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# Efficacy of vitamin D in the treatment of depression: a systematic review and meta-analysis

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## ABSTRACT

**Introduction.** Vitamin D is a fat-soluble vitamin that performs multiple functions in the body. In addition to regulating calcium and phosphate levels in the body and contributing to bone mineralization, it participates in various brain and neurocognitive processes. In fact, the deficiency of this vitamin has also been linked to various psychiatric disorders, including depression.

**Objective.** To review if the administration of vitamin D is effective in the treatment of depression in adults compared to placebo.

**Methodology.** An electronic search was carried out in 4 databases (PubMed, Embase, Web of Science-Science Citation Index and Scopus) of randomized clinical trials (RCT) to assess the efficacy of vitamin D, in adults with depression compared to placebo, from 2013 to date of search (2019). The outcome measure used for the effect size calculation was the depressive symptom score. The effect sizes for the trials were calculated using the standardized mean difference and the $I^2$ test was used to assess sample heterogeneity. The critical evaluation of the articles was carried out using the funnel plot tool.

**Results.** A total of 10 RCTs involving 1.393 participants were included in the study. Given the heterogeneity of the studies, the random effects model was used. The result of the meta-analysis indicates that oral administration of vitamin D did not have a significant effect on the reduction of post-intervention depression scores. The standardized mean difference for the pooled data was -0,91 (95% confidence interval -2,02 – 0,19).

**Conclusions.** This study has not detected a significant therapeutic effect in the administration of vitamin D in depression.

KEY WORDS: Vitamin D; Depression; Treatment; Efficacy, Placebos.

*Actas Esp Psiquiatr 2021;49(1):12-23 | ISSN: 1578-2735*

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## EFICACIA DE LA VITAMINA D EN EL TRATAMIENTO DE LA DEPRESIÓN: REVISIÓN SISTEMÁTICA Y METAANÁLISIS

## RESUMEN

**Introducción.** La vitamina D es una vitamina liposoluble que desempeña múltiples funciones en el organismo. Además de regular los niveles de calcio y fosfato y contribuir a la mineralización ósea, participa en diversos procesos cerebrales y neurocognitivos. De hecho, el déficit de esta vitamina también se ha relacionado con diversos trastornos psiquiátricos, incluida la depresión.

**Objetivo.** Revisar si la administración de la vitamina D es eficaz en el tratamiento de la depresión en adultos frente a placebo.

**Metodología**. Se realizó una búsqueda bibliográfica en 4 bases de datos (PubMed, Embase, Web of Science-Science Citation Index y Scopus) de ensayos clínicos aleatorizados (ECA) para valorar la eficacia de la vitamina D en adultos con depresión frente a placebo, desde 2013 hasta septiembre de 2019. La medida de resultado utilizada para el cálculo del tamaño del efecto fue la puntuación de los síntomas depresivos. Los tamaños del efecto para los ensayos se calcularon utilizando la diferencia de media estandarizada y la prueba $I^2$ se utilizó para evaluar la heterogeneidad de la muestra. La evaluación crítica de los artículos se realizó mediante la herramienta del *funnel plot*.

**Resultados.** Un total de 10 ECA que implicaron 1.393 participantes fueron incluidos en el estudio. Dada la heterogeneidad de los estudios se utilizó el modelo de efectos aleatorios. El resultado del metaanálisis indica que la administración oral de vitamina D no obtuvo un efecto significativo en la disminución de las puntuaciones de depresión postintervención. La diferencia de media estandarizada para los datos agrupados fue de -0,91 (intervalo de confianza del 95 %: -2,02 - 0,19).

**Conclusiones**. Este estudio no ha detectado un efecto terapéutico significativo en la administración de la vitamina D en la depresión.

PALABRAS CLAVE: Vitamina D; Depresión; Tratamiento; Eficacia, Placebo.

*Actas Esp Psiquiatr 2021;49(1):12-23 | ISSN: 1578-2735*

## INTRODUCTION

Vitamin D, although belonging to the group of fat-soluble vitamins, also functions as a true hormone since it is synthesized in the body, is transported through the blood and acts on some target cells. We can find vitamin D in foods of animal origin (cholecalciferol or vitamin D3 from cholesterol) or in plant foods (ergocalciferol or vitamin D2 from ergosterol). In humans, most of the vitamin D comes from the skin transformation in the presence of sunlight of 7-dehydrocholesterol into cholecalciferol. Regardless of whether vitamin D comes from food or from synthesis in the skin, to exert its metabolic action it still needs to go through two hydroxylations, one in the liver and the other in the kidney, finally giving rise to the active hormone (1, 25 (OH) 2 vitamin D or calcitriol).

Vitamin D has multiple functions. The most important and known is the regulation of calcium and phosphate levels, promoting intestinal absorption and reabsorption of calcium at the renal level. In addition, it contributes to bone formation by promoting bone remodeling and mineralization. It also has a regulatory function of the immune system and antiproliferative action in tumor cell cultures[1].

Today it is known that vitamin D participates in multiple brain processes, such as cognitive processes and modulation of neuronal plasticity. Vitamin D deficiency has been identified as a possible risk factor in the development of several psychiatric disorders, including schizophrenia, depression, attention deficit disorder, and autism spectrum disorder[2].

Regarding the relationship of vitamin D as a risk factor for the development of depression, there are studies that find a higher prevalence of depression in people with low levels of vitamin D[3] and on the contrary, other studies do not show this association[4]. It has also been suggested that the administration of vitamin D could be effective in improving depressive symptoms, however, the effect of vitamin D as an antidepressant remains unclear, with contradictory results. In a meta-analysis Li et al. (2014) [5], did not find a significant effect of vitamin D in the treatment of depression. Six randomized clinical trials (RCTs) with 1,203 patients (72% women) were included in this meta-analysis, five of the studies included adults at risk of depression, and one trial used depressed patients (n = 71).

Vellekkatt and Menon[6] however, in a more recent meta-analysis (2019) did obtain a positive result in favor of the antidepressant effect of vitamin D. They included 4 studies with a pooled sample of 948 patients. Of the 4 trials, 3 were double blind RCTs and the fourth was an unblinded randomized trial.

## REVIEW OBJECTIVE

The objective of this review was to find out the most recent scientific evidence on the efficacy of vitamin D, administered orally, for the treatment of depression in adults over 18 years old.

## MATERIAL AND METHOD

This systematic review was carried out on the basis of the PRISMA guide (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes)[7].

### Inclusion and exclusion criteria

The inclusion criteria were: a) randomized clinical trials (RCTs) evaluating the efficacy of vitamin D in depressed patients versus placebo; b) that included adult participants over 18 years old with a clinical diagnosis of depression according to the ICD-10, APA and other standardized scales; c) whose intervention was the oral administration of vitamin D, which may vary in dose and duration; d) that the result was the quantitative change in depressive symptoms using depression assessment scales, in order to assess the improvement, worsening or lack of response to treatment, e) published in peer-reviewed journals, in Spanish and English, and finally, f) new articles that had been published from 2013 until the time of the search (September 2019), since in the most recent systematic review[5] the search spanned until July of that year (2013).

The exclusion criteria were: a) non-randomized clinical trials, cohort studies, case-control studies, case studies, or systematic reviews; b) that include any participant under 18 years old; c) studies where vitamin D was administered in conjunction with other interventions (exercise, nutrients, other vitamins, etc.) and, in general, different from that considered in the inclusion criteria; d) the measurement of the result was different from the one previously stated; e) published in journals or conferences without peer review and in a language other than English or Spanish.

### Information sources and search strategy

Four complementary databases were used to obtain the relevant works: PubMed, Embase, Web of Science-Science Citation Index (WoS-SCI) and Scopus. The search strategies for each of them (Annex I) were constructed from the concepts Depression and Vitamin D. To define the type of study, the terms recommended by Lefebvre, Manheimer and Glanville were used [8].

In PubMed and Embase, the search was carried out using the Mesh and Emtree descriptors, respectively, as well as in the title and abstract fields. In the case of WoS-SCI and Scopus, the search was carried out in the title, abstract and keyword fields. The search and download of the bibliographic records was carried out on September 21, 2019.

### Papers selection process

After downloading each of the databases, and once the duplicate bibliographic records were eliminated, two authors (AL and MH) independently reviewed the title and abstract of each record to determine its relevance. In this process, a concordance in the selection of 90.7% was obtained, resolving the discrepancies by consensus. Subsequently, from the records considered initially relevant, the full text was obtained and it was reviewed by three authors equally independently (AL, MR, CC). The discrepancies about their inclusion or not, were resolved through the arbitration of a fourth author (MH).

### Analysis of the information

AL, MR and CC analyzed the following aspects of each study: study population, sample size, instrument used to measure depression, type of intervention, outcome and study time. MH checked the analysis to assess consistency between investigators. Discrepancies were resolved by consensus.

### Evaluation of the quality of the studies

The quality of individual clinical trials was assessed using the Cochrane Collaboration Tool[9] that assesses risk of bias in various domains. These domains include information on random sequence generation (selection bias), details on allocation concealment (selection bias), blinding of study participants and staff (performance bias), blinding of outcome assessor (detection bias), incomplete data handling (attrition bias), and selectively reporting the originally mentioned results (reporting bias). The authors, after examining the full texts of the included articles, categorized each trial according to the cited parameters, which were reported as present, absent or unclear.

### Assessment of publication bias

Publication bias was visually examined using the funnel plot showing effect size versus standard error. In addition, the Egger[10] test was performed to contrast the symmetry hypothesis in the funnel plot.

### Statistics

A meta-analysis was conducted by pooling the articles to assess the efficacy of oral vitamin D in the treatment of depression. Efficacy was measured with the mean in the treated group and in the control group with depression evaluation scales. Total heterogeneity[9] was studied using the $I^2$ index based on a chi-square test. It was agreed to use the random effects model in case of a Cochran's Q test <0.05 or an $I^2$ index greater than 50%.

Since the evaluation of depression had been carried out by different methods, it was also decided to perform a meta-regression to study the effect of the administration of vitamin D within each method.

All analysis were carried out in R (version 3.6.2).

## RESULTS

### Results of the selection of the works

The initial search yielded 1,264 bibliographic records (Figure 1) which, after eliminating duplicates, were 722 unique references. After reading the title and abstract, 55 were selected, and their relevance was assessed from reading the full text. Of these 55 studies, 2 of them were eliminated because they were the same study, 6 of them because the

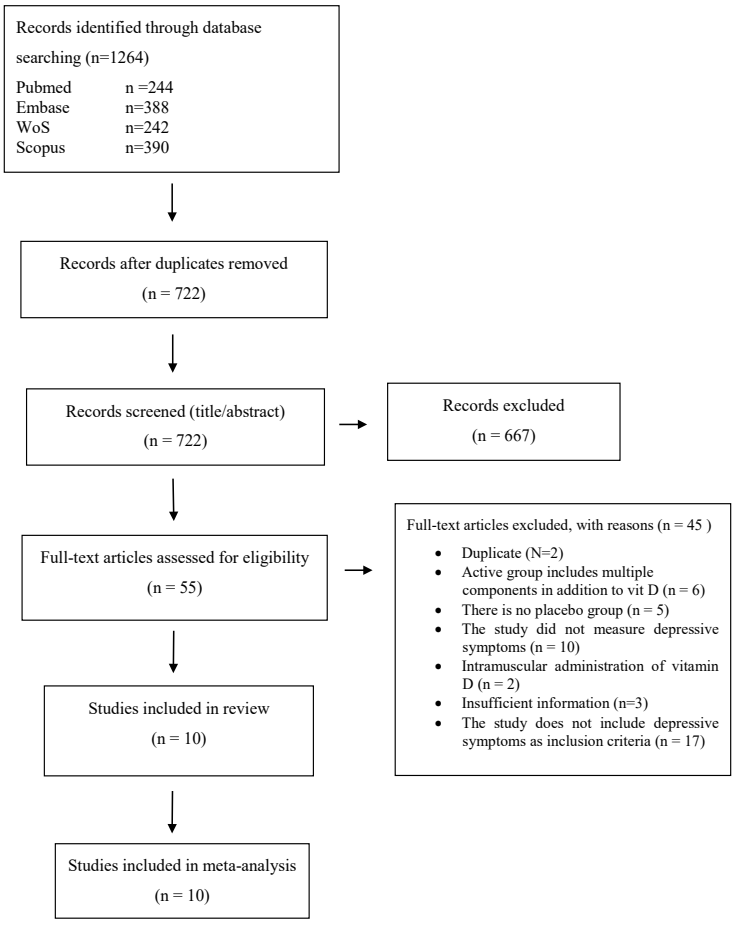



**Figure 1** Flow chart of study selection

active group included multiple components in addition to vitamin D, 5 of them because there was no placebo group, 10 because it did not measure depressive symptoms, 2 of them because vitamin D was administered intramuscularly, 3 of them because the information presented was insufficient, 17 of them because the presence of depressive symptoms was not included in the inclusion criteria. Finally, 10 studies were selected for review and meta-analysis. These 10 RCTs include a total of 1,393 participants.

## Characteristics of the included studies

There were ten RCTs included in the analysis (Table 1), four were conducted in Iran[11,12,13,14], two in Denmark[15,16,] two in China[17,18], one in the Netherlands[19] and one in the USA[20].

A total of 1,393 participants were randomized, with a mean age ranging from 24 years[13] to 68 years[11].

The 10 RCTs included patients diagnosed with major depressive disorder (MDD) or had mild-moderate depressive symptoms and their main variable was the study of the efficacy of oral administration of vitamin D in the treatment of depression.

Baseline vitamin D levels ranged from 9.2 ng / ml[14] to 24.5 ng / ml[18].

All the studies administered vitamin D3 (cholecalciferol) with a dose range ranging from 1,000 IU / d[13] to 100,000 IU / week (14,285 IU / d)[18].

The duration of the vitamin D administration time was also highly variable, between 8 weeks [11,14,18] and 52 weeks [17].

The scales to measure depression in the identified studies included the Beck Depression Inventory (BDI)[12,14,17,18], the Hamilton Depression Scale (HAM)[15], the Center for Epidemiologic Studies Depression Scale (CES-D)[19], the geriatric depression scale (GDS)[11], the structured interview of the Hamilton depression scale adapted for seasonal affective disorders (SIGH-SAD)[16], the Montgomery-Åsberg depression scale (MADRS)[20] and the Edinburgh Postnatal Depression Scale (EPDS)[13].

## Efficacy of oral administration of vitamin D in the treatment of depression

Only 3 studies[11,12,13] of the 10 selected studies (see Table 1), found a favorable result for the administration of vitamin D compared to placebo in the treatment of depression. The 3 studies were conducted in the same country (Iran) although by different authors.

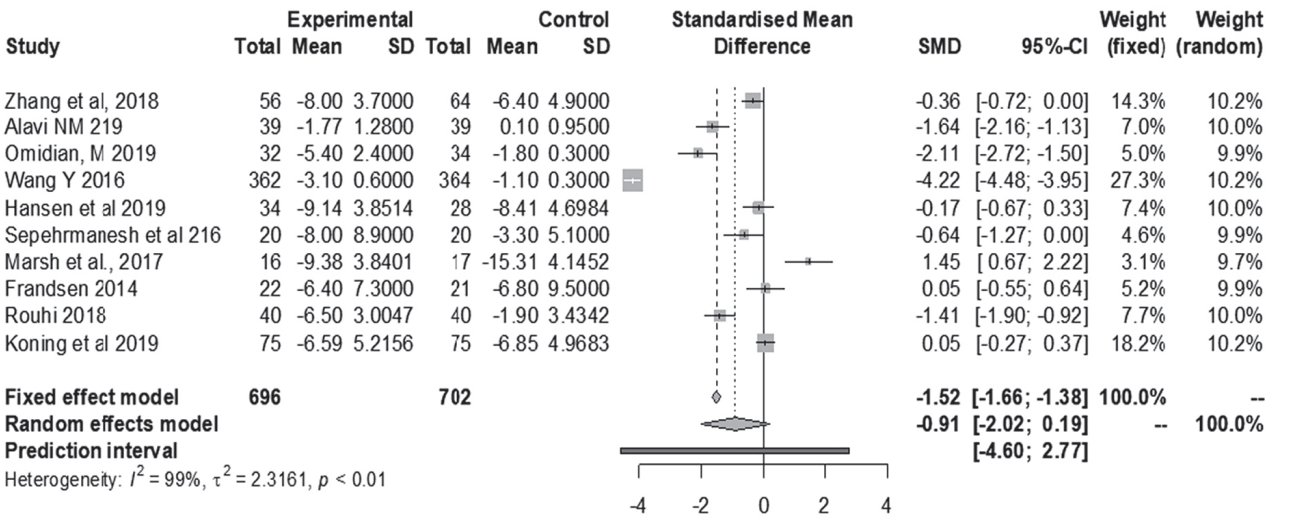
The estimated efficacy point for each RCT and the total result of the meta-analysis for the vitamin D group versus placebo is presented in Figure 2. The $I^2$ index is greater than 50% and the heterogeneity between the studies is significant ($p < 0.01$) so the random effects model was used.

Given the high heterogeneity ($I^2$ 99%, $p > 0.01$), it was decided to make an analysis using the scatter plot proposed by Baujat et al. (2002)[21] and it was found that the study by Wang (2016)[17] is the one that most influences this heterogeneity, followed by the study by Koning et al. (2019)[19] (See Annex II). However, even running the analysis again and removing such studies, heterogeneity remains high.

**Table 1** Characteristics of included RCTs

| First author, year (Ref.) | Country | Sample size and age (years) | Selection criteria | Basal level of Vitamin D (ng / ml) | Instruments and Baseline Scores Depression (mean (SD)) | Vitamin D doe | Duration of intervention (weeks) | Post-intervention vitamin D level | Post-intervention depression score (mean (SD) or difference of means) | p |
|---|---|---|---|---|---|---|---|---|---|---|
| Zhang and cols., 2018 | China | 123 people over 18 years of age MA: 39 | Tuberculosis patients with MDD criteria according to DSM-IV | GD 22,9 (7,1) ng/ml GP 24,5 (−−6) ng/ml | BDI-II GD 24,6 (13,1) GP 23,3 (10,5) | 100.000 vit D IU/ weekly 14285 ui/d | 8 | GD 27,1 (8,3) ng/ml GP 23,6 (8,1) ng/ml | GD 16,6 (9,4) GP16,9 (8,3) | 0,38 |
| De Koning EJ and cols., 2019 | Holland | 155 people between 60-80 years old. MA: 67 | People in the community with significant depressive symptoms | GD 46 [32,5–57] nmol/L GP 44 [36–55,25] nmol/L (13,26 y 12,6 ng/ml respectively) | CES-D GD 22 GP 21 | 1.200 ui/d | 48 | GD 43,48 ± 9,5 nmol/L GP 25,9 ± 15,3 nmol/L | – 0,25 (– 2,37, 1,87) | 0,82 |
| Alavi NM and cols., 2019 | Iran | 78 people over 60 years old MA: 68 | People with moderate-severe depression | GD 22,57 ± 6,2 ng/ml GP 21,2 ± 5,8 ng/ml | GDS-15 GD9,25 (2,4) GP 8,9 (2,3) | 50.000 ui / weekly 7.142 ui/d | 8 | GD 43,48 ± 9,5 ng/ml GP 25,9 ± 15,3 ng/ml | GD 7,48 (1,66) GP 9 (2,1) | 0,0001 |
| Omidian M and cols., 2019 | Iran | 66 people between 30-60 years MA: 50 | Patients with diabetes mellitus and mild-moderate depressive symptoms | GD 15,5 ± 8,8 ng/ml GP 14,6 ± 11,4 ng/ml | BDI-II GD 15,2 (9,6) GP 15,5 (11,2) | 4.000 ui/d (=100 µg/d) | 12 | GD 32,2 ± 8,9 ng/ml | GD 9,8 (7,2) GP 13,7 (11,5) | 0,02 |
| Wang Y and cols., 2016 | China | 726 people MA: 53 | Dialysis patients with MDD according to DSM - IV | GD 21,9 ± 4,1 ng/ml GP 23,2 ± 5,8 ng/ml | BDI-II GD 22,7 (4,3) GP 21,9 (5,4) | 50.000 IU/ sem vit D3 7.142 ui /d | 52 | GD 41,3 (13,7) ng/ml GP 23,1 (7,5) ng/ml | GD 19,6 (3,7) GP 20,8 (5,1) | 0,06 |
| Hansen and cols., 2019 | Denmark | 62 people between 18-65 years MA: 39 | Patients with MDD according to ICD 10 | GD 43,2 (24,6) nmol/L GP 44,3 (24,1) nmol/L (12,4 y 12,7 ng/ml respectively) | HAM-17 GD 18,4 (5,73) GP 18,0 (6,01) | 2.800 ui/d Vit D3 (70 µg/d) | 12 | GD 94,5 (30,0) nmol/L GP 44,4 (25,0) nmol/L | GD 10,6 (5,40) GP 9,50 (5,48) | 0,73 |
| Sepehrmanesh Z and cols., 2016 | Iran | 36 people between 18-65 years MA: 36 | Patients with MDD according to DSM IV | GD 13,6 ± 7,9 µg/L (ng/ml) GP 9,2 ± 6,0 µg/L (ng/ml) | BDI GD 25,2 (9,2) GP 28,5 (10,8) | 50.000 VIT D ui/ weekly 7.142 ui /d | 8 | GD 8,3 ± 4,0 ng/ml GP 34,0 ± 9,1 ng/ml | GD 17,2 (10,6) GP 25,2 (9,9) | 0,06 |
| Frandsen TB and cols., 2014 | Denmark | 34 health professionals (18-65 years) MA: 44 | People with a history of Seasonal Affective Disorder who have moderate depressive symptoms | 68,3 (25,3) nmol/L (19,6 ng/ml) | SIGH-SAD GD 18,56 (8,25) GC 18,67 (8,25) | 2.800 IU/d 70 µg/d vit D | 12 | Not available | Decrease GD −6,4 (7,3) GP −6,8 (9,5); | 1,00 |
| Marsh WK and cols., 2017 | USA | 33 people 18-70 years MA: 44 | Patients with bipolar depression and vitamin D deficiency (<30 ng / ml) | GD 19,2 (5,8) ng/ml GP 19,3 (5,5) ng/ml | MADRS GD 21,3 (6,4) GP 22,8 (6,9) | 5.000 ui/d Vit D | 12 | INCREASE GD 9,9 ± 8,2 ng/ml GP 1,3 ± 4,3 ng/ml | GD 9,54 GP 6,42 | 0,89 |
| Rouhi M and cols., 2018 | Iran | 80 primiparous women MA: 24 | Women who score> 13 on the depression scale (EPDS) and> 20 on the Fatigue scale | Not valued | EPDS GD 15,05 GP 15,27 | 1.000 ui/d vit D | 24 | Not available | GD -7 points (CI=3,02–5,35; GP No significant differences | 0,001 |

**Figure 2** Forest Plot para los estudios incluidos




The result of using the pooled data of the 10 studies does not show that vitamin D is effective for the treatment of depression compared to placebo (Standardized mean difference: -0.91; 95% Confidence Interval: -2, 02-0.19).

Table 2 shows the results obtained by meta-regression. It is concluded that, within the BDI-II method, the efficacy of vitamin D for the treatment of depression is not demonstrated either (Standardized Mean Difference: -1.021; 95% Confidence Interval: -3.355-1.313).

The assessment of the risk of bias, as mentioned above, was assessed using the Cochrane collaboration tool[9]. The results of the categorization of each trial are presented in Table 3.

Figure 3 shows the funnel plot associated with the 10 included studies with the aim of studying possible publication bias. It is observed that the point cloud is not symmetrically distributed around the global estimate of the effect. The p-value associated with this test was 0.01.

**Table 2** Results by subgroups

| Method | Number of studies | Standardized mean difference | Confidence interval (95%) | Q | $\tau^2$ | $\tau$ | $I^2$ (%) |
|---|---|---|---|---|---|---|---|
| BDI-II | 3 | -1,021 | (-3,355; 1,313) | 23,69 | 0,780 | 0,88 | 91,6 |
| CES-D | 2 | -0,783 | (-11,540; 9,974) | 29,82 | 1,344 | 1,159 | 96,6 |
| BDI | 1 | -4,216 | (-4,477; -3,954) | 0 | | | |
| HAM-17 | 1 | -0,170 | (-0,670; 0,332) | 0 | | | |
| MADRS | 1 | 1,446 | (0,669; 2,224) | 0 | | | |
| SIGH-SAD | 1 | 0,047 | (-0,552; 0,645) | 0 | | | |
| EPDS | 1 | -1,412 | (-1,904; -0,920) | 0 | | | |

**Tabla 3** **Assessment of risk of bias in included studies**

| Study | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and staff (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data were addressed (attrition bias) | Selective reporting (reporting bias) |
|---|---|---|---|---|---|---|
| Sepehrmanesh et al. 2015 | Yes | Yes | Yes | Yes | No | No |
| Hansen et al.- 2019 | Yes | Yes | Yes | ? | No | No |
| Frandsen et al. 2014 | Yes | Yes | Yes | ? | No | No |
| Marsh et al . 2017 | Yes | Yes | Yes | Yes | No | No |
| Rouhi et al.- 2018 | Yes | Yes | Yes | Yes | No | No |
| Zhang et al. (2018). | Yes | Yes | Yes | Yes | Yes | Yes |
| De Koning et al. (2019). | Yes | Yes | Yes | Yes | Yes | Yes |
| Alavi et al. (2019). | Yes | Yes | Yes | Yes | Yes | Yes |
| M. Omidian et al. (2019) | Yes | Yes | No | Yes | Yes | No |
| Wang et al. (2016). | Yes | Yes | Yes | Yes | Yes | Yes |

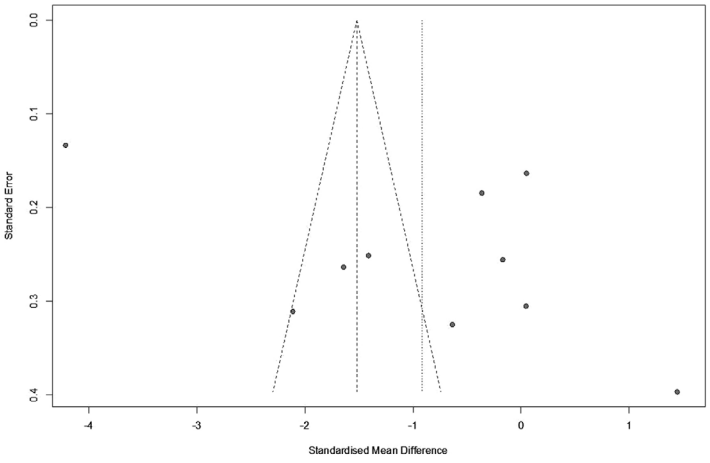



**Figure 3** Funnel Plot para los estudios incluidos

## DISCUSSION

The present systematic review identified 10 RCTs focused on the study of the efficacy of the administration of vitamin D in the treatment of depression. For this reason, it involves the analysis of a greater number of RCTs compared to other systematic reviews of a similar nature. These reviews do not present conclusive results regarding the association between vitamin D and depression, so this work represents an advance in the knowledge of this association.

In general, the results provided do not show that the oral administration of vitamin D has had a significant effect on the symptomatic treatment of depression. This is a result that is consistent with the studies by Li et al. (2014) [5] that included fewer RCTs than the present review (6) and that of Wang et al.[22] (2018) that, focused on depression in women in pre and postpartum, included only 9 longitudinal studies. Also, in this case they did not find an association between vitamin D deficiency and depressive symptoms during pregnancy. Finally, Gowda et al.[23], in a meta-analysis that included nine trials with 4923 participants, also did not find a significant effect of vitamin D in the treatment of depression.

However, other reviews did find this association (Angling et al.[24], Spedding[25] Vellekkatt&Menon, 2019[6]) although the scope of the studies they reviewed represents a limitation compared to the present study. Thus, in the case of the review by Anglin[24] et al. (2013) only included observational studies (one case-control study, 3 cohort studies and 10 cross-sectional studies), not including RCTs. On the other hand, Spedding[25] (2014) only included 2 RCTs in the meta-analysis. Finally, the review by Vellekkatt and Menon, 2019[6], with a similar objective and methodology to that of the present study, only included 4 RCTs. The difference in the number of RCTs included in this study (4) compared to the results presented here (10) could be the consequence of a smaller scope of the search (August 2017) compared to our results (September

2019) and would explain the difference obtained for the association between vitamin D and depression.

When looking at the reviewed studies in detail, one of the characteristics found is methodological diversity, a fact already highlighted by Spedding[25]. Thus, the population included in the review was varied, including people with tuberculosis[18], diabetes[12], fatigue[13], on dialysis[17] or bipolar depression[20], among others. On the other hand, the scales used to measure depressive symptoms were also varied, including the Beck depression inventory BDI-II[12 17 18] and BDI[14] (in this article the authors did not specify the version of BDI used), the Hamilton depression scale (HAM)[15], the geriatric depression scale (GDS)[11], the structured interview of the Hamilton depression scale adapted for seasonal affective disorders (SIGH-SAD)[16], the Montgomery-Åsberg depression scale (MADRS)[20] and the Edinburgh Postnatal Depression Scale (EPDS)[13]. This methodological diversity is a limitation to obtain conclusive results. Another limitation is the fact that in some studies [11, 14,18] , the intervention time was very short (8 weeks), an aspect that may influence the results. In this case, two studies found no association between vitamin D and depression and one did find it[11].

Possible explanations for the high heterogeneity found ($I^2$ 99%, p> 0.01) even after removing the studies by Wang (2016)[17] and Koning (2019)[19], would be, on the one hand, clinical heterogeneity (differences between types of patients, baseline levels of vitamin D, dose and duration of treatments) and methodological (variability in the designs) which could cause disparities in the results obtained. On the other hand, this heterogeneity could also indicate that vitamin D is not an important prognostic factor in the results.

Regarding the lack of symmetry in the results of the study of publication bias of the 10 included studies, we consider that this asymmetry would be more related to the heterogeneity of the studies than to a possible publication bias. The review carried out includes both studies with positive and negative results for the use of vitamin D, the latter being the majority. Furthermore, as the overall effect of vitamin D administration was not significant in the current review, it is possible that publication bias did not influence our results.

### Strengths and limitations

The present review has started from an exhaustive search both for the four bibliographic databases used, the ones with the greatest coverage in the field of biomedical literature, and for the number of terms used in the search strategy. This search ensures that the results presented show the best scientific evidence published to date. On the other hand, it facilitates the updating of the results of other reviews of a similar nature. Additionally, this study has focused on randomized, double-blind, placebo-controlled trials; in which the study of depression in depressed patients has been the main variable of the study. In this way, we have sought to reduce the variability and biases of other studies.

However, there are two limitations that must be taken into account when assessing the results. On the one hand, the heterogeneity of the general analysis, related to the different scales used and the diversity of the depressive population studied, may affect the quality of the evidence obtained. On the other hand, 4 of the 10 studies come from the same country (Iran), which represents 39.8% of the total weight of articles in the meta-analysis (random model), which could limit the generalizability of the results.

## CONCLUSION

The current state of knowledge on the efficacy of vitamin D administration in the treatment of depression presents contradictory results. The result of our systematic review does not support the efficacy of vitamin D in the treatment of depressive symptoms and it is considered necessary to perform more RCTs using patients with depressive disorder. With the currently available evidence, the use of vitamin D in the treatment of depression cannot be recommended.

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| **Anexo 1** | **Search strategy** |
|---|---|

## PUBMED

| | |
|---|---|
| #1 | "Search "Vitamin D""[Mesh]" |
| #2 | "Search (Calcifediol[Title/Abstract] OR Calciferol[Title/Abstract] OR Calciol[Title/Abstract] OR Calcitriol[Title/Abstract] OR Cholecalciferol[Title/Abstract] OR colecalciferol[Title/Abstract] OR Dihydrotachysterol[Title/Abstract] OR Dihydroxycholecalciferol[Title/Abstract] OR "Dihydroxyvitamin D"[Title/Abstract] OR Ergocalciferol[Title/Abstract] OR Hydroxycholecalciferol[Title/Abstract] OR "Hydroxyvitamin D"[Title/Abstract] OR lunacalcipol[Title/Abstract] OR "Vitamin D"[Title/Abstract] OR "Vitamin D2"[Title/Abstract] OR "Vitamin D3"[Title/Abstract])" |
| #3 | "Search #1 OR #2" |
| #4 | "Search ""Depressive Disorder""[Mesh] OR ""Depression""[Mesh]" |
| #5 | "Search "Affective disorder"[Title/Abstract] OR "bipolar disorder"[Title/Abstract] OR Depress*[Title/Abstract] OR dysphori*[Title/Abstract] OR Dysthymi*[Title/Abstract] OR "Involutional Paraphrenia"[Title/Abstract] OR "Involutional Psychos*"[Title/Abstract] OR Melancholia*[Title/Abstract] OR "Mood Disorder*"[Title/Abstract] OR "mourning syndrome"[Title/Abstract] OR "Perry syndrome"[Title/Abstract] OR pseudodementia" |
| #6 | "Search #4 OR #5" |
| #7 | "Search "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]" |
| #8 | "Search #3 AND #6 AND #7" |
| #9 | "Search (""2013/01/01""[Date - Publication] : ""2019""[Date - Publication])" |
| #10 | "Search #8 AND #9" |

## EMBASE through EMBASE.COM

| | |
|---|---|
| #1 | 'vitamin d'/exp |
| #2 | calcifediol:ab,ti OR calciferol:ab,ti OR calciol:ab,ti OR calcitriol:ab,ti OR cholecalciferol:ab,ti OR colecalciferol:ab,ti OR dihydrotachysterol:ab,ti OR dihydroxycholecalciferol:ab,ti OR 'dihydroxyvitamin d':ab,ti OR ergocalciferol:ab,ti OR hydroxycholecalciferol:ab,ti OR 'hydroxyvitamin d':ab,ti OR lunacalcipol:ab,ti OR 'vitamin d':ab,ti OR 'vitamin d2':ab,ti OR 'vitamin d3':ab,ti |
| #3 | #1 OR #2 |
| #4 | 'depression'/exp |
| #5 | 'affective disorder':ab,ti OR 'bipolar disorder':ab,ti OR depress*:ab,ti OR dysphori*:ab,ti OR dysthymi*:ab,ti OR 'involutional paraphrenia':ab,ti OR 'involutional psychos*':ab,ti OR melancholia*:ab,ti OR 'mood disorder*':ab,ti OR 'mourning syndrome':ab,ti OR 'perry syndrome':ab,ti OR pseudodementia:ab,ti |
| #6 | #4 OR #5 |
| #7 | 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti |
| #8 | #3 AND #6 AND #7 |
| #9 | #8 AND (2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) |
| 10 | #8 AND (2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND [embase]/lim |

## WoS- Core Collection

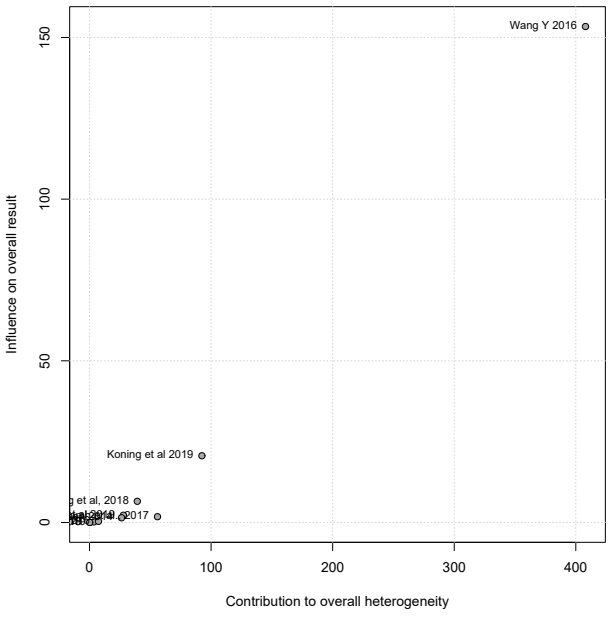
| | |
|---|---|
| 1 | TOPIC: (Calcifediol OR Calciferol OR Calciol OR Calcitriol OR Cholecalciferol OR colecalciferol OR Dihydrotachysterol OR Dihydroxycholecalciferol OR "Dihydroxyvitamin D" OR Ergocalciferol OR Hydroxycholecalciferol OR "Hydroxyvitamin D" OR lunacalcipol OR "Vitamin D" OR "Vitamin D2" OR "Vitamin D3") |
| 2 | TOPIC: ("Affective disorder" OR "bipolar disorder" OR Depress* OR dysphori* OR Dysthymi* OR "Involutional Paraphrenia" OR "Involutional Psychos*" OR Melancholia* OR "Mood Disorder*" OR "mourning syndrome" OR "Perry syndrome" OR pseudodementia) |
| 3 | TOPIC: (random* or placebo* or "clinic* trial*" or "singl* blind*" or "doubl* blind*" OR rct) |
| 4 | #3 AND #2 AND #1 |
| 5 | #3 AND #2 AND #1<br><br>Refined by: PUBLICATION YEARS: ( 2019 OR 2018 OR 2017 OR 2016 OR 2015 OR 2014 OR 2013 ) |

## SCOPUS

| | |
|---|---|
| 1 | TITLE-ABS-KEY ( calcifediol OR calciferol OR calciol OR calcitriol OR cholecalciferol OR colecalciferol OR dihydrotachysterol OR dihydroxycholecalciferol OR "Dihydroxyvitamin D" OR ergocalciferol OR hydroxycholecalciferol OR "Hydroxyvitamin D" OR lunacalcipol OR "Vitamin D" OR "vitamin D2" OR "Vitamin D3" ) |
| 2 | TITLE-ABS-KEY ( "Affective disorder" OR "bipolar disorder" OR depress* OR dysphori* OR dysthymi* OR "Involutional Paraphrenia" OR "Involutional Psychos*" OR melancholia* OR "Mood Disorder*" OR "mourning syndrome" OR "Perry syndrome" OR pseudodementia ) |
| 3 | TITLE-ABS-KEY ( random* OR placebo* OR "clinic* trial*" OR "singl* blind*" OR "doubl* blind*" OR rct ) |
| 4 | 1 AND 2 AND 3 |
| 5 | ( LIMIT-TO ( PUBYEAR , 2019 ) OR LIMIT-TO ( PUBYEAR , 2018 ) OR LIMIT-TO ( PUBYEAR , 2017 ) OR LIMIT-TO ( PUBYEAR , 2016 ) OR LIMIT-TO ( PUBYEAR , 2015 ) OR LIMIT-TO ( PUBYEAR , 2014 ) OR LIMIT-TO ( PUBYEAR , 2013 ) ) |
| 6 | 4 AND 5 |

## Annex 2

Data dispersion graph (Baujat 2002) that includes the 10 studies of the meta-analysis




Data dispersion graph (Baujat 2002) excluding the study by Wang (2016)