The Role of the Microbiome in the Developmental Origins of Health and Disease

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Although the prominent role of the microbiome in human health has been established, the early-life microbiome is now being recognized as a major influence on long-term human health and development. Variations in the composition and functional potential of the early-life microbiome are the result of lifestyle factors, such as mode of birth, breastfeeding, diet, and antibiotic usage. In addition, variations in the composition of the early-life microbiome have been associated with specific disease outcomes, such as asthma, obesity, and neurodevelopmental disorders. This points toward this bacterial consortium as a mediator between early lifestyle factors and health and disease. In addition, variations in the microbial intrauterine environment may predispose neonates to specific health outcomes later in life. A role of the microbiome in the Developmental Origins of Health and Disease is supported in this collective research. Highlighting the early-life critical window of susceptibility associated with microbiome development, we discuss infant microbial colonization, beginning with the maternal-to-fetal exchange of microbes in utero and up through the influence of breastfeeding in the first year of life. In addition, we review the available disease-specific evidence pointing toward the microbiome as a mechanistic mediator in the Developmental Origins of Health and Disease.

During the past decade, the microbiome has emerged as a major contributor to human health.[1] It has been suggested in current studies that the early-life microbiome is a crucial factor for proper immune development and long-term health.[2,3] Transient microbial dysbiosis during this time period has been associated with the development of immune-mediated, metabolic, and neurodevelopmental disorders.[4–7] In addition, increasing evidence has been used to support a vital role of the maternal and intrauterine microbiomes in childhood health and development.[8] Collectively, these findings have been used to support the microbiome as a key participant in the Developmental Origins of Health and Disease (DOHaD). In this review, we will discuss the current research surrounding the maturation of the early-life microbiome and how transient variations in this bacterial consortium can have long-term consequences for human health.

THE DOHAD: WHERE DOES THE MICROBIOME FIT?

The developmental origins hypothesis proposes variations in fetal and infant programming through environmental exposures during a critical window of early life.[9] Termed originally as the Barker hypothesis,[10,11] in which the association between fetal malnutrition and hypertension later in life was a focus, this theory has since expanded to account for many types of early-life exposures and birth outcomes associated with long-term health and development. For example, high birth

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weight is associated with an increase in breast and colon cancer risk,[12,13] and the underlying mechanism of this association may be related to intrauterine exposure to high levels of growth hormones.[9]

Early-life infections and microbial exposures were not originally associated with DOHaD but were proposed as significant environmental influences on infant immune development in the hygiene hypothesis of allergic disease.[14] With the advancement of human microbiome research, a modern extension of the hygiene hypothesis has since been proposed, known as the microflora hypothesis.[15] In the microflora hypothesis, it is suggested that early-life environmental exposures alter the development of the human microbiome.[15] Shifts in the composition of the microbiome are thought to bias maturation of the immune system toward a hypersensitive and/or hyperinflammatory state.[15] For example, the innate and adaptive branches of the immune system are both highly involved in promoting an inflammatory response. However, exposure to microbes typically evokes a T-helper 1–mediated response, which suppresses the T-helper 2 activity often associated with immune-mediated and hypersensitivity reactions.[3] Discussion of the mechanisms regulating the interface between the immune system and the microbiota is beyond the scope of this review; please see Tamburini et al[3] for a recent in-depth discussion on this topic.

Analogous to DOHaD, an early-life critical window of development has also been proposed for the microbiome. Transient microbial dysbiosis (unhealthy microbial state) during this time frame has been associated with long-term immune and metabolic health issues,[2] meriting its exploration within the developmental origins field (Fig 1).

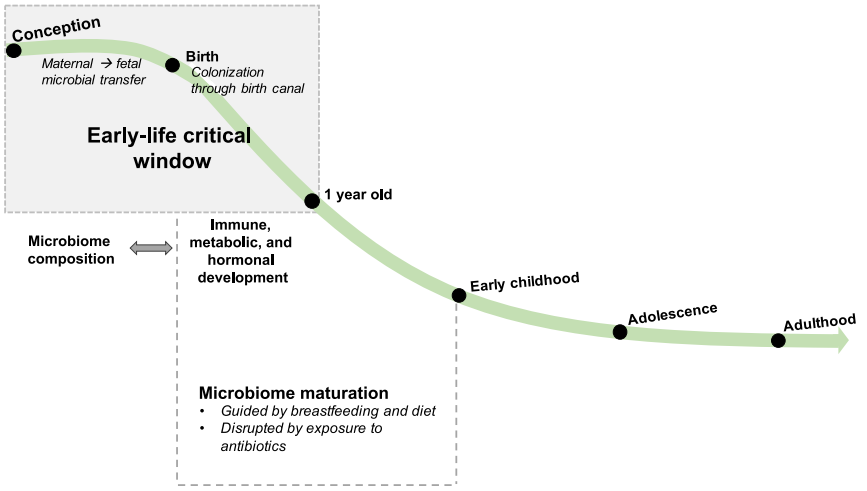

FIGURE 1

The infant microbiome is most vulnerable to environmental influences in early life. Maternal to fetal microbial transfer, mode of birth, antibiotics, and diet can alter the colonization and maturation of the early-life microbiome. These lifestyle-induced variations in microbiome composition and function can have prolonged influences on human health and may lead to the development of disease later in life.

EARLY-LIFE DEVELOPMENT OF THE MICROBIOME

The human microbiota is a composite organism, composed of 10 trillion to 100 trillion microbial cells (bacteria, archaea, and microbial eukaryotes) and viruses.[16,17] To highlight the impressive functional potential of the microbiota, the genomic catalog of this super organism, the microbiome, is composed of ~3.3 million nonredundant genes.[16] Although the terms "microbiota" and "microbiome" are descriptive of the microbial composition and genomic catalog, respectively, they are used interchangeably within this research field. The following sections are devoted to delineating the initial colonization and establishment of the human bacterial microbiota in infancy, from conception through the first year of life.

Maternal-to-Fetal Microbial Transfer

Until recently, the intrauterine environment was perceived as sterile.[18] However, nonpathogenic bacteria have since been detected by molecular techniques in the amniotic fluid and placentas of healthy infants,[19,20] suggesting a maternal-to-fetal exchange of microbes. In addition, through comparisons of the amniotic, placental, and meconium microbiotas, Collado et al[21] report that the meconium microbiota of infants delivered via cesarean delivery shares ~55% of its bacterial taxa with the placenta and amniotic fluid microbiotas. The prenatal maternal microbiome may also modulate the infant immune system. For example, gestation-only colonization with *Escherichia coli* HA107 was reported to modify the intestinal mucosal innate immune system and transcriptome of the offspring.[22]

In humans, variations in the placental microbiome composition have been associated with maternal pregnancy-related (stress and gestational diabetes) and neonatal health outcomes (birth weight, preterm birth).[7,23–25] The placental microbiome of infants born preterm was also reported to differ in composition according to gestational weight gain,[26] suggesting that this bacterial consortium may mediate

fetal development depending on the health status of the mother.

Isolation of bacteria from the placenta is often associated with a pathophysiological state, which threatens the health of the mother and child. Because of the lack of culture-based analyses of the placental microbiome, there is some controversy surrounding its validity.[27] In addition, inclusion of appropriate controls to address background contamination is also lacking in many molecular-based studies characterizing the intrauterine microbiome.[28]

It is also possible that the placenta does not harbor any viable bacteria but rather is composed of phagocytosed microbial by-products or cell wall components.[8,22,29] The lack of viable bacteria does not negate the capacity of the placental microbiome to modulate fetal development because interactions with pathogen-associated molecular patterns may still regulate cell differentiation and proliferation.[8,22,29] In addition, upon implementation of stringent validation strategies for placental metagenomic analyses, the placental microbiome might be referenced as a biomarker for maternal and fetal health and disease. Few studies have been conducted to explore the function of the placental microbiome,[23,25] emphasizing an opportunity for future research in this area. Analysis of microbial metabolites and the application of metatranscriptomic approaches to characterize the functional capacity of the placental microbiome will be key in defining its role in DOHaD.

Vaginal Birth: The First Step in Postnatal Microbial Colonization

Postnatal bacterial colonization of the infant begins during birth, at which time neonates are exposed to the maternal fecal and vaginal microbiotas.[30] Within 24 hours of delivery, the microbiotas across various body sites (oral, skin, meconium, etc) of cesarean delivered infants are initially populated with bacteria residing on the mother's skin (eg, *Staphylococcus* spp.), whereas vaginally delivered infants are populated with typical vaginal bacteria (eg, *Prevotella*, *Atopobium* spp.).[30] In a recent study, Chu et al[31] suggest this finding may be specific to the neonatal gut microbiome. In their study of 81 mother and infant dyads, the microbiomes of other body sites (nares, skin, etc) from infants delivered vaginally revealed a bimodal pattern of maternal origin, populated by both the mothers' vaginal and skin bacteria rather than by one or the other.[31] However, it is suggested in both studies that the microbiotas of infants are homogeneously distributed across body sites (eg, meconium, skin, nares, etc) immediately after birth.[30]

Profiling of the neonatal intestinal microbiome immediately after birth and up to age 2 years suggests that birth mode can result in prolonged infant gut microbial dysbiosis.[32] In a study of 43 mother and infant dyads, infants delivered via cesarean delivery exhibited increased phylogenetic diversity immediately after birth.[32] However, after 1 month of age, the phylogenetic diversity of infants delivered via cesarean delivery declined below that of vaginally delivered infants.[32] Chu et al[31] challenge this finding slightly. In their recent study, birth mode was associated with variations in the microbiomes of the nares, skin, and oral cavity immediately after birth but not with variations in the infant meconium microbiome. Researchers of both studies do support the influence of birth mode on neonatal colonization in general; however, more research is needed to determine the influence of this early-life factor on the microbiomes of specific body sites.

Because of the health benefits associated with vaginal birth,[33] Dominguez-bello et al[34] conducted the first study aimed at recolonizing infants delivered via cesarean delivery with vaginal bacteria. After swabbing neonates with maternal vaginal fluids within 2 minutes of birth, the authors report partial restoration of the microbiota of infants delivered via cesarean delivery to that of vaginally delivered infants.[34] However, the long-term health effects and composition of the infant microbiome are not yet known.[34] Future analysis of these cesarean delivered infants exposed to the vaginal microbiome will be extremely valuable in determining the benefits of vaginally derived bacteria in long-term human health. In addition, the establishment of prospective human studies and animal models attempting similar colonization with vaginal bacteria among offspring delivered via cesarean delivery will be crucial in elucidating the role of vaginal microbes in the development of disease.

Breastfeeding Furthers Microbiota Maturation in Early Life

As the neonate grows, the homogeneous microbiome populating his or her body diverges into microbe-specific body niches.[18,31] The maturation of the total infant microbiome has been studied for the first year of life, but beyond this time point, most researchers focus specifically on the gut microbiome. Driven in large part by breastfeeding and infant diet, the human gut microbiome continues to mature until the child reaches 2 to 3 years of age, after which its composition stabilizes.[35]

Breastfeeding seeds the infant gut microbiome through contact with maternal areolar and breast milk microbes and provides key energy sources for many bacteria (human milk oligosaccharides).[36–39] In a study of 107 mother and infant dyads, infants who were breastfed during the first 30 to 40 days of life

received a mean of ~28% of their bacteria from breast milk and ~10% from maternal areolar skin.[38] The authors also report a dose-dependent association between the infant gut microbiome composition and the proportion of daily breastfeeding.[38]

There is a clear compositional distinction between breastfed and formula-fed infants, with breastfed infants being populated with higher proportions of *Bifidobacteria* and *Lactobacillus* spp. and formula-fed infants being populated with a greater prevalence of clostridiales and proteobacteria.[32,40] In addition, formula-fed infants exhibit decreased diversity and bacterial richness even after the first year of life (12–24 months of age).[32] In a study of 30 preterm infants, the effect of breastfeeding (versus formula feeding) was also reported to mask the influence of birth weight on the infant microbiome, highlighting breastfeeding as being potentially protective (at least with regard to the infant microbiome) against a traditional DOHaD risk factor.[41] Epidemiologic evidence provides further support for the beneficial roles of breastfeeding in promoting infant health. Formula feeding has been associated with an increased risk of various hyperinflammatory and immune-mediated diseases.[42,43] In addition, researchers of a recent epidemiologic study reported that breastfeeding protects against wheezing during the first year of life among infants born to mothers with asthma.[43] With the work discussed in this section, we suggest that the microbiome may be a mediator between these associations.

Gestation-Associated Maternal Diet Shapes the Developing Infant Microbiome

Recent evidence has been used to support a significant role of gestation-associated maternal diet in shaping the microbiome of infancy. A maternal high-fat diet during pregnancy and breastfeeding was reported to induce dysbiosis in the offspring microbiome of Japanese macaques.[44] These maternal diet–induced microbial variations persisted in juvenile macaques.[44] In addition, a postweaning, low-fat control diet was unable to correct this maternal high-fat diet–induced dysbiosis.[44] In a prospective cohort of 26 mother and infant dyads, a high-fat maternal gestational diet was associated with distinct variations in the neonatal gut microbial composition (meconium), which persisted to 4 to 6 weeks of age.[45] In a mouse model, a maternal high-fiber diet was associated with increased short-chain fatty acid (SCFA) production in the offspring.[46] Emphasizing the immune-modulatory capacity of the maternal diet–driven microbiome during pregnancy, higher frequencies of thymic T-regulatory cells were also found in these pups.[46] Finally, demonstrating the effect of maternal diet on the functional capacity of the infant microbiome, piglets born of sows that were fed a western diet (high-energy, high-fat, fructose-based diet) during pregnancy displayed decreased SCFA production.[47] In these studies, the importance of the microbiome as a mediator linking gestation-associated maternal diet to infant health is supported, substantiating the role of the microbiome in DOHaD. Future studies may shed more light on the prolonged health and developmental effects of gestation-associated maternal diet.

Antibiotics Alter Infant Colonization and Decrease Microbiota Maturation

Perhaps unsurprisingly, pre- and postnatal antibiotic exposure is a major early-life environmental stressor on the infant microbiome. Prenatal maternal antibiotic exposure has been reported to alter the diversity of both the neonatal[48–50] and maternal[51] microbiotas. Intrapartum antibiotic exposure was also reported to alter the infant oral microbiome composition.[52] Specifically, the bacterial families *streptococcaceae* and *gemellaceae* and the order lactobacillales were decreased, whereas bacterial families in the proteobacteria phylum were enriched among infants whose mothers received intrapartum antibiotics.[52] In addition, among infants whose mothers received antibiotics, the infant oral microbiome composition was further differentiated depending on whether the mother received a cocktail of antibiotics compared with if she received only 1 antibiotic.[52]

Postnatal antibiotic courses given to the infant in the first 3 to 9 months of life were reported to alter abundances of specific gut bacterial taxa (namely, *Ruminococcus* and clostridiales).[32] In addition, antibiotic use in the first 6 to 12 months of life has been associated with decreased maturation of the infant microbiota.[32] This suggests antibiotics may stunt the development of the microbiota if administered during this time period, which could potentially predispose infants to microbiome-associated diseases later in life.[32]

In epidemiologic studies, it has been suggested that antibiotic-induced dysbiosis in infancy promotes the development of many noncommunicable diseases in later childhood and adulthood (ie, obesity, asthma, inflammatory bowel disease [IBD]).[53–56] However, these epidemiologic analyses do not address whether these diseases are causally related to early-life antibiotic use or whether they are indicative of early-life immune deficiencies or propensity for infection. Nevertheless, there are some promising animal models and prospective human cohort studies that attempt to address this quandary and provide additional support for the microbiome as a key developmental mediator in DOHaD.

DYSBIOSIS-ASSOCIATED NONCOMMUNICABLE DISEASES PROVIDE ADDITIONAL SUPPORT FOR THE MICROBIOME IN DOHAD

The Critical Window in Early Life

As mentioned at the beginning of this review, DOHaD emphasizes a critical window of susceptibility from conception to early life in which environmental stressors most profoundly affect long-term human health. A similar critical window has emerged for the development of the microbiome. Scientists have narrowed the microbiome early-life critical window to the time period between conception and the first year of life (Fig 1).[1] Though more research is needed to confirm this theory, the microbiome's vulnerability to environmental influences appears to be time varying, more substantial earlier in life and lessening as it matures toward that of an adult (Fig 1). In the following sections, we will discuss disease-specific research (specifically, necrotizing enterocolitis [NEC], asthma and atopic disease, obesity, and neurodevelopmental disorders) that points toward this early-life critical window and further supports the role of the microbiome in DOHaD (summarized in Table 1).

NEC

In addition to the health risks associated with preterm birth, preterm infants display marked neonatal microbial dysbiosis. This dysbiosis enhances their susceptibility to disease, particularly NEC, which may be modified by exposure to antibiotics during this critical time period.[57] Through analysis of existing 16S ribosomal RNA gene sequence data, the authors identified differential abundances of proteobacteria, firmicutes, and bacteroidetes, which preceded the onset of NEC.[57] Gut dysbiosis characterized by similar variations in bacterial taxa was also reported to precede NEC in a study of 122 extremely low birth weight neonates.[58] The increase in proteobacteria along with increased enterocyte Toll-like receptor 4 activity in these neonates with NEC suggest a hyperinflammatory response to a dysbiotic microbiome.[59] However, a recent study was conducted in which researchers identified uropathogenic *E coli* colonization as a significant risk marker for NEC.[59] This suggests an invasive microbial species may be synergistic in driving this dysbiosis-associated disorder. In addition, infants treated with antibiotics for 7–14 days (regardless of NEC status) were enriched for *E coli* relative to infants treated with antibiotics for 0–6 days.[59] This supports a role of neonatal antibiotic-induced dysbiosis in NEC, which may enhance the vulnerability of the neonatal gut microbiome to pathogen invasion. Because of the apparent link between microbial dysbiosis and NEC, probiotic supplementation of preterm neonates is becoming a prominent research area for NEC prevention and treatment.[109,110] In a systematic review and meta-analysis of 26 probiotic intervention studies for NEC, it is suggested that probiotic intervention does prevent NEC.[60] However, the particular strains to be used and the effects on high-risk populations (extremely low birth weight infants) requires further study.[60] Nonetheless, it may be possible in the near future to optimize the neonatal microbiome to combat development of this disease and prevent associated infant mortality.

Asthma and Atopic Disease

NEC studies highlight the dynamic relation between the gut microbiome and the developing immune system. However, although the neonatal immune system is on high alert for pathogenic invaders, researchers who have conducted studies of asthma and atopic diseases (food allergies, atopic dermatitis, etc) suggest its development is strongly influenced by commensal bacteria.

In a recent assessment of the microbiome in asthma development, a more substantial role of the maternal microbiota in fetal development is supported than what was previously thought. In a mouse model of allergic airway inflammation, high-fiber (which has been reported to stimulate production of SCFAs by the microbiome[111]) or acetate (a SCFA) feeding of pregnant mice modulated the maternal microbiota and protected the subsequent offspring from developing allergic airway disease.[73] The authors of this study also provided preliminary evidence of this association in humans; high acetate levels in the serum of pregnant individuals correlated with reduced general practitioner visits for coughing and wheezing in the offspring during the first 12 months of life.[73]

Postnatal early-life dysbiosis in both the human gut[2,4,5,70] and airway[78] microbiomes is also associated with asthma and atopic disease development in children. This dysbiosis is characterized by shifts in the prevalence of specific bacterial[4,5] and fungal taxa,[70] which are transient and most prominent between birth and 3 months of life. The majority of human studies in this research area reveal only correlative evidence to link the early-life dysbiosis with asthma. However, Arrieta et al[4] provide preliminary evidence of causality related to early-life transient dysbiosis and immune development in the context of asthma. In this study, inoculation of previously germ-free (GF) mice with 4 bacterial species, which were reduced in infants at high risk of asthma, ameliorated allergic airway inflammation in these mice.[4]

There is also evidence to support a role of the early-life microbiome in food allergies. Azad et al[74] report a decrease in microbial diversity at

TABLE 1 Studies in Which Researchers Relate the Early-Life Microbiome With Health Outcomes in Later Childhood and Adulthood

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
NEC						
To assess microbial dysbiosis before NEC in a systematic review and meta-analysis	Systematic review and meta-analysis of 14 human fecal microbiome studies of NEC	None	Variations in the microbiome before NEC development	NEC at ∼30 wk postconception	Increased proteobacteria and decreased firmicutes and bacteroidetes preceded NEC onset. Antibiotics, diet, and mode of delivery do contribute to microbial dysbiosis associated with NEC. However, causality related to these factors cannot be determined	57
To determine if 1 or more gut bacterial taxa differ between cases of NEC and controls	Prospective human cohort analysis (primary cohort, *n* = 122; secondary cohorts, *n* = 44)	None	Variations in the microbiome before NEC development	NEC in very low birth wt infants	Increases in gammaproteobacteria and decreases in negativicutes and clostridia-negativicutes classes over time preceded NEC development	58
To enhance strain-level resolution of NEC-associated pathogens by using deep shotgun metagenomics sequencing	Prospective human cohort analysis (*n* = 166)	None	Variations in the microbiome before NEC development	NEC in infancy	Variations in the microbiome were detected before NEC development. However, at 17–22 d postpartum, infants with high antibiotic treatment were enriched for *E coli*. The group later identified uropathogenic *E coli* as a major risk factor for NEC and associated death	59
To compare the efficacy and safety of enteral probiotic administration in preventing NEC	Systematic review and meta-analysis of 24 randomized or quasi-randomized controlled trials in humans	None	Enteral probiotic supplementation before NEC development	Stage II and stage III NEC in infancy	Enteral probiotic supplementation significantly reduced the incidence of NEC and mortality in infants	60
To assess the intestinal microbiota composition before NEC development in infants who developed NEC and controls	Prospective human cohort analysis (*n* = 38)	None	Variations in the microbiome before NEC development	NEC in infancy	An average of 7 samples were collected per subject and the temporal changes in microbiome composition were assessed. Throughout early life, before the development of NEC, different microbial populations dominate the gut and are associated with NEC development. In addition, the microbiome compositional progression appears to be associated with the timing of NEC onset	61
To identify microbial and metabolic biomarkers of NEC	Nested case-control design (*n* = 35)	None	Variations in the microbiome before NEC development	NEC in infancy	Lower α diversity 4–9 d postbirth was associated with NEC development. Microbiomes of subjects tended to cluster according to NEC status. These microbial variations were associated with shifts in urine metabolites, namely alanine and histidine	62

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To determine if gut microbiome composition can be used to predict NEC severity	Prospective human cohort analysis ($n = 30$)	None	Variations in the microbiome before NEC development	NEC in infancy	Variations in the microbiome were not associated with NEC severity. There were also no differences in the microbiome post-NEC compared with controls	63
To assess whether fecal microbiota transplantation is an effective treatment of NEC	Wild-type and *Grx1*−/− mouse models of NEC	None	Fecal microbiota transplant from 1 to 4 d postbirth	NEC 5 d postbirth	Fecal microbiota transplant from healthy 6–8-wk-old mice to mouse pups conditioned for NEC reduced NEC incidence and severity compared with controls. This was dependent on *Grx1*. The mechanism of action is potentially through TLR-mediated inflammation and gut permeability	64
To determine if patients at risk for NEC can be identified by their meconium and early postnatal microbiota	Prospective human cohort analysis ($n = 33$)	Early enteral feeding and breast milk	Variations in meconium microbiome and neonatal microbiome before NEC	NEC in infancy	*Clostridium perfringens* and *Bacteroides dorei* were increased in the meconium of infants who developed NEC. *C perfringens* abundance persisted in neonatal stool samples. The amount of breast milk before NEC and earlier enteral feeding was negatively associated with NEC and associated with increased lactate-producing bacilli	65
To compare enteral versus parenteral antibiotics in preventing formula-induced NEC lesions in pigs	Piglet model of NEC	Antibiotic-induced	Enteral and parenteral antibiotic treatment (for 5 d post birth)	NEC in preterm piglets	Enteral antibiotics prevented NEC lesions, whereas lesions in piglets that were treated with parenteral antibiotics were increased. Enteral antibiotics decreased bacterial load and abundances of Gram-positive bacteria in the intestine. It is suggested that delayed colonization (particularly with Gram-positive bacteria) may prevent NEC. However, although microbiome variations correlate with NEC, they do not necessarily precede NEC	66
To determine if total parenteral nutrition, before the start of enteral feeding, can prevent NEC-associated gut dysfunction and inflammation	Piglet model of NEC	Enteral and total parenteral nutrition	Variations in the microbiome after feeding methods	NEC in preterm piglets	Enteral feeding increased microbial diversity and the abundance of *Clostridium* species. Density of *C perfringens* was associated with NEC severity. Microbiome variations correlate with NEC but do not necessarily precede NEC	67
To identify microbial profiles before NEC diagnosis	Prospective human cohort analysis ($n = 369$)	None	Variations in the microbiome before NEC diagnosis	NEC in infancy	Identification of 2 fecal microbiota profiles associated with NEC development (*C perfringens* type A dominant and *Klebsiella* dominant)	68

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To characterize epigenome to microbiome crosstalk at critical neonatal stages of development	Tissue-based (immature enterocytes) and mouse models (dexamethasone or 5-azacytidine to induce epigenetic changes)	Prenatal dexamethasone or 5-azacytidine treatment	Microbiome to epigenome crosstalk in perinatal life	TLR and tight junction-signaling pathways in offspring	Prenatal dexamethasone and azacytidine treatment alters DNA methylation of tight junction and TLR genes and associated inflammatory pathways in fetuses and guts of 2-wk-old offspring. Both prenatal exposures also altered the offspring microbiome. Azacytidine treatment induces global demethylation, suggesting that the pre- and neonatal epigenome influences neonatal microbial colonization	69
Asthma and atopic disease						
To analyze the microbiome of infants before atopic disease development at 1 y of age	Nested case-control design (n = 319) and Ovalbumin-challenged mouse models of asthma	None	Variations in the 3-mo-old gut microbiome	Atopy and wheezing at 1 y of age	Four bacterial taxa (*Faecalibacterium*, *Lachnospira*, *Veillonella*, and *Rothia*) were decreased among infants with atopy and wheezing at 1 y of age. Supplementation of asthma-induced mice with these 4 bacteria ameliorated airway inflammation	4
To analyze the microbiota of infants before asthma development by 4 y of age	Nested case-control design (n = 319)	None	Variations in the 3-mo-old gut microbiome	Asthma by 4 y of age	Decreased *Lachnospira*/*Clostridium neonatale* ratio at 3 mo of age was associated with asthma by 4 y of age	5
To characterize the bacterial and fungal microbiomes in neonates before asthma development at 4 y of age	Prospective human cohort analysis (n = 168)	None	Variations in gut microbiome 35 d postbirth	Asthma at 4 y of age	Variations in bacterial and fungal taxa at 35 d postbirth associated with highest relative risk of asthma. Sterile fecal water from the highest-risk group induces CD4+ T-cell dysfunction	70
To characterize the early-life critical window associated with exacerbated allergic airways responses in mice	Ovalbumin-challenged mouse model	Antibiotic-induced	Perinatal (in utero and through weaning)	Asthma induced later in life	Perinatal vancomycin exposure promotes expansion of firmicutes and exacerbates airway inflammation in mice	71
To analyze the effects of perinatal antibiotic treatment on development of hypersensitivity pneumonitis	Th1/Th17-mediated mouse model	Antibiotic-induced	Perinatal antibiotic exposure	Hypersensitivity pneumonitis in adulthood	Perinatal streptomycin promotes expansion of bacteroidetes and results in exaggerated hypersensitivity pneumonitis	72
To characterize the cellular mechanisms associated with diet or microbiota-mediated immune regulation	Wild-type, Gpr43−/−, and HDAC9−/− house dust mite mouse models of AAD; nested case-control design (n = 40)	Maternal acetate or high-fiber diet; maternal serum levels of acetate	Prenatal antibiotic exposure; prenatal acetate exposure	AAD induced in adulthood; coughing and wheeze by 1 y of age	High-fiber diet or acetate feeding of dams in pregnancy prevents robust AAD in adult offspring. Maternal serum levels of acetate were inversely associated with general practitioner visits for coughing and wheezing in the first 12 mo of life	73

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To analyze the infant microbiota in association with food sensitization	Nested case-control design (n = 166)	None	Variations in the gut microbiome at 3 mo of age	Food sensitivity at 1 y of age	Decreased α diversity and increased enterobacteriaceae/bacteroidaceae ratio associated with food sensitization to at least 1 food allergen (milk, egg, peanut, soy) at 1 y of age.	74
To analyze the early-life microbiota in association with resolution of cow's milk allergy	Nested case-control design (n = 226 subjects with milk allergy)	None	Variations in the gut microbiome at 3–6 mo of age	Milk allergy resolution by 8 y of age	Firmicutes and clostridia were enriched in microbiomes of subjects whose milk allergy resolved by 8 y of age. Bacteroidetes and *Enterobacter* were enriched among those whose milk allergy did not resolve by 8 y of age	75
To investigate age-dependent microbial modulation of iNKTs in mouse models of IBD and asthma	Ovalbumin-challenged mouse model	None	Exposure to maternal gut microbiome at birth	Asthma induced later in life	Neonatal exposure to a conventional microbiota (compared with GF conditions) increased iNKT in the lungs and protected against allergic asthma induced in adulthood. In addition, hypomethylation of CXCL16, driven by the microbiome, was associated with iNKT induction, implicating the microbiome in gene regulation	76
To analyze the role of the early-life lung microbiota in allergen-induced airway inflammation	Mouse model of house dust mite–induced airway inflammation	None	2-wk window of susceptibility (lung microbiome)	Asthma induced later in life	Variations in the lung microbiome (shift from gammaproteobacteria and firmicutes to bacteroidetes) associated with decreased aeroallergen responsiveness and increased Helios$^-$ T-regulatory cells. This is mediated by PD-L1. Blockage of PD-L1 in the first 2 wk of life results in enhanced allergic airway inflammation	77
To analyze the nasopharyngeal microbiome in infancy in association with respiratory disease later in life	Prospective human cohort study (n = 234)	None	Variations in the nasopharyngeal microbiome 7–9 wk postbirth	Chronic wheezing at 5–10 y of age	Children who developed chronic wheezing at 5–7 y of age and were atopic by age 2 were twice as likely to have been colonized with asymptomatic *Streptococcus*	78
To determine if variations in the skin microbiome in early life are associated with atopic dermatitis	Nested case-control design (n = 20)	None	Variations in the skin (antecubital fossa) microbiome at 2 mo of age	Atopic dermatitis at 1 y of age	Colonization of antecubital fossa at 2 mo of age with *Staphylococcus* was associated with decreased incidence of atopic dermatitis at 1 y of age	79
To analyze associations between neonatal gut *Bifidobacterium* species and eczema or atopy development in the first year of life	Nested case-control design (n = 117)	Colonization patterns influenced by household pets, number of siblings, and maternal allergic status	Variations in *Bifidobacterium* species at 1 wk and 3 mo of age	Atopic dermatitis at 1 y of age	Variations in *Bifidobacterium* species at 1 wk and 3 mo of age were associated with risk of eczema at 1 y of age. However, the microbiome was not analyzed after 3 mo of age	80

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To analyze associations between proportions of IgA coating and bacteria bound to IgA in infancy and allergy development later in life	Nested case-control design (n = 48)	None	IgA and total bacterial load measured at 1 wk and 1 y of age	Asthma, allergic rhinoconjunctivitis, allergic urticaria, and eczema by 7 y of age	At 12 mo of age, children with allergic disease (particularly asthma) displayed a lower proportion of IgA bound to fecal bacteria. IgA recognition patterns for the microbiota varied between children with allergies and healthy children at 1 wk of age	81
To analyze fecal microbial diversity and bacterial abundances in the first year of life in association with asthma and allergies later in life	Nested case-control design (n = 47)	None	Microbial diversity at 1 mo of age	Asthma at 7 y of age	Children with asthma displayed lower overall microbial diversity than children without asthma	82
To investigate the infant intestinal microbiota composition in association with maternal prenatal stress and infant health	Nested case-control design (n = 56)	Prenatal stress	Variations in the microbiome at postnatal days 7, 14, 28, 80, and 110	GI symptoms and allergic response by 3 mo of age	Infants exposed to prenatal stress displayed more GI symptoms (38% compared with 22%) and allergic reactions (43% compared with 0%), which were associated with variations in the microbiome. This microbiome was characterized by less lactic acid bacteria and *Akkermansia* and greater *Escherichia*, *Enterobacter*, and *Serratia*	83
Obesity and metabolism						
To analyze if the early-life microbiota composition is associated with childhood BMI and if antibiotic use modifies this association	Nested case-control design from 2 cohorts (Bibo cohort, n = 87; Flora cohort, n = 75)	Antibiotic treatment	Variations in the gut microbiome at 3 mo of age	BMI at 5–6 y	In the 3-mo-old microbiome, relative abundance of streptococci was positively associated with BMI at 5–6 y of age, and relative abundance of bifidobacteria was negatively associated with BMI at 5–6 y of age. Among children with a history of multiple antibiotic courses, the firmicutes phylum was significantly associated with BMI. However, microbiome composition was not measured at any other time point	84
To analyze the impact of diet on the early-life microbiome in a primate model	Primate model (high-fat versus standard diet)	Maternal high-fat diet during pregnancy and breastfeeding	Variations in the offspring microbiome composition	Shifts in microbial metabolic pathways	In this study, a link to a specific health outcome was not established. However, a maternal high-fat diet did alter the microbiome composition of offspring macaques, which persisted in juvenile macaques. Offspring displayed altered metabolic pathways on the basis of maternal diet. Additionally, these functional pathways (amino acid, carbohydrate, and lipid metabolism) correlated with abundances of specific gut bacteria	44

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To determine if the placental microbiome varies in association with birth wt	Prospective human cohort analysis (n = 24)	None	Variations in the placental microbiome composition	Birth wt	Low birth wt infants displayed lower gut microbiome richness and variations in the abundances of specific bacterial taxa compared with normal birth wt infants. *Lactobacillus* percentage was positively correlated with birth wt	24
To analyze the effect of early-life microbial perturbation with antibiotic treatment on host metabolism and adiposity	Mouse model (high-fat versus standard diet)	Antibiotic-induced	LDP exposure from birth through weaning	Body composition in adulthood	Compared with controls and mice exposed to long-term LDP, mice exposed to LDP for 4 or 8 wk after birth displayed elevated caloric intake and faster total mass and fat mass accumulation. The authors also report that the penicillin-selected microbiota can induce metabolic changes when transferred to GF mice	6
To better understand how early-life antibiotic use alters the gut microbiome composition and metabolic development	Mouse model (high fat versus standard diet)	Antibiotic-induced	Pulsed antibiotic treatment completed shortly after weaning	Body composition from 3–6 wk	Early-life pulsed antibiotic treatment accelerates total mass and bone growth. The authors also report that response to high-fat diet is altered depending on the particular antibiotic and number of courses used to perturb the microbiota	85
To analyze the impact of maternal prepregnancy BMI on the infant gut microbiome composition and functional potential	Nested case-control design (n = 39)	Maternal prepregnancy obesity	Variations in infant microbiome composition and function	Infant metabolism at 18 mo of age	Firmicutes were reported enriched in children born to mothers at a normal wt, whereas bacteroidetes were enriched in infants born to women who were obese. In this study, a link to an infant health outcome was not established, but differential microbiome metabolic functions that were based on whether infants were born to mothers at a normal wt or to women who were obese was identified	86
To investigate the effect of cadmium exposure on the early-life gut microbiota and metabolism in adulthood	SPF mouse model	Cadmium exposure 1 wk before parental mating	Variations in the microbiome composition observed at 8 wk and at adulthood (20 wk)	Body composition measured in adulthood	Cadmium exposure in parental mice resulted in increased fat accumulation in male offspring. Alterations in microbiome composition occurred before measurements of body composition. In addition, through microbiota transfer experiments, the group reported that fat accumulation was driven by the cadmium-exposed microbiome	87
To determine if the early-life gut microbiota composition is associated with wt development in early childhood	Nested case-control design (n = 49)	None	Variations in the microbiome composition between 6 and 12 mo of age	BMI measured at 7 y of age	Greater abundance of *Staphylococcus aureus* in children who were obese in infancy. Greater abundances of bifidobacteria in children at a normal wt in infancy	88

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To investigate the effects of early-life factors on the trajectory of gut microbial development and childhood adiposity	Prospective human cohort analysis ($n = 75$)	Gestational age and delivery mode	Variations in the microbiome before 6 mo of age	Adiposity at 18 mo of age	Infants with high *Bifidobacterium* and *Collinsella* at a later age displayed lower adiposity at 18 mo of age. Infants who acquired these taxa at 6 mo showed the lowest adiposity at 18 mo. In addition, acquisition of these bacterial taxa was influenced by length of gestation and delivery mode	89
To analyze the effect of subtherapeutic antibiotic administration on the gut microbiome and host metabolism	Mouse model of antibiotic-induced adiposity	Antibiotic-induced	Variations in the microbiome measured before sacrifice	Body composition measured in adulthood (16–20 wk)	The authors generated a mouse model of adiposity by exposing mice in early life to antibiotics. Variations in microbial composition before adiposity measurement was not assessed. However, the antibiotics did alter the microbiome composition, SCFA metabolism, and hepatic metabolism of fatty acids and lipids	90
To analyze the association between the early-life gut microbiome composition and BMI in childhood	Prospective human cohort analysis ($n = 138$)	None	Variations in the microbiome composition within the first year of age	BMI SD score between 1 and 3 y of age	Abundance of *Bacteroides fragilis* at 3 and 26 wk of age is associated with BMI SD score between 1 and 3 y of age. Abundance of *Staphylococcus* at 3 and 52 wk is inversely associated with BMI SD score between 1 and 3 y	91
Neurodevelopment						
To determine if limited nesting stress alters offspring microbiota, corticosterone levels, and intestinal permeability	Rat model of limited nesting stress	Limited nesting stress	Variations in the gut microbiome composition 21 d post birth (at weaning)	Limited nesting stress from postnatal days 2–10	Limited-nesting pups had hypercorticosteronemia, enhanced intestinal permeability, decreased microbial diversity, and variations in specific microbial taxa	92
To determine if maternal high-fat-diet-induced obesity is associated with social behavioral deficits and altered microbiota in the offspring	High-fat diet mouse model	Maternal high-fat diet	Variations in the gut microbiome composition in offspring	Behavior exams on 7–12-wk-old offspring mice	A maternal high-fat diet induces compositional variations in the gut microbiome of offspring mice. Offspring mice of mothers on a high-fat diet cohoused with mice born of mothers raised on a regular diet displayed normal social behavior. In addition, reintroduction of *L reuteri* (lacking in offspring mice of a mother on a high-fat diet) restored normal social behavior in these mice	93

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To determine if cognitive ability is associated with particular infant gut microbiota profiles	Prospective human cohort analysis ($n = 89$)	Group 2 was more likely to have been breastfed, less likely to have been born by cesarean delivery, and associated with white ethnicity. Having older siblings was associated with increased α diversity	3 groups of subjects were identified on the basis of their 1-y microbiome analysis	Cognitive outcomes at 1 and 2 y of age	Three groups of subjects were identified on the basis of their microbiome. Group 1 displayed high abundance of *Faecalibacterium*, group 2 displayed high abundance of *Bacteroides*, and group 3 displayed high abundance of ruminococcaceae. Individual Mullen scales differed between groups. α diversity was negatively associated with individual Mullen scales at 2 y of age (expressive language and visual reception)	94
To determine if maternal prenatal stress alters the microbial intrauterine environment and behavior in offspring	Mouse model of prenatal stress	Prenatal stress	Variations in placental microbiome and fecal microbiome of offspring	Anxiety-like behavior in offspring	Prenatal maternal stress was associated with variations in the microbiome of dams, offspring, and in the placenta. Additionally, prenatal stress is associated with increased IL-1β in the placenta and reduced brain-derived neurotrophic factor in placenta and adult offspring amygdala	7
To determine if probiotic administration in early life modifies maternal separation-induced gut dysfunction	Rat model (stress induced by maternal separation)	Maternal separation in early life (day 4 to day 19)	Variations in microbiome and gut function in offspring	Hypothalamus-pituitary-adrenal axis activity	Increased corticosterone levels and altered colonic mucosal barrier function in maternally separated rat pups. Early-life administration of probiotics (composed of *Lactobacillus rhamnosus* and *Lactobacillus helveticus* strains) to rat pups ameliorates these findings and persists to adulthood	95
To determine if early-life stress alters the gut-brain axis	Rat model (stress induced by maternal separation)	Maternal separation in early life	Variations in microbiome composition in rat pups	Symptoms of psychiatric disorders and irritable bowel syndrome	Increased plasma corticosterone and increased tumor necrosis factor-α and interferon-γ. Also, the microbiome composition varied in the maternally separated group compared with the rats that were not maternally separated	96
To examine the effects of prenatal and early-life exposure to propionic acid and LPS on offspring gut microbial metabolism, locomotor activity, and anxiety-like behavior	Rat model	None	Pre- and postnatal LPS or propionic acid exposure	Behavior traits in offspring	Prenatal propionic acid increased anxiety-like behavior in male and female adolescent offspring. Postnatal propionic acid increased anxiety-like behavior in female offspring only. Prenatal propionic acid and LPS induced developmental delays (including delays in eye opening)	97

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To determine if colonization by gut microbiota in early life impacts brain development and adult behavior	GF and SPF mouse models	None	Offspring of previously GF mice colonized with SPF microbiota	Behavior in adulthood	Adult colonized offspring displayed similar behaviors compared with SPF mice. These mice spent less time exploring the open arms in the maze (less locomotor activity). Additionally, colonized mice expressed less synaptophysin and PSD-95 in the striatum compared with GF mice, suggesting the microbiome is involved in programming brain development	98
To determine if a maternal high-fat-diet-altered microbiome can modify offspring behavior	Mouse model colonized with maternal high-fat-diet-shaped microbiota	Maternal high-fat diet	Female mice transplanted with high-fat diet microbiome	Behavior traits in offspring	Female mice were transplanted with a high-fat-diet- or control low-fat-diet-associated gut microbiome. Offspring of these mice displayed altered behavior in a sex-dependent manner. Offspring mice displayed less stress after maternal separation. Male offspring displayed decreased exploratory and cognitive behaviors, which is indicative of increased anxiety. Female mice displayed increases in adiposity and body wt	99
To analyze the microbial and molecular mechanisms that underlie the gut-brain axis	GF and conventionally raised mouse models	None	GF mice colonized after weaning	Neuronal activity in the amygdala	Absence of a microbiota in early life results in differential gene expression, exon usage, RNA editing, and upstream gene regulation in the amygdala. This was similar to mice who were raised GF for their entire lives but varied when compared with conventionalized mice	100
To examine whether variations in the vaginal microbiome are associated with varied offspring programming	Mouse model of prenatal stress	Prenatal stress	Variations in the maternal vaginal and neonatal gut microbiome	Metabolic and neurologic programming and in offspring	*Lactobacillus* abundance is decreased in the vaginal microbiome and in neonates born to dams exposed to early prenatal stress. Other bacterial population abundances also varied in offspring exposed to early prenatal stress. Early prenatal stress altered metabolic profiles and amino acid availability in the brain	101
Immune-mediated diseases (IBD, T1D, etc)						
To investigate age-dependent microbial modulation of iNKTs in mouse models of IBD and asthma	Mouse model of oxazolone-induced colitis	None	SPF-colonization during pregnancy lead to SPF-colonized offspring	Colitis induced later in life	Neonatal exposure to a conventional microbiota compared with GF conditions protected mice from oxazolone-induced colitis	76

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To determine if and how early-life exposure to antibiotics changes susceptibility to IBD	Mouse model DSS-induced colitis	Antibiotic-induced	LDP after weaning	Colitis induced later in life	LDP-treated mice displayed transient gut microbial compositional alterations, including eradication of segmented filamentous bacteria. In addition, after DSS-induced colitis, LDP mice displayed reduced colitis symptoms, Il-17 expression, and ileal Th17 differentiation compared with mice exposed to metronidazole, enrofloxacin, and controls. Finally, the authors report penicillin's effects are dependent on eradiation of segmented filamentous bacteria, implicating the microbiome as the mediator between this early life exposure and colitis development	102
To explore the influence of gut dysbiosis in the progression of T1D	NOD mouse model	Antibiotic-induced	Antibiotic treatment in early life (conception until 40 wk postnatal)	Spontaneous diabetes later in life	Antibiotics were administered to NOD mice from conception until 40 wk postnatal development. Treatment with antibiotics increased incidence of T1D in male mice. Antibiotic treatment also resulted in near ablation of the gut microbiome at 8 wk of age, which may partially explain the increased T1D incidence in male mice	103
To determine if exposure to prenatal antibiotics can protect offspring from T1D	NOD mouse model	Antibiotic-induced	Prenatal antibiotic treatment induced variations in offspring and maternal microbiomes	Spontaneous diabetes later in life	Prenatal neomycin and vancomycin treatment resulted in differential shifts in the offspring and maternal microbiomes. Offspring treated prenatally with neomycin were protected from T1D development, whereas offspring treated prenatally with vancomycin displayed accelerated T1D development. The antibiotic treatment also resulted in altered immune profiles, such as increased T-cell–mediated inflammation in mice treated with vancomycin and altered antigen-presenting cell phenotypes in mice treated with neomycin	104
To determine the impact of targeting Gram-negative gut bacteria at various time points in early life on T1D development	NOD mouse model	Antibiotic-induced	Prenatal antibiotic treatment induced variations in offspring microbiome	Spontaneous diabetes later in life	Pregnant, NOD mice treated with an antibiotic mixture (neomycin, polymyxin B, and streptomycin) were protected from T1D compared with mice treated postnatally. Microbiota transfer from these mice to untreated mice resulted in protection from T1D	105

TABLE 1 Continued

Research Objective	Study Population or Animal Model	Early-Life Factors and Timing of Exposure	Timing of Microbiome Analysis or Intervention	Health Outcome and Timing of Assessment	Summary of Findings	Ref. No.
To compare the effects of pulsed therapeutic antibiotics or continuous low-dose antibiotics in early life on T1D development	NOD mouse model	Antibiotic-induced	Pulsed antibiotic treatment induced variations in 6-wk-old microbiome	Spontaneous diabetes later in life	Pulsed postnatal treatment with tylosin altered the mouse microbiome and accelerated T1D development compared with mice treated with subtherapeutic penicillin from pregnancy to week 12	106
To analyze the association between the infant gut microbiome and T1D development	Prospective human cohort analysis ($n = 33$)	None	Variations in the microbiome before diagnosis with T1D	T1D diagnosis at ∼3 y of age	T1D disease state was distinguishable by the gut microbiome composition. Seroconverted subjects diagnosed with T1D displayed a marked decrease in α diversity before diagnosis when compared with seroconverted subjects not diagnosed with T1D and nonseroconverted subjects	107
To analyze the effect of peripartum cefoperazone administration on the maternal and offspring microbiota and IBD in the offspring	SPF IL-10 knock-out mouse model combined with DSS-induced colitis	Antibiotic-induced	Peripartum antibiotic treatment induced gut dysbiosis in offspring that persists to adulthood	Spontaneous colitis later in life	Peripartum exposure to cefoperazone increases risk of spontaneous colitis in offspring. Antibiotics also contribute to immune skewing and promote gut dysbiosis that persists to adulthood. Additionally, as demonstrated by fecal transplant to GF IL-10 knock-out dams, immune skewing is mediated by the antibiotic-induced dysbiosis	108
To analyze the impact of a maternal high-fiber diet on T-regulatory cell differentiation in the offspring	SPF GPR41−/− mouse model	Maternal high-fiber diet during pregnancy and breastfeeding	Increased plasma SCFAs	Increased thymic and peripheral T-regulatory cells	Compared with offspring from maternal mice fed a normal diet, high-fiber diet during pregnancy and breastfeeding resulted in increased plasma SCFAs in the offspring. These offspring also displayed higher frequencies of thymic and peripheral T-regulatory cells, which may be prompted by increased SCFA levels	46

AAD, allergic airways disease; CD4+, cluster of differentiation 4; CXCL16, chemokine ligand 16; DSS, dextran sodium sulfate; GI, gastrointestinal; GPR41, G protein–coupled receptor 41; GPR43, G protein–coupled receptor 43; Grx1, Glutaredoxin-1; HDAC9, histone deacetylase 9; IgA, immunoglobulin A; IL-1β, interleukin 1 beta; IL-10, interleukin 10; IL-17, interleukin 17; iNKT, invariant natural killer T cell; LPS, lipopolysaccharide; NOD, nonobese diabetic; PD-L1, programmed death ligand-1; PSD-95, postsynaptic density protein 95; Ref., reference; Th1, T-helper 1; Th17, T-helper 17; TLR, Toll-like receptor; T1D, type 1 diabetes.

3 months of age and an increased enterobacteriaceae/bacteroidaceae ratio at 3 months and 1 year of age, which was associated with increased food sensitization among 1-year-old children. Variations in the gut microbiome at 3 and 6 months of age have also been associated with the resolution of a milk allergy by 8 years of age.[75] Thus, authors of the current microbiome research for asthma and allergies suggest the time period between birth and 1 year of age as the developmental origins window for this disease. These immune hypersensitivities persist into later childhood and adulthood despite the transient nature of microbial dysbiosis.

Obesity

Similar to asthma and atopic disease, prospective studies reveal early-life gut microbiome compositional variations, which precede the development of obesity.[88,91] A recent study reveals temporal and compositional microbiome associations with early childhood adiposity.[89] Specifically, infants with high *Streptococcus* abundance at 6 months of age displayed increased adiposity at 18 months of age.[89] This emphasizes the importance of both microbiome composition and timing of microbiome maturation in the development of childhood obesity.

Mouse model studies have been used to mechanistically support the potential metabolic effects of early-life microbial dysbiosis and emphasize the obesity-inducing abilities of antibiotics. In a study by Cho et al,[90] antibiotics administered to mice in early life resulted in subsequent increases in adiposity and metabolic hormones. Cox et al[6] furthered this research by manipulating the early-life microbiota using low-dose penicillin (LDP). Here, they report LDP exposure during early life increased the effect of a high-fat diet on the microbiota, which could be transferred to GF mice to induce obesity.[6] It will be important for future researchers to incorporate both prospective human studies and animal models to determine the microbiome-associated effects of early-life antibiotic exposure on human health.

Neurodevelopmental Disorders

A less intuitive role of the gut microbiome in human health and development is the impact of early-life microbial dysbiosis in neurodevelopment (ie, the gut-brain axis). There is increasing evidence to support early-life microbial compositional variations in stress response and anxiety. In animal models, it is suggested that neonatal stress after maternal separation results in long-term compositional changes to the intestinal microbiota,[95,96] and treating rat pups with probiotics can counter the resulting elevated corticosterone levels.[95] Prenatal exposure to the SCFA, propionic acid, was also reported to increase anxiety-like behavior in mice.[97] In a recent study, Gur et al[7] report the influence of prenatal maternal stress in mice and its ability to alter both the maternal and neonatal intestinal microbiomes. Adult offspring exposed to prenatal maternal stress also displayed increased anxiety-like behavior.[7] Additionally, prenatal stress also induced variations in the placental microbiome.[7] This suggests that the intrauterine microbial environment is a potential mediator of maternal prenatal stress and resulting stress in the offspring.

Variations in the gut microbiome have also been associated with many facets of social behavior. Adult offspring of conventionalized dams (previously GF but colonized with the microbiome of specific pathogen–free [SPF] mice) were reported to display decreased motor activity compared with offspring from GF dams.[98] Buffington et al[93] report impaired social behavior (similar to that observed in autism spectrum disorder) in the offspring of dams that were fed a high-fat diet, which is mediated by variations in the offspring microbiome. In addition, using shotgun metagenomic sequencing, this group identified a significant reduction in *Lactobacillus reuteri* among the maternal high-fat diet–fed offspring.[93] Supplementation of drinking water with *L reuteri* resulted in restoration of offspring social deficits.[93] Notably, the majority of studies with researchers focusing on the early-life critical window in relation to neurodevelopment have been conducted in animal models. However, there is recent evidence to support a role of the infant gut microbiome in cognitive development in humans. Carlson et al[94] reported variations in gut microbiome α diversity in 1-year-old children, which correlated with their cognitive abilities measured at age 2. Additional studies in humans will substantiate this evidence. However, it is interesting to note that researchers consistently identify the time period between pregnancy and the first year of life as the most influential in human development.

Collectively, this disease-specific research is used to support a role of the early-life microbiome in fetal and childhood development in a variety of contexts. However, prediagnostic variations in the early-life microbiome composition have been associated with other chronic noncommunicable diseases in later childhood and adulthood (ie, IBD and type 1 diabetes, Table 1).[1] In addition, Harris et al[112] identified an association between adolescent diet and breast cancer diagnosed in adulthood, suggesting that the timing of susceptibility for the microbiome may also be disease specific. The future of research surrounding the microbiome in DOHaD is thus ripe with opportunity.

CONCLUSIONS AND FUTURE DIRECTIONS

In this review, we summarize evidence supporting the role of the microbiome as a fundamental part of human physiology and key to our understanding of DOHaD. Pre- and postbirth exposures alter the microbiome composition and functional potential in the neonate. In turn, this dysbiosis results in a number of health and disease outcomes later in life. Collaborative translational efforts using both animal models and human samples will mechanistically define the extent to which the microbiome plays a causal role during this critical window of developmental plasticity. Multiomics approaches, combining epigenetic, transcriptome, and microbiome analyses in large, prospective, human birth cohorts will enhance our current understanding of how the microbiome may interact with host components to drive aspects of infant development. In addition, as it is becoming clearer that the microbiota (both maternal and placental) can influence fetal development, more research surrounding the vaginal and intrauterine microbiomes is needed to paint a fuller picture of the fetal and neonatal origins of disease. We propose revisiting DOHaD and incorporating the microbiome into our current understanding of the many aspects of early human development associated with long-term health.

ABBREVIATIONS

DOHaD: Developmental Origins of Health and Disease
GF: germ free
IBD: inflammatory bowel disease
LDP: low-dose penicillin
NEC: necrotizing enterocolitis
SCFA: short-chain fatty acid
SPF: specific pathogen free

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