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The effects of vitamin D supplementation on mental health, and biomarkers of inflammation and oxidative stress in patients with psychiatric disorders: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: In the current meta-analysis of randomized controlled trials (RCTs), the effects of vitamin D supplementation on mental health, and biomarkers of inflammation and oxidative stress in patients with psychiatric disorders are assessed.

Methods: The following databases were search up to March 2019: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The quality of the relevant extracted data was assessed according to the Cochrane risk of bias tool. Data were pooled by the use of the inverse variance method and expressed as mean difference with 95% Confidence Intervals (95% CI).

Results: Eleven effect sizes from nine studies were included in the final analyses. A pooled analysis of 9 effect sizes showed a significant reduction in Beck Depression Inventory (BDI) score following supplementation with vitamin D [weighted mean difference (WMD): -3.91; 95% CI: -5.15 -2.66), I^2= 85.9%]. Combining data from two available studies on the effects of vitamin D supplementation on Pittsburgh Sleep Quality Index (PSQI) also revealed a significant reduction in this score following the intervention (WMD: -1.78; 95% CI: -2.28, -1.28). In addition, there were significant increase in glutathione (GSH) through 3 studies (WMD: 180.70; 95% CI: 6.76, 354.64), and in total antioxidant capacity (TAC) through 3 studies (WMD: 90.09; 95% CI: 56.36, 123.82) after vitamin D supplementation. Combining data from five studies, we found a significant reduction in C-reactive protein (CRP) concentrations after vitamin D supplementation (WMD: -1.74; 95% CI: -2.82, -0.66).

Conclusions: Overall, the current meta-analysis demonstrated that taking vitamin D supplements among patients with psychiatric disorders had beneficial effects on BDI, PSQI, GSH, TAC and CRP levels, but did not affect other biomarkers of inflammation and oxidative stress.

1. Introduction

Psychiatric disorders, as a group of diseases which mainly included depression, anxiety, substance-related disorders and schizophrenia, are prevalent worldwide (Hyman et al., 2006). Almost one third of adults experienced a common mental disorder across their lifetimes (Steel et al., 2014). These conditions are associated with excess premature all-cause mortality and increased global burden of disease (Charlson et al., 2015). Current estimates indicated that psychiatric disorders accounted for 13% of global disability-adjusted life-years (Vigo et al., 2016). Chronic inflammatory state and elevated reactive oxygen species (ROS) present as major components of mental illness pathology (Najjar et al., 2013).

Based on the results of observational studies, psychiatric disorders

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are associated with lower vitamin D status (Belvederi Murri et al., 2013). Vitamin D is a lipid-soluble vitamin, which has several hormonal functions. Beside to calcium-phosphorus homeostasis and bone metabolism, it involves in antioxidant defense system, anti-inflammatory process, and immune modulation (Sassi et al., 2018). Vitamin D is proposed to act as a membrane antioxidant. It also increases the gene expression levels of antioxidants agents (Brown and Slatopolsky, 2008). Vitamin D also decreases cytokine generation via inhibitory effects on the activation and expression of nuclear factor kappa B (NF-κB) and other related genes (Cohen-Lahav et al., 2006). The evidence has suggested that vitamin D may improve mood and behavior by modulating the biosynthesis of neurotransmitters and neurotrophic factors (Macova et al., 2017).

Previously, Spedding (2014) performed a meta-analysis to examine the effects of vitamin D supplementation in the management of depression and concluded that taking vitamin D supplements improved depressive symptoms in studies without biological flaws. Another meta-analysis by Li et al. (2014) showed that vitamin D supplementation did not improve depressive score in adults; while, all of the included trials except one, conducted among participants without clinical depression. Two other meta-analyses failed to find any beneficial effects of vitamin D supplementation on depressive symptoms among individuals with different health conditions (Gowda et al., 2015; Shaffer et al., 2014). Several evidence evaluated the effects of vitamin D supplementation on oxidative stress and inflammatory markers. Recently, a systematic review and meta-analysis conducted by Sepidarkish et al. (2019) revealed that vitamin D supplementation significantly increased some antioxidants levels and led to a remarkable decrease in malondialdehyde (MDA) values, while the serum nitric oxide (NO) concentrations were unchanged. Our previous study indicated that vitamin D supplementation improved plasma levels of oxidative stress markers and decreased C-reactive protein (CRP) values among patients with diabetes (Mansournia et al., 2018). Several randomized clinical trials (RCTs) have indicated a promising effect of vitamin D supplementation on mental health, inflammatory and oxidative stress parameters in patients with psychiatric disorders; others did not report such effect. However, the sample size of these trials was small, the dosage and frequency of supplementation were different, the quality of studies was variable; therefore, the results were inconsistent.

This meta-analysis was carried out to summarize the available evidence of RCTs to clarify the effects of vitamin D supplementation on parameters of mental health, inflammation and oxidative stress markers in patients with psychiatric disorders.

2. Methods

2.1. Search strategy

We used the relevant published articles which are extracted from Medline, Embase, Cochrane Library, and Web of Science databases until March 2019 for identifying Eligible RCTs using manually searching the reference list of the retrieved papers. In this regard, we applied the Databases of International Standard Randomized Controlled Trial Number Register and Meta-register for obtaining the RCTs for all ongoing trials. Reports retrieved that assessed the effects of vitamin D supplementation on various mental health parameters, and oxidative stress and inflammation markers by applying the following MeSH and text words, including intervention [("*colecalciferol*" AND "vitamin D" AND "*ergocalciferol*" AND "supplementation" OR "intake")], and outcomes ["Beck Depression Inventory (BDI)" OR "CRP" OR "NO" OR "MDA" OR "total antioxidant capacity (TAC)" OR "glutathione (GSH)"], and patients ["psychotic disorder" OR "depressive disorders" OR "mental disorder" OR "mental health" OR "mood" OR "depression" OR "attention deficit disorder with hyperactivity" OR "attention deficit hyperactivity disorder (ADHD)" OR "autism spectrum disorder" OR "Tourette syndrome" OR "obsessive-compulsive disorder" OR "anxiety disorder" OR "AD" OR "schizophrenia" OR "bipolar disorder"]. Moreover, we used additional manual searches (i.e., reference lists of associated reports; former review studies were assessed to elevate sensitivity in search procedure.

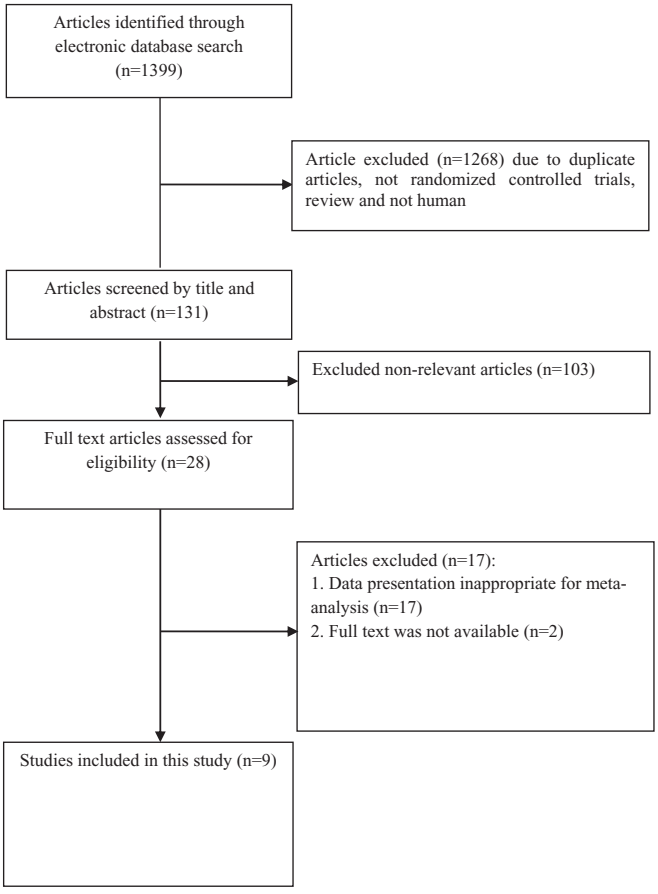


Fig. 1. Literature search and review flowchart for selection of studies.

2.2. Inclusion and exclusion criteria

All CTs with either parallel or cross-over design that investigated the effect of any dosages of vitamin D supplementation on mental health parameters, and oxidative stress and inflammation markers, and used placebo as the control group among patients with psychiatric disorders were included. Animal experiments, *in vitro* studies, case reports, observational studies, studies that did not have a control group, and those studies that did not achieve the least quality score were excluded. Studies in which vitamin D analogs were used as the intervention and those without placebo group were also excluded.

2.3. Data extraction and quality assessment

We employed two authors (EA and HM) independently which extracted the data and evaluated its quality applying the Cochrane Collaboration risk of bias tool and standard forms, respectively (Higgins et al., 2011; Mansournia et al., 2017). This tool is depended on information from the following domains, including allocation concealment, blinding of cases and outcome evaluation, randomization generation, selective outcome reporting, incomplete outcome data, and other sources of bias. The disagreements among two authors were resolved by third author (ZA). Eligible studies based on the following characteristics were abstracted: publication year, first authors' name, study design, study location, age, sex, and body composition and/or metabolic profiles of study subjects and related measures of variance,

Table 1
Characteristics of the studies included in the analysis.

Authors (ref)	Publication year	Country	Sample size (control/ intervention)	Duration (wk)	Age (years)	Intervention (type and dosage)
Mozaffari-Khosravi et al. (2013)	2013	Iran	34/36	12	20–60	150,000 IU vitamin D single injection
			34/39	12	20–60	300,000 IU vitamin D single injection
Khoraminya et al. (2013)	2013	Iran	20/20	8	18–65	1,500 IU vitamin D3 + 20 mg fluxetine
Sepehrmanesh et al. (2016)	2016	Iran	18/18	8	18–65	50,000 IU/week vitamin D
Wang et al. (2016)	2016	China	364/362	52	≥ 18	50,000 IU/week vitamin D3
Ghaderi et al. (2017)	2017	Iran	34/34	12	25–70	50,000 IU/2 weeks vitamin D
Majid and Ahmad (2018)	2018	Iran	45/44	8	20–50	50,000 IU/2 weeks vitamin D
Zhang et al. (2018)	2018	China	64/56	8	≥18	100,000 IU/week vitamin D3
Ghaderi et al. (2019)	2019	Iran	30/30	12	25–65	50,000 IU/2 weeks vitamin D + probiotic
Far et al. (2018)	2018	Iran	20/19	8	18–65	50,000 IU/week vitamin D3 + cognitive behavioral therapy
			13/13	8	18–65	50,000 IU/week vitamin D3 + drug therapy

Table 2
The effects of vitamin D supplementation on markers of mental health, inflammation and oxidative stress.

Variables	Number of effect sizes	Weighted mean difference	CI 95%	Heterogeneity	
				I^2 (%)	P-value heterogeneity
BDI	9	-3.91	-5.15, -2.66	85.9	< 0.001
PSQI	2	-1.78	-2.28, -1.28	0.0	0.32
GSH	3	180.70	6.76, 354.64	85.8	< 0.01
TAC	3	90.09	56.36, 123.82	0.0	0.55
MDA	2	-0.19	-0.77, 0.40	86.9	< 0.01
NO	2	-0.82	-1.97, 0.32	11.1	0.28
CRP	5	-1.74	-2.82, -0.66	89.3	< 0.001

BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; GSH, Glutathione; TAC, Total Antioxidant Capacity; MDA, Malondialdehyde; NO, Nitric Oxide; CRP, C-Reactive Protein.

number of cases in the control and intervention groups, and duration of the intervention.

2.4. Heterogeneity and publication biases

In the present meta-analysis study, chi-square test (Overvad et al., 1999), and quantified by the I^2 statistic (Higgins et al., 2003) were used for assessing the heterogeneity of the results in the included reports. The funnel plot used for evaluating the publication bias and also Egger's test performed to assess statistical significance (Egger et al., 1997).

2.5. Summary measures

We obtained the mean difference and carried out the meta-analyses for the impacts of vitamin D supplementation on oxidative stress and inflammation markers and different mental health parameters, for all included RCTs by applying the inverse variance approach. To reach the impact sizes the change score approach was applied, because the correlations between end measurements and baseline were more than 1/2 (Matthews, 2006). The random effect model was employed to study the pooled mean difference with 95 % confidence intervals (CIs). If heterogeneity was high between studies, random effect model was used to calculate the pooled estimates. Baseline and final values of the mentioned outcomes for both intervention and placebo groups were extracted from the included studies to calculate mean changes with standard deviation (SD) for each variable. In addition, we used subgroup analysis to detect probable sources of heterogeneity using a fixed-effects model. P-values < 0.05 were obtained as statistically significant. Review Manager 5.3 and Stata version 11.0 (Stata Corp., College Station, TX) were used for statistical analyses.

3. Results

3.1. Study characteristics

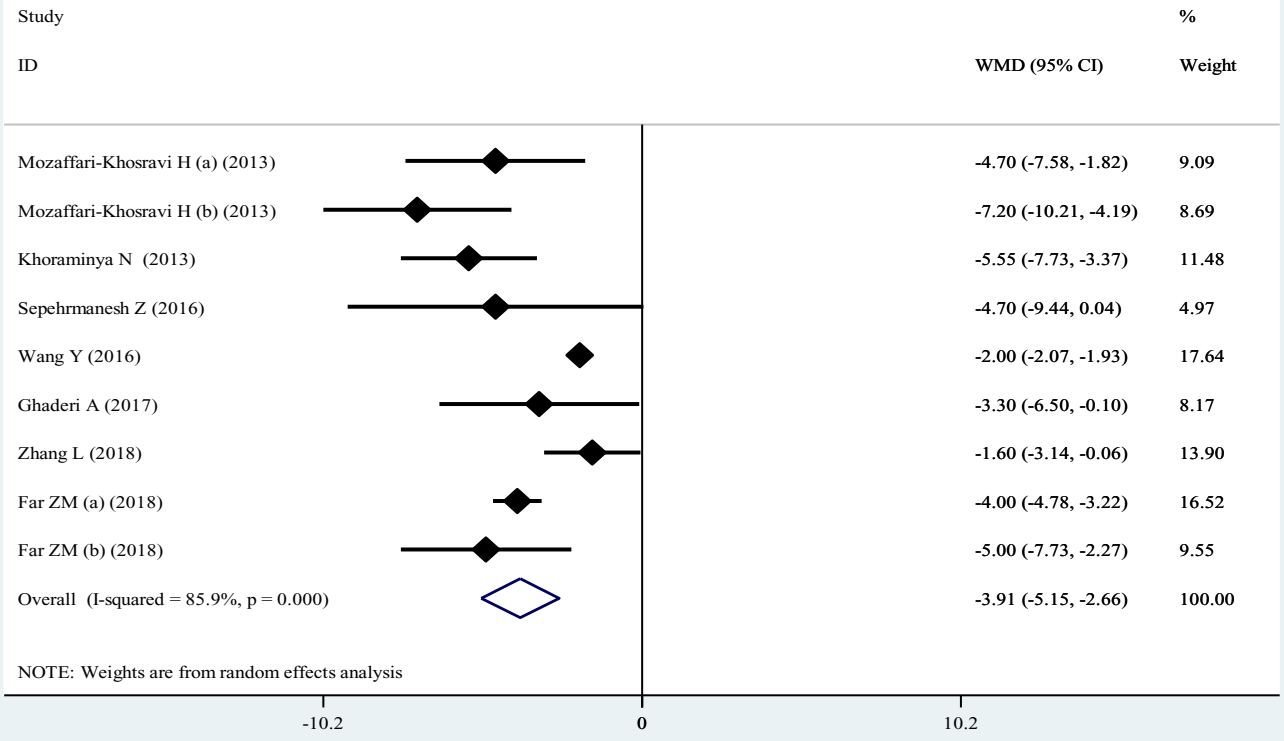
In total, data from nine studies with 11 effect sizes were included in the current meta-analysis. Flow-diagram of study selection is shown in Fig. 1. Characteristics of included studies are presented in Table 1. A total of 1348 individuals aged 18 to 65 years old (671 in intervention and 677 in control groups) were participated in these studies. The study duration was varied between 8 and 52 weeks. Vitamin D was used in usual dose (50,000 IU) in some studies, while the others used high dosages of vitamin D.

3.2. Findings for the effects of vitamin D supplementation on parameters of mental health

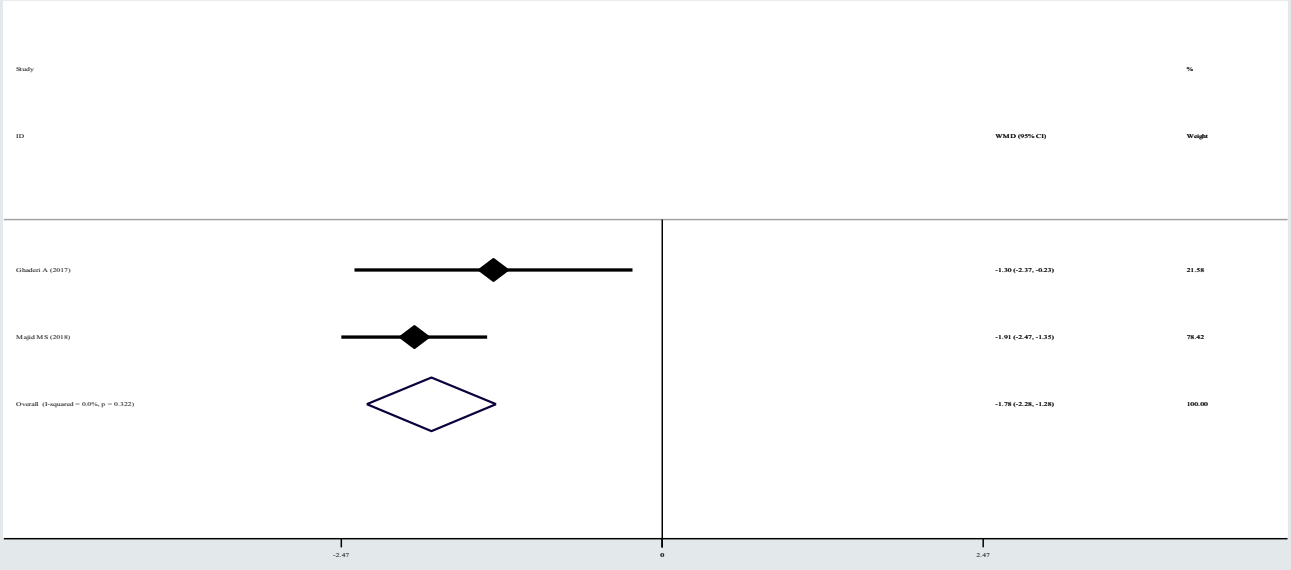
A pooled analysis of 9 effect sizes from 8 studies showed a significant reduction in BDI score following vitamin D supplementation [weighted mean difference (WMD): -3.91; 95% CI: -5.15, -2.66), I^2 = 85.9%] (Table 2 & Fig. 2A). Subgroup analyses were performed to investigate the potential sources of between-study heterogeneity. We stratified studies based on study location, supplement dosage, study duration (< 12 vs. ≥12 weeks), study sample size (< 50 vs. ≥50), and outcome assessment method (BDI/DSM-IV/other methods or combination) (Table 3). Findings remained unchanged in all subgroup analyses. In addition, combining data from two available studies on the effects of vitamin D supplementation on PSQI also revealed a significant reduction in this score following the intervention (WMD: -1.78; 95% CI: -2.28, -1.28) (Table 2 & Fig. 2B).

3.3. Findings for the effects of vitamin D supplementation on oxidative stress

Our meta-analysis showed a significant increase in GSH through 3 studies (WMD: 180.70; 95% CI: 6.76, 354.64) and in TAC levels

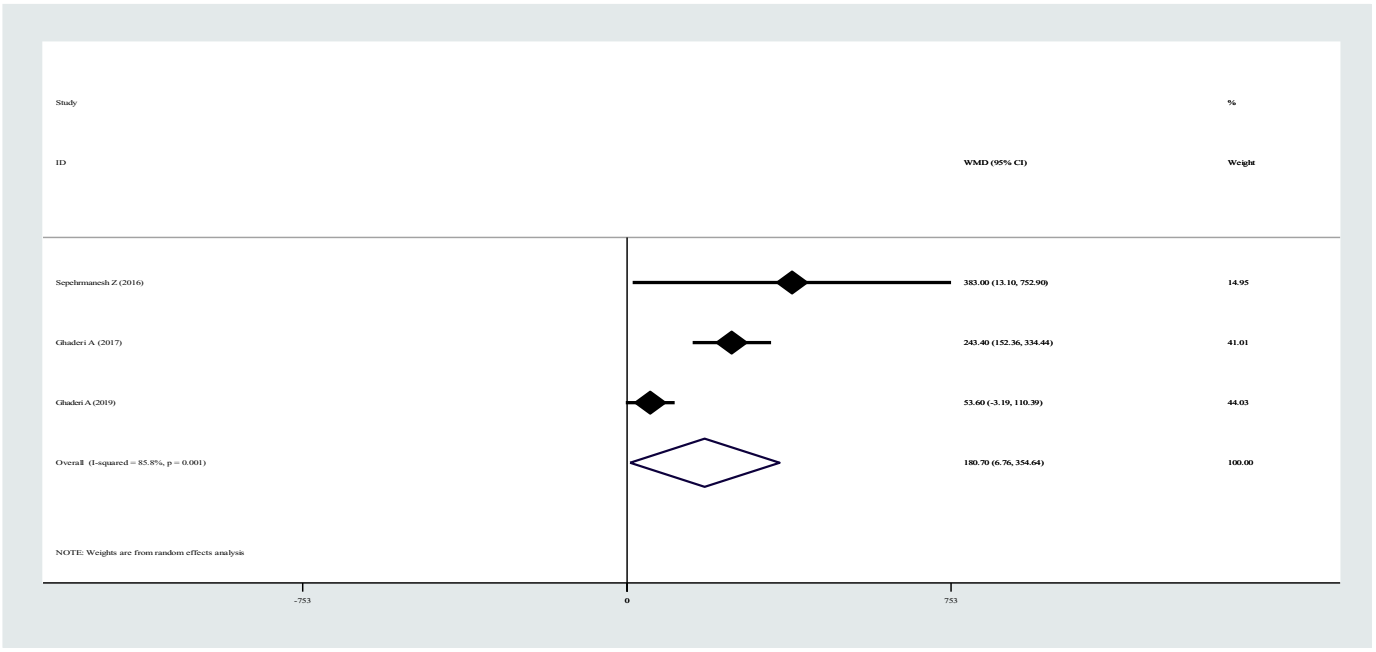


A



B

Fig. 2. Meta-analysis mental health and biomarkers of inflammation and oxidative stress weighted mean difference estimates for A) BDI, B) PSQI, C) GSH, D) TAC, E) MDA, F) NO, and G) CRP in the vitamin D supplements and placebo groups (CI = 95%).



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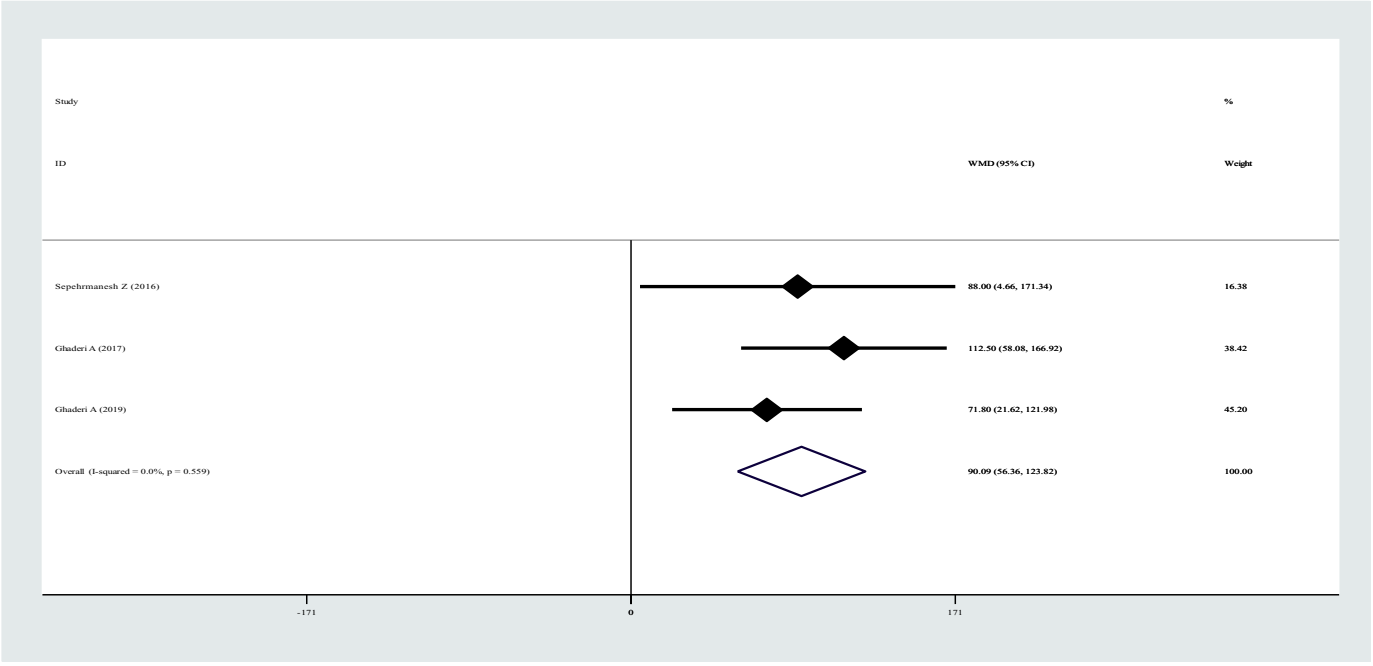


D

Fig. 2. (*continued*)

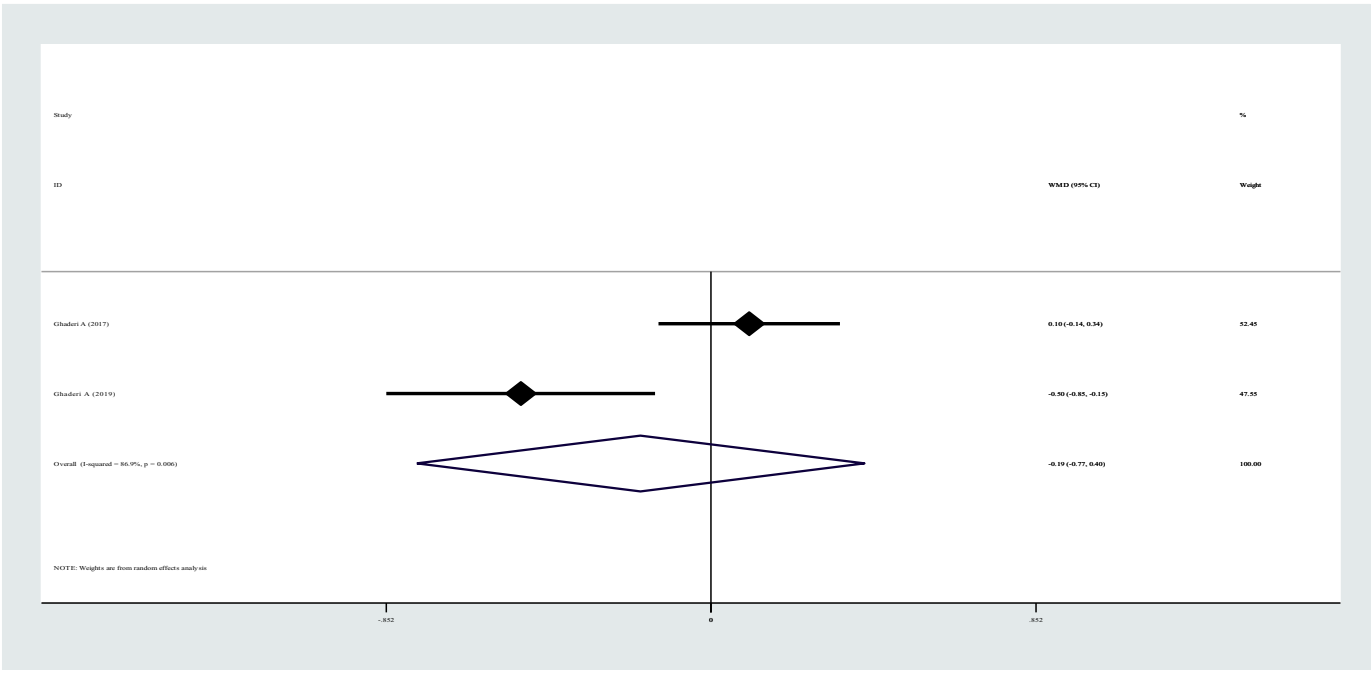
through 3 studies (WMD: 90.09; 95% CI: 56.36, 123.82) after vitamin D supplementation (Table 2 & Fig. 2C and D). In contrast, no significant change was found in MDA through 2 studies (WMD: -0.19; 95% CI: -0.77, 0.40) and NO levels through 2 studies (WMD: -0.82; 95% CI: -1.97, 0.32) following vitamin D supplementation (Table 2 & Fig. 2E and F).

3.4. Findings for the effects of vitamin D supplementation on CRP levels

Combining data from five studies, we found a significant reduction in CRP concentrations after vitamin D supplementation (-1.74; 95% CI: -2.82, -0.66) (Table 2 & Fig. 2 G), which remained unchanged in all subgroup analyses, even in stratification by the participants' health condition (depression/other mental disorders) (Table 3).

4. Discussion

In this meta-analysis, for the first time, we pooled data from available evidence of vitamin D supplementation in patients with psychiatric disease. The results of present study revealed that the consumption of vitamin D supplements improved BDI, PSQI, GSH, TAC and CRP levels, but did not affect other biomarkers of inflammation and oxidative



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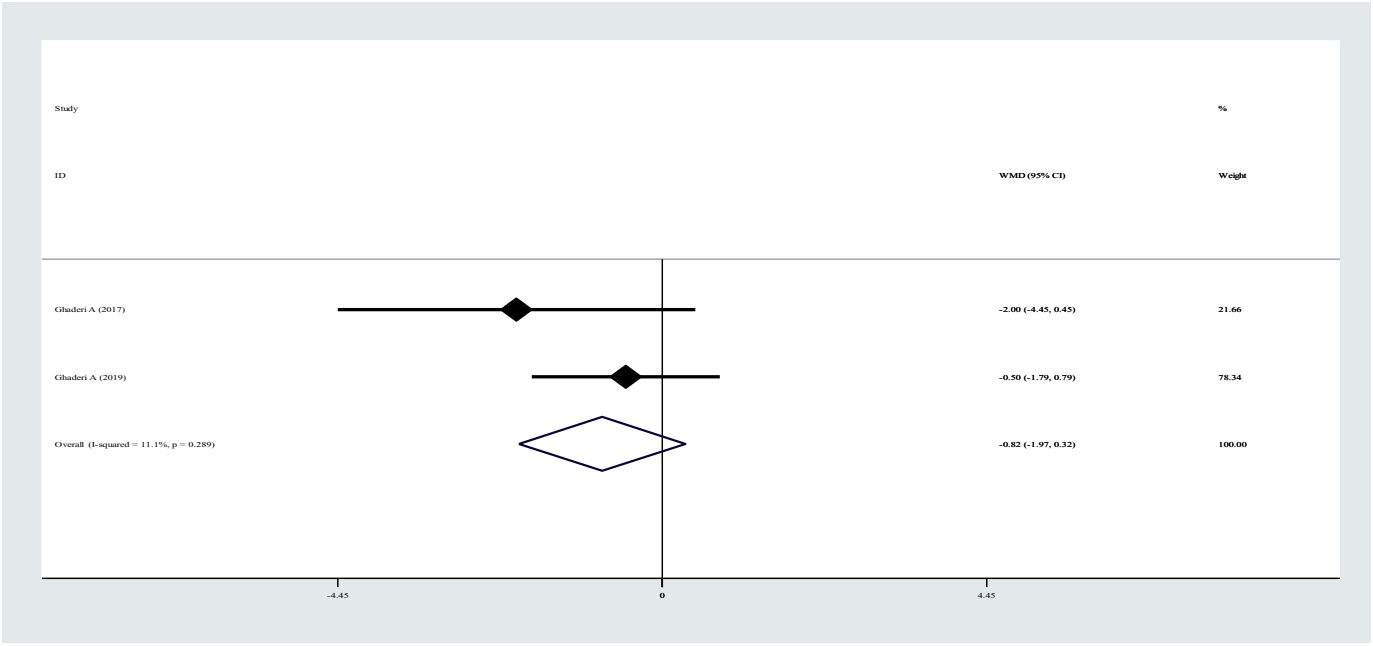


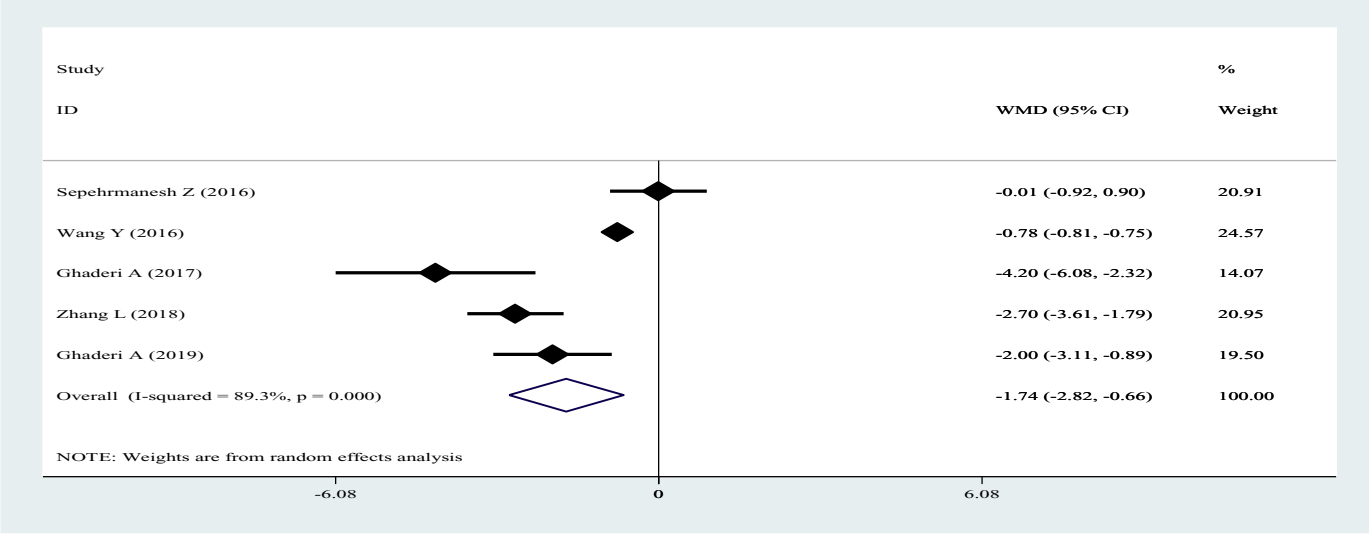
F

Fig. 2. (*continued*)

stress.

4.1. Effects on mental health

Psychiatric disorders are associated with mood and emotional challenges leading to impaired individual function and quality of life (Hyman et al., 2006). These conditions are accompanied by increased oxidative stress and the inflammatory state (Maes et al., 2011). In the present study, we demonstrated that vitamin D supplementation decreased BDI score and PSQI in patients with psychiatric diseases. Similar to our findings a meta-analysis by Spedding (2014) revealed that vitamin D supplementation led to a significant reduction in the indicators of depression in studies without biological flaws. Whereas, Shaffer et al. (2014) demonstrated that vitamin D supplementation had no significant effects on depressive symptoms in patient with various underlying conditions, while the authors found a moderate improvement across trials that recruited patients with depression. In contrast to our findings, in a meta-analysis by Gowda et al. (2015), vitamin D supplementation resulted in no significant reduction in depression symptoms. Another meta-analysis by Li et al. (2014) also revealed that



G

Fig. 2. (*continued*)

Table 3
Subgroup analyses for the effects of vitamin D supplementation on markers of mental health, inflammation and oxidative stress.

Variables		Subgroups	Number of effect sizes	Pooled WMD	95% CI	I^2 (%)	Between-study I^2 (%)
BDI	Study location	Iran	7	-4.34	-4.99, -3.69	0.7	< 0.001
		China	2	-2.00	-2.07, -1.93	0.0	
	Supplement dosage	Usual	6	-2.02	-2.09, -1.95	88.1	< 0.001
		High	3	-3.03	-4.27, -1.79	82.3	
	Study duration	< 12 weeks	5	-3.79	-4.43, -3.15	65.0	< 0.001
		≥12 weeks	4	-2.00	-2.07, -1.94	79.0	
	Study sample size	n < 50	4	-4.24	-4.94, -3.54	0.0	< 0.001
		n ≥ 50	5	-2.00	-2.07, -1.93	72.5	
	Outcome assessment method	BDI	4	-4.25	-4.96, -3.55	31.3	< 0.01
		DSM-IV	3	-3.04	-4.25, -1.82	77.6	
		Not reported	2	-2.00	-2.07, -1.93	0.0	
CRP	Study location	Iran	3	-1.23	-1.89, -0.57	89.1	0.18
		China	2	-0.78	-0.81, -0.75	94.2	
	Outcome assessment method	DSM-IV	3	-1.52	-2.08, -0.97	88.8	0.009
		Not reported	2	-0.78	-0.81, -0.75	92.1	
	Health condition	Depression	3	-0.78	-0.81, -0.75	99.89	< 0.001
		Other mental disorders	2	-2.57	-3.53, -1.61	74.3	
	Study duration	< 12 weeks	2	-1.36	-2.01, -0.72	94.1	0.07
		≥12 weeks	3	-0.78	-0.81, -0.75	88.4	

BDI: Beck Depression Inventory; CRP: C–Reactive Protein.

vitamin D supplementation had no significant effects on depressive symptoms in adults; however, most of the included RCTs investigated the effects of vitamin D supplementation in participants at risk of depression and only one study was conducted in patients with MDD. Based on previous investigations, depressive symptoms increase the risk of suicide in patients with psychiatric disease (Fiedorowicz et al., 2019). This may suggest that improving depression scores in patients suffered from mental disorders could have protective effects against fatality rate. In addition, there is an association between BDI score and health-related quality of life (Riihimaki et al., 2016). There are several mechanisms by which vitamin D may improve psychological symptoms. It is proposed that vitamin D activates receptors in the brain, in areas which it is implicated in the regulation of behavior, stimulates neurotrophin release, and protects the brain against oxidative damages and inflammation (Cherniack et al., 2009). In addition, it is proposed that increased neural levels of calcium as a result of increased glutamate, is a major factor for the onset of depression. Vitamin D modulates the expression of calcium pumps and buffers which results in decreasing calcium levels and regulating calcium signaling pathways (Berridge, 2017). Moreover, vitamin D induces the transcription of serotonin-synthesizing gene tryptophan hydroxylase 2 in the brain, which contains a vitamin D response element (VDRE) and contributes to improving psychiatric symptoms (Patrick and Ames, 2014).

4.2. Effects on biomarkers of oxidative stress

Results of the present study showed that vitamin D supplementation significantly improved TAC and GSH levels, but did not influence MDA levels. Recently, in a study conducted by Sepidarkish et al. (2019), vitamin D supplementation significantly increased TAC and GSH levels, and led to a remarkable reduction in MDA levels; while serum NO concentrations were unchanged. Our previous work indicated that vitamin D supplementation in diabetic patients increased NO, GSH and TAC levels and decreased MDA values (Mansournia et al., 2018). Another meta-analysis revealed that vitamin D supplementation led to a significant rise in TAC and a significant decrease in MDA levels, while GSH and NO levels remained unchanged (Akbari et al., 2018). The elevated oxidative burden may contribute to endothelial dysfunction

which is a shared mechanism for the association between depressive disorders and CVD (Najjar et al., 2013). Oxidative stress increases the risk of atherosclerosis in individuals with depression (Yager et al., 2010). Decreased antioxidant capacity and increased ROS damage protein, DNA, and membrane fatty acids which results in cell apoptosis, neurodegeneration and volumetric changes in the brain (Maes et al., 2011). Moreover, multiple studies have reported that antioxidant therapy improved clinical symptoms of psychiatric disorders (Pandya et al., 2013). The evidence suggests that vitamin D may increase the gene expression of several antioxidants including GSH, glutathione peroxidase, and superoxide dismutase through binding to VDRE (Brown and Slatopolsky, 2008). In addition, the structural similarities between vitamin D and cholesterol and ergosterl are responsible for its membrane antioxidant properties (Wiseman, 1993). Vitamin D intake can improve oxidative stress through its antioxidant properties (Cetinkalp et al., 2009), and decreasing production of *ROS* and pro-inflammatory cytokines (Jain and Micinski, 2013).

4.3. Effects on inflammatory markers

Our findings indicated that vitamin D supplementation significantly reduced CRP, but did not affect NO levels. While other studies indicated that vitamin D supplementation significantly decreased CRP levels in all (Sepidarkish et al., 2019), as well as, among patients with diabetes (Mansournia et al., 2018), or had beneficial effects on serum CRP concentrations (Akbari et al., 2018). However, a meta-analysis by Rodriguez et al. (2018) failed to find any significant improvement in plasma CRP values among patients with heart failure. Activation of inflammatory responses is one of the contributing mechanisms which increase the risk of metabolic syndrome in patients with psychiatric disorders (Penninx and Lange, 2018). The difference in dosages of vitamin D used, the type of vitamin D used (vitamin D alone or vitamin D combined with other nutrients), study design, and characteristics of study populations are some of the possible reasons explaining discrepant results regarding the effect of vitamin D on mental health, inflammation and oxidative stress markers among these studies.

4.4. Limitations

This meta-analysis has few limitations. There were few eligible RCTs and a modest number of participants to be included in the meta-analysis to analyze the clinical effectiveness of vitamin D on mental health, and biomarkers of inflammation and oxidative stress. Due to the heterogeneity between studies, as a result of the variations in duration of vitamin D supplementation, the dosage or frequency of vitamin D used, the results of this meta-analysis should be interpreted with caution.

5. Conclusions

Overall, the current meta-analysis demonstrated that vitamin D supplementation among patients with psychiatric disorders had beneficial effects on BDI, PSQI, GSH, TAC and CRP levels, but did not affect other biomarkers of inflammation and oxidative stress.

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Competing interests

The authors declare no conflict of interest.

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Author contributions

ZA, EA and AM contributed in conception, design, statistical analysis and drafting of the manuscript. HM, HJ, FK, MZ and AG. contributed in conception, data collection and manuscript drafting. The final version was confirmed by all authors for submission.

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Conflict of interest

None.

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