**ORIGINAL ARTICLES**

# The effect of vitamin D on patients with depression symptoms: A systematic review and meta-analysis

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## ABSTRACT

**Objective:** 1- to estimate the effect size of vitamin D on depression symptoms, 2- to analyze and discuss the effect size of different Vitamin D doses.

**Method:** This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) in search of eligible studies on multiple databases. The quality of included studies would be evaluated by the Jadad scale. Inclusion and exclusion criteria were based on PICOTS standards. Meta-analyses were performed using R Studio and presented in the forest plot.

**Results:** Of the total 1274 records identified in multiple databases, ten RCTs were eligible for inclusion, with 60% of them having good quality. The result of our meta-analysis indicated that, compared to placebo, vitamin D supplementation demonstrated a better effect on reducing -0.78 depression points (Standardized Mean Differences (SMD) =−0.78, 95%CI= -1.26; -0.30). Moreover, vitamin D3 was found to relieve depression symptoms among individuals who were assessed by BDI scales (SMD=-1-15), took ≥3000 International Unit (IU) of Vitamin D3 per day (SMD=-1.02), and studied for 8 weeks (SMD=-0.88).

**Conclusion:** This study demonstrated the clinical implications of vitamin D supplementation by relieving symptoms of depression. Our findings might suggest the use of vitamin D supplements as an alternative to antidepressants or adding vitamin D to current treatment guidelines.

***Keywords:*** *Depression, nutritional intervention, vitamin D, effect.*

## INTRODUCTION

Depression is a common mental disorder that involves a depressed mood or loss of pleasure or interest in activities for long periods of time. According to the World Health Organization (WHO), approximately 350 million people worldwide are currently suffering from depression, and the disorder is expected to be a major cause of disability by 2030 (1). Although its pathogenesis has not been fully described, there are several factors that contribute to the development of depression, including biologic, medical and psychosocial (2, 3). The WHO estimated that approximately 700000 annual suicides were linked to depression (1). Treatment for depression often requires medications combined with psychological therapy. Vitamin D is a fat-soluble vitamin that has long been known to help the body absorb and retain calcium and phosphorus, thereby strengthening muscle and bones (4, 5). Along with its contribution to physical well-being, vitamin D is now increasingly recognized for its influence on mental health (6). Meanwhile, observational studies found that people with

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depression tended to have insufficient levels of vitamin D concentration (7) however, with respect to what a healthy minimum level of circulation (8). Evidence supports the hypothesis that vitamin D helps to improve depression symptoms were not strong enough due to inconsistent results of studies worldwide (9, 10). Therefore, we implemented this study with two specific objectives: 1- to estimate the effect size of vitamin D on depression symptoms, 2- to analyze and discuss the effect size of different Vitamin D doses, time of intervention, and depression assessment tools through subgroup analyses.

## METHODS

**Study design:** This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).

**Study site and time:** The study in search of eligible studies on multiple databases, including PubMed, Google Scholar, and Web of Science from 01/01/2019- 01/01/2024.

**Study subjects:** In this step, we followed the PICOTS framework to gather desired studies serving for study objectives

**Table 1. PICOTS framework to select eligible studies**

| Criteria | Inclusion | Exclusion |
|---|---|---|
| **General** | Original research that was peer-reviewed and written in English | Non-original research: Review papers, meta-analysis, study protocol, conference reports, opinion pieces. Studies not published in English |
| **Population (P)** | People diagnosed with depression, or appeared depression symptoms | Animal studies. People with other mental disorders |
| **Intervention (I)** | Vitamin D supplement only | Vitamin D supplement along with other vitamins. Multivitamins that contain vitamin D |
| **Comparison (C)** | Placebo | Not receiving placebo |
| **Outcome (O)** | Changes in depression points after intervention measured by Mean differences (MD) | Other data and indicators not serving to measure depression |
| **Timing (T)** | Within 5 years (01/01/2019- 01/01/2024) | Out of that time |
| **Study design (S)** | Randomized controlled trials | Other study designs |

### Sample size and sampling methods

The study selection process of this systematic review and meta-analysis was based on the description of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (Figure 1) (11). The four main keywords we used include “depression”, “nutritional intervention”, “vitamin D”, and “effect”, combined with the search functions OR, AND.

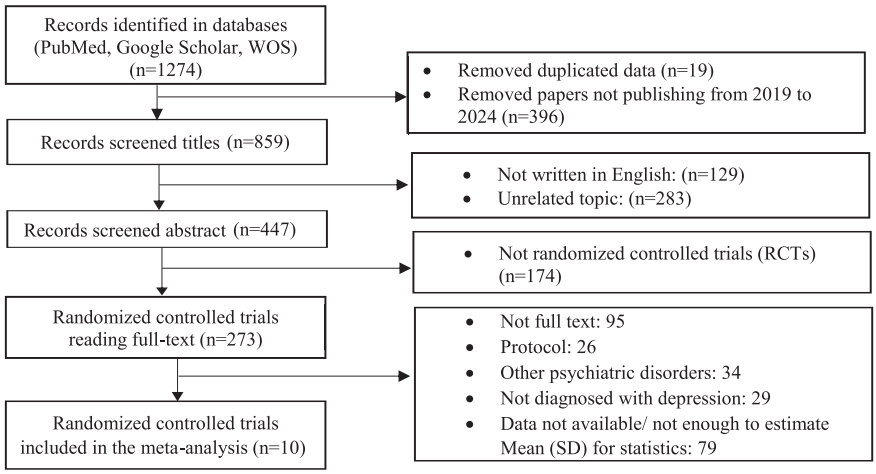


**Figure 1. The process of study selection for systematic review and meta-analysis**

**Tools and methods of data collection:** After reviewing articles that met the inclusion criteria, the retrieved papers were independently screened by two authors. Extracted data were study characteristics including: authors, country, year of publication, study subjects, time of intervention, sample size, depression assessment instruments, mean differences (MD), and standard deviation (SD) within groups.

### Processing and analyzing data

The outcome for meta-analysis was Mean differences ± Standard Deviation (MD ± SD). The statistical data in the included studies were measured as changes in depression points within the vitamin D and placebo groups. From that, we would identify the Standardized Mean differences (SMD), which indicate the general effect size of our meta-analysis. Results would be analyzed and presented in the forest plot. The $I^2$ statistic was used to quantify heterogeneity, and an $I^2$ value of 0% indicated no observed heterogeneity, with larger values showing increased heterogeneity. Due to the differential in study characteristics, we believed the random-effects model could be more appropriate. However, fixed-effects models would be applied when $I^2$ <75%. Variables for subgroup analyses were depression assessment instruments, time of intervention, and forms/doses of vitamin D. Three cut-off points of the intervention time were ≤8 weeks, 8-12 weeks, and 12-24 weeks. Administration <3000 IU/ day would be regarded as a lower dose group and ≥3000 IU/ day would be classified into the higher dose group. Data analysis was performed by using Excel 2019 and R Studio version 3.6.

## RESULT

### The quality of included randomized controlled trials

The study depicted the quality of the randomized controlled trials based on the Jadad Scale criteria. Six studies had Good quality, accounting for 60% of the total included studies. The mean point of this group was 4.17 with 0.41 points of SD. Four remaining studies was considered fair quality. The mean point of this group was 3.0 points.

### Basic characteristics of included studies

Ten eligible studies were included in our meta-analysis model (12–21). The extracted scales used to measure depression in the identified studies included the BDI, DASS-21, HDRS-17, CES-D, EPDS, and GDS-15. Mean serum 25(OH)D concentration of participants at baseline between studies varied considerably, ranging around 20 to 30 ng/ml. All studies used oral Vitamin D3 (cholecalciferol) except the study of Chimeh, whose study participants received an intramuscular injection (18). Vitamin D3 doses ranged from 1200 IU to 7100 IU per day, and the duration varied from 4 weeks to 24 weeks.

**Table 2. Basic characteristics of included RCTs**

| Author (Study number) | Year of publication | Country | Baseline 25(OH)D (Mean ± SD) | Follow-up (week) | Post intervention 25(OH)D (Mean ± SD) | Forms/doses of Vitamin D | Sample size | | Characteristics of study participants | Depression assessment instrument | Changes of depression points ¥ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Intervention | Control | | | |
| Kaviani (1) | 2022 | Iran | Intervention: 87.1±28.5 (nmol/L) Control: 73.64±31.9 (nmol/L) | 8 | Intervention: 127.9±24.9 (nmol/L) Control: 78.7 ±27.0 (nmol/L) | Oral vitamin D3 (50000 IU/ 2 weeks) | 28 | 28 | Patients from 18-65 with mild to moderate depression with no other psychiatric disease | BDI | Vitamin D: -11.8(6.4) Placebo: -3.6(10.4) |
| Omidian (2) | 2019 | Iran | Intervention: 15.5 ± 8.8 (ng/ml) | 12 | Intervention: 32.2 ± 8.9 (ng/ml) | Oral vitamin D3 (4000 IU/ day) | 32 | 34 | Type 2 diabetic patients with mild to moderate depressive symptoms | BDI | Vitamin D: -5.4(2.4) Placebo: -1.8(0.3) |
| Rajabi-Naeeni (3) | 2021 | Iran | Intervention: 21.43 ±8.0 (ng/d) Control: 25.47 ±5.83 (ng/d) | 8 | Intervention: 29.71±12.1 (ng/d) Control: 20.9 ±6.63 (ng/d) | Oral Vitamin D3 (50000 IU/ 2 weeks) | 42 | 42 | Women aged 15 to 50 years old with pre-diabetes, hypovitaminosis D, and depression symptoms | DASS-21 | Vitamin D: -2.1(7.0) Placebo: - 0.2(6.1) |
| Libuda (4) | 2020 | Germany | Intervention: 8.66 ± 1.97 (ng/ml) Control: 8.56 ± 2.05 (ng/ml) | 4 | Intervention: 23.9 ± 6.11 (ng/ml) Control 10.4 ± 4.31 (ng/ml) | Oral vitamin D3 (2640 IU/ day) | 52 | 48 | Patients aged 11–18 years with hypovitaminosis D and concurrent (at least) mild depressive symptoms | BDI | Vitamin D: -4.3(8.5) Placebo: -5.2(8.8) |
| Fazelian (5) | 2019 | Iran | Intervention: 87.1± 28.5 (nmol/L) Control: 73.6±31.9 (nmol/L) | 16 | Intervention: 127.9±24.9 (nmol/L) Control: 78.7±27.0 (nmol/L) | Oral vitamin D3 (50000 IU/2 weeks) | 26 | 25 | Type 2 Diabetes (T2DM) women between 20 to 60 years old diagnosed with mild, moderate, or severe depression | DASS-21 | Vitamin D: -2.0(4.4) Placebo: -1.4(4.1) |

| Author (Study number) | Year of publication | Country | Baseline 25(OH)D (Mean ± SD) | Follow-up (week) | Post intervention 25(OH)D (Mean ± SD) | Forms/doses of Vitamin D | Sample size | | Characteristics of study participants | Depression assessment instrument | Changes of depression points ¥ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Intervention | Control | | | |
| Hansen (6) | 2019 | Denmark | Intervention: 43.2±24.6 (nmol/L) Control: 44.3±24.1 (nmol/L) | 12 | Intervention: 97.9± 25.0 (nmol/L) Control 52.0± 33.5 (nmol/L) | Oral vitamin D3 (2800 IU/day) | 28 | 34 | People aged from 18-65 years old with mild to severe depression | HDRS-17 | Vitamin D: -9.6(6.2) Placebo: -7.1(6.2) |
| Chimeh (7) | 2019 | Iran | Intervention: 14.9 ± 1.4 (ng/ml) Control: 14.2 ± 1.6 (ng/ml) | 8 | Intervention: 29.3± 4.8 ng/ml Control: 12.7 ±2.8 (ng/ml) | Intramuscular injection of vitamin D3 (300000 IU at baseline and end of week 4) | 38 | 38 | Women from 18 to 45 years old with sexual dysfunction and depression symptoms | BDI | Vitamin D: -21.9(12.4) Placebo: -2.7(9.7) |
| Amini (8) | 2020 | Iran | Not available | 8 | Not available | Oral vitamin D3 (50000 IU/2 weeks) | 26 | 24 | Women with postpartum depression (PPD) score >12 | EPDS | Vitamin D: -4.2(5.9) Placebo: 0.2(2.8) |
| Alavi (9) | 2019 | Iran | Intervention: 22.57 ± 6.2 (ng/ml) Control: 21.2 ± 5.8 (ng/ml) | 8 | Intervention: 43.48 ± 9.5 (ng/ml) Control: 25.9 ± 15.3 (ng/ml) | Oral vitamin D3 (50000 IU per week) | 39 | 39 | Adults aged over 60 years with moderate to severe depression | GDS-15 | Vitamin D: -1.8(1.3) Placebo: 0(0.9) |
| Koning (10) | 2019 | Netherlands | Intervention: 46 (nmol/L) Control: 45 (nmol/L) | 24 | Intervention: 85 ± 16 (nmol/L) Control: 43 ± 18 (nmol/L) | Oral vitamin D3 (1200 IU/ day) | 75 | 75 | People aged 60–80 years who had clinically relevant depressive symptoms | CES-D | Vitamin D: -6.6(5.2) Placebo: -6.8(5.0) |

*(BDI: Beck's Depression Inventory; DASS-21: Depression, Anxiety and Stress Scale - 21 Items; HDRS-17: Hamilton Depression Rating Scale- 17 Items; EPDS: Edinburgh Postnatal Depression Scale; GDS-15: Geriatric Depression Scale- 15 Items; CES-D: Center for Epidemiologic Studies Depression Scale)*

*¥ Mean differences ± Standard deviation (MD ± SD) after intervention within groups (vitamin D and placebo) calculated by paired t-test*

**Effects of vitamin D supplementation on the improvement of depression**

A total of 773 individuals were recruited in our meta-analysis. In which 386 participants were in the experimental group, the another 387 were in the control group (Figure 2). Half of the total included RCTs showed statistically significant results for the administration of vitamin D compared to placebo (12,13),(18–20), while the remaining 5 studies did not demonstrate a statistically significant difference between the intervention and control group (14–17,21). Due to the high percentage of heterogeneity ($I^2$ =90%), the random effects model was applied to the analysis. Our meta-analysis result indicated that vitamin D supplements showed more beneficial effects than placebo (SMD= -0.78; 95% CI=-1.26, -0.30).

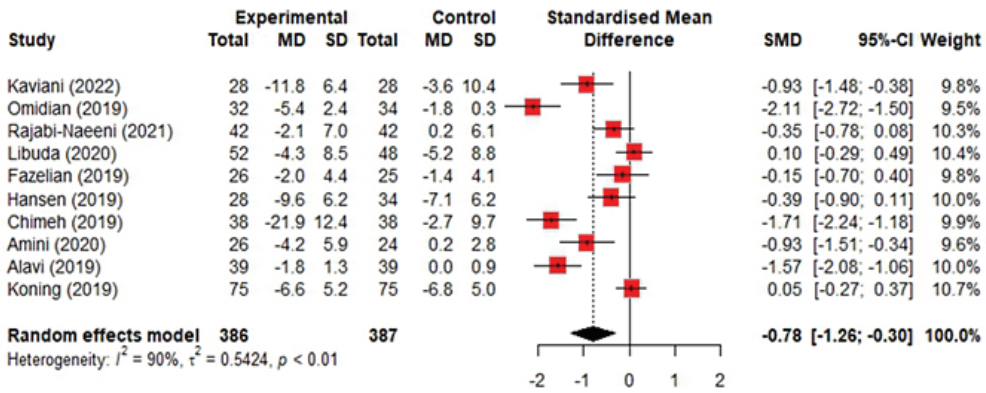


**Figure 2. Forest plot of standardized mean differences of depression points between the experimental and control groups**

Table 3 analyzed the effect size of vitamin D on subgroups. Vitamin D showed positive effects in subgroups: BDI scale (SMD= -1.15, p<0.01), taking ≥3000 IU/day (SMD= -1.02, p<0.01), and intervention ≤8 weeks (SMD=-0.88, p<0.01). In addition, those who were in the group taking oral vitamin D and intramuscular injection also indicated statistically significant results, with the effect size equaled to -0.68 and -1.71, respectively.

**Table 3. Subgroup analysis**

| Subgroup | Number of studies | Standardized mean differences (95% C.I) | Q | $\tau^2$ | $\tau$ | $I^2$ (%) |
|---|---|---|---|---|---|---|
| **Depression assessment instrument** | | | | | | |
| BDI- II; BDI | 4 | -1.15[α] (-2.11; -0.18) | 49.16 | 0.89 | 0.94 | 93.9 |
| DASS-21 | 2 | -0.27[α] (-0.61; -0.15) | - | - | - | - |
| CES-D | 1 | 0.05 (-0.27; 0.37) | - | - | - | - |
| HDRS-17 | 1 | -0.39 (-0.9; 0.11) | - | - | - | - |
| EPDS | 1 | -0.93[α] (-1.51; -0.34) | - | - | - | - |
| GDS-15 | 1 | -1.57[α] (-2.08; -1.06) | - | - | - | - |

| Subgroup | Number of studies | Standardized mean differences (95% C.I) | Q | $\tau^2$ | $\tau$ | $I^2$ (%) |
|---|---|---|---|---|---|---|
| **Time of intervention** | | | | | | |
| 8 weeks | 6 | -0.88[α] (-1.45; -0.31) | 44.63 | 0.66 | 0.43 | 88.8 |
| 8 - 12 weeks | 2 | -1.24 (-2.93; 0.44) | 18.1 | 1.18 | 1.39 | 94.5 |
| 12- 24 weeks | 2 | 0 ( -0.28; 0.28) | - | - | - | - |
| **Doses of vitamin D** | | | | | | |
| <3000 IU per day | 4 | -0.44 ( -1.19; 0.31) | 32.4 | 0.73 | 0.53 | 90.7 |
| ≥3000 IU per day | 6 | -1.02[α] (-1.62; -0.41) | 37.52 | 0.7 | 0.49 | 86.7 |
| **Form of Vitamin D3** | | | | | | |
| Oral | 9 | -0.68[α] (-1.17; -0.19) | 70.7 | 0.49 | 0.7 | 89 |
| Intramuscular injection | 1 | -1.71[α] (-2.24; -1.18) | - | - | - | - |

[α] *p<0,01*

## DISCUSSION

### The quality of full-text papers

Regarding the quality assessment scale, the Jadad Scale determined that 60% of included RCTs had good quality and the remaining 40% had fair quality. However, some studies did not specify the method for blinding criteria (Study 3;6;10) and some did not appropriately describe the double-blinding method (Study 5;8). In Study 7, only participants were blinded, while clinicians were still aware of the supplementation and the placebo, thereby increasing the likelihood of bias in performing trials (single-blinded).

### The characteristics of included RCTs

#### *Depression assessment instruments*

In our study, the BDI was the most frequently used instrument among all included studies. In addition, other instruments such as DASS-21, HDRS-17, CES-D, EPDS, and GDS-15 were also commonly used in research to diagnose and measure depression (22). These self-assessment instruments' prominent features were efficient, time-saving, and cost-effective (23).

#### *Forms and doses of Vitamin D*

Vitamins D2 (ergocalciferol) and D3 (cholecalciferol) are two dominant forms of Vitamin D. But D2 is produced in plants and fungi, and D3 in animals, including humans. All included studies supplemented their participants with vitamin D3, and in fact, vitamin D supplements were mainly manufactured in the form of D3. First, vitamin D3 was the main form that the human body synthesized and stored, therefore, our body would easily recognize and use vitamin D3 rather than D2. Moreover, compared to vitamin D2, Vitamin D3 has a more stable structure in the natural environment (oxygen, light, and temperature). Regarding the effectiveness, comparative studies also found that vitamin D3 was clearly superior to vitamin D2 in raising total 25(OH)D concentrations.

It was noticeable that the majority of included studies used oral vitamin D3, while only Chimeh's study used intramuscular vitamin D3. In addition to its lower price, the oral form was considered a noninvasive and easy-to-implement measure in clinical studies with large sample sizes. Intramuscular vitamin D3 was recommended solely for specific clinical

cases, such as malabsorption or severe vitamin D deficiency with symptoms. As calculated per day, the highest oral vitamin D doses were approximately 7100 IU (20), while the lowest were 1200 IU, which were in excess of the current recommendation of 600 IU for adults and 800 IU for the elderly (21, 24).

***Time of intervention***

There was a significant difference in the intervention duration between trials. We found 50% of the total included studies were designed with up to an 8-week follow-up period, while Koning and his team carried out their 24-week intervention. At this point, if the follow-up time was too short, it may not fully reflect the change in the patient's depression symptoms, and clinicians might fail to observe the intervention effect over time because they stopped early. However, if the follow-up time was too long, it could lead to the loss of patients, thereby increasing the risk of biases in the evaluation of RCTs.

***25(OH)D concentration of subjects at baseline***

Measuring the mean vitamin D concentration of the subjects, we found that almost all had vitamin D concentrations of less than 30 ng/mL, which was considered "vitamin D deficiency" according to the definition of the American Geriatric Society. A previous cross-sectional study found a critically low serum 25(OH) D level in patients with depression symptoms and people with a history of depression (8). According to the author's statement, depressed people tended to consume a less nutritious diet, particularly low-fat diets that could adversely affect the absorption of vitamin D. Additionally, people with depression preferred to stay indoors, exercise less, and limit their exposure to sunlight, thereby interfering their body to synthesize vitamin D through the skin.

**The effect size model**

Herein, we found that Vitamin D demonstrated an overall effect of -0.78 depression points, which was in line with the previous study of Xie, who indicated a decline in depression points in the vitamin D group (25).

Our analysis indicated significant effects of vitamin D on depressive symptoms with daily supplementary doses ≥3000 IU. It was suggested that taking higher doses of vitamin D3 might be more beneficial in the treatment of depression, while lower doses might be futile. This finding was similar to Xie's study but different from Li's study (25, 26). The discrepancy might be attributed to the different cutoff points between the two studies (4000 IU/day in Li's study) (26).

Nine out of ten included RCTs provided their subjects with oral vitamin D3, while only participants in Chimeh's study received intramuscular injected. After removing Chimeh's study from the model, the meta-analysis of nine studies still pointed out positive results in the vitamin D groups compared to the placebo (18). Meanwhile, the study of Chimeh alone also found significant improvement in depression among the experimental group. In other words, vitamin D supplementation worked well in both oral and intramuscular injectable forms and provided considerable improvement in depression.

It was suggested that intervention of ≤8 weeks could be considered as the most appropriate time point that could trigger the effectiveness of vitamin D. Our result was aligned with the study of Xie, who also found remission among those in the group of intervention ≤8 weeks (25). In fact, the improvement of symptoms and the impact of vitamin D would be based on multiple factors such as the severity of depression, the level of vitamin D deficiency, and other factors affecting Vitamin D absorption, such as sun exposure, chronic conditions, or medications. This could be a plausible explanation for why taking vitamin D for longer periods (8-12 weeks and 12-24 weeks) might not guarantee the effect of vitamin D.

## CONCLUSION

In this meta-analysis, vitamin D supplementation was found to be positively associated with a decrease in the symptoms of depression. People with depression are encouraged to participate in outdoor activities to absorb enough vitamin D. Vitamin D supplements or high fat diets from fishes, fish oil, and animal fat are also recommended to increase absorption of vitamin D. To strengthen to scientific evidence, future studies should consider larger and more diverse samples are essential for improving the generalizability of results.

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