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Review article

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The gut microbiota in malnutrition

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Abstract

Malnutrition poses a substantial global health burden with long-lasting physical, social and economic effects. Now recognized as an spectrum of interrelated conditions, malnutrition manifests differently based on an individual's geography, health-care access and lifestyle. There is growing evidence that malnutrition is also driven by defects in the composition and function of the gut microbiota, a metabolically active 'virtual organ' known to play a central role in intestinal barrier function, energy harvest, immune regulation and metabolic signalling. Across the malnutrition spectrum, perturbed microbial composition and function have been consistently observed in both children and adults. This 'malnourished microbiota' is associated with impaired nutrient utilization, chronic inflammation and altered energy balance and is known to persist despite nutritional interventions. This Review synthesizes evidence from human cohorts and animal models showing that the gut microbiota functions as a central player in malnutrition. We discuss implications for diagnostic and therapeutic strategies, arguing that microbiome restoration could provide a partial solution for malnutrition. This reframing is particularly relevant given current challenges such as armed conflict, climate change and declining international support, all of which are associated with an increased global burden of malnutrition. Thus, integrating microbiota-based strategies could protect vulnerable populations and accelerate progress towards overcoming malnutrition.

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Introduction

Malnutrition encompasses both undernutrition and overnutrition, which are distinct yet interrelated conditions (Box 1). Undernutrition refers to deficiencies in energy, protein and essential micronutrients. Overnutrition, by contrast, involves excessive intake of energy and nutrients and, similar to undernutrition, is associated with substantial health consequences including metabolic dysregulation and increased risk of disease[1–6]. Traditionally, undernutrition has been more comprehensively studied in paediatric populations, which are particularly vulnerable to its detrimental effects, as well as in hospitalized adults, often with underlying chronic illnesses[1–6]. Conversely, overnutrition is studied in both children and adults across all contexts. Regardless of age, both undernutrition and overnutrition are linked by common underlying biological mechanisms. These include metabolic dysfunction affecting glucose and lipid metabolism, alterations in body composition (for example, sarcopenia), immune dysregulation and, more recently, gut microbiota dysfunction and imbalance[1–6]. Malnutrition remains one of the most pressing global health and developmental challenges, contributing to nearly half of all deaths in children under 5, but also affecting health outcomes over an individual's entire lifespan[7]. Although undernutrition, affecting more than 2 billion people, remains the leading cause of morbidity and mortality in low-income and middle-income countries (LMICs), overnutrition is rising at an alarming rate worldwide[7]. Overnutrition and its associated pathologies now affect more than 2.5 billion people globally[8]. Consequently, LMICs are experiencing a 'double burden of malnutrition', in which undernutrition and overnutrition coexist within the same country, population, household or even within a single individual. This spectrum of malnutrition is driven by a complex interplay of factors, including poverty, food insecurity, unequal health-care access, shifts towards ultra-processed diets, urbanization and environmental stressors[9–11]. Moreover, ongoing disruptions to global food systems, driven by climate change, armed conflicts and harmful marketing of unhealthy foods, together with increased consumption of nutrient-poor, calorie-dense foods, economic instability and the reverberating effects of the COVID-19 pandemic, such as disruptions in food supply chains, continue to threaten progress towards Zero Hunger by 2030[10–14].

Over the past two decades, a growing body of evidence has argued for an important microbial contribution to malnutrition, positioning the gut microbiota as a central mediator of nutritional status and growth. The gut microbiota comprises bacteria, archaea and eukaryotic microorganisms residing in the gastrointestinal tract. Although the terms 'microbiota' and 'microbiome' are often used interchangeably in the literature, microbiome more broadly refers to the collective genomes and functional potential of these microorganisms, including their metabolic outputs and surrounding environment. In this Review,

Box 1 | Malnutrition in all its forms

Malnutrition includes undernutrition, overnutrition and the double burden of malnutrition, which involves the coexistence of undernutrition and overweight or obesity. Once considered distinct, these conditions are now recognized as a spectrum of interrelated disorders shaped by dietary intake, food insecurity, sanitation, disease states and other contextual factors[186,187]. Malnutrition may also arise in the context of acute and chronic diseases, termed disease-related malnutrition.

Undernutrition

Undernutrition results from insufficient intake of protein, calories and/or essential micronutrients. In 2022, an estimated 735 million people worldwide were undernourished, 122 million more than pre-COVID-19 levels[11]. Low-income and middle-income countries bear the greatest undernutrition burden, with undernutrition contributing to approximately 45% of deaths in children under 5 (ref. 188) and increasing the risk of cognitive delay, immune dysfunction, impaired growth and cardiometabolic disease in adulthood[35,48,189,190].

Key indicators and consequences:

- Stunting: low height-for-age due to chronic undernutrition; affects 149 million children under age 5 years worldwide[35,191]
- Protein-energy malnutrition, wasting and kwashiorkor[36]
- Metabolic dysregulation: impaired glucose, insulin and abnormal lipid levels[2,173,174]
- Immune dysfunction leading to infection susceptibility[87,175]
- Gut and systemic inflammation[87,175]
- Micronutrient deficiencies: a critical subcategory of undernutrition, affect more than half of the world's population and occur across the malnutrition spectrum[176,177]

Overnutrition

Overnutrition arises from excessive caloric intake relative to energy expenditure. In 2022, 2.5 billion people were overweight and 890 million had obesity[8], including 390 million children and adolescents aged 5–19 years and 37 million children under the age of 5 (ref. 8).

Key indicators and consequences:

- Increased body mass index (>25), waist circumference and body fat[8]
- Metabolic disorders: glucose intolerance, insulin resistance and non-communicable diseases[192]
- Hypertension and abnormal lipid levels[178]
- Respiratory problems (for example, asthma and sleep apnoea)[179,193]
- Micronutrient deficiencies due to poor diet quality[194]
- Increased gut and systemic inflammation[195]

Double burden of malnutrition

This refers to the coexistence of undernutrition and overnutrition at the individual, household, population or country level. Key indicators and consequences reflect those of both undernutrition and overnutrition, which often occur simultaneously[196–199].

Disease-related malnutrition

This occurs when acute or chronic illnesses drive malnutrition via reduced food intake, impaired absorption and metabolism, or increased nutrient requirements[136,200,201].

Key indicators and consequences:

- Unintentional weight loss and sarcopenia[200,201]
- Inflammation-associated metabolic alterations[136]
- Impaired recovery, increased complications and mortality[200,201]

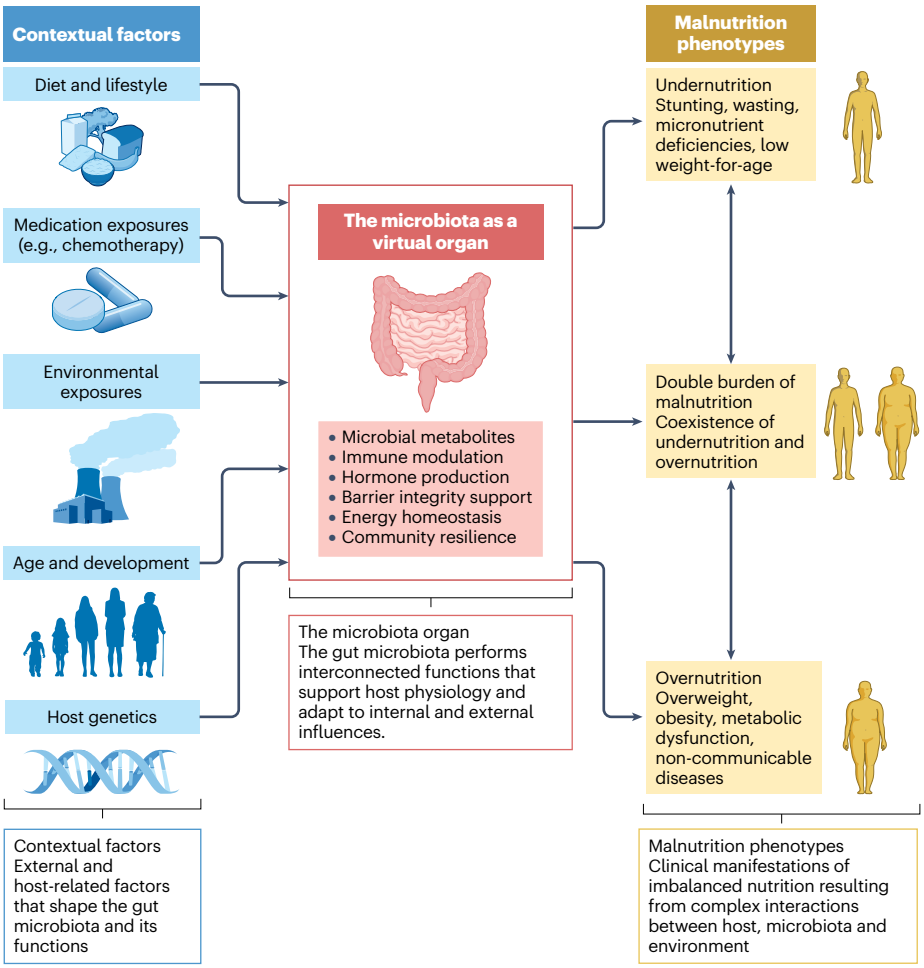

Fig. 1 | The gut microbiota as a virtual organ across the malnutrition spectrum. The gut microbiota can be conceptualized as a virtual organ, the composition and functional capacity of which are shaped by diet, environmental exposures, medication use and host developmental stage. This system produces a range of functional outputs, including microbial metabolites, immune-modulatory signals and factors that support intestinal barrier integrity, while also harbouring mechanisms for community resilience. In parallel, the microbiota is associated with key metabolic processes such as energy homeostasis and hormone production, which can influence growth, body composition and host systemic physiology. Across the malnutrition spectrum, alterations in these host–microbiota interactions are associated with undernutrition, overnutrition and the double burden of malnutrition, linking nutritional exposures with intestinal and system outcomes.

we use the term 'microbiota' to refer to the microbial community itself and consider its metabolic products as key functional outputs relevant to host physiology[15]. Despite its central role in health and disease, the concept of a 'healthy microbiota' remains a controversial and unresolved issue. A recent perspective argues that, rather than creating a single universal definition of 'microbiome health' based on taxonomic composition, the field should move towards a contextual and functional framework[16]. In this view, microbiome health is defined by the capacity of a microbial community to support its host's physiological functions, maintain ecosystem stability and remain resilient and adaptable to environmental and developmental changes[16]. For example, specific microbiota members ferment non-digestible fibres and resistant starches to produce short chain fatty acids (SCFAs), including butyrate, acetate and propionate. These metabolites represent key functional outputs through which the microbiota influences host energy balance, immune function and metabolic health[17]. Microbial communities also play an important role in nutrient absorption and utilization by modulating intestinal epithelial barrier function and bile acid (BA) metabolism and regulating the efficiency of fat and carbohydrate utilization[18].

Building on this perspective, the gut microbiota can be considered a resilient, metabolically dynamic, organ-like system that, in a healthy host, efficiently transforms dietary components into key metabolites that support overall health and physiological well-being. Much like adipose tissue, which is not a distinct anatomical organ such as the liver or heart yet is recognized as a complex and highly active endocrine organ, the gut microbiota should be similarly viewed as an organ-like system[19]. The concept of the gut microbiome as a 'virtual endocrine organ' was proposed more than a decade ago[20]. Within this organ-like framework, the gut microbiota can be viewed as a central metabolic system through which contextual factors, such as environmental exposures, medication use and host developmental factors, are integrated. Rather than acting as the sole driver of malnutrition, it serves as a key interface linking these inputs to downstream malnourished phenotypes. Thus, malnutrition is not only a consequence of inadequate or excessive nutrient intake but also involves impaired microbial processes that influence nutrient utilization, epithelial barrier maintenance, energy balance, immune function and metabolic signalling across the lifespan (Fig. 1). In this Review, we first summarize shared features of gut microbiota disruption across the malnutrition spectrum. We then examine how these compositional and functional changes manifest in undernutrition, overnutrition and the double burden of malnutrition. We also consider disease-related malnutrition, focusing on how gut microbiota alterations may contribute to impaired nutrient utilization, metabolic dysfunction, inflammation and clinical outcomes in chronic diseases. Within these sections, we integrate current evidence and seminal studies relating to microbial

metabolism and host–microorganism interactions. Finally, we discuss microbiota-targeted interventions and their potential to address malnutrition across diverse populations and settings.

Malnutrition and the gut microbiota

To provide context for the sections that follow, we first summarize key compositional and functional features of the gut microbiota that are shared across the malnutrition spectrum. Across humans and animal models, different forms of malnutrition are consistently associated with shifts in microbial diversity, taxonomic abundance and metabolite production, reflecting dynamic interactions between diet, microbiota and host metabolism[4,7,21–27]. As most microbiota studies rely on faecal samples, these observations largely reflect aggregate microbial composition rather than spatially resolved populations, and interactions among microorganisms are often inferred rather than directly measured because of technological limitations. These perturbations are commonly characterized by altered microbial composition, including decreased diversity, loss of beneficial taxa and expansion of opportunistic taxa, consistent with reduced ecological stability[4,7,21–28]. Advances in functional profiling further reveal altered production of microbial metabolites such as SCFAs, dysregulated host nutrient utilization and increased capacity for energy harvest[29–32]. Evidence from animal studies supports a causal role for the microbiota in malnutrition, as microbial transfer can recapitulate both obese and stunted (that is, undernourished) phenotypes in recipient hosts[24,26,33,34]. The term 'immature microbiome' was coined to refer a gut microbial population that is underdeveloped for a child's age, characterized by reduced diversity and altered composition, and associated with impaired linear growth and nutrition[24,27]. Collectively, observations from animal and human studies highlight shared disruptions in both microbial composition and function across the malnutrition spectrum (Fig. 2). In the following sections, we examine how these shared patterns manifest across the malnutrition spectrum and consider their implications within a microbial 'virtual organ' framework (Fig. 3).

Undernutrition and the gut microbiota

Undernutrition primarily arises from deficiencies in energy, protein and micronutrients, which frequently co-occur in clinical and population settings[35–40]. Stunting is the most prevalent manifestation of chronic undernutrition and reflects sustained deficits in protein and essential micronutrients. Although most gut microbiota studies in undernourished children have focused on stunting, similar microbiota-associated alterations have been reported across a broader range of populations, including non-stunted undernourished children and adults in both clinical and community settings[35–40]. Randomized controlled trials and systematic reviews suggest that many forms of undernutrition are largely refractory to nutritional interventions[41–47]. Although dietary interventions can improve weight and nutrient status in the short term, they often fail to completely restore linear growth or reverse associated persistent impairments such as stunting. They also often fail to substantially reduce infant and childhood mortality or prevent long-term negative consequences including cognitive delay and an increased risk of metabolic disease later in life[41–47]. Together, these observations suggest that recovery from undernutrition may be constrained by biological factors that extend beyond nutrient availability alone and thus remain incompletely understood.

Analyses of the gut microbiota, primarily from faecal samples, have identified a set of recurring compositional and functional patterns

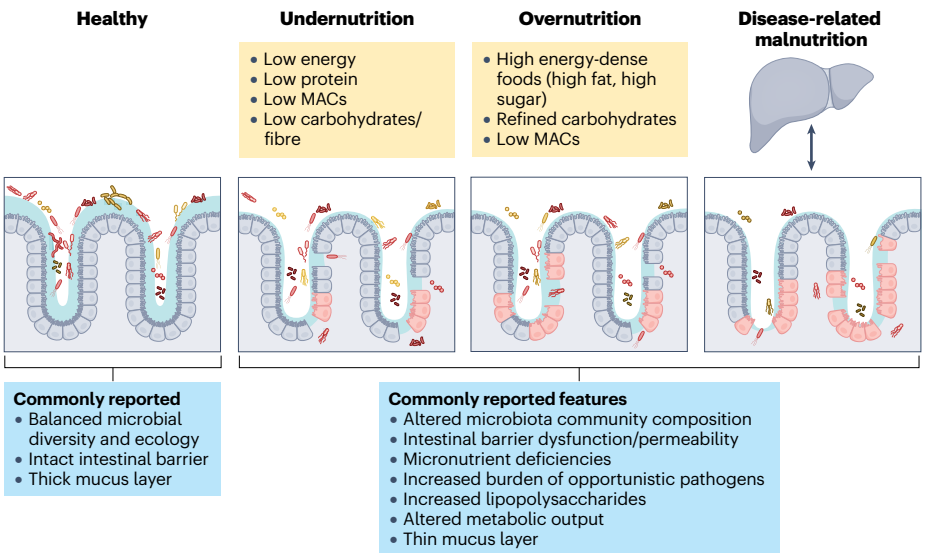

Fig. 2 | Microbial and epithelial features of malnutrition. Undernutrition and overnutrition are associated with distinct yet overlapping microbial and intestinal epithelial characteristics. The left panel depicts a healthy gut, with commonly reported features of a balanced microbiota, an intact epithelium and a thick protective mucus layer. In malnutrition, both undernutrition and overnutrition are associated with commonly reported shared features, including reduced microbial diversity, altered community composition and function, and increased presence of opportunistic pathogens. These states are also linked to epithelial alterations, including intestinal barrier dysfunction, increased permeability, bacterial translocation, higher lipopolysaccharide (LPS) levels, thinner mucus layer and micronutrient deficiencies. The double burden of malnutrition reflects the coexistence of undernutrition and overnutrition and may present shared characteristic features. Across clinical conditions such as inflammatory bowel disease and chronic liver disease, these microbial and epithelial features and micronutrient deficiencies also persist and may be further modified or exacerbated by underlying disease pathology. MACS, microbiota-accessible carbohydrates.

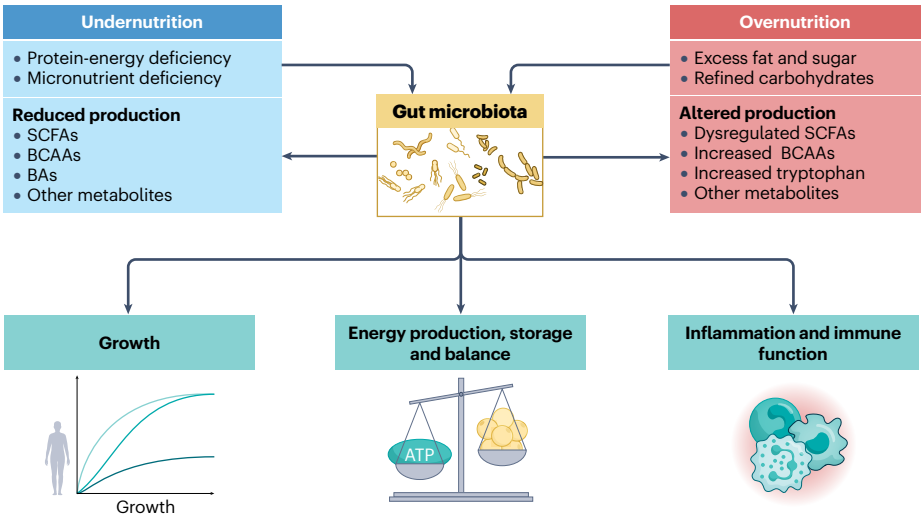

Fig. 3 | Altered metabolic output in undernutrition and overnutrition. The gut microbiota functions as a metabolic system that converts dietary substrates into active metabolites that influence host growth, energy balance, immune function and metabolic health. In undernutrition, protein-energy and micronutrient deficiencies are associated with reduced microbial production of key metabolites, including short-chain fatty acids (SCFAs), branched-chain amino acids (BCAAs), bile acids (BAs) and other metabolites. In overnutrition, excessive calorie intake from dietary fat, sugar and refined carbohydrates drives shifts in microbial output, resulting in dysregulated SCFA and BCAA metabolism, altered tryptophan metabolism, increased trimethylamine *N*-oxide production and changes in other metabolites. Across both forms, disrupted microbial outputs contribute to impaired growth trajectories, altered energy production, storage and balance, and heightened inflammation and immune dysregulation.

associated with undernutrition. These include reduced microbial diversity, expansion of opportunistic taxa and delayed or immature microbiota development[7,9,21,24,48–51]. In some contexts, these alterations also include decompartmentalization, defined as the loss of regional separation of microorganisms due to excessive translocation along the length of the gastrointestinal tract[52], loss of microbial diversity, and expansion of pathogens and other opportunistic taxa[7,9,21,24,48–51]. Collectively, these findings describe a microbiota profile that is associated with an altered ecological structure and reduced functional capacity. These compositional changes are accompanied by shifts in microbial metabolic output, including reduced production of SCFAs such as butyrate, altered levels of tryptophan-derived metabolites and changes in other important microbial products, which are involved in maintaining intestinal barrier integrity, immune function and host metabolism[7,9,21,24,48–51]. SCFAs serve as a major energy source for colonocytes and regulate intestinal gluconeogenesis via G protein-coupled receptors (GPR41 and GPR43), stimulating an increase in glucagon-like peptide 1, peptide YY and serotonin from the enteroendocrine L cells. They also promote the growth of beneficial bacteria such as *Bifidobacterium* spp. and *Lactobacillus* spp.[53]. Reduced SCFA availability is associated with impaired epithelial barrier function and altered host–microorganism signalling, although direct causal relationships remain incompletely defined.

Beyond carbohydrate fermentation, microbial metabolism of amino acids is also altered in undernutrition. Tryptophan is metabolized into indoles and tryptamine mainly by Bacillota, including *Clostridium*, *Ruminococcus*, *Blautia* and *Lactobacillus* species, which are often under-represented in malnourished individuals[54]. Indoles and tryptamine are known to directly affect intestinal health and nutrient acquisition by preventing inflammation, regulating epithelial permeability and promoting proper mucosal immune responses, primarily through the orphan aryl hydrocarbon receptor and the pregnane X receptor[55–60]. Reduced abundance of these taxa in undernourished populations is therefore consistent with altered production of these metabolites with functional consequences to the host and microbial environment.

Branched-chain amino acids (BCAAs) represent another metabolic interface between diet, microbiota and host physiology. A malnourished diet low in proteins but rich in carbohydrates and fats is likely to reduce the microbial synthesis of BCAAs, as well as their catabolism into branched-chain α-keto acids, branched fatty acids, 3-hydroxyisobutyrate and acylcarnitine[61,62]. The role of BCAAs in intestinal health is multifaceted, encompassing both positive and negative aspects. Whereas some pathogenic taxa, including members of Enterobacteriaceae, depend on BCAAs for growth, stress resistance and virulence, BCAAs also contribute to the maintenance of intestinal integrity by promoting incretin secretion from enteroendocrine cells and increasing intestinal immunoglobulin A secretion. Altered protein intake and microbial composition in undernutrition are therefore likely to influence BCAA-related metabolic pathways, with context-dependent effects on host physiology[63–68].

BAs are cholesterol derivatives synthesized primarily in the liver and secreted via the gall bladder into the intestines. Most primary BAs are reabsorbed in the terminal ileum, with only 5% proceeding into the colon, where they undergo modification by commensal bacteria, transforming them into secondary BAs that are then recirculated via portal vein to the liver[69]. This microbial transformation plays an important role in lipid digestion, absorption of fat-soluble vitamins (that is, vitamins A, D, E and K) and host metabolic signalling[70]. Alterations in BA metabolism have been reported in undernutrition[69]. In severe acute malnutrition, BA metabolism has been shown to be impaired, resulting in increased serum levels of secondary BAs, mainly glycine conjugates, which are negatively associated with liver health[69]. Disruptions in BA metabolism may therefore contribute to host growth impairment via fat-soluble vitamin malabsorption and various other adverse outcomes, chief among which are altered immunological functions and increased intestinal pathology[69,71].

Trimethylamine is another metabolite produced through the microbial metabolism of dietary choline, L-carnitine, ergothioneine and betaine and has been associated with cardiometabolic risk and adverse outcomes in multiple populations[72–74]. In clinical settings, including individuals on maintenance haemodialysis, higher circulating trimethylamine *N*-oxide (TMAO) levels have been correlated with protein-energy wasting and lower nutritional status indices[75]. However, these associations are difficult to interpret mechanistically, as TMAO levels are strongly influenced by renal function, inflammation

and overall disease burden. As such, current evidence supports a role for TMAO as a context-dependent biomarker rather than a consistent driver of malnutrition-related pathophysiology.

Several cohort studies have shown how these functional impairments manifest across different geographical settings. A cohort of children with stunting from Indonesia showed markedly lower abundance of Bacteroidota and higher Bacillota compared with children without stunting[76]. At the genus level, *Lachnoclostridium*, *Faecalibacterium* and *Veillonella* were also significantly increased in children with stunting[77]. Although these taxa are commonly associated with SCFA metabolism and lactate utilization, their enrichment in this context probably reflects an ecological adaptation of the gut microbiota to chronic undernutrition, in which both microbial composition and function shift to compensate for nutrient scarcity. Despite these changes, the altered microbiota remains unable to restore nutrient homeostasis to support healthy growth in children with stunting. Similar microbiota patterns have been reported across Asian cohorts, with increased abundance of Bacillota and Bacteroidota observed[78], although findings are not uniform and some studies have found no specific microbial signature for stunting[79]. Nevertheless, microbial shifts are consistently observed across children with stunting, with some heterogeneity related to age. One Bangladeshi cohort of young children with stunting found higher abundance of Pseudomonadota, *Bifidobacterium longum* and *Escherichia coli* and lower abundance of *B. adolescentis* compared with a control cohort of children without stunting[80]. Older children with stunting, however, seemed to have a different taxonomic profile, with greater abundance of *Klebsiella pneumoniae* and *E. coli*. This pattern of expansion of opportunistic taxa such as Pseudomonadota and *E. coli* reflects known effects of gut inflammation, which may further impair nutrient absorption and epithelial barrier integrity. These age-related patterns suggest that, although microbial composition shifts during development in children with stunting, the resulting inflammatory features of the gut environment persist and are therefore not dependent on age alone. Although these associations do not establish causality, they support a model in which microbial community structure and host inflammatory responses are closely linked in undernutrition, including impaired linear growth.

Similar features of gut microbiota instability have also been observed in children with stunting versus children without stunting in Africa. One study[52] demonstrated a strong association between stunting and the gut microbiota using faecal 16S rRNA gene amplicon sequencing, together with culture-based quantification of small intestinal bacterial overgrowth (SIBO) from duodenal aspirates. This association was characterized by microbial decompartmentalization, with an overrepresentation of oral bacteria residing in the stomach, small intestine and colon in children with stunting[52]. This translocation of bacteria to regions of the gut has important implications for malnutrition persistence, as misplaced microorganisms can often disrupt normal gastrointestinal function. For example, the small intestine is a critical site for the absorption of protein, carbohydrates, fats, vitamins and minerals as well as BA reabsorption[81]. Therefore, an increase in its microbial burden would intensify competition for nutrient resources while also potentially damaging the epithelium, further exacerbating malnutrition[81]. Furthermore, this loss of spatial organization may disrupt normal digestive processes, particularly in the small intestine where nutrient absorption is prominent. Indeed, SIBO contributes to nutritional deficiencies through nutrient competition, impaired digestion and absorption, and diarrhoea-associated losses[82,83]. A strength of the study is the integration of culture-based and sequencing methods in analysing the small intestine. This approach enabled multi-site characterization of microbial alterations along the gastrointestinal tract. However, as a cross-sectional study, it cannot establish causality or determine whether the observed microbial shifts are a cause or a consequence of stunting.

Other forms of undernutrition show related but distinct microbial features. In Gambian children with severe, non-oedematous undernutrition, reduced microbial richness and biomass, together with an enrichment of Enterobacteriaceae, including *E. coli* species, have been reported[84]. In addition, dysregulation of key energy hormones, including suppressed levels of leptin and insulin-like growth factor 1 (IGF1) and paradoxically elevated levels of ghrelin and soluble leptin receptor, was observed[84]. These findings highlight a breakdown of both microbial and host metabolic control, further supporting the view that the microbiota acts as an organ-like system that influences host physiology in malnutrition.

Most studies examining the gut microbiota in adults have been conducted in clinical settings, where undernutrition often co-occurs with acute illness, chronic disease or advanced age[85,86]. This complicates disentangling host-driven factors from microbiota-associated features of undernutrition. Nevertheless, similar patterns are observed to those seen in undernourished children, with altered microbial diversity linked to malnutrition severity[85]. A recent analysis of a longitudinal study of older adults receiving hospital care found that malnutrition severity was associated with reduced microbial diversity and distinct compositional changes, including significantly lower abundances of butyrate-producing taxa such as *Lachnospiraceae* NK4A136, *Subdoligranulum* spp. and *Faecalibacterium prausnitzii*, together with increased abundances of *Corynebacterium* spp., Ruminococcaceae Incertae Sedis and *Fusobacterium* spp. These patterns are frequently associated with ecological imbalance linked to inflammation and were noted to be strong predictors of worsened clinical outcomes in this setting[85,87,88]. Similar associations have been reported in community-dwelling older adults, in whom altered microbiome features were linked to poor appetite and undernutrition, including reduced abundance of *Blautia* spp. and lower faecal acetate levels. Notably, transferring microbiota from these individuals to germ-free mice recapitulated several clinical features such as reduced weight gain and altered body composition, supporting a causal role for the microbiota in shaping host nutritional outcomes in a community setting[89].

Not all studies, however, identify consistent microbiota differences. A community-based study in a rural and urban slum in Karnataka, India, comparing adults with low BMI across different environments, did not find consistent differences in overall microbial diversity but did report alterations in specific taxa and predicted microbial metabolic pathways, including carbohydrate and amino acid metabolism[90]. These functional profiles were inferred from 16S rRNA gene sequencing data and computationally mapped to Kyoto Encyclopedia of Genes and Genomes (KEGG) metabolic pathways. The study suggests that geography, lifestyle and demographic factors may exert a stronger influence on gut microbiota composition than nutritional status alone in these non-clinical settings and that predicted functional differences may occur even when overall diversity seems to be unchanged. Collectively, these findings, observed in both children and adults, suggest that undernutrition is consistently associated with a gut microbiota that is ecologically and functionally altered and support the concept that impaired microbiota development and function disrupt nutrient utilization and may constrain recovery from undernutrition even in the presence of nutritional repletion.

Micronutrient deficiencies represent an additional dimension of undernutrition with important implications for the gut microbiota. Deficiencies in vitamins and minerals can impair gut function, compromise intestinal barrier integrity and exacerbate the functional limitations of the microbiota observed in undernourished populations[91]. Although most studies have focused on supplementation and fortification, available data suggest that deficiency states are associated with reduced microbial diversity and compositional shifts and functional activity[91–98]. For example, a recent double-blind, cluster-controlled trial in school-aged Cambodian children found an association between vitamin A and iron deficiency and a specific microbiota pattern characterized by lower microbial α-diversity and evenness and altered β-diversity compared with non-deficient and older children, respectively[99]. Interestingly, iron-deficient anaemia was found to correlate with enrichment of *Prevotella* spp., whereas vitamin A deficiency was associated with enrichment of bacilli (Lactobacillaceae), *Gordonibacter* spp. and *Romboutsia* spp. Another study in children from Qatar found that vitamin D deficiency (that is, serum 25(OH)D <75 nmol l^{-1}) was associated with decreased microbial β-diversity and a significantly higher Bacillota-to-Bacteroidota ratio, together with dominance of the genus *Prevotella*, compared with children with sufficient levels of vitamin D[100]. Functional analysis showed enrichment of pathways linked to lipopolysaccharide (LPS) biosynthesis and primary immunodeficiency in the deficient group, whereas pathways involved in fatty acid and amino acid metabolism were enriched in children with sufficient levels of vitamin D. Although these findings are based on predicted functional profiles rather than direct metabolite or enzymatic measurements, they are consistent with vitamin D influencing gut microbial function indirectly through host-mediated mechanisms[101,102]. For example, vitamin D is known to support epithelial barrier integrity and regulate mucosal immune responses via vitamin D receptor-dependent signalling, which may in turn shape gut microbiota structure and functional potential[101,102]. Moreover, this pattern is therefore consistent with a state in which vitamin D deficiency is associated with weakened intestinal barrier and immune regulation, permitting expansion of taxa with greater LPS-producing capacity and a more pro-inflammatory functional profile. By contrast, vitamin D sufficiency has been associated with differences in gut microbial composition and predicted functional profiles, although these findings are not consistent across studies[100,101]. Expansion of Enterobacteriaceae in severe malnutrition and enrichment of taxa and pathways associated with LPS biosynthesis in micronutrient deficiency are consistent with a shift towards a more inflammatory and metabolically inefficient microbial state. Within this organ-like framework, these findings represent a transition from a gut microbiota optimized for nutrient processing and utilization that supports the host to one characterized by reduced functional capacity, increased immune activation and altered metabolic signalling.

Animal studies provide complementary mechanistic insight into this relationship. Sprague–Dawley rats fed a vitamin B6-deficient diet for 6 weeks were found to have a lower abundance of Verrucomicrobiota compared with rats fed a diet high in vitamin B6. Furthermore, levels of the SCFAs propionate and butyrate were markedly reduced in rats fed a low-vitamin B6 diet, with both gut and serum analyses indicating impairment of arginine biosynthesis, lysine degradation and nicotinate/nicotinamide pathways, suggesting that vitamin B6 deficiency constrains host metabolic capacity. Further analysis showed that *Lachnospiraceae* NK4A136 and *Bacteroides* spp. were the main drivers of the microbial changes observed in the vitamin B6-deficient groups[103].

We also recently showed that multiple micronutrient deficiencies (low iron, vitamin A, zinc, vitamin B12 and folate) in an early-life murine model significantly altered both host and microbial energy metabolism[3]. Mice fed a deficient diet for 4 weeks showed a shift in microbial composition, including increased relative and absolute abundances of Pseudomonadota and Enterobacteriaceae, respectively, and altered abundances of taxa involved in carbohydrate and amino acid metabolism. Our metagenomic analyses also showed reduced microbial function related to glycolysis/gluconeogenesis and SCFA production[3]. Host metabolic profiles also showed altered lipid and glucose metabolism, suggesting that nutrient scarcity constrained both microbial and host metabolic pathways.

Across models, these findings indicate that micronutrient deficiency consistently disrupts microbial fermentative capacity and energy-producing pathways, alongside a shift towards taxa such as Enterobacteriaceae that are associated with reduced metabolic efficiency and inflammation. Together, these findings suggest that undernutrition and micronutrient deficiency independently exert a substantial impact on the gut microbiota, contributing to impaired host energy production and other metabolic pathways. Evidence across humans and animals indicates that undernutrition is associated with alterations in gut microbial composition and metabolic function. These changes are consistent with disruption of a metabolically active, organ-like system that contributes to host energy balance, barrier integrity and immune regulation. However, the extent to which these microbial alterations act as causal drivers versus consequences or amplifiers of undernutrition remains an important area for further investigation.

Overnutrition and the gut microbiota

In contrast to undernutrition, overnutrition represents a distinct but related state in which chronic nutrient excess may drive characteristic alterations in the gut microbiota. As with undernutrition, these changes extend beyond microbial composition to altered metabolic output, including metabolites that influence the gut environment, epithelial barrier integrity, host metabolism and immune function[17,32,104]. Much like adipose tissue that responds to excess nutrients by storing energy and modulating endocrine signalling, the gut microbiota responds to dietary inputs by adapting its metabolic capacity and signalling pathways. Within this organ framework, these changes reflect functional adaptation to nutrient excess, although their downstream effects on host metabolism may be context dependent and correlative in nature. However, similar to undernutrition, the strength, direction and consistency of these findings vary across populations and study design. Importantly, host nutritional status does not necessarily reflect microbial substrate availability. Microbiota-accessible carbohydrates (MACs), largely derived from dietary fibre, represent a primary energy source for gut microorganisms[105,106]. Diets associated with overnutrition, particularly Western dietary patterns, are often energy dense but low in MACs, creating a relative state of substrate limitation for the gut microbiota despite host energy excess, functionally resembling a state of microbial undernutrition[105]. Under these conditions, reduced microbial fermentation may shift microbial reliance towards host-derived substrates, such as mucin glycans, a shift that has been associated with decreased production of SCFAs and mucosal thinning in experimental models[105,106]. In this section, we summarize reported features of the intestinal microbial community in overnourished populations across adults and children, highlighting mechanisms that may contribute to energy harvest, metabolic regulation and obesity-related disease risk.

Consistent with this, SCFAs are the most widely studied microbial metabolites produced from carbohydrate fermentation and are frequently reported to be altered in obesity; however, findings are inconsistent across studies[107–109]. Differences in SCFA production, however, seem to reflect differences in dietary intake, microbial composition and intestinal transit time, which limits their utility as sole markers of microbial energy harvest in humans[107–109]. These observations argue that metabolite profiles alone do not fully capture microbiota function, particularly in the context of excessive nutrient intake. Across both adult and paediatric populations, studies commonly show that the gut microbiota is also ecologically disturbed, including changes in community composition, structure and function[17,32,104]. Functionally, these microbial changes have been associated with increased capacity for energy harvest, impaired BA signalling and low-grade inflammation, although causal relationships remain incompletely determined.

Experimental studies have provided important insights into potential microbiota-mediated mechanisms linking the gut microbiota to host metabolic regulation in overnutrition. A seminal study demonstrated that a specific microbiome signature established during obesity contributes to the development and persistence of body weight gain. Using a 'yo-yo' diet model in mice, the authors showed that microbiota from mice that had previously been obese transmitted increased weight gain and metabolic dysregulation to germ-free recipient mice following faecal microbiota transplantation (FMT)[110]. Importantly, this work highlighted a potential explanation for why weight is rapidly regained after repeated on–off dieting or binge-eating cycles[110]. Notably, translating these findings to humans remains an active and ongoing area of research[111,112]. A recent double-blind, randomized, placebo-controlled trial examined FMT in adolescents with obesity over a 4-year follow-up period, during which participants received either placebo or capsules derived from lean donors[111]. No sustained differences in BMI or total body fat following the intervention were observed between the groups, and obesity prevalence remained unchanged at follow-up. Despite this, FMT was associated with persistent shifts in gut microbiota composition and inferred functions in a manner consistent with long-term engraftment. These changes were accompanied by modest and variable cardiometabolic effects in a subset of participants, including differences in fat distribution and insulin sensitivity, as well as alterations in pathways related to carbohydrate metabolism and microbial fermentation. However, these effects were not consistent across all participants. Nonetheless, these findings indicate that a single FMT intervention in adolescence can induce sustained changes in the gut microbial community and its functional capacity, but these changes do not translate into body weight changes. This supports a model in which the gut microbiota modulates host metabolic responses rather than directly determining obesity. These findings reinforce the notion that the gut microbiota contributes to host metabolism through regulatory signalling functions that extend beyond energy harvest alone. Whether or not FMT emerges as an effective therapy for obesity warrants further investigation.

Evidence from a randomized crossover feeding trial further supports a functional role for the gut microbiota in altering energy utilization. In a strictly controlled metabolic ward study, researchers used a 'microbiome enhancer diet', designed to directly deliver more fermentable carbohydrates to the colon[17]. This intervention increased microbial fermentation and total microbial biomass, diverting more dietary energy into growing microorganisms and their fermented metabolites, which were lost in faeces, and consequently resulting in a reduction in the amount of dietary energy available to the host. This study provides a mechanistic demonstration that the gut microbiota can actively divert energy away from the host through fermentation processes, thereby directly influencing host energy harvest efficiency, a mechanism that has been implicated in obesity development. Although these results are compelling, they were obtained from a small, tightly controlled setting, and broader applicability remains to be determined.

Evidence from multiple studies suggests that children with obesity may exhibit altered gut microbiota profiles compared with control cohorts without obesity, although findings are inconsistent across cohorts, particularly with respect to α-diversity[5,113,114]. For example, in the Dutch KOALA Birth Cohort, specific gut microbial taxa, rather than overall microbial diversity, were associated with increased body weight, with inverse associations observed for *Akkermansia*, *Prevotella* and *Sutterella* species and a positive association between *Streptococcus bovis* and being overweight[115]. Notably, despite its relatively large and well-characterized population, the KOALA study found that anthropometric measures explained only a small portion of the overall variation in microbiota composition, highlighting that effect sizes in population-based cohorts may be modest even when statistically significant associations with specific taxa are observed. Similar inconsistencies have been reported across other studies, with some cohorts demonstrating reduced microbial diversity in obesity and others identifying taxonomic shifts in the absence of diversity changes[104]. This heterogeneity probably reflects, in part, differences in study design, including variation in DNA extraction methods, sequencing approaches, reference databases and bioinformatic pipelines, as well as underlying population, dietary and environmental differences.

Other studies have shown an intergenerational effect, whereby maternal high-fat or high-fructose diets during pregnancy can adversely affect hepatic metabolism and increase susceptibility to steatotic (that is, fatty) liver disease in the offspring by differentially regulating the gut microbial composition[116,117]. In the Growing Life, Optimizing Wellness (GLOWING) cohort, the offspring of mothers with obesity were found to have a significant reduction in SCFA-producing bacteria such as *Ruminococcus*, *Turicibacter* and *Roseburia* species at 1 month of age[113]. The data suggest that disruption of those taxa linked to regulation of the immune system through SCFA production could potentially increase the risk of chronic diseases in later life[118,119]. Many of these studies, however, are correlative in nature, and causal mechanisms remain incompletely understood. Despite these limitations, the literature highlights the potential for microbial contributions to host energy balance, metabolism and inflammatory status in overnutrition[30,104,113–115,118]. In summary, overnutrition during early life, from conception through the first year of life, can alter gut microbiota maturation through persistent nutritional skewing, with effects that extend beyond dietary intake alone. They may thus contribute to long-term metabolic dysfunction, increasing the risk of being overweight or obese later in adult life. Together, these findings suggest that, although the gut microbiota is associated with obesity, its contribution is complex and context dependent and may be better understood in terms of functional capacity and host–microorganism interactions rather than diversity metrics alone.

Double burden of malnutrition and the gut microbiota

As previously discussed, LMICs are experiencing a rapid increase in the double burden of malnutrition (Box 1). The concept of the metabolic capacity load, developed by Wells, provides a useful framework for understanding this phenomenon by distinguishing early-life

metabolic capacity, including organ development and lean body mass, which determine the body's ability to maintain homeostasis, from later-life metabolic load, such as excess body fat and energy-dense diets[120]. Constraints on metabolic capacity during early life, including growth faltering or nutrient deficiencies, may limit the body's ability to appropriately respond to later excessive metabolic loads.

Within this framework, the gut microbiota can be viewed as a central player in metabolic capacity. Undernutrition has been associated with delayed or immature microbiota development and impaired metabolic function, which may influence energy utilization and host metabolic regulation. By contrast, overnutrition introduces a sustained metabolic load that may negatively interact with these early-life constraints potentially limiting the body's ability to effectively respond to nutritional excess.

The predictive adaptive response (PAR) theory proposed by Gluckman and colleagues argues that early-life nutritional and environmental exposures can programme a host's physiological responses for anticipated future conditions[121]. The PAR posits that organisms adapt their physiology during critical windows of development in anticipation of similar future environmental conditions, and when there is a mismatch between predicted and actual environments, disease risk may increase[121]. Emerging evidence suggests that the gut microbiota may participate in these adaptive processes, although further work is needed to understand the mechanisms[122,123]. Nevertheless, studies consistently show that early-life perturbations have lasting consequences. For example, early-life factors, including caesarean section birth, formula feeding, antibiotic exposure and undernutrition, have been associated with altered microbial colonization patterns and persistent changes in host–microbiota interactions[4,48,124]. These adaptations may confer short-term advantages in resource-limited settings but potentially become maladaptive when environmental conditions change.

Although research specifically examining the gut microbiota within the context of the double burden of malnutrition remains limited, a small but growing body of evidence suggests that there are distinct microbial patterns associated with this phenomenon. A study comparing school-aged Mexican children found that both undernourished children and children with obesity exhibited lower faecal bacterial richness and diversity compared with children without obesity[125]. Undernourished children had higher abundances of Bacillota and Lachnospiraceae, whereas children with obesity showed overrepresentation of Pseudomonadota, with these taxa correlating with energy intake, leptin levels and dietary fat intake. These findings suggest that the gut microbiota may also contribute to metabolic differences across the malnutrition spectrum within the double burden of malnutrition. These results are also correlative, and further mechanistic and longitudinal studies are needed to help to clarify any causal relationships and build a more robust understanding of microbiota-driven effects in this form of malnutrition.

Disease-related malnutrition and the gut microbiota

Beyond the various forms of malnutrition, nutritional deficiencies are highly prevalent among individuals with chronic metabolic and gastrointestinal conditions, such as cancer, chronic liver disease and inflammatory bowel disease (IBD)[126–129]. In these conditions, malnutrition may arise from increased nutrient demands due to infection or inflammation, reduced dietary intake or malabsorption[130–133]. Importantly, disease manifestations often co-occur within a complex host–microbiota environment where impaired nutrient metabolism and alterations in gut microbial ecology are closely interrelated, making their relative contributions difficult to disentangle[15,134]. IBD provides a well-studied example of this complexity, as it is a chronic inflammatory disorder marked by an inappropriate immune response against an altered gut microbiota in genetically susceptible individuals[126,135]. Both children and adult patients often exhibit deficiencies in micronutrients such as zinc, iron, folate and vitamin D that are not fully explained by dietary intake alone, suggesting that disease-related factors such as malabsorption, inflammation and microbial alterations may contribute. These deficiencies probably reflect a combination of reduced dietary intake, inflammation-associated metabolic alterations and impaired intestinal absorption, which are often attributed to mucosal damage and dysregulated host–microbial interactions[127,136–138]. Indeed, individuals with IBD often feature an altered gut microbiota compared with healthy individuals, characterized by reduced diversity, depletion of taxa such as *Faecalibacterium prausnitzii* and *Roseburia* spp. and expansion of opportunistic bacteria such as *Escherichia coli* and other Enterobacteriaceae[139]. These compositional changes are associated with shifts in microbial metabolic output, including reduced butyrate production, which may compromise epithelial barrier integrity and immune homeostasis[139].

Studies have also demonstrated that diet is a major determinant in shaping the IBD-associated microbiota, further complicating efforts to isolate disease-specific causal relationships[140]. A recent study examining colonic mucosal microbiota in individuals with IBD and concurrent protein–calorie malnutrition (PCM) found no significant differences in overall microbiota diversity when compared with individuals with IBD but without PCM even after adjusting for age, sex, body mass index and disease type[126]. Moreover, no differences in diversity metrics were observed even after accounting for disease duration, location, medication use or localized inflammation at the biopsy site. However, species-level differences were observed with increases in *Lachnoclostridium* spp., Pseudomonadota spp. and *Intestinibacter bartlettii* and reductions in *B. longum*, *Bacteroides thetaiotaomicron* and other beneficial microorganisms[126]. These taxonomic shifts are consistent with patterns associated with altered carbohydrate metabolism and fermentation[126,141]. Such changes support a potential role for gut microbiota dysfunction in IBD-associated malnutrition, possibly involving reduced nutrient processing capacity, although these functional consequences cannot be directly inferred from taxonomic data alone.

Similar microbiota–malnutrition interactions have been observed in other chronic disease states. In cancer, both microbial metabolites and inflammatory signals by tumour cells can disrupt energy metabolism, resulting in anorexia, cachexia and malnutrition[128]. Emerging evidence suggests that the gut microbiota may be involved in cancer-associated malnutrition, although current evidence remains largely associative and mechanistic understanding is still evolving[128,142]. In chronic liver disease, dysregulation of BA metabolism and portal hypertension are associated with gut microbial alterations, including shifts towards increased abundance of Pseudomonadota and reduced levels of beneficial commensals such as SCFA-producing taxa. This was accompanied by increased intestinal permeability, facilitating the translocation of microbial products into the circulation and promoting systemic inflammation[129,143]. This is further linked to disruptions in protein and energy metabolism, including increased proteolysis and impaired muscle protein synthesis, as well as worsening liver condition, reflecting a bidirectional gut–liver axis[143]. Importantly, malnutrition in chronic liver disease may occur in both states of nutrient deficiency and

excess, as seen in sarcopenic obesity, in which adiposity can coexist with progressive skeletal muscle loss[129]. This highlights that altered host metabolic regulation, rather than nutrient availability alone, contributes to changes in body composition and energy pathways in chronic disease states. However, across these conditions, disentangling the independent effects of disease, diet and gastrointestinal dysfunction remains challenging, although converging evidence implicates gut microbiota-associated effects. These observations are consistent with the concept that the gut microbiota functions as a metabolic interface that modulates host nutrient processing and systemic metabolism across multiple disease and pathological conditions.

Gut microbiota targeted interventions for undernutrition

Despite recognition of the gut microbiota as a key metabolic interface of host nutrient processing and systemic health, several conventional strategies aimed at addressing undernutrition and overnutrition have demonstrated only limited or inconsistent success[144–149]. For example, evidence for the water, sanitation and hygiene (WASH) programme in preventing and treating acute malnutrition in children under 5 has been limited, as it did not lead to meaningful changes in health or sanitation behaviours associated with malnutrition[149]. Similarly, the Sanitation Hygiene Infant Nutrition Efficacy (SHINE)[144] trial did not show significant improvements in preventing enteric infections in children. Both studies also showed little or no impact on the gut microbiome, and only marginal effects on stunting were observed[4].

Interventions aimed at preventing or treating childhood and adult obesity through diet, lifestyle modifications and pharmacological intervention have also shown mixed success[146–148,150,151]. Although calorie restriction, behavioural counselling and structured physical activity interventions can produce reductions in BMI and improve metabolic biomarkers, effects in many cases can be modest and short lived. These recalcitrant features highlight why the obesity epidemic remains a substantial health challenge[146–148,150]. More recently, researchers have turned their attention to targeting the gut microbiota as a therapeutic strategy in both undernourished and overnourished contexts[152–157]. This shift reflects growing interest in whether the altered or maladapted microbiota states observed in malnutrition can be functionally restored through targeted nutritional interventions. Microbiota-directed complementary foods (MDCFs) have shown promising effects in undernutrition, although evidence remains context specific. A study supplied three MDCF formulation prototypes to undernourished Bangladeshi children aged 12 to 18 months[156]. Notably, compared with standard ready-to-use supplementary food, children who received the MDCF-2 formula containing ingredients such as chickpea, peanut paste, soy flour, green banana, micronutrients, and oils, gained more body weight and showed favourable alterations in their gut microbiome, resulting in a microbiota composition similar to that of healthy control individuals. They also showed an improved serum proteome including bone growth, neurocognitive and immune-related proteins[156].

Preliminary insights from the BE-GONE trial highlight the potential for prebiotic foods to modulate the gut microbiota and improve metabolic health in patients at high risk for metabolic disease[158]. The trial demonstrated that adding beans to the diets of individuals with obesity and a history of colorectal neoplasia led to an increase in their gut microbiota diversity and shifted microbial populations, alongside associated changes in circulating metabolites and inflammatory biomarkers, although clinical end points remain exploratory[158]. Other trials are currently underway to directly target the gut microbiota in acute undernourished children (ClinicalTrials.gov identifier number NCT06155474)[159] and obesity (ClinicalTrials.gov identifier number NCT04780477)[160], reflecting growing interest in microbiota-based therapeutic strategies.

Two recent systematic reviews and meta-analyses suggest that probiotic supplementation, as a microbiota-targeted intervention, frequently demonstrates beneficial effects on weight and growth markers in studies of undernourished children in LMICs[155,161]. However, results vary across studies and are highly strain specific. Moreover, many trials did not consistently assess changes in gut microbiota composition or function. Studies have also examined prebiotics and synbiotics, and although effects were variable, these supplements did moderately improve weight gain and growth, potentially supporting their role as complementary strategies alongside standard nutritional interventions[155,161]. Additionally, emerging products such as synbiotics (combinations of live bacteria and prebiotics) that can promote the growth and function of beneficial microorganisms represent an attractive therapeutic approach that remains to be further explored in the malnutrition field[162].

At present, there is limited clinical data on FMT in undernourished children and adults. A prospective observational study of washed microbiota transplantation (WMT) in children with gastrointestinal disease-related malnutrition showed promise[163]. WMT involves processing donor stool through repeated microfiltration, centrifugation and washing, producing a purified microbial suspension with a higher safety profile compared with traditional FMT. The suspension is then delivered via an enteral tube to the patients' intestine. At the end of the trial, approximately 48% of treated children achieved a clinical response, including significant increases in serum albumin and prealbumin levels and marked reductions in diarrhoea, abdominal pain and hematochezia[163].

By contrast, microbiota-targeted interventions for obesity have produced more variable and, in many cases, modest yet promising effects[26,153,154,164,165]. Multiple meta-analyses of randomized controlled trials report that probiotic supplementation as a microbiota-targeted therapy is associated with statistically significant reductions in body weight, BMI, body fat percentage, waist circumference and visceral adiposity compared with placebo controls[166–168]. However, the effect sizes across these studies have been limited, and substantial variability in probiotic strains, intervention duration and methodological assessment has limited clinical interpretation and subsequent implementation of probiotics as a stand-alone therapy for obesity. Nonetheless, combination interventions that integrate microbiota-targeted therapy with lifestyle modification show some promise. In a longitudinal intervention study, the authors evaluated the effects of prebiotics, probiotics and regular exercise on body composition and metabolic markers of obesity and found significant differences in the body composition, gut microbiota and metabolic and anthropometric markers of obesity in Egyptian women over a 3-month period[169]. Although the intervention resulted in significant reductions in body weight, BMI and metabolic markers of obesity such as leptin and aspartate aminotransferase, the authors did not report the magnitude of these changes. They also found positive changes in the gut microbiota including increases in the abundance of *Bifidobacterium*, *Lactobacillus* and species within Bacteroidota. These findings suggest that, although combined microbiota-targeted and exercise interventions can produce positive outcomes for obesity, their effects are often modest and may not be sustained without longer-term follow-up and standardized protocols.

FMT has also been explored as a microbiota-targeted intervention for obesity and related metabolic disorders, and like many other therapies, the evidence at present remains inconsistent[26,112,170,171]. Multiple randomized controlled trials and meta-analyses demonstrate that FMT consistently alters gut microbial composition and yields short-term improvements in insulin sensitivity, glycaemic control and selected cardiometabolic markers. Unfortunately, robust and persistent effects on body weight or BMI have not been found[26,112,170,171]. Overall, results from these studies suggest that this approach could offer potential benefits in reducing abdominal adiposity and inflammation, improving lipid profiles and regulating glucose homeostasis, although the effects are generally transient. A more recent follow-up study of adolescents with obesity treated with FMT showed that, 4 years after using a single-donor FMT, there were no statistically significant differences in BMI between the donor recipients and the placebo group. However, significant improvements were found in body composition, including reduced waist circumference, and in metabolic markers such as reduced systemic inflammation and higher high-density lipoprotein (HDL) cholesterol compared with placebo. Moreover, donor-derived bacterial strains persisted long term in the recipient gut microbiota, demonstrating sustained engraftment over time[111]. Another randomized controlled trial in adults undergoing bariatric surgery found that FMT had no significant effect on body weight either before or after surgery and no meaningful impact on obesity-related metabolic biomarkers such as HDL, triglycerides and fasting glucose, except for a modest reduction in total body cholesterol levels[111,171–179]. Personalized approaches, such as combining dietary interventions with FMT or using engineered microbiota consortia to restore gut microbiota balance, may therefore hold promise[180].

It should be noted that improving intestinal structure and function remains paramount in malnutrition. In addition to microbiota-targeted therapies, reinforcing intestinal mucosal barriers with bioengineered mucus represents another therapeutic alternative. The authors of a review describe how engineered mucus, including synthetic mucin — the main structural component of mucus — generated using hydrogels and engineered glycans, can help to restore gut architecture[181]. They also highlight that using engineered mucus in physiologically relevant systems, such as organoids (three-dimensional mini gut structures) and gut-on-a-chip systems (microfluidic devices lined with organoid-derived intestinal epithelial cells), provides a practical way to test how these systems reinforce the epithelial barrier and modulate the microbiota structure and function. Indeed, others have already begun using organoids and gut-on-a-chip models to study malnutrition and its effects on the gut. One study developed a method to produce malnourished intestinal organoids by culturing them in media deficient in both macronutrients and micronutrients[182]. These organoids recapitulated key features of the undernourished epithelium, including increased paracellular permeability and heightened susceptibility to bacterial infection, specifically with *Shigella flexneri*. An intriguing finding was the increased gene and protein expression of MUC2, the main mucin protein in the gut, which probably reflects a stress-induced compensatory attempt to maintain a failing epithelial barrier. Moreover, studying undernutrition in vitro has long been challenging owing to the difficulties of maintaining cell viability under nutrient-depleted conditions; thus, this model represents a new, physiologically relevant system to investigate the epithelial and metabolic consequences of nutrient deficiency. Importantly, it also provides a platform to mechanistically explore why simple nutrient replacement often fails to rescue undernutrition. It would be intriguing to test whether similar nutrient-modified media could be applied to mimic overnutrition in an organoid model.

Another study also examined undernutrition by exposing a human intestine-derived gut-on-a-chip system, generated from intestinal cells obtained from malnourished children, to nutrient-deficient conditions that mimic aspects of environmental enteric dysfunction (EED), a chronic malnutrition-associated intestinal disorder[183]. When these intestinal chips were cultured in media deficient in niacinamide and tryptophan, they recapitulated multiple features of EED, including significantly reduced growth of villous-like structures, compromised barrier function and impaired fatty acid and amino acid transport. Nutrient deficiency also produced gene expression changes in the chips that overlapped with the transcriptional profiles seen in intestinal tissues from EED donors, including downregulation of pathways involved in nutrient uptake and metabolism, further validating the relevance of the model. This tool provides a powerful approach to dissecting the

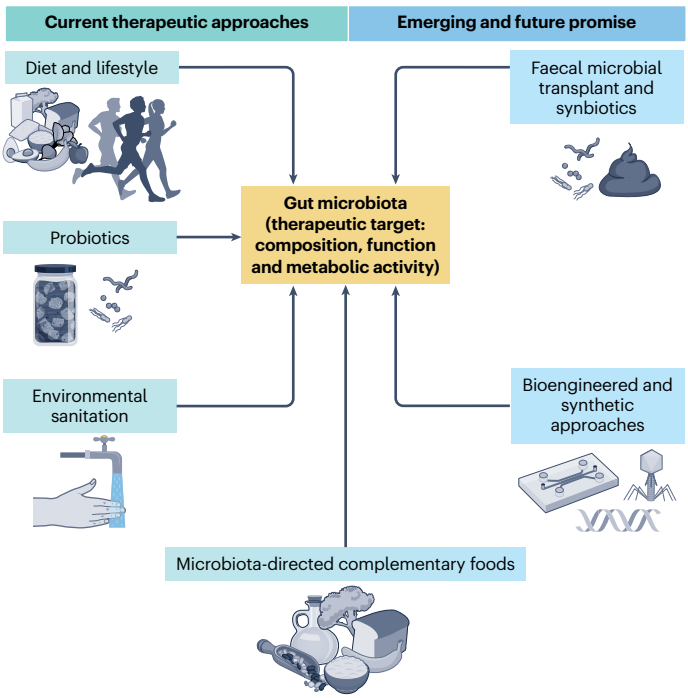

Fig. 4 | Current and emerging therapeutic approaches targeting the microbiota in malnutrition. Conventional strategies to address malnutrition have focused on lifestyle and environmental interventions, including dietary modification and physical activity in overnutrition, as well as improved sanitation and hygiene in undernutrition and limited use of probiotics in both. Despite decades of implementation, these approaches have achieved variable success, and global rates of malnutrition across the spectrum remain largely unchanged. Growing recognition of the importance of the gut microbiota in health and disease has shifted attention towards microbiota-targeted interventions in malnutrition. Emerging approaches include microbiota-directed complementary foods, faecal microbial transplantation with or without prebiotics or synbiotics, and strategies aimed at reinforcing the intestinal barrier through bioengineered mucus. In conjunction, advanced in vitro models such as organoids and gut-on-a-chip systems provide physiologically relevant platforms to interrogate malnutrition mechanisms and nutrient–microbiota interactions relevant to precision therapies. By integrating microbiota-targeted interventions with bioengineered models, this framework positions the microbiota organ as a central player in more effective malnutrition therapies.

molecular, genetic and functional basis of intestinal injury caused by nutritional deficiencies. Similarly, this model could be used to explore overnutrition.

Furthermore, co-culturing organoids and gut-on-a-chip platforms with microbiota would enhance their physiological relevance and enable the investigation of host–microorganism interactions and microbial influences on nutrient metabolism[184,185].

Overall, evidence suggests that microbiota-targeted therapies show clear promise for addressing undernutrition, whereas in overnutrition, a deeper understanding of the microbiota structure and function is needed to develop effective interventions, in the same way that advances in other organ systems have enabled new approaches for therapies, such as stem cell regenerative therapy or immunotherapy for cancer. The recent switch in the field towards recognizing the microbiota as a functional entity that can be directly targeted for therapeutic benefit further underscores its potential as an actionable component of health, including in malnutrition. Framing the gut microbiota as a functional and targetable organ should pave the way for a new generation of precision microbiota-based therapies that move beyond the standard 'one-size-fits-all' nutritional approaches. As highlighted throughout this Review, malnutrition is not driven by a single microorganism but rather reflects collective shifts in microbial communities, the genes they encode and the metabolic pathways they regulate. Accordingly, a holistic focus on microbial function, rather than taxonomic composition alone, is essential for understanding how microbial metabolism influences nutrient utilization, barrier integrity and host immune responses. This functional perspective supports the development of context-dependent interventions that are adaptable across the malnutrition spectrum and underpins emerging strategies (Fig. 4).

Conclusions

An emerging paradigm shift now recognizes malnutrition as a condition that reflects impairments in both nutrition and host–microbiota interactions within the gut ecosystem. Although most current interventions continue to prioritize diet, sanitation and environmental factors, their limited and often inconsistent results across different forms of malnutrition point to a critical gap in how we conceptualize and treat malnutrition. Specifically, these approaches largely overlook the gut microbiota as a contributing biological component of nutritional status and metabolic flexibility. To effectively address all forms of malnutrition, future strategies must move beyond nutritional supplementation alone and integrate approaches that restore both nutrient homeostasis and microbial function. Synthesizing evidence across the fields of undernutrition and overnutrition helps to reveal shared microbial and metabolic patterns and provides a framework for mechanistic and translational research that can better guide the development of more effective and context-dependent interventions.

The gut microbiota functions as a dynamic organ-like system, producing a diverse set of microbial metabolites that regulate the host's nutrient absorption, energy balance, immune function and systemic physiology. Across the malnutrition spectrum, disruptions in microbial composition and substrate availability have been shown to alter these outputs, contributing to impaired growth, metabolic dysregulation and increased susceptibility to disease. Research on specific microbial metabolites, including SCFAs, BAs and other bioactive microbial molecules, underscores the importance of linking microbial composition to functional outcomes rather than relying on taxonomic profiles.

Emerging therapeutic interventions targeting the gut microbiota provide proof-of-principle evidence that restoring microbial function can influence clinical outcomes. Microbiota-directed complementary foods in undernourished children seem to hold the most promise. Moreover, dietary, prebiotic and probiotic approaches in overnutrition demonstrate to varying degrees that microbial metabolism is modifiable and clinically relevant. More extreme interventions, such as FMT, hold promise to conceptually position the gut microbiota as a functional organ by directly replacing a disrupted microbial composition with one that either carries its own metabolic function or restores the function of the original.

Together, this framework places the gut microbiota at the centre of efforts to understand and address malnutrition. By prioritizing microbial function in concert with host nutrition, this conceptualization opens the door to precision, mechanism-driven interventions that may be adaptable across different forms of malnutrition and developmental stages. Continued integration of microbiota science with clinical research and public health initiatives offers the potential to develop innovative, sustainable and globally relevant strategies for addressing malnutrition and improving health outcomes for vulnerable populations worldwide.

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Author contributions

P.T.L. researched data for the article. P.T.L. and B.B.F. contributed substantially to discussion of the content. P.T.L., R.H. and B.B.F. wrote the article. All authors reviewed and/or edited the manuscript before submission.

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