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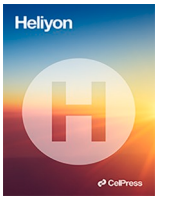

Research article

Vitamin D improves irritable bowel syndrome symptoms: A meta-analysis

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ABSTRACT

Background & aims: Approximately 5%–10% of the population in most geographical regions suffer from irritable bowel syndrome (IBS), which creates a significant burden on individual patients, their families, and society. Recent advances in IBS therapies have indicated that vitamin D supplementation is potential to relieve its symptoms, but evidence of this is lacking. This meta-analysis aimed to estimate the effect of vitamin D on gastrointestinal (GI) symptoms in IBS patients.

Methods: The PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were searched from their inception to March 2022. Statistical analyses were performed with Stata 12.0 and Review Manager 5.4, and statistical significance was defined as $P < 0.05$. The pooled results are presented as weighted mean differences (WMD) and 95% confidence intervals (CI).

Results: The meta-analysis including 6 randomized controlled trials (RCT) with 572 patients found a significant difference in IBS symptom severity score (WMD, −34.88; 95% CI, −62.48 to −7.27; $P = 0.013$; random-effects model) but no significant difference in IBS quality of life score (WMD, 3.33; 95% CI, −5.12 to −11.77; $P = 0.440$; random-effects model).

Conclusions: Overall, IBS patients may benefit from vitamin D supplementation to reduce the GI symptoms.

1. Introduction

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) diseases involving abdominal pain associated with a change in stool form or frequency that affects approximately 5%–10% of the population in most geographical regions [1]. IBS creates a significant burden for individual patients, their families, and society [2]. Unfortunately, its complex pathophysiology, which involves the gut-brain axis, altered motility, visceral hypersensitivity, the gut microenvironment, stress, and other factors, is not yet fully understood [3]. Current IBS treatments primarily focus on relieving symptoms and are limited or even invalid [4]. Thus, it is necessary to explore new ways to relieve GI symptoms. Interestingly, many studies have consistently reported the presence of a vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) < 50 nmol/L or 20 ng/mL) in IBS patients [5,6]. Moreover, some randomized controlled trials (RCT) reported that taking vitamin D supplements improve IBS symptoms [7–11].

Vitamin D is a prohormone mainly derived from synthesis in the skin by sunlight exposure, diet, and oral supplementation and is

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sequentially subjected to hepatic and renal dihydroxylation to yield 25(OH)D, the main form in the plasma, and 1,25(OH)D, the active form. Therefore, all studies use serum 25(OH)D levels to measure vitamin D levels in participants. Regarding the mechanism of vitamin D in IBS, it may effectively improve bowel function to reduce symptoms by modulating the immune system and inflammatory processes, regulating the gut microbiome, and even influencing neural activity [12]; however, this hypothesis has not been proven. The current meta-analysis of RCT investigated the effect of vitamin D versus control placebo on the GI symptoms and quality of life (QoL) of patients with IBS.

2. Methods

The meta-analysis was registered in PROSPERO (registration number: CRD42021291742) and the study was executed and reported according to the PRISMA statement guidelines [13].

2.1. Selection criteria

Studies were included if they met the following criteria: (1) Patients with confirmed IBS; (2) vitamin D as the intervention and placebo as the control; and (3) the availability of sufficient information about baseline and follow-up IBS symptom severity scores (IBS-SSS) or a self-reported IBS-specific QoL measure (IBS-QoL); (4) RCT design. Identical trials were excluded.

2.2. Search strategy and selection procedure

English language records published from inception to March 2022 were queried by searching the PubMed, Embase, and Cochrane Central Register of Controlled Trials databases. The titles and abstracts were searched for synonyms, variations, and combinations of IBS, vitamin D, and RCT. Search strategy for each database is detailed in Supplementary Table S1.

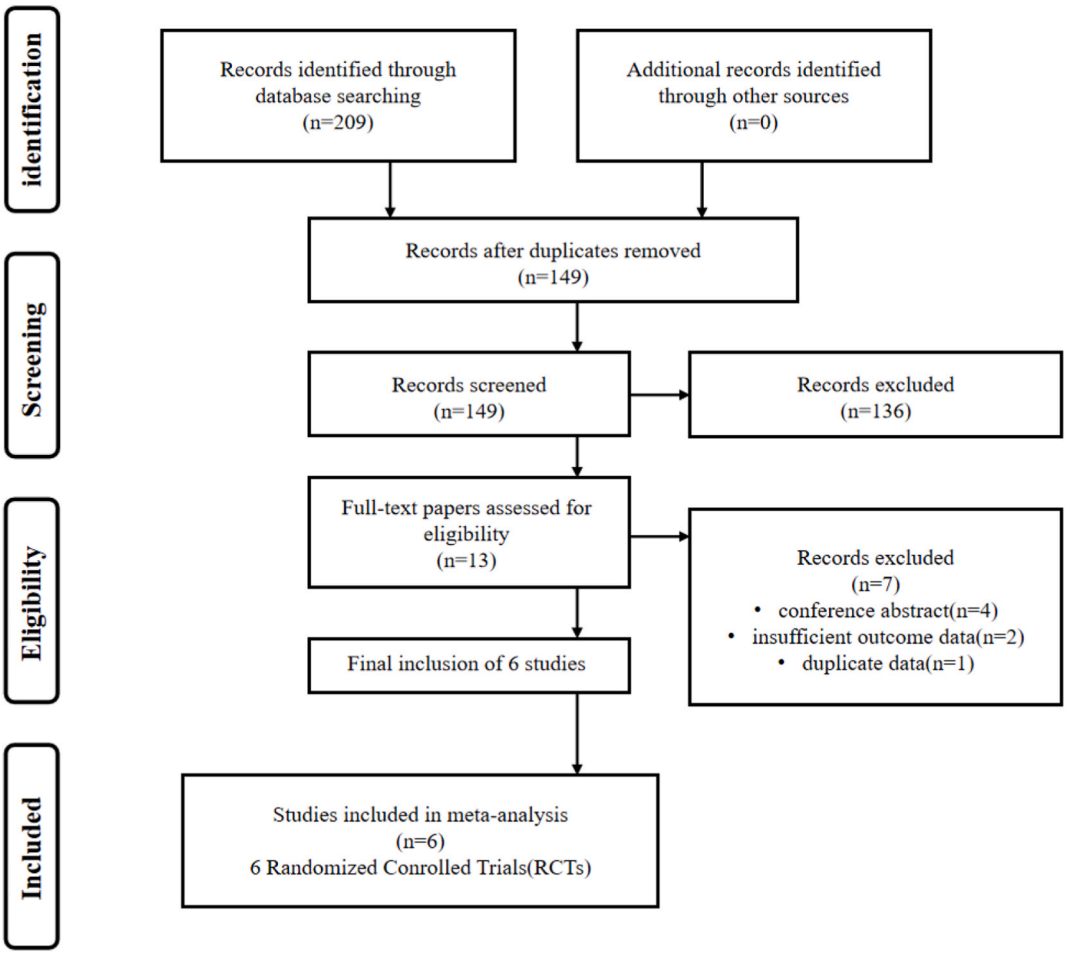


Fig. 1. Flowchart of study selection.

The duplicates were removed after all studies were acquired in accordance with the electronic search strategy. The potential studies were selected step by step through the titles, abstracts, and full texts to conform to inclusion criteria. The above procedure was conducted independently by two investigators; if any disagreements occurred, a third investigator was consulted. The detailed steps for the selection of included researches is shown in Fig. 1.

2.3. Data extraction, transformation, and risk of bias (RoB) assessments

Two researchers independently collected the data including first author's name, publication year, nation, sample size, sex (% female), intervention (vitamin D dosage), treatment duration, serum 25(OH)D levels (baseline), and IBS-SSS and IBS-QoL score (baseline and post-intervention).

The widely used and highly recognized IBS symptom severity questionnaire was used to assess GI symptom intensity with higher scores meaning more severe symptoms [14]. QoL was assessed by using a questionnaire named IBS-QoL with 34 items and 8 subscales that were summed and averaged for a total score and then transformed to a 0–100 scale, with higher scores indicating better QoL [15–18]. The primary outcome measure was the IBS-SSS and the secondary outcome measure was IBS-QoL score; their effect sizes are represented as mean difference (MD) and standard deviation (SD). However, the data of Jalili et al., 2016 [7] were represented as MD and standard error, those of Sikaroudi et al., 2020 [11] as median and first and third quartiles, and those of Jalili et al., 2019 [10] as only baseline and change MD and standard error. All data were converted to MD and SD according to the Cochrane Handbook [19] and the McGrath et al. study [20]. The data transformation methods are listed in Supplementary Table S2.

RoB assessments were performed using version 2 of the Cochrane RoB tool for randomized trials, the recommended tool for use in Cochrane Reviews, including bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result [21,22]. Once any discrepancies emerged among the data extracted, transformed, and assessed by two researchers, a third one was designated to resolve these problems.

2.4. Statistical analysis

All statistical analyses were performed using Review Manager 5.4 and Stata 12.0. The pooled results are presented as weighted mean differences (WMD) and 95% confidence intervals (CI). A random-effects model was chosen to estimate the overall effect. Heterogeneity was assessed with the Q and I^2 statistics. The upper limit of I^2 values for low and moderate levels of heterogeneity were 25% and 50%, respectively, and I^2 values exceeding 50% were considered high level of heterogeneity. Additionally, subgroup analyses according to different dose classifications of vitamin D (low-dose daily vs. high-dose weekly or biweekly), regional differences (Middle East vs. Europe), and serum 25(OH)D levels (vitamin D deficiency vs. non-deficiency) were performed to address whether the summary effects vary with the three specific characteristics above. Meta-regression analyses were to identify the potential factors contributing to heterogeneity. Sensitivity analyses were performed to analyze the impact of removing individual study data on the overall results. Publication bias was analyzed with a funnel plot, whose symmetry was assessed by Egger's test.

3. Results

3.1. Included trial characteristics and RoB assessments

A total of 209 records were obtained through the database search. 60 duplicates and 136 ineligible papers were removed based on the title and abstract screening. Eventually, a full-text assessment excluded 7 papers for different reasons, leaving 6 RCT ultimately included in the meta-analysis. Descriptive data for each trial are summarised in Table 1.

A total of 572 subjects participated in the 6 RCT that explored the effect of vitamin D on GI symptoms in IBS patients. The cohort

Table 1
Characteristics of the included RCT studies in the meta-analysis.

Author (ref.)	Year (Published)	Nation	Patients (vitamin D/ control)	Female (%)	Follow-up	Dose of Vitamin D Supplementation	Serum 25(OH)D (vitamin D, baseline)	Serum 25(OH)D (control, baseline)
Jalili et al. [7]	2016	Iran	25/25	100	6 weeks	50,000 IU/biweek	21.10 ± 8.23 ng/mL	21.23 ± 8.45 ng/mL
Abbasnezhad et al. [8]	2016	Iran	44/41	57/85	6 months	50,000 IU/biweek	19.65 ± 10.35 ng/mL	18.62 ± 11.23 ng/mL
Amrousy et al. [9]	2018	Egypt	56/56	62/112	6 months	2000 IU/d	17.2 ± 1.3 ng/mL	17.5 ± 1.1 ng/mL
Jalili et al. [10]	2019	Iran	58/58	not available	6 weeks	50,000 IU/week	21.10 ± 5.23 ng/mL	21.10 ± 5.23 ng/mL
Sikaroudi et al. [11]	2020	Iran	39/35	39/74	9 weeks	50,000 IU/week	18.59 ± 7.58 ng/mL	18.59 ± 7.92 ng/mL
Williams et al. [23]	2021	United Kingdom	68/67	106/135	12 weeks	3000 IU/d	48.75 ± 27.91 nmol/L	49.71 ± 27.05 nmol/L

size of the studies ranged from 50 to 135, while the mean patient age ranged from 16 to 42 years old. The study duration ranged from 6 weeks to 6 months. Four studies were conducted in Iran, 1 in Egypt, and 1 in the United Kingdom. The subjects in the 6 trials received vitamin D supplements as an intervention.

With respect to RoB, only Sikaroudi et al. [11] did not state whether intention-to-treat or modified intention-to-treat analyses have been used. The result of RoB assessments are shown in Fig. 2a, b.

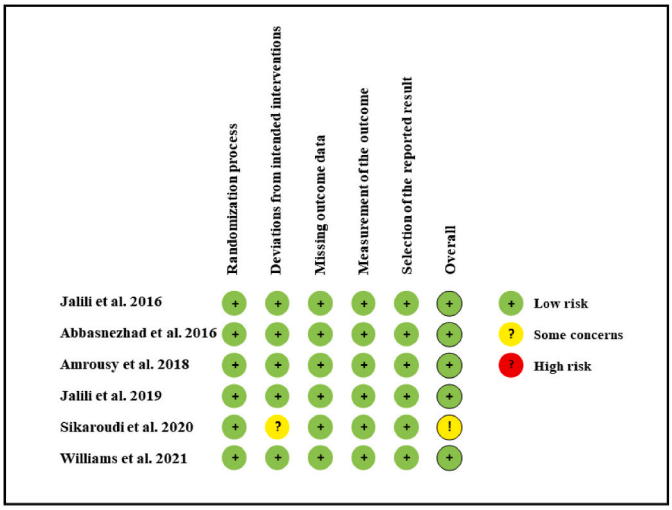
3.2. Primary outcomes

3.2.1. IBS symptom severity score

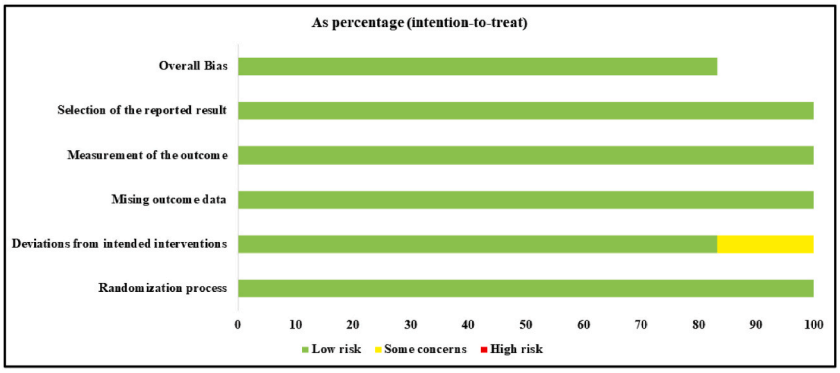
The outcomes of the meta-analysis for 6 trials involving 572 subjects are observed in Fig. 3. IBS-SSS decreased significantly in vitamin D intervention group versus controls (WMD, −34.88; 95% CI, −62.48 to −7.27; $P = 0.013$; random-effects model). However, a high degree of heterogeneity was observed across the 6 trials ($I^2 = 78.8\%$). The funnel plot drawn using Stata software (Fig. 4) was roughly symmetrical according to Egger's test ($P = 0.390$).

3.2.2. Subgroup analysis

All grouping types were extracted based on known baseline variables. Subgroup analyses according to different dose classifications of vitamin D (Fig. 5a), regional differences (Fig. 5b), and degree of serum 25(OH)D levels (Fig. 5c) were performed. The heterogeneity of the 2 groups divided by different doses and serum 25(OH)D levels did not decrease significantly. Because only 1 study was performed in Europe, no heterogeneity of that region was available. The Middle East region (WMD, −48.71; 95% CI, −65.14 to −32.28; $P < 0.001$) showed significant effects on IBS-SSS and had a low degree of heterogeneity ($I^2 = 29.8\%$).



(a)



(b)

Fig. 2. Risk of bias assessments: (a) Upper panel presents risk of bias for each included study; (b) Lower panel presents overall risk of bias of included studies; green indicates low risk, red indicates high risk, yellow indicates some concerns.

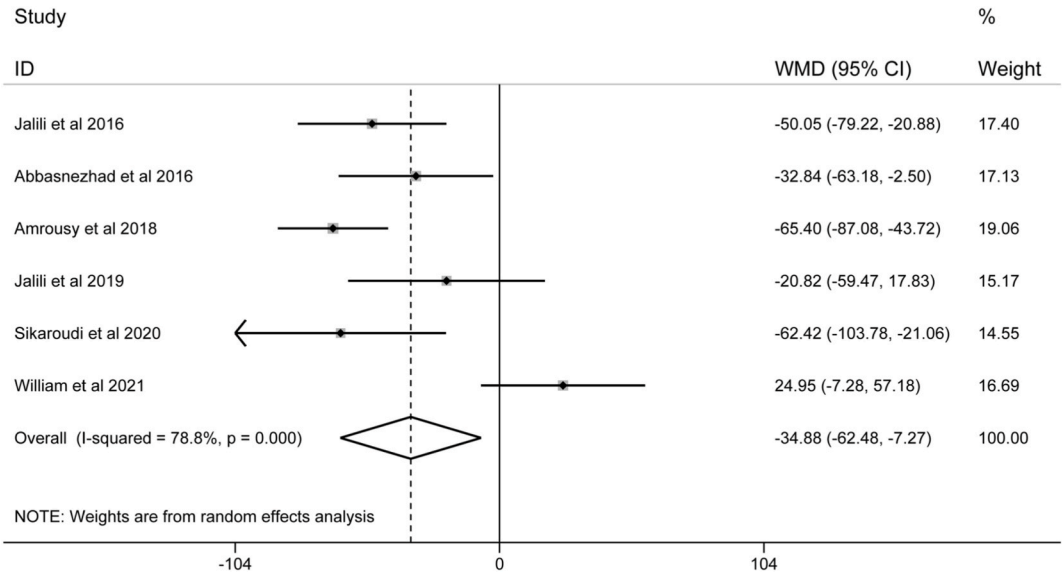


Fig. 3. Forest plot comparing IBS-SSS between intervention and control groups. IBS-SSS, inflammatory bowel syndrome-symptom severity score.

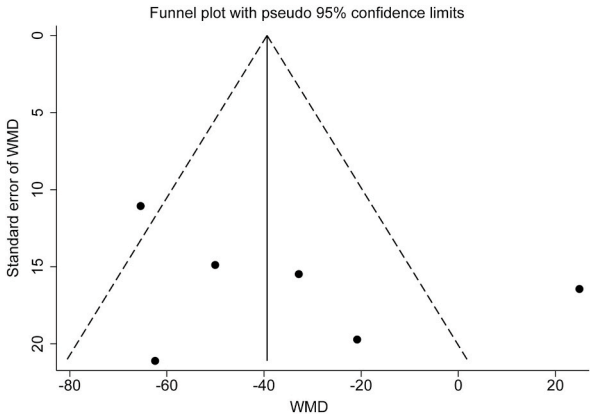


Fig. 4. Funnel plot: each dot represents 1 RCT.

3.2.3. Meta-regression

Meta-regression analyses were used to determine the potential factors extracted based on known baseline variables that might cause heterogeneity, and explore the correlation between these factors and existing heterogeneity. Homogeneity of included studies can be significantly influenced by factors with values of $P < 0.05$. To detect the origins of high degree heterogeneity, different doses of vitamin D, regional differences, and serum 25(OH)D levels were analyzed in the meta-regression.

The meta-regression results showed that different doses of vitamin D ($P = 0.422$), regional differences ($P = 0.067$), and serum 25 (OH)D levels ($P = 0.097$) had no significant impact on heterogeneity (Supplementary Figure S1).

3.2.4. Sensitivity testing

Sensitivity analyses were performed to assess the relative influence of each study by excluding the studies individually to confirm the relative stability of the results (Fig. 6).

3.3. Secondary outcomes

3.3.1. IBS-QoL score

Four studies provided data on IBS-QoL scores [7–9,23]. The outcome of the meta-analysis (Fig. 7) showed no significant differences between the vitamin D intervention and control groups (WMD, 3.33; 95% CI, −5.12 to −11.77; $P = 0.440$; random-effects model). Moreover, a high degree of heterogeneity was observed across the 4 trials ($I^2 = 89.2\%$).

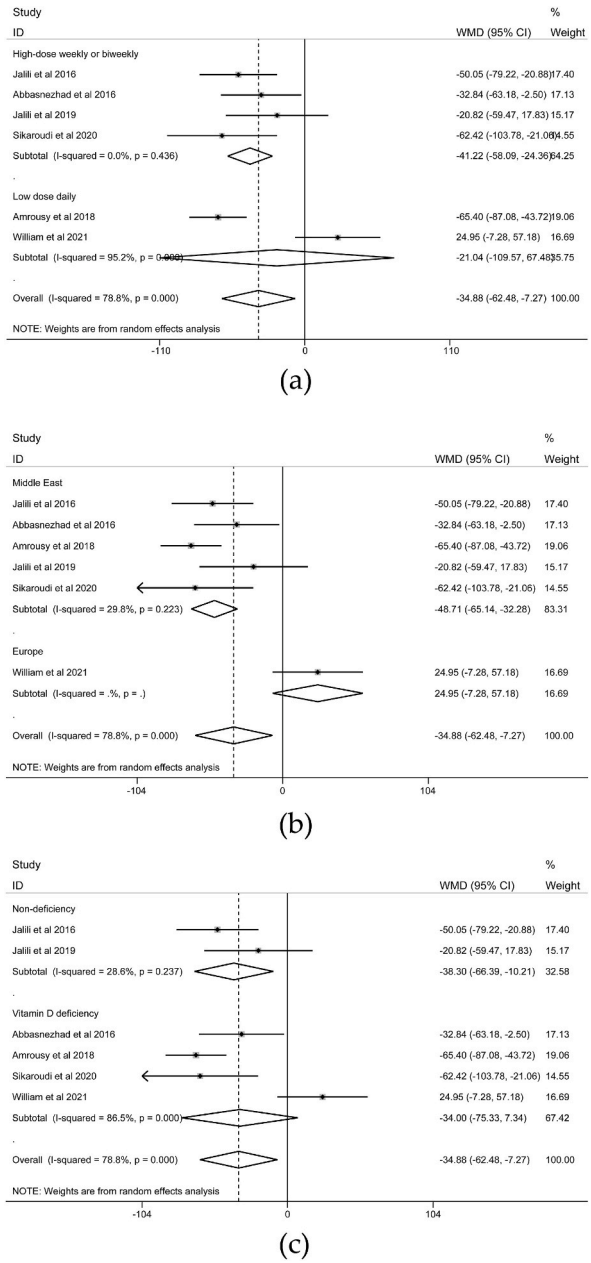


Fig. 5. Subgroup analyses according to different dose classifications of vitamin D (low-dose daily vs. high-dose weekly or biweekly), regional differences (Middle East vs. Europe), and serum 25(OH)D levels (vitamin D deficiency vs. non-deficiency): (**a**) Forest plot for IBS-SSS comparison of vitamin D with different doses; (**b**) Forest plot for IBS-SSS comparison of different regions; (**c**) Forest plot for IBS-SSS comparison of different serum 25(OH)D levels. IBS-SSS, inflammatory bowel syndrome-symptom severity score.

4. Discussion

Overall, our study implied that vitamin D supplementation helps reduce IBS severity. However, IBS-SSS heterogeneity across the included studies was too high to ignore, and the subgroup analysis and meta-regression revealed that different doses, regions, and serum 25(OH)D levels did not affect the overall results and were not responsible for the existing heterogeneity, while the sensitivity analysis showed that the results were relatively stable. Due to the small number of studies, the meta-regression may have had false negative errors and may not have identified all sources of heterogeneity. Moreover, the heterogeneity risk was decreased to low after the exclusion of the William et al. study [23]. Therefore, this study was considered the main source of heterogeneity.

To explore the reason why that particular study [23] produced the high heterogeneity, we further generalised the characteristics of all included studies. Each [7–11,23] showed high compliance rates, low dropout rates, and robust designs despite their small sample

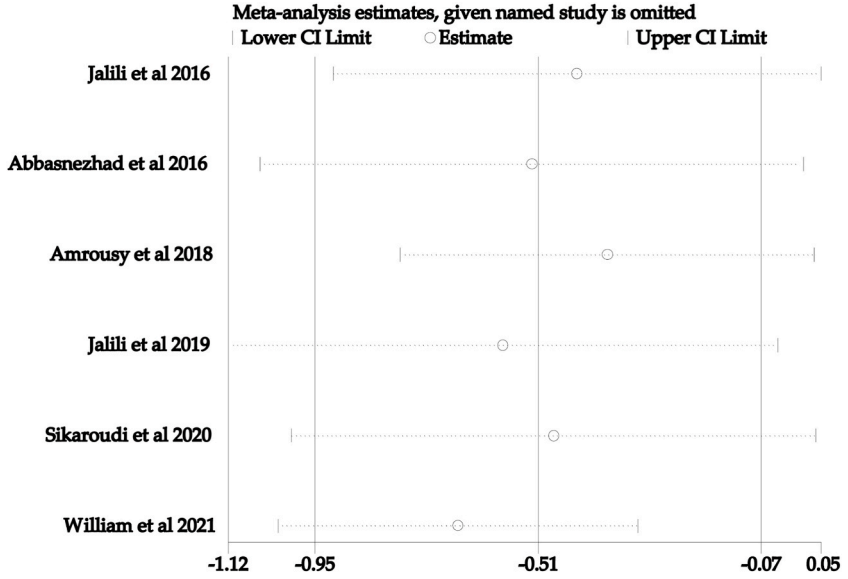


Fig. 6. Sensitivity testing of IBS-SSS. IBS-SSS, inflammatory bowel syndrome-symptom severity score.

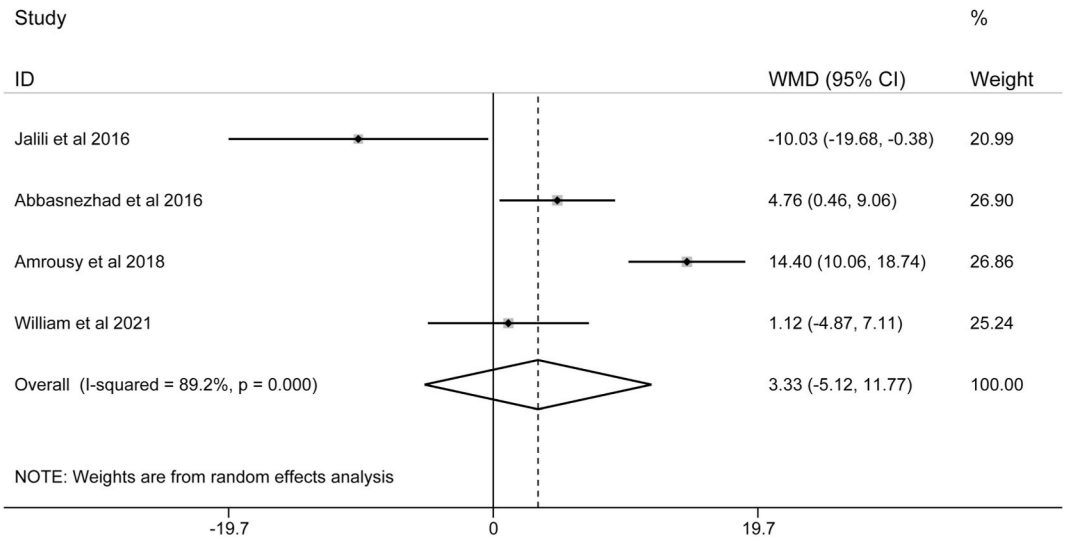


Fig. 7. Forest plot comparing IBS-QoL score between intervention and control groups. IBS, inflammatory bowel syndrome; IBS-QoL, a self-reported IBS-specific QoL measure.

sizes (25–68 patients/arm). Vitamin D deficiency was indeed widespread in IBS patients, and no adverse effects of its supplementation were reported in these studies. Jalili et al., 2016 [7] included only 25 patients per arm recruited from Iran who received 50,000 IU/biweek of vitamin D for 6 weeks and reported a significant ($P < 0.05$) difference in terms of IBS-SSS and IBS-QoL scores. A significant reduction in IBS-SSS scores ($P < 0.001$) was reported in Abbasnezhad et al. [8] which recruited 45 patients per arm in Iran to a biweekly dose of 50,000 IU and used a longer intervention (6 months). Amrousy et al. [9] recruited 56 patients per arm from Egypt and used a smaller daily dose of 2000 IU for 6 months, again reporting a significant improvement in IBS-SSS ($P < 0.001$). Jalili et al., 2019 [10] recruited 58 patients per arm from Iran to a weekly dose of 50,000 IU for 6 weeks and found a significant benefit of vitamin D supplementation ($P < 0.05$). A significant improvement in terms of IBS-SSS scores was stated in Sikaroudi et al. [11] with 88 Iran subjects dosing with 50,000 IU of vitamin D per week for 9 weeks. Finally, William et al. [23] treated the largest sample size (155 patients) from the United Kingdom with 2000 IU/day for 12 weeks but reported a large placebo effect and no significant ($P > 0.05$) response. Overall, studies confirming the effectiveness of vitamin D for improving IBS symptoms had consistent features, with most patients recruited from the Middle East and most using higher doses of vitamin D, which suggests that caution is needed in generalizing from these findings to the wider population of IBS patients. Moreover, 1 trial [24] that was excluded owing to lack of data recruited 35

subjects in the United Kingdom, dosing them with 3000 IU/day for 12 weeks and reporting a significant ($P < 0.001$) benefit to total symptom severity score of IBS. The features of that study were similar to those of William et al. [23]; although there was no significant difference in IBS-SSS between the vitamin D and placebo groups, IBS-SSS reduced numerically compared to baseline. In summary, vitamin D supplementation as a long-term IBS management is a feasible option.

Meta-analysis suggested no significant improvement in IBS-QoL score following vitamin D supplementation contrary to symptom score relief. The result is not fully credible because the way QoL is measured in previous IBS studies has lacked consistency and may introduce bias in the results. It may be possible to classify IBS-QoL score results from different scale systems for meta-analysis in the future. Fortunately, the main study subjects of this paper are IBS-SSS scores whose data came from the same scale system.

Vitamin D supplementation may improve the GI symptoms in IBS, but the association of vitamin D with the complex pathophysiology of IBS involving the gut-brain axis, altered motility, visceral hypersensitivity, the gut microenvironment, stress, and other factors, is not well understood. Some studies showed that vitamin D can increase vitamin D receptor expression and thus reduce mucosal inflammatory responses to avoid bacterial invasion by reducing mucosal barrier damage [25,26]. Inflammation may play a pathogenic role in IBS and chronic, low-grade, subclinical inflammation is thought to perpetuate the symptoms of IBS [27]. Therefore, vitamin D may reduce symptoms of IBS through its anti-inflammatory effects.

The threshold for vitamin D deficiency and sufficiency is defined as a serum 25(OH)D level of 50 nmol/L (20 ng/mL) and 75 nmol/L (30 ng/mL), respectively [28]. Using this definition, it was easy to determine that the average serum 25(OH)D level in each of the six studies was less than 75 nmol/L (30 ng/mL). Therefore, our study population should be limited to IBS patients with vitamin D insufficiency or even deficiency, consistent with the prevalence of vitamin D deficiency reported by some researches [6]. Before using vitamin D as a clinical treatment for IBS, we must determine the serum 25(OH)D levels of IBS patients as well as the effective dose and safety of vitamin D supplements. First, serum 25(OH)D levels are not routinely examined in IBS patients; however, we recommend routine serum 25(OH)D testing of IBS patients to guide the need for vitamin D supplementation. Second, no studies have reported the recommended vitamin D supplement dose for IBS treatment. Charoenngam et al. [29] reported no downside to increasing one's intake of vitamin D to maintain a serum 25(OH)D level of at least 75 nmol/L (30 ng/mL) and preferably increasing it to 100–150 nmol/L (40–60 ng/mL) to achieve optimal overall health benefits of vitamin D [29], which may be a reference for vitamin D supplementation. Finally, the safety of vitamin D supplementation is critical. Many vitamin D–replete people take vitamin D supplements without clear benefits [30], and its overdose can lead to acute poisoning [31]. In summary, IBS patients with vitamin D insufficiency or deficiency should take appropriate vitamin D supplements and undergo regular serum 25(OH)D level monitoring to avoid poisoning or, conversely, underdosing.

In recent systematic reviews and meta-analyses, Huang et al. [32] and Chong et al. [33] concluded that vitamin D significantly improved IBS-SSS, which is consistent with our findings. But Abuelazm et al. [34] indicated that vitamin D was ineffective in reducing GI symptoms in patients of IBS, which is contradictory to our findings. Abuelazm et al. [34] should explain how to get the difference of the baseline and final MD and SD as effect value so that it is beneficial to understand the cause of the difference in outcome. Huang et al. [32] may need a better and more refined searching technique to capture all the available studies so far, and it is best to describe in detail how to deal with the problem of inconsistent data forms in each included study. Likewise, the meta-analysis of Chong et al. [33] included Tazzyman et al. [24] that used the Visual Analogue Scale for IBS, which is a different scale system with IBS-SSS. Therefore, the study of Tazzyman et al. [24] should be excluded to make the remaining data more homogeneous. The doubts and suggestions above were listed in Supplementary Table S3. Overall, controversy exists regarding whether vitamin D improves IBS symptoms in recent meta-analyses, which requires not only more rational meta-analysis but also more clinical evidence-based data, especially the results of multi-center research to support.

5. Study limitations

There is no denying that this meta-analysis has some limitations. First, despite our efforts to broaden the scope of the search, it was difficult to retrieve a large number of eligible trials. Second, this meta-analysis transformed the retrieved data to a uniform effect size, which could have increased the risk of heterogeneity. Third, the follow-up period of the trials was not long, so the long-term effects of vitamin D on IBS remain unclear. Last but not the least, this meta-analysis lacked control for possible confounding factors. Some of the included studies did not specifically exclude the participants treated with diet therapy, recent antibiotic use, active medications and other interfering factors that could influence outcome measures.

6. Conclusion

Given the existing data, vitamin D supplementation may be associated with a reduction in IBS-SSS but not an increase in IBS-QoL scores. Thus, it is recommended that IBS patients, especially those with vitamin D insufficiency or deficiency take appropriate vitamin D supplements and regularly undergo serum 25(OH)D monitoring.

Author contributions

Chenxi Yan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Chenmin Hu, Xiaolong Chen: Performed the experiments; Analyzed and interpreted the data.

Xinyi Jia: Conceived and designed the experiments; Performed the experiments.

Zhenya Zhu, Diya Ye: Analyzed and interpreted the data.
Yuhao Wu: Contributed reagents, materials, analysis tools or data.
Rui Guo: Performed the experiments.
Mizu Jiang: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e16437.

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