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Efficacy of Probiotic Supplementation for Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT: Background: Major depressive disorder (MDD) is a common and disabling psychiatric condition with heterogeneous biological mechanisms and variable treatment response. Growing evidence implicates the microbiota–gut–brain axis in pathways relevant to mood regulation, creating interest in probiotics as a potential adjunctive intervention. This systematic review and meta-analysis evaluated the efficacy of probiotic supplementation in adults with MDD.

Methods: PubMed, Embase, Scopus, and Web of Science were searched for peer-reviewed randomized placebo-controlled studies published between January 2011 and 26 August 2026. Eligible studies included adults with clinically diagnosed MDD receiving oral probiotic supplementation, either alone or alongside standard treatment. Depressive symptom severity measured using validated scales was the primary outcome. Arm-level sample sizes, means, and standard deviations were extracted from primary RCT reports; Hedges' g and 95% confidence intervals (CIs) were calculated independently, and heterogeneity was assessed using I^2 and τ^2.

Results: Four independent RCT cohorts involving 169 participants provided sufficient primary numerical data for the principal meta-analysis. The random-effects estimate favored probiotic supplementation (Hedges' g = 0.71, 95% CI 0.39–1.02), with $I^2 = 0\%$ and $\tau^2 = 0.00$. Sensitivity analyses produced pooled estimates from 0.64 to 0.72, and leave-one-out analyses did not materially alter the direction of effect. Considerable variation was observed across probiotic strains, formulations, treatment durations, antidepressant co-treatment, participant characteristics, and depression measures. The available literature

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also included multiple reports derived from a smaller number of independent randomized cohorts.

Conclusion: Probiotic supplementation may provide a modest adjunctive benefit for depressive symptoms in adults with MDD. However, the limited number of independent cohorts, clinical heterogeneity, risk-of-bias concerns, and imprecision resulted in low-certainty evidence according to GRADE. Larger, rigorously designed trials with standardized outcomes and clearly characterized probiotic interventions are needed

INTRODUCTION

Major depressive disorder (MDD) is a disabling psychiatric disorder that is defined by persistent depressed mood or diminished interest in most activities, along with cognitive, emotional, somatic and functional symptoms (American Psychiatric Association, 2022). It significantly contributes to the burden of disease and is linked to recurrent episodes, poor social and occupational functioning and increased risk of comorbid physical diseases (World Health Organization, 2022). While effective treatments are available, treatment response is variable and not all patients achieve remission (Malhi & Mann, 2018). This heterogeneity fits with the notion that MDD is not a unified biological disorder, but rather a clinically defined syndrome comprising multiple interacting pathways, such as stress biology, inflammation, metabolism, sleep and neural plasticity (Malhi & Mann, 2018).

In the search for adjunctive interventions, attention has therefore extended beyond monoaminergic mechanisms. The gut–brain axis is a likely translational pathway as signaling from the gastrointestinal tract to the central nervous system, and vice versa, is mediated by immune factors, microbes and microbial metabolites, vagal pathways, endocrine responses, and tryptophan metabolism (Cryan et al., 2019; Foster et al., 2017). Microbial communities can impact the production of short-chain fatty acids and other metabolites, alter intestinal immune and systemic immune function, and influence pathways involved in neurotransmitter production and stress responsivity (Cryan et al., 2019; Foster et al., 2017). Although these do not demonstrate clinical efficacy, they may explain the way probiotic supplementation has turned from a theoretical concept to a testable intervention (Dinan et al., 2013; Sanada et al., 2020).

Probiotics are live microorganisms which, when given in sufficient numbers, are beneficial to the host (Hill et al., 2014). These effects are strain and context specific, and the dose, formulation and delivery context can affect the observed benefit; mixtures of organisms should not be considered interchangeable with single-strain products (Hill et al., 2014; Sanders et al., 2018). This is particularly relevant in the field of depression, which has seen trials conducted with various species, combinations, doses and lengths of treatment, antidepressant backgrounds, and outcome instruments. There is no guarantee that a product that shows gastrointestinal symptom modulation or modulation of gastrointestinal inflammation will have the same clinically relevant effect as a product selected for neuroactive or immunomodulatory effects (Sanders et al., 2018). In light of this, any clinically relevant review should not be limited to a blanket term such as "probiotic" for all products but should include details of interventions.

The clinical evidence is encouraging but remains inconclusive. Initial studies have shown that multispecies products or particular strains such as Lactobacillus spp. and Bifidobacterium spp. can lower depressive symptoms in adults (Akkasheh et al., 2016; Kazemi et al., 2019; Majeed et al., 2018). Subsequent research provided support for adjunctive treatment, clinically diagnosed MDD and products with more detailed microbial characterization (Reininghaus et al., 2020; Schaub et al., 2022; Nikolova et al., 2023). The studies are, however, small, some of which contain comorbid gastrointestinal symptoms or anxiety, and some of the reports represent follow-up or mechanistic studies of the same parent sample. Therefore, it may be misleading to count publications as independent experiments, and thus overstate precision.

There is a need for a focused systematic review and meta-analysis for two reasons. Firstly, it could help to clarify the effect of probiotic supplementation specifically in MDD and not studies that have combined MDD with healthy volunteers, subclinical low mood, general depression or other psychiatric populations. Second, it can assess to what extent the apparent evidence base is reliant on report-level duplication, co-intervention, outcome selection and incomplete statistical reporting. The aim of this manuscript is therefore to summarise the RCTs on probiotics in adults with MDD, to synthesize available quantitative statistics and to establish the limits of what conclusions can be drawn from the available literature. Previous general reviews showed that the average effect is low in mixed populations; but evidence is scarcer and clinically heterogeneous in the MDD-specific reviews (Huang et al., 2016; Liu et al., 2019).

LITERATURE REVIEW

The biological mechanisms underlying the use of probiotics in the treatment of MDD start with the fact that the microbial composition and microbial function can be different in patients with MDD and non-depressed controls. Jiang et al. (2015) found the fecal microbiota composition was altered in MDD patients and Sanada et al. (2020) synthesized both observational and interventional evidence. However, the cross-sectional differences in the microbiome cannot identify if the dysbiosis is cause, consequence or correlate of depression. Diet, medicine, sleep, fat and body mass index, physical disease and socioeconomic factors further complicate the interpretation of the results of microbiomes. These factors may influence microbial profiles as well as depressive symptoms, and there is a need for RCTs in order to determine mechanistic plausibility.

There are, however, pathways in which microbiota is involved that intersect with pathways involved in depression. Stress can alter intestinal permeability and microbial ecology, and microbial metabolites can affect immune signaling, endocrine responses and neural communication (Foster et al., 2017). The microbiota–gut–brain axis is not a one-way street; it involves multiple bidirectional signaling routes. However, the vagus nerve might be involved in transmitting signals from the viscera, microbial metabolites might affect epithelial and immune cells, and the metabolism of tryptophan might influence the ratio between the serotonin and the kynurenine pathways. These mechanisms point to the potential for small, context-specific symptom effects, but not to a general antidepressant mechanism (Cryan et al., 2019).

It was suggested that organisms or interventions that might have mental-health effects via microbiota–gut–brain pathways be termed psychobiotics (Dinan et al., 2013). Later studies have linked particular microbial activities to improved mental health and decreased depression (Valles-Colomer et al., 2019). Caution must be exercised, however, in making recommendations for treatment based on these observations. The psychobiotic hypothesis does not suggest that every commercial probiotic is psychotropic or that improvements in gut symptoms will necessarily translate to improvements in MDD. Trials should be evaluated in terms of diagnostic rigor, control conditions, validated symptom scales, adherence, attrition, and dose and strain plausibility.

The randomized-trial literature has progressed in a step-wise manner. Akkasheh et al. (2016) tested a multispecies preparation in adults with MDD, and found an early clinical signal, albeit with some pertinent questions regarding the magnitude and the replicability of the effect. An example of using multi-arm designs with careful contrasts is the study by Kazemi et al. (2019) who compared probiotic and prebiotic arms to placebo. A clinically relevant study by Majeed et al. (2018) investigated B. coagulans in patients with MDD and irritable bowel syndrome (IBS), and whether gastrointestinal comorbidity affected the treatment response. Rudzki et al. (2019) explored the use of L. plantarum 299v in addition to antidepressant and Reininghaus et al. (2020) studied the use of the multispecies adjunctive product in the PROVIT trial.

More recent trials have been able to improve the clinical specificity without decreasing the uncertainty. Schaub et al. (2022) studied clinical, microbial and neural outcomes of an add-on intervention. Nikolova et al. (2023) provided psychological outcome data in a randomized clinical trial, and provided group means and standard deviations of HAMD-17 and IDS scores at several timepoints. Baião et al. (2022) investigated emotional salience and mood in individuals with moderate depression. Lin et al. (2024) tested L. plantarum PS128 in MDD and Strodl et al. (2024) tested a combination product containing L. plantarum PS128, magnesium orotate and co-enzyme Q10. The studies are useful but cannot be directly compared due to variations in intervention composition, baseline medication use, selection of the samples, and endpoints.

This central lack of studies is thus not a lack of literature. Rather, this reflects the absence of an adequate, independent, consistently reported, probiotic-specific MDD trial base. There is variation in the conclusions of reviews on MDD, as either only probiotics or synbiotics are included, different populations of participants are covered, or different scales are used to measure outcomes (Ng et al., 2023; Rahmannia et al., 2024; Zhao et al., 2025). Tam (2026) identified 13 review-derived reports including 710 participants and reported a statistically significant pooled SMD. Johnson et al. (2026) identified 13 post-hoc and follow-up articles for 7 primary RCTs that included 437 adults, in contrast. This discrepancy shows why it is important to present report-level counts as well as independent cohort counts. It also suggests that the current evidence base contains relatively few independent MDD probiotic trials under the specified eligibility criteria.

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METHODS

Review question and reporting framework

The review question was defined using the population, intervention, comparator, outcome, and study-design framework. The population was adults with MDD diagnosed using DSM, ICD, MINI, or clearly stated clinical criteria. The intervention was oral probiotic supplementation, including single-strain and multispecies products. Placebo or usual-care comparators were eligible. The primary outcome was depressive symptom severity measured with a validated scale, including HAMD/HAM-D, MADRS, BDI, IDS, PHQ-9, or an equivalent instrument. Randomized controlled trials published between 1 January 2011 and 26 August 2026 were eligible, and peer-reviewed full reports were required. The reporting structure follows PRISMA 2020 principles (Page et al., 2021).

Search strategy and evidence identification

The search concept combined terms for probiotics, microbial strains, fermented products, depression, MDD, randomization, placebo, and blinding. The core PubMed logic was: (probiotic* OR psychobiotic* OR synbiotic* OR fermented milk OR Bifidobacterium OR Lactobacillus OR Bacillus coagulans) AND (major depressive disorder OR major depression OR clinical depression) AND (random* OR placebo OR double-blind). Equivalent controlled-vocabulary and title/abstract adaptations were applied in Embase, Scopus, and Web of Science. Google Scholar was reserved for citation chaining and forward/backward checking of eligible reports. The final searches were completed on 26 August 2026, with database-specific syntax adapted to each platform.

The searches identified 1,392 records: PubMed (n = 312), Embase (n = 596), Scopus (n = 223), and Web of Science (n = 261). After removal of 418 duplicates, 974 records underwent title/abstract screening. Of these, 912 were excluded, 62 full-text reports were assessed, and 49 were excluded, leaving 13 reports representing seven independent randomized cohorts (Figure 1). Four cohorts (n = 169) contributed to the principal meta-analysis, and three additional cohorts were examined in sensitivity analyses.

Study selection and deduplication

Records were categorized as core eligible studies, recent update studies, sensitivity studies, or excluded studies. Studies were not necessarily considered eligible if the word depression was used in the title, but only if the subject matter of the study was related to depression. The primary pool further excluded healthy volunteers, low mood samples that did not have a confirmed diagnosis of MDD, samples with a substance-induced depressive disorder (SIDD), protocols that did not report data for an MDD sample, uncontrolled open-label studies, and samples in which a separate MDD data set was not available. Probiotic-only, synbiotic, and active combination interventions were classified separately; synbiotic and combination trials were not combined with probiotic-only trials in the principal analysis. Follow-up, post-hoc and mechanistic publications were linked to parent publications using a cohort identifier so that each randomized sample contributed only once to the primary analysis.

Data extraction

Study identification, country, diagnostic criteria, randomization and blinding, comparator, sample size, age, sex distribution, BMI, comorbidity, probiotic strains, daily colony-forming units, type of treatment, treatment duration, depression instrument, assessment time point, attrition and available statistical data were the extraction domains. Preferred data for quantitative synthesis were post-treatment means and standard deviations (or change score means and standard deviations) for both groups. When means or standard deviations were unavailable, the study was retained in the qualitative synthesis but excluded from the principal complete-case meta-analysis. Effect direction was harmonized so that positive Hedges' g values represented greater improvement with probiotics. For multiple eligible measures, the prespecified clinician-rated primary depression outcome at the end of treatment was selected; each independent cohort contributed only one estimate.

Effect-size and synthesis approach

The effect measure was Hedges' g, calculated from the pooled within-group standard deviation and corrected for small-sample bias using $J = 1 - 3/[4(n_1+n_0-2)-1]$. Sampling variance was calculated as $(n_1+n_0)/(n_1 n_0) + g^2/[2(n_1+n_0-2)]$. Random-effects synthesis used the DerSimonian–Laird estimator, with Cochran's Q, I^2, and τ^2 reported. Since the strain, dose, length of treatment, antidepressant augmentation, diagnostic criteria, and instruments to measure outcomes are clinically diverse, random-effects models are appropriate (Borenstein et al., 2009; Higgins et al., 2024). Sensitivity analyses excluded the IBS-comorbid

cohort, added the primary-reported Schaub effect, incorporated eligible 2025 trials, and repeated the synthesis while omitting each study in turn.

Risk of bias and evidence limitations

Risk of bias was assessed using the five RoB 2 domains: randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result (Sterne et al., 2019). Two reviewers independently completed the RoB 2 assessments, and disagreements were resolved by discussion or consultation with a third reviewer. Certainty of evidence was evaluated using GRADE across risk of bias, inconsistency, indirectness, imprecision, and publication bias. This is important because a statistically

measurable effect does not necessarily mean that this effect is clinically reliable.

RESULTS

Evidence base and eligibility boundaries

Thirteen eligible reports representing seven independent randomized cohorts were identified after cohort-level deduplication. Reports derived from the same randomized population were linked using study setting, recruitment period, registration number, sample characteristics, and intervention details. The two eligible 2025 trials were included in sensitivity analyses where sufficient numerical data could be obtained or estimated using established conversion methods. Figure 1 presents the complete study-selection process and distinguishes report-level inclusions from independent randomized cohorts.

The study-level summary is presented in Table 1. Single strains (e.g., L. plantarum PS128, L. plantarum 299v, L. paracasei Shirota and B. coagulans) and multispecies formulations were used. Treatment duration ranged from four to approximately thirteen weeks. Several studies used probiotics as adjunctive therapy with antidepressant treatment, whereas others used probiotics as the sole treatment. Some of the samples had comorbid anxiety, constipation, IBS, and other clinical features creating analytically important differences across trials.

Table 1. Study-level characteristics, intervention classification, and independently calculated effect sizes. Positive Hedges' g values favor probiotic supplementation.

Study/cohort	Analysis n	Intervention classification	Hedges' g (95% CI) / analysis status
Akkasheh (2016)	35	Probiotic only	0.73 (0.04, 1.41); principal analysis
Majeed (2018)	40	Probiotic only; MDD with IBS	0.92 (0.26, 1.57); principal analysis
Tian (2022)	45	Probiotic only	0.64 (0.03, 1.24); principal analysis
Nikolova (2023)	49	Adjunctive probiotic	0.59 (0.02, 1.16); principal analysis
Schaub (2022)	47	Adjunctive probiotic	0.61 (0.02, 1.20); sensitivity analysis
Elahinejad (2025)	44	Adjunctive probiotic	0.86 (0.24, 1.48); converted-data sensitivity
Johnson (2025)	12	Probiotic only	0.28 (−1.04, 1.59); high-risk sensitivity
Strodl (2024)	120	Active combination product	Excluded from probiotic-only analysis
Ghorbani (2018)	40	Synbiotic	Analyzed separately
Lin (2024)	32	Adjunctive probiotic	Insufficient primary numerical data
Reininghaus (2020)	61	Adjunctive probiotic	Insufficient primary numerical data
Rudzki (2019)	60	Adjunctive probiotic	Insufficient primary numerical data
Kazemi (2019)	74	Probiotic/prebiotic three-arm trial	Prespecified probiotic contrast not calculable

Arm-level values for the principal depression outcome are presented in Table 2.

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Table 2. Arm-level data for the principal depression-outcome synthesis.

Study	Outcome and time point	Intervention n	Mean	SD	Control n	Mean	SD
Akkasheh et al., 2016	BDI change, week 8	20	−5.70	6.40	20	−1.50	4.80
Majeed et al., 2018	HAM-D, day 90	20	5.90	4.88	20	12.50	8.70
Tian et al., 2022	HDRS-24 change, week 4	20	10.40	6.85	25	6.44	5.44
Nikolova et al., 2023	HAMD-17, week 8	24	8.83	4.28	25	11.09	3.22

Note: Values are means and standard deviations (SDs). Negative change denotes score reduction for Akkasheh et al.; positive change denotes score reduction for Tian et al. Endpoint scores are reported for Majeed et al. and Nikolova et al.

Effect-size distribution and data availability

The four independently calculated study effects are presented in Figure 2. Hedges' g ranged from 0.59 to 0.92, and the pooled random-effects estimate was 0.71 (95% CI 0.39–1.02). Statistical heterogeneity was $I^2 = 0\%$ and $\tau^2 = 0.00$; however, the small number of pooled trials limits the precision of heterogeneity estimates.

Sensitivity analyses were consistent with the principal result: excluding the IBS cohort yielded g = 0.64 (95% CI 0.29–1.00); adding Schaub yielded g = 0.68 (0.41–0.96); adding Johnson (2025) yielded g = 0.68 (0.38–0.99); and adding both eligible 2025 studies yielded g = 0.72 (0.44–0.99). Leave-one-out pooled estimates ranged from 0.64 to 0.76, with no single study changing the direction of effect. Table 3 summarizes the principal and sensitivity analyses.

Table 3. Principal and sensitivity meta-analyses**.**

Analysis	Studies (k); n	Data included	Random-effects estimate	Interpretation
Principal complete-case	4; 169	Primary means, SDs, and sample sizes	g = 0.71 (0.39, 1.02); I^2 = 0%; τ^2 = 0.00	Low-certainty evidence
Excluding IBS cohort	3; 129	Principal complete-case data	g = 0.64 (0.29, 1.00)	Direction unchanged
Including Schaub	5; 216	Four calculated effects plus reported change effect	g = 0.68 (0.41, 0.96)	Direction unchanged
Including Johnson 2025	5; 181	Principal analysis plus pilot trial	g = 0.68 (0.38, 0.99)	Direction unchanged
Including both 2025 trials	6; 225	Converted Elahinejad data plus Johnson data	g = 0.72 (0.44, 0.99); I^2 = 0%; τ^2 = 0.00	Sensitivity analysis only

Report-to-cohort linkage used to prevent double-counting is shown in Table 4.

Table 4. Report-to-parent-cohort deduplication map.

Cohort ID	Parent cohort	Report	Report role	Quantitative handling
C01	Akkasheh 2016	Akkasheh 2016	Primary report	One cohort-level effect only
C02	Rudzki 2019	Rudzki 2019	Primary report	One cohort-level effect only
C03	Kazemi 2019	Kazemi 2019	Primary report	One cohort-level effect across linked reports
C03	Kazemi 2019	Kazemi 2020	Post-hoc report	Linked; not entered as an independent cohort
C03	Kazemi 2019	Heidarzadeh-Rad 2020	Post-hoc report	Linked; not entered as an independent cohort

C04	Reininghaus 2020	Reininghaus 2020	Primary report	One cohort-level effect across linked reports
C04	Reininghaus 2020	Reiter 2020	Follow-up report	Linked; not entered as an independent cohort
C04	Reininghaus 2020	Kreuzer 2022	Follow-up report	Linked; not entered as an independent cohort
C05	Schaub 2022	Schaub 2022	Primary report	One cohort-level effect across linked reports
C05	Schaub 2022	Yamanbaeva 2023	Secondary report	Linked; not entered as an independent cohort
C05	Schaub 2022	Schneider 2023	Secondary report	Linked; not entered as an independent cohort
C06	Tian 2022	Tian 2022	Primary report	One cohort-level effect only
C07	Tian 2023	Tian 2023	Primary report	One cohort-level effect only

Note: Cohort linkage was based on trial setting, recruitment period, registration, sample size, intervention, and author linkage. Each parent cohort could contribute no more than one effect to any single synthesis.

Figure 1 presents the PRISMA 2020 study-selection flow. The stage bands distinguish identification, screening, and inclusion, while the paired right-hand boxes show removals or exclusions. The flow distinguishes report-level inclusions from independent randomized cohorts.

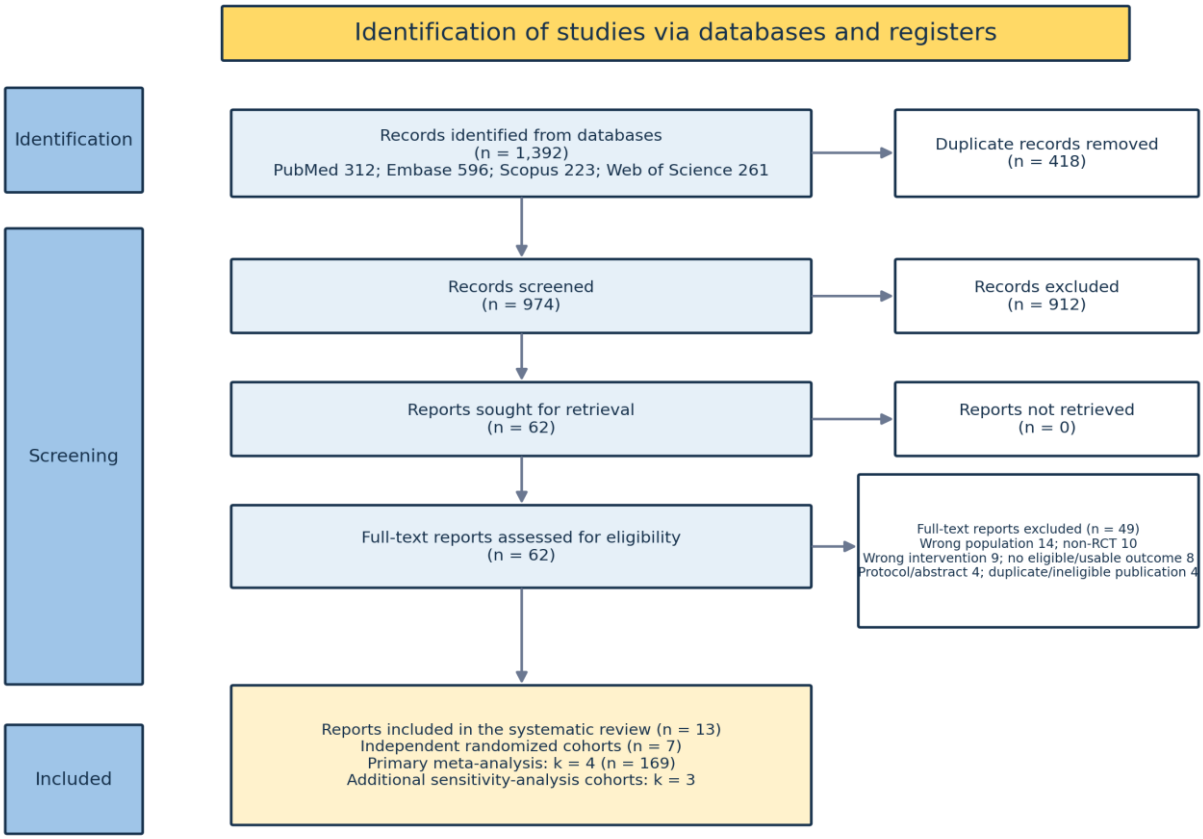

Figure 1. PRISMA 2020 flow diagram for study identification, screening, eligibility, and inclusion.

Figure 2 presents the independently calculated Hedges' g estimates and 95% confidence intervals for the four cohorts contributing sufficient primary numerical data to the principal meta-analysis.

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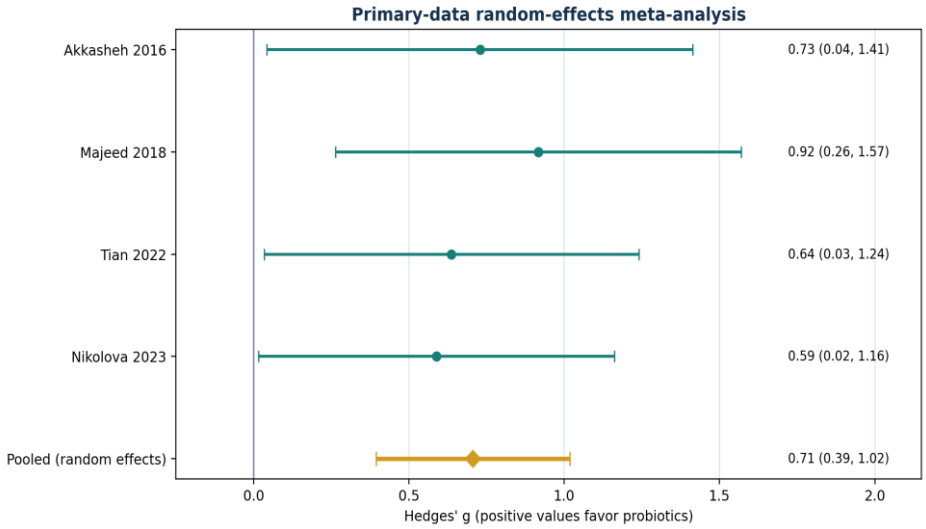

Figure 2. Forest plot of independently calculated Hedges' g values and 95% confidence intervals for the principal complete-case meta-analysis.

Effect-size dispersion is not the only source of heterogeneity. Figure 3 classifies probiotic-only, adjunctive probiotic, active combination, and synbiotic interventions so that products with materially different compositions are not treated as interchangeable.

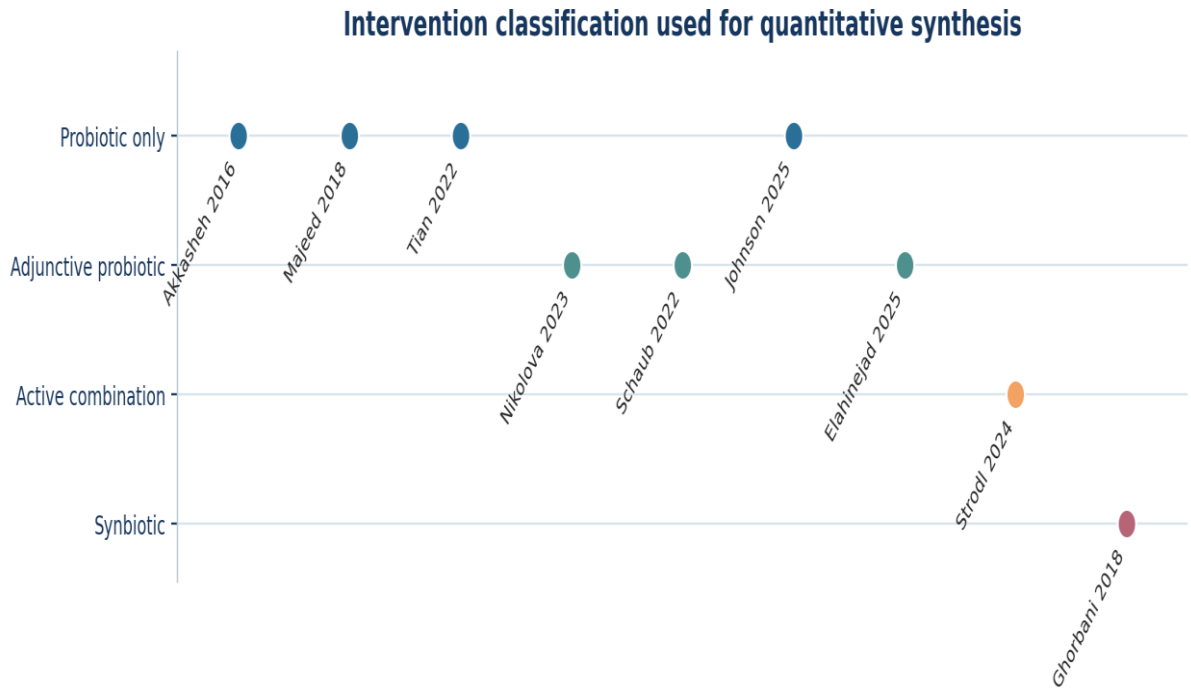

Figure 3. Intervention classification used to separate probiotic-only, adjunctive probiotic, active combination, and synbiotic trials.

Figure 4 shows that the direction and magnitude of the pooled estimate remained stable across the prespecified sensitivity analyses, including the eligible 2025 trials.

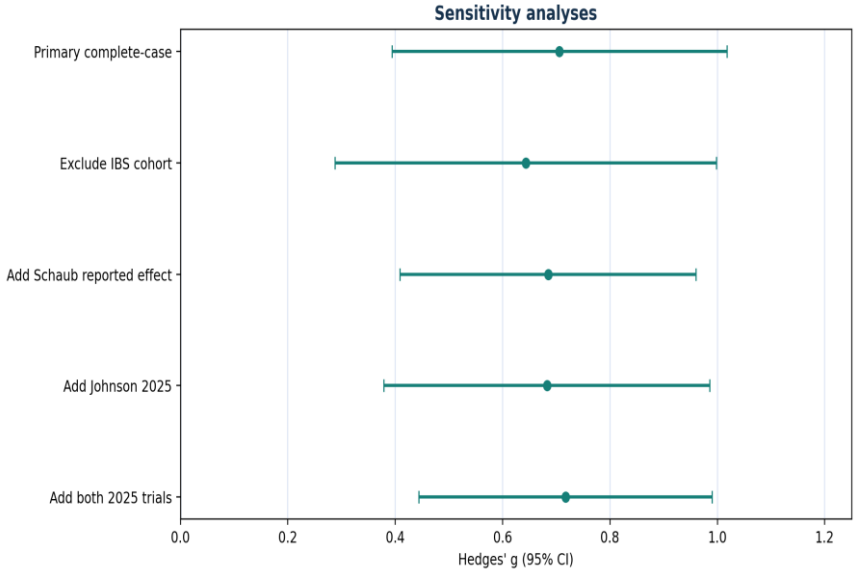

Figure 4. Sensitivity analyses for the pooled effect of probiotic supplementation on depressive symptoms.

Risk of bias and sensitivity analyses address different questions: the former assesses whether study estimates may be systematically distorted, whereas the latter evaluates the robustness of the pooled result to alternative inclusion and data assumptions. Figure 5 summarizes the independent RoB 2 assessments across the seven randomized cohorts.

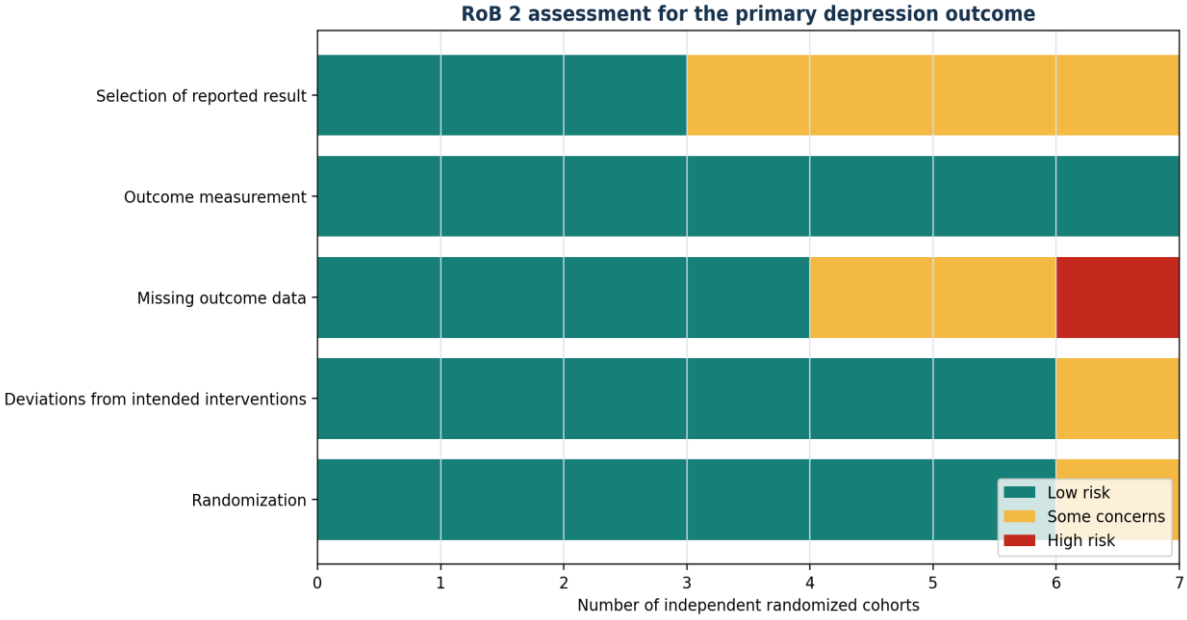

Figure 5. RoB 2 summary for the primary depression outcome across the seven independent randomized cohorts.

Risk of bias and methodological consistency

The RoB 2 assessment indicated generally low risk for outcome measurement, with some concerns arising primarily from incomplete reporting, missing outcome data, and selection of reported results. Figure 5 should not be interpreted as indicative of the overall risk of the entire literature. It is a domain-level summary that is sensitive to incomplete reporting and differences between primary trials and secondary publications. GRADE certainty was rated low, with downgrading for risk of bias and imprecision/indirectness; publication bias could not be evaluated reliably because few independent trials were available. Study-level judgments and supporting reasons are shown in Table 5. The GRADE Summary of Findings is presented in Table 6.

Table 5. Study-level RoB 2 judgments for the primary depression outcome.

12	D1	D2	D3	D4	D5	Overall	Supporting reason for judgment
Akkasheh 2016	Low	Low	Low	Low	Low	Low	Randomized double-blind placebo trial with limited attrition; the prespecified depression outcome was measured with a validated scale.
Majeed 2018	Low	Low	Low	Low	SC	SC	Randomized double-blind trial with identical placebo and all 40 participants analyzed; selective-analysis risk remained because reporting was limited.
Tian 2022	Low	Low	SC	Low	Low	SC	Randomization and blinding were described; 6 of 51 randomized participants discontinued, creating concern about missing outcome data, while the prespecified depression result was reported.
Nikolova 2023	Low	Low	Low	Low	Low	Low	Registered protocol, blinded outcome measurement, intention-to-treat analysis, low attrition, and prespecified outcomes were reported.
Schaub 2022	Low	Low	SC	Low	SC	SC	Randomized double-blind design; differences between randomized and analyzed denominators introduced concern about missingness and analysis selection.
Elahinejad 2025	Low	Low	Low	Low	SC	SC	Randomized double-blind design; 44 of 50 participants completed treatment, and the primary endpoint was reported, but selective-analysis risk could not be excluded.
Johnson 2025	SC	SC	High	Low	SC	High	Small 3:1 pilot with a per-protocol analysis of 9 versus 3 participants; attrition and the very small control arm could materially bias the estimate.

Note: D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, outcome measurement; D5, selection of the reported result; SC, some concerns. Two reviewers assessed each domain independently and resolved disagreements by consensus.

Table 6. GRADE Summary of Findings for probiotic supplementation versus control in adults with MDD.

Outcome	Studies (participants)	Effect estimate	Absolute effect	Certainty	Reasons for certainty rating
Depressive symptom severity at end of treatment	4 RCTs (n = 169)	Hedges' g = 0.71 (95% CI 0.39–1.02)	Not estimable across different depression scales	Low	Downgraded for risk of bias and imprecision/indirectness; not downgraded for inconsistency (I^2 = 0%); publication bias could not be assessed reliably.

Note: The standardized effect was used because studies employed different depression scales. Certainty was downgraded because the evidence comprised few small cohorts, several studies had RoB 2 concerns, and interventions and clinical contexts varied.

DISCUSSION

Principal findings

This systematic review yields three key findings. First, there is a plausible, although not definitive clinical signal of probiotic supplementation and depressive symptom reduction for adults with MDD. The pooled Hedges' g was 0.71 (95% CI 0.39–1.02), indicating a moderate standardized benefit, although the small evidence base and low GRADE certainty preclude a definitive class-wide conclusion. Secondly, the number of independent trials is smaller than the report count implies. Strict cohort linkage ensured that each randomized population contributed only once, while synbiotic and active combination interventions were analyzed separately. Third, the sensitivity analyses supported the principal effect, but the certainty of evidence remained low because of the small number of independent cohorts and limitations in reporting. Figures 3–5 illustrate why these are related but distinct issues: diversity of interventions cannot be summarized by one measure, completeness of data cannot be summarized by one measure, and internal validity cannot be summarized by one measure.

Interpretation in relation to the gut–brain literature

The results are biologically plausible in light of the literature on the gut–brain axis, but do not establish a single mechanism. Probiotic preparations can alter the function of the intestinal barrier, microbial metabolites, immune signaling, stress responses and tryptophan metabolism, but each clinical product may intervene in a unique combination of pathways (Cryan et al., 2019; Foster et al., 2017). Thus the most robust interpretation is that some strains or combinations might improve depressive symptoms in some patient subgroups, perhaps as an add-on to standard care, whereas others might be ineffective. This is more appropriate than treating the commercial probiotic category as one pharmacologic entity. It also matches the newer strain-specific results: Rahmannia et al. (2024) reported that results varied depending on the depression scale, with a more consistent signal on BDI compared to HAMD, DASS and MADRS; and Ng et al. (2023) reported modest symptom effects, but no consistent change in microbiota diversity. Modification of the microbiome should, therefore, be viewed as a related, but not identical outcome of clinical improvement.

Size and independence of the evidence base

The population is restricted to MDD and the intervention to probiotics, which is consistent with the review question, but also restricts the evidence base that is included. The number of studies could be increased by broadening the population to healthy volunteers, subclinical low mood, general depression, or substance-induced depressive disorder, but in doing so the review question would be altered. In the same way, any synbiotic product, protocol, uncontrolled open-label pilot or follow-up/post-hoc report would count as a separate trial, which would lead to an overestimate of the number of independent RCTs. It is not appropriate to inflate the study count in a way that obscures the limited number of independent eligible RCTs; rather, the evidence gap should be reported explicitly.

Clinical and research implications

Probiotics should be viewed as a potential, research-supported adjunctive intervention, not as a substitute for evidence-based MDD treatment. Despite the apparent benefits, no specific strain or dose can be recommended due to variation in formulations, patient characteristics, and antidepressant background. Future trials should include a definite diagnosis of MDD, should pre-specify a primary depression outcome, report intention-to-treat and per-protocol results, give means and standard deviations of the data at prespecified time points, and include adherence and adverse-event reporting. The trial reports should also include the strain ID, dose administered, how the strain(s) were stored, co-intervention, dietary exclusion criteria, and whether the product was a probiotic alone or combined with prebiotics, minerals, or other supplements.

For future evidence syntheses, it should be determined in advance what will be done with multiple scales and multiple publications from a single cohort. A single independent cohort should not contribute multiple correlated estimates without a model or prespecified selection rule. When different instruments are used, the use of Hedges g is appropriate, with prespecified justification for instrument and time-point selection. It is likely that a component network or meta-regression of strain, dose, duration, antidepressant co-treatment, and gastrointestinal comorbidity will be useful in future, but the number of independent cohorts is currently too small for reliable high-dimensional moderator analysis (Higgins et al., 2024).

STRENGTHS AND LIMITATIONS

The primary strength is the clear alignment between the review question and the eligibility boundary. The review aims to distinguish eligible MDD studies from out-of-scope studies, differentiate between report-level and independent-cohort counts, and document quantitative data availability without assuming that all studies are equally informative. The manuscript also clearly specifies the direction of the SMD and presents the individual estimates instead of just a pooled estimate.

There are a number of caveats. Although the search and screening procedures were structured according to PRISMA 2020, the modest number of independent cohorts limits precision and the assessment of small-study effects. Only effects supported by sufficient primary numerical data were included in the principal meta-analysis. The 2025 studies were restricted to sensitivity analyses because one required distributional conversion and the other had a very small per-protocol sample. Wallace et al. (2021) is included for transparency but not in the main pool of RCTs due to concern raised by the available original report that it was an open-label design. In conclusion, there is clinical and statistical heterogeneity caused by variations in diagnosis, comorbidity, co-intervention, probiotic composition and depression instrument, and this may not be fully reflected by a single SMD. The pooled estimate should therefore be interpreted cautiously as a complete-case synthesis that may be influenced by selective availability of numerical data.

CONCLUSION

Within the defined review question, the independently calculated complete-case meta-analysis favored probiotic supplementation (Hedges' g = 0.71, 95% CI 0.39–1.02). The finding is clinically relevant but not definitive because it is based on a small number of independent cohorts and the GRADE certainty was low. Further, the lack of homogeneity among the different strains, product combinations, antidepressant use, diagnostic processes, depression scales, and follow-up periods make it difficult to consider all products as being one homogeneous intervention.

The most cautious interpretation is that probiotics are a promising, but not yet well-established adjunctive intervention, and not a substitute for MDD treatment. Future trials and evidence updates should report complete arm-level statistics, prespecify outcome selection, maintain clear cohort identifiers, and distinguish probiotic-only products from synbiotic and active combination interventions. These steps will determine if a benefit is present, and the field will be able to identify which strains, doses, patient subgroups and treatment contexts are clinically useful. In the meantime, the evidence supports cautious optimism but remains subject to important limitations.

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