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The effect of vitamin D supplement on negative emotions: A systematic review and meta-analysis

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Abstract

Background: The several meta-analyses of the effect of vitamin D on depression have produced inconsistent results and studies dealing with anxiety were not incorporated. There has been no comprehensive analysis of how results are affected by the nature of the sample or the dosage and duration of supplementation. The study is aimed to investigate whether vitamin D supplementation reduces negative emotions and to analyze the possible influence of sample and regimen.

Method: We conducted a systematic review and meta-analysis of randomized controlled trials comparing the effect of vitamin D and placebo on negative emotion. Databases were searched for relevant articles published before February 2019.

Results: The analysis covered 25 trials with a total of 7,534 participants and revealed an effect of vitamin D on negative emotion (Hedges' $g = -0.4990$, 95% CI [−0.8453, −0.1528], $p = .0047$, $I^2 = 97.7\%$). Subgroup analysis showed that vitamin D had an effect on patients with major depressive disorder and on subjects with serum 25(OH)D levels ≤50 nmol/L. The pooled data from trials of vitamin D supplementation lasting ≥8 weeks and dosage ≤4,000 IU/day indicated that vitamin D had an effect.

Conclusions: Our results support the hypothesis that vitamin D supplementation can reduce negative emotions. Patients with major depressive disorder and individuals with vitamin D deficiency are most likely to benefit from supplementation. But to interpret the results with high heterogeneity should still be cautious.

KEYWORDS

anxiety/anxiety disorders, depression, dysthymic disorder, mood disorders, pharmacotherapy

1 | INTRODUCTION

The association between vitamin and mental health has been explored extensively (Landel & Wion, 2017; Lim et al., 2016). In previous decades, the effects of vitamin B were the major target of investigation (Mikkelsen, Stojanovska, & Apostolopoulos, 2016; Sachdev et al., 2005; Tiemeier et al., 2002), but vitamin D has also attracted much attention in recent years (Berk et al., 2007; Berridge, 2017; Landel & Wion, 2017; McGrath, 2017; Pittampalli, Mekala, Upadhyayula, & Lippmann, 2018). Vitamin D is a secosteroid hormone and is involved in the absorption of calcium and phosphorus in the intestine as well as being important for osteogenesis (Holick, 2004). There are several forms of vitamin D, D1–D5; D2 (ergocalciferol) and D3 (cholecalciferol) are the forms most frequently used in oral supplements (Hammami & Yusuf, 2017). Exposure to light is required for manufacture of vitamin D, so limited exposure to sunlight and a predominance of indoor activities may cause vitamin D deficiency (Bouillon, 2017). As well as being involved in calcium regulation, vitamin D also acts on the central nervous system (Hausler & Weber, 2019). Vitamin D3 is

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able to cross the blood–brain barrier (Kalueff & Tuohimaa, 2007). Vitamin D receptors are widespread in several brain regions, such as prefrontal cortex, substantia nigra, and hypothalamus (Bertone-Johnson, 2009; Humble, 2010; Kalueff & Tuohimaa, 2007). Vitamin D has also been related to synthesis of monoamines (serotonin, dopamine, and noradrenaline) and its steroidal features may allow it to modulate the activity of GABA-A receptors (Bertone-Johnson, 2009; Humble, 2010; Maguire, Ferando, Simonsen, & Mody, 2009; Marsh, Penny, & Rothschild, 2017; Panzica & Melcangi, 2008; Patrick & Ames, 2014). In addition several studies have shown that vitamin D is associated with nerve growth factor enhancement and antioxidant effects in the central nervous system (Humble, 2010; Moradi, Sohrabi, Taheri, Khodashenas, & Movahedi, 2018; Pertile, Cui, Hammond, & Eyles, 2018; Sepehrmanesh et al., 2016). It is therefore biologically plausible that vitamin D would have psychiatric applications and the possibilities are worthy of investigation (Bertone-Johnson, 2009; Humble, 2010).

There have been many studies exploring the potential associations between vitamin D and psychological phenomena or psychiatric disorders, including depression (Alavi, Khademalhoseini, Vakili, & Assarian, 2018; Amini, Jafarirad, & Amani, 2018; Bertone-Johnson et al., 2012; Dumville et al., 2006; Ghaderi et al., 2017; Jorde, Sneve, Figenschau, Svartberg, & Waterloo, 2008; Khoraminya, Tehrani-Doost, Jazayeri, Hosseini, & Djazayery, 2013; Pittampalli et al., 2018), anxiety (Armstrong et al., 2007; Huang et al., 2014; Pu et al., 2018), psychotic disorders (Chiang, Natarajan, & Fan, 2016), cognitive impairment (Degner, 2016; Etgen, Sander, Bickel, Sander, & Forstl, 2012), sleep disturbance (Gao et al., 2018; Ghaderi et al., 2017), autism spectrum disorder (Moradi et al., 2018; Patrick & Ames, 2014), and substance use (Ghaderi et al., 2017). Studies investigating the relationship between vitamin D and depression are the most common. Several studies found that depression subsided after vitamin D supplement (Alavi et al., 2018; Ghaderi et al., 2017; Jorde et al., 2008; Khoraminya et al., 2013). This phenomenon has been discussed in several systematic reviews and meta-analyses, although the conclusions are somewhat controversial (Anglin, Samaan, Walter, & McDonald, 2013; Gowda, Mutowo, Smith, Wluka, & Renzaho, 2015; Li et al., 2014; Marsh et al., 2017; Sarris et al., 2016; Shaffer et al., 2014; Sparling, Henschke, Nesbitt, & Gabrysch, 2017; Spedding, 2014; Vellekkatt & Menon, 2018). Other research indicates that serum level of vitamin D is negatively associated with the severity of depression (Jorde et al., 2008; Jozefowicz, Rabe-Jablonska, Wozniacka, & Strzelecki, 2014; Kim, Seok, & Kim, 2016; Kjaergaard et al., 2012; Kolade, 2012; van den Berg et al., 2016). In addition anxiety and depression are often comorbid in clinical practice; they can be examined together in a negative emotions framework (Tully, Baker, Turnbull, Winefield, & Knight, 2009). There have also been studies investigating the relationship between vitamin D and anxiety; some of which found that vitamin D supplementation relieved anxiety (Jamilian et al., 2018; Tartagni et al., 2016). Therefore, although meta-analyses of the effects of vitamin D supplementation on depression have already been carried out we believe that combining studies of the effects of vitamin D on depression with studies looking at the relationship between vitamin D and anxiety may improve our understanding of the psychological effects of vitamin D.

Although there have been some meta-analyses exploring the influence of vitamin D on depression, we have noted that they have several limitations. The conclusions of previous meta-analyses were controversial, though some results (such as the positive effect on clinically meaningful depression) were similar (Anglin et al., 2013; Gowda et al., 2015; Li et al., 2014; Sarris et al., 2016; Shaffer et al., 2014; Sparling et al., 2017; Spedding, 2014; Vellekkatt & Menon, 2018). An explanation of the inconsistent results is the issue of "trials with flaw," which means the study population may not be vitamin D deficient, or the regimen of vitamin D supplement may be inadequate (Spedding, 2014). Our review revealed that, in addition to the flawed trials issue, the results were influenced by several factors, such as age and depression status (Anglin et al., 2013; Li et al., 2014; Sarris et al., 2016; Shaffer et al., 2014; Sparling et al., 2017; Spedding, 2014; Vellekkatt & Menon, 2018). The factors described in situations with flaw (such as inadequate dosage or duration, subjects without vitamin D deficiency) can be analyzed separately; however, the subgroup analyses results about these factors were also inconsistent in previous meta-analyses (Anglin et al., 2013; Li et al., 2014; Sarris et al., 2016; Shaffer et al., 2014; Sparling et al., 2017; Spedding, 2014; Vellekkatt & Menon, 2018). We believed, therefore, that in addition to extending the scope of analysis to include anxiety studies, performing subgroup analyses or meta-regression with the above factors would provide more insight into possible clinical applications of vitamin D.

On the basis of the evidence reviewed above we reviewed relevant literature and performed a new meta-analysis, which primary aim was to determine whether vitamin D supplementation reduces negative emotions, including the level of depression and anxiety. We also analyzed how the effects of vitamin D supplementation varied across groups (patients with major depressive disorder; healthy individuals; elderly people; people with vitamin D deficiency) and with baseline serum level of vitamin D and dose and duration of supplementation. Our approach is to integrate as more data as possible, then use subgroup analyses, meta-regression to investigate "whether vitamin D supplement is helpful for managing negative emotions in specific situations." This meta-analysis is not only focused on ones with definite diagnoses of anxiety or depression; because for individuals without diagnoses, whether vitamin supplement works on improving emotional disturbance is also a common question.

2 | METHODS AND MATERIALS

2.1 | Data sources and search strategy

This systematic review and meta-analysis was prepared according to the PRISMA statement guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). We conducted an electronic search of PubMed, the Cochrane Library, EMBASE, and PsychoINFO from the earliest available date to February 2019. The literature search was conducted by three researchers (Y.-C. Cheng, Y.-C. Huang, and W.-L. Huang) and employed the three sets of key

terms: ("vitamin D" OR "25-hydroxyvitamin D" OR "25-hydroxyvitamin D3" OR "25 hyrdoxycalciferol" OR "1,25 dihydroxyvitamin D3" OR "1,25 dihydroxycholecalciferol" OR "25(OH)D" OR "cholecalciferol" OR "calcifero" OR "ergocalciferol") AND ("depression" OR "*dysthymia*" OR "*anxiety*" OR "*mood disorders*" OR "*negative emotion*" OR "*negative affect*") AND ("*controlled clinical trial*" OR "*randomized study*" OR "*randomized trial*"). Several terms for each of these three concepts were used to search keywords, text, titles, and subject headings, as appropriate for each database. Detailed searching string of Pubmed was showed in the Appendix of this article, and searching strings of other databases could be found in the Supplementary Material. The full texts of all publications with titles meeting the inclusion were retrieved and reviewed. Original studies investigating the effect of vitamin D supplementation on negative emotions, specifically depression and anxiety, were eligible for review. Additional eligible studies were sought by searching the reference lists of primary articles and relevant reviews to try to uncover relevant publications not retrieved through the electronic search.

2.2 | Inclusion and exclusion criteria

We aimed to determine the effects of vitamin D supplementation on symptoms of depression and anxiety in several clinical and nonclinical populations: people with depression, anxiety, or comorbid depression and anxiety and people with subclinical symptoms of depression or anxiety. Eligible studies were: (a) randomized clinical trials; (b) clinical trials in which vitamin D supplements were administered and emotion symptoms were measured at baseline and at the end of the intervention in both treatment and control groups; (c) published in English. Exclusion criteria were: (a) studies performing light therapy; (b) comparing the effects of different vitamin D doses (without placebo); (c) articles reporting a case or series of cases; (d) conference abstracts for which no full text was available.

2.3 | Data extraction and quality assessment

Three investigators (Y.-C. Cheng, Y.-C. Huang, and W.-L. Huang) independently extracted relevant information from the included studies and evaluated the methodological quality of eligible trials using the Cochrane Collaboration risk of bias tools (Higgins et al., 2011). The following data on studies were obtained: last name of first author; year of publication; geographical location; participants' characteristics; study design; sample and groups sizes; duration and dosage of vitamin D supplementation; baseline serum level of 25(OH)D; baseline and endpoint emotion scores. The means and standard deviations of changes from baseline were extracted. If the studies reported data of emotion scores using several different scales, priority was given to a combined measure of depression and anxiety, followed by a validated measure of depression, then anxiety. For the different depression scales in a single study, we gave preference to the Beck Depression Inventory (BDI) or Beck Depression Inventory-II (BDI-II) for self-rating questionnaires and the Hamilton Depression/Anxiety Rating Scale (HAM-D/HAM-A) for rater-administered scales. The incorporated measurements should be well-known or have psychometric data, such as BDI, BDI-II, HAM-A, Hospital Anxiety, and Depression Scale, General Health Questionnaire.

Where emotional symptoms had been assessed at multiple time points we only extracted the data for baseline and endpoint. In the case of studies where relevant data were unreported we contacted the authors to request the necessary information. All potentially relevant manuscripts were independently reviewed by two investigators (Y.-C. Cheng and Y.-C. Huang) and areas of disagreement or uncertainty were adjudicated by a third investigator (W.-L. Huang).

The Cochrane Collaboration's tool was used to evaluate seven domains of risk of bias: selection bias (sequence generation and concealment), performance bias (blinding of participants and assessors), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective outcome reporting, and other bias. Each domain was classified as having a low, high, or unclear (if there was insufficient information to make a judgment) risk of bias. Disagreements between the two investigators were resolved through discussion.

2.4 | Efficacy outcomes

The primary efficacy outcome for the negative emotion were measured by the change in the scores of depression, anxiety, or related emotions before and after intervention in vitamin D and control groups, measured using any clinically validated rating scale.

2.5 | Statistical analysis

For each comparison between vitamin D and placebo group, the total differences in changes in symptoms of depression and anxiety were pooled to compute the overall effect sizes of vitamin D intervention. Using the data reported in each study, we estimated the effect size by calculating standardized mean differences (*SMD*; Hedges' *g*) with 95% confidence intervals. Hedges' *g* is related to Cohen's *d* and can be interpreted using the same conventions: a value of 0.2 indicates a small effect, a value of 0.5 indicates a medium effect, and a value of 0.8 or larger indicates a large effect (Cohen, 1988). An added benefit of Hedges' *g* is correction for the biases found in small sample sizes. A negative value indicates a larger change in the intervention group than the control group. Where the standard deviations (*SDs*) of the change scores were not reported we calculated them using the formula (SD = square root $[(SD \text{ pretreatment})^2 + (SD \text{ posttreatment})^2 - (2R \times SD \text{ pretreatment} \times SD \text{ posttreatment})]$, assuming a correlation coefficient (R) = 0.5). When only the standard errors of the means (*SEMs*) were reported we calculated *SDs* by multiplying *SEMs* by the square root of the sample size. Where median and range were reported we calculated means and *SDs* using the formulae given in the Cochrane guidelines (Higgins & Green, 2011; Hozo, Djulbegovic, & Hozo, 2005). Possible sources of heterogeneity or inconsistency in the magnitude or direction of effects were investigated. Heterogeneity was estimated using the

I^2 test (Higgins & Thompson, 2002). A random effect model was employed if significant heterogeneity was detected (Cochrane's Q $p < .1$ and $I^2 > 50\%$). Subgroups analysis were used to assess the potential variables that may have impacted the effects of vitamin D supplementation on negative emotions. The potential variables contained: duration of vitamin D supplementation (<8 weeks; ≥8 weeks), dosage of vitamin D (≤4,000 IU/day; >4,000 IU/day or ≤2,000 IU/day; >2,000 IU/day), baseline levels of 25(OH)D (≤50 nmol/L; >50 nmol/L), participant type (patients with major depressive disorder; healthy people), mean age of sample (18–65-year-old; >65-year-old). Publication bias was examined using a funnel plot of effect size against the standard error for asymmetry. Egger's regression test was also used to assess publication bias (Egger, Davey Smith, Schneider, & Minder, 1997). Leave-one-study-out sensitivity analysis was performed, excluding trials one at a time to determine whether this affected the pooled effects. Sensitivity analysis was also conducted by excluding studies with biological flaws, that is those where the intervention was inappropriate, produced the opposite effect to that which was intended, did not increase serum levels of vitamin D, those where baseline 25(OH)D level was not reported and those which included patients with normal levels of 25(OH)D (Spedding, 2014).

To explore the potential effect of trial-level modifiers we carried out several meta-regressions, each including a single covariate. Meta-regression allows the investigation of the effects of continuous and categorical characteristics. Three covariates were defined: mean age, mean daily dosage of vitamin D, and baseline serum 25(OH)D level. All meta-analytic computations were performed with the R software (R x 64 3.5.1; The Cochrane Collaboration, Oxford, UK).

3 | RESULTS

3.1 | Baseline characteristics of included studies

Figure 1 summarizes the review flowchart in accordance with the PRISMA statement (Moher et al., 2009). Twenty-seven of the 182 original studies screened met the inclusion criteria for qualitative synthesis. A summary of studies included in the qualitative review and their results are presented in Table 1. Eleven studies concluded that vitamin D supplementation had clinical benefit on negative emotion, while 16 studies found no difference between vitamin D and placebo. Two of the studies included in the qualitative review were excluded from quantitative analysis because they did not report sufficient data and the corresponding authors could not be contacted. The 25 trials included in the meta-analysis were conducted in Australia (4 trials: Dean et al., 2011; Lansdowne & Provost, 1998; Mousa, Naderpoor, de Courten, & de Courten, 2018; Sanders et al., 2011), Iran (8 trials: Alavi et al., 2018; Ghaderi et al., 2017; Jamilian et al., 2018; Khoraminya et al., 2013; Mozaffari-Khosravi, Nabizade, Yassini-Ardakani, Hadinedoushan, & Barzegar, 2013; Raygan, Ostadmohammadi, Bahmani, & Asemi, 2018; Sepehrmanesh et al., 2016; Vaziri et al., 2016), Norway (4 trials: Grung et al., 2017; Jorde & Kubiak, 2018; Jorde et al., 2008; Kjaergaard et al., 2012), United States (4 trials: Arvold et al., 2009; Bertone-Johnson et al., 2012; Mason et al., 2016; Yalamanchili & Gallagher, 2012), Denmark (1 trial: Frandsen, Pareek, Hansen, & Nielsen, 2014), China (1 trial: Wang et al., 2016), Netherlands (1 trial: Rolf et al., 2017), Sweden (1 trial: von Berens et al., 2018), and New Zealand (1 trial: Choukri, Conner, Haszard, Harper, & Houghton, 2018). Sample size ranged from 34 to 726. Dosage of vitamin D varied from 400 to about 200,000 IU. Duration of intervention ranged between 5 days and 36 months. The results of quality assessment of the trials included in the meta-analysis, based on the Cochrane Collaboration tool and the authors' judgments about each risk of bias item, are presented in Supporting Information Figures S1 and S2.

3.2 | Overall effects of vitamin D supplementation on negative emotion

Table 2 displays result of the main meta-analysis of negative emotion outcome. The main meta-analysis included 25 trials involving 7,534 participants and yielded a pooled effect of vitamin D on negative emotion (Hedges' $g = -0.4990$, 95% CI [−0.8453, −0.1528], $p = .0047$, $I^2 = 97.7\%$; Figure 2). Visual inspection of a funnel plot (Supporting Information Figure S3) and the use of an Egger test did not suggest the presence of publication bias ($t = 1.53$, $df = 23$, $p = .1394$).

3.3 | Subgroup analysis

In subgroup analysis a vitamin D effect was observed in the subset of trials evaluating anxiety symptoms (Hedges' $g = -0.2404$, 95% CI [−0.4694, −0.0115], $p = .0396$, $I^2 = 52.6\%$) and in people with major depressive disorder (Hedges' $g = -1.0976$, 95% CI [−1.5538, −0.6413], $p < .0001$, $I^2 = 79.7\%$; Figure 3), but not healthy people (Hedges' $g = -0.1114$, 95% CI [−0.2488, 0.0260], $p = .1121$, $I^2 = 73.5\%$). If separating the level of depression according to the common cut-off values of scales, no matter above or under the cut-off values, the effects of vitamin D on negative emotions were not significant. In trials where vitamin D was administered for ≥8 weeks it had an effect on negative emotion (Hedges' $g = -0.4794$, 95% CI [−0.8444, −0.1145], $p = .0100$, $I^2 = 97.9\%$). The effects of vitamin D were both significant for the duration 8–12 weeks and at least 12 weeks. In the subset of trials where vitamin D was administered to people with baseline serum 25(OH)D levels ≤50 nmol/L, it also had an effect (Hedges' $g = -0.3262$, 95% CI [−0.5404, −0.1121], $p = .0028$, $I^2 = 71.1\%$), but not for trails including people with baseline serum 25(OH)D levels >50 nmol/L with (Hedges' $g = -0.5769$, 95% CI [−1.1555, 0.0017], $p = .0507$, $I^2 = 98.9\%$). The pooled data showed that vitamin D supplementation at doses of ≤4,000 IU/day had an effect on negative emotion (Hedges' $g = -0.2311$, 95% CI [−0.3664, −0.0958], $p = .0008$, $I^2 = 76.6\%$), but doses >4,000 IU/day did not (Hedges' $g = -0.8105$, 95% CI [− 1.9859, 0.3649], $p = .1766$, $I^2 = 98.9\%$). Using a threshold of 2,000 IU/day, the pooled data showed an effect of vitamin D supplementation at doses ≤2,000 IU/day (Hedges' $g = -0.1675$, 95% CI [−0.3288, −0.0062], $p = .0418$, $I^2 = 75.7\%$), and doses >2,000 IU/day

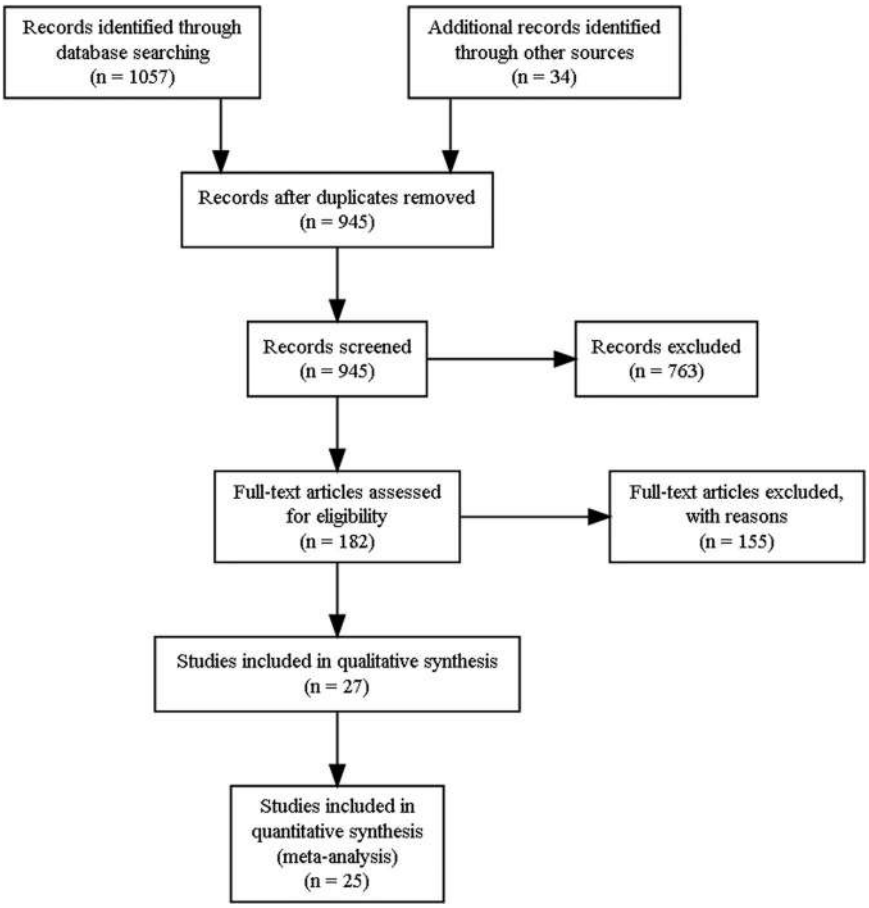

FIGURE 1 Flowchart of the study selection process for the systematic review and meta-analysis

(Hedges' $g = -0.6081$, 95% CI [−1.2095, −0.0068], $p = .0475$, $I^2 = 98.1\%$). There was a vitamin D effect in pooled data from trials where the groups' mean ages were between 18 and 65 years (Hedges' $g = -0.5464$, 95% CI [−1.0637, −0.0292], $p = .0384$, $I^2 = 98.2\%$), but not for the subset of trials including people aged >65-year-old (Hedges' $g = -0.3761$, 95% CI [−0.7668, 0.0147], $p = .0593$, $I^2 = 89.9\%$). There was a vitamin D effect in the subset of trials without flaws (Hedges' $g = -0.721$, 95% CI [−1.3837, −0.0583], $p = .0330$, $I^2 = 98.1\%$) but not in those with flaws (Hedges' $g = 0.0091$, 95% CI [−0.0464, 0.0645], $p = .7490$, $I^2 = 0\%$). Finally, considering the status of combining antidepressants, the effects of vitamin D on negative emotions were not significant for ones taking and not taking antidepressants. However, for studies not reporting using antidepressants or not, the effect of vitamin D was significant. The results of these subgroup analyses were shown in Table 2 and Supporting Information Figures S4–S10.

3.4 | Sensitivity analysis

The stability of the meta-analysis and subgroup analyses was tested through sensitivity analysis. In the following subgroup analyses the sensitivity analysis indicated instability, and so these results should be treated with caution: trials evaluating the effect of vitamin D on anxiety symptoms; people with baseline serum 25(OH)D levels >50 nmol/L; doses ≤2,000 IU/day; doses >2,000 IU/day; trials where the groups' mean ages were between 18 and 65 years; trials without flaws.

3.5 | Meta-regression

Analyses of study-level covariates showed no effects of age, vitamin D dosage, baseline 25(OH)D levels, or treatment duration (Supporting Information Table S1 and Supporting Information Figure S11). The results indicated that the moderator variables had no influence on our results ($p > .05$).

4 | DISCUSSION

Our analyses yielded the following main findings. (a) Overall, vitamin D supplementation reduces negative emotion. (b) This effect is greater if flawed trials are excluded from the analysis. (c) In patients with major depressive disorder vitamin D supplementation has a large effect (Hedges' $g = -1.1086$). (d) In healthy people vitamin D does not affect emotion. (e) Vitamin D reduces anxiety, although the effect is small (Hedges' $g = -0.2404$). (f) Vitamin D affects the level of negative emotions if supplements are taken for longer than 8 weeks. (g) High doses (>4,000 IU/day) of vitamin D are not effective. (h) Vitamin D supplementation reduces negative emotion in people with

TABLE 1 Characteristics of the included studies

Author year	Country	Population	Dose	Sample size (vitamin D vs. control)	Mean age (*SD* or range)	Duration	Baseline 25 (OH) D (nmol/L)	Assessment scale measure	Major finding	Study design
Lansdowne and Provost (1998)	Australia	Healthy subjects during winter	400 IU/day 800 IU/day	44 (22 vs. 22)	22.0 (6.57)	5 days	NR	PANAS	Favoring vitamin D group	RCT
Dumville et al. (2006)	United Kingdom	Women ≥70 years old	800 IU/day	2,117 (912 vs. 1,205)	Vitamin D: 77.2 (5.2); Placebo: 76.6 (5)	6 months	NR	SF-12; MCS	No difference	RCT
Jorde et al. (2008)	Norway	Obese adults	2,000 IU/day 4,000 IU/day	334 (106 vs. 116 vs. 112)	47.0 (21–70)	12 months	52.5 (11.1–111.5)	BDI	Favoring vitamin D group, but two doses were similar	RCT
Arvold et al. (2009)	United States	Mild and moderate vitamin D deficiency outpatients	50,000 IU/week	90 (48 vs. 42)	Vitamin D: 59.7 (14); Placebo: 57.8 (15.8)	8 weeks	Vitamin D: 44.67 (8.8); Placebo: 45.1 (10)	FIQ	No difference	RCT
Dean et al. (2011)	Australia	Healthy young adults	5,000 IU/day	128 (63 vs. 65)	Vitamin D: 21.5 (2.9); Placebo: 22.1 (15.8)	6 weeks	Vitamin D: 76.2 (19.1); Placebo: 77.3 (20.1)	BDI; STAI	No difference	RCT
Sanders et al. (2011)	Australia	Community older women (≥70 years old)	500,000 IU/year	2,012 (1,001 vs. 1,011)	Vitamin D: 76.4 (73.1–80.5); Placebo: 76.3 (73.1–79.8)	3–5 years	53	SF-12; MCS; GHQ	No difference	RCT
Kjaergaard et al. (2012)	Norway	Healthy with low 25(OH) D levels	40,000 IU/week	230 (120 vs. 110)	Vitamin D: 53.4 (10.3); Placebo: 53.3 (10.1)	6 months	47.4 (15.8)	BDI-II; HADS; MADRS	No difference	RCT
Bertone-Johnson et al. (2012)	United States	Women with low 25(OH) D levels	400 IU/day	2,252 (1,109 vs. 1,143)	NR	2 years	52.9 (21.1)	Burnam scale	No difference	RCT
Yalamanchili and Gallagher (2012)	United States	Older postmenopausal women	0.25 g/bi-day (2 million IU)	246 (123 vs. 123)	Vitamin D: 71.8 (3.4); Placebo: 71.1 (3.7)	36 months	Vitamin D: 76.5 (23.5); Placebo: 79.3 (27.5)	GDS-30	No difference	RCT
Khoraminya et al. (2013)	Iran	MDD outpatients	1,500 IU/day	40 (20 vs. 20)	Vitamin D: 38.1 (10.1) Placebo: 39.7 (8.2)	8 weeks	Vitamin D: 58.8 (10.1); Placebo: 57.5 (11)	BDI-II; HAM-D	Favoring vitamin D group	RCT

TABLE 1 (Continued)

Author year	Country	Population	Dose	Sample size (vitamin D vs. control)	Mean age (*SD* or range)	Duration	Baseline 25 (OH) D (nmol/L)	Assessment scale measure	Major finding	Study design
Mozaffari-Khosravi et al. (2013)	Iran	MDD patients	300,000 IU/ 3 months 150,000 IU/ 3 months	120 (40 vs. 40 vs. 40)	Vitamin $D_{300,000}$: 32.6 (9) Vitamin $D_{150,000}$: 32.7 (8.4); Placebo: 33 (8.8)	3 months	Vitamin $D_{300,000}$: 21.3; Vitamin $D_{150,000}$: 23; Placebo: 25.4	BDI-II	Favoring vitamin D group, higher dose group was more effective than low-dose group	RCT
Frandsen et al. (2014)	Denmark	Healthy	2800 IU/day	34 (16 vs. 18)	Vitamin D: 44.2 (11.5) Placebo: 44.4 (10)	12 weeks	Majority with sufficient level	SIGH-SAD	No difference	RCT
Mason et al. (2016)	United States	Overweight (BMI ≥ 25) postmenopausal women	2,000 IU/day	180 (89 vs. 91)	59.6 (5.1)	12 months	53.5 (12.7)	BSI-18; SF-36	No difference	RCT
Wang et al. (2016)	China	Dialysis patients	50,000 IU/week	726 (362 vs. 364)	NR	52 weeks	Vitamin D: 54.8 (10.2); Placebo: 58 (14.5)	BDI-II	Favoring vitamin D group in dialysis patients with vascular depression	RCT
Vaziri et al. (2016)	Iran	Pregnant women	2,000 IU/day	150 (75 vs. 75)	Vitamin D: 26.4 (4.9); Placebo: 26.2 (4.3)	12 weeks	Vitamin D: 32 (19.7); Placebo: 29.7 (16)	EPDS	Favoring vitamin D group	RCT
Marsh et al. (2017)	United States	Bipolar depression patients	5,000 IU/day	33 (16 vs. 17)	Vitamin D: 45.2 (13.3); Placebo: 43.3 (12.9)	12 weeks	Vitamin D: 48.5 (13.8); Placebo: 48 (14.5)	MADRS; HAM-A	No difference	RCT
Sepehrmanesh et al. (2016)	Iran	MDD patients	50,000 IU/week	36 (18 vs. 18)	Vitamin D: 36.5 (8.7); Placebo: 36.1 (6.9)	8 weeks	Vitamin D: 34 (19.7); Placebo: 23 (15)	BDI-II	A trend favoring vitamin D group	RCT
Rolf et al. (2017)	Netherlands	Patients with multiple sclerosis	14,000 IU/day	40 (20 vs. 20)	Vitamin D: 37.6 (9.6); Placebo: 38.5 (7.8)	48 weeks	Vitamin D: 53 (43–63); Placebo: 58 (38–82)	HADS-D	No difference	RCT
Grung et al. (2017)	Norway	Healthy adolescents	38 μg/day (1,600 IU/day)	46 (23 vs. 23)	NR	3–4 months	Vitamin D: 44 (14) Placebo: 39 (16)	YSR-CBCL	No difference	RCT

(Continues)

TABLE 1 (Continued)

Author year	Country	Population	Dose	Sample size (vitamin D vs. control)	Mean age (*SD* or range)	Duration	Baseline 25 (OH) D (nmol/L)	Assessment scale measure	Major finding	Study design
Ghaderi et al. (2017)	Iran	Patients with maintenance methadone treatment	50,000 IU/bi-week	68 (34 vs. 34)	Vitamin D: 40.1 (9.2); Placebo: 42.5 (8.9)	12 weeks	Vitamin D: 34.7 (11.2); Placebo: 33.7 (11.2)	BDI BAI	Favoring vitamin D group in BDI, but no difference in BAI	RCT
Jorde and Kubiak (2018)	Norway	Healthy with low 25(OH) D levels	100,000 IU bolus and 20,000 IU/ week	385 (192 vs. 193)	Vitamin D: 51.3 (8.4); Placebo: 52.6 (8.8)	4 months	Vitamin D: 32.8 (11.2); Placebo: 35.4 (13.7)	BDI-II	No difference	RCT
Mousa et al. (2018)	Australia	Overweight or obese adults (BMI ≥ 25)	100,000 IU bolus and 4,000 IU/day	48 (26 vs. 22)	Vitamin D: 31.5 (8.1); Placebo: 32.0 (9.9)	16 weeks	Vitamin D: 31.7 (13); Placebo: 35 (9.5)	BDI-II	No difference	RCT
von Berens et al. (2018)	Sweden and United States	Older adults (≥70 years old)	800 IU/day	133 (68 vs. 65)	Vitamin D: 78.1 (5.8); Placebo: 76.9 (4.9)	6 months	Vitamin D: 44.3 (14.8); Placebo: 49.3 (17)	CES-D	No difference	RCT
Alavi et al. (2018)	Iran	Geriatric depression patients	50,000 IU/week	78 (39 vs. 39)	Vitamin D: 68.7 (7); Placebo: 67 (6.3)	8 weeks	Vitamin D: 56.3 (15.4); Placebo: 53 (14.5)	GDS-15	Favoring vitamin D group	RCT
Raygan et al. (2018)	Iran	Diabetic patients with coronary heart disease	50,000 IU/ bi- week	60 (30 vs. 30)	Vitamin D: 71.5 (10.9); Placebo: 67.3 (11)	12 weeks	Vitamin D: 36.7 (11.7); Placebo: 34.4 (7.5)	BDI; BAI; GHQ	Favoring vitamin D group in BDI, BAI, GHQ	RCT
Jamilian et al. (2018)	Iran	Women with PCOS	50,000 IU/ bi- week	60 (30 vs. 30)	Vitamin D: 26.8 (4.4); Placebo: 25.1 (3.7)	12 weeks	Vitamin D: 30.2 (7.8); Placebo: 31.7 (6.7)	BDI-II; DASS; GHQ	Favoring vitamin D group in BDI, DASS, GHQ	RCT
Choukri et al. (2018)	New Zealand	Healthy adult women	50,000 IU/months	150 (76 vs. 74)	Vitamin D: 24.4 (6.4); Placebo: 23.9 (5.6)	6 months	Vitamin D: 77.7 (26.1); Placebo: 74 (26.1)	CES-D; HADS-A	No difference	RCT

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; BMI, body mass index; BSI-18, Brief Symptom Inventory Depression Subscale; CES-D, Center for Epidemiological Studies Depression Scale; DASS-21, Depression Anxiety and Stress Scales 21-item Short Form; EPDS, Edinburgh Postnatal Depression Scale; FIQ, Fibromyalgia Impact Questionnaire; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MCS, Mental Health Component Score; MDD, major depressive disorder; PANAS, Positive and Negative Affect Schedule; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; SF-12, The 12-Item Short Form Healthy Survey; SF-36, The 36-Item Short Form Health Survey; SIGH-SAD, The Structured Interview Guide for the Hamilton Rating Scale for Depression–Seasonal Affective Disorder version; STAI, State-Trait Anxiety Inventory; YSR-CBCL, Youth Self-report version of the Child Behavior Checklist.

TABLE 2 Meta-analyses results about the effect of vitamin D supplementation (including subgroup analyses and sensitivity analyses)

	Study no.	Patients/ control	Effect sizes (95% CI)	Effect size *p*- value	Heterogeneity I^2 (%)
Groups by all participants	25	3,750/3,784	−0.4990 (−0.8453, −0.1528)	.0047	97.7
Subgroups analyses					
Groups by anxiety scale	6	353/343	−0.2404 (−0.4694, −0.0115)	.0396	52.6
Different vitamin D dosage					
>2,000 IU/day	18	1,424/1,415	−0.6081 (−1.2095, −0.0068)	.0475	98.1
≤2,000 IU/day	9	2,482/2,521	−0.1675 (−0.3288, −0.0062)	.0418	75.7
>4,000 IU/day	9	812/792	−0.8105 (−1.9859, 0.3649)	.1766	98.9
≤4,000 IU/day	17	3,054/3,104	−0.2311 (−0.3664, −0.0958)	.0008	76.6
Baseline vitamin D level					
Serum 25(OH)D >50 nmol/L	12	3,024/3,080	−0.5769 (−1.1555, 0.0017)	.0507	98.9
Serum 25(OH)D ≤50 nmol/L	12	704/682	−0.3262 (−0.5404, −0.1121)	.0028	71.1
Treatment duration					
≥8 weeks	23	3,665/3,697	−0.4794 (−0.8444, −0.1145)	.0100	97.9
<8 weeks	2	85/87	−0.7254 (−1.8704, 0.4196)	.2144	89.4
8–12 weeks (including 12 weeks)	12	615/614	−0.3727 (−0.6053, −0.1400)	.0017	71.6
≥12 weeks	19	3,540/3,578	−0.4223 (−0.8262, −0.0184)	.0404	98.2
Age					
18–65 years old	19	2,466/2,493	−0.5464 (−1.0637, −0.0292)	.0384	98.2
>65 years old	5	1,261/1,268	−0.3761 (−0.7668, 0.0147)	.0593	89.9
Study population					
Patients with major depressive disorder	5	329/321	−1.0976 (−1.5538, −0.6413)	<.0001	79.7
Healthy participants	11	2,765/2,799	−0.1114 (−0.2488, 0.0260)	.1121	73.5
Patient with clinically meaningful depression (≥cut-off values of scale)	11	792/789	−0.9664 (−1.9618, 0.0290)	.0571	98.4
Patient without clinically meaningful depression (<cut-off values of scale)	6	530/535	−0.0291 (−0.1494, 0.0911)	.6349	0.0
Only studies adopting BDI or BDI-II	12	2,024/2,031	−0.6700 (−1.3985, 0.0585)	.0715	98.8
Taking antidepressants	4	291/292	−0.7135 (−1.5258, 0.0988)	.0851	93.4
Not taking antidepressants	6	699/695	−1.0306 (−2.6408, 0.5797)	.2097	99.3
Not mentioning about taking antidepressants or not	13	2,706/2,743	−0.1494 (−0.2778, −0.0210)	.0226	66.1
Female	7	2,503/2,547	−0.1268 (−0.2800, 0.0263)	.1045	77.6
Sensitivity analyses					
Excluding studies with biological flaws	17	1,271/1,262	−0.7210 (−1.3837, 0.0583)	.0330	98.1
Studies with biological flaw	8	2,479/2,522	0.0091 (−0.0464, 0.0645)	.7490	0.0

Abbreviations: BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II.

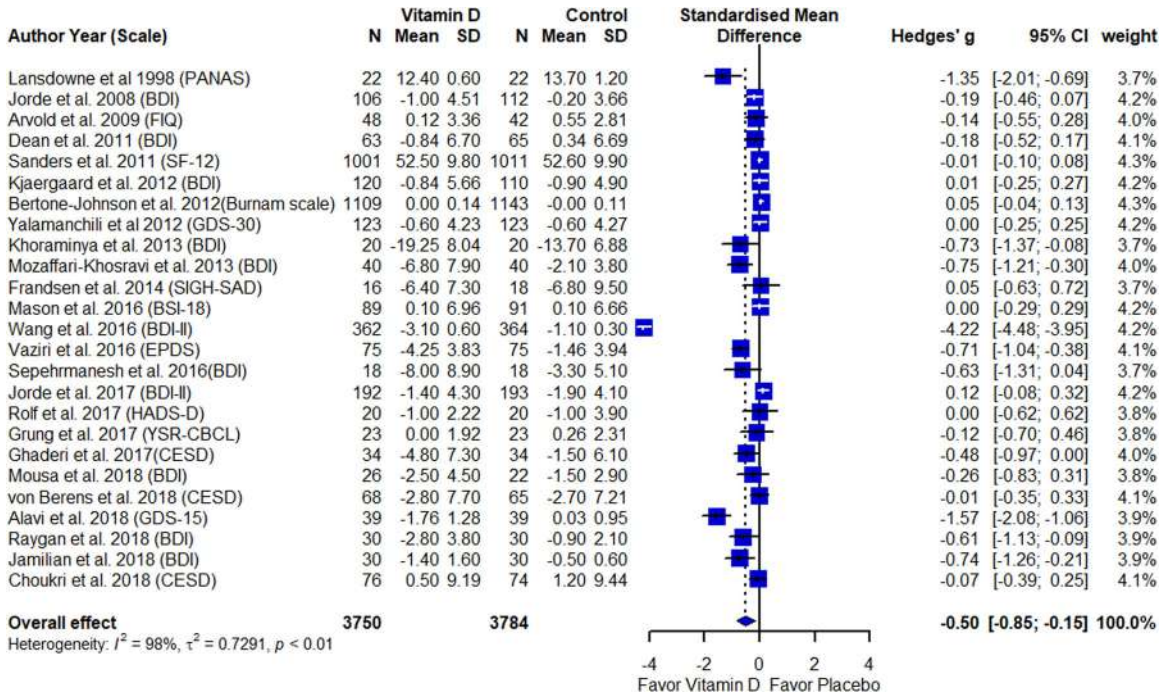

FIGURE 2 Forest plot of the effect of vitamin D supplementation on negative emotion

low (<50 nmol/L) serum levels of vitamin D at baseline, and the effect is marginal in people with serum levels >50 nmol/L at baseline. (i) Vitamin D supplementation is not helpful in elderly people (age >65 years) but is effective in adults aged 18–65 years; this is a medium to large effect. These findings are worthy of discussion.

Our main analysis revealed that vitamin D reduces negative emotions. The results of analyses of all eligible studies and only studies without flaws were similar. This result supports the hypothesis that vitamin D plays a role in the central nervous system, although the mechanism is currently unclear. There was no effect of vitamin D on emotion in the meta-analysis of flawed trials, which implies that the unflawed trials contributed more to the overall analysis. Our subgroup analysis of flawed and unflawed trials produced similar results to that performed by Spedding (2014). Our results suggest that the effects of vitamin D depend on the population and dosage. Therefore, these factors related with flawed situations should be analyzed delicately.

Vitamin D produced an emotional improvement in patients with major depressive disorder but not in healthy individuals. This may represent a floor effect: levels of negative emotion in healthy individuals are sufficiently low that there is little room for reduction and therefore a reduction is hard to detect through statistical analysis. Even if vitamin D has protective or preventive effect on emotion in healthy people it would be difficult to detect over a period of weeks. Another possible explanation is that healthy people are less likely to be deficient in vitamin D and therefore may not benefit from vitamin D supplementation (Jozefowicz et al., 2014). Our finding that vitamin D reduces negative emotion in people with major depressive disorder is similar to the analysis of Vellekkatt and Menon (2018). This finding should be treated with caution, however, as the interpretation of results is to some extent dependent on whether vitamin D is given alone or in combination with other evidence-based treatments (such as antidepressants or psychotherapy), and not all the studies we analyzed reported details of concurrent treatments (Alavi et al., 2018; Khoraminya et al., 2013; Mozaffari-Khosravi et al., 2013; Sepehrmanesh et al., 2016;

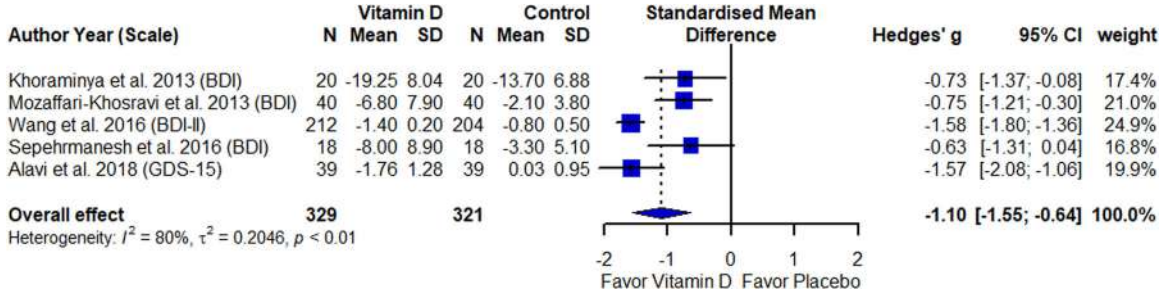

FIGURE 3 Forest plot for trials with patients having diagnosis of major depressive disorder

Wang et al., 2016). Besides, separating subjects with the cut-off values of scales could not present significant effects of vitamin D. An possible explanation is that the clinically meaningful depression defined by the scales is relatively mild to major depressive disorder. The heterogeneity of scales may also have influence.

In addition to its effect on depression vitamin D also seems to have an effect, albeit small, on anxiety. Depression and anxiety are often viewed as emotions with overlapping biological pathways, involving serotonin, related brain regions, and neuroinflammation (Calcia et al., 2016). These mechanisms have also been supposed to be associated with vitamin D (Humble, 2010). We consider that the effects of vitamin D on depression and anxiety are capable of explanation by a common mechanism. However, there have been fewer studies of anxiety and a greater diversity of tools have been used to measure anxiety (Choukri et al., 2018; Dean et al., 2011; Ghaderi et al., 2017; Jamilian et al., 2018; Kjaergaard et al., 2012; Raygan et al., 2018; Tartagni et al., 2016), so the finding that vitamin D supplementation reduces anxiety should be viewed conservatively.

As for the regimen of vitamin D supplement, our results indicate that high doses (>4,000 IU/day) are not beneficial and that supplementation needs to last at least 8 weeks. We also divided the studies by dosage, using a threshold of 2,000 IU/day; there was a vitamin D effect in both groups (>2,000 IU/day and ≤2,000 IU/day), but sensitivity analyses indicated that neither effect was robust. In vitamin D supplementation in adults the common dose is 600–800 IU/day, with doses greater than 4,000 IU/day considered high (Ross, Taylor, Yaktine, & Del Valle, 2011; EFSA Panel on Dietetic Products, 2016). High doses of vitamin D (4,000 IU/day) have been used to manage bone and calcium problems in people with vitamin D deficiency; the common duration of this regimen is also 8 weeks (Iraj, Ebneshahidi, & Askari, 2012). In some countries, such as the United States, 4,000 IU/day is also the upper limit of recommended intake as an excess of vitamin D can be toxic (Ross et al., 2011). Vitamin D is a secosteroid hormone and steroid-like chemicals usually act via transcription in the nucleus and thus take long period to work (Becker, 2013). Only a small proportion of the studies included in this meta-analysis assessed short-term (<8 weeks) supplementation, so further studies are needed to determine the effectiveness of such regimes. On the other hand, the effects of vitamin D with treatment duration of 8–12 weeks, at least 12 weeks were both significant. It indicates that "at least 8 weeks" can be viewed as a sufficient duration of observing the response to vitamin D; it can be examined in future interventional research.

Subgroup analysis of the effects of vitamin D in different populations showed that supplementation is beneficial in people with low vitamin D levels (<50 nmol/L) and adults aged ≤65 years. The standard criterion for vitamin D deficiency is a serum levels of 25(OH)D lower than 50 nmol/L (20 ng/ml), with levels of 50–75 nmol/L (20–30 ng/ml) being considered insufficient (van Groningen et al., 2010). Adequate serum levels of vitamin D are required if it is to play its role in calcium and phosphorus absorption and osteogenesis (Holick et al., 2011). It is not surprising, therefore, that an adequate level is necessary to fulfillment of its normal role in the central nervous system. Vitamin D supplementation has more effect on osteogenesis in people with vitamin D deficiency than those with adequate levels (Shuler, Wingate, Moore, & Giangarra, 2012). Our analysis also indicated that vitamin D supplementation has no effect in people who are not deficient. This issue can be explained with the finding "vitamin D supplement is more helpful in major depressive disorder patients than in healthy ones." If patients with major depressive disorder are more likely to be vitamin D deficient than the general population, the two findings may be related. There are actually studies that provide evidence of a relationship between depression and vitamin D deficiency (Jozefowicz et al., 2014; Szpunar, 2019). As for the limited response in elderly people it is difficult to offer an explanation due to the presence of confounding factors. For example, 3 of the 5 studies of elderly people included subjects without clinically meaningful depression (Alavi et al., 2018; Raygan et al., 2018; Sanders et al., 2011; von Berens et al., 2018; Yalamanchili & Gallagher, 2012) and baseline vitamin D levels and dosage were variable (Alavi et al., 2018; Raygan et al., 2018; Sanders et al., 2011; von Berens et al., 2018; Yalamanchili & Gallagher, 2012). The recommended dose for vitamin D supplementation is higher for elderly people than other age groups (Bacon, Gamble, Horne, Scott, & Reid, 2009; Hanley et al., 2010). As sensitivity analysis indicated that the two findings about populations (with/without vitamin D deficiency and age groups) were not robust they should be treated with more caution than our other findings. Besides, though vitamin D is extensively supplied in different age groups, the lowest mean age in our incorporated studies was 22 years old. Therefore, our findings about young to middle-age adults cannot be extended to adolescents or children.

For investigating the influence of combining antidepressants, we separated the studies into three categories: taking antidepressants, not taking antidepressants, not mentioning taking antidepressants or not. The significant effect on negative emotion was only found in the last situation. It seems uneasy to explain. However, from the statistical viewpoint, the numbers of "not mentioning taking antidepressants or not" studies are highest (13 articles). Therefore, if the effect sizes in these situations are similar, it is the most possible to reveal significance in this group. The clinical value of combining antidepressants and vitamin D still awaits more future studies to explore.

Several limitations of our study should be discussed. First, the studies incorporated into our meta-analysis are heterogeneous with respect to a number of factors such as the population from which the sample was drawn, definition of the degree of negative emotions, and the vitamin D supplementation regime. Although we analyzed several specific subgroups, not all heterogeneity could be managed in this manner. The tools that were used to measure symptoms of anxiety and depression assessed slightly different constructs. For example, the BDI measures both cognitive/affective and somatic/vegetative aspects of depression, whereas the Geriatric Depression Scale emphasizes the cognitive/affective features (Balsamo, Cataldi, Carlucci, Padulo, & Fairfield, 2018). Several instruments are available for evaluating anxiety; the Beck Anxiety Inventory focuses on somatic aspects, paying less attention to free floating anxiety

(Julian, 2011). Considering only the most frequently used tools BDI and BDI-II, the effect of vitamin D supplement is not significant. It reminds us to notice the influence of distinct measurement tools. Under different measurements, the level of depression or anxiety cannot be examined with meta-regression. The populations, co-morbidities across studies also contribute to heterogeneity. Besides, ethnicity, levels of outdoor activity and sun exposure are also possible to affect the efficacy of vitamin D, but they were not recorded in most studies. Second, the quality of evidence was variable. Some studies did not have double-blind design and in some emotion was evaluated via a self-administered instrument, whereas in others it was rated by medical staff. These factors may increase the possibility of observational bias. Third, most studies did not perform head-to-head comparisons between vitamin D supplementation and antidepressants. For these reasons the results should be interpreted cautiously; there is no evidence to suggest that vitamin D can replace antidepressants. Fourth, there was little detailed information on concurrent psychosocial interventions and use of antidepressant medication in the studies we analyzed, particularly those examining patients with major depressive disorder (Alavi et al., 2018; Khoraminya et al., 2013; Mozaffari-Khosravi et al., 2013; Sepehrmanesh et al., 2016; Wang et al., 2016) and so the possibility that the observed improvement in depression in major depressive disorder patients was due to concurrent psychological intervention or use of antidepressants cannot be excluded. Finally, though the subgroup analyses regarding duration of supplement and baseline serum level revealed distinct findings in different subgroups, meta-regressions for these two factors disclosed nonsignificant results. The possible explanations included the interference of outliers, the nonlinear association between these factors and treatment effects, and the complexity among factors (e.g., subjects with low serum vitamin D level did not necessarily receive enough dose of supplement; this cannot be managed in analytical manner due to insufficient data). But since these hypotheses cannot be directly examined, the related results should be interpreted cautiously.

To our knowledge, this is the first meta-analysis to explore the effects of vitamin D supplementation on both anxiety and depression. Our results indicate that vitamin D is helpful in both depression and anxiety; the population most likely to benefit from vitamin D supplements is patients with major depressive disorder. As for the question of what supplementation regimes are most effective, we found that supplementation was more likely to be effective if carried for more than 8 weeks and that high doses (>4,000 IU/day) of vitamin D seemed not effective. However, because of the high heterogeneity of the incorporated data, and some of them cannot be managed with subgroup analyses or meta-regression, the results should be interpreted cautiously. Further research is required to confirm the clinical implications of these findings. We did not examine the association between serum level of vitamin D and the severity of negative emotions, and vitamin D supplement cannot be directly understood as the increase of serum vitamin D level. This point should also be examined in the future.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Y.-C. Cheng and W.-L. Huang reviewed the literature and designed this study. Y.-C. Cheng and Y.-C. Huang analyzed and interpreted the data. Y.-C. Cheng and W.-L. Huang drafted the manuscript.

DATA AVAILABILITY STATEMENT

The data of integrated studies have been listed in the tables of this meta-analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX: SEARCHING STRING OF PUBMED

Search	Query	Items found
#4	Search ((((((((((((((((Vitamin D) OR hydroxyvitamin d) OR vitamin D2) OR vitamin d3) OR 25 hydroxyvitamin d3) OR 25 OH VIt D) OR dihydroxyvitamin D3) OR 25 hydroxycalciferol) OR hydroxycholecalciferol) OR 1,25 dihydroxycholecalciferol) OR calcifediol) OR calciferol) OR calcitriol) OR cholecalciferol) OR ergocalciferol)) AND (((((((((Depression) OR Depressive Disorder) OR dysthymia) OR depress) OR mood disorder) OR anxiety) OR negative emotion) OR negative affect)) AND ((((((((((randomized controlled trial) OR controlled trials) OR clinical study) OR placebo.ab) OR randomized) OR trial) OR clinical) OR therapy) OR randomly) OR controlled)	751
#3	Search (((((((((randomized controlled trial) OR controlled trials) OR clinical study) OR placebo.ab) OR randomized) OR trial) OR clinical) OR therapy) OR randomly) OR controlled	11,733,317

(Continues)

#2	Search (((((((Depression) OR Depressive Disorder) OR dysthymia) OR depress) OR mood disorder) OR anxiety) OR negative emotion) OR negative affect	619,464
#1	Search ((((((((((((((Vitamin D) OR hydroxyvitamin d) OR vitamin D2) OR vitamin d3) OR 25 hydroxyvitamin d3) OR 25 OH VIt D) OR dihydroxyvitamin D3) OR 25 hydroxycalciferol) OR hydroxycholecalciferol) OR 1,25 dihydroxycholecalciferol) OR calcifediol) OR calciferol) OR calcitriol) OR cholecalciferol) OR ergocalciferol	85,388