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ORIGINAL ARTICLE

The association between low vitamin D and depressive disorders

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It has been hypothesized that hypovitaminosis D is associated with depression but epidemiological evidence is limited. We investigated the association between depressive disorders and related clinical characteristics with blood concentrations of 25-hydroxyvitamin D [25(OH)D] in a large cohort. The sample consisted of participants (aged 18–65 years) from the Netherlands Study of Depression and Anxiety (NESDA) with a current ($N = 1102$) or remitted ($N = 790$) depressive disorder (major depressive disorder, dysthymia) defined according to DSM-IV criteria, and healthy controls ($N = 494$). Serum levels of 25(OH)D measured and analyzed in multivariate analyses adjusting for sociodemographics, sunlight, urbanization, lifestyle and health. Of the sample, 33.6% had deficient or insufficient serum 25(OH)D ($< 50\ \text{nmol l}^{-1}$). As compared with controls, lower 25(OH)D levels were found in participants with current depression ($P = 0.001$, Cohen's $d = 0.21$), particularly in those with the most severe symptoms ($P = 0.001$, Cohen's $d = 0.44$). In currently depressed persons, 25(OH)D was inversely associated with symptom severity ($\beta = -0.19$, s.e. $= 0.07$, $P = 0.003$) suggesting a dose-response gradient, and with risk (relative risk $= 0.90$, 95% confidence interval $= 0.82$–0.99, $P = 0.03$) of having a depressive disorders at 2-year follow-up. This large cohort study indicates that low levels of 25(OH)D were associated to the presence and severity of depressive disorder suggesting that hypovitaminosis D may represent an underlying biological vulnerability for depression. Future studies should elucidate whether—the highly prevalent—hypovitaminosis D could be cost-effectively treated as part of preventive or treatment interventions for depression.

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INTRODUCTION

Depression is a major public health problem and is projected to be the second most important cause of disability worldwide in 2020.[1] This trend is accompanied by soaring costs for treatment and reduced productivity.[2] Depression etiology and pathophysiology have not yet been fully elucidated. Recent advances in basic and clinical research highlighted the potential role of new biological factors that may affect mood in combination with the more traditional neurochemical and neuroendocrine mechanisms.

For instance, vitamin D has been increasingly related to cognitive decline and mental health and it has been hypothesized that hypovitaminosis D may contribute to depression.[3,4] Studies in humans confirmed the presence of vitamin D receptors (VDR) and 1α-hydroxylase that catalyzes the synthesis of 1,25-dihydroxyvitamin D (calcitriol, the bioactive form of vitamin D) within brain structures such as prefrontal cortex, the amygdala and the hippocampus.[5,6] Vitamin D metabolites protect the integrity of neurons through upregulation of neurotrophic factors (nerve growth factor, neurotrophin-3 and neurotrophin-4) present in the hippocampus and neocortex.[7,8] Moreover, vitamin D affects inflammatory pathways (downregulating autoimmune pathways producing proinflammatory cytokines and promoting anti-inflammatory pathways through VDR-mediated gene transcription)[9–11] that in turn have been linked to depression.[12,13]

To date, epidemiological evidence concerning the association between vitamin D and depression is limited and non-conclusive: several studies identified associations between depression and low vitamin D levels, but there were also a number of studies with non-significant results.[14,15] Moreover, the majority of clinical studies had small sample sizes, while population-based studies were more commonly performed in older persons and measured depression generally through symptoms questionnaires instead of assessing psychiatric diagnoses by means of clinical interviews.[14–20]

In the present study, we examined the association between vitamin D and depression in a large and relatively young cohort well-characterized in terms of psychiatric diagnoses taking important confounding factors into account. The main aim of the study was to compare the serum level of 25-hydroxyvitamin-D [25(OH)D] (and parathyroid hormone (PTH)) in depressed patients, persons with remitted depression and healthy controls. Moreover, we explored whether in persons with current depressive disorders serum 25(OH)D was associated with specific clinical features and the course of depression. We hypothesized that serum 25(OH)D levels would be lower in currently depressed patients and persons with remitted depression as compared with healthy controls, and that low 25(OH)D concentrations in depressed patients would be associated with less favorable clinical characteristics and subsequent course.

MATERIALS AND METHODS

Study population

Participants were part of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing cohort study into the long-term course and consequences of depressive and anxiety disorders. A description of the

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study rationale, design and methods is given elsewhere.[21] Briefly, in 2004–2007 participants aged 18–65 years were recruited from the community (19%), general practice (54%) and secondary mental health care (27%), reflecting therefore various settings and developmental stages of psychopathology in order to obtain a full and generalizable picture of the course of psychiatric disorders. A total of 2981 participants were included, consisting of persons with a current or past depressive and/or anxiety disorder and healthy controls. After 2 years, a face-to-face follow-up assessment was conducted with a response of 87.1%.[22] The research protocol was approved by the ethical committee of participating universities, and all respondents provided written informed consent.

At baseline, participants provided blood samples and underwent medical examinations and psychiatric interviews. Presence of DSM-IV[23] diagnoses of depressive (major depressive disorder, dysthymia) and anxiety (social phobia, generalized anxiety disorder, panic disorder and agoraphobia) disorders was ascertained using the Composite Interview Diagnostic Instrument (CIDI)[24] administered by specially trained research staff. For the present analyses, we initially selected participants with a current (that is, within the past 6 month; $N=1158$) or remitted (that is, lifetime, but not current; $N=815$) depressive disorder and healthy controls ($N=511$) without any lifetime depressive/anxiety disorder and a score on the Inventory of Depressive Symptoms (IDS)[25] below 14 points. Of these 2484 persons, we excluded 54 with missing values and 44 with values above 3 s.d. for 25(OH)D ($N=11$, $\geqslant 151\,\mathrm{nmol\,l^{-1}}$) and PTH ($N=33$, $\geqslant 12.9\,\mathrm{pmol\,l^{-1}}$). This left 2386 participants as the primary sample. Excluded participants, as compared with those included, were older (44.4 vs 41.7 years, $P=0.04$) but did not differ in terms of sex, years of education and depressive disorder status. Finally, analyses on the course of depressive disorders were based on 902 participants currently depressed at baseline who participated in the 2-year follow-up and had complete data on outcome indicators.

Vitamin D and PTH assays

Vitamin D status was measured by assessing circulating levels of 25(OH)D, which is the combined product of cutaneous synthesis from solar exposure and dietary sources. Fasting blood samples were obtained in the morning around 8 am and kept frozen at $-80\,^{\circ}\mathrm{C}$ and never thawed before analysis. Serum 25(OH)D was measured using isotope dilution—online solid phase extraction liquid chromatography–tandem mass spectrometry (ID-XLC-MS/MS),[26] which is an accurate method for the quantification of 25(OH)D, known to be a difficult analyte to measure.[27] In short, 25(OH)D was released from its binding protein(s) and a deuterated internal standard (IS: 25(OH)D3-d6) was added. Samples were extracted and analyzed by XLC-MS/MS (a Symbiosis online SPE system (Spark Holland, Emmen, the Netherlands) coupled to a Quattro Premier XE tandem mass spectrometer (Waters Corp., Milford, MA, USA). Concentrations of $25(OH)D_2$ and $25(OH)D_3$ were measured separately and added to report total 25(OH)D. Limit of quantitation was $4.0\,\mathrm{nmol\,l^{-1}}$, intra-and inter-assay coefficients of variation were $<6\%$ and $<8\%$ for concentrations between 25 and $180\,\mathrm{nmol\,l^{-1}}$. The Institute of Medicine[28] has set the optimal serum 25(OH)D at $50\,\mathrm{nmol\,l^{-1}}$ ($20\,\mathrm{ng\,ml^{-1}}$) or higher. A serum 25(OH)D lower than $25\,\mathrm{nmol\,l^{-1}}$ ($10\,\mathrm{ng\,ml^{-1}}$) is considered vitamin D deficient, as it may be associated with clinical skeletal disease, and a level from 25–$50\,\mathrm{nmol\,l^{-1}}$ is considered insufficient. As some experts[29] consider serum 25(OH)D $>75\,\mathrm{nmol\,l^{-1}}$ ($30\,\mathrm{ng\,ml^{-1}}$) as optimal, we also looked at the persons with a serum 25(OH)D between 50 and $75\,\mathrm{nmol\,l^{-1}}$ ($30\,\mathrm{ng\,ml^{-1}}$).

Serum intact PTH was determined using an immunometric assay (Abbott Laboratories, Abbott Park, Illinois) with a limit of quantification of $0.5\,\mathrm{pmol\,l^{-1}}$ and both intra- and inter-assay coefficients of variations of $<5\%$.

Clinical characteristics

For participants with current depressive disorders, various clinical characteristics were further assessed. The severity of depression was measured using the 28-item self-report IDS.[25] The clinical cutoffs of the IDS were also applied, classifying symptoms severity in none/mild ($\leqslant 25$), moderate (26–38), severe (39–48) and very severe ($\geqslant 49$). Depressive symptoms duration during the past 4 years was measured using the Life Chart Interview method,[30] which uses a calendar approach to assess depressive symptoms: the percent of time (0–100%) with depressive symptoms was calculated. Data on age of onset and presence of comorbid anxiety disorders were derived from the CIDI. To examine a potential pathophysiological impact of treatment, medication use was assessed based on drug container inspection of all drugs used in the past month and classified according to the Anatomical Therapeutic Chemical classification system.[31] Antidepressant medications were only considered when taken on a regular basis (at least 50% of the time) and included selective serotonin reuptake inhibitors (N06AB), serotonin-norepinephrine reuptake inhibitors (N06AX16, N06AX21) and tricyclic antidepressants (N06AA).

Course of depressive disorders

Course was determined using two different outcome measures: (1) the presence (yes/no) of a DSM-IV depressive diagnosis (6-month recency) at 2-year follow-up was ascertained through a CIDI interview at 2-year follow-up; (2) duration of depressive symptoms as calculated with the Life Chart Interview assessing presence and severity of symptoms at each month during the 2-year follow-up. Duration of symptoms was calculated as the percentage of time during follow-up with symptoms of at least mild severity. Two indicators were constructed: a continuous score ranging from 0 (no symptoms at all during follow-up) to 100% (symptoms during the entire follow-up period) and a dichotomous indicator assessing whether persons had (yes/no) depressive symptoms for $>75\%$ (highest quartile) of the follow-up period.

Confounders

Putative confounders were a priori selected on the basis of previously reported associations with vitamin D and depression. Sociodemographic characteristics included age, sex and years of education. The following lifestyle characteristics were assessed: smoking status (never/former/current); alcohol use was assessed by the Alcohol Use Disorder Identification Test, with higher scores (range 0–40) indicating hazardous and harmful use;[32] body mass index calculated as $\mathrm{kg\,m^{-2}}$ and categorized as normal (<25), overweight (25–29.99) and obese ($\geqslant 30$); physical activity measured with the International Physical Activity Questionnaire[33] and expressed in MET-minutes (ratio of energy expenditure during activity compared with rest times the number of minutes performing the activity) per week. Number of self-reported chronic diseases for which persons received treatment (including cardiovascular disorders, diabetes, lung disease, arthritis, cancer, ulcer, intestinal problem, liver disease, epilepsy and thyroid gland disease) was calculated as a global marker of poor physical health. To account for effects of renal function on 25(OH)D levels, creatinine clearance was calculated using plasma creatinine and the Cockroft–Gault formula.[34] Plasma creatinine was assessed using the Roche enzymatic creatinine method (Roche Diagnostics, GmbH, Mannheim, Germany). Use of vitamin D supplements was assessed using Anatomical Therapeutic Chemical codes and included vitamin D and analogs (A11CC) or vitamin D in combination with calcium (A12AX) and with other vitamins (multivitamin, A11B). Instead of using season of blood collection as a proxy for sunlight irradiation, as commonly used in vitamin D research, we used data on the actual amount of sunlight. The number of sunlight hours in the 10 weeks preceding blood drawing was measured using pyranometers at the weather station of the Dutch Royal Metereological Institute (Supplementary eMethods). Degree of urbanization (number of inhabitants per $\mathrm{km^2}$) was assessed as described by Snijder *et al.*[35] as a possible factor affecting sunlight exposure.

Statistical analyses

Variables were reported as percentages or means ± s.d. as appropriate. Differences in baseline characteristics were tested according to depressive disorder status using χ^2-tests or analyses of variance as appropriate. Partial correlations between 25(OH)D and major covariates were examined using Pearson's or Spearman's coefficients controlling for age and sex. Adjusted mean levels of 25(OH)D and PTH levels across depressive disorder status groups were compared using analyses of covariance. For significant differences, *post-hoc* tests between groups were performed using Tukey's test and Cohen's d[36] was calculated as a measure of effect size. To investigate possible differences due to sex or sunlight levels, depression-by-sex and depression-by-sunlight interaction terms were entered in fully adjusted models. Multinomial logistic regressions were used to compare the odds of desirable, deficient and inadequate versus adequate 25(OH)D levels across depressive disorder status groups. To test whether specific clinical characteristics were associated with 25(OH)D and PTH levels, linear regression analyses were performed for each characteristic within the group of participants with a current depressive disorder. In the same group, the association between serum 25(OH)D and categorical course indicators was calculated using the "modified Poisson" approach proposed

Table 1. Characteristics of the study population

Characteristics	*Controls* (n = 494)	*Depressive disorders*		P
		Remitted (n = 790)	*Current* (n = 1102)	
Sociodemographic				
Age (years) (mean ± s.d.)	40.1 ± 14.9	43.4 ± 12.5	40.9 ± 12.1	<0.0001
Sex (F)(%)	60.7	69.4	67.2	0.01
Education (years) (mean ± s.d.)	13.0 ± 3.2	12.4 ± 3.2	11.6.9 ± 3.3	<0.0001
Determinants of sunlight exposure				
Sunlight previous 10 weeks (h)(mean ± s.d.)	565.3 ± 210.2	534.7 ± 226.9	515.1 ± 232.9	0.002
Level urbanization (*N* inabitants per km^2) (%)				0.01
<500	5.7	5.5	5.6	
500–1000	5.9	8.6	10.9	
1000–1500	15.9	14.6	15.3	
1500–2500	9.4	14.7	13.5	
>2500	63.2	56.5	54.7	
Lifestyle and health indicators				
Smoking status *(%)*				<0.0001
Non smoker	37.9	23.4	26.7	
Former smoker	35.8	37.2	27.9	
Current smoker	26.3	39.4	45.5	
Alcohol AUDIT score (mean ± s.d.)	4.7 ± 3.4	4.7 ± 4.4	4.9 ± 5.4	0.55
Physical activity (MET-min per week)(mean ± s.d.)	3880.8 ± 3037.1	3811.0 ± 3044.0	3497.7 ± 3226.1	0.04
Body mass index (%)				0.02
Normal	55.9	50.7	52.1	
Overweight	30.2	33.6	28.6	
Obesity	14.0	15.7	19.3	
No. of chronic diseases (mean ± s.d.)	0.6 ± 0.9	0.9 ± 1.1	1.0 ± 1.1	<0.0001
Creatinine clearance (ml min^{-1}) (mean ± s.d.)	125.4 ± 35.5	124.2 ± 35.5	130.6 ± 40.0	0.001
Vitamin D supplements use (%)	9.5	9.6	10.2	0.89
Clinical characteristics				
IDS score (mean ± s.d.)	5.3 ± 3.5	17.7 ± 10.1	32.4 ± 12.1	<0.0001
Duration (% time depressed) (mean ± s.d.)			38.2 ± 0.30	
Age of onset (years) (mean ± s.d.)			27.0 ± 12.4	
Comorbid anxiety (%)			65.6	
Antidepressant use (%)				
No antidepressant	99.6	78.7	61.2	<0.0001
SSRI	0.4	15.6	27.9	
SNRI	0.0	3.0	6.9	
TCA	0.0	2.7	4.1	
Vitamin D and parathyroid hormone				
25(OH)D (nmol l^{-1}) (mean ± s.d.)	68.0 ± 26.7	63.1 ± 27.1	59.9 ± 27.8	<0.0001
PTH (pmol l^{-1}) (mean ± s.d.)	5.0 ± 1.9	5.4 ± 2.0	5.6 ± 2.1	<0.0001
2-Year outcome indicators[a]				
Depression disorders at 2-year folllow-up (%)			45.2	
% Follow-up with depression (mean ± s.d.)			34.6 ± 0.32	

Abbreviations: AUDIT, alcohol use disorder identification test; IDS, inventory of depressive symptoms; PTH, parathyroid hormone; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; 25(OH)D, 25-hydroxyvitamin D.
[a]Data available for 902 participants currently depressed at baseline who participated in the 2-year follow-up.

by Zou[37] that allow to estimate relative risks, which are preferable over the odds ratios approximation when outcome events occur in >10% of subjects.[38] The association between 25(OH)D and the continuous measure of symptom duration was tested using left-censored regression (Tobit) models,[39] because of the large cluster at the zero value (25.2%) of the distribution. All analyses were performed using SAS (v. 9.2, SAS Institute, Inc., Cary, NC, USA). Significance level was set at $P<0.05$, two-tailed.

RESULTS

The mean age of the study sample was 41.7 (± 12.9) years and 66.6% were women. Subjects with remitted or current depressive disorders were more often women, were older and less educated (Table 1). Currently depressed had the least favorable profile on almost all of the lifestyle and health characteristics and were less likely to live in highly urbanized areas. Moreover, depressed persons participated in the blood drawing after a period with less sunlight. Only 9.9% of the sample used vitamin D supplements. Given this low prevalence and the lack of association with depression status, this variable was not retained in subsequent analyses. After age- and sex-adjustment, serum 25(OH)D was significantly correlated with PTH ($r=-0.26$, $P<0.0001$), sunlight in previous 10 weeks ($r=0.36$, $P<0.0001$), physical activity ($r=0.07$, $P=0.001$), body mass index ($rs=-0.15$, $P<0.0001$) and urbanization level ($rs=0.06$, $P=0.004$).

Table 2 shows adjusted means of 25(OH)D and PTH across depression groups. After adjustment for sociodemographics, sunlight and urbanization, a significant (*P*-for-trend <0.0001) progressively lower level of 25(OH)D was found from healthy controls to those with remitted depression to those with current depression. As compared with controls, significantly lower 25(OH)D levels were found for subjects with remitted depression ($P=0.004$, d = 0.18) and for those with current depression

Table 2. Adjusted means of serum 25(OH)D and PTH across depression groups

	25(OH)D					*PTH*				
	Controls	*Remitted depression*		*Current depression*		*Controls*	*Remitted depression*		*Current depression*	
	mean (s.e.)	*mean (s.e.)*	P[a]	*mean (s.e.)*	P[a]	*mean (s.e.)*	*mean (s.e.)*	P[a]	*mean (s.e.)*	P[a]
Model 1	67.7 (1.16)	63.0 (0.91)	0.004	60.5 (0.77)	<0.0001	5.13 (0.09)	5.36 (0.07)	0.10	5.64 (0.06)	<0.0001
Model 2	66.6 (1.17)	63.2 (0.92)	0.06	61.2 (0.79)	0.001	5.10 (0.09)	5.37 (0.07)	0.06	5.60 (0.06)	<0.0001

Abbreviations: PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D. Model 1: adjusted for age, sex, education, sunlight and level of urbanization. Model 2: additionally adjusted for smoking, alcohol, BMI, physical activity, chronic diseases and creatinine clearance. Unit of measure: 25(OH)D, nmol l^{-1} (multiply by 0.4 to obtain ng ml^{-1}); PTH, pmol l^{-1}.
[a]From *post-hoc* comparison (Tukey's test) with mean 25(OH)D levels of the controls.

($P<0.0001$, d = 0.28). Additional adjustment for lifestyle and health status did not substantially modify these associations (*P*-for-trend = 0.001): differences with controls were slightly reduced for those with remitted depression ($P=0.06$, d = 0.13) and remained significant for those currently depressed ($P=0.001$, $d=0.21$). No significant interactions of depression status with sex (depression-by-sex $P=0.74$) or sunlight (depression-by-sunlight $P=0.24$) was found. Finally, we repeated the analyses after dividing currently depressed patients according to IDS clinical cutoffs.[27] As compared with controls, 25(OH)D level was significantly and progressively lower in 445 patients with moderate (61.1, s.e. 1.2 nmol l^{-1}; $P=0.01$, $d=0.22$), 224 with severe (59.0, s.e. 1.7 nmol l^{-1}; $P=0.004$, $d=0.30$) and 103 with very-severe (55.3, s.e. 2.6 nmol l^{-1}; $P=0.001$, $d=0.44$) symptoms, suggesting a dose-response relationship (Supplementary eFigure1). Analyses with PTH showed progressively higher concentrations (*P*-for-trend < 0.0001) from controls to depressed subjects.

One third of the sample (33.6%) had insufficient (< 50 nmol l^{-1}) 25(OH)D levels and 7% had deficient (< 25 nmol l^{-1}) levels. The proportion of participants with deficient 25(OH)D levels increased from healthy controls (4.7%) to those with remitted (5.8%) and current (9.0%) depression (Figure 1). Table 3 reports the odds of desirable, insufficient and deficient 25(OH)D levels estimated by multinomial logistic regressions in which adequate status (> 75 nmol l^{-1}) was set as the reference category. In fully adjusted models, as compared with controls, those with current depression had a 1.80-fold ($P=0.001$) and 2.17-fold ($P=0.01$) increased risk for insufficient and deficient 25(OH)D levels, respectively. Subjects with remitted depression, as compared with controls, had a 1.68-fold ($P=0.004$) increased risk for insufficient 25(OH)D levels and a non-significant increased risk for deficient levels (probably attributable to low number of subjects, only 46, in the latter category). Finally, results from Tables 2 and 3 were unchanged (data not shown) in confirmatory analyses after (1) additional adjustment for vitamin supplements use, (2) exclusion of 120 participants (5.0%) of non north-European ancestry (including a few persons with dark skin) and (3) including the 44 participants initially excluded for outliers value of the studied biomarkers.

Clinical characteristics

Linear regression models tested the association of specific psychiatric characteristics with 25(OH)D and PTH within the group ($N=1102$) with current depressive disorders (Table 4). After full adjustment, depression severity as measured by the IDS was inversely associated with 25(OH)D levels ($\beta=-0.19$, s.e. = 0.07, $P=0.003$), in line with a dose-response relationship. These results were not modified by additional adjustment for PTH. In contrast, the tendency towards significance ($P=0.08$) in the association between severity and higher PTH disappeared after further adjustment for 25(OH)D ($P=0.30$), suggesting that the association was largely driven by 25(OH)D. No associations were found in fully adjusted models for duration, age of onset or comorbidity of anxiety disorder. Use of antidepressants, as compared with being drug-free, was significantly associated with higher PTH (serotonin-norepinephrine reuptake inhibitors, $P=0.01$; tricyclic antidepressants, $P<0.0001$; selective serotonin reuptake inhibitors, $P=0.002$) even when including IDS score, in order to take into account that medicated participants may represent the most severe cases.

Course of depressive disorders

We examined whether serum 25(OH)D predicted depression course in 902 (81.9%) participants with current depressive disorders and available data at 2-year follow-up (Table 5). In fully adjusted models, each s.d. increase of 25(OH)D concentrations was associated with a 10% decreased risk ($P=0.03$) of having a depressive disorder at follow-up (45.2% prevalence). Furthermore, higher serum 25(OH)D was also associated with lower duration of depressive symptoms during follow-up ($P=0.01$) and with lower risk of having depressive symptoms for > 75% (highest quartile) of the follow-up period ($P=0.001$). As compared with participants with adequate 25(OH)D, those with insufficient and deficient levels had, respectively, a 1.55 (95% confidence interval (CI) = 1.07–2.24, $P=0.02$) and 1.74 (95% CI = 1.07–2.84, $P=0.03$) higher risk of having depressive symptoms for > 75% of the follow-up period. Results were unchanged when selecting more stringent cutoffs at 80 and 90%, with relative risks for 25(OH)D s.d.-increase of, respectively, 0.76 (95% CI = 0.64–0.91, $P=0.002$) and 0.57 (95% CI = 0.43–0.75, $P<0.0001$).

DISCUSSION

In a large cohort of depressed persons and controls, to our knowledge the largest of its kind, we found that after considering a wide set of possible confounding factors, low serum level of 25(OH)D was associated with the presence and severity of depressive disorders. Although the overall association between depression status and 25(OH)D was of rather small effect size (comparable to those found for inflammatory markers,[12] brain-derived neurotrophic factor[40] and cortisol[41]), the effect size was more pronounced in subjects with the most severe symptoms. Clinically insufficient and deficient 25(OH)D levels were more likely to be found in subjects with either remitted and current depression. Moreover, in patients with current depression low serum 25(OH)D was associated with a less favorable course over a 2-year follow-up. In the present study, we also found that being depressed was associated with higher PTH, although this association was partially driven by low 25(OH)D. Secondary hyperparathyroidism has been proposed as the principal mechanism whereby vitamin D deficiency could contribute to

the pathogenesis of osteoporosis. The reduction of intestinal calcium absorption due to vitamin D deficiency triggers the release of PTH, which corrects serum calcium by promoting bone resorption with mobilization of calcium and consequent bone loss.[42,43] Intriguingly, depression has been associated with accelerated bone loss. A recent meta-analysis[44] showed that depression, especially when diagnosed according to DSM criteria, was associated with significantly reduced bone mineral density and an increased bone resorption markers. Furthermore, we found that in depressed patients antidepressant treatment was associated with increased PTH, while no differences were found in 25(OH)D levels. Although there is evidence of hyperparathyroidism induced by long-term treatment with lithium,[45] the relationship between antidepressant treatments and PTH has not been systematically studied. Epidemiological studies in older persons showed that use of antidepressants were associated with fragility fractures and low bone mineral density even beyond the effects of depression itself.[46–48] Whether PTH may have a role in this association is unknown. Further research aimed specifically at disentangling this relationship is needed.

The current study has some limitations. First, as the study design is mainly cross-sectional, no inference on the directionality of the association can be made. We were not able to adjust the detected association for dietary intake of vitamin D, because nutritional data were not available. However, only a small part of circulating 25(OH)D is determined by dietary intake,[49] very few foods naturally contain vitamin D and fortification of food in the Netherlands is limited.[50] Moreover, as we reported, supplementation was largely absent. Our study has some important strengths, including the large sample size, clinical diagnoses of depression, a gold-standard method to assay 25(OH)D and adequate adjustment for potential confounders, including a measure of the actual sunlight irradiation.

In summary, our findings provide strong confirmative evidence to prior literature, which was mainly based on older samples with symptom reports, by showing the link between vitamin D and depression in a large and relatively young cohort including psychiatric cases of depression. Remarkably, low serum levels of 25(OH)D were found in subjects with both current and remitted depression. Furthermore, among currently depressed patients those with lower serum 25(OH)D had a less favorable course over time. However, no definite conclusions about directionality in this association can be extrapolated from the present findings. Hypovitaminosis D may also be the consequence of depression, due to the fact that depression impacts on health-related lifestyle such as physical activity, diet and obesity, all of which have been linked to serum 25(OH)D levels.[50–53] Adjusting for these factors (plus sunlight and urbanization) did not attenuate the association between 25(OH)D and presence, severity and course of depression. Our results should stimulate further longitudinal and experimental studies demonstrating consistent time-sequenced associations in order to further explore causality in the depression-vitamin D link. Demonstrating an involvement of vitamin D in the pathway to depression may have important implications. Depression is a highly heterogeneous disorder, and hypovitaminosis D may be relevant only in specific subgroups of patients. Although hypovitaminosis D is highly prevalent,[54] potentially modifiable determinants of vitamin D status, such as dietary habits, use of dietary supplements and behavior related to sun exposure, could provide new selective cost-effective strategies aimed at preventing depression and its disease burden.[2] In a randomized controlled trial,[55] involving overweight and obese

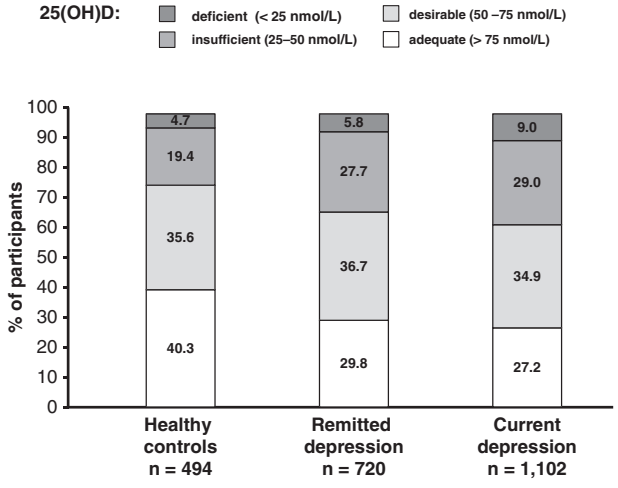

Figure 1. Clinical classification of serum 25(OH)D levels across depression groups. 25(OH)D, 25-hydroxyvitamin D. Unit of measure 25(OH)D: nmol l^{-1} (multiply by 0.4 to obtain ng ml^{-1}).

Table 3. Adjusted associations between depressive disorder status and clinical classification of serum 25(OH)D

		25(OH)D status								
Depression status	*Adequate* (n = *734*)	*Desirable* (n = *850*)			*Insufficient* (n = *634*)			*Deficient* (n = *168*)		
		OR	*95% CI*	P	*OR*	*95% CI*	P	*OR*	*95% CI*	P
Model 1										
Healthy controls	Reference category	1.00			1.00			1.00		
Depressed—remitted		1.35	(1.03–1.78)	0.03	1.90	(1.38–2.63)	0.0001	1.73	(0.99–3.05)	0.06
Depressed—current		1.40	(1.08–1.82)	0.01	2.09	(1.53–2.85)	<.0001	2.80	(1.67–4.7)	<0.0001
Model 2										
Healthy controls	Reference category	1.00			1.00			1.00		
Depressed—remitted		1.30	(0.98–1.74)	0.07	1.68	(1.19–2.37)	0.004	1.48	(0.81–2.70)	0.20
Depressed—current		1.37	(1.04–1.81)	0.03	1.80	(1.29–2.51)	0.001	2.17	(1.24–3.80)	0.01

Abbreviations: CI, confidence interval; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D. Model 1: adjusted for age, sex, education, sunlight and level of urbanization. Model 2: additionally adjusted for smoking, alcohol, BMI, physical activity, chronic diseases and creatinine clearance. 25(OH)D status clinical classification: adequate, >75 nmol l^{-1} (>30 ng ml^{-1}); desirable 75–50 nmol l^{-1} (30–20 ng ml^{-1}); insufficient, <50 nmol l^{-1} (<20 ng ml^{-1}); deficient, <25 nmol l^{-1} (<10 ng ml^{-1}).

Table 4. Adjusted associations of depression characteristics with serum 25(OH)D and PTH in participants with current depressive disorders (N = 1102)

	25(OH)D			
Clinical characteristics	*Model 1*		*Model 2*	
	β (s.e.)	P	*β* (s.e.)	P
Severity (IDS score)	− 0.28 (0.07)	<.0001	− 0.19 (0.07)	0.003
Duration (% time depressed)	− 4.43 (2.67)	0.10	− 3.90 (2.69)	0.15
Age of onset (years)	0.07 (0.08)	0.39	0.09 (0.08)	0.22
Comorbid anxiety	− 3.52 (1.67)	0.04	− 3.20 (1.67)	0.06
Antidepressant use[a]				
No antidepressant	Ref		Ref	
SSRI	− 3.40 (1.82)	0.06	− 3.43 (1.82)	0.06
SNRI	− 3.90 (3.17)	0.22	− 1.39 (3.19)	0.66
TCA	− 8.63 (4.04)	0.03	− 7.10 (4.05)	0.08
	PTH			
Clinical characteristics	Model 1		Model 2	
	β (s.e.)	P	*β* (s.e.)	P
Severity (IDS score)	0.01 (0.01)	0.01	0.01 (0.01)	0.08
Duration (% time depressed)	0.38 (0.21)	0.07	0.22 (0.22)	0.32
Age of onset (years)	− 0.001 (0.01)	0.92	− 0.002 (0.01)	0.68
Comorbid anxiety	− 0.010 (0.13)	0.46	− 0.04 (0.13)	0.78
Antidepressant use[a]				
No antidepressant	Ref		Ref	
SSRI	0.36 (0.14)	0.01	0.39 (0.14)	0.01
SNRI	1.05 (0.25)	<0.0001	1.16 (0.25)	<0.0001
TCA	0.97 (0.32)	0.002	1.01 (0.32)	0.002

Abbreviations: IDS, inventory of depressive symptoms, PTH, parathyroid hormone; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; 25(OH)D, 25-hydroxyvitamin D. Model 1: adjusted for age, sex, education, sunlight and level of urbanization. Model 2: additionally adjusted for smoking, alcohol, BMI, physical activity, chronic diseases and creatinine clearance.
[a]Additionally adjusted for symptoms severity (IDS score).

Table 5. Multivariate analyses[a] on serum 25(OH)D as predictor of the 2-year depression course among persons with a current depressive disorder at baseline (*n* = 902)

	Presence (yes/no) of depressive disorders after 2 years				*Percent of time with depressive symptoms during 2-year follow-up*						
					0–100%			*>75% (Highest quartile)*			
	%	*RR*	*95% CI*	P	*Estimate*	s.e.	P	*%*	*RR*	*95% CI*	P
25(OH)D per s.d. increase	45.2	0.90	(0.82–0.99)	0.03	− 0.03	0.01	0.01	25.0	0.78	(0.67–0.91)	0.001
25(OH)D status											
Adequate (*n* = 246)	42.7	Ref.			Ref.			20.3	Ref.		
Desirable (*n* = 325)	45.5	1.12	(0.92–1.37)	0.27	0.02	0.03	0.55	24.0	1.25	(0.89–1.75)	0.79
Insufficient (*n* = 258)	44.6	1.16	(0.93–1.46)	0.19	0.07	0.03	0.02	29.5	1.55	(1.07–2.24)	0.02
Deficient (*n* = 73)	54.8	1.41	(1.06–1.89)	0.03	0.06	0.05	0.17	28.8	1.74	(1.07–2.84)	0.03

Abbreviations: CI, confidence interval; RR, relative risk; 25(OH)D, 25-hydroxyvitamin D. 25(OH)D, s.d. = 27.5 nmol l^{-1} (11 ng ml^{-1}).
[a]Adjusted for age, sex, education, sunlight, level of urbanization, smoking, alcohol, BMI, physical activity, chronic diseases and creatinine clearance.

non-depressed individuals aged 21–70 years, the supplementation of high dosage vitamin D was associated with an improvement in depressive symptoms over the following 12 months. In contrast, two recent trials based on samples of postmenopausal women in the United States[56] and the adult general population in Norway[57] reported no benefit of vitamin D supplementation on depressive symptoms after a follow-up of, respectively, 2 years and 6 months. However, none of the trials included clinically depressed patients and additional factors such as assessment of depression with symptom questionnaires only, exclusion of participants with the most severe symptoms and concomitant calcium supplementation may have influenced the results. In the meantime, treatment of clinically relevant hypovitaminosis D in the high-risk population of severely depressed patients may positively impact on health-related outcomes such as bone health and physical function, which subsequently can contribute to a favorable impact on mood. If further intervention trials will be undertaken, important methodological aspects, such as optimal target levels of serum 25(OH)D, type and dosage of supplementation (with consideration of potential harmful effects) should be systematically evaluated. Addressing these issues successfully will allow us to determine whether normalization of 25(OH)D levels may become a potential future strategy to prevent and treat depression and its deleterious consequences on health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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