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META-ANALYSIS

Vitamin D supplementation for irritable bowel syndrome: A systematic review and meta-analysis

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Abstract

Background and Aim: Irritable bowel syndrome (IBS) is a prevalent and complex gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits. Observational studies have suggested a relationship between serum vitamin D levels and IBS symptoms. This systematic review and meta-analysis aimed to investigate the clinical effects of vitamin D supplementation on IBS symptom severity and quality of life (QoL) measures.

Methods: Medline, Embase, Scopus, Web of Science, and The Cochrane Library databases were systematically searched. Data abstraction and quality assessment were conducted by four authors independently, and discrepancies were resolved through consensus from the senior author. Continuous data were pooled with standardized mean difference (SMD) using the DerSimonian and Laird's random-effects model. Sensitivity analysis by risk of bias and potentially "predatory" publication were performed as well.

Results: A total of 685 patients across eight studies were included in the meta-analysis. Vitamin D supplementation significantly improved IBS symptom severity scale scores, with a SMD of −0.77 (95% confidence interval [CI] −1.47 to −0.07, $P = 0.04$, $I^2 = 91\%$). Improvements in IBS-QoL scores were also observed, albeit not statistically significant (SMD 0.54; 95% CI −0.34 to 1.41, $P = 0.15$, $I^2 = 87\%$). However, small sample sizes, a relatively young study population, limited ethnicities, and varied vitamin D dosing strategies across the studies were notable limitations.

Conclusions: Vitamin D supplementation could be part of our clinical armamentarium when managing IBS patients due to the potential efficacy and good safety profile. Further randomized, controlled trials are required to confirm the therapeutic effects.

Introduction

Irritable bowel syndrome (IBS) is a prevalent gastrointestinal problem, which affects 4% to 21% of the general population.[1-3] The diagnosis of IBS is established clinically using the updated ROME IV diagnostic criteria, characterized by recurrent abdominal pain for 1 day a week in the previous 3 months with symptom onset of at least 6 months before diagnosis, and associated with two or more of the following: (1) pain related to defecation, (2) change in appearance of stool, or (3) change in stool frequency.[4,5] IBS symptoms are associated with psychological distress, impaired social and personal functions, worsened well-being, and a decline in the patient's quality of life (QoL), even more so than other chronic diseases.[6,7] Also strongly correlated with an impaired QoL, a high prevalence of depression has been noted in IBS patients. There is hence compelling reason to improve management of IBS. Despite its prevalence and often chronic, relapsing nature, the pathophysiology of IBS remains poorly

understood and treatment strategies suboptimal.[8-10] Several theories relating to gastrointestinal mucosal permeability, inflammation and visceral hypersensitivity, and gut microbiota alterations have been proposed.[10,11]

With its diverse pathophysiological mechanisms and presenting symptoms, there is currently no definitive treatment for IBS beyond supportive treatment and symptomatic relief.[12–14] Management of IBS can be classified into dietary modification, modification of gut microbiome, and pharmacotherapy aimed at altering motility, sensation, and intraluminal environment. However, current treatments may have limited long-term benefits, marginal effects on QoL, or bothersome adverse effects.[14–16]

Burgeoning studies have suggested a relationship between vitamin D deficiency and multiple disease states, including IBS.[17,18] Vitamin D has putative functions in influencing cellular mechanisms, regulating gut microbiome, and modulating immune system and inflammatory processes.[17,18] Observational studies have also noted a high prevalence of vitamin D deficiency in IBS patients (up to 82%),[17,19] suggesting a potential therapeutic role for vitamin D supplementation.

To our knowledge, no published systematic review or meta-analysis has investigated the clinical effects of vitamin D supplements on IBS symptom severity and QoL measures. There are also conflicting conclusions pertaining to the efficacy of vitamin D supplements.[20–23] Therefore, this study aimed to summarize the existing data to clarify the efficacy of vitamin D supplementation for IBS patients.

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24] The study protocol was registered in the International Prospective Register of Systematic Reviews under the number CRD42022301706.

Search strategy. A systematic literature search was performed in the OVID Medline, Embase, Scopus, Web of Science, and The Cochrane Library databases from inception to December 22, 2021 for articles that reported on vitamin D supplements in IBS patients. The search strategy was developed in consultation with a medical information specialist (Medical Library, National University of Singapore). Key search terms such as "Irritable Bowel Syndrome," "Vitamin D," and "Cholecalciferol" were used in the search strategy. No restrictions on date, language, or subject were implemented on the database search. The detailed search strategy can be found in Table S1. Abstracts were imported into Covidence (Melbourne, Victoria, Australia) and screened by four independent researchers (C.Y.Y.L, R.I.H.C, S.E.T, and C.Y.L.L.). Full texts were obtained for all abstracts of relevance, and their respective reference lists were hand-searched to identify additional relevant articles. Forward searching of prospective citations of the relevant full texts was also performed, and authors of the respective articles were contacted if necessary to provide additional data.

Inclusion and exclusion criteria. The selection of articles for inclusion was conducted by four researchers (C.Y.Y.L, R.I.H.C, S.E.T, and C.Y.L.L.). Each article was reviewed by at least two researchers blinded to each others' decision. Disputes were resolved through consensus from the senior author (Q.X.N.). The predefined criteria for inclusion were as follows: (1) articles reporting outcomes (either IBS symptom severity scale [IBS-SSS] or IBS quality of life [IBS-QoL]) of vitamin D supplementation in IBS patients, (2) original articles (randomized controlled trials [RCTs], case control studies, and cohort and cross-sectional studies), and (3) articles written or translated into the English language. The criteria for exclusion were as follows: (1) studies which reported serum blood values as the only outcome and (2) commentaries, consensus-based guidelines, case reports, case series, review articles, and conference abstracts.

Data abstraction. Data were abstracted into an Excel spreadsheet (Microsoft Corp, New Mexico, United States) by four authors (C.Y.Y.L, R.I.H.C, S.E.T, and C.Y.L.L.) and double-coded, to ensure accuracy. Data abstracted included study characteristics (e.g. author name, year of publication, and country or region), study population characteristics (e.g. sample size, age, gender, diagnostic criteria, and follow-up time), and primary outcomes reported (e.g. IBS severity score and QoL outcomes). The IBS-SSS is a questionnaire that consists of five items about the severity of abdominal discomfort, frequency of discomfort, severity of flatulence, satisfaction after defecation, and interactive impact of IBS symptoms with everyday life. Each item was scored on a scale from 0 to 100, and the sum of these five items was the score of IBS severity (range 0–500). Scores of 75–175, 175–300, and > 300 indicated mild, moderate, and severe cases, respectively.[25] QoL outcomes were measured using the IBS-QoL questionnaire. IBS-QoL questionnaire has 34 items including dysphoria (8 items), body image (4 items), health-oriented worries (3 items), sexual related worries (2 items), social behavior (4 items), intervene with everyday activity (7 items), and personal relationship (3 items). This questionnaire was based on a five-choice scale (0–4), and the summed total score was transformed to a numerical scale ranging from 0 (*poor QoL*) to 100 (*maximum QoL*).

For continuous variables, mean and standard deviation (SD) were reported. Where these data were unavailable, appropriate formulae were applied to transform the data from median and range or interquartile range to mean and SD.[26] Unreported SDs were calculated as a pooled SD based on other included studies.[27]

Statistical analysis. Data analyses were conducted using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed statistical significance was set at P value < 0.05. To account for any different units of analysis, continuous data were pooled with standardized mean difference (SMD), expressed as Hedges' g.[28] As some heterogeneity was expected, the DerSimonian and Laird's random-effects model weighted by the inverse variance method was used.[29] Heterogeneity was quantified using the Cochran Q test and I^2 statistics. I^2 value thresholds of 25%, 50%, and 75% signified low, moderate, and high heterogeneity, respectively.[30] Assessment of publication bias was performed via inspection of funnel-plots and Egger's regression test.[31]

Two sensitivity analyses were performed, one excluding studies rated mod-to-high risk of bias by the Cochrane's Risk of Bias 2 (RoB2) tool[32] and the other excluding studies published in potentially "predatory" journals. Predatory journals were taken to be

journals that were not indexed in PubMed or the Directory of Open Access Journals and not a member of Committee On Publication Ethics.[33]

Risk of bias assessment. The RoB2 tool was used for RCTs. The RoB2 tool assesses quality on five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurements, and reporting.[32,34]

Results

Literature retrieval and summary of included articles. The database search yielded 643 records, from which 221 duplicates were removed. Of the remaining 422 records, 389 were excluded on the basis of their titles and abstracts. Thirty-three full-texts were reviewed, of which seven articles were eligible. One additional article was identified from reviewing references of eligible articles. Therefore, eight articles were included for analysis.[20–23,35–38] The selection process and reasons for excluding articles were illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Fig. 1).

All included studies were RCTs. A total of 685 patients were included across eight studies. Three hundred and forty-six patients were given vitamin D supplements while 339 patients were given placebos. Mean age ranged from 16.4 to 41.3 years in the vitamin D group, while it ranged from 16.2 to 39.8 years in the placebo group. In terms of the country of origin of study populations, the majority of studies were from Iran ($n = 4$), two studies were from Egypt, and two studies were from the United Kingdom. Follow-up duration ranged from 9 to 24 weeks. Five studies[20–22,35,37] used the ROME III criteria to diagnose IBS while the remaining three studies[23,36,38] used the newer ROME IV criteria. A summary table of the included articles was available in Table 1.

All included RCTs were classified to be of low to moderate risk of bias, and only Zeid *et al.*'s study[38] was published in a potentially predatory journal. The detailed risk of bias assessment results were summarized in Figure 2.

IBS symptom severity scale outcomes. As seen in Figure 3, in pooled analysis (using a random-effects model) of eight studies totaling 685 patients (346 taking vitamin D supplements and 339 taking placebo), it was found that patients who received vitamin D supplements had a significant improvement of IBS-SSS (SMD −0.77; 95% CI −1.47 to −0.07, $P = 0.04$, $I^2 = 91\%$). There was no evidence of publication bias, based on a nonsignificant Egger regression test ($P = 0.1124$) (Table S2) and a visually symmetrical funnel plot (Fig. S1).

However, sensitivity analysis excluding five trials at mod-to-high risk of bias found that patients taking vitamin D supplements did not experience a significant improvement of IBS-SSS (SMD −0.52; 95% CI −2.67 to 1.62, $P = 0.4$, $I^2 = 93\%$) (Fig. 4). There was evidence of publication bias, based on a significant Egger regression test ($P = 0.0357$) (Table S2) and a visually asymmetrical funnel plot (Fig. S2). Sensitivity analysis excluding one study published in a potentially predatory journals revealed that patients taking vitamin D supplements experienced a significant improvement of IBS-SSS (SMD −0.52; 95% CI −1.00 to −0.05, $P = 0.40$, $I^2 = 82\%$) (Fig. 5). There was no evidence of publication bias,

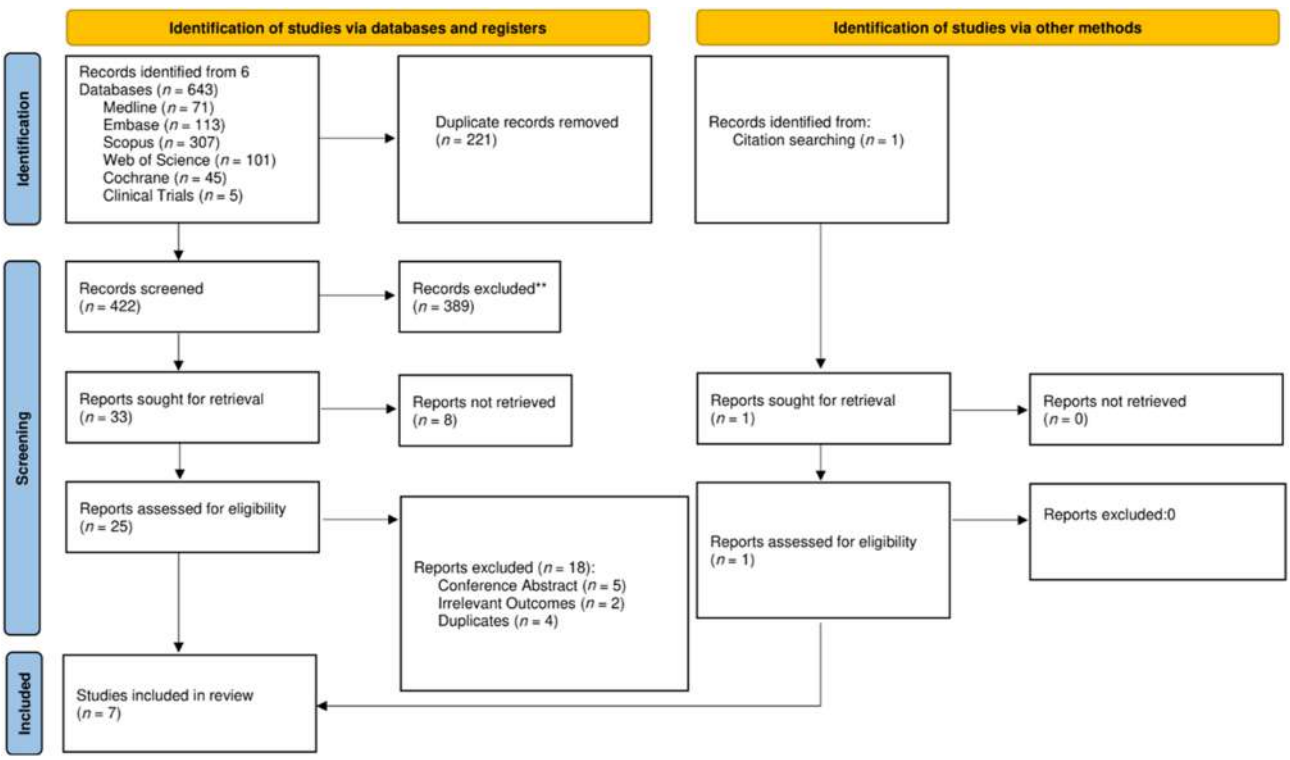

Figure 1 PRISMA flowchart showing abstraction process.

Table 1 Characteristics of studies reviewed (arranged alphabetically by first author's last name)

Study	Location	Study design	Diagnostic criteria	IBS subtype	Follow-up time	Male gender, *N*(%) (i) Vitamin D (ii) Placebo	Mean age in years (SD) (i) Vitamin D (ii) Placebo	Sample size (i) Vitamin D (ii) Placebo	Vitamin D dose	Risk of bias	Published in a potentially "predatory" journal
Abbasnezhad *et al*. (2016)[21]	Iran	Randomized, double-blind, placebo-controlled trial	ROME III	IBS-C IBS-D IBS-A	24 weeks	(i) 36.40 (ii) 29.30	(i) 37.45 (8.11) (ii) 38.34 (9.85)	(i) 44 (ii) 41	50 000 IU fortnightly	Low	No
El Amrousy *et al*. (2018)[22]	Egypt	Prospective randomized controlled trial	ROME III	IBS-C IBS-D IBS-M IBS-U	24 weeks	(i) 48.20 (ii) 42.86	(i) 16.40 (1.50) (ii) 16.20 (1.10)	(i) 56 (ii) 56	2000 IU per day	Some concerns	No
Jalili *et al*. (2016)[20]	Iran	Factorial blinded randomized clinical trial	ROME III	IBS-C IBS-D IBS-M IBS-U	10 weeks	(i) NR (ii) NR	(i) 41.32 (12.62) (ii) 39.76 (12.99)	(i) 25 (ii) 25	50 000 IU biweekly	Some concerns	No
Jalili *et al*. (2019)[35]	Iran	Randomized, double-blind, placebo-controlled clinical trial	ROME III	NR	10 weeks	(i) NR (ii) NR	(i) 42.24 (12.26) (ii) 40.06 (13.37)	(i) 58 (ii) 58	50 000 IU weekly	Low	No
Sikaroudi *et al*. (2020)[36]	Iran	Randomized, double-blind, placebo-controlled trial	ROME IV and World Gastroenterology Organization questionnaire	IBS-D	9 weeks	(i) 53.80 (ii) 51.40	(i) 34.56 (12.02) (ii) 36.57 (8.36)	(i) 39 (ii) 35	50 000 IU weekly	Some concerns	No
Tazzyman *et al*. (2015)[37]	United Kingdom	Randomized, double-blind, three-arm parallel design trial	ROME III	IBS-C IBS-D IBS-M	12 weeks	(i) 11.76 (ii) 5.56	(i) 34.00 (12.00) (ii) 36.00 (15.00)	(i) 17 (ii) 18	3000 IU per day	Some concerns	No
Williams *et al*. (2021)[23]	United Kingdom	Randomized, double-blind, placebo-controlled, two-arm parallel trial	ROME IV	NR	12 weeks	(i) 19.10 (ii) 23.90	(i) 28.94 (10.03) (ii) 31.10 (10.85)	(i) 68 (ii) 67	3000 IU per day	Low	No
Zeid *et al*. (2020)[38]	Egypt	Randomized, double-blind, placebo-controlled trial	ROME IV	NR	12 weeks	(i) NR (ii) NR	(i) 37.64 (11.13) (ii) 38.03 (6.37)	(i) 39 (ii) 39	4000 IU per day	Some concerns	Yes

IBS-A, alternating; IBS-C, constipation; IBS-D, diarrhea; IBS-M, mixed; IBS-U, unsubtyped; *N*, Number; SD, standard deviation; NR, not reported.

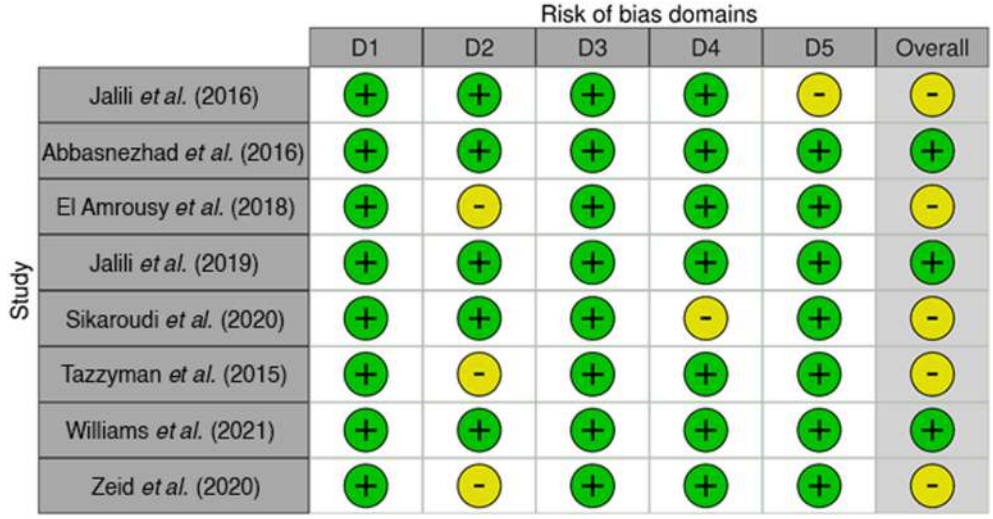

Figure 2 Included studies rated using the Cochrane risk of bias assessment tool. Domains: D1, bias arising from the randomization process; D2, bias due to deviations from the intended intervention; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection the reported results. Judgement: -, some concerns; +, low.

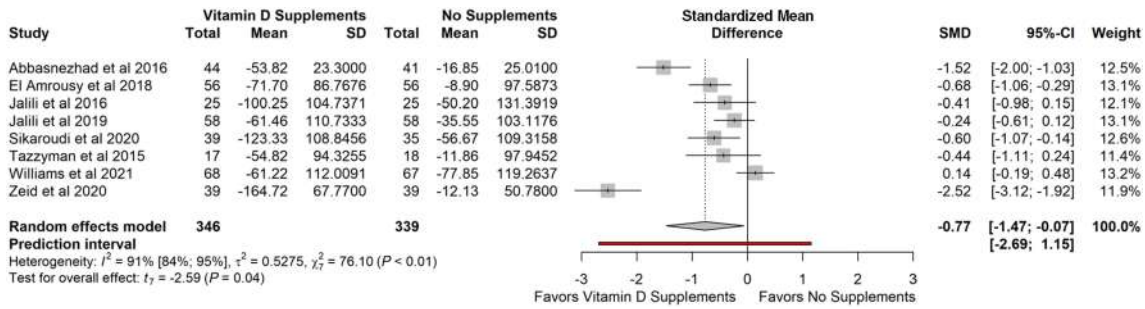

Figure 3 Forest plot showing meta-analysis of vitamin D supplementation on IBS-SSS scores.

based on a non-significant Egger regression test ($P = 0.3087$) (Table S2) and a visually symmetrical funnel plot (Fig. S3). The sensitivity analysis did call into question the validity and robustness of the initial findings reported in Figure 3 as the effect size was markedly reduced after excluding studies with at least moderate risk of bias from the meta-analysis.

We also performed a subgroup analysis of studies that used the Rome IV criteria versus the Rome III criteria for diagnosing IBS. Five studies[20–22,35,37] used the ROME III criteria to diagnose IBS while the remaining three[23,36,38] used the newer ROME IV criteria. Interestingly, the SMD was significant for studies that used the Rome III criteria (Fig. 6) but not significant when analyzing studies that used the Rome IV criteria (Fig. 7). A possible explanation is that although most Rome III-diagnosed IBS patients will likely still fulfill the Rome IV criteria for IBS, the Rome IV-diagnosed patients may constitute a more severe group of patients in terms of their symptoms.[39] Compared with the Rome III criteria for IBS, the Rome IV criteria required the presence of abdominal pain (not discomfort), and the expected frequency was increased to at least 1 day per week. In view of the more severe symptoms and the relative modest effects of vitamin D, it may not reach statistical significance in this patient group.

IBS quality of life outcomes. In pooled analysis (using a random-effects model) of four studies containing 448 patients (226 taking vitamin D supplements and 222 taking placebo), it was found that patients who received vitamin D supplements did not experience a significant improvement in their IBS-QoL scores (SMD 0.54; 95% CI −0.34 to 1.41, $P = 0.15$, $I^2 = 87\%$) (Fig. 8). There was no evidence of publication bias, based on a non-significant Egger regression test ($P = 0.0575$) (Table S2) and a visually symmetrical funnel plot (Fig. S4).

Sensitivity analysis by excluding five studies with mod-to-high risk of bias revealed that patients taking vitamin D supplements did not experience a significant improvement of IBS-QoL scores (SMD 0.48; 95% CI −1.15 to 2.11, $P = 0.33$, $I^2 = 90\%$) (Fig. 9). There was no evidence of publication bias, based on a non-significant Egger regression test ($P = 0.1218$) (Table S2) and a visually symmetrical funnel plot (Fig. S5).

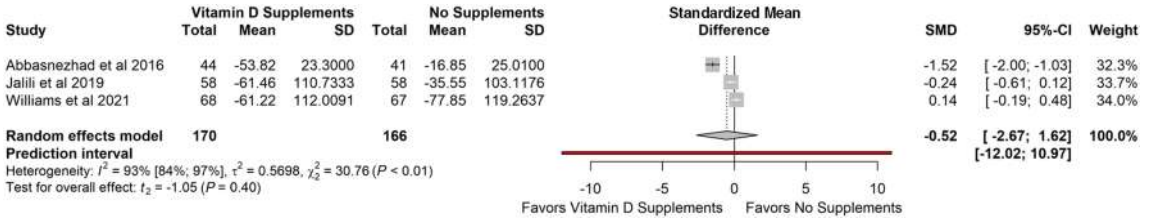

Figure 4 Sensitivity analysis for IBS-SSS by excluding studies with mod-to-high risk of bias.

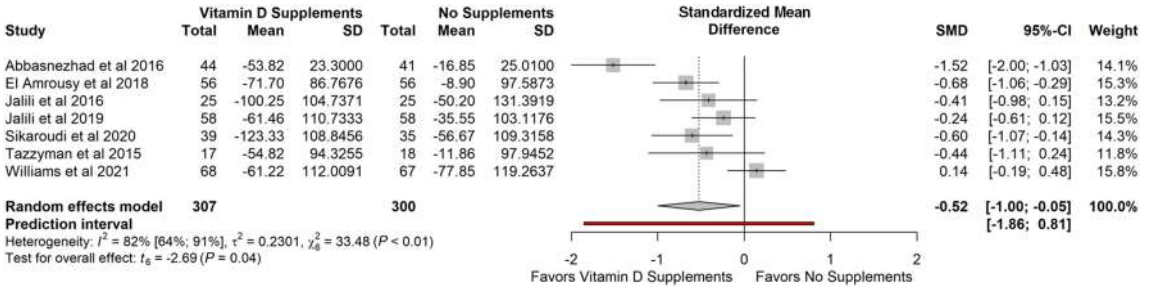

Figure 5 Sensitivity analysis for IBS-SSS by excluding study published in 'predatory' journal.

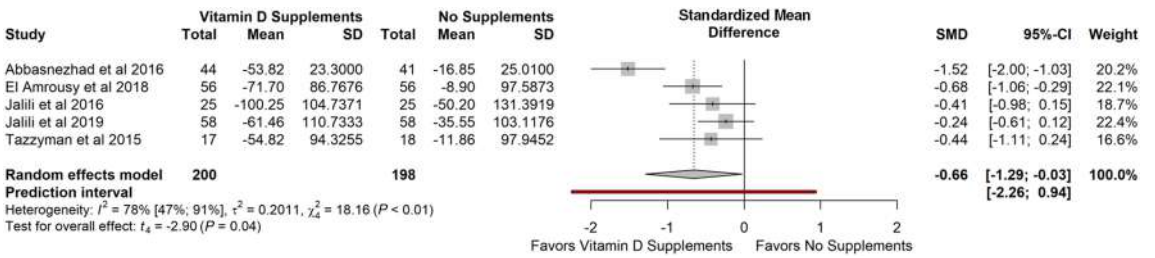

Figure 6 Subgroup analysis of studies that used the Rome III criteria for diagnosis of IBS.

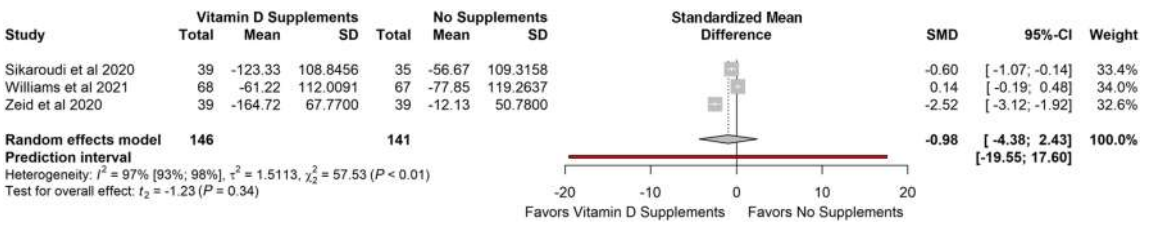

Figure 7 Subgroup analysis of studies that used the Rome IV criteria for diagnosis of IBS.

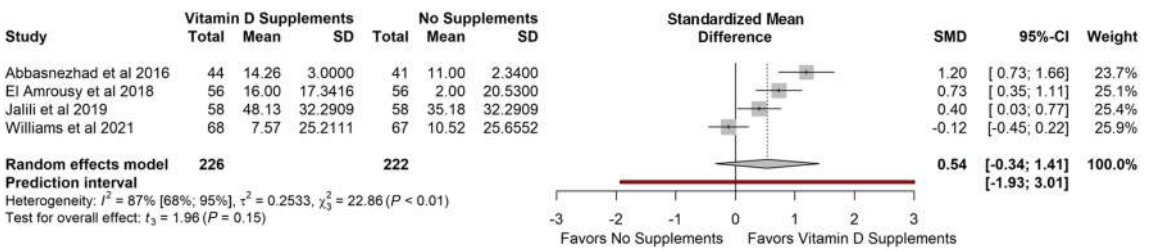

Figure 8 Forest plot showing meta-analysis of vitamin D supplementation on IBS-QoL scores.

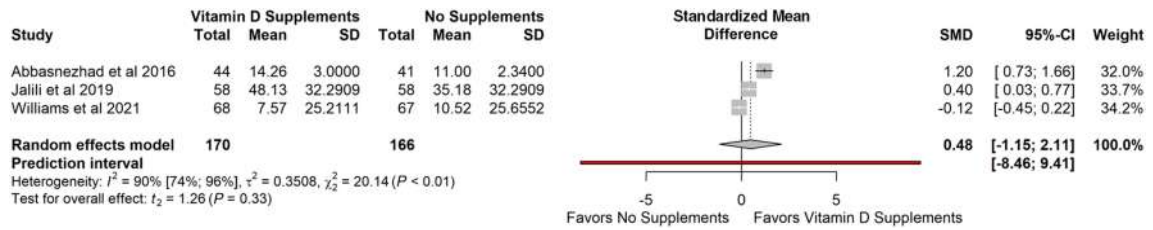

Figure 9 Sensitivity analysis for IBS-QoL by excluding studies with mod-to-high risk of bias.

Discussion

In this systematic review and meta-analysis, the effects of vitamin D supplementation on IBS-SSS and IBS-QoL scores were studied. Overall, there was a significant improvement in IBS-SSS (SMD −0.77, 95% CI: −1.47 to −0.07, $P = 0.04$, $I^2 = 91\%$) but not for IBS-QoL (SMD 0.54, 95% CI: −0.34 to 1.41, $P = 0.15$, $I^2 = 87\%$). To our knowledge, this is the first meta-analysis to investigate the effects of vitamin D supplements on IBS symptomatology.

At present, IBS treatment is generally aimed at symptom relief and current therapies include nonpharmacologic (e.g. the elimination of dietary fermentable oligosaccharides, disaccharides, monosaccharides and polyols, or low FODMAP diet) and pharmacologic methods (e.g. peppermint oil, and antidepressant medications).[17,40–43] Previous studies have shown that a low FODMAP diet[40], dietary fiber[41], peppermint oil,[42] and tricyclic antidepressants[43] can improve IBS symptoms. Based on the findings of this meta-analysis, IBS-SSS improvement through the use of vitamin D supplements (SMD: −0.77, 95% CI −1.47 to −0.07, $P = 0.04$, $I^2 = 91\%$) was comparable with the popular low FODMAP diet (SMD: −0.66, 95% CI: −0.88 to −0.44, $I^2 = 54\%$, $P < 0.01$).[44] Similarly, peppermint oil, which was found in studies to improve IBS-SSS by 90.8 ± 75.3 points,[45] was comparable with the mean improvements reported in this meta-analysis.

Vitamin D supplements appeared safe, with no serious adverse events reported in any of the trials. This may make it a more attractive option than other therapies. For example, elimination diets may have long-term health risks, including the development of eating disorders[46] and micronutrient deficiencies.[47] Tricyclic antidepressants have various side effects, including dry mouth, insomnia, constipation, flushing, palpitations, and loss of appetite due to their anticholinergic actions.[48] However, vitamin D supplements do fall short in improving IBS-QoL scores. This meta-analysis found that the improvements in IBS-QoL scores were not statistically significant (SMD 0.54; 95% CI −0.34 to 1.41, $P = 0.15$, $I^2 = 87\%$). Similarly, peppermint oil, although a popular remedy for IBS, has also not consistently demonstrated significant improvements in IBS-QoL scores.[45] Based on a 2021 meta-analysis, a low FODMAP diet has significant beneficial effects on IBS-QoL scores compared with a control diet[44]; however, questions about nutritional adequacy and the long-term effects of such a diet on gut microbiome still remain unanswered. Nonetheless, vitamin D supplements are a suitable alternative for treatment of IBS patients, with its comparable efficacy and minimal side effects.

In terms of the range of doses investigated, the studies used 2000 IU/day to 50 000 IU/biweekly of vitamin D. Importantly, no serious adverse events were reported. In general, vitamin D is safe and potential side effects include acute manifestations of severe hypercalcemia secondary to vitamin D toxicity, which range from fatigue, constipation, back pain, and forgetfulness to nausea, vomiting, weight loss, and refractory status epilepticus. However, this is rare and typically occurs with excessive long-term intake of vitamin D, or in individuals with aberrant vitamin D metabolic pathways, such as the intestinal calcium hyperabsorption or the metastatic calcification of soft tissues.[49] Furthermore, Hathcock *et al*. showed that there was no association between harm and intake of 10 000 IU/day of vitamin D, suggesting that a high dose of vitamin D is necessary to induce toxicity related to hypercalcemia.[50] Therefore, to avoid adverse effects of vitamin D, the recommended dietary allowance of vitamin D is approximately 600 IU/day, with an upper limit of 4000 IU/day. Additionally, it was found that the best regimen to supplement vitamin D in healthy adults consists of an initial large bolus dose of 600 000 IU monthly by intramuscular injections or a monthly oral dose of 200 000 IU or a weekly oral dose of 50 000 IU for 8 weeks, followed by a maintenance dose of 50 000 IU monthly or bimonthly.[51]

The precise pathophysiology of IBS is not well-understood. It is hypothesized to involve interactions at the level of the gut microbiome, alterations in intestinal permeability, gut immunity, visceral sensation, and brain–gut interactions.[9–11] Vitamin D could have beneficial effects on all these probable shared and disparate pathophysiologies. Vitamin D may help alleviate dysbiosis, an imbalance in the inflammatory processes and shift of the gut microbiome, contributing to the improvement in IBS symptoms.[52,53] In terms of the effects on gut microbiome, vitamin D deficiency may lead to the overgrowth of certain pathogens such as *Haemophilus* and *Veillonella*,[54] while supplementation of vitamin D may prevent this.[55] Furthermore, vitamin D has been found in earlier studies to improve intestinal barrier function, increase production of antimicrobial peptides, and modulate adaptive and innate immunity.[18,56,57] With regard to immunity, vitamin D is a key regulator of T-cell function and receptor recognition.[58] It acts to inhibit Th1 and Th17 cells while inducing regulatory T cells, thus potentially ameliorating inflammation in the gut and maintaining an acceptable level of immune tolerance in the gut.[59] Lastly, as inflammation leads to a heightened central sensitivity, which results in visceral hypersensitivity and abdominal pain perception, the reduction of inflammation with vitamin D supplementation should theoretically improve overall IBS symptoms.[10,60]

Interestingly, while most included studies were in agreement that vitamin D improves overall IBS symptoms, Williams *et al*.[23] showed that vitamin D supplements had no significant effects on IBS-SSS for all the IBS subtypes. A possible explanation for this

differing result could be due to vitamin D suppressing tryptophan hydroxylase 1 enzymes in the gut.[61] This enzyme is the synthetic rate-limiting enzyme for serotonin production in the gut, and repression of this enzyme results in decreased serotonin levels.[62] Such derangements in serotonin metabolism have been implicated in the pathogenesis of IBS and could explain this conflicting result. Further research is warranted to unravel the pathways in which vitamin D supplements affect IBS, in order to better understand its role as a treatment for IBS.

Furthermore, IBS is a complicated disease with different subtypes, such as that of IBS with predominant constipation, predominant diarrhea (IBS-D), mixed IBS, and unspecified IBS.[63] Therapy for IBS is known to be influenced by its subtype, with specific medications such as lubiprostone and linaclotide for IBS with predominant constipation and rifaximin and eluxadoline for IBS-D being approved by the FDA.[64] In the case of vitamin D supplements, majority of the studies included in this review have not grouped the IBS patients into their different subtypes, and hence, additional studies of longer duration in selected IBS subtypes are necessary to better define its role and optimal doses. There may be differences in treatment response for the different IBS subtypes. In fact, an earlier study found that the serum concentrations of 25-hydroxyvitamin D (25(OH)D) were statistically lower only in IBS-D patients compared with healthy controls, when analyzing the different IBS subtypes.[65]

Another aspect of treatment effectiveness in IBS would be the QoL improvements. While the results of this meta-analysis showed that vitamin D supplements did not significantly improve QoL outcomes of IBS patients, vitamin D supplements may help improve mood in vitamin D deficient IBS patients. In IBS patients, depression and anxiety[66,67] and vitamin D deficiency[19] are prevalent. Depression is multifactorial, with vitamin D deficiency as a potential contributing factor, even among healthy individuals.[68] Normally, intracellular levels of calcium are maintained at a low level due to regulation via vitamin D. When there is a deficiency in vitamin D, there is an increase in calcium levels intracellularly, which has been shown to be associated with depressive symptoms.[69] Vitamin D is also related to the synthesis of 5-hydroxytryptamine via stimulation of tryptophan hydroxylase 2.[61,62] 5-Hydroxytryptamine stimulates the expression of DNA demethylases that are involved in the homeostasis of neuronal activity which prevent depression.[70] Thus, vitamin D supplementation may improve mood symptoms in IBS patients with vitamin D deficiency, thereby improving the physical symptoms.

Limitations. The findings of the present meta-analysis should be interpreted in light of some limitations. High heterogeneity was detected in the meta-analysis. The studies included in this meta-analysis were rather heterogeneous and limited in generalizability for the following reasons. First, given the heterogeneous nature of IBS as a condition, whereby there are several subtypes, each with their own complex of symptoms, the treatment should be based on the predominant symptom and subtype. The potential of vitamin D as a therapy for various IBS subtypes requires further clarification, considering how among the various subtypes, only IBS-D patients were found to have a lower serum vitamin D concentration when compared with healthy controls.[65] Second, the dosing regimen of vitamin D supplements used among the trials was different, and potential dose-dependent relationships between vitamin D supplements and improvement of IBS symptoms or effects on QoL may have been overlooked. There were also other confounding factors such as diet and physical activity, which have not been controlled for. There is a paucity of data on the effects of nutritional sources of vitamin D as opposed to active vitamin D supplements. Lastly, six out of the eight studies included were from the Middle East, further limiting the generalizability of the findings. Moreover, the studies also had relatively small sample sizes and recruited predominantly younger persons (mean age ranged from 16.20 to 42.24 years in the vitamin D group). This is relevant as the severity of abdominal pain/discomfort and QoL may differ in IBS patients of different ages.[71]

Given that the statistical significance of the findings was not maintained in the sensitivity analysis, recommendations for future research would include more rigorous placebo-controlled RCTs to investigate the effects of vitamin D supplements in each individual subtypes of IBS, as well as the dose-dependent relationships of vitamin D with IBS symptoms and QoL improvements. Future studies could also be performed using a larger sample and with populations derived from regions where vitamin D deficiencies are more prevalent, such as South Asia, Europe, the United States, and Canada.[72]

Conclusion

This meta-analysis supported the potential clinical role of vitamin D supplementation in improving IBS symptom severity and QoL measures. It may represent an addition to the current therapeutic armamentarium for IBS sufferers. Further research is required to elucidate the generalizability, dosing strategy, and long-term effects of vitamin D supplements.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search Strategy for Medline.
Table S2. Egger Regression Analysis.
Figure S1. Funnel Plot for IBS-SSS Analysis.
Figure S2. Funnel Plot for IBS-SSS after excluding mod-to-high risk of bias studies.
Figure S3. Funnel Plot for IBS-SSS after excluding article published in potentially 'predatory' journal.
Figure S4. Funnel Plot for QoL.
Figure S5. Funnel Plot for QoL after excluding mod-to-high risk of bias studies.
Table S3. PRISMA-P 2020 Checklist.