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Original Article

Impact of Probiotics or Synbiotics Supplementation on Weight Gain and Diarrhea in Children with Severe Acute Malnutrition: A Systematic Review and Meta-Analysis

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Abstract:

Background: Malnutrition remains a critical global health concern, with both short- and long-term consequences. Children suffering from malnutrition frequently exhibit gut dysfunction, which leads to growth retardation, impaired absorption of essential nutrients and vitamins, and immune dysfunction. Diarrhea is one of the most common conditions in children with malnutrition and can further worsen their condition. Probiotics have been proposed as a potential adjunctive therapy in malnutrition due to their role in modulating gut microbiota. This study aims to evaluate the effects of probiotics on weight gain and diarrhea specifically in children with severe acute malnutrition (SAM).

Methods: A systematic literature search was conducted across six databases (PubMed, Cochrane Library, ProQuest, EBSCOhost, ScienceDirect, Google Scholar) using relevant keywords. Data were extracted and analyzed using Review Manager for meta-analysis.

Result: Four studies, encompassing a total 1662 patient met the inclusion criteria. Probiotics are proven to reduce significantly the duration of diarrhea and improve the recovery (SMD -0.70; 95% CI -0.89 to -0.50; $I^2 = 0\%$, $p < 0.00001$). However, they are not diminishing the incidence of diarrhea. Moreover, this study concluded that the use of probiotics or synbiotics did not significantly impact weight gain.

Conclusion: Probiotics demonstrated efficacy in reducing the duration of diarrhea, but not its incidence, potentially contributing to improved recovery outcomes. However, their impact on weight gain in children with SAM remains inconclusive. Further research with larger studies is warranted to identify factors influencing probiotic efficacy and to explore their potential role in the comprehensive management of SAM.

Keyword: diarrhea, probiotics, severe acute malnutrition, synbiotics, weight gain

Introduction

Severe acute malnutrition (SAM), as defined by the World Health Organization, is characterized by one or more of the following: a weight-for-height z-score (WHZ) below -3 standard deviations, a mid-upper arm circumference (MUAC) less than 11.5 mm in children aged 6-59 months, or the presence of bilateral pitting edema.[1] SAM arises from a complex interplay of factors, including inadequate food consumption and chronic infections.[2] This condition significantly increases morbidity and mortality in children, with long-term consequences such as impaired cognitive development, metabolic disorders, and diminished adult potential.[3]

Globally, SAM affects an estimated 18.7 million children, with a disproportionate burden in low- and middle-income countries (LMICs).[1] Malnutrition remains a significant public health challenge in Indonesia. Based on World Health Organization (WHO) criteria and Indonesian population data from 2017, the estimated number of children under five with SAM was approximately 805,000 in that year.[3] According to the 2022 Indonesian Nutritional Status Survey, the prevalence of wasting (low weight-for-height) in Indonesia was 7.7%, an increase from 7.1% in 2021.[4]

The management of SAM consist of emergency stabilization, correction of electrolyte imbalances, infections management if present, and the provision of therapeutic feeding to promote catch-up growth.[3] However, therapeutic food interventions have limitations, such as the potential for relapse and incomplete recovery. Notably, evidence shows that the gut microbiome plays a crucial role in the recovery process.[5]

Probiotic administration has been observed to advance weight gain through the modulation of gut microbiota.[6] When administered in sufficient amounts, probiotics may provide health benefits to the host.[7] The most utilized microorganism include *Lactobacillus* and *Bifidobacterium* in probiotic formulations. Probiotics benefit the host by modulating the host's immune system, preventing pathogen adhesion to the intestinal epithelium, and improving nutrient absorption.[8]

Prebiotics are a group of nutrients that are fermented by gut microorganisms but are not digested. These indigestible compounds produce beneficial physiological effects for the host, such as promoting the growth of native bacteria and encouraging the production of short-chain fatty acids. These short-chain fatty acids, in turn, inhibit the growth of pathogenic microorganisms, thereby strengthening the body's defenses.[9]

Furthermore, the combined use of probiotics and prebiotics, known as symbiotic, result in a synergistic effect that, amplifies their positive effect. A systematic review by Mugambi et al. demonstrated that synbiotic supplementation has a positive impact on child developmental anthropometric indicators. [10]

Diarrhea is a prevalent condition among children with malnutrition, potentially delaying recovery and increasing the risk of mortality. Therefore, effective diarrhea management is essential. Probiotics have been shown to be safe and demonstrate clear benefits in reducing the duration and severity of diarrhea in pediatric.[11, 12]

Previous evidence suggests that probiotic, prebiotic, and synbiotic interventions can promote weight gain and diarrhea in malnourished children.[13, 14] However, the effects of probiotic, prebiotic, or synbiotic administration specifically in children with SAM remain understudied. Therefore, this systematic review and meta-analysis synthesizes existing evidence to assess their potential on weight gain and diarrhea in SAM children.

Method

Data Source and Search Strategy

A comprehensive literature search was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart. Literature search was initiated across six databases (PubMed, Cochrane Library, ProQuest, EBSCOhost, ScienceDirect, and Google Scholar). The search strategy utilized a combination of keywords such as "Severe Acute Malnutrition," "Children," "Probiotic," and "Weight Gain," combined with Boolean operators (AND, OR) to refine the search results. **Table 1** details the specific search queries for each database. Articles were independently screened by authors to remove duplicates and identify relevant studies, which were then compiled into a spreadsheet for further review.

Data Extraction

A standard data extraction was created using Microsoft Sheets with multiple reviewers independently pulling information from four randomized clinical trials (RCTs). For each study, key details were recorded, including the first author, publication year, study design, participant demographics, setting, age range, intervention specifics (e.g., probiotic strain, dosage), control group (e.g., placebo, standard care), intervention duration, follow-up period, and outcomes like diarrhea duration, weight gain, and hospitalization rates. Additional data on breastfeeding, antibiotic use, and HIV status were collected to account for potential confounders.

Studies were included if they met specific criteria: had to be randomized clinical trials involving severe acute malnutrition participants, clearly describe probiotic interventions, and report relevant outcomes such as diarrhea duration or weight gain. Studies were excluded if they were not randomized, lacked a control group, involved animal models, full text did not accessible, or did not provide sufficient data on the outcomes of interest. Additionally, studies with unclear methods or those not published in peer-reviewed sources were left out. This thorough and structured approach helped ensure the accuracy and reliability of the data for further analysis.

Data Synthesis

A meta-analysis was performed to synthesize the results of the included studies, focusing on comparable outcomes such as weight gain, and diarrhea duration. This statistical approach enabled a quantitative summary of the overall effect size and assessed heterogeneity across the studies. A random-effects model was employed for continuous meta-analysis, using standard mean difference as the effect size to account for variability in study designs and populations. The findings were visualized through forest plots, providing a clear representation of the pooled effect estimates and the degree of consistency among the studies. This synthesis aimed to evaluate the efficacy of prebiotic, probiotic, and synbiotic interventions in improving outcomes for children with severe acute malnutrition (SAM), while accounting for potential cofounding factors such as antibiotic use, HIV status, and breastfeeding practices.

Table 1. Search queries and first-hit results of each database

Database	Keyword	First-Hits Articles
PubMed	("Severe Acute Malnutrition" OR "SAM") AND ("Children" OR "Infant" OR "Child") AND ("Probiotics" OR "Probiotic Supplementation") AND ("Growth" OR "Weight Gain" OR "Anthropometry" OR "Growth Indices")	7
Cochrane Library	(("Severe Acute Malnutrition" OR "SAM") AND ("Children" OR "Infant" OR "Child")) AND (("Probiotics" OR "Probiotic Supplementation") AND ("Growth" OR "Weight Gain" OR "Anthropometry" OR "Growth Indices"))	18
ProQuest	(("Severe Acute Malnutrition" OR "SAM") AND ("Children" OR "Infant" OR "Child")) AND (("Probiotics" OR "Probiotic Supplementation") AND ("Growth" OR "Weight Gain" OR "Anthropometry" OR "Growth Indices"))	4660
EBSCOhost	("Severe Acute Malnutrition" OR "SAM" OR "Malnutrition, Severe Acute") AND ("Probiotic Supplementation" OR "Probiotics" OR "Probiotic Therapy") AND ("Growth" OR "Weight Gain" OR "Anthropometry" OR "Growth Indices") AND ("Children" OR "Pediatric" OR "Child" OR "Infant")	9

ScienceDirect	("Severe Acute Malnutrition" OR "SAM") AND "Probiotics" AND ("Growth" OR "Weight Gain") AND "Children"	142
Google Scholar	"prebiotics" "severe acute malnutrition" "children" "randomized controlled trial"	323

Quality Assessment

The quality of the included studies was assessed using the Risk of Bias for RCT tool. The quality assessment was conducted independently by all reviewers, with disagreements resolved through consensus deliberation.

Result

Population and Study Characteristic

A total of 5159 studies were identified on initial search from 6 databases. Nine duplicate records were removed, and 3521 articles were disqualified as they are ineligible records from automation tools. Other 1612 titles/abstracts were excluded because they did not match the study questions. Six articles were excluded due to the unavailability of articles and additional 7 articles were further excluded after full text reading because the outcome is not relevant to this study. At last, 4 studies were included and analyzed in this study (**Figure 1**). The quality of each study was assessed using Risk of Bias. Based on the result, we found that all studies exhibited low risk of bias (**Figure 2).**

The characteristics of studies included are summarized in **Table 2**. Among the total of 1662 participants, 820 patients received probiotics, 23 received synbiotic, and 819 received placebo. Three studies were conducted in both inpatient and outpatient settings, while 1 study was limited to outpatient participants. Multiple strains of probiotics were also utilized, with *Bifidobacterium* and *Lactobacillus* being the most frequently used genera in this study.

Two of the studies also reported the breastfeeding status of the participants in their study. Nuzhat et al. reported that the breastmilk intake for each study was 6.42% in the probiotic group, 4.92% in the placebo group, and 0% in the synbiotic group. Kambale et al. reported higher prevalence of breastfeeding, with 142 patients in probiotics (71.0%) and 46 patients in placebo (73.0%) being breastfed. [15, 16]

Furthermore, three of the studies administered probiotics during antibiotic treatment. Grenov et al. administered antibiotics as part of standard treatment for a minimum 5 days, with ampicillin and gentamicin as first-line antibiotics, and chloramphenicol,

ceftriaxone, cloxacillin, and ciprofloxacin were used as second- and third- line antibiotics. All patients in Kerac et al. received cotrimoxazole, and 50% of the participants had other types of parenteral antibiotics. Kambale et al used amoxicillin as a 5-days course of treatment in their study. Meanwhile, Nuzhat et al. administered the probiotics after completion of antibiotic treatment. [15-18]

Three of the studies also included HIV status in their studies. Kambale et al. reported that all the children enrolled in their study were HIV negative. Meanwhile, Grenov et al. and Kerac et al. revealed that the HIV positivity rates between their study participants were 14% and 95%, respectively.[16-18]

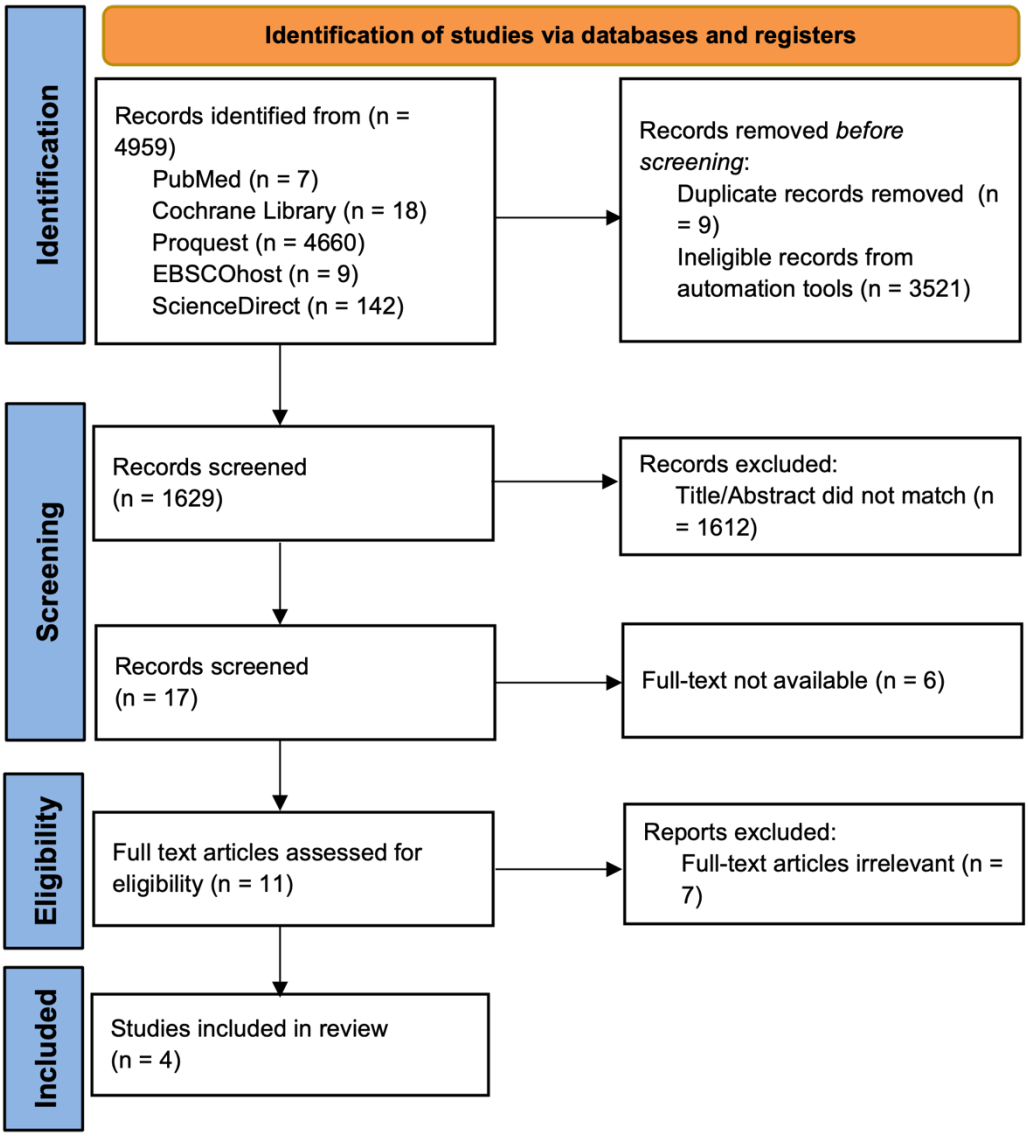

Figure 1. PRISMA Diagram

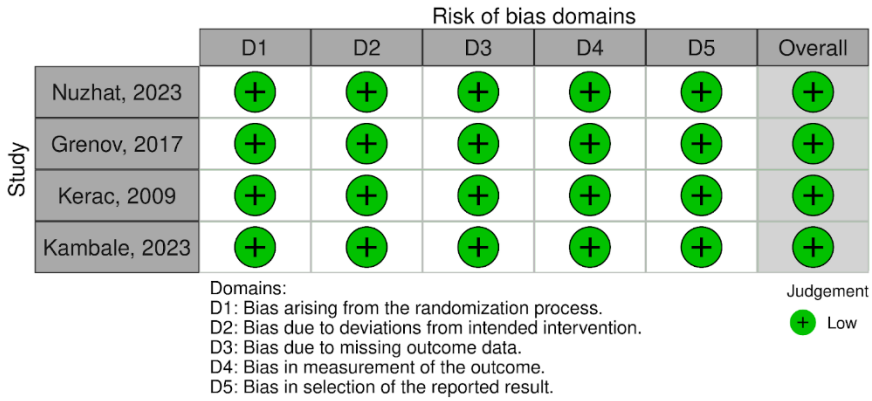

Figure 2. Risk of Bias Results

Table 2. Characteristics of included studies

Author, year	Study Design	Study Population	Age (mo)	Intervention	Control	Duration	Follow up	Outcomes
Nuzhat et al., 2023[15]	Single-blind RCT	Probiotic (21) Synbiotic (23) Placebo (23)	2-6	Probiotic: B. infantis EVC001 Synbiotic: (B. infantis EVC001, 8 billion CFU/day) + Prebiotic (Lacto-N-neotetraose - LNnT)	Lactose	28 days	4 weeks post supplementation	1.Hospitalization 2.Rate weight gain 3.Duration of diarrhea
Grenov et al., 2017[17]	Double-blind RCT	Probiotic (200) Placebo (200)	6-59	Bifidobacterium animalis subsp lactis Lactobacillus rhamnosus	Maltodextrin	During hospitalization followed by an 8- to 12-weeks outpatient treatment period	Depend on patients recovery rate	1.Incidence of diarrhea 2. Pneumonia 3.Weight gain 4.Recovery 5.Hospitalization 6.Fever 7.Vomit
Kerac et al., 2009[18]	Double-blind RCT	Probiotic (399)	5-168	Pediococcus pentosaceus	No placebo (RUTF	Depend on patients	Until nutritional	1.Nutritional cure 2.Death

		Placebo (396)		16:1 LMG P-20608, Leuconostoc mesenteroides 23-77:1 LMG P-20607, Lactobacillus paracaseissp paracasei F-19 LMG P-17806, Lactobacillus plantarum 2362 LMG P-20606) and 4 prebiotic-fermentable bioactive fibres (2·5 g of each per 10^{11} bacteria) (oat bran [rich in β-glucans], inulin, pectin, and resistant starch).	without any placebo supple-menta-tion	reco-very rate (median 33 days)	reco-very was achi-eved	3.Weight gain 4.Time to cure 5.Incidence of diarrhea
Kambale et al., 2023[16]	Double -blind RCT	Probiotic (200) Placebo (200)	6-24	Lacticase-bacillus rhamnosus GG Limosi-lactobacillus reuteri DSM 17938	Coco-nut oil	1 month	Until nutri-tional reco-very or the end of 12-week period	1.Duration of diarrhea 2.Risk of diarrhea 3.Nutri-tional recovery 4.Weight gain 5.Frequen-cy of pneumonia 6.Transfer to inpatient care rate

Weight Gain

Four studies reported weight gain after interventions. Our study showed that the overall analysis [0.30 (95% CI -0.11 to 0.71); I^2 = 92%, p = 0.15] as well as the subgroup analysis on probiotic-only [0.45 (95% CI -0.21 to 1.10); I^2 = 93%, p = 0.18] and synbiotic-only [0.02 (95%CI: -0.12 to 0.15); I^2 = 0%, p = 0.79] did not exhibit any statistical significance compared to the placebo. Furthermore, the overall and probiotic subgroup analysis exhibited high level of heterogenicity (**Figure 3**).

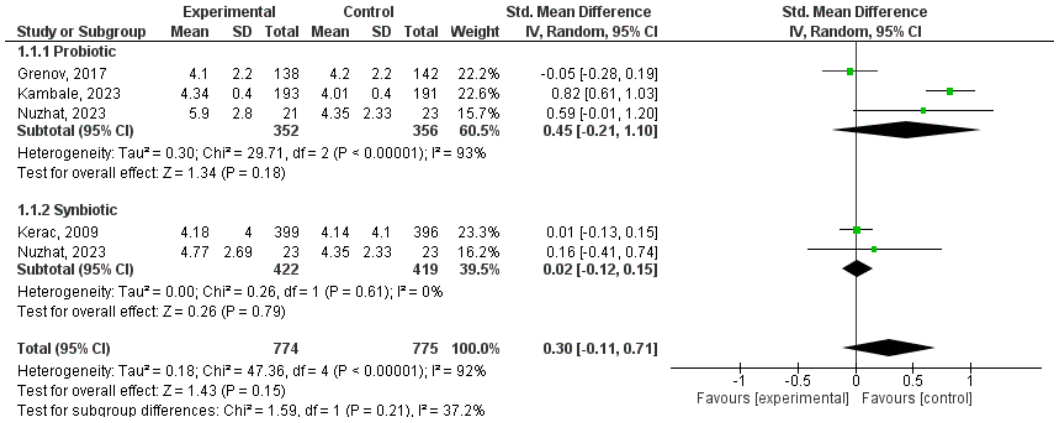

Figure 3. Forest plots for weight gain outcomes. SD: standard deviation, CI: confidence interval

Incidence of Diarrhea

Two studies reported the incidence of diarrhea after probiotic (experimental) and placebo (control) interventions, categorized by inpatient and outpatient settings. Among inpatient participants, there was no significant difference between the two groups [72.8% vs 64.2%; RR = 1.11 (95% CI 0.85 to 1.47); I^2 = 94%, p = 0.44). Interestingly, probiotics slightly lowered diarrhea incidence, despite being not statistically significant [27.1% vs 30.9%; RR = 0.90 (95% CI 0.80-1.01); I^2 = 0%, p = 0.08]. Overall, the studies showed no significant difference in diarrhea incidence between probiotics and placebo [50.8% vs 48.1%; RR = 1.02 (95% CI 0.89-1.17); I^2 = 79%, p = 0.81] (**Figure 4**).

Duration of Diarrhea

Two studies reported the duration of diarrhea after probiotic (experimental) and placebo (control) interventions. Kambale et al. found a shorter duration in the probiotic group, while Nuzhat et al. observed a smaller, non-significant decrease. Overall, probiotics significantly shortened diarrhea duration, with a mean difference of -0.70 (95% CI -0.89 to -0.50); I^2 = 0%, $p < 0.00001$ (**Figure 5**).

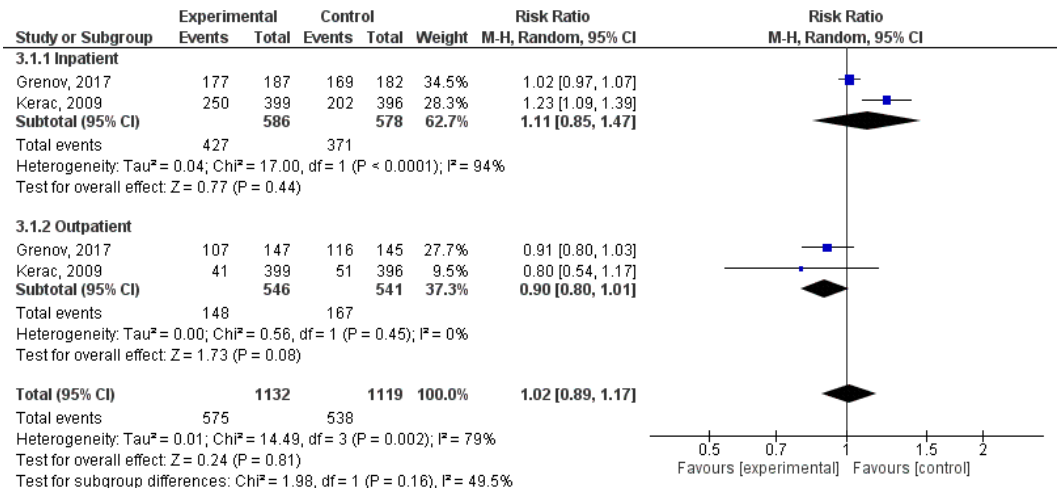

Figure 4. Forest plots for incidence of diarrhea outcomes. CI: confidence interval.

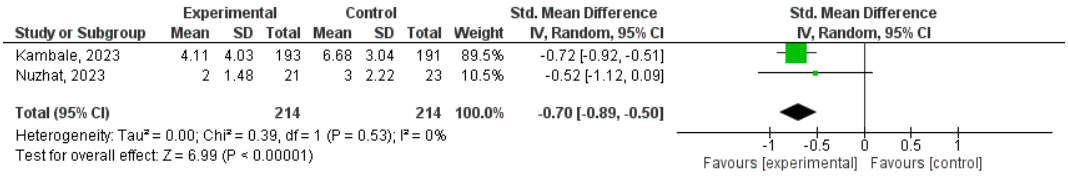

Figure 5. Forest plots for duration of diarrhea outcomes. SD: standard deviation, CI: confidence interval.

Discussion

The four studies included in this study reveal differences in design, population, settings, and interventions. Most studies used double-blind designs with sample sizes ranging from 21 to 399 participants, ages from 2 months to 168 months. Settings included both inpatient and outpatient treatments, with some studies transitioning from hospital care to community-based follow-up (e.g., Grenov et al., 2017; Kerac et al., 2009).[17, 18] Interventions involved probiotic strains like *Bifidobacterium* and *Lactobacillus*, often combined with prebiotics such as galacto-oligosaccharides, compared to placebos like lactose or maltodextrin. Study durations varied from 28 days to 12 weeks, with follow-up until nutritional recovery or 4–12 weeks post-intervention. All studies have a low risk of bias.

In children with severe acute malnutrition (SAM), gut function is significantly compromised due to gut junction impairment and increased permeability, leading to both intestinal and systemic inflammation.[19] This dysfunction can manifest as diarrhea, poor nutrient absorption, bacterial overgrowth in the small intestine, intestinal damage, and weakened immune system. Research indicates that SAM is also linked to an unbalanced gut microbiome (dysbiosis), which restricts children's growth and worsens malnutrition.[20] Probiotics are expected to support child growth by preventing

infections and enhancing nutrient and vitamin absorption through modulation of the gut microbiota.[21] Previous meta-analyses suggest that malnourished children receiving prebiotics and probiotics experience significantly greater weight gain compared to those in the control group.[13] Conversely, our meta-analysis indicated that weight gain was greater in the control group compared to the probiotic group, although this difference was not statistically significant (SMD = 0.3; 95% CI -0.11 to 0.71; p = 0.15). These differences in findings may be attributed to several factors. The study population in our analysis exhibited more severe clinical conditions compared to previous meta-analyses, which primarily included children with underweight status without complication. This can be seen from the high heterogeneity exhibited in the analysis. Additionally, one randomized controlled trial by Batool et al. reported a significant difference in weight between the probiotic and control groups after the intervention.[22] There is a distinguishing factor in this study, as the Batool et al. study included children with uncomplicated SAM undergoing outpatient treatment, whereas in majority of our studies focused on hospitalized children with more severe forms of SAM requiring inpatient care.[17, 18] This finding underscores the importance of illness severity in determining the efficacy of probiotics.

Among the four included studies, three studies (Grenov et al., Kerac et al., Kambale et al.) reported a greater weight gain in the probiotic group compared to the control group, however, the difference was not statistically significant.[16-18] Conversely, one study by Nuzhat et al. demonstrated a significant difference in weight gain between the probiotic, symbiotic, and placebo groups.[15] A key distinction in the Nuzhat et al. study was that the intervention was administered after the completion of antibiotic treatment, which may have influenced the observed effects. Antibiotics may decrease gut colonization and viability of the probiotics, thereby reducing the effectiveness of the treatment.[16, 18]

According to Suez et al., antibiotics disrupt the natural balance of the gut microbiome, causing dysbiosis and reducing microbial diversity. It also impairs the microbiome's ability to recolonize, which leads to prolonged dysbiosis. After antibiotics disrupt the gut microbiome, probiotics rapidly occupy the vacant spots, thereby outcompeting the native commensal bacteria for adhesion sites and nutrients. This competitive exclusion impedes the regrowth of the host's original microbiota. Furthermore, the probiotics themselves can release soluble factors, particularly from *Lactobacillus* species, that inhibit the growth of native bacteria, further impairing microbiome recovery. This combination of disrupted colonization by antibiotics and probiotics-induced inhibition reduces the effectiveness of probiotics in restoring a healthy gut microbiome after antibiotic use.[23]

Our meta-analysis indicates that there was a slightly higher risk of diarrhea in the probiotic group in inpatients, but the difference was not statistically significant (RR = 1.1 [95% CI: 0.85, 1.47]). In contrast, in the outpatient group, there was a possible reduction in diarrhea incidence with probiotics, although it is not statistically significant (RR = 1.02 [95% CI: 0.89, 1.17]). These results suggest that probiotics did not significantly impact the incidence of diarrhea compared to the control group, despite the observed trend towards lower diarrhea incidence in the outpatient participants. These results may be attributed to severe illness and antibiotic use in both studies.[17, 18]

Among the two included studies which analyzed diarrhea duration, only one study reported a significant difference between the probiotic and control groups. A key difference between these studies was that among the study population reported by Nuzhat et al., greater severity of illness was observed compared to the other included study.[15] Additionally, in the Kambale et al. study, all children were HIV-negative, which may have influenced the outcome.[16] In HIV patients, there are changes in gut microbial composition, significant loss of CD4+ T cells in the gastrointestinal tract, inflammation and immune activation, and the formation of viral reservoirs.[24] However, the overall meta-analysis revealed that probiotics significantly reduced diarrhea duration compared to the control (SMD = -0.70 [95% CI: -0.89, -0.50]; $p < 0.00001$). This finding suggests that while probiotics may not significantly prevent diarrhea in SAM children, they could be effective in shortening its duration, potentially improving recovery outcomes.

HIV status has become an important factor to investigate, there had been concerns that, due to the high prevalence of HIV among subjects, probiotic administration might cause sepsis due to the immunocompromised status.[21] HIV patients often undergo prolonged antibiotic treatment, which can result in lasting changes to the gut microbiota. Extended antibiotic use may significantly reduce gut bacterial concentrations, and in some cases, lead to the complete loss of specific bacterial communities.[25]

The type of strain used may also influence efficacy of the treatment. Among the four studies, the study that demonstrated significant weight gain was using *Bifidobacterium infantis* as the probiotics.[15] Human milk oligosaccharides (HMOs) are sugar present in breast milk that function as selective growth promoters for beneficial gut bacteria, especially Bifidobacteria.[26] In the probiotic group, breast milk intake was the highest, which may have contributed to the significant weight gain observed in this group. *B. infantis* is a key gut bacterium in infancy that is depleted in severely malnourished infants, leading to immature gut microbiota. The SYNERGIE trial found that B. infantis EVC001 supplementation improves weight gain and reduces intestinal

inflammation in malnourished infants.[15, 27] This strain may also explain why significant weight gain and reduced diarrhea duration were observed in studies with a population under two years old. This could be due to the fact that many children in this age group are still consuming breast milk, where human milk oligosaccharides (HMOs) enhance the effectiveness of probiotics.

We acknowledge that our study has limitations, including variations in probiotic strains, dosages, and treatment durations, which make comparisons challenging. We recognize that the concurrent use of antibiotics likely reduced probiotic efficacy, and the inclusion of HIV-positive children may have introduced confounding factors. Additionally, the lack of long-term follow-up limits our understanding of the sustained effects on weight gain and overall health outcomes in SAM children. Thus, further research is required to analyze these factors and their role in determining probiotic effectiveness. Investigating specific strains like *Bifidobacterium infantis* could provide more effective treatment options.

Conclusion

This systematic review and meta-analysis revealed that probiotics and synbiotics did not noticeably enhance weight gain in children with severe acute malnutrition when compared to placebo. Nonetheless, probiotics were linked to shorter durations of diarrhea, which could aid in recovery. The effectiveness of probiotics seems to be affected by various factors, including the severity of illness, antibiotic use, HIV status, breastfeeding, and age. These observations underline the importance of further studies to better understand the interactions between probiotics and these influencing factors, ultimately aiming to improve treatment strategies for malnourished children.

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Conflict of Interest

None declared

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