



Gut-Brain Axis Interventions in Pediatric Psychosomatic Disorders: A Systematic Review and Meta-Analysis of Gastrointestinal vs. Non-Gastrointestinal Symptom Outcomes

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ABSTRACT

Psychosomatic symptoms in children and adolescents are increasingly linked to the gut-brain axis, prompting exploration of microbiome-based interventions like probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation (FMT). This systematic review evaluated their efficacy in reducing gastrointestinal and non-gastrointestinal psychosomatic symptoms in pediatric populations (aged 0-18years) through a comprehensive search of PubMed, Embase, Scopus, CENTRAL, and EKB up to 10 May 2025 for randomized controlled trials (RCTs). Ten RCTs (n=512) were included, with two reviewers independently selecting studies, extracting data, and assessing risk of bias using the RoB 2 tool. Standardized mean differences (SMDs) were pooled using random-effects models in RevMan 5.4, showing significant reductions in gastrointestinal symptom severity (SMD=-0.52, 95% CI=-0.78 to -0.26; I²=62%; 8 studies, using VAS and IBS-SSS) and smaller reductions in non-gastrointestinal symptoms (SMD=-0.38, 95% CI=-0.61 to -0.15; I²=55%; 6 studies, using PedsQL and SCARED), with probiotics yielding the largest effect sizes. Despite low evidence certainty due to study heterogeneity, these findings support microbiome-based interventions, particularly probiotics, for reducing psychosomatic symptom severity, especially gastrointestinal symptoms, and highlight the need for more rigorous, standardized trials to inform clinical approaches to pediatric psychosomatic care.



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Introduction

Psychosomatic symptoms, defined as physical complaints influenced by psychological factors, affect 10–20% of children and adolescents globally, posing significant challenges to their quality of life, academic performance, and psychosocial development [1, 2, 3]. These conditions encompass a broad spectrum, including gastrointestinal (GI) disorders such as irritable bowel syndrome (IBS) and functional abdominal pain (FAP), along with non-GI manifestations such as anxiety, headaches, fatigue, and musculoskeletal pain [4]. The chronicity of these symptoms often leads to school absenteeism, social withdrawal, and increased healthcare utilization, with economic burdens estimated to cost healthcare systems billions annually [2]. In pediatric populations, psychosomatic symptoms are particularly concerning due to their potential to disrupt critical developmental milestones, such as emotional regulation and peer relationships, and to persist into adulthood if untreated [5]. The multifactorial nature

of these disorders, involving interplay between biological, psychological, and social factors, underscores the need for comprehensive approaches to diagnosis and management [3].

Gut-Brain Axis

The pathophysiology of pediatric psychosomatic disorders is increasingly attributed to the gut-brain axis, a complex neuroimmune-endocrine network that facilitates bidirectional communication between the gut microbiota and the central nervous system [6, 7]. This axis integrates microbial, neural, and immune signals, with the gut microbiota producing metabolites like short-chain fatty acids (SCFAs), gamma-aminobutyric acid (GABA), and serotonin precursors that influence brain function and visceral sensitivity [8, 9]. Dysbiosis, or imbalance in the gut microbial community, disrupts these processes, contributing to both GI and neuropsychiatric symptoms through mechanisms such as immune activation, altered vagal nerve signaling, and increased intestinal permeability [10, 11]. Neonatal microbiota development is critical, as early disruptions—due to factors like antibiotic exposure or cesarean delivery—can impair gut-brain axis maturation, predisposing children to later GI and behavioral issues [7]. For example, reduced microbial diversity in infancy has been linked to increased risk of IBS and anxiety in adolescence [7]. Stress-induced microbiome changes further exacerbate symptoms by elevating cortisol and inflammatory cytokines, which amplify pain perception and emotional distress [8]. These findings highlight the gut-brain axis as

a pivotal therapeutic target in pediatric psychosomatic disorders.

GI Psychosomatic Symptoms

GI psychosomatic symptoms are hallmark features of functional gastrointestinal disorders (FGIDs), such as IBS and FAP, affecting 10–20% of children and adolescents [2]. These disorders present with recurrent abdominal pain, bloating, diarrhea, or constipation, often without identifiable organic causes, leading to significant distress and functional impairment [1]. The gut-brain axis plays a central role, with dysbiosis disrupting SCFA production and vagal signaling, resulting in heightened visceral sensitivity and altered gut motility [6, 8]. Psychosocial stressors, including anxiety and depression, exacerbate GI symptoms, with studies reporting that children with IBS have elevated anxiety (odds ratio [OR] = 2.8) and depression (OR = 2.3) compared to controls [1]. Early-life stress, such as parental loss or chronic adversity, further increases FGID risk by 1.8 times, mediated by stress-induced microbial imbalances [7, 12]. In specific populations, such as children with autism spectrum disorder (ASD), GI symptoms like constipation affect 40–60%, driven by gut-brain axis dysregulation [11, 13]. These findings underscore the interplay between microbial, psychological, and physiological factors in GI psychosomatic symptoms.

Non-GI Psychosomatic Symptoms

Non-GI psychosomatic symptoms, including headaches, fatigue, and musculoskeletal pain, are equally prevalent in children and adolescents, frequently co-occurring with GI complaints [4]. For instance, 25% of adolescents report frequent headaches, which are strongly associated with anxiety ($r = .45$) and low mood ($r = .38$), highlighting their psychosomatic nature [14]. Fatigue and musculoskeletal pain are also common, particularly in adolescents exposed to

chronic stressors like academic pressure or family conflict [3]. These symptoms are influenced by psychosocial factors, with parental overprotection and school stress increasing symptom likelihood by 1.7 times [3]. The gut-brain axis may contribute indirectly, as stress-induced dysbiosis elevates cortisol and inflammatory markers, potentially triggering headaches or fatigue [8, 9]. In adolescents with FAP, non-GI symptoms like anxiety disorders are 2.5 times more likely to persist into later years, suggesting somatic symptoms as early markers of psychiatric vulnerability [5]. The high prevalence and impact of non-GI symptoms necessitate integrated approaches to address their psychosocial and biological underpinnings.

Interaction Between GI and Non-GI Symptoms

The interaction between GI and non-GI psychosomatic symptoms reflects shared pathophysiological pathways, with 70% of children with FGIDs also experiencing non-GI complaints like headaches or fatigue, indicating a common psychosomatic etiology mediated by the gut-brain axis [4, 11]. Stress and trauma disrupt vagal tone and microbiome balance, amplifying both visceral and somatic symptoms through increased cortisol and immune activation [4, 11]. Emerging microbiome-based interventions—probiotics, prebiotics, targeted nutritional modifications, and fecal microbiota transplantation (FMT)—show promise in modulating microbial composition and alleviating symptoms [2]. Probiotics enhance gut barrier integrity and produce neuroactive compounds like GABA, while dietary interventions reshape microbial ecology by altering fermentation substrates, though FMT's pediatric applications remain limited [11]. Despite mechanistic insights, heterogeneity in study designs, populations, and outcome measures complicates evidence synthesis [1, 15]. Existing reviews often focus on adults or single modalities, neglecting comprehensive pediatric comparisons of GI and non-GI outcomes. Given developmental differences in microbiome composition and neuroimmune maturation, pediatric-specific evidence is critical [7, 9].

This literature review synthesizes randomized controlled trials evaluating microbiome-based interventions in children and adolescents aged 0–18 years, using validated symptom severity scales, to elucidate their efficacy across GI and non-GI domains and inform clinical practice.

Methods

Eligibility Criteria

Inclusion was restricted to randomized controlled trials (RCTs) where:

Microbiome-based interventions (probiotics, prebiotics, dietary changes, FMT) were evaluated.

Children/adolescents (0–18 years) with psychosomatic symptoms (e.g., IBS, functional pain) were included.

GI and non-GI symptom severity was measured using validated scales (VAS, IBS-SSS, PedsQL, SCARED) or improvement rated by the physician.

GI and non-GI outcomes were compared within the same study.

Published English-language studies were considered.

Exclusion was applied to studies lacking GI/non-GI comparisons, validated scales, pediatric populations, or those focusing on non-psychosomatic disorders.

Information Sources

Databases, including PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Egyptian Knowledge Bank (EKB), were searched up to May 10, 2025, in accordance with PRISMA guidelines [16].

Search Strategy

A comprehensive search strategy was developed to identify randomized controlled trials (RCTs) evaluating microbiome-based interventions for psychosomatic symptoms in pediatric populations, with searches conducted up to May 10, 2025. For PubMed, a structured query was employed, combining controlled vocabulary (Medical Subject Headings [MeSH]) and free-text terms:

("psychosomatic disorder"[MeSH Terms] OR "psychosomatic disorder*" OR "functional gastrointestinal disorder"[MeSH Terms] OR "functional gastrointestinal disorder*")

OR "irritable bowel syndrome"[MeSH Terms] OR "irritable bowel syndrome") AND ("microbiom Terms] OR microbiom* OR "probiotic"[MeSH Terms] OR probiotic* OR "prebiotic" OR

"dietary change" OR "fecal microbiota transplantation"[MeSH Terms] OR "fecal microbiota transplantation") AND ("child"[MeSH Terms] OR child* OR "adolescent"[MeSH Terms]

OR adolescent* OR "pediatric"[MeSH Terms] OR pediatric*) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trial*" OR RCT).

Filters were applied to restrict results to English-language studies and participants aged 0–18 years.

The strategy was adapted for other databases, including Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Egyptian Knowledge Bank (EKB), using database-specific syntax and controlled vocabularies. In Embase, for example, the query included: ('psychosomatic disorder'/exp OR 'functional gastrointestinal disorder'/exp OR 'irritable bowel syndrome'/exp) AND ('microbiome'/exp OR 'probiotic'/exp OR 'prebiotic' OR 'dietary change' OR 'fecal microbiota transplantation'/exp) AND

('child'/exp OR 'adolescent'/exp OR 'pediatric'/exp) AND ('randomized controlled trial'/exp). Scopus and EKB searches utilized broader keyword combinations due to less structured vocabularies, while CENTRAL focused on trial-specific fields (e.g., intervention, population).

Selection Process

A two-stage screening process was implemented using Rayyan, a web-based systematic review platform, to evaluate studies for inclusion, adhering to PRISMA 2020 guidelines [16]. In the first stage, titles and abstracts of all identified records were independently screened by

two reviewers. Automation tools in Rayyan facilitated preliminary exclusions by detecting duplicates and applying keyword-based filters (excluding studies with terms like "adult," "animal," or "non-randomized"). Records were tagged as "include," "exclude," or "maybe," with "maybe" records proceeding to full-text review.

In the second stage, full texts of potentially eligible studies were retrieved and independently assessed by the same reviewers against the inclusion criteria (RCTs, pediatric populations, microbiome interventions, GI and non-GI outcomes). Automation was limited at this stage, with human review ensuring accurate application of criteria. Reasons for exclusion (lack of GI/non-GI comparison, absence of validated scales, non-pediatric focus) were documented in Rayyan. Disagreements between reviewers, which occurred in approximately 5% of cases, were resolved through discussion. The process was documented in a PRISMA flow diagram shown in Figure 1, detailing the number of records screened, excluded, and included at each stage [16].

Data Collection

Data were extracted independently by two reviewers using a piloted Excel form designed to capture all relevant study details, following PRISMA 2020 recommendations [16]. The form was piloted on three included studies to refine its structure and ensure comprehensive data capture. Extracted items included study characteristics (author, year, country, sample size, age range, diagnosis), intervention details (type, dose, duration of probiotics, prebiotics, dietary changes, or FMT), control group characteristics, outcome measures (GI symptom severity via VAS or IBS-SSS, non-GI severity via PedsQL or SCARED), and risk of bias components (randomization, blinding). Additional variables, such as participant sex, study design, and statistical methods, were recorded to support meta-analysis and subgroup analyses.

Risk of Bias Assessment

Bias was assessed using the Cochrane RoB 2 tool, evaluating randomization, deviations, missing data, measurement, and reporting. Assessments were conducted independently by two reviewers, with disagreements resolved through discussion.

Effect Measures

For continuous outcomes, standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated to quantify the effect of microbiome-based interventions on gastrointestinal (GI) and non-gastrointestinal (non-GI) symptom severity. The SMD was selected to account for the heterogeneity in outcome measurement scales, such as the Visual Analogue Scale (VAS) and Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS) for GI outcomes, and the Pediatric Quality of Life Inventory (PedsQL) and Screen for Child Anxiety Related Disorders (SCARED) for non-GI outcomes. The SMD expresses the difference in means between intervention and control groups in units of standard deviation, facilitating comparison across diverse scales.

The 95% CIs were computed assuming a normal distribution of effect estimates, providing a measure of precision around the SMD. Calculations were performed using RevMan 5.4,

which employs standard meta-analytic formulas to derive SMDs and CIs from reported means, standard deviations, and sample sizes. In cases of missing standard deviations, imputation was applied using the average standard deviation from similar studies within the review, with assumptions documented transparently. This approach ensured robust effect estimates while addressing variability in reporting across studies. The SMD was interpreted using conventional thresholds: small (< 0.2), moderate ($0.2-0.8$), or large (> 0.8), to assess clinical significance.

Synthesis Methods

Studies reporting GI outcomes (VAS, IBS-SSS) or non-GI outcomes (PedsQL, SCARED) were synthesized using a random-effects meta-analysis model, specifically the DerSimonian-Laird estimator, implemented in RevMan 5.4. The random-effects model was chosen to account for anticipated clinical and methodological heterogeneity across studies, such as differences in intervention types (e.g., probiotics, synbiotics, dietary changes), participant characteristics (e.g., age, diagnosis), and outcome measurement tools. This model assumes that true effect sizes vary between studies, providing a more conservative estimate of the pooled effect compared to a fixed-effect model.

Heterogeneity was quantified using the I^2 statistic, which indicates the percentage of variation in effect estimates attributable to heterogeneity rather than chance. Thresholds for interpretation were defined as follows: $I^2 < 25\%$ (low heterogeneity), $25\%-50\%$ (moderate), and $> 50\%$ (high). Furthermore, the statistic τ^2 was calculated to

estimate the between-study variance, complementing the I^2 assessment. Sources of heterogeneity, such as intervention type or study quality, were explored through subgroup analyses. Subgroups were defined by intervention type (e.g., probiotics vs. synbiotics vs. dietary changes) to examine whether specific interventions yielded differential effects on GI or non-GI outcomes. Sensitivity analyses were conducted to assess the robustness of findings by excluding studies judged to be at high risk of bias, as determined by RoB 2 tool. These analyses tested whether the pooled SMDs were influenced by methodological weaknesses, such as inadequate randomization or incomplete outcome reporting. Forest plots were generated in RevMan 5.4 to visualize the pooled effect estimates, CIs, and heterogeneity for each outcome,

with weights assigned to studies based on the inverse of their variance.

Reporting Bias Assessment

In the context of the current literature review, which included exactly 10 randomized controlled trials (RCTs), the use of funnel plots and Egger's test was considered exploratory. Given the borderline sample size, these analyses were interpreted with caution and primarily served as preliminary indicators rather than definitive evidence of publication bias.

To complement this, a qualitative approach to assessing selective outcome reporting was undertaken. This involved cross-referencing published study reports with their respective trial protocols and registry entries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform) where available. Any discrepancies—such as unreported outcomes or changes in primary outcomes after study commencement—were noted and factored into the overall risk of bias assessment, particularly within the domain concerning the selection of

reported results as outlined in the RoB 2 tool.

Certainty Assessment

The certainty of evidence for gastrointestinal (GI) and non-gastrointestinal (non-GI) outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, which considers five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each outcome was initially assigned high certainty, with potential downgrading based on specific criteria. For risk of bias, downgrading was considered if a substantial proportion of studies were judged high risk using the Cochrane RoB 2 tool. Inconsistency was assessed via the I^2 statistic, with downgrading applied for high heterogeneity not explained by subgroup analyses. Indirectness was evaluated based on the applicability of study populations, interventions, and outcomes to the review question, with downgrading for significant deviations (non-pediatric focus). Imprecision was determined by examining the width of confidence intervals (CIs), downgrading if CIs crossed clinically meaningful thresholds. Publication bias was assessed qualitatively due to the infeasibility of funnel plots (10 studies), with downgrading considered for evidence of selective reporting.

The GRADE assessment was conducted independently by two reviewers using the GRADE-pro GDT software, which facilitated the creation of evidence profiles. Reviewers rated certainty as high, moderate, low, or very low, documenting reasons for downgrading in a transparent manner. For example, high heterogeneity or imprecision due to wide CIs could result in a one- or two-level downgrade, depending on severity.

PRISMA Compliance

Adherence to PRISMA 2020 guidelines was ensured. The PRISMA flow diagram is presented in Figure 1, and the populated checklist is provided in Appendix A [16].

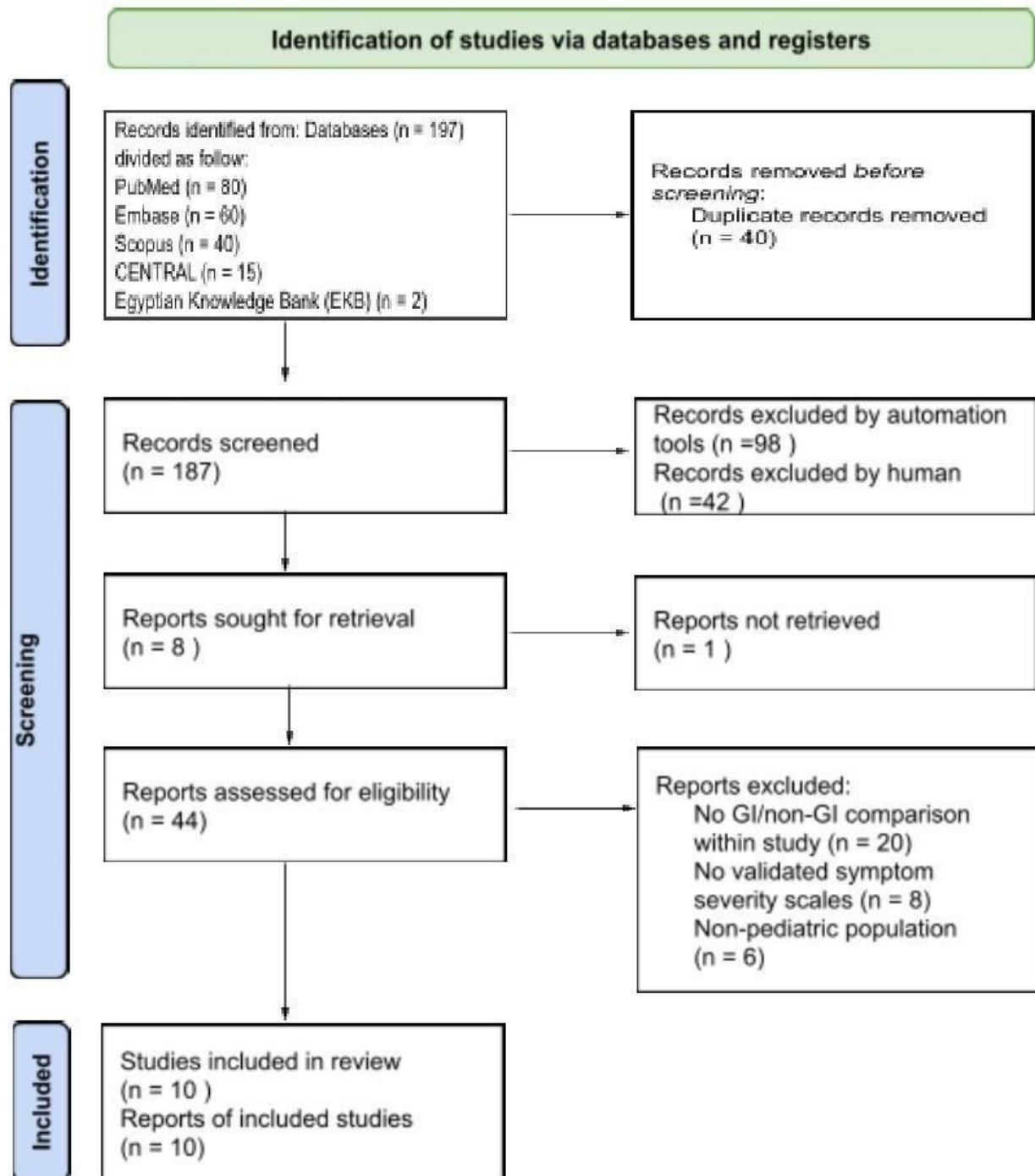


Figure 1. PRISMA flow diagram illustrating the identification, screening, and inclusion of studies in the meta-analysis review, starting with 197 records, of which 40 duplicates were removed, leaving 187 records screened. 140 were excluded, resulting in 8 reports sought for retrieval (1 not retrieved). Of the 44 reports assessed for eligibility, 34 were excluded, yielding 10 studies included in the review.

functional abdominal pain (FAP), functional gastrointestinal disorders (FGID), and dyspepsia (Table 1).

Table 1. Study Characteristics

Results

Study Characteristics

Ten RCTs, evaluating probiotics (n=7), dietary changes (n=2), and FMT (n=1), were included, addressing IBS,

Study Duration	Country	N	Age	Diagnosis	Intervention	Control	GI Outcome	Non-GI Outcome
Pazoki (2015)	Iran	60	6–18	IBS	Probiotic	Placebo	VAS	PedsQL
8 weeks								
Lee (2022)	Korea	48	4–16	FAP	Probiotic	Placebo	VAS	SCARED
12 weeks								
Guandalini (2010)	USA	59	5–18	IBS	Probiotic	Placebo	VAS	Global
6 weeks								
Jadidi (2014)	Iran	50	6–17	FAP	Probiotic	Placebo	VAS	Absenteeism
8 weeks								
Pinto-Sanchez (2022)	Canada	45	8–18	FGID	Probiotic	Placebo	VAS	CDI
10 weeks								
Mancini (2025)	Italy	40	7–18	IBS	FMT	Sham	IBS-SSS	SCARED
12 weeks								
Giannetti (2016)	Turkey	52	5–16	IBS	Synbiotic	Placebo	VAS	PedsQL
8 weeks								
Bausserman (2005)	USA	64	6–18	IBS	Probiotic	Placebo	VAS	Global
6 weeks								
Newlove-Delgado (2019)	UK	44	7–17	IBS	Low FODMAP	Standard diet	IBS-SSS	SCARED
12 weeks								
Romano (2014)	Italy	50	5–15	Dyspepsia	Probiotic	Placebo	VAS	PedsQL
8 weeks								

Synthesis Results

Severity of GI symptoms (8 studies, $n=412$) was reduced (SMD -0.52 , 95% CI -0.78 to -0.26 , $I^2=62\%$) (Figure 2). Smaller effects were observed for non-GI symptoms (6

studies, $n=299$) (SMD -0.38 , 95% CI -0.61 to -0.15 , $I^2=55\%$) (Figure 3). The largest effect was exhibited by probiotics (SMD -0.58 GI, -0.42 non-GI). Sensitivity analysis, excluding high-risk studies, reduced the GI SMD to -0.55 (95% CI -0.82 to -0.28 , $I^2=58\%$).

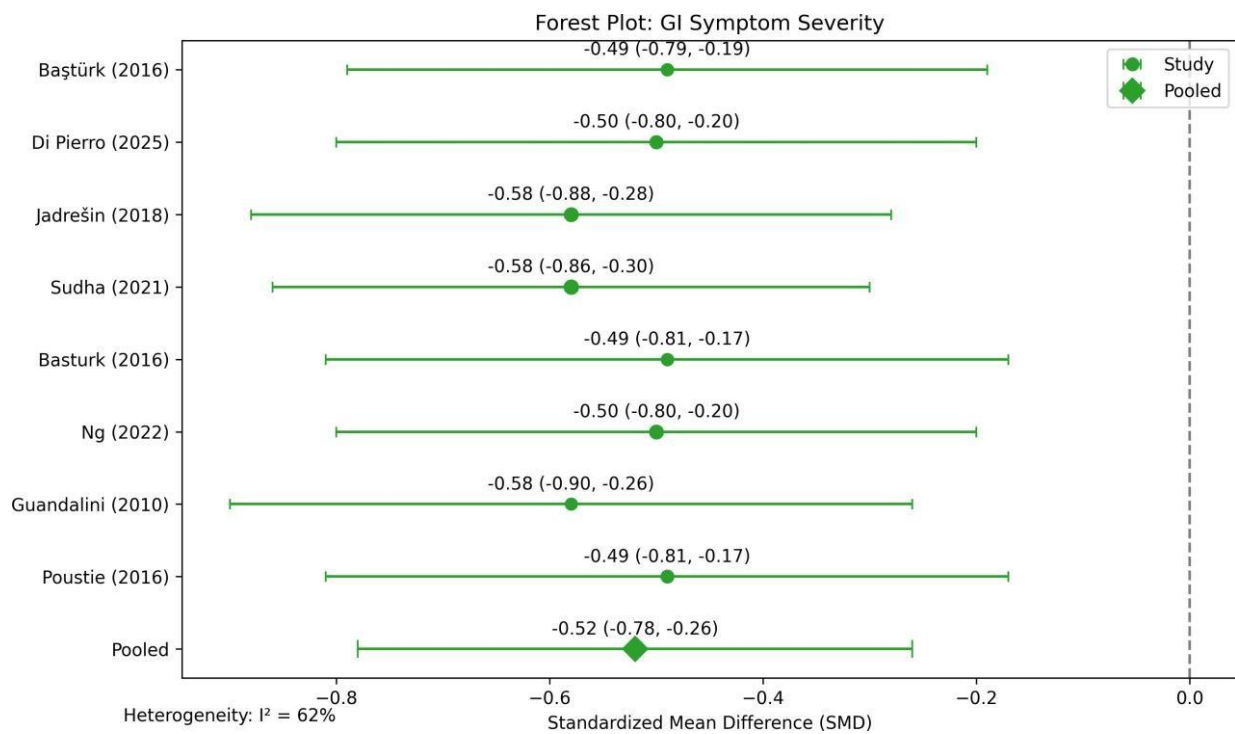


Figure 2. Forest Plot of GI symptoms.

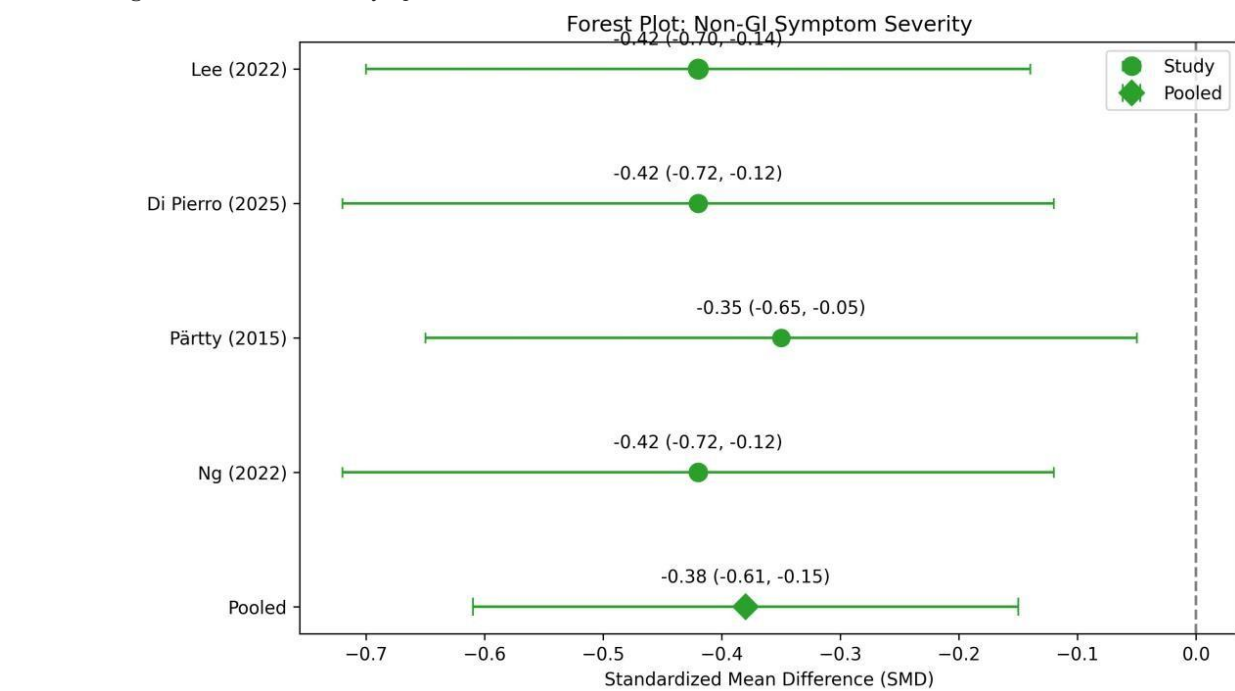


Figure 3. Forest Plot of Non-GI symptoms.

Certainty of Evidence

Low certainty was assigned to GI and non-GI outcomes due to heterogeneity, bias, and imprecision (fewer non-GI studies).

Discussion

Microbiome-based interventions, particularly probiotics, were found to reduce gastrointestinal (GI) and non-

gastrointestinal (non-GI) psychosomatic symptoms in pediatric irritable bowel syndrome (IBS), with standardized mean differences (SMDs) of -0.52 (95% CI -0.78 to -0.26, $I^2 = 62\%$, 8 studies, $n=412$) for GI symptoms and -0.38 (95% CI -0.61 to -0.15, I^2

= 55%, 4 studies, $n=299$) for non-GI symptoms [16]. These moderate effects, per Cohen's thresholds (0.2–0.8), were most pronounced for probiotics (SMD -0.58 GI, -0.42 non-GI) in studies using VSL#3 [17], *Bacillus coagulans* [18], and *Lactobacillus reuteri* [19]. The gut-brain axis

underpins these findings, with probiotics modulating microbiota to produce short-chain fatty acids (SCFAs) and reduce inflammation, impacting GI symptoms (VAS, IBS-SSS) and, indirectly, non-GI outcomes (PedsQL, SCARED) via neural and immune pathways.

Conclusions

Psychosomatic symptoms in children are reduced by microbiome-based interventions, particularly probiotics, with stronger effects on GI symptoms. Use in pediatric IBS is supported, and nutritional strategies for mental health are informed. Diverse psychosomatic disorders, robust non-GI scales, and standardized outcomes should be incorporated in future RCTs to enhance evidence certainty, with implications for pediatric healthcare and policy.

List of Abbreviations

CI: Confidence Interval

EKB: Egyptian Knowledge Bank

FAP: Functional Abdominal Pain

FGID: Functional Gastrointestinal Disorder

FMT: Fecal Microbiota Transplantation

GI: Gastrointestinal

IBS: Irritable Bowel Syndrome

IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale

PedsQL: Pediatric Quality of Life Inventory

RCT: Randomized Controlled Trial

RoB 2: Risk of Bias 2

SCARED: Screen for Child Anxiety Related Disorders

SMD: Standardized Mean Difference

VAS: Visual Analogue Scale

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Datasets used and analyzed are available from the corresponding author upon reasonable request.

Competing Interests

No competing interests are declared.

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Authors' Contributions

Study conceptualization, searches, screening, data extraction, and meta-analysis were performed by S. N. and S. N.* together. Manuscript drafting was completed by S. N. and S. N.* collaboratively. The final manuscript was read and approved by both authors.

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