REVIEW ARTICLE

Unraveling the link between gut microbiota and failure to thrive: a narrative review of emerging evidence

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ABSTRACT

Background: Childhood undernutrition and failing to thrive (FTT) are significant global health problems that are related to the long-term physical and neurodevelopmental consequences. The information obtained recently suggests that the pathophysiology of FTT relies primarily on the immaturity of gut microbiota thus impacting the immune system, the nutrient uptake, and development. Understanding the characteristics of gut microbiota of malnourished children can reveal novel biomarkers and treatment goals to promote early childhood development and growth.

Methods: This narrative review synthesized peer-reviewed studies published from database inception through April 30, 2025, investigating gut microbiota in children with clinically defined FTT or closely related pediatric undernutrition conditions, including stunting, moderate acute malnutrition, and severe acute malnutrition, where growth outcomes were reported. Literature was identified through PubMed, Scopus, Web of Science, and Google Scholar. Eligible evidence included observational studies, randomized controlled trials, and mechanistic gnotobiotic animal studies that contributed to understanding the relationship between gut microbiota and impaired growth. Data extracted included study characteristics, participant demographics, microbiota assessment methods, anthropometric indicators, and microbial composition and diversity.

Results: Ten eligible studies, comprising human observational studies, randomized controlled trials, and complementary gnotobiotic animal experiments, were included. In all studies, FTT/malnourished children exhibited consistently immature gut microbiota possessing lower alpha diversity, decreased abundance of key commensal taxa (e.g., Bacteroides, Bifidobacterium, and Faecalibacterium), and atypical age-dependent colonization patterns. Z-scores of microbiota-for-age were significantly reduced and positively related to anthropometric indicators in malnourished children. Several studies involving interventions such as microbiota-directed complementary foods (MDCF) reported an increase in microbial maturity and growth indicators (Weight-for-age Z-score, Height-for-age Z-score, Weight-for-Length Z-score) when using interventions. Gnotobiotic mouse models confirmed that malnourished microbiota would induce growth faltering, hence a causal relationship.

Conclusion: It is concluded that immature microbiota is a core characteristic and possible pathogen of FTT and childhood malnutrition. Returning microbial diversity and functional maturation would also be a potential treatment to enhance growth outcomes. Special microbiota development interventions such as MDCF and precision nutrition programs must be considered as being under nutrition management protocols. Future studies should examine the long-term effects, sustainability, and feasibility of implementation in various pediatric populations.

Introduction

Failure to thrive (FTT) has been a clinical issue of concern, especially in the pediatric population, where it is described as the poor physical development of a child or the inability to achieve anticipated growth patterns in terms of weight and height by age and sex [1,2]. Conventionally, FTT has been linked to various

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factors, such as inadequate caloric intake, malabsorption, chronic conditions, or psychosocial issues [3,4]. Recent developments in microbiome studies have, however, provided light as to a possible and hitherto understudied cause of this multifactorial disorder: the gut microbiota [5,6].

The gut microbiota, which is a trillion microorganisms that inhabit the gastrointestinal system, is vital in digestion, development of the immune system, and metabolism of nutrients [7]. During early life, this microbial ecosystem experiences rapid changes, depending on the mode of delivery, feeding habits, exposure to antibiotics, and environmental conditions [8]. Recent research has also pointed out that the abnormal development of the gut microbiome, which is commonly known as dysbiosis, can be closely associated with the maladaptive growth patterns of infants and young children [9,10].

Specifically, the recent discoveries in both human cohorts and animal models have indicated that children who are affected by FTT might have different gut microbial profiles as compared to their healthy counterparts [11]. These changes could cause a reduction in energy harvesting, inflammation, or nutrient use, which may worsen growth retardation [11]. In addition, the gut microbiota-based interventions, including the consumption of prebiotics, probiotics, or microbiota-directed complementary foods (MDCFs), have demonstrated potential in enhancing weight gain and nutritional status of malnourished children [12].

Although these observations have been made, the exact pathways by which gut microbial composition is a risk factor of FTT are yet to be fully elucidated, and discrepancies are still present among the studies [11,12]. The study designs, population traits, and methods of microbiome profiling are also different, and this makes it difficult to make conclusive findings. In its turn, it implies that a detailed synthesis of available evidence is required to understand whether the gut microbiota has a role in FTT and what targets can be addressed to prevent and treat the condition.

This is a narrative review that will examine and summarize the existing literature on the relationship between gut microbiota and FTT among children. It aims to clarify the contribution of microbial dysbiosis in the pathophysiology of FTT and assess the role of microbial modulation in diagnostic interventions, growth, and nutritional interventions in children with the condition.

Methods

The present study was based on the narrative review design in order to synthesize and contextualize the emerging evidence on the gut microbiota and FTT relationship in pediatric populations. A narrative approach was deemed to be suitable since the available literature is heterogeneous, as it is based on different study designs, methods of assessing microbiota, definitions of outcomes, and clinical settings. A narrative review, unlike systematic reviews, offers the capacity of integrating clinical, microbiological, and mechanistic research, thus enabling a thorough interpretation of how changes in gut microbiota can impact growth, nutrition, and developmental outcome in children with FTT. This method also allowed the investigations of theoretical frameworks and clinical implications that are not restricted to quantitative estimates of effects.

A structured literature search was conducted on several electronic databases, such as PubMed, Scopus, Web of Science, and Google Scholar. The search was conducted in the databases from the beginning of the database up to April 30, 2025. Search terms Medical Subject Headings and free-text words were used to search gut microbiota and growth disorders, such as: “gut microbiota” OR intestinal microbiome OR microbial dysbiosis AND failure to thrive or growth faltering or malnutrition and infants, children, or pediatrics. Sensitivity was optimized using the use of the Boolean operators (AND/OR), and search strings were changed to meet the indexing needs of each database. Manual screening of reference lists of pertinent articles was done to identify more eligible studies. Gray literature (abstracts of conferences, theses, and non-peer-reviewed reports, etc.) was excluded to guarantee methodological rigor and reliability of the data.

The a priori eligibility criteria were used to ensure that they remained relevant to the research question. The studies included were peer-reviewed articles published in English that involved human participants aged 0-12 years diagnosed with FTT or related pediatric undernutrition conditions (stunting, MAM, or SAM) or animal models and studied gut microbiota composition, diversity, or microbiota-targeted interventions (e.g., probiotics, prebiotics, or microbiota-directed nutritional supplements). The study designs that were eligible were cohort, case-control, cross-sectional studies, and randomized controlled trials. Exclusion criteria included studies that only dealt with adult populations, animal models that were not directly relevant in pediatric FTT, or those studies that did not include specific data on the association between the findings of gut microbiota and growth outcomes. Opinion pieces, commentaries, and editorials were also not included in which there was no primary or systematically analyzed data. These criteria were used so that there would be clinical applicability and to restrict conceptual overlap with no empirical evidence.

The selection of the studies was done in two steps. First, titles and abstracts were filtered through relevancy, and then full-text screening of potentially eligible articles was done to ensure inclusion. Finally, ten studies were included in all criteria. The relatively few included studies, even with broad inclusion criteria, both indicate the lack of pediatric research that specifically correlates gut microbiota phenotypes with clinically defined FTT outcomes and also the exclusion of studies involving animals only and non-peer-reviewed literature. This observation indicates the newness of this research field and the necessity of more properly designed pediatric studies.

A standardized form (author and year of publication, country, study design, population characteristics (age range, sample size, and FTT diagnostic criteria), microbiota assessment methods (e.g., 16S rRNA

sequencing or metagenomic analysis), key microbiota-related findings, details of any microbiota-directed interventions, and reported growth or nutritional outcomes) was used to extract data. One of the reviewers performed screening and data extraction, and the uncertainties were discussed with the supervising author. The application of one reviewer is recognized as a methodological weakness because it can cause selection or extraction bias, but to some extent, it was countered through pre-established eligibility criteria and systematic extraction protocols.

Although the criteria of inclusion were quite broad, ten studies were selected since the existing literature that directly addresses the relationship between gut microbiota and clinically defined FTT in pediatric groups is still very limited. Most of the identified publications initially were on general pediatric malnutrition, stunting, or growth patterns with no clear definition of FTT as a clinical condition or no direct correlation of microbiota results to quantifiable growth outcomes. Moreover, a significant level of research was performed on animal models or adult groups of people, and thus, it was disqualified because of its minimal relevance to pediatric FTT. Other articles were not included as they did not have a detailed characterization of microbiota, or they did not have extractable data that could be used in the review objectives. All these factors significantly narrowed down the list of available studies and point to the novelty of this research topic, which makes it necessary to conduct more carefully designed pediatric studies that would investigate gut microbiota in connection with FTT.

The results of the included studies were synthesized in a narrative manner and grouped into thematic areas, such as the differences in gut microbial profiles between children with FTT and healthy controls, the hypothesized biological processes of the microbiota changes in relation to impaired growth (nutrient absorption and immune modulation), and the effect of microbiota-targeted interventions on growth parameters. The methodological heterogeneity, limitations of individual studies, and gaps in the current literature were critically discussed, with the focus on their implications on pediatric clinical practice and future research.

Since this review was based only on published information, it did not need any ethical approval. The review also followed the standards of academic integrity, such as proper citation and plagiarism avoidance. Whereas no formal risk-of-bias evaluation was conducted because of the narrative design, the quality of included studies was qualitatively evaluated on the basis of study design, sample characteristics, methodology clarity, and relevance to the research objectives, and more interpretative weight was placed on the results of studies with more robust study designs.

Results

The ten studies included [11,13-21] a range of research designs, including cross-sectional, longitudinal observational studies, and randomized controlled trials, highlighting the diversity of methodological approaches in examining gut flora in connection to FTT and malnutrition. With FTT often defined as Z-scores below -2, the diagnostic criteria for growth faltering included standard anthropometric indices such as weight-for-length (WLZ), height-for-age (HAZ), and weight-for-age (WAZ). Most research employed sophisticated microbiota analysis methods, including 16S rRNA gene sequencing, shotgun metagenomics, and multi-omics approaches. The targeted pediatric populations varied in age, from neonates and toddlers as young as a few months to children up to three years of age, with sample sizes ranging from as little as 14 to over 600 individuals. Studies captured varied sociodemographic and nutritional settings across many geographic areas, including China [11], Bangladesh [13,14,17,19], Malawi [13,15], India [20], Spain [16], and some African countries [18,21]. Several also employed developmental or maturity indices of the microbiota, such as microbiota-for-age Z-scores (MAZ), to correlate microbial age with chronological development. Collectively, these studies offer a robust and multifaceted overview of microbiota composition in nutritionally vulnerable pediatric populations (Table 1).

FTT refers to inadequate physical growth resulting from insufficient weight gain over time and is a broad clinical diagnosis that may arise from nutritional, medical, or psychosocial causes. In contrast, stunting reflects chronic undernutrition and is defined as a HAZ < -2 SD, whereas moderate acute malnutrition (MAM) and severe acute malnutrition (SAM) represent acute forms of undernutrition characterized by wasting, with SAM indicating the most severe clinical presentation. Across these conditions, studies consistently demonstrated that gut microbiota development was disrupted, although the patterns varied according to disease phenotype and study setting. In children with FTT, microbial immaturity was characterized by reduced alpha diversity, including lower Shannon indices and observed operational taxonomic units (OTUs), together with delayed age-dependent colonization and depletion of beneficial taxa such as *Bacteroides* and *Bifidobacterium* [11]. These alterations were associated with lower birth weight, poorer WAZ and HAZ scores, smaller head circumference, and increased gastrointestinal symptoms. Studies conducted in chronically undernourished or stunted children similarly reported immature microbial communities, reduced abundance of beneficial genera including *Bacteroides*, *Lactobacillus*, and *Faecalibacterium*, and lower microbiota maturity scores (MAZ), which correlated with impaired linear growth [13,14,20]. In children with acute malnutrition, particularly kwashiorkor and SAM, microbiota disturbances were more pronounced, with marked reductions in microbial maturity and metabolic capacity, enrichment of pathogenic taxa such as *Proteobacteria* and *Klebsiella*, and depletion of key anaerobic commensals [15,19,21]. Experimental transplantation studies further demonstrated that microbiota from children with kwashiorkor induced growth faltering in germ-free mice, supporting a causal role of gut dysbiosis in malnutrition [15]. Intervention studies performed primarily in children with MAM showed that microbiota-directed complementary foods (MDCF) promoted microbial maturation, increased beneficial bacterial taxa, and

Table 1. *Study characteristics and patient information.*

Author	Year	Study Design	Country	Age (Mean ± SD / Range)	Sample Size	Patients' Characteristics / Diagnostic Criteria	Microbiota Analysis Method
Zhang et al. [11]	2022	Cross-sectional	China	6.13 ± 2.5 (3-12 months)	152	FTT group (LAZ < -2), preterm NFTT (LAZ 0 to -2), healthy NFTT infants	16S rRNA gene sequencing
Gough et al. [13]	2015	Secondary analysis of twin cohort	Malawi, Bangladesh	Malawi: 10.2 mo; Bangladesh: 0.3 mo	69	Stunted children (HAZ < -2)	Whole genome (Malawi), relative abundance (BD)
Gehrig et al. [14]	2019	RCT + multi-omics + gnotobiotic animals	Bangladesh	15.2 ± 5.1 (6-36 months)	343	SAM (based on WHO), transition to MAM by anthropometry	Metagenomics (16S V4); MAZ score modeling
Smith et al. [15]	2013	Longitudinal cohort + gnotobiotic mice	Malawi	<3 years	634 (317 pairs)	WHO criteria: Kwashiorkor (edema); Marasmus (WHZ < -3)	Shotgun metagenomic sequencing
Arboleya et al. [16]	2017	Observational longitudinal	Spain	NA	63	Preterm neonates; weight gain over 3 months	qPCR, SCFA by gas chromatography
Chen et al. [17]	2021	Randomized Controlled Trial	Bangladesh	13.1 ± 1.8 (12-18 months)	123	MAM (WLZ < -2)	16S rRNA + metagenomics
Robertson et al. [18]	2023	Longitudinal Observational	Zimbabwe	1-18 months	335	General infant population incl. HIV-exposed, LAZ < -2	Whole Metagenome Sequencing
Monira et al. [19]	2011	Cross-sectional	Bangladesh	2.5 ± 0.5 (2-3 years)	14	Healthy versus malnourished children	16S rRNA gene pyrosequencing
Dinh et al. [20]	2016	Longitudinal Cohort	India	24 months	20	10 stunted (HAZ < -2) versus 10 non-stunted	16S rRNA + metagenomics
Alou et al. [21]	2017	Observational (Case-Control)	Niger, Senegal	13.4 ± 17.8	15	10 with kwashiorkor, 5 healthy controls; clinical diagnosis	Culturomics + 16S Rrna

produced modest but consistent improvements in anthropometric indices, including WAZ and WLZ, while also enhancing biomarkers of growth, immune function, and neurodevelopment [14,17]. Collectively, these findings indicate that although microbial dysbiosis is a common feature across FTT, stunting, and acute malnutrition, the specific microbial alterations and their clinical consequences differ according to the underlying nutritional disorder, highlighting the importance of disease-specific microbiota-targeted therapeutic strategies (Table 2).

Discussion

The existing body of evidence synthesis highlights a strong and biologically feasible relationship between childhood undernutrition, such as FTT, and impaired or delayed gut microbiota maturation. In the ten studies that were included (representing different geographic regions and using cross-sectional, longitudinal, randomized controlled, and translational animal models), a common microbial signature of growth faltering appeared. The children with FTT or other types of undernourishment had lower microbial diversity, loss of age-specific commensal taxa, and deviated developmental patterns of the intestinal microbiome than children in good health. Figure 1 summarizes the principal findings of the included studies and illustrates the proposed conceptual framework linking disrupted microbiota maturation with impaired growth outcomes and the potential role of microbiota-directed nutritional interventions. These combined findings suggest that gut microbiota immaturity is consistently associated with pediatric growth faltering and may contribute to impaired somatic development through multiple interconnected biological pathways. However, because much of the available evidence remains observational, causality cannot yet be considered definitive in human populations.

In observational studies, continued microbial immaturity despite traditional nutritional rehabilitation was always present as indicated by reduced alpha diversity indices (e.g., Shannon index, observed operational taxonomic units) and slower acquisition of major taxa. As an illustration, in China, infants with FTT exhibited much lower levels of microbial diversity and changes in colonization patterns of *Bacteroides*, *Bifidobacterium*, and *Streptococcus* as well as strong relationships between microbiota maturity and anthropometric parameters including length-for-age (LAZ), WAZ, and HAZ scores [11]. Cohorts in NigerSenegal, Malawi, India, and Bangladesh were also reported to have similar dysbiotic patterns, with loss of beneficial commensals (Bacteroides, Lactobacillus, Faecalibacterium and methanogenic archaea) and gain of potentially pathogenic taxa (*Proteobacteria*, *Klebsiella*, and *Escherichia*) [13,18,19,21]. Taken together, these repeated observations in heterogeneous environments support the idea of impaired microbiome ontogeny as an epitome of pediatric undernutrition [22-25].

Notably, the development of metagenomic age modeling has made it possible to quantitatively evaluate the development of the microbiome in comparison to chronological age. MAZ and relative microbiota maturity scores have been developed as reproducible markers of microbial ontogeny and were highly correlated with growth outcomes even after the contribution of common genetics and environmental exposures as was shown in Malawi twin studies. In the seminal study by Gehrig

Table 2. *Microbiota findings and growth-related outcomes.*

Author	Underdeveloped Microbiota	Alpha Diversity	Colonization Pattern	Growth Outcomes	Other Notable Findings
Zhang et al. [11]	Yes	Lower OTUs & Shannon index in FTT	Disrupted age-dependent colonization (e.g., Bacteroides, Bifidobacterium)	Lower birth weight/ length, WAZ/HAZ < –2, reduced HC, GI problems in FTT	Microbiota age positively correlated with LAZ, WAZ, HAZ; trend for BAZ (NS)
Gough et al. [13]	Yes	Lower in stunted children (both cohorts)	Reduced Bacteroides, Lactobacillus, others	NA	Acidaminococcus linked to future growth deficits; community-wide interactions altered
Gehrig et al. [14]	Yes	Lower MAZ, correlating with anthropometry	Disrupted colonization; gnotobiotic model validated	Persistent stunting (HAZ), MDCF improved GI and biomarker status	MAZ correlated with WHZ/HAZ/ WAZ; IGF-1 stayed low; MDCF improved neuro, immune, bone markers
Smith et al. [15]	Yes, esp. in kwashiorkor	Lower maturity and metabolic function	Regressed post-RUTF; delayed in kwashiorkor	WHZ < –2 in kwashiorkor; frequent GI problems	Transplanted kwashiorkor microbiota induced weight loss in mice; confirmed causal role
Arboleya et al. [16]	NA	NA	Group differences at 1 month (Bactericides)	Group 3 had WAZ = –2.37 ± 2.24 at 3 months	Early microbiota explained 73.5% of 1-month weight variance; Enterococcus & others linked to growth
Chen et al. [17]	Yes	Improved more in MDCF-2 group	MDCF-2 enhanced maturation	WLZ and WAZ improved more with MDCF-2	MDCF-2 increased beneficial taxa and plasma proteins linked to growth
Robertson et al. [18]	Yes	Increased gene richness in HIV-exposed	Over-maturity, programmed colonization	18%-34% stunting prevalence	Functional microbiota predicted growth; maternal HIV associated with over-diversification
Monira et al. [19]	Yes	Health: 546 OTUs versus Malnourished: 310 OTUs	Reduced beneficial genera; dominant pathogens	NA	174-fold ↑ Klebsiella, ↑ Escherichia, ↑ Proteobacteria (46% *vs.* 5%) in malnourished
Dinh et al. [20]	Yes	No diversity difference, but compositional	↑ Bacteroidetes, ↓ Proteobacteria, Actinobacteria	Stunted: low BW, HAZ < -2, 100% had ≥1 diarrhea	Stunted enriched with Desulfovibrio, Campylobacterales; more antibiotic exposure
Alou et al. [21]	Yes	Shannon Index lower in kwashiorkor	↓ anaerobes; disrupted ecosystem	NA	Enrichment in Proteobacteria, Fusobacteria; depletion in M. smithii; 12 probiotics absent in kwashiorkor

LAZ: Length-for-age Z-score; WAZ: Weight-for-age Z-score; HAZ: Height-for-age Z-score; BAZ: BMI-for-age Z-score; MAZ: Microbiota-for-Age Z-score; OTUs: Operational Taxonomic Units; MDCF / MDCF-2: Microbiota-Directed Complementary Food.

et al. [14], children who had moderate and severe acute malnutrition had systematically underdeveloped microbiota despite the usual refeeding interventions, and these shortcomings strongly correlated with the impairment of linear and ponderal development. These metagenomic maturity measures have a consistent predictive value, which justifies their possible use as non-invasive biomarkers, as well as targets of microbiota-directed interventions [26,27]. Although MAZ have demonstrated promising associations with growth outcomes, their clinical applicability remains uncertain because reference microbiome trajectories differ across geographic regions, dietary practices, environmental exposures, and sequencing platforms. Consequently, future validation studies are required before MAZ can be incorporated into routine clinical assessment of children with FTT.

Evidence supporting a potential causal contribution of gut microbiota to growth impairment is strengthened by microbiota-directed intervention studies and complementary gnotobiotic animal experiments. Nevertheless, direct causal inference in humans remains limited because relatively few randomized clinical trials have been performed and most mechanistic evidence originates from experimental animal models. Two clinical trials in Bangladesh showed that microbiota-guided complementary food (MDCF2) led to much better changes in WAZ and WHZ scores than conventional nutritional supplements and recovery of age-discriminatory microbial taxa [14,17,22,27,28]. Longitudinal studies also showed an increase in circulating biomarkers associated with bone formation, immune development, and neurodevelopment [27]. Similar gnotobiotic mouse experiments revealed that microbial community structure was perturbed by transplantation of microbiota of malnourished children, which led to growth impairment, and that MDCF2 administration restored these effects by reestablishing microbial community structure and hastening microbiome development, which once again supported a mechanistic interaction between microbial development and host growth [17,22,24,26,28-30].

Microbial immaturity and dysbiosis can also disrupt growth at a mechanistic level by affecting growth in several interlinked biological pathways. The decrease in the abundance of short-chain fatty acid-producing microbes, including *Faecalibacterium* and *Ruminococcus*, restricts the synthesis of acetate, propionate, and butyrate-metabolites that are crucial in the provision of energy to colonocytes, regulation of appetite, and insulin-like growth factor signaling and

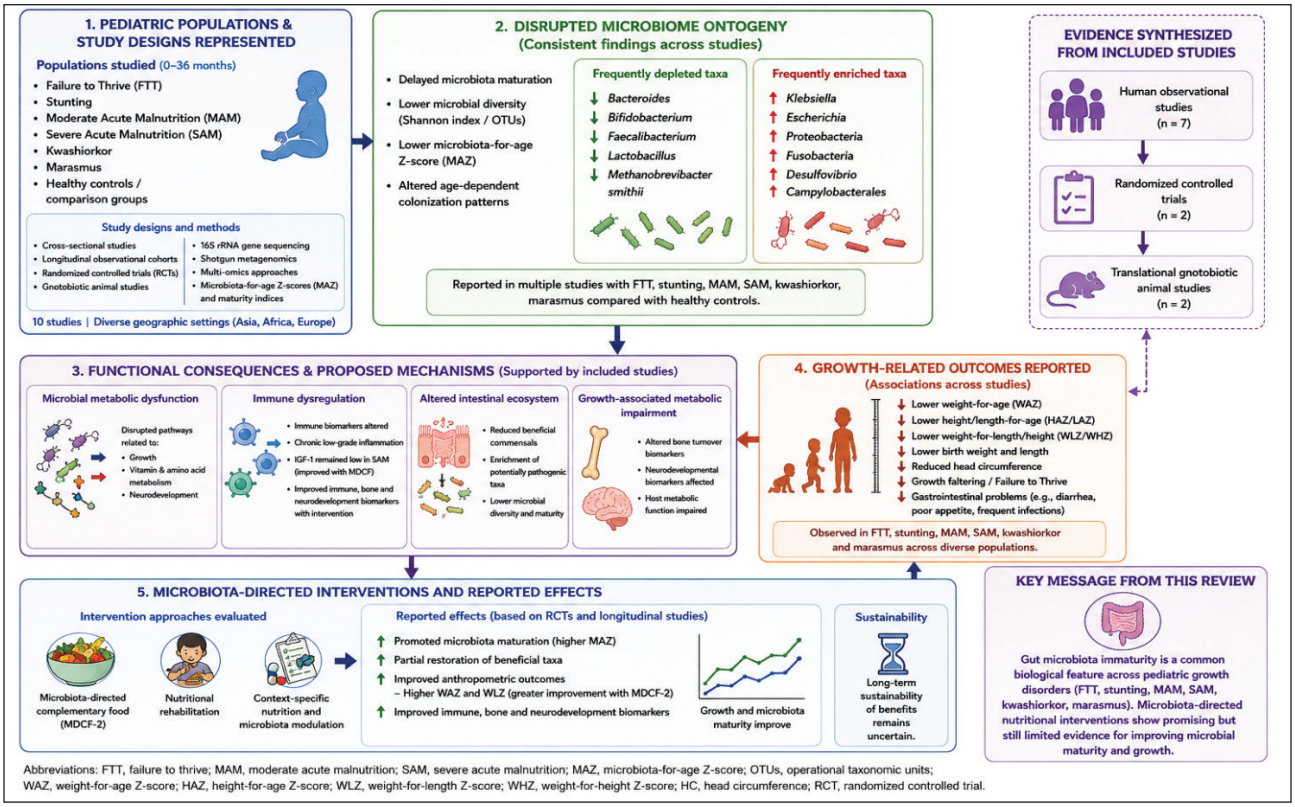

Figure 1. *Conceptual framework summarizing the principal findings of the ten included studies on gut microbiota maturation and pediatric failure to thrive (FTT) and related under nutrition.*

controlling of the systemic inflammatory state. The changed bile acid metabolism, which is caused by the disturbed microbial deconjugation and transformation pathways, can also undermine lipid absorption and vitamin bioavailability in fats. Simultaneously, dysbiosis is a factor that leads to the decreased integrity of the gut barrier through the dysfunction of tight junctions and mucus layer maintenance, which enables the translocation of microbes and the activation of the chronic immune response. All these processes favor environmental enteric dysfunction (EED), a subclinical inflammatory disorder of the small intestine that is closely linked with malabsorption, systemic inflammation, and linear growth failure. A number of studies reported the decreased microbial pathways in amino acids, nucleotide, and B-vitamin biosynthesis in malnourished children and partial recovery after MDCF2 intervention [17,22,26,27,29].

Immune maturation and inflammatory tone also influence host microbiome interactions. Microbial signals early in life are essential in the education of mucosal and systemic immunity and thus immature microbiome maturation can lead to hyperinflammatory reactions to enteric pathogen, higher infection load, and diversion of metabolic resources off growth. Importantly, these mechanisms are substantially modified by environmental and socioeconomic determinants. Poor sanitation repeated enteric infections, antibiotic exposure during critical developmental windows, inadequate dietary diversity, and food insecurity may all disrupt normal microbiome ontogeny, thereby amplifying microbial immaturity and reducing responsiveness to nutritional or microbiota-directed interventions [29]. These contextual factors likely explain a considerable proportion of the variability observed across studies.

Collectively, observational, interventional, and mechanistic data can be used to support the idea that gut microbiota immaturity is an active cause of FTT and pediatric undernutrition and not a passive association. The strategies extending beyond caloric repletion to support age-specific microbiome development and functional metabolic capacity seem to be fundamental to recovery of growth. The growing number of microbiota-directed complementary foods, which selectively enrich beneficial taxa and reestablish important metabolic pathways, represents a change towards precision nutrition strategies that consider both physiology and microbial ecology of the host [30,31]. Nevertheless, there are still significant issues. Subsequent research shows that the increase in the maturity and growth of microbiota can partially reverse once the MDCF2 is stopped, which casts doubt on the sustainability of such interventions in the long term [32,33]. In addition, small and context-specific probiotic actions underscore the importance of taking into consideration the baseline of microbial maturity, environmental exposures, and pressure of infection in developing microbiome-based treatment.

Exposures at an early age such as poor dietary consumption, frequent infections, the use of antibiotics, and poor sanitation interfere with normal gut microbiota ontogeny at critical developmental stages. This

perturbation leads to microbiota immaturity, which is low microbial diversity, slow age-discriminatory taxa acquisition, and low MAZ. The immature microbiome has poor metabolic potential, such as decreased SCFA production, poor microbial synthesis of amino acids, vitamins, and nucleotides, and disturbed bile acid metabolism, which result in an inefficient extraction and absorption of nutrients. Microbial dysbiosis, at the same time, undermines the integrity of gut barriers, enhances intestinal permeability and encourages EED, and disrupts immune maturation and maintains chronic low-grade inflammation. These interdependent pathways augment metabolic requirements, repress growth-associated hormonal signaling, and channel energy toward immune reactions, which eventually leads to growth failure and clinical inability to flourish. The impairment of growth is further reinforced by feedback loops of persistent infection, inflammation, and dysbiosis. Microbiota-directed interventions, including microbiota-directed complementary foods, are partially capable of reversing this cycle by enhancing microbial maturation, reinstating metabolic activity, and enhancing growth-related outcomes.

The current evidence is associated with a great degree of heterogeneity, which complicates its interpretation. Study design, characteristics of study population, definitions of FTT and undernutrition, microbiota assessment methods, and outcomes were variable. Studies that were included were cross-sectional observational studies through to longitudinal cohorts, randomized controlled studies, and translational gnotobiotic animal studies, each bringing a varying degree of causal inference. Differences in methods of microbiome profiling including 16S rRNA gene sequencing and whole-metagenome shotgun sequencing did not allow direct comparability of microbial taxa, functional pathways and maturity indices across studies. Moreover, the diagnosis of FTT and malnutrition varied and some studies used only anthropometric Z-scores as a diagnostic tool whilst others considered clinical or biochemical measures. This heterogeneity highlights the importance of standardized definitions, harmonized microbiome analytic pipelines, and standard measures of growth outcomes to enhance cross-study comparability and synthesis.

The visual regional and contextual disparities also influenced the associations that were observed between gut microbiota and growth outcomes. The majority of interventional and mechanistic studies have been done in low- and middle-income countries especially South Asia and sub-Saharan Africa where undernutrition is a combination of high infection burden, poor sanitation, and food insecurity. In such environments, microbiota immaturity is probably a cumulative stressor of the environment such as frequent enteric infections, EED, and frequent exposure to antibiotics. Conversely, research in higher-income areas was more likely to study milder growth faltering and showed distinct microbial patterns, indicating that the initial composition of microbiota, dietary diversity, and access to healthcare might alter microbiota-growth interactions. Such context variations indicate that the gut microbiota-specific intervention might not be universally applicable and should be adapted to local ecological and nutritional and infectious disease settings.

Although there is mounting evidence to suggest that microbiota immaturity is associated with FTT, there are still a number of key gaps. To begin with, there is a lack of long-term longitudinal data that would trace the development and growth patterns of the microbiomes and the neurodevelopmental outcomes of individuals in later life stages than in early childhood. It is yet to be determined how long-lasting microbiota-directed interventions are especially following supplementation termination. Second, bacterial communities have been studied most, with little research on other microbiome constituents, including viruses, fungi, and archaea, which can also impact the ecology of the gut and host metabolism. Third, mechanistic mechanisms - especially those of bile acid signaling, endocrine control and host-microbic epigenetics are yet to be fully described in human populations. In the future, the focus of research should be on well-powered, multicenter longitudinal studies, combination of multi-omics methodologies, and randomized trials of sustained or gradual microbiota-directed therapy. Contextual modifiers such as sanitation, infection burden, antibiotics exposure, and dietary diversity will also be incorporated to increase the accuracy of precision nutrition strategies in children with FTT.

Limitations

There are various limitations of this narrative review that must be taken into account during the interpretation of the results. First, the narrative design did not permit quantitative synthesis and risk-of-bias evaluation in a formal way and constrained the possibility of estimating the pooled effect sizes and conclusively ranking the strength of evidence. Second, the selection of studies and data extraction were conducted by one reviewer, which can result in selection or interpretative bias, but it was minimized due to the predetermined eligibility criteria and formal data extraction processes. Third, the study included only the English-language and peer-reviewed articles, and there is a risk of publication and language bias, as well as there could have been a risk of omitting the relevant data possessed by gray literature or non-English studies. Lastly, the limited amount of eligible studies is also indicative of how new this field is and restricts the generalizability of the results across different pediatric groups. In spite of these limitations, the similarity of the results in heterogeneous study designs and geography provides increased confidence in the core of the role of gut microbiota immaturity in the pathophysiology of failure to thrive.

Conclusion

Current evidence consistently demonstrates that altered gut microbiota development is associated with failure to thrive and related pediatric undernutrition conditions, although definitive causal relationships in humans remain to be established. The available findings suggest that impaired microbiome maturation, disrupted microbial metabolism, altered immune development, compromised

intestinal barrier integrity, and environmental enteric dysfunction together may contribute to impaired growth through interconnected biological pathways. From a clinical perspective, microbiota-directed nutritional strategies represent promising adjuncts to conventional nutritional rehabilitation, but their long-term efficacy, sustainability, and applicability across diverse populations require further evaluation. At the public health level, interventions aimed at improving sanitation, reducing infectious burden, promoting dietary diversity, and minimizing unnecessary antibiotic exposure should accompany microbiome-targeted approaches to maximize their effectiveness. Future multicenter longitudinal studies incorporating standardized definitions of FTT, harmonized microbiome analytical methods, multi-omics technologies, and long-term follow-up are needed to clarify causal mechanisms and translate microbiome science into evidence-based pediatric practice.

List of Abbreviations

EED	Environmental enteric dysfunction
FTT	Failing to thrive
HAZ	Height-for-age
MDCF	Microbiota-directed complementary foods
MAM	Moderate Acute Malnutrition
OTUs	Operational taxonomic units
SAM	Severe Acute Malnutrition
WAZ	Weight-for-age
WLZ	Weight-for-length

Conflicts of interest

The authors declared no conflict of interest.

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Consent for publication

Not applicable. This manuscript does not contain any identifiable personal information or images of patients.

Ethical approval

Since this review was based only on published information, it did not need any ethical approval. The review also followed the standards of academic integrity, such as proper citation and plagiarism avoidance.

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Supplementary content (if any) is available online.

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