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Research Article

Low 25-Hydroxyvitamin D Concentrations Predict Incident Depression in Well-Functioning Older Adults: The Health, Aging, and Body Composition Study

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Abstract

Background. Cross-sectional studies suggest that low 25-hydroxyvitamin D (25[OH]D) may be a risk factor for depression; however, there are few prospective studies. We examined the association between 25(OH)D and depressive symptoms in community-dwelling persons aged 70–79 years in the Health, Aging, and Body Composition (Health ABC) Study (***n*** = 2598).

Methods. Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression Scale (CES-D) at baseline and 2-, 3- and 4-year follow-up. Serum 25(OH)D was measured at 1-year follow-up and categorized as <20, 20–<30, and ≥30 ng/mL. Mixed models were used to examine change in CES-D scores according to 25(OH)D categories. The association between 25(OH)D categories and incident depression (CES-D short score ≥10 or antidepressant medication use) were assessed using Cox proportional hazards models. Analyses were adjusted for socio-demographic and behavioral characteristics, season, and chronic conditions.

Results. Thirty-three percent of participants had 25(OH)D <20 ng/mL. Serum 25(OH)D was not associated with CES-D scores at baseline (***p*** = .51); however, CES-D scores increased over time and were significantly associated with 25(OH)D at 2-year (***p*** = .003) and 4-year follow-up (***p*** < .001). Among 2,156 participants free of depression at the 1-year follow-up, the cumulative incidence of depression was 26.9%. Participants with 25(OH)D <20 ng/mL were at greater risk of developing depression (HR [95% CI]: 1.65 [1.23–2.22]) over 4 years of follow-up compared with those with 25(OH)D ≥30 ng/mL.

Conclusion. Low 25(OH)D was independently associated with a greater increase in depressive symptom scores and incident depression in community-dwelling older adults.

Key Words: Depression—Epidemiology—Risk factors—Nutrition.

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Low serum 25-hydroxyvitamin D (25[OH]D) and depression are both common in older adults. A growing body of literature suggests that low 25(OH)D may be associated with depression in later life, although methodological concerns and inconsistent results have limited the strength of evidence (1,2). An association could have significant public health implications, as identifying modifiable risk factors for depression is an important health care priority.

Vitamin D insufficiency (25(OH)D <20 ng/mL) is associated with a number of poor health outcomes (3) and affects roughly one-third of the older adult population (4). Older adults are predisposed to low 25(OH)D by behavioral and physiologic changes associated with aging, such as reduced exposure to sunlight and decreased efficiency of UV-mediated synthesis of vitamin D in the skin (5).

Major depression affects 1–5% of the community-dwelling older adult population, with an additional 8–20% experiencing clinically significant depressive symptoms. Beyond personal suffering and family disruption, these individuals are at risk for disability, morbidity and all-cause mortality (6–11). Furthermore, depression in late-life is a heterogeneous and poorly understood disorder. Multiple etiologic pathways are suspected to underlie the broad spectrum of symptoms, natural history, and response to therapy observed among older adults.

A possible role for vitamin D in the etiology of depression is supported by the presence of vitamin D receptors and activating enzymes concentrated in areas of the human brain known to be associated with mood regulation (12–14). Some (15–20), but not all (21,22), cross-sectional studies suggest that 25(OH)D and mood are associated in older adults. However, it is difficult to determine from cross-sectional studies whether low 25(OH)D precedes the onset of depression or whether individuals have low 25(OH)D because they are depressed and have less sun exposure and endogenous 25(OH)D synthesis. The few prospective studies have found an increased risk of depression among older adults with low 25(OH)D (23–25); however, one of these studies was limited to men (24) and another to patients with cardiovascular disease (25). Thus, the objective of this study was to examine the association between 25(OH)D and changes in depressed mood and incident depression over 4 years of follow-up in community-dwelling older black and white men and women in the Health, Aging, and Body Composition (Health ABC) Study.

Methods

Study Population

The Health ABC Study is a prospective cohort study investigating the associations between body composition, weight-related health conditions, and incident functional limitations in older adults. A total of 3,075 community-dwelling black and white men and women aged 70–79 years were enrolled between April 1997 and June 1998. Participants were recruited from a random sample of white and all black Medicare-eligible residents in Pittsburgh, Pennsylvania (40.4°N latitude) and Memphis, Tennessee (35.2°N latitude). Eligibility criteria included: (i) self-report of no difficulty walking one-fourth of a mile, climbing up 10 steps, or performing activities of daily living; (ii) absence of life-threatening illness; (iii) plan to remain in the geographic area for at least 3 years; and (iv) no current enrollment in lifestyle intervention trials. All participants provided written informed consent, and all protocols were approved by the institutional review boards at each study site.

Participants who attended the 1-year follow-up visit (1998–1999), when 25(OH)D was measured, were eligible for these analyses (n = 2998). Those with missing serum 25(OH)D (n = 205), baseline depression (n = 36), or covariates (n = 159) were excluded, resulting in a cross-sectional sample of 2,598 participants. The sample for the longitudinal analysis of change in CES-D scores over time (n=2,504) further excluded those who did not have CES-D scores at either the 2- or 4-year follow-up visit (n = 94). For the incident depression analysis (n = 2,156), participants with prevalent depression at baseline (n = 193 total; n = 50 antidepressant medication, n = 126 CES-D ≥10, n = 17 both) or at 1-year follow-up (n = 184 total; n = 21 antidepressant medication, Geriatric Depression Score [GDS] ≥4, n = 157, n = 6 both), or those lacking follow-up (n = 65) were excluded from the original cross-sectional sample.

Assessment of 25(OH)D Concentrations

Serum 25(OH)D was obtained at the 1-year follow-up visit when dietary data were collected. Fasting serum 25(OH)D was measured using a two-step radioimmunoassay (25-hydroxyvitamin D I RIA Kit, DiaSorin, Stillwater, Minnesota) in a laboratory which met the Vitamin D External Quality Assessment Scheme quality criteria. The inter-assay coefficient of variation was 6.7% for log-transformed values. Serum 25(OH)D was categorized as <20, 20–<30, or ≥30 ng/mL based on recently recommended cut-points from the Endocrine Society (26).

Assessment of Depression

Depressive symptoms were assessed at baseline and at 2-, 3-, and 4-year follow-up with the Center for Epidemiologic Study Depression short form (CES-D 10), a 10-item self-report scale scored 0–30. Although not a diagnostic measure of depression, the CES-D 10 has been used extensively in older adults and is considered to be a reliable screening instrument for detecting clinically significant depressive symptoms, or "depression," in this population (27). Participants with a CES-D 10 score ≥10 were classified as having depressive symptoms. The 15-item GDS (28), a validated screening tool for depressive symptoms in older people, was administered at the 1-year follow-up visit only (when 25[OH]D was measured) and participants with a score ≥4 were classified as having depressive symptoms. Antidepressant medication use was collected at baseline and 1-, 2- and 4-year follow-up.

Prevalent depression was defined as a CES-D10 score ≥10 or taking antidepressant medication at baseline or a GDS score ≥4

or taking antidepressant medication at 1-year follow-up. Incident depression was defined as the first occurrence of a CES-D 10 score ≥10 or antidepressant medication use over 4 years of follow-up among those without prevalent depression at baseline or 1-year follow-up.

Covariates

At the baseline clinic visit, demographic (age, sex, race, field site, education, marital status) and lifestyle characteristics (smoking status, alcohol use) were ascertained using interviewer-administered questionnaires. Body weight and height were measured using a standard balance-beam scale and Harpenden stadiometer (Holtain Ltd., Crosswell, UK), and body mass index (BMI) was calculated as weight (kg)/height (m^2). Physical activity was self-reported as number of minutes spent walking over the past 7 days. Cognition was assessed using the Modified Mini-Mental State Examination (3MS) (29). Information on prevalent cardiovascular disease and diabetes was obtained from self-report and medication use. History of depression at baseline was defined by an affirmative answer to the question "Have you ever been treated for depression?" Serum creatinine was used to calculate the estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease equation; a value of <60 mL/min/1.73m^2 indicates kidney disease. Intact PTH was measured in EDTA plasma with a two-site immunoradiometric assay kit (N-tact PTHSP, DiaSorin, Stillwater, Minnesota). Dietary supplement and medication use was determined by reviewing all medications and supplements brought to each clinic visit by the participant. Supplements with ≥4 vitamin or mineral ingredients were considered multivitamins. Vitamin D-containing supplements were defined as those containing vitamin D and ≤2 additional ingredients. The season during which the blood sample was obtained was included to account for seasonal effects on 25(OH)D and was categorized as winter (December–February), spring (March–May), summer (June–August) and fall (September–November).

Statistical Analyses

Analyses of 25(OH)D and depression were conducted using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, North Carolina). Baseline characteristics were compared across 25(OH)D categories using Cochran–Mantel–Haenszel tests for trend for categorical variables and linear regression for trend for continuous variables. Cronbach's alpha was used to measure the internal consistency of the CES-D 10 items in this population by year. To test the cross-sectional association between 25(OH)D categories and prevalent depression, we fit logistic regression models. Minimally adjusted models included age, sex, race, education, site, and season. Fully adjusted models additionally included diabetes, cardiovascular disease, BMI, kidney disease, 3MS score, smoking status, alcohol consumption, marital status, and physical activity.

To estimate mean change in CES-D scores in the longitudinal sample from baseline to 2- and 4-year follow-up by 25(OH)D categories, general linear mixed models were used, including a time-varying covariate for antidepressant medication and the other variables described in the aforementioned fully adjusted model. Because information on antidepressant medication was not available at the 3-year follow-up visit, CES-D scores at the 3-year follow-up visit were not included in the change analyses. The cumulative incidence of depression at 2-, 3-, and 4-year follow-up was calculated using the life-table method with discrete 6-month intervals overall and by 25(OH)D categories and compared using the log-rank test. Participants were censored at the date of their last visit. Cox proportional hazards models were used to calculate the adjusted hazard ratios of incident depression by 25(OH)D categories; the discrete likelihood method was used for ties. Minimally and fully adjusted models were examined as described earlier; however, the fully adjusted model also included history of depression at baseline. Proportionality was assessed statistically by testing for a time interaction and the proportional hazard assumption was met.

Gender, race, and season by serum 25(OH)D interactions and site by season interactions were tested in the fully adjusted cross-sectional, change in CES-D scores, and incident depression analyses and were not significant. A two-sided alpha level of .05 was considered significant.

Results

Participants included in the baseline sample (n = 2,598) had a mean age of 75 years and 51.5% were female and 39.7% black. Table 1 describes the study sample by 25(OH)D categories. One-third of the participants had 25(OH)D <20 ng/mL; however, only 4% had 25(OH)D <10 ng/mL and, thus, were included in the <20 ng/mL category. These individuals were more likely to have been assessed during the winter or spring. They were also more likely to be single, black, female, a current smoker, and to have less education; were less likely to be active and drink alcohol; and more likely to have chronic disease, higher BMI and eGFR, and lower 3MS scores compared with those who had higher 25(OH)D. Participants with 25(OH)D <20 ng/mL were also less likely to report vitamin D or multivitamin supplement use.

Participants excluded from the analysis due to missing data were compared with the final analytical sample. Those who were missing serum 25(OH)D, baseline depression or covariates (n = 400) had higher CES-D scores (3.5 vs 3.0, p = .007) compared with those in the analysis sample (n = 2,598). They also had lower BMI and 3MS scores and were more likely to have been assessed during the winter or spring and to be single, black, a current smoker, less active, and have less education compared with those in the final sample (p < .05). Of the 2,598 participants in the cross-sectional analysis, 94 were missing at least one follow-up visit. Incomplete follow up was not associated with baseline CES-D score, age, site, season, education, marital status, alcohol consumption, physical activity, or having diabetes, but was associated with lower 25(OH)D, 3MS scores, and BMI, and being male, black, a current smoker, and having CVD and kidney disease (p < .05).

At baseline, 7.4% of participants were depressed (CES-D ≥10, 4.8%; antidepressant medication use, 1.9%; both, 0.7%) with a mean (SD) CES-D score of 3.0 (3.3). At the 1-year follow-up, when 25(OH)D was measured, 11.2% were depressed (GDS ≥4, 8.1%; antidepressant medication use, 2.1%; both, 1.0%) with a mean (SD) GDS score of 1.4 (1.8). The prevalence of depression at either baseline or 1-year follow-up (14.5%) did not vary by 25(OH)D category in fully adjusted models (OR [95% CI]: 1.00 [0.73, 1.36] and 1.04 [0.79–1.37] for <20 and 20–<30 vs ≥30 ng/mL, respectively).

Mean CES-D scores within each 25(OH)D category increased significantly over the 4-year follow-up (p < .001), with the greatest increase in participants with the lowest 25(OH)D concentrations (p for interaction, <.001) as shown in Figure 1. In the fully adjusted model, mean (SE) increases in CES-D scores from baseline to the 4-year follow-up were 2.40 (0.15), 2.04 (0.14), and 1.49 (0.15) in those with 25(OH)D <20, 20–<30, and ≥30 ng/mL, respectively. The internal consistency of the CES-D over the 4-year follow-up was high (all Cronbach's alpha > .70).

Table 1. Baseline Characteristics by 25(OH)D Categories: The Health ABC Study*

		Serum 25(OH)D			
	Overall (n = 2,598)	<20 ng/mL (n = 851)	20–<30 ng/mL (n = 915)	≥30 ng/mL (n = 832)	p for Trend
Age, years	74.7 (2.9)	74.6 (2.9)	74.8 (2.9)	74.6 (2.8)	.88
Female gender, %	51.5	57.0	49.9	47.5	<.001
Black race, %	39.7	65.0	34.5	19.5	<.001
Site, %					
Memphis	51.1	48.2	52.3	52.6	.07
Pittsburgh	48.9	51.8	47.7	47.4	
Less than high school education, %	23.5	32.4	21.9	16.2	<.001
Married, %	57.2	46.8	59.0	65.7	<.001
Current smoker, %	9.4	13.7	7.8	6.6	<.001
Drinking, %					
No consumption in past year	62.9	68.2	62.6	57.7	.008
≤7 drinks/wk	28.1	22.8	28.4	33.1	
>7 drinks/wk	9.1	9.0	9.0	9.3	
Season, %					
Winter	26.2	31.8	26.2	20.4	<.001
Spring	31.3	33.5	30.6	29.7	
Summer	16.9	11.9	18.3	20.6	
Fall	25.6	22.8	24.9	29.3	
BMI, kg/m^2	27.3 (4.8)	28.6 (5.5)	27.2 (4.5)	25.9 (3.9)	<.001
Physical activity (minutes walking/wk), %					
0	40.3	49.6	37.8	33.7	<.001
1–149	31.5	31.1	31.7	31.7	
≥150	28.1	19.3	30.5	34.6	
eGFR, mL/min/1.73 m^2	72.4 (16.2)	74.4 (17.6)	72.3 (16.0)	70.4 (14.6)	<.001
Prevalent disease, %					
Diabetes	20.1	26.2	19.0	15.0	<.001
Cardiovascular disease	28.3	31.1	28.1	25.6	.01
3MS score	90.1 (8.1)	87.8 (9.0)	90.9 (7.6)	91.7 (7.0)	<.001
Vitamin D supplementation, %	10.5	2.7	10.6	18.3	<.001
Multivitamin use, %	35.7	13.9	37.2	56.5	<.001
CES-D 10 score (range, 0–30)	3.0 (3.3)	3.1 (3.3)	2.9 (3.2)	3.0 (3.5)	.40

Notes: BMI = body mass index; CES-D10 = Center for Epidemiologic Studies Depression Scale short form; eGFR = estimated glomerular filtration rate; 3MS = Modified Mini-Mental State Examination.
*Means (*SD*) or frequencies with Cochran–Mantel–Haenszel or linear regression trend test to evaluate the distribution across categories of 25(OH)D.

Figure 2 shows the incidence of depression among the 2,156 participants without depression at baseline or at 1-year follow-up (when 25[OH]D was measured). The cumulative incidence of depression was 26.9% over a median follow-up time of 4.0 years, ranging from 18.1% in those with 25(OH)D ≥30 ng/mL to 35.8% in those with 25(OH)D <20 ng/mL. In minimally adjusted models, individuals with 25(OH)D <20 and 20–<30 ng/mL were at greater risk of developing depression than individuals with 25(OH)D ≥30 ng/mL (Table 2). The association persisted for those with 25(OH)D <20 ng/mL in the fully adjusted model.

Results for the cross-sectional, change in CES-D scores, and incident depression analyses were similar after further adjustment for parathyroid hormone (data not shown).

Discussion

Although we did not observe a cross-sectional association between 25(OH)D concentrations and depression in this cohort of well-functioning older adults, there was a significant association between 25(OH)D concentrations and change in CES-D scores over time, with individuals with 25(OH)D <20 ng/mL experiencing a greater increase in depressive symptoms than those with higher 25(OH)D concentrations. Furthermore, individuals with 25(OH)D <20 ng/mL were at greater risk of developing depression over 4 years of follow-up than those with 25(OH)D ≥30 ng/mL, independent of a wide range of potential confounders.

Estimates of the prevalence and incidence of depression in older adults vary with the choice of diagnostic instrument, with a prevalence reaching nearly 50% among community dwelling elders (30), over half of whom may experience their first event later in life (31). Because the Health ABC population was selected to be well-functioning, the baseline prevalence of depression was low (7.4%). The low prevalence of depression may explain why we did not observe a cross-sectional association with 25(OH)D concentrations. Although some cross-sectional studies have observed an association between 25(OH)D and depression (15–20), others have not (21,22).

The overall cumulative incidence of depression over 4 years of follow-up was 27%, with incidence rates differing significantly by 25(OH)D concentration. The overall incidence rate over 4 years is similar to the InCHIANTI study which found an overall incidence of depressive symptoms of 31% over 6 years of follow-up (23). Furthermore, we found an increased risk of depression among those with lower 25(OH)D concentrations similar to that reported in the InCHIANTI study.

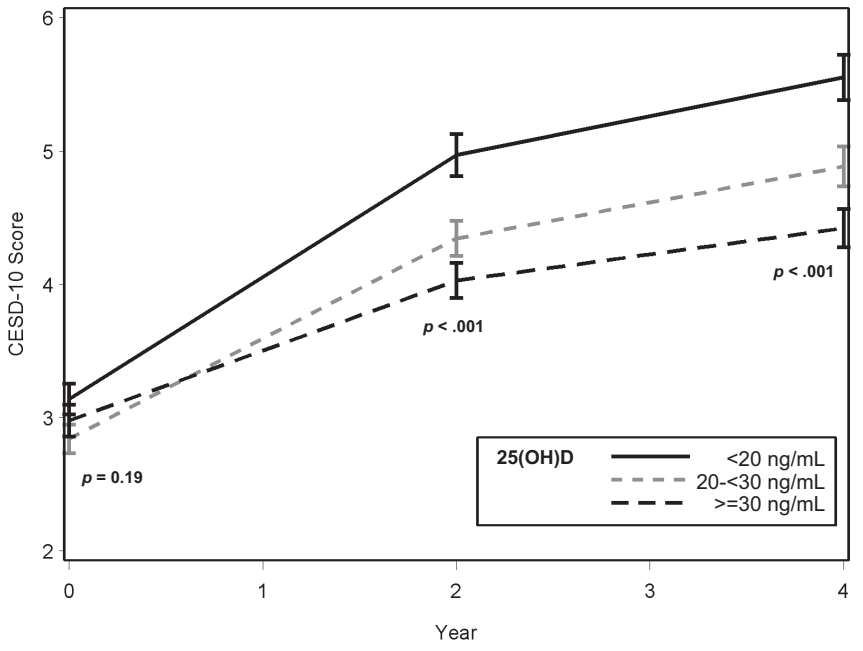
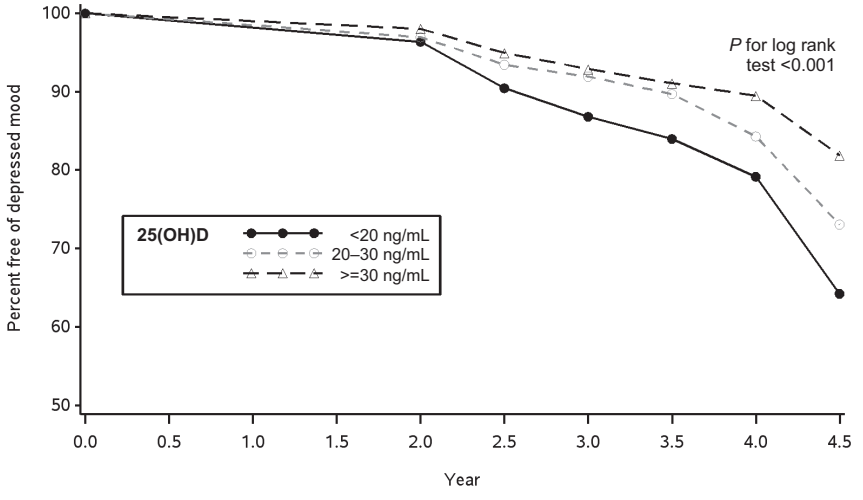


Figure 1. Unadjusted CES-D scores (mean [*SE*]) over time according to 25(OH)D categories at 1-year follow-up: the Health ABC Study ($N = 2,504$). Dashed black line: 25(OH)D ≥ 30 ng/mL; dashed gray line: 25(OH)D 20–<30 ng/mL; solid black line: 25(OH)D < 20 ng/mL.



Number of Participants	<20 ng/mL:	events	25	40	24	18	23	27
		at risk	693	658	604	562	523	259
	20-<30 ng/mL:	events	23	26	11	16	29	21
		at risk	760	723	687	666	639	294
	>=30 ng/mL:	events	14	21	14	12	8	14
		at risk	703	684	645	623	597	315

Figure 2. Cumulative Kaplan–Meier estimates of proportion remaining free of depression according to 25(OH)D categories at 1-year follow-up: the Health ABC study ($N = 2,173$). Dashed black line: 25(OH)D ≥ 30 ng/mL; dashed gray line: 25(OH)D 20–<30 ng/mL; solid black line: 25(OH)D < 20 ng/mL.

The hypothesis that vitamin D may have a central role in depression was posited by Stumpf and Privette (32) in 1989, generating a surge of interest in the potential role of vitamin D in the central nervous system. A leading hypothesis is that vitamin D may have a neuroprotective role, as inflammation has been implicated as a key etiologic process underlying depression (33). A recent meta-analysis reports that higher concentrations of pro-inflammatory cytokines are present in depressed compared with non-depressed young adults (34), and findings in older adults appear to be consistent. In a cross-sectional study of older adults in the Longitudinal Aging Study, Amsterdam, Bremmer and colleagues (35) found an association of major depression with elevated IL-6 independent of age, chronic disease, cognitive function, and anti-depressant use. Although the mechanism of this apparent association is unknown, there is growing evidence that vitamin D has potent immunosuppressant activity and may influence pro-inflammatory cytokines, such as IL-6, in the brain. (36).

Vitamin D may also be neuroprotective by reducing oxidative stress through its influence on the gene expression of the enzyme

Table 2. Risk of Incident Depression* Over 4 years of Follow-up According to 25(OH)D Categories at 1-year Follow-up: The Health ABC Study

HR (95% CI)	Serum 25(OH)D			*p* for Trend
	<20 ng/mL (*n* = 759)	20–<30 ng/mL (*n* = 821)	≥30 ng/mL (*n* = 745)	
Model 1†	1.72 (1.29, 2.29)	1.35 (1.02, 1.79)	1.00	*p* < .001
Model 2‡	1.65 (1.23, 2.22)	1.31 (0.99, 1.74)	1.00	*p* < .001

Notes: BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale short form; eGFR = estimated glomerular filtration rate; HR = hazard ratio; 3MS = Modified Mini-Mental State Examination.

*Incident depression defined as CES-D ≥ 10 or antidepressant medication use among participants without prevalent depression at baseline or 1-year follow-up visit.

†Model 1—adjusted for age, sex, race, site, season, and education.

‡Model 2—adjusted for covariates in Model 1 plus diabetes, cardiovascular disease, BMI, 3MS score, kidney disease (eGFR < 60), smoking status, alcohol consumption, marital status, physical activity, and history of depression.

γ-glutamyl transpeptidase, which is necessary in the formation of glutathione, one of the most important antioxidants of the brain (37). Vitamin D has additionally been shown to influence the availability of dopamine, noradrenaline, and adrenaline through activation of the gene expression of the enzyme tyrosine hydroxylase, considered to be the rate-limiting step in the synthesis of catecholamines (38). Similarly, it increases the availability of the neurotransmitter acetylcholine by both enhancing production and reducing degradation (39).

Our study has several strengths. In this large representative sample of community-dwelling older adults, we were able to adjust for a variety of confounders including geographic location, season, physical activity, chronic illness, cognition, and various demographic and health-related measures. We were able to assess depressive symptoms at multiple time-points which provided not only an estimate of incident depression, but also of change in depressive symptoms over time. Although a recent systematic review and meta-analysis concluded that the totality of evidence supports the association of depression with low 25(OH)D (2), only three contributing studies were longitudinal, two of which are not representative of the larger population (24,25).

Potential methodological considerations of this study merit discussion. Although it is biologically plausible that low 25(OH)D could be associated with depression, the observational nature of this study does not allow us to evaluate a causal association. Because depressed mood may lead to behaviors predisposing individuals to low 25(OH)D, we also cannot rule out the possibility of reverse causality.

Serum 25(OH)D was measured only once and not contemporaneously with the baseline depression assessment; however, prior work suggests that serum 25(OH)D concentrations at a single time point may be a useful biomarker of vitamin D status over a 5-year period (40). Serum 25(OH)D was obtained throughout the year and is known to fluctuate seasonally, with the lowest concentrations occurring during the winter and spring months. To account for this variation, follow-up visits were scheduled during the same season as the baseline visit whenever possible. Although we adjusted for geographic location (Memphis vs Pittsburgh) and for participation in physical activity, more-specific measures of sunlight exposure and use of sunscreen, which have been identified as determinants of 25(OH)D in older adults in other population-based studies, were not available.

Finally, the operationalization of depression in this study warrants comment. Depression identified by a CES-D10 score ≥10 or GDS ≥4 was not confirmed with a definitive clinical diagnosis. However, subthreshold depression and depressive disorders are common and important in their own right, contributing to poor physical health, physical disability, and reduced quality of life (8). Because the CES-D queries symptoms experienced over the preceding week, our case finding may not have captured the fluctuating natural history of depression. It is unknown whether the incident cases in our analysis represent a first diagnosis or a recurrence of depression occurring prior to enrollment in the study.

In conclusion, low 25(OH)D concentrations were associated with greater increases in depressive symptoms over time and with incident depression in this sample of well-functioning older adults. Given that approximately one-third of older adults are vitamin D insufficient and vitamin D insufficiency is easily treatable, vitamin D supplementation trials are needed to determine whether remediating low 25(OH)D concentrations could have an impact on prevention and management of depression.

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