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Relationship between vitamin D levels and depression in women with polycystic ovary syndrome

Povezanost između nivoa vitamina D i depresije kod žena koje imaju sindrom policističnih jajnika

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Abstract

Background/Aim. Polycystic ovary syndrome (PCOS) is a common gynecological disorder in women of reproductive age. Depression is a common PCOS-related comorbidity that affects women's mental state. Although vitamin D deficiency (VDD) has been associated with affective dysregulation through immuno-inflammatory and neuroendocrine pathways, evidence in PCOS remains limited. The aim of this study was to determine the relationship between serum 25-hydroxyvitamin D [25(OH)D] deficiency and Beck Depression Inventory (BDI) scores in women with PCOS. **Methods.** This cross-sectional study included 80 women with PCOS who completed the BDI on the same day when their fasting serum 25(OH)D levels were measured. Multivariable models were prespecified to compare depressive symptom (DS) severity across vitamin D status, adjusting for key confounders such as age, body mass index, season, and insulin resistance. **Results.** Women with VDD experienced a greater burden of DSs than women without VDD ($p < 0.05$). This association persisted after adjusting for covariates in sensitivity analyses. **Conclusion.** Among women with PCOS, VDD was associated with greater DS severity. However, causal relationships cannot be established, and further longitudinal and interventional studies are needed.

Keywords:
depression; polycystic ovary syndrome; surveys and questionnaires; turkish people; vitamin d deficiency.

Apstrakt

Uvod/Cilj. Sindrom policističnih jajnika (*polycystic ovary syndrome* – PCOS) je čest ginekološki poremećaj kod žena u reproduktivnom dobu. Depresija je čest komorbiditet povezan sa PCOS-om koji utiče na mentalno stanje žena. Iako se nedostatak vitamina D (vitamin D *deficiency* – VDD) povezuje sa afektivnom disregulacijom posredovanom mehanizmima imunsko-inflamacijskih i neuroendokrinih puteva, dokazi o ovoj povezanosti kod PCOS i dalje su oskudni. Cilj ove studije bio je da se utvrdi odnos između nedostatka 25-hidroksivitamina D [25(OH)D] u serumu i rezultata Bekove skale depresivnosti (*Beck Depression Inventory* – BDI) kod žena koje imaju PCOS. **Metode.** Studijom preseka obuhvaćeno je 80 žena sa PCOS koje su popunile BDI istog dana kada im je natašte izmeren nivo 25(OH)D u serumu. Multivarijantni modeli određeni su unapred da bi se uporedila težina simptoma depresije u odnosu na status vitamina D, uz prilagođavanje za ključne zbunjujuće faktore kao što su životno doba, indeks telesne mase, godišnje doba i insulinska rezistencija. **Rezultati**. Žene sa VDD imale su značajno veće opterećenje simptomima depresije u odnosu na žene bez VDD ($p < 0,05$). Ta povezanost ostala je prisutna i nakon prilagođavanja kovarijablama u analizama osetljivosti. **Zaključak.** Kod žena koje imaju PCOS, VDD je bio povezan sa težim stepenom simptoma depresije. Međutim, ne mogu se utvrditi uzročno-posledične veze i potrebna su dalja longitudinalna i interventna istraživanja.

Ključne reči:
depresija; jajnik, policistični, sindrom; ankete i upitnici; turska; vitamin d, nedostatak.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder that affects reproduction, metabolism, and mental health in women of reproductive age worldwide [1, 2]. Individuals with PCOS are more likely to experience significant anxiety and depressive symptoms (DSs) than those without the condition. Women with PCOS are particularly vulnerable to anxiety and depression during the transition from adolescence to adulthood [3, 4].

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Vitamin D (VD) deficiency (VDD) is widespread in countries with significant seasonal and latitudinal variability, such as Türkiye, and has been associated with increased risk of anxiety and DSs [5, 6]. VD plays a role in neurobiological processes that influence depression by regulating proinflammatory cytokines, connecting with the hypothalamic–pituitary-adrenal axis, and modulating serotonergic pathways by controlling the tryptophan hydroxylase gene. PCOS is a disorder characterized by obesity, insulin resistance, and chronic low-grade inflammation, all of which may influence these pathways [7–9].

Studies have shown that low 25-hydroxyvitamin D [25(OH)D] levels are associated with an increased risk of DSs. VDD is also particularly common among women with PCOS. Estimates range from 40% to 80%, and deficiency is linked to adverse metabolic and reproductive outcomes [3, 10–12]. While some studies suggest that VD supplementation could improve metabolic or reproductive factors, its effect on mood has not been adequately investigated [13–16].

Studies have found that women with PCOS tend to experience lower quality of life and higher levels of DSs [17, 18]. In addition to the inflammatory and neuroendocrine aspects of PCOS, diminished VD levels have been associated with mood disturbances in perinatal populations [19].

The aim of the study was to determine the relation between VD levels and Beck Depression Inventory (BDI) scores in women with PCOS.

Methods

Study design and participants

The study was prepared in accordance with the Declaration of Helsinki and was approved by the Çanakkale Onsekiz Mart University, Faculty of Medicine, Clinical Research Ethics Committee, Çanakkale, Türkiye (No. 2023/11-02, from August 16, 2023). All participants provided written informed consent after receiving a comprehensive explanation of the study's aims, procedures, potential risks, and confidentiality safeguards. No incentives were contingent on questionnaire responses.

This study was designed as a single-center, analytical cross-sectional study conducted exclusively among women diagnosed with PCOS. The primary analytical framework involved stratifying participants according to VD status (deficient vs. non-deficient) to examine its association with DS severity. No external non-PCOS control group was included in the primary statistical analyses. The study included 80 consecutive women, aged 18–45 years, who had received a clinical diagnosis of PCOS according to contemporary, guideline-consistent criteria at the time of recruitment [2, 20]. The diagnosis of PCOS was determined by a specialist physician using clinical or biochemical hyperandrogenism and ultrasonographic evaluation according to the 2003 Rotterdam criteria [21].

Inclusion criteria were reproductive age, a confirmed PCOS diagnosis, and the ability to complete self-report measures in Turkish. Exclusion criteria included current pregnancy or being less than 6 months postpartum, a major known psychiatric disorder other than unipolar depression, endocrine disorders that mimic PCOS (e.g., nonclassic congenital adrenal hyperplasia, Cushing syndrome, hyperprolactinemia, and thyroid dysfunction not on stable therapy), chronic kidney or liver disease, an active infection or inflammatory disease flare-up within the last 4 weeks, high-dose VD therapy (> 2,000 IU/day within the last 3 months) or recent parenteral VD supplementation, and photosensitizing drugs that could alter VD status. Current use of antidepressants or anxiolytics was recorded and considered in sensitivity analyses.

The following parameters were recorded: age, parity, smoking status, physical activity (self-reported categories), and prior psychiatric diagnosis. Anthropometric measurements included height, weight, and body mass index (BMI). Fasting glucose and insulin were measured to compute the homeostasis model assessment of insulin resistance (HOMA-IR) [22], where available. In addition, self-reported information on prior psychiatric history and current use of psychopharmacological medications (including antidepressants and anxiolytics) was collected. Physical activity was assessed using categorical self-report measures. Although the season of blood sampling was recorded as a proxy for sunlight exposure, detailed quantitative measures such as daily sunlight exposure duration, dietary VD intake, and over-the-counter supplementation were not systematically assessed.

BDI is a 21-item self-report scale that assesses the current severity of DSs. Each item is rated on a 4-point scale (0–3), with possible total scores ranging from 0 to 63. A cutoff score of 17 or higher indicates depression. The Turkish validity and reliability of the scale were established by Hisli [23]. BDI scores of 11 or higher were considered indicative of depression: scores 11–16 indicate mild DSs, and scores of 17 or higher indicate moderate to severe DSs [12, 23, 24]. Standard severity ranges were used for descriptive reporting, while analyses modeled scores continuously.

Serum 25(OH)D levels were measured in fasting blood samples using a standardized method aligned with the Vitamin D Standardization Program, where available [25, 26]. The institutional laboratory documented internal quality controls and interassay coefficients of variation. Additional routine analytes (e.g., thyroid-stimulating hormone – TSH) were assessed as required for clinical purposes. Reference ranges for routine biochemical parameters were determined according to the institutional laboratory standards and current international clinical guidelines.

The primary exposure was defined as VDD, *a priori* defined as 25(OH)D < 20 ng/mL (50 nmol/L). This threshold is widely used in clinical and research contexts, particularly before the Endocrine Society shifted away from fixed sufficiency cut-points in 2024. To ensure comparability, we present our findings using this conventional threshold and provide sensitivity analyses using alternative cutoffs (below 12 ng/mL and between 12 and 20 ng/mL). These alternative cutoffs reflect updated perspectives distinguishing VDD from insufficiency [25, 27]. The VD-deficient group (Group 1) included 40 patients with serum 25(OH)D levels below

20 ng/mL. VD-sufficient group (Group 2) included 40 women with serum 25(OH)D levels at or above 20 ng/mL.

Sample size and power

A *post hoc* precision assessment indicated that, with n = 80 and an anticipated standard deviation (SD) of ~ 9–10 points for the BDI, the study could detect a between-group difference of ~ 5 points with 80% power at $\alpha = 0.05$ (two-tailed), or a standardized effect size of ~ 0.5. These estimates are typical for mood symptom studies in PCOS and inform the interpretation of null vs. positive findings in sensitivity checks.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the sample. Group comparisons by VD status used *t*-tests, Mann-Whitney *U* tests, or Chi-squared/Fisher's exact tests as appropriate. The primary analysis used multivariable linear regression with the BDI score as the dependent variable and VDD as the main predictor. The analysis was adjusted for the prespecified confounders of age, BMI, season (winter/spring vs. summer/autumn), and HOMA-IR (or metformin use when HOMA-IR was unavailable). Model diagnostics were used to evaluate linearity, residual normality, collinearity (variance inflation factors – VIF < 5), and influential observations. Sensitivity analyses included excluding participants taking antidepressants, performing ordinal regression across BDI severity strata, and evaluating alternative VD thresholds. Two-sided $p < 0.05$ denoted statistical significance. The statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). All analyses were restricted to the PCOS cohort, and comparisons were performed between VD status subgroups rather than between PCOS and non-PCOS populations. Sensitivity analyses were conducted to evaluate the robustness of findings after excluding participants using antidepressant or anxiolytic medications.

Variables included in the study were selected based on *a priori* clinical relevance and evidence from a multivariable logistic regression model in the literature indicating their potential associations with both VD status and DSs. Specifically, age, BMI, and insulin resistance (HOMA-IR) were included as key confounders. Given the relatively modest sample size, the number of covariates was restricted to minimize the risk of model overfitting. Multicollinearity was assessed using VIF, and model assumptions were evaluated prior to final model specification.

The discriminative performance of the logistic regression model was further evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated.

Results

Participants with PCOS were stratified according to serum 25(OH)D status into two groups: Group 1 (n = 40) with serum 25(OH)D < 20 ng/mL and Group 2 (n = 40) with serum 25(OH)D ≥ 20 ng/mL (Table 1). The average age of the

Table 1

Sociodemographic and lifestyle characteristics of women with PCOS according to 25(OH)D level

Variables	Group 1 (n = 40)	Group 2 (n = 40)	*p*-value
Age, years	25.08 ± 0.80	25.80 ± 1.04	0.58
Education level			0.09
elementary	2 (2.5)	8 (10.0)	
high school	14 (17.5)	14 (17.5)	
university and higher	24 (30.0)	18 (22.5)	
Employment status			0.78
employed	16 (20.0)	14 (17.5)	
student	1 (1.3)	2 (2.5)	
unemployed	23 (28.7)	24 (30.0)	
Place of residence			0.49
urban	25 (31.3)	21 (26.3)	
rural	15 (18.7)	19 (23.7)	
Smoking status			0.43
never	28 (35.0)	32 (40.0)	
former	12 (15.0)	8 (10.0)	
Physical activity			0.79
yes	10 (12.5)	9 (11.3)	
no	30 (37.5)	31 (38.7)	
Family history of PCOS			0.80
yes	12 (15.0)	13 (16.3)	
no	28 (35.0)	27 (33.7)	

PCOS – polycystic ovary syndrome; 25(OH)D – 25-hydroxyvitamin D; n – number of respondents.
Data are presented as mean ± standard deviation and as numbers (percentages).
***Note*: Group 1 consisted of respondents with 25(OH)D < 20 ng/mL, while Group 2 consisted of respondents with 25(OH)D ≥ 20 ng/mL.**

patients in Group 1 was 25.08 ± 0.80 years, while the average age of the patients in Group 2 was 25.80 ± 1.04 years (p = 0.58). No statistically significant differences were observed in educational status, employment, place of residence, smoking status, physical activity, or family history of PCOS between the groups (p > 0.05). However, participants in Group 1 had significantly higher BDI scores than those in Group 2 (p = 0.04). The mean difference in BDI scores between the groups was approximately 4.4 points. Additionally, participants with VDD exhibited higher DS severity than those without deficiency (p = 0.02) (Table 2).

Correlation analysis performed across the entire sample demonstrated a significant inverse relationship between serum 25-(OH) D levels and BDI scores (r = -0.23, p = 0.04). Lower VD levels were associated with higher DS severity.

A multivariate logistic regression analysis was performed to determine whether VDD was independently associated with DSs (BDI ≥ 11). After adjusting for age, BMI, and HOMA-IR, VDD remained significantly associated with an increased likelihood of DSs [odds ratio (OR) = 2.84, 95% confidence interval (CI): 1.03–7.82, p = 0.04] (Figures 1 and 2). None of the other variables included in the model showed a

Table 2

Clinical and biochemical characteristics according to 25(OH)D level

Variables	Reference ranges	Group 1 (n = 40)	Group 2 (n = 40)	*p*-value
BMI, kg/m²	18.5–22.4	25.46 ± 1.03	26.50 ± 0.90	0.45
Glucose, mg/dL	70–99	89.72 ± 1.76	89.09 ± 2.28	0.82
Total cholesterol, mg/dL	< 200	171.47 ± 5.01	185.78 ± 6.55	0.08
LDL-C, mg/dL	< 100	95.78 ± 4.51	107.80 ± 5.89	0.42
HDL-C, mg/dL	> 50 (women)	55.85 ± 1.51	63.95 ± 2.49	0.03
Triglycerides, mg/dL	< 150	105.74 ± 8.90	108.27 ± 7.37	0.82
HOMA-IR	< 2.5*	2.92 ± 0.24	4.67 ± 1.03	0.10
BDI score	0–10 normal**	15.85 ± 1.84	11.40 ± 1.20	0.04
BDI ≥11		25 (31.25)	14 (17.50)	0.02

25(OH)D – 25-hydroxyvitamin D; n – number of respondents; BMI – body mass index; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; HOMA-IR – homeostasis model assessment of insulin resistance; BDI – Beck Depression Inventory.

Data are presented as mean ± standard deviation and as numbers (percentages).

***Note*: Group 1 consisted of respondents with 25(OH)D < 20 ng/mL, while Group 2 consisted of respondents with 25(OH)D ≥ 20 ng/mL. *HOMA-IR values < 2.5 were considered within the normal range. **BDI scores: 0–10 minimal/no depressive symptoms; 11–16 mild depressive symptoms; ≥ 17 moderate-to-severe depressive symptoms.**

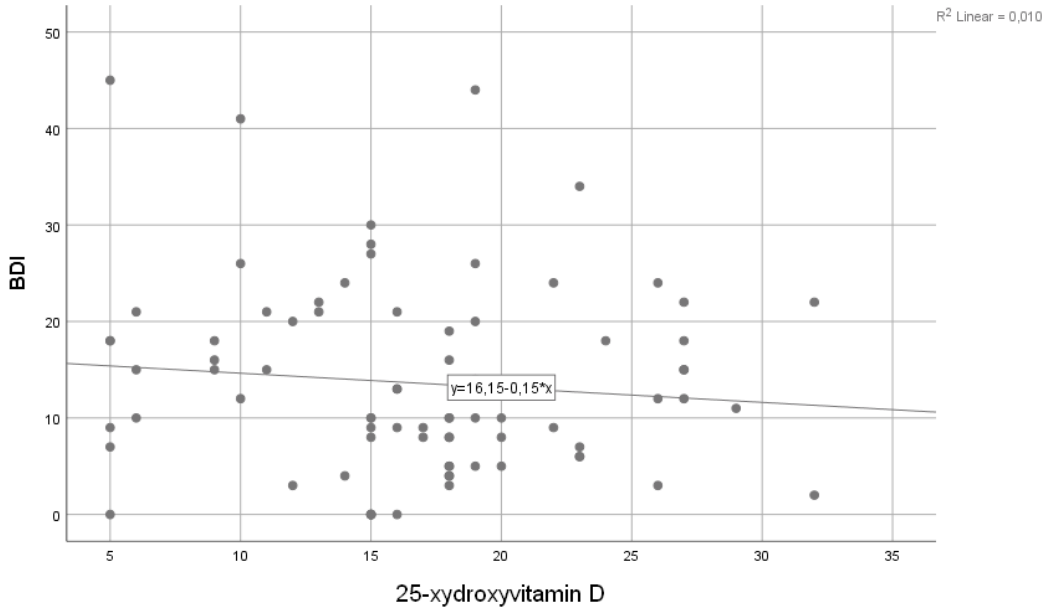

Fig. 1 – Scatter plot illustrating the inverse relationship between serum 25-xydroxyvitamin D levels and Beck Depression Inventory (BDI) scores.

The fitted linear regression line demonstrates a modest negative correlation (r = - 0.23, p = 0.04).

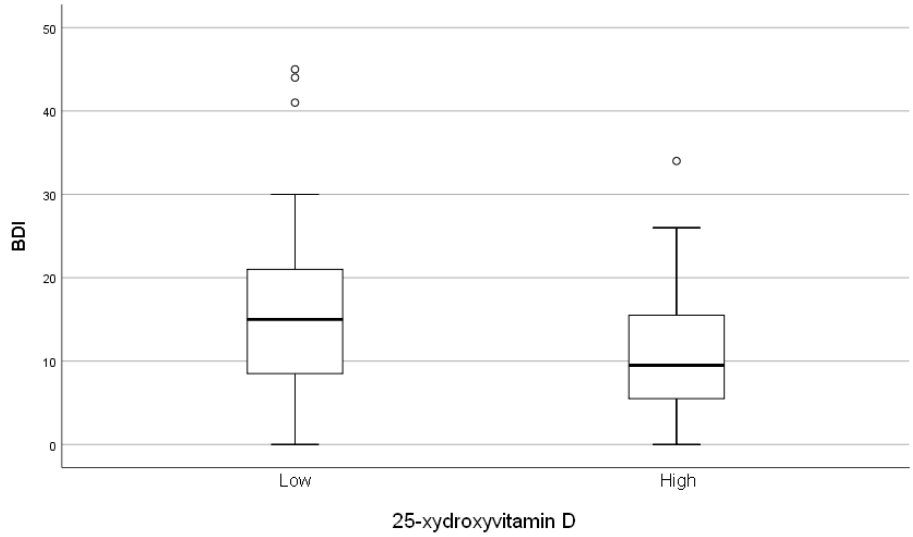

Fig. 2 – Box plot comparing Beck Depression Inventory (BDI) score distributions between participants with 25-xydroxyvitamin D deficiency (< 20 ng/mL) and those with sufficient levels (≥ 20 ng/mL).

Table 3

Multivariate logistic regression analysis for depressive symptoms

Variable	OR	95% CI	*p*-value
25(OH)D	2.84	1.03–7.82	0.04
Age	1.05	0.88–1.25	0.56
BMI	1.08	0.83–0.99	0.32
HOMA-IR	1.06	0.94–1.19	0.32

OR – odds ratio; CI – confidence interval; 25(OH)D – 25-hydroxyvitamin D; BMI – body mass index; HOMA-IR – homeostasis model assessment of insulin resistance.

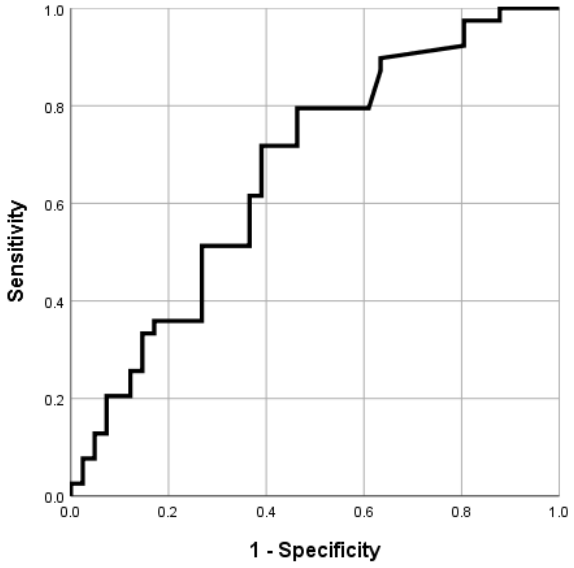

Fig. 3 – Receiver operating characteristic (ROC) curve demonstrating the discriminative performance of the multivariable logistic regression model for predicting depressive symptoms (Beck Depression Inventory – BDI ≥ 11).
***Note*: Diagonal segments are produced by ties.**

statistically significant association with DSs (Table 3). The ROC curve analysis was performed to evaluate the discriminative performance of the multivariable logistic regression model. The model demonstrated acceptable discrimination, with an AUC of 0.668 (95% CI, p = 0.010) (Figure 3).

Discussion

This study examined the association between serum VD levels and DS severity in women with PCOS. Importantly, it is a within-PCOS analysis rather than a case–control comparison. The study found that low VD levels were associated with higher BDI scores in individuals diagnosed with PCOS. This finding aligns with previous studies that have linked low serum 25(OH)D levels to DSs [3, 17, 18]. Our results support studies indicating that women with PCOS experience high levels of depressive symptomatology and compromised quality of life [17, 28]. Furthermore, there is evidence that VDD is prevalent in individuals with PCOS and that correcting it could potentially improve non-mood symptoms [3, 7, 16, 19]. Lifestyle and socioeconomic factors may also confound the observed association. The ROC analysis showed acceptable but limited discriminative performance of the model. However, the modest AUC value suggests that VD status and the included covariates alone may not fully explain the variability in DSs, highlighting the multifactorial nature of depression in women with PCOS.

These findings are biologically plausible *via* converging pathways. First, VD affects serotonin generation by regulating the expression of tryptophan hydroxylase isoforms. This may influence mood regulation [29]. Secondly, VD has immune-modulating functions that reduce cytokine-induced "sickness behavior". This action is increasingly being linked to DSs [8, 30]. Third, PCOS is characterized by low-grade chronic inflammation. This includes elevated levels of C-reactive protein and interleukin-6, as well as changes in immune cell profiles that may increase susceptibility to mood changes when VD levels are low [7, 8, 30]. Furthermore, insulin resistance and excess weight, which are common in PCOS, are associated with lower serum 25(OH)D levels due to mechanisms such as dilution and sequestration, as well as with DSs. These factors present potential feedback loops.

Although the difference in BDI scores between groups was statistically significant, its clinical relevance warrants careful interpretation. The observed mean difference of approximately 4–5 points may reflect a shift within adjacent severity categories (e.g., from minimal to mild or from mild to moderate DSs), rather than a clear threshold for clinical diagnosis or intervention. Therefore, while the findings suggest a greater burden of DSs among women with VDD, they do not necessarily indicate clinically actionable depression requiring treatment. From a clinical perspective, these findings may help identify subgroups of patients with PCOS who are more vulnerable to depressive symptomatology. However, the results should not be interpreted as sufficient to guide clinical decision-making in isolation. Comprehensive psychiatric evaluation and established clinical criteria remain essential for diagnosis and management. Accordingly, the observed association should be considered clinically informative but not practice-changing.

Randomized trials in the general population produce inconsistent results. For instance, the large Vitamin D and Omega-3 Trial-Depression Endpoint Prevention – VITAL-DEP trial did not observe a reduction in new depression cases among adults with adequate VD levels [11]. However, meta-analyses of individuals with VDD or clinical depression indicate small yet significant symptom reductions with supplementation. These findings suggest that baseline VD levels and clinical presentation are important factors [7, 25, 31, 32]. In PCOS, newer meta-analyses indicate that VD supplementation can improve certain metabolic, hormonal, and reproductive indices [10, 11, 16, 19, 25, 27, 32]. However, mood has rarely been the primary focus. Our findings emphasize the need for PCOS-specific randomized controlled trials to address VDD and evaluate mood outcomes.

In clinical practice, the updated 2024 Endocrine Society guidelines advise against screening the general population. The guidelines advocate moving away from very strict sufficiency thresholds but support targeted testing in high-risk individuals or those presenting symptoms [27]. Individuals with PCOS who exhibit symptoms of depression, particularly those related to winter or higher-latitude environments, could fall into this high-risk category. From a clinical perspective, these findings highlight a potential area of interest rather than a basis for intervention. Any consideration of VD assessment or supplementation in this population should be guided by existing clinical guidelines rather than the results of this study alone. Where deficiency has been confirmed, supplementation should adhere to current safety guidelines and consider repletion strategies [10, 27, 30, 33].

The findings of this study indicate a significant association between VDD and increased DS severity among women with PCOS. However, these results should be interpreted as evidence of an association rather than as direct evidence of a therapeutic effect of VD on DSs. Given the cross-sectional nature of the study, causal inferences cannot be established. Nevertheless, several biological mechanisms may help explain the observed relationship.

VD plays an important role in neurobiological processes related to mood regulation. Experimental and clinical evidence suggests that VD may influence serotonin synthesis through the regulation of tryptophan hydroxylase expression, thereby contributing to the modulation of emotional states and depressive symptomatology [29, 30]. In addition, VD has immunomodulatory effects and may reduce systemic inflammation by regulating proinflammatory cytokines. Since chronic low-grade inflammation is frequently observed in PCOS, this pathway may partially explain the association between VDD and DSs. Furthermore, VD has been implicated in the regulation of the hypothalamic-pituitary-adrenal axis, which is closely linked to stress response and mood disorders.

Despite these plausible mechanisms, the cross-sectional design of the present study precludes determining whether VDD contributes to DSs or whether DSs themselves influence lifestyle behaviors that affect VD status, such as reduced outdoor activity or dietary intake. Therefore, the findings should be interpreted cautiously. Longitudinal studies and randomized controlled trials focusing specifically on mood outcomes are required to clarify the direction and clinical significance of this relationship.

While the association between VDD and DSs observed in this study is noteworthy, it should be interpreted with cau-

tion. The findings do not support causal inference, nor do they justify immediate changes in clinical practice. Instead, they should be considered hypothesis-generating and serve as a basis for future prospective and interventional research.

Limitations of the study

The strengths of the current study include same-day assessments of mood and VD levels, predetermined adjustments for confounding factors, and sensitivity analyses based on new guidelines and alternative cutoff points. This study has several limitations that should be considered when interpreting the findings. First, the cross-sectional design precludes the establishment of causal relationships between VDD and DSs. Second, the study was conducted at a single center with a relatively modest sample size, which may limit the generalizability of the findings. Third, although several potential confounders—such as age, BMI, season, and insulin resistance—were adjusted for, other factors that may influence VD levels, including detailed dietary intake, precise sunlight exposure, and duration of outdoor activity, were not quantitatively assessed. In addition, PCOS phenotypes were not analyzed separately due to the limited sample size, which may have influenced the interpretation of the results. Finally, DSs were assessed using a self-report instrument rather than a structured psychiatric interview. Additional multicenter longitudinal studies with larger samples and more comprehensive assessments of lifestyle factors are needed to further clarify the relationship between VD status and DSs in women with PCOS.

Despite adjustment for several key confounders, the possibility of residual confounding cannot be excluded. Important variables known to influence both VD status and DSs—such as quantitative sunlight exposure, dietary VD intake, socioeconomic status, and detailed physical activity patterns—were not comprehensively measured. Although seasonality was included as a proxy for sunlight exposure and self-reported physical activity was recorded, these measures may not fully capture individual variability. In addition, while psychopharmacological medication use and prior psychiatric history were documented and considered in sensitivity analyses, the study was not powered to fully disentangle their potential modifying effects. These limitations should be considered when interpreting the observed associations.

Conclusion

Our findings indicate that lower vitamin D levels are associated with greater depressive symptom severity among women with polycystic ovary syndrome. However, given the cross-sectional design of the study, these results should be interpreted as evidence of association rather than causation. The observed relationship may reflect complex interactions between biological, behavioral, and environmental factors. Therefore, no direct clinical implications regarding vitamin D supplementation or screening can be inferred from the present findings. Future longitudinal studies and randomized controlled trials are required to clarify the directionality and clinical relevance of this association. The clinical significance of these findings remains to be clarified in prospective studies evaluating patient-centered outcomes.

Conflict of interest

The authors declare no conflict of interest.

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