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REVIEW

Interactions of the maternal microbiome with diet, stress, and infection influence fetal development

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Humans and other animals contain multitudes of microorganisms including bacteria, fungi, and viruses, which make up a diverse microbiome. Across body sites including skin, gastrointestinal tract, and oral cavity there are distinct microbial niches that are made up of trillions of microorganisms that have co-evolved to inhabit and interact with the host. The microbiome also interacts with the changing environment. This tripartite interaction between the host, microbiome, and environment suggests microbial communities play a key role in the biological processes of the host, such as development and behaviors. Over the past two decades, emerging research continues to reveal how host and microbe interactions impact nervous system signaling and behaviors, and influence neurodevelopmental, neurological, and neurodegenerative disorders. In this review, we will describe the unique features of the maternal microbiome that exist during the perinatal period and discuss evidence for the function of the maternal microbiome in offspring development. Finally, we will discuss how the maternal environment interacts with the microbiome and nervous system development and then postulate how the maternal microbiome can modify early offspring development to have lasting influence on brain health.

Microbiome during pregnancy and early life

During pregnancy, the body undergoes striking changes in growth, metabolism, immunity, and cognitive function [1–5]. Concomitantly, the maternal microbiome, which consists of distinct oral, skin, breast milk, vaginal, and gut microbial communities, also experience notable changes in bacterial composition and abundance during pregnancy and up to 6 months postpartum [6–12]. Using metatranscriptomic sequencing, Gosalbes *et al.* described changes in the human maternal gut microbial transcriptome during pregnancy, noting in late pregnancy an increased expression of microbial genes that signal a state of increased carbohydrate and polysaccharide processing, and increased glucose storage in the form of glycogen [3]. Similarly, shotgun metagenomic sequencing of nonhuman primate fecal microbiomes revealed increased abundance of pathways associated with carbohydrate metabolism and transport [13]. A separate study using shotgun metagenomics on stool samples collected every 3 weeks from 10 pregnant women showed diverse gut microbial communities and enrichment of fermentation pathways [7]. These gene changes are coupled with distinct microbiome changes that occur during pregnancy [7].

The oral microbiome of pregnant women is diverse but remains stable, with little changes in abundance [7,14,15]. Like the oral microbiome, the breast milk microbial diversity remains relatively stable and is

Abbreviations
ABX, antibiotic-treated; BDNF, brain-derived neurotrophic factor; E, gestational or embryonic day; GF, germ-free; LPS, lipopolysaccharide; poly I:C, polyinosinic:polycytidylic acid; SCFAs, short-chain fatty acids; SPF, specific pathogen-free.

dominated by *Staphylococcus* and *Streptococcus* during lactation [8,16]. Conversely, during the course of pregnancy the gut and vaginal microbiome experiences selective shifts in microbial communities [6,7,16,17]. The vaginal microbiome undergoes significant changes, including lower richness and diversity, and increased abundance of *Lactobacillus* species, bacteria that regulate vaginal pH [7,8,14,15,17]. Pregnancy is characterized by changes in hormone levels, metabolic demand, and immune state in response to the developing fetus. Levels of secreted hormones such as progesterone and estrogen increase dramatically. Metabolic adaptations include an exchange from anabolism during the initial stages of pregnancy to increase energy storage, followed by a shift to catabolism to support fetal growth towards the end of pregnancy. Complex immune changes that range in inflammatory states occur to support implantation, placentation, fetal growth and development, and delivery of the baby [18]. Correspondingly, the maternal gut microbiota dynamically remodels during the different phases of pregnancy. In several prospective studies, healthy pregnant women show changes in gut microbiota diversity from the first to the third trimester, including a decrease in Firmicutes, increase in Bacteroidetes and increased *Proteobacteria* and *Actinobacteria* [9,10,19]. While in a separate longitudinal study of 40 pregnant women (11 women delivered preterm) in the United States, the researchers used a linear-mixed effects model to measure alpha diversity throughout gestation and found no difference in vaginal, gut, tooth, or salivary microbiome composition [15]. Notably, abundance and diversity changes seen in the pregnant gut microbiota of humans are similarly observed in animal models. For example, in the pregnant gut microbiota of nonhuman primates, rodents, and sows, there was increased abundance of *Alloprevotella*, *Lactobacillaceae*, *Lachnospiraceae*, and *Coriobacteriaceae* [13,20,21]. However, exactly how the human maternal microbiota at different stages of pregnancy informs obstetric outcomes, maternal health, and fetal health requires more investigation.

While controversial, there are reports investigating the presence of the placental microbiome. Aagaard *et al*. used whole genome sequencing and identified a placental microbiome composed of nonpathogenic microbes from the phyla *Firmicutes*, *Tenericutes*, *Proteobacteria*, and *Bacteroides*, and a composition that was most similar to the oral microbiome or nonpregnant controls [22]. 16S rRNA gene sequencing of the placental microbiome from monozygotic twins showed a distinct placental microbiome which was significantly different from maternal skin, vaginal, fecal, and infant fecal microbiomes [23]. However, other groups have failed to identify significant levels of 16S bacterial gene sequences using 16S rRNA gene sequencing or shotgun metagenomic sequencing from placental samples [24]. Additionally, in mouse models, researchers were not able to identify a unique placental microbiome [25]. Evidence supporting the existence of a placental microbiome is contradictory but if a placental microbiome is indeed present, further studies are needed to confirm its functional significance for obstetric, maternal, and offspring health outcomes.

The microbiome is vertically transmitted from the mother to the infant, whereby the composition of the initial colonization of the infant gut microbiome is determined by mode of delivery and is further shaped by environmental factors such as antibiotics exposure and diet such as breast-fed vs formula-fed [26–34]. While some recent reports suggest amniotic fluid contains low abundance of bacterial DNA, as identified by 16S rRNA gene sequencing and proteomics, this does not confirm a microbiota in amniotic fluid from healthy pregnancies as there is no significant number of live bacteria, suggesting the maternal microbiota during pregnancy likely impacts the fetus through metabolites [35–38]. Thus, the changes in the maternal microbiota during pregnancy and the early postpartum period suggest that the maternal environment and factors influencing it can play key roles in maternal health, obstetric outcomes, and the growth and development of the offspring.

Environmental factors and the gut microbiome

Exposure to environmental factors such as perinatal stress, nutritional status, and maternal immune activation during pregnancy and postparturition informs the overall growth and developmental trajectory of the offspring. These environmental factors can disrupt and interact with the maternal microbiomes to impose a lasting influence on offspring development [29,39–42]. As a critical component of the pregnancy environment, the maternal microbiome modifies immune, metabolic, and brain developmental processes that can have long-term consequences on offspring health outcomes. While a number of studies describe associations between alterations of the maternal gut microbiome and offspring outcomes, few studies outline mechanisms directly linking specific maternal gut microbes to offspring outcomes. More studies are needed to elucidate how interactions between the microbiome and external factors during pregnancy contribute to specific brain and behavioral alterations in the offspring.

Table 1. Human studies of interactions between the microbiome and environmental factors.

Model	Impact on maternal gut microbiome	Impact on offspring gut microbiome	Impact on offspring	Reference
Gestational stress				
Adverse childhood experiences (childhood)	↑ *Prevotella* (20–26 weeks gestation)			Hantsoo *et al.* [39]
Prenatal general anxiety (0–39-week gestation)	↑ *Oxalobacter*, *Rothia*, *Acetotomaculum*, *Staphylococcus*, and *Acidaminococcus* (third trimester)			Hechler *et al.* [46]
Prenatal stress and cortisol levels (third trimester)			Increased Proteobacterial taxa Decreased Lactobacillus, Lactococcus, Aerococcus, and Bifidobacteria	Zijlmans *et al.* [45]
Maternal diet				
Reduced fat and increased complex carbohydrate diet (24–28-week gestation)	↑ *Bifidobacteria* (30–31 or 36–37 weeks of gestation)	↑ Postnatal Alpha diversity (2 weeks, 2 months, and 4–5 months old)	Reduced postnatal obesity diagnosis and promoted healthy postnatal immune development (birth, 2 weeks, 2 months, and 4–5 months old)	Sugino *et al.* [32]
Maternal high-fat diet (third trimester)		↑ Postnatal *Enterococcus* ↓ Postnatal *Bacteroides* (birth)		Chu *et al.* [29]
Maternal vegetarian diet (0–16-week gestation)	↑ *Lachnospiraceae* and *Roseburia* ↓ *Collinsella* and *Holdemania* (0–16-week gestation)			Barrett *et al.* [59]
Maternal infection				
Maternal SARS-CoV-2 infection (anytime during gestation)	↑ *Dialister* ↓ *Bacteroides* (before delivery)	↑ Prenatal *Enterococcus* ↓ Prenatal *H. parainfluenzae* (1–2 days old)		Leftwich *et al.* [70]
Maternal HIV infection (20–39-week gestation)	↑ *Actinomyces* and *Clostridium* ↓ *Bacteroides* and *Bifidobacterium* (20–39 weeks of gestation)		Association with birth weight	Chandiwana *et al.* [71]

Gestational stress

The effects of gestational stress on the microbiome

Prenatal stress refers to psychosocial or physical stress experienced during pregnancy, affecting up to 78% of pregnant individuals [43]. Maternal stress increases the risk of pre-eclampsia, preterm birth, and low birth weight [44]. Additionally, high maternal prenatal stress is associated with alterations in the infant microbiota (birth to 110 days of life) including increased Proteobacteria taxa and decreased lactic acid-producing bacteria compared to infants from low maternal stress (Table 1) [45]. The maternal gut microbiota also changes in response to stress experienced during pregnancy. In a study of 70 pregnant women from the Netherlands, general anxiety throughout pregnancy was associated with increased abundance of the genera *Oxalobacter*, *Rothia*, *Acetitomaculum*, *Acidaminococcus*, and *Staphylococcus*, but did not affect richness or diversity [46]. In late gestation, mothers that had decreased perceived stress, as measured using the Perceived Stress Scale-10, displayed a more diverse gut microbiome [47]. In a recent study, pregnant women with high scores in the Adverse Childhood Experience (ACE) survey, a self-reported measure of childhood abuse and

neglect, exhibited increased abundance of *Prevotella* and a trending decreased abundance of *Erysipelotrichaceae* and *Phascolarctobacterium*. However, they did not display significant inflammatory response to acute stress, contrary to prior evidence that exposure to childhood adversity is associated with an exaggerated pro-inflammatory response [39]. Interestingly, an exploratory analysis of results from pregnant women with high ACE scores and high dietary intake of polyunsaturated fatty acids (PUFAs) showed a reduced inflammatory response to acute stress, suggesting PUFAs may have protective effects on populations exposed to stress [39]. Overall, the changes in the microbiome are inconsistent, and the exact effects on obstetric outcomes, maternal-fetal health, and postnatal offspring health remain to be defined. Future studies with standardized characterization of stress (when, type, frequency) along with mechanistic research examining the interactions between stress, the microbiome, maternal inflammatory state, and fetal and postnatal offspring health are needed.

Linking the effects of gestational stress and microbiome interactions on offspring development

Although prenatal stress appears to modify the maternal gut microbiome, it is also linked to alterations in the infant gut microbiota (birth to 110 days of life), including increased Proteobacteria taxa and decreased lactic acid-producing bacteria compared to infants from low maternal stress [45]. To better understand the effects of gestational stress on offspring development, we turn to animal models. In a model of maternal stress, gestating rats were exposed to chronic unpredictable stress, which induced maternal depression-like behaviors along with decreased abundance of *Ruminococcaceae* and increased abundance of *Prevotellaceae* in the pregnant dams compared to unstressed controls (Table 2) [48]. Jašarević *et al*. demonstrate that early variable prenatal stress during days 1–7 of gestation, such as restraint stress, predatory odor exposure, noise stress, and unstable home cage environment, also altered the gut microbiome diversity and composition in murine dams during pregnancy and postpartum [49]. However, it is unclear whether microbiome changes were the direct result of stress or an indirect result of depression-induced factors such as reduced physical activity and liquid consumption. Such alterations in the maternal gut microbiome following prenatal stress can be vertically transmitted to impact offspring behavior and development. In a model of chronic restraint stress during gestation, stressed pregnant mice exhibited altered gut microbiome composition that coincided with changes in gut microbial community structure in both female and male offspring compared to nonstressed controls [50,51]. In a separate study, postnatal day 28 male offspring that experienced early prenatal stress showed differential community structure compared to unstressed male controls, but this microbiome change was not observed in female offspring [52]. These findings are further supported in a nonhuman primate model, whereby prenatal stress was induced in pregnant females using a 6-week acoustic startle paradigm during early or late gestation. Offspring gut microbiota from stressed dams displayed reduced *Lactobacillus* spp. and *Bifidobacterium* spp. compared to unstressed controls [53]. Together, these findings suggest maternal stress during gestation can regulate maternal microbiota and offspring microbiota.

Gestational stress had differential effects on female and male offspring's brain and behaviors. For example, female offspring that experienced prenatal stress displayed increased amygdala IL-1β mRNA, decreased amygdala BDNF, decreased novel object preference, and increased anxiety-like behavior compared to unstressed controls [50,51]. Whereas male offspring had increased cortical IL-1β and IL-6 mRNA, decreased cortical serotonergic metabolism, decreased social interactions, and increased corticosterone levels in response to social interactions [51]. In a separate study, control offspring that were gavaged with vaginal inoculant from dams exposed to early prenatal stress showed reduced abundance of *E. coli*, *S. acidominimus*, and *S. thoraltensis* DSM 12221 in the gut along with increased plasma corticosterone levels compared to untreated controls [52]. Additionally, the male offspring also displayed changes in the paraventricular nucleus transcriptome, suggesting prenatal stress exposure and the vaginal microbiota can predispose the offspring to stress-induced alterations in the brain [52].

While these results demonstrate dynamic interactions between the gut microbiome and prenatal stress, how stress at different stages of pregnancy changes the maternal nutritional, endocrine, or immune environments to inform maternal gut and offspring bacterial communities warrants further investigations. Future studies, such as microbiota transplants, select bacteria colonization, or cross-fostering experiments will be needed to elucidate how prenatal stress may directly alter offspring brain and behaviors, and how maternal vs offspring microbial changes may mediate stress effects on brain and behavioral responses.

Maternal diet

Diet is a potent modulator of the gut microbiome [54–56]. How maternal diet during pregnancy impacts the structure of the maternal gut microbiome, the

Table 2. Animal studies of interactions between the microbiome and environmental factors.

Model	Impact on maternal gut microbiome	Impact on offspring gut microbiome	Impact on offspring	Reference
Gestational stress				
Chronic unpredicted mild stress (E0-21)	↑ *Prevotellaceae* ↓ *Ruminococcaceae* (E22)			Wang *et al.* [48]
Early prenatal stress (E1-7)	↑ *Mucispirillum* (E0-birth)	↓ Postnatal *Lactobacillus* and *Streptococcus* (2, 6, 28 days old)		Jašarević *et al.* [49]
Prenatal restraint stress (E10-16)		↑ Postnatal Proteobacteria ↓ Postnatal Bacteroidetes (4 months old)	Postnatal memory deficits and decreased amygdala BDNF at postnatal timepoints (4 months old)	Gur *et al.* [51]
Acoustic startle stress (E50-92 and 105–147)		↑ Postnatal *Lactobacillus* and *Bifidobacterium* (2 days old, 2, 8, 16, and 24 weeks old)		Bailey *et al.* [53]
Maternal diet				
Maternal high-fat diet (8 weeks prior to mating-weaning)		↓ Postnatal microbial diversity (7–8 weeks old)	Impaired sociability, Decreased number of oxytocin+ neurons in PVN at postnatal timepoints (7–8 weeks old)	Buffington *et al.* [65]
Maternal high-fat diet (transplantation 10 days prior to mating and every 2 weeks throughout gestation)	↑ Bacteroidetes (gestation and lactation) ↓ Firmicutes (gestation and lactation)	↓ Postnatal Firmicutes (birth and 12 weeks old)	Increased postnatal body weight and adiposity in females (8, 10, and 21 days old). Increased postnatal stereotyped and compulsive behavior in males (10–12 weeks old)	Bruce-Keller *et al.* [64]
Maternal high-fat diet (12 weeks prior to mating-weaning)	↑ Verrucomicrobia ↓ Proteobacteria	↑ Postnatal *Bacteroides* ↓ Postnatal *Allobaculum* (8–10 weeks old)	Long-term memory deficit Impaired sociability at postnatal timepoints (8–10 weeks old)	Liu *et al.* [68]
Maternal high-fat diet (6 weeks prior to mating-E18.5)	↑ *Akkermansia* and *Clostridium* ↓ *Lachnospiraceae* and *Ruminococcus* (E0.5-E18.5)		Increased prenatal intestinal NFKB (E18.5)	Gohir *et al.* [63]
Maternal low-fat diet (E0-P0)	↑ Firmicutes ↓ Bacteroidetes (E18.5)		Increased anxiety-like behavior, impaired locomotor ability at postnatal timepoints (6 weeks old)	Yu *et al.* [67]
Maternal immune activation				
Poly I:C (E12.5)	↓ Alpha diversity (after E12.5)		Immune primed postnatal phenotype via epigenetically primed CD4+ cells (7–8 weeks old)	Kim *et al*, 2022 [74]
Poly I:C (E12.5)	Presence of *Segmented filamentous bacteria* (7 days prior to mating-P0)		Increased anxiety and repetitive behaviors social deficits at postnatal timepoints (8–12 weeks old)	Kim *et al.* [73]
Poly I:C (E12.5)		↑ Postnatal *Porphyromonadaceae*, *Prevotellaceae* and *Lachnospiraceae* (8–10 weeks old)	Increased stereotyped behavior and social deficits at postnatal timepoints (6 weeks old)	Hsiao *et al.* [75]

establishment of the offspring gut microbiome and fetal and postnatal offspring development is an active area of investigation.

The effects of maternal diet on maternal and offspring gut microbiome in humans

Chu *et al*. evaluated 81 pregnant women that consumed a diet that was higher in fat compared to controls, as measured by a dietary questionnaire on fat, sugar, and fiber intake during late third trimester and 4–6 weeks postpartum. The neonatal gut microbiome from the maternal high-fat diet during pregnancy was distinct compared to control groups that had lower fat intake during pregnancy, including enrichment of *Enterococcus* and decreased abundance of *Bacteroides*. This was not a result of differences in prepregnancy BMI, antibiotic usage, mode of delivery, gestational diabetes, or gestational weight gain [29]. While the maternal gestational high-fat diet-induced persistent changes from the neonate to the 6-week infant microbiota, the neonatal and infant gut microbiome from controls also showed significant taxonomic changes, indicating early life is a period of general gut microbiome restructuring. Notably, relative abundance of *Bacteroides* was significantly decreased in neonates and 6-week-old, infants from the maternal high-fat gestational diet group compared to controls, therefore, further mechanistic studies are needed to elucidate the role of *Bacteroides* species in offspring development and how *Bacteroides* species may protect against the adverse effects of maternal gestational high-fat diet [29]. In contrast, in a separate study of pregnant women, those that consumed more fat, sodium, and protein in the third trimester, according to questionnaire responses, were associated with a gut microbiome that was dominated by *Bacteroides* [57]. It is important to note the variations between the two studies, including how the questionnaires were designed, what was considered a maternal 'high-fat diet', how increased consumption of other nutrients such as sodium and protein may affect results, and whether maternal or offspring microbiota was characterized.

Other diets consumed during pregnancy such as a high-fiber diet, vegetarian diet, omnivorous diet, and the intake of vitamins and cholesterol contribute to varying shifts in the microbiota. For example, in early pregnancy of overweight women, fiber intake was positively associated with maternal gut microbiota diversity and richness. In contrast, a low-fiber and high-fat diet was associated with increased *Bacteroidaceae* family in the maternal gut microbiota and linked to increased low-grade inflammation marker GlycA, raising the question of how diet and microbiome interactions can inform inflammatory state during pregnancy [58]. On the other hand, the early gestational microbiota of pregnant women that consumed a vegetarian diet displayed reduced beta diversity, lower abundance of *Collinsella*, *Holdemania*, *Eubacterium*, increased abundance of *Lachnospiraceae* and *Clostridium*, and had a gut microbiome that correlated with more acetate and butyrate production compared to omnivore controls [59]. Moreover, women who consumed more vitamin D, cholesterol, and mono-unsaturated fat during the second trimester of pregnancy had a gut microbiota shortly following delivery that displayed increased abundance of *Proteobacteria*, which is a phylum associated with pro-inflammatory properties. Conversely, those who consumed more vitamin E, protein, and saturated fats had decreased abundance of *Proteobacteria* [60]. Others observed vitamin D supplementation during pregnancy had no significant effect on the late pregnancy gut microbiome diversity but prevented the enrichment of *Desulfovibrio*, a sulfate-reducing bacteria that is associated with intestinal inflammation [61]. Together, these studies illustrate how composition of the maternal diet can differentially modify the maternal and offspring gut microbiota. More clinical studies with detailed tracking of maternal diet during the perinatal period are needed to tease apart how changes in the maternal or offspring gut microbiota induced by different diets at different stages of pregnancy or postpartum can impact maternal health and offspring growth and developmental trajectories.

Probing effects of maternal high-fat diet and gut microbiome interactions on offspring development

Preclinical studies begin to elucidate how diet consumed during pregnancy alters the maternal and offspring gut microbiome to impact offspring development, brain, and behaviors (Table 2). In the macaque, maternal high-fat diet during gestation altered the abundance of indigenous gut bacteria in the dam including decreased *Treponema* and increased *Prevotella* compared to isocaloric control diet groups [62]. To explore the temporal effects of diet on the offspring microbiome, macaque offspring from dams on control or high-fat diet during pregnancy were maintained on the same diet until weaning (6–7 months postbirth), after which, offspring from each group were given the same or opposing diet (control or high-fat diet) after weaning displayed persistent microbiome composition at 1 year of age that was nominally modified by postweaning diet. Control diet

postweaning could partially normalize offspring microbiota from the maternal high-fat diet cohort, however, dietary exposure during gestation and breastfeeding were more likely to determine postweaning offspring microbiome community, suggesting *in utero* and early postnatal environment is a period of unique susceptibility for microbiome programming [62]. Gohir and colleagues demonstrated that a high-fat diet during gestation in a murine model altered the maternal gut environment during gestation including decreased abundance of cecal short-chain fatty acids, increased abundance of *Akkermansia* and *Clostridium*, decreased abundance of *Ruminococcus*, and *Lachnospira*, impaired gut barrier integrity and elevated intestinal inflammation compared to control dams [63]. Correspondingly, high-fat diet during gestation and changes to the maternal gut environment were associated with altered placental growth and development including increased expression of markers for hypoxia, atypical placental vasculature, decreased placental carnitine metabolites, and increased nuclear factor-kappa B activation in the fetal small intestine [63]. These results suggest gestational high-fat diet has long-ranging consequences that extend beyond the maternal microbiota to influence obstetrics and fetal development.

To examine the causal effects of a maternal high-fat diet-associated microbiota on offspring development researchers employ gnotobiotic techniques. One study used cecal and colonic high-fat microbiota to colonize antibiotic-treated female mice that were maintained on a control diet and paired for breeding. The maternal high-fat diet-associated microbiota decreased vocalization in male and female offspring, perturbed exploratory, stereotypical, and compulsive behaviors in male offspring, and increased adiposity and body weight in female offspring, compared to control diet offspring [64]. Both male and female offspring from dams with the high-fat diet-associated microbiota displayed significant differences in their microbiota community composition compared to control offspring, suggesting maternal microbiota differences may not account for all behavioral differences, rather the postnatal microbiota may contribute to sex-specific effects on behaviors [64]. In a separate study, dams were maintained on a high-fat diet from 8 weeks before breeding until offspring were weaned and subsequently placed on the control diet. The 7–12-week-old male offsprings displayed gut microbiota changes, decreased oxytocin neurons in the hypothalamus, social deficits, and attenuated long-term potentiation in the ventral tegmental area following social interaction compared to male offspring from dams that were consecutively maintained on a control diet [65]. Interestingly, by maintaining female mice on high-fat diet from 6 weeks before breeding until offspring were weaned can impact first- and second-generation offspring microbiome and behaviors. The first-generation female offspring from maternal high-fat diet dams have reduced microbial richness compared to control diet offspring. The second-generation male and female offspring did not exhibit microbiota differences but displayed abnormal social function in the three-chamber social interaction test, suggesting behavioral deficits are in part determined by the maternal microbiota rather than intrinsic offspring microbiota [66]. Given the disruption of the microbiota and behavioral deficits were primarily observed in male mice, future studies are needed to determine whether male offspring from dams on a maternal high-fat diet could elicit microbiota or behavioral deficits in second-generation offspring.

Levels of fiber content in the maternal diet during pregnancy can impact offspring development. For example, low-fiber diet during gestation was associated with a maternal gut microbiota that had decreased *Bacteroides* and increased *Firmicutes* abundance and reduced maternal serum levels of propionate and butyrate compared to normal fiber diet controls. Offspring from maternal low-fiber diet dams displayed impaired synaptic plasticity and cognitive function compared to normal fiber diet controls. The neurocognitive deficits could be prevented by maternal supplementation with butyrate during gestation, suggesting gestational manipulations of microbial metabolism or metabolite signaling pathways can support development of neural circuits [67]. Similarly, in a model of maternal high-fat diet, high-fiber intake during gestation or supplementing offspring with acetate and propionate after weaning, prevented, or reversed cognitive and social behavioral deficits in the offspring, implicating short-chain fatty acids as key players of the maternal microbiota and its effects on offspring development [68]. Together, these reports demonstrate the maternal gut microbiota during pregnancy and early postnatal period responds to diet to influence offspring microbiota and brain and behaviors.

Maternal immune activation

Infection during pregnancy modifies the human maternal microbiome

Previous studies have shown the pregnant population is particularly vulnerable to infectious diseases, for reasons that are not clearly known [69]. While there are numerous studies of maternal infection, review of existing literature reveals few clinical studies have

investigated the impacts of infection during pregnancy while considering the role of the maternal microbiome. SARS-CoV-2 infection during pregnancy, particularly during the first trimester, showed decreased alpha diversity in maternal gut and vaginal microbiome compared to uninfected controls [70]. Similarly, in a study conducted in Zimbabwe, HIV-infected pregnant women displayed reduced species richness in gut microbiota, which was characterized by reduced abundance of *Clostridium*, *Turicibacter*, *Ruminococcus*, *Parabacteroides*, *Bacteroides*, *Bifidobacterium*, *Treponema*, *Oscillospira*, and *Faecalibacterium*, and increased abundance of *Actinomyces* and *Succinivibrio*, however, the investigators did not find differences in the HIV-associated microbiota that correlated with immune competence, such as levels of CD4+ cells [71]. Taken together, there is emerging clinical research that supports interactions between maternal infection during pregnancy and the maternal microbiota. To better understand how the interactions between gestational immune activation and the gestational maternal microbiota can impact offspring health outcomes, future investigations will need to move beyond microbiota profiling.

Animal models of maternal immune activation reveal interactions with the microbiota to influence offspring development

In preclinical settings, immune activation following exposure to bacteria and viruses can interact with the maternal gut microbiota to influence offspring development (Table 2). For example, the gut microbiota from pregnant macaques infected with the bacteria *Listeria monocytogenes* during the first trimester displayed decreased alpha diversity, loss of microbial richness, and minor changes in abundance of *Eubacterium ruminantium*, *Methanobrevibacter*, *Prevotella*, and *Treponema* genera compared to nonpregnant controls [72]. Microbial changes were not significantly associated with incidence and severity of diarrhea observed in *L. monocytogenes* exposure or pregnancy. How these bacterial community changes contribute to maternal health, pregnancy outcomes, and offspring growth and development remain to be elucidated.

To begin parsing the effects of maternal infection and microbiota interactions on offspring development, researchers use animal models of pregnant dams exposed to viral (poly I:C, Zika virus) or bacterial (LPS) infections. In one study, pregnant dams were treated with poly I:C at E12.5. This induced cortical patches in the dysgranular zone of the primary somatosensory cortex and alterations in social, repetitive, and anxiety behaviors in male offspring. Notably, dams that were natively colonized with the bacterium-segmented filamentous bacteria (SFB) were more likely to yield offspring with brain morphological and behavioral deficits compared to dams without SFB in their gut microbiota [73]. Further investigation suggests SFB in the maternal gut regulates the number of Th17 cells in the maternal small intestine and levels of IL-17 in maternal plasma IL-17 levels to mediate the effects of maternal infection on offspring brain and behaviors through neuroimmune interactions [73]. In the same poly I:C maternal immune activation model, Kim *et al.* demonstrate postnatal offspring from maternal infection dams were more susceptible to developing intestinal inflammation in response to *C. rodentium* exposure compared to untreated controls [74]. Exactly how this heightened inflammatory state in the offspring contributes to neuroinflammation and regulates neurobehavioral outcomes requires further investigation. In a separate study, poly I:C administration into pregnant dams at E12.5 yielded offspring with increased abundance of *Porphyromonadaceae*, *Prevotellaceae*, and *Lachnospiraceae* in the gut microbiota and increased levels of serum metabolites including 4-ethylphenylsulfate. Probiotic treatment with the bacteria *B. fragilis* in adult offspring from poly I:C treated dams rescued sensorimotor, repetitive, anxiety-like and communication behaviors, ameliorated gut permeability issues, and normalized serum metabolite levels, cytokine production, and tight junction gene expression, suggesting there is a postnatal window for microbes and microbial metabolite interventions [75].

In a study of Zika virus infection during pregnancy (E4-7) in mice, the presence or absence of the microbiota modulated offspring susceptibility to infection, whereby comparison of infection rates between SPF and GF dams revealed 78% of pregnant GF dams were infected while 25% of pregnant SPF dams were infected following exposure to Zika virus [76]. Additionally, offspring from SPF dams were less likely to display fetal growth impairments and placental infections compared to offspring from GF dams, suggesting the microbiota may regulate immune development of the placenta in response to infection to protect the pregnancy and fetus [76].

Finally, in model of maternal bacterial infection, pregnant rats were intraperitoneally injected with lipopolysaccharide (LPS), a bacterial cell wall component, on E17. The pregnant dams showed increased levels of calprotectin in the gut, a marker of intestinal inflammation. The postnatal maternal and neonatal brain showed increased APP, β- and γ-secretase, and decreased gene expression of brain-derived

neurotrophic factor (BDNF) [77]. Further, administering probiotics to LPS exposed dams dampened the LPS-induced increase in APP, β-secretase, and γ-secretase levels in neonatal brains, and partially normalized BDNF gene expression in the maternal and offspring brain. The dual effects of infection on maternal gut inflammation and maternal brain gene expression suggest the effects on offspring can be mediated by inflammatory signals or maternal health and behaviors. Together, these studies demonstrate the type of infection, severity of infection, and when the infection occurs can variably modify the maternal microbiota to shape offspring development.

Maternal microbiome impacts offspring immune, metabolic, and brain development

The maternal microbiome influences offspring immune development

The homeostatic and disrupted maternal microbiota during pregnancy plays a key role in shaping offspring immune development. Nyangahu *et al*. reported that disrupting the mouse maternal gut microbiome during pregnancy using vancomycin altered the 14-day postpartum maternal and offspring gut microbiota, increased number of lymphocyte and CD4+ T cells in the 14-day postnatal offspring, and altered maternal immunity as evidenced by increased IgG and IgM in breast milk [78]. While disruption of the maternal microbiota during pregnancy may directly influence offspring immunity, postpartum factors such as immune changes in breastmilk can also influence offspring microbiota and immunity [78]. Further, offspring from GF dams or dams treated with antibiotics displayed abnormal antibody response following immunization with Ovalbumin and complete freund adjuvant, underscoring the importance of a complex maternal gut profile to ensure immune development and appropriate immune response in the postnatal offspring [79]. Pregnant mice that were treated with poly I:C at E12.5 displayed reduced alpha diversity in the maternal gut microbiome and their postnatal offspring displayed an exaggerated immune response to *C. rodentium* infection as characterized by increased colonic IL-17A, INF-γ producing T cells, and CD4+ T cells [74]. In a separate study, pregnant GF murine dams that were transiently colonized (E4-E15—gestational colonization) during pregnancy with Escherichia coli HA107, a unique strain that does not persist in the intestine, yielded pups with increased intestinal group 3 innate lymphoid cells and alterations in the intestinal transcriptome compared to uncolonized GF controls [80]. Further, the effects of gestational colonization on offspring immune development require dam's antibodies and microbial metabolites that passed across the placenta to fetus and was present in maternal milk and postnatal offspring [80]. Additionally, systemic or intestinal postnatal colonization of adult GF mice with E. coli HA107 affects B cell repertoires, and combined or sequential exposures to transient microbial taxa affect IgA and IgG clonal diversity [81]. This suggests the source, timing, and order of microbial taxa exposure during gestation can have differential impacts on postnatal offspring immune development and responses. Further, pups from dams colonized with a defined consortia of eight bacteria, altered Schaedler flora, displayed increased NKp46+ ILC3 and F4/80 + CD11c + iMNC populations compared to pups from GF dams [80]. Studies like these illustrate the importance of the maternal microbiota before and after birth in establishing a healthy immune profile in the offspring.

The maternal microbiome regulates offspring metabolic development

Gnotobiotic animal models are also used to study the effects of maternal microbiome on fetal growth and metabolism. For example, differential gene expression analysis and metabolomics in intestinal tissue from SPF and GF fetuses reveal gene changes in lipid metabolism, aromatic compound biosynthesis, and tRNA metabolism and strongly associated with TMAO, 5-AVAB, Glu-TRP, and fatty acid derivatives, with these metabolites being down regulated in GF compared to SPF controls [82]. Postnatal offspring from GF dams that are postnatally conventionalized are still more susceptible to metabolic dysfunction, such as increased glucose intolerance and increased weight gain compared to SPF controls [83]. Notably, certain metabolic features such as glucose intolerance were ameliorated by maternal supplementation with short-chain fatty acids, consistent with studies demonstrating short-chain fatty acid supplementation during gestation can ameliorate diet-induced deficits in offspring brain and behaviors [66,67,83]. In a murine model, Lopez-Tello *et al*. reported that E18.5 fetuses from GF dams displayed reduced fetal weight and liver size and were hypoglycemic at E16.5 compared to those from conventionally colonized dams [84]. Supplementation of GF dams with *B. breve* up regulated fatty acid transporter levels in the placenta, altered placental structure, and upregulated pathways involved in oxygen transport-binding and hemoglobin in fetal livers [84]. Given that both the

microbiota and liver play an important role in nutrient metabolism, changes in liver size and expression of genes related to liver function suggest the altered metabolic output of GF mice may in part be due to the absence of the microbiota and microbiota-induced liver abnormalities. Further investigation on liver morphogenesis and metabolic efficiencies in offspring from different microbiota conditions are needed.

While the causal effects of microbial metabolites on gene expression continue to be explored, a comprehensive metabolomic profiling of fetal intestine, fetal brain, and placenta from conventionally colonized and GF animals can begin to unravel the role of the homeostatic maternal microbiota and metabolites. In a study using a sheep model, modifying the maternal microbiota using diet showed changes in maternal metabolites including pyroglutamic acid, methionine, oleamide, CAR(3:0 (OH)), and 15-HeTrE, exactly how these metabolites contribute to fetal development will require further studies [85]. E18 GF fetal brain and intestine had reduced abundance of microbial molecules: TMAO, 5-AVAB, fatty acid derivatives, aryl sulfates, Glu-Trp, and other dipeptides compared to conventionally colonized controls [82]. Finally, in a model of maternal microbiota depletion using broad-spectrum antibiotics during gestation, male and female offspring showed decreased bodyweight, increased food, water, and sucrose intake compared to conventionally colonized controls [86]. With the emerging link between the microbiota, growth and metabolism, future studies understanding microbiota-based interventions should include observations of growth and metabolic changes that extend across gestation and postnatal time periods, and in metabolic organs such as the placenta and liver.

The maternal microbiome impacts offspring brain development

The maternal environment, including the maternal gut microbiota, influences offspring brain, and behavior during critical windows of brain development. GF mice show distinct brain features compared to SPF mice. This includes altered fetal brain gene expression, altered serum levels, reduced embryonic thalamocortical axons, altered embryonic and adult microglia transcriptome and morphology, decreased myelination throughout the brain, and decreased gray and white matter volume [75,82,83,87–93]. These changes in the GF brain were associated with behavioral abnormalities including social deficits, increased anxiety, decreased mobility, altered cognition, and decreased tactile sensation compared to SPF control animals [65,75,83,87,88]. Similarly, antibiotic depletion of the maternal microbiome revealed sex-dependent changes in the offspring including decreased bodyweight, atypical movement, abnormal eating habits in female offspring, and abnormal emotional regulation behaviors in male offspring [86]. Notably, the effects of the maternal microbiota on brain development can occur directly on the fetus and developing brain, or indirectly through modifications of maternal behaviors. For example, Lee and colleagues showed that pregnant dams with abnormal levels of gut *Escherichia coli* displayed altered maternal behavior, such as reduced nest building, that negatively affected offspring nourishment and growth [94].

Modifying the maternal microbiota using diet, infection, selective colonization with a consortium of bacteria, or probiotic colonization can disrupt or protect offspring brain architecture and behaviors. For example, a maternal high-fat diet disrupted the maternal gut microbiota, reduced oxytocin-expressing cells in the offspring hypothalamus, and decreased sociability behaviors in the offspring [65]. Similarly, maternal infection via poly I:C, resulted in disrupted maternal and offspring gut microbiota, cortical patches in the offspring, and increased repetitive behaviors and decreased social preference in the offspring [73,75]. Additionally, selective colonization with a consortium of *Clostridia*-dominant spore-forming bacteria during gestation can prevent neurodevelopmental abnormalities that were induced by a deficient or depleted maternal microbiota [87]. While some offspring deficits can be prevented with microbiome-based interventions that are administered during gestation, it is important to note an additional postnatal window for bacterial colonization in the offspring that can rescue brain and behavioral abnormalities. For example, in the maternal infection via poly I:C model, colonizing offspring at weaning with human *B. fragilis* rescues anxiety-like, communicative, and stereotypic behaviors, and corrects intestinal barrier integrity [75,95]. In addition, in the maternal high-fat diet model, colonizing male offspring at weaning with the commensal microbe *L. reuteri* rescued loss of oxytocin neurons in offspring PVN hypothalamus and corrected social deficits in the offspring [65,66]. Together, these studies illustrate how the maternal gut microbiome mediates the influence of environmental factors on offspring immune, metabolic, brain, and behavior changes.

Targeting maternal microbiome to promote healthy outcomes in the offspring

While microbiome-based interventions such as diets, prebiotics, probiotics, dietary supplementations, and

microbiota transplantations are methods that alter the microbiome state and have promise to promote offspring health, most of the evidence supporting these interventions are conducted in animal models. For example, in mice, probiotic supplementation with *Lactobacillus salivarius* and *Bifidobacterium infantis* corrected neuroinflammation and intestinal inflammation profiles in offspring from dams exposed to LPS [77]. Maternal probiotic supplementation with *Lactobacillus acidophilus* and *Bifidobacterium infantis* from E16.5 to weaning, promotes neuronal and oligodendrocyte development in the postnatal offspring, and protects postnatal offspring brain from postnatal IL-1B-induced neuroinflammation, such as microglia and astrocyte activation, blood–brain barrier permeability, leukocyte recruitment and extracellular matrix damage [96]. Postnatal probiotic pretreatment with *L. helveticus R0052* and *B. longum R0175* ameliorates postnatal LPS-induced neuronal apoptosis in the hippocampus [97]. Additionally, probiotic supplementation with *Lactobacillus reuteri* of pregnant dams during gestation or postnatal offspring prevented hyperactivity, disruption in neural activity in the ventral tegmental area, and social deficits in the offspring from maternal high-fat diet conditions [65,98].

Alternatively, researchers are now investigating how changing microbial function may confer beneficial health outcomes. For example, researchers are manipulating microbial metabolite levels via metabolite supplementation or metabolite antagonists. Butyrate supplementation to dams that were fed a low-fiber diet prevented impairments in cognitive function and synaptic plasticity in postnatal offspring [67]. Short-chain fatty acid supplementation to antibiotic-treated, germ-free, and protein restriction-diet fed dams during gestation promotes placental growth and vascularization [99]. GF and antibiotic-treated pregnant dams supplemented with a selection of microbial metabolites from E7.5-E14.5 prevented disruptions in fetal brain axonogenesis and adult offspring sensory behavior deficits [87]. More recently, a gut-derived metabolite, 4-EPS, was associated with increased functional activity in the hippocampus, thalamus, amygdala, and hypothalamus, reduced oligodendrocyte maturation, decreased neuronal myelination, and atypical communicative, stereotyped, anxiety-like, and sensorimotor behaviors in mice [75,91]. Administration of a phenol absorbent that binds and sequesters aromatic metabolites such as 4-EPS for 8 weeks to 30 adolescents (29 males and 1 female) that were diagnosed with ASD yielded a reduction in several metabolites in urine, including 4-EPS, reduced anxiety and irritability scores, and mild adverse effects [100]. Future studies are needed to dissect when and how often metabolites or molecules that manipulate metabolite levels should be administered, the specificity of individual or selection of metabolite effects on the host, and the long-term effects of metabolite supplementation.

Finally, cross-fostering experiments provide temporal insight to microbiome manipulations, whereby postnatal reconstitution of the microbiota can rescue behaviors, however, in some cases, normalizing the microbiota during postnatal timepoints is not sufficient. For example, co-housing offspring from maternal high-fat diet dams with control diet offspring prevented social and gut microbial dysfunction [65]. In a separate study, offspring from western diet fed dams show head dysmorphia, hyperactivity, and stereotyped behaviors that could be corrected by *in utero* probiotic *L. reuteri* supplementation [98]. Atypical behaviors in offspring from western diet fed dams persisted following cross-fostering with control diet dams. Whereas beneficial effects of *in utero L. reuteri* supplementation were maintained despite cross-fostering with western diet fed dams [98]. Together these findings support the hypothesis that the maternal microbiota during gestation regulates offspring development and behaviors.

Conclusion

The human and animal studies summarized in this review highlight the role of the maternal microbiome during pregnancy and early postpartum in offspring health and disease. Characterization of the maternal gut microbiome during pregnancy reveals a dynamic window during gestation to which microbial diversity is shaped by external features such as stress, diet, and infection. While the microbiota continuously responds to extrinsic inputs to regulate maternal and fetal health, the taxonomic and functional changes are variable, therefore more reproducible studies with detailed host information are needed to determine a signature maternal microbiota composition that can be predictive of a healthy or disease state. Moreover, as animal studies elucidate how we can manipulate the gut microbiome to promote health and provide intervention, it is important to identify the molecular, genetic, and temporal mechanisms of how the gestational gut microbiome contributes to fetal development and the lasting impacts on offspring health. Indeed, targeted colonization studies have provided powerful proof-of-concept evidence that microbiome-based interventions can reshape a dysregulated maternal microbial state to prevent negative health outcomes in the offspring. Increasingly evident is the need to consider multiple modifiers of the maternal state when interpreting

effects on offspring health, such as the window of perturbation, type of environmental challenge, and frequency of insults. Moreover, identifying how and when the individual components of the maternal microbiome - gut, vaginal, oral, and breast—contribute to maternal and offspring health or disease conditions will provide a target and window for microbiome interventions. Mapping microbiota and environmental interactions during pregnancy are necessary for developing effective interventions for neurodevelopmental and behavioral abnormalities.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

CHP and HEV conceptualized and wrote the manuscript and generated tables and abstract figure. MK, MA, and ML wrote the manuscript.

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