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Vitamin D protects against depression: Evidence from an umbrella meta-analysis on interventional and observational meta-analyses

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ABSTRACT

Meta-analyses of interventional and observational studies investigating the efficacy and the relationship between vitamin D and depression provided inconsistent results. The current umbrella meta-analysis was conducted to assess the available evidence and provide a conclusive outcome in this regard. The following international databases were systematically searched till March 2022: PubMed, Scopus, Embase, Web of Science, and Google Scholar. Random-effects model was carried out to calculate the pooled point estimates and their respective 95 % confidence intervals (CI). Ten meta-analyses of randomised controlled trials (RCTs) revealed significant reduction in depression symptoms comparing participants on vitmain D supplements to those on placebo (Pooled standardised mean difference: − 0.40; 95 % CI: − 0.60, − 0.21, $p < 0.01$: $I^2 = 89.1$ %, $p < 0.01$). Four meta-analyses of cohort studies (with one having two subgroups) revealed that participants with lower levels of serum vitamin D were at increased odds of depression than those with higher levels of serum vitamin D (Pooled odds ratio: 1.60; 95 % CI: 1.08, 2.36, $p < 0.01$; $I^2 = 91.3$ %, $p < 0.01$). The present umbrella meta-analysis confirms the potential benefits of vitamin D supplementation and higher serum vitamin D levels in reducing the development and symptoms of depression.

1. Introduction

Depression is a mental disorder that causes disabling effects of mood and anxiety disorders. Depression has also become a leading global cause of disease burden [1,2]. Based on the evidence from the World Health Organization, more than 264 million people are affected by depression worldwide [3]. In the wake of the COVID-19 outbreak, a number of studies have demonstrated a rise in depression psychopathology and suicide tendencies across a variety of countries [4]. Depressive symptoms were the most common mental health condition during the COVID-19 pandemic, ranging from 14.6 % to 48.3 % across all populations, according to a systematic review [5]. People who suffer from depression may feel sad, anxious, hopeless, helpless, irritable, worthless, guilty, or ashamed [6]. There might also be decreased

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appetite or overeating, and inability to exercise, or even suicide among them [7]. Antidepressants, which have been used for many years to treat depression, have raised concerns about their effectiveness and tolerance [8–10]. Furthermore, the failure of depression to respond to a wide range of pharmaceutical treatments [11] indicates that other mechanisms are involved in the pathogenesis of depression, such as those affecting neuroendocrine, immunological, neurotrophic, and metabolic systems [12]. In spite of these challenges, complementary treatments for depression appears to be helpful.

Vitamin D is a unique neurosteroid hormone that may play a role in depression [13]. Vitamin D has numerous functions in the brain such as neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity, and brain development [14]. Also, vitamin D receptors can be found on the neurons and glia in many parts of the brain, including the cingulate cortex and the hippocampus [15]. Vitamin D deficiency may have played a significant role in stress-related depression during the COVID-19 pandemic, according to a growing body of literature [16]. Vitamin D is thought to influence the serotoninergic system and contribute to the maintenance of circadian rhythms, both of which are associated with depressive symptoms [16,17]. As a result, it is biologically plausible that vitamin D might play an important role in the treatment of depressive disorders [13]. However, evidence is accumulating that vitamin D may have beneficial effects regarding the depressive disorders. In this context, many meta analyses of RCTs and observational studies have been published over the last few years. Several RCT studies showed a beneficial effect of vitamin D supplementation on depression [18–21]. On the other hand, other studies did not report a significant effect [22–24].

Therefore, as the results are conflicting and no definite conclusion could be obtained from the existing meta-analyses, the present umbrella meta-analysis was conducted to propose whether vitamin D supplementation or higher serum vitamin D levels had a protective role against depression and could hence be considered as a reliable therapeutic approach.

2. Methods

2.1. Search strategy and study selection

EMBASE, Scopus, Web of Science, Cochrane Central Library, and PubMed scientific databases in addition to Google Scholar were checked for relevant papers published up to March, 2022. The search strategy is shown in Suppl. Table 1.

To improve the sensitivity of our search strategy, we used the wildcard term"*". Only studies published in English were included in the current study. Additionally, the reference list of related articles was checked for any missing eligible studies.

2.2. Inclusion and exclusion criteria

In the current study, we included meta-analyses of randomised controlled trials (RCTs) and of observational studies (cohort and cross-sectional) that investigated the effect of vitamin D supplementation on depression symptoms considering the following criteria: reporting standardised mean difference (SMD), or odds ratio (OR) and their corresponding confidence intervals (CI) for vitamin D supplementation on depression symptoms. Other studies were excluded from this review, including original experimental studies, case reports, *in vitro*, *ex-vivo*, and *in vivo* investigations.

2.3. Data extraction

Two independent reviewers (ZK and MK) screened papers based on the eligibility criteria. In the first step, the reviewers reviewed papers by titles and abstracts. Then, they evaluated the full texts of relevant papers to determine suitability for the meta-analysis. Any disagreement was settled by consensus with the third reviewer (MZ).

The following data were extracted from the selected papers: publication year, sample size, the dosage and duration of the intervention of vitamin D supplementation in RCTs, follow-up duration in observational studies, and the SMD or OR and their 95 % confidence intervals.

2.4. Quality assessment

Two reviewers (ZK and MK) independently assessed the methodological quality of the qualifying papers using the assessment of multiple systematic reviews (AMSTAR2) questionnaire. The AMSTAR2 questionnaire includes 16 items that asks reviewers to reply 'Yes' or 'Partial Yes' or 'No' or 'No Meta-analysis'. The AMSTAR2 checklist was categorised into "critically low quality", "low quality", "moderate quality", and "high quality" [25]. Also the third reviewer (RM) solved any disagreements.

2.5. Data synthesis and statistical analysis

The overall effect sizes were calculated by pooling the point estimates and their respective 95 % CIs for observational and RCT studies, separately using the random effects model by DerSimonian and Laird [26]. To detect statistical heterogeneity, the I^2 index and Cochrane's Q test were utilised. An I^2 value of more than 40 % or a $P < 0.1$ for the Q-test was considered as significant between-study heterogeneity. When feasible, we conducted subgroup analyses based on vitamin D dosage (< 4000; 4000–5000; > 5000 IU/day), intervention duration (≤ 20, > 20 weeks), and average age (≤ 50/> 50 years) to detect possible heterogeneity sources. We also conducted a sensitivity analysis in which each study was excluded to examine the impact of that study on the pooled point estimate. For outcomes with at least 10 meta-analyses, the small-study effect was examined performing the formal tests of Egger's [27] and Begg's [28] and if these last were significant, a visual evaluation of funnel plots was conducted. If an asymmetry was found in the funnel plot and contingent on publication bias being the reason, the trim-and-fill method was used to detect the effect of the potentially missing small studies on the overall effect. We used version 16.0 of STATA to conduct all statistical analyses (Stata Corporation, College Station, TX). Unless otherwise specified, significant level was defined as a p-value < 0.05.

3. Results

3.1. Study selection

Following a thorough search of electronic databases, a total of 300 papers were found. After removing 61 duplicates, 239 studies were discarded due to their irrelevant titles and abstracts (n = 179), animal studies (n = 20), and review studies (n = 17). In the end, 23 full texts were reviewed. Eight studies were excluded for lack of required information. Finally, 14 meta-analyses (One meta-analysis reported separate pooled point estimates for RCT studies and for observational studies, finally, 10 effect size for RCTs and five effect size for observational studies) met all of our inclusion criteria. Note that four of these meta-analyses reported separate pooled point estimates for cohort studies and for cross-sectional studies.The study selection process is schematically depicted in the PRISMA study flow chart in Fig. 1.

3.2. Study characteristics

In the umbrella meta-analysis of RCTs, there were 10 meta-analyses (24,510 participants from 49 RCTs) that reported weighted mean differences in depression risk score comparing the vitamin D arm to the placebo arm. The included meta-analyses were performed between 2014 and 2021. The number of subjects ranged between 66 and 42,226. The average age of participants ranged between 37 and 57 years.

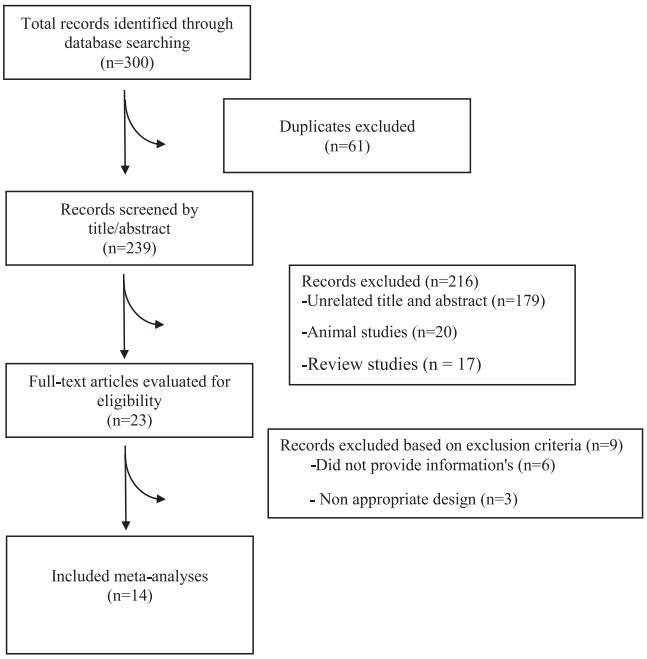

Fig. 1. PRISMA flowchart diagram.

Intervention duration was between 8 and 74 weeks. Vitamin D dosages used varied between 2500 and 6000 IU/day (Table 1). Jamilian et al. [29] presented data as weighted mean difference (WMD) (− 3.9;1 95 % CI; − 5.15, − 2.66), which was converted to SMD (−0.17; 95 % CI; − 0.23, − 0.12) based on statistical methods.

In the umbrella meta-analysis of cohort studies, there were five meta-analyses (38,237 participants from 16 cohort studies) that reported weighted OR for depression comparing lower serum levels of vitmain D (vitamin D deficiency) to higher levels. The included meta-analyses were performed between 2013 and 2021. The number of subjects ranged between 383 and 12,648. The average age of participants ranged between 28 and 73 years. Follow-up duration was between 6 months and 3.5 years.

In the umbrella meta-analysis of cross-sectional studies, three meta-analyses reported OR (66,409 participants from 13 cross-sectional studies). The included meta-analyses were conducted between 2013 and 2021. The number of participants ranged from 796 to 43,137 with an average age of 25–63 years.

3.3. Risk of bias assessment

The findings of the AMSTAR2 questionnaire-based quality assessment was shown in Supplementary Table 2. Out of ten meta-analyses of RCTs, eight [29–36] were of high-quality and two [37,38] were of moderate-quality. Also, four meta-analyses [13,39–41] of observational studies had high-quality and one [37] had moderate-quality.

3.4. Effects of vitamin D supplementation on depression according meta-analyses of RCTs

Vitamin D supplementation had (Table 2) a significant effect on decreasing depression symptoms (ES_{SMD}: − 0.40; 95 % CI: − 0.60, − 0.21, $p < 0.01$), according to the pooled analysis of 10 meta-analyses (Fig. 2**A**). There was a significant between-study heterogeneity (I^2 = 89.1 %, p-heterogeneity < 0.01) which the dosage of vitamin D, sample size, and duration of intervention were determined as its sources, after performing subgroup analyses (Table 3). Vitamin D supplementation in dosage of 4000–5000 IU/day, or intervention duration of ≤ 20-weeks appeared to have a stronger reduction in depression symptoms compared to other respective subgroups (Table 3**)**. Based on the one-study removal analysis, no significant change was observed after removing a single study at a time (Suppl. File. 1). There was no significant small-study effect according to the results of Egger's (p = 0.21) and Begg's tests (p = 0.78). However, visual inspection of the funnel plot showed an asymmetric distribution of studies indicating a potential

Table 1
Characteristics of included meta-analyses of RCT studies.

Study, year, country	No. of studies in the meta-analysis	No. of participants in the meta-analysis	Mean age	Duration of intervention	Intervention/daily dose	Quality assessment scale and outcome	Measured outcomes and results
Li, 2014, Canada	6	1203 (healthy and with depression)	57	74 weeks	Vit D/3700 IU/day	NR	Depression → ↓
Spedding et al. 2014 Australia	15	42,226 (healthy and with depression)	NR	41 weeks	Vit D/5200 IU/day	Yes (Cochrane) 10/15 high	Depression → ↓
Shaffer et al. 2014 Columbia	7	3191 (healthy and with depression)	47	34 weeks	Vit D/2500 IU/day	Yes (Cochrane) 3/7 high	Depression → not significant effect
Gowda et al. 2015 Australia	9	4923 with depression	45	61 weeks	Vit D/3070 IU/day	Yes (Cochrane) 7/9 high	Depression → not significant effect
Firth et al. 2019 Australia	4	948 with unipolar depression	NR	NR	Vit D/4300 IU/day	NR	Depression → ↓
Vellekkatt et al. 2019 India	4	948 with major depression	NR	20 weeks	Vit D/4800 IU/day	Yes (Cochrane) 2/4 high	Depression → ↓
Jamilian et al. 2019 Iran	9	1347 with psychiatric disorders	40	13 weeks	Vit D/6000 IU/day	NR	Depression → ↓
Cheng et al. 2020 Taiwan	25	9840 (healthy and with depression)	47	32 weeks	Vit D/4200 IU/day	NR	Depression → ↓
Jeremiah et al. 2020 Ireland	2	66 with depression	37	8 weeks	Vit D/4250 IU/day	Yes (Cochrane) 0/2 high	Depression → ↓
Nicoláse et al. 2021 Spain	10	1393 with depression	46	20 weeks	Vit D/5250 IU/day	Yes (Cochrane) 8/10 high	Depression → not significant effect

IU: International units; NR, not reported; vit D, vitamin D.

Table 2
Characteristics of the included meta-analyses for observational studies.

Study, year	Study design	Participants	Gender	Mean age, years	Follow-up duration	Outcome
Meta-analyses of cohort studies						
†Anglin, 2013, Canada	Cohort	8815	Both genders	73	3.6 Years	↑ risk of depression
†Ju, 2013, Korea	Cohort	12648	Both genders	65	NR	↑ risk of depression
Li, 2014, Canada	Cohort	383	Female	73	3.5 years	No statistically significant association
§Wang,2018, China	Cohort	8470	Female	28	6 months	↑ risk of postpartum depression
§Wang, 2018, China	Cohort	8470	Female	28	6 months	No statistically significant association during pregnancy
†Tan, 2021, China	Cohort	7921	Both genders	28	NR	↑ risk of depression
Meta-analyses of cross-sectional studies						
†Anglin, 2013, Canada	Cross-sectional	22,476	Both genders	63	NR	↑ risk of depression
†Ju, 2013, Korea	Cross-sectional	43,137	Both genders	50	NR	↑ risk of depression
†Tan, 2021, China	Cross-sectional	796	Both genders	25	NR	↑ risk of depression

NR, not reported; vit D, vitamin D.
† These meta-analyses reported separate pooled point estimates for cohort studies and for cross-sectional studies.
‡ Only the subgroup of original studies that included participants not on antidepressants was included.
§ Wang et al. was stratified in two groups, one for pregnant women and one for women post-delivery.

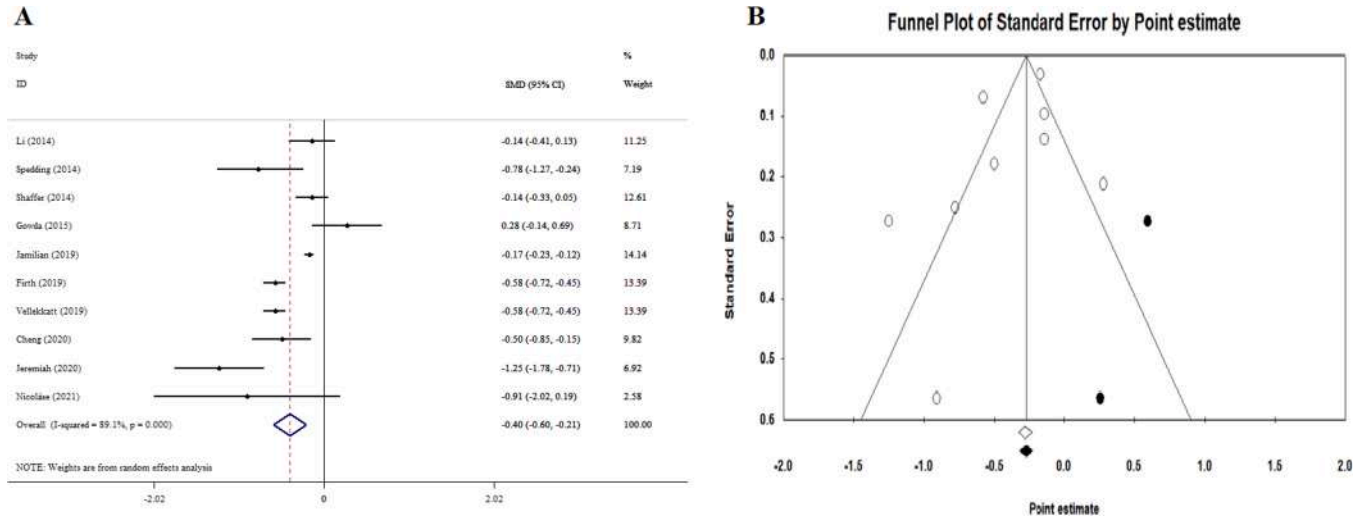

Fig. 2. Forest plot (A) funnel plot with mean difference and 95 % confidence intervals (CIs) (B) publication bias in the studies the effects of vitamin D supplementation on depression symptoms.

presence of small study effect (Fig. 2**B**). Therefore, the trim and fill method was carried out with 12 studies (two imputed studies) and results remained significant (ES_{SMD}: − 0.33; 95 % CI: − 0.52, − 0.13, $p < 0.05$).

3.5. Association between vitamin D and depression according to meta-analyses of cohort studies

The association between Vitamin D and protection against depression risk was examined in four meta-analyses with five effect sizes that included 38,237 participants. Our findings revealed a significant protective association between serum vitamin D and overall depression risk (Pooled ES_{OR}: 1.60; 95 % CI: 1.08, 2.36, $p < 0.01$) (Fig. 3). The level of heterogeneity was high (I^2 = 91.3 %, p-heterogeneity < 0.01). Subgroup analysis showed that the protective association between higher levels of serum vitamin D and depression was stronger among participants aged ≤ 50 years old than their older peers (Table 3). Furthermore, after excluding the study of Tan et al. [40], and Wang et al. [41], using one-study removal analysis, the significance was lost (ES_{OR}: 1.43; 95 % CI: 0.98, 2.10), and (ES_{OR}: 1.41; 95 % CI: 0.95, 2.09) (Suppl. File. 1). One meta-analysis by Anglin et al. [13] presented a pooled hazard ratio (HR) from three cohort studies and was hence not included in our umbrella meta-analysis of cohort studies which reported mainly OR. The direction of the results of the HR were in line with our findings suggesting an increased hazard of depression in the lowest serum vitmain D compared to the highest (pooled HR = 2.21; 95 % CI; 1.40, 3.49).

3.6. Association between serum vitamin D and depression according to meta-analyses of cross-sectional studies

The association between serum vitamin D and depression was reported in three meta-analyses of cross-sectional studies with 66,411 participants.The summary effect size for overall depression indicated no significant protective association between serum vitamin D and overall depression (Pooled ES_{OR}: 1.19; 95 % CI: 0.95, 1.49, $p = 0.14$; I^2 = 53.9 %, $p = 0.11$) (Fig. 4). No subgroup analysis was performed on these meta-analyses.

4. Discussion

The current umbrella meta-analysis summarised 15 meta-analyses, which included 65 RCTs, and 31 observational (cohort and cross-sectional) studies. According to the results, vitamin D supplementation was efficient in alleviating symptoms of depression and an inverse association was observed between higher serum levels of vitamin D intake and overall depression. Based on sub-group analyses, vitamin D supplementation in studies using dosage of > 5000 IU/day, and

Table 3
Subgroup analyses for the effects of vitamin D supplementation on depression symptoms.

Variables	No. studies	Pooled point estimate (95 % CI)	P-value	I^2 (%)	P-heterogeneity
Meta-analysis of RCTs (SMD)					
Overall	10	-0.40 (− 0.60, − 0.21)	< 0.001	89.1	< 0.001
Dosage (IU/day)			0.234		
< 4000	3	-0.09	< 0.001	42.0	0.178
4000–5000	4	(− 0.23,	< 0.001	51.1	0.105
> 5000	3	0.06)		71.5	0.030
		-0.59 (− 0.68, − 0.50)			
		-0.18 (− 0.23, − 0.12)			
Intervention duration (weeks)					
	4	-0.24	< 0.001	93.4	< 0.001
≤ 20	5	(− 0.29,	0.004	70.1	0.010
> 20	1	− 0.19)	< 0.001	–	–
NR		-0.19 (− 0.32, − 0.06)			
		-0.58 (− 0.71, − 0.44)			
Meta-analysis of cohort studies (OR)					
Overall	5	1.60 (1.08, 2.36)	< 0.001	91.3	< 0.001
Sex					
	3	1.55 (1.13,	0.007	69.7	0.037
Female	2	2.13)	< 0.001	97.3	< 0.001
Both		1.19 (1.12, 1.26)			
Age (years)					
	3	2.02 (1.71,	< 0.001	51.8	0.126
≤ 50	2	2.39)	< 0.001	0.0	0.973
> 50		1.12 (1.05, 1.19)			

IU: international unit; RCT; randomized control trial, NR; not reported; OR: odds ratio; SMD: standardized mean difference.

intervention duration of ≤ 20-weeks exhibited stronger effects in lowering symptoms of depression. Moreover, the inverse association between lower serum vitamin D levels and depression was stronger among participants aged ≤ 50 years.

Recent studies have shown a significant association between vitamin D insufficiency or deficiency and depressive disorders [32]. Receptors of vitamin D and 1-alphahydroxylase enzymes, involved in the hydroxylation of 25-hydroxy vitamin D (25OHD) to the active form 1,25-dihydroxy vitamin D, are present on neurons and glia in multiple regions of the brain, including prefrontal cortex, substantia nigra, cingulate cortex and hippocampus and hypothalamus which have an important role in the pathophysiology of depression [13,30,34,39]. Vitamin D is involved in the synthesis of neurotrophic factors and neurotransmitters (serotonin, dopamine, adrenalin, and noradrenaline) through VDRs in the adrenal cortex and due to its steroidal structure, modulates the hypothalamic-pituitary-adrenal axis and GABA-A receptors activity [30,34].

During depression, inflammatory markers increase [34]. Meanwhile, vitamin D displays antioxidant effects in the central nervous system, enhances nerve growth factors and the gene expression of antioxidant agents, down-regulates cytokines and inflammatory mediators such as nuclear factor-kB, which is linked to psychosocial stress and depression [32]. In general, vitamin D prevents the onset of depression by taking role in six main pathways: 1) Controlling the expression of calcium homoeostasis genes; 3) Controlling serotonin synthesis *via* alleviating tryptophan hydroxylase 2 (TPH2) expression and repressing tryptophan hydroxylase1 (TPH1); 4) Controlling inflammation by reducing the expression of inflammatory cytokines; 5) Controlling the expression of mitochondrial proteins that preserve normal mitochondrial respiration; and 6) Preventing the hypermethylation of gene promotors such as Jumonji domain-containing protein 1A and 3 (JMJD1A, JMJD3) and lysine-specific demethylase 1 and 2 (LSD1, LSD2). These genes have a significant role in the activation of GABAergic neurons [29,42]. Fig. 5 exhibits the mechanism of action of vitamin D in preventing and lowering symptoms of depression.

Although the majority of RCTs have reported beneficial effects of vitamin D supplementation on depression and observational studies have confirmed the inverse association between serum vitamin D levels and depression, a significant between-study heterogeneity was observed among the included studies and a few studies observed contradictory results. Explanation for the inconsistent results in cohort studies can be found below: First, various study populations were included (tuberculosis, diabetes, fatigue, dialysis, and bipolar depression). Second, various scales were administered for measuring depressive symptoms. Third, some interventions had a shorter duration than others. Fourth, there were differences in baseline vitamin D level, dose, and study design [38]. In Gowda et al.'s study, subjects had a low depression level at baseline and not all of the patients were diagnosed as clinically depressed. Whereas, vitamin D is considered beneficial for depressed individuals rather than healthy ones. In fact, individual's baseline vitamin D level was not considered in the majority of studies. Hence, according to findings, it is possible that individuals who have low serum 25(OH)D level are expected to show greater benefit of vitamin D supplementation on depressive symptoms. Longitudinal studies have indicated that low vitamin D level was associated with developing depression in the future. Also, Vitamin D deficiency is common among the elderly, adolescents, obese individuals, people who are homebound and have limited sun exposure, and those with chronic illness. These individuals are already at high risk for developing depression. Multiple cross-sectional studies had unrepresentative samples, used self-reports of depression, and had small sample sizes [13]. Furthermore, heterogeneity attributed to analytic strategies and participant characteristics, various diagnostic criteria for depression and different methods for measuring 25(OH)D were also mentioned as sources of bias in cross-sectional studies [39].

In RCT studies, variability in the dose of vitamin D administered is an important factor affecting the results of studies. Few studies used high doses of vitamin D (more than the tolerable upper-level intake) and few studies administered lower doses which was not sufficient enough to achieve desirable results. It is evident that depression develops gradually, continues for several years, and symptoms change over time. Thus, in order to observe changes in symptoms of depression, organised longitudinal studies are recommended. The small number of studies with different study designs, substantial heterogeneity, and uncertain allocation concealment, along with limitations in blinding were other important factors for the high risk of bias observed in several RCTs [13,32,39] In addition, other factors such as administrating various doses of vitamin D for participants with and without clinical depression symptoms were also mentioned for the inconsistent results observed in previous studies. In a few studies, vitamin D supplementation was administered alongside fluoxetine therapy (known as a selective serotonin reuptake inhibitor). The different sources of vitamin D supplementation, either administered *via* intramuscular injection, capsule, or food were another source of heterogeneity [31,37].

Two of the meta-analyses of cohort studies [40,41] summarised the association between vitamin D deficiency and antepartum and postpartum depression. Several physiological and methodological factors have been mentioned for the inconsistent findings. During pregnancy,

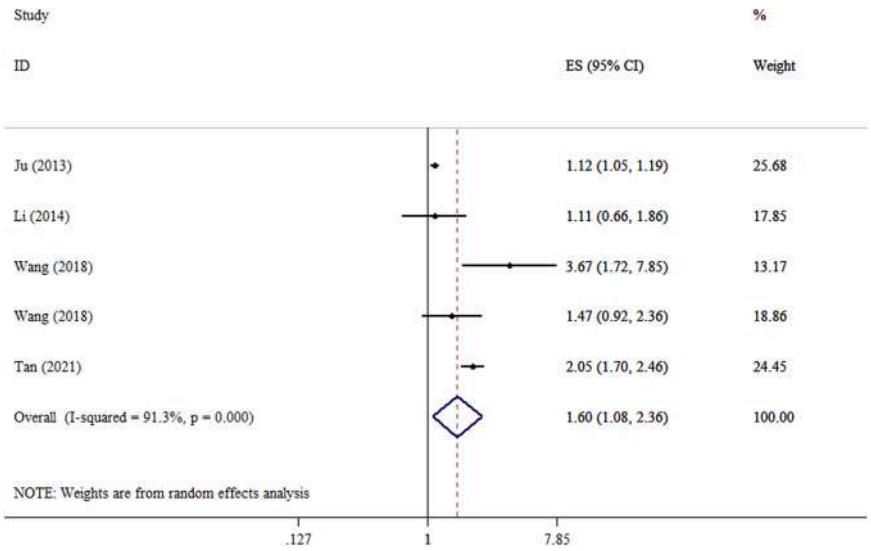

Fig. 3. Forest plot with mean difference and 95 % confidence intervals (CIs), the relationship between vitamin D and depression symptoms according to meta-analyses of cohort studies.

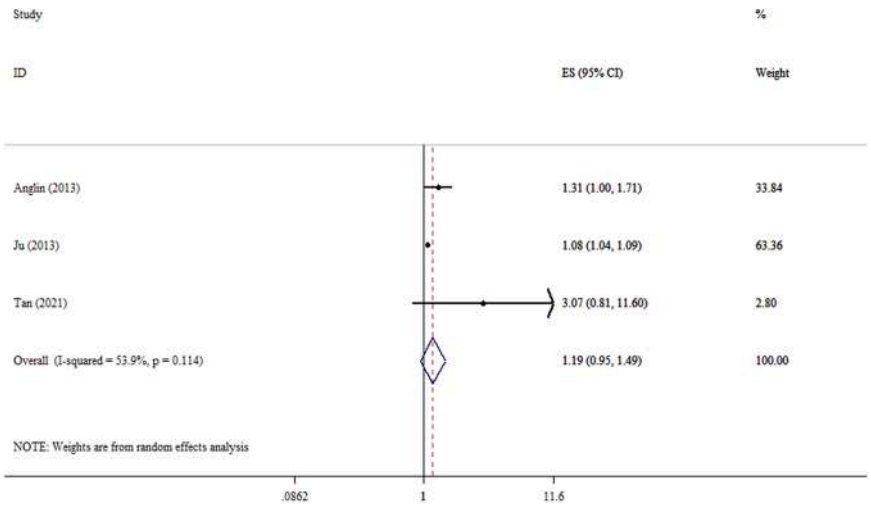

Fig. 4. Forest plot with mean difference and 95 % confidence intervals (CIs), the relationship between vitamin D and depression symptoms according to meta-analyses of cross-sectional studies.

vitamin D-binding proteins enhance and affect the concentration of measured vitamin D. Also, due to physiological adaptations, maternal 25-(OH) D concentration changes in order to supply the foetus with appropriate amounts of calcium for bone mineralisation. The short duration of the intervention and the small number of participants, previous history of depression, variations in the origin and period of depression, different cut-offs and methods for measuring vitamin D, and moderate-class quality of the included studies were mentioned as methodological biases. Moreover, most observational studies used a scaled cut-off instead of a clinical depression diagnosis and did not adjust for covariates such as life stress, social support and exercise. Additionally, in a meta-analysis by Tan et al., 2021, the therapeutic effects of both 25(OH)D2 and 25(OH)D3 were not analysed separately [40]. Due to the vascular changes during pregnancy, the maternal cerebral environment is sensitive to inflammation. Hence, the inflammatory nature of depression and anti-inflammatory and immunomodulatory features of vitamin D bring a connection between vitamin D deficiency and depression. The mechanism of action is mainly related to the hypothalamic–pituitary–adrenal (HPA) axis, the levels of estradiol, and pro-inflammatory cytokines involved in postpartum depression. Vitamin D decreases the production of pro-inflammatory cytokines. In addition, the sudden drop in oestrogen level after delivery reduces maternal calcium deposits and influence the gonadotropin-releasing hormone (GnRH) through the HPA axis. GnRH plays a significant role in the physiological regulation of neuronal activity and fertility cycle and decreases oestrogen levels [41]. However, due to limited outdoor activities and exposure to sunlight, less nutritious food consumption, and less physical activity engagement, pregnant women are prone to vitamin D deficiency. Thus, in cross-sectional studies, the reverse causality in which patients who have less exposure to sun end up having lower serum vitamin D levels is not ruled out [13, 40].

Our subgroup analyses for meta-analyses of RCTs indicated that when studies administered vitamin D in dosage of greater than 5000 IU/day for a duration of $\leq$ 20-weeks, stronger results were obtained. Findings indicated that studies which used less than the recommended tolerable upper-level intake of vitamin D ($<$ 4000 IU/d) didn't observe desirable effects. One study claimed that lower doses of vitamin D were not sufficient to cause any change in the occurrence and symptoms of depression [32]. When vitamin D is administered at insufficient doses,

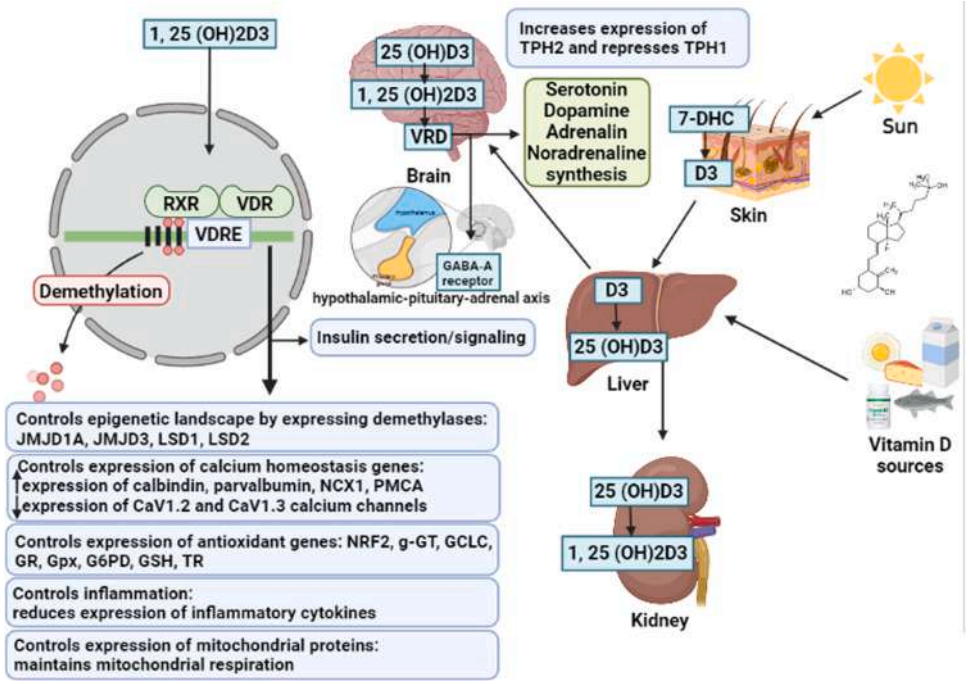

Fig. 5. The mechanism of action of vitamin D in preventing and declining symptoms of depression.

the upregulation of the level of 25OHD from deficient to sufficient is not expected. However, higher doses of vitamin D are beneficial when administered for patients with vitamin D deficiency (< 50 nmol/L serum levels of vitamin D at baseline) [30]. Another study indicated that vitamin D supplementation had a large effect in major depressive disorders; whereas, vitamin D did not affect emotions in healthy subjects. Several studies claimed that the positive effects of vitamin D on emotions were expressed when administered for more than eight weeks [29, 32,34]. Depression develops gradually, continues for several years, and symptoms change over time; supplementation must be applied for at least eight weeks and according to sub-group analyses, superior effects are observed when administered for ≤ 20-weeks, because compliance is weak in long duration interventions. Moreover, vitamin D is known as a secosteroid hormone and steroid-like elements act by transcription in the nucleus; Hence, it requires several weeks to take effect [32]. Cheng et al., investigated the effect of using antidepressants along with vitamin D administration on depression. In this regard, they separated studies into three categories: taking antidepressants, not taking antidepressants, not mentioning taking antidepressants. The significant effect on negative emotion was only observed in the last situation. However, it must be noted that the number of studies mentioning the last item was higher. Thus, for studies not reporting using antidepressants or not, the effect of vitamin D was significant [34].

Subgroup analyses for meta-analyses of cohort studies indicated that the association between lower serum vitamin D levels and depression was stronger in participants ≤ 50 years. One study mentioned that vitamin D supplementation was not effective in individuals aged more than 65 years; however, subjects aged 18–65 years achieved more benefits [34]. Jeremiah et al., also confirmed more beneficial effects of vitamin D supplementation for patients younger than 50 years than for those older than 50 years. This might be due to the fact that older individuals reveal chronic courses of depression and respond less to antidepressant therapies in comparison to younger ones. Depression has a bidirectional relationship with insulin resistance; therefore, impairment in β-cell function and adaptation to insulin resistance caused by aging might limit the effectiveness of vitamin D supplementation in elderly depressed subjects [35]. Moreover, due to diminished dietary intake, limited sun exposure, restriction of outdoor activities, and kidneys' declined capacity for hydroxylation to produce adequate amounts of calcitriol, older adults are at major risk of developing vitamin D deficiency [39]. Ju et al., reported significant differences in the association between 25(OH)D levels and depression. In fact, they indicated a significant 4 % reduction in depression risk in individuals less than 60 years and a 10 % in elderly greater than 60 years. Despite the comorbidities in elderly, due to the effectiveness of vitamin D supplementation among depressed patients with vitamin D deficiency and the higher doses administered to this age group, vitamin D supplementation is rather beneficial for this age group. However, because of the limited number of studies conducted on this age group, findings should be interpreted with caution [39]. In this umbrella meta-analysis, only the subgroup of original studies that included participants not on antidepressants were included. Comparing the efficiency of vitamin D supplementation among females or both genders did not indicate any major differences because significant effects were observed in both categories. This may explain the benefits of vitamin D supplementation in both genders. Based on sub-group analyses, cohort studies expressed an inverse relationship between vitamin D deficiency and depression better than cross-sectional studies. In cross-sectional studies, the biases caused by reverse causality (eg, less outdoor activity/nutrient intake, and thus low Vit D) were not ruled out. Moreover, cross-sectional studies had small sample sizes with misleading samples, unadjusted data (life stress, social support, exercise), and self-reported depression. In contrast, cohort studies are methodologically of better quality compared to cross-sectional studies [13].

The limitations of the present study are the various ranges of study populations with different characteristics such as maternal depression along with other types of depression (moderate and/or severe depression). Moreover, environmental factors such as sunlight, altitude, or diet on serum 25(OH)D status were not considered in the included meta-analyses. Also, individuals baseline serum vitamin D level was not measured and reported in all of the trials, as some participants had low serum vitamin D level which could affect the symptoms of depression and the treatment with vitamin D supplementation. Despite these limitations, several strengths could be attributed to the present umbrella meta-analysis. The inclusion of multiple high and/or moderate quality observational studies and RCTs according to the AMSTAR2

questionnaire is the most notable strength of this study. Another strength was performing sub-group analyses for meta-analyses of RCTs and meta-analyses of cohort studies.

5. Conclusion

The present umbrella meta-analysis confirms the potential benefits of vitamin D supplementation in reducing symptoms of depression and an inverse relationship between higher serum levels of vitamin D and overall depression. Vitamin D supplementation in studies using dosage of $>$ 5000 IU/day and intervention duration of $\leq$ 20-weeks exhibited better effects in lowering depression symptoms. Moreover, a greater risk of depression was shown among participants aged $\leq$ 50 with lower serum vitamin D levels.

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Declaration of Interest

The authors declare that there is no conflict of interests.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106605.

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