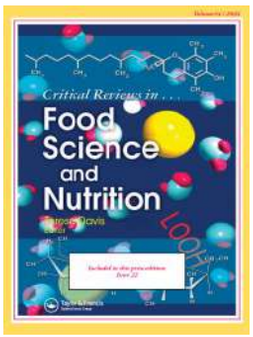

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REVIEW ARTICLE

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The effects of vitamin D intake and status on symptom severity and quality-of-life in adults with irritable bowel syndrome (IBS): a systematic review and meta-analysis

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ABSTRACT

Importance: Many individuals with irritable bowel syndrome (IBS) have insufficient or deficient serum 25-hydroxyvitamin D [25(OH)D] status; however, it is not clear if improved vitamin D nutritional status through higher intake can improve symptom severity and quality of life.

Objective: This systematic review and meta-analysis aimed to identify if changes in vitamin D intake or status affect symptom severity and quality of life in adults with IBS.

Data Sources: MEDLINE®, Cochrane Central Register of Controlled Trials, Global Health, EMBASE, and Web-of-Science databases were systematically searched for relevant articles to August 12, 2024, in the English language.

Study Selection: Clinical trials, prospective observational studies, and Mendelian randomization (MR) analyses reporting the effect of vitamin D intake or status on IBS-related outcomes were included.

Data Extraction and Synthesis: Article review and data extraction were conducted by 2 authors following the PRISMA guidelines. Random effects meta-analyses and the Nutrition Quality Evaluation Strengthening Tools to assess risk of bias were employed for randomized controlled trials.

Main Outcome(s) and Measure(s): Primary outcomes included measures of serum 25(OH)D status, symptom severity, and quality of life.

Results: 12 studies from 15 articles were included ($n=7$ RCTs; $n=3$ single-arm interventions; $n=2$ MR). Seven study populations had deficient (<20 ng/mL) and three had insufficient (21–29 ng/mL) baseline serum 25(OH)D status. RCTs measured changes in serum 25(OH)D after 6–26 wks with 3,000 IU daily to 50,000 IU bi-weekly vitamin D dosages. Meta-analyses of low risk-of-bias RCTs revealed increased 25(OH)D levels in groups treated with oral vitamin D compared to placebo ($n=5$; Pooled mean difference [95% CI]: 20.33 [12.91, 27.74] ng/mL; $I^2 = 97.9\%$). Quality of life scores improved significantly in deficient populations ($n=3$; 3.19 [2.14, 4.24]; $I^2 = 0.0\%$). Non-significant decreased trends in IBS symptom severity were shown across populations ($n=6$: −25.89 [-55.26, 3.48]; $I^2 = 92.8\%$).

Conclusion: Moderate level evidence indicate vitamin D supplementation may improve status in adults with IBS and quality of life in those with deficient status at baseline.

KEY POINTS

Question: Do changes in vitamin D intake or status affect symptom severity and quality of life in adults with irritable bowel syndrome?

FindingsIn this systematic review and meta-analysis, moderate level evidence supports vitamin D supplementation for improving serum 25-hydroxyvitamin D status in adults with IBS and for increasing quality of life scores in those with deficient status at baseline.

Meaning: Vitamin D supplementation may improve quality of life in IBS patients with deficient serum 25-hydroxyvitamin D status.

KEYWORDS

Vitamin D; irritable bowel syndrome; IBS; quality of life; nutritional status

Introduction

Irritable Bowel Syndrome (IBS) is a chronic condition marked by persistent abdominal pain and irregular bowel habits, occurring without any identifiable organic etiology (Canavan, West, and Card 2014). This syndrome significantly impacts patients' quality of life (QoL) and imposes a financial burden on individuals and society as a whole (Peery et al. 2022). Research suggests that approximately 10%-25% of the population experiences symptoms consistent with IBS (Canavan, West, and Card 2014). Although not all individuals seek medical attention, those affected represent a significant portion of outpatient visits to gastroenterology clinics (Peery et al. 2022). Based on current Rome IV diagnostic criteria, symptoms typically include constipation, diarrhea, or a mix of constipation and diarrhea, and abdominal bloating/distention (Grad and

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Dumitrascu 2020). As such, the disorder encompasses three primary subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), and IBS with mixed symptoms (IBS-M), also referred to as alternating IBS (IBS-A). IBS with bowel habits not fitting the above categories is diagnosed as Unspecified (IBS-U).

IBS is a complex disorder with multiple factors contributing to its symptomatology. These factors include gastrointestinal dysmotility, inflammation, visceral hypersensitivity, and dysregulated gut-brain axis (Grad and Dumitrascu 2020). Dietary patterns and exposure to stress have also been identified as potential contributors (Heitkemper, Jarrett, and Jun 2013). Furthermore, genetic predisposition and environmental factors, such as familial susceptibility and psychosocial stressors, are thought to play roles in its pathogenesis (Fukudo and Kanazawa 2011; Ng et al. 2024). As a result, treatment options are mainly aimed at managing symptoms (Grad and Dumitrascu 2020). Pharmaceutical approaches may include the use of anti-spasmodic and anti-depressive medications. Dietary regimens, like low-FODMAP diets and other exclusion-based approaches, are also used for symptomatic management (Whelan et al. 2018). Additionally, disruptions in the gastrointestinal tract can lead to intestinal hyperpermeability and result in malabsorption of nutrients in patients with IBS (Zhou et al. 2019), so supplementation methods, such as probiotics and prebiotics (Ford et al. 2018), glutamine (Zhou et al. 2019), and especially vitamin D (Chong et al. 2022) have gained recent increased interest among scientists and clinicians.

Vitamin D is a prohormone that can be obtained through dietary sources or synthesized endogenously, with the latter serving as the primary source for most individuals, and a large majority of individuals falling short of recommended dietary intakes (Bouillon et al. 2019). The process involves the photoconversion of 7-dehydrocholesterol, a derivative of cholesterol, within the skin's sebaceous glands, leading to the formation of vitamin D3. Subsequent hepatic and renal hydroxylation result in its conversion to 25-hydroxyvitamin D (abbreviated 25(OH)D) and then to 1,25(OH)D. Guidelines from authoritative bodies widely recognize serum 25(OH)D as the best indicator of nutritional status, and the Endocrine Society designates levels below 20 ng/mL as deficient, between 21–29 ng/mL as insufficient, and between 30–100 ng/mL as sufficient and safe for use in clinical practice (Sempos and Binkley 2020); these levels are slightly higher than the National Academy of Medicine's public health guidelines. Aside from its fundamental role in maintaining mineral (e.g., calcium, magnesium, and phosphorus) homeostasis, vitamin D may directly or indirectly influence the immune system, inflammatory processes, gut microbiome, and release of antimicrobial peptides. Vitamin D receptors (VDRs) has been identified as critical to maintaining intestinal mucosal barrier homeostasis and in restoring the healing capacity of the colon (Kong et al. 2008). Observational studies further suggest patients with IBS have a higher risk of inadequate serum 25(OH)D levels (Khayyat and Attar 2015; Nwosu, Maranda, and Candela 2017); and therefore, augmentation through clinically supervised supplementation may have utility as a therapeutic adjuvant for this condition.

Supplementation has been suggested to be beneficial for repleting individuals with low 25(OH)D status (Bouillon et al. 2019), but it is not clear if this improvement impacts symptom severity and quality of life for patients with IBS. Augmentation of inadequate serum 25(OH)D levels through clinically supervised supplementation could provide additional therapeutic effects as an adjuvant strategy for improving symptom severity and quality of life in patients with IBS. While recent systematic reviews of randomized controlled trials have been conducted on this topic (Chong et al. 2022; Huang et al. 2022; Abuelazm et al. 2022), a high-quality comprehensive review on the totality of evidence across study designs does not yet exist. Therefore, our objective was to conduct a systematic review of all available literature on the effect of vitamin D intake and in adults with IBS and to conduct a meta-analysis to identify whether improved vitamin D nutritional status leads to changes in IBS symptom severity and quality-of-life. We hypothesized that dietary vitamin D augmentation would improve serum 25(OH)D status, symptom severity, and quality-of-life in adult patients with IBS.

Methods

This study followed the National Academy of Medicine's Standards for Systematic Reviews (Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research 2011) and was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, version 6.4 ("Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)" 2023), and the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al. 2021). The review protocol was registered on The International Prospective Register of Systematic Reviews prior to data extraction (https://www.crd.york.ac.uk/prospero/; PROSPERO CRD42023492631), and we did not deviate from or amend the protocol.

Data sources and searches

Search strategies were developed in consultation with two university librarians. The initial search strategy was developed for bibliographic databases on the Ovid platform including MEDLINE® (1946 to August 12, 2024), Cochrane Central Register of Controlled Trials (1991 to August 12, 2024), and Global Health (1910 to August 12, 2024). The strategy was then adapted for searching Embase (1974 to August 12, 2024) and the Web-of-Science databases including the "Core Collection" (1900 to August 12, 2024) and "All Databases" (1637 to August 12, 2024). Search strategies included keywords related to all forms of dietary and supplemental vitamin D (e.g., cholecalciferol, 25-hydroxyvitamin D), keywords related to all forms of IBS and associated symptoms (e.g., IBS-C, IBS-D, constipation, diarrhea), and indexing terms tailored to each database (e.g., Medical Subject Headings [MeSH] for MEDLINE® and Emtree terms for Embase). No limitations were applied to the searches

(e.g., no language or publication date limits). The complete Ovid MEDLINE® search strategy is included in the **Supplemental Materials** as an example. In addition to searching bibliographic databases, we performed reference mining in relevant former narrative and systematic reviews to ensure no relevant studies were missed.

Study selection

Abstracts and titles from database searches were screened by two independent investigators using Rayyan online software (Ouzzani et al. 2016), and conflicts were resolved by consensus. For included abstracts and all records identified through reference mining, full-text articles were pulled and screened for eligibility criteria by the lead investigator (KCC). Exclusion of any article at this stage was confirmed by a second investigator (SFT), and there were no disagreements. Eligibility criteria, presented in Table 1, followed the Population Intervention/Exposure Comparator Outcome (PI/ECO) framework which is recommended for comprehensive systematic reviews (Methley et al. 2014).

Studies of vitamin D interventions or exposures in adult populations (≥ 18 years of age) with IBS, or healthy cohorts prospectively followed for IBS outcomes, were eligible for inclusion in this review. We excluded nonhuman studies and human studies on infants, children, adolescents, or populations with diseases other than IBS. Eligible study designs included clinical trials of any form (i.e., parallel or crossover randomized controlled trials; non-randomized controlled trials such as quasi-experimental, crossover, and controlled before-after studies; and uncontrolled trials including single arm studies), prospective cohort studies, nested case-control studies, case-cohort studies, and Mendelian randomization studies. Studies reporting only cross-sectional associations or not reporting associations between vitamin D intake or status and IBS outcomes were excluded. To be included, study reports needed to quantify serum vitamin D or dietary intake of vitamin D from foods, beverages, or supplements and quantify change in serum vitamin D and/or any IBS-related outcomes. We included studies examining different doses, sources, and status of vitamin D as well as those comparing vitamin D intake to a placebo or no comparator. However, studies that compared vitamin D interventions/exposures only to other vitamins, multivitamins, other mixed supplements, or non-vitamin supplements were excluded.

Data extraction

We created separate data extraction tables for study and participant characteristics and quantitative results. Study characteristics data included registration number, location, funding source, design, duration, and cohort description or data source (where relevant). We also extracted data for the vitamin D intervention/exposure source, type, dose, frequency, dietary assessment tool, and serum vitamin D assessment method; the comparator type and description; and each study's primary and secondary outcome(s). Participant characteristics data included sample size enrolled/randomized and analyzed, percent male, race/ethnicity, health status, and how presence of IBS was determined in the study. We also extracted mean baseline data for age, body mass index (BMI), and serum 25(OH)D levels.

Table 1. Criteria used to determine eligibility for inclusion in the systematic review[1].

Category	Inclusion criteria	Exclusion criteria
Study participants	Human subjects	Non-human subjects (animals or cells)
Age of study participants	Adults (≥18 years) including populations with: • Mean/median age ≥18 years • Age range mid-point ≥18 years	Infants Children Adolescents
Health status of participants	Irritable bowel syndrome (IBS) at baseline Healthy (prospective cohorts)	Populations with diseases other than IBS Populations with IBS in addition to other diseases
Intervention or exposure	Dietary vitamin D intake from foods, beverages, or supplements Vitamin D status (e.g., serum vitamin D or 25-OH-D)	No quantified vitamin D intake or status
Comparator	Different vitamin D doses, sources, and status Placebo No comparator	Other vitamins Multivitamins Other mixed supplements or non-vitamin supplements
Outcomes	Vitamin D status changes IBS diagnosis (prospective cohorts) IBS symptom severity or activity scores (e.g., ROME criteria) Quality of life scores Any reported IBS-associated outcomes (e.g., constipation, diarrhea, etc.)	No IBS-related outcomes and no post-intervention vitamin D outcomes
Study design	Clinical trials including: • Randomized controlled trials (parallel or crossover) • Non-randomized controlled trials including quasi-experimental, crossover, and controlled before-after studies • Uncontrolled trials (e.g., single arm studies) Mendelian randomization studies Prospective cohort studies Nested case-control studies Case-cohort studies	Retrospective cohort studies Case-control studies Cross-sectional studies Narrative reviews Systematic reviews Meta-analyses Letters to the editor Case studies or case series Conference proceedings Abstracts
Publication status	Articles published in peer-reviewed journals	Articles not published in peer-reviewed journals, including unpublished data, manuscript reports, abstracts, pre-prints, and conference proceedings
Language of publication	English	Languages other than English

[1]No restrictions for study duration, sample size, date of publication, or study country.

Quantitative results were extracted for outcomes reported by three or more RCTs. If studies reported multiple analysis models, we extracted results from the most adjusted model. For studies with repeated measures, we extracted only baseline and endpoint results and/or reported change statistics (e.g., mean change). Quantitative data were extracted by one investigator (KCC) and exhaustively checked by another investigator for agreement (SFT and HFA). Only one error was detected and was resolved by consensus. When relevant data were only presented in figures, we extracted those data using WebPlotDigitizer online software, version 4.6 (Rohatgi 2022). We contacted study authors for clarification or additional data when published results were not reported with sufficient details.

Meta-analyses

To prepare data from RCTs for meta-analysis, we performed several assumptions-free calculations. Serum 25(OH)D values in nmol/L were divided by 2.496 and converted to ng/mL (Young 1990). One article reported IBS Quality of Life scores on a scale of 34 to 170 with higher scores indicating lower quality of life (Khalighi Sikaroudi, Mokhtare, Shidfar, et al. 2020a), so these scores were reversed then converted to a scale of 0–100 to match what was reported in all other studies. Reported median and IQR values were converted to mean and SD using the methods and calculator provided by Wan, et al. (Wan et al. 2014), and reported SE was converted to SD by a standard equation ($\sqrt{n} \times SE$). When articles did not report mean differences, we calculated these from available baseline and endpoint data. Estimating SD of change for these mean differences required an assumption. Data from included studies where SD of change was reported showed Pearson's $r = 0.99$ between study arms. We used a more conservative $r = 0.90$ to impute SD of change with this equation: $\sqrt{SD_1^2 + SD_2^2 - \left(2 \times r \times SD_1 \times SD_2\right)}$, where SD_1 represents the standard deviation at baseline, and SD_2 represents the standard deviation at endpoint for one study arm. In sensitivity analyses, we repeated all meta-analyses where SD of change was imputed with more conservative values of $r = 0.8$ and $r = 0.7$, when two articles with data reporting issues were removed (Tazzyman et al. 2015; Jalili et al. 2016), and when one article with some potential for bias was included (Zeid et al. 2020). Conclusions from sensitivity analyses for imputed SD of change were similar to those from primary analyses, so we have reported the primary results. For conclusions changed by the addition or exclusion of individual articles, we present findings from both primary and sensitivity analyses.

In light of clinical heterogeneity (e.g., differences in vitamin D intake and status and in study populations across studies), random-effects meta-analyses were conducted using the restricted maximum likelihood (REML) method and unstandardized mean differences when ≥3 clinical trials with low potential risk-of-bias reported the same outcome of interest ("Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)" 2023). These mean differences were based on change-from-baseline measures to estimate the degree to which vitamin D interventions changed each outcome on average compared to a placebo ("Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)" 2023). We avoided double counting of participants from studies reported in more than one publication by only analyzing data from different outcomes reported in those publications.

To explore potential sources of heterogeneity, we originally planned to conduct dose-response meta-regressions and perform multiple subgroup analyses. However, due to differences in study designs and a small number of included studies addressing each outcome, meta-regression was deemed inappropriate, and subgroup analyses were not possible for certain characteristics (e.g., sex and vitamin D intervention dose, frequency, and duration). We were able to conduct subgroup analyses for baseline vitamin D status and BMI status, which we planned for the following reasons: (1) subjects with deficient or insufficient serum 25(OH)D status often have an enhanced response to oral vitamin D therapy, and (2) differences in treatment effects have been reported between individuals with normal and high BMI due to the simple volumetric dilution of this fat-soluble vitamin in fat tissue. Included studies used various ranges to define vitamin D status in their study populations. To standardize definitions for deficient and insufficient vitamin D status for the purpose of our analyses, we applied the Endocrine Society guidelines, which were designed for clinical practice, rather than the National Academy of Medicine public health guidelines, which were designed for the generally healthy non-diseased population (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium 2011; Holick et al. 2011).

Meta-analysis results were deemed statistically significant if the confidence intervals for pooled effect sizes excluded zero. Cochrane's Q statistic was calculated to quantify heterogeneity where $p \leq 0.1$ was considered significant, and I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. Stata SE software (version 18.0; Stata Corp., College Station, TX) was used for all calculations and meta-analyses.

Risk-of-bias and strength-of-evidence

For all included randomized controlled trials, two investigators independently performed risk of bias (ROB) assessments at the study and outcome levels using the Nutrition Quality Evaluation Strengthening Tools (NUQUEST) for RCTs (Kelly et al. 2021). Studies were assessed on 14 total items across four domains measuring potential bias due to the selection of participants, comparability of study groups, nutrition-specific considerations, and the ascertainment of outcomes. An internally developed scoring system and rating algorithm was then applied where each ROB item was assigned a score based on the following answer choices: yes, probably yes, probably no, and no. One item in the "comparability of study groups" domain was not applicable to included RCTs so was removed from scoring. Total scores were tallied across the 13 remaining items, and ratings of good (low ROB), neutral (some ROB), or poor (high ROB)

were assigned to the four domains and the study overall. The scoring system and rating algorithm are presented in **Supplemental Tables S1 and S2**.

For each outcome included in our meta-analyses, we used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al. 2011; Guyatt et al. 2008) to determine collective strength-of-evidence (SoE) across the clinical trials. MR studies were excluded from the GRADE evaluation. SoE profile tables were compiled to report the number and design of studies measuring each outcome; the overall limitations, imprecision, inconsistency, indirectness, and publication bias identified in this review; summary of findings statements; and SoE grades (i.e., *very low*, *low*, *moderate*, or *high*). These grades indicate our degree of confidence that estimated effects from reviewed evidence were close to the true effect.

Results

Study and participant characteristics

After screening 954 records, we included 15 articles reporting on 12 studies in this systematic review ($n=7$ RCTs; $n=3$ single arm interventions; $n=2$ MR) (Figure 1). Although prospective observational studies were eligible for this review, none met our inclusion criteria. Articles excluded during the full-text extraction stage ($n=12$) are listed with their exclusion reasons in **Supplemental Table S3**. Included RCT and single arm intervention studies ranged in size from 40 to 135 participants in populations aged 18 to 75 years, as shown in Table 2. The two MR studies ranged in size from 187,028 to 496,946 and did not report age ranges. Based on reported mean BMI, studies were conducted in populations with overweight ($n=3$) or healthy weight ($n=2$; $n=7$ did not report BMI). Mean (SD) baseline serum 25(OH)D levels for intervention study groups ranged from 11.68 (8.17) to 21.33 (5.54) ng/mL with all populations having deficient (<20 ng/mL, $n=7$) or insufficient (21 to 29 ng/mL, $n=3$) baseline vitamin D status according to Endocrine Society standards (Sempos and Binkley 2020; Holick et al. 2011). One MR study was conducted in a population with insufficient baseline vitamin D status (28.04 ± 13.9 ng/mL) (Xu et al. 2023), while the second MR study (Xie et al. 2022) and one RCT (Zeid et al. 2020) did not report 25(OH)D levels. Most studies were conducted in countries from the greater Middle East (Iran, $n=4$; Egypt, $n=2$; Pakistan, $n=1$) with others conducted in China ($n=2$), the UK ($n=2$), and the US ($n=1$).

Although all studies included participants with IBS, the predominant symptoms in the study populations varied (IBS-C, $n=4$; IBS-D, $n=6$; IBS-M or IBS-A, $n=4$; IBS-U, $n=1$) with several studies conducted in populations with multiple IBS subtypes ($n=4$) or subtypes that were not specified ($n=6$). Two studies included only participants with IBS-D (Khalighi Sikaroudi, Mokhtare, Shidfar, et al. 2020a; Khalighi Sikaroudi, Mokhtare, Janani, et al. 2020b; Kesavan et al. 2023). For the interventions, IBS status was evaluated by Rome III ($n=4$) or Rome IV ($n=3$) diagnostic criteria and/or clinical diagnosis ($n=4$). These studies investigated effects of daily, weekly, or bi-weekly vitamin D supplementation administered over 6 to 26 wks. Four intervention studies administered supplementation of 3,000–5,000 IU vitamin D daily, four administered 50,000 IU weekly or bi-weekly, and one administered 42,000 IU weekly (Ibrahim et al. 2020). One study specified four VD injections provided weekly and two subsequent doses monthly but did not report dose administered (Alvi et al. 2022).

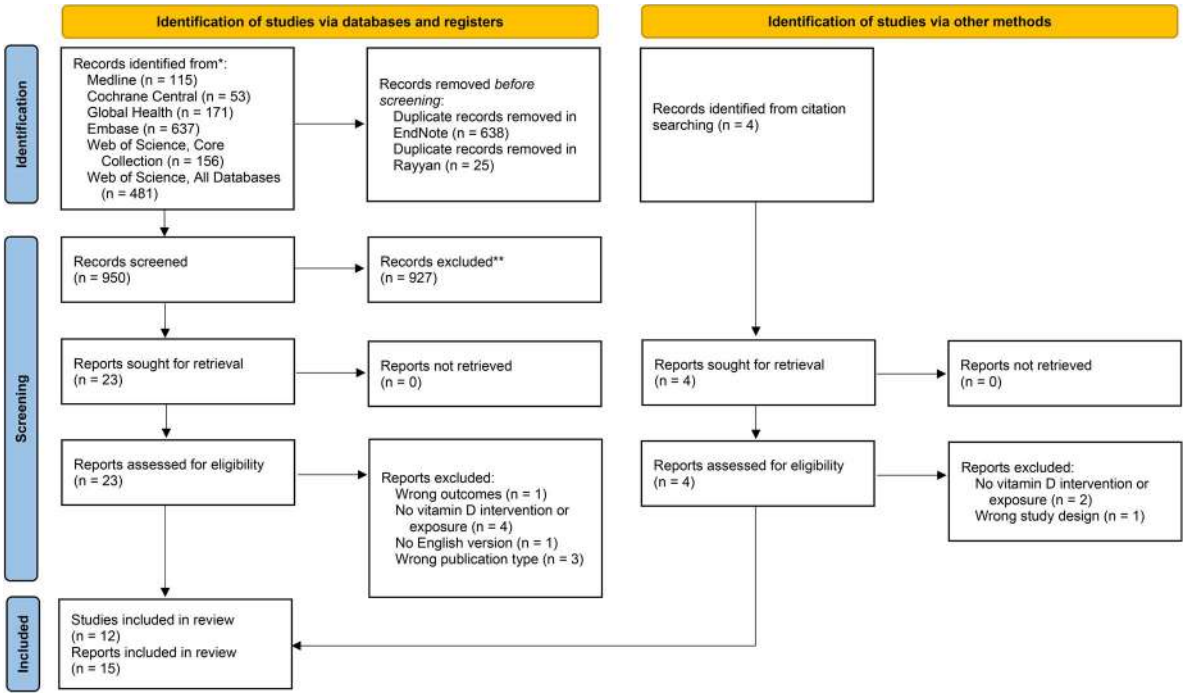

Figure 1. Flowchart of the literature search and study selection process.

Table 2. Study characteristics for included studies,[1] by study type.

Author (year); Registration	Location; Funding type	Study design; Cohort or data source	IBS type; Criteria	Enrolled/analyzed, n; Male %	Mean/median (SD) age, y; range	**Mean (SD) BMI (kg/m^2)**	Mean (SD) baseline 25(OH)D, ng/mL; 25(OH)D range = study group %	Vit. D dose, IU; Study duration, wk	Outcome(s) reported
Randomized Controlled Trials (RCTs)									
Abbasnezhad, et al. (2016); **NCT02579902**	Iran; Nonprofit	RCT, parallel	IBS-C, IBS-D, IBS-A; Rome III criteria	90/85; ~32.9%	37.9; 18–73	VD: 25.21 (2.72) Placebo: 24.98 (2.90)	VD: 19.65 (10.35) ng/mL; <20 = 65.9%, 20–30 = 18.2%, >30 = 15.9% Placebo: 18.62 (11.23) ng/mL; <20 = 63.4%, 20–30 = 22%, >30 = 14.6%	50,000 bi-weekly; 26	25(OH)D, IBS severity score, gastrointestinal symptoms (abdominal pain, abdominal distension, flatulence, rumbling, dissatisfaction with bowel habits, overall symptom), IBS quality of life
Amani, et al. (2018); **NCT02579902**	Iran; Nonprofit	RCT, parallel	IBS-C, IBS-D, IBS-A; Rome III criteria	90/85; ~32.9%	37.9; 18–73	VD: 25.21 (2.72) Placebo: 24.98 (2.90)	VD: 19.65 (10.35) ng/mL; NR Placebo: 18.62 (11.23) ng/mL; NR	50,000 bi-weekly; 26	25(OH)D, inflammatory cytokines (IL-17, IL-10, TNF-α), biomarkers of oxidative stress (total antioxidant capacity, malondialdehyde)
Jalili, et al. (2016); **NCT02026518**	Iran; Nonprofit	RCT, parallel	IBS-C, IBS-D, IBS-M, IBS-U; Rome III criteria	50/50; 0%	VD: 41.32 (12.62); Placebo: 39.76 (12.99); 18–75	VD: 26.04 (4.15) Placebo: 25.35 (3.93)	VD: 21.10 (8.23) ng/mL; NR Placebo: 21.23 (8.45) ng/mL; NR	50,000 bi-weekly; 6	IBS symptom severity scores, disease-specific quality of life, and total score
Jalili, et al. (2019a); IRCT20140223401O N11	Iran; Nonprofit	RCT, parallel	IBS unspecified; Rome III criteria	116/116; 0%	VD: 42.24 (12.26); Placebo: 40.06 (13.37); NR	VD: 25.85 (3.78) Placebo: 25.27 (4.07)	VD: 21.10 (5.23) ng/mL; NR Placebo: 21.33 (5.54) ng/mL; NR	50,000 weekly; 6	25(OH)D, IBS symptoms, quality of life, total IBS score
Jalili, et al. (2019b); **NCT02026518**	Iran; Nonprofit	RCT, parallel	IBS-C, IBS-D, IBS-M, IBS-U; Rome III criteria	50/50; 0%	VD: 41.32 (12.62); Placebo: 39.76 (12.99); 18–75	VD: 26.04 (4.15) Placebo: 25.35 (3.93)	VD: 21.10 (8.23) ng/mL; NR Placebo: 21.23 (8.45) ng/mL; NR	50,000 bi-weekly; 6	Plasma TNF-a, leukocyte NF-kb activity, plasma TAC and fecal serine protease
Khalighi Sikaroudi, Mokhtare, Shidfar, et al. (2020a); **IRCT201701162709N**42	Iran; None	RCT, parallel	IBS-D; Rome IV criteria and World Gastroenterology Organization (WGO) questionnaire	88/74; 46.6%	35.07 (10); 18–65	VD: 24.52 (4.63) Placebo: 26.22 (4.41)	VD: 18.59 (7.58) ng/mL; NR Placebo: 18.59 (7.92) ng/mL; NR	50,000 weekly; 9	25(OH)D, IBS severity score, quality of life, stress and depression, visceral sensitivity, serum serotonin, 5-hydroxyindole acetic acid
Khalighi Sikaroudi, Mokhtare, Janani, et al. (2020b); **IRCT201709232709N**45	Iran; Nonprofit	RCT, parallel	IBS-D; Rome IV criteria	88/88; 46.6%	35.07 (10); 18–65	VD: 24.71 (4.81) Placebo: 25.78 (4.30)	VD: 17.68 (7.69) ng/mL; NR Placebo: 17.83 (7.84) ng/mL; NR	50,000 weekly; 9	25(OH)D, symptom severity, serum CRH, serum IL-6
Tazzyman, et al. (2015); ICTRN 6116003917 and ISRCTN75474149	UK; Industry	RCT, parallel	IBS-C, IBS-D, IBS-M; Clinical diagnosis of IBS and Rome III criteria	51/51; 7.8%	~34.71 (NR); NR	NR	VD [2]: 15.8 (8.0) ng/mL; <12.5 =, 20–50 = 22.2% Placebo [2]: 15 (8.4) ng/mL; 20–50 = 18.5%	3,000 daily; 12	25(OH)D, total IBS symptoms, abdominal pain severity and duration, abdominal distension, bowel movements per day, satisfaction with bowel habits, life disruption
Williams, et al. (2022); ISRCTN13277340	UK; Nonprofit and industry	RCT, parallel	IBS-C, IBS-D, IBS-A; Clinical diagnosis and total IBS-SSS >=150	135/165; 21.5%	30.01 (10.46); >=18	VD: 23.15 (2.76) Placebo: 23.58 (3.00)	VD: 19.53 (11.18) ng/mL[3]; <10 = 26.5%, < 20 = 58.8% Placebo: 19.92 (10.84) ng/mL[3]; <10 = 14.9%, <20 = 61.2%	3,000 daily; 12	25(OH)D, symptom severity, quality of life
Zeid, et al. (2020); NR	Egypt; NR	RCT, parallel	IBS unspecified; Rome IV criteria	80/78; 30%	VD: 37.64 (11.13); Placebo: 38.03 (6.37); >=18	NR	NR; NR	4,000 daily; 12	Symptom severity
Other intervention studies									

(*Continued*)

Table 2. Continued.

Author (year); Registration	Location; Funding type	Study design; Cohort or data source	IBS type; Criteria	Enrolled/analyzed, n; Male %	Mean/median (SD) age, y; range	**Mean (SD) BMI (kg/m^2)**	Mean (SD) baseline 25(OH)D, ng/mL; 25(OH)D range = study group %	Vit. D dose, IU; Study duration, wk	Outcome(s) reported
Alvi, et al. (2022); NR	Pakistan; None	Single arm intervention; Patients, consecutively treated	IBS unspecified; Clinical diagnosis	111/97; 54%	35.97 (9.89); 18–60	NR	14.59 (7.66) ng/mL; NR	NR; four VD injections weekly then two doses monthly; 13	IBS symptoms (abdominal fullness, bloating, heartburn, constipation, diarrhea)
Ibrahim, et al. (2020); NR	Egypt; NR	Single arm intervention; Nutritional Assessment of Medical Students of Ain Shams University (NAMS/ASU) project on undergraduate medical students	IBS unspecified; Rome IV criteria	40/40; 35%	22.33 (1.37); NR	NR	11.68 (8.17) ng/mL; <20 ng/mL = 100%	42,000 weekly; 12	25(OH)D, IBS symptoms (not specified)
Kesavan, et al. (2023); NR	US; None	Single arm intervention; Gulf War Veterans	IBS-D; Clinical diagnosis based on serologies and standards of United European Gastroenterology and European Society for Neurogastroenterology and Motility	69/69; 100%	NR; 25–75 (based on Figure 1A)	NR	20.06 (7.10) ng/mL; <30 ng/mL = 100%	3,000–5,000 daily; NR	25(OH)D, number of bowel movements
Mendelian randomization studies									
Xie, et al. (2022); NR	China; Government	Two-sample Mendelian randomization; EBI database (ebi-a-GCST90000618) from the IEU OpenGWAS database	IBS unspecified; NR	496946/496946; NR	NR; NR	NR	NR; NR	NA; NA	Genetically predicted risk of IBS, genetically predicted vitamin D levels
Xu, et al. (2023); NR	China; Nonprofit	Two-sample Mendelian randomization; FinnGen biobank database (finn-b-K11_IBS) from the IEU Open GWAS database	IBS unspecified; NR	187028/187028; NR	NR; NR	NR	28.04 (13.9) ng/mL[3]; NR	NA; NA	Genetically predicted risk of IBS

NA, not applicable; NR, not reported.
[1]Study registration numbers in bold indicate studies reported in multiple articles included in this review.
[2]Due to discrepancies between tables, values reported here were taken from the article's text first and then supplemented with values reported in tables.
[3]Values were reported as nmol/L which we converted to ng/mL using a conversion factor of 2.496.

Randomized controlled trials

Altogether, seven RCTs reported in 10 articles were included in this review (see Table 2). The most reported outcomes across studies were change in serum 25(OH)D levels ($n=5$), IBS quality of life ($n=5$), IBS symptom severity ($n=7$), and individual IBS symptoms ($n=6$) including abdominal distension severity, abdominal pain duration, abdominal pain severity, bowel habit satisfaction, life disruption, flatulence, and rumbling. Three articles reported on various inflammation and oxidative stress measures (Amani et al. 2018; Jalili et al. 2019b; Khalighi Sikaroudi, Mokhtare, Janani, et al. 2020b), while one other paper reported on stress and depression, visceral sensitivity, serum serotonin, and 5-hydroxyindole acetic acid (Khalighi Sikaroudi, Mokhtare, Shidfar, et al. 2020a). Risk of bias was found to be low for most studies ($n=6$) with one study rated as neutral due to some potential for bias in the selection of participants and high potential for bias in the nutrition-specific domain (Zeid et al. 2020). ROB results are presented in **Supplemental Table S4**. Due to a lack of complete results reported for other outcomes, we only meta-analyzed results for changes in serum 25(OH)D, IBS quality of life, and IBS symptom severity reported in six RCTs with low risk of bias (Abbasnezhad et al. 2016; Jalili et al. 2016; Jalili et al. 2019a; Khalighi Sikaroudi, Mokhtare, Shidfar, et al. 2020a; Tazzyman et al. 2015; Williams, Williams, and Corfe 2022). Results from these meta-analyses are presented by outcome in Figure 2 and below.

Serum 25(OH)D or vitamin D status

Five RCTs assessed the effects of vitamin D supplementation on change in serum 25(OH)D levels (Abbasnezhad et al. 2016; Jalili et al. 2019a; Khalighi Sikaroudi, Mokhtare, Shidfar, et al. 2020a; Tazzyman et al. 2015; Williams, Williams, and Corfe 2022). All had low risk of bias so were included in meta-analyses. Random-effects meta-analysis results (pooled mean difference [95% CI]) indicated a significant increase in 25(OH)D levels in groups treated with vitamin D compared to a placebo ($n=5$; 20.33 [12.91, 27.74] ng/mL), and heterogeneity across populations was high (I^2 = 97.89%). Findings from subgroup analyses showed similar results across populations with deficient baseline vitamin D status ($n=4$; 21.58 [12.50, 30.66] ng/mL, I^2 = 98.11%) and healthy BMI ($n=2$; 22.28 [11.29, 33.27] ng/mL, I^2 = 98.13%) or overweight BMI status ($n=2$; 23.05 [7.93, 38.17] ng/mL, I^2 = 97.96%; $n=1$ did not report BMI). See **Supplemental Figures S1 and S2**.

IBS quality of life

Five RCTs with low ROB reported on the effect of treatment with vitamin D on change in IBS Quality of Life (IBS-QoL) with scores ranging from 0 (poor quality of life) to 100 (great quality of life). Results from a random-effects meta-analysis (pooled mean difference [95% CI]) revealed no difference in IBS-QoL scores for participants treated with vitamin D compared to a placebo ($n=5$; −0.05 [−10.62, 10.53]), and high heterogeneity across populations (I^2 = 97.45%). Subgroup analyses similarly showed no effects in

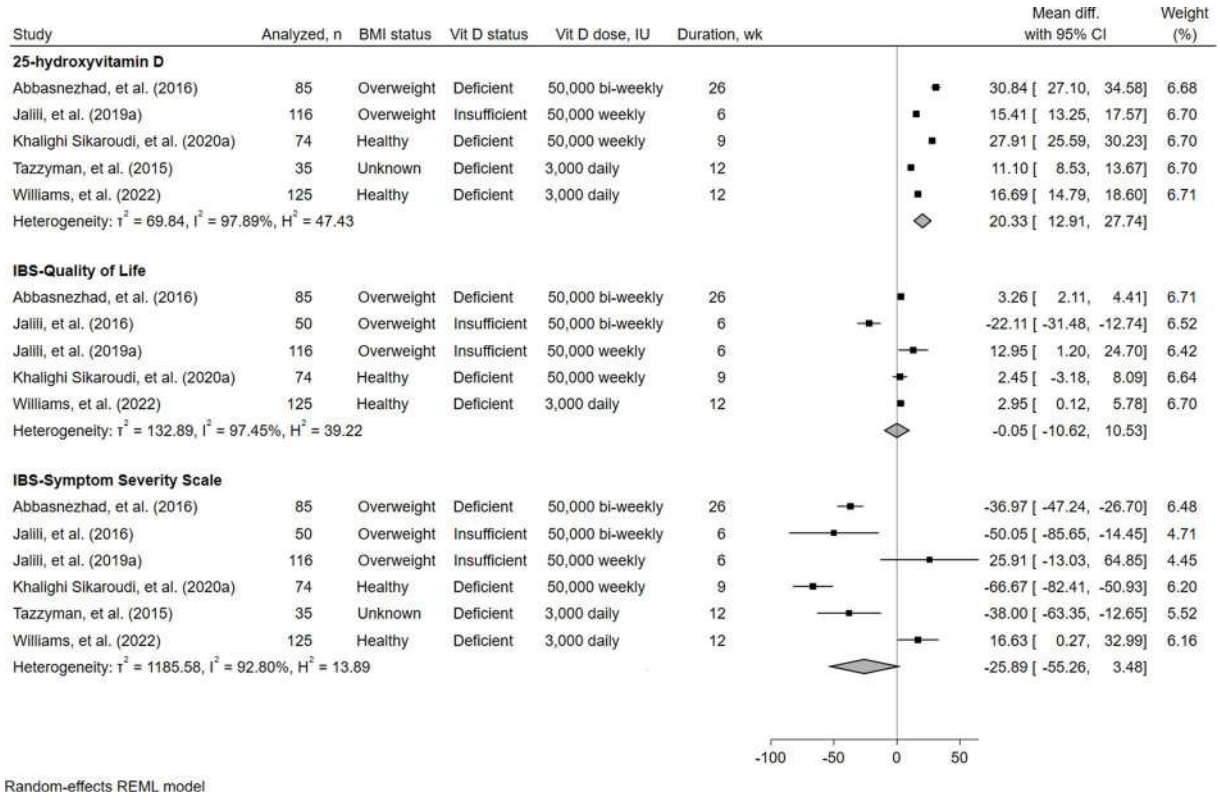

Figure 2. Random effects meta-analysis with pooled mean differences between vitamin D and placebo groups for change in primary outcomes: serum 25(OH)D levels, IBS quality of life, and IBS symptom severity.

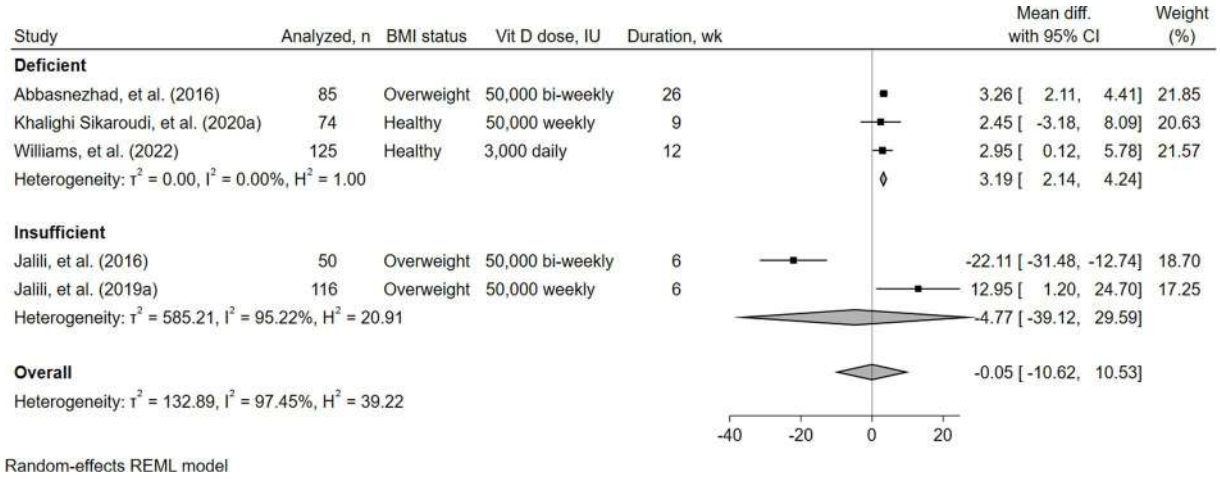

Figure 3. Random effects meta-analysis with pooled mean differences between vitamin D and placebo groups for change in IBS quality of life scores by baseline vitamin D status subgroups.

populations with overweight BMI status ($n = 3$; −2.03 [−22.08, 18.02], I^2 = 95.40%; **Supplemental Figure S3**). However, compared to a placebo, oral treatment with vitamin D significantly improved IBS-QoL for populations with deficient serum 25(OH)D status at baseline ($n = 3$; 3.19 [2.14, 4.24]; Figure 3) with no heterogeneity across studies (I^2 = 0.00%). In sensitivity analyses, where one study with data reporting issues was removed (Jalili et al. 2016), the conclusion for IBS-QoL changed to show significantly improved IBS-QoL scores in participants (regardless of baseline status) treated with vitamin D compared to a placebo ($n = 4$; 3.27 [2.22, 4.31]) and no heterogeneity across studies (I^2 = 0.00%; **Supplemental Figure S4**).

IBS symptom severity

Seven studies assessed the effects of vitamin D supplementation on IBS symptom severity, and all seven used the IBS symptom severity scale (IBS-SSS) which uses a 100-mm visual analogue scale to measure the severity of symptoms across five areas for a total score ranging from 0 (no symptoms) to 500 (severe symptoms). We meta-analyzed six of these studies with low risk of bias. To avoid double-counting participants from one study reported in two articles (Khalighi Sikaroudi, Mokhtare, Janani, et al. 2020b; Khalighi Sikaroudi, Mokhtare, Shidfar, et al. 2020a), we only analyzed results from the article reporting the most complete data across outcomes of interest (Khalighi Sikaroudi, Mokhtare, Shidfar, et al. 2020a). As depicted in Figure 2, random effects meta-analysis results (pooled mean difference [95% CI]) indicated a non-significant decrease in symptom severity for participants treated with vitamin D compared to a placebo ($n = 6$; −25.89 [−55.26, 3.48]), and heterogeneity across populations was high (I^2 = 92.80%). Subgroup analyses showed similar results for populations with deficient baseline vitamin D status ($n = 4$; −31.22 [−65.61, 3.18], I^2 = 94.77%; **Supplemental Figure S5**) and with overweight BMI status ($n = 3$; −22.23 [−65.03, 20.56], I^2 = 85.73%; **Supplemental Figure S6**). It is worth noting that when one study with neutral risk of bias was included in meta-analyses (Zeid et al. 2020), the overall pooled effect showed significantly decreased symptom severity after treatment with vitamin D compared to a placebo ($n = 7$; −43.42 [-86.82, −0.01], I^2 = 97.07%), but results from subgroup analyses remained non-significant (**Supplemental Figures S7 and S8**).

Single-arm interventions

Three single arm intervention studies were included in this review. The first study examined the effects of vitamin D replacement over 3 months (four injections weekly then two injections monthly; dose not reported) in consecutively treated patients with IBS and deficient vitamin D status at baseline from a hospital in Pakistan (Alvi et al. 2022). Of 97 analyzed patients, 56.7% showed complete relief from IBS symptoms (abdominal fullness, bloating, heartburn, constipation, and diarrhea), while 36.1% showed considerable improvement and 6.2% showed moderate relief. The second study was from a medical university in Egypt and involved 40 undergraduate medical students with IBS, based on Rome IV criteria, and with deficient vitamin D status at baseline (Ibrahim et al. 2020). After 12 wks supplementation with 42,000 IU/week cholecalciferol (oral drops) and advice to increase intakes of vitamin D rich foods, 97.5% of participants showed replete vitamin D status (>40 ng/mL), 47.5% showed no IBS symptoms, and 52.5% showed partial relief of symptoms (symptoms not specified). Participants with no IBS symptoms had significantly higher 25(OH)D levels compared to those with partial relief ($p = 0.01$). The third single arm intervention involved white, non-Hispanic, male U.S. veterans of the Gulf War ($n = 69$) who had diarrhea predominant IBS (IBS-D) and deficient vitamin D status at baseline (Kesavan et al. 2023). The study reported that after vitamin D supplementation at 3,000 to 5,000 units (based on weight; duration not reported), the veterans' vitamin D levels increased significantly ($p < 0.0001$), and their number of bowel movements per day decreased significantly ($p < 0.0001$).

Mendelian randomization studies

Two MR studies were included in this review. One conducted a bi-directional two-sample MR analysis in a population of 496,946 European descendants drawn from the European Bioinformatics Institute (EBI) database (Xie et al. 2022). This study first explored the effects of genetic instrumental variables (IVs) related to vitamin D status from serum 25(OH)D levels on genetically predicted risk of IBS and found no causal association across three analysis methods: inverse variance weighted ($p = 0.94$), MR Egger ($p = 0.95$), and weighted median ($p = 0.76$). Next, the study explored IBS as a risk factor of genetically predicted levels of vitamin D and again found no causal association across the same three methods ($p > 0.5$ for all). The second study conducted a two-sample MR analysis of 187,028 European descendants drawn from the FinnGen biobank (Xu et al. 2023). This study examined the effects of genetic IVs for both vitamin D intake and serum 25(OH)D on IBS. Vitamin D intake was not causally association with IBS across six analysis methods ($p > 0.1$ for all), and serum 25(OH)D was not causally association with IBS across four analysis methods ($p > 0.05$ for all). However, serum 25(OH)D showed a negative causal relationship with IBS using the inverse variance weighted (fixed effects) method (OR = 0.83; 95% CI: 0.70, 1.00; $p = 0.04$, adjusted $p = 0.17$) and the maximum likelihood method (OR = 0.83; 95% CI: 0.70, 0.99; $p = 0.04$).

Strength-of-evidence

SoE was assessed using GRADE criteria for the three outcomes included in our meta-analyses: change in 25(OH)D levels, IBS quality of life, and IBS symptom severity. For each outcome, we summarized the SoE across all intervention studies in this review, including single-arm studies reporting outcome results, and the GRADE SoE is summarized in Table 3. For the assessment of study limitations, single-arm interventions were automatically determined to have high risk of bias due to the lack of randomization and controls in the study design. SoE across five RCTs and two single-arm studies was found to be moderate and indicated that treatment with vitamin D supplementation may increase serum 25(OH)D in adults with IBS regardless of insufficient or deficient baseline vitamin D status. Across five RCTs reporting IBS quality of life outcomes, SoE was rated as very low and indicated that treatment with vitamin D may have no effect on quality of life in adults with IBS overall; however, for populations with deficient vitamin D status at baseline, moderate SoE from three RCTs suggested that treatment with vitamin D may improve quality of life. For IBS symptom severity, SoE from seven RCTs and two single-arm interventions was found to be very low and indicated that treatment with vitamin D may have no effect on IBS symptom severity in adults with IBS regardless of baseline vitamin D status.

Discussion

This systematic review and meta-analysis show oral vitamin D supplementation to be effective in repleting serum 25(OH)D levels in adult IBS patients with inadequate or deficient status (moderate SoE), and that repletion in patients with deficient (but not inadequate) serum 25(OH)D levels may improve self-reported quality of life (very low SoE) but not symptom severity (very low SoE). Future research in this area is important, as augmentation of inadequate serum 25(OH)D levels through clinically supervised supplementation could provide additional therapeutic effects as an adjuvant strategy managing IBS. Our results should come as no surprise to those in the field; IBS is a multifaceted disease and vitamin D, much like other classic nutrients, exhibits innate complexities in its actions and interactions, influencing countless biological mechanisms. It is important to note that international recommendations for adequate serum 25(OH)D status, including those from the Endocrine Society, are based on bone-related outcome measures (Holick et al. 2011) and not IBS. It is likely that (if present) vitamin D asserts a threshold effect; therefore, consideration of participant baseline status in the inclusion and exclusion criteria of future trials can help ensure accuracy of the response to treatment with vitamin D. Vitamin D, like many other nutrients, has also been known to display a non-linear relationship with health outcomes, where low and high levels are associated with suboptimal physiological function, and optimal function occurs over a range of intake (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium 2011). In recent years, the utility of administering pharmacological mega-doses vitamin D, as seen in the majority studies included this our systematic review, may place patients at increased risk of adverse effects, particularly hypercalcemia (Malihi et al. 2019; Taylor and Davies 2018; Rizzoli 2021). Several other nutrients are known to interact with vitamin D and its metabolism and can likely modulate individual response to vitamin D supplementation. For example, several steps in vitamin D metabolism are dependent of magnesium, a nutrient low in the diets of IBS patients (Roth et al. 2022; El-Salhy et al. 2012), as a cofactor, including the binding of vitamin D to vitamin D binding protein, 25(OH)D synthesis, and vitamin D receptor activation that is needed for cellular effects (Lemay and Gascon-Barre 1992; Zitterman 2013).

Our findings differ from those of a former small systematic review that combined RCTs of adult ($n = 3$) and adolescent ($n = 1$) populations with IBS and showed improvement in both symptom severity and quality of life (Huang et al. 2022). Our findings also differ from another recent systematic review of adult patients with IBS that suggests vitamin D supplementation improves symptom severity but not quality of life (Chong et al. 2022). However, the approach of using pooled standardized mean differences within the meta-analyses present in this systematic review is problematic for analyzing data from small RCTs, where variability across study populations is expected to be high ("Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023)" 2023). Since all studies included in our meta-analyses used the same IBS-SSS and IBS-QoL, we pooled non-standardized mean differences; this approach better accounts for actual variability among study participants. Similar to our findings, another systematic review of RCTs in adults and adolescents

Table 3. GRADE strength of evidence profiles for outcomes assessed by three or more included clinical trials (RCTs or single-arm interventions).

Studies		Quality assessment						
n	Design	Limitations	Imprecision	Inconsistency	Indirectness	Publication bias	Summary of findings	Strength of evidence [1]
Serum 25(OH)D level								
7	5 RCTs 2 single-arm interventions	**No serious limitations:** Most information is from studies at low risk of bias. All 5 RCTs had low potential for bias overall. One RCT each had some potential for bias in the "comparison of study groups" and "nutrition-specific" domains. There was high ROB in the single-arm interventions due to study design.	**No serious imprecision:** The total sample size from a random effects meta-analysis on 5 RCTs ($n = 435$) was > OIS, and the pooled mean difference CIs excluded "no effect" (12.91, 27.74).	**No serious inconsistency**: A random effects meta-analysis on 5 RCTs showed minimal overlapping CIs with high and significant heterogeneity (I^2 = 97.9%, $p < 0.0001$); point estimates across individual studies varied, but all suggested increased serum 25(OH)D levels.	**Indirect**: Surrogate outcome.	**Undetected:** RCTs showed significant effects. Two studies reported industry funding, and one was a pilot study. No unpublished (completed) studies were identified on trial registries.	Treatment with vitamin D supplementation may increase serum 25(OH)D in adults with IBS.	⊕⊕⊕◯MODERATE
IBS quality of life								
5	RCTs	**No serious limitations:** Most information is from studies at low risk of bias. All 5 RCTs had low potential for bias overall. One RCT each had some potential for bias in the "comparison of study groups" and "nutrition-specific" domains.	**Serious imprecision:** The total sample size for a random effects meta-analysis on all 5 RCTs ($n = 450$) was > OIS, but the pooled mean difference CIs did not exclude "no effect" (-10.62, 10.53).	**Very serious inconsistency:** A random effects meta-analysis on all 5 RCTs showed mostly overlapping CIs with high and significant heterogeneity (I^2 = 97.5%, $p < 0.0001$); point estimates across individual studies varied widely and suggested benefit, harm, and no effect.	**Direct**: Clinical outcome.	**Undetected:** RCTs showed significant and null effects. One study reported industry funding. No unpublished (completed) studies were identified on trial registries.	Treatment with vitamin D supplementation may have no effect on quality of life in adults with IBS.	**All populations:** ⊕◯◯◯VERY LOW
			No serious imprecision: The total sample size for a random effects meta-analysis on 3 RCTs in populations with deficient vitamin D status at baseline ($n = 284$) was > OIS, and the pooled mean difference CIs excluded "no effect" (2.14, 4.24).	**Serious inconsistency:** A random effects meta-analysis on 3 RCTs in populations with deficient vitamin D status at baseline had overlapping CIs and no heterogeneity (I^2 = 0.0%, $p = 0.95$); point estimates across individual studies were similar and suggested benefit or no effect.			Treatment with vitamin D supplementation may improve quality of life in adults with IBS and deficient baseline vitamin D status.	**Populations deficient in vitamin D:** ⊕⊕⊕◯MODERATE
IBS symptom severity								
9	7 RCTs 2 single-arm interventions	**No serious limitations:** Most information is from studies at low risk of bias. 6 RCTs had low potential for bias overall, where one RCT each had some potential for bias in the "comparison of study groups" and "nutrition-specific" domains. One RCT had potential for bias overall (neutral rating) due to "selection of participants" and "nutrition-specific" domains. There was high ROB in the single-arm interventions due to study design.	**Serious imprecision:** The total sample size for a random effects meta-analysis on 6 RCTs with low ROB ($n = 485$) was > OIS, but the pooled mean difference CIs did not exclude "no effect" (-55.26, 3.48).	**Very serious inconsistency:** A random effects meta-analysis on 6 RCTs with low ROB showed minimally overlapping CIs with high and significant heterogeneity (I^2 = 92.80%, $p < 0.0001$); point estimates across individual studies varied widely and suggested benefit, harm, and no effect. The 2 single-arm studies reported complete relief of IBS symptoms after supplementation in 48% to 57% of participants with all participants showing some improvement.	**Direct**: Clinical outcome.	**Undetected:** 5 RCTs showed significant and null effects. Two studies reported industry funding, and one was a pilot study. No unpublished (completed) studies were identified on trial registries.	Treatment with vitamin D supplementation may have no effect on IBS symptom severity in adults with IBS.	⊕◯◯◯VERY LOW

CI, confidence interval(s); GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; OIS, optimal information size; RCT, randomized controlled trial; ROB, risk of bias.

[1]Symbols indicate the following strength of evidence: ⊕⊕⊕⊕, High (We are very confident that the true effect lies close to that of the estimate of the effect.); ⊕⊕⊕◯, Moderate (We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.); ⊕⊕◯◯, Low (Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.); and ⊕◯◯◯, Very low (We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.).

found no difference in symptom severity between but improvement in IBS-QoL (Abuelazm et al. 2022). This systematic review also included a GRADE SoE assessment and, like our study, found SoE for serum 25(OH)D to be moderate and SoE for symptom severity and quality of life overall to be very low. However, unlike our study, this review did not include subgroup analyses to identify potential sources of heterogeneity (they did perform leave-one-out analyses). Our approach suggests baseline vitamin D status may influence vitamin D treatments effectiveness, at least in regard to self-reported quality of life. None of the former systematic reviews employed RoB tools designed for nutrition studies. There are known factors such as uncertainties in dietary intake assessment, interrelated biological functions of nutrients, and baseline nutritional status that can influence RoB in nutrition-related research (Lichtenstein, Yetley, and Lau 2008).

Our study has several strengths and limitations. The major strength of our study was the rigorous design that enabled a thorough review of the peer-reviewed English language scientific literature. Sub-analyses by baseline 25(OH)D status increases the accuracy of results owing to the heterogeneity between these groups. Several major limitations are also apparent. Low statistical power, due to the small sample sizes present within included trials, likely affected our ability to detect modest effects and further explore heterogeneity using meta-regression or subgroup meta-analysis techniques. A major limitation of involved incomplete reporting of results among included articles, which restricted our ability to perform meta-analyses on individual IBS symptoms. Along these lines, two articles reported conflicting data between figures, tables, and text (Tazzyman et al. 2015; Jalili et al. 2016), and based on our sensitivity analyses, these discrepancies are likely to influence quality of life findings. We took these limitations into consideration when making SoE evaluations.

Conclusion

Moderate SoE demonstrates oral vitamin D supplementation to be effective in repleting serum 25(OH)D levels in adult IBS patients with inadequate or deficient status. Very low SoE supports repletion of deficient (but not inadequate) 25(OH)D levels improve self-reported quality of life but not symptom severity in adult patients with IBS. Future RCTs with sufficient power are greatly needed to fully elucidate the effects of vitamin D supplementation, past repleting inadequate or deficient serum 25(OH)D levels, in adults with IBS.

Author contributions

Taylor C. Wallace and Kelly C. Cara contributed to the study conception and design. Data collection was performed by Kelly C. Cara, Salima F. Taylor, and Haya F. Alhmly. Material preparation and analyses were performed by Kelly C. Cara. The first draft of the manuscript was written by Kelly C. Cara, Salima F. Taylor, and Haya F. Alhmly, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

All data collection forms, extracted data from included studies, data used for analyses, and the analytic code are available upon reasonable request from the corresponding author.

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