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Diet mediates the gut microbiome composition and assembly processes in infant and toddler populations

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ABSTRACT

Infancy and toddlerhood are critical phases of life, as the gut microbiota is established here, which influences current and future health. During this period, the microbiota was relatively less stable and highly responsive to environmental factors. Therefore, it is important to understand how dietary factors affect this complex stage of microbial assembly. The effect of feeding practices (breast milk/formula) on microbial colonization in early infancy has been actively studied; however, studies on the effect of diet on the gut microbiota during the complementary feeding period are sparse. The introduction of complementary foods provides abundant new dietary compounds for the gut microbiota, which induces a shift in gut microbiota and metabolism from milk-adapted toward a more mature and diverse adult-like community. Herein, we discuss the impact of dietary nutrients (carbohydrates, proteins, fats, vitamins, and minerals) on microbiome of infants and toddlers. Furthermore, this review summarizes the effects of complementary feeding patterns, specific foods (such as cereals; legumes and nuts; vegetables and fruits; meats; dairy products), food additives, and malnutrition (undernutrition or overnutrition) on gut microbiota of this populations. These findings might deepen our comprehension of the complex interactions between diets and the development and establishment of the gut microbiota. This may facilitate the tailoring of interventions aimed at promoting beneficial modifications within the gut microbial community. Furthermore, the insights gained could inform the design and implementation of safe and efficacious complementary feeding practices.

1. Introduction

Infants and toddlers are not merely 'little adults' with smaller but essentially identical organ systems. Their physiology is unique and highly adapted to their specific requirements, and the developing gut microbiota is no exception to this rule. In healthy neonates, the composition of the gut microbiome undergoes large-scale longitudinal changes[1]. Aerotolerant and facultative anaerobes such as Enterobacteriaceae, *Staphylococcus* spp. and *Lactobacillus* are the major initial colonizers of the neonatal gut; however, their proportions decline rapidly over days to weeks, and the gut microbiota of breastfed infants begins to be dominated by breastmilk-promoted anaerobic Bifidobacteriaceae[2-4]. The abundance of other anaerobic bacterial families (e.g., Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae) increases during infancy and toddlerhood[5]. The gut microecosystem does not mature into an adult-like microbiome until the child is 3 years of age. However, before reaching this stage, the gut microbiota is sensitive to extrinsic factors[1-2].

Any solid or liquid food that is not breast milk or infant formula is considered complementary[6]. The complementary feeding period begins at 4–6 months of age, and although the age at which infants are first introduced to complementary foods varies, most infants

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worldwide are exposed to grains for the first time[7]. The first solid foods to which other infants are exposed may be vegetables or meat[8-9]. No consensus exists regarding the order in which foods should be introduced, except for iron supplementation at 6 months of age is recognized as important[10-11]. Gradually increase consistency, intake, and variety of food as the infant gets older, adapting to their requirements and abilities. Plant-based foods offer many nutritional benefits for infants: cereals provide digestible carbohydrates and B vitamins; vegetables and fruits are rich in indigestible carbohydrates and various vitamins such as vitamin C and vitamin K; legumes are high in plant proteins; seeds are abundant in plant proteins and oils, primarily unsaturated fatty acids. Animal-based foods, including meat, poultry, fish, eggs, and dairy products, supply infants with ample proteins, fats, minerals, and vitamins such as vitamin B_{12}, vitamin A, and vitamin D. Some infants also receive fortified complementary foods or vitamin and mineral supplements, as needed, including iron, calcium, vitamin D, vitamin C, and vitamin B_1. Complementary foods also provide calories for infants and toddlers, accounting for approximately 1/3 of the total energy needs of infants aged 6–8 months old, 1/2 of infants aged 9–11 months, and approximately 2/3 of infants aged 12–23 months[12].

Diet is a major driver of the composition, diversity, and function of gut bacteria after the introduction of complementary foods[13-14]. Certain dietary components (such as fat, protein and carbohydrates) and downstream metabolites can interact directly with intestinal microbes to promote or inhibit their growth[15]. The human genome encodes a limited number of glycoside hydrolases and no polysaccharide lyases. Thus, glycans, including resistant starch, pectin, and cellulose reach the large intestine in their undigested forms. In contrast to humans, the intestinal microbiome encodes tens of thousands of carbohydrate-active enzymes, particularly in *Bacteroides* spp. and *Ruminococcus* spp., which allow them to ingest undigested carbohydrates as nutritional substrates[16]. Furthermore, compounds of dietary including antigens can indirectly shape the gut microbiota by influencing host metabolism and immune responses[17]. Additionally, certain dietary components may disrupt the intestinal barrier, potentially affecting the host-microbiome interface and leading to dysbiosis[17]. Several studies have suggested that the specific emulsifiers[18], fat-rich diets[19], Western-style diets[20], or low-fiber diets[21] can disrupt barrier function. Moreover, the diet also serves as a vehicle for the transfer of microbial species inherently present in foods into the native gut microbial ecosystem[22]. For instance, *Lactobacillus delbrueckii* subsp. bulgaricus and *Streptococcus thermophilus* found in yogurt, *Lactiplantibacillus plantarum* in kimchi, and *Bacillus subtilis* natto in natto can be introduced into the gut microbial ecosystem through dietary consumption, enriching its diversity and influencing its function.

Regarding the effect of early diet on gut microbiota, most pediatric microbiome research has focused on the differences between breast- and formula-fed infants during the first year of life[23-24]. Few studies have evaluated the effect of diet on the gut microbiota from the introduction of complementary foods until 3 years of age (infancy and toddlerhood). Indeed, changes in microbes during this period may have enormous implications in shaping the lifelong gut microbiota. Therefore, this review discusses the current evidence on the role of dietary composition, dietary patterns, specific foods, dietary diversity, food additives, and nutritional status on the gut microbiota during infancy and early childhood. These findings are relevant for the assembly of gut microbiota early in life, may help identify windows of opportunity for interventions for certain gut microbiota-related diseases in childhood and adulthood, and may inform the design and implementation of such interventions.

2. Nutrients in a diet affecting the gut microbiota of infants and toddlers

During the transition from a milk-based diet (breast milk and/or infant formula) to an adult-like diet, there is an increase in the diversity and richness of the microbiota composition[25]. The introduction of complementary foods is accompanied by a significant increase in Lachnospiraceae, Ruminococcaceae, *Blautia*, *Bacteroides*, and *Akkermansia*, and a decrease in *Bifidobacterium*, Veillonellaceae, Lactobacillaceae, Enterobacteriaceae, and Enterococcaceae[26-28]. As energy-producing substrates change during weaning, the metabolic capacity of the infant's gut microbiota is altered, and genes associated with starch, central carbon, and pyruvate metabolism are enriched[29]. Correspondingly, there is a decrease in the relative abundance of bacteria (bifidobacterial species like *Bifidobacterium longum* subsp. *infantis*, *Bifidobacterium bifidum*, and *Bifidobacterium breve*) that use human milk oligosaccharides (HMOs) or galacto-oligosaccharides as substrates and an increase in microorganisms capable of degrading complex polysaccharides, such as Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae[30].

Interestingly, the microbiota of breastfed infants living in Italy (urban areas) and Burkina Faso (rural areas) showed similarities in composition and structure, albeit with vastly different diets and environments of the 2 countries[31]. Burkina Faso is located in Africa and has a predominantly vegetarian diet rich in starch, fiber and plant polysaccharides, whereas Italian children eat a typical Western diet high in animal protein, sugar, starch and fat. However, once breastfeeding was replaced with solid foods, the differences in microbiota between the 2 populations increased, with the microbiota of Burkina Faso children being dominated by Bacteroidetes, whereas that of Italian children was enriched by Firmicutes[31]. This study highlights the dominance of dietary specialization in shaping young gut microbiota. Fig. 1 shows the effects of dietary nutrients on the gut microbiota of infants and toddlers.

2.1 Carbohydrates

A portion of the diet, primarily indigestible carbohydrates, passes through the stomach and small intestine, and is utilized by the microbiota in the colon. A considerable proportion of dietary starch is not digested during the early stages of weaning because pancreatic function, small intestine absorption, and fermentation ability are weak. Increased intake of non-digestible carbohydrates is often mentioned as a driver of gut microbiota diversification during weaning[32-33]. The dominant phyla Proteobacteria and Actinobacteria are replaced by Firmicutes and Bacteroidetes, which are closer to the adults[34]. For instance, De Filippo et al.[31] discovered that Burkina Faso infants exposed to a fiber-rich diet had significantly lower levels of Proteobacteria compared with European infants who consumed significantly less fiber, supporting a potential link between dietary fiber intake and a decrease in proteobacterial species. At the genus

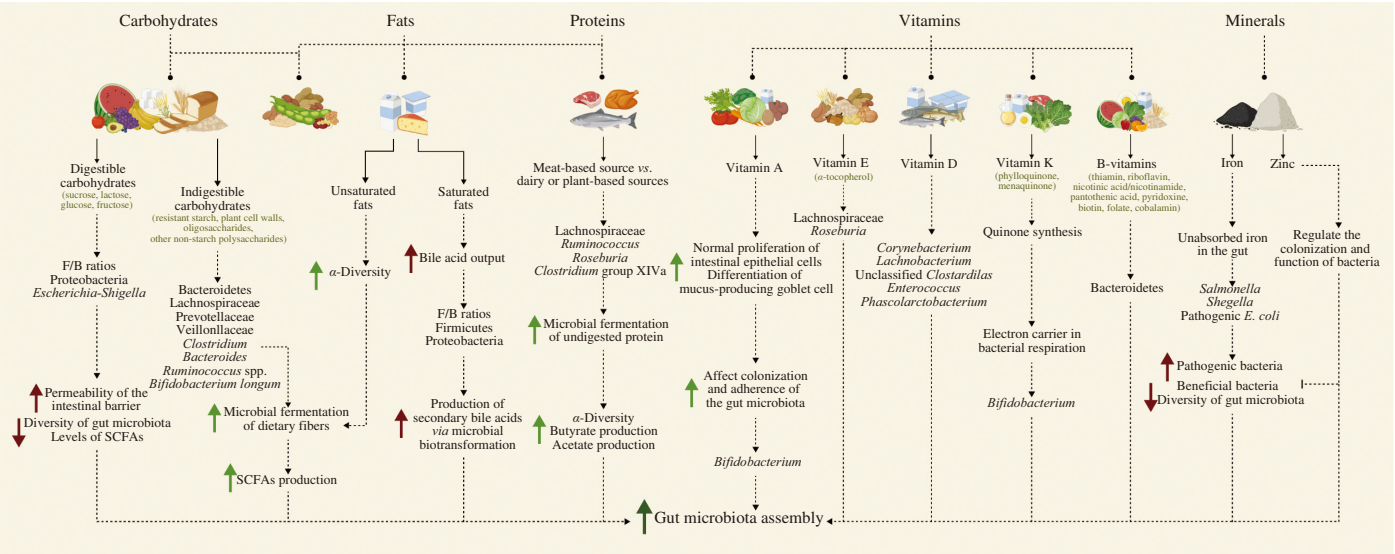

Fig. 1 Effects of dietary nutrients on the gut microbiota of infants and toddlers.

level, there was an increase in *Atopobium*, *Clostridium*, *Akkermansia*, *Bacteroides*, Lachnospiraceae, and *Ruminococcus* spp.; concurrently there is a decrease in *Escherichia* and *Staphylococcus* spp.[30,35]. Additionally, Eubacteriaceae, Pasteurellaceae, Prevotellaceae, Veillonellaceae, and Fusobacteriaceae were found to be positively associated with fiber intake in two different cohorts of Danish infants born to either of healthy mothers or of obese mothers[33]. With the introduction of solid foods, the dominant strains in the intestinal microbiota undergo turnover due to changes in selective pressures. A good example is *B. longum*, a common species in the gut microbiome of breastfed infants, which is also found in the microbiomes of post-weaning children. As the type of carbohydrate intake changes, the dominant strains of *B. longum* in infants gut shift from those that can utilize HMOs to those that thrive by fermenting non-HMO carbohydrates[36]. A recent study that longitudinally analyzed the fecal microbiomes and metabolomes of Bangladeshi young children during the first two years of life identified a distinct clade of *B. longum* that thrives during weaning[37]. This clade contains enzymes that utilize both HMOs and complex glycans found in plant foods, is associated with a number of other intestinal taxa and metabolites, suggesting that this clade may play a key role in the gut ecosystem and host development during the weaning phase[37].

Akin to non-digestible carbohydrates, digestible carbohydrates may influence the gut microbiota. Digestible carbohydrates, such as sucrose or lactose, are degraded to monosaccharides (e.g., glucose and fructose) by a series of gastrointestinal enzymes and then absorbed in the small intestine[38]. However, the small intestine cannot metabolize high doses of monosaccharides. Therefore, excess monosaccharides overflows into the large intestine[39]. Excessive dietary sugar intake can cause deleterious functional changes in the intestinal microbiome. The study revealed that high-sucrose conditions directly limited colonic development, which was associated with reduced proliferative gene expression, adenosine triphosphate levels, and pyruvate accumulation[40]. Mice on a high-sugar diet (50% sucrose) showed increased permeability of the intestinal barrier and decreased diversity of gut microbiota and levels of short-chain fatty acids (SCFAs), resulting in increased susceptibility to colitis and increased concentrations of pro-inflammatory cytokines in the colon[40]. Infant cereals are usually manufactured with added sugars[41]. Sweetened commercial supplemental foods consumption is common in Germany, Belgium, Poland, Italy, and Spain, and is most popular in Italy, Poland and Spain[42]. In Spain, more than 95% of children aged 9–12 months consume sweetened commercial supplemental foods[42]. Plaza-Diaz et al.[43] analyzed the changes in the microbial composition of fecal samples from 4- to 7-month-old Spanish infants who consumed infant cereals with varying whole grain and sugar contents as their first weaning food. Compared to infants consuming 50% whole-grain cereal with 12 g sugar, the relative abundance of Proteobacteria and *Escherichia-Shigella* were higher in fecal samples from infants consuming 0% whole-grain cereal with 24 g sugar[43]. A high-sugar diet is a characteristic of the Western diet. A study conducted in Mexico reported that malnourished-children had higher Firmicutes/Bacteroidetes (F/B) ratio than normal weight children of the same age, which might predispose them to obesity in the future[44]. They attributed this phenomenon to the high-sugar and low-fiber diets consumed by these children[44]. An animal study also confirmed that high- glucose or fructose consumption causes an increase in the F/B ratios of the gut microbiota[45].

During weaning, ingestion of non-digestible carbohydrates leads to an increase in the populations of Bacteroidetes, Lachnospiraceae, Prevotellaceae, Veillonellaceae, as well as *Clostridium*, *Bacteroides*, *Ruminococcus* spp., and *B. longum*. These microbiotas are known for their ability to produce large amounts of SCFAs, which may benefit the intestinal microecosystem. Conversely, consuming excess digestible carbohydrates may result in an elevated F/B ratio, an increase in Proteobacteria and *Escherichia-Shigella*, reduced microbial diversity, lower SCFA levels and increased gut barrier permeability, which may adversely affect the intestinal microecosystem. Reducing the sugar content of infant cereals and appropriately increasing the whole grains content may be beneficial to infant health and contribute to the achievement of recommendations for sustainable healthy diets.

2.2 Proteins

Proteins provide a nitrogen source for bacteria. Protein can be obtained from meat, dairy, and plant, etc. Various proteins have

different effects on the gut microbiota. A cohort in Colorado, USA, confirmed that differential growth patterns of gut microbiota were observed in formula-fed infants aged 5–12 months who consumed a supplemental diet based on meat or dairy products (total protein intake was approximately 3 g/kg·day in both groups)[46]. α-Diversity increased over time in the meat group but not in the dairy group[46]. Compared with the dairy group, an increased abundance of *Ruminococcus* and *Roseburia* was observed in the meat group, accompanied by a significant increase in butyrate and acetate production[46]. In another cohort, commercially available meat purees served as the first supplemental food for infants and as a consistent part of their diets from approximately 6 to 9 months of age[47]. The results showed that the median relative abundance of *Clostridium* group XIVa clade (phylum Firmicutes) increased by 40% in the meat group but only by 10% in the control groups of iron-fortified and iron-zinc-fortified cereals[47]. In 2 independent Danish infant cohorts, 1 cohort of infants was born to healthy mothers and another was born to obese mothers, which revealed that protein intake was significantly positively associated with Lachnospiraceae but significantly negatively associated with Bifidobacteriaceae[33]. These findings indicate that the transition from early grain-based infant foods to family foods containing more protein plays a significant role in altering the gut microbial composition during late infancy.

Overall, consumption of meat-derived proteins during weaning is associated with increased populations of Lachnospiraceae, *Ruminococcus*, *Roseburia*, and *Clostridium* group XIVa clade, as well as an increase in α-diversity, butyrate, and acetate production by intestinal microbiota, as compared to proteins sources from dairy or plants.

2.3 Fats

Although the majority of dietary fat is absorbed in the small intestine, there is growing evidence showing that fat can impact the gut microbiota. A previous study found that a high-fat diet induces dramatic changes in the gut microbiota, including a decreased abundance of Bacteroidetes and an increased abundance of Firmicutes and Proteobacteria[48]. These results were observed in both genotypes (wild-type and RELM β-knockout-type) of mice, regardless of their obesity status, suggesting that the high-fat diet itself, rather than obesity, is primarily attributable to the observed altered gut microbiota[48]. The effects of dietary fat on the gut microbiota of infants and toddlers remain unclear. The American Academy of Pediatrics advises against restricting fat or cholesterol for infants under 2 years of age, who require high energy intake for rapid growth and neurological development, unless there are concerns about obesity or a family history of cardiovascular disease[49]. However, the excessive intake of saturated fat in infants and young children is a concern. Demmer et al.[50] explored the consumption patterns of infants and children in the USA based on NHANES 2011–2012 and 2013–2014 dietary data for children aged 0–5 years (n = 2 431). The results showed a substantial increase (> 500%) in solid fat intake in the groups aged 12–23 months compared to the 0–11 months[50]. Herman et al.[51] investigated the dietary habits of American children aged between 2 and 9 years and found that although 28% of the study participants had total fat values lower than the Acceptable Macronutrient Distribution Ranges (AMDRs), 82.7% of the study participants had a saturated fat intake higher than the AMDRs.

Unsaturated fats serve as health-promoting factors. Recently, several studies have investigated the influence of unsaturated fatty acids on the gut microbiota of infants and toddlers. A cross-sectional study examined the gut microbiota of 10- to 18-month-old children living in an urban slum in Mumbai and determined its association with comprehensive nutritional status[52]. Redundancy analysis showed that 5% of the variance in Faith's phylogenetic diversity was attributable to polyunsaturated fatty acid intake[52]. Another study was designed to analyze the effects of a fish and safflower oil mixture (rich in omega-3 polyunsaturated fatty acids) on the gut microbiota of preterm infants undergoing small bowel enterostomy[53]. Compared to standard nutritional therapy, the intervention, lasted 9 weeks, increased microbial α-diversity, decreased abundance of potentially pathogenic bacteria (Enterobacteriaceae, *Clostridium*) and enriched predictive gene function for carbohydrate metabolism[53]. Among the several diet types, the Mediterranean diet is high in omega-3 polyunsaturated fatty acids. Researchers have found that adherence to the Mediterranean diet has positive health effects, including SCFAs production and anti-inflammatory properties, which may reduce the risk of chronic inflammatory diseases such as type II diabetes[54]. Currently, there is no direct evidence of adherence to the Mediterranean diet and changes in the gut microbiota in infants and toddlers. In adolescents, Shankar et al.[55] uncovered microbial and metabolic differences in the gut environment between Egyptian counterparts consuming a Mediterranean diet and USA counterparts consuming a typical Western diet (average age of approximately 13 years). The results showed that the gut environment of Egyptian adolescents was characterized by higher levels of SCFAs, whereas American children had higher level of intestinal vitamin-associated compounds[55].

Excessive consumption of saturated fats may decrease the abundance of Bacteroidetes while increasing the abundance of Firmicutes and Proteobacteria in the gut microbiota of infants and toddlers. Intake of unsaturated fats can enhance microbial α-diversity and reduce populations of potentially pathogenic bacteria. The above findings suggest that careful selection and combination of fat types in infant and toddlers' diets may promote a healthy gut microbiota.

2.4 Vitamins

Vitamins are small molecules that are essential for human health, and recent research has found that they influence the composition of the gut microbiota. Vitamin A plays a crucial role in ensuring the integrity of the intestinal barrier and facilitating the regeneration of damaged mucosal epithelium, especially the normal proliferation of intestinal epithelial cells and differentiation of mucus-producing goblet cell[56]. These functions impact the colonization and adherence of the gut microbiota[56]. A recent study examined the effects of vitamin A supplementation on the neonatal gut microbiota, which increased the relative abundance of intestinal *Bifidobacterium* in male infants in early life (6–15 weeks of age), and was associated with an increase in the abundance of Bacteroidetes in 2 years of age female infants above the median birth weight[57].

Vitamin E acts as an antioxidant primarily through α-tocopherol activity. Vitamin E reduces oxidative potential, so taking it with iron may ameliorate the effects of iron-associated inflammation, improving gut microbiota outcomes[58-59]. A study of infants and toddlers with

iron deficiency or iron deficiency anemia between 9 to 24 months of age in the USA found that 6 mg/kg iron plus 18 mg of vitamin E daily for 2 months did not result in changes in bacterial diversity, but did result in differences in changes in relative abundance of specific gut microbiota[58]. Over time, compared with the iron group, the combination of vitamin E and iron led to a decrease in the abundance of Bacteroidaceae (phylum Bacteroidetes) and an increase in the abundance of Lachnospiraceae and *Roseburia* (phylum Firmicutes)[58].

A systematic review of 10 studies involving changes in the gut microbiome associated with vitamin D and immune pathways in children from infancy to 18 years of age suggested that vitamin D supplementation or vitamin D levels may have an impact on the composition of the gut microbiota in children: the relative abundance of the phylum Actinobacteria (*Corynebacterium*) and Firmicutes (*Lachnobacterium*, unclassified_Clostardilas, *Enterococcus*, and *Phascolarctobacterium*) increased, and that of phylum Bacteroidetes (*Prevotella*, *Alistipes marseille*, *Alistipes indistinctus*, and *Bacteroides massillensis*) decreased, as vitamin D levels increased[60].

Phylloquinone is a dietary vitamin K quinone found in green leafy vegetables and some vegetable oils, menaquinones are vitamin K quinones that are both consumed in the diet (mainly in animal products such as meat, cheese and eggs) and produced by the gut microbiota[61]. Menaquinones are used as an electron carrier in bacterial respiration and quinone synthesis is widespread in the gut[61]. Recent work suggested that some members of the gut microbiota, which have lost the ability to synthesize menaquinones may be able to utilize vitamin K quinone or precursors derived from neighboring bacteria or from the host diets[62]. Direct evidence on vitamin K and the gut microbiome in infants and toddlers is not yet available. A study revealed that the total counts and the number of bifidobacteria in the feces of infants with vitamin K deficiency were lower than those of healthy infants, whereas *Bacteroides*, *Veillonella*, and *Enterococci* were more abundant in the feces of infants with vitamin K deficiency[63]. Similar results were found when analyzing differences in the gut microbiota of Japanese women on low- and high-vitamin K diets[64].

The quantitative linkages between dietary B vitamins and gut microbial composition were tested in a study of 80 children aged 2–8 years in Los Angeles, USA[65]. The relative abundance of Bacteroidetes phylum was found to be higher in individuals who consumed more B vitamins (folate) in their diets[65]. Bacteroidetes are predicted to synthesize all 8 kinds of B vitamins and have specialized transporters to salvage these metabolites[66].

In general, there is relatively limited evidence regarding the impact of vitamins on the gut microbiome of infants and toddlers. Available findings suggest that vitamin A and vitamin K supplementation may be associated with an increase in the relative abundance of intestinal *Bifidobacterium*; vitamin E supplementation may decrease the abundance of Bacteroidaceae (phylum Bacteroidetes) and increase the abundance of Lachnospiraceae and *Roseburia* (phylum Firmicutes); vitamin D supplementation may tend to reduce the abundance of phylum Bacteroidetes while increasing phylum Actinobacteria and Firmicutes; B-vitamins supplementation may be linked to an increased abundance of phylum Bacteroidetes. Given that gut bacteria can recover intermediates and obtain vitamins directly from other species, in addition to being able to absorb and transform vitamins to produce cofactors for a variety of reactions, different bacterial species use distinct metabolic pathways to ingest or metabolize vitamins. Expanding the evidence base to identify cooperation among microorganisms and appropriate doses that are physiologically beneficial for infants and toddlers is warranted.

2.5 Minerals

Infants and young children are particularly vulnerable to iron deficiency owing to their rapid growth[67]. Meat and meat products are vital sources of iron. However, meat intake among infants and toddlers is very limited. Iron fortification in the form of oral micronutrient powders (MNP) is a common corrective strategy for the prevention of iron deficiency[67]. Iron supplements are also available in the form of iron drops, fortified formulas, or fortified supplemental foods[68]. However, iron supplementation for infants and toddlers remains controversial. A growing number of studies have reported the adverse effects of iron on infants and toddlers, especially those who are iron-replete. These effects include decreased growth (linear growth and weight gain), heightened susceptibility to illnesses (typically manifesting as diarrhea), a disturbance of the gut microbiota with a shift towards more pathogenic bacteria and a decrease in beneficial bacteria, and increased inflammatory markers[67-71]. Tang et al.[71] found that home fortification with iron-containing MNP significantly reduced the relative abundance of *Bifidobacterium*, but not the relative abundance of *Escherichia* in the gut of generally non-anemic breastfed African infants at 6–9 months of age, compared with infants receiving no iron or no MNP at all. Consistent results were observed in an intervention study of ferrous sulfate drops in 6-month-old iron-sufficient Swedish infants[70]. Iron is an essential growth-limiting nutrient for many intestinal bacteria, including most Gram-negative bacteria (e.g., *Salmonella*, *Shigella*, or pathogenic *Escherichia coli*)[71]. These pathogenic bacteria acquire effective mechanisms for obtaining iron from the environment, such as the secretion of iron chelators[67]. Excessive iron intake, whether through fortification or supplementation, results in unabsorbed iron in the gut, which in turn fosters the proliferation of these pathogens and disrupts the equilibrium among microbial species[71].

Therefore, there is an urgent need to improve the absorption of iron supplements to reduce the amount of iron entering the colon. This can be accomplished by adding ingredients to the MNP sachets to enhance iron absorption. In children aged 24–31 months, iron absorption was approximately 50% higher in foods fortified with a mixture of 2 mg iron as ferrous sulfate and NaFeEDTA than with 4 mg ferrous sulfate[72]. In addition, iron supplements should contain ingredients that mitigate the adverse effects of iron fortification on the gut microbiome, such as oligogalactans. MNP plus oligogalactans were found to increase *Bifidobacterium* and *Lactobacillus* abundance, decrease virulence and toxin gene abundance of pathogens, and reduce enterocyte damage compared to those with MNP administration alone[69].

The colonization and function of commensal and pathogenic bacteria in the gut may be regulated by zinc[73]. A randomized controlled trial on micronutrient supplementation in 80 Pakistani children aged 12 and 24 months examined the effects of zinc on the gut microbiota of children supplemented with MNP[74]. The results showed that gut bacterial diversity was reduced in children receiving MNP, and vitamins and iron were associated with an increased carriage of specific protozoa and mucormycetes, an effect that was attenuated by zinc addition. Additionally, zinc significantly reduced

the prevalence of *Toxoplasma*. Another study of 6-month-old infants who consumed cereals fortified with iron and zinc or iron found that zinc counteracted the potentially adverse effects of iron fortification on the gut microbiota observed in the iron-only group[47].

There are complex interactions between iron/zinc and the gut microbiota of infants and toddlers. Excess iron can disrupt the intestinal microecological balance, reducing gut diversity, fostering the growth of pathogenic bacteria such as *Salmonella*, *Shigella*, and pathogenic *E. coli*, and reducing beneficial microbes such as *Bifidobacterium*, which may lead to adverse health effects like slowed growth and diarrhea. In contrast, zinc supplementation appears to mitigate some of the negative effects of iron on the gut microbiota. Minerals supplementation strategies should carefully consider nutrient balance and absorption to optimize gut microbial health and minimize adverse effects.

3. Dietary patterns affecting the gut microbiota of infants and toddlers

Laursen et al.[33] compared the gut microbiota profiles of 2 different cohorts of Danish infants (n = 495) at 9 and 18 months of age to examine the association between specific characteristics of the gut microbiota and a complementary diet. Early infant food consists of breast milk, formula and porridge, and the food introduced in late infancy changes to a high content of meat, milk, cheese, animal fats, and rye bread. Both of the independent cohorts, family food dietary pattern (with high protein and fiber contents), was negatively associated with the abundance of Bifidobacteriaceae and Enterococcaceae, but positively associated with the abundance of Lachnospiraceae and Sutterellaceae. The results also showed a positive correlation between Pasteurellaceae and health-conscious foods, consisting of low levels of sweets/cakes, sugar beverages, and fast foods and high levels of fruits, vegetables, fats (vegetables), potatoes, and fish. Dietary patterns of family foods and to a lesser extent the health-conscious foods were both significantly positively correlated with the Shannon index (α-diversity), contributed mainly by cheese, meat, and rye bread. These results indicate that the development of diverse and intricate microbiota occurs gradually during infancy and toddlerhood, primarily as a consequence of the transition from breastfeeding to family-like food. However, complementary diets or home foods received in infancy and toddlerhood could vary depending on dietary habits, cultural (religious beliefs), educational level, and socioeconomic status, which may lead to selective advantages for the establishment of specific microorganisms in the gut. Thus, it is necessary to discuss the effects of different dietary patterns on the development and establishment of the gut microbiota in infants and toddlers.

3.1 USA or Europe (low in fiber and high in animal protein, fats, and refined carbohydrates) vs. Africa or South America (rich in grains, legumes, vegetables, and complex carbohydrates)

Compared to the diets of infants and toddlers living in rural countries, those of infants and toddlers living in Western countries are typically quite low in fiber and contain large amounts of fat and refined carbohydrates. In the USA, up to 27% of infants aged 6–18 months do not eat any vegetables on a given day, and up to 23% do not eat any fruits on a given day[75]. The decrease in vegetable/fruit intake is partly associated with the consumption of commercially prepared infant foods[76]. Several studies have compared the gut microbiota of infants and toddlers in the USA and Europe with that of infants and toddlers in Africa and South America. By comparing cohorts of children aged 1–6 years, De Filippo et al.[31] found that the gut microbiota of children living in rural African villages who consumed a diet based on grains, legumes, and vegetables was more enriched in Actinobacteria and Bacteroidetes than that of children living in Italy who consumed a typical Western diet high in animal protein, sugar, starch, and fat and low in fiber (63.7% *vs*. 27.3% and 6.7% *vs*. 0.8%, respectively). In addition, diets rich in complex carbohydrates led to an increase in the abundance of several specialized starch-degrading bacterial taxa, such as *Prevotella*, *Xylanibacter*, and *Treponema* in rural African village children, whereas these bacteria were not found in Italian children. In contrast, the gut microbiomes of Italian children were enriched in Firmicutes (63.7% *vs*. 27.3%) and Proteobacteria (6.7% *vs*. 0.8%), possibly because of their low-fiber but calorie-rich diet. This is in line with the results of De Goffau et al.[77], who determined the gut microbiota of 7- to 37-month-old children (n = 616) living in rural Gambia. They reported that *Prevotella copri*, *Faecalibacterium prausnitzii*, and *Sorodiplophrys stercorea* were the most abundant species in these populations (35%, 11% and 7%, respectively), with *P. copri* rapidly becoming the dominant species after weaning and showing clusters of bacterial trophic networks centered on *Prevotella stercorea*. Xiao et al.[78] collected 13 776 stool samples or datasets from 1 956 infants aged 1–3 years to analyze the characteristics of the gut microbiota based on a multi-population cohort covering 17 countries. In developing countries such as South Africa, Peru and Brazil, *Bifidobacterium*-predominating enterotypes 2 is prevalent in the first 3 years of life. In contrast, developed Nordic countries have proposed *Bacteroides*-predominating enterotype 3 for most months.

3.2 Hunter-gatherer lifestyle vs. transitional lifestyle vs. industrialized lifestyle

A recent study analyzed the microbiome assembly processes and microbial and functional profiles of infants from different lifestyles and confirmed that the main driver of gut microbiota differences stems from lifestyle[79]. This study included approximately 1 900 16S rRNA and 700 metagenomic and sequencing samples from infants and toddlers following 3 lifestyles: hunter-gatherer/nonindustrialized (Tanzania, Bolivia, and Nigeria), transitional (Bangladesh, India, Malawi, Nigeria, Peru, Karelia, South Africa, EI Salvador, Estonia, and Ethiopia), and industrialized (Brazil, Colorado, Estonia, Finland, Georgia, Germany, Sweden, and Washington). *Bifidobacterium-Streptococcus* microbial coabundance groups (CAG) dominated all lifestyles early in life (0–6 months), with *Bacteroides-Ruminococcus gnavus* CAG blossoming over time (6–36 months) in industrialized children, *Prevotella-Faecalibacterium* CAG expanding in children living in transitional or non-industrialized lifestyles. Compared with toddlers with industrialized lifestyle, a higher relative abundance of *Lactobacillus ruminis*-Clostridiaceae CAG and a lower relative abundance of *Blautia-Ruminococcus bromii* CAG were observed in toddlers with transitional or nonindustrialized lifestyles. In addition, 23.4% of the metagenome-assembled genomes (MAGs) of the

Hadza (Tanzania, a hunter-gatherer lifestyle) infant and toddler feces represented novel species compared to the Unified Human Gastrointestinal Genome collection, and 63 gut microbiota species of the Hadza cohort were extinct (never detected) in infants living in industrialized or transitional lifestyles. Together, these patterns suggest that lifestyle may be a causative factor in the assembly of the infant microbiome and that more species are lost than gained with the industrialization of lifestyles. Fig. 2 shows the differences in the composition and function of the gut microbiome in infants and toddlers with different lifestyles and dietary habits.

3.3 High dietary diversity vs. low dietary diversity

Globally, only 29.4% of children meet minimum dietary diversity standards[80]. In Ethiopia, only 23.7% of children have acceptable dietary diversity, with cereals and legumes as the main dietary sources and a very low intake of vegetables, fruits, and animal foods[81]. The development of the infant gut microbiota primarily occurs within the initial 3 years of life, starting with a relatively simple community of low richness and diversity towards an adult-like complex community. Dietary diversity enhances microbial diversity by providing a variety of substrates for the gut microbiota[82]. In 2 geographically distinct cohorts of healthy infants (Canada and the Netherlands), an increase in dietary diversity appeared to stabilize the gut microbiome[83]. With the introduction of supplementary foods, microbial richness and diversity increased over time and were positively correlated with dietary diversity scores[83]. Proteobacteria and Bacteroidetes utilize proteins and sugars, which may allow members of these phyla to persist during their transition to solid foods[84]. Many microbial families and species from the phylum Firmicutes collectively provide the enzymatic capacity to utilize carbohydrates, proteins, saccharides, and other microbial fermentation by-products[85]. This metabolic diversity empowers the Firmicutes phylum to efficiently occupy and exploit novel resource niches that emerge during dietary diversification, as confirmed in a study analyzing 12 500 fecal samples from children aged 3–46 months from 3 European countries and 3 American states[2]. This study showed a significant increase in 110 unique bacterial species (89 from Firmicutes phylum) at 3–14 months after the discontinuation of breastfeeding. Factors influencing complementary foods diversity and meal frequency include household production diversity, the proportion of household income allocated to food, place of residence, household ethnicity, caregiver occupation, caregiver marital status, and family size[86].

3.4 Other dietary patterns

Recently, Matsuyama and colleagues[5] were able to link dietary patterns to the composition of the gut microbiome of 1- to 2-year-old Australian toddlers. They found that toddlers' adult-like diets could be further divided into 2 groups: a healthy diet characterized by meat/fish, fruits, vegetables, eggs/beans, and bread/pasta, and an unhealthy diet characterized by processed meats, salty snacks, hot-chips/French fries, and cakes. These dietary groups were associated with differences in microbiome composition: 'Healthy' adult-like diets corrected with a different unspecified *Coprococcus* genus; 'Unhealthy' adult-like diets corrected with unspecified members of Lachnospiraceae family. Further, members of the unspecified families of Lachnospiraceae, a *Ruminococcus* genus, and a *Bacteroides* genus were positively associated with unprocessed foods (e.g., meat/fish, fruits) but negatively associated with processed food groups (e.g., processed meats, savory snacks), *Blautia* and *Clostridium* genera were exactly the opposite of these bacteria. Processed foods epitomize modern Western diets. These bacteria, which are positively associated with processed foods, are also enriched in European weaning children[33,87].

4. Specific foods affecting the gut microbiota of infants and toddlers

The earliest research on the ability of diet to modulate the composition and function of the human and other mammalian gut microbial communities was published nearly 100 years ago[88]. Dietary effects on the functional aspects of microbiota may help explain how specific metabolic inputs alter microbiota composition over time[89]. Certain metabolic inputs can select pathways and organisms that contain them[89]. For example, the microbial-encoded degradation

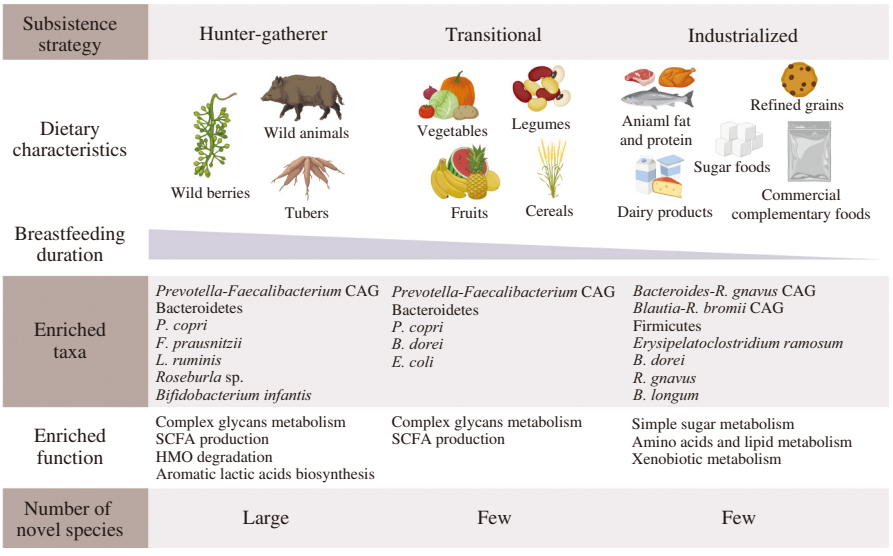

Fig. 2 Differences in the composition and function of the gut microbiome in infants and toddlers with different lifestyles and dietary habits.

system for porphyran, a polysaccharide found in some edible seaweeds, is rare in the microbiota of Westerners, but is prominent in Japanese populations that regularly consume seaweeds[90]. Herein, we summarize the effects of specific foods in the diet on the gut microbiota of infants and toddlers, highlighting the dietary drivers of microbiota assembly early in life (Table 1).

Overall, cereal intake increased the diversity of the gut microbiota in infants and toddlers, the relative abundance of the Bacteroidetes phylum, *Bacteroides* and *Lachnoclostridium*, and decreased the relative abundance of the Proteobacteria phylum[33,43,51,71,91]. Legume intake was positively associated with the relative abundance of *Lachnospira* and *Bacteroides*, and negatively associated with the Firmicutes phylum (including Clostridiales, *Coprococcus*, and *Blautia*)[5,51,92-93]. Fruit intake was positively correlated with the relative abundance of *Lachnospira* and negatively correlated with the F/B phylum ratio[5,51,93]. Apple/pear intake was negatively associated with the relative abundance of *Ruminococcus gnavus* but no significant associations were observed between serve intakes of the citrus subgroup and any taxa[93]. Meat intake increased the diversity of the gut microbiota and the relative abundances of *Ruminococcus*, *Roseburia*, *Clostridium*, and Lachnospiraceae, which belong to the phylum Firmicutes[5,33,46-47,51,94]. Dairy product intake was positively associated with the relative abundance of *Streptococcus* and negatively associated with those of *Alistipes* and *Bacteroides*[5,33,51,93].

These findings demonstrate the contribution of diet to the microbiome assembly, corresponding to the characterization of the microbiota of specific infant and toddler populations. For instance, reductions in the relative abundance of Bacteroidaceae, Lachnospiraceae, Ruminococcaceae, *Roseburia*, and *Clostridium* are commonly observed in the intestines of undernourished children[95]. These bacteria have been shown to be enriched by meat (Table 1). The diet of undernourished children (mostly in low- and middle-income countries from sub-Saharan Africa and the South) is frequently restricted to starchy foods lacking meat. The oral introduction of some Lachnospiraceae species (such as *R. gnavus* and *Clostridium symbiosum*) has been shown to promote growth and bone development in mice previously transplanted with an undernourished gut microbiota[96], and the relative abundance of this species has been shown to be boosted by meat in infant populations[5].

5. Food additives affecting the gut microbiota of infants and toddlers

One of the major changes in human diet over the past few decades has been the increased consumption in processed foods, which often contain synthetic or natural additives such as sweeteners, emulsifiers, and preservatives. Although these additives are generally recognized as safe (GRAS), they have been shown to negatively impact the gut microbiota.

5.1 Sugars/sweeteners

Indeed, for children under 2 years of age, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the American Heart Association recommend avoiding added sugars, while the WHO European National Precautionary Measures (NPM) advises against any added sugars or sweeteners for children under 36 months of age[97-98]. However, a 2019 report from the WHO found that 53% of commercially produced complementary foods (CPCFs) in the UK, 57% in Denmark, and 44% in Spain had total sugar levels above the WHO's recommended levels. Likewise, a survey of approximately 2 500 CPCF products from seven countries (Australia, Brazil, Chile, Mexico, the United Arab Emirates, the UK, and the USA) found that many of the CPCFs contained at least one added sugar or sweetener, with the proportion ranging from 7.3% to 47.4% in 7 countries[99].

Consuming overly sweet products at a young age may influence taste preferences and form habits that persist into late childhood and beyond[100]. Sugar or sweeteners may also affect the process of assembling the gut microbiota in infants and toddlers. Studies on the direct effects of sweeteners on the composition of the gut microbiota in infants and toddlers are still in progress. This prospective study included 100 infants (3–12 months old) whose mothers consumed or did not consume artificially sweetened beverages during pregnancy[101]. The comparison of the gut microbiome composition of these infants revealed β-diversity as well as *Bacteroides* sp. abundance were decreased, and *P. copri* was enriched in infants born to mothers who consumed artificially sweetened beverage compared to infants of mothers who did not consume during pregnancy[101]. The consumption of artificially sweetened beverages during pregnancy was also associated with higher levels of spermine and succinate in infants' urinary metabolites, which are known to be produced by the metabolism of putrescine microorganisms in the gut[101]. Succinate was significantly and positively associated with infant BMI at 1 year of age[101]. Increased levels of circulating succinate are linked to obesity and impaired glucose metabolism[102]. These results support the role of artificially sweetened beverages in the taxonomic and functional changes in the early life microbiome. Notably the sweeteners investigated in this study were artificial sweeteners, whereas natural sugars/sweeteners are generally added to the CPCFs, and there are significant structural differences between the 2 types of sugar. Thus, the specific effects of natural sugars and sweeteners on the gut microbiota of infants and toddlers need to be investigated in depth.

5.2 Emulsifiers

Food emulsifiers are defined by the Codex Alimentarius as additives that form or maintain two-phase or multi-phase homogeneous emulsions in foods. Food additive emulsifiers in young children's foods may be common in baked products such as breads, pastries, biscuits, muffins and cookies. The Irish National Food Ingredient Database compiled the prevalence of food additives in packaged branded foods in the Irish food supply, indicating mono- and diglycerides of fatty acids and lecithin were the most commonly used emulsifiers[103], which was in line with the findings of the USA dietary intake study[104] and also consistent with our investigation on the addition of emulsifiers to Chinese infants and young children foods. One project investigated the intake of 6 groups of food emulsifiers in 8 European countries[105]. The results showed that in an assessment based on a combination of individual consumption data and maximum permissible levels, the intake of polysorbates exceeded the acceptable daily intake (ADI) for children in 4 countries (the UK, Italy, France, and Ireland). Even in toddlers (1–4 years of age), the intake of stearoyl lactylate exceed the ADI in the UK and Ireland.

Table 1
Summary of studies exploring effects of specific foods on gut microbiota in infants and toddlers.

Food category	Food	Impact on gut microbiota	Country of study, age range, and number of participants	Method of microbiota assessment	Study design	References
Cereals	Rye bread	Positively associated with α-diversity	Denmark 9 months n = 311 (SKOT I) and n = 184 (SKOT II)	the Ion OneTouch and Ion personal genome machine (PGM) systems with an Ion 318 chip kit	Observational longitudinal cohort study	[33]
	Breads and cereals	Positively associated with α-diversity (Shannon index and number of OTUs) at 12 months of age	New Zealand 7 months n = 74	V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[91]
	Whole-grain (based on wheat, corn, rice, oat, barley, rye, sorghum, and millet)	Increased in *Bacteroides* and *Lachnoclostridium* and a decreased in Proteobacteria phylum and *Escherichia-Shigella* over time	Spain 4–5 months (7 weeks of intervention) n = 48	V3–V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[43]
	Grain or non-whole grain	Grain correlated with the β-diversity (Weighted UniFrac); Non-whole grain correlated with the β-diversity (Weighted UniFrac and Unweighted UniFrac)	USA 2–9 years n = 75	V4 16S rRNA by Illumina MiSeq	Cross-sectional	[51]
	Maize	The relative abundance of Bacteroidetes increased and Proteobacteria decreased	Kenya 6 months (3 months of intervention) n = 33	V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[71]
	Cowpea	Compared with bean or corn-soy blend flour groups, higher relative abundance of *Bifidobacterium* during the ages of > 9 to 12 months, lower relative abundances of *Prevotella* during the ages of 6–12 months, and lower relative abundances *Escherichia*/*Shigella* during the ages of 6–9 months	Malawi 6–12 months n = 236	V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[92]
Legumes and nuts	Soy, pulses, and nuts	Vegetable protein (soy, pulses, and nuts) intake negatively associated with the relative abundance of the Firmicutes phylum and Clostridiales, and positively associated with *Lachnospira*, *Bacteroides xylanisolvens*	Australia 2–3 years n = 37	V6–V8 16S rRNA by Illumina MiSeq	Cross-sectional	[93]
	Nuts, soy, and legumes SoyNuts/seeds	Nuts, soy, and legumes correlated with the α-diversity (Shannon index); Soy and nuts/seeds correlated with the β-diversity (Unweighted UniFrac), respectively; Legumes intake negatively associated with *Coprococcus*	USA 2–9 years n = 75	V4 16S rRNA by Illumina MiSeq	Cross-sectional	[51]
	Beans	Positively associated with unspecified family members of Lachnospiraceae and *Bacteroides*, and negatively associated with *Blautia*	Australia 1–2 years n = 48	V3–V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[5]
Vegetables and fruits	Fruit Apple/pear Citrus	Fruits intake negatively associated with the Firmicutes/Bacteroidetes phylum ratio, Erysipelotrichaceae, and *R. gnavus*; Apple/pear intake negatively associated with the *R. gnavus*; No significant associations were observed between serve intakes of the citrus sub–group and any taxa	Australia 2–3 years n = 37	V6–V8 16S rRNA by Illumina MiSeq	Cross-sectional	[93]
	Citrus/melon/berries Tomato	Citrus/melon/berries and tomato correlated with the β-diversity (Weighted UniFrac), respectively; Fruit total intake positively correlated with *Lachnospir*a	USA 2–9 years n = 75	V4 16S rRNA by Illumina MiSeq	Cross-sectional	[51]
	Fruit	Positively associated with unspecified family members of Lachnospiraceae, *Bacteroides*, and *Clostridium*, and negatively associated with *Bifidobacterium*	Australia 1–2 years n = 48	V3–V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[5]
Meats	Meat	Positively associated with α-diversity	Denmark 9 months n = 311 (SKOT I) and n = 184 (SKOT II)	the Ion OneTouch and ion personal genome machine (PGM) systems with an Ion 318 chip kit	Observational longitudinal cohort study	[33]
	Meat	Increased relative abundances of *Ruminococcus* and *Roseburia*, and increased of butyrate and acetate productions	USA 5–12 months n = 59	16S rRNA sequencing	Randomized controlled trial	[46]
	Meat	Increased relative abundances of butyrate producing *Clostridium* group XIVa	USA 5–9 months n = 14	V1–V3 16S rRNA by 454 pyrosequencing	Randomized controlled trial	[47]
	Beef	Increased relative abundances of Enterobacteriaceae and Proteobacteria phylum	USA 4–6 months (2–4 weeks of intervention) n = 82	V3–V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[94]
	Include beef, pork, veal, lamb, game, organ meats, sausages, luncheon meat, poultry, and fish and shellfish	Correlated with the α-diversity (Shannon index)	USA 2–9 years n = 75	V4 16S rRNA by Illumina MiSeq	Cross-sectional	[51]
	Poultry	Correlated with the α-diversity (Shannon index)	USA 2–9 years n = 75	V4 16S rRNA by Illumina MiSeq	Cross-sectional	[51]

Table 1 (*Continued*)

	Meat/fish	Positively associated with unspecified family members of Lachnospiraceae, *Ruminococcus*, and *Bacteroides*, and negatively associated with *Blautia*	Australia 1–2 years n = 48	V3–V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[5]
	Cheese	Positively associated with α-diversity	Denmark 9 months n = 311 (SKOT I) and n = 184 (SKOT II)	the Ion OneTouch and ion personal genome machine (PGM) systems with an Ion 318 chip kit	Observational longitudinal cohort study	[33]
Dairy products	Dairy Yoghurt	Dairy intake negatively associated with Bacteroidetes, *Parabacteroides*, *F. prausnitzii*, *Fusicatenibacter*, species richness (Chao1) and diversity (Shannon index) and positively with *Erysipelatoclostridium* spp., *Streptococcus salivarius* subsp. *thermophilus*, *Lachnoclostridium* and the F/B ratio; Yoghurt intake positively associated with *S. salivarius* subsp. *thermophilu* and negatively with *Alistipes* and *Bacteroides*	Australia 2–3 years n = 37	V6–V8 16S rRNA by Illumina MiSeq	Cross-sectional	[93]
	Yogurt	Correlated with the α-diversity (Phylogenetic Diversity) and β-diversity (Unweighted UniFrac)	USA 2–9 years n = 75	V4 16S rRNA by Illumina MiSeq	Cross-sectional	[51]
	Milk/milk products	Positively associated with *Blautia* and *Coprococcus* and negatively associated with *Bifidobacterium*	Australia 1–2 years n = 48	V3–V4 16S rRNA by Illumina MiSeq	Randomized controlled trial	[5]

Recently, a series of studies have raised concerns regarding the safety of specific emulsifiers, particularly their effects on the intestinal environment[104,106-109]. Some food emulsifiers have been found to alter the intestinal lumen and/or mucosal microbiota, increase intestinal permeability, and promote intestinal inflammation, all of which are associated with the development of colitis[110]. A recent study confirmed that the ingestion of polysorbate 80 by female mice delayed intestinal development, disrupted the intestinal barrier, and induced low-grade intestinal inflammation in the offspring mice[111]. Interestingly, maternal ingestion of polysorbate 80 resulted in dysbiosis of the gut microbiota of the offspring that lasted from the weaning period to adulthood (3–8 weeks of age), with a significant decrease in bacteria positively associated with intestinal proliferation and differentiation (*Mucispirillum*, *Clostridium* XI, and *Parabacteroides*) and an increase in deleterious bacteria such as Proteobacteria, Helicobacteraceae, Campylobacterales, and Desulfovibrionales[111]. However, there are limitations to these studies, most of which were conducted *in vitro* or in animal models, and thus cannot be fully extrapolated to humans, especially infants and toddlers. Most of these studies were on emulsifiers such as carrageenan, polysorbate 80, and carboxymethylcellulose, which are not commonly used in food for infants and toddlers. An emerging risk report from the European Food Safety Authority stated that "food emulsifiers, gut microbiome, and long-term health effects" need to be investigated urgently[112].

6. Malnutrition affecting the gut microbiota of infants and toddlers

6.1 Undernutrition

Undernutrition remains one of the most pressing global health challenges today, affecting about 1 in 5 children worldwide[113]. Forms of undernutrition in infants and children include wasting, stunting, underweight, and deficiencies in vitamins and minerals[26]. Nearly half of all under-five deaths are caused by undernutrition, and in 2020, an estimated 149 million children under the age of 5 were still stunted and an estimated 45 million were wasted[114]. Undernourished children live mostly in low- and middle-income countries from sub-Saharan Africa and the South.

When diets evolve from an exclusive breastmilk/formula diet to one that includes complementary foods during the first period of life, food deficiencies or improper feeding may result in undernutrition. Several studies have identified differences of gut microbiomes between healthy and undernourished infants and toddlers. For instance, in a Swedish cohort, children with slower-than-expected weight gain (reference curve between 12 months and 5 years of age) were characterized by lower microbial diversity and a lower relative abundance of Ruminococcaceae, *Faecalibacterium*, and *Roseburia* at 12 months of age than those in children with normal or accelerated weight development[115]. In Bangladesh, the composition of the gut microbiota of severely undernourished toddlers (2 and 3 years of age) was significantly different from that of healthy toddlers, with a reduced α-diversity, a decreased abundance of Bacteroidetes and a dramatic increased abundance of Proteobacteria, including pathogenic genera (e.g., *Klebsiella*, *Escherichia*, *Shigella*, and *Streptococcus*)[116]. Of these, the abundances of *Klebsiella* and *Escherichia* were 174 and 9 folds of those in their healthy counterparts. These differences may be due to undernourished toddlers being less likely to have access to foods such as meat, milk, fish, and eggs, because poor families cannot afford protein-rich foods[116]. Million et al.[95] investigated children (6–59 months of age) with severe acute malnutrition in 5 different African and Asian countries and reported a decrease in several species of Bacteroidaceae, Eubacteriaceae, Lachnospiraceae, and Ruminococcaceae, as well as the methanogenic archaeal species *Methanobrevibacter smithii*, whereas potential pathogens such as *Enterococcus faecalis*, *E. coli*, and *S. aureus* were consistently enriched. *M. smithii* is a key player in energy harvesting, and its importance was confirmed in another study in Mali, where severe acute malnutrition was highly correlated with the loss of this taxon[117]. The gut bacterial species with the greatest distinction between healthy and undernourished children (6–24 months old) were *F. prausnitzii*, *Ruminococcus* spp., and *Dorea* spp.[96,118-119]. In undernourished children, the 'microbiota-for-age *Z*-score' is lower because maturation is severely impaired[120]. Children with undernutrition may also have a functionally immature gut microbiome with disrupted pathways

of carbohydrate and amino acid metabolism, vitamin B production, and nucleotide biosynthesis[121-122]. Notably, studies have shown that changes associated with undernutrition can be transferred to animal models through fecal microbial transplantation, suggesting that the gut microbiome may also play a causal role in the multiple manifestations of undernutrition[96,123].

Microbiota-directed complementary food (MDCF) has provided encouraging results in clinical trials in undernourished children. After 3 months of the MDCF-2 (chickpea, peanut, banana, and soy flour) intervention, Bangladeshi children (12–18 months of age) with moderate acute malnutrition showed favorable changes in key anthropometric measures[124]. Furthermore, the gut microbiota of children receiving MDCF-2 was completely repaired, with the largest bacterial increase occurring in *P. copri* and *F. prausnitzii*, and the largest decrease in *Bifidobacterium* spp. (probably *B. longum*), indicating a successful development of the gut community[124]. However, conventional therapeutic food approaches in Bangladesh, although effective in addressing severe acute malnutrition in children, do not support microbiome restoration or maturation[114,119].

6.2 Overnutrition

Although not as well-researched as undernutrition, overnutrition is a growing global health problem, with an estimated 38 million children under the age of 5 being obese or overweight[125]. This nutritional imbalance is not limited to affluent countries, but is becoming increasingly common in developing countries as well[126]. In infants and toddlers, the high protein and energy content of complementary foods and noncompliance with feeding guidelines during the weaning period may be associated with overnutrition[127]. In addition, pre-pregnancy BMI of the mother, high birth weight and height, formula feeding during the first year, and frequent consumption of fast food, have been identified as risk factors for childhood overweight or obesity[128]. A recent cross-sectional study of 72 900 children from 17 countries found that the strongest risk factor associated with a dose-response was the frequency of fast food consumption[129]. Understanding the interrelationships between obesity and the gut microbiota early in life could contribute to the development of 'healthy' microbiota.

Previous studies have compared obese animals and humans with their lean counterparts to describe the differences in the composition of the gut microbiota. Obese mice and humans exhibited an increase in the relative abundance of the Firmicutes and a decrease in the relative abundance of the Bacteroidetes, which was reversed after diet-induced weight loss[130-132]. The results of a systematic review of children aged 3 weeks to 13 years were comparable to those of adults, showing that the F/B ratio was positively associated with obesity[133]. Some studies have also characterized the composition of the gut microbiota in obese/overweight and healthy-weight children, identifying the presence of specific gut microbes associated with overweight and obesity. Karvonen et al.[128] investigated 146 of 502 children who are 3-year-old in the USA who were categorized as overweight/obese. They reported that a high relative abundance of *Parabacteroide* (Bacteroidetes) and an unassigned genus within the Peptostreptococcaceae family was negatively associated with overweight/obesity, whereas a high relative abundance of *Dorea* (Firmicutes) was positively associated with overweight/obesity[128]. In addition, they did not find an association between diversity indices and overweight/obesity[128]. Another prospective birth cohort study (n = 3 405) based on a Canadian population found differences in gut microbiota composition in the first year of life in rapidly growing infants[134]. Infants with a rapid growth trajectory acquired less microbiota diversity in the first year of life and a decrease in the relative abundance of *Akkermansia* and an increase in the abundance of *Ruminococcus* (Firmicutes) and *Clostridium* (Firmicutes) compared to normal infants[134]. In contrast, Houtman et al.[135] found no relationship between the B/F ratio and BMI Z-scores (zBMI) in the first 12 years of life among 160 Dutch children. Exploratory analyses showed that the relative abundance of Firmicutes and Bacteroidetes and microbial richness were independently negatively associated with zBMI from infancy to childhood, and the SCFA-producing genera *Subdolicapsulum* and *Alistipes* were negatively associated with future zBMI in children[135]. The authors explained that their observations may be a result of the small number of obese children in the study (28/1160 zBMI were considered obese), and that the Dutch children's samples (< 1% abundance of Bacteroidetes in some of the samples) may have fewer Bacteroidetes than their counterparts from other geographies[135]. An increase in the F/B ratio reflects an increased ability to ferment dietary polysaccharides into SCFAs. SCFAs are estimated to account for 10% of the total human dietary energy supply and Firmicutes include many known SCFAs producers[136-137].

7. Conclusion

An important window of opportunity to modify the structure of the developing microbiota occurs during the complementary feeding period when the diet gradually changes from milk-based infant feeding to family-based solid foods. In this review, we summarize available evidence from nutritional intervention trials that have tested the effects of complementary foods practices on microbiome-related outcomes in infants and toddlers, primarily based on data from observational cohort studies. These findings might deepen our comprehension of the complex interactions between diets and the development and establishment of the gut microbiota. This may facilitate the tailoring of interventions aimed at promoting beneficial modifications within the gut microbial community. Furthermore, the insights could inform the design and implementation of safe and efficacious complementary feeding practices.

Overall, during the complementary feeding period, healthy development of the gut microbiota necessitates appropriate amounts of grains, vegetables, fruits, meat, fish, eggs, legumes, and dairy products as needed. Dietary diversity should be maintained to ensure the diversity of the gut microbiota. In some cases, infants and toddlers might require nutritional supplements (vitamins and minerals), but careful attention should be paid to the possible adverse effects of excess intake such as those from iron on the gut. Excessive intake of digestible dietary sugars or saturated fats has been associated with detrimental functional changes in the gut microbiota. Thus, it is advisable to increase the proportion of whole grains and limit saturated fats while opting for appropriate unsaturated fats. Additionally, CPCFs containing added sugars, sweeteners, or emulsifiers are not recommended.

8. Suggestions and future directions

Diet provides an attractive opportunity to modulate the assembly processes of the gut microbiome in infants and toddlers. To date, only a few studies have evaluated diet during the complementary feeding phase and compared it with the development of the gut microbiota. To decipher the effects of dietary factors on gut microbial development, a detailed assessment of the complementary dietary components is required. Traditional food frequency questionnaires, designed for assessing long-term or habitual diets, may not capture rapid dietary changes effectively during this critical period. A more precise method is to maintain food records for multiple consecutive days during the complementary feeding phase. In addition, a combination of frequent fecal sampling and state-of-the-art microbiome (obtaining species- and strain-level resolution) and metabonomics analyses, as well as in-depth genomic and phenotypic characterization of fecal microbial isolates, could identify key diet-microbe-metabolite interactions. Future studies should include prospective cohort and targeted intervention studies to establish a causal relationship between dietary components and gut microbial composition. Finally, animal experiments based on germ-free mice or specific models of human diseases can be used to determine the exact mechanisms and physiological significance of the effects of specific dietary components on the microbiome. In summary, these future study designs will allow us to expand our understanding of the effects of complementary foods on the gut microbiota of infants and toddlers, aiming to address topical issues such as the timing and type of complementary food introduction, the long-term health effects of the microbiota early in life, and the optimization and safety of nutritional supplements.

Conflict of interests

Qixiao Zhai is an associate editor for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors declare there is no conflict of interest.

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