ASSOCIATION BETWEEN SERUM VITAMIN D LEVELS AND DEPRESSION AMONG ELDERLY: DETERMINATION OF AN OPTIMAL CUT-OFF VALUE USING ROC ANALYSIS

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Abstract: Evaluating The Threshold of Vitamin D Levels For Depression Prevention in The Elderly: A Cross-Sectional Study. *Major depressive disorder adversely affects psychological well-being and is marked by persistent low mood and loss of interest in previously pleasurable activities. Depression prevalence varies across countries, with reported rates of 33.8% in Indonesia, 30.3% in Japan, and 17.2% in Vietnam. This study aimed to identify a vitamin D threshold associated with depression prevention in older adults. Using a cross-sectional design, the study was conducted at Panti Bina Bhakti and included 93 participants aged 60 years and above. Serum vitamin D levels were measured using the enzyme-linked immunosorbent assay (ELISA), while depressive symptoms were assessed with the Geriatric Depression Scale (GDS). The findings revealed a significant association between lower vitamin D concentrations and greater severity of depressive symptoms. ROC analysis identified a serum vitamin D threshold of 9 ng/mL associated with the presence of depression. This threshold yielded an AUC of 0.729 (p = 0.003), with a sensitivity of 21.1% and a specificity of 49.1%. These results suggest that vitamin D deficiency is common among the elderly and that higher vitamin D levels were associated with lower depression prevalence. Despite identifying a potential threshold, this study has limitations, including its cross-sectional design and the absence of randomized controlled trials to establish a causal effect of vitamin D supplementation on depression risk.*

Keywords : *Major Depressive Disorder, Vitamin D Threshold, Geriatric Depression Scale; Vitamin D Deficiency*

Abstrak: Penilaian Ambang Batas Kadar Vitamin D untuk Pencegahan Depresi pada Lansia: Studi Potong Lintang. Gangguan depresi mayor berdampak negatif pada kesejahteraan psikologis dan ditandai dengan mood yang hipotim secara persisten serta hilangnya minat terhadap aktivitas yang sebelumnya menyenangkan. Prevalensi depresi bervariasi antar negara, dengan tingkat prevalensi 33,8% di Indonesia, 30,3% di Jepang, dan 17,2% di Vietnam. Studi ini bertujuan untuk mengidentifikasi ambang batas vitamin D yang terkait dengan pencegahan depresi pada lansia. Menggunakan desain potong lintang, studi ini dilakukan di Panti Bina Bhakti dan melibatkan 93 peserta berusia 60 tahun ke atas. Kadar vitamin D dalam serum diukur menggunakan metode *enzyme-linked immunosorbent assay* (ELISA), sementara gejala depresi dievaluasi dengan *Geriatric Depression Scale* (GDS). Temuan menunjukkan adanya hubungan yang signifikan antara kadar vitamin D yang lebih rendah dan tingkat keparahan gejala depresi yang lebih tinggi. Analisis ROC mengidentifikasi ambang batas kadar vitamin D dalam serum sebesar 9 ng/mL yang terkait dengan adanya depresi. Ambang batas ini menghasilkan nilai AUC sebesar 0,729 (p = 0,003), dengan sensitivitas 21,1% dan spesifisitas 49,1%. Hasil-hasil ini menunjukkan bahwa kekurangan vitamin D umum terjadi di kalangan lansia dan bahwa kadar vitamin D yang lebih tinggi dikaitkan dengan prevalensi depresi yang lebih rendah. Meskipun mengidentifikasi ambang batas potensial, studi ini memiliki

keterbatasan, termasuk desain cross-sectional dan ketidakhadiran uji klinis terkontrol acak untuk menetapkan efek kausal suplemen vitamin D terhadap risiko depresi.

Kata Kunci : Gangguan Depresi Mayor, Ambang Batas Vitamin D, Skala Depresi Geriatri, Defisiensi Vitamin D

INTRODUCTION

The psychological well-being of the elderly is a complex personal experience that develops through their life activities and interactions with others. Psychological well-being is influenced by various factors, including personal aspects (subjective age, self-actualization, and self-regulation), cognitive, socio-emotional (neuroticism, depression, and self-compassion), as well as other factors (Oh and Spivak, 2018). Major depressive disorder is one of the mental disorders that affect psychological well-being, characterized by pervasive and persistent feelings of sadness and a loss of pleasure in activities that were previously considered enjoyable. This disorder has an incidence rate of 20% in the population of every individual's life (Sepehrmanesh *et al.*, 2016). Based on research conducted by Taizo Wada et al., in the elderly living in communities in three different Asian countries, namely Vietnam, Indonesia, and Japan, it was found that around 17.2 - 33.8% experienced depression with the prevalence in Indonesia reaching 33.8%, Japan 30.3%, and Vietnam 17.2%. This shows that the number of elderly experiencing depression is still very high in Indonesia (Wada *et al.*, 2005).

Vitamin D is a neurohormone with broad physiological impacts. Many studies have shown that Vitamin D has various effects on biological processes that regulate calcium and phosphorus metabolism as well as affecting cell proliferation, differentiation, apoptosis, immune regulation, genome stability, and neurogenesis (Wang *et al.*, 2017). Vitamin D is closely related to CYP27B1 metabolism. The CYP27B1 enzyme, known as CYP27B1, is expressed in neurons and glial cells in both fetuses and adults, particularly in the substantia nigra supraoptic and paraventricular hypothalamus. Furthermore, the hypothalamus, pons, basal ganglia, hippocampus, and developing brain tissue have significant expression of VDR receptors, indicating a potential role for Vitamin D in brain development and function (Harms *et al.*, 2011). Vitamin D status is an important indicator of overall health and has been identified as a factor that may beneficially affect the prevention and management of several chronic diseases (Anglin et al., 2013). In addition, its established involvement in neural functions, including neuroplasticity and neuroimmunomodulation, suggests a potential role for vitamin D in psychiatric conditions such as depression (Eyles et al., 2005). Elucidating the diverse biological roles of vitamin D remains a focus of ongoing research.

Vitamin D deficiency is common in the elderly population, particularly those with limited mobility or living in long-term care facilities (Samefors *et al.*, 2014; Boettger *et al.*, 2018). A study conducted in northwestern China reported that 75.2% of elderly participants were vitamin D deficient (Zhen *et al.*, 2015). A large cohort study of 56,366 U.S. women aged 50–79 years demonstrated that higher vitamin D intake was associated with a significantly lower risk of depression, further supporting the link between vitamin D deficiency and neuropsychiatric disorders (Bertone-Johnson et al., 2011). Available evidence indicates that vitamin D enhances the expression of calcium-binding proteins. (Eyles *et al.*, 2005). Previous research has shown that vitamin D exerts neuroprotective effects by enhancing antioxidant defenses (Kesby et al., 2011). Furthermore, vitamin D has been reported to modulate the synthesis, release, and activity of serotonin within the central nervous

system (Patrick and Ames, 2015). Despite growing evidence supporting the association between vitamin D deficiency and depression, the optimal serum vitamin D threshold associated with depressive symptoms remains unclear. A study conducted in Brazil (dos Santos et al., 2024) reported that serum vitamin D levels below 12 ng/mL were significantly associated with higher depressive symptom scores among older adults. In contrast, studies from the United Kingdom (Di Gessa et al., 2021) and Kuwait (Albolushi et al., 2022) identified a higher cut-off value of <20 ng/mL, which was also significantly associated with increased depressive symptom scores. These findings suggest considerable variability in the vitamin D threshold associated with depressive symptoms across different geriatric populations.

To date, evidence regarding the optimal serum vitamin D threshold associated with depressive symptoms among older adults in Indonesia remains limited. Given the high prevalence of both vitamin D deficiency and depression in the geriatric population, establishing a population-specific cut-off value may contribute to more targeted screening and preventive strategies. Therefore, this study aimed to determine the serum vitamin D cut-off associated with the absence of depressive symptoms among Indonesian older adults using receiver operating characteristic (ROC) analysis.

METHODS

This study employed a cross-sectional design and was carried out at Panti Bina Bhakti in May 2024. The objective was to examine the association between serum vitamin D levels and the severity of depression among elderly. The study population consists of residents of Panti Bina Bhakti who meet the inclusion criteria, which include being at least 60 years old. Exclusion criteria encompass respondents who are uncooperative, unable to communicate bilaterally, or have other conditions that hinder participation. The sampling method used is total sampling, with a target minimum sample size of 60 respondents.

The main variables in this study are the levels of vitamin Din venous blood and the level of depression. The measurement of vitamin D levels is performed using the Enzyme-Linked Immunosorbent Assay (ELISA) method. ELISA is an immunological technique used to measure the concentration of an antigen (in this case, 25-OH-D3) in a blood sample using antibodies specific to that antigen. This process involves adding the blood sample to a microtiter well coated with specific antibodies, followed by the addition of a substrate that produces a color change that can be quantitatively measured with a spectrophotometer. The normal healthy range for serum vitamin D levels is typically between 30 to 50 ng/mL (Bischoff-Ferrari *et al.*, 2006).

Depression was evaluated using the Geriatric Depression Scale (GDS), a validated screening tool designed specifically for use in elderly populations. The instrument consists of binary (‟yes”/‟no”) questions that assess emotional state, activity level, and engagement in daily life. Total scores are calculated from responses indicative of depressive symptoms, with higher scores corresponding to greater symptom severity. According to standard GDS criteria, scores are categorized as no depression (0–4), mild depression (5–8), moderate depression (9–11), and severe depression (12–15). A meta-analysis of 31 studies encompassing 8,897 participants reported a pooled sensitivity of 0.80 (95% CI: 0.78–0.82), demonstrating strong diagnostic performance in older adults, and a pooled specificity of 0.79 (95% CI: 0.78–0.80), confirming the tool’s reliability and validity (Park and Kwak, 2021).

Ethical approval was obtained from the Tarumanagara University Human Research Ethics Committee, Institute of Research and Community Engagement (No. 013-UTHREC/UNTAR/VI/2024).

Written informed consent was obtained from all participants prior to data collection.

Data analysis is performed using ROC (Receiver Operating Characteristic) analysis to determine the optimal threshold value of vitamin D levels that provide protection against depression. The ROC curve is used to evaluate the ability of vitamin D levels to predict the risk of depression by displaying sensitivity (the ability of the test to detect positive cases) and specificity (the ability of the test to detect negative cases) at various threshold points. From the ROC curve, the area under the curve (AUC) is calculated to assess the overall diagnostic accuracy of vitamin D levels. Additionally, the analysis will identify the lowest vitamin D levels that pose a significant risk for developing severe depression, determined through sensitivity and specificity analysis at various vitamin D threshold points. The results of this analysis are expected to provide recommendations for optimal vitamin D levels for the prevention of depression in the elderly.

Results

This study included 93 research respondents who met the inclusion criteria. The characteristics of the research respondents are described in Table 1. The results of the Kruskall Wallis test revealed that there was at least one group that had a significant difference in Vitamin D levels when compared to the other groups (p-value: 0.038). Clinical investigations showed that the group without depression had the highest levels of Vitamin D, namely 9.2 (5.8 – 25.60) ng/mL when compared with other groups with depression. (Table 2)

Table 1. Characteristics of Research Respondents

Parameter	N (%)	Med (Min-Max)
Age		75 (61 – 97)
Sex		
● Men	16 (17,2%)	
● Women	77 (82,8%)	
Vitamin D 25 OH levels		7,5 (1,07 – 25,60)
Geriatric Depression Scale (GDS)		3 (0 – 15)
● Normal	55 (59,1%)	
● Mild	19 (20,4%)	
● Moderate	9 (9,7%)	
● Severe	10 (10,8%)	

The x-axis displays categories of depression severity as defined by the Geriatric Depression Scale, namely no depression (0–4 points), mild depression (5–8 points), moderate depression (9–11 points), and severe depression (12–15 points). The y-axis denotes serum vitamin D concentrations expressed in ng/mL. Each box plot illustrates the distribution of vitamin D levels within each depression severity group. Statistical comparisons yielded p-values of 0.023 for no depression versus mild depression, 0.772 for mild versus moderate depression, 0.068 for no depression versus moderate depression, and 0.968 for moderate versus severe depression. Notably, a significant difference in vitamin D levels was observed only between individuals without depression and those with depression ($p = 0.023$). In contrast, progressively lower vitamin D concentrations were not associated with increasing severity of depressive symptoms (Table 2, Figure 1).

Table 2. Difference in Average Vitamin D Levels between Depression Severity

Parameter		N	Med (Min – Max)	Mean Rank	p-value
Geriartric Depression Scale (GDS)	Normal	55	9.2 (5,8 – 25,60)	53,75	0,038
	Mild	19	6,5 (5,7 – 21,23)	37,16	
	Moderate	9	7,1 (5,7 – 20,11)	37,83	
	Severe	10	6,9 (1,07 – 16,40)	36,80	

Statistical analysis used Kruskall Wallis due to non-normal data distribution according to the Kolmogorov Smirnov and Shapiro Wilk tests
The significance value set is p-value <0.05

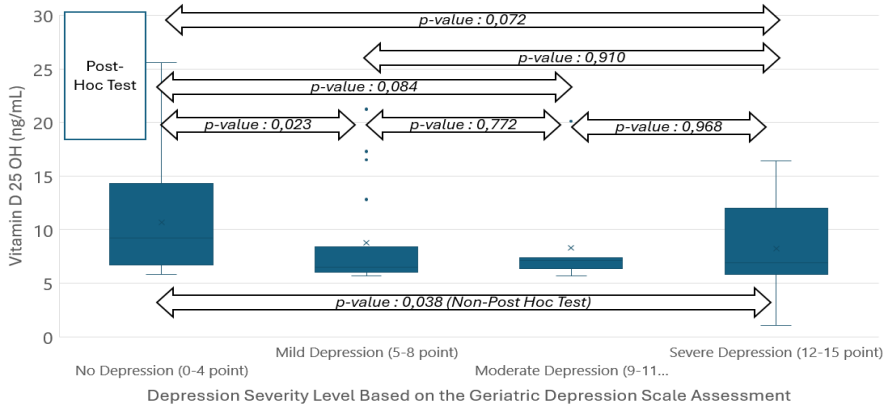


Figure 1. Analysis of Differences in Average Vitamin D Levels between Depression Severity (Post Hoc Test)

The area under the curve (AUC) value for vitamin D levels as a predictor of outcomes without depression in the elderly group (Table 3) in this analysis is 0.729, indicating a moderate ability to predict outcomes without depression. The p-value is 0.003, suggesting that the result is statistically significant, supporting the predictive power of vitamin D levels. The 95% confidence interval (CI) for the AUC value for vitamin D levels as a discriminative ability of outcomes without depression in the elderly group ranges from 0.617 to 0.842. In conclusion, this analysis suggests that vitamin D levels have moderate predictive ability for outcomes without depression in the elderly population.

Table 3. Area Under the Curve Value for Vitamin D Levels as a Predictor of Outcomes Without Depression in the Elderly Group

			Asymptotic 95% Confidence Interval	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
0.729	0.057	0.003	0.617	0.842

Test Result Variable(s): Vitamin D(ng/mL)
Value of state variable: No Depression
The test result variable(s): Vitamin D(ng/mL) has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

The ROC (Receiver Operating Characteristic) curve (Figure 2) illustrates the diagnostic performance of a binary classifier system. The x-axis represents the false positive rate (1 - specificity), and the y-axis represents the true positive rate (sensitivity). The closer the curve follows the top-left border, the more accurate the test. An optimal cutoff point balances sensitivity and specificity. This graph (Figure 2-3) shows sensitivity and specificity values for predicting depression in the elderly based on Vitamin D levels. ROC analysis identified an optimal serum vitamin D cut-off value of 9 ng/mL, with a sensitivity of 21.1%, specificity of 49.1%, positive predictive value (PPV) of 22.2%, and negative predictive value (NPV) of 47.3%.

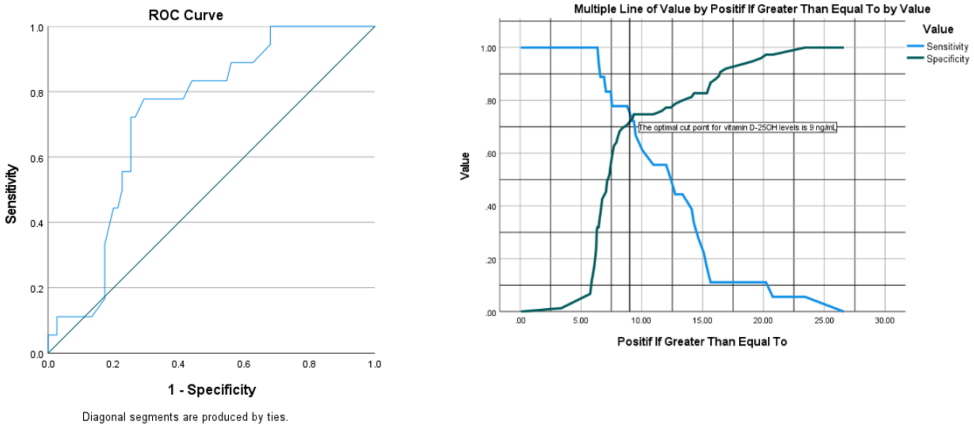
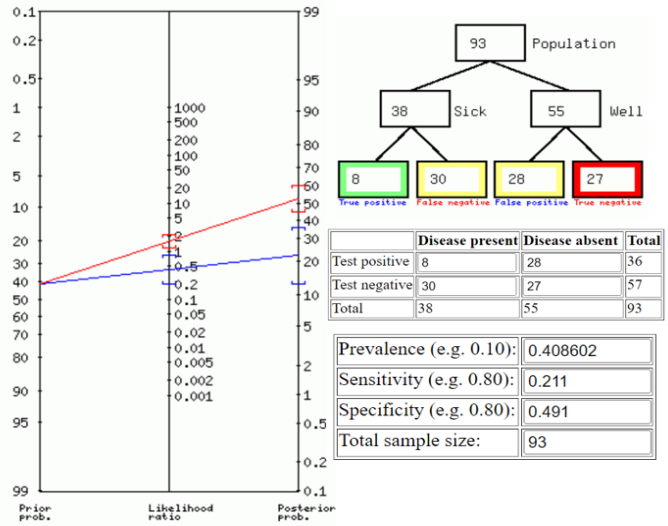


Figure 2. ROC Curve of Predictor Variables Causing Mortality in Acute Coronary Syndrome Cases (Left); Bargaining Graph of Sensitivity and Specificity Value of Vitamin D Levels in Predicting Depression in the Elderly Group (Right)



	Disease present	Disease absent	Total
Test positive	8	28	36
Test negative	30	27	57
Total	38	55	93

Prevalence (e.g. 0.10):	0.408602
Sensitivity (e.g. 0.80):	0.211
Specificity (e.g. 0.80):	0.491
Total sample size:	93

Figure 3. Likelihood ratio (LR) graph of Vitamin D levels as a test to evaluate depression in the elderly group

DISCUSSION

Based on our study's analysis, it was determined that a vitamin D threshold of at least 9 ng/mL is necessary to prevent depression in the geriatric population. Notably, our results

show that vitamin D (25-OH-D_3) concentrations below this threshold display variable patterns, indicating that vitamin D levels may not have a significant influence on depression severity in this population.

Our findings are consistent with those of dos Santos et al., who reported an inverse association between vitamin D deficiency and depressive symptoms among older adults. Similarly, Di Gessa et al. demonstrated that declining vitamin D concentrations were associated with increased depressive symptoms during follow-up. However, the threshold identified in our study was lower than values reported in several Western populations, which generally ranged from 12–30 ng/mL. (dos Santos et al., 2024; Di Gessa et al., 2021)

The lower vitamin D threshold identified in our study may be explained by several factors. First, substantial variability exists in the definition of vitamin D deficiency across clinical guidelines. Recommended cut-off values range from <12 ng/mL (30 nmol/L) to <30 ng/mL (75 nmol/L), depending on whether the threshold is based primarily on skeletal outcomes or broader health benefits. For example, the Institute of Medicine defines vitamin D deficiency as serum levels below 20 ng/mL (50 nmol/L) based on bone health outcomes, whereas the Endocrine Society previously recommended a sufficiency threshold of ≥30 ng/mL (75 nmol/L), although strict definitions have recently been reconsidered due to insufficient evidence supporting universal cut-off values (Demay et al., 2024; Grant et al., 2025). Second, methodological differences in vitamin D measurement may contribute to discrepancies among studies. Variability in assay techniques and the lack of complete standardization across laboratories can substantially influence measured serum vitamin D concentrations, resulting in differences in reported prevalence rates and proposed threshold values (Pang et al., 2022). Third, population-specific characteristics may affect the optimal vitamin D threshold. Genetic background, skin pigmentation, sunlight exposure, geographical location, seasonal variation, dietary habits, and food fortification practices all influence vitamin D status and may limit the applicability of a single universal cut-off value across different populations (Harvey et al., 2024). Finally, the optimal vitamin D threshold may vary according to the health outcome being evaluated. While strong evidence supports the relationship between vitamin D deficiency and skeletal health, the evidence regarding extra-skeletal outcomes, including depression, remains less consistent (Grant et al., 2025). Consequently, there is currently no consensus regarding the most appropriate vitamin D threshold for preventing or reducing the risk of depression. These factors may collectively explain why the vitamin D cut-off identified in our study was lower than those reported in previous studies.

The absence of a clear dose-response relationship below 9 ng/mL suggests that depression in older adults is likely multifactorial. A comprehensive systematic review of longitudinal studies among individuals aged 65 years and older reported that chronic disease, sleep initiation difficulties, mobility impairment, IADL limitations, and visual impairment were the most consistently identified predictors of depression. Furthermore, female sex, lower educational level, poorer self-perceived health status, cognitive impairment, and older age were commonly associated with a higher risk of depression; however, the strength and consistency of these associations varied across studies (Zenebe et al., 2021).

These findings highlight a potential association between severe vitamin D deficiency and depressive symptoms in older adults. However, given the cross-sectional nature of the study, no causal relationship can be inferred. Nevertheless, assessment of vitamin D status may be considered as part of a

comprehensive evaluation of older adults presenting with depressive symptoms.

Several biological mechanisms may explain the association between vitamin D deficiency and depression. Vitamin D plays a critical role in maintaining calcium homeostasis by regulating the expression of calcium-binding proteins, calcium transporters, and calcium channels. Deficiency of vitamin D disrupts intracellular calcium regulation, leading to neuronal dysfunction that has been implicated in the pathophysiology of depression (Bergantin, 2020; Glaser *et al.*, 2019; Anwar *et al.*, 2023). In addition, vitamin D enhances antioxidant defenses, thereby protecting neurons from oxidative stress and cellular damage, both of which have been associated with depressive disorders (Sabir *et al.*, 2020) (Figure 4). Vitamin D also contributes to mental health through its effects on neurotransmission, inflammation, mitochondrial function, and epigenetic regulation. It promotes serotonin synthesis by regulating tryptophan hydroxylase expression, suppresses pro-inflammatory cytokine production, and supports normal mitochondrial respiration and energy metabolism (Grozić *et al.*, 2022; Huiberts and Smolders, 2021; Holick *et al.*, 2023). Furthermore, vitamin D helps preserve the expression of genes involved in neuronal function by modulating DNA methylation processes. Consequently, vitamin D deficiency may contribute to depression through multiple interconnected pathways involving calcium dysregulation, oxidative stress, impaired serotonin signaling, neuroinflammation, mitochondrial dysfunction (Giménez-Palomo *et al.*, 2021), and altered epigenetic regulation (Maitra *et al.*, 2020; Wang *et al.*, 2020; Fiori and Turecki, 2020) (Figure 5).

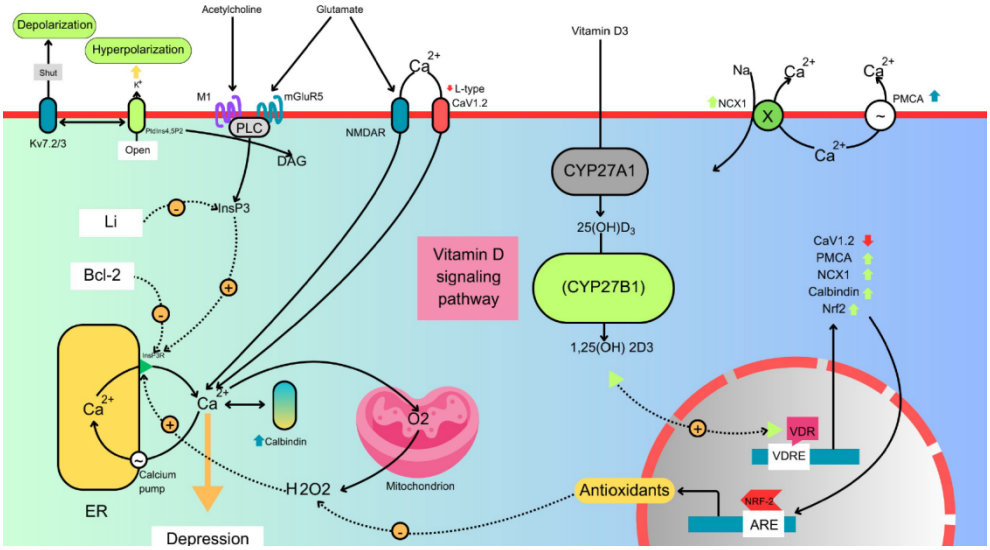


Figure 4. The Role of Ca^{2+} Signaling in Depression

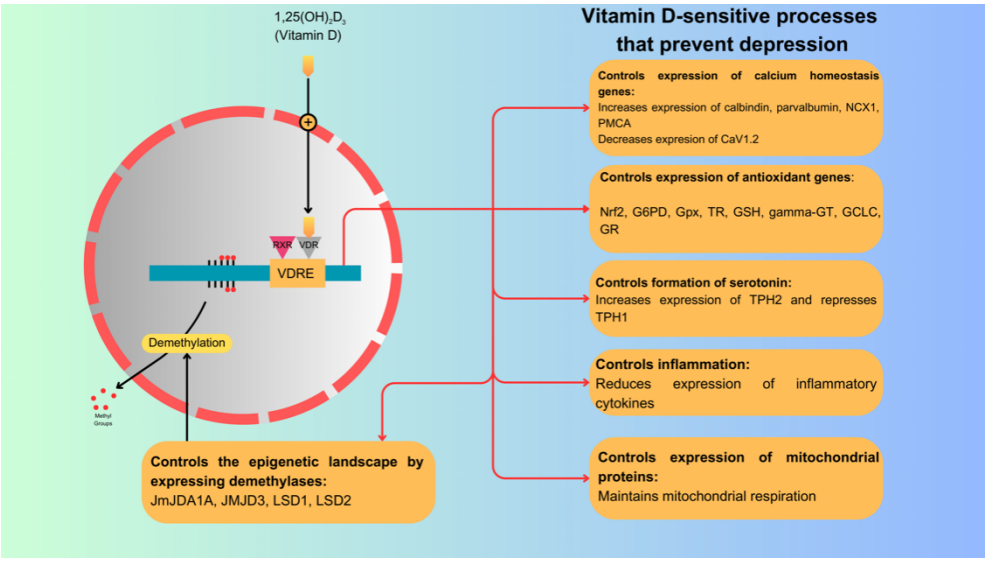


Figure 5. Vitamin D plays a crucial role in preventing the onset of depression by activating several processes essential for maintaining healthy neurons. Once inside the nucleus, vitamin D (25-OH-D_3) forms a heterodimer with the retinoid X receptor (RXR) and binds to vitamin D response elements (VDREs) within the regulatory regions of multiple genes. Through this genomic action, it maintains calcium homeostasis by upregulating the expression of calbindin, parvalbumin, the Na^+/Ca^{2+} exchanger 1 (NCX1), and the plasma membrane Ca^{2+}-ATPase (PMCA), while concurrently downregulating the expression of the CaV1.2 calcium channel. Vitamin D also promotes the expression of various antioxidant genes, including nuclear factor-erythroid-2-related factor 2 (NRF2), γ-glutamyl transpeptidase (γ-GT), glutamate cysteine ligase (GCLC), glutathione reductase (GR), and glutathione peroxidase (Gpx). Furthermore, it modulates serotonin production by increasing tryptophan hydroxylase 2 (TPH2) levels and repressing tryptophan hydroxylase 1 (TPH1). Vitamin D mitigates inflammation by downregulating inflammatory cytokines and supports mitochondrial function by regulating the expression of key mitochondrial proteins. Furthermore, it modulates the epigenetic environment by inducing the expression of DNA demethylating enzymes, including Jumonji domain–containing proteins 1A and 3 (JMJD1A, JMJD3), as well as lysine-specific demethylases 1 and 2 (LSD1, LSD2).

Study limitation

Our findings identified a vitamin D threshold of 9 ng/mL associated with depression status among older adults. However, this study did not demonstrate that vitamin D supplementation effectively reduces the risk of developing depression. A randomized controlled trial by Alavi et al. demonstrated that administering vitamin D supplementation at a dose of 50,000 IU weekly for eight weeks to adults aged 60 years and older with moderate to severe depression significantly reduced mean depression scores from 9.25 to 7.48 ($p = 0.0001$) (Alavi et al., 2019).

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes establishing temporal or causal relationships between serum vitamin D levels and depressive symptoms. Second, the study was conducted in a single nursing home, which may limit the generalizability of the findings to other elderly populations in Indonesia. Third, potential confounding factors, including comorbidities, physical activity, nutritional status, and medication use, were not comprehensively assessed. Furthermore, no follow-up assessment was performed; therefore, changes in vitamin D levels and depressive symptoms over time could not be evaluated. Finally, important determinants of vitamin D status, such

as sunlight exposure and dietary vitamin D intake, were not measured and may have influenced the observed association.

Additional prospective studies with larger and more diverse populations are required to validate the identified vitamin D threshold and to clarify the potential role of vitamin D supplementation in reducing the risk of depression among older adults in Indonesia.

CONCLUSION

A serum vitamin D concentration of 9 ng/mL was identified as the optimal cut-off associated with the absence of depressive symptoms among elderly participants. Further longitudinal and interventional studies are required to determine whether maintaining vitamin D levels above this threshold can reduce depression risk.

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