

Review Article

Protocol registration: PROSPERO
(CRD42022309640).

Cite this article: Ghaemi S, Zeraattalab-Motlagh S, Jayedi A, Shab-Bidar S (2024). The effect of vitamin D supplementation on depression: a systematic review and dose–response meta-analysis of randomized controlled trials. *Psychological Medicine* **54**, 3999–4008. <https://doi.org/10.1017/S0033291724001697>

Received: 1 November 2023
Revised: 20 May 2024
Accepted: 5 August 2024
First published online: 18 November 2024


Keywords:

anxiety; depression; dose–response; randomized controlled trials; Vitamin D₃

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The effect of vitamin D supplementation on depression: a systematic review and dose–response meta-analysis of randomized controlled trials

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Abstract

The impact of vitamin D supplementation on depressive symptoms remains uncertain. This study aimed to investigate the dose-dependent effects of vitamin D supplementation on depressive and anxiety symptoms in adults. We systematically searched PubMed, Scopus, and Web of Science up to December 2022 to identify randomized controlled trials evaluating the effects of vitamin D₃ supplementation on depression and anxiety symptoms in adults. Using a random-effects model, we calculated the standardized mean difference (SMD) for each 1000 IU/day vitamin D₃ supplementation. The GRADE tool assessed the certainty of evidence. Our analysis included 31 trials with 24189 participants. Each 1000 IU/day vitamin D₃ supplementation slightly reduced depressive symptoms in individuals with and without depression (SMD: −0.32, 95% CI −0.43 to −0.22; GRADE = moderate). The effect was more pronounced in those with depressive symptoms (SMD: −0.57, 95% CI −0.69 to −0.44; *n* = 15). The greatest reduction occurred at 8000 IU/day (SMD: −2.04, 95% CI −3.77 to −0.31). Trials with follow-up ≤8 weeks (SMD: −0.45, 95% CI −0.70 to −0.20; *n* = 8) and 8 to ≤24 weeks (SMD: −0.47, 95% CI −0.70 to −0.24; *n* = 15) showed stronger effects compared to those lasting 24 to ≤52 weeks (SMD: −0.13, 95% CI −0.28 to 0.02; *n* = 5) or longer than 52 weeks (SMD: 0.14, 95% CI −0.16 to 0.44; *n* = 3) (*p* group difference <0.001). Vitamin D₃ supplementation had no significant effects on anxiety symptoms. In summary, this study suggests that vitamin D₃ supplementation may effectively reduce depressive symptoms in short term. Further high-quality trials are warranted for a conclusive assessment of its impact on anxiety.

Introduction

Depression is the most common psychiatric disease worldwide, with an immense cognitive, social, and economic burden (Malhi & Mann, 2018). Currently, approximately 280 million people are affected by depression (GBD 2019 Diseases and Injuries Collaborators, 2020), making depression the leading cause of losing years of life due to disability (Friedrich, 2017; World Health, 2017). The World Health Organization ranked major depression as the third leading cause of disease worldwide and predicted that it will be the first public health concern by 2030 (World Health, 2008). Anxiety is also one of the most common mental health problems, with global estimates ranging from 3.8 to 25% across countries. Since 1990, there has been a 50% increase in the absolute number of patients with anxiety disorders (Z. Zhang et al., 2021). Additionally, research around the world has reported an increase in the prevalence of anxiety and depression symptoms during the COVID-19 outbreak (COVID-19 Mental Disorders Collaborators, 2021).

During the past decades, many prominent basic and clinical studies have been carried out to elucidate the underlying causes of depression (Saveanu & Nemeroff, 2012). A variety of factors including genetic predisposition, cognitive dysfunctions, stressful life events, interpersonal dysfunction, biological differences, and inherited traits are implicated in developing depression and anxiety (Altemus, Sarvaiya, & Neill Epperson, 2014; Hammen, 2018; Morssinkhof et al., 2020; Penner-Goeke & Binder, 2019). Studies in nutritional psychiatry have suggested some evidence of the role of dietary factors in developing depression and management of depressive symptoms (Marx et al., 2021; Pano et al., 2021). Furthermore, some studies investigated the effect of single micronutrient supplementation such as folate (Altaf, Gonzalez, Rubino, &

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Nemec, 2021; Jin *et al.*, 2022), zinc (Yosae *et al.*, 2022), alpha-tocopherol (Lee *et al.*, 2022), iron (Huang, Bilgrami, & Hare, 2022), and vitamin D (Parker, Brotchie, & Graham, 2017) on depression management. Of note, due to its possible role in the function of the brain, vitamin D has received much attention among micronutrients (Anglin, Samaan, Walter, & McDonald, 2013).

Vitamin D is a neuroprotective hormone, representing important roles in immune system regulation, promoting cell growth and differentiation, and anti-inflammatory pathways (Holick, 2007). It also regulates many essential genes involved in the brain function (Sultan *et al.*, 2020). Several meta-analyses of epidemiological studies have suggested a positive relationship between vitamin D deficiency and risk of developing depression (Anglin *et al.*, 2013; Ju, Lee, & Jeong, 2013).

Although some review studies have presented suggestions of a beneficial effect of vitamin D supplementation on depressive symptoms (Anglin *et al.*, 2013; Cheng, Huang, & Huang, 2020; Mikola *et al.*, 2023; Shaffer *et al.*, 2014; Xie *et al.*, 2022), none of these reviews have examined the potential dose-dependent effects of vitamin D supplementation on depressive symptoms to determine the optimum dose of intervention. Some of the available reviews, owing to the limited number of trials and methodological biases, were of low quality (Anglin *et al.*, 2013; Cheng *et al.*, 2020; Li *et al.*, 2014; Shaffer *et al.*, 2014). Considering these uncertainties, we aimed to fill this gap by conducting a systematic review and dose-response meta-analysis of randomized control trials (RCTs) to determine the optimum dose and shape of the effects of vitamin D supplementation on depression and anxiety symptoms in adults regardless of their health status.

Methods

We conducted the meta-analysis per instructions outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement for Systematic Reviews of Interventions (Page *et al.*, 2021) and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Handbook (Schunemann, 2008). The review protocol was registered with PROSPERO (CRD42022309640).

Data sources and searches

PubMed, Scopus, and Web of Science were systematically searched to find relevant literature up to 15 December 2022. Only English-language articles were included. Two investigators (SG and SZM) independently performed the systematic search and screened the titles and abstracts and then full-text articles to find eligible studies. Disagreements were resolved under the supervision of a third reviewer (SS-B). We also checked out the reference lists of published meta-analyses of RCTs of the effect of vitamin D supplementation. Further details about the search strategy in the databases are represented in online Supplementary Table 1.

Study selection

Inclusion and exclusion criteria were defined according to the framework of PICOS (population, intervention/exposure, comparator, outcome, and study design). Published human intervention studies were considered eligible for inclusion in the present meta-analysis if they had the following criteria: (1) RCTs, with

a minimum intervention period of 4 weeks, conducted in adults aged 18 years or older, regardless of medication use and their health status; (2) evaluated the effects of vitamin D supplementation alone, regardless of type (vitamin D₃, vitamin D₂), method of advice (orally, injection), and dosing regimen against a control group; (3) provided a dose of vitamin D supplementation in the intervention group; and (4) provided effect estimates in the form of mean difference and its 95% confidence interval (CI) for continuous outcomes and odds ratio (OR) with its 95% CI for binary outcome, or reported sufficient information to estimate those measures. Eligible control group included usual diet, no advice, no intervention, or placebo. Trials that compared two doses of vitamin D supplementation in intervention and control arms were eligible. Except trials that used vitamin D in combination with calcium, others that implemented a multicomponent intervention including vitamin D in combination with another supplement (for example, omega-3) were excluded from our review.

Outcomes

Our primary outcomes were (1) the anxiety and depressive symptoms and (2) remission of depression. Moreover, our secondary outcomes included quality of life and its domains and total and serious adverse events.

Data extraction

The full texts of potentially eligible trials were examined separately by two investigators (SG and SZM). From studies considered eligible, the same two reviewers independently extracted the following characteristics from each trial: author and year of publication; population location, study design, and duration, characteristics of the population (% female, mean age \pm s.d., baseline body mass index, and health status), total sample size, intervention characteristics (dose of vitamin D supplementation in the intervention group), comparison group, vitamin D deficiency (yes/no/mixed), use of antidepressant medication (yes/no/mixed), dropout, baseline depression risk, outcome measures and main results for the outcomes included.

Risk of bias assessment

Version 2.0 of the Cochrane tool was used to assess the risk of bias of the eligible RCTs (Higgins *et al.*, 2011). Two authors (SG and SZM) independently performed risk of bias assessment. Disagreements were resolved by discussion with a third reviewer (SS-B).

Data synthesis and analysis

We considered standardized mean difference (SMD) and its 95% CI for continuous outcomes (anxiety and depressive symptoms, comorbidity index, stress, overall quality of life, bodily image, dysphoria, food avoidance, healthy worry, relationship, sexual and social reaction) and OR and risk difference (RD) for binary outcomes (depression remission, adverse events, as well as serious adverse event) to report the results. For the analyses of continuous outcomes, we first computed the mean and s.d. of changes from baseline measures for each study arm in each trial. For the studies that did not report these changes, we estimated these values using the reported means and SDs of outcomes before and after the

intervention per instructions in the Cochrane Handbook (Chandler, Cumpston, Li, Page, & Welch, 2019). We converted trial data to *s.d.* if they reported standard errors rather than *s.d.* (Higgins & Green, 2008). If neither *s.d.* nor standard error were reported in the trials, we used the average *s.d.* obtained from other trials for the analyses (Furukawa, Barbui, Cipriani, Brambilla, & Watanabe, 2006). Second, we calculated SMD and its 95%CI for each 1000 IU/day vitamin D₃ supplementation in each trial using the method introduced by Crippa and Orsini (Crippa & Orsini, 2016). Trial-specific results were pooled using a random-effect model (DerSimonian & Laird, 1986). The following items were needed for this method: the dose of vitamin D₃ supplementation in the intervention and control arms, the mean and its related *s.d.* of change in outcomes in each study arm (treatment and control groups), and the total number of participants in each group. For trials that implemented vitamin D supplementation on a weekly or monthly basis (e.g. 30 000 IU per week or 50 000 IU per month), we converted the dosing regimen to IU per day. Finally, we conducted a dose–response meta-analysis to evaluate the shape of the dose-dependent effects of vitamin D₃ supplementation on depressive and anxiety symptoms outcomes (Crippa & Orsini, 2016).

Then we performed pre-specified subgroup analyses based on the risk of bias (low/some concerns/high), intervention duration (≤ 8 , 9–24, 24–52, > 52 weeks), sex (both/men/women), weight status (normal weight, obese/overweight, not reported), vitamin D deficiency (yes/no/mixed), health status, medication use (yes/no/mixed), and baseline risk of depression (low/medium/high). According to eight criteria determined by the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN), we examined the credibility of subgroup differences (Schandelmaier et al., 2020). We used meta-regression analyses to compute the *p*-values for subgroup differences. For publication bias, we applied Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997) and Begg's test (Begg & Mazumdar, 1994) and inspected the funnel plots for asymmetry. The heterogeneity of effects among studies was quantified using the *I*² statistic and χ^2 test ($P_{\text{heterogeneity}} > 0.10$) (Higgins, Savovic, Page, Elbers, & Sterne, 2019).

For the analyses of binary outcomes (adverse event, depression remission), we calculated OR, RD, and their 95%CI using the number of participants and events in the intervention and control groups. Moreover, for depression remission judgment, every study defined specific criteria for recognition. For instance, in our review, only one study considered depression remission (Marsh, Penny, & Rothschild, 2017) and defined it as when participants had Montgomery-Åsberg Depression Rating Scale (MADRS) score was 12 or less. We used STATA software version 17.0 for our analyses. A two-tailed *p*-value less than 0.05 was regarded as statistically significant.

Grading the evidence

The GRADE approach was applied to judge the certainty of the evidence (Guyatt et al., 2011). According to the GRADE, evidence obtained from RCTs starts at high certainty that can be downgraded or upgraded based on pre-defined criteria. Detailed criteria that were applied for use the GRADE tool are described in online Supplementary Table 2. In order to interpretation of the magnitude of effect sizes, the estimated SMDs were interpreted as a trivial effect (0.0–0.2), a small effect (0.2–0.6), a moderate

effect (0.6–1.2), a large effect (1.2–2.0), a very large effect (2.0–4.0), and an extremely large effect (≥ 4.0) (Hopkins, Marshall, Batterham, & Hanin, 2009; Varangot-Reille, Suso-Martí, Romero-Palau, Suárez-Pastor, & Cuenca-Martínez, 2022).

Results

Systematic search

The literature search yielded 2243 records, with 1 additional record identified through manual search. After excluding 607 duplicates and 1582 irrelevant records, 55 full texts were reviewed in detail for eligibility. After reviewing the full texts, 31 trials were eligible for inclusion in this dose–response meta-analysis (Alavi, Khademalhosseini, Vakili, & Assarian, 2019; Alghamdi et al., 2020; Bertone-Johnson et al., 2012; Choukri, Conner, Haszard, Harper, & Houghton, 2018; de Koning et al., 2019; Dean et al., 2011; Eid et al., 2019; Fazelian, Amani, Paknahad, Kheiri, & Khajehali, 2019; Frandsen, Pareek, Hansen, & Nielsen, 2014; Gaughran et al., 2021; Ghaderi et al., 2017, 2020; Hansen et al., 2019; Jorde & Kubiak, 2018; Jorde, Sneve, Figenschau, Svartberg, & Waterloo, 2008; Kaviani, Nikooyeh, Zand, Yaghmaei, & Neyestani, 2020; Khalighi Sikaroudi et al., 2020; Krivoy et al., 2017; Kusmiyati, Suryani, Herawati, & Firdausi, 2020; Marsh et al., 2017; Okereke et al., 2020; Omidian et al., 2019; Rolf et al., 2017; Sepehrmanesh et al., 2016; Sharifi, Vahedi, Nedjat, Mohamadkhani, & Hosseinzadeh Attar, 2019; Vellekkatt, Menon, Rajappa, & Sahoo, 2020; Vieth, Kimball, Hu, & Walfish, 2004; Wang et al., 2016; L. Zhang, Wang, Zhu, & Yang, 2018; Zheng et al., 2019; Zhu et al., 2020) (online Supplementary Figure 1). The list of studies excluded through full-text evaluation with reasons is reported in online Supplementary Table 3.

Characteristics of original articles

Characteristics of 31 trials included in the present dose–response meta-analysis are presented in online Supplementary Table 4. The included trials comprised 24 189 participants, of which, 12 091 subjects were in the control arm and 12 098 subjects were in the intervention arm. Twenty-nine trials used vitamin D₃ supplement as an intervention. In one of the RCTs, vitamin D supplementation was performed in combination with calcium (Bertone-Johnson et al., 2012). In another one of the RCTs, vitamin D supplementation was combined with omega-3 supplementation (Okereke et al., 2020). The intervention duration ranged from 4 to 256.8 weeks, of which, 8 trials lasted ≤ 8 weeks (Alavi et al., 2019; Choukri et al., 2018; Dean et al., 2011; Kaviani et al., 2020; Krivoy et al., 2017; Kusmiyati et al., 2020; Sepehrmanesh et al., 2016; Zhang et al., 2018), fifteen trials lasted > 8 to ≤ 24 weeks (Alghamdi et al., 2020; Eid et al., 2019; Fazelian et al., 2019; Frandsen et al., 2014; Gaughran et al., 2021; Ghaderi et al., 2017, 2020; Hansen et al., 2019; Jorde & Kubiak, 2018; Khalighi Sikaroudi et al., 2020; Marsh et al., 2017; Omidian et al., 2019; Sharifi et al., 2019; Vellekkatt et al., 2020; Zhu et al., 2020), five trials lasted > 24 to ≤ 52 weeks (de Koning et al., 2019; Jorde et al., 2008; Rolf et al., 2017; Vieth et al., 2004; Wang et al., 2016), and three trials lasted > 52 weeks (Bertone-Johnson et al., 2012; Okereke et al., 2020; Zheng et al., 2019). Fifteen trials were conducted in patients with depression (Alavi et al., 2019; Alghamdi et al., 2020;

Bertone-Johnson et al., 2012; Frandsen et al., 2014; Gaughran et al., 2021; Ghaderi et al., 2017, 2020; Hansen et al., 2019; Jorde et al., 2008; Kaviani et al., 2020; Omidian et al., 2019; Sepehrmanesh et al., 2016; Vellekkatt et al., 2020; Wang et al., 2016; Zhang et al., 2018), six trials were carried out on healthy subjects (Choukri et al., 2018; de Koning et al., 2019; Dean et al., 2011; Jorde & Kubiak, 2018; Kusmiyati et al., 2020; Okereke et al., 2020), two studies were carried out on subjects with anxiety (Eid et al., 2019; Fazelian et al., 2019), and other trials were carried out in patients with chronic diseases including schizophrenia (Krivoy et al., 2017), bipolar disorder (Marsh et al., 2017), multiple sclerosis (Rolf et al., 2017), ulcerative colitis (Sharifi et al., 2019), and irritable bowel syndrome (Khalighi Sikaroudi et al., 2020). Five of the 30 RCTs were carried out in individuals with normal weight (Choukri et al., 2018; Vellekkatt et al., 2020; Wang et al., 2016; Zheng et al., 2019; Zhu et al., 2020), 15 were carried out in individuals with overweight or obesity (body mass index ≥ 25 kg/m²) (Alghamdi et al., 2020; de Koning et al., 2019; Fazelian et al., 2019; Gaughran et al., 2021; Ghaderi et al., 2017, 2020; Jorde & Kubiak, 2018; Jorde et al., 2008; Kaviani et al., 2020; Khalighi Sikaroudi et al., 2020; Krivoy et al., 2017; Omidian et al., 2019; Sepehrmanesh et al., 2016; Sharifi et al., 2019; Zheng et al., 2019), and the remaining 11 studies did not report the participants' weight status (Alavi et al., 2019; Bertone-Johnson et al., 2012; Dean et al., 2011; Eid et al., 2019; Frandsen et al., 2014; Hansen et al., 2019; Kusmiyati et al., 2020; Marsh et al., 2017; Okereke et al., 2020; Rolf et al., 2017; Vieth et al., 2004). Participants in the 17 trials had vitamin D deficiency (Alavi et al., 2019; de Koning et al., 2019; Eid et al., 2019; Fazelian et al., 2019; Ghaderi et al., 2017, 2020; Khalighi Sikaroudi et al., 2020; Krivoy et al., 2017; Marsh et al., 2017; Omidian et al., 2019; Rolf et al., 2017; Sepehrmanesh et al., 2016; Vellekkatt et al., 2020; Wang et al., 2016; Zhang et al., 2018; Zheng et al., 2019; Zhu et al., 2020), six trials were conducted in those without vitamin D deficiency (Choukri et al., 2018; Dean et al., 2011; Frandsen et al., 2014; Jorde & Kubiak, 2018; Rolf et al., 2017; Vieth et al., 2004), while the other eight trials were conducted in individuals with mixed vitamin D status (Alghamdi et al., 2020; Gaughran et al., 2021; Hansen et al., 2019; Jorde et al., 2008; Kaviani et al., 2020; Kusmiyati et al., 2020; Okereke et al., 2020; Sharifi et al., 2019). Five trials were rated as low risk of bias (Dean et al., 2011; Frandsen et al., 2014; Gaughran et al., 2021; Hansen et al., 2019; Vellekkatt et al., 2020), twelve trials were rated to have some concerns (Choukri et al., 2018; de Koning et al., 2019; Fazelian et al., 2019; Ghaderi et al., 2017, 2020; Jorde et al., 2008; Krivoy et al., 2017; Okereke et al., 2020; Omidian et al., 2019; Vieth et al., 2004; Wang et al., 2016; L. Zhang et al., 2018), and the other 14 trials were rated to have a high risk of bias (Alavi et al., 2019; Alghamdi et al., 2020; Bertone-Johnson et al., 2012; Eid et al., 2019; Jorde & Kubiak, 2018; Kaviani et al., 2020; Khalighi Sikaroudi et al., 2020; Kusmiyati et al., 2020; Marsh et al., 2017; Rolf et al., 2017; Sepehrmanesh et al., 2016; Sharifi et al., 2019; Zheng et al., 2019; Zhu et al., 2020) (online Supplementary Table 5).

Primary outcomes

A total of 31 trials with 12 098 participants in the intervention group and 12 091 participants in the control group provided data on the effect of vitamin D₃ supplementation on the depressive symptoms (Alavi et al., 2019; Alghamdi et al., 2020; Bertone-Johnson et al., 2012; Choukri et al., 2018; de Koning

et al., 2019; Dean et al., 2011; Eid et al., 2019; Fazelian et al., 2019; Frandsen et al., 2014; Gaughran et al., 2021; Ghaderi et al., 2017, 2020; Hansen et al., 2019; Jorde & Kubiak, 2018; Jorde et al., 2008; Kaviani et al., 2020; Khalighi Sikaroudi et al., 2020; Krivoy et al., 2017; Kusmiyati et al., 2020; Marsh et al., 2017; Okereke et al., 2020; Omidian et al., 2019; Rolf et al., 2017; Sepehrmanesh et al., 2016; Sharifi et al., 2019; Vellekkatt et al., 2020; Vieth et al., 2004; Wang et al., 2016; Zhang et al., 2018; Zheng et al., 2019; Zhu et al., 2020). Every 1000 IU/day vitamin D₃ supplementation slightly reduced depressive symptoms (SMD: -0.32 ; 95% CI -0.43 to -0.22 ; $I^2 = 98\%$; $P_{\text{heterogeneity}} < 0.001$, GEADE = moderate) (online Supplementary Figure 2). Of note, vitamin D supplementation resulted in a larger improvement in depressive symptoms in those with a history of depression (SMD: -0.57 , 95% CI -0.69 to -0.44 ; $n = 15$ trials) (**Table 1**).

Table 1 presents the subgroup analysis of the effects of vitamin D₃ supplementation (each 1000 IU/day) on depressive symptoms. There were several potential effect modifications by intervention duration, sex, weight status, vitamin D status, and health status. However, the credibility of these subgroup differences was rated low (online Supplementary Table 6). For instance, we found a stronger effect in trials with an intervention duration of ≤ 8 weeks and 8 to ≤ 24 weeks, and a nonsignificant effect in trials longer than 24 weeks (p group difference < 0.001); however, only a few trials were available with follow-up longer than 52 weeks (**Table 1**). By using Egger's test ($p = 0.23$), Begg's test ($p = 0.16$), and an inspection of the funnel plot, we did not detect any evidence of publication bias (online Supplementary Figure 3).

The effects of different doses of vitamin D₃ on depressive symptoms are shown in **Table 2** and **Fig. 1**. The analysis showed that depression symptoms decreased proportionally with increase in the dosage of vitamin D₃ supplementation up to 8000 IU/day (SMD_{8000 IU/d}: -2.04 ; 95% CI -3.77 to -0.31), with no further change in effect estimate at higher doses ($P_{\text{dose-response}} < 0.001$, $P_{\text{nonlinearity}} = 0.208$; $n = 31$, **Fig. 1** and **Table 2**).

One study reported the effect of vitamin D₃ supplementation on the odds of depression remission (Marsh et al., 2017). Vitamin D₃ supplementation had no significant effect on depression remission (online Supplementary Figure 4 and **Table 3**).

A total of seven trials with 332 individuals in the intervention group and 309 individuals in the control group provided data on the effect of vitamin D₃ supplementation on the severity of anxiety (Choukri et al., 2018; Dean et al., 2011; Fazelian et al., 2019; Ghaderi et al., 2017, 2020; Khalighi Sikaroudi et al., 2020; Zhu et al., 2020). Our analysis showed that every 1000 IU/day of vitamin D₃ did not significantly reduce the severity of anxiety (online Supplementary Figure 6 and **Table 3**).

Secondary outcomes

The effect of vitamin D₃ supplementation on secondary outcomes is demonstrated in online Supplementary Figure (7–20) and **Table (3)**.<TE: Please check this is supplementary table citation or actual table citation?. Opening bracket missing here.> Vitamin D₃ supplementation had no effects on secondary outcomes including adverse events and different aspects of quality of life.

Grading of the evidence

The GRADE evidence rating for primary and secondary outcomes is presented in online Supplementary Table 8. The certainty of the

Table 1. Subgroup analyses of the effects of vitamin D₃ supplement (each 1000 IU/d) on depressive symptoms

	<i>n</i>	Standardized mean difference (95% CI)	<i>I</i> ² , <i>P</i> _{heterogeneity}	<i>P</i> subgroup difference ^a
All trials	31	−0.32 (−0.43, −0.22)	98%, <0.001	–
Risk of bias				0.92
Low	5	−0.40 (−0.70, −0.09)	96%, <0.001	
Some concerns	12	−0.31 (−0.45, −0.19)	95%, <0.001	
High	14	−0.36 (−0.56, −0.15)	98%, <0.001	
Intervention duration				<0.001
≤8 weeks	8	−0.45 (−0.70, −0.20)	95%, 0.41	
8 to ≤24 weeks	15	−0.47 (−0.70, −0.24)	97%, <0.001	
24 to ≤52 weeks	5	−0.13 (−0.28, 0.02)	97%, 0.01	
>52 weeks	3	0.14 (−0.16, 0.44)	98%, 0.54	
Sex				<0.001
Men	4	−0.21 (−0.43, 0.02)	39%, 0.22	
Women	1	−0.54 (−0.82, −0.47)	–	
Both	26	−0.34 (−0.45, −0.20)	98%, <0.001	
Weight status				0.01
Normal weight	5	−0.53 (−0.74, −0.33)	31%, 0.54	
Overweight/obese	15	−0.43 (−0.64, −0.21)	48%, 0.06	
Not reported	11	−0.11 (−0.29, 0.02)	91%, <0.001	
Vitamin D deficiency				<0.001
Yes	17	−0.26 (−0.42, −0.10)	98%, <0.001	
No	6	0.10 (−0.28, 0.08)	32%, 0.01	
Mixed	8	−0.91 (−1.29, −0.52)	96%, <0.001	
Health status				<0.001
Depressed	15	−0.57 (−0.69, −0.44)	96%, <0.001	
Healthy	6	−0.19 (−0.44, 0.06)	37%, 0.42	
Anxiety	2	−0.37 (−0.76, 0.01)	21%, 0.36	
Cognitive decline	1	−0.38 (−0.65, −0.12)	–	
Schizophrenia	1	0.55 (0.34, 0.86)	–	
Bipolar disorder	1	0.92 (0.66, 1.18)	–	
Multiple sclerosis	1	0.00 (−0.04, 0.04)	–	
Ulcerative colitis	1	−1.20 (−1.42, −0.98)	–	
Irritable bowel syndrome	1	−0.07 (−0.13, 0.00)	–	
Thyroid clinic outpatients	1	−0.35 (−0.50, −0.20)	–	
Knee osteoarthritis	1	0.39 (0.34, 0.45)	–	
Medication use				0.23
Yes	9	−0.54 (−0.85, −0.23)	66%, 0.01	
No	13	−0.28 (−0.40, −0.16)	97%, <0.001	
Mixed	3	−0.44 (−0.71, −0.18)	2%, 0.74	
Not reported	6	−0.51 (−0.79, −0.22)	55%, 0.04	
Baseline risk of depression				0.05
Low	5	−0.12 (−0.27, 0.02)	48%, 0.15	
Medium	5	−0.22 (−0.53, 0.10)	37%, 0.24	
High	21	−0.41 (−0.56, −0.25)	98%, <0.001	

^aObtained by meta-regression analysis.

Table 2. The effects of vitamin D₃ on depressive symptoms from the nonlinear dose–response meta-analysis (standardized mean difference and 95% confidence interval)

Vitamin D ₃ (IU/d)	0 (ref)	1000	3000	5000	6000	7000	8000	9000	12 000	15 000
Depressive symptoms	0	−0.63 (−1.10, −0.16)	−1.44 (−2.25, −0.63)	−1.82 (−2.66, −0.98)	−1.91 (−2.94, −0.89)	−1.98 (−3.32, −0.64)	−2.04 (−3.77, −0.31)	−2.09 (−4.25, 0.06)	−2.27 (−5.78, 1.24)	−2.44 (−7.35, 2.47)

evidence was rated moderate for the effects of vitamin D₃ supplementation on depressive symptoms due to a downgrade for inconsistency and an upgrade for the dose–response gradient. The certainty of evidence was rated very low to low for other outcomes (×Table 3). Of note, the effects of vitamin D₃ supplementation on depressive symptoms surpassed the threshold set as large effect size (SMD: −1.2 to −2) in the nonlinear dose–response meta-analysis, suggesting that supplementation with vitamin D₃ at a dose of 8000 IU/day could lead to a large improvement in depressive symptoms.

Discussion

To our knowledge, this is the first meta-analysis to investigate the dose-dependent effect of vitamin D supplementation on depression and anxiety symptoms in adults. Our results presented evidence of moderate certainty of the beneficial effects of vitamin D supplementation on depressive symptoms in adults. We did not find any significant effects of vitamin D supplementation on depression remission and anxiety symptoms. Vitamin D₃ supplementation had no effects on quality of life.

Evidence from population-based epidemiological studies is consistent with the hypothesis that low serum vitamin D concentration is associated with a higher risk of depression (Anglin et al., 2013; Ju et al., 2013). Furthermore, our findings are consistent with existing evidence presented by meta-analysis of RCTs about the effects of vitamin D supplementation on depressive symptoms. A recent meta-analysis of 11 trials indicated that vitamin D₃ supplementation improved the Beck Depression Inventory score in patients with psychiatric disorders (Jamilian et al., 2019). The results of another recent meta-analysis including 29 trials with 4504 participants indicated that the use of vitamin

D₃ may be beneficial to decrease the incidence of depression and improvement of depression symptoms (Xie et al., 2022). Moreover, another meta-analysis of four trials with 948 participants showed that vitamin D₃ supplementation positively impacted depression rating in patients with major depression (Vellekkatt & Menon, 2019). However, there is some conflicting evidence, suggesting that oral administration of vitamin D₃ did not have a significant effect on the reduction of post-intervention depression score (Lázaro Tomé et al., 2021).

Although the beneficial effects of vitamin D supplementation on depressive symptoms have been ascertained in previous research, the optimum dose of supplementation for reducing depressive symptoms has not been determined in previous studies. Our primary findings indicated that every 1000 IU/day of vitamin D₃ supplementation significantly reduced depressive symptoms. We found that depressive symptoms decreased proportionally with the increase of the dosage of intervention up to 8000 IU/day. We found the greatest impact at 8000 IU/day, and that higher doses had no added values for treatment of depressive symptoms.

Our subgroup analyses indicated a stronger effect on depressive symptoms in women than in men. This is consistent with the literature, which suggests that the relationship between vitamin D₃ deficiency and depression risk was stronger in women than in men (Harse et al., 2021; Landel, Annweiler, Millet, Morello, & Féron, 2016; Lerchbaum, 2014). There are physiological interactions between the effects of vitamin D and estrogen. Vitamin D deficiency may lead to lower estrogen levels, which can cause depression. This can make women more vulnerable to the effects of vitamin D deficiency (Harse et al., 2021; Landel et al., 2016; Lerchbaum, 2014). However, there was only one trial in women, and the credibility of subgroup difference was rated low. Therefore, the potential sex difference in the effect of vitamin D₃ supplementation on depressive symptoms should be interpreted with caution.

Our subgroup analyses also highlighted a significant subgroup difference by intervention duration, where trials with an intervention duration of ≤8 weeks and 8 to ≤24 weeks indicated a stronger effect than those with 24 to ≤52 weeks. Of note, an increasing effect was seen among trials with an intervention duration of >52 weeks. Regarding the length of the intervention, ‘8 weeks’ was identified as the window of time that may start the vitamin D response, whether in the prevention or therapy of depression (Xie et al., 2022). The decline in the efficacy of vitamin D supplementation in reducing depressive symptoms can be explained by attrition bias, lower compliance, and higher dropout in trials with longer intervention durations.

There are several possible physiological mechanisms to explain why vitamin D₃ supplementation is effective in treating depression. These mechanisms include its impacts on cellular signaling, neurotropic and immunomodulatory processes, serotonin synthesis, expression of mitochondrial proteins, increasing the expression

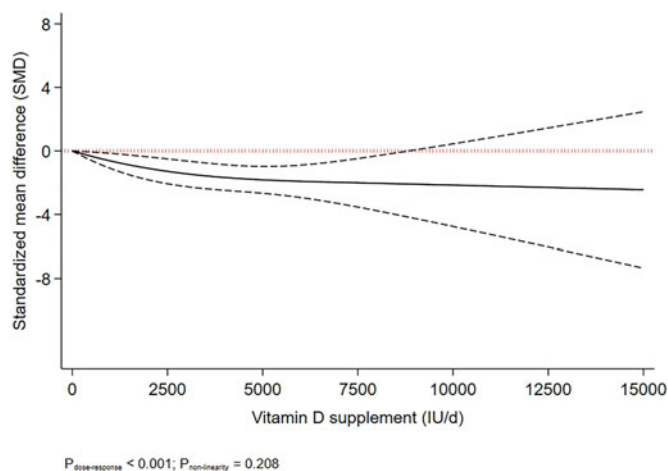


Figure 1. Dose-dependent effect of vitamin D supplement on depressive symptoms. Solid lines represent standardised mean difference and dashed lines represent 95 % CI.

Table 3. The effect of vitamin D₃ supplementation (per 1000 IU/day) on primary and secondary outcomes

Outcome (s)	Number of trials (participants)	Type of effect size	Effect size (95% CI)	GRADE certainty
Depressive symptoms	31 (24 189)	Standardized mean difference	-0.32 (-0.43, -0.22)	Moderate
Depression remission	1 (25)	Odds ratio	0.20 (0.03, 1.15)	Low
		Risk difference	-0.33 (-0.64, -0.03)	Low
Severity of anxiety	7 (641)	Standardized mean difference	-0.33 (-0.92, 0.25)	Low
Adverse events	8 (3672)	Odds ratio	1.20 (1.00, 1.45)	Very low
		Risk difference	0.01 (0.01, 0.02)	Low
Serious adverse events	2 (2115)	Odds ratio	1.00 (0.51, 1.97)	Low
		Risk difference	0.00 (-0.11, 0.11)	Low
Comorbidity index	1 (726)	Standardized mean difference	0.18 (-0.90, 1.26)	Low
Stress	1 (51)	Standardized mean difference	0.18 (-0.90, 1.26)	Low
Overall quality of life	2 (120)	Standardized mean difference	-0.24 (-0.63, 0.15)	Low
Bodily image	1 (74)	Standardized mean difference	-0.30 (-0.99, 0.39)	Low
Dysphoria	1 (74)	Standardized mean difference	-0.40 (-1.09, 0.29)	Low
Food avoidance	1 (74)	Standardized mean difference	0.02 (-0.41, 0.45)	Low
Healthy worry	1 (74)	Standardized mean difference	-0.16 (-0.63, 0.31)	Low
Relationship	1 (74)	Standardized mean difference	-0.13 (-0.50, 0.24)	Low
Sexual	1 (74)	Standardized mean difference	0.00 (-1.47, 1.47)	Low
Social reaction	1 (74)	Standardized mean difference	0.00 (-0.35, 0.35)	Low

of vitamin D₃ receptors in important brain regions, and decreasing levels of C-reactive protein, as an inflammatory marker linked to depression (Geng et al., 2019). Moreover, oxidative stress can be a contributing factor to depression. Vitamin D has important antioxidant properties and thus, may have therapeutic effects against depressive symptoms (Penckofer et al., 2022; Thurfah, Christine, Bagaskhara, Alfian, & Puspitasari, 2022; Vellekkatt & Menon, 2019). Vitamin D may also affect the serotonin system and maintain circadian rhythms, which are linked to depression (Casseb, Kaster, & Rodrigues, 2019; Ceolin, Mano, Hames, Antunes, & Moreira, 2021).

Additionally, the possible benefits of vitamin D on physical health in the long term were as follows: Vitamin D supplementation has been shown to have long-lasting benefits such as reducing the risk of falls and fractures, as demonstrated in the ViDA trial (Khaw et al., 2017). It has also been found to lower central blood pressure among vitamin D deficient participants (Sluyter et al., 2017) and lower the risk of overall mortality (Chowdhury et al., 2014).

Despite the aforementioned findings, we could not find a significant association between vitamin D₃ supplementation and depression remission. Furthermore, we could not observe a significant relationship between vitamin D₃ supplementation and the severity of anxiety. Nevertheless, some previous studies demonstrated that vitamin D supplementation was effective in alleviating anxiety symptoms (Borges-Vieira & Cardoso, 2023; Eid et al., 2019; Zaromytidou et al., 2022). These controversies may be attributed to the low number of trials available in this field, design of the studies, initial serum 25(OH)D concentrations of the participants, dose and type of vitamin D supplement (D₂ v. D₃), intervention duration, method of supplementation and age of the target group.

There were several strengths to our study. Our study updated earlier findings by including more recent RCTs in this field (Alavi et al., 2019; Alghamdi et al., 2020; de Koning et al., 2019; Eid et al., 2019; Fazelian et al., 2019; Gaughran et al., 2021; Ghaderi et al., 2020; Hansen et al., 2019; Kaviani et al., 2020; Kusmiyati et al., 2020; Omidian et al., 2019; Sharifi et al., 2019; Vellekkatt et al., 2020; Zheng et al., 2019; Zhu et al., 2020). Additionally, to the best of our knowledge, this is the first meta-analysis that investigated the dose-dependent effects of vitamin D₃ supplementation on depression and anxiety symptoms in adults. We also applied the GRADE approach to rate the certainty of evidence. The Cochrane risk of bias tool (Version 2.0) was utilized to assess the methodological quality of included RCTs. Lastly, Pre-specified subgroup analyses were conducted based on various study characteristics, including risk of bias, intervention duration, sex, weight status, vitamin D deficiency, health status, medication use, and baseline risk of depression. This comprehensive approach enabled the exploration of potential effect modifiers.

However, there were also some limitations in the present meta-analysis. First, other factors may act as a moderator in the association between vitamin D supplementation and depressive symptoms. Although we did several subgroup analyses by participants and study characteristics, several unknown variables can affect the results. Second, we had limited evidence about the effects of vitamin D supplementation on depression remission and severity of anxiety. In addition, a subgroup analysis by intervention duration suggested that vitamin D supplementation was no longer effective in reducing depressive symptoms at follow-up longer than 52 weeks. Also, we included adults regardless of their depression, anxiety, and health status. Finally, despite efforts to identify all relevant studies, publication bias may have influenced

the findings, as studies with statistically significant results are more likely to be published. Therefore, more trials are needed to test the long-term efficacy of vitamin D supplementation on depressive symptoms, as well as on depression remission and anxiety symptoms.

Conclusion

Our dose–response meta-analysis of randomized trials demonstrated that vitamin D supplementation may result in a large improvement in depressive symptoms at follow-up shorter than 24 weeks. The greatest impact was seen at 8000 IU/day, and higher doses had no added value in reducing depressive symptoms. Vitamin D supplementation had no effects on depression remission and anxiety symptoms. More trials with high quality are needed to test the long-term efficacy of vitamin D supplementation, considering baseline vitamin D levels of individuals, on depressive symptoms, as well as on depression remission and anxiety symptoms.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291724001697>.

Data availability statement. The data sets generated or analyzed during the current study are not publicly available but are available from the corresponding author at reasonable request.

Acknowledgements. None.

Author contributions. SS-B designed the research process. SG and SZM searched the databases and extracted the data and necessary information. AJ performed statistical analyses. SG wrote the manuscript. AJ and SS-B critically revised the manuscript. All authors confirmed the final manuscript for submission. SS-B is the guarantor.

Funding statement. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Competing interests. None.

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