

## **Estado de la vitamina D en el síndrome del intestino irritable y el impacto de la suplementación en los síntomas: una revisión sistemática y metaanálisis**

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*Estado de la vitamina D en el síndrome del intestino irritable y el impacto de la suplementación en los síntomas: una revisión sistemática y metaanálisis*

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**ABSTRACT**

**Background:** latest studies have shown that vitamin D deficiency is related to the occurrence of irritable bowel disease (IBS), and taking vitamin D as a supplement can alleviate the symptoms of irritable bowel disease. However, clinical treatment of irritable bowel disease with vitamin D is controversial.

**Objective:** we conducted a meta-analysis of all clinical trials to evaluate the associations between vitamin D and irritable bowel disease.

**Methods:** we screened all randomized controlled trials that were published before December 20, 2021 from the following databases: Medline, Web of Science, China National Knowledge Infrastructure (CNKI), Cochrane Central, and Clinical Trial. We used RevMan 5.4.1 and Stata 16.1 to analyze the relevant data. The standardized mean difference (SMD) with 95 % confidence interval (95 % CI) was used to report effect sizes. Serum vitamin D concentration, risk of vitamin D deficiency among patients with IBS, Symptom Severity Score (SSS), and Quality of Life (QoL) score are the main endpoint outcomes in this study.

**Results:** data from twelve clinical trials with 1331 IBS patients were included. Patients with IBS have relatively low vitamin D levels in their serum. Vitamin D supplementation improves the Quality of Life (QoL) score but has no significant effect on the Symptom Severity Score (SSS).

**Conclusions:** vitamin D deficiency is associated with the pathogenesis of irritable bowel syndrome. Serum vitamin D levels decreased in patients with irritable bowel syndrome, and vitamin D supplementation could improve patient quality of life.

**Keywords:** Vitamin D. Irritable bowel syndrome. Meta-analysis. Gastroenterology.

## RESUMEN

**Antecedentes:** los últimos estudios han demostrado que la deficiencia de vitamina D está relacionada con la aparición de la enfermedad del intestino irritable (SII) y que tomar vitamina D como suplemento puede aliviar los síntomas de la enfermedad del intestino

irritable. Sin embargo, el tratamiento clínico de la enfermedad del intestino irritable con vitamina D es controvertido.

**Objetivo:** se realizó un metanálisis de todos los ensayos clínicos para evaluar las asociaciones entre la vitamina D y la enfermedad del intestino irritable.

**Métodos:** se examinaron todos los ensayos controlados aleatorios que se publicaron antes del 20 de diciembre de 2021 en las siguientes bases de datos: Medline, Web of Science, China National Knowledge Infrastructure (CNKI), Cochrane Central y Clinical Trial. Se utilizaron RevMan 5.4.1 y Stata 16.1 para analizar los datos relevantes. Se utilizó la diferencia de medias estandarizada (DME) con intervalo de confianza del 95 % (IC 95 %) para presentar los tamaños del efecto. La concentración sérica de vitamina D, el riesgo de deficiencia de vitamina D entre los pacientes con SII, la puntuación de gravedad de los síntomas (SSS) y la puntuación de calidad de vida (CdV) son los principales criterios de valoración de este estudio.

**Resultados:** se incluyeron datos de doce ensayos clínicos en 1331 pacientes con SII. los pacientes con SII tienen niveles relativamente bajos de vitamina D en el suero. La suplementación con vitamina D mejora la puntuación de calidad de vida (CdV), pero no tiene un efecto significativo en la puntuación de gravedad de los síntomas (SSS).

**Conclusiones:** la deficiencia de vitamina D se asocia con la patogénesis del síndrome del intestino irritable. Los niveles séricos de vitamina D disminuyeron en pacientes con síndrome del intestino irritable, y la suplementación con vitamina D podría mejorar la calidad de vida de los pacientes.

**Palabras clave:** Vitamina D. Síndrome del intestino irritable. Metaanálisis. Gastroenterología.

## **INTRODUCTION**

### **Background and available evidence**

Irritable bowel syndrome (IBS) is one of the common functional gastrointestinal diseases (1,2). With the deepening of research and the improvement of medical workers' understanding of the disease, the diagnostic rate of IBS has also increased. According to the latest Rome IV standard, irritable bowel syndrome is a non-organic disease characterized by abdominal pain with changes in bowel habits or stool traits (3-5). The prevalence of IBS in Chinese people is about 6.5 % and is on the rise. The possible pathogenesis of IBS includes visceral hypersensitivity, changes in gastrointestinal motility, abnormal regulation of brain and intestinal axis, intestinal flora disorder, mental and psychological factors, and a regulatory mechanism of the nerve-immune-endocrine network that has attracted attention in recent years has been reported (6). Treatment of IBS emphasizes individualized comprehensive treatment, including psychological and behavioral intervention, diet adjustment, and drug therapy, but the overall treatment effect is unsatisfactory, seriously affecting the quality of life of patients, bringing heavy psychological and social burdens. Therefore, it is urgent to explore safe and effective new therapies for IBS treatment (7,8). The main function of vitamin D is to regulate calcium and phosphorus metabolism, but new ideas suggest that vitamin D can inhibit inflammation and regulate immune response (9). Vitamin D deficiency occurs in 30 to 50 % of the global human population and also accounts for a similar proportion in people with gastrointestinal diseases. Recent studies have found that the serum vitamin D level in IBS patients is significantly lower than that in healthy people. Vitamin D deficiency (VDD) has a high incidence in IBS patients, but the relationship between vitamin D and the severity of gastrointestinal symptoms in IBS patients is not clear (10). In recent years, foreign cases and small-sample clinical studies have reported that vitamin D supplementation may alleviate clinical

symptoms in IBS patients (11,12). Our initial intention in this review is to synthesize existing studies to provide solid evidence for vitamin D in the treatment of IBD.

### **Value of this review**

In the United States, the medical costs for IBS are as high as \$ 20 billion a year. The current treatment regimen is unsatisfactory, seriously affecting the quality of life of patients, bringing heavy psychological and social burdens. Therefore, it is urgent to explore safe and effective new therapies for the treatment of IBS.

## **METHOD**

### **Search strategy**

We selected all randomized controlled trials associated with vitamin D and irritable bowel syndrome from the following databases: Medline, Web of Science, CNKI, Cochrane Central, and Clinical Trial, and any limitations of language were rejected. We also searched the references of earlier meta-analyses related to the selected studies to determine any additional potential studies. The trials were limited to human studies.

### **Study selection**

Two independent and trained reviewers screened the title/abstract and full text to determine the included literature. The different opinions between reviewers would be solved by another experienced doctor. The criteria for excluding literature were as follows: 1) the study was performed on randomized controlled trials; 2) participants received at least 3,000 IU of vitamin D per day for 4 weeks; 3) enrollment of patients with no organic digestive diseases; 4) data are complete or available; 5) any conference papers, reviews, case reports, experience summaries, and repeated literature (only the

earliest one is retained in the papers published in multiple languages) were also rejected.

### **Assessment of risk of bias**

Two experienced reviewers used Revman 5.4.1 (RevMan; The Cochrane Collaboration, Oxford, UK) to evaluate the publication bias of articles according to the Cochrane Handbook for Systematic Reviews of Interventions. Quality evaluation was generated in the following assessments: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; 7) other biases. A summary of bias risks is provided in figure 2.

### **Data extraction**

Two reviewers assessed and extracted relevant data independently, including demographic characteristics of participants, clinical diagnosis types, treatment duration, type and dose of administration, and sample size. We summarized the curative effect of vitamin D on irritable bowel syndrome (IBS) in the following measures: 1) risk of vitamin D deficiency among patients with IBS; 2) SSS; 3) QoL; 4) serum vitamin D concentration. These outcomes were summarized in figures 3 A-D.

### **Statistical analysis**

Each outcome was represented by using standardized mean difference (SMD) with a 95 % confidence interval (CI). In addition, a sensitivity analysis was carried out when necessary.

We used the STATA software (Stata Corporation, College Station, TX) to perform forest plot graphics and funnel plots. All statistical tests were bilateral significant levels: p-value was set at 0.05.

Q-statistic and  $I^2$  test were used to calculate the heterogeneity of all studies. When p-value is less than 0.1 or  $I^2$  is bigger than 40 %,

heterogeneity is considered to be significant, and we use a random effects model. On the contrary, when  $p$  is bigger than 0.1 or  $I^2$  is less than 40 %, we used the fixed-effect model.

Publication bias was evaluated with a funnel plot, Egger's test, and Begg's test. Egger's and Begg's linear regression tests were used to evaluate asymmetry, and the level of significance was set as  $p < 0.05$  (Fig. 4 A-D).

Three researchers (Bin Yang, Lili Yuan, and Kang Liao) independently conducted the screening of titles, abstracts, and the full text of all studies. Study exclusion and inclusion were based on the criteria we set before. Two reviews (Bin Yang, Lili Yuan) extracted the relevant data from included studies: characteristics of participants, outcomes measures, treatment duration, etc., and quality assessments of the studies were performed according to the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreement was reported to an experienced doctor. Another researcher double-checked the consistency between the statistical results converted into software and the data provided in the original literature to avoid any wrong inputs. One reviewer (Bin Yang) performed the statistical analysis using STATA16.1 to obtain the results of each outcome. The whole process was under the guidance of the Cochrane Handbook. All patient data were derived from published literature.

## RESULTS

### Selection of studies

The literature retrieval strategy is shown in Appendix 1. We identified a total of 793 studies associating vitamin D and irritable bowel syndrome (IBS), from which we ultimately included a total of 12 RCTs in 1331 patients, and details of these studies are shown in table I. Any studies that did not meet the criteria were excluded. We provide a flow chart for the progress of literature retrieval and the inclusion or



exclusion of studies in **figure 1**. The risk of bias of all included trials was assessed using the Cochrane method.

### **Included studies**

1. Abbasnezhad A, Amani R, Hajiani E, Alavinejad P, Cheraghian B, Ghadiri A. Effect of vitamin D on gastrointestinal symptoms and health-related quality of life in irritable bowel syndrome patients: a randomized double-blind clinical trial. *Neurogastroenterol Motil* 2016;28(10):1533-44.
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## **Meta-analysis**

### ***Risk of vitamin D deficiency among patients with IBS***

A total of 974 patients were enrolled in three studies, which provide the risk of vitamin D deficiency among patients with IBS. Data show that people with vitamin deficiency are more likely to suffer from irritable bowel syndrome (relative risk (RR) = 1.78, 95 % CI (1.45, 2.12)). The heterogeneity test for the included studies was done by STATA 16.1, and results showed  $p = 0.000$  and  $I^2 = 91.5\%$ , a very high heterogeneity, for which we decided to use the random effect model. The results were summarized in **figure 3A** and the result of publication biases is shown in **figure 4A**.

### ***Serum vitamin D concentration***

Nine studies including 1331 samples reported serum vitamin D levels in patients with irritable bowel syndrome and controls. After summarizing the data, we found that serum vitamin D levels in

patients with irritable bowel syndrome were significantly lower than those in the control group (SMD, -0.84, 95 % CI (-0.18, -0.50)). We used STATA 16.1 to test the heterogeneity of 9 studies, and the results showed that  $p = 0.000$ ,  $I^2 = 81\%$ , indicating high heterogeneity, for which a random effect model is needed. Revman 5.4.1 (Revman 2020) provided a forest plot for each outcome measure. The results were summarized in figure 3B and the result of publication bias is shown in figure 4B.

### ***The SS scores***

Five studies enrolling 536 participants reported the effect of vitamin D supplementation on the SS score in patients with IBS. The forest plot showed that vitamin D supplementation had no significant effect on SS score in IBS patients (SMD, -0.43, 95 % CI (-0.89, 0.03)). The heterogeneity test included in the study was carried out by STATA 16.1, where  $p = 0.000$ ,  $I^2 = 85.6\%$ , a very high heterogeneity than that we previously set. the source of heterogeneity may be the insufficient number of included studies and small sample size. The publication bias of these 5 studies was done by STATA 16.1. These results are summarized in figure 3 and the result of publication bias is shown in figure 4C.

### ***The QoL score***

A total of 448 people in the four studies reported the effect of vitamin D supplementation on QoL scores of patients with IBS. The summarized data of four studies show that vitamin D supplementation can significantly increase the QoL score of IBS patients (SMD, 0.65, 95 % CI (0.14, 1.15)), which means that the quality of life of patients is significantly improved. We underwent the heterogeneity test for the 4 studies by STATA 16.1, in which  $p = 0.000$  and  $I^2 = 85.6\%$ , a very high heterogeneity, and for which we decided to use the random effect model. The results were summarized in figure 3D and the result of publication bias is shown in figure 4D.

## **DISCUSSION**

Although the pathogenesis of IBS has not been fully understood, many scholars believe that functional bowel disease is caused by multiple factors. The recognized pathogenesis of IBS is as follows: gastrointestinal motility disorder, visceral sensitivity abnormality, poor food tolerance, intestinal immune system abnormality, and bacterial-intestinal-brain axis dysfunction (13,14). In addition, social-psychological factors, dietary habits, intestinal flora imbalance, intestinal infection, abnormal endogenous cannabinoid system, and vitamin D deficiency are closely related to IBS. Vitamin D deficiency has become a research hotspot (12,15-17).

Vitamin D is an essential vitamin for the human body and belongs to the fat-soluble vitamins group. In addition to the regulation of calcium and phosphorus balance, vitamin D also has anti-inflammatory and immune regulatory effects. Many studies suggest that vitamin D deficiency is widespread in IBS patients (18,19). In addition, a retrospective study of children and adolescents in the United States found that compared with the control group, IBS patients have lower 25(OH)D concentrations. Only 7 % of IBS children and adolescents have sufficient vitamin D. More than half of IBS patients have vitamin D deficiency, which may be caused by dietary restriction, sunlight exposure, living habits, gender, hypoproteinemia, and other factors (20,21).

Individuals can acquire exogenous vitamin D from foods rich in vitamin D, but more vitamin D<sub>3</sub> (about 70 %) is produced in the skin under ultraviolet light. If the yield from the skin is sufficient, it can even make individuals no longer need to take it from food. The prevalence of vitamin D deficiency in IBS patients may be associated with excessive indoor activity time and sunscreen habits inspired by concerns about the risk of skin cancer caused by exposure to ultraviolet light. These habits affect the normal outdoor activity time of individuals to some extent, resulting in insufficient sources of

vitamin D. In conclusion, increasing outdoor activities, ensuring adequate sunshine hours, and appropriate supplementation of vitamin D supplements can provide new ideas for the prevention and treatment of IBS (22,23).

Epidemiological surveys have shown that the prevalence of IBS varies in different regions, different countries, and even within the same country, which may be due to different survey populations and different survey methods. The long course of IBS consumes a lot of medical resources, which seriously affects the quality of life of IBS patients and their families, and causes a serious social burden (24,25). Therefore, it is of great significance for the prevention of IBS to actively carry out an epidemiological investigation and follow-up of IBS for various populations and to promote the health of IBS-related knowledge and health education. Although the pathogenesis of IBS is still unclear, an in-depth study of the pathogenic factors can provide valuable direction for the prevention and treatment of IBS.

We have included four outcome measures from twelve studies and 1331 patients in this review, from which we summarized the following evidence: vitamin D deficiency is a risk factor for irritable bowel syndrome (RR, 1.76, 95 % CI [1.45, 2.12]) and serum vitamin D levels in patients with irritable bowel syndrome are significantly lower than in normal people (SMD, -0.84, 95 % CI [-1.18, 0.50]). In addition, vitamin D supplementation in patients with irritable bowel syndrome can significantly improve their quality of life (SMD, 0.65, 95 % CI [0.14, 1.15]). However, vitamin D supplementation had no significant effect on the SS score of patients with irritable bowel syndrome (SMD, -0.43, 95 % CI [-0.89, 0.03]).

Finally, we concluded that vitamin D deficiency is associated with irritable bowel syndrome: vitamin D deficiency patients are more likely to suffer from irritable bowel syndrome, taking vitamin D can improve the quality of life of patients with irritable bowel syndrome.

Currently, serum 25(OH)D value is used as an indicator of Vitamin D level internationally, for which the universally accepted criteria are

that serum 25(OH)D < 20 ng/mL is considered as vitamin D deficiency, serum 25(OH)D between 20 and 30 ng/mL as vitamin D insufficiency, and serum 25(OH)D  $\geq$  30 ng/mL as vitamin D sufficiency (26). In addition to the IBS studied in this paper, vitamin D levels are also closely related to the skeletal, muscular, and cardiovascular systems. A minimum serum 25(OH)D concentration of 20 ng/mL should be achieved in the general population, and 30 ng/mL should be maintained in high-risk groups to ensure bone health (27). In addition, vitamin D is associated with maintaining muscle function and reducing the risk of cardiovascular diseases, for which the optimal vitamin D levels are not yet clear. By searching and exploring studies of vitamin D and IBS, future population-based and multicenter prospective studies with larger samples, especially randomized controlled trials, are warranted to verify the causal relationship between vitamin D and IBS. We reviewed the previous literature and suggested at least 4 consecutive weeks of active intervention and up to 6 months of follow-up analysis for IBS patients to continuously validate the effect of the intervention. In the subsequent experiments, the data on vitamin D intake of the subjects need to be obtained using food-recall questionnaires whenever possible to accurately record the intake of each subject. This is particularly critical because some populations, such as patients with severe dietary restrictions and lifestyle choices that limit sun exposure, may have lower concentrations of vitamin D than normal subjects. Therefore, a more objective way is needed for the collection of vitamin D levels, and food-recall questionnaires provide a superior avenue to address this shortcoming. The effect of family history on the relationship between vitamin D and IBS should also be taken into consideration in the later statistical analysis, as this factor is an extremely crucial covariate for model adjustment in association analysis.

## **CONCLUSIONS**

Vitamin D deficiency is associated with the pathogenesis of irritable bowel syndrome. Serum vitamin D levels decreased in patients with irritable bowel syndrome, and vitamin D supplementation could improve the quality of life of patients.

## Appendix 1. The search strategy

PubMed	
Search strategy	
Number	Items
#1	irritable bowel syndrome[Mesh]
#2	Irritable Bowel Syndromes[Title/Abstract]
#3	Syndrome, Irritable Bowel [Title/Abstract]
#4	Syndromes, Irritable Bowel[Title/Abstract]
#5	Colon, Irritable[Title/Abstract]
#6	Irritable Colon [Title/Abstract]
#7	Colitis, Mucous[Title/Abstract]
#8	Colitides, Mucous[Title/Abstract]
#9	Mucous Colitides[Title/Abstract]
#10	Mucous Colitis[Title/Abstract]
#11	#1 OR #2 OR #3 OR #4 OR #5 OR # 6 OR # 7 OR # 8 OR # 9 OR 10
#12	Postprandial distress syndrome[Mesh]
#13	#11 AND #12



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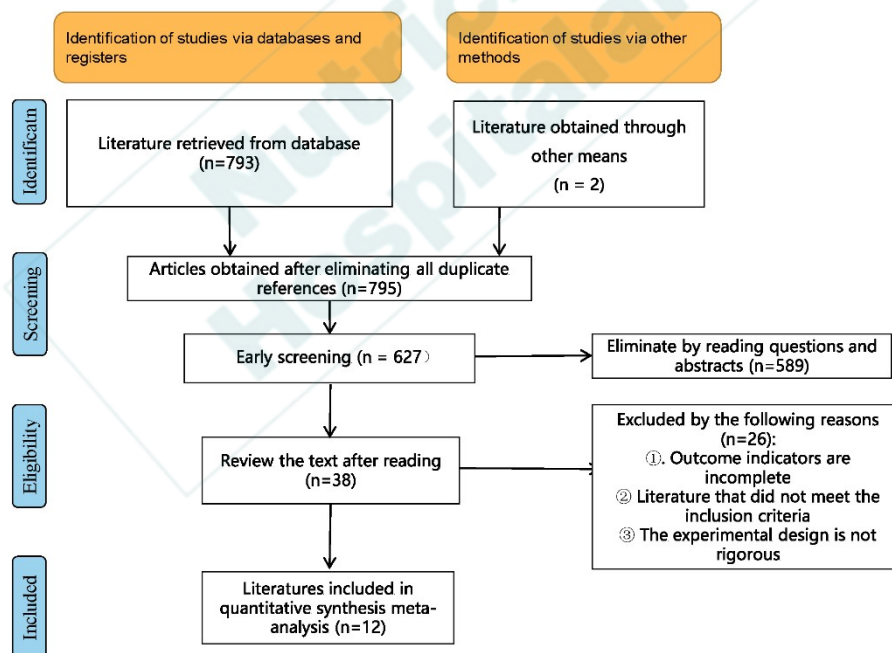


Figure 1. The flow chart of literature search and data selection. The figure describes the routine for inclusion in the study. Of the 795 studies from databases and other studies, 12 experiments met our inclusion criteria.

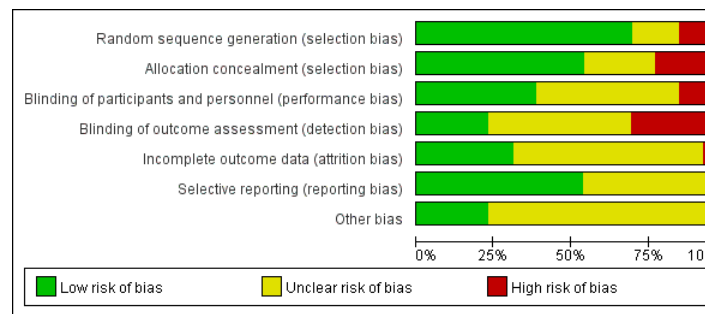


Figure 2A

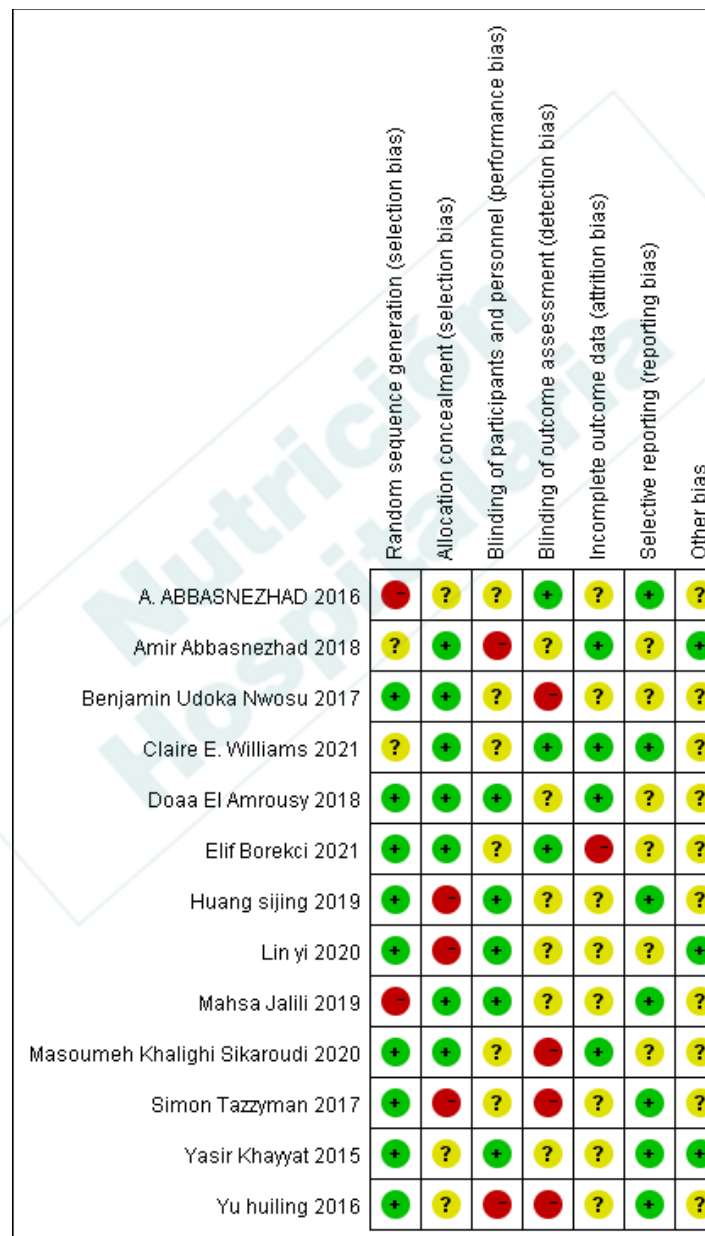
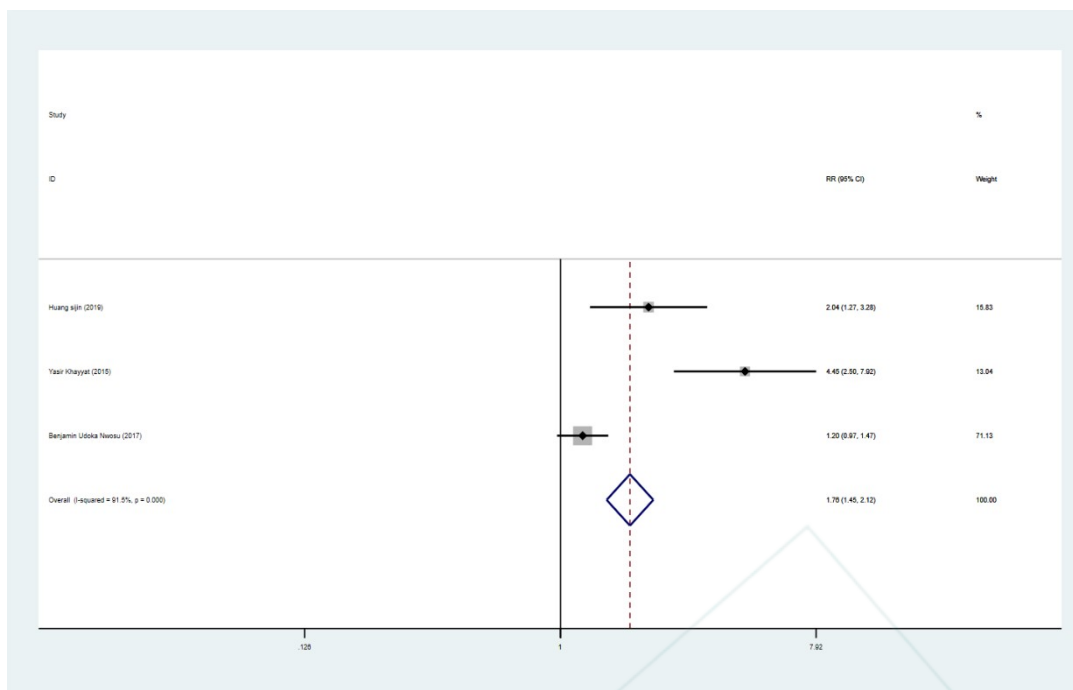


Figure 2B

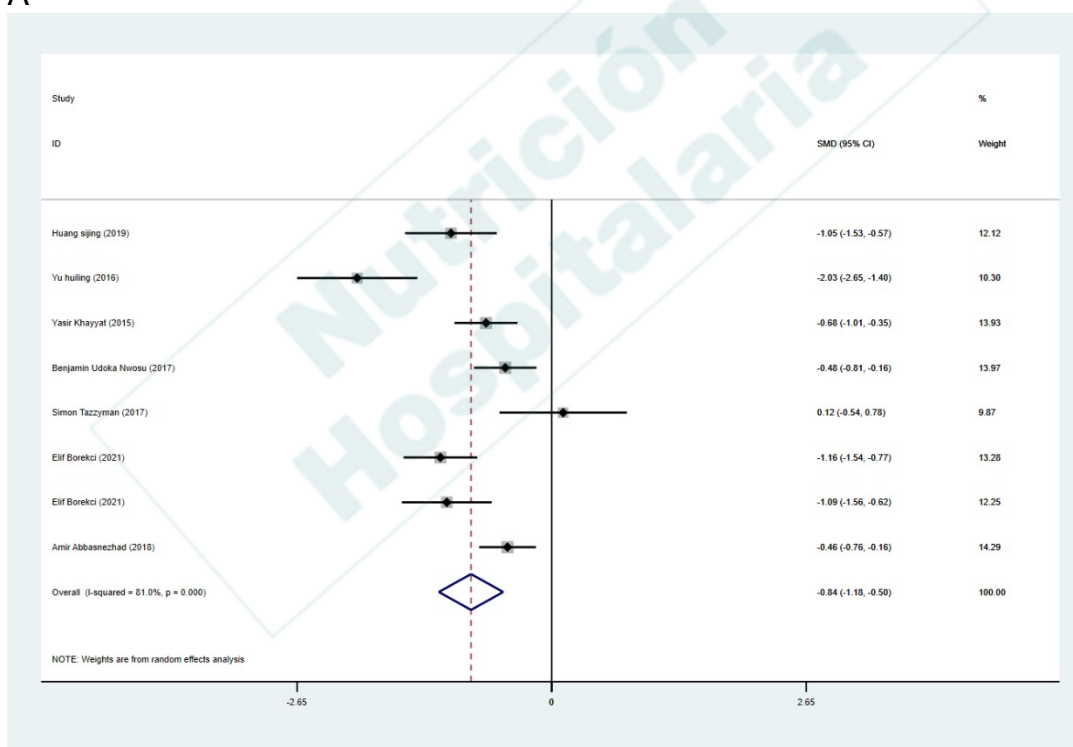
Figure 2. 2A is a summary of all the bias

Risk of bias. summary of risks

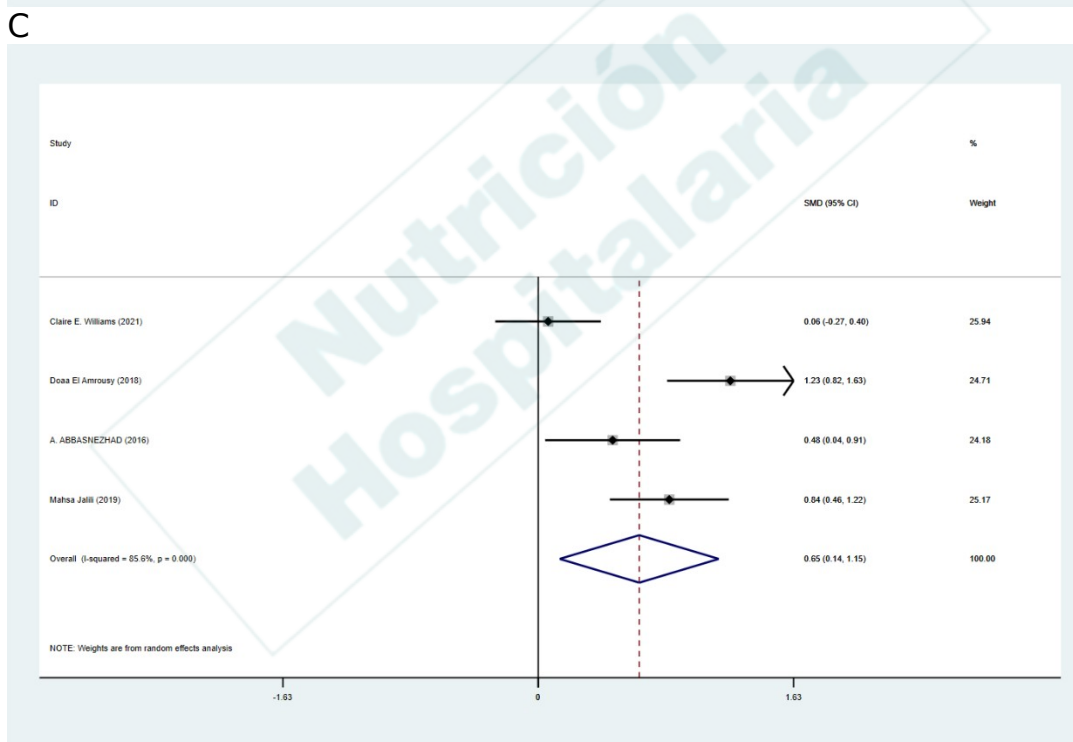
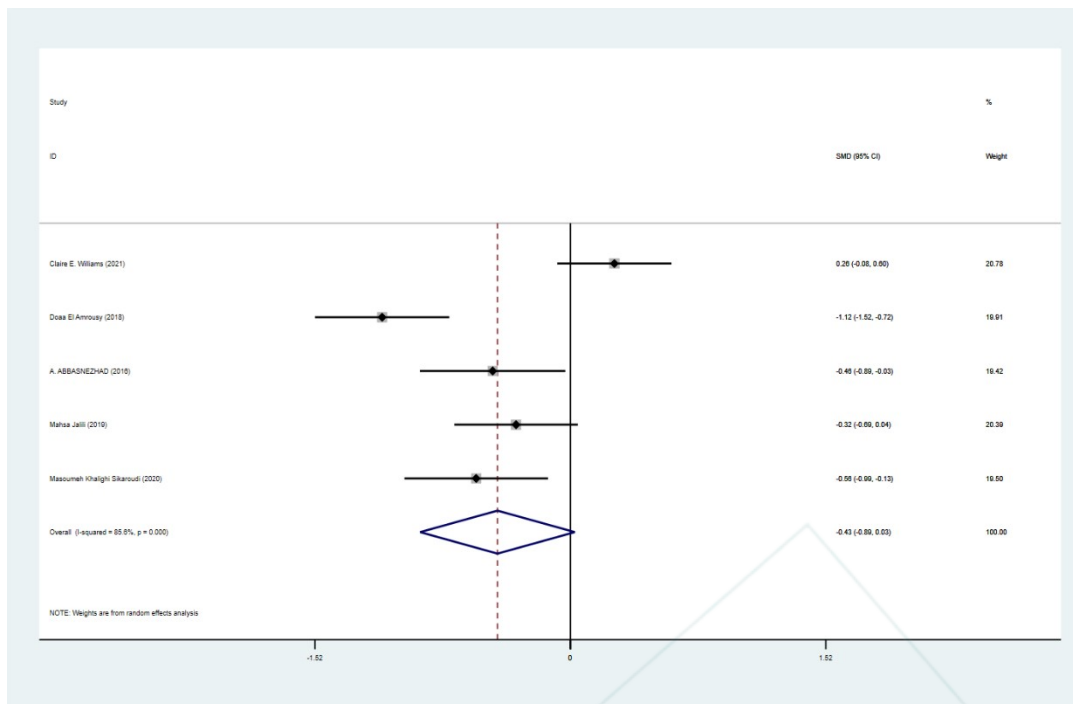
included in the study; 2B details the bias of each study.



A



B



D

Figure 3. A. Shows a forest plot that demonstrates the risk of vitamin D deficiency among patients with IBS. Compared with the control group using the random-effect model, people with vitamin D deficiency are more likely to suffer from irritable bowel syndrome. There is also obvious heterogeneity evidence between the experiments. In Meta-analysis, the size of grey squares are proportional to the weight; black lines represent confidence intervals;

the virtual line represents the combined effect. Risk factor, RR; p-value is shown in the supplementary material. Shows a forest plot showing serum vitamin D concentrations. The p-value is shown in the supplementary material. C. Shows the forest map showing the changes in the SSS scores of patients after vitamin D treatment. The p-value is shown in the supplementary material. Shows the forest map showing the changes in QoL of patients after vitamin D treatment. The p-value is shown in the supplementary material.

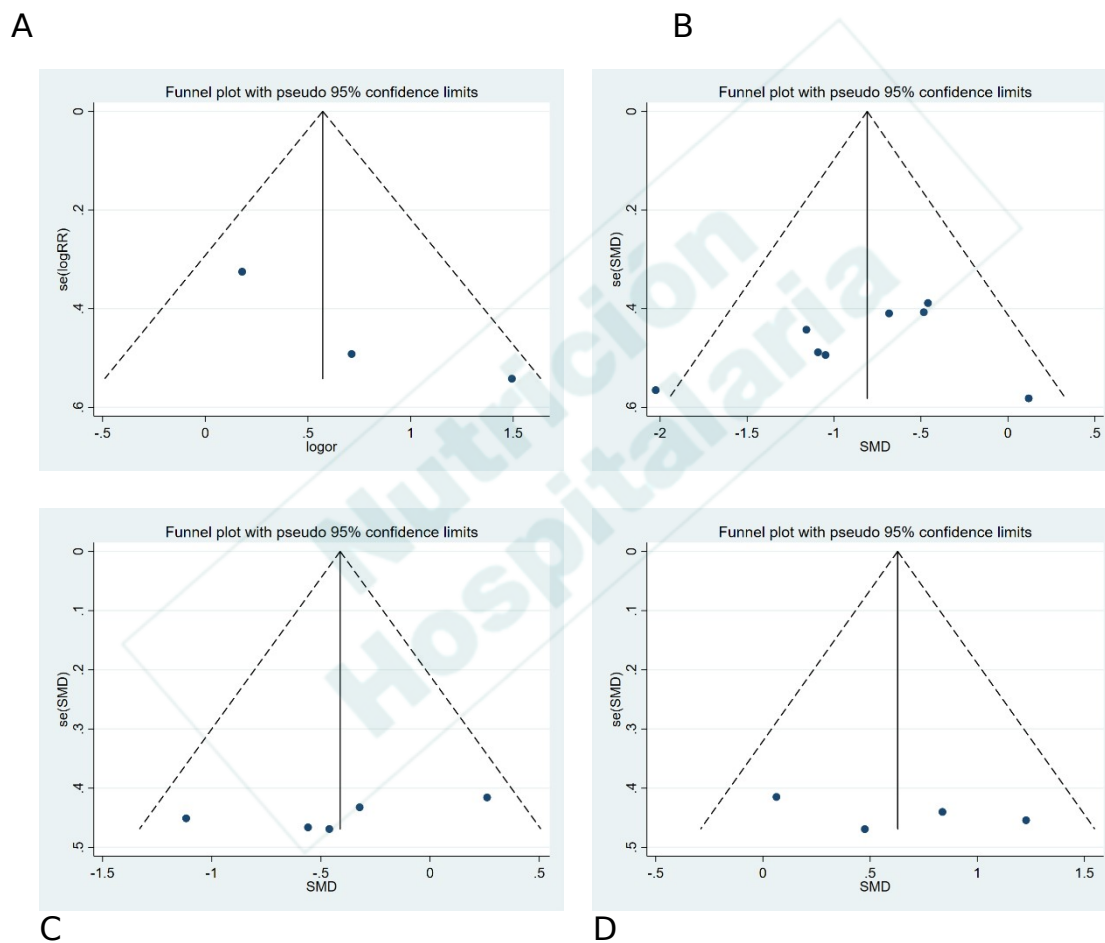


Figure 4. Publication bias of each outcome. The effect sizes were pooled by using the random-effects model. The standardized mean difference and standard error are described in this funnel plot. The black circles are published literature, and the cone region surrounded by virtual lines on both sides represents the 95 % confidence interval. A. Risk of vitamin D deficiency among patients with IBS. B. Serum

vitamin D levels of IBS patients and controls. C. Changes in SSS scores of patients after vitamin D treatment. D. changes in QoL of patients after vitamin D treatment.

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The 26 trials included in this meta-analysis were randomized controlled trials. They were summarized as participants' country, sample size, gender, and age. Data were reported in means and standard deviations (SD).

T: trial; C: control; USA: United States of America.