INPLASY

Prophylactic Probiotic Use for the Prevention of Feeding Intolerance in Preterm Infants: A Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 August 2026 and was last updated on 27 August 2026.

INTRODUCTION

Review question / Objective Feeding intolerance (FI) is a common and significant morbidity in preterm infants, delaying nutritional autonomy and prolonging hospital stay. This systematic review and meta-analysis aimed to evaluate the effect of prophylactic probiotics on FI in preterm infants (<37 weeks gestational age) admitted to neonatal intensive care units (NICUs).

Rationale Feeding intolerance (FI) is a pervasive and clinically significant challenge in the management of preterm infants, particularly those admitted to neonatal intensive care units (NICUs). Defined as the inability to adequately digest enteral feedings, it typically manifests as gastric residuals, abdominal distension, or emesis, leading to frequent interruptions in the feeding regimen . This condition is not merely a transient inconvenience; it is a critical obstacle to achieving optimal nutrition, often necessitating prolonged parenteral nutrition and its associated risks, including central line-associated bloodstream infections and cholestasis. The prevalence of FI is directly linked to the degree of prematurity, driven by the functional immaturity of gastrointestinal motility, digestive enzyme activity, and mucosal barrier function. While the majority of the 15 million infants born preterm annually are at risk, the most vulnerable are those born before 32 weeks of gestation, who face the highest incidence of feeding difficulties and related comorbidities.

Current management strategies for FI are largely supportive and lack robust evidence. Approaches range from conservative measures, such as trophic feeds and standardized feeding protocols, to pharmacological interventions, such as erythromycin, a motilin agonist. However, the efficacy of even these interventions remains controversial. For instance, a Cochrane review found insufficient evidence to support the use of erythromycin for promoting gastrointestinal motility in preterm infants, highlighting the therapeutic vacuum that exists . This underscores a critical gap in clinical practice: the absence of a safe,

effective, and standardized prophylactic strategy to prevent the development of FI.

In this context, probiotics have emerged as a promising intervention. The rationale is grounded in the role of intestinal dysbiosis as a hallmark of gastrointestinal pathology in preterm infants, particularly necrotizing enterocolitis (NEC). By introducing beneficial bacteria with immunomodulating and anti-inflammatory functions, probiotics may stabilize the gut microbiome, enhance barrier function, and improve motility. However, the literature on probiotics for FI is marked by significant heterogeneity. Trials vary widely in the strains used (e.g., Lactobacillus, Bifidobacterium, Saccharomyces), dosing regimens, and outcome definitions, making it difficult to draw definitive conclusions. This inconsistency in study design and reporting has precluded a clear clinical consensus on their role in preventing FI.

To address these uncertainties, we conducted a systematic review and meta-analysis of parallel-group randomized controlled trials (RCTs). This study aims to evaluate the effect of prophylactic probiotics initiated within the first 7 days of life on objective measures of feeding intolerance in preterm infants (<37 weeks' gestational age). Unlike previous reviews that have focused on severe endpoints like NEC, this analysis specifically targets FI, a more common and immediate barrier to enteral nutrition. By employing rigorous methodology—including a comprehensive search of major databases, dual-independent screening, and a pre-specified statistical plan to handle heterogeneity—we seek to provide a robust synthesis of the available evidence. Our findings are intended to clarify the role of probiotics in this specific clinical context, potentially informing evidence-based feeding protocols and improving nutritional outcomes for this vulnerable population.

Condition being studied Feeding intolerance (FI) is a pervasive and clinically significant challenge in the management of preterm infants, particularly those admitted to neonatal intensive care units (NICUs). Defined as the inability to digest enteral feedings adequately, it typically manifests as gastric residuals, abdominal distension, or emesis, leading to frequent interruptions in the feeding regimen. This condition is not merely a transient inconvenience; it is a critical obstacle to achieving optimal nutrition, often necessitating prolonged parenteral nutrition and its associated risks, including central line-associated bloodstream infections and cholestasis. The prevalence of FI is directly linked to the degree of prematurity, driven by the functional immaturity of gastrointestinal motility, digestive enzyme activity, and mucosal barrier function. While the majority of the 15 million infants born preterm annually are at risk, the most vulnerable are those born before 32 weeks of gestation, who face the highest incidence of feeding difficulties and related comorbidities.

METHODS

Search strategy We conducted a comprehensive literature search in Web of Science, PubMed, EMBASE, and the Cochrane Library on August 26, 2026, limited to studies published up to this date. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to the patient population and intervention: ("preterm infant" OR "premature infant" OR "preterm neonate" OR "premature neonate" OR "low birth weight" OR "very low birth weight" OR "extremely low birth weight") AND ("probiotic" OR "Lactobacillus" OR "Bifidobacterium" OR "Saccharomyces" OR "probiotic" OR" synbiotic") AND ("feeding intolerance" OR "feeding difficulty" OR "gastric residual" OR "feeding delay" OR "feeding tolerance" OR "gastrointestinal dysfunction" OR "enteral feeding" OR "feeding problems") AND ("randomized controlled trial" OR "RCT" OR "controlled clinical trial" OR "random*" OR "trial"). Only studies published in English were considered. Additional relevant studies were identified by manually screening the reference lists of included articles.

Participant or population Participants were preterm infants (gestational age < 37 weeks) of any birth weight admitted to neonatal intensive care units (NICUs) or similar settings, without major congenital gastrointestinal anomalies, necrotizing enterocolitis (NEC) at enrollment, or prior probiotic exposure. We excluded studies including infants with severe comorbidities or those requiring surgical intervention at baseline to reduce confounding.

Intervention The intervention was prophylactic administration of any probiotic strain(s) (single or multi-strain preparations, including Lactobacillus, Bifidobacterium, Saccharomyces, or Streptococcus species), initiated within the first 7 days of life, with any dosage, formulation (e.g., powder, drops, capsule), route (oral or via feeding tube), and duration (minimum of 7 days or until full enteral feeding).

Comparator The comparator was infants receiving placebo, no intervention, or standard care without probiotics; studies with active comparators were

excluded to isolate the effect of probiotics versus non-probiotic controls.

Study designs to be included Randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), and prospective or retrospective cohort studies with a comparator group. Studies were included if they had a minimum follow-up period of 7 days or until hospital discharge. Cross-sectional studies, case series, case reports, narrative reviews, editorials, and studies without primary data were excluded. Only studies published in English or with an available English translation were considered.

Eligibility criteria Inclusion criteria encompassed several key aspects. Participants were preterm infants (gestational age < 37 weeks) of any birth weight admitted to neonatal intensive care units (NICUs) or similar settings, without major congenital gastrointestinal anomalies, necrotizing enterocolitis (NEC) at enrollment, or prior probiotic exposure. We excluded studies including infants with severe comorbidities or those requiring surgical intervention at baseline to reduce confounding. The intervention was prophylactic administration of any probiotic strain(s) (single or multi-strain preparations, including Lactobacillus, Bifidobacterium, Saccharomyces, or Streptococcus species), initiated within the first 7 days of life, with any dosage, formulation (e.g., powder, drops, capsule), route (oral or via feeding tube), and duration (minimum of 7 days or until full enteral feeding). The comparator was infants receiving placebo, no intervention, or standard care without probiotics; studies with active comparators were excluded to isolate the effect of probiotics versus non-probiotic controls. Eligible outcomes included at least one objective measure of feeding intolerance, defined as time to achieve full enteral feeds, number or volume of feeding interruptions, incidence of feeding intolerance, need for parenteral nutrition duration, or validated feeding intolerance scores, assessed during the neonatal period. Studies reporting only subjective assessments were excluded. Regarding study design, only parallel-group randomized controlled trials (RCTs) with a minimum follow-up of 14 days or until hospital discharge were included; crossover trials, quasi-experimental designs, observational studies, case series, and review articles were excluded. Only full-text articles published in peer-reviewed journals were considered.
Exclusion criteria included studies published in languages other than English or Chinese unless a full translation could be obtained, studies where the full text was inaccessible, studies with a follow-up period of less than 14 days where the infant was not discharged, studies where primary outcome data could not be quantitatively synthesized, studies where the probiotic was co-administered with a prebiotic or synbiotic whose effects could not be isolated, and duplicate publications or secondary analyses of already included trial data.

Information sources We conducted a comprehensive literature search in Web of Science, PubMed, EMBASE, and the Cochrane Library on August 26, 2026, limited to studies published up to this date.

Main outcome(s) Eligible outcomes included at least one objective measure of feeding intolerance, defined as time to achieve full enteral feeds, number or volume of feeding interruptions, incidence of feeding intolerance, need for parenteral nutrition duration, or validated feeding intolerance scores, assessed during the neonatal period. Studies reporting only subjective assessments were excluded.

Additional outcome(s) No.

Data management Literature Screening
Two independent experts performed the initial screening of all retrieved records, meticulously examining titles, abstracts, and keywords to assess relevance. Based on this evaluation, each record was categorized as “included,” “excluded,” or “uncertain.” Records clearly meeting primary inclusion criteria were labeled “included,” while those clearly not meeting were marked “excluded.” Citations providing insufficient information or ambiguous findings were assigned to the “uncertain” group. This process served as a broad filter to eliminate studies that were obviously irrelevant.
Following this, a full-text review was conducted by three senior reviewers who independently examined the complete manuscripts of records classified as “included” or “uncertain.” Each reviewer applied a detailed set of predefined eligibility criteria. Discrepancies were resolved through consensus discussions, with a fourth senior researcher consulted as a final arbiter if necessary. This multi-stage approach minimized selection bias and enhanced the reliability of the final study pool.

Data Extraction
In the data extraction phase, we systematically collected key information from each eligible study. For each included publication, we recorded the first author's last name and publication year as a

unique identifier. Additionally, we extracted basic participant characteristics, including total sample size, mean age, and/or age range, and the proportion of female participants. Two independent reviewers performed the extraction using a standardized pre-piloted form in Microsoft Excel. Discrepancies were resolved through discussion or consultation with a third reviewer. To minimize bias, raw data or exact values from tables and figures were extracted whenever feasible. For studies with missing or ambiguous data, we contacted corresponding authors to obtain additional details. The extraction process was blinded to study outcomes where possible, and all extracted data were double-checked for accuracy before entry into meta-analytic software.

Quality assessment / Risk of bias analysis
Quality Assessment
Two independent reviewers assessed the risk of bias for each included randomized controlled trial using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). The assessment covered five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For each domain, risk of bias was judged as 'low risk', 'some concerns', or 'high risk'. We determined an overall risk-of-bias judgment for each study An overall risk-of-bias judgment for each study was determined based on assessments across all domains. Discrepancies were resolved through discussion or by consulting a third reviewer.
Ris of bias analysis
Publication bias was assessed visually using funnel plots and statistically via Egger's linear regression test. A p-value less than 0.05 was considered statistically significant for asymmetry, indicating potential publication bias. In cases of significant bias, the trim-and-fill method was applied to adjust for missing studies. Additionally, subgroup analyses and meta-regression were performed to explore potential sources of heterogeneity, focusing on study design, population characteristics, or intervention types. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant unless specified otherwise.

Strategy of data synthesis Statistical analyses were performed using the meta and metafor packages in R (Version 4.x). Heterogeneity among studies was assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. If the I^2 value was less than 50%, a fixed-effects model was applied to pool effect sizes. Conversely, when $I^2 \geq 50\%$, a random-effects model (DerSimonian and Laird method) was employed to account for between-study variability.
For binary outcomes, effect sizes were expressed as odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes, standardized mean differences (SMDs) or mean differences (MDs) were calculated depending on the consistency of measurement scales. Sensitivity analyses were conducted by sequentially omitting each study to evaluate the robustness of pooled estimates.
Publication bias was assessed visually using funnel plots and statistically via Egger's linear regression test. A p-value less than 0.05 was considered statistically significant for asymmetry, indicating potential publication bias. In cases of significant bias, the trim-and-fill method was applied to adjust for missing studies. Additionally, subgroup analyses and meta-regression were performed to explore potential sources of heterogeneity, focusing on study design, population characteristics, or intervention types. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant unless specified otherwise.

Subgroup analysis Subgroup analyses and meta-regression were performed to explore potential sources of heterogeneity, focusing on study design, population characteristics, or intervention types. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant unless specified otherwise.

Sensitivity analysis Sensitivity analyses were conducted by sequentially omitting each study to evaluate the robustness of pooled estimates.

Language restriction No language or publication type restrictions were applied.

Country(ies) involved China.

Other relevant information No.

Keywords Feeding intolerance, Meta-analysis, Prophylactic probiotics, Preterm Infants, Randomized Controlled Trials.

Dissemination plans No.

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