The Microbiota and Malnutrition: Impact of Nutritional Status During Early Life

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Abstract

According to the developmental origins of health and disease hypothesis, our health is determined by events experienced in utero and during early infancy. Indeed, both our prenatal and postnatal nutrition conditions have an impact on the initial architecture and activity of our microbiota. Recent evidence has underlined the importance of the composition of the early gut microbiota in relation to malnutrition, whether it be undernutrition or over-nutrition, that is, in terms of both stunted and overweight development. It remains unclear how early microbial contact is linked to the risk of disease, as well as whether alterations in the microbiome underlie the pathogenesis of malnutrition or are merely the end result of it, which indicates that the

question of causality must urgently be answered. This review provides information on the complex interaction between the microbiota and nutrition during the first 1,000 days of life, taking into account the impact of both undernutrition and overnutrition on the microbiota and on infants' health outcomes in the short- and long-term.

Contents

1. INTRODUCTION

The intimate interrelationship that exists between an individual's diet, the key regulatory systems of the body, and the microbiome has been widely recognized when explaining an individual's susceptibility to disease, with the related phenotypes ranging from allergic, autoimmune, and inflammatory diseases to obesity (147).

Our understanding of the concept of nutrition is continuously evolving. The primary role of an individual's diet is to provide the nutrients necessary to meet the body's energy and metabolic requirements, as well as to ensure the growth and development of children. Perhaps somewhat belatedly, the position of an individual's diet in relation to health and well-being has been strengthened as the science of nutrition has evolved. Because diet has the ability to regulate specific target functions within the body, its use to promote health and reduce the risk of disease has become increasingly important (104).

Furthermore, the idea that microbes always cause infection has been refuted (7). In the field of medicine, microbes have traditionally been viewed cautiously and defensively, as pathogens that cause disease. Recently, the host–microbe interaction has been identified, which points to the fundamental capacity of the microbiome to extend the host's genome, thereby providing an expanded range of metabolic and functional capacities (56).

The dogma concerning fetal development in sterile conditions is likewise changing. New evidence suggests that the mother may actually provide the inoculum of microbial colonization in utero (33) since bacteria have been detected in the meconium and amniotic fluid as well as in the placenta, and other biological tissues involved in the maternal–fetal interface. A dramatic shift in the gut microbiota toward a proinflammatory profile occurs during pregnancy, which is evidenced by signs of systemic inflammation during the third trimester and the associated weight gain (146). Pregnancy also influences the oral microbiota composition toward a proinflammatory profile (45). Traditionally, the gut colonization process in infants has been determined by the mode of delivery and breastfeeding, with maternal immunological and metabolic health having an impact, although the focus of research is now shifting to the prenatal period (79).

The importance of both the timing of the initial microbial contact and the composition of the microbiota become clear when considering the risk of noncommunicable diseases (NCDs) (138). According to the developmental origins of health and disease hypothesis, human health will be endangered if the environment following birth significantly differs from that encountered by the fetus during pregnancy. Indeed, restricted in utero nutrition and later overnutrition, as occurs in the lifestyle of developed countries, increase human risk and susceptibility to metabolic problems (99). Epidemiological evidence of early programming of metabolic diseases suggests that it depends on maternal nutrition, both undernutrition and overnutrition (44). In fact, the gestational and perinatal periods are considered to be the most critical stages in terms of the risk of developing NCDs. Maternal microbiota dysbiosis may be transferred to the infant via different routes, for example, during pregnancy, birth, and breastfeeding. These factors also have an impact on the composition of breast milk (51, 82), which is the most important source of nutrients, human milk oligosaccharides (HMOs), and microorganisms needed for microbial colonization during early infancy.

One explanation for the rise in immune and metabolic morbidity in recent years concerns the fact that our genome is not yet equalized to the contemporary abundance and continuous availability of foods, which have been influenced by intensive agricultural and food-processing practices. Consequently, the process of adaptation to the modern diet that must be undertaken by the complex microbial gene collection (the microbiome) remains incomplete (11). However, resilience to unfavorable changes witnessed during this critical period of maturation may be achieved through the introduction of specific next-generation personalized diets based on individual risk algorithms. One candidate source of the active compounds necessary in this regard could be a healthy, age-appropriate gut microbiota (135).

This review focuses on the key interaction between the gut microbiota and an individual's nutritional status during the first 1,000 days of life. We address the impacts of both undernutrition and overnutrition on the microbiota, as well as the microbiota's effects on short- and long-term health outcomes.

2. DEVELOPMENT OF THE HUMAN GUT MICROBIOTA

2.1. Prenatal Exposure to Microbes

It has been suggested that the exposure to microbes is initiated even earlier than generally believed. In fact, the fertilization process itself may be influenced by the vaginal and seminal microbiota (91). It is known that the amniotic fluid has a relatively rich microbiota composition, although there are only low numbers of bacteria. As the amniotic fluid is ingested, it provides the initial inoculum for the primary colonization of the gastrointestinal tract by those microbes present in it. Evidence of this colonization has been found by analyzing the microbial signatures of both the amniotic fluid and the meconium (36, 110). The first colonizing microbes present in the amniotic fluid, which

have also been recovered from the meconium, belong to the Proteobacteria genera *Escherichia* and *Enterobacter* and also to Firmicutes, mainly dominated by lactic acid bacteria, including *Enterococcus*, *Lactobacillus*, *Leuconostoc*, and *Lactococcus* (33). These may be also impacted by the composition of the HMOs in the amniotic fluid (142).

2.2. The Impact of Birth: Microbial Pioneers of the Neonatal Gut

The exposure to specific bacterial species during the neonatal period is facilitated by the mode of delivery, since vaginally delivered infants are exposed to microbes from the vagina, including *Prevotella* and *Lactobacillus*, as well as to the genera *Bacteroides*, *Bifidobacterium*, *Parabacteroides*, and *Escherichia*, among others (127). The maternal gut represents an important source of bacteria, with 72% of gut bacteria in vaginally delivered newborns being derived from the maternal intestine compared with 41% in newborns delivered by Caesarean section (9). Moreover, it appears that these differences in the composition of the gut bacteria are accentuated in the case of elective Caesarean section compared with emergency Caesarean section, whereby the mechanisms of labor increase the gut permeability during delivery (8). Hence, infants delivered by elective Caesarean section are mostly colonized by bacteria associated with the maternal skin and mouth or the maternal environment, including the hospital and place of birth.

Several studies have documented the reduced fecal abundance of *Bacteroides* or the reduced diversity of the Bacteroidetes phylum in the infant gut following delivery via Caesarean section (11, 114, 127). In such cases, the fecal microbiome may consist of *Enterobacter*, *Staphylococcus* (including *S. aureus*), *Streptococcus*, and *Veillonella*, among others. The *Bifidobacterium* species tend to be less abundant in Caesarean-born infants when compared with the abundance seen in vaginally delivered infants. Caesarean-born infants also harbor more *Clostridium difficile*, which may introduce imbalances to the microbiota by means of Clostridia overgrowth and possibly even toxin production.

Moreover, antibiotics have been reported to significantly alter the early gut colonization profile and to have relatively long-lasting effects, which result in reduced diversity and a particularly low abundance of Actinobacteria (83). The use of antibiotics appears to have the most pronounced impact on the composition of the microbiota in infants born by Caesarean section, with the use of intrapartum antibiotics being more frequent during such births. The consequences of neonatal antibiotic exposure have been reported to include an increased abundance of proinflammatory Proteobacteria, as well as significantly reduced numbers of Actinobacteria (105). More specifically, antibiotic treatment appears to lead to a reduced number of potentially protective *Bifidobacterium* genera (5, 9, 64). These changes can be long-lasting, and they may play a significant role in programming infants for a propensity to develop overweight and obesity.

2.3. Early Postnatal Development of the Intestinal Microbiota (Age 0–6 Months)

Following birth, the type of feeding (i.e., breastfeeding or formula-feeding) directly shapes the microbiota, thereby influencing both diversity and richness. Breastfeeding generally favors the predominance of bifidobacteria in the infant gut, and the composition and activity of the bifidobacteria together with the lactic acid bacteria form the basis for the development of the microbiota (98). During infancy, the most important step in the colonization process is the rapid succession of anaerobic bacteria, including the genera *Bifidobacterium* and *Bacteroides* and also *Eubacterium* and *Clostridium*. It has been reported that in exclusively breastfed neonates, early in life up to 90% of the gut microbiota may be composed of different species of *Bifidobacterium* (112). The most

common *Bifidobacterium* species in the neonatal gut are *B. breve*, *B. infantis*, and *B. longum*, while the *Lactobacillus acidophilus* group or *Lactobacillus gasseri* are the most common lactobacilli found in the gut of both breastfed and formula-fed infants (112, 116).

Breastfeeding is also a vehicle for transferring maternal skin bacteria, as well as certain environmental bacteria also via the skin (99). Breast milk bacterial profiles are generally similar to those seen in infant feces, while similarities with maternal blood samples have also been reported (38). Such similarities suggest that there exists a link between the various sites. Hence, the breast milk microbiota contains similar bacterial communities to those found on the skin, and in the gut, vagina, and oral cavity (106).

By contrast, formula-fed infants have been found to be more commonly colonized by various genera of Clostridiales and Proteobacteria, including *E. coli* and *Clostridium* species, as well as by *Akkermansia muciniphila*, *Bacteroides fragilis*, and lactobacilli (21, 145), with the majority of these species having an environmental origin. These differences could explain the higher risks of infection and immune-mediated and metabolic-related diseases—such as atopy, asthma, and related allergies—obesity, and other problems faced by formula-fed infants (62).

2.4. Development of the Intestinal Microbiota During the Postnatal Developmental Phase (Age 6 Months to 2 Years)

Weaning causes a rapid and major change in the gut colonization process, and it starts to guide the microbiota composition and activity toward those of the adult microbiota. The steady introduction of complementary food can serve to remove differences between breastfed and formula-fed neonates (11). At the same time, the numbers of *Bacteroides*, *Eubacterium*, *Clostridium*, and other anaerobic bacteria increase, with particular increases being seen in the numbers of enterobacteria, such as *E. coli*, and also some lactic acid bacteria, such as *Enterococcus* (106). During this phase, rapid changes and fluctuations in the numbers and diversity of species occur, particularly in the *Bacteroides* species, which are able to harvest energy from the fiber components of a diet. During the second year of life, the steps involved in the development of the microbiota composition include increases in diversity and in the numbers of *Bacteroides*, *Veillonella*, and *Fusobacterium*. The numbers of uncultivable or unidentifiable microbes also increase, which renders the characterization of the complete microbiota challenging. Nevertheless, children appear to harbor higher numbers, as well as different species, of bifidobacteria and enterobacteria than adults for some time until, eventually, the microbiota becomes similar to that seen in adults (128).

3. CONTRIBUTIONS OF THE MICROBIOTA TO THE HOST'S NUTRITION

Commensal bacteria are able to influence the host's nutritional status in several ways (**Figure 1**), including through nutrient absorption, the bioconversion of compounds from the diet to bioactive compounds, the regulation of energy, and the production of micronutrients, vitamins, and other microbial metabolites (103). Therefore, the intestinal microbiota should be recognized as an important part of the human digestive system that plays a key role in nutrition (93). The interplay between the gut microbiota and the host's nutritional status, as well as evidence concerning the impact of diet on the gut microbiota (34, 117), highlight the interdependence of these factors in the homeostasis of the human body (103). This means that dysbiosis in the gut microbiota can be both a cause and a consequence of malnutrition.
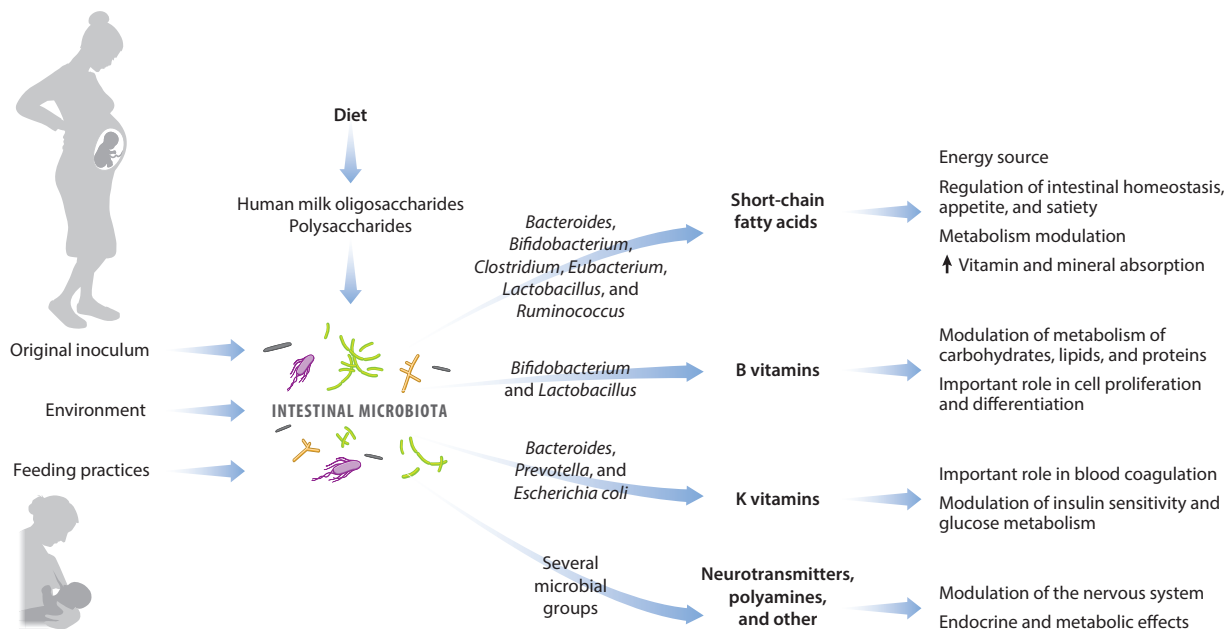
Figure 1

Microbial metabolites in nutrition and health. The main factors modulating the composition of the intestinal microbiota in early life are related to perinatal events, environmental exposures, and feeding practices. Intestinal microbiota produce nutrients and other metabolites that can be easily absorbed in the gut and contribute to a beneficial health status. It is well known that different microbial populations produce different metabolites, and deficiencies in these bacterial metabolites are linked to several diseases.

3.1. The Microbiota and Nondigestible Carbohydrates

The term nondigestible carbohydrate refers to all of the carbohydrates—including resistant starch, plant cell–wall material, and oligosaccharides—that resist gastrointestinal digestion (96). The microbiome encodes the genes necessary for polysaccharide digestion, thereby hydrolyzing and fermenting these nondigestible carbohydrates in the large intestine (22).

Breast milk is the first source of nondigestible oligosaccharides, which are known as HMOs. These are structurally diverse, and the composition of breast milk depends on several factors, including genetic and environmental factors (20). HMOs directly influence the infant's gut microbiota by acting as substrates for specific commensal gut bacteria; by acting as antiadhesive antimicrobials and decoy molecules interfering with pathogen-, virus-, and toxin-binding receptors; and also by indirectly modulating immune response (65). *Bifidobacterium* and *Bacteroides* species use HMOs as carbon sources to promote their growth, although this ability is modulated in a strain-specific way (65). Following the introduction of complementary feeding, other polysaccharides become available to the gut bacteria. The main genera related to polysaccharide digestion in the human gut are *Bacteroides*, *Bifidobacterium*, and *Ruminococcus*, as well as *Clostridium*, *Eubacterium*, and some *Lactobacillus* (96), all of which contribute an additional 6–10% of the energy derived from carbohydrates, mainly in the form of short-chain fatty acids (SCFAs) (13, 81, 103). The main SCFAs produced are acetate, succinate, propionate, butyrate, and formate (113). Moreover, several studies have indicated that SCFAs, in addition to supplying energy, also exert bioactive properties, such as modulating the endocrine system, thereby having a positive impact on the mechanisms that regulate energy intake, appetite, intestinal function, lipid metabolism, insulin release, and

glucose homeostasis (103, 111). The rapid absorption and metabolism of SCFAs make it difficult to quantify their production, although it has been estimated that in a healthy individual who consumes a typical Western diet, about 100–200 mM of SCFAs are produced daily in the gut, of which approximately 90–95% are absorbed in the colon (81).

SCFAs have a significant impact on intestinal health because they are the main source of energy for colonocytes, as well as being related to the regulation of both intestinal homeostasis and epithelial integrity (52). The rate of production of SCFAs and the amount of SCFAs vary depending on the composition and density of the colon microbiota in combination with other factors, such as age, diet, pH of the colon luminal content, gut transit time, and also the type of dietary fiber available for microbial fermentation (58, 81). In terms of the composition of the microbiota, *Bacteroides*, *Bifidobacterium*, *Eubacterium*, and *Propionibacterium* are all acetate producers; butyrate is produced by microorganisms belonging to *Clostridium* clusters IV (including *Ruminococcus bromii* and *Faecalibacterium prausnitzii*) and XIV (*Blautia coccoides*, *Eubacterium rectale*, *Roseburia* species, and *Butyrivibrio fibrisolvens*), among others; *Bacteroides*, Clostridia, and Propionibacteriaceae produce propionate; lactic acid bacteria and members of *Clostridium* cluster XIVa convert lactate to butyrate; while members of *Clostridium* cluster IX transform lactate into propionate (109). The SCFAs that are not utilized by colonocytes are transported in the blood, thereby exerting an effect on other tissues. Butyrate appears to play critical roles in regulating both intestinal motility and the enteric nervous system (90). In the liver, propionate serves as a substrate for gluconeogenesis, and it can also modulate cholesterol synthesis (134), while acetate is used for lipogenesis and cholesterol synthesis (13, 81).

Moreover, in addition to their direct impact on nutrition, the SCFAs produced by the microbiota can modulate vitamin and mineral absorption. It has previously been demonstrated that SCFAs induce the expression of the vitamin D receptor and the calcium transporter in intestinal epithelial cells (103). Further, SCFA production reduces the luminal pH of the colon, an effect that stimulates the absorption of divalent cations in the cecum (109). Similar to how different microbiota profiles might lead to different rates of carbohydrate fermentation and the production of different metabolites, altered microbiota profiles may influence infant development in unusual ways, with both short- and long-term consequences (52).

3.2. Microbiota Production of Vitamins and Other Bioactive Compounds

Vitamins are considered to be essential micronutrients: They act as the enzyme precursors needed for essential biochemical reactions in the human body. Humans are not able to synthesize most vitamins and of those they can synthesize, they are unable to synthetize a sufficient amount to fulfill their requirements, consequently vitamins must be obtained exogenously. The most important uptake of microbial-produced vitamins occurs in the large intestine, mainly in the colon, in contrast to the vitamins obtained through the diet, which are adsorbed mostly in the small intestine (86).

It has been shown that the gut microbiota, mainly the bacteria present in the distal colon, are able to produce and synthesize several vitamins, including vitamin K in the form of menaquinones (vitamin K_2), as well as B group vitamins, including thiamine (B_1), riboflavin (B_2), nicotinic acid (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_8), folate (B_9), and cobalamin (B_{12}) (86).

The B vitamin group includes eight different water-soluble vitamins that all play essential roles in some metabolic pathways, including carbohydrate and protein metabolism, and DNA replication, repair, and methylation. Some microorganisms belonging to the genera *Lactobacillus* and *Bifidobacterium* contribute to the production of B vitamins (103), thereby supplementing or compensating for dietary intake. An example of this can be seen in the production of vitamin B_{12} by

Table 1 Vitamins produced by intestinal microbiota species (70, 85, 86, 103)

Bacteria	Vitamins produced
Bacteroides spp.	K_2
Bifidobacterium adolescentis	B_9
Bifidobacterium bifidum	B_9
Bifidobacterium breve	B_9
Bifidobacterium lactis	B_1
Bifidobacterium longum	B_1, B_6, B_9
Bifidobacterium pseudocatenulatum	B_9
Escherichia coli	K_2
Klebsiella spp.	B_{12}
Lactobacillus helveticus	B_1, B_6
Lactobacillus plantarum	B_2, B_9
Lactobacillus reuteri	B_{12}
Lactobacillus rhamnosus	B_1, B_2, B_9
Prevotella spp.	K_2
Pseudomonas spp.	B_{12}

intestinal bacteria, which appears to be adequate to meet the daily requirements of some vegan populations in India and Iran (3, 12, 57).

In addition to the production of B group vitamins, different isoforms of vitamin K_2 are produced by different species of commensal bacteria, with short-chain isoforms being produced in the ileum and long-chain menaquinones being produced in the colon (103). Beyond its classical role in blood coagulation, vitamin K appears to exert anti-inflammatory effects (124). Recent studies have reported that variations in commensal intestinal bacteria produce different forms of vitamin K with different bioavailability, bioactivity, and functions, which may cause differences in both vitamin K status and general health (70, 103).

Examples of vitamin-producing bacteria are shown in **Table 1**. Given that a high percentage of commensal bacteria possesses the necessary biosynthesis pathways for vitamins (85), the amount and the isoforms of the vitamins produced in the gastrointestinal tract under different conditions and different dietary patterns need further study.

In addition to vitamins, the intestinal microbiota produces a vast number of other bioactive compounds, such as polyamines, taurine, indole derivatives, urolithin A, and flavonoid derivatives (52, 90), which are all involved in regulating key physiological functions in the host's immune, metabolic, and nervous systems. For example, the indole derivatives produced by *Lactobacillus reuteri* and *Lactobacillus johnsonii* from tryptophan are involved in regulating immune homeostasis in the gut (90). As in the case of carbohydrates, different microbiota profiles might be associated with differences in metabolite production, with such changes potentially influencing an infant's development.

3.3. The Microbiota and Feeding Behavior

The gut–brain axis integrates the central nervous system with the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic arms of the autonomic nervous system, the hypothalamic–pituitary–adrenal (HPA) axis, the enteric nervous system, and the gut microbiota. This gut–brain axis integrates bidirectional communication between the nervous system and gut microbiota by means of specific signaling and specific compounds and metabolites. Brain signals

influence the sensory, motor, and secretory gut functions by producing specific compounds, such as neuropeptides and hormones, while gut visceral messages also influence brain function, mood, and behavior. An accumulation of data suggests a link between the central nervous system and gut microbiota, with this relationship being able to modulate human food preferences and eating behavior, as well as appetite, food choice and intake, and the host's metabolism (4, 87, 132). The gut microbiota have also been suggested to play a role in neuropsychiatric disorders, such as autism, anxiety, depression, stress, Alzheimer's disease, and anorexia nervosa (84).

The gut microbiota metabolites derived from the consumption and fermentation of dietary nutrients may influence appetite, eating behavior, and food intake by directly modulating nutrient sensing and appetite, as well as the intestinal satiety pathways (42, 132). These microbial metabolites include SCFAs and other neuroactive compounds, as described in several reports (66, 67, 143). Alterations in the gut microbiota have been associated with inflammation, metabolic, immunological, and also behavioral disorders, which suggests a potential role in the etiology and development of these disorders (74). The effects on the gut–brain axis have been proposed to result from the mechanisms linking microbial perturbation and energy metabolism through altered levels of SCFAs and their impact on appetite-regulating hormones (107). These proinflammatory microbial-related compounds, such as lipopolysaccharide and flagellin produced by the Enterobacteriaceae family, have been linked to both an impairment in diet-driven satiety and the development of hyperphagia (75), as well as to weight gain and insulin resistance (25). Indeed, all of these bacterial metabolites can be detected in the systemic circulation, which may enable them to act directly on the hypothalamic neurons.

Furthermore, it has also been reported that the consumption of a high-fat and/or high-energy diet is related to an increase in both meal size and hyperphagia over time (131). Gut satiety peptides, such as cholecystokinin, signal via the vagus nerve to control food intake. Additionally, evidence suggests that the vagus nerve may play a key role in transmitting gut microbiota signals to the brain, thus affecting feeding behavior (74).

It should also be noted that functional genetic variation in the taste genes, for example, *TAS2R38*, is relevant to the perception of bitter compounds or food (97, 118). In addition to perception, there appears to be a link between genotype and food preferences, choices, and intake in the case of vegetable consumption (39, 60, 120), which can impact the intestinal microbiota both in mothers and children. It has recently been reported that the host–microbiota interaction evidenced by the link between the oral microbiota and the genetic variation in the bitter taste receptor TAS2R38 could influence food preferences, food choices, and eating behavior (119).

4. MALNUTRITION AND THE MICROBIOTA

Malnutrition is a term that includes both undernutrition (reduced consumption or utilization of one or more nutrients and/or energy) and overnutrition (excessive food intake in relation to energy requirements) (139).

Undernutrition can be a consequence of two situations: First, exogenous or environmental undernutrition is the prevalent form observed in developing countries. This type occurs due to a lack of food consumption resulting from insufficient intake or poor food quality, or both, and it is also linked to poor hygiene and a repeated number of infections, including gastrointestinal infections and intestinal parasites, and tuberculosis, measles, and malaria, among others (95, 121). According to the World Health Organization (WHO), undernourished populations are mainly found in Asia, sub-Saharan Africa, and Latin America, with undernutrition also common in countries suffering from wars and refugee crises. Second, endogenous undernutrition is caused by specific diseases that either impair nutritional or physiological processes—such as intake,

absorption, or metabolism—or enhance nutritional requirements. This type is related to disease, and it is prevalent in developed countries due to the high survival rates associated with most severe and chronic diseases (50).

When children suffer from acute undernutrition in situations of poverty (in which there are unbalanced diets, poor hygiene, and repeated infections), first they become underweight and then, when their condition deteriorates, they suffer from severe wasting [in children under 5 years, defined as having body mass index (BMI) that is 3 standard deviations (SDs) below the average for their age] (139). The percentage of children in developing countries affected by severe wasting ranges from 2% to 20%; furthermore, when this situation is long-lasting or chronic, children stop developing, which triggers stunting. The definition of stunting (linear growth delay) is a height-for-age z-score that is below two SDs from the median of WHO's reference guidelines (139). The prevalence of stunting is a significant concern in children in Africa and Asia who are under the age of 5 years.

Depending on the nutrients involved, undernutrition may present clinically in two different ways: If the deficit affects the energy supply, marasmus develops, whereas protein deficiency leads to kwashiorkor, which is later accompanied by edema and intense immunodeficiency. Kwashiorkor is the most common form of undernutrition observed in developing countries where there is a lack of access to food and there is consumption of poor-quality nutrients with less protein of high biological value (50).

Furthermore, a number of poorer countries worldwide experience the double burden of malnutrition caused by simultaneously suffering high rates of child undernutrition and anemia, as well as rising rates of overweight and obesity (140). In 2016, the number of chronically undernourished people in the world was estimated to be 815 million, of whom 55 million were children under the age of 5 years (41). The groups considered most sensitive to undernutrition include the fetus during pregnancy, children during the first 5 years of life, adolescents, pregnant and lactating women, and the elderly (99). In 2016, wasting was found to have affected 52 million children under the age of 5 years, more than half of whom lived in southern Asia, while 41 million children under 5 years were found to be overweight (41).

Undernutrition in children is responsible for short- and long-term sequelae, including growth failure and neurodevelopmental impairment (14). In addition, overweight and obesity are associated with high economic costs, as well as being the fifth leading cause of death worldwide (15). Overweight and obesity are considered to be important predisposing factors for an increased risk of developing several diseases and disorders, particularly metabolic syndrome, diabetes, and cardiovascular disorders (73). All of these NCDs are characterized by high morbidity and mortality, contributing to some 41 million deaths every year (140). The Global Burden of Disease Obesity Collaborators reported that disability-adjusted life years and deaths due to cardiovascular disease have increased in recent years in parallel with the increase seen in the adult BMI (1).

Dysbiosis refers to an imbalance or alteration in the taxonomic composition of the microbiota. An age-appropriate microbiota composition is pivotal to maintain health (61). Precocious maturation of the gut microbiota has been linked to the development of overweight in a Singaporean birth cohort, which is in accordance with previous reports from Finland concerning lower abundance and prevalences of bifidobacteria in breastfed children who became overweight later in life. In contrast, undernourished Bangladeshi and Malawian children exhibited a younger gut microbiota profile than was expected for their chronological age (18).

Recently, the Afribiota project designed a study to compare the microbiota composition (i.e., in the stomach, small intestine, and feces) of a cohort of stunted children aged 2 to 5 years with that in nonstunted children (recruited in the Central African Republic and Madagascar), as well as to determine the association of microbiota composition with enteropathy (136). They hypothesized

that dysbiosis must play a role in the chronic gut inflammatory status in stunted children and that the chronic inflammation is potentially associated with long-lasting epigenetic causative effects (e.g., increase in susceptibility to infection, decreased nutrient degradation, and micronutrient deficiencies) (136).

The opposite of dysbiosis, that is, a healthy microbiota, is more difficult to define. Indeed, the microbiota represent a moving target for any preventive and therapeutic measures since we do not know whether the changes in the microbiome underlie the pathogenesis of NCDs or whether they are a result of them. Aiming to define a healthy microbiota by assessing targeted nutritional interventions intended to reduce the risk of disease will be accomplished only through labor-intensive prospective studies of healthy infants who remain healthy during long-term follow-up. Whether the definition thus achieved will remain applicable to rapid environmental evolution remains an open question.

The extent to which the microbiota are associated with malnutrition has yet to be elucidated, although some potential mechanisms through which the gut microbiota may influence energy homeostasis in relation to malnutrition have been suggested (35). Undernutrition, mainly among infants, has been considered to be part of a vicious cycle that includes an unbalanced immune response, increased episodes of infections, poor nutrition, and host genetics (53, 72). All of these factors have been linked to gut microbiota dysbiosis (**Table 2**), which may impact the immune response, propensity for infection, and nutritional status, thereby resulting in the main consequences of undernutrition, which are similar to those related to overweight. In conclusion, an intimate relationship exists among malnutrition, the immune system, and the microbiota (**Figure 2**).

4.1. Early Nutrition Programming

The first 1,000 days of life (from conception to 2 years of age) are considered to be an essential period due to the high energy and nutrient needs associated with the rapid growth and development seen during the prenatal and postnatal periods (43). This is also a critical period in terms of plasticity in metabolic, immunological, cognitive, and educational development. According to the developmental origins of health and disease hypothesis (60), this sensitive period will potentially have short- and long-term consequences for somatic and intellectual development, as well as for the risk of obesity and the development of metabolic, inflammatory, allergic, and autoimmune diseases (2). From this perspective, perinatal factors, such as the mode of delivery, antibiotic use, and the type of feeding, may have important effects on the microbiome and on future health. Thus, perinatal factors alter the composition of the gut microbiota, and those alterations may have consequences for health (76, 98). Furthermore, maternal factors, such as diet, obesity, and metabolic diseases, as well as environmental and genetic factors, influence the maternal microbiota and these, in turn, influence the vertical transmission of microbes from mothers to their offspring (98). Moreover, epidemiological studies have reported that adverse gestational and postnatal environments may affect the programming of health in infants. There is increasing evidence to suggest that an adverse nutritional environment—that is, both under- and overnutrition—during these periods may play determining roles in the early programming of NCDs (40, 77). The potential mechanism through which nutrition modulates epigenetic mechanisms may involve changes in the intestinal microbiota. For example, perinatal alterations in the ratio of Firmicutes to Bacteroidetes have been associated with epigenetic modifications in the *SCD5* and USF family genes, which alter lipid metabolism and increase the risk of overweight and obesity (62, 68).

4.2. Undernutrition During the Perinatal Period

In response to maternal stimuli, the fetus exhibits predictable responses that theoretically result in long-lasting adjustments to the homeostatic systems that are intended to achieve better

Table 2   Summary of the main studies analyzing the link between undernutrition and the microbiota

Location	Study type	Participants	Age	Findings	Reference
South Africa	Intervention in kwashiorkor	$N = 33$	No data	Different microbial composition in kwashiorkor patients	136
Guatemala	Observational	$N = 13$ participants with acute protein–energy undernutrition $N = 4$ control	1–6 years	↓ Anaerobic bacteria ↓ *Bifidobacterium* spp. ↑ Enterobacteriaceae, and *Proteus* and *Pseudomonas* spp.	95
India	Observational	$N = 1$ undernourished female infant $N = 1$ female infant control	16 months	↑ Enterobacteriaceae ↓ Archaea	55
Bangladesh	Observational	$N = 7$ undernourished children $N = 7$ control children	2–3 years	↓ Bacterial diversity ↑ Proteobacteria and *Streptococcus* and *Fusobacterium* spp. ↓ *Lactobacillus* and *Bifidobacterium* spp.	102
Malawi	Observational	$N = 9$ pairs of control twins $N = 13$ twin pairs discordant for kwashiorkor	<3 years	Blockade of microbiome maturation; no taxonomic signature (probable overmatching bias)	125
India	Observational	20 children with varying nutritional status: $N = 6$ healthy $N = 8$ borderline undernourished $N = 6$ severely undernourished	<5 years	↑ Proteobacteria and *Veillonella* and *Streptococcus* spp. ↓ Anaerobic Firmicutes (*Roseburia*, *Faecalibacterium*, and *Butyrivibrio* spp.)	49
Bangladesh	Observational	$N = 64$ severely undernourished children $N = 50$ control children	0–2 years	↑ *Escherichia coli*, *Enterococcus faecalis*, and *Streptococcus gallolyticus* ↓ Anaerobic Firmicutes, Bacteroidetes, and *Bifidobacterium* and *Lactobacillus* spp.	129
Niger and Senegal	Observational	$N = 4$ children with kwashiorkor (Senegal) $N = 6$ children with kwashiorkor (Niger) $N = 3$ control children (Senegal) $N = 2$ control children (Niger)	2.2 months–4 years	↓ Bacterial diversity ↓ Oxygen-sensitive prokaryotes, including *Methanobrevibacter smithii* ↑ Potentially pathogenic Proteobacteria, Fusobacteria, and *Streptococcus gallolyticus*	130

Adapted from References 69 and 99.

↑ indicates increase; ↓indicates decrease.
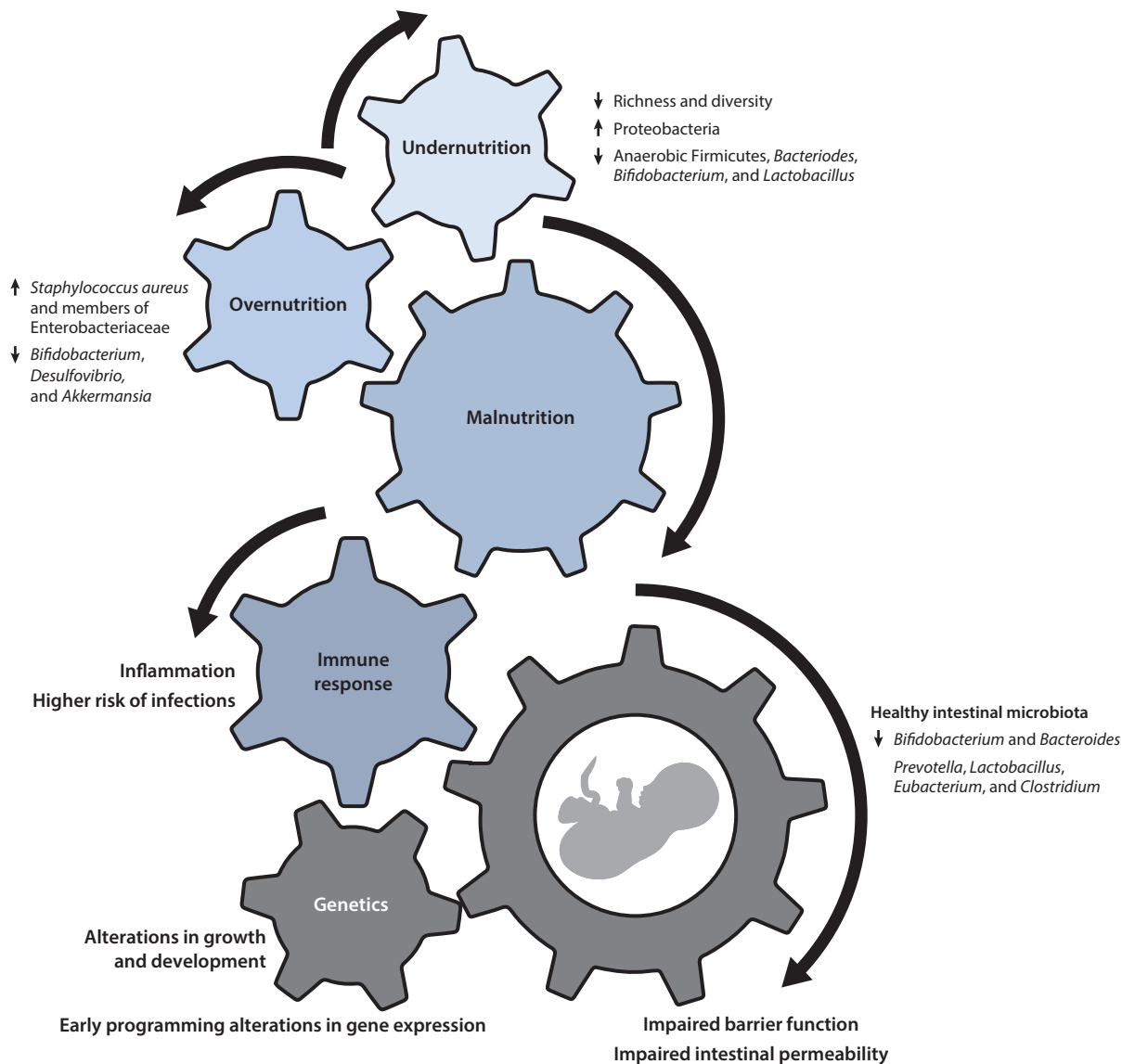
Figure 2

Consequences of malnutrition in early life are expressed through alterations in the immune response, microbiota composition and activity, and gene expression.

adaptation to postnatal life. In certain situations, a mismatch may occur, and such adjustments might ultimately prove disadvantageous because they increase the risk of future diseases (62).

Maternal undernutrition modifies this epigenetic programming and has a negative impact on fetal gene expression, thereby resulting in potential long-term consequences for offspring (89). Experiments conducted in animal models have associated maternal undernutrition with alterations in the expression of the *IGF1* and *PDX1* genes, thus increasing metabolic abnormalities and glucose dyshomeostasis (62).

Only a few studies have investigated the gut microbiota in undernourished pregnant women. Although anorexia nervosa represents a completely different physiological situation, it also is characterized by reduced food intake and altered energy homeostasis. Anorexia nervosa has previously been associated with an altered gut microbiota composition, an increase in methane-producing archaea, and a reduction in the *Clostridium coccoides* group, *Bacteroides fragilis*, *Clostridium leptum*, and *Roseburia* and *Streptococcus* species (35). Similar alterations may be associated with undernutrition during pregnancy, and they may alter both fetal development and microbial colonization during birth, thereby resulting in the production of metabolites that may affect fetal development.

Moreover, little is known about the impact of undernutrition during the first month of life. During early life, the maturity of the gut microbiota seems to be a crucial factor in relation to the prevalence and severity of kwashiorkor (126). Severe acute malnutrition has been linked to an index of relative microbiota immaturity, as measured by the difference between the microbiota of malnourished and healthy infants of the same chronological age (127). Experiments conducted in animal models have shown that undernutrition during the early stages of life is characterized by an overall loss of richness and diversity in the microbial community, together with alterations in microbial metabolic pathways that result in the less efficient extraction of energy from nondigestible dietary components (108). However, few data concerning the impact of undernutrition on neonates are available. Breast milk contains nutrients and a wide range of bioactive compounds, including HMOs, microbes, proteins, and peptides, as well as immune-related compounds, all of which could potentially impact infants' health. Significant differences in HMO profiles have been reported in Malawian breast milk samples from mothers of healthy infants compared with samples from mothers of malnourished infants (27). Moreover, sialylated HMOs were found to be significantly less abundant in the breast milk samples from mothers of severely stunted infants when compared with those from mothers of healthy infants. Furthermore, the reduction in sialylated HMOs was also linked to severe retardation of infant growth.

4.3. Overweight and Obesity During the Perinatal Period

It has been observed that the composition of the microbiota could play an important role in the development of obesity and associated metabolic disorders (24, 29, 77), although most human data concerning the maternal microbiota are related to the association between maternal obesity and the maternal microbiota (47, 63).

Studies in animals and humans have demonstrated that the composition and diversity of the gut microbiota differ between normal weight and obese individuals. Many studies have shown that obese individuals exhibit a reduced abundance of Bacteroidetes, an increase in Firmicutes, and a decrease in bacterial diversity when compared with normal weight individuals (88). Maternal obesity introduces unfavorable changes in the architecture and activity of the gut microbiota of infants, alongside early increases in the proinflammatory Proteobacteria.

In addition, obesity during pregnancy is associated with a higher risk of delivery via Caesarean section (47). Moreover, Caesarean section, in turn, is associated with higher rates of adiposity and a higher BMI during infancy and childhood (19, 133). Children born by Caesarean section are colonized by different and less diverse microbes than infants born vaginally (5, 64). Likewise, Caesarean section is linked to the administration of antibiotics. Both factors affect the initial establishment and later development of the gut microbiota in the offspring (9). Several studies have associated Caesarean delivery and the use of antibiotics with a higher risk of childhood overweight and obesity (10, 115). Further, excessive weight gain during gestation has been linked to specific gut microbial changes in the mothers that can be transferred to their offspring (30, 31). According to several studies, overweight mothers, obese mothers, and mothers who gain an excessive amount

of weight during gestation exhibit lower levels of *Bifidobacterium* species than do healthy mothers (30). Other studies have reported similar findings in overweight mothers at the end of gestation, including lower concentrations of *Bacteroides*; higher numbers of *Staphylococcus*, *Escherichia coli*, and Actinobacteria; and also decreased bacterial richness (78, 122). Recent studies have shown that children whose mothers were obese also present a different colonization profile (31, 46), which may predict the risk of obesity during childhood (77, 80).

It has been suggested that various maternal factors, such as the environment, nutrition, and the mode of delivery, have an impact on breast-milk microbes and other compounds, such as hormones and polyamines (6, 23, 32, 51, 123). Thus, promoting better breast milk composition, which favors the presence of higher concentrations of certain bacterial groups and bioactive compounds, may protect infants against overweight and obesity. In any event, breastfeeding promotes neonatal gut enrichment of *Bifidobacterium*, and it also protects against several diseases, including obesity (54).

Collado et al. (31) reported an association between increased maternal weight during pregnancy and infant microbiota development during the first 6 months of life. Infants with overweight mothers or mothers who gained excessive weight during pregnancy exhibited significantly higher numbers of *Staphylococcus aureus* and lower numbers of bifidobacteria. In later studies, higher numbers of *Akkermansia* were reported in obese women and their 6-month-old infants (31). Thus, maternal obesity represents a risk factor for alterations in the infant's microbiota. However, the extent to which maternal obesogenic factors have an impact on both the infant microbiota and the development of overweight in the long term remains unknown.

Rapid weight gain during the first months of life and infant formula-feeding have consistently been associated with obesity during adulthood (28). There is a clear association between formula-fed infants and alterations in the intestinal colonization pattern, as discussed previously (21, 145). In the case of rapid weight gain, studies conducted in animal models have explained the increased risk of obesity in adults through a reduction in adaptive thermogenesis in brown adipose tissue, disturbed lipid metabolism, and impaired sympathetic nervous system regulation (144). A wide range of metabolites are produced by the intestinal microbiota, including secondary bile acids, SCFAs, and trimethylamine *N*-oxide, all of which have an effect on hepatic lipid and bile metabolism, cholesterol transport, energy expenditure, and insulin sensitivity (48). In addition, the intestinal microbiota can modulate the sympathetic nervous system through the production of γ-aminobutyric acid, dopamine, SCFAs, and lactate (146). Furthermore, gut colonization has been linked to the development of the HPA axis, which is associated with both the stress response and visceral obesity (92).

Moreover, alterations in the intestinal microbiota during early life might increase the risk of obesity in later life through epigenetic factors. Different microbes in the infant's gastrointestinal tract may have different metabolic capabilities, producing metabolites such as SCFAs, methionine, and folate, which not only can exert profound endocrine and metabolic effects but also change epigenetic status, thereby leading to obesity and insulin resistance (26).

4.4. Undernutrition During the Postnatal Developmental Phase

An accumulation of evidence indicates there is a link between severe acute undernutrition and the gut microbiota. However, only a few studies concerning the gut microbiome have been conducted in stunted children during the first year of life (16). Additionally, there is a lack of studies about the gut microbiota in malnourished adults. The gut microbiota composition of Bangladeshi infants was found to differ significantly between healthy and acutely undernourished infants (102), with a dramatic increase in undernourished children in the number of Proteobacteria (9.2 times higher) alongside a reduction in the α-diversity. Another study showed alterations in the gut microbiota

and a core set of 23 genera in children from India with varying nutritional status (49). Notably, the malnourished condition is transferrable via fecal transplantation into animal models (99).

Recent studies have focused on undernutrition in different geographical locations. For instance, a longitudinal study conducted in southern India characterized the gut microbiota of children with low birth weight and persistent stunting (cases) and children with normal birth weight and no stunting (controls) from birth to 2 years of age (37). The results showed the enriched presence of proinflammatory Proteobacteria (*Desulfovibrio* genus and Campylobacterales order) in the stunted infants, while *Bifidobacterium longum* and *Lactobacillus mucosae* were enriched in the microbiota of the controls.

Moreover, the composition and diversity of the gut microbiota have been shown to be related to the pathogenesis of kwashiorkor. The results obtained from Malawian twin pairs showed lower microbial diversity and a reduction in the strictly anaerobic species, mainly *Methanobrevibacter smithii* (125), in twins discordant for kwashiorkor. The reduction in anaerobic microbial diversity was linked with a high redox potential and also with a higher presence of aerobic microbial species (100). A recent study conducted among kwashiorkor patients in Niger and Senegal found a global decrease in species diversity, a decrease in anaerobic species (again, mainly *Methanobrevibacter smithii*), and the enrichment of proinflammatory and pathogenic bacteria, including Proteobacteria, Fusobacteria, and *Streptococcus gallolyticus* (130). Interestingly, this study noted a core of 12 bacterial species found exclusively in healthy children, which were identified as protective biomarkers.

The role of the intestinal microbiota in undernutrition has been confirmed by studies in animal models. For instance, fecal transplantation of the microbiota from malnourished Malawian children into germ-free mice has been performed (18). The results showed that those mice who harbored the microbiota from the malnourished children gained substantially less weight and showed impaired growth when compared with the control group, which received fecal transplantation of the microbiota from healthy children. *Ruminococcus gnavus* and *Clostridium symbiosum* were identified as the main bacteria responsible for the weight gain seen in well-nourished Malawian children, with both being able to ameliorate the impaired growth phenotype transmitted to the mice via an undernourished donor's microbiota (18). Hence, it seems clear that the gut microbiota play a key role in the etiology of undernutrition, while the specific bacterial strains present in the developing microbiota in healthy individuals could represent novel therapeutic targets for improving the treatment of severe acute undernutrition by reestablishing a healthy gut microbiota (17).

It has been suggested that the effects of undernutrition on the development of the gut microbiota could be modified during postnatal life via the administration of probiotics or symbiotics (53). A recent study has demonstrated that the transplantation of gut microbiota from undernourished 24-month-old Bangladeshi children to mice resulted in drastic weight loss, which was transmissible from the dams to their offspring (137). It is important to highlight the potential effect of antibiotics on the management of malnutrition, as well as their effect on reducing mortality in children with kwashiorkor. In a recent systematic review of studies conducted between 2010 and 2017, seven studies supported the use of oral amoxicillin for the treatment of children with severe acute malnutrition (141).

4.5. Overweight and Obesity During the Postnatal Developmental Phase

Several systematic reviews have noted that obese infants are more likely to be obese between the ages of 5 and 18 years than normal weight infants (101), and they have an associated increase in the risk of developing adverse health outcomes in the future. Recent studies have observed differences in early microbial composition according to BMI during childhood. Some studies conducted

among children have demonstrated differences in the composition of the gut microbiota between children with excessive body weight versus those with normal weight (68, 71).

Some bacterial groups, such as *Bifidobacterium*, *Desulfovibrio*, and *Akkermansia*, that are associated with health are commonly found in normal weight children, whereas an increase in potential pathogens, such as *Staphylococcus aureus* and members of the Enterobacteriaceae family, has been found in overweight children (68, 71). Similar to the colon microbiota, the small intestine microbiota seem to play an important role in energy metabolism. Experiments conducted in mice have shown that when germ-free mice are conventionalized with a high-fat diet–induced microbiota their microbiota exhibited increased lipid absorption even when they were later fed a low-fat diet (94).

5. RESEARCH PRIORITIES

Taken together, the evidence shows that undernourished children exhibit a more immature composition of their gut microbiota than normal weight children and children who experienced excessive weight gain after having a low birth weight. Thus, one approach to undernutrition has been to target the microbiota. This approach uses the model of a healthy age-adjusted gut microbiota for a given population. Based on this rationale, the composition of the gut microbiota of a healthy and exclusively breastfed child is considered to be a representative model of infant feeding, as well as a model of beneficial health outcomes in the short- and long-term. It is important to recognize that our knowledge of the nutrition–microbiota–host health triad remains insufficient for specific recommendations to be offered. Sparse data are available concerning the relevance of the nutrition–microbiota–host axis during the first 1,000 days of life or its impact on maternal and neonatal health. Furthermore, little is currently known about the impact of nutrition on the reproductive microbes that play a key role in fertility. Maternal microbes during pregnancy could have a pivotal impact on early microbial exposure at conception and during gestation. The potential microbiota exposure during fetal life, as well as its relevance for human health, need to be explored to link the findings of epidemiological studies to demonstrate the impact of early microbial exposure on obesity and other metabolic problems in both the short- and long-term.

Moreover, the target of any intervention during this critical time frame should be the clinical benefit to the host and his or her future health. Thus, nutrition can be seen as the intervention, the microbiota as the mechanism, and the host's health as the outcome. The gut microbiota—as an important source of genetic material and regulator of the impact of the environment on the development of the key regulatory systems in the body—exhibit the potential to adapt to internal and external environments. We should not disregard the lesson from the developmental origins of health and disease hypothesis (59) that human health is particularly endangered if the environment after birth differs from the situation during pregnancy since prenatal exposures aim to induce adaptation to the anticipated postnatal environment. Restricted in utero nutrition followed by the abundant nutrition that is characteristic of the lifestyle in developed countries increases an individual's susceptibility to obesity and related NCDs. On this basis, the nutrition of the mother, that is, the pregnant woman, requires additional attention from the scientific community. According to our current understanding, pregnancy is the most critical stage of an individual's life, as well as the optimal target for interventions aimed at reducing the risk of NCDs in later life. Targeted interventions in the form of nutritional counseling, probiotics, prebiotics, symbiotics, antibiotics, and other microbiota-related interventions could represent new tools for effectively managing malnutrition.

Furthermore, it is important to highlight the relevance of the environment to both nutrition and the microbiota. Specific foods, dietary patterns, and food preferences across the world

influence the microbiota, which, in turn, has a key effect on health. The world is experiencing climate change, which will potentially have an impact on the availability of food, change the seasons, and alter temperatures to the extreme, all of which might affect our physiology and microbiota, thereby affecting our nutritional status.

SUMMARY POINTS

1. The microbiota play a key role in the host's nutrition and energy metabolism, including the extraction and storage of energy from the available sources.

2. Adequate microbial colonization during the first 1,000 days of life is pivotal for appropriate immune system maturation, metabolic activities, and brain development.

3. Maternal nutrition, the mode of delivery, and perinatal environmental exposures have impacts on the gut microbiota of the neonate, thereby affecting the infant's nutritional status and his or her health in later life.

4. Aberrations in intestinal colonization patterns may direct the microbiota toward overnutrition or undernutrition.

FUTURE ISSUES

1. Multidisciplinary approaches should be used to obtain more evidence about the nutrition–microbiota–host axis during early life.

2. It is important to ensure a healthy maternal microbiota and maternal nutrition prior to conception due to their potential impacts on infant health programming.

3. Nutritional programming during pregnancy may affect the neonatal microbiota, with potential implications for human health and for effects that will be transmitted to the next generation.

4. Interventions are being explored to manage nutritional programming.

5. One of the greatest challenges for the future of health care is to modulate the microbiota to correct malnutrition during early life.

DISCLOSURE STATEMENT

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