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Review

# Gut microbiota alterations and dietary modulation in childhood malnutrition – The role of short chain fatty acids

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SUMMARY

The gut microbiome affects the health status of the host through different mechanisms and is associated with a wide variety of diseases. Both childhood undernutrition and obesity are linked to alterations in composition and functionality of the gut microbiome. One of the possible mechanisms underlying the interplay between microbiota and host metabolism is through appetite-regulating hormones (including leptin, ghrelin, glucagon-like peptide-1). Short chain fatty acids, the end product of bacterial fermentation of non-digestible carbohydrates, might be able to alter energy harvest and metabolism through enteroendocrine cell signaling, adipogenesis and insulin-like growth factor-1 production. Elucidating these mechanisms may lead to development of new modulation practices of the gut microbiota as a potential prevention and treatment strategy for childhood malnutrition. The present overview will briefly outline the gut microbiota development in the early life, gut microbiota alterations in childhood undernutrition and obesity, and whether this relationship is causal. Further we will discuss possible underlying mechanisms in relation to the gut–brain axis and short chain fatty acids, and the potential of probiotics, prebiotics and synbiotics for modulating the gut microbiota during childhood as a prevention and treatment strategy against undernutrition and obesity.



## 1. Introduction

Childhood obesity has reached epidemic levels in both developed and developing countries and it can profoundly affect social and emotional well-being of the children as well as non-communicable disease risk in later life [1,2]. Childhood undernutrition, in the other end of the malnutrition spectrum, accounts for 45% of all deaths for children under 5 years worldwide [3,4]. Children who survive undernutrition have increased risk of altered cognitive and motor development, in addition to obesity and non-communicable diseases in later life [5]. Thus, the etiology of childhood malnutrition and strategies towards prevention and treatment are of major interest and the gut microbiota might be a potential target for prevention and treatment of childhood malnutrition.

The human gut microbiota consists of trillions of microorganisms with more than 1000 different bacterial species [6–8]. The two approaches to culture-independent techniques: 16S rRNA amplicon sequencing and shotgun metagenomics are widely used to characterize the gut microbiome. 16S rRNA amplicon sequencing targets marker genes for taxonomic classification [9]. 16S rRNA sequences can be clustered into Operational Taxonomic Units (OTUs) according to sequence similarities. OTUs are assigned to taxonomic groups at different levels further to be used for characterization of the microbiota through estimates of α- (within sample) and β- (between sample) diversity indices, composition

*Abbreviations:* BMI, body mass index; CNS, central nervous system; COGs, clusters of Orthologous Groups; EECs, enteroendocrine cells; FFA, free fatty acid receptor; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; GIT, gastrointestinal tract; GF, germ-free; GLP-1, glucagon-like peptide-1; GPCRs, G-protein coupled receptors; HAZ, height for age z-score; HIV, human immunodeficiency virus; HMOs, human milk oligosaccharides; IGF-1, insulin-like growth factor-1; IOTF, international obesity task force; MAZ, microbiota-for-age z-score; MAM, moderate acute malnutrition; OTUs, operational taxonomic units; PYY, polypeptide YY; RUTF, ready to use therapeutic food; SAM, severe acute malnutrition; SCFAs, short chain fatty acids; SDS, standard deviation score; TLR, toll like receptor; WAZ, weight for age z-score; WHZ, weight for height z-score; WHO, world health organization; FUT2, α-1,2 fucosyltransferase; FUT3, α-1,3/4 fucosyltransferase; 16S rRNA, 16S ribosomal ribonucleic acid.

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and richness [10]. Metagenomics (whole-metagenome shotgun sequencing) provides more specific taxonomic and functional identification by massive parallel sequencing of whole "microbiota genomes" [11]. Superior to amplicon sequencing, whole-metagenome shotgun sequencing allows direct functional profiling of microbial communities as it is not limited with single marker gene amplification [12].

The commensal bacteria and their genome affect the health status of the host through modulation of energy harvest, immune system, metabolic and hormonal signaling and metabolism of xenobiotics [13]. Through these mechanisms the gut microbiota has been associated with a wide variety of conditions including obesity and undernutrition (32–34). Possible mechanisms underlying the interplay between microbiota and nutritional status involve the gut–brain axis [14]. Short chain fatty acids (SCFAs), the end product of bacterial fermentation of non-digestible carbohydrates, might be able to alter energy harvest and metabolism through enteroendocrine cell (EEC) signaling, adipogenesis and insulin-like growth factor-1 (IGF-1) production [15–17]. However, to what extent these mechanisms play a role in the etiology and prognosis of childhood malnutrition is not clear. Thus, elucidating these mechanisms may lead to development of new modulation practices of the gut microbiota as a potential prevention and treatment strategy for childhood malnutrition.

The aim of this critical review is to discuss the establishment of gut microbiota in the early life, the link between the gut microbiota and childhood malnutrition, the possible underlying mechanisms in relation to gut–brain axis and short chain fatty acids, and the potential of nutritional interventions aimed at modulating the gut microbiota during the childhood as a prevention and treatment strategy towards undernutrition and obesity.

## 2. Methods

We searched two electronic databases (Pubmed and Web of Science), using key terms such as ((malnutrition OR malnourished OR undernutrition OR growth impairment OR growth faltering OR severe acute malnutrition OR moderate acute malnutrition OR stunting) OR (obesity OR obese OR overweight OR weight gain OR excessive body weight OR body mass index)) AND (gut microbiota OR dysbiosis OR gut microbiome OR metagenomics OR gut microbiota immaturity OR intestinal microflora OR culturomics OR prebiotics OR probiotics OR synbiotics OR human milk oligosaccharides) with age (birth-18 years) and language (English) filter. We included human studies and animal models. The last literature search is made on January 3, 2018. In order to supplement the search results, we searched reference lists of the reviewed studies.

## 3. Gut microbiota in early life

Until recently, the fetal gastrointestinal tract was considered to be sterile, but new findings suggest that prenatal mother-to child transmission of commensal bacteria may take place. Low numbers of bacteria were shown to be present in first-pass meconium samples from healthy term infants [18,19], and genetically labelled strains have been isolated from the offspring of inoculated pregnant mice [20]. However, the contribution of in-utero transmission to fetal gut colonization remains controversial [21,22]. During and after delivery, the colonization of the gut takes place under influence of factors such as mode of delivery, gestational age, maternal body mass index (BMI) and microbiota, infant feeding, host genetics, antibiotic exposure, pets, number of siblings and geographical habitat [21,23–25]. Infants delivered by cesarean section are initially colonized with skin associated species and vaginally born infants are colonized with their mothers vaginal and fecal microbiota [26]. Maternal BMI and delivery mode can affect the vertical transmission of gut microbiota from mother to infant [27]. Excess maternal pre-pregnancy weight is associated with enrichment in *Bacteroides* and depletion in *Enterococcus, Acinetobacter, Pseudomonas* and *Hydrogenophilus* in neonatal gut microbiota following vaginal, but not cesarean delivery [28]. Contradictive results have been published regarding the link between delivery mode and establishment of gut microbiota. A cohort of breastfed infants confirmed that early neonatal microbiota composition and urine metabolome is affected by mode of delivery and gestational age during the first 6 months of life [29]. During the first year of life, delayed colonization and prominent differences in taxonomic composition were observed in gut microbiota of cesarean compared to vaginal delivered infants but the difference is less pronounced after the first 5 months of life [30]. A recent systematic review suggests that gut microbiota composition differs between vaginally born and C-section delivered infants during the first 3 months, whereas delivery mode has less effect on colonization and diversity of gut microbiota at 6–12 months which corresponds to transition to complementary feeding [31]. However, in a longitudinal study of infant microbiota across body sites, the structure and function of the gut microbiota dodoes not differ between vaginally and cesarean delivered infants [32]. The authors speculated that the reorganization of infant microbiota during the first 6 weeks of life is mainly driven by body site, not by delivery mode.

Breastmilk not only provides energy and nutrients for the infant but also contains a diverse microbiome and human milk oligosaccharides (HMOs) with prebiotic properties [33]. The composition of the human milk microbiome varies in accordance to geographical location, mode of delivery, maternal BMI and duration of lactation [34,35]. The mature breast milk is dominated by bacteria typical to the oral cavity (e.g. *Veillonella*, *Leptotrichia*, and *Prevotella*), in addition to lactic acid bacteria [35]. Previously, *Bifidobacterium, Bacteroides, Parabacteroides* and several butyrate producing members of Clostridia have been shown to be present in breast milk, maternal and neonatal feces, indicating that vertical transmission from mother to neonate via breastfeeding may occur [36]. In a pilot study in 10 mother–infant pairs, shared genera with human breast milk accounted for 70–88% of the total relative abundance in infant fecal samples [37]. Breastfeeding and transition to complementary feeding are proposed to be the main driver of gut microbiota shifts during the first years of life [38]. Gut microbiota of breastfed infants is dominated by *Bifidobacterium*, *Lactobacillaceae* and *Enterobacteriaceae*, whereas the gut microbiota of infants on complementary feeding are enriched in species belonging to Clostridia, *Bacteroides, Lachnospiraceae* and *Ruminococcaceae*. [24,38,39]. Fecal *Bifidobacterium* are found to be more pronounced in breastfed infants compared to standard formula fed infants [40]. Exclusively breastfed infants have enriched levels of bacterial genomes involved in oxidative phosphorylation and synthesis of riboflavin, tetrahydrofolate, biotin and α-amylase compared to formula fed infants [24]. Moreover, breastfeeding influences the gut microbiota metabolites. Exclusively breastfed compared to mainly formula fed infants have a higher proportion of fecal acetate relative to other SCFAs [41]. Transition from breastfeeding to regular foods with high protein and fiber content is linked to increased α-diversity indices (Shannon diversity index, observed genera and Pielou's evenness) indicating a progression to a more complex and balanced microbial community [38,42]. Introduction of cereal + fruit and meat was leading to increased gut microbiota richness in a randomized controlled trial (RCT). However, relative abundance of dominant bacterial phyla and families were not different across different types of first complementary foods (cereal, cereal + fruit and meat) [43]. The carbohydrate profile of infant cereals may affect the fermentation by gut microbes. Two months' intervention with

infant cereal with a higher ratio of complex vs. simple carbohydrates resulted in higher fecal butyric acid concentration and lower pH without any significant change in the composition of the gut microbiota in a double-blind RCT [44].

The complex and dynamic ecosystem of the gut microbiota is mainly shaped during the first years of life, and microbiota-modulating exposures during these years might be crucial in terms of maturation of the immune system and resemblance to a balanced adult-like microbiota [45]. The composition and network structure of infant gut microbiota seems to be adapting to resources feeding the community, available energy substrates and other environmental factors [24]. Although there is a growing evidence regarding the importance of the infant feeding regime on the establishment of their gut microbiota, more research is needed to optimize knowledge on the introduction time and composition of the complementary feeding to promote the development of a balanced gut microbiota [38].

## 4. Gut microbiota alterations in childhood malnutrition

### 4.1. Childhood undernutrition

Definitions of childhood undernutrition includes underweight (low weight-for height < -2SD), wasting (low weight for age < -2SD) and stunting (low height for age < -2SD), where underweight often is linked to acute and/or chronic malnutrition, wasting to acute malnutrition, and stunting to chronic malnutrition [4,56,57]. There are two clinical forms of undernutrition; Marasmus, described as a wasting syndrome without edema, and kwashiorkor, characterized by edema [58]. Even though undernutrition often is a consequence of inadequate food intake, the etiology of childhood undernutrition cannot simply be explained by limited access to macro- and micro-nutrients, but may be due to a complex interplay between factors such as food insecurity, impaired absorption due to recurrent infections, decreased immune function, host genotype together with alteration in gut microbial structure and function [59]. The development and maturity of the gut microbiota can be disturbed by childhood undernutrition [60]. Subramanian et al. [49] defined 'relative microbiota maturity index' and 'microbiota-for-age Z-score (MAZ)' in a Bangladeshi birth cohort. Further they showed that children with moderate acute malnutrition (MAM) and severe acute malnutrition (SAM) have lower relative microbiota maturity and lower Shannon diversity index (α-diversity) compared to healthy controls. Moreover, several taxa positively linked to relative microbiota maturity were found to be depleted in all phases of SAM [49]. The difference in MAZ and microbiota maturity remained after intake of ready to use therapeutic food (RUTF) and locally produced rice-lentil based (khichuri-halwa) undernutrition treatment within and beyond 3 months follow-up. The link between microbiota immaturity and undernutrition is validated by Blanton et al. [51], where they showed a positive correlation between MAZ score and weight for height Z-score (WHZ) and weight for age Z-score (WAZ). Additionally, MAZ at 12 months was found to be positively related to WHZ and WAZ at 18 months of age suggesting that MAZ may be a predictor of future growth.

Several studies showed taxonomic and functional alterations of the gut microbiota in childhood undernutrition. In a cross-sectional study of Bangladeshi children, undernutrition linked to a less diverse microbiota, defined by the lower number of OTUs in undernourished microbiota characterized with higher Proteobacteria and lower Bacteroidetes compared to the healthy controls. Moreover, higher abundance of *Klebsiella* and *Escherichia* was found in the gut microbiota of malnourished children [46]. Kwashiorkor microbiota associated with lower β diversity and specifically a lower anaerobic diversity including depletion in *Methanobrevibacter smithii*. Additionally kwashiorkor microbiota is enriched with the potentially pathogenic Proteobacteria, Fusobacteria and *Streptococcus gallolyticus* [55]. In contrast, no significant difference was found in β-diversity and the abundance of specific genera with respect to oedema in SAM in a cross sectional study of Ugandan children. However, α-diversity found to be lower in gut microbiota of children hospitalized with non-oedematous SAM compared to children with oedematous SAM [53]. In a cross-sectional study of Indian children with varying nutritional status, abundance of *Escherichia, Streptococcus*, *Shigella*, *Enterobacter* and *Veillonella* genera are increasing with deteriorated nutritional status. In addition, the microbial genes related to energy production and conversion, amino acid and carbohydrate transport and metabolism were positively linked to the nutritional index (calculated from WHZ, WAZ and height for age Z-score). This may indicate a better utilization of nutrients in healthy compared to malnourished children [48]. Time series from Malawian twin pairs discordant for kwashiorkor revealed a decrease in relative abundance of Actinobacteria in children with kwashiorkor but not in their healthy co-twins after 2 weeks of ready to use therapeutic food (RUTF) treatment. Microbiota transfer from discordant twins to gnotobiotic mice displayed 37 species that differed between gnotobiotic mice harboring kwashiorkor compared to healthy microbiota [47]. Two twin cohorts (Malawi and Bangladesh) linked chronic malnutrition to a lower α-diversity. Stunting is associated with depletion of the *Prevotella, Bacteroides, Eubacterium* and *Blautia* genera in the Malawi cohort and to the *Lactobacillus, Olsenella, Dorea*, and *Blautia* genera in the Bangladesh cohort. Additionally, relative abundance of *Acidaminococcus* sp. is linked to lower future linear growth [50]. A longitudinal birth cohort study conducted on low birth weight Indian children demonstrated that stunting is associated with enrichment in *Prevotella stercorea*, *Prevotella copri*, *Desulfovibrio* and *Catenibacterium* genera, and the Campylobacterales order, which have inflammogenic properties. Unlike in the Malawian and Bangladeshi cohort, they found no difference in α-diversity indices or in the rates of their increase by age between low birth weight and persistent stunting versus healthy controls [52]. Contradictory results may be due to different sequencing methods and platforms, geographic location, variation in the antibiotic use, breastfeeding and weaning practices. A meta-analysis of 5 studies including children from Niger, Senegal, Malawi, Bangladesh and India revealed a dramatic depletion of obligate anaerobes in undernutrition regardless of age, sex and recruitment center. Undernutrition linked to depletion of several species from *Bacteroidaceae*, *Eubacteriaceae*, *Lachnospiraceae* and *Ruminococceae* families and enrichment of several aerotolerant species with potential pathogenic effects such as *Escherichia coli, Enterococcus faecalis and Staphylococcus aureus* [54].

Both cross-sectional and longitudinal studies indicate that childhood undernutrition is associated with gut microbiota immaturity, altered diversity, enrichment in potentially pathogenic and inflammogenic species, depletion in obligate anaerobes and less efficient nutrient utilization (see Table 1).

### 4.2. Childhood obesity

WHO defines childhood obesity as: weight-for-height >3 SDS up to 5 years of age and BMI-for age >2 SDS thereafter [80]. Host genotype is one factor that can contribute to obesity. However, polygenic susceptibility needs to be coupled with contributing environmental and behavioral factors in order to cause obesity [2]. Childhood obesity is linked to gut microbiota alterations, with an increased Firmicutes/Bacteroidetes ratio being characteristic for children with obesity in various geographical regions [69,71,77,81].

**Table 1**
Summary of main findings from studies of microbiota alterations in childhood undernutrition. Abbrevations: COGs: Clusters of Orthologous Groups; DGGE: Denaturing Gradient Gel Electrophoresis GF: Germ-free; GM: Gut microbiota; HAZ: Height for age Z score; LBW: Low birth weight, MALDI-TOF/MS: Matrix-assisted laser desorption/ionization-Time of flight/Mass spectrometry; MAZ:Microbiota-for-age Z-score; MAM: Moderate acute malnutrition; OTUs: Operational Taxonomic Units; RF: Random forest; RUTF:Ready to use therapeutic food; rRNA: ribosomal RNA; SAM:severe acute malnutrition; WAZ: Weight for age Z-score; WHZ: Weight for height Z-score; WHO: World Health Organization.

| Subjects, country and reference | Design | Method | Sampling | Malnutrition criteria | Diet | Antibiotic and/or medicine information | Main findings |
|---|---|---|---|---|---|---|---|
| Healthy (n = 7) and malnourished (n = 7) children between 2 and 3 years, Bangladesh, [46] | Cross-sectional | 16S rRNA amplicon sequencing (V5–V6 regions) | Single sampling | WHZ ≥100% for healthy and ≤70% for malnourished children | Both groups received usual Bangladeshi foods, e.g., rice, meat, fish, milk, egg, fruits and vegetables. | No antibiotics use for the last 2 months. | Higher microbiota diversity in healthy children (higher number of OTUs). Bacterial population of the phyla Proteobacteria and Bacteroidetes accounted for 46% and 18% in malnourished children; 5% and 44% in healthy children respectively. *Klebsiella* and *Escherichia* were 174-fold and 9-fold higher in malnourished children. |
| Monozygotic and dizygotic twin pairs (n = 317 and < 3 years old), Malawi, [47] | Longitudinal (follow-up to 36 month) and GM transplantation from twin pairs discordant for kwashiorkor to GF mice | 16SrRNA amplicon sequencing (V4 region) and shotgun pyrosequencing | 3 time points (initial, initial+3 months, initial+6months) | WHO criteria | SAM treated with RUTF and MAM treated with soy-peanut ready-to-use supplementary food.<br>GM transplantation to GF mice: Malawian diet vs. RUTF intervention. | No antibiotics use at the time of sampling | Children with kwashiorkor manifested a decrease in Actinobacteria with the introduction of RUTF, unlike their healthy co-twins.<br>GM transplantation to GF mice: Combination of fecal transplantation of kwashiorkor co-twin's microbiota and Malawian diet resulted in greater weight loss in 3 weeks. 30 species-level taxa significantly changed in kwashiorkor microbiota transplant recipients.Species characteristic for a kwashiorkor related microbiota were *Bilophila wadsworthia* (Proteobacteria, Desulfovibrio) and *Clostridium innocuum* |
| 5-60 months old children with varying nutritional status (n = 20), India, [48] | Cross-sectional | Whole genome sequencing | Single sampling | 'Cumulative Nutritional Index' based on HAZ, WAZ, WHZ | No specific dietary history. | No antibiotics for at least 4 weeks before sampling. | Taxa characterized with *Escherichia, Streptococcus, Shigella, Enterobacter, Veillonella* increased in their abundance with the decreasing nutritional index. *Roseburia, Faecalibacterium, Butyrivibrio* had positive correlations with nutritional index. Several COGs related to secondary metabolites biosynthesis, transport and catabolism, energy production and conversion, amino acid and carbohydrate transport and metabolism were positively correlated with nutritional index. Several COGs related to lipid transport and metabolism, virulence and bacterial pathogenesis are negatively correlated with nutritional index. |
| 64 children with SAM between 6 and 20 months, Bangladesh, [49] | Randomized intervention study | 16S rRNA amplicon sequencing (V4 region) | Before intervention, during intervention (every 3 days) and post-intervention (every months for >4 months) | WHO criteria for SAM - and/or bilateral pedal edema | Peanut-based RUTF (n = 32) vs locally produced rice-lentil based therapeutic foods (Khichuri-Halwa) (n = 32) intervention | Parenteral ampicillin/ gentamicin and oral amoxicillin treatment for SAM before dietary intervention. | WHZ scores significantly and inversely correlated with relative microbiota maturity and MAZ scores. Age discriminatory taxa depleted across all phases of SAM were *Faecalibacterium prausnitzii, Clostridium* sp., *Dorea formicigenerans, Ruminococcus* sp *5 1 39BFAA, Ruminococcaceae* sp., *Catenibacterium mitsuokai, Haemophilus parainfluenzae*. Lower age adjusted Shannon Diversity Index at enrollment, during the treatment and follow up periods of children with SAM compared to healthy. |

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|---|---|---|---|---|---|---|---|
| Stunted children from Malawian twin pairs cohort(case n = 10, control n = 8) and Bangladesh cohort (case n = 6, control n = 5), Malawi and Bangladesh, [50] | Secondary case −control data analysis of longitudinal twin cohorts | Malawian Cohort: whole genome shotgun sequencing datasets<br>Bangladesh Cohort: Relative OTUs abundance | Followed for median 9,7 and 14,5 months respectively. | WHO criteria | Only available for Bangladesh cohort [49] | Only available for Bangladesh cohort [49] | Less diverse gut microbiota with greater covariance network density is associated with stunting severity. Increase in the relative abundance of *Acidaminococcus* sp. is associated with lower future linear growth in both cohorts. In the Malawi cohort, *Prevotella, Bacteroides, Eubacterium* and *Blautia* showed the largest decrease in relative abundance in cases vs controls. In the Bangladesh cohort, *Lactobacillus, Olsenella, Dorea, Blautia,* and unclassified genera in the *Coriobacteriaceae* and *Enterococcaceae* showed the largest decrease in relative abundance in cases vs controls. |
| Twin pairs concordant for healthy growth from Malawian cohort [47], Malawi, [51] | Longitudinal and GM transplantation from healthy or malnourished donors to GF mice | 16SrRNA amplicon sequencing (V4 region) | Malawian cohort: 220 fecal samples from 27 twin pairs | For transplantation: Moderately or severely underweight and stunted based on WHO criteria | Germ-free mice fed with representative Malawian diet with low caloric and nutrient density | No antibiotics use at the time of sampling | Positive correlation between microbiota-for-age Z-score (MAZ score) and weight for height Z-score (WHZ) and weight for age Z-score (WAZ). 25 age discriminatory taxa were defined which are also growth discriminatory. Combination of malnourished microbiota transplantation and deficient Malawian diet transmitted impaired growth phenotype to mice. Cohousing of healthy and malnourished microbiota recipient mice resulted in invasion of taxa- from the healthy donor's microbiota into the malnourished microbiota recipient mice and prevented growth impairments. Improved growth by adding growth-discriminatory taxa to the malnourished microbiota recipient mice. |
| Low birth weight, persistently stunted (n = 10) vs. Controls with normal birth weight (n = 10), India, [52] | Longitudinal Birth Cohort | 16S rRNA amplicon sequencing (V4 region) | 8 time points-Every 3 months up to 2 years | LBW: <2500 g<br>Persistent stunting: HAZ score < −2 SD at least 6 of 8 three monthly periods | The diet mainly consists of rice, lentils and vegetables. The major protein sources are milk, eggs and lentils. No difference in exclusive breastfeeding and weaning between groups. | Average of 8.1 and 1.9 episodes of antibiotic use during 24 months for cases and control, respectively. | No difference in α-diversity indices (observed OTUs, Chao, Shannon, Equitability, Phylogenetic diversity) or in the rates of their increase with the age between cases and controls. Significant increase in β-diversity (UniFrac distance) in cases compared to controls at the 12 month, but not at other time points. Taxa enriched in the cases *Prevotella stercorea, Prevotella copri*, *Desulfovibrio* and *Catenibacterium* and Campylobacterales (inflammogenic species). |
| 6-24 months old hospitalized children with oedematous (n = 54) vs. Non-oedematous (n = 33) SAM, Uganda, [53] | Cross-sectional | DGGE and 16S rRNA amplicon sequencing (V3−V4 regions) | Single sampling | WHO criteria | Therapeutic diets F75 and F100 and RUTF after stability | Empiric anti-biotics treatment | Alpha diversity was significantly higher in oedematous children compared to non-oedematous. Beta diversity (un-weighted Unifrac distance) revealed a minor significant difference between oedematous and non-oedematous children. No significant difference in the abundance of specific genera were observed between SAM types. |
| <60 months old children with varying nutritional status from Niger (n = 34) And Senegal (n = 52).<br><br>For the meta-analysis: SAM (n = 107) vs controls (n = 77) from 5 studies | Case control and meta-analysis | 16S rRNA amplicon sequencing (V3−V4 regions) | Single sampling | WHO criteria | In Senegal, an energy milk drink (milk, oil, sugar) was given. In Niger, children were recruited immediately on diagnosis, before any nutritional supplements was administered. | No antibiotic use <2 months before stool collection. | Total gut bacterial concentration and *Methanobrevibacter Smithii* were significantly depleted in SAM whereas gut redox potential was significantly higher. Relative depletion of obligate anaerobes and enrichment of aerotolerant organisms in SAM. SAM is associated with anaerobic depletion regardless of age, sex and recruitment center.<br>The meta-analysis: Depletion of several obligate anaerobes, including several Firmicutes (*Eubacteriaceae, Lachnospiraceae, Ruminococcaceae, Erysipelotrichaceae*), |

(*continued on next page*)

**Table 1** (*continued*)

| Subjects, country and reference | Design | Method | Sampling | Malnutrition criteria | Diet | Antibiotic and/or medicine information | Main findings |
|---|---|---|---|---|---|---|---|
| (Bangladesh, India, Malawi, Niger and Senegal), [54] | | | | | | | Bacteroidetes (*Bacteroidaceae*) and Actinobacteria (*Eggerthella, Coriobacteriaceae*). Conversely, some aerotolerant bacteria were enriched in SAM, including *Enterococcus faecalis, Escherichia coli*, and *Staphylococcus aureus*, which all represent potential pathogens. |
| Children with kwashiorkor (n = 10) vs. healthy controls (n = 5) (mean age 13.4 and 25.1 months, respectively), Senegal and Niger, [55] | Cross-sectional | Culturomics in 18 different conditions: colonies identified using MALDI-TOF/MS and 16S rRNA amplicon sequencing (V3-V4 regions) | Single sampling | WHO criteria | No specific dietary history. | Not ascertain that mothers have not given antibiotics prior to admission | Decreased β-diversity and anaerobic diversity and increased Proteobacteria and *Streptococcus gallolyticus* in malnourished group. 12 species with possible probiotic effects identified representing missing repertoire in Kwashiorkor patients: Firmicutes (*Anaerostipes caccae, Bacillus lichenjformis, Bacillus subtilis, Intestinimonas butyriciproducens, Lactobacillus parabuchneri, Lactobacillus perolens, Lactobacillus vaccinostercus,Terrisporobacter glycolicus*), Bacteroidetes (*Alistipes indistinctus, Bacteroides salyersiae*)and Actinobacteria (*Bifidobacterium adolescentis*) |

These results are similar to what has been found in adults with obesity [82]. Although the shifts in the Bacteroidetes and Firmicutes might occur in obesity, it is important to note that functional variability in the human gut microbiome may not be explained by the dominant phyla [83]. Most of the studies show that gut microbiota diversity is not significantly affected in childhood obesity. In a case control study conducted in Italy, microbial biodiversity was not correlated with BMI z-score [78]. Consistent with these results, two studies showed no significant difference in number of observed OTUs, α-diversity, β-diversity and richness in the gut microbiota of Italian [77] and Korean [73] children/adolescents with obesity, compared with lean individuals. However, α-diversity tended to be lower in overweight and pre-school children with obesity [68]. Cross-sectional studies revealed that some of the microbiota members were altered in childhood obesity. The overweight/obese microbiota was enriched in *Lactobacillus* spp. and depleted in *Bacteroides vulgatus* belonging to *Bacteroides fragilis* group in Belgian children between 6 and 16 years, compared to lean controls [71]. Lower abundance of *Akermansia muciniphyla, Faecalibacterium prausnitzii and Saccharomyces* spp. were reported for Italian children with obesity, compared to normal weight children [78]. At genus level *Bacteroides, Faecalibacterium* and *Oscillibacter* were found to be less abundant, and *Prevotella* and *Alistipes* were found to be enriched in Korean adolescents with obesity, compared to lean adolescents [73]. Balamurugan et al. [64]. reported enrichment in *F. prausnitzii* in Indian adolescents with obesity, and Ignacio et al. [76] showed higher concentration of *Bacteroides fragilis* and *L.* spp. in Brazilian children with obesity between 3 and 11 years. Higher *E. coli* and lower *Bifidobacterium* count observed in Chinese school age children with obesity [72]. Karlsson et al. [68] reported higher concentration of *Enterobacteriaceae* and lower concentration of *Desulfovibrio* and *Akermansia muciniphila* in pre-school children with overweight/obesity. It is important to note that some of these studies target specific genera/groups which can explain the variable results. Gut microbiota alteration in childhood obesity seems to be modifiable by diet and physical activity. Weight loss intervention and increased physical activity in Spanish overweight adolescents resulted in increased *Bacteroides fragilis* and *Lactobacillus*, decreased *Clostridium coccoides, Bifidobacterium longum* and *Bifidobacterium adolescentis* [63]. Moreover, differences in early gut microbiota were linked to obesity in the later childhood. A nested case control study revealed that children becoming obese at the age of 7 years have higher counts of fecal *S. aureus* and lower counts of bifidobacteria at the age of 6 and 12 months [61]. In a subcohort of Dutch and Finnish children the relative abundance of streptococci positively correlated with BMI at 3 months of age and the relative abundance of bifidobacteria negatively correlated with BMI at the age of 5–6 years [79]. The associations were found to be stronger among children with a higher lifetime exposure of antibiotics supporting previous findings regarding the link between early antibiotic exposure and childhood obesity [84,85]. Two longitudinal studies have reported an association between *Bacteroides fragilis* and childhood weight development. *Bacteroides fragilis* concentration was found positively correlated to BMI at the age of 3 and 26 weeks in Belgian healthy term infants. Additionally a low *Staphylococcus/Bacteroides fragilis* ratio at the age of 3 weeks was linked with higher BMI during the first 3 years of life [66]. In the KOALA birth cohort study [74], colonization with *Bacteroides fragilis* at the age of 1 month was linked to 0.34 higher BMI z-score in the follow-up examinations up to 10 years of age and higher counts of *Bacteroides fragilis* were positively associated with the BMI z-score, however, only in children consuming a high fiber diet (>15 g/day).

Childhood obesity linked with altered gut microbiota composition, just as childhood undernutrition. Several studies show that *Bifidobacterium* colonization in the early life negatively associated

with later childhood weight gain whereas *Bacteroides fragilis* colonization positively linked with childhood weight development. Overall, these results suggest a link between dietary intake, antibiotic exposure and gut colonization in early life and the later development of childhood obesity (see Table 2).

### 4.3. Is this a causal relationship?

Characterization of 'core' microbial signatures of adults with obesity and their lean twins at the gene level revealed that deviations from this 'core microbiome' is associated with different physiological states such as obesity [86]. Fecal microbial communities of children from different geographical regions and populations are different in a way that makes it difficult to define a common 'core microbiome' [45,87]. Defining the 'core' microbiome at both taxonomic and functional level and determining what a normal/healthy microbiota is and whether normal in one population can be generalized to others are major challenges when testing microbiota-malnutrition hypothesis [88]. Microbiota transplantation from obese mice to germ-free (GF) mice resulted in increased capacity for dietary energy harvest and greater body fat gain compared to microbiota transplantation from lean mice [89]. Microbiota transplantation from twins discordant for obesity to gnotobiotic mice modulate adiposity and metabolic phenotypes, as the mice that received microbiota from the obese co-twin exhibited greater fat mass gain. Moreover co-housing lead to invasion of members of the lean microbiota into the gut of the obese microbiota recipient mice and ultimately prevented adiposity in a diet dependent manner [90]. In the case of undernutrition, fecal microbiota transplantation from healthy versus undernourished infants to GF mice resulted in lower weight and body mass gain in the mice that received undernourished microbiota. Subsequent co-housing lead to invasion of bacteria from the healthy to the undernourished microbiota recipient mice that prevented the growth impairment [51]. Fecal microbiota transplantation from twin pairs discordant for kwashiorkor to gnotobiotic mice showed that the combination of a deficient diet and kwashiorkor microbiota resulted in weight loss in the recipient mice. Additionally weight loss was accompanied by amino acid, carbohydrate and intermediary metabolism perturbations. The authors proposed that a kwashiorkor microbiota challenges the energy metabolism especially when accompanied with a macro- and micro-nutrient deficient diet [47]. These results support the possible causal relationship between microbiota perturbations and childhood malnutrition. On the other hand, structural and functional intestinal changes due to food deprivation may also alter gut microbiota by hampering mucin synthesis, gut mucosal integrity and epithelial gut barrier [91,92]. An experimental model of diet and exercise induced anorexia in rats showed that extreme food restriction has a negative impact on the diversity of the bacterial community and promotes the growth of mucin degrading bacteria which may hamper the gut mucosal barrier [93]. Recently, a mechanism has been proposed that links angiotensin-converting enzyme 2 (ACE2) to undernutrition and microbiota. ACE2 is necessary for the intestinal expression of the Hartnup amino acid transporter (B(0)AT1) that plays a major role in tryptophan uptake [94]. Mice fed with tryptophan-free diet exhibited aberrant mTOR activation that leads to impaired expression of antimicrobial peptides. Thus, it has been proposed that impaired expression of antimicrobial peptides may result in gut microbiota changes and inflammation in the protein deficient state [95]. Gut microbiota composition was changed in mice fed with tryptophan free or protein free diet resulting in weight loss and intestinal inflammation [96]. Therefore a bidirectional complex relationship between microbial perturbation and malnutrition is more likely [97].

## 5. Potential mechanisms focusing on gut–brain axis and short chain fatty acids

### 5.1. Gut-brain axis

Gut-brain axis is a bidirectional communication between gut and the brain that regulates brain neurochemistry and gastrointestinal homeostasis [98]. This interaction plays an important role not only in energy homeostasis, digestion and appetite [99] but also in behavior, cognitive functions and decision making [98,100]. Gut-brain communication takes place through different mechanisms. In the gastrointestinal tract, sensory information is transformed into neural, hormonal, and immunological signals, which are transmitted to the central nervous system (CNS) in order to maintain the energy homeostasis [99]. The gut microbiota and its products may influence energy metabolism by affecting the peripheral and central nervous system [101]. GF mice exhibit higher levels of pro-obesity peptides (neuropeptide-Y and agouti-related protein) and altered levels of anti-obesity peptides (higher GLP-1 precursor proglucagon and lower pro-opiomelanocortin) in the brainstem and hypothalamus compared to conventionally raised mice, although it might be a secondary result of reduced fat mass in the GF mice [102]. Animal models have also linked gut microbiota to development of the peripheral nervous system. Decreased excitability of afferent neurons [103], lower nerve density and decreased numbers of neurons per ganglion in the myenteric neurons of GF mice have been reported [104]. These findings suggest that the gut microbiota may play a role in the adaptation of the enteric nervous system to the extrauterine environment [101,104].

The gut microbiota is involved in intestinal nutrient sensing mechanisms mainly through EECs. EEC signaling is a key regulator of nutrient sensing mechanisms related to the gut–brain axis [101]. EECs sense luminal nutrients and bile acids mainly through the GPCR family and elicit hormonal and neuronal signaling as a response [105]. A subpopulation of EECs, the L cells, are widely distributed in the distal small intestine and in the proximal colon and they mainly secrete GLP-1, GLP-2 and polypeptide YY (PYY) in response to food intake [15]. GLP-1 and PYY are involved in appetite regulation through both peripheral and central pathways by decreasing intestinal motility, regulating glucose homeostasis and energy expenditure, and suppressing appetite and food intake [99,106–108]. These gut peptides can either enter the circulation and act in an endocrine fashion or display their actions in a paracrine fashion by stimulating the afferent neurons that innervate the gut wall [109]. Ghrelin differs from the other gut hormones with opposite fluctuations in plasma and opposite functions such as stimulation of gastric emptying, appetite sensation, and glucagon secretion and inhibition of insulin secretion and thermogenesis [110]. The small intestine is partially contributing to the ghrelin production and food stimulated ghrelin suppression in the plasma requires post-gastric feedback [15,111,112].

Gut peptides involved in the appetite and metabolic regulation are likely to be affected by the gut microbiota [14]. The involvement of microbiota is primarily explained by SCFAs produced by the bacterial fermentation [113]. SCFAs are mainly sensed through GPR41, GPR43 [114] and in a toll like receptor (TLR) dependent manner [115] and generally result in increased release of PYY [115–119] and GLP-1 [117–119]. However, increased GLP-1 levels in plasma has been reported in GF and antibiotic treated mice, which have severely reduced SCFA production [120]. Authors speculated that this may be an adaptive response to the insufficient energy availability in the colon that slows intestinal transit to improve nutrient absorption. The gut microbiota potentially influences EEC numbers and nutrient receptor expressions [101]. The Firmicutes to Bacteroidetes ratio is positively correlated with

**Table 2**
Summary of main findings from studies of microbiota alterations in childhood obesity. Abbrevations: BMI: Body mass index; CDC: Centers for Disease Control; FISH: Fluorescence In Situ Hybridization; FFQ: Food Frequency Questionnaire; IOTF: International Obesity Task Force; MALDI-TOF/MS: Matrix-assisted laser desorption/ionization-Time of flight/Mass spectrometry; OTUs: Operational Taxonomic Units; qPCR: Quantitative polymerase chain reaction; rRNA: ribosomal RNA; SCFAs: Short chain fatty acids; SDS: Standard deviation score; TGGE: Temperature gradient gel electrophoresis; T-RFLP: Terminal restriction fragment length polymorphism.

| Subjects, country and reference | Design | Method | Sampling | Malnutrition criteria | Diet | Antibiotic and/or medicine information | Main findings |
|---|---|---|---|---|---|---|---|
| Overweight/obese (n = 25) and leant children (n = 24) at 7 years of age, Finland, [61] | Nested case control study | FISH and qPCR | Sampling at the ages of 6 and 12 months old. | IOTF criteria | Exclusive and total breastfeeding duration is not different between groups | Antibiotic exposure is not different between groups at the age of sampling | Numbers of bifidobacteria in fecal samples during infancy were higher in children remaining normal weight at 7 years old. *Staphylococcus aureus* numbers in infancy were higher in children who were obese at age 7 years. |
| Overweight and obese adolescents (n = 39) with mean age 14.8, Spain, [62,63] | Longitudinal intervention | FISH and qPCR | Baseline and after the 10 week intervention | IOTF criteria | %10–40 calorie restriction and increased physical activity for 10 weeks | No antibiotic use during the intervention | FISH findings: *Clostridium histolyticum and E. rectale/C. coccoides* ratio reductions were significantly correlated with weight and BMI z-score. Total fecal energy content was reduced in high weight loss group (>4 kg)<br>qPCR findings: Intervention increased counts of *Bacteroides fragilis, Lactobacillus* and decreased *Clostridium coccoides, Bifidobacterium longum, Bifidobacterium adolescentis*. Total bacteria counts, *B. fragilis*, *Clostridium leptum* and *Bifidobacterium catenulatum* significantly higher; *C. coccoides*, *Lactobacillus, Bifidobacterium*, *Bifidobacterium breve* and *Bifidobacterium bifidum* were significantly lower in the high weight loss group (>4 kg) before and after the intervention. |
| Obese (n = 15) and lean (n = 13) adolescents between 11 and 14 years, India, [64] | Cross-sectional | qPCR | Single sampling | WHO criteria | Similar energy, carbohydrates, fat and protein intake between groups for the previous 3 months. | No antibiotic use for the last 1 month | *Faecalibacterium prausnitzii* were significantly more abundant in the obese group. No significant difference in *Bacteroides-Prevotella, Bifidobacterium species*, *Lactobacillus acidophilus* or *Eubacterium rectale*. |
| Obese (n = 15) and lean children (n = 15) between 8 and 14 years, Switzerland, [65] | Cross-sectional | qPCR and TGGE | Single sampling | CDC criteria | Similar baseline dietary intake between groups. | No antibiotics use within the last 3 months | No significant quantitative differences in gut microbiota communities. Higher butyrate and propionate, lower intermediate metabolites in faeces of obese group. |
| Healthy term infants (n = 138), Belgium, [66] | Birth Cohort | Culture on selective media for 6 bacterial genera | 3, 26 and 52 weeks of age | BMI SDS based on Flemish growth curves [67] | Adjustment for formula/breastfeeding | Adjustment for antibiotic use | Positive correlation between BMI SDS and *Bacteroides fragilis* concentration at 3 and 26 weeks. There was a negative correlation between BMI SDS and *Staphylococcus* concentration at 3, 52 weeks. A low *Staphylococcus/Bacteroides fragilis* ratio at the age of 3 weeks is associated with higher BMI SDS during the first 3 years of life. |
| Overweight-obese (n = 20) and lean children (n = 20) between 4 and 5 years old, Sweden, [68] | Cross-sectional | qPCR and T-RFLP | Single sampling | IOTF criteria | No dietary info | No info about medicine | A higher concentration of *Enterobacteriaceae* and lower concentration of *Desulfovibrio* and *Akermansia muciniphila* was observed in the overweight/obese group. No difference was found for *Lactobacillus*, *Bifidobacterium* or *Bacteroides fragilis*. The dominating bacterial community tended to be less diverse (Shannon index and Simpson index) in the overweight/obese group. |
| Obese (n = 22), overweight (n = 62) and lean (n = 91) children aged between 7 and 13,, Kazakhstan, [69] | Case-control | qPCR | Single sampling | China Obesity Task Force Criteria [70] | No dietary info | No antibiotic use for the last 2 weeks | Bacteroidetes and Bacteroidetes/Firmicutes ratio were significantly lower in the obese group compared to the overweight and lean groups. Bacteroidetes and the Bacteroidetes/Firmicutes ratio negatively correlated with BMI. |
| | Cross-sectional | | Single sampling | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Overweight/obese (n = 26) and lean children (n = 27) between 6 and 16 years, Belgium, [71] | | Selective plating −qPCR and MALDI-TOF MS | | Extended IOTF criteria | Similar dietary intake between groups | No Antibiotic and corticosteroids before sampling | Elevated Firmicutes/Bacteroidetes in obese group compared to lean group. Lower relative proportions of *B. vulgatus* belonging to *Bacteroides fragilis* group. Higher relative proportions of *Lactobacillus spp*. and *Staphylococcus spp*. were positively correlated with energy intake in both groups. |
| Obese (n = 63) and lean children (n = 63) with mean age 6.8 years, China, [72] | Case-control | qPCR | Single Sampling | WHO criteria | No dietary info | No antibiotic and probiotic use within the last 4 weeks | Higher *E. coli* and lower *Bifidobacterium* content in obese group. Lower *Bifidobacterium/E. coli* ratio in obese group. |
| Obese (n = 67) and lean adolescents (n = 67) between 13 and 16 years, Korea, [73] | Cross-sectional study | 16S rRNA amplicon sequencing V1−V3 regions) | Single sampling | Obese: BMI≥30 kg/m2 or ≥99th BMI percentile | No dietary info | No antibiotics use within the last 4 weeks | No significant difference in number of observed OTUs, Shannon index (α-diversity), β-diversity and Firmicutes/Bacteroidetes ratio between obese and lean adolescents. At genus level *Bacteroides, Faecalibacterium* and *Oscillibacter* significantly decreased, *Prevotella* and *Alistipes* were enriched in obese adolescents |
| Infants (n = 909) enrolled for KOALA Birth Cohort Study, Netherlands, [74] | Birth Cohort | qPCR | Single sampling (at 1 month of age) | BMI Z-scores based on Dutch standards [75] | Adjustment for the type of infant feeding | No antibiotic use before sampling | Growth were followed up between 9 and 117 months of age. Early colonization with *B. fragilis* was associated with 0.34 higher BMI z-score among children with low fiber intake. Higher counts of *B. fragilis* were positively associated with BMI z-score in children consuming high-fiber diet (>15 g/day) and inversely associated with low-fiber diet. |
| Obese (n = 30)-overweight (n = 24) and lean children (n = 30) between 3 and 11 years old, Brazil, [76] | Cross-sectional study | Culture technique and qPCR | Single sampling | WHO criteria | No dietary info | No antibiotics use within the last 3 months | Higher concentration of *B. fragilis* group and *Lactobacillus* spp. in obese children. *B. fragilis* and *Lactobacillus* spp. were positively correlated with BMI. More pronounced Bifidobacterium spp. in lean group. |
| Obese (n = 42) and lean children (n = 36) between 6 and 16 years old, Italy, [77] | Cross-sectional | 16S rRNA sequencing | Single sampling | IOTF criteria | FFQ at recruitment | No antibiotic and probiotic use within the last 6 months | α-diversity (Shannon and Simpson) and richness (Chao1) were similar between groups. The Firmicutes/Bacteroidetes ratio was higher in obese group. Obese children have increased correlation density and clustering of OTUs. SCFAs level was higher in the faeces in the obese group. Acetate positively linked with BMI z-score. |
| Obese (n = 28) and lean children (n = 33) with mean age 10 years, Italy, [78] | Case-Control study | 16S rRNA amplicon sequencing (V2−V3 region) and DGGE | Single sampling | WHO criteria | Higher energy and macronutrients intake in the obese group | No antibiotic and prebiotic/probiotic use within the last 1 month | Lower abundance of *Akermansia muciniphyla, Faecalibacterium prausnitzii, Bacteroides/Prevotella* in obese group compared to lean. Microbial biodiversity was not significantly correlated with BMI Z-score. |
| Healthy children from Netherlands (n = 87) and Finland (n = 75), [79] | Sub-cohort selected from 2 longitudinal studies | 16S rRNA amplicon sequencing (V1 and V6 region) | Sampling at 3 months of age | BMI were calculated at 5−6 years | Two cohorts do not differ in duration of breastfeeding | Life time antibiotic use recorded | At 3 months of age the relative abundance of *Streptococcus* was positively, while relative abundance of *Bifidobacterium* was negatively associated with the BMI outcome at 5−6 years. The association was stronger among children with higher lifetime antibiotic exposure. |

GPR43 expression in the colon of diet induced obese mice [121]. In an intestinal epithelial cell culture model, bacteria belonging to the Bacteroidetes, Proteobacteria and Firmicutes phyla are linked to altered GPR120 expression [122]. The gut microbiota may affect the host appetite and metabolism by its relation to other appetite regulating hormones with anorexigenic (e.g. leptin) and orexigenic (e.g. ghrelin) properties [14]. In rats, *Bifidobacterium* and *Lactobacillus* positively correlated with serum leptin levels whereas *Clostridium* and *Prevotella* negatively correlated. Serum ghrelin levels are negatively correlated with *Bifidobacterium, Lactobacillus and B. coccoides-Eubacterium rectale* and positively correlatedwith *Prevotella* [93]. In a rat model, *Bacteroides* and total bacterial counts were positively linked with the ghrelin level after prebiotic fiber administration [123]. However, it is not clear whether the gut microbiota composition is causally related to leptin and ghrelin levels. Although ghrelin producing cells are enriched in GPR43 and GPR120, there is lack of knowledge on whether dietary and gut microbiome derived metabolites stimulate these receptors and result in ghrelin production [110]. One proposed mechanism regarding leptin is that circulating leptin may modulate the gut microbiota by stimulating gut cell mucin production [124] and ultimately favor the growth of specific bacteria [125]. On the other hand, high-fat diet induced gut microbiota and fat mass alterations may affect circulating leptin levels [126]. Leptin may also act independently from the food intake to modulate gut microbial composition in a mouse model [127]. A cohort of breastfed infants showed that infants born from mothers with obesity are exposed to two-fold higher leptin and insulin from the breastmilk and exhibit altered microbiota composition and function [128]. Evidence of the cross-talk between gut microbiota and the gut–brain axis is mostly based on animal models of obesity [99,129,130] and research is scarce in the case of undernutrition. More evidence from human studies for both childhood undernutrition and obesity is needed to clarify whether modulation of appetite regulating hormones through gut microbiota can be a prevention or treatment strategy towards childhood malnutrition.

### 5.2. Short chain fatty acids

Production of SCFAs in the gut is influenced by availability of fermentable carbohydrates, microbiota composition and gastric transit time [131,132]. Butyrate is primarily used as an energy source for colonic epithelial cells, whereas propionate and acetate are mainly utilized as substrates for lipogenesis and gluconeogenesis by the liver and peripheral tissues [133]. Additionally butyrate may be involved in immune homeostasis by suppressing lipopolysaccharide induced metabolic reprogramming of human dendritic cells [134] and by inhibition of the NF-κβ signaling pathway in macrophage cells [135]. Production of SCFAs via bacterial fermentation is an energy harvest mechanism for the host. As discussed above SCFAs are involved in the gut brain-axis via EEC signaling or through direct stimulation of afferent nerve fibers that innervate the gut wall. GPR43 deficient mice fed a high-carbohydrate, high-fat diet preserved lower body mass and higher lean mass compared to wild-type mice, suggesting a role for SCFAs in metabolic regulation [136]. Moreover SCFAs may interact with adipose tissue through free fatty acid receptor 2 (FFA2/GPR 43) (and possibly through FFA3/GPR41). There are contradictory results on whether SCFAs alter adipogenesis and leptin expression from adipose tissue [117,137,138]. I*n vitro* stimulation of GPR43 with acetate and propionate was linked to reduced lipolysis. Further, *in vivo* stimulation of GPR43 by acetate resulted in suppressed plasma free fatty acid levels [139]. On the contrary acetate and propionate are linked to adipogenesis through upregulation of GPR43 in adipose tissue of mice. The authors noted that GPR43 upregulation in adipose tissue was diet dependent which may explain the contradictory results [140]. Involvement of SCFAs in energy metabolism and growth may also be through hepatic IGF-1 production. Colonization of GF and specific pathogen-free mice resulted in increased serum IGF-1, a hormone mainly produced by liver stimulating growth. Further, antibiotic treatment of conventional mice caused decreased serum IGF-1 levels and bone formation, which were restored by SCFA supplementation [16] (see Fig. 1).

Both undernutrition and obesity appear to be the linked to altered SCFA production in the gut. Lower faecal SCFA concentrations were observed before nutritional recovery in severely malnourished children with cholera. Additionally, SCFAs concentration increases in parallel with faecal bacterial number during clinical recovery [141]. Lower levels of butyrate and propionate were measured in faeces of Malawian children who died from complicated SAM compared to those who recovered. Moreover, mortality in SAM were predicted with a mixed model including presence of diarrhea, high intestinal and systemic inflammation, and low fecal SCFA concentrations [142]. Children with obesity have higher butyrate and propionate content in faeces compared to lean children [65]. A cross-sectional study reported higher SCFA levels in childhood obesity with a positive correlation between fecal acetate level and BMI z-score [77]. Moreover, a weight loss intervention in Spanish overweight adolescents resulted in reduced total faecal energy content [62].

The gut microbiota may affect nutritional status partly through its production and utilization of SCFAs. Alteration in microbial genetic pathways, including N-glycan and inositol phosphate pathways were observed in a protein-energy malnourished mouse model, which may cause less efficient microbial energy extraction from non-digestible dietary components such as glycans and phytates [143]. This is supported by a cross-sectional study of Indian children, where nutritional status negatively correlated with the abundance of microbial genes encoding enzyme groups that selectively degrade peptidoglycans and complex plant carbohydrates [48]. Increased levels of faecal SCFAs in obesity could reflect greater microbial fermentation and energy harvest [144]. Increased fecal content of SCFAs could also reflect larger fermentable input to the colon due to increased dietary intake. On the other hand, it could be an adaptation to a high energy intake to decrease the absorption of SCFAs and other energy contributing components in the gut content. Therefore dietary intake can be a confounding factor when evaluating the effect of SCFA on energy metabolism. Another research question could be whether certain SCFAs affect appetite regulating hormones and thus nutritional status differently. Further research to define SCFA production dynamics in relation to gut microbiota may lead the development of novel prevention and treatment strategies for childhood malnutrition.

## 6. Dietary modulation of microbiota in childhood malnutrition

Probiotics are defined as ‘live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host’ [145]. Members of the bifidobacteria and lactobacilli as well as *Saccharomyces Boulardii* and *Bacillus coagulans* are often used as single strains or as mixtures [146]. Based on a limited number of studies, multi-strain probiotics appear to be more effective than single strains [147]. Recently, a mixture of 12 species from *Firmicutes*, *Bacteroidetes* and *Actinobacteria* were proposed as a possible probiotic treatment to replace missing bacteria of Kwashiorkor microbiota observed in children from Niger and Senegal. However, the efficacy of this mixture on growth outcomes in Kwashiorkor

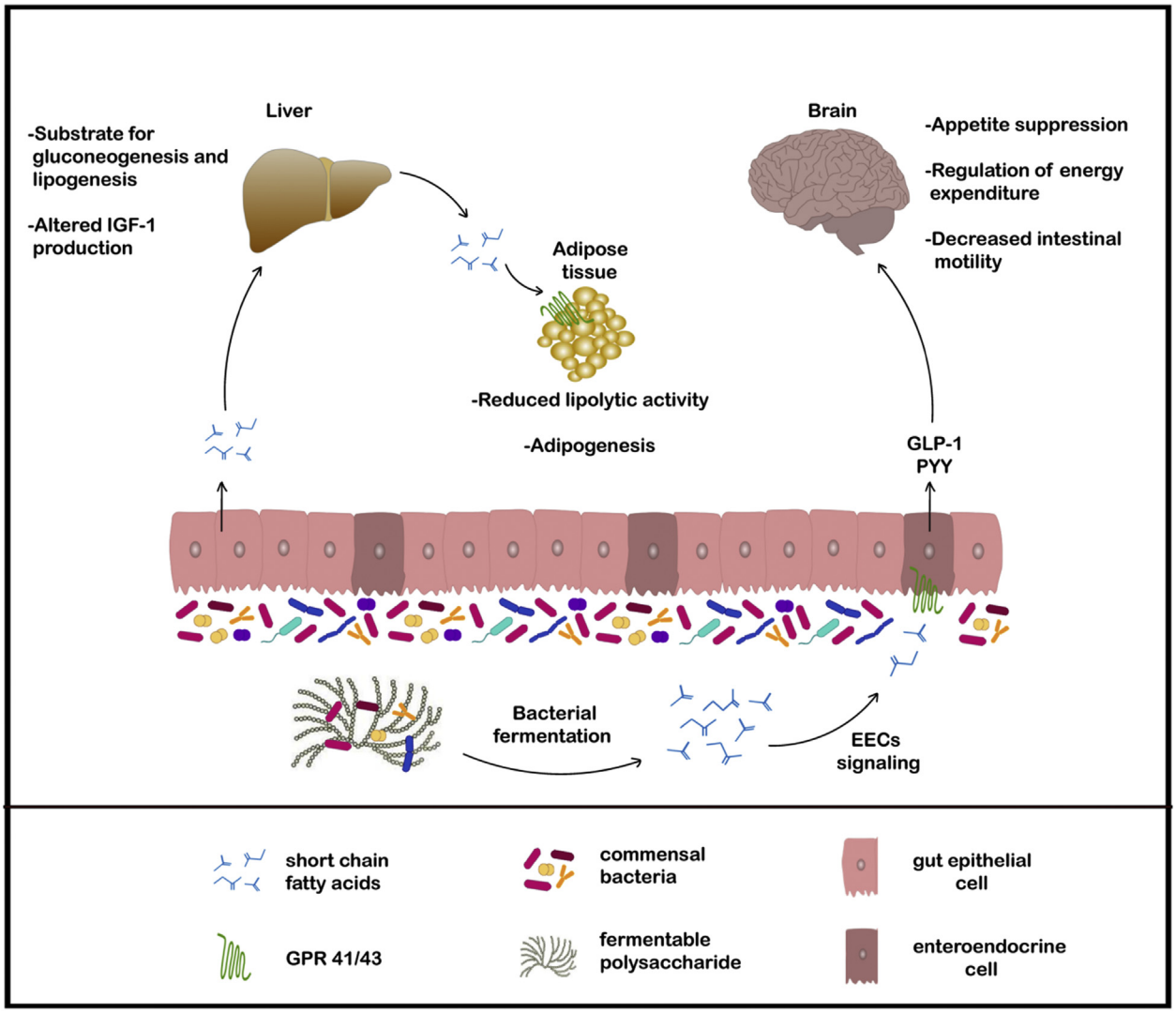


**Fig. 1.** Potential influence of SCFAs on energy metabolism. SCFAs may modulate energy metabolism by stimulating GLP-1 and PYY production. These gut peptides can act in endocrine and/or paracrine fashion and contribute to appetite suppression, regulation of energy expenditure, regulation of glucose homeostasis and decreased intestinal motility. SCFAs can be used as substrate for gluconeogenesis and lipogenesis and may alter IGF-1 production in the liver. *In vivo* and *in vitro* models linked SCFAs with both reduced lipolytic activity and adipogenesis. Abbreviations: EECs, enteroendocrine cells; GLP-1, glucagon-like peptide-1; GPR 41/43, g-protein coupled receptors 41 and 43; IGF-1, insulin-like growth factor-1; PYY, polypeptide YY; SCFAs, short chain fatty acids.

still needs to be tested [55]. The major mechanisms of action for probiotics appear to be modulation of gut microbiota, enhancement of epithelial barrier, inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microbial substances, degradation of toxins and modulation of the immune system [148]. Additionally, a probiotic mixture may affect food intake through the interaction between SCFA and gut peptides. Probiotic treatment increase the release of GLP-1 in a butyrate dependent manner, resulting in decreased food intake and improved glucose tolerance in cell culture and mouse models [149]. Several animal models showed reduced bowel wall atrophy [150], recovery of colonic goblet cells and colon wall strata [151,152], improved systemic immune response [153,154] and enhanced recovery from undernutrition [155] with probiotic treatment. The efficacy of probiotics has been widely tested in adults for conditions such as obesity and diabetes [156,157]. However, only a limited number of studies have tested the effect of probiotics in childhood malnutrition. In a double-blind RCT, a perinatal *Lactobacillus rhamnosus* intervention during the first 6 months of life moderated the excessive weight gain until 48 months of age [158]. Six months of *Lactobacillus Acidophilusacidophilus* supplementation in a daily prepared curd matrix promoted greater weight and height gain and fewer cases of diarrhea in stunted Indian toddlers compared to control group receiving an isocaloric supplement [159]. Efficacy of probiotics on child growth may differ according to nutritional status. A recent systematic review suggests that probiotics may have more profound effects on undernourished children compared to healthy children living in developing countries [160]. On the other hand, *Enterococcus faecium* IS-27526 intervention resulted in significant weight gain only in normal weight children. For underweight children, *E. faecium* IS-27526 supplementation in a milk matrix has positive effects on humoral immune response, measured with salivary SIgA, but not on weight gain [161]. Mixed results following probiotic supplementation may be due to factors affecting the efficacy of probiotics. In a rat model, susceptibility of the resident gut microbiota to modulation by transient bacteria is linked to the basal gut microbiota composition [162]. This is supported by an *in vitro* study showing that microbiota modulation

with bifidobacterium strains and FOS is strongly dependent on the basal microbiota composition and the study population. Different responses to probiotic and prebiotic incubations of fecal samples were observed among adults and premature, breastfed and formula fed infants [163]. Therefore, stratifying categories of malnourished children by taking into account the baseline gut microbiota composition, population characteristics and geographical location may lead to the development of efficient approaches to prevention and treatment of malnutrition with probiotics [164]. Locally sourced probiotics for undernutrition and chronic enteric infections may be a good approach to provide affordable, accessible and sustainable solutions in developing countries. Additionally, locally fermented foods may be more resistant to locally used spices and herbs and therefore may be more advantageous for the stability and viability of the probiotics [165].

Prebiotics are defined as 'nondigestible compounds that, through microbial metabolism in the gut, modulate the composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host' [166]. Inulin, FOS, galactooligosaccharides (GOS), lactulose, dietary fibers, resistant starches and other non-digestible oligosaccharides are the main prebiotics [167]. Prebiotics mainly confer their health benefits by promoting the growth of specific bacteria (mainly bifidobacteria and lactobacilli), production of short chain fatty acids, enhanced uptake of micronutrients, delayed gastric emptying, and modulation of the immune system [168–170]. Sixteen weeks of oligofructose-enriched inulin supplementation increased the relative abundance of *Bifidobacterium* while decreasing the relative abundance of *B. vulgatus* in children with overweight/obesity between 7 and 12 years of age. Changes in their microbiota composition were accompanied by decreased body weight z-score, percent of body fat, percent of trunk fat and serum triglycerides in the intervention group [171]. On the other hand, 12 weeks of oligofructose supplementation did not lead to significant changes in BMI z-score and total body fat in children with overweight/obesity between 7 and 18 years of age [172]. Pubertal stage can be a confounder in paediatric clinical trials, which may account for the contradictory results [173]. Prebiotics potentially modulate the gut microbiota also in the early life [174]. Growth of infant fecal bacteria has been tested with two types of commercial prebiotics (GOS vs FOS) and both stimulate the growth of bifidobacteria and lactobacilli in the same manner. Infant formula enriched with GOS, beta-palmitate and acidified milk led to increased fecal bifidobacteria counts compared to standard formula [175]. The addition of prebiotics to infant formula may promote increased abundance of bifidobacteria in the gut microbiota of formula-fed infants similar to that of breast-fed infants [176–178].

Human milk oligosaccharides are an important source of prebiotics in early life and they are mostly unique to human milk [179]. The HMO composition of human milk is quite diverse with more than 200 different structures containing monomers such as glucose, galactose, N-acetylglucoseamine, fucose and sialic acid [180]. Although the utilization of HMOs are strain specific, *in vitro* studies show that predominant members of the early gut microbiota such as *Bifidobacterim* and *Bacteroides* spp. are able to ferment HMO structures [181]. The maternal expression of HMOs vary in accordance with Lewis blood type and secretor locus that encodes α-1,2 fucosyltransferase (FUT2) and α-1,3/4 fucosyltransferase (FUT3) [182]. Secretor mothers have higher concentrations of sialylated, fucosylated and total HMO in their breastmilk [183,184]. Age, BMI, delivery mode, lactation stage, season and geographical location are among maternal factors associated with HMO composition [185–187]. HMOs are more abundant in the later stage of lactation and vaginal delivery is linked to higher concentrations of sialylated HMOs in the human milk [186]. HMOs and acidic oligosaccharides that contain sialic acid residues (such as sialyllactose) have potential effects on gut maturation, growth of bifidobacteria and bacteroides, resistance to pathogens, immune function and cognitive development [188,189]. One of the mechanisms underlying the negative association between breastfeeding and childhood obesity points to direct and indirect effects of HMOs [190]. Diversity and evenness of HMO composition in breastmilk are associated with growth and body composition in healthy infants during the first 6 months of life [191]. Sialylated milk oligosaccharides have been linked to microbiota dependent growth in infant undernutrition [192]. Breastmilk profiling of Malawian mothers to healthy or severely stunted infants revealed that non-secretor mothers with severely stunted infants have lower total, fucosylated and sialylated HMO concentrations in their breastmilk compared to non-secretor mothers with healthy infants. Furthermore, fecal microbiota transplanted from stunted underweight infants to GF and gnotobiotic mice followed by sialylated HMO supplementation promoted bone growth, body weight and lean body mass gain and also conferred metabolic effects in liver, muscle and brain. Since HMO supplementation failed to promote growth of GF mice, growth promotion with sialylated HMOs seems dependent on a gut microbiota. A longitudinal study of 4–20 weeks old Gambian infants at risk of malnutrition showed that the 3′-sialyllactose level in human milk is a good indicator of infant weight-for-age. Higher lacto-N-fucopentose levels in the human milk were linked to decreased infant morbidity which may decrease the risk of undernutrition [187].

Synbiotics are synergistic combinations of pre- and probiotics developed to overcome possible survival difficulties for probiotics during storage and passage through the upper GI tract [146,170]. *Bifidobacterium Lactis* HN019 and prebiotic oligosaccharides fortified milk were administered to healthy and stunted Indian toddlers for a 1 year period. The main weight velocity among children consuming the synbiotic milk was higher compared to controls (0.13 kg/year), while the change in z-scores from baseline was unaffected [193]. In a double-blind RCT conducted in 795 Malawian children with severe acute malnutrition, participants were administered RUTF with or without a synbiotic (median 33 days). Nutritional theraphy was not different between groups, however a trend towards reduced outpatient mortality in the synbiotic group was observed [194]. Synbiotic sachets containing fructo-oligosaccharides and *B. coagulans* were administered to Iranian children with failure to thrive for 6 months in a triple-blinded RCT. A higher weight gain in the intervention group was observed along with a similar increment of height compared to controls [195]. Eight weeks of synbiotic capsule intervention containing *Lactobacillus casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus* with fructo-oligosaccharides in children with overweight-obesity between aged 6–18 years decreased BMI z-score, waist circumference and waist-to-hip ratio compared to controls [196].

Probiotics, prebiotics and synbiotics seem to have the potential to improve growth outcomes and decrease morbidity in undernourished children and to ameliorate overweight/obesity in pediatric populations. However, more clinical trials are needed to clarify how, when and which probiotics, prebiotics and synbiotics should be used in childhood malnutrition.

## 7. Conclusion

The composition and functional capacity of the gut microbiota seems to be altered in both childhood undernutrition and obesity. Undernourished microbiota is linked with gut microbiota immaturity, altered diversity, enrichment in potentially pathogenic and

inflammogenic species, depletion in obligate anaerobes and less efficient nutrient utilization. Early colonization, antibiotic exposure and diet seem to contribute to weight gain in the later childhood. Effects on the gut–brain axis are among the possible mechanisms related to microbial perturbation and energy metabolism. However, it is not currently possible to make a clear conclusion from human studies on whether altered levels of SCFAs result in modulation of appetite regulating hormones and affect nutritional status through this mechanism. Dietary modulation of the gut microbiota could be a strategy for prevention and treatment of childhood malnutrition. However, more randomized clinical trials are needed to test the efficacy of probiotics, prebiotics and synbiotics while stratifying by the malnutrition type, geographical region, pubertal stage, and baseline composition of the microbiota.

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