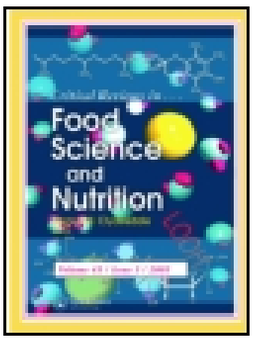

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REVIEW

Gut dysbiosis during early life: causes, health outcomes, and amelioration via dietary intervention

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ABSTRACT

The colonization and maturation of gut microbiota (GM) is a delicate and precise process, which continues to influence not only infancy and childhood but also adulthood health by affecting immunity. However, many perinatal factors, including gestational age, delivery mode, antibiotic administration, feeding mode, and environmental and maternal factors, can disturb this well-designed process, increasing the morbidity of various gut dysbiosis-related diseases, such as type-1-diabetes, allergies, necrotizing enterocolitis, and obesity. In this review, we discussed the early-life colonization and maturation of the GM, factors influencing this process, and diseases related to the disruption of this process. Moreover, we focused on discussing dietary interventions, including probiotics, oligosaccharides, nutritional supplementation, and exclusive enteral nutrition, in ameliorating early-life dysbiosis and diseases related to it. Furthermore, possible mechanisms, and shortcomings, as well as potential solutions to the drawbacks of dietary interventions, were also discussed.

KEYWORDS

Early life; gut dysbiosis; health outcomes; dietary intervention

Introduction

Following the rapid advances in analyzing the composition and functions of microbes, knowledge regarding the correlation between early-life microbiomes, especially gut microbiomes, and short- and long-term health, has expanded significantly in recent years (Wernroth et al. 2020; Zheng et al. 2020). During homeostasis, adult gut microbiota is stable and mainly composed of bacteria, virus and fungi, which can inhibit the proliferation and translocation of (potential) pathogens, ferment the otherwise indigestible polysaccharides to produce short-chain fatty acids, and modulate the host immunity. The early GM is different to adult GM and changes dynamically during early life (Akagawa et al. 2019; Bäckhed et al. 2015). It has been established that early-life dysbiosis is closely linked to various diseases, including type 1 diabetes (T1D) (Wernroth et al. 2020), allergy (Mitselou et al. 2018), necrotizing enterocolitis (NEC) (Gopalakrishna et al. 2019), pediatric Crohn's disease (CD), and malnutrition (Subramanian et al. 2014), as well as childhood and adulthood obesity (Li et al. 2017; Tun et al., 2018), based on epidemiological investigations and animal studies. Furthermore, numerous studies have made efforts to treat these diseases by modifying early-life GM (Korpela et al. 2018; Mischke et al. 2018; Roggero et al. 2020; Singer et al. 2019). However, some effective approaches, such as fecal microbiota transplantation (FMT) and antibiotics that are commonly used in adults to modify the GM are inappropriate in young children, considering the safety of this approach (Papanicolas et al. 2020) and that antibiotic treatment per se is one of the significant disruptive factors in the GM of (young) children (Rogawski et al. 2017), leaving dietary interventions as the main effective method for regulating (young) children's GM.

Factors influencing the colonization and maturation of early-life GM

The colonization and maturation of early-life GM

It is generally believed that vaginally delivered newborns acquire their first microbiota from the vagina during birth, which colonizes in the neonatal gut via swallowing (Robertson et al. 2019). Recently, pros and cons for this dogma have both emerged. A study of the microbiome of ten mother-infant dyads at the time of delivery via cesarean section (C-section) demonstrated the existence of bacterial DNA in the meconium and oral cavity of the newborns, with a predicted origination from utero sources, including the placenta (Younge et al. 2019). Similar to humans, samples collected from pregnant and fetal mice at different gestational ages (GA) under well-controlled sterile conditions demonstrated the existence of bacterial DNA in the utero compartment and fetal intestine. Moreover, via the culture-based method, viable bacteria were identified during the

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mid-gestation but not the late gestation of mice (Younge et al. 2019).

However, a recent study of the microbiome of 537 human placentas with strict negative and positive controls demonstrated the absence of microbiome in healthy human placenta samples: all bacterial DNA signals except for *Streptococcus agalactiae* detected in the placenta samples originated from the environmental contamination, the DNA extraction process, and library construction (de Goffau et al. 2019). Similar results have also been reported in another study of microbiome of human placenta samples with strict negative and positive controls (Leiby et al. 2018). These results suggested that the "uterine microbiome" if it exists, might dynamically change at different gestational stages (de Goffau et al. 2019; Younge et al. 2019). Nonetheless, the influence of this uterine microbiome on the first microbiota that colonizes the neonatal gut is minimal, regardless of its existence or not (de Goffau et al. 2019; Leiby et al. 2018). Therefore, microbiota encountered by neonates at birth remains the main factor influencing the microbes that first colonize in the neonatal gut.

During the first days of life, the GM of full-term, breastfed, vaginally delivered healthy infants primarily consists of aerobic/facultative anaerobic bacteria belonging to Gammaproteobacteria and Firmicutes, such as *Enterobacteriaceae* members, *Escherichia/Shigella* and *Klebsiella*, *Enterococcus* spp., *Lactobacillus,* and *Staphylococcus* spp. (Akagawa et al. 2019; Bäckhed et al. 2015). The abundance of these facultative bacterial taxa decreases rapidly because of the consumption of oxygen and intestinal SIgA, along with the expansion of anaerobic bacteria *Bifidobacterium* and *Clostridium* during the first months of life (Bäckhed et al. 2015; Mirpuri et al. 2014; Planer et al. 2016). Then, *Bifidobacterium* experiences a decrease while the abundance of *Bacteroides* (Bacteroidetes) increases following the introduction of solid food and weaning (Bäckhed et al. 2015; Planer et al. 2016), and an adult-like GM is formed at $1 \sim 3$ years of age (Planer et al. 2016; Yatsunenko et al. 2012). A similar pattern of GM maturation was also found in mice (Mirpuri et al. 2014), piglets (Chen et al. 2018), goats (Zhuang et al. 2020), and cows (Yeoman et al. 2018), indicating a conservative process of GM maturation among mammals.

Similar to the gut bacteria, gut virome experiences quick changes during early life but stabilizes after maturation (Cadwell 2015). Various eukaryotic viruses such as HIV, rubella, cytomegalovirus and influenza can transfer to infants through placenta or vagina. In amniotic fluid, adenovirus, CMV, herpes simplex virus, enterovirus, Epstein–Barr virus, respiratory syncytial virus, and human parvovirus B191 have been identified (Lim, Wang, and Holtz 2016). However, for healthy infants, the level of virus-like particles in meconium and early feces is fairly low or cannot be detected, which increases quickly and reaches to 10^9/g feces within one month, a similar level to that found in adults (Liang et al. 2020). The colonization of the infant gut by virus is stepwise, first mainly by temperate bacteriophages induced from pioneer bacteria such as *Bifidobacterium* and *lactobacillus*, and later by viruses that replicate in human cells such as *Adenoviridae*, *Anelloviridae*, *Caliciviridae* and *Picornaviridae* (Liang et al. 2020; Lim et al. 2015).

Unlike the gut bacterial microbiota and virome, moderate changes in the diversity, mainly a modest increase in alpha-diversity, of mycobiota during early life are evident (Schei et al. 2017). Similar to adults, the infant gut mycobiota is dominated by *Saccharomycetales* that contains many common yeasts, and *Malasseziales* that contains many common skin fungi, which matures from five to eleven months to an elimination of *Malasseziales* while the reservation of *Saccharomycetales* (Fujimura et al. 2016). Within *Saccharomycetales*, a transform from *Debaryomyces hansenii* to *Saccharomyces cerevisiae* during the first year of life was observed (Schei et al. 2017).

Factors influencing early-life GM maturation

In contrast to the relatively stable GM in adults (Faith et al. 2013), the colonization and maturation of early-life GM are vulnerable and can be disturbed by many pre- and post-parturient factors, including GA, antibiotics, delivery and feeding modes, the environment, and maternal physiological status (Figure 1 and Table 1).

Gestational age

Concerning full-term babies, the development of the gut immunity and integrity of premature infants is insufficient, resulting in a different gut ecosystem for microbe colonization (Ma et al. 2018; Schreurs et al. 2019). In a study of the GM of 95 preterm (28.83 ± 3.37 weeks) infants, prematurity resulted in a dominance of Bacilli, instead of Gammaproteobacteria as observed in full-term infants, in the first days after parturition (Grier et al. 2017). This dominance of Bacilli in the premature GM is not a particular case or caused by contingency factors such as the hospitalization environment, since many other studies revealed similar results (Graspeuntner et al. 2019; Ho et al. 2018; La Rosa et al. 2014). In addition, the delivery mode and changes in the vaginal microbiome are also not causes of this phenomenon, since the richness of Bacilli member, *Lactobacillus,* increases throughout the second and third trimesters (Romero et al. 2014; Serrano et al. 2019) and only parts of the preterm infants are delivered by C-section (Graspeuntner et al. 2019; Ho et al. 2018; La Rosa et al. 2014). Therefore the inherent properties of the intestinal ecosystem of the preterm infants mediate the dominance of Bacilli (Graspeuntner et al. 2019). A succession from Bacilli to Gammaproteobacteria to Clostridia then occurs during the several weeks after parturition in preterm infants, similar to that in full-term infants but at a later timeline, suggesting a delayed GM maturation in prematurity based on chronological age (Grier et al. 2017; Ho et al. 2018; La Rosa et al. 2014).

The GA is also an independent factor influencing the colonization of *Bifidobacterium* (Butel et al. 2007). A study analyzed the microbiome in the feces of 52 preterm infants

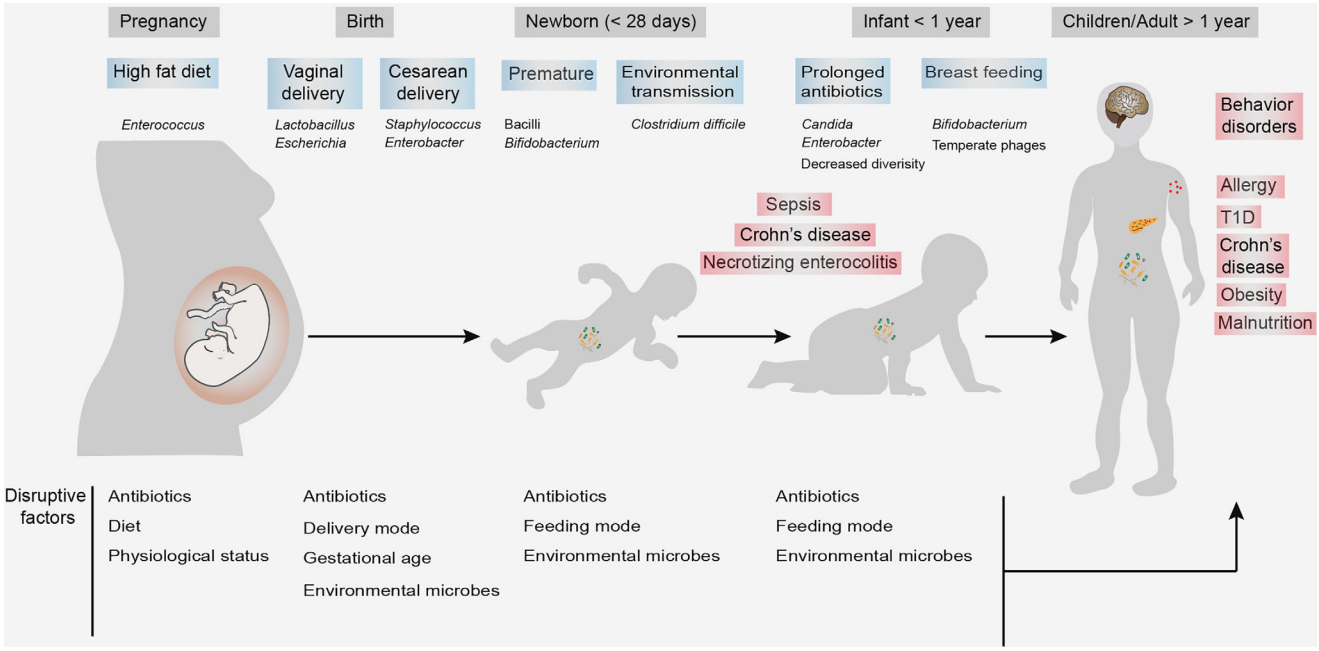

Figure 1. Factors influencing the neonatal bacterial microbiota and its related diseases. During pregnancy, maternal diet and physiological status and antibiotics can influence the maternal gut and vaginal microbiota, therefore affecting the microbiota transferred to newborns. At birth, delivery modes mainly influence the first microbiota encountered by newborns; while gestational age can affect the neonatal microbiome through the influences on intestinal immunity and maternal vaginal microbiota. After birth, antibiotics, feeding modes, and environmental microbes together shape the infant microbiome and an adult-like microbiota is formed at 1-3 years of age. Gut dysbiosis of infants induced by these factors increases the susceptibility to various diseases later in life. T1D, type 1 diabetes.

(GA 33.4 ± 1.2 weeks, 28 vaginally delivered), which were collected twice a week for at least two weeks after birth. *Bifidobacterium* can only be detected in the fecal samples of infants with a GA larger than 32.9 weeks (Butel et al. 2007). Consistent with these results, the richness of *Bifidobacterium* in maternal GM only experiences an increase during late pregnancy (Nuriel-Ohayon et al. 2019). However, not all infants with a GA larger than 32.9 weeks exhibited the existence of *Bifidobacterium* in their feces, suggesting that other perinatal factors, such as delivery mode, also influence the colonization of *Bifidobacterium* (Butel et al. 2007).

In conclusion, GA affects the colonization and maturation of infant GM through both the influence of gut immunity and maternal gut and vaginal microbiome.

Delivery mode

The use of the C-section is significantly prevalent, and in Latin America and the Caribbean region, C-sections have accounted for 44.3% of all births in 2015 (Boerma et al. 2018). The delivery mode influences the first main microbiota newborns encounter (Bäckhed et al. 2015; Dominguez-Bello et al. 2010). The fecal microbiome of vaginally-delivered infants is similar to the vaginal microbiome of their mothers, such as *Escherichia/Shigella*, *Lactobacillus*, *Prevotella*, and *Bacteroides*, while infants delivered by C-section showed an initial fecal microbiome similar to skin and environmental microbes, such as *Enterobacter*, *Haemophilus*, *Corynebacterium,* and *Staphylococcus* (Bäckhed et al. 2015; Dominguez-Bello et al. 2010). Notably, some studies demonstrated that there was no significant difference between the microbiota in meconium samples collected within 24 h after the birth of infants delivered vaginally and via C-section (Dong et al. 2015; Liu et al. 2019). This result suggests that the microbes in the meconium display no or deficient vitality, which is consistent with the GF results obtained from animals delivered by C-section, while further emphasizing the importance of microbiota encountered during birth (Perez-Muñoz et al. 2017). The difference in GM induced by birth mode decreases following GM maturation even though bacterial signals related to C-section delivery can be identified for a long time (up to 4 years) (Bäckhed et al. 2015; Fouhy et al. 2019). In addition to bacteria, C-sections have also been shown to delay the colonization and succession of micro-eukaryotes and archaea (Wampach et al. 2017).

Antibiotics

The exposure of infants to antibiotics, either through their mothers during pregnancy, post-partum, and lactation, or direct administration, during early life, is prevalent. In the US, more than 30% of pregnant women receive intrapartum antibiotic prophylaxis (IAP) to prevent group B *Streptococcus* (GBS) infection, which is related to early-onset sepsis (EOS), in newborns (Verani, McGee, and Schrag 2010). A large population-based American study revealed that ~160,000 out of ~800,000 children had used antibiotics before 6 months of age (Zven et al. 2020). A high antibiotic exposure rate (95% before 4 years old) has also been reported in a Zelanian study of 6,853 children (Chelimo et al. 2020). Antibiotics used during early life are mainly broad-spectrum antibiotics, such as β-lactam, macrolides, and cephalosporins (Chelimo et al. 2020; Zven et al. 2020), which can affect a wide range of bacterial taxa. IAP decreases the transfer of *Lactobacillus* from mothers to infants while it increases certain Proteobacteria members, such as *Neisseriaceae* and *Comamonadaceae*, in the oral

Table 1. Factors influencing the colonization and maturation of the GM

Influence factors	Subjects	Samples	Characteristics of the GM	Ref.
GA	A cohort of 120 infants including 95 pre-term infants (GA 28.83 ± 3.37 wk) and 25 full-term infants (GA 39.72 ± 1 wk).	Stool samples collected spaning PMA 24 to 46 wk.	Dominance of class Bacilli at early PMA; followed by a transmission to Gamaproteobacteria to Clostridia within several weeks of postnatal age.	(Grier et al. 2017)
	Fifty-eight pre-term infants (GA 25.6 ∼ 29.0 wk).	Stool samples collected spaning severals day to at least 30 days after birth.	Dominance of class Bacilli at early days of life; followed by a transmission to Gamaproteobacteria to Clostridia within several weeks of postnatal age.	(La Rosa et al. 2014)
	Fourty-five pre-term infants (GA 27.9 ± 2.2 wk) with very low birth weight (birth weight 1126 ± 208 g).	Stool samples collected at ≤ 2 wk and during the 3rd and 4th weeks after birth.	Dominance of class Bacilli at ≤ 2 wk postnatal age; followed by a transmission to Gamaproteobacteria to Clostridia within two weeks of postnatal age.	(Ho et al. 2018)
	Fifty-two pre-term infants (GA 33.4 ± 1.2 wk).	Stool samples collected twice a week for at least two wk right after birth.	Bifidobacterium can be only detected in the feces of infants with a GA larger than 32.9 wk.	(Butel et al. 2007)
Delivery mode	Nine-eight full-term infants (15 were delivered by C-section) and their mothers.	Stool samples colloected during the first days of life and at 4 and 12 months of age.	Less prevalence of vaginal microbiota-like microbes, such as *Escherichia*/*Shigella* and *Bifidobacterium*, in cesarean infants in the first days of life and decreased *Bacteroides* at 4 and 12 months of age in these babies.	(Bäckhed et al. 2015)
	A longitudinal study enrolled 70, 57, and 32 children at years one, two, and four, respectively.	Stool samples collected at years one, two and four	Differences of the GM in genus level, such as *Akkermansia*, *Ruminiclostridium*, and *Clostridium* can be detected between vaginally- and cesarean-delivered children throughout the four-year study.	(Fouhy et al. 2019)
	A one-year long study enrolled 15 children (GA 38.7 ± 1.8 wk).	Stool samples collected around days 1, 3, 5, 28, 150, and 365	Delayed colonziation and succession of microeukaryotes and archaea in cesarean-delivered children.	(Wampach et al. 2017)
Feeding	A part of a prospective birth cohort study enrolled 1032 infants.	Stool samples collected at one month of age.	Decrease in *Bifidobacterium* and increases in in *E. coli* and *C. difficile* in breastfed infants.	(Penders et al. 2006)
	A longitudinal cohort study of 1,249 mother-infant dyads.	Milk and fecal (infants) samples collected at 3 months after birth and additional fecal samples collected at 1 year of age.	Decreases in *Streptococcus*(3), *B. bifidum*, *Haemophilus parainfluenzae*, and *Veillonella dispar* and increases in *Blautia*, *Dorea*, *Streptococcus*(2) and unclassified Lachnospiraceae(2,3) in infants that were partially breastfed compared to exclusively breastfed.	(Fehr et al. 2020)
	A longitudinal study of the human virome of 20 healthy infants.	Stool samples were collected longitudinally at 0–4 days after birth, month 1 and month 4.	Increase in virus that can infect humans and decrease in temperate phages of *Bifidobacterium* and *Lactobacillus* at 4 months of age in formula-fed infants.	(Liang et al. 2020)
Antibiotics	Forty-five mother–newborn (full-term, 41 vaginally delivered) pairs.	Vaginal and oral cavity samples were collected several days before and at birth, respectively.	Newborns whose mothers received IAP showed decreased colonziation of *Lactobacillus*.	(Keski-Nisula et al. 2013)
	Twenty full-term, vaginally delivered infants (10 of whose mothers received IAP before birth).	Stool samples collected 6-7 days after birth.	Reductions of bacterial diversity and richness, an enrichment of Enterobacteriaceae, and a decrease in *Bifidobacterium* spp. were found in infants whose mothers received IAP.	(Aloisio et al. 2016)
	Seventy-four pre-term infants (GA ≤ 32 wk).	Serial stool samples were collected at week 1 (4-7 days), week 2 (10-16 days), and week 3 (20-23 days of age).	Infants who received prolonged antibiotics showed lower bacterial diversity at weeks 2 and 3 and increased Enterobacter at week 1.	(Greenwood et al. 2014)
	A cohort of 85 children (aged from 10.1 to 15.5 years) with pediatric CD and 26 healthy controls.	Stool samples collected at baseline, 1 wk, 4 wk, and 8 wk following initiation of the treatment.	Antibiotics exposure increased the fungal proportions, including *Saccharomyces cerevisiae*, *Clavispora lusitaniae*, *Cyberlindnera jadinii*, *Candida albicans*, and *Kluyveromyces marxianus*, in children with CD.	(Lewis et al. 2015)
Hospitalization and environment	A one year longitudinal prospective cohort study enrolled 121 premature neonates (GA 31.2 ± 2.8 wk).	Stool samples collected during hospitalization at one week and one month of postnatal age, at hospital discharge, and throughout the first year of life.	C. difficile increases during hospitalization and decreases after discharge.	(Ferraris et al. 2019)

(*continued*)

Table 1. Continued.

Influence factors	Subjects	Samples	Characteristics of the GM	Ref.
	A large subsample of 746 infants from the CHILD cohort.	Stool samples collected at the mean age of 3.3 months.	Pre- and postnatal furry pet exposure enriched the abundance of *Oscillospira* and/or *Ruminococcus* ($P < 0.05$).	(Tun et al., 2017)
Maternal obesity	Ger-free mouse study using fecal samples collected from full-term infants (GA > 37 wk).	Stool samples collected from infants at 2-week old.	Mice received fecal microbiota from infants whose mothers were obese showed an increase in Firmicutes and a decrease in Bacteroidetes.	(Soderborg et al. 2018)
Maternal diet	A representative cohort study enrolled 163 preganant women and their babies.	Stool and meconium samples collected from neonates at delivery and by 6 weeks of age.	Infants whose mother consuming a high fat diet during pregnancy showed an enrichment of *Enterococcus* (at birth) and a reduction of Bacteroides (at birth and 6 weeks of age).	(Chu et al. 2016)

PMA, postmenstrual age; IAP, intrapartum antibiotic prophylaxis; CD, Crhon's disease; GM, gut microbiota; GA, gestational age

cavity of the infant at birth (Gomez-Arango et al. 2017; Keski-Nisula et al. 2013). The abundance of *Bifidobacterium* is also reportedly reduced 7 d after birth in healthy full-term infants whose mothers received IAP, which became insignificant at 30 d (Corvaglia et al. 2016). Interestingly, this IAP-induced effect on *Bifidobacterium* may be (partially) mediated by breastfeeding, as IAP decreased the abundance of *Bifidobacterium* in milk at 7 d but not 30 d after birth (Padilha et al. 2019). At the phylum level, a decrease in Firmicutes and Actinobacteria and an increase in Proteobacteria has also been reported (Aloisio et al. 2016). Differences of the GM induced by IAP decreases following GM maturation, but decreases in bacterial diversity and richness can still be identified at 1 year old (Aloisio et al. 2016; Coker et al. 2020).

Similar to IAP, direct administration of antibiotics to young children mainly results in the reduction of bacterial diversity and overrepresentation of (potential) pathogens, such as *Streptococcus*, *Pseudomonas*, and *Enterococcus* (Greenwood et al. 2014; Zhu et al. 2017). Contrary to the class of antibiotics, duration seems to be a more effective factor influencing neonatal GM (Zhu et al. 2017), which may be because most antibiotics used are broad-spectrum. In addition to the direct influence on bacteria, antibiotic administration also results in the expansion of fungi, such as *Candida*, in the gut, along with exaggerated dysbiosis and intestinal inflammation in children with CD (Lewis et al. 2015).

Of all the factors that influence early-life GM discussed here, antibiotics are the only one that can profoundly affect the overall census of the GM (Aloisio et al. 2016; Coker et al. 2020). Although the impact decreases after some time, this leads to a unique health outcome on health, as discussed below.

Hospitalization and environment

Hospitalization mainly influences the transfer of the microbes in the ward to infants (Brooks et al. 2014). Prolonged stays in a neonatal intensive care unit (NICU) are associated with the colonization of *C. difficile*, a common infection source in the hospital, in the gut of preterm infants (Ferraris et al. 2019). Intriguingly, concerning vaginal birth, infants delivered by C-section are more vulnerable to the colonization of environmental microbes (Johnson and Versalovic 2012), which may be attributed to the priority effect (Sprockett, Fukami, and Relman 2018), that is, the neonatal guts of vaginally-delivered infants are first colonized by the vaginal and fecal microbiota of their mothers during birth, resisting environmental microbes colonization.

The hospital environment can be seen as a "dirty environment" enriched by specific pathogens (Brooks et al. 2014). However, an excessively clean environment may dampen the interaction between the GM and immune system, known as the hygiene hypothesis (Wasko, Nichols, and Clark 2020). Pet-ownership is associated with increased bacterial diversity in the house dust (Fujimura et al. 2010). A study involving 746 Canadian infants demonstrated that exposure to furry pets during pregnancy or the postnatal period enriched the abundance of *Oscillospira* and *Ruminococcus* ($P < 0.05$), which have been negatively associated with childhood atopy and obesity (Tun et al., 2017). Consistently, children who were exposed to pets before the first year of life were associated with lower allergy and asthma morbidity at 6-7 years of age (Ownby, Johnson, and Peterson 2002).

Generally, the influence of hospitalization on early-life GM is relatively weak, as the hospital stays are short for healthy infants (generally < 3 d for vaginally-delivered healthy infants) (Stein et al. 2020). Prolonged hospitalization is usually seen in very low birth weight neonates, whose GM can be significantly influenced by microbiota in NICU(Brooks et al. 2014).

Feeding

Different feeding modes, including breastfeeding, regular formula, fermented formula, or combinations of these, profoundly affect the GM maturation and intestinal immunity of infants. Weaning, rather than the introduction of solid food, induces the formation of an adult-like microbiota in children (Bäckhed et al. 2015). Human milk contains abundant structurally complex, unconjugated glycans, namely human milk oligosaccharides (HMOs), which is one of the major differences from cow's milk (Engfer et al. 2000). HMOs are resistant to gastrointestinal digestion and can reach the infant colon, where they are fermented almost exclusively by infant-specific *Bifidobacterium* members, such as *B. longum* ssp. *infantis*, while those found in adults, such as *B. longum* ssp. *longum* cannot utilize HMOs (Engfer et al. 2000). Consequently, in contrast to the dominance of *Bifidobacterium* in breastfeeding infants, those who are exclusively formula-fed show enrichment of *E. coli* and *C.*

difficile in their fecal microbiota at one month of age (Penders et al. 2006). HMOs can also regulate intestinal immunity and prevent the adherence of pathogens to intestinal epithelial cells (IECs) by binding to the receptors of immune cells and the surfaces of pathogens, respectively (Triantis, Bode, and Van Neerven 2018).

Human milk also contains various bacterial taxa, such as *Bifidobacterium*, *Streptococcus*, *Staphylococcus*, *Acinetobacter*, and *Lactobacillus*, which supposedly originated from the mouths and skin of babies and, especially, the gut of mothers (Fehr et al. 2020; Wan et al. 2020). Specific bacterial taxa such as *L. lactis* MG1614 and *L. reuteri* consumed orally by lactating women and animals can later be detected in their milk (Abrahamsson et al. 2009; De Andrés et al. 2017). This transfer of bacteria from the gut to the mammary glands primarily occurs during late pregnancy and is mediated by dendritic cells (DCs) and macrophages (Moossavi and Azad, 2020). Milk microbes can colonize in the infant's gut, thereby influencing the GM composition (Fehr et al. 2020). The infant fecal microbes share some taxa, such as *Streptococcus* spp. and *Veillonella dispar* with the milk microbes of their mothers, and a positive correlation of their abundance between feces and milk was found (Fehr et al. 2020). GF mice orally gavaged with human milk collected from a mother 2 d after vaginal delivery exhibited stable colonization of milk microbiota (37 out of 88 OTUs) in the gut 8 weeks after gavage (Wang, Lu, et al. 2017). This maternal gut-milk-neonatal gut transfer of microbes reflects the influence of maternal GM on infant GM, which may contribute to the vertical transmission of core microbiomes across generations (Fischbach and Segre 2016).

IgA contained in the human milk may also favor the vertical transmission of GM. IgA-producing plasma cells (PCs) in the mammary gland originate from the gut and are educated by the gut antigens, resulting in similar repertoires of PC and IgA between the mammary gland and gut (Lindner et al. 2015; Morteau et al. 2008). As a master controller of GM, IgA then may tend to shape the infant GM similarly to their mothers, contributing to the establishment of a stable GM (Kubinak and Round 2016). With respect to normal-raised mice, mouse pups fed on milk lacking IgA showed a different GM composition at weaning and adult (70 d of life) and translocations of aerobic bacteria, such as the opportunistic pathogen, *Ochrobactrum anthropic,* occurred from the gut into draining lymph nodes during weaning (Rogier et al. 2014). Similar to IgA, IgG induced by the maternal GM can protect neonatal mice from being infected with pathogen enterotoxigenic *E. coli* through breastfeeding (Zheng et al. 2020).

Besides bacteria, breastfeeding also influences the intestinal colonization of viruses (Liang et al. 2020). A longitudinal study of the human virome of 20 healthy infants revealed that breastfed infants carry a lower load of viruses that can infect human cells compared to exclusively formula-fed infants at 4 months of age, while the temperate phages of *Bifidobacterium* and *Lactobacillus* are higher in breastfed infants (Liang et al. 2020). This selective regulation of the gut virus may be achieved through the enhanced

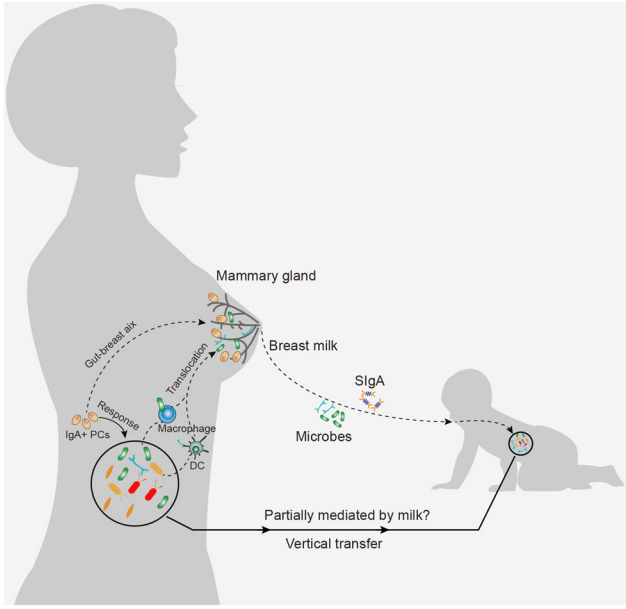

Figure 2. The maternal gut-milk-infant gut axis of microbial transfer. IgA-producing PCs generating in the gut in respond to gut antigens can migrate to mammary gland and produce IgA there. IgA produced by these PCs is secreted into breast milk as secretory IgA, which can shape the infant gut microbiota. Similar to IgA, gut microbes can also translocate from the gut to mammary gland with the help of DCs and macrophages. These microbes then colonize into the infant gut following the suck of breast milk by infants. PCs, plasma cells; DCs, dendritic cells.

proliferation of *Bifidobacterium* and *Lactobacillus* (Liang et al. 2020) or the regulation of viruses by HMOs, IgA, and IgG (Morozov et al. 2018; Zheng et al. 2020).

Therefore, HMOs, the gut-originated milk microbiomes, and the gut antigens-selected antibodies existing in the milk confer the ability to regulate neonatal GM to milk, making it an essential vehicle mediating the vertical transmission of the GM (Figure 2).

Maternal obesity and diet

Maternal obesity influences the metabolome and microbiome of milk and the GM of mothers (Moossavi et al. 2019; Soderborg et al. 2018). Through the transfer of fecal microbiota to GF mice, a recent study demonstrated that fecal microbiota of 2-week-old infants whose mothers were obese increased adiposity, hepatic inflammation, and susceptibility to nonalcoholic fatty liver disease in GF mice, compared to that of infants whose mothers' body weights were normal (Soderborg et al. 2018). The GM in mice receiving an "obese GM" is also different from those receiving a "normal GM," with an increase in Firmicutes and a decrease in Bacteroidetes (Soderborg et al. 2018). In addition to the physiological status of mothers, maternal diet can also have a long-lasting influence on the GM of their babies. Consumption of a high-fat diet (HFD) during pregnancy significantly ($P = 0.001$) altered the GM in infants, with enrichment of *Enterococcus* and a reduction of *Bacteroides*, which lasted until 6 weeks of age (only for *Bacteroides*) (Chu et al. 2016). These results emphasized the central role of maternity in the establishment of a healthy infant GM.

Collectively, the colonization and maturation of the GM during early life are vulnerable to various disturbing factors (Table 1). Although changes in the infant GM induced by all these factors decrease with time, their impact on immunity and metabolism persist for a long time, even for a lifetime (discussed below).

The health outcomes of early-life dysbiosis

Regulation of the intestinal immune system by the GM

Proper interaction between the intestinal immune system and gut antigens during early life imprints the immune system with immunotolerance to commensals, preventing excessive inflammatory responses in later life (Vatanen et al., 2016). Lipopolysaccharides (LPS) of *E. coli* can down-regulate the immune responses to infections and induce the generation of regulatory T (Treg) cells, thereby increasing the immunotolerance of endotoxins (Vatanen et al., 2016). Contrarily, LPS derived from *Bacteroides* suppressed the immunotolerance induced by *E. coli*-derived LPS (Vatanen et al., 2016). Therefore, infants in Finland and Estonia have highly abundant *Bacteroides* in their GM compared to Russian infants, along with higher morbidity of autoimmune diseases, such as allergies in these two countries (Vatanen et al., 2016). Not all *Bacteroides* members tend to induce inflammatory responses, for example, polysaccharide A derived from *B. fragilis* induces differentiation of Treg cells through the activation of toll-like receptor (TLR) 2 in these cells and inhibits T helper 17 (Th17) cell generation, which can only occur during early life (An et al. 2014).

Why is early life a unique time for the interaction between the immune system and GM? Recent animal studies have shed some light on this important question. During the critical time window of 11 d to 21 d of life, GC-associated antigen passage (GAP) formation in the colonic goblet cells allows the interaction between specific commensal bacterial antigens and the immune system, resulting in the proliferation of peripheral Foxp3$^+$ Treg cells, thereby increasing the tolerance to commensals (Knoop et al. 2017). Around the time of weaning, a "weaning reaction" characterized by the high expression of tumor necrosis factor-α and interferon-γ, as well as the generation of Foxp3$^+$ Treg cells in the terminal ileum, further imprints the intestinal immune system immunotolerance to commensals (Al Nabhani, Dulauroy, Lécuyer, et al. 2019). Colonic GAP formation before 10 d of life and an ileal "weaning reaction" before weaning are inhibited by the epidermal growth factor (EGF) existing in the breast milk (Al Nabhani, Dulauroy, Lécuyer, et al. 2019; Knoop et al. 2017). Altering the timing of GAPs formation or the inhibition of the "weaning reaction" by antibiotics results in blunting the Foxp3$^+$ Treg induction, increasing susceptibility to intestinal injury and colitis during adulthood (Al Nabhani, Dulauroy, Lécuyer, et al. 2019; Knoop et al. 2017). Although these patterns are not examined in humans, human milk contains an abundance of EGF and human IECs express the EGF receptor (Carpenter 1980; Knoop and Newberry 2018), indicating that similar mechanisms may exist in humans.

Intestinal virus can influence the education of early gut immunity either through the direct interaction with immune system or indirectly through the effects on bacterial microbiota. Certain eukaryotic viruses can directly cause disease. For example, rotavirus-induced diarrhea in young children is the leading causes of diarrhea-related death (Harris et al. 2018). Through infecting and killing bacterial cells, bacteriophages belonging to the gut virome can influence the bacterial microbiota, thereby influencing the development of gut immunity as discussed above. In addition, the gut immune responses to virus and bacteria are synergistic. Infecting germ-free or antibiotic-treated mice with murine norovirus activates the type 1 interferon pathway in these mice and protects them from intestinal injury and pathogenic bacterial infection(Kernbauer, Ding, and Cadwell 2014). On the contrary, gram-negative bacteria can induce the anti-virus activity in the intestine in a necrosis factor κB (NF-κB)-dependent manner (Sansone et al. 2015).

Antibiotic usage can usually lead to the expansion of fungi in developing gut of both humans and mouse, which is associated with certain diseases such as sepsis and Crohn's disease (Dong et al. 2015; Jiang et al. 2017; Lewis et al. 2015; Ward, Knights, and Gale 2017). The majority of antibiotics cannot directly act on fungus; by contrast, they may influence the mycobiota indirectly through killing bacteria. For example, a healthy mouse gut is resistant to the colonization of *C. albicans* unless treating preliminary with antibiotics (Jiang et al. 2017). Close interaction among the gut bacteria, fungi and immunity has also been observed. Commensal anaerobic bacteria, such as clusters IV and XIVa of *Clostridia*, resist the colonization of *C. albicans* by hypoxia-inducible factor-1α-mediated generation of LL-37 in mice (Fan et al. 2015). On the contrary, colonization of fungi *C. albicans* or *S. cerevisiae* confers protection to mice from dextran sulfate sodium-induced colitis and influenza A infection (Jiang et al. 2017).

Consequently, during this specific time of early life, proper interaction between the GM, immune system, and other factors, such as breast milk at the right time and place, is pivotal for immune education and the establishment of immunotolerance (Al Nabhani, Dulauroy, Lécuyer, et al. 2019; An et al. 2014; Knoop et al. 2017; Vatanen et al., 2016). Disrupting this delicate process (for example, through dysbiosis) results in the impairment of Treg cell generation and changes in the B cell repertoire (generally from IgA to IgG production partially because of the decreased expression of factors, such as interleukin-10), leading to decreased immunotolerance to commensals, while increasing the morbidity of chronic inflammation-related diseases, such as allergies, autoimmune diseases, and obesity (Tamburini et al. 2016) (Table 3).

Allergies and type 1 diabetes

As discussed above, certain kinds of LPS can imprint immunotolerance onto the immune system (Vatanen et al., 2016). In a study involving 319 children, a reduction of LPS at 3 months of age was observed in the group that developed

atopy and wheezing at 1 year of age, compared to the control (Arrieta et al., 2015). Subjects in this group also showed the elimination of *Faecalibacterium*, *Lachnospira*, *Rothia,* and *Veillonella* in their GM at 3 months of age (Arrieta et al., 2015). Importantly, the transfer of these four bacterial taxa to a GF mouse model with airway inflammation ameliorated their symptoms, suggesting a causal role of these bacterial taxa in averting asthma development (Arrieta et al., 2015).

The development of T1D, a common autoimmune disease, is associated with the GM. Antibiotic exposure during the first year of life is linked to increased susceptibility to T1D, especially in children delivered by C-section (Wernroth et al. 2020). Consistent to the observations in human, neonatal non-obese diabetic (NOD) mice, a mouse model that is genetically susceptible to T1D, were exposed to continuous low-dose antibiotics or pulsed therapeutic antibiotics (PAT), mimicking childhood exposures. PAT exposure decreased the richness and influenced the β-diversity of the GM, reduced the ileal Foxp3$^+$ Treg cells, and increased the susceptibility to T1D in mice (Livanos et al. 2016). Interestingly, continuous low-dose antibiotics, which also influenced the composition but had no significant influence on the richness of the GM (Cho et al. 2012), did not influence the morbidity of T1D in mice (Livanos et al. 2016). Similarly, in humans, antibiotic administration during pregnancy, which had a limited effect on the richness of the GM in their babies, was not related to the T1D risk in their children (Haupt-Jørgensen et al. 2018). Moreover, the transfer of the GM from children with T1D to GF NOD mice failed to enhance the development of T1D but instead delayed its development (Neuman et al. 2019). These recent studies suggest a scenario where the development of T1D may be more sensitive to the richness (α-diversity) of the GM, instead of the composition (β-diversity). Consistent with this assumption, as discussed above, a weaning reaction characterized by the induction of Foxp3$^+$ Treg cells in the ileum (decreased in PAT-exposed mice), is closely related to bacterial loads (Al Nabhani, Dulauroy, Lécuyer, et al. 2019). Furthermore, the GM composition can influence this progress indirectly through bacterial metabolites, including short-chain fatty acids (SCFAs) and retinoic acid that are also important for the weaning reaction (Al Nabhani, Dulauroy, Lécuyer, et al. 2019). A cohort study of 17,055 newborn babies from the southeast of Sweden demonstrated that the GM of 1-year-old children with different levels of T1D risk, as predicted by human leukocyte antigen allele combinations, were structurally different, with enrichment of genera *Intestinibacter* and *Romboutsia*, certain members of which are known to produce SCFAs (He et al. 2019; Kang et al. 2019), in children with low T1D risk (Russell et al. 2019).

Necrotizing enterocolitis and pediatric crohn's disease

NEC is a disease with high morbidity and mortality in preterm infants. The precise pathogenesis of NEC is unclear; however, gut dysbiosis is usually seen prior to NEC onset and is believed to contribute it (Gopalakrishna et al. 2019; Morrow et al. 2013; Pammi et al. 2017). An enrichment of Proteobacteria members, especially Gammaproteobacteria and a decrease in bacterial diversity, are typical characteristics of the GM in feces collected from 4 d to 40 d of age in infants who later developed NEC (Gopalakrishna et al. 2019; Heida et al. 2017; Morrow et al. 2013; Pammi et al. 2017). These changes in the GM are also usually seen in infants who are fed on formula or exposed to antibiotics (Gasparrini et al. 2019; Greenwood et al. 2014), and in accordance, increased morbidity of NEC has been reported in these infants (Raba et al. 2019; Repa et al. 2015). In fact, animal studies showed that lacking IgA in milk can result in the over-proliferation of Proteobacteria members such as *Enterobacteriaceae* (Mirpuri et al. 2014; Rogier et al. 2014), the typical dominant bacteria taxon in NEC (Pammi et al. 2017). Therefore, IgA may (partially) mediate the protective role of breast milk in NEC development. Indeed, a recent study demonstrated that a decrease in IgA-bound bacteria is associated with the development of NEC in infants during the first month of life (Gopalakrishna et al. 2019). An enrichment of *Enterobacteriaceae* was also observed in the IgA-unbound fraction of the microbiota in infants with NEC (Gopalakrishna et al. 2019). Of note, mice fed on milk lacking IgA were more susceptible to NEC compared to those fed on IgA-containing milk, highlighting the critical role of IgA, rather than the other ingredients in the milk in mediating the protective effect of milk on NEC (Gopalakrishna et al. 2019).

Enrichment of Proteobacteria, especially *Enterobacteriaceae*, is also a characteristic of pediatric CD (Brusaferro et al. 2019). The expansion of Proteobacteria may be the cause, as well as the result of NEC and pediatric CD. On the one hand, certain members of Proteobacteria, such as *Enterobacter* spp. are pathogenic and invasive, promoting inflammatory responses in the intestine, thereby aggravating NEC and pediatric CD (Gopalakrishna et al. 2019). On the other hand, the NEC- and CD-induced damage of IECs decrease the oxygen consumption by IECs, resulting in an increase in oxygen diffusion from the gut mucosa to the lumen, which, in turn, enhances the proliferation of aerobic/facultative anaerobic Proteobacteria (Byndloss and Baumler 2018). Moreover, decreases in commensals result in a reduction in SCFAs production (Wang et al. 2018), decreasing the oxygen consumption and Treg generation (Byndloss et al., 2017), further leading to exaggerated inflammation.

Sepsis

Sepsis includes EOS and late-onset sepsis (LOS). EOS occurs before 3 d of life and is mainly caused by the GBS infection, while LOS is related to the infections by commensals in the gut and skin, including *E. coli* and *Klebsiella pneumonia* belonging to *Enterobacteriaceae*, *Staphylococcus* spp., and fungi such as *Candida* spp. (Dong and Speer 2015). With respect to EOS, LOS is more common in preterm infants, and prolonged antibiotic therapy ($\geq$ 5d) used to prevent

EOS increases the morbidity of LOS (Kuppala et al. 2011). In line with this, preterm infants and prolonged antibiotic treatment delay the maturation of GM, as discussed above, resulting in the overrepresentation of Proteobacteria members (Aloisio et al. 2016; Coker et al. 2020; Grier et al. 2017). In addition, antibiotic exposure increases the abundance of fungi, such as *Candida,* in infants (Ward, Knights, and Gale 2017). This high consistency between the alteration of GM induced by the risk factors of LOS and the changes in the GM seen in young children with LOS indicates that gut dysbiosis plays a crucial role in LOS development. Indeed, a recent study demonstrated serum IgA boosted by the intestinal Proteobacteria protected mice from polymicrobial sepsis, indicating that gut antigens are involved in the development and prevention of sepsis (Wilmore et al. 2018).

Obesity and malnutrition

The correlation between GM and obesity and obesity-related metabolic syndrome (MetS) are well established compared to other GM-related diseases(Cani and Jordan 2018). Almost all perinatal factors, including delivery and feeding modes, antibiotic, maternal overweight and diet, and gestational diabetes, that can influence infant GM have effects on the development of childhood and adult obesity(Chavarro et al. 2020; Chelimo et al. 2020; García-Mantrana et al. 2020; Ley et al. 2020; Shao et al. 2017; Tun et al., 2018). However, despite that numerous studies have revealed the close correlation between early-life GM disturbance and obesity, the investigation of the underline mechanism(s) is scarce(Chavarro et al. 2020; Chelimo et al. 2020; García-Mantrana et al. 2020; Ley et al. 2020; Shao et al. 2017; Tun et al., 2018). A large-scale longitudinal birth cohort study revealed that the infection, rather than antibiotics administration, during infancy increased the childhood obesity rates(Li et al. 2017). This suggest that the enhanced inflammatory responses induced by the gut dysbiosis during infancy, as induced by various factors discussed above, induced the development of obesity through the reduction of Treg and IgA-producing B cells (Knoop et al. 2017; Luck et al. 2019; Tamburini et al. 2016).

Gut dysbiosis is also associated with malnutrition in children (Kau et al. 2015). A study determined the interaction between the GM and childhood undernutrition using GF mice receiving microbiota derived from Malawian twins discordant for malnutrition. A significant overrepresentation of *Enterobacteriaceae* and a reduction in *Akkermansia muciniphila* were found in the IgA-bound microbiota of gnotobiotic mice receiving microbiota from the malnourished twins, along with weight loss, sepsis, and the rapid disruption of the small intestinal and colonic epithelial barrier in these mice in a diet-dependent manner (Kau et al. 2015). Further transfer of an *Enterobacteriaceae*-containing, 11-strain, cultured bacterial consortium derived from these gnotobiotic mice to GF mice further transmitted these phenotypes. These results highlighted the pivotal role of the GM in mediating childhood malnutrition(Kau et al. 2015). Overproliferation of *Enterobacteriaceae* is associated with intestinal inflammatory responses (Gopalakrishna et al. 2019), which has been shown to suppress the Gata4-related metabolic functions in mice (Shulzhenko et al. 2011). This led to lipid malabsorption and decreased deposition of body fat that may contribute to the malnutrition observed in young children (Shulzhenko et al. 2011).

Behavioral disorders

Certain gut bacteria and their metabolites, such as 5-hydroxytryptamine and LPS, can influence brain function directly through vagal stimulation or indirectly through neuroendocrine and immune systems, known as microbiota-gut-brain axis (Torres-Fuentes et al. 2017). This affects the basic neurogenerative processes, such as the formation of the blood-brain barrier, myelination, and neurogenesis, while also regulating a wide range of social and affective behaviors, such as anxiety, depression, cognition, and autism spectrum disorder (ASD), which is especially significant during early life, a critical time window for neurodevelopment (Sharon et al. 2016). A longitudinal population-based study of children in Finland revealed that antibiotic exposure during pregnancy or the first two years of life was associated with an increased risk for the childhood development of psychopathology, such as sleep disorders, attention deficit hyperactivity disorder, conduct disorder, as well as mood and anxiety disorders (Lavebratt et al. 2019). In addition to antibiotics, C-section is also linked to the increased risk of neurodevelopmental disorders, such as ASD and attention-deficit/hyperactivity disorder (Zhang et al. 2019). Animal studies have shown that maternal HFD resulted in a shift in the GM in their offspring, mediating the social deficits in pups (Buffington et al. 2016). This GM-mediated impairment of neurodevelopment may be attributed to enhanced neuroinflammation, known to induce neurological conditions (Wee Yong 2010), in neonatal mice, as dysbiosis in the neonatal gut, leading to enhanced inflammatory responses in the gut (Tamburini et al. 2016), which are closely linked to neuroinflammation (Giau et al. 2018).

Therefore, it can be concluded that the inappropriate interaction between the GM and the gut immune system imprints inflammatory properties to the immune system, mainly the reduction of Treg and IgA-producing B cells, which increases the susceptibility to not all, but most of these gut dysbiosis-related diseases (Table 2).

The influence of dietary interventions on gut dysbiosis and health

As discussed above, the typical characteristics of gut dysbiosis during early life mainly include the delay of GM maturation, over-proliferation of pathogens, and a decrease in beneficial microbes, such as *Bifidobacterium* and *Lactobacillus*. Therefore, ideas that directly come to mind are restoring the balance of GM via probiotic supplementation, pathogen restriction, and GM maturation enhancement (Figure 3 and Table 3).

Table 2. Diseases related to the early-life gut dysbiosis

Diseases	Characteristics of the GM	Possible mechanism(s)	Risking factors	Ref.
Allergy	Enrichment of *Bacteroides* and *B. dorei* (throughout the first 3 years of life) and decreases in *Bifidobacterium* (during the first year of life), *Fecalibacterium*, *Lachnospira*, *Rothia* and *Veillonella* (at 3 months of age); a reduction in fecal LPS levels (at 3 months of age).	Bacterial antigens such as LPS derived from certain bacteria such as *E. coli* induce the generation of Treg cells while LPS derived from certain *Bacteroides* members such as *B. dorei* induces inflammatory responses and reduces Treg cells generation.	Not mentioned in these studies.	(Arrieta et al., 2015; Vatanen et al., 2016)
T1D	Decrease in α-diversity of the GM and (or) SCFAs-producing bacteria at early life (for human, $<$ 1 year; for mouse, before weaning).	Decreased bacterial loads and (or) gut SCFAs levels disturbed the weaning reaction that can induce Treg cells generation in the ileum.	Prolonged antibiotic administration during the first year of life, C-section.	(Livanos et al. 2016; Russell et al. 2019; Wernroth et al. 2020)
NEC	Enrichment of Proteobacteria members especially Enterobacteriaceae (generally after 10 days of life).	The abundance of Proteobacteria that should decrease after the first days of life keep high in some infants. Many members of Poteobacteria are pathogens that can induce inflammatory responses in the intestine thereafter.	Non-breast feeding, prolonged antibiotics therapy before, during, or after birth.	(Gopalakrishna et al. 2019; Morrow et al. 2013; Pammi et al. 2017; Raba et al. 2019)
Sepsis	Enrichment of Proteobacteria members especially Enterobacteriaceae and fungi such as *Candida* spp..	Over proliferation and translocation of specific pathogens such as *Klebsiella pneumonia*.	Prolonged antibiotic therapy in newborns, premature.	(Kuppala et al. 2011; Singer et al. 2019)
Obesity	Various gut dysbiosis during infancy/early childhood is associated with later-life obesity.	Early childhood gut dysbiosis is generally associated with enhanced inflammatory responses, which reduced Treg and IgA-producing B cell generation and may contribute to later-life obesity.	C-section, remature, antibiotics administration pre- and post-birth, non-breast feeding, maternal obesity, and maternal high fat diet.	(Chavarro et al. 2020; Chelimo et al. 2020; García-Mantrana et al. 2020; Ley et al. 2020; Shao et al. 2017; Tun et al., 2018)
Malnutrition	Enrichment of Enterobacteriaceae and a reduction in *Akkermansia muciniphila* in IgA + fraction.	Enhanced intestinal inflammatory responses induced by Enterobacteriaceae suppressed the Gata4-related metabolic functions, resulting in lipid malabsorption and decreased deposition of body fat.	Not mentioned in these studies.	(Gopalakrishna et al. 2019; Kau et al. 2015; Shulzhenko et al. 2011)
Behavioral disorders	A reduction in bacterial alpha-diversity and an increases in Proteobacteria.	Dysbiosis impaires gut barrier, resulting in the translocation of bacterial toxins such as LPS, which induces neuroinflammation and contributes to neurological conditions.	Maternal high fat diet, antibiotics exposure during pregnancy or the first two years of life, C-section.	(Buffington et al. 2016; Lavebratt et al. 2019; Yang et al. 2019; Zhang et al. 2019)

NEC, necrotizing enterocolitis; T1D, type 1 diabetes; GM, gut microbiota; LPS, lipopolysaccharide; C-section, cesarean section; SCFAs, short chain fatty acids

Probiotics

Probiotics are live microorganisms that supposedly provide health benefits to the host when administered in adequate amounts. However, dead bacteria and (or) their components, such as proteins, can also exhibit probiotic properties (Plaza-Diaz et al. 2019; Wang, Liu, et al. 2017). Probiotics are believed to improve the health of hosts by regulating inflammatory responses, enhancing IgA production, and improving intestinal integrity (Plaza-Diaz et al. 2019). The effect of probiotics on pediatric diseases, such as allergies, obesity, gastrointestinal infections, and colitis have been widely studied, despite the controversy that exists regarding their efficiency (Suez et al. 2019). The most commonly used probiotics are *Lactobacillus* and *Bifidobacterium* spp. Supplementation with probiotics can generally increase the abundance of these specific bacteria and last for a while. *L. johnsonii* La1 supplementation increased the total *Lactobacillus* counts, as compared to placebo controls, and live bacterial cells could still be detected in the feces of 17% of the newborns at least 2 weeks after its last administration (Brunser et al. 2006).

A double-blind, placebo-controlled randomized clinical trial evaluated the effect of mixed probiotics, including *B. breve* Bb99, *Propionibacterium freundenreichii* subsp. shermanii JS, *L. rhamnosus* Lc705 and LGG, on the restoration of C-section- or antibiotic-induced infant gut dysbiosis. The probiotic administration partially counteracted the influence of C-section and antibiotics on infant GM, including an increase in *Bifidobacterium* and a reduction in Proteobacteria and *Clostridia*, in breastfed but not formula-fed 3-month-old infants (Korpela et al. 2018). Multiple strains of probiotics belonging to *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* have been shown to decrease the morbidity and (or) mortality of NEC(Chang et al. 2017), which may also depend on breastfeeding (Repa et al. 2015). These results are consistent to a recent study showing that *Lactobacillus* can utilize SIgA to colonize into

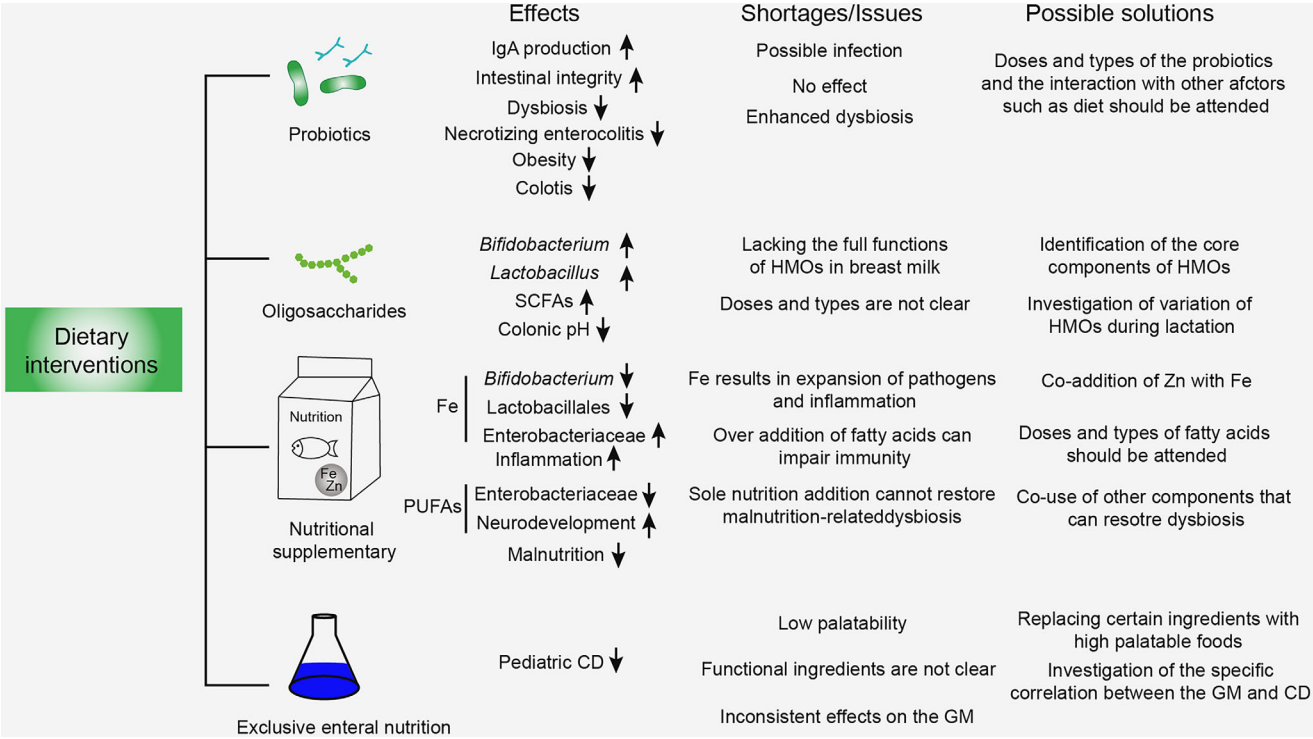

Figure 3. Dietary interventions used to improve early-life gut dysbiosis. Probiotics administration to young children can enhance IgA production and intestinal integrity, which decreases the susceptibility to various diseases. However, possible infections, enhanced dysbiosis and ineffective results can also happen; therefore, the doses and types of probiotics and interactions with other factors should be attended. Oligosaccharides (OS) supplementation is associated with decrease in colonic pH and increases in beneficial microbes and SCFAs production, while doses and types of OS addition are still not clear. Investigation of the components and variation of HMOs in milk can provide help for solving these key questions. Supplementation of Fe cannot significantly decreases the morbidity of anemia while enhances the proliferation of (potential) pathogens and intestinal inflammation. Co-addition of Zn with Fe partially counteracts these deleterious effects of Fe. Supplementary of PUFAs during pregnancy or lactation is associated with the reduction in (potential) pathogens and improvement of neurodevelopment in infants while over-addition of fatty acids during pregnancy impairs the immunity of mouse pups and increases the susceptibility to colitis in adult. Therefore, doses and types of fatty acids should be examined when supplementing. Sole nutritional supplementation can improve malnutrition but cannot restore malnutrition-related dysbiosis while supplementation of other components such as probiotics can provide help. Exclusive enteral nutrition leads to high remission rates of pediatric CD but its palatability is low and its functional ingredients are not clear. Therefore identification of its functional ingredients and improve its palatability are pivotal for the management of CD. SCFAs, short chain fatty acids; HMOs, human milk oligosaccharides; PUFAs, polyunsaturated fatty acids; CD, Crohn's disease.

the deep mucus layer (Huus et al. 2020). In addition, the protection against NEC and restriction of Proteobacteria by probiotics could be also (partially) mediated by their IgA-inductive ability (Wang, Liu, et al. 2017), as IgA has been shown to protect infants from NEC (Gopalakrishna et al. 2019) and Proteobacteria is one of the major bacterial taxa bound by IgA (Bunker et al. 2015).

The administration of *L. salivarius* CECT 9145 in GSB-positive pregnant women during 26 to 38 weeks of GA efficiently eradicated the GSB in rectal (72%) and vaginal (68%) samples, suggesting a promising alternative to antibiotics in preventing GSB infection-induced EOS (Martín et al. 2019). Similar results were reported using *L. rhamnosus* GR-1 (Ho et al. 2016). The production of organic acid and peroxide hydrogen, as well as co-aggregation with GBS by this strain of *Lactobacillus,* may contribute to the inhibition of GBS (Martín et al. 2019). However, the abundance of these bacterial strains in the vagina after administration has not been reported (Ho et al. 2016; Martín et al. 2019), leaving the critical question of whether these orally consumed probiotics can efficiently transfer to the vagina, unsolved. Recently, a randomized, placebo-controlled, double-blind crossover study showed that orally administrated *L. paracasei* LPC-S01 transferred to the vagina but at a low rate (2 out of 23 subjects) (Koirala et al. 2020). These results suggest that other indirect mechanism(s) may exist for the GBS-inhibiting effect of these probiotics in the vagina, which merits further investiagtion. Moreover, administration of other strains of *Lactobacillus*, including *L. murinus* V10 and *L. johnsonii* G2A, has also been reported to prevent the development of LOS by restricting the translocation of *K. pneumonia* (Singer et al. 2019).

In addition to the direct supplementation of probiotics in a formula, fermenting the formula using probiotics seems to be a better choice. In a randomized, placebo-controlled, clinical trial involving 78 healthy full-term neonates, with respect to regular formula-fed infants, the administration of *L. paracasei* CBA L74-fermented formula enhanced the intestinal SIgA production at 90 (90 ± 5) d of age, accompanied by similar developments in the GM and immune system of breastfed infants (Roggero et al. 2020). Notably, the delivery mode also had an impact on the effect of probiotic-fermented formula(Roggero et al. 2020), suggesting a complex interaction between the factors affecting the infant GM. Instead of the relatively short-term effects exhibited in humans, animal studies showed a long-lasting influence on the metabolism of the host during early life probiotic administration. The transient treatment of neonatal mice with probiotics (LGG(Yan et al. 2017) or *B. breve* M-16 V plus prebiotics(Mischke et al. 2018)) enhanced IgA production and intestinal integrity, reduced susceptibility to DSS-

Table 3. Dietry interventions used to improve early-life dysbiosis and its related diseases

Treatments	Study design	Samples	Changes in the microbiota	Health outcomes	Ref.
Probiotics	B. breve Bb99, Propionibacterium freundenreichii subsp. shermanii JS, L. rhamnosus Lc705 and LGG were orally given to pregnant women from 35 wk of GA and to infants until 6 months of age after birth.	Stool samples of infants were ceollected at 3 months of age.	Increase in Bifidobacteria and reduction in Proteobacteria and *Clostridia* were observed in breastfed infants supplemented with probiotics.	Not mentioned.	(Korpela et al. 2018)
	L. acidophilus and B. infantis were orally given to pre-term (GA $<$ 34 wk) infants from birth to discharge or 37 wk of PMA.	Not collected.	Not analyzed.	Probiotics administration reduced the morbility of NEC in breastfed but not formula-fed infants.	(Repa et al. 2015)
	L. salivarius CECT 9145 was given to GBS-positive pregnant women from week 26 to week 38 of the pregnancy.	Rectal and vaginal exudates samples were collected at 28, 32 and 38 wk.	At week 38, 72% and 68% of pregnant women received probiotic were GBS-negative in the rectal and vaginal samples, respectively.	Not mentioned here but the elimination of GBS contributes to the prevention of GBS-induced EOS in newborns.	(Martín et al. 2019)
	Standard or L. paracasei CBA L74-fermented formula were given to healthy full-term (GA 38.5 ± 1.0 wk) infants from birth to three months of age.	Stool samples were collected at the enrollment (from birth to 7 days of life) and 90 ± 5 days of life.	Increased heterogeneous and α-diversity of the GM were observed in infants fed on standard formular, as compared to breast- and fermented formula-feeding.	Fermented formula enhanced SIgA production in infants at 90 (90 ± 5) days of life.	(Roggero et al. 2020)
	One daily dose of a combination B. *aimalis* subsp. *lactis* BB-12 and LGG or placebo was given to children (aged from 6 to 59 months) with SAM for 8-12 wk.	Stool samples were collected at admission, discharge, and after 8 wk of outpatient treatment.	At discharge and two months after the treatment, probiotics treatment increased the α-diversity of the GM.	Probiotics treatment reduced the incidence of diarrhea during the outpatient phase.	(Castro-Mejía et al. 2020)
	Postnatal diets were supplemented with *B. breve* M-16V and prebiotics until 42 days of age of mice.	Stool samples were collected at 21, 42 and 98 days of age; metabolic parameters were determined at 98 days of age.	Increases in *Bifibacterium* (throughout the experiment) and bacterial diversity (at 21 and 42 days of age) were increased in synbiotics-supplemented mice.	Early life synbiotics supplementation protected mice from a HFD-induced body weight increase and fat accumulation.	(Mischke et al. 2018)
	Juvenile mice (21 days of age) fed on a HFD were gavaged with *Akkermansia muciniphila* twice a day for 28 days.	Microbial samples were not celloected while neuronal development and cognitive functions were evaluated.	Not analyzed.	Supplementation of *A. muciniphila* corrects gut permeability, restores neuronal development and synapse plasticity, and ameliorates defects in learning and memory in HFD-fed mice.	(Yang et al. 2019)
Oligosaccharides	2'Fucosyllactose and Lacto-N-neotetraose were supplemented to healthy full-term infants began at 0-14 days of age.	Stool samples were collected at 3 months of age.	Main discriminants between control and supplemented group were *Bifidobacterium, Escherichia* and Peptostreptococcaceae.	Not mentioned.	(Steenhout et al. 2016)
	Short-chain fructoolisaccharides (scFOS) were supplemented to full-term healthy infants at 0-6 days of age for 3 months.	Stool samples were collected at enrollment, and 2, 3, and 4 months of age.	Supplementation of scFOS in the formula increased the abundance of *Bifidobacterium* at 2 and 3 months of age compared to controls.	There was a trend ($P = 0.08$) toward increased fecal SIgA levels in infants fed on scFOS-supplemented formula.	(Paineau et al. 2014)
Nutritional supplements	Pureed meats, iron- and zinc-fortified infant cereals, or iron-only fortified infant cereals	Stool samples were collected at monthly intervals from 5 months through 9	Iron-only supplementation decreased the abundance of *Bifidobacterium* and	No significant differences in linear growth, weight gain, and	(Krebs et al. 2013)

(*continued*)

Table 3. Continued.

Treatments	Study design	Samples	Changes in the microbiota	Health outcomes	Ref.
	were supplemented to 45 exclusively breastfed, full-term, vaginal delivered 5-month-old infants for 4-5 months.	months; blood samples were also collected.	Lactobacillales while increased Bacteroidales in infants; the abundance of Enterobacteriaceae was associated with the total dietary iron intake.	anemic were observed among treatments.	
	Iron-fortified biscuits were given to 6-14-year-old children 4 times a week for 6 months.	Blood and stool samples were collected at basline and at the end (6 months) of the study.	Six-month iron supplementation increased the abundance of Enterobacteria while decreased Lactobacilli.	Iron supplementation had no significant effects on, anemia, or hookworm prevalence but increased the fecal calprotectin levels.	(Zimmermann et al. 2010)
	Ninety-one women (44 controls) with full-term infants were daily supplemented with fish oil or not for 6 months after their babies were born.	Infant stool samples were collected at 1 wk of age, and once per month until 6 months; breast milk samples from the mothers were collected the morning of infant stool collection.	Maternal fish oil supplementation resulted in increase in the fecal *Bifidobacterium* (at week 1 and months 3 and 4) and a decrease in Gammaproteobacteria members at month 4.	Fish oil supplementation decreased SIgA (at month 5), increased IL-10 production (at all time points), and elevated (at months 1, 4, and 5) eicosapentaenoic acid levels in milk.	(Quin et al. 2020)
	Enteral supplementation of a blend of fish oil and safflower oil were given to premature infants (geatational age $<$ 37 weeks, postnatal age $<$ 2 months) with an enterostomy.	Stool ostomy output was collected weekly from the time of study enrollment to the time of bowel reanastomosis (up to a maximum of 10 weeks).	Supplementation of the oil decreased Proteobacteria (weeks 2-8), *Escherichia* (weeks 1-9), *Serratia* (weeks 2-9), *Pantoea* (weeks 2-9), and *Clostridium* (weeks 2-9).	Not mentioned.	(Younge, Yang, and Seed 2017)
Exclusive enteral nutrition	Children with CD were treated with EEN diet for 8 weeks accompied with other medication.	Stool samples were collected from 23 CD and 21 healthy childrenl for CD children, stool samples were collected before, during EEN, and when patients returned to their habitual diets.	EEN rapidly decreased the α-diversity of GM in children with CD; among 34 significantly influenced genera by EEN, 33 were decreased.	Improvement of disease conditions were observed upon EEN treatment.	(Quince et al. 2015)
	Children with newly diagnosed CD were treated with EEN diet for 8 weeks with no other medication.	Stool samples were collected at enrollment and two and eight (end of the treatment) weeks after treatment start.	EEN increased the bacterial richness and similarity to healthy controls in children who responded.	Improvement of disease conditions were observed upon EEN treatment.	(Tang et al. 2020)
	The effects of a modified EEN diet (CD-TREAT) on CD and GM were evaluated in healthy individuals, rat models and children with CD.	Stool samples were collected from healthy individuals and rats with colitis.	Similar influences on the GM of healthy individuals were found between EEN and CD-TREAT diets: in OTU level:43.1% of the EEN-induced OTU changes were replicated by CDTREAT and 73.4% of CD-TREAT-induced OTU changes were observed in EEN; in genus level, 48.3% of the EEN effect was replicated by CDTREAT and 73.7% of the CD-TREAT effect was observed in EEN.	Three out of five children with CD reached clinical remission upon a 8-week treatment of CD-TREAT diet.	(Svolos et al. 2019)

PMA, postmenstrual age; GA, gestational age; NEC, necrotizing enterocolitis; GM, gut microbiota; CD, Crhon's disease; EEN, exclusive enternal nutrition

induced colitis(Yan et al. 2017), and resisted diet-induced obesity in adult mice(Mischke et al. 2018). Short-term stimulation has been shown to enhance IgA production for a long time (at least for 3 months) in mice (Tran et al. 2019). Considering the pivotal role of IgA in controlling bacterial encroachment that related to MetS and colitis (Luck et al. 2019; Tran et al. 2019), these transient probiotic treatment-induced long-term protective effects may also be mediated by the enhancement of IgA production (Tamburini et al. 2016; Yan et al. 2017).

Recently, animal studies demonstrated that *A. muciniphila*, a mucin degrader, seems to present a new promising probiotic in treating obesity, colitis, and neurological conditions (Ansaldo et al. 2019; Dao et al., 2016; Yang et al. 2019). Supplementation with it has been shown to prevent the early-life HFD-induced impairment of contextual/spatial learning and memory (Yang et al. 2019). However, human studies involving *Akkermansia muciniphila* are relatively scarce, especially regarding infants, as its safety still requires further investigation despite a well tolerance has been reported in adults (Depommier et al. 2019).

Despite numerous studies supporting the advantages of probiotics, considerable research has reported on their non-effective or even deleterious effects (Freedman et al. 2018; Schnadower et al. 2018; Suez et al., 2018; Yelin et al. 2019; Zmora et al., 2018). Two recent randomized, double-blind trials involving 3-month to 4-year-old children found that LGG or *L. rhamnosus* R0011 plus *L. helveticus* R0052 could not improve pediatric gastroenteritis (Freedman et al. 2018; Schnadower et al. 2018). However, it should be noted that none of these studies thoroughly considered the effects of interfering factors, such as mode of delivery and feeding, which, as specified above, can significantly influence the outcome of probiotic administration and may contribute to the ineffective results observed in these studies (Freedman et al. 2018; Schnadower et al. 2018). In addition, certain strains of *Lactobacillus,* such as LGG and *L. acidophilus* have been shown to translocate into the blood of intensive care unit patients and contribute to bacteremia, especially for those under 4 years old (Yelin et al. 2019), suggesting that the administration of probiotics should be approached with caution, especially regarding young children with severe health conditions. In healthy adults, probiotics dampen the GM reconstitution after antibiotic treatment, as compared to spontaneous recovery and autologous FMT (Suez et al., 2018).

In conclusion, probiotic administration during early life remains a promising approach for improving the intestinal and overall health of infants, while interfering factors and possible deleterious effects should be assessed.

Oligosaccharides

One of the primary differences between standard formula and breast milk is the lack of HMOs in formula (Vandenplas, Zakharova, and Dmitrieva 2015). The degradation of HMOs, mainly by *Bifidobacterium*, as well as by other bacterial taxa, such as *Bacteroides* and *Streptomyces,* results in the production of lactic acid and SCFAs (Shen et al. 2011). By decreasing the colonic oxygen level and enhancing the generation of IgA (Fehervari 2016), SCFAs can suppress the proliferation of aerobic/facultative anaerobic Proteobacteria (MX et al., 2017). Therefore, one of the main differences presented by the GM in formula-fed infants is the overrepresentation of Proteobacteria (Lee et al. 2015). To mimic the function of HMOs, certain oligosaccharides (OS), including galacto-OS, fructo-OS, and polydextrose, have been added to the formula. Supplementing the formula with OS resulted in a decrease in colonic pH, an increase in SCFA production, a reduction in pathogens, such as *E. coli* and the enrichment of *Bifidobacterium* and *Lactobacillus*, similar to those observed in breast-feeding infants (Vandenplas, Zakharova, and Dmitrieva 2015). However, the influence of OS supplementation on formula-fed-related long-term diseases, such as obesity and allergies, have not been adequately explored. Consequently, the long-term influence of OS supplementation still needs to be determined (Paineau et al. 2014; Steenhout et al. 2016).

In addition, OS supplemented into the formula lack the intrinsic complexity of HMOs regarding monosaccharide composition, linkage, and structural diversity (Sela and Mills 2010), making it quite difficult to fully achieve the HMO functions, such as immune regulation and the prevention of pathogenic adherence (Akkerman, Faas, and de Vos 2019). Therefore, it is essential to determine that whether there is a "core components" of HMOs, in terms of the monosaccharide composition, linkage types, and structural characteristics, that can fulfill all, or the majority, of the functions of HMOs? A recent study found that exercise during pregnancy increased 3′-sialyllactose levels in the milk of humans and mice, which mediated the beneficial effects of maternal exercise on the metabolic health of the offspring of mice, including a decrease in body weight and body fat percentage, as well as an improvement in glucose metabolism when fed an HFD (Harris et al. 2020). Although the function of 3′-sialyllactose has not been verified in humans, it provides an approach for the identification of key OS in breast milk (Harris et al. 2020). For example, maternal obesity can result in the alteration of HMOs in breast milk and is associated with increased obese morbidity in their babies (Lagström et al. 2020; Tun et al., 2018). Analysis of this correlation may contribute to the identification of the OS that is related to obesity. Furthermore, the number of HMOs decreases, and their composition changes following lactation (Thurl et al. 2010; Xu et al. 2017). Is there biological significance to these changing patterns? It is well-established that for a balanced GM maturation process, the abundance of *Bifidobacterium*, the main utilizer of HMOs, increases and then declines during the first year of life (Bäckhed et al. 2015; Planer et al. 2016; Yatsunenko et al. 2012), which is consistent with the alteration of HMOs, and seems not to be a coincidence. Investigation of these critical questions is pivotal for the supplementation of OS into a formula.

Nutritional supplements

The effect of nutritional supplements on the infant GM and overall health have also been characterized. In a study of the microbiome of 45 exclusively breastfed, full-term, vaginal delivered 5-month-old infants, the influence of iron-fortified cereals or iron- and zinc-fortified cereals supplementation on the gut microbiome was studied. The iron-fortified group showed a decreased abundance of *Bifidobacterium* and Lactobacillales compared to primary food (pureed meats) and iron- and zinc-fortified groups, while the differences of GM between the primary food group and iron- and the

zinc-fortified group was relatively small (Krebs et al. 2013). Iron is a pivotal and rare source for gut microbes. Increased iron levels in the gut enhance the proliferation of pathogens, resulting in inflammation (Bessman et al. 2020). Consistent with this, the abundance of *Enterobacteriaceae* in infants is associated with total dietary iron intake (Krebs et al. 2013). Moreover, dietary supplementation with iron in 6- to 14-year old African children resulted in a reduction in *Lactobacilli* and increases in pathogenic Enterobacteria and fecal calprotectin, an indicator for intestinal inflammation (Zimmermann et al. 2010). These observations emphasize that more attention should be paid to the GM when supplementing iron in infant food, while zinc seems to (partially) counteract the deleterious effects of iron on the GM (Krebs et al. 2013).

Fish oil that contains abundant polyunsaturated fatty acids (PUFAs) is also often supplemented to infants with the purpose to enhance infant health. The supplementation of fish oil during lactation by mothers increased eicosapentaenoic acid in breast milk and exhibited an increase in the fecal *Bifidobacterium* at 1 week, as well as 3 and 4 months of age while decreasing Gammaproteobacteria members such as *Enterobacteriaceae* at 4 months of age in infants (Quin et al. 2020). The direct administration of fish oil to infants showed similar results: prematurely born infants who were enterally supplemented with a blend of fish oil, and sunflower oil showed a decrease in *Enterobacteriaceae* members, such as *Escherichia* and *Serratia* (Younge, Yang, and Seed 2017). These results indicate that PUFAs may contribute to the management of pathogenic *Enterobacteriaceae*-related diseases, such as NEC, LOS, and neurological conditions (Frost and Caplan 2019; Yang et al. 2019; Zhu et al. 2020). Indeed, although controversies exist, animal and human studies show that early-life supplementation with PUFAs is associated with improved development in neurological functions and decreased sensitivities to NEC and LOS (Hamazaki et al., 2020; Lu et al. 2007; Yang et al. 2014). The inhibition of aerobic/facultative anaerobic Gammaproteobacteria members by PUFAs may be (partially) attributed to their enhancement of β-oxidation in IECs, which increases the consumption of oxygen, and enhances intestinal hypoxia (Byndloss and Baumler 2018; Hofmanová et al. 2012; Hofmanová et al. 2005).

However, attention should be focused on the supplementation of additional nutrients to infants, as nutritional status interacts with the immune system, and nutritional imbalance leads to disturbed immunity (Macpherson, de Agüero, and Ganal-Vonarburg 2017). A recent study demonstrated that excessive calorie intake by neonatal mice through maternal HFD, forced feeding of neonates or low litter competition resulted in increases in intestinal permeability, the expression of pro-inflammatory cytokines, and hydrogen sulfide production by the microbiota, leading to increased susceptibility to colitis in adults (Al Nabhani, Dulauroy, Marques, et al. 2019).

Pure nutritional supplementation with two widely used formulas reportedly reduced the mortality in Bangladeshi children with severe acute malnutrition (SAM). However, the dysbiosis associated with SAM, including immaturity and reduced α-diversity, was only partially restored (one formula transiently improved, while another had no significant influence on the reduced α-diversity) (Subramanian et al. 2014). Therefore, modifying the ingredients of the present nutritional interventions or the co-use of probiotics may be needed to achieve better clinical outcomes in malnutrition. (Subramanian et al. 2014). Consistent with this assumption, a recent study of 400 Ugandan children (22 controls, 17.0 ± 8.5 months of age) determined the influence of extra probiotic (LGG and *B. animalis* subsp. *lactis* BB-12) supplementation (standard treatment was also provided to the children) on the GM and disease conditions of SAM. Children with SAM showed reduced α-diversity, similar to that seen in Bangladeshi children with SAM (Castro-Mejía et al. 2020; Subramanian et al. 2014). Probiotic treatment reduced the cumulative incidence of diarrhea during the outpatient phase, while increasing the α-diversity at discharge and two months (time the last microbial samples were collected) after the treatment, compared to the standard treatment-only (placebo) group (Castro-Mejía et al. 2020).

Exclusive enteral nutrition

Exclusive enteral nutrition (EEN) is the first-line therapy and the only established dietary treatment for pediatric CD with remission rates of 60–80% (Ashton, Gavin, and Beattie 2019; Svolos et al. 2019). In EEN, the normal dietary components are replaced with a formula consisting exclusively of liquid nutrients. Changes in the GM upon EEN treatment were believed to play a pivotal role in achieving remission, although heterogeneous results of the GM alteration were obtained from different studies (Ashton, Gavin, and Beattie 2019). A study assessed 23 children aged 6.9-14.7 with active CD, of which 15 received EEN for 8 weeks. The intervention resulted in an amelioration of the disease condition, a rapid reduction in bacterial α-diversity, and a decrease in basically all bacterial genera (33 out of 34 significantly changed genera), leading to an even more dissimilar GM from the controls (Quince et al. 2015). On the contrary, a recent study involving Chinese children with CD revealed that those who responded to an 8-week EEN treatment showed an increase in bacterial richness and similarities to healthy controls compared to those who did not (Tang et al. 2020). Differences in the EEN formula and other medications may contribute to this discrepancy (Quince et al. 2015; Tang et al. 2020).

Despite its success in individuals with pediatric CD, the acceptability of EEN is relatively low because of its poor palatability and delivery method (tube feeding), making it challenging to maintain prolonged use (Tamburini et al. 2016). Therefore, the development of a modified EEN diet with high palatability and comparable or better efficiency in treating CD is meaningful. A recent study provided some insights into this (Svolos et al. 2019). In this study, some of the original ingredients, such as gluten, lactose, and alcohol of a popular EEN diet were removed, and macronutrients, vitamins, minerals, and fiber were replaced with ingredients

as close as possible to ordinary food (Svolos et al. 2019). The modified EEN diet, called CD-TREAT diet, had an increase in acceptability and had a similar impact on the GM (43.1% of the EEN-induced OTU changes were replicated by CDTREAT, and 73.4% of CD-TREAT-induced OTU changes were observed in EEN for healthy individuals) as EEN. Moreover, this ordinary food-based CD-TREAT diet improved disease conditions and colonic inflammation in children with CD, while reducing ileitis in a colitis rat model (Svolos et al. 2019), indicating a promising avenue for CD management. Furthermore, this result also suggests that the effective constituents in EEN are still largely unknown and should be investigated. Considering the key role of GM in mediating the effect of EEN, the precise determination of the interaction between specific microbes and pediatric CD may assist in determining the effective components in EEN (Gerasimidis et al. 2014; Quince et al. 2015). Therefore, a more acceptable diet able to accurately modulate the specific CD-relating microbial taxa may significantly contribute to the daily management of pediatric CD (Svolos et al. 2019).

Conclusions and perspectives

Various factors can disturb the colonization and maturation of the GM during early life, primarily defined by a delay in maturation, a reduction in beneficial microbes, such as *Bifidobacterium*, and an overrepresentation of (potential) pathogens, such as *Enterobacteriaceae*. This early-life gut dysbiosis is associated with various diseases, while the determination of causality is scarce in human studies. Animal studies did find causal links between early-life dysbiosis and certain diseases, including obesity, allergies, malnutrition, and behavioral disorders. However, investigations into their applicability for humans and the underlying mechanisms remain inadequate.

Dietary interventions are the main approaches in regulating the GM during early life, while issues exist during application. The efficiency of probiotic supplementation has been verified in certain diseases, such as NEC, while its long-term effect on health is not well determined. Moreover, a more effective influence of probiotics is generally observed in breastfed children and, therefore, a formula that can mimic breast milk is essential when breast milk is not available. To better mimic the function of breast milk, multifarious OS is supplemented into the formula as a substitution for HMOs. However, key issues, including the type and number of OS, need to be addressed when making these additions. The determination of the core components of HMOs and their variations during lactation can be substantially useful for the supplementation of OS into a formula (Figure 3).

In addition, human milk contains abundant antimicrobial antibodies, such as IgA and IgG, which are pivotal for the prevention of pathogenic infection and the regulation of GM composition and intestinal immunity in infants. In the future, more research is warranted to determine whether it is necessary and how to supplement or substitute them into formula while retaining similar functionality.

Disclosure statement

The authors declare no conflicts of interest.

Abbreviations

T1D	type 1 diabetes
NEC	necrotizing enterocolitis
CD	Crohn's disease
GM	gut microbiota
FMT	fecal microbiota transplantation
GF	germ-free
GA	gestational age
IAP	intrapartum antibiotic prophylaxis
EOS	early-onset sepsis
NICU	neonatal intensive care unit
IEC	intestinal epithelial cell
HMO	human milk oligosaccharide
DC	dendritic cells
PC	plasma cells
HFD	high-fat diet
LPS	lipopolysaccharide
Treg	regulatory T
TLR	toll-like receptor
Th17	T helper 17
GAP	GC-associated antigen passage
EGF	epidermal growth factor
NOD	neonatal non-obese diabetic
PAT	pulsed therapeutic antibiotics
SCFA	short-chain fatty acid
LOS	late-onset sepsis
OS	oligosaccharides
PUFA	polyunsaturated fatty acid
SAM	severe acute malnutrition
EEN	Exclusive enteral nutrition

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