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The Association Between Vitamin D and Irritable Bowel Syndrome: A Meta-Analysis of Randomized Controlled Trials and Observational Studies

Vitamin D ile İrritabl Bağırsak Sendromu Arasındaki İlişki: Randomize Kontrollü Çalışmalar ve Gözlemsel Araştırmaların Meta-Analizi

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Abstract: This meta-analysis aimed to evaluate the effects of vitamin D supplementation on irritable bowel syndrome (IBS) symptoms and serum 25-hydroxy vitamin D 25(OH)D levels by synthesizing data from randomized controlled trials. Additionally, it aimed to compare baseline serum 25(OH)D levels between healthy individuals and IBS patients. The study is a meta-analysis of randomized controlled trials (RCTs) and observational studies. In the study conducted in accordance with PRISMA guidelines, 11 studies were evaluated and IBS-SSS, IBS-QoL and serum 25(OH)D levels were examined. Data were analyzed using the I^2 test to assess heterogeneity. The meta-analysis results showed that vitamin D supplementation improved the quality of life of IBS patients (mean difference [MD] for IBS-QoL: 6.48, 95% CI: 1.14-11.83, p=0.02). However, it had no significant effect on IBS symptom severity (IBS-SSS) (MD: 3.91, 95% CI: -60.99-68.81, p=0.91). Serum 25(OH)D levels were significantly increased by vitamin D supplementation (MD: 17.13, 95% CI: 8.09-26.17, p<0.0002). When serum 25(OH)D levels were compared between healthy individuals and IBS patients, a significant decrease was observed in IBS patients (standard mean difference [SMD]: -10.17, 95% CI: -15.57 to -4.77, p=0.0005). Vitamin D supplementation may be effective in improving quality of life and increasing serum vitamin D levels in IBS patients. However, more homogeneous and large-scale studies are needed to clarify its effect on symptom severity. These results provide a valuable perspective on the role of vitamin D supplementation in the management of IBS.
Keywords: Vitamin D, Irritable Bowel Syndrome, Meta-analysis, Randomized Controlled Trials

Özet: Bu meta-analiz, randomize kontrollü çalışmalardan elde edilen verileri sentezleyerek D vitamini takviyesinin irritabl bağırsak sendromu (IBS) semptomları ve serum 25-hidroksi D vitamini 25(OH)D düzeyleri üzerindeki etkilerini değerlendirmeyi amaçlamıştır. Ek olarak, sağlıklı bireyler ve IBS hastaları arasındaki bazal serum 25(OH)D düzeylerini karşılaştırmayı amaçlamıştır. Çalışma, gözlemsel ve randomize kontrollü çalışmaların (RCT) bir meta-analizidir. PRISMA kılavuzlarına uygun olarak yürütülen çalışmada, 11 çalışma değerlendirilmiş ve IBS-SSS, IBS-QoL ve serum 25(OH)D düzeyleri incelenmiştir. Veriler, heterojenliği değerlendirmek için I^2 testi kullanılarak analiz edilmiştir. Meta-analiz sonuçları, D vitamini takviyesinin IBS hastalarının yaşam kalitesini iyileştirdiğini göstermiştir (IBS-QoL için ortalama fark [MD]: 6,48, %95 GA: 1,14-11,83, p=0,02). Ancak IBS semptom şiddeti (IBS-SSS) üzerinde anlamlı bir etkisi olmadı (MD: 3.91, %95 GA: -60.99-68.81, p=0.91). Serum 25(OH)D düzeyleri D vitamini takviyesi ile anlamlı şekilde arttı (MD: 17.13, %95 GA: 8.09-26.17, p<0.0002). Serum 25(OH)D düzeyleri sağlıklı bireyler ve IBS hastaları arasında karşılaştırıldığında, IBS hastalarında anlamlı bir azalma gözlendi (standart ortalama fark [SMD]: -10.17, %95 GA: -15.57 ila -4.77, p=0.0005). D vitamini takviyesi IBS hastalarında yaşam kalitesini iyileştirmede ve serum D vitamini düzeylerini artırmada etkili olabilir. Ancak semptom şiddeti üzerindeki etkisini açıklığa kavuşturmak için daha homojen ve geniş ölçekli çalışmalara ihtiyaç vardır. Bu sonuçlar IBS yönetiminde D vitamini takviyesinin rolü hakkında değerli bir bakış açısı sağlar.
Anahtar Kelimeler: D vitamini, İrritabl Bağırsak Sendromu, Meta-analiz, Randomize Kontrollü Çalışmalar

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1. Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain and alterations in bowel habits in the absence of identifiable structural abnormalities (1). Affecting an estimated 10–25% of the global population, IBS imposes a substantial burden on patients' quality of life (QoL) and healthcare systems. It presents in multiple subtypes—diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M), or unclassified (IBS-U)—which complicates diagnosis and management strategies. Despite extensive research, the multifaceted pathophysiology of IBS, involving dysfunction in the gut-brain axis, visceral hypersensitivity, immune dysregulation, and altered gut microbiota, remains incompletely understood (2).

Current IBS treatment options, including dietary modifications, pharmacotherapy, and psychological interventions, offer symptomatic relief but often fail to address the underlying pathophysiological mechanisms, leaving many patients unsatisfied (3). In recent years, the role of vitamin D in gastrointestinal health has garnered significant attention (4). Beyond its established function in calcium-phosphorus metabolism, vitamin D exhibits immunomodulatory and anti-inflammatory properties that may influence intestinal mucosal integrity and the gut microbiota. These effects suggest a potential therapeutic role for vitamin D in IBS management (5, 6).

Epidemiological studies indicate a high prevalence of vitamin D deficiency among individuals with IBS, with several reports suggesting an inverse association between serum 25-hydroxyvitamin D levels and symptom severity (7-9). Observational and interventional studies have explored the therapeutic potential of vitamin D supplementation in IBS, but the findings remain inconsistent (10). These discrepancies may stem from methodological heterogeneity, including differences in dosage regimens (e.g., 2,000 IU/day to 50,000 IU/week), treatment durations (ranging from 1.5 to 6 months), study populations (age, sex, ethnicity), geographic factors (e.g., sunlight exposure), and variation in IBS subtypes (e.g., IBS-D, IBS-C). Such variability makes it difficult to draw definitive conclusions and highlights the need for a comprehensive synthesis of existing evidence (7, 9, 11).

Recent meta-analyses have attempted to synthesize these findings, suggesting that the benefits of vitamin D supplementation may be more pronounced in patients with baseline vitamin D deficiency. However, high heterogeneity across studies, likely due to variations in supplementation regimens, follow-up durations, and study populations, limits the generalizability of these conclusions. Addressing these gaps requires a comprehensive synthesis of existing evidence to delineate the role of vitamin D in IBS management (7, 9, 11).

This study aims to comprehensively evaluate the effects of vitamin D supplementation on IBS symptoms and serum 25-hydroxyvitamin D [25(OH)D] levels by conducting a meta-analysis of randomized controlled trials (RCTs). The primary outcomes include the impact of vitamin D supplementation on IBS-SSS) IBS-QoL) and post-supplementation 25(OH)D levels across eight RCTs. Additionally, the secondary outcome focuses on comparing serum 25(OH)D levels between healthy controls and IBS patients to investigate the relationship between vitamin D status and IBS. By integrating data from diverse studies, this analysis aims to provide robust evidence for the role of vitamin D in the management of IBS and its potential implications for clinical practice.

2. Materials and Methods

2.1. Study Design

This meta-analysis assessed the impact of 25-hydroxy vitamin D on IBS symptoms and quality of life. The study followed PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions (3, 12).

2.2. Search Strategy

A comprehensive literature search was conducted across five electronic databases: PubMed, Scopus, Web of Science, EBSCOhost, and Cochrane Library, encompassing studies published from January 2002 to December 2024. The search strategy utilized both Medical Subject Headings (MeSH) terms and free-text keywords to enhance sensitivity. The following search terms were employed:

Vitamin D-related terms: "vitamin D," "cholecalciferol," "ergocalciferols," "25-hydroxyvitamin D," "calcifediol."

IBS-related terms: "irritable bowel syndrome," "functional gastrointestinal disorders," "irritable colon," "functional abdominal pain."

Boolean operators: Queries combined these terms using "AND" and "OR" operators, with results limited to studies published in English.

The complete search string was as follows:

(("vitamin D"[MeSH Terms] OR "vitamin D"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]) AND ("irritable bowel syndrome"[MeSH Terms] OR ("irritable"[All Fields] AND "bowel"[All Fields] AND "syndrome"[All Fields]) OR "irritable bowel syndrome"[All Fields])) AND (2002:2024[pdat])

2.3. Inclusion and Exclusion Criteria

To ensure the quality and relevance of the included studies, we applied strict inclusion and exclusion criteria.

Inclusion Criteria

Population: Adult IBS patients (all subtypes) diagnosed based on validated criteria (e.g., Rome III or IV) (13).

Intervention: 25-hydroxy vitamin D supplementation, regardless of dosage or treatment duration.

Comparison: Placebo or no supplementation.

Outcomes: Primary outcomes were IBS Severity Scoring System (IBS-SSS) scores, IBS-related Quality of Life (IBS-QoL) scores, and serum 25-hydroxy vitamin D levels.

Data: Studies reporting results only as mean and standard deviation

Study Design: Randomized controlled trials (RCTs) with full-text availability.

Exclusion Criteria

For the intervention-based meta-analysis, we excluded observational studies, pilot studies, animal studies, in vitro studies, reviews, case reports, conference abstracts, and studies without outcome measures of interest. However, for the secondary analysis comparing serum 25(OH)D levels between healthy controls and IBS patients, we included relevant observational studies.

2.4. Study Selection

The process of study selection was conducted systematically in accordance with PRISMA guidelines. Initial screening of records was performed using Endnote software to remove duplicate entries. Two independent reviewers (N.D.O. and H.H.A.) assessed the titles and abstracts of the remaining records to determine their relevance based on predefined eligibility criteria. Subsequently, full-text articles of potentially relevant studies were retrieved and reviewed for inclusion.

Any discrepancies between the two reviewers regarding the inclusion or exclusion of studies were resolved through discussion and consensus. If disagreements persisted, a third reviewer was consulted to make the final decision. The detailed study selection process is illustrated in the PRISMA flow chart (Figure 1), which outlines the number of records identified, screened, excluded, and ultimately included in the meta-analysis.

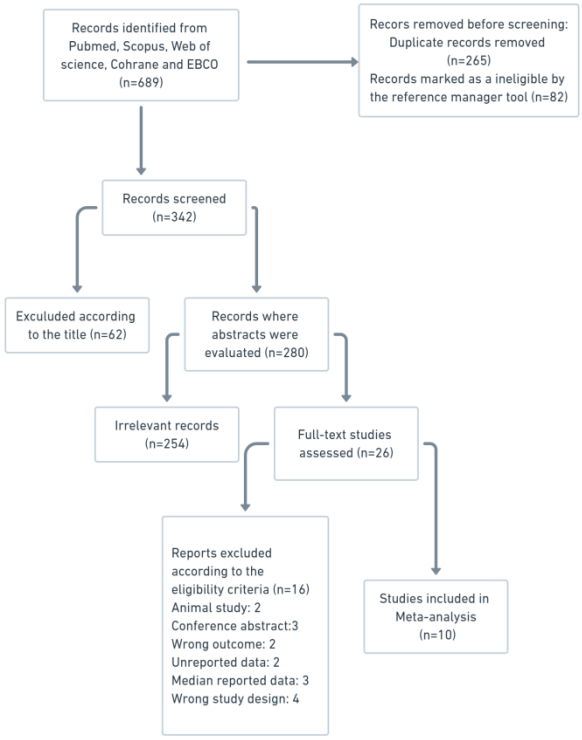

Figure 1. PRISMA flow chart of the screening process.

2.5. Data Synthesis and Analysis

Two reviewers (N.D.O and H.H.A.) independently conducted data extraction using a pre-designed data extraction form. The extracted data included study characteristics (author, year, country, sample size, intervention details), participant demographics (age, sex, baseline IBS-SSS, IBS-QoL scores and serum 25-hydroxy vitamin D levels), and outcomes.

The Cochrane Collaboration's Risk of Bias Tool was employed to evaluate the methodological quality of the included studies across domains such as randomized assignment of participants (selection bias), concealment of group assignment (selection bias), masking of participants and study personnel (performance bias), prevention of detection bias in outcome measurement (detection bias), handling of missing data (attrition bias), evaluation of comprehensive data reporting (reporting bias), and other biases. Discrepancies in data extraction or quality assessment were resolved through discussion or by a third reviewer (Y.Y.Ü.).

2.6. Statistical Software

Statistical analysis was performed using RevMan Web software. The study evaluated the effects of 25-hydroxy vitamin D supplementation on IBS-SSS (IBS Severity Score), IBSQoL (IBS Quality of Life Score), and 25-hydroxy vitamin D levels in patients with IBS. Analysis of continuous variables was performed using the pooled mean difference (MD) and standard deviation (SD) of pre- and post-treatment changes in the treatment group and placebo group (14). Pooled MD was calculated using the Mantel-Haenszel method and the results were presented with 95% confidence interval (CI). A p-value of <0.05 was accepted for statistical significance. Heterogeneity between studies was assessed using I-square and chi-square tests. The chi-square test was used to assess whether there was significant heterogeneity, while the I-square test was used to measure the magnitude of heterogeneity. With reference to the Cochrane Handbook (Chapter 9), I-square results were interpreted as follows: 0–40%: insignificant heterogeneity, 30–60%: moderate heterogeneity, 50–90%: high heterogeneity. In case of significant heterogeneity, a random-effects model was applied, and in case of low or insignificant heterogeneity, a fixed-effects model was applied.

3. Results

3.1. Search results

In the search results, a systematic search of PubMed, Scopus, Web of Science, Cochrane Library and EBSCO databases yielded a total of 689 records. Of these records, 265 were removed because they were duplicates and 82 were excluded because they were marked as inappropriate by the reference management tool. The remaining 342 unique records were screened, and 62 articles were excluded as they were found to be irrelevant to the study topic after the title screening. Then, the abstracts of 280 records were evaluated and 254 records were excluded because they did not meet the study criteria. Twenty-six articles were selected for full-text evaluation, but 16 articles were excluded at this stage because they did not meet the study criteria. The reasons for exclusion included animal studies (n=2), conference abstracts (n=3), inaccurate outcome measures (n=2), incompletely reported data (n=2), only median reported data (n=3) and incorrect study design (n=4). Ten studies that met all eligibility criteria were finally included in the meta-analysis. The study selection process is presented as a PRISMA flow diagram in Figure 1.

3.2. Primary Outcomes

3.2.1. Study Characteristics

This meta-analysis reviewed eight RCTs involving 695 participants: 352 in vitamin D groups and 343 in placebo groups. The mean age for the vitamin D groups was 16.4 to 52.2 years, and for placebo groups, it was 16.2 to 40.1 years. Females made up 63.6% to 100% of the vitamin D group and 50% to 100% of the placebo group.

The studies were conducted in Iran (four), Egypt (two), and the UK (two), all being double-blinded RCTs with one multicenter trial and others single-center trials. Follow-up lasted from 1.5 to 6 months, with vitamin D doses ranging from 2000 IU daily to 50,000 IU weekly or fortnightly.

Outcomes measured included the mean difference in IBS-SSS scores, revealing substantial heterogeneity (I^2=80.3%, p<0.01). Baseline and post-intervention serum vitamin D levels varied among participants. Population demographics, study design, and intervention protocols are detailed in Table 1.

Table 1. The characteristics of the studies included in the meta-analysis.

					Vitamin D supplementation group					Placebo group			
Total	Country	Design	Total Participant	Follow-up period Month	Subject number	Female	Age (mean)	Serum Vit D	Dose	Subject number	Female	Age (mean)	Serum Vit D
Abbasnezhad 2016 (15)	Iran	single center double blinded rct	85	6	44	28(63,6)	37,45(8,11)	19,65(10,35)	50,000IU fortnighlty	41	29 (70,7)	38,45 (9,85)	18,62 (11,23)
El Amrousy 2018 (16)	Egypt	single center double blinded rct	112	6	56	29(52)	16,4(1,5)	17,2(1,3)	2000IUdaily	56	33 (59)	16,2(1,1)	17,5(1,1)
Jalili 2019(17)	Iran	multicenter double blinded rct	116	1,5	58	58(100)	52,24(12,26)	N/A	50,000IU weekly	58	58 (100)	40,06 (13,37)	N/A
Jalili 2016(18)	Iran	single center double blinded rct	50	1,5	25	25	41.32 (12.62)	21.10 (8.23)	50,000IU weekly	25	25	39.76 (12.99)	21.23 (8.45)
Sikaroudi 2020 (19)	Iran	single center double blinded rct	88	2	44	25(56.8)	35,07(11,73)	17,68(7,69)	50,000IU weekly	44	22 (50)	35,61 (8)	17,83 (7,84)
Tazyman 2015 (20)	UK	single center double blinded rct	35	3	17	15	34(12)	14(8,3)	3000IUdaily	18	17	36(15)	15(8,4)
Willims 2022 (21)	UK	single center double blinded rct	135	3	68	55(80.9)	28,9(10,03)	48,75(27,91)	3000IUdaily	67	51 (76,1)	31,1(10,85)	49,71 (27,05)
Zeid 2020 (22)	Egypt	single center double blinded rct	80	3	40	N/A	37,64(11,3)	N/A	4000IUdaily	40	N/A	38,03 (6,37)	N/A

*Data presented for the vitamin D group include the number of participants, percentage of females, mean age (±SD), baseline serum vitamin D levels (±SD), and vitamin D supplementation dosage. Corresponding data for the placebo group are also included, highlighting baseline serum vitamin D levels, mean age (±SD), and percentage of females.*UK: United Kingdom. IU: International Unite

3.2.2. Risk of Bias

The risk of bias was evaluated for all included studies using the Cochrane Collaboration's Risk of Bias tool. The results are summarized in Figures 2. Across the domains assessed, a majority of studies demonstrated a low risk of bias in the areas of randomized assignment of participants (selection bias) and concealment of group assignment (selection bias), reflecting robust methodologies for randomization and allocation concealment.

However, there were uncertainties in some studies regarding the masking of participants and study personnel (performance bias) and prevention of detection bias in outcome measurement (detection bias). A few studies showed unclear or high risk in handling of missing data (attrition bias) and evaluation of comprehensive data reporting (reporting bias), indicating potential limitations in data completeness and reporting transparency.

"Other biases" were observed in select studies, reflecting inconsistencies in study design or unreported methodological elements. Despite these limitations, the overall methodological quality was considered satisfactory for deriving reliable conclusions.

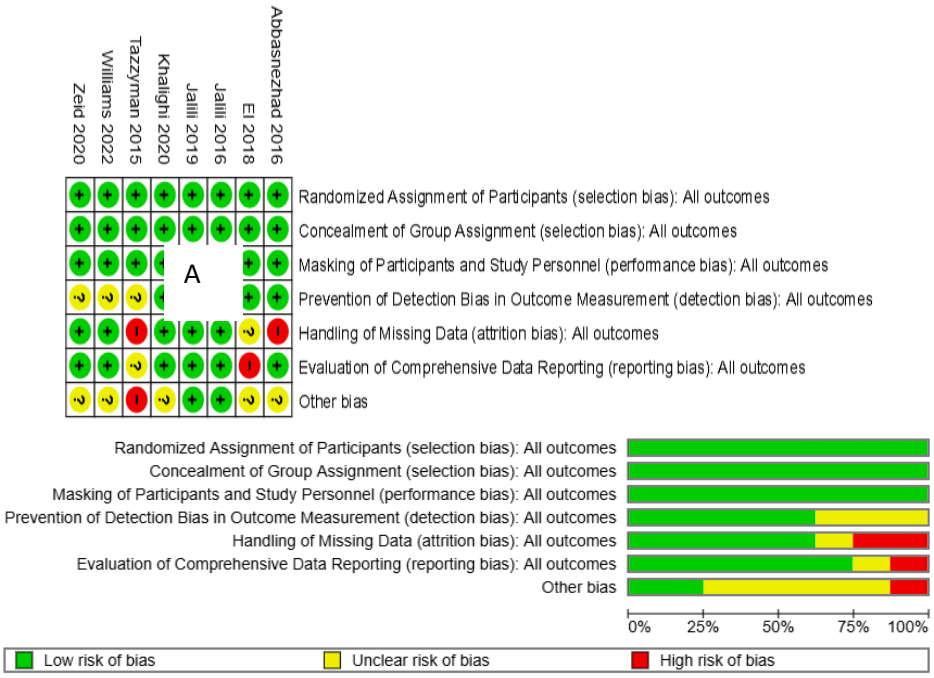

Figure 2. Summary and Distribution of Risk of Bias Across Included Studies.

3.2.3. Publication bias

To evaluate potential publication bias in the meta-analysis, funnel plots were generated for the primary outcomes, including IBS Symptom Severity Score (IBS-SSS), IBS Quality of Life (IBS-QoL), and serum 25-hydroxyvitamin D (25-OH Vit D) levels.

The funnel plot for IBS-SSS revealed a symmetric distribution of studies around the mean effect size. This suggests that there is no significant publication bias affecting the pooled analysis of IBS symptom severity scores (Figure 3A).

For IBS-QoL, the funnel plot exhibited a relatively symmetrical distribution with slight deviations, indicating a low likelihood of publication bias. The absence of extreme asymmetry strengthens the validity of the aggregated findings (Figure 3B).

The funnel plot for serum 25-OH vitamin D levels demonstrated a balanced spread of studies on either

side of the mean effect size, supporting the robustness of the meta-analysis. No significant small-study effects were observed (Figure 3C).

In conclusion, the symmetrical nature of the funnel plots across all outcomes indicates minimal risk of publication bias in the analyzed studies.

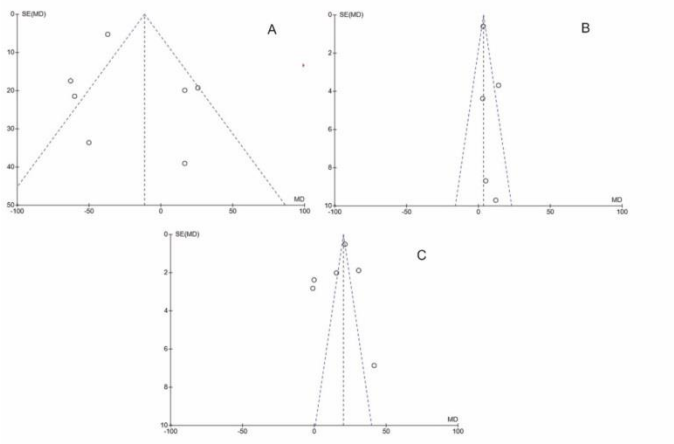

Figure 3. The publication bias assessment by funnel plot. 3A: IBS-SS, 3B: IBS-QoL and 3C: 25-hydroxy Vitamin D.

3.2.4. Outcome Analysis

The meta-analysis for IBS-SSS, including seven studies with a total of 352 participants in the Vitamin D supplementation group and 343 participants in the placebo group, revealed no significant overall effect (mean difference [MD]: 3.91, 95% CI: [-60.99, 68.81], p = 0.91). A high level of heterogeneity was observed (I^2 = 97%, p < 0.00001). Despite substantial heterogeneity, the individual study outcomes varied, with both positive and negative mean differences reported. The heterogeneity might be attributed to differences in study populations, Vitamin D dosages, and duration of intervention (Figure 4A).

Five studies assessed the impact of Vitamin D supplementation on IBS-QoL, involving 229 participants in the Vitamin D group and 246 participants in the placebo group. The meta-analysis revealed a statistically significant improvement in IBS-QoL with Vitamin D supplementation (MD: 6.48, 95% CI: [1.14, 11.83], p = 0.02). Heterogeneity was moderate (I^2 = 56%, p = 0.06), suggesting some variation among the included studies. The results indicate that Vitamin D supplementation might have a beneficial effect on quality of life in IBS patients, but further studies with consistent methodologies are warranted (Figure 4B).

Six studies contributed to the analysis of 25-OH Vitamin D levels, including 267 participants in the Vitamin D group and 264 participants in the placebo group. The pooled results demonstrated a significant increase in serum 25-OH Vitamin D levels in the supplementation group (MD: 17.13, 95% CI: [8.09, 26.17], p < 0.0002). However, a high level of heterogeneity was present (I^2 = 97%, p < 0.00001). The variation in Vitamin D dosages and baseline Vitamin D status across studies might explain the heterogeneity. These findings highlight the effectiveness of Vitamin D supplementation in improving serum Vitamin D levels among IBS patient (Figure 4C).

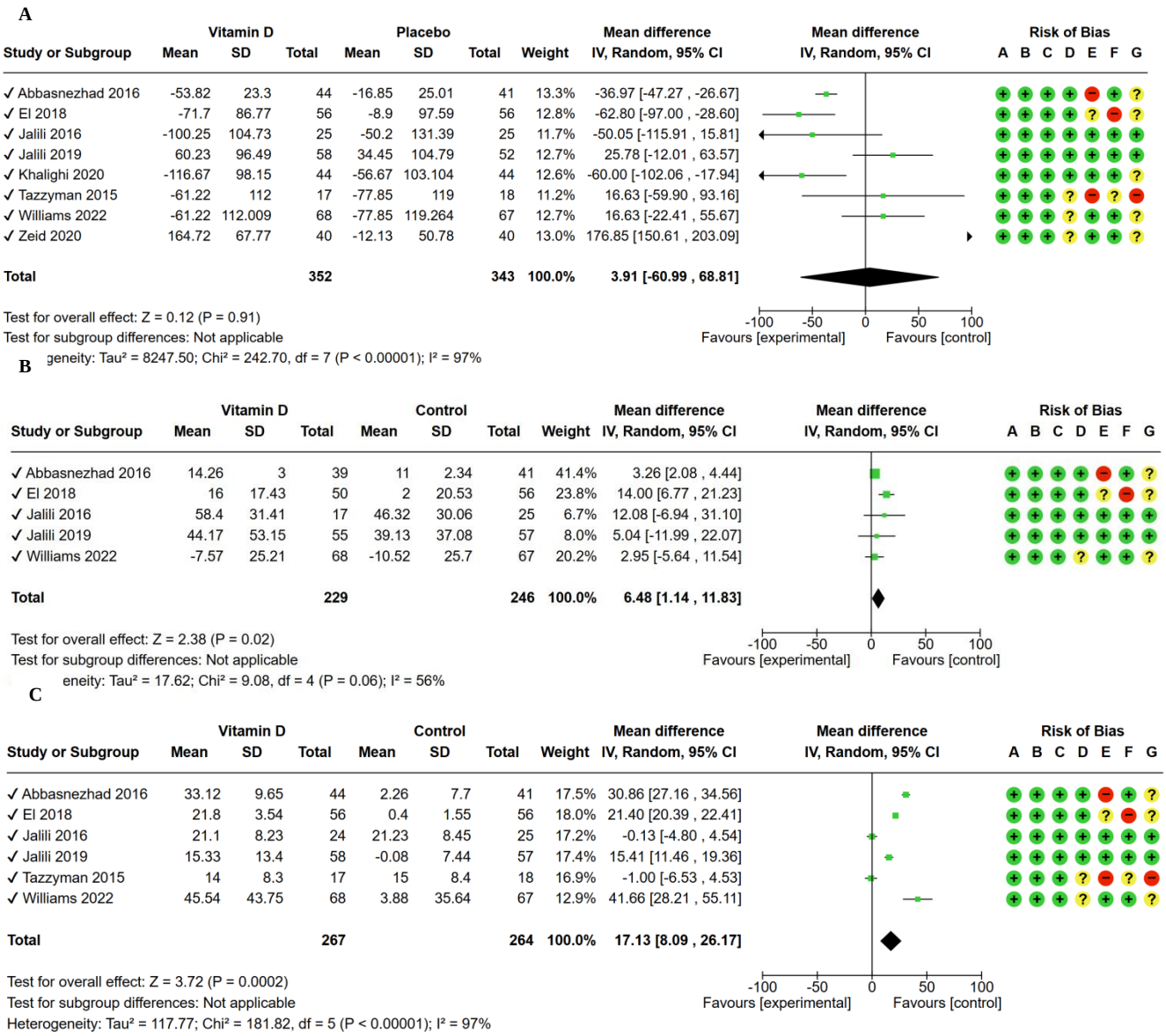

Figure 4. The forest blot analysis for IBS-SSS (A), IBS-QoL (B) and 25-hydroxy Vitamin D level (C).

3.2.4.1 Subgroup Analysis: Effect of 50,000 IU/Week Vitamin D Supplementation

This subgroup analysis included only studies that administered a weekly dose of 50,000 IU vitamin D. InFigure 5A, no statistically significant effect of vitamin D supplementation on IBS symptom severity (IBS-SSS) was found (MD: -28.47; 95% CI: -66.39, 9.45; p = 0.14). However, there was high heterogeneity (I^2 = 80%), which may be due to differences in treatment duration, population, and sample. In Figure 5B, a significant improvement in IBS-QoL scores was seen (MD: 3.31; 95% CI: 2.17–4.44; p < 0.00001). These results, together with low heterogeneity (I^2 = 0%), support the positive effects of vitamin D on quality of life.

In Figure 5C, a significant increase in serum 25(OH)D levels was observed, but remained at the limit of statistical significance (MD: 15.42; 95% CI: -2.10, 32.94; p = 0.08). Heterogeneity was quite high (I^2 = 98%), which may be due to differences in baseline levels and methodological diversity across studies.

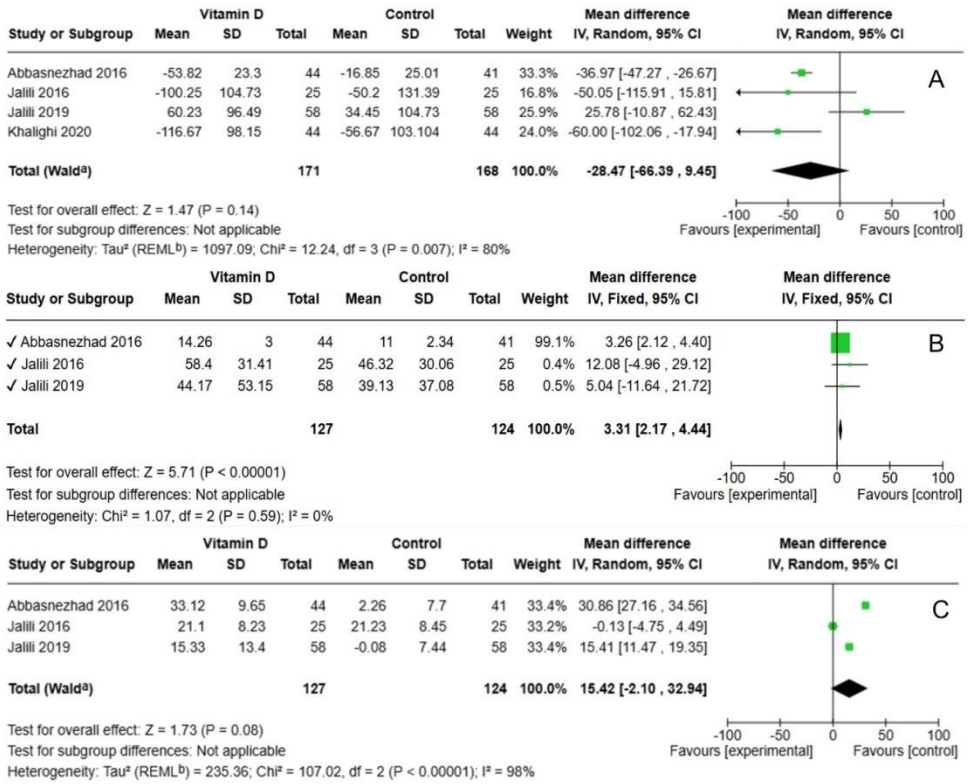

Figure 5. Subgroup analysis: effect of weekly 50,000 IU vitamin D supplementation on clinical parameters in IBS patients. (A), IBS-QoL (B) and 25-hydroxy Vitamin D level (C).

3.2.5. Sensitivity Analysis

Sensitivity analysis was performed to assess the robustness of the meta-analysis findings by excluding one study at a time from the overall pooled analysis for each outcome: IBS-SSS, IBS-QoL, and serum 25-hydroxy vitamin D levels.

For the IBS-SSS outcome, the overall pooled mean difference (MD) from all studies was 3.91 (95% CI: -60.99 to 68.81) with substantial heterogeneity (I^2 = 97%). Sensitivity analysis revealed that excluding individual studies did not significantly alter the overall pooled effect, with MD values ranging between -23.82 (95% CI: -50.07 to 2.43) when Zeid et al. 2020 was excluded, to 13.59 (95% CI: -60.83 to 88.01) when El Amrousy et al. 2018 was excluded. Heterogeneity remained high ($I^2 \geq 97\%$) across all sensitivity analyses, indicating that no single study contributed disproportionately to the heterogeneity or overall effect.

The pooled effect for IBS-QoL was significant, with an MD of 6.48 (95% CI: 1.14 to 11.83) and moderate heterogeneity (I^2 = 56%). Sensitivity analysis showed that the exclusion of individual studies slightly changed the pooled effect size. For instance, excluding Abbasnezhad et al. 2016 increased the MD to 8.85 (95% CI: 2.47 to 15.24) and decreased heterogeneity (I^2 = 26%), while excluding El Amrousy et al. 2018 resulted in the smallest MD of 3.3 (95% CI: 2.13 to 4.46) with no observed heterogeneity (I^2 = 0%). This indicates that Abbasnezhad et al. 2016 contributed moderately to the heterogeneity observed in the overall analysis.

The pooled analysis for serum 25-hydroxy vitamin D levels demonstrated a significant MD of 17.13 (95% CI: 8.09 to 26.17) with high heterogeneity (I^2 = 97%). Sensitivity analysis revealed minimal variability in the pooled effect size upon the exclusion of individual studies. For instance, excluding Jalili et al. 2016 resulted in the largest MD of 20.48 (95% CI: 11.98 to 29.98), while excluding Abbasnezhad et al. 2016 yielded an MD of 14.36 (95% CI: 3.6 to 25.12). Heterogeneity remained consistently high ($I^2 \geq 87\%$) across all analyses, suggesting that heterogeneity was not primarily driven by any single study.

The sensitivity analysis indicates that the overall findings for IBS-SSS, IBS-QoL, and serum 25-hydroxy vitamin D levels are robust and not unduly influenced by any single study. However, the high heterogeneity observed, particularly for IBS-SSS and serum 25-hydroxy vitamin D levels, underscores

the potential influence of methodological differences or population variations among the included studies.

Table 2. The sensitivity analysis

Outcome	Subject number (Vitamin D/Control) IBS-SSS	No of Trial	Quantitative Data Analysis			Heterogeneity Analysis		
			MD (95%CI)	Z Value	P value	df	P value	I^2 (%)
All studies	352/343	8	3.91(-60.99-68.81)	0.12	0.91	7	0.001	97%
Omitting Abbasnezhad et al., 2016	308/302	7	9.84 (-71.55-91.24)	0.24	0.81	6	0.001	96%
Omitting El et al., 2018	296/287	7	13.59 (-60.83-88.01)	0.36	0.72	6	0.001	97%
Omitting Jalili et al., 2016	327/318	7	11.05 (-59.51-81.60)	0.31	0.76	6	0.001	98%
Omitting Jalili et al., 2019	294/291	7	0.64 (-73.36-74.63)	0.02	0.99	6	0.001	97%
Omitting Khalighi et al., 2020	308/299	7	13.05(-59.66-85.75)	0.35	0.73	6	0.001	97%
Omitting Tazzyman et al., 2015	335/325	7	2.27 (-67.82-72.35	0.06	0.95	6	0.001	98%
Omitting Williams et al., 2022	284/276	7	1.98 (-71.94-75.89)	0.05	0.96	6	0.001	98%
Omitting Zeid et al., 2020	312/303	7	-23.82 (-50.07-2.43)	1.78	0.08	6	0.001	73%
	IBS-QoL							
All studies	229/246	5	6.48 (1.14-11.83)	2.38	0.02	4	0.06	56%
Omitting Abbasnezhad et al., 2016	190/205	4	8.85 (2.47-15.24)	2.72	0.007	3	0.26	26%
Omitting El et al., 2018	179/190	4	3.3 (2.13-4.46)	5.54	0.004	3	0.83	0%
Omitting Jalili et al., 2016	212/221	4	6.13 (0.37-11.89)	2.09	0.04	3	0.04	64%
Omitting Jalili et al., 2019	174/189	4	6.79 (0.66-12.92)	2.17	0.03	3	0.03	67%
Omitting Williams et al., 2022	161/179	4	7.86 (0.45-15.26)	2.08	0.04	3	0.03	67%
	25-hydroxy Vitamin D							
All studies	267/264	6	17.13 (8.09-26.17)	3.72	0.02	5	0.001	97%
Omitting Abbasnezhad et al., 2016	223/223	5	14.36 (3.6-25.12)	2.62	0.009	4	0.002	97%
Omitting El et al., 2018	211/208	5	16.71 (2.65-30.76)	2.33	0.02	4	0.001	87%
Omitting Jalili et al., 2016	243/239	5	20.48 (11.98-28.9)	4.73	0.001	4	0.001	96%
Omitting Jalili et al., 2019	209/207	5	17.7 (6.33-29.06)	3.05	0.001	4	0.001	98%
Omitting Tazzyman et al., 2015	250/246	5	20.63 (11.77-29.48)	4.67	0.001	4	0.001	97%
Omitting Williams et al., 2022	199/197	5	13.5 (3.94-23.06)	2.77	0.006	4	0.001	98%

IBS-SSS: Irritable Bowel Syndrome- IBS-Severity Scoring System, IBS-QoL: Irritable Bowel Syndrome- IBS-quality of life, MD. Mean Difference, df: Degrees of Freedom and I2: Inconsistency

3.3. Secondary Outcome

3.3.1. Comparison of the 25-hydroxy Vitamin D levels

The demographic characteristics of the participants included in the meta-analysis are summarized in Table 3. A total of three studies provided detailed demographic data, including healthy control groups and IBS patient groups. The total sample size across the studies was 276 participants in the healthy control group and 236 participants in the IBS patient group.

Table 3. Demographic Characteristics of Healthy Controls and IBS Patients in Studies Included for Serum 25-hydroxy Vitamin D levels.

	Healthy Control Group				IBS Patients Group			
Study	**N**	**F/M**	**Age**	**BMI**	**N**	**F/M**	**Age**	**BMI**
Abbasnezhad et al. (2018) (23)	90	61/29	38.69±9.21	24.56±3	90	61/29	37.66±8.84	25.12±2.78
Khayyat and Attar (2015) (24)	100	11/89	47±14.55	N/A	60	23/37	44.2±16	N/A
Panarese et al. (2019) (25)	86	73/13	50±17.1	25.6±3.4	86	73/13	49.9±17.4	23.7±2.8

F/M: Female/Male, BMI, Body Mass Index, N/A: Not Assayed

The meta-analysis compared serum vitamin D levels between IBS patients and healthy controls across three included studies. The pooled standard mean difference (SMD) was -10.17 (95% CI: -15.57 to -4.77), indicating a lower serum vitamin D level in the IBS group compared to the healthy control group. Heterogeneity was significant (I^2 = 87%, p = 0.0005) (Figure 6).

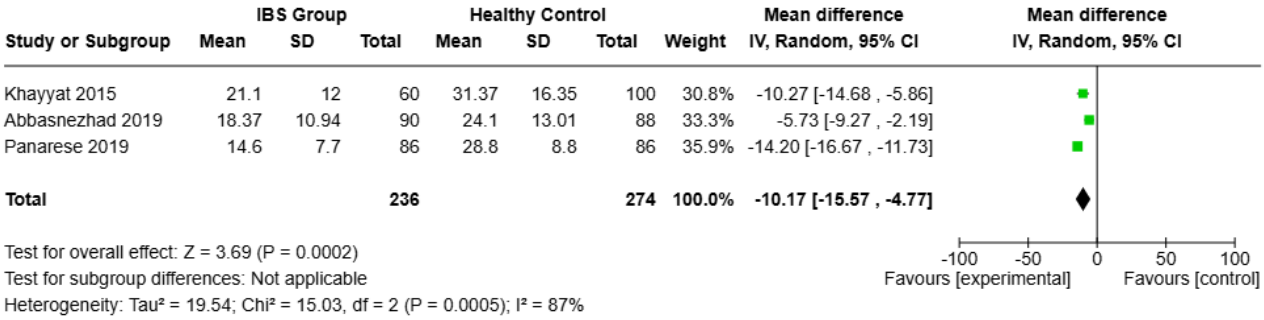

Figure 6. The forest blot analysis for serum 25-hydroxy Vitamin D levels in healthy control and IBS patient groups.

Publication bias

The funnel plot for the included studies assessing serum vitamin D levels in IBS and healthy control groups demonstrates a symmetric distribution of study effect sizes around the pooled estimate. This symmetry suggests no apparent publication bias in the meta-analysis. However, the limited number of studies analyzed may reduce the reliability of funnel plot-based conclusions (Figure 7).

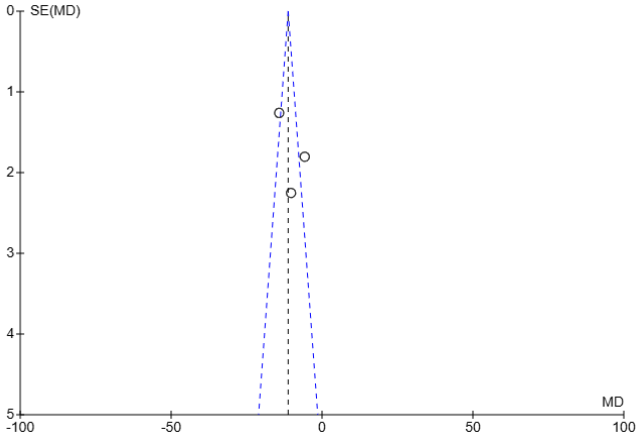

Figure 7. The publication bias assessment by funnel plot for serum 25-hydroxy Vitamin D levels in healthy control and IBS patient groups.

4. Discussion

This meta-analysis underscores the multifaceted role of vitamin D supplementation in improving the quality of life and potentially addressing physiological deficiencies in individuals with IBS. Our primary outcome analysis reveals a statistically significant improvement in IBS-QoL among individuals receiving vitamin D supplementation, aligning with prior studies emphasizing the immunomodulatory and anti-inflammatory effects of vitamin D in gastrointestinal disorders (5, 26). The pooled mean difference in IBS-QoL scores reflects the potential for this intervention to ameliorate IBS-related functional impairments and improve patient well-being, albeit with moderate variability across studies. This variability may be attributed to heterogeneity in study designs, geographic regions, and baseline vitamin D levels (9, 21). Consistent with our findings, a study by Tazzyman et al. reported significant symptom relief in IBS patients following vitamin D supplementation, highlighting the therapeutic promise of addressing vitamin D deficiency in this population (20). However, the high heterogeneity observed across different studies underscores the need for personalized approaches to supplementation, considering factors such as baseline deficiency, geographic region, and IBS subtype. Further high-quality, large-scale RCTs are needed to clarify the role of vitamin D supplementation in IBS management, particularly focusing on these variables.

The lack of significant improvement in IBS symptom severity (IBS-SSS) scores observed in our meta-analysis warrants further investigation. Despite some individual trials reporting notable symptom relief, the high heterogeneity across studies limits the generalizability of this finding. This is consistent with previous meta-analyses, such as those by Cara et al and Abboud et al. which reported similar challenges due to variability in diagnostic criteria, supplementation protocols, and patient demographics (9, 27).

Several studies suggest that patients with severe baseline vitamin D deficiency or specific IBS subtypes may experience more pronounced benefits from vitamin D supplementation. For instance, Chong et al. reported significant symptom improvement in vitamin D-deficient IBS patients following supplementation (28). Additionally, our findings on serum 25(OH)D]levels corroborate the efficacy of vitamin D supplementation in addressing vitamin D deficiency, a condition prevalent among IBS patients. The pooled mean difference highlights the robust impact of supplementation on serum levels.

The considerable heterogeneity observed in the meta-analyses can stem from several sources, including differences in geographical locations, ethnic backgrounds, dosing regimens, and treatment durations across the included studies. For example, some studies were conducted in Middle Eastern countries (Iran, Egypt), while others originated from Western regions (UK), introducing potential variation due to differences in sunlight exposure, dietary patterns, and genetic factors influencing vitamin D metabolism. Moreover, the dosage of vitamin D supplementation varied markedly—from daily doses of 2000–4000 IU to weekly doses of 50,000 IU—and follow-up durations ranged from 1.5 to 6 months. These inconsistencies likely contributed to outcome variability and reduced comparability between trials. While our subgroup analysis focusing exclusively on studies using 50,000 IU/week provided more consistent results in terms of quality of life, the lack of standardized intervention protocols across the broader dataset may limit generalizability. Future research should consider stratified analyses by dose, duration, geographic region, and genetic markers to better elucidate the sources of heterogeneity.

Given the substantial heterogeneity observed in the overall analyses for IBS symptom severity and serum 25(OH)D levels, we conducted a subgroup analysis to examine whether differences in vitamin D dosage contributed to this variability. Specifically, we focused on studies that administered a standardized high dose of 50,000 IU of vitamin D per week. This approach allowed for the evaluation of outcomes under more consistent intervention conditions. The subgroup analysis revealed that while symptom severity did not significantly improve, quality of life scores showed more uniform enhancement across studies, and heterogeneity was notably reduced. These findings suggest that variations in supplementation regimens—particularly dosage and frequency—may be important sources of heterogeneity in the literature. Therefore, future studies should consider standardizing vitamin D dosing protocols to improve comparability and clarity regarding its clinical efficacy in IBS.

The secondary outcome of this meta-analysis—comparing serum 25(OH)D levels between IBS patients and healthy controls—revealed a significant

difference, with IBS patients exhibiting lower levels (SMD: -10.17, 95% CI: -15.57 to -4.77, p = 0.0005). These findings reinforce the growing body of evidence suggesting a link between vitamin D deficiency and IBS pathophysiology. Hypotheses include the role of vitamin D in modulating gut permeability, reducing low-grade inflammation, and influencing the gut-brain axis. Despite these associations, the directionality and causality of this relationship remain unclear, necessitating further research.

The implications of these findings are clinically significant. First, the demonstrated improvements in IBS-QoL and serum vitamin D levels advocate for routine screening and management of vitamin D deficiency as part of IBS care. Second, the variability in IBS-SSS outcomes highlights the need for personalized approaches to supplementation, considering factors such as baseline deficiency, geographic region, and IBS subtype. Lastly, the observed difference in baseline serum 25(OH)D levels between IBS patients and controls suggests that addressing vitamin D deficiency could serve as a preventative strategy or adjunctive treatment for IBS.

Limitations

This meta-analysis has several limitations. The high level of heterogeneity observed in most analyses reduces the generalizability of the findings and highlights the variability in study designs, supplementation regimens, and populations. Additionally, the limited number of included studies for certain outcomes restricts the ability to perform subgroup analyses, such as by IBS subtype or baseline vitamin D status.

5.Conclusion

In conclusion, this meta-analysis suggests that vitamin D supplementation may improve IBS-QoL and effectively increase serum 25(OH)D levels in IBS patients. However, its effect on symptom severity remains inconclusive. Further high-quality, large-scale RCTs are needed to clarify the role of vitamin D supplementation in IBS management, particularly focusing on baseline vitamin D status and IBS subtypes. Addressing vitamin D deficiency may represent a promising avenue for improving patient outcomes in this challenging and multifactorial condition.

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