



## VITAMIN D DEFICIENCY LINKED TO DEPRESSION (SYSTEMATIC REVIEW: META SYNTHESIS)

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### ABSTRACT

**Background:** Depression is a mood disorder that is marked by a persistent feeling of sadness, loss of interest; reduced energy and vitality; feelings of low self-worth or guilt; loss of appetite; disturbed sleep or insomnia; and slowness of thought or action. Vitamin D deficiency has been associated with depression. When the level of Vitamin D and serotonin is low, that leads to depression. **Objective:** To analyze whether vitamin D deficiency or insufficiency is associated with depression. **Method:** This is a Systematic Review Report. Samples were gathered from two journals – PubMed and Science Direct with specific search terms used were vitamin D and depression, then were adjusted based on the inclusion criteria and research question. After that, the findings are combined in order to reach a conclusion so that the research question is well answered. **Results:** There are eleven journals that describe a link between low level of Vitamin D and symptoms of depression. The connection between the two is formed due to the neuroprotector and immunomodulatory effects of Vitamin D. **Conclusion:** Previous studies have shown that Vitamin D deficiency linked to depression.

**Keywords :** *Depression, level of vitamin D, vitamin D serum.*

### INTRODUCTION

Depression is a serious health problem in community. According to the World Health Organization (WHO), depression is a common mental disorder characterized by a depressed mood, loss of pleasure or interest, feeling of a loss of energy, feeling of guilt or low self-worth, disturbed appetite or sleep, and low concentration. Based on the results of the 2018 Basic Health Research (Riset Kesehatan Dasar/Riskesdas) conducted by the Ministry of Health of the Republic of Indonesia, depression prevalence rate among people aged over 15 years in Indonesia reaches 6.1%. The study also found that people age 75 years and older have the highest rate of depression, which is 8.9%. Women are more vulnerable to depression than men. It was recorded that women had a higher depression prevalence rate than men, namely 7.4% vs 4.7% respectively.<sup>1</sup>

Depression is caused by various factors, including significant past experiences, socioeconomic and biological status, age, gender, and nutritional factors whereby vitamin D intake is thought to have an effect on the incidence of depression.<sup>2</sup> Vitamin D consists of 2 forms, namely ergocalciferol (D2) and cholecalciferol (D3). Vitamin D2 is found in vegetables and some species of fish,

whereas vitamin D3 is produced when the skin is exposed to ultraviolet B (UVB) of the sunlight.<sup>3</sup>

The major metabolites of vitamin D that is widely circulating in the body is 25-Hydroxyvitamin D [25 (OH) D] and its serum level of 25 (OH) D indicates the most reliable status of vitamin D.<sup>4</sup> Identification of vitamin D receptor (VDR) in the central nervous system (CNS) suggests that vitamin D may have a functional role in the nervous system. The existence of vitamin D receptor in the prefrontal cortex and limbic system illustrates the role of vitamin D in influencing functions such as affect, emotion, and cognitive functions.<sup>5</sup>

Some literatures on meta-analysis show that depression is associated with a Vitamin D deficiency in the body and it is also said that vitamin D supplementation is beneficial for the treatment of depression. A study conducted by Patrick and Ames found that vitamin D affects neuroendocrine function, namely the serotonin hormone.<sup>6</sup> Low level vitamin D can lead to serotonin level, which may cause depression.<sup>7</sup>

Based on the study conducted by Parker G. et al. in 2011, there was no clear relationship between the effect of vitamin D intake and the onset of depressive disorder at various ages. There has been debate whether vitamin D level have been linked with depressive disorder. Therefore, further study is



needed to explore the relationship between vitamin D level and depressive disorder. In this study, a systematic review method will be adopted to identify and evaluate study results which are relevant to topic on the relationship between vitamin D level and depressive disorder.

## METHOD

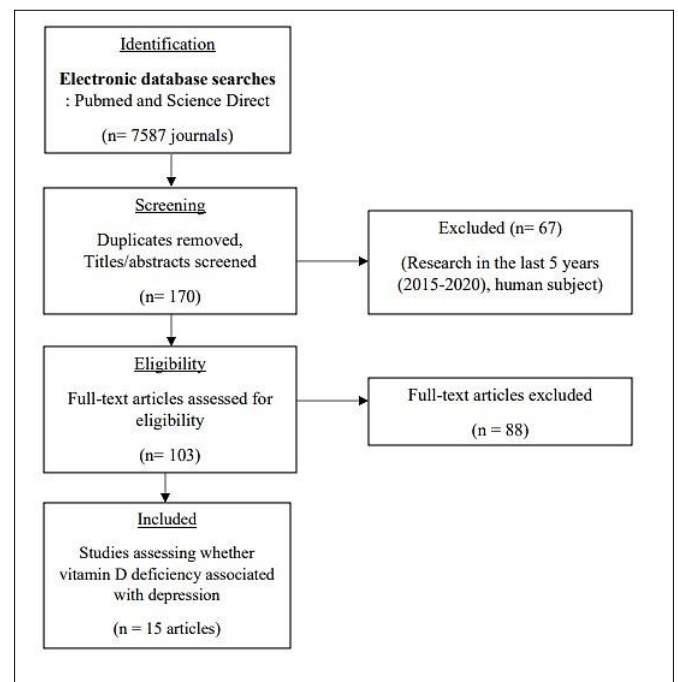
This study was carried out using a Systematic Review methodology. The study examined the relationship between vitamin D level and depressive disorder. Samples were obtained by searching for journals with predetermined keywords in the online Pubmed and Science Direct database and then were made in line with the inclusion criteria and research questions.

The inclusion criteria of the study are those published in 2015-2020 with human subject, study which contains keywords of vitamin D level and depression, study included in Pubmed and Science Direct and in English language version. The exclusion criteria are study using experimental animals.

As shown in Figure 1, based on search on Pubmed and Science Direct with keywords of vitamin D level and depression, the researchers found 7,587 best matching journals. A total of 170 journals of those all matching journals were then screened, 67 journals were excluded due to a lack of full-text articles. Feasibility assessment on 103 full-text journals was carried out, 88 journals which were not in accordance with the scientific search topic were excluded, resulted in 15 full-text journals to review.

Journals of the Research which satisfy the inclusion criteria were then collected and summary of the journals was made, including the name of researcher, the journal publication year, the country where the research was carried out, the title of the research, the method and summary of the results or findings. The summary of journals of the research was incorporated in a table.

To further clarify the analysis, abstracts and full-text version of the journals were read and examined. The summary of the journals was then analyzed with respect to the content of the research objectives and the research results/findings. Analysis was carried out based on PRISMA checklist and meta-synthesis method.



**Figure 1.** Flow Diagram of Journal Review

Findings from the journals which had been collected were then synthesized to answer research questions and draw conclusions. This study does not require ethical clearance because it does not involve human and experimental animals as subjects

## RESULTS

### Results of Journal Selection

The journal articles selected from Pubmed and Science Direct were then listed in a table including the name of researcher, year, research design, measurement method, statistical analysis, and results. Once the journals were collected and incorporated to tabular form (Table 1), an analysis was then carried out based on the feasibility of the journals in accordance with the inclusion criteria and formulation of problem.

Of the 15 journals that had been reviewed and met the inclusion criteria, only 11 journals identified a relationship between low level of vitamin D and the onset of depressive symptoms. There have been different results among the journals due to restrictive condition on each research, such as short research duration or limited number of the samples.



### Journal Search Quality

Based on the results of extraction of data which have met the inclusion criteria, 15 journals were deemed relevant to the research topic, namely the relationship between vitamin D levels and depressive disorders.

The journals were then selected to see whether the research results support the research hypothesis. Table 1 indicates the results of the assessment quality

indicating whether or not the data are used in this study.

Journals with check mark provide results that support the hypothesis of this study, namely that there is a relationship between low level of vitamin D and symptoms of depression. Meanwhile, journals with cross mark do not show a relationship between vitamin D level and the onset of symptoms of depression.

**Table 1.** List of articles that made up the systematic review

Author	Year	Study Design	Sample	Statistical Analysis	Result	Conclusion
Wang <i>et al.</i>	2017	Cross-sectional	2786	The serum 25(OH)D levels were significantly lower in diabetic patients with depression than those patients without depression [P < 0.0001].	✓	Researcher observed a significant negative association between serum levels of 25 (OH)D and depression in Chinese patients with T2DM.
Woo <i>et al.</i>	2019	Retrospective	196	The baseline HDRS total score was significantly higher (24.0±6.3) in the insufficiency/deficiency group compared with the sufficiency group (21.6±4.9; p=0.037).	✓	Researcher found that symptoms related to the HDRS factor reflecting core depressive symptoms were significantly increased in patients with insufficient/deficient vitamin D compared with those having sufficient vitamin D.
Song <i>et al.</i>	2016	Cross-sectional	2942	Men with severe depression tend to have lower 25 (OH)D (P value = 0,020).	✓	Lower concentrations of vitamin D are independently associated with depressive symptoms in older Korean adults.
Kerr <i>et al.</i>	2015	Cross-sectional	185	Lower W1 vitamin D3 predicted clinically significant depressive symptoms across W1–W5 ( $\beta$ = -0.20, P< 0.05)	✓	Findings are consistent with a temporal association between low levels of vitamin D and clinically meaningful depressive symptoms.
Mohaddesi <i>et al.</i>	2019	Cross-sectional	100	Women's depression scores showed a significant inverse correlation with the serum level of vitamin D (r= -0.21, P= 0.03)	✓	The results of this study showed there was correlation between women's depression score and their vitamin D levels.
Oliveira <i>et al.</i>	2018	Cross-sectional	10.601	Overall, there was a significant association between low 25OHD levels and elevated depressive symptoms (odds ratio [OR] = 1.58, 95% confidence interval [CI] = 1.20–2.07 for the lowest quartile; OR = 1.45, 95% CI = 1.15–1.83 for a wide range of covariates of clinical significance	✓	The independent and inverse association found between low 25OHD levels and elevated depressive symptoms suggests that vitamin D deficiency may be a risk factor for late-life depression, particularly among women.



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Ren <i>et al.</i>	2016	Cross-sectional	194	Vitamin D levels were significantly lower in smokers than in nonsmokers ( $p = 0.002$ ). Patients with depression symptoms showed lower vitamin D levels than those with no depression symptoms ( $p = 0.03$ ).	✓	Higher rates of depression in smokers with acute ischemic stroke may be associated with lower vitamin D levels induced by smoking.
Hyun <i>et al.</i>	2017	Cross-sectional	633	Additionally, the prevalence of depression was significantly higher in CKD patients with (vs. without) vitamin D deficiency (32.5% vs. 50.0%, $P < 0.001$ ).	✓	Depression was highly prevalent in CKD patients, in whom vitamin D deficiency was a significant independent predictor of depression.
Elseesy <i>et al.</i>	2020	Observational descriptive	75	There was no statistically significant correlation between levels of vitamin D and severity of depression, age of onset or number of episodes, as well as levels of vitamin D in relation to scores of different cognitive tests done ( $P = 0.231$ ).	X	MDD was associated with vitamin D deficiency but no statistical significant correlation could be established neither between levels of vitamin D and severity of depression nor between levels of vitamin D and cognitive dysfunction.
Zhu <i>et al.</i>	2019	Cross-sectional	50	There were significant negative correlations between HAMD score and TIV ( $P < 0.001$ ) and negative indirect effect of the serum vitamin D concentration on HAMD score through TIV in patients with MDD, on HAMD score was significant ( $P = 0.025$ ).	✓	In patients with MDD, HAMD score was negatively correlated with TIV and serum vitamin D concentration, and TIV was positively correlated with serum vitamin D concentration.
Mousa <i>et al.</i>	2018	Cross-sectional	63	There were no associations between 25(OH)D concentrations and total BDI (Beck Depression Inventory) scores or BDI subscales (all $p > 0.1$ ).	X	Vitamin D deficiency may not be related to increased risk of depression in individuals without clinically significant depression.
Ikonen <i>et al.</i>	2019	Cohort	4987	There is no differences in serum 25(OH)D between schizophrenia, other psychoses, non-psychotic depression and control groups ( $P=0.23$ ).	X	Researcher did not find any difference in vitamin D status between schizophrenia, psychoses, non-psychotic depression and control groups.
Osvaldo <i>et al.</i>	2015	Cross-sectional	3105	The adjusted hazard ratio of incident depression for men with plasma vitamin D $< 50$ nmol/L was 1.03 (95% CI = 0.59, 1.79; adjusted for age, living arrangements, season, and prevalent cardiovascular diseases).	X	The results do not support a role for vitamin D in the causation of depression.



Zhou <i>et al.</i>	2019	Cross-sectional	186	Patients with depression showed significantly lower 25(OH)D levels as compared to patients without depression (P,0.001). Significant differences in 25(OH)D quartiles of gout patients were observed between the patients with depression and the patients without depression (P=0.003).	✓	This study demonstrates an important association between serum vitamin D levels and depression in patients with gout.
Fond <i>et al.</i>	2018	Cohort	140	In multivariate analysis, hypovitaminosis D has been significantly associated with respectively higher depressive symptoms (p = 0.02) and current anxiety disorder (p = 0.001), independently of age and gender.	✓	Hypovitaminosis D is frequent and associated with depressive symptoms and anxiety disorders in schizophrenia.

## DISCUSSION

Based on metanalysis study, it was generally found that the low level of vitamin D may cause depression disorder. The relationship between them is supposed to be formed because human brain has vitamin D receptor (VDR) which may cause psychiatric disorder through mechanisms as follows:<sup>8</sup>

1) In some parts of human brain such as thalamus, cerebellum, amygdala and hippocampus can express  $1\alpha$ -hydroxylase enzymes which are able to metabolize 25(OH)D to  $1,25(\text{OH})_2\text{D}_3$ ; 2). There is relationship between the presence of vitamin D and its receptors (VDR) in human brain with CYP 24A1 and CYP 27B1 enzymes, pointing to a role of vitamin D as a neuroactive hormone involved in key function as neuroprotection; 3) Vitamin D may play its role as neuroprotective role in the body inflammatory process. There has been increased inflammatory cytokines and vitamin D to assist the immunomodulation process.

The best strategy for estimating vitamin D levels in the body is by testing serum 25(OH)D levels by taking blood samples. Serum 25(OH)D is considered to be the best marker for assessing vitamin D status in which it is the active form of vitamin D with the highest level reported in the blood circulatory system.

Study on the relationship between vitamin D levels and depressive disorder has been conducted on men and women respondents. A study conducted by Y.S Woo *et al.* showed that the total score of Hamilton Depression Rating Scale (HDRS) is significantly higher in patients with vitamin D insufficiency or deficiency with probability of  $(21.6 \pm 4.9; p=0.037)$ .<sup>9</sup>

A study by Kerr *et al.* identified that color-skinned women are at a higher risk of vitamin D insufficiency and are prone to depression compared to the other races. In addition, low level of vitamin D is also influenced by season.<sup>10</sup> Another study on female respondents was conducted by Mohaddesi *et al.* showing that women's depression score indicates a significant inverse correlation with serum vitamin D level ( $r = -0,21, P = 0,03$ ).<sup>11</sup>

The relationship between depression and vitamin D level has also been tested in the elderly population. A study by Oliveira *et al.* using male and female respondents aged  $\geq 50$  years found that respondents with low level of serum 25(OH)D have an increased risk in depressive symptoms, especially in women. The symptoms are influenced by several factors such as age, economic conditions, health conditions, habits, physical function, and cognitive function.<sup>12</sup>





Several other studies on depression and vitamin D level in patients with a particular medical condition have also been conducted. First, a study by Fond et al. on depression with hypovitaminosis D in schizophrenic patients which found that the hypovitaminosis D in schizophrenic patients is associated to depression and anxiety symptoms. Based on multivariate analysis, hypovitaminosis D is significantly associated with depressive symptoms ( $p = 0.02$ ).<sup>13</sup>

Second, a study by Ren et al. showing that smokers have lower vitamin D levels and depressive symptoms compared to non-smokers. Patients with depressive symptoms showed lower level of vitamin D than those without depressive symptoms ( $P = 0.03$ ). Smoking can reduce vitamin D level because the unhealthy lifestyle and lack of exposure to direct sunlight can reduce the synthesis of vitamin D. Smoking can also decrease the function of the hormone serotonin. Therefore, the number of depression cases among smokers with acute ischemic stroke remains high.<sup>14</sup>

Third, research by Zhou et al. on patients with gout. The relationship between gout illness and depression is indicated by repeated attacks in several joints causing depression on patients. At the same time, the relationship between gout and vitamin D is indicated by the presence of chronic inflammatory reaction in gout which causes an increased IL-6 and IL-1 $\beta$ . Vitamin D, which is immunomodulatory, can modulate the secretion of inflammatory cytokines by affecting the body's immune system. Based on a multivariate analysis, 25(OH)D level ( $\leq 40.0$  nmol/L) is closely related to depression in gouty patients ( $P=0.009$ ).<sup>15</sup>

Fourth, a study Jong Hyun et al. on the association between vitamin D deficiency and the incidence of depression in patients with chronic renal failure. Older patients with chronic renal failure, history of diabetes and low hemoglobin level have low vitamin D level. Kidney failure patients with lower outdoor physical activities and lack of direct sun exposure are likely to develop low vitamin D level.<sup>16</sup>

Based on the synthesis on the results of studies on the journals, it can be said low vitamin D level in the body is caused by various factors such as age, gender, race/ethnicity, skin color, season, illness, and vitamin D supplement intake.

Weaknesses of this study lie in the fact that it only reviews journals published by the Pubmed and Science Direct media. The number of journal articles reviewed is not yet maximal, as the journal articles were probably overlooked. Therefore, it is necessary to conduct second review on the journals published by other media. In addition, most of the study locations of the journals reviewed were outside Indonesia, due to rarely or lack of data on the recent study on relationship between vitamin D level and depressive disorder in Indonesia. This study is therefore expected to provide a reference for the Indonesian researchers to conduct similar study.

## CONCLUSIONS AND RECOMMENDATIONS

### Conclusions

Based on the review conducted, 11 journal articles report the relationship between low vitamin D levels and depression. Several factors contribute to hamper the studies on the relationship between vitamin D and depression, including the fact that vitamin D deficiency is just one of the many factors that may contribute depression. In addition, the effects of Vitamin D on depression may take a long time to work, meaning that adequately long period of studies such as cohorts are needed.

### Recommendations

It is necessary to carry out further and long-term research on the relationship between vitamin D level and depressive disorder. Furthermore, any additional researches using systematic review methodology may include more journal articles from various journal database.

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