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ORIGINAL ARTICLE

Vitamin D serum concentration is prospectively associated with depressive symptoms in the EpiFloripa Aging Cohort Study: a structural equation modeling approach

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Objective: To evaluate the direct, indirect, and total prospective effects of serum concentrations of 25-hydroxycholecalciferol (25[OH]D) on depressive symptoms in older adults.
Methods: Data from the second (2013-2015) and third (2017-2019) waves of the EpiFloripa Aging Cohort Study ($\geqslant$ 60 years) were analyzed. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale. 25(OH)D levels were measured using the microparticle chemiluminescence method. A directed acyclic graph was constructed to identify the minimum set of adjustments. Structural equation modeling analysis was used to determine the effects of 25(OH)D on depressive symptoms.
Results: Data from 574 older adults (63.1% female) were analyzed. In the follow-up (n=390), 16.2% of them presented severe depressive symptoms ($\geqslant$ 6 points). Structural equation modeling analysis revealed that 25(OH)D had a small direct negative effect (β = -0.11, $p < 0.05$) and an overall negative effect (β = -0.13; $p < 0.05$) on depressive symptoms in wave 3 (increased 25[OH]D led to decreased depressive symptoms). No direct or indirect effect on depressive symptoms was found in wave 2.
Conclusion: Our findings indicate a prospective association between 25(OH)D and depressive symptoms, suggesting a long-term effect in older adults from southern Brazil.

Keywords: Vitamin D; aging; depression; longitudinal studies

Introduction

Major depressive disorder, or simply depression, is a prevalent and multifactorial disorder that affects 28.4% of the older adult population worldwide.[1] Its impact is particularly high in individuals from low- and middle-income countries due to challenges in accessing treatment.[2] Concurrently, the prevalence of vitamin D deficiency ($<$ 20 ng/mL) among older adults has been estimated at 17 to 87%.[3] Both depression and vitamin D deficiency are associated with an increased risk of frailty, disability, and mortality in this population.[4-7]

Many processes involved in brain aging and the pathophysiology of major depressive disorder are regulated by vitamin D and its metabolites, including neurotransmitter actions and neuroendocrine system functions.[8,9] Vitamin D may affect major depressive disorder by maintaining cellular calcium (Ca^{2+}) homeostasis, expressing antioxidant genes that regulate serotonin and dopamine function, and reducing inflammatory cytokine expression.[8,10,11]

Previous studies have explored the association between 25-hydroxycholecalciferol (25[OH]D) deficiency and depression in older adults in different scenarios, including clinical, cross-sectional, and longitudinal studies.[9] However, most of these studies have included mixed populations of adults and older adults, which has led to high methodological variability, such as different vitamin D cut-off points and different screening tools for depressive symptoms. As a result, the association is still unclear.

Only six longitudinal studies have been conducted exclusively with older adults ($\geqslant$ 60 years),[12-17] and none

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took place in low- and middle-income countries, where depressive symptoms are more prevalent than in developed countries. Moreover, none of these studies tested the mediating effect of previous depressive symptoms on current depressive symptoms.[9]

Data from the second (2013-2015) and third (2017-2019) waves of the "Health Conditions of the older adults in the Florianópolis – EpiFloripa Aging Cohort Study," a population-based study, were used for this analysis (Figure 1). Details about the study's design, methods, and sample have been published previously.[18,19] In brief, the inclusion criteria at baseline were people aged ⩾ 60 years who lived in metropolitan Florianópolis, Santa Catarina, Brazil. Individuals in long-term care institutions, hospitals, or prisons were excluded. All older adults who participated in the study's first wave (2009-2010, n=1,702) were invited to participate in the second and third waves. In the second wave, all participants (n=1,197) were invited to complete complementary examinations, including blood sample collection, resulting in a sample of 574 participants (33.7% retention rate from wave 1). The third wave included only those from whom blood samples were collected in wave 2, resulting in 390 participants (67.9% retention rate).

A structured questionnaire was administered by trained interviewers for data collection during home visits. In the second stage, additional examinations, including blood sample collection, were conducted at the Universidade Federal de Santa Catarina (UFSC). The time between blood sample collection and the third wave interview was 3.7 ± 0.5 years (with a minimum of 2.7 and a maximum of 5.7 years). The study's consistency analysis and quality control were conducted by telephone interviews, in which a shortened version of the questionnaire was applied to 10% of randomly selected participants.[18]

Measurements

Vitamin D

Blood samples were collected from each participant at UFSC's Laboratório de Metabolismo e Dietética and analyzed at the clinical analysis laboratory of Hospital Universitário Polydoro Ernani de São Thiago. Participants were asked to fast for 8-10 hours before blood collection, and 30 mL of peripheral venous blood was collected from each participant.[19]

Serum 25(OH)D concentrations (ng/mL) were measured using the microparticle chemiluminescence method

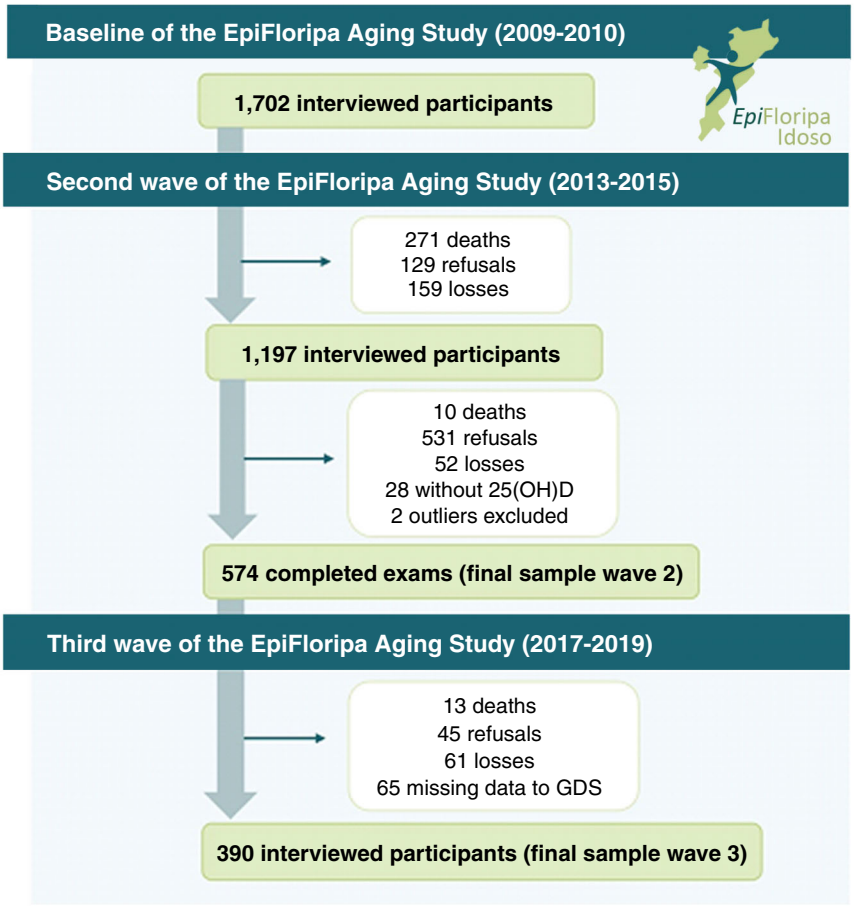


Figure 1 Flowchart of the EpiFloripa Aging Cohort Study. 25(OH)D = 25-hydroxycholecalciferol; GDS = Geriatric Depression Scale.

in LIAISON (DiaSorin, São Paulo, SP, Brazil) according to manufacturer instructions.[20] LIAISON is a rapid, accurate, and precise assay with a functional sensitivity of $\leqslant$ 2.0 ng/mL and inter-assay imprecision of $<$ 20%.[20] It was certified for total 25-hydroxyvitamin D assays in 2014 by the U.S. Centers for Disease Control and Prevention Vitamin D Standardization-Certification Program.[21]

Severity of depressive symptoms

Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS). This instrument is recommended by the Brazilian Ministry of Health[22] as a useful tool for the rapid screening of depressive symptoms in older adults at primary healthcare centers. The scale was translated and adapted for Brazilian outpatients aged $\geqslant$ 60 years who met the ICD-10 and DSM-IV criteria for major depressive disorder (current or in remission).[23,24]

In the descriptive analysis, we followed the cut-off points suggested by Almeida & Almeida,[23,24] considering $\geqslant$ 6 points as severe depressive symptoms.[23,25] For the structural equation modeling (SEM) analysis, we used questions with dichotomous answers (No/Yes) to determine a latent variable from both waves. These questions were: 1) Are you basically satisfied with your life?; 2) Have you dropped many of your activities and interests?; 3) Do you feel that your life is empty?; 4) Do you often get bored?; 5) Are you in good spirits most of the time?; 6) Are you afraid that something bad is going to happen to you?; 7) Do you feel happy most of the time?; 8) Do you feel helpless?; 9) Do you prefer to stay at home, rather than going out and doing new things?; 10) Do you feel you have more problems with memory than most?; 11) Do you think it is wonderful to be alive now?; 12) Do you feel pretty worthless the way you are now?; 13) Do you feel full of energy?; 14) Do you feel that your situation is hopeless?; and 15) Do you think that most people are better than you are?

Covariates

A directed acyclic graph, also known as causal Bayesian networks, was constructed using DAGitty software to represent the theoretical model and elucidate the involvement of covariates in the longitudinal association between 25(OH)D levels and depressive symptoms (Figure 2).[26] In this graph, we considered depressive symptoms in wave 2 as a possible mediator between 25(OH)D and depressive symptoms in wave 3. The criteria for adjusted covariates were used to define a minimum set of covariates to adjust for confounding and to reduce variable selection bias.[27,28] The covariates suggested by the backdoor criteria to adjust for confounding were sex, age, education, family income, alcohol consumption, leisure-time physical activity (LTPA), number of general medical comorbidities, and body mass index (BMI).

The sociodemographic variables were sex (male/female), age (years), education (years), and per capita family income in multiples of the federal minimum salary ($\leqslant$ 1, $>$ 1 to $\leqslant$ 3, $>$ 3 to $\leqslant$ 5, $>$ 5 to $\leqslant$ 10, and $>$ 10) during 2013 (minimum salary = BRL 678.00) and 2014 (BRL 724.00). The behavioral factor was LTPA, which was assessed using the International Physical Activity Questionnaire and classified as insufficiently active $<$ 150 min or active $\geqslant$ 150 min.[29,30] The health variables included BMI, calculated as the ratio of weight (kg) to height squared (m^2),[31] and medical comorbidities (sum of diagnosed diseases: spine or back pain, arthritis, cancer, diabetes, bronchitis, cardiovascular or renal conditions, tuberculosis, cirrhosis, stroke, osteoporosis, hypertension, and depression).

Statistical analysis

Descriptive analysis of the data is presented as absolute and relative frequencies and mean and SD. SEM was performed to analyze direct effects, the overall indirect effect (the sum of all indirect effects), specific indirect effects (each indirect effect), and the overall effect (the sum of direct and indirect effects) of 25(OH)D on depressive symptoms using standardized coefficients (β). The covariates suggested by the backdoor criteria were included in the model. For the analysis, three latent variables were considered: two including all 15 questions of GDS for each wave (GDS2 for wave 2 and GDS3 for wave 3) and one combining education and income as socioeconomic status (Supplementary Table S1). First, the latent variables were tested through confirmatory factor analysis. After confirming their validity, all paths were included in the measurement model (final model).

The robust weighted least square mean and variance adjusted and THETA parameterization were used to control for differences in residual variance. The "mod-indices" command was used to indicate new paths in the initial theoretical model that could better fit the model. When the modification suggestions were considered plausible from a theoretical point of view, a new model was developed and analyzed if the modification index value was $>$ 10.[32] To determine whether the model presented a good fit, the following fit indices were considered: $p > 0.05$ for the chi-square test,[33] $p < 0.05$, and an upper limit of the 90%CI < 0.08 for the root mean square error of approximation[32]; values > 0.90 for the comparative fit index and the Tucker-Lewis index[34]; values < 0.05 for the standardized root mean square residual; and $p < 0.05$ for factor loading > 0.5, as a good indicator of convergent validity, i.e., a correlation of moderately high magnitude between the observed variables and construct.[33]

The analysis was performed using Stata 14.0 software, considering sample weights through the command *svy*. MPLUS 8.4 was used for all SEM analyses, with $p < 0.05$ considered statistically significant. By default, MPLUS estimates the model using all available data (full information maximum likelihood) to handle the missing data. This approach directly estimates each parameter and considers all 574 participants in the model.

The sample size power (1 - β error probability) was calculated *a posteriori* (post-hoc) in G*Power 3.1.9.7, using the following parameters: a quadratic regression

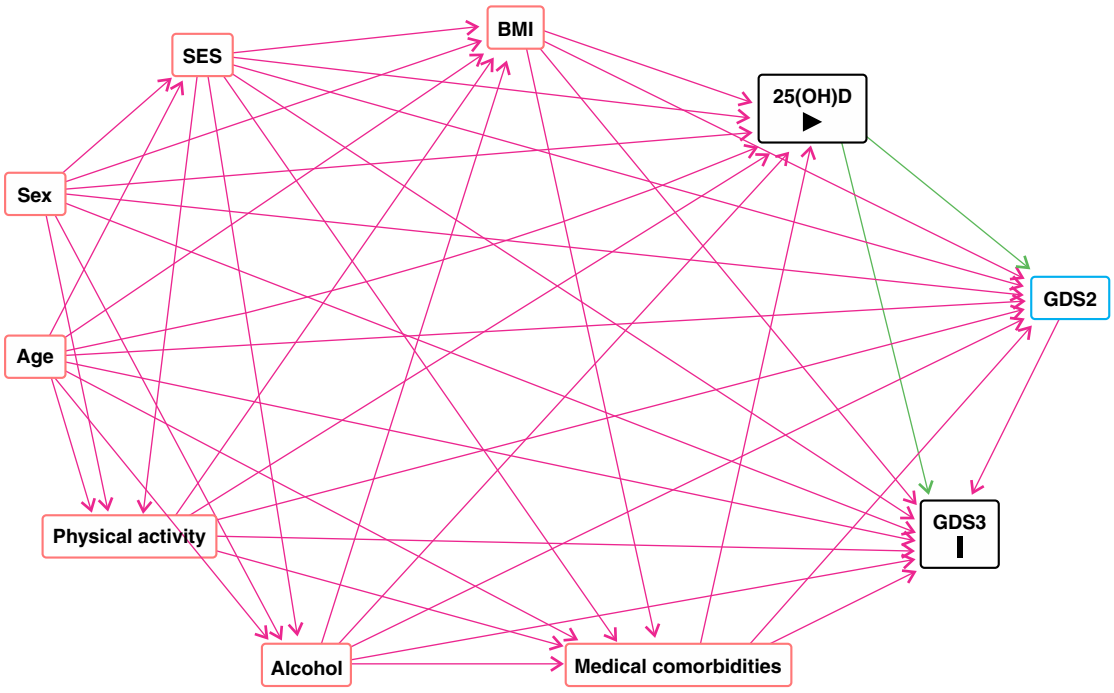


Figure 2 Theoretical model of the minimum set of adjustment covariates indicated by directed acyclic graphing of the association between 25(OH)D and depressive symptoms. The graph used to determine the minimum set of adjustment covariates for confounding was based on associations described in the literature to test the direct effect of 25(OH)D (exposure variable, play symbol) on depressive symptoms according to the GDS3, from wave 3 (stop symbol). The variables in red are the antecedents of exposure and outcome; GDS2, from wave 2 (blue) is both the antecedent and mediator of the outcome. The arrows represent the causal association between each variable. Pink arrows are the biasing paths, and green arrows are the causal path between the exposure and the outcome (GDS3) and between exposure and the mediator (GDS2). 25(OH)D = 25-hydroxycholecalciferol; BMI = body mass index; GDS = Geriatric Depression Scale; SES = socioeconomic status.

coefficient of 0.11 and a sample size of 574 (power = 0.99).

Ethics statement

The EpiFloripa Aging Cohort Study was conducted in accordance with the Declaration of Helsinki.[35] The second and third waves were approved by the UFSC Human Research Ethics Committee (numbers: 329,650 and 526,126 [second wave] and 1,957,977 [third wave]). Written informed consent was provided by all participating older adults.

Results

A total of 574 participants were included in the analysis (Table 1). Most were women (63.1%), the mean age was 72.3 (SD, 6.4) years, and the mean serum vitamin D concentration was 26.2 (SD, 8.5) ng/mL. In wave 2, 16% of the participants presented severe depressive symptoms, which increased to 16.7% in wave 3.

The simplified theoretical model based on SEM is presented in Figure 3 (the complete diagram is shown in Supplementary Figure S1). Standardized coefficients of direct, overall, and indirect effects of 25(OH)D on depressive symptoms are shown in Table 2 (direct effects between covariates are shown in Supplementary Table S2). In wave 2, 25(OH)D presented a small direct negative effect (β = -0.11; $p < 0.05$), and an overall negative effect (β = -0.14; $p < 0.05$) on depressive symptoms in wave 3. This suggests that increased 25(OH)D resulted in a prospective decrease in depressive symptoms, indicating that 25(OH)D had a long-term effect on depressive symptoms. Notably, 25(OH)D had neither a direct effect in wave 2 nor an indirect effect in wave 3, which suggests no mediating effect on depressive symptoms in wave 2 (Table 3). Depressive symptoms in wave 2 had a significant and high positive effect on depressive symptoms in wave 3 (β = 0.63; $p < 0.001$).

The analysis also examined the covariates' direct, overall, and overall indirect effects (Table 2), and their specific indirect effects (Table 3) on depressive symptoms. Socioeconomic status had a small direct negative effect (β = -0.20; $p < 0.05$) on GDS2, an overall negative effect (β = -0.25; $p < 0.001$), an overall indirect negative effect (β = -0.20; $p < 0.001$) on GDS3, and a specific indirect negative effect (β = -0.12; $p < 0.05$) on GDS3 mediated by GDS2. This suggests that increased socioeconomic status was associated with decreased depressive symptoms.

LTPA had a small direct negative effect (β = -0.18; $p < 0.05$) on GDS2, an overall indirect negative effect on GDS3 (β = -0.15; $p < 0.05$), and a specific indirect negative effect (β = -0.11; $p < 0.05$) on GDS3 mediated

Table 1 Sample characterization according to demographic, socioeconomic, and health characteristics of the EpiFloripa Aging Cohort Study (2013-2019)

Participant characteristics (n=574)	n (%)	95%CI
Sex (wave 2)		
Male	199 (36.9)	32.0-42.0
Female	375 (63.1)	58.0-68.0
LTPA (min/week, n=573, wave 2)		
Insufficiently active $\leqslant$ 150	411(71.9)	67.9-75.3
Active $>$ 150	162 (28.7)	23.6-34.3
Alcohol use (wave 2)		
None	332 (57.8)	53.7-61.8
Moderate	158 (27.5)	24.0-31.3
High	84 (14.6)	11.9-17.8
Depressive symptom severity in wave 2 (n=555)		
High severity ($\geqslant$ 6 points)	89 (16.0)	13.2-19.3
Low severity ($\leqslant$ 5 points)	466 (84.0)	80.7-86.8
Depressive symptom severity in wave 3 (n=390)		
High severity ($\geqslant$ 6 points)	65 (16.7)	13.3-20.7
Low severity ($\leqslant$ 5 points)	325 (83.3)	79.3-86.7
	Mean (SD)	Min-Max
Age (years, wave 2)	72.3 (6.4)	63-93
Education (years, n=573, wave 2)	7.9 (5.7)	0-28
Family income (minimum wages, n=555, wave 2)	6.64 (7.0)	0.7-49.7
25(OH)D (ng/mL, wave 2)	26.2 (8.5)	4-50
BMI (kg/m^2; n=567, wave 2)	28.2 (5.2)	16.4-54.2
Medical comorbidities (wave 2)	3.1 (1.8)	0-9
GDS2 (total score, n=555)	3.2 (2.7)	0-14
GDS3 (total score, n=390)	3.1 (2.7)	0-12

25(OH)D = 25-hydroxycholecalciferol concentration; BMI = body mass index; GDS = Geriatric Depression Scale; GDS2 = GDS from wave 2; GDS3 = GDS from wave 3; LTPA = leisure-time physical activity.

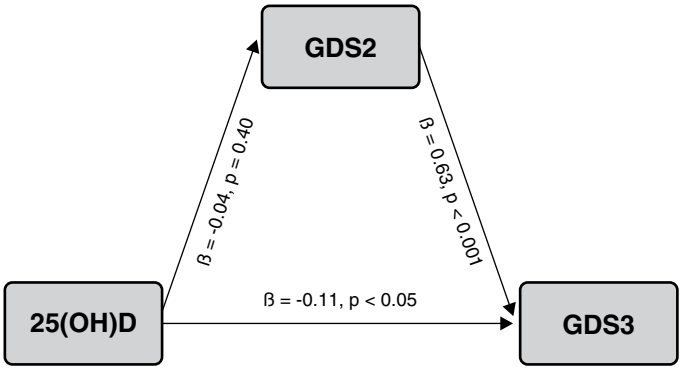


Figure 3 The simplified theoretical model of the effects of 25(OH)D on depressive symptoms. Structural equation modeling analysis used standardized coefficients (β). The main variables are represented in the box, with the arrows representing the direction of the effect. Serum vitamin D concentration had a significant negative direct effect on depressive symptoms according to GDS scores in wave 3 (GDS3), but not in wave 2 (GDS2). Depressive symptoms in wave 2 (GDS2) had a positive direct effect on depressive symptoms in wave 3 (GDS3). The model was adjusted for socioeconomic status, sex, age, leisure-time physical activity, and body mass index. 25(OH)D = 25-hydroxycholecalciferol; GDS = Geriatric Depression Scale.

by GDS2. This suggests that increased LTPA resulted in decreased depressive symptoms. Additionally, LTPA had a direct positive effect on 25(OH)D, indicating that increased LTPA is associated with increased 25(OH)D (Supplementary Table S2).

Medical comorbidities had a medium direct positive effect ($\beta = 0.31$; $p < 0.001$) on GDS2, an overall positive effect ($\beta = 0.20$; $p < 0.001$), an overall indirect positive effect ($\beta = 0.19$; $p < 0.001$) on GDS3, and a specific indirect positive effect ($\beta = 0.19$; $p < 0.001$) on GDS3 mediated by GDS2. This indicates that increased medical comorbidities leads to increased depressive symptoms.

BMI did not have a direct effect on GDS2 or GDS3, but it had a small overall positive effect ($\beta = 0.19$; $p < 0.001$)

Table 2 Direct effects of 25(OH)D and covariates on GDS and total and total indirect effects on GDS in the third wave (n=574) of the EpiFloripa Aging Cohort Study, Florianópolis, Santa Catarina, Brazil, 2013-2015

Pathways and estimates	Standardized coefficient	Standard error	p-value
Direct effects on GDS2 and GDS3			
GDS2 → GDS3	0.63	0.07	< 0.001
25(OH)D → GDS2	-0.04	0.05	0.40
25(OH)D → GDS3	-0.11	0.05	< 0.05
SES → GDS2	-0.20	0.06	< 0.05
SES → GDS3	-0.06	0.06	0.39
Sex → GDS2	-0.03	0.05	0.61
Sex → GDS3	-0.02	0.06	0.70
Age → GDS2	0.00	0.05	0.99
Age → GDS3	0.08	0.06	0.16
LTPA → GDS2	-0.18	0.07	< 0.05
LTPA → GDS3	0.09	0.07	0.20
BMI → GDS2	0.07	0.05	0.16
BMI → GDS3	0.08	0.05	0.13
Medical comorbidities → GDS2	0.31	0.05	< 0.001
Medical comorbidities → GDS3	0.01	0.06	0.84
Alcohol use → GDS2	-0.11	0.06	0.08
Alcohol use → GDS3	-0.01	0.08	0.95
Total effects on GDS3			
25(OH)D	-0.14	0.06	< 0.05
Socioeconomic status	-0.25	0.06	< 0.001
BMI	0.19	0.05	< 0.001
LTPA	-0.06	0.07	0.35
Medical comorbidities	0.20	0.06	< 0.001
Alcohol use	-0.09	0.08	0.23
Total indirect effects on GDS3			
25(OH)D	-0.03	0.03	0.41
Socioeconomic status	-0.20	0.05	< 0.001
BMI	0.11	0.03	< 0.001
LTPA	-0.15	0.06	< 0.05
Medical comorbidities	0.19	0.04	< 0.001
Alcohol use	-0.09	0.04	0.05

25(OH)D = 25-hydroxycholecalciferol concentration; BMI = body mass index; GDS = Geriatric Depression Scale; GDS2 = GDS from wave 2; GDS3 = GDS from wave 3; LTPA = leisure-time physical activity.
Results of the structural equation modeling analysis of direct effects of serum vitamin D (25[OH]D) concentration and covariates on GDS scores in the second (GDS2) and third waves (GDS3). The model was adjusted for socioeconomic status, sex, age, LTPA, and BMI. Adjustment parameters that validated the models: $\chi^2 = < 0.001$, root mean square error of approximation = 0.03, upper limit of 90%CI = 0.03, probability = 1.00, comparative fit index = 0.93, Tucker-Lewis index = 0.92, and standardized root mean square residual = 0.12.

Table 3 The specific indirect effects of covariates on depressive symptoms in wave 3, EpiFloripa Aging Cohort Study, Florianópolis, Santa Catarina, Brazil, 2013-2014 and 2017-2019

Pathways and estimates	Standardized coefficient	Standard error	p-value
Specific indirect effects from 25(OH)D			
25(OH)D → GDS2 → GDS3	-0.03	0.03	0.41
Specific indirect effects from SES			
SES → GDS2 → GDS3	-0.12	0.04	< 0.05
SES → Alcohol → Medical comorbidities → GDS2 → GDS3	-0.01	0.005	< 0.05
Specific indirect effects from BMI			
BMI → Medical comorbidities → GDS2 → GDS3	0.05	0.01	< 0.001
Specific indirect effects from LTPA			
LTPA → GDS2 → GDS3	-0.11	0.05	< 0.05
Specific indirect effects from medical comorbidities			
Medical comorbidities → GDS2 → GDS3	0.19	0.04	< 0.001
Specific indirect effects from alcohol use			
Alcohol → Medical comorbidities → GDS2 → GDS3	-0.03	0.01	< 0.05

25(OH)D = 25-hydroxycholecalciferol concentration; BMI = body mass index; GDS = Geriatric Depression Scale; GDS2 = GDS from wave 2; GDS3 = GDS from wave 3; LTPA = leisure-time physical activity; SES = socioeconomic status.
Structural equation modeling analysis results of the statistically significant specific indirect effects of covariates on depressive symptoms in wave 3.

and an indirect overall positive effect (β = 0.11; $p < 0.001$) on GDS3, as well as a specific indirect positive effect (β = 0.05; $p < 0.001$) on GDS3 mediated by medical comorbidities and GDS2. BMI also had a small direct negative effect on 25(OH)D, which suggests that increased BMI is associated with decreased 25(OH)D (Supplementary Table S2).

We observed two modification indices that indicated correlational relationships between two GDS questions (questions 3 and 7) from the latent variables across waves. Although this correlation may be attributed to measurement error, it contributed to a better fit in the adjusted model parameters (Supplementary Table S1).

Discussion

This study found that 25(OH)D concentrations had a small long-term negative effect on depressive symptoms in older adults, suggesting that increased 25(OH)D in wave 2 was associated with decreased depressive symptoms in wave 3. Interestingly, 25(OH)D concentrations had no significant effect on depressive symptoms in wave 2. Furthermore, despite having a significant impact on wave 3 depressive symptoms, wave 2 depressive symptoms did not mediate this prospective effect.

This study is notable for being the first to utilize SEM analysis to explore the association between 25(OH)D and depressive symptoms. The most distinctive aspect of our results is the long-term effect of 25(OH)D on depressive symptoms, which was not mediated by depressive symptoms from the initial assessment. Few longitudinal studies on 25(OH)D and depressive symptoms have exclusively involved older adults ($\geqslant$ 60 years), and only two found a longitudinal association.[12-17] In 4 years of follow-up in the United States, individuals with 25(OH)D levels $<$ 20 ng/mL had a greater risk of developing depression (hazard ratio = 1.65; 95%CI 1.23-2.22) than those with levels $\geqslant$ 30ng/mL.[14] In 3 and 6 years of follow-up in Italy, women with 25(OH)D levels $<$ 50 nmol/L ($<$ 20 ng/mL) had an increased risk of depressive mood (hazard ratio = 2.0; 95%CI 1.2-3.2).[17]

Despite a substantial body of pre-clinical evidence suggesting that vitamin D has potential effects on depression,[8-11] clinical and observational studies still inconclusive.[9] Methodological variability is a notable challenge in these studies, encompassing both clinical trials and observational investigations. Several clinical studies that included older adults ($>$ 65 years) failed to demonstrate significant improvement in depressive symptoms with 25(OH)D supplementation, which may be due to lower vitamin D doses, short study duration, a sample including adults and older adults, or not specifically targeting older individuals diagnosed with depression.[9] Additionally, in observational studies that did not find an association, researchers either stratified the analysis by sex,[15] included men only,[13,16] focused solely on older adults with depression,[12] or included both adults and older adults.

Studies conducted with clinically depressed individuals, including those diagnosed and undergoing treatment, enable researchers to investigate the influence of 25(OH)D on the course and/or remission of depression, as evidenced by Van Den Berg et al.[12] In contrast, the present study draws from a community sample, which is distinct from a clinically depressed sample, thus providing a representative cohort for exploring the potential impact of 25(OH)D on the prevalence and incidence of depressive symptoms. Hence, it is plausible to hypothesize that 25(OH)D may have a preventive, rather than a treatment, effect on depression. Moreover, it is crucial to recognize that older adults are in a distinct phase of life due to the aging process, which is associated with a reduced ability to maintain homeostasis. This age-related vulnerability could result in susceptibility to pathological abnormalities, including low circulating levels of vitamin D and neuropsychiatric disorders, such as depression.[36,37] Conversely, older adults with depression face a higher mortality risk,[4] as do those with vitamin D deficiency.[6]

It is noteworthy that low levels of 25(OH)D might influence depression through other conditions, such as bone and muscle weakness. Van Den Berg et al.[38] identified an association between 25(OH)D and frailty, suggesting the possibility of an indirect effect on depression. Additionally, our previous research identified an association between severe dependency in activities of daily life and low serum levels of vitamin D,[39] possibly due to limited exposure to sunlight. This might also impact depression, as demonstrated by another study from the EpiFloripa Aging Cohort Study, which linked activities of daily life to depressive symptoms.[40]

Although we did not measure 25(OH)D levels in the third wave, it should be pointed out that vitamin D's half-life in the blood is short ($\sim$15-25 days).[41] Despite the prevalence of vitamin D deficiency in older adults,[3] in a previous publication (using the same sample from wave 2), we found a high prevalence of vitamin D insufficiency (43.7%; 21-29 ng/mL) and deficiency (23.5%; $\leqslant$ 20 ng/mL). Additionally, few participants (6.2%) were taking vitamin D supplements during wave 2[40] or wave 3 (8.5%) (data not shown), which could imply inadequate blood levels of vitamin D and indicate that only a small portion of those with vitamin D deficiency receive vitamin D supplementation.

Although not the primary focus of this study, socioeconomic status, LTPA, medical comorbidities, and BMI had significant and stronger effects on depressive symptoms than vitamin D. Furthermore, vitamin D had concurrent effects in wave 2 but long-term effects in wave 3. None of the covariates had a direct effect on depressive symptoms in wave 3. However, socioeconomic status, LTPA, and medical comorbidities had a direct effect in wave 2 and an indirect effect in wave 3 that was mediated by depressive symptoms in wave 2, indicating a long-term effect. BMI only had an indirect effect on depressive symptoms, which was mediated by medical comorbidities and depressive symptoms in wave 2.

Higher socioeconomic status could provide resources and support, thus influencing depressive symptoms. Additionally, regular physical activity has been associated with enhanced mood and well-being, potentially alleviating depressive symptoms. Although the association

between BMI and depression has not been firmly established, it has been suggested that obesity and depressive symptoms share some associated factors.[42-46] Overall, these findings underscore the importance of considering multiple factors when investigating the relationship between vitamin D and depressive symptoms in older adults, highlighting the multifaceted nature of depression, to which vitamin D may contribute in the long term.

One possible study limitation was that the clinical and biochemical examinations were conducted at the university, which may have led to the selection of individuals with relatively better health than those who did not participate. Due to the logistics of data collection, blood samples were not collected at the same time as the interview, and they were not collected in wave 3. Although we used a technique certified by the U.S. Centers for Disease Control and Prevention's Vitamin D Standardization-Certification Program to measure 25(OH)D, it may differ in some respects from the gold standard method.[47] Moreover, possible limitations in the GDS' psychometric properties should be considered. However, in a large epidemiological study, such as the EpiFloripa Aging Cohort Study, and considering the interview duration and the collection of other variables, the GDS was the most feasible measure for evaluating the severity of depressive symptoms. Although our sample had good statistical power and the SEM analysis employed a robust method to handle missing data (full information maximum likelihood), we should be mindful of attrition over the years and that our study is based on a subsample of the original cohort.

One of the strengths of this study is that the sample exclusively included older adults, a population at risk for low vitamin D levels and distinct in terms of metabolic changes and life cycle aspects. This study involved highly accurate methods of data quality assurance, including trained interviewers who conducted face-to-face interviews and who were supervised for quality control. Using directed acyclic graphing, a recommended approach, helped define the minimum set of variables and reduce bias. Additionally, SEM analysis allows for a deeper understanding of long-term effects in epidemiological data, providing insight into the association between 25(OH)D and depressive symptoms.

In conclusion, this study found a prospective association between serum vitamin D levels and depressive symptoms in older adults, indicating a small negative long-term effect, which implies that increased 25(OH)D led to decreased depressive symptoms. These findings suggest that vitamin D might have a long-term preventive effect on depressive symptoms. Given that depression is a complex and multifactorial disorder, further exploration is needed to better understand the role of vitamin D in its pathophysiology. Future studies could benefit from directed acyclic graphing to identify a minimum set of confounders and reduce bias. Additionally, using SEM to examine the same hypothesis could help unravel the relationship between vitamin D and depressive symptoms, providing valuable insight for clinical and preventive strategies.

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Disclosure

The authors report no conflicts of interest.

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