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SYSTEMATIC REVIEW

The Effect of Probiotics on Obesity with Comorbid Depression: A Systematic Review and Meta-Analysis

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Abstract

Aims/Background Obesity and depression frequently co-occur, and the relationship between them is bidirectional. Being obese or overweight increases the risk of depression, and conversely, depression increases the risk of obesity or overweight. Emerging clinical research has shown that probiotics may be effective in treating obesity and associated depression. Modulating gut microbiota with probiotics may improve obesity-related depression, but current evidence is inconsistent.

Methods We systematically searched PubMed, EMBASE, Web of Science, and Cochrane Library for randomized controlled trials examining probiotics for depression in obese adults. Mean difference (MD) in depression scores between probiotic and placebo groups was pooled across studies using random-effects models. Heterogeneity was assessed using I^2 to explain heterogeneity in meta-regression analysis. To detect the publication bias of the included studies, a funnel plot, and Begg and Egger tests, were used. Possible heterogeneity moderators were detected by subgroup and sensitivity analyses, Galbraith plot, and graphic display of study heterogeneity (GOSH) analysis. Leave-one-out and Influence analyses were performed to assess sensitivity.

Results Five trials (n = 488) were included. Overall, probiotics did not significantly improve depressive symptoms versus placebo (MD = 0.08, 95% confidence interval [CI] = –0.63 to 0.79, $p = 0.82$). Considerable heterogeneity among studies was observed ($I^2 = 63\%$). In subgroup analyses, probiotics significantly reduced depression as measured by the Edinburgh Postnatal Depression Scale (MD = –0.60, 95% CI = –1.17 to –0.03, $p = 0.04$) with no heterogeneity ($I^2 = 0\%$). Probiotics also decreased depressive symptoms after 12 weeks of supplementation (MD = –0.78, 95% CI = –1.58 to –0.01, $p = 0.05$) versus placebo. No publication bias was found using Begg and Egger tests. The GOSH diagnostics revealed three outliers, among the clusters identified by K-means, DBSCAN (Density-based spatial clustering of applications with noise algorithm), and GMM (Gaussian Mixture Model) analyses.

Conclusion Overall, probiotics did not improve depressive symptoms in obesity. However, beneficial effects were observed with the Edinburgh Postnatal Depression Scale and short-term use of probiotic. Additional rigorous randomized controlled trials are warranted to elucidate the therapeutic potential of probiotics for obesity-related depression.

Key words: probiotics; obesity; depression; gut microbiota

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Introduction

Obesity is a multifactorial disease characterized by the accumulation of excess body fat, which has detrimental effects on health. The prevalence of obesity is rapidly increasing, giving rise to an unprecedented epidemic that shows no significant signs of abating in the near future. Elevated body mass index (BMI) serves

as a risk factor for noncommunicable diseases, including diabetes, cardiovascular disorders, and musculoskeletal conditions, leading to a significant deterioration in both quality of life and life expectancy. Obesity and depression are two highly prevalent health conditions that frequently coexist and exacerbate each other (Vancampfort et al, 2016). A bidirectional relationship has been established between obesity and depression, where obesity increases the risk of developing depressive symptoms, and vice versa (Lopresti and Drummond, 2013). For example, results of previous studies (Lopresti and Drummond, 2013; Simon et al, 2006) suggest that maternal obesity is linked to an increased presence of anxiety and depression symptoms. Both during and after pregnancy, obesity is associated with heightened levels of anxiety and depression (Griffiths et al, 2024; Wang et al, 2019).

The comorbidity between obesity and depression leads to worse health outcomes and reduced quality of life compared to either condition alone (Simon et al, 2006). Moreover, the relationship between obesity and mental health symptomology may be influenced by socioeconomic status and ethnicity.

In recent years, the gut microbiota has emerged as a potential link between obesity and depression (Roager and Licht, 2018). The gut microbiota is the collection of microorganisms present in the human gut, including bacteria, fungi, viruses and other microorganisms. The gut microbiota plays an important ecological and functional role in the gut. Gut microbiota has an important impact on human health. It is involved in a variety of physiological processes, such as food digestion, immunomodulation, and maintenance of intestinal barrier function. It also synthesizes certain vitamins and other beneficial substances and inhibits the growth of potentially pathogenic microorganisms. In recent years, an increasing number of studies have demonstrated the close relationship between the gut microbiota and the occurrence and progression of various diseases, such as inflammatory bowel disease, obesity, metabolic disorders (such as diabetes mellitus), autoimmune diseases, and cardiovascular diseases. The study suggested that regulating and improving the gut microbiota may represent a novel approach for the prevention and treatment of these conditions (Vancampfort et al, 2016).

Alterations in the gut microbial composition, known as dysbiosis, have been associated with obesity, inflammation, impaired metabolism, and psychiatric disorders like depression (Jiang et al, 2017). Modulating the gut microbiome with probiotics has shown promising results in improving obesity-related parameters as well as mental health outcomes (Ng et al, 2018). Several systematic reviews have examined the antidepressant effects of probiotics, but few have specifically focused on obese populations with co-existing depression (El Dib et al, 2021; Sanchez et al, 2017).

Therefore, we aimed to conduct a systematic review and meta-analysis of Randomized controlled trials (RCTs) examining the effect of probiotics on depressive symptoms in patients with obesity and comorbid depression. We performed subgroup analyses to evaluate whether probiotic effects varied by the type of depression scale used or the duration of supplementation. Findings from this meta-analysis will provide insights into the therapeutic potential of probiotics for improving mental health in individuals with obesity.

Methods

Search Strategy and Selection Criteria

We systematically searched PubMed, EMBASE, Web of Science, and Cochrane Library databases up until October 2023 using the following search terms: (probiotic OR microbiota OR microbiome OR *Lactobacillus* OR *Bifidobacterium*) AND (obesity OR obese) AND (depression OR depressive disorder OR depressed mood). No language or date restrictions were applied. Reference lists of relevant reviews and included studies were hand-searched for additional studies.

Inclusion criteria: (1) RCTs comparing probiotics versus placebo in obese adults. (2) Assessment of depression symptoms using validated scales. (3) Sufficient data reported to calculate the mean difference (MD) and its standard error (SE) in depression scores between the probiotic and placebo groups.

Exclusion criteria: (1) Reviews, non-human studies, and non-RCTs. (2) Studies with fewer than 50 participants. (3) Studies lacking sufficient data for the calculation of MD and standard error (SE) in depression scores between groups.

Data Extraction and Quality Assessment

Two reviewers independently performed study selection, data extraction, and quality assessment using a standardized form. Extracted data included: first author, year, country, participant demographics, probiotic strains and doses, depression scale used, follow-up duration, and pre-post MD in depression scores.

Scoring Criteria for Different Scales

Five papers utilized commonly used depression assessment scales, namely the Beck Depression Inventory (BDI), Edinburgh Postnatal Depression Scale (EPDS), and Depression, Anxiety, and Stress Scale-21 (DASS-21). The BDI is a widely used self-report questionnaire that assesses the severity of depressive symptoms. It consists of 21 items, and each item is scored on a scale of 0 to 3. The total score on the BDI can be interpreted as follows: 0–13 = Minimal or no depression; 14–19 = Mild depression; 20–28 = Moderate depression; 29–63 = Severe depression. Edinburgh Postnatal Depression Scale (EPDS): The EPDS is a specific screening tool for postnatal depression. It consists of 10 items, and each item is scored on a scale of 0 to 3. The total score on the EPDS is interpreted as follows: 0–9 = Normal range; 10–12 = Mild depression; 13–15 = Moderate depression; 16 and above = Severe depression. The Depression, Anxiety, and Stress Scale-21 (DASS-21) is a self-report questionnaire that measures the severity of symptoms related to depression, anxiety, and stress. It consists of 21 items, with each item scored on a scale from 0 (not at all) to 3 (most of the time). The scores on the DASS-21 can be categorized as follows: 0–9 = Normal range; 10–13 = Mild depression; 14–20 = Moderate depression; 21 and above = Severe depression.

Quality Assessment

The GRADE system was used to grade the quality of evidence (Schünemann et al, 2013). The level of evidence for outcome indicators was evaluated based on five criteria (risk of bias, inconsistency, indirectness, inaccuracy, and publication

bias). Grade divides evidence quality into: high quality (confident that effect size estimates are close to the true effect), moderate quality (effect size estimates are likely close to the true effect, but there is still the possibility that the two are substantially different), low quality (confidence in the estimate of effect size is limited, may differ substantially from the true effect), very low quality (very little confidence in the estimate of effect size, is likely to differ substantially from the true effect).

Statistical Analysis

Data were processed and analyzed using R software 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) for processing and analysis. All analyses were performed using R software. The 'meta' and 'dmetar' packages were used for the meta-analysis. Heterogeneity was analyzed using the Q-test, and a p value > 0.1 was considered to indicate no significant heterogeneity between the studies, at which point the variables were included in a fixed-effects model to calculate statistics. A p value ≤ 0.1 was considered to indicate significant heterogeneity between studies, and the variables were included in a random-effects model. p value < 0.05 was considered statistically significant. A random-effects model was used to pool MD in depression scores between probiotic and placebo groups across studies.

Publication bias was evaluated visually using funnel plots and statistically using the Begg test and Egger regression test. The Begg rank correlation test is based on the rank correlation between the effect size estimates and their standard errors. The null hypothesis of this test is that there is no correlation between the effect size estimates and their standard errors, meaning that there is no funnel plot asymmetry. The alternative hypothesis is that there is a correlation between them, meaning that there is funnel plot asymmetry. The Egger test is based on the linear regression of the effect size estimates on their standard errors. The null hypothesis of this test is that the intercept of the regression line is zero, meaning that there is no funnel plot asymmetry. The alternative hypothesis is that the intercept of the regression line is not zero, meaning that there is funnel plot asymmetry.

The meta-analysis also used two graphical methods to assess the presence of heterogeneity and outliers in the studies. The first method was the Baujat plot for the meta-analysis of probiotics on depressive symptoms in obese patients. The second method was the Galbraith plot, which is a scatter plot of the standardized residual (y-axis) against its reciprocal standard error (x-axis). The standardized residual is the same as in the Baujat plot, and it measures how far each study effect size is from the pooled effect size. The meta-analysis also used a trim-and-fill method to adjust for possible funnel plot asymmetry, which may indicate the presence of publication bias or other sources of heterogeneity.

Sensitivity analyses included leave-one-out analysis and influence analysis to assess the robustness of results and impact of individual studies. Sources of heterogeneity were explored using subgroup analyses based on depression scale type and follow-up duration. Graphic display of study heterogeneity (GOSH) diagnostics using K-means, Density-based spatial clustering of applications with noise algorithm

(DBSCAN), and Gaussian Mixture Models (GMMs) were used to identify potential outliers and clusters. The p value < 0.05 was considered statistically significant.

Results

Overall Meta-Analysis

In this meta-analysis, a systematic screening process was conducted to identify and select relevant studies. A total of 382 records were initially identified through database searching from PubMed, EMBASE, and Web of Science. After removing duplicates, 213 records were eliminated. The remaining 169 records were screened, and 78 were excluded based on the review of titles and abstracts. Subsequently, 91 records underwent a full-text assessment for eligibility. Among the 91 full-text articles assessed, several articles were excluded from the meta-analysis based on specific criteria. Eight articles were excluded because they were reviews or meta-analyses. Twelve articles were excluded due to a sample size of less than 50 participants, and 66 articles were excluded because they had insufficient data for inclusion in the meta-analysis. As a result, a total of 5 studies were included in the final meta-analysis (Fig. 1). The systematic review followed PRISMA guidelines and a PRISMA check list is provided as a supplementary material (**PRISMA Checklist**).

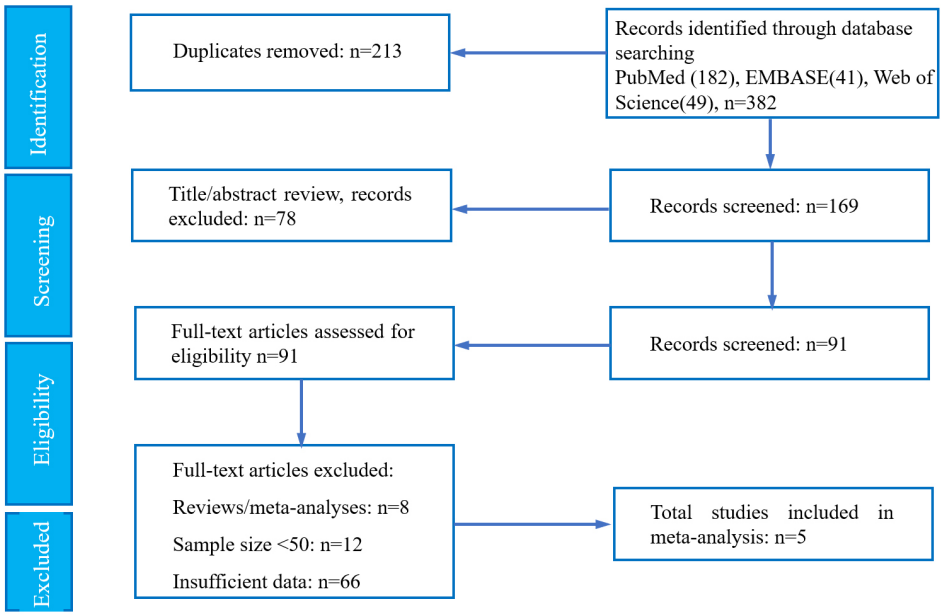

Fig. 1. Flow diagram of study selection process.

The included studies differed in several aspects, including their region, participant demographics, grouping, sample sizes, scale types, probiotics used, and the effect of high-fat diet (HFD) versus control on metabolism. The following are the key characteristics of the five studies included in the meta-analysis. The studies used different types of scales to measure depressive symptoms, such as BDI, DASS-21, and EPDS (Table 1). The results of the quality assessment are shown in

Table 1 (Rao et al, 2019; Hadi et al, 2019; Dawe et al, 2020; Hulkkonen et al, 2021; Mahboobi et al, 2022).

Forest Plot Analysis of Effects of Probiotics on Depressive Symptoms

The meta-analysis was conducted to examine the effect of probiotics (gut microbiota) on obese patients with comorbid depression. The meta-analysis included 11 papers that reported the MD and its 95% confidence interval (CI) for depressive symptoms between probiotic and placebo groups. The depressive symptoms were measured by various scales, such as the Beck Depression Inventory (BDI), Depression, Anxiety, and Stress Scale-21 (DASS-21), Edinburgh Postnatal Depression Scale (EPDS), and State-Trait Anxiety Inventory (STAI). The probiotic products contained different strains and doses of bacteria, such as *Lactobacillus rhamnosus*, *Bifidobacterium longum*, *Lactobacillus casei*, and *Lactobacillus acidophilus*. The duration of probiotic supplementation ranged from 4 to 24 weeks.

The results showed that the overall pooled MD was 0.0441 [–0.3770–0.4652] for the fixed-effects model and 0.0834 [–0.6268–0.7936] for the random-effects model, and these differences were not statistically significant ($z = 0.21$, $p = 0.84$ for fixed-effects model; $z = 0.23$, $p = 0.82$ for random-effects model). Thus, there were no significant differences in depressive symptoms between probiotic and placebo groups across all studies. The heterogeneity among the studies was quantified by tau^2, tau, I^2, and H statistics. The results showed that there was moderate to high heterogeneity among the studies ($tau^2 = 0.865$ [0.081–3.857]; $tau = 0.9299$ [0.2847–1.9640]; $I^2 = 63\%$ [28%–81%]; $H = 1.64$ [1.18–2.27]). The test of heterogeneity also confirmed that there was significant heterogeneity among the studies ($Q = 26.78$, $df = 10$, $p = 0.003$) (Fig. 2).

Funnel Plot Analysis of Effects of Probiotics on Depressive Symptoms

The funnel plot for the meta-analysis of effects of probiotics on depressive symptoms in obese patients is shown in Fig. 3. The funnel plot shows that most of the studies are within the 95% CI of the pooled MD, and that they are roughly symmetrically distributed around it. This suggests that there is no significant publication bias or heterogeneity among the studies. However, there is one exception, which is Mahboobi et al (2022). This study is located at the bottom right corner of the funnel plot, and there is no corresponding study on the left side. This indicates that this study has a large SE and a large positive MD, meaning that it has a low precision and a high effect size. This study may be an outlier or an influential point that deviates from the overall trend. A total of 6 papers (Hulkkonen et al (2021) (to late pregnancy), Hulkkonen et al (2021) (to 3 months postpartum), Hulkkonen et al (2021) (to 6 months postpartum), Hulkkonen et al (2021) (to 12 months postpartum), Sanchez et al (2017) (Phase 1-baseline|Men), and Sanchez et al (2017) (Phase 1-baseline|Women)) are distributed within the left 95% CI, one paper (Sanchez et al (2017) (Phase 2-baseline|Men)) is within the right 95% CI, and 2 papers (Hadi et al (2019) (8 weeks), and Sanchez et al (2017) (Phase 2-baseline|Women)) are distributed outside the right 95% CI.

Table 1. Characteristics of randomized controlled trials assessing the metabolic effects of prebiotics in obese patients with comorbid depression included in the systematic review.

Study	Region	Sex	Age (Trial/Control)	Grouping	Sample sizes	Scale type	Probiotics	Effect HFD vs. Control (Metabolism)	Quality assessment
(Rao et al, 2019)	Canada	Male and female	35.0 ± 10.0/37.0 ± 10.0	Placebo group & Intervention group	62/63	BDI	*Lactobacillus rhamnosus CGMCC1.3724*	A decrease in the Beck Depression Inventory score ($p = 0.05$) that was significantly different from the change noted in the placebo group ($p = 0.02$)	High quality
(Hadi et al, 2019)	Iran	Male and female	34.49 ± 6.02/36.64 ± 7.26	Placebo group & Intervention group	30/29	DASS-21	*Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*	A significant between-group decrease in depression ($p = 0.03$) was found in the synbiotic group compared to the placebo	Medium quality
(Dawe et al, 2020)	New Zealand	Female	29.39 ± 5.39/30.06 ± 5.51	Placebo group & Intervention group	88/76	EPDS	Lactobacillus *rhamnosus GG & Bifdobacterium lactis BB12*	Depression scores remained stable and did not difer between the probiotic (M = 7.18, SD = 3.80) and placebo groups (M = 6.76, SD = 4.65) at 36 weeks ($p > 0.05$)	High quality
(Hulkkonen et al, 2021)	Finland	Female	30.6 ± 4.6	Probiotics + placebo & Placebo + placebo	96/92	EPDS/STAI-6/SF-12-v2	*Lactobacillus rhamnosus HN001 & Bifidobacterium animalis ssp. lactis 420*	The intervention had a modest impact on depressive symptoms during pregnancy and 12 months postpartum (Trial group: EPDS = 1.1, Control group: EPDS = 0.85, $p = 0.017$)	High quality
(Mahboobi et al, 2022)	Iran	Male and female	38.94 ± 7.19/35.90 ± 8.64	Placebo group & Intervention group	28/24	BDI	Lactobacillus *rhamnosus (LGG) & Bifidobacterium animalis subsp. Lactis (BB-12)*	Changes in BDI-II scores were not significantly different between intervention (−7.13 ± 5.67, 1.20 ± 2.16, respectively) and placebo (−5.42 ± 6.71, 1.94 ± 1.86, respectively) groups ($p > 0.05$)	Low quality

Note: STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; HFD, high-fat diet; EPDS, Edinburgh Postnatal Depression Scale; DASS-21, Depression, Anxiety, and Stress Scale-21.

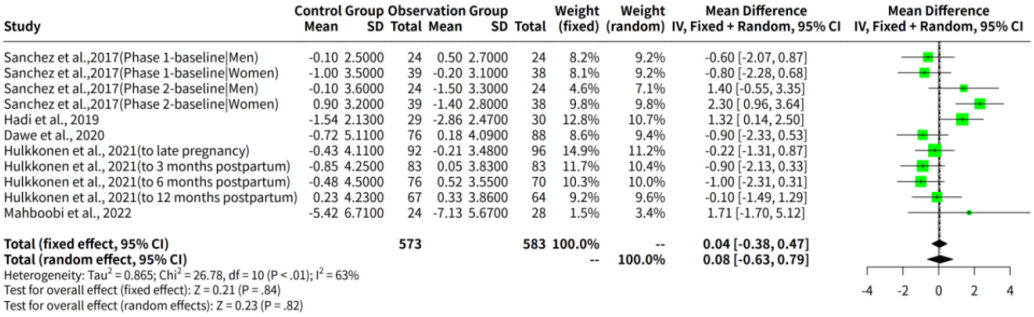

Fig. 2. Forest plot of the meta-analysis of probiotics on depressive symptoms in obese patients.

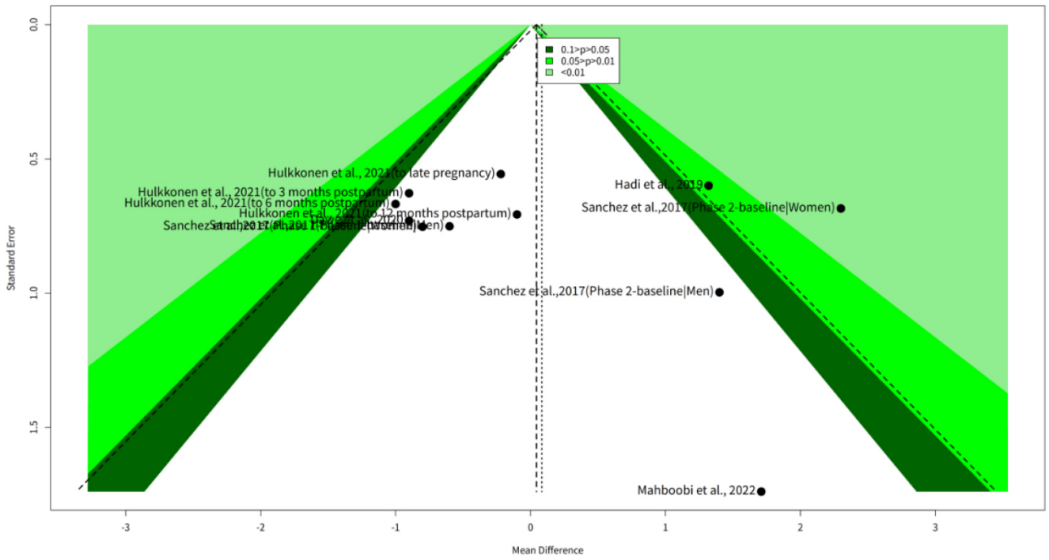

Fig. 3. Funnel plot of the meta-analysis of effects of probiotics on depressive symptoms in obese patients.

Publication Bias Assessed Using the Begg Test and Egger Test

The results of the Begg rank correlation test were not significant ($z = 0.39$, $p = 0.70$). This means that the Begg rank correlation test did not reject the null hypothesis, and thus did not provide evidence for funnel plot asymmetry. The Begg rank correlation test result is shown in Fig. 4A.

The results of the Egger test were not significant ($t = 0.57$, $df = 9$, $p = 0.58$). The Egger linear regression test result is shown in Fig. 4B.

Thus, both the Begg test and the Egger test showed that there was no significant publication bias or other sources of funnel plot asymmetry in the meta-analysis of effects of probiotics on depressive symptoms in obese patients.

Baujat and Galbraith Analysis

The Baujat plot (Fig. 5A) shows that most of the studies are clustered near the origin, meaning that they have low contributions to both heterogeneity and overall effect size. However, there is one exception, which is Sanchez et al (2017) (Phase

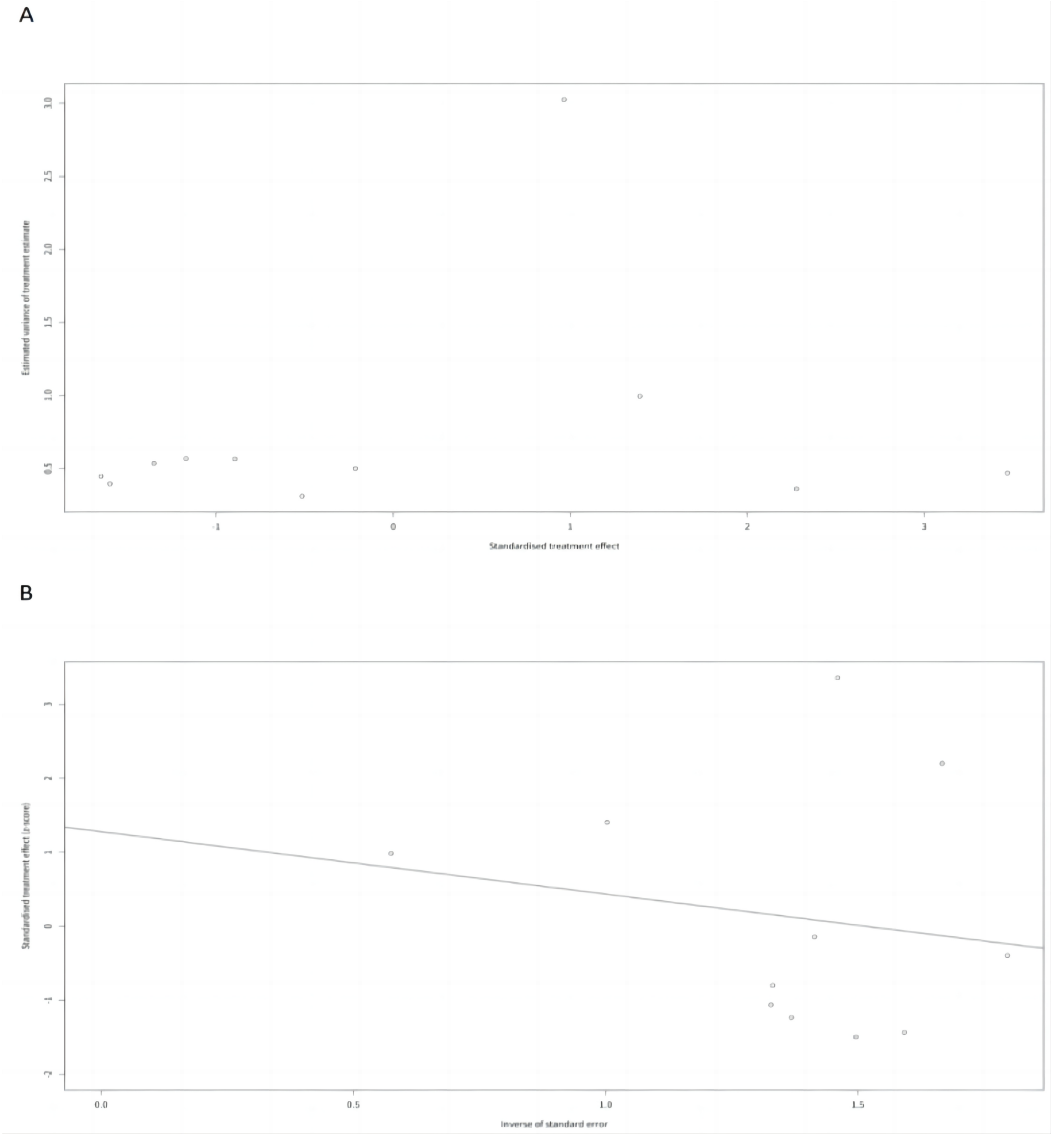

Fig. 4. Assessment of publication bias. (A) Begg's rank correlation test and (B) Egger's linear regression test.

2-baseline|Women). This study is located at the top right corner of the Baujat plot, meaning that it has high contributions to both heterogeneity and overall effect size. This indicates that this study has a large positive effect size and a large residual, meaning that it has a high precision and a high deviation from the pooled effect size. This study may be an outlier or an influential point that affects the meta-analysis results (Fig. 5A).

The Galbraith plot shows that all the studies are distributed in four regions, which are defined by two horizontal lines at y = ±1.96 and two vertical lines at x = ±3 (Fig. 5B). The Galbraith plot shows that Sanchez et al (2017) (Phase 2-baseline|Women) and Hadi et al (2019) are located above the upper horizontal line and within the vertical lines. This means that they have significant positive effect sizes but moderate standardized residuals. Thus, both the Baujat plot and the Galbraith plot showed that there was moderate to high heterogeneity among the studies,

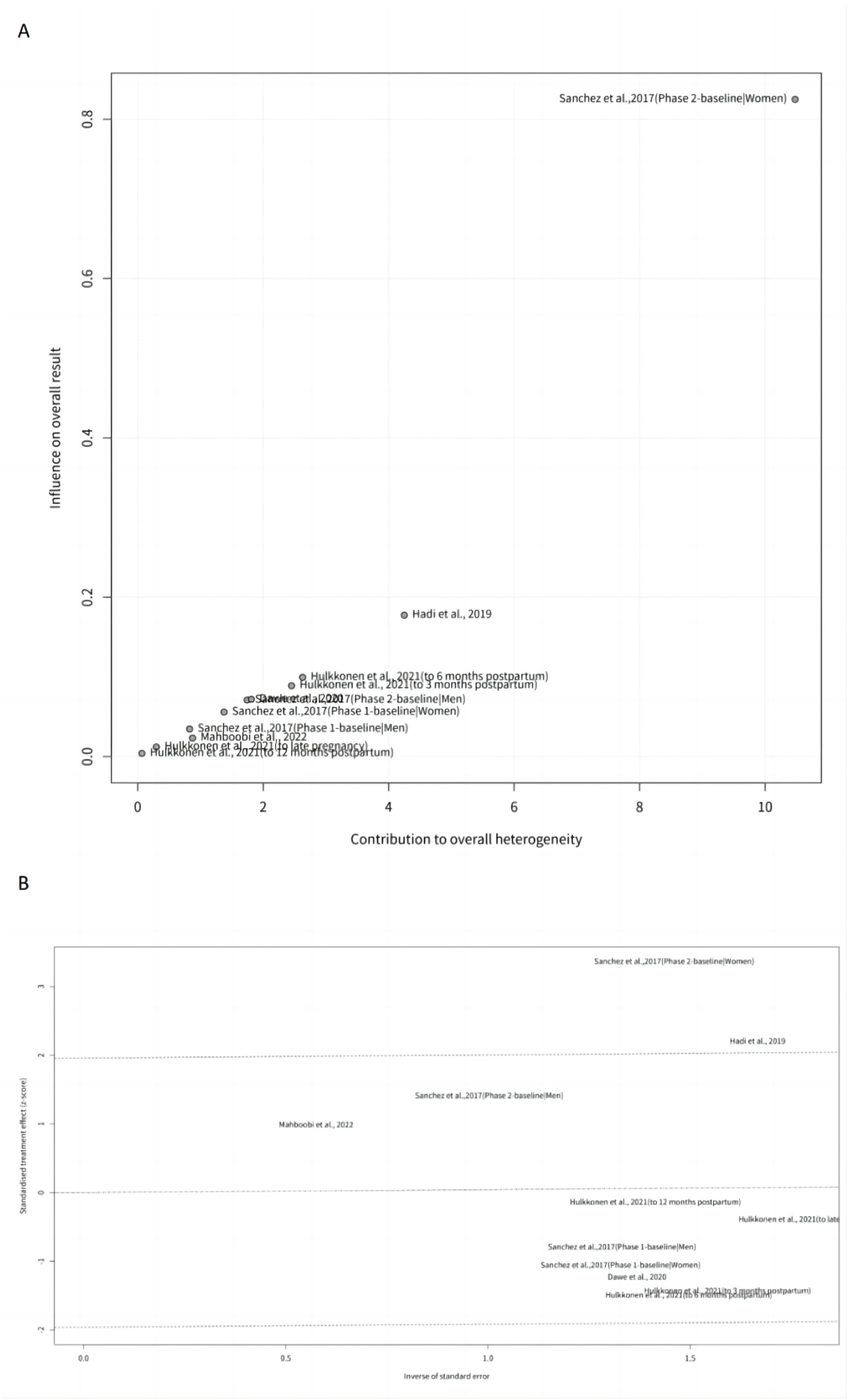

Fig. 5. Analysis of the origin of heterogeneity. (A) Baujat plot: contribution to heterogeneity and overall effect. (B) Galbraith plot: standardized residual and reciprocal standard error.

Table 2. Baujat diagnostics sorted by heterogeneity contribution for the meta-analysis of effects of probiotics on depressive symptoms in obese patients.

Study	Lables	Heterogeneity contribution	Influence effect size
Sanchez et al (2017) (Phase 2-baseline|Women)	BDI.3	10.854	1.185
Hadi et al (2019)	DASS-21	4.525	0.666
Hulkkonen et al (2021) (to 6 months postpartum)	EPDS.3	2.442	0.282
Hulkkonen et al (2021) (to 3 months postpartum)	EPDS.2	2.260	0.300
Sanchez et al (2017) (Phase 2-baseline|Men)	BDI.2	1.850	0.090
Dawe et al (2020)	EPDS	1.670	0.158
Sanchez et al (2017) (Phase 1-baseline|Women)	BDI.1	1.257	0.111
Mahboobi et al (2022)	BDI.4	0.918	0.014
Sanchez et al (2017) (Phase 1-baseline|Men)	BDI	0.735	0.066
Hulkkonen et al (2021) (to late pregnancy)	EPDS.1	0.225	0.039
Hulkkonen et al (2021) (to 12 months postpartum)	EPDS.4	0.042	0.004

Note: BDI, Beck Depression Inventory; EPDS, Edinburgh Postnatal Depression Scale; DASS-21, Depression, Anxiety, and Stress Scale-21.

and that Sanchez et al (2017) (Phase 2-baseline|Women) was an outlier or an influential point that deviated from the overall trend.

The Baujat diagnosis for the meta-analysis of probiotics on depressive symptoms in obese patients is shown in Table 2 (Sanchez et al, 2017; Hadi et al, 2019; Hulkkonen et al, 2021; Dawe et al, 2020; Mahboobi et al, 2022), which shows that Sanchez et al (2017) (Phase 2-baseline|Women) had the largest influence on the heterogeneity, as it contributed 10.854 units to the heterogeneity, and increased the pooled effect size by 1.185 units when included. The table also shows that Hadi et al (2019) and Hulkkonen et al (2021) (to 6 months postpartum) had moderate influences on the heterogeneity, as they contributed 4.525 and 2.442 units to the heterogeneity, respectively, and increased or decreased the pooled effect size by 0.666 and –0.282 units, respectively, when included. The table also shows that Mahboobi et al (2022) had a small influence on the heterogeneity, as it contributed 0.918 units to the heterogeneity, and decreased the pooled effect size by –0.014 units when included. The table also shows that Sanchez et al (2017) (Phase 1-baseline|Men), Hulkkonen et al (2021) (to late pregnancy), and Hulkkonen et al (2021) (to 12 months postpartum) had negligible influences on the heterogeneity, as they contributed less than 1 unit to the heterogeneity, and changed the pooled effect size by less than 0.1 units when included.

Trim-and-Fill Analysis

The trim-and-fill method with the L-estimator is shown in Fig. 6. Sanchez et al (2017) (Phase 2-baseline|Women) was trimmed and filled on the left side of the funnel plot. This study had a large positive effect size and a large standard error, and it was an outlier or an influential point in the previous analyses. The results showed that the adjusted pooled MD was –0.1485 [–0.9495–0.6526] under the random-effects model, which was not statistically significant (z = –0.36, *p* =

Table 3. Leave-one-out analysis for the meta-analysis of probiotics on depressive symptoms in obese patients.

Study	Lables	Effect	LLCI	ULCI	I^2
Sanchez et al (2017) (Phase 2-baseline|Women)	BDI.3	0.202	–0.241	0.646	0.389
Hadi et al (2019)	DASS-21	0.144	–0.307	0.595	0.583
Hulkkonen et al (2021) (to 6 months postpartum)	EPDS.3	–0.164	–0.609	0.280	0.626
Hulkkonen et al (2021) (to 3 months postpartum)	EPDS.2	–0.169	–0.617	0.279	0.628
Sanchez et al (2017) (Phase 2-baseline|Men)	BDI.2	0.022	–0.409	0.453	0.638
Dawe et al (2020)	EPDS	–0.133	–0.574	0.307	0.639
Sanchez et al (2017) (Phase 1-baseline|Women)	BDI.1	–0.119	–0.558	0.320	0.646
Mahboobi et al (2022)	BDI.4	–0.018	–0.443	0.406	0.652
Sanchez et al (2017) (Phase 1-baseline|Men)	BDI	–0.101	–0.541	0.338	0.654
Hulkkonen et al (2021) (to late pregnancy)	EPDS.1	–0.090	–0.547	0.366	0.661
Hulkkonen et al (2021) (to 12 months postpartum)	EPDS.4	–0.059	–0.501	0.383	0.663

Note: BDI, Beck Depression Inventory; EPDS, Edinburgh Postnatal Depression Scale; DASS-21, Depression, Anxiety, and Stress Scale-21.

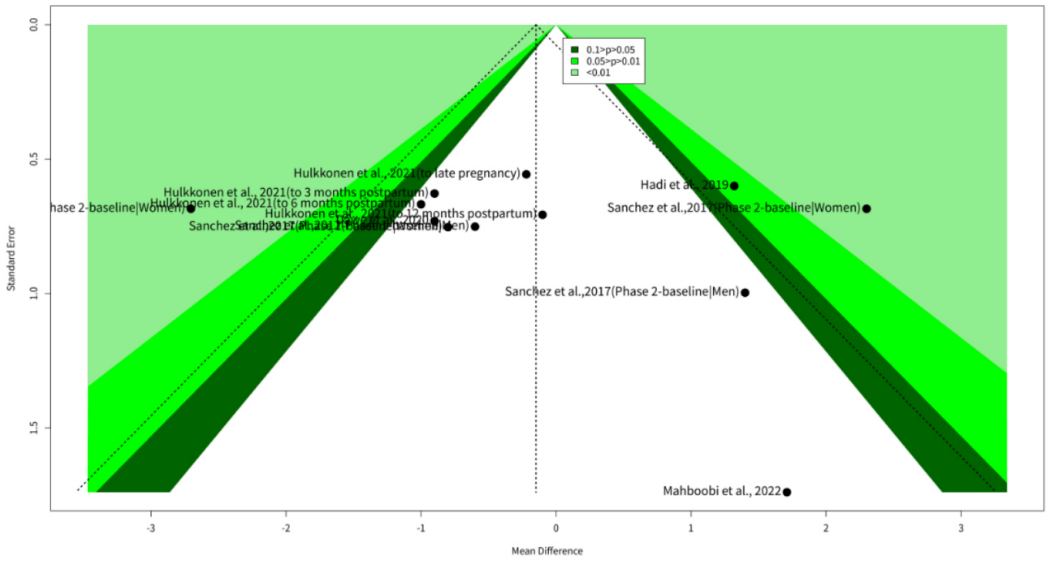

Fig. 6. Funnel plot with trim-and-fill method for the meta-analysis.

0.72). Thus, there was no significant difference in depressive symptoms between probiotic and placebo groups after adjusting for funnel plot asymmetry. The heterogeneity among the studies was still moderate to high (tau^2 = 1.413 [0.407–5.200]; tau = 1.1887 [0.6378–2.2804]; I^2 = 73% [53%–85%]; H = 1.94 [1.46–2.59]). The test of heterogeneity also confirmed that there was still significant heterogeneity among the studies (Q = 41.44, df = 11, $p < 0.001$).

Leave-One-Out Analysis

The leave-one-out analysis for the meta-analysis of probiotics on depressive symptoms in obese patients is shown in Table 3 (Sanchez et al, 2017; Hadi et al, 2019; Hulkkonen et al, 2021; Dawe et al, 2020; Mahboobi et al, 2022). The table

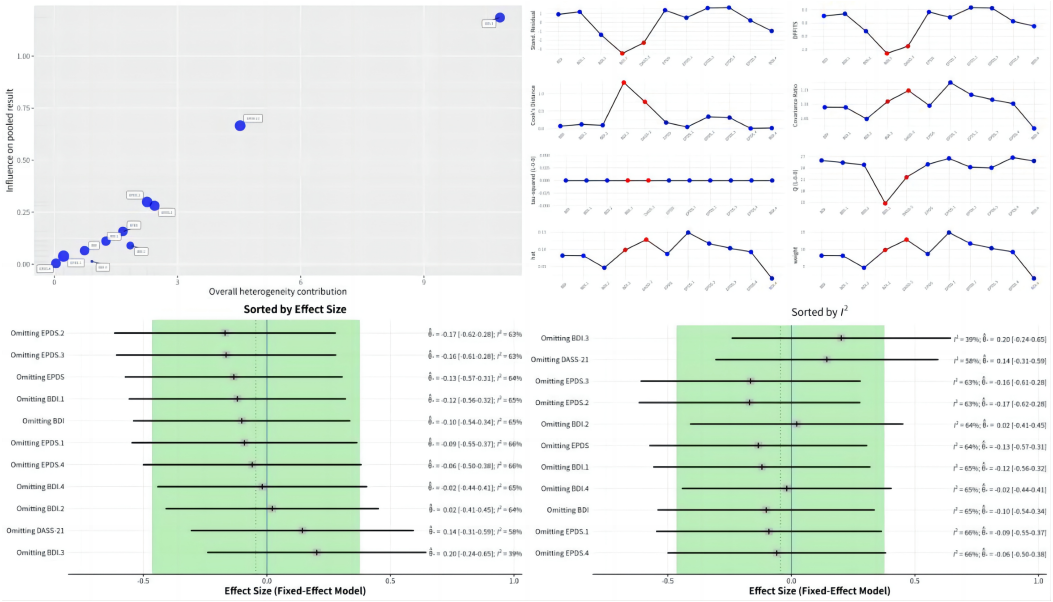

Fig. 7. Galbraith plot for the meta-analysis of probiotics on depressive symptoms in obese patients.

shows the effect size (MD) and 95% CI of each study, as well as the heterogeneity (I^2) of the meta-analysis after excluding each study. The table shows that Sanchez et al (2017) (Phase 2-baseline|Women) had the largest influence on the meta-analysis results, as it reduced the heterogeneity from 63% to 39% when excluded, and increased the pooled effect size from 0 to 0.202 when included. This study was also an outlier or an influential point in the previous analyses, such as the Baujat plot, the Galbraith plot, and the trim-and-fill method. This suggests that this study had a large positive effect size and a large residual, meaning that it had a high precision and a high deviation from the pooled effect size. The table also shows that Hadi et al (2019) and Hulkkonen et al (2021) (to 6 months postpartum) had moderate influences on the meta-analysis results, as they reduced the heterogeneity from 63% to 58% and 63% to 63%, respectively, when excluded, and increased or decreased the pooled effect size from 0 to 0.144 or –0.164, respectively, when included. These studies were also located above or below the upper horizontal line in the Galbraith plot, meaning that they had significant positive or negative effect sizes but moderate standardized residuals. The table also shows that Mahboobi et al (2022) had a small influence on the meta-analysis results, as it increased the heterogeneity from 63% to 65% when excluded, and decreased the pooled effect size from 0 to –0.018 when included. This study was also located outside the right vertical line in the Galbraith plot, meaning that it had a non-significant positive effect size but a large standardized residual (Fig. 7).

Influence Analysis

We also performed an influence analysis, which is shown in Table 4 (Sanchez et al, 2017; Hadi et al, 2019; Hulkkonen et al, 2021; Dawe et al, 2020; Mahboobi et al, 2022), to assess the impact of each study on the pooled effect size and heterogeneity.

Table 4. Influence analysis of the meta-analysis of effects of probiotics on depressive symptoms in obese patients.

Study	Labels	Rstudent	Dffits	Cook.d	Cov.r	Qe.del	Hat	Weight	Infl
Sanchez et al (2017) (Phase 1-baseline|Men)	BDI	0.895	0.267	0.071	1.089	25.976	0.082	8.182	
Sanchez et al (2017) (Phase 1-baseline|Women)	BDI.1	1.170	0.348	0.121	1.089	25.409	0.081	8.141	
Sanchez et al (2017) (Phase 2-baseline|Men)	BDI.2	–1.393	–0.307	0.095	1.049	24.836	0.046	4.645	
Sanchez et al (2017) (Phase 2-baseline|Women)	BDI.3	–3.470	–1.147	1.315	1.109	14.737	0.098	9.845	*
Hadi et al (2019)	DASS-21	–2.278	–0.874	0.764	1.147	21.586	0.128	12.829	*
Dawe et al (2020)	EPDS	1.352	0.416	0.173	1.095	24.948	0.086	8.650	
Hulkkonen et al (2021) (to late pregnancy)	EPDS.1	0.514	0.215	0.046	1.175	26.512	0.149	14.902	
Hulkkonen et al (2021) (to 3 months postpartum)	EPDS.2	1.600	0.583	0.339	1.133	24.217	0.117	11.705	
Hulkkonen et al (2021) (to 6 months postpartum)	EPDS.3	1.650	0.560	0.314	1.115	24.053	0.103	10.339	
Hulkkonen et al (2021) (to 12 months postpartum)	EPDS.4	0.214	0.068	0.005	1.102	26.731	0.092	9.235	
Mahboobi et al (2022)	BDI.4	–0.965	–0.12	0.014	1.016	25.845	0.015	1.526	

“infl = ”, a small impact on the meta-analysis.
“infl = *”, a significant impact on the meta-analysis.

The table shows that Sanchez et al (2017) (Phase 2-baseline|Women) had the largest impact on the meta-analysis results, as it had a large negative studentized residual (–3.47), a large negative DFFITS (–1.147), a large Cook's distance (1.315), and a large influence (infl = *). The table also shows that Hadi et al (2019) had a moderate impact on the meta-analysis results, as it had a large negative studentized residual (–2.278), a large negative DFFITS (–0.874), a large Cook's distance (0.764), and a large influence (infl = *). The table also shows that Mahboobi et al (2022) had a small impact on the meta-analysis results, as it had a small negative studentized residual (–0.965), a small negative DFFITS (–0.12), a small Cook's distance (0.014), and a negligible influence (infl =).

GOSH Diagnostics

We also performed GOSH diagnostics to assess the presence of outliers and clusters in the studies. The GOSH diagnostics is shown in Fig. 8. K-means detected three clusters of studies, which are shown as red circles, blue triangles, and green squares in Fig. 8A. K-means also detected two outliers, which are Sanchez et al (2017) (Phase 2-baseline|Women) and Hadi et al (2019).

DBSCAN detected five clusters of studies, which are shown as red circles, blue triangles, green squares, yellow diamonds, and purple stars in Fig. 8B. DBSCAN also detected three outliers, which are Sanchez et al (2017) (Phase 2-baseline|Women), Hadi et al (2019), and Sanchez et al (2017) (Phase 2-baseline|Men).

GMM detected six clusters of studies, which are shown as red circles, blue triangles, green squares, yellow diamonds, purple stars, and orange pentagons in Fig. 8C. GMM also detected three outliers, which are Sanchez et al (2017) (Phase 2-baseline|Women), Hadi et al (2019), and Sanchez et al (2017) (Phase 2-baseline|Men). These studies are shown as black crosses in Fig. 8C.

Subgroup Meta-Analysis by Scale Type

The results for the subgroups based on the scale type are shown in Fig. 9. The subgroup analysis showed that there was a significant difference in depressive symptoms between the probiotic and placebo groups for the EPDS subgroup (MD = –0.5993, 95% CI = –1.1680 to –0.0306, z = –2.05, $p = 0.04$), but not for the BDI subgroup (MD = 0.6883, 95% CI = –0.7345 to 2.1112, z = 0.66, $p = 0.51$) or the DASS-21 subgroup (MD = 1.32, 95% CI = 0.1443 to 2.4957, z = 2.19, $p = 0.03$). This means that probiotics had a beneficial effect on reducing depressive symptoms in obese patients measured by EPDS, but not by BDI or DASS-21.

The heterogeneity within the subgroups was low for the EPDS subgroup ($Tau^2 = 0$, Tau = 0, $I^2 = 0\%$, H = 1), moderate for the BDI subgroup ($tau^2 = 1.738$, tau = 1.3183, $I^2 = 70\%$, H = 1.84), and not applicable for the DASS-21 subgroup (only one study). The test of heterogeneity within the subgroups was not significant for the EPDS subgroup (Q = 1.72, df = 4, $p = 0.79$), but significant for the BDI subgroup (Q = 13.22, df = 4, $p = 0.01$). The heterogeneity between the subgroups was also moderate to high, as indicated by the tau^2 value of 0.865.

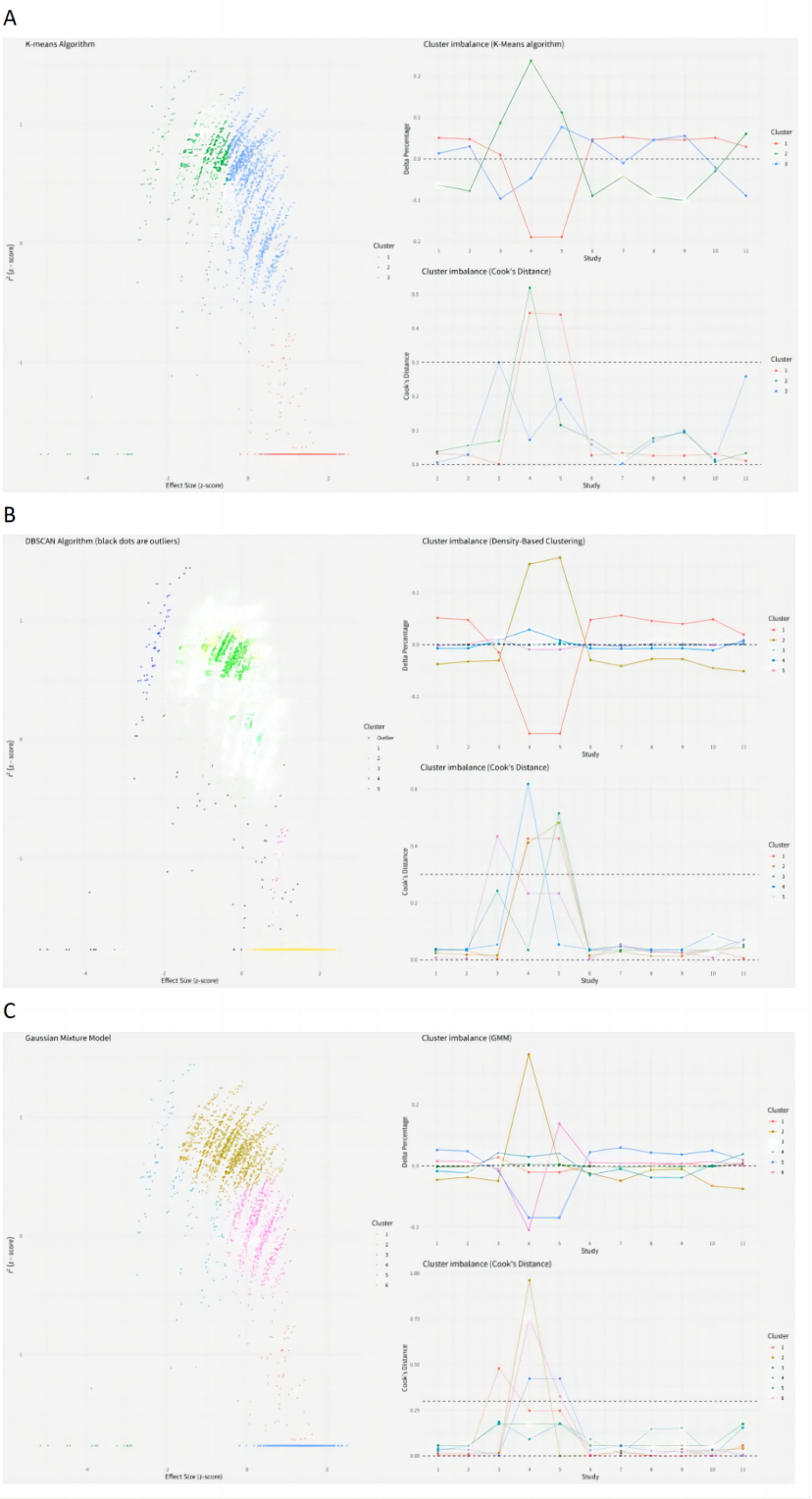

Fig. 8. Graphic display of study heterogeneity (GOSH) diagnostics for the meta-analysis. (A) K-means analysis. (B) Density-based spatial clustering of applications with noise algorithm (DBSCAN) analysis. (C) Gaussian Mixture Model (GMM) analysis.

Subgroup Meta-Analysis by Follow-Up Period

The results for the subgroups based on the follow-up period are shown in Fig. 10. The subgroup analysis showed that there was a significant difference in

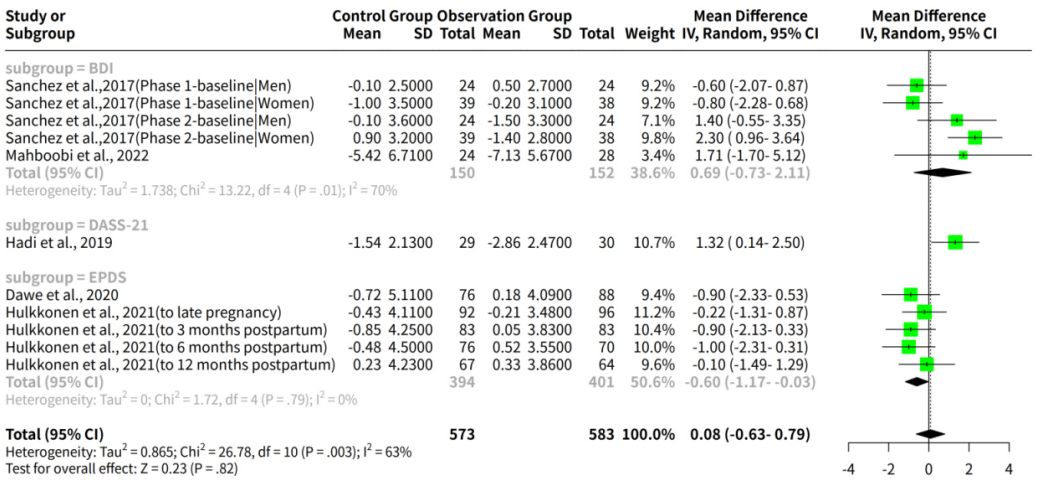

Fig. 9. Forest plot for the meta-analysis of effects of probiotics on depressive symptoms in obese patients by scale type.

depressive symptoms between the probiotic and placebo groups for the 12-week subgroup (MD = –0.7834, 95% CI = –1.5788 to –0.0120, z = –1.97, $p = 0.05$), but not for the other subgroups (24-week: MD = 0.8732, 95% CI = –1.2946 to 3.0410, z = 0.64, $p = 0.52$; less than 12-week: MD = 0.6619, 95% CI = –0.5865 to 1.9103, z = 1.05, $p = 0.29$; 36-week: MD = –0.9, 95% CI = –2.3318 to 0.5318 , z = –1.22 , $p = 0.22$; 48-week: MD = –0.1, 95% CI = –1.4857 to 1.2857, z = –0.08, $p = 0.94$). Thus, probiotics had a beneficial effect on reducing depressive symptoms in obese patients after a follow-up period of 12 weeks, but not after other follow-up periods.

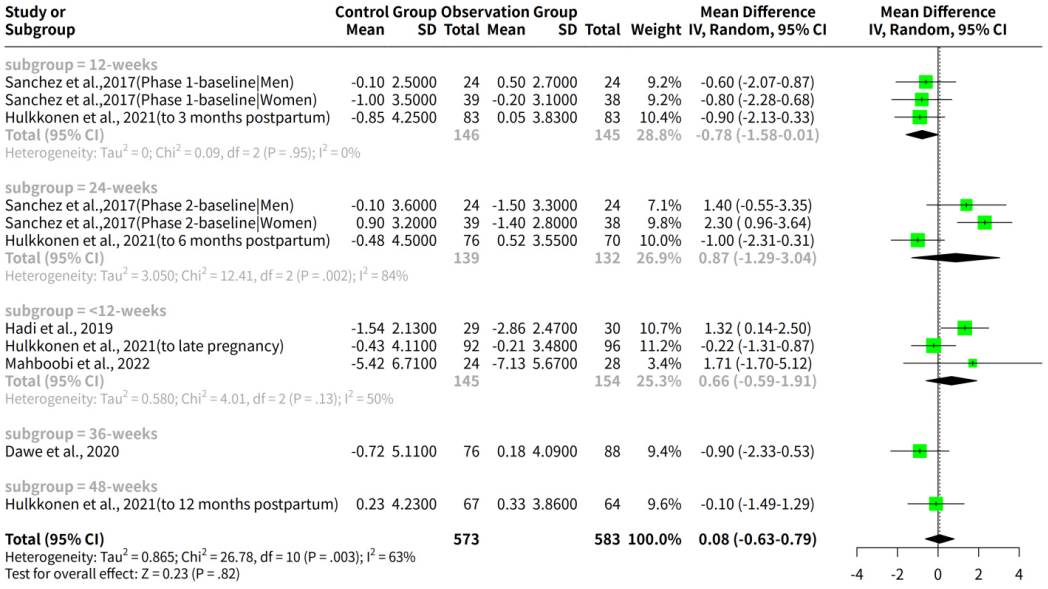

Fig. 10. Forest plot for the meta-analysis of effects of probiotics on depressive symptoms in obese patients by follow-up period.

The heterogeneity within the subgroups was low for the 12-week subgroup ($tau^2 = 0$, tau = 0, $I^2 = 0\%$, H = 1), high for the 24-week subgroup ($tau^2 = 3.050$,

tau = 1.7465, I^2 = 84%, H = 2.51), moderate for the less than 12-week subgroup (tau^2 = 0.580, tau = 0.7618, I^2 = 50%, H = 1.41), and not applicable for the 36-week and 48-week subgroups (only one study each). The test of heterogeneity within the subgroups was not significant for the 12-week and less than 12-week subgroups (Q = 0.09, df = 2, p = 0.96; Q = 4.01, df = 2, p = 0.13), but significant for the 24-week subgroup (Q = 12.41, df = 2, p = 0.002). The heterogeneity between the subgroups was also moderate to high, as indicated by the tau^2 value of 0.865.

Discussion

In this meta-analysis of 5 RCTs, we found no significant overall effect of probiotic supplementation on depressive symptoms in obese adults. The pooled MD in depression scores between probiotic and placebo groups was small and non-significant. Considerable heterogeneity was observed across the included studies.

Obesity and depression are global health issues, and behavioral intervention approaches have the potential to effectively manage these conditions. Motivational Interviewing (MI) is a widely utilized behavioral intervention method in the health field, aiming to modify unhealthy behaviors by enhancing motivation and willingness within individuals. There is a bidirectional relationship between obesity and major depressive disorder (MDD). Firstly, obesity may increase the risk of developing depression. The physical condition and weight issues associated with obesity can lead to decreased self-esteem, social isolation, dissatisfaction with body image, and ultimately increase the likelihood of developing depression. A previous meta-analysis revealed a noteworthy positive correlation between obesity and the development of major depressive disorder (MDD) in prospective studies. However, the presence of heterogeneity and inadequate reporting of weight-related variables hindered the calculation of weight changes (Crider et al, 2022). Secondly, depression can contribute to the occurrence and exacerbation of obesity. Symptoms of depression often include emotional instability, changes in appetite, and reduced energy expenditure. These factors can lead to disrupted eating behaviors, decreased physical activity, and ultimately result in weight gain and obesity. Traditional treatment for depression primarily relies on interpersonal psychotherapy (Crider et al, 2022). Furthermore, obesity and depression may also influence each other through shared biological and physiological mechanisms. Factors such as abnormalities in the neuroendocrine system, increased inflammatory response, and changes in brain chemistry may play a role in the development of both obesity and depression. Research suggests that patients whose obesity is accompanied by depression may have impaired neuronal synaptic plasticity, leading to impaired emotion regulation and dysregulated appetite control (Lv et al, 2022). It is important to note that the relationship between obesity and depression is complex and individual differences exist. Not all individuals with obesity will experience symptoms of depression, and not all individuals with depression will develop obesity (Peng et al, 2022).

In the present study, subgroup analyses indicated beneficial effects of probiotics in specific populations. Probiotic supplementation significantly reduced depressive symptoms measured by the EPDS scale in obese patients. The EPDS is

designed to screen postpartum depression, suggesting that probiotics may improve mood in postpartum women with obesity.

Additionally, probiotics alleviated depressive symptoms after 12 weeks of supplementation. Short-term interventions may be optimal for observing probiotics' central effects. In a meta-analysis by Ng et al (2018), antidepressant benefits of probiotics were significant at 8 weeks but not at later timepoints (El Dib et al, 2021). Transient changes in gut microbiota and their metabolites may mediate probiotics' acute psychological effects (Michalopoulou et al, 2022).

Probiotics failed to improve depression measured by the BDI or DASS-21 scales. Differences in the psychological constructs assessed by various scales may account for the divergent effects. The underlying mechanisms relating gut dysbiosis to depression also remain unclear. Several pathways have been proposed, including microbial regulation of inflammatory cytokines, vagus nerve signaling, tryptophan metabolism, and production of neuroactive compounds (Purgato et al, 2018).

There are some limitations of this study. Although we observed some positive effects, we also acknowledge that there is a need for more clinical trials to elucidate the therapeutic effects of probiotics on obesity-related depression. More research is warranted to elucidate the role of gut-brain interactions in neuropsychiatric conditions like depression. Larger, longer RCTs stratifying participants by depression severity and adiposity phenotypes are needed. Future studies should also collect fecal samples for microbiome analyses and examine blood biomarkers associated with depression pathophysiology.

Conclusion

Overall, this meta-analysis does not support probiotic supplementation as an effective strategy for reducing depressive symptoms in obese populations. Additional well-designed RCTs are warranted to determine the therapeutic utility of modulating gut microbiota in obesity-related depression.

Key Points

- The intestinal flora has a positive effect on obese patients with depression.
- The intestinal flora of obese individuals enhances the body's capacity to extract energy from the diet.
- Probiotic supplementation improves weight management and depressive symptoms in individuals with obesity and comorbid depression.

Availability of Data and Materials

The datasets used and/or analyzed during the current study were available from the corresponding author on reasonable request.

Author Contributions

LC and JHZ designed the study. All authors conducted the study. TX, LWX and CLY collected and analyzed the data. LC and TX participated in drafting the manuscript, and all authors contributed to critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors participated fully in the work, take public responsibility for appropriate portions of the content, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0161.

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