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Address for correspondence: Lisa F. Stinson, Department of Obstetrics and Gynaecology, The University of Western Australia, 374 Bagot Rd, Subiaco, WA 6008, Australia.
Email: lisa.stinson@uwa.edu.au

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Establishment of the early-life microbiome: a DOHaD perspective

Lisa F. Stinson

Division of Obstetrics and Gynaecology, Faculty of Health & Medical Sciences, The University of Western Australia, Perth, WA, Australia

Abstract

The human microbiome plays a number of critical roles in host physiology. Evidence from longitudinal cohort studies and animal models strongly supports the theory that maldevelopment of the microbiome in early life can programme later-life disease. The early-life microbiome develops in a clear stepwise manner over the first 3 years of life. During this highly dynamic time, insults such as antibiotic use and formula feeding can adversely affect the composition and temporal development of the microbiome. Such experiences predispose infants for the development of chronic health conditions later in life. This review highlights key factors that disrupt the early-life microbiome and highlights major non-communicable diseases which are underpinned by early-life dysbiosis.

Background

The human microbiome is the ecosystem of microorganisms that inhabit the human body. The majority of these microbes are found in the human intestines, where they play important roles in epithelial barrier function, fermentation of dietary fibre, synthesis of vitamins, calibration of the immune system, and defence against pathogens.[1] This community has also been found to play some surprising roles in angiogenesis,[2,3] brain development,[4–6] and behaviour.[6,7]

Given the various functions of the human-associated microbiota, it is unsurprising that aberrations in this community (dysbiosis) have been associated with a range of non-communicable diseases (NCDs), including obesity,[8–12] diabetes,[12,13] inflammatory bowel disease,[14,15] metabolic syndrome,[16,17] some types of cancer,[18–20] asthma,[21–23] allergy,[24–26] non-alcoholic fatty liver disease (NAFLD),[27] and even certain neuropsychiatric disorders.[28] NCDs such as these are a significant and increasing burden on our health systems and on society. The rise of NCDs, which has been described as 'a public health emergency in slow motion',[29] has coincided with environmental, medical, and lifestyle changes that are known to impact on the human microbiome. Such practices include antibiotic use, dietary antimicrobials, increased hygiene, formula feeding, and reduced exposure to animals and farming environments.[30–33]

The developmental origins of health and disease (DOHaD) paradigm provides a framework through which to understand programming of disease by the human microbiome. The DOHaD theory states that exposures during the highly plastic period of early life can programme later-life disease risk. The human microbiome is seeded, established, and stabilises in early life.[34,35] During the first 2–3 years of life, the human gut microbiome is highly dynamic and is shaped by numerous environmental factors.[35] Early life (from gestation to early childhood) appears to be a critical window for microbiome-driven programming of NCDs. Here, the evidence that certain NCDs have an early-life microbiome origin is reviewed, with a focus on insults that can disrupt early-life establishment of the human microbiome.

The early-life microbiome contributes to later-life disease

The microbiome is established in a clear, stepwise manner in the first years of life.[35–38] At birth, the human gut microbiome is highly dynamic, with a low biomass, a low level of intra-individual (alpha) diversity, and a high level of inter-individual (beta) diversity.[39,40] At around 1 year of age, the gut microbiome shifts from a developmental stage to a transitional phase.[35] During this period, the composition of the microbiome changes, as alpha diversity increases and beta diversity decreases. Finally, 2–3 years after birth, the gut microbiome matures to a stable, adult-like phase.[35] A range of chronic health conditions have been shown to be preceded by or associated with dysbiosis during this early-life critical window of microbiome development.

Asthma

Evidence from longitudinal cohort studies suggests that a change in the early-life intestinal microbiota precedes development of wheeze and asthma in childhood. Stokholm *et al.* reported

an association between an immature gut microbiome at 1 year of age and development of asthma at 5 years of age in a cohort of 690 children.[41] Importantly, this association was only evident in the children of asthmatic mothers, suggesting that the double hit of genetic predisposition and lack of microbial stimulation in infancy triggers asthma development. In another study of 1176 children, faecal colonisation with *Clostridium difficile* at 1 month of age was correlated with wheezing throughout the first 6–7 years of life and asthma at 6–7 years of age.[42] Similarly, Fujimura *et al.* analysed stool samples from 298 infants aged 1–11 months and found that infants with a lower relative abundance of particular bacteria (such as *Bifidobacterium*, *Akkermansia*, and *Faecalibacterium*), and a higher relative abundance of the fungal genera *Candida* and *Rhodotorula* had an increased risk of asthma at 4 years of age.[43] In a smaller study of just 47 infants, children who developed asthma by 7 years of age ($n = 8$) showed decreased gut microbiome diversity at 1 week and 1 month of age, but not at 12 months.[21] However, with such a low number of participants, and such a high level of inter-individual variation at these time points, these data should be interpreted with caution. Antibiotic use in the first 2 years of life increases the risk of wheeze[44] and asthma[45] in later childhood in a dose-dependent manner. Together these studies demonstrate that dysbiosis of the intestinal microbiome in the first year of life underpins later-life risk of asthma.

Further evidence from animal studies supports the notion that the early-life microbiome plays a role in asthma development. In germ-free mice, invariant natural killer T cells accumulate in the colonic lamina propria and lung, leading to increased disease severity in an ovalbumin-challenged mouse model of allergic asthma.[46] Colonisation of these mice with conventional murine microbiota protects them from asthma, but only if performed in the neonatal period. Arrieta *et al.* found four bacterial genera (*Faecalibacterium*, *Lachnospira*, *Rothia*, and *Veillonella*) were decreased in 3-month-old stool samples from CHILD study participants who went on to develop wheeze and asthma in later life.[22] Importantly, when these four taxa were inoculated into pregnant germ-free mice, their adult progeny were protected from airway inflammation.

There is evidence to suggest that the mechanism by which the early-life gut bacteria protect children from developing asthma is via their production of short-chain fatty acids (SCFAs). SCFAs are immune-modulating bacterial metabolites which are produced in the intestines as a result of fibre fermentation and are distributed systemically. Thorburn *et al.* found that, in a mouse model of allergic airway inflammation, maternal gestational high-fibre diet or supplementation with the SCFA acetate altered the maternal microbiome and subsequently protected the offspring from asthma.[23] The offspring of the high-fibre diet/acetate-supplemented dams showed an increase in T-regulatory cell number and function, as well as epigenetic changes in the Foxp3 promotor. Further, high serum acetate levels in pregnant women correlates with reduced risk of wheeze in their offspring in the first year of life.[23] Similarly, high intestinal acetate at 3 months of age,[22] and propionate and butyrate at 12 months of age[47] in infants correlates with a decreased risk for wheeze and asthma in later life. These studies demonstrate the importance of the early-life gut bacteria in shaping appropriate immune functions via the actions of SCFAs.

Allergy and atopy

Dysbiosis of the intestinal microbiome has been shown to precede development of allergy and atopy. In mice, neonatal antibiotic exposure alters the intestinal microbiota and enhances food allergen sensitisation.[48] In the CHILD study cohort, an increased Enterobacteriaceae/Bacteroidaceae ratio at 3 months and 1 year of age was associated with increased food allergen sensitisation at 1 year.[49] In the KOALA study cohort, *Escherichia coli* colonisation in stool samples taken at 1 month of age was associated with eczema diagnosis by 2 years of age in a dose-dependent fashion, while *C. difficile* colonisation was associated with both eczema and allergic sensitisation.[42,50] In this same cohort, the effect of intestinal colonisation with *E. coli* on eczema development was modified by genetic variations in CD14 (cluster of differentiation 14) and TLR4 (Toll-like receptor 4), suggesting that host gene–microbiota interactions determine atopy development in early life.[51] In a study of 138 infants, discordant temporal development of Enterobacteriaceae and *Parabacteroides* spp. and decreased abundance of *Eubacterium* spp. and *Anaerostipes* spp. over the first 26 weeks of life were observed in those that were diagnosed with eczema by 18 months of age ($n = 52$).[52] These infants also had decreased levels of the SCFA butyrate in their stool in the first 26 weeks of life. This finding has been expanded upon in another study showing that gut dysbiosis and decreased stool SCFA levels at 3 months of age correlated with atopy at 1 year of age.[53] Children with the highest levels of stool butyrate have been shown to have the lowest risk of food allergy and allergic rhinitis in later life.[47] These data suggest that early-life dysbiosis drives alterations in the SCFA profiles of infants, which may underpin the risk of atopy and allergy.

Obesity

There is a wealth of literature implicating the human gastrointestinal microbiome in the aetiology of obesity. An obesogenic ('Western') diet causes the microbiome to shift to an obesogenic state,[54–56] while an obesogenic microbiome contributes to the development of obesity and metabolic syndrome.[57–60] Mechanistically, an obesogenic microbiome is more efficient at extracting energy from food, increasing intestinal permeability, modulating satiety hormones, increasing lipogenesis, and inducing chronic inflammation.[57–60]

The rise in childhood obesity rates over the past three decades has paralleled the rise in maternal obesity. Recent models predict that more than half (57%) of today's children will be obese by age 35.[61] Disruptions in the development of the early-life intestinal microbiota are associated with later-life development of obesity. Dogra *et al.* reported that changes in the temporal development of the gut microbiome in the first 6 months of life were predictive of adiposity at 18 months of age.[62] Specifically, infants with high levels of *Streptococcus* and low levels of *Bifidobacteria* and *Collinsella* at 6 months of age showed increased adiposity at 18 months. Another prospective study of 165 children found that the composition of the gut microbiome at 10 days and 2 years was significantly associated with childhood BMI (at age 12).[63] In this cohort, the gut microbiota composition at 2 years of age explained over 50% of the variation in childhood BMI. Antibiotic administration in the first year of life has been repeatedly shown to increase the risk of adiposity and obesity in later childhood.[64–66] These observations are supported by studies in mice, which show that even sub-therapeutic doses of antibiotics in the neonatal period result in increased adiposity and metabolic hormones, as well as an increased susceptibility to a high-fat diet (HFD) in later life.[67,68]

The maternal microbiome also appears to contribute to the risk of obesity in her offspring. Maternal antibiotic administration

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during the second and third trimesters increases the risk of obesity in her children at 7 years of age by 84%.[69] Similarly, maternal HFD during pregnancy is associated with changes in the neonatal gut microbiome independently of maternal BMI.[70] Evidence from animal models supports the notion that dysbiosis of the maternal microbiome results in neonatal dysbiosis and obesity development. In mice, maternal HFD alters the gut microbiome in offspring, leading to the development of obesity and metabolic syndrome.[71,72] In a non-human primate model, maternal HFD caused changes in the composition of the neonatal gut microbiome which persist even after weaning and transfer to a control diet.[73]

Neuropsychiatric

In adults, the intestinal microbiota interact with the brain and the nervous system via their production of inflammatory and endocrine molecules and microbial metabolites.[74–78] Additionally, they are able to signal through the gut–brain axis via the vagus nerve.[74–78] Several neuropsychiatric disorders have been associated with gut dysbiosis in adults, including autism,[79] Parkinson's,[80] Alzheimer's,[81] depression,[82] and schizophrenia.[83] Emerging evidence suggests that neuropsychiatric disorders might be programmed through early-life microbial exposure. In a cohort study of 7794 people, periconceptional genital/reproductive tract infections significantly increased the risk of schizophrenia in the offspring.[84] In a larger study of almost 2 million people, maternal infections during pregnancy and childhood infections during the first 13 years of life have been associated with the development of psychosis.[85] However, in these cases, it is difficult to ascertain whether the involved mechanism is the maternal infection *per se*, or the inflammatory response to the infection. The early-life microbiome has also been associated with cognitive development in children. One study reported an inverse relationship between gut microbiome alpha diversity at 1 year of age and cognitive abilities at 2 years of age.[86] In a study of 309 children, gut microbiome composition at 3–6 months of age was associated with cognitive development at 3 years of age.[87] Many of the associations observed in this study were driven by taxa within the order Clostridiales.

These observations have been further explored in mechanistic animal studies. Diaz Heijtz *et al.* reported that germ-free mice showed altered motor activity and anxiety-like behaviour which was coupled with altered expression of genes involved in second messenger pathways and synaptic long-term potentiation in brain regions implicated in these behaviours.[6] Importantly, they could rescue these aberrant behaviours by conventionalising germ-free mice with normal gut microbiota in the gestational and neonatal period, but not adulthood. Germ-free mice also show impaired social behaviour and abnormal microglial development.[88] Modulation of the maternal microbiome is sufficient to cause behavioural and neurological changes in the offspring in mice. Administration of non-absorbable antibiotics to pregnant mice reduces exploratory behaviour in their offspring.[89] Fostering these offspring with untreated dams from postnatal day 1 partially rescued this phenotype, suggesting that the maternal microbiome during gestation is involved in programming this behaviour. Stress induces changes to the gut microbiome. In mice, maternal prenatal stress alters both the maternal and offspring gut microbiota, and increases anxiety-like behaviour in the offspring.[90] These changes are accompanied by differences in cytokine expression in the placenta and the adult offspring amygdala. Modulation of the maternal microbiome using a HFD results in dysbiosis of the offspring microbiome coupled with altered social behaviour and neurological changes (specifically, changes in signalling in the mesolimbic reward system, oxytocin levels in the hypothalamus, and neural activity in the ventral tegmental area).[91] Importantly, this phenotype could be rescued after transferring stool from control mice to the offspring of HFD dams, demonstrating a causal link between maternal diet-induced dysbiosis, offspring dysbiosis, and the development of behavioural abnormalities. These authors were able to pinpoint a single bacterial species, *Lactobacillus reuteri*, which was drastically reduced in offspring of HFD dams. Treatment with *L. reuteri* restored social behaviour in these mice. The ability of *L. reuteri* to rescue social deficits in other models of autism spectrum disorder (including genetic, environmental, and idiopathic) has since been established.[92] Together, these animal studies support observational evidence that the maternal and early-life microbiomes may influence neurological development and modulate the risk of neuropsychiatric disorders later in life.

Disruptions to the early-life microbiome

The human microbiome is vulnerable to disturbance in early life (Fig. 1). Dysbiosis of the maternal microbiome, intrapartum or neonatal antibiotic exposure, formula feeding, and delivery mode have all been shown to influence the early-life microbiome. Disturbances during this highly dynamic period appear to be transient in nature and are corrected after weaning.[36,93–95] Nevertheless, these events can have long-lasting impacts on the risk for later-life disease.

Early-life antibiotics

Antibiotics are powerful disrupters of the gut microbiome across the lifespan; however, while the adult microbiome is generally able to recover from antibiotic exposure in a timely manner,[96] early-life antibiotics have longer-lasting effects. Antibiotics can have profound effects on the development of the early-life microbiome, although this is dependent on the type, dose, duration, and timing of administration.[97] In one study of 142 Finnish children aged 2–7 years, early-life antibiotic use (from birth to the study period) was associated with long-lasting shifts in gut microbiota composition and metabolism.[98] In this study, macrolides (drugs that inhibit bacterial protein biosynthesis, such as azithromycin) were shown to have a greater effect than β-lactams (drugs that inhibit bacterial cell wall biosynthesis, such as penicillin). In a randomised control trial, the effects of three commonly prescribed antibiotics were assessed in preschool-aged children.[99] Children were randomised to receive amoxicillin, azithromycin, cotrimoxazole, or placebo for 5 days, with rectal swabs analysed before and after treatment. Azithromycin was found to decrease bacterial alpha diversity, while cotrimoxazole and amoxicillin had no discernible effect on diversity. Yassour *et al.* performed a longitudinal study of the gut microbiome of 39 children (half of whom were administered multiple course of antibiotics in the first 3 years of life) which included whole-genome shotgun sequencing of monthly stool samples, allowing strain-level resolution of the microbiome.[100] Stool samples of antibiotic-exposed children had a lower level of bacterial diversity at both the species and the strain level. Further, the gut microbiome of antibiotic-treated children was less stable than that of untreated children.

Maternal antibiotic administration during pregnancy and birth has also been shown to disrupt the neonatal microbiome.[101–106] Intrapartum antibiotic prophylaxis (IAP) has been shown to decrease bacterial diversity while decreasing the relative abundance of *Bifidobacteria* spp., *Bacteroides* spp., and *Lactobacillus* spp., and

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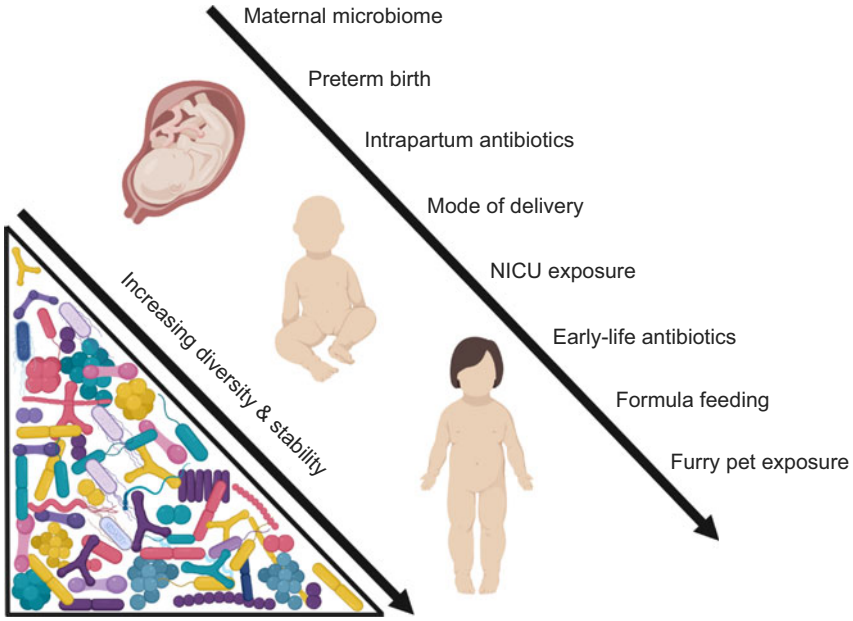

Fig. 1. Insults to the microbiome in early life (from gestation to early childhood).

increasing the relative abundance of *Enterococcus* spp., and *Clostridium* spp.[107] The mechanism by which maternally administered antibiotics affect the neonatal microbiome is unclear. Direct transmission of antibiotics via the placenta or breast milk may occur. Alternatively, antibiotics may cause temporary dysbiosis in the mother, resulting in transmitting her disrupted microbiota to her infant during the critical phases of early life. Perinatal antibiotic exposure has been associated with an increased risk of developing asthma,[108–111] allergies,[112,113] and obesity.[64–66,69] These are important considerations, as administration of antibiotics during labour and delivery is a common practice. IAP is administered to all mothers delivering by caesarean section (CS; 34% of births in Australia[114]), all mothers who deliver vaginally and are vaginally or rectally colonised with group B streptococcus (20%–24% of births in Australia[115–117]), as well as all mothers who experience prolonged rupture of membranes. Combined, these prophylactic interventions result may place a significant portion of the population at risk of early-life dysbiosis and associated later-life diseases.

Mode of delivery

Internationally, the rate of caesarean delivery has steadily increased between 2000 and 2015.[114] In Australia, 34% of infants were born via CS in 2015.[114] This is a significant concern as CS delivery has been repeatedly associated with early-life gut dysbiosis.[36,38,118–122] CS-delivered infants are also at a greater risk of childhood asthma,[123–125] atopic disease,[126–128] allergies,[128,129] obesity,[130] type 1 diabetes mellitus,[131] inflammatory bowel disease,[124,132] and impaired cognition.[133] Some have ascribed this dysbiosis to a lack of exposure to the maternal vaginal microbiota at birth. Indeed, postnatal 'vaginal seeding' (i.e., swabbing of the maternal vaginal fluid across the skin and orifices of the newborn) has been trialled in an attempt to correct this supposed issue.[134] However, the act of passing through the vagina at birth may not be the factor that differentiates the microbiomes of CS-delivered and vaginally delivered infants. Instead, intrapartum antibiotic administration is likely a key factor in the observed CS microbiome.[107] All CS-delivered infants are exposed to IAP, while the majority of vaginally delivered infants are not. Indeed, the gut dysbiosis caused by CS delivery closely mirrors that seen in vaginally delivered infants that are exposed to IAP, with a decrease in the abundance of *Bacteroides* and *Bifidobacteria*, and an increase in the abundance of *Clostridium*, *Streptococcus*, and *Enterococcus*.[107] Further, women who deliver via CS tend to have higher BMIs,[135–141] lower gestational age at delivery,[142] and reduced rates of breastfeeding.[143–145] Regardless of the mechanism (IAP exposure or lack of vaginal microbiota exposure), mode of delivery is certainly associated with the microbiome in early life.

Preterm birth/NICU exposure

There is evidence to suggest that the human microbiome is seeded prior to birth.[36,39,40,146–149] However, this is a controversial topic and there is also evidence to suggest that bacterial exposure does not occur until birth.[150] If humans are seeded with bacteria *in utero*, these are likely to play a significant role in the development of the fetal immune system.[151] There is an increase in the rate of bacterial translocation across the intestines and an increase in trafficking of live bacteria around the body in the final trimester of pregnancy.[152] This may suggest that bacterial exposure increases or perhaps commences in late pregnancy. Preterm birth may therefore bypass this prenatal exposure.

Additionally, preterm infants are subject to a range of medical interventions that have been associated with neonatal dysbiosis. In particular, preterm infants are exposed to the neonatal intensive care unit (NICU), the environment of which is likely to influence the neonatal microbiome.[153] These infants are also more likely to consume formula or donor breast milk (which is sterilised prior to use) and to experience less skin-to-skin contact with their mothers. Further, preterm infants are more likely to be delivered by CS[142] and to be administered antibiotics.[154] The sum of these aberrant early-life exposures is a significant difference in the neonatal gut microbiome of preterm infants compared to their full-term counterparts.[155–158]

Breastfeeding

Breast milk contains a rich and diverse microbiome. Breastfeeding has been repeatedly shown to influence the development of the

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infant gut microbiome.[35,102,119,159–164] Exposure to breast milk bacteria and their metabolites modifies host gene expression and immune development.[162–164] Over a third of the gut bacteria of breastfed infants are vertically derived from their mothers' breast milk and breast skin.[165] Additionally, breast milk contains prebiotics which modulate the infant gut microbiome and metabolome.[166] A recent meta-analysis found that the gut microbiomes of exclusively breastfed infants persistently differed in composition, diversity, and function from non-exclusively breastfed infants.[167] In the TEDDY study, breastfeeding (exclusive or partial) was the most significant factor that shaped the gut microbiome in the first 4 years of life.[35] In this study, there were many factors which significantly altered the infant gut microbiome at the genus and species level, but breastfeeding was the only factor that influenced the function of the microbiome. This is an important distinction, as it demonstrates a certain level of redundancy in the functional capacity of the early-life gut microbiome, which is considerably shaped by breastfeeding. The cessation of breastfeeding drives the maturation of the infant gut microbiome to an adult-like state.[35,36]

Given the important role of breastfeeding in the development of the infant microbiome, it is not surprising that formula feeding is associated with early-life dysbiosis[38,168–170] and the development of later-life NCDs.[168,171,172] However, the effect of expressing and bottle-feeding breast milk is less clear. Source-tracking studies have demonstrated that the skin around the areola is the source of approximately 10% of the breastfed infant microbiome.[165] Bottle-fed infants may therefore miss out on maternal skin microbes. Further, expressed breast milk is often stored frozen and thawed before use. The effect of these common practices on the infant gut microbiome is currently unknown, although there is evidence to suggest that hand-expressed milk varies in bacterial composition from pump-expressed milk.[173]

Maternal microbiome

The maternal microbiome is the largest donor of bacteria to the infant microbiome.[39,40] Therefore, maternal dysbiosis will negatively impact on the development of the infant microbiome. Factors that may skew the maternal microbiome include diet, stress, medications, dietary antimicrobials, diabetes, and obesity.

The gut microbiota of infants of obese mothers varies from that of infants of lean mothers,[174–178] although this effect may be birth mode-dependent.[176] When stool from 2-week-old infants born of obese mothers (Inf-ObM) or infants born of lean mothers was transferred to germ-free mice, the Inf-ObM colonised mice showed gut dysbiosis, increased intestinal permeability, and increased susceptibility to obesity when exposed to a Western diet.[179] These mice also displayed hallmarks of NAFLD. Importantly, all mothers in this study delivered vaginally, were not exposed to perinatal antibiotics, and exclusively breastfed. This suggests that maternal obesity is a causative factor in microbiome-mediated offspring obesity and NAFLD. Maternal transmission of an obesogenic microbiome may contribute to the intergenerational transmission of obesity. With approximately a third of all women of childbearing age classified as obese,[180] it is likely that a significant portion of the population is exposed to an obesogenic microbiome from birth. Further, obesity is a risk factor for other microbiome-modulating events, such as CS delivery[181] and reduced breastfeeding.[182]

The maternal diet during gestation also shapes the offspring gut microbiome. In mice, 2-week-old pups of dams exposed to a Western diet had altered gut microbiota and sex-specific changes to colonic gene expression.[183] In a primate model, a perinatal maternal HFD, but not obesity *per se*, persistently altered the offspring gut microbiome.[73] Offspring dysbiosis could not be fully corrected with a low-fat postnatal diet, suggesting that microbial exposures *in utero* and in early life programme long-term metabolism.

Perinatal stress can modulate the maternal and offspring microbiome and increase the risk of later-life disease. In a study of 56 vaginally delivered infants, maternal prenatal stress (both self-reported and inferred from serum cortisol levels) was associated with offspring gut dysbiosis, including a reduction in the relative abundance of *Lactobacilli* and *Bifidobacteria*, and an increase in the relative abundance of *Escherichia*, *Serratia*, and *Enterobacter*.[184] In a mouse model, maternal stress in early pregnancy disrupted the normal maternal microbiome adaptations to pregnancy (both gut and vaginal), resulting in temporal disruptions to the offspring microbiota.[185] The effects of maternal stress on the offspring microbiota in mice have been implicated in altered hypothalamic pituitary adrenal (HPA) axis responses, immune dysfunction, and aberrant neural development, and can last long into adulthood.[186,187]

Another major maternal condition which may detrimentally affect the early-life acquisition of microbes is diabetes. The intestinal and vaginal microbiota of women with gestational diabetes mellitus (GDM) varies from that of normoglycaemic pregnant women.[188–191] This maternal dysbiosis is mirrored in the infant gut microbiome.[191] Importantly, there is evidence to suggest that both GDM and pre-existing maternal diabetes mellitus are associated with changes in the amniotic fluid and meconium microbiomes.[191,192] These data might suggest that diabetes can alter the human microbiome prior to birth. One study, which analysed stool samples from mothers ($n = 128$) with and without GDM and their children ($n = 109$) 5 years after birth, found that the maternal microbiome had recovered at this time, while the microbiomes of children of GDM mothers remained altered.[193] Given that gestational diabetes is a significant and increasing concern in the pregnant population, the impact of this disease on the early-life microbiome should be considered in more depth. In particular, the effect of diabetes and diabetic medication on the breast milk microbiome should be explored.

Household environment

Infants and young children spend the vast majority of their time inside the family home. The microbiome of the residential built environment is therefore an important consideration in the development of the early-life microbiome. Lynch *et al.* prospectively collected dust samples from homes with children <1 year old ($n = 104$) and measured atopy and wheeze in these children at 3 years of age.[194] The household dust of children who did not develop atopy or wheeze by 3 years of age was richer and more diverse than that of affected children. These results suggest that household microbial exposures contribute to early-life immune development and may confer protection against common immune-mediated diseases.

The presence of furry pets[35,195,196] and older siblings[35,197] also has a significant effect on the early-life microbiome. Dust from homes with furry pets is microbially richer than that of homes without pets.[195] There is a well-established link between pet ownership in early life and protection from allergy.[198–200] To test the hypothesis that this protection is conferred through exposure to pet-associated microbes, Fujimura *et al.* collected house dust from

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dog-owning and pet-free houses.[196] Mice were exposed to these dust samples prior to and during an airway allergen challenge. Those animals sensitised with dog-residence dust had significant changes in the composition of their gut microbiomes and were protected from airway inflammation. This suggests that diversity within the environmental microbiome (particularly in cases of cohabitation with animals) confers a benefit to the developing microbiome.

Conclusions

The first years of life are a critical window for the development of the microbiome. Insults such as antibiotic use, maternal dysbiosis, and formula feeding during this time disrupt the early-life microbiome, increasing the risk for later-life metabolic, neuropsychiatric, and immunological disease. The prevalence of such microbiome-disrupting practices has increased over the past three decades and may have contributed to the rise of NCDs during this time. Importantly, the human microbiome is more readily changeable than the human gene content. Therefore, interventions to optimise the microbiome during gestation and infancy may help to lessen the societal burden of NCDs.

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References

1. Fujimura KE, Slusher NA, Cabana MD, Lynch SV. Role of the gut microbiota in defining human health. *Expert Rev Anti Infect Ther*. 2010; 8(4), 435–454.
2. Schirbel A, Kessler S, Rieder F, *et al*. Pro-angiogenic activity of TLRs and NLRs: a novel link between gut microbiota and intestinal angiogenesis. *Gastroenterology*. 2013; 144(3), 613–623e619.
3. Stappenbeck TS, Hooper LV, Gordon JI. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. *Proc Natl Acad Sci USA*. 2002; 99(24), 15451–15455.
4. Ceppa F, Mancini A, Tuohy K. Current evidence linking diet to gut microbiota and brain development and function. *Int J Food Sci Nutr*. 2018; 70, 1–19. doi: 10.1080/09637486.2018.1462309
5. Lu J, Lu L, Yu Y, Cluette-Brown J, Martin CR, Claud EC. Effects of intestinal microbiota on brain development in humanized gnotobiotic mice. *Sci Rep*. 2018; 8(1), 5443.
6. Diaz Heijtz R, Wang S, Anuar F, *et al*. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci USA*. 2011; 108(7), 3047–3052.
7. Clarke G, O'Mahony SM, Dinan TG, Cryan JF. Priming for health: gut microbiota acquired in early life regulates physiology, brain and behaviour. *Acta Paediatr*. 2014; 103(8), 812–819.
8. Boulange CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Med*. 2016; 8(1), 42.
9. Ley RE. Obesity and the human microbiome. *Curr Opin Gastroenterol*. 2010; 26(1), 5–11.
10. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci USA*. 2005; 102(31), 11070–11075.
11. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006; 444(7122), 1022–1023.
12. Moreno-Indias I, Cardona F, Tinahones FJ, Queipo-Ortuno MI. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. *Front Microbiol*. 2014; 5, 190.
13. Tilg H, Moschen AR. Microbiota and diabetes: an evolving relationship. *Gut*. 2014; 63(9), 1513–1521.
14. Papa E, Docktor M, Smillie C, *et al*. Non-invasive mapping of the gastrointestinal microbiota identifies children with inflammatory bowel disease. *PLoS ONE*. 2012; 7(6), e39242.
15. Ni J, Wu GD, Albenberg L, Tomov VT. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol*. 2017; 14(10), 573–584.
16. Parekh PJ, Balart LA, Johnson DA. The influence of the gut microbiome on obesity, metabolic syndrome and gastrointestinal disease. *Clin Transl Gastroenterol*. 2015; 6, e91.
17. Chassaing B, Gewirtz AT. Gut microbiota, low-grade inflammation, and metabolic syndrome. *Toxicol Pathol*. 2014; 42(1), 49–53.
18. Dahmus JD, Kotler DL, Kastenberg DM, Kistler CA. The gut microbiome and colorectal cancer: a review of bacterial pathogenesis. *J Gastrointest Oncol*. 2018; 9(4), 769–777.
19. Dai Z, Coker OO, Nakatsu G, *et al*. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. *Microbiome*. 2018; 6(1), 70.
20. Flemer B, Lynch DB, Brown JM, *et al*. Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut*. 2017; 66(4), 633–643.
21. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy*. 2014; 44(6), 842–850.
22. Arrieta MC, Stiemsma LT, Dimitriu PA, *et al*. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med*. 2015; 7(307), 307ra152.
23. Thorburn AN, McKenzie CI, Shen S, *et al*. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat Commun*. 2015; 6, 7320.
24. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol*. 2001; 108(4), 516–520.
25. Debarry J, Garn H, Hanuszkiewicz A, *et al*. *Acinetobacter lwoffii* and *Lactococcus lactis* strains isolated from farm cowsheds possess strong allergy-protective properties. *J Allergy Clin Immunol*. 2007; 119(6), 1514–1521.
26. Subbarao P, Anand SS, Becker AB, *et al*. The Canadian Healthy Infant Longitudinal Development (CHILD) Study: examining developmental origins of allergy and asthma. *Thorax*. 2015; 70(10), 998–1000.
27. Kolodziejczyk AA, Zheng D, Shibolet O, Elinav E. The role of the microbiome in NAFLD and NASH. *EMBO Mol Med*. 2019; 11(2), pii: e9302.
28. Warner BB. The contribution of the gut microbiome to neurodevelopment and neuropsychiatric disorders. *Pediatr Res*. 2019; 85(2), 216–224.
29. Ki-moon B. *Secretary-General, in Concluding Remarks to Forum, Emphasizes Importance of Partnerships in Race to Meet Health-Related Millennium Development Goals*. (ed. Nations U), 2009. https://www.mja.com.au/journal/2011/194/4/time-global-action-chronic-disease, https://www.who.int/nmh/events/un_ncd_summit2011/3rd_plenary_meeting.pdf
30. Bailar JC 3rd, Travers K. Review of assessments of the human health risk associated with the use of antimicrobial agents in agriculture. *Clin Infect Dis*. 2002; 34(Suppl. 3), S135–143.
31. Jernberg C, Lofmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology*. 2010; 156(Pt 11), 3216–3223.
32. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med*. 2016; 8(1), 39.
33. Thorsen J, McCauley K, Fadrosh D, *et al*. Evaluating the effects of farm exposure on infant gut microbiome. *Journal of Allergy and Clinical Immunology*. 2019; 143(2), AB299.
34. Hornef M. Microbiome and Early Life. In *The Gut Microbiome in Health and Disease* (ed. Haller D), 2018; pp. 31–47. Springer International Publishing, Cham.

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35. Stewart CJ, Ajami NJ, O'Brien JL, *et al.* Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature*. 2018; 562(7728), 583–588.
36. Wampach L, Heintz-Buschart A, Hogan A, *et al.* Colonization and succession within the human gut microbiome by archaea, bacteria, and microeukaryotes during the first year of life. *Front Microbiol*. 2017; 8, 738.
37. Bergstrom A, Skov TH, Bahl MI, *et al.* Establishment of intestinal microbiota during early life: a longitudinal, explorative study of a large cohort of Danish infants. *Appl Environ Microbiol*. 2014; 80(9), 2889–2900.
38. Backhed F, Roswall J, Peng Y, *et al.* Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe*. 2015; 17(5), 690–703.
39. Ferretti P, Pasolli E, Tett A, *et al.* Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host Microbe*. 2018; 24(1), 133–145.e5.
40. Yassour M, Jason E, Hogstrom LJ, *et al.* Strain-level analysis of mother-to-child bacterial transmission during the first few months of life. *Cell Host Microbe*. 2018; 24(1), 146–154.e4.
41. Stokholm J, Blaser MJ, Thorsen J, *et al.* Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun*. 2018; 9(1), 141.
42. van Nimwegen FA, Penders J, Stobberingh EE, *et al.* Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol*. 2011; 128(5), 948–955.e3.
43. Fujimura KE, Sitarik AR, Havstad S, *et al.* Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med*. 2016; 22(10), 1187–1191.
44. Kummeling I, Stelma FF, Dagnelie PC, *et al.* Early life exposure to antibiotics and the subsequent development of eczema, wheeze, and allergic sensitization in the first 2 years of life: the KOALA Birth Cohort Study. *Pediatrics*. 2007; 119(1), e225–231.
45. Hoskin-Parr L, Teyhan A, Blocker A, Henderson AJ. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: a dose-dependent relationship. *Pediatr Allergy Immunol*. 2013; 24(8), 762–771.
46. Olszak T, An D, Zeissig S, *et al.* Microbial exposure during early life has persistent effects on natural killer T cell function. *Science*. 2012; 336(6080), 489–493.
47. Roduit C, Frei R, Ferstl R, *et al.* High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy*. 2019; 74(4), 799–809.
48. Stefka AT, Feehley T, Tripathi P, *et al.* Commensal bacteria protect against food allergen sensitization. *Proc Natl Acad Sci USA*. 2014; 111(36), 13145–13150.
49. Azad MB, Konya T, Guttman DS, *et al.* Infant gut microbiota and food sensitization: associations in the first year of life. *Clin Exp Allergy*. 2015; 45(3), 632–643.
50. Penders J, Thijs C, van den Brandt PA, *et al.* Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. *Gut*. 2007; 56(5), 661–667.
51. Penders J, Thijs C, Mommers M, *et al.* Host-microbial interactions in childhood atopy: toll-like receptor 4 (TLR4), CD14, and fecal *Escherichia coli*. *J Allergy Clin Immunol*. 2010; 125(1), 231–236.e5.
52. Wopereis H, Sim K, Shaw A, Warner JO, Knol J, Kroll JS. Intestinal microbiota in infants at high risk for allergy: effects of prebiotics and role in eczema development. *J Allergy Clin Immunol*. 2018; 141(4), 1334–1342.e5.
53. Stiemsma LT, Arrieta M-C, Dimitriu PA, *et al.* The early life gut microbiota and atopic disease. *Allergy Asthma Clin Immunol*. 2014; 10(Suppl. 2), A63–A63.
54. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med*. 2009; 1(6), 6ra14.
55. Wu GD, Chen J, Hoffmann C, *et al.* Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011; 334(6052), 105–108.
56. Turnbaugh PJ, Backhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe*. 2008; 3(4), 213–223.
57. Tseng CH, Wu CY. The gut microbiome in obesity. *J Formos Med Assoc*. 2019; 118(Suppl. 1), S3–S9.
58. Al-Assal K, Martinez AC, Torrinhas RS, Cardinelli C, Waitzberg D. Gut microbiota and obesity. *Clinical Nutrition Experimental*. 2018; 20, 60–64.
59. Sun L, Ma L, Ma Y, Zhang F, Zhao C, Nie Y. Insights into the role of gut microbiota in obesity: pathogenesis, mechanisms, and therapeutic perspectives. *Protein Cell*. 2018; 9(5), 397–403.
60. Cornejo-Pareja I, Munoz-Garach A, Clemente-Postigo M, Tinahones FJ. Importance of gut microbiota in obesity. *Eur J Clin Nutr*. 2018; 72(Suppl 1), 26–37. doi: 10.1038/s41430–018–0306–8.
61. Collaborators GBDO, Afshin A, Forouzanfar MH, *et al.* Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017; 377(1), 13–27.
62. Dogra S, Sakwinska O, Soh SE, *et al.* Dynamics of infant gut microbiota are influenced by delivery mode and gestational duration and are associated with subsequent adiposity. *MBio*. 2015; 6(1), 193.
63. Stanislawski MA, Dabelea D, Wagner BD, *et al.* Gut microbiota in the first 2 years of life and the association with body mass index at age 12 in a Norwegian Birth Cohort. *MBio*. 2018; 9(5), pii: e01751-18.
64. Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. Infant antibiotic exposures and early-life body mass. *Int J Obes (Lond)*. 2013; 37(1), 16–23.
65. Azad MB, Bridgman SL, Becker AB, Kozyrskyj AL. Infant antibiotic exposure and the development of childhood overweight and central adiposity. *Int J Obes (Lond)*. 2014; 38(10), 1290–1298.
66. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr*. 2014; 168(11), 1063–1069.
67. Cho I, Yamanishi S, Cox L, *et al.* Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature*. 2012; 488(7413), 621–626.
68. Cox LM, Yamanishi S, Sohn J, *et al.* Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell*. 2014; 158(4), 705–721.
69. Mueller NT, Whyatt R, Hoepner L, *et al.* Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. *Int J Obes (Lond)*. 2015; 39(4), 665–670.
70. Chu DM, Antony KM, Ma J, *et al.* The early infant gut microbiome varies in association with a maternal high-fat diet. *Genome Med*. 2016; 8(1), 77.
71. Paul HA, Bomhof MR, Vogel HJ, Reimer RA. Diet-induced changes in maternal gut microbiota and metabolomic profiles influence programming of offspring obesity risk in rats. *Sci Rep*. 2016; 6, 20683.
72. Wankhade UD, Zhong Y, Kang P, *et al.* Enhanced offspring predisposition to steatohepatitis with maternal high-fat diet is associated with epigenetic and microbiome alterations. *PLoS ONE*. 2017; 12(4), e0175675.
73. Ma J, Prince AL, Bader D, *et al.* High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. *Nat Commun*. 2014; 5, 3889.
74. Bravo JA, Forsythe P, Chew MV, *et al.* Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA*. 2011; 108(38), 16050–16055.
75. Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. *Psychoneuroendocrinology*. 2012; 37(9), 1369–1378.
76. Erny D, Hrabe de Angelis AL, Jaitin D, *et al.* Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci*. 2015; 18(7), 965–977.
77. Konig J, Wells J, Cani PD, *et al.* Human intestinal barrier function in health and disease. *Clin Transl Gastroenterol*. 2016; 7(10), e196.
78. Dinan TG, Cryan JF. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *J Physiol*. 2017; 595(2), 489–503.
79. Liu F, Li J, Wu F, Zheng H, Peng Q, Zhou H. Altered composition and function of intestinal microbiota in autism spectrum disorders: a systematic review. *Transl Psychiatry*. 2019; 9(1), 43.
80. Sampson TR, Debelius JW, Thron T, *et al.* Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell*. 2016; 167(6), 1469–1480.e12.
81. Vogt NM, Kerby RL, Dill-McFarland KA, *et al.* Gut microbiome alterations in Alzheimer's disease. *Sci Rep*. 2017; 7(1), 13537.

82. Valles-Colomer M, Falony G, Darzi Y, *et al.* The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol.* 2019; 4(4), 623–632.
83. Zheng P, Zeng B, Liu M, *et al.* The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. *Sci Adv.* 2019; 5(2), eaau8317.
84. Babulas V, Factor-Litvak P, Goetz R, Schaefer CA, Brown AS. Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. *Am J Psychiatry.* 2006; 163(5), 927–929.
85. Blomstrom A, Karlsson H, Gardner R, Jorgensen L, Magnusson C, Dalman C. Associations between maternal infection during pregnancy, childhood infections, and the risk of subsequent psychotic disorder–a Swedish cohort study of nearly 2 million individuals. *Schizophr Bull.* 2016; 42(1), 125–133.
86. Carlson AL, Xia K, Azcarate-Peril MA, *et al.* Infant gut microbiome associated with cognitive development. *Biol Psychiatry.* 2018; 83(2), 148–159.
87. Sordillo JE, Korrick S, Laranjo N, *et al.* Association of the infant gut microbiome with early childhood neurodevelopmental outcomes: an ancillary study to the VDAART randomized clinical trial. *JAMA Netw Open.* 2019; 2(3), e190905.
88. Forssberg H. Microbiome programming of brain development: implications for neurodevelopmental disorders. *Dev Med Child Neurol.* 2019; 61, 744–749. doi: 10.1111/dmcn.14208.
89. Tochitani S, Ikeno T, Ito T, Sakurai A, Yamauchi T, Matsuzaki H. Administration of non-absorbable antibiotics to pregnant mice to perturb the maternal gut microbiota is associated with alterations in offspring behavior. *PLoS ONE.* 2016; 11(1), e0138293.
90. Gur TL, Shay L, Palkar AV, *et al.* Prenatal stress affects placental cytokines and neurotrophins, commensal microbes, and anxiety-like behavior in adult female offspring. *Brain Behav Immun.* 2017; 64, 50–58.
91. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell.* 2016; 165(7), 1762–1775.
92. Sgritta M, Dooling SW, Buffington SA, *et al.* Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. *Neuron.* 2019; 101(2), 246–259.e6.
93. Schloss PD, Iverson KD, Petrosino JF, Schloss SJ. The dynamics of a family's gut microbiota reveal variations on a theme. *Microbiome.* 2014; 2, 25.
94. Koenig JE, Spor A, Scalfone N, *et al.* Succession of microbial consortia in the developing infant gut microbiome. *Proc Natl Acad Sci USA.* 2011; 108(Suppl. 1), 4578–4585.
95. Fallani M, Amarri S, Uusijarvi A, *et al.* Determinants of the human infant intestinal microbiota after the introduction of first complementary foods in infant samples from five European centres. *Microbiology.* 2011; 157(Pt 5), 1385–1392.
96. Rashid MU, Zaura E, Buijs MJ, *et al.* Determining the long-term effect of antibiotic administration on the human normal intestinal microbiota using culture and pyrosequencing methods. *Clin Infect Dis.* 2015; 60(Suppl. 2), S77–84.
97. Berardi A, Pietrangiolillo Z, Bacchi Reggiani ML, *et al.* Are postnatal ampicillin levels actually related to the duration of intrapartum antibiotic prophylaxis prior to delivery? A pharmacokinetic study in 120 neonates. *Arch Dis Child Fetal Neonatal Ed.* 2017; 103(2), F152–F156. doi: 10.1136/archdischild-2016–312546
98. Korpela K, Salonen A, Virta LJ, *et al.* Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat Commun.* 2016; 7, 10410.
99. Oldenburg CE, Sie A, Coulibaly B, *et al.* Effect of commonly used pediatric antibiotics on gut microbial diversity in preschool children in Burkina Faso: a randomized clinical trial. *Open Forum Infect Dis.* 2018; 5(11), ofy289.
100. Yassour M, Vatanen T, Siljander H, *et al.* Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Sci Transl Med.* 2016; 8(343), 343ra381.
101. Nogacka A, Salazar N, Suarez M, *et al.* Impact of intrapartum antimicrobial prophylaxis upon the intestinal microbiota and the prevalence of antibiotic resistance genes in vaginally delivered full-term neonates. *Microbiome.* 2017; 5(1), 93.
102. Azad MB, Konya T, Persaud RR, *et al.* Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG.* 2016; 123(6), 983–993.
103. Mazzola G, Murphy K, Ross RP, *et al.* Early gut microbiota perturbations following intrapartum antibiotic prophylaxis to prevent group B streptococcal disease. *PLoS ONE.* 2016; 11(6), e0157527.
104. Aloisio I, Mazzola G, Corvaglia LT, *et al.* Influence of intrapartum antibiotic prophylaxis against group B streptococcus on the early newborn gut composition and evaluation of the anti-streptococcus activity of bifidobacterium strains. *Appl Microbiol Biotechnol.* 2014; 98(13), 6051–6060.
105. Fallani M, Young D, Scott J, *et al.* Intestinal microbiota of 6-week-old infants across Europe: geographic influence beyond delivery mode, breast-feeding, and antibiotics. *J Pediatr Gastroenterol Nutr.* 2010; 51(1), 77–84.
106. Fouhy F, Guinane CM, Hussey S, *et al.* High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin. *Antimicrob Agents Chemother.* 2012; 56(11), 5811–5820.
107. Stinson LF, Payne MS, Keelan JA. A critical review of the bacterial baptism hypothesis and the impact of cesarean delivery on the infant microbiome. *Front Med (Lausanne).* 2018; 5, 135.
108. Lapin B, Piorkowski J, Ownby D, *et al.* Relationship between prenatal antibiotic use and asthma in at-risk children. *Ann Allergy Asthma Immunol.* 2015; 114(3), 203–207.
109. Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. *Clin Exp Allergy.* 2015; 45(1), 137–145.
110. Ortqvist AK, Lundholm C, Kieler H, *et al.* Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ.* 2014; 349, g6979.
111. Stensballe LG, Simonsen J, Jensen SM, Bonnelykke K, Bisgaard H. Use of antibiotics during pregnancy increases the risk of asthma in early childhood. *J Pediatr.* 2013; 162(4), 832–838.e3.
112. McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. *Am J Respir Crit Care Med.* 2002; 166(6), 827–832.
113. Wohl DL, Curry WJ, Mauger D, Miller J, Tyrie K. Intrapartum antibiotics and childhood atopic dermatitis. *J Am Board Fam Med.* 2015; 28(1), 82–89.
114. OECD. *Health at a Glance 2015*, 2015. OECD Indicators, OECD Publishing, Paris. doi: 10.1787/health_glance-2015-en
115. Angstetra D, Ferguson J, Giles WB. Institution of universal screening for Group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. *Aust N Z J Obstet Gynaecol.* 2007; 47(5), 378–382.
116. Furfaro LL, Nathan EA, Chang BJ, Payne MS. Group B streptococcus prevalence, serotype distribution and colonization dynamics in Western Australian pregnant women. *J Med Microbiol.* 2019; 68(5), 728–740.
117. Hiller JE, McDonald HM, Darbyshire P, Crowther CA. Antenatal screening for Group B Streptococcus: a diagnostic cohort study. *BMC Pregnancy Childbirth.* 2005; 5, 12.
118. Azad MB, Konya T, Maughan H, *et al.* Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ.* 2013; 185(5), 385–394.
119. Penders J, Thijs C, Vink C, *et al.* Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics.* 2006; 118(2), 511–521.
120. Bokulich NA, Chung J, Battaglia T, *et al.* Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med.* 2016; 8(343), 343ra382.
121. Jakobsson HE, Abrahamsson TR, Jenmalm MC, *et al.* Decreased gut microbiota diversity, delayed bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut.* 2014; 63(4), 559–566.
122. Martin R, Makino H, Cetinyurek Yavuz A, *et al.* Early-life events, including mode of delivery and type of feeding, siblings and gender, shape the developing gut microbiota. *PLoS ONE.* 2016; 11(6), e0158498.

123. Debley JS, Smith JM, Redding GJ, Critchlow CW. Childhood asthma hospitalization risk after cesarean delivery in former term and premature infants. *Ann Allergy Asthma Immunol*. 2005; 94(2), 228–233.
124. Sevelsted A, Stokholm J, Bonnelykke K, Bisgaard H. Cesarean section and chronic immune disorders. *Pediatrics*. 2015; 135(1), e92–98.
125. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between caesarean section and childhood asthma. *Clin Exp Allergy*. 2008; 38(4), 629–633.
126. Laubereau B, Filipiak-Pittroff B, von Berg A, *et al*. Caesarean section and gastrointestinal symptoms, atopic dermatitis, and sensitisation during the first year of life. *Arch Dis Child*. 2004; 89(11), 993–997.
127. Negele K, Heinrich J, Borte M, *et al*. Mode of delivery and development of atopic disease during the first 2 years of life. *Pediatr Allergy Immunol*. 2004; 15(1), 48–54.
128. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy*. 2008; 38(4), 634–642.
129. Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol*. 2003; 112(2), 420–426.
130. Darmasseelane K, Hyde MJ, Santhakumaran S, Gale C, Modi N. Mode of delivery and offspring body mass index, overweight and obesity in adult life: a systematic review and meta-analysis. *PLoS ONE*. 2014; 9(2), e87896.
131. Cardwell CR, Stene LC, Joner G, *et al*. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia*. 2008; 51(5), 726–735.
132. Li Y, Tian Y, Zhu W, *et al*. Cesarean delivery and risk of inflammatory bowel disease: a systematic review and meta-analysis. *Scand J Gastroenterol*. 2014; 49(7), 834–844.
133. Polidano C, Zhu A, Bornstein JC. The relation between cesarean birth and child cognitive development. *Sci Rep*. 2017; 7(1), 11483.
134. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, *et al*. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med*. 2016; 22(3), 250–253.
135. Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. *Obes Rev*. 2015; 16(8), 621–638.
136. Al-Kubaisy W, Al-Rubaey M, Al-Naggar RA, Karim B, Mohd Noor NA. Maternal obesity and its relation with the cesarean section: a hospital based cross sectional study in Iraq. *BMC Pregnancy Childbirth*. 2014; 14, 235.
137. Berendzen JA, Howard BC. Association between cesarean delivery rate and body mass index. *Tenn Med*. 2013; 106(1), 35–37, 42.
138. Cresswell JA, Campbell OM, De Silva MJ, Slaymaker E, Filippi V. Maternal obesity and caesarean delivery in sub-Saharan Africa. *Trop Med Int Health*. 2016; 21(7), 879–885.
139. Kyvernitakis I, Kohler C, Schmidt S, *et al*. Impact of maternal body mass index on the cesarean delivery rate in Germany from 1990 to 2012. *J Perinat Med*. 2015; 43(4), 449–454.
140. Roman H, Goffinet F, Hulsey TF, Newman R, Robillard PY, Hulsey TC. Maternal body mass index at delivery and risk of caesarean due to dystocia in low risk pregnancies. *Acta Obstet Gynecol Scand*. 2008; 87(2), 163–170.
141. Tun HM, Bridgman SL, Chari R, *et al*. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. *JAMA Pediatr*. 2018; doi: 10.1001/jamapediatrics.2017.5535.
142. Delnord M, Blondel B, Drewniak N, *et al*. Varying gestational age patterns in cesarean delivery: an international comparison. *BMC Pregnancy Childbirth*. 2014; 14, 321.
143. Dewey KG, Nommsen-Rivers LA, Heinig MJ, Cohen RJ. Risk factors for suboptimal infant breastfeeding behavior, delayed onset of lactation, and excess neonatal weight loss. *Pediatrics*. 2003; 112(3), 607–619.
144. Bai DL, Wu KM, Tarrant M. Association between intrapartum interventions and breastfeeding duration. *J Midwifery Womens Health*. 2013; 58(1), 25–32.
145. Evans KC, Evans RG, Royal R, Esterman AJ, James SL. Effect of caesarean section on breast milk transfer to the normal term newborn over the first week of life. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88(5), F380–382.
146. Collado MC, Rautava S, Aakko J, Isolauri E, Salminen S. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Sci Rep*. 2016; 6, 23129.
147. Stinson LF, Keelan JA, Payne MS. Characterization of the bacterial microbiome in first-pass meconium using propidium monoazide (PMA) to exclude nonviable bacterial DNA. *Lett Appl Microbiol*. 2019; 68(5), 378–385.
148. Stinson LF, Payne MS, Keelan JA. Planting the seed: origins, composition, and postnatal health significance of the fetal gastrointestinal microbiota. *Crit Rev Microbiol*. 2016; 1–18. doi: 10.1080/1040841X.2016.1211088
149. Jimenez E, Marin ML, Martin R, *et al*. Is meconium from healthy newborns actually sterile? *Res Microbiol*. 2008; 159(3), 187–193.
150. Perez-Munoz ME, Arrieta MC, Ramer-Tait AE, Walter J. A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: implications for research on the pioneer infant microbiome. *Microbiome*. 2017; 5(1), 48.
151. Romano-Keeler J, Weitkamp JH. Maternal influences on fetal microbial colonization and immune development. *Pediatr Res*. 2015; 77(1–2), 189–195.
152. Perez PF, Dore J, Leclerc M, *et al*. Bacterial imprinting of the neonatal immune system: lessons from maternal cells? *Pediatrics*. 2007; 119(3), e724–732.
153. Taft DH, Ambalavanan N, Schibler KR, *et al*. Intestinal microbiota of preterm infants differ over time and between hospitals. *Microbiome*. 2014; 2, 36.
154. Patel K, Konduru K, Patra AK, Chandel DS, Panigrahi P. Trends and determinants of gastric bacterial colonization of preterm neonates in a NICU setting. *PLoS ONE*. 2015; 10(7), e0114664.
155. Ardissone AN, de la Cruz DM, Davis-Richardson AG, *et al*. Meconium microbiome analysis identifies bacteria correlated with premature birth. *PLoS ONE*. 2014; 9(3), e90784.
156. Arboleya S, Binetti A, Salazar N, *et al*. Establishment and development of intestinal microbiota in preterm neonates. *FEMS Microbiol Ecol*. 2012; 79(3), 763–772.
157. Hill CJ, Lynch DB, Murphy K, *et al*. Evolution of gut microbiota composition from birth to 24 weeks in the INFANTMET Cohort. *Microbiome*. 2017; 5(1), 4.
158. La Rosa PS, Warner BB, Zhou Y, *et al*. Patterned progression of bacterial populations in the premature infant gut. *Proc Natl Acad Sci USA*. 2014; 111(34), 12522–12527.
159. Thompson AL, Monteagudo-Mera A, Cadenas MB, Lampl ML, Azcarate-Peril MA. Milk- and solid-feeding practices and daycare attendance are associated with differences in bacterial diversity, predominant communities, and metabolic and immune function of the infant gut microbiome. *Front Cell Infect Microbiol*. 2015; 5, 3.
160. Harmsen HJ, Wildeboer-Veloo AC, Raangs GC, *et al*. Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *J Pediatr Gastroenterol Nutr*. 2000; 30(1), 61–67.
161. Martin V, Maldonado-Barragan A, Moles L, *et al*. Sharing of bacterial strains between breast milk and infant feces. *J Hum Lact*. 2012; 28(1), 36–44.
162. Rogier EW, Frantz AL, Bruno ME, *et al*. Secretory antibodies in breast milk promote long-term intestinal homeostasis by regulating the gut microbiota and host gene expression. *Proc Natl Acad Sci USA*. 2014; 111(8), 3074–3079.
163. Schwartz S, Friedberg I, Ivanov IV, *et al*. A metagenomic study of diet-dependent interaction between gut microbiota and host in infants reveals differences in immune response. *Genome Biol*. 2012; 13(4), r32.
164. Praveen P, Jordan F, Priami C, Morine MJ. The role of breast-feeding in infant immune system: a systems perspective on the intestinal microbiome. *Microbiome*. 2015; 3, 41.
165. Pannaraj PS, Li F, Cerini C, *et al*. Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. *JAMA Pediatr*. 2017; 171(7), 647–654.
166. Marcobal A, Sonnenburg JL. Human milk oligosaccharide consumption by intestinal microbiota. *Clin Microbiol Infect*. 2012; 18(Suppl. 4), 12–15.
167. Ho NT, Li F, Lee-Sarwar KA, *et al*. Meta-analysis of effects of exclusive breastfeeding on infant gut microbiota across populations. *Nat Commun*. 2018; 9(1), 4169.
168. Forbes JD, Azad MB, Vehling L, *et al*. Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life association of breastfeeding with gut microbiota and risk of overweightassociation of breastfeeding with

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gut microbiota and risk of overweight. *JAMA Pediatr*. 2018; 172(7), e181161.
169. Rautava S. Early microbial contact, the breast milk microbiome and child health. *J Dev Orig Health Dis*. 2015; 7(1), 1–10. doi: 10.1017/S2040174415001233
170. Bezirtzoglou E, Tsiotsias A, Welling GW. Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH). *Anaerobe*. 2011; 17(6), 478–482.
171. Kelishadi R, Farajian S. The protective effects of breastfeeding on chronic non-communicable diseases in adulthood: A review of evidence. *Adv Biomed Res*. 2014; 3, 3.
172. Akobeng AK, Ramanan AV, Buchan I, Heller RF. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Arch Dis Child*. 2006; 91(1), 39–43.
173. Moossavi S, Sepehri S, Robertson B, *et al*. Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. *Cell Host Microbe*. 2019; 25(2), 324–335.e4.
174. Sugino KY, Paneth N, Comstock SS. Michigan cohorts to determine associations of maternal pre-pregnancy body mass index with pregnancy and infant gastrointestinal microbial communities: late pregnancy and early infancy. *PLoS ONE*. 2019; 14(3), e0213733.
175. Galley JD, Bailey M, Kamp Dush C, Schoppe-Sullivan S, Christian LM. Maternal obesity is associated with alterations in the gut microbiome in toddlers. *PLoS ONE*. 2014; 9(11), e113026.
176. Mueller NT, Shin H, Pizoni A, *et al*. Birth mode-dependent association between pre-pregnancy maternal weight status and the neonatal intestinal microbiome. *Sci Rep*. 2016; 6, 23133.
177. Lemas DJ, Young BE, Baker PR 2nd, *et al*. Alterations in human milk leptin and insulin are associated with early changes in the infant intestinal microbiome. *Am J Clin Nutr*. 2016; 103(5), 1291–1300.
178. Collado MC, Isolauri E, Laitinen K, Salminen S. Effect of mother's weight on infant's microbiota acquisition, composition, and activity during early infancy: a prospective follow-up study initiated in early pregnancy. *Am J Clin Nutr*. 2010; 92(5), 1023–1030.
179. Soderborg TK, Clark SE, Mulligan CE, *et al*. The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD. *Nat Commun*. 2018; 9(1), 4462.
180. Chen C, Xu X, Yan Y. Estimated global overweight and obesity burden in pregnant women based on panel data model. *PLoS ONE*. 2018; 13(8), e0202183.
181. Chu SY, Kim SY, Schmid CH, *et al*. Maternal obesity and risk of cesarean delivery: a meta-analysis. *Obes Rev*. 2007; 8(5), 385–394.
182. Lepe M, Bacardi Gascon M, Castaneda-Gonzalez LM, Perez Morales ME, Jimenez Cruz A. Effect of maternal obesity on lactation: systematic review. *Nutr Hosp*. 2011; 26(6), 1266–1269.
183. Steegenga WT, Mischke M, Lute C, *et al*. Maternal exposure to a Western-style diet causes differences in intestinal microbiota composition and gene expression of suckling mouse pups. *Mol Nutr Food Res*. 2017; 61(1).
184. Zijlmans MAC, Korpela K, Riksen-Walraven JM, de Vos WM, de Weerth C. Maternal prenatal stress is associated with the infant intestinal microbiota. *Psychoneuroendocrinology*. 2015; 53, 233–245.
185. Jasarevic E, Howard CD, Misic AM, Beiting DP, Bale TL. Stress during pregnancy alters temporal and spatial dynamics of the maternal and offspring microbiome in a sex-specific manner. *Sci Rep*. 2017; 7, 44182.
186. Golubeva AV, Crampton S, Desbonnet L, *et al*. Prenatal stress-induced alterations in major physiological systems correlate with gut microbiota composition in adulthood. *Psychoneuroendocrinology*. 2015; 60, 58–74.
187. Gur TL, Bailey MT. Effects of stress on commensal microbes and immune system activity. *Adv Exp Med Biol*. 2016; 874, 289–300.
188. Ferrocino I, Ponzo V, Gambino R, *et al*. Changes in the gut microbiota composition during pregnancy in patients with gestational diabetes mellitus (GDM). *Sci Rep*. 2018; 8(1), 12216.
189. Crusell MKW, Hansen TH, Nielsen T, *et al*. Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. *Microbiome*. 2018; 6(1), 89.
190. Cortez RV, Taddei CR, Sparvoli LG, *et al*. Microbiome and its relation to gestational diabetes. *Endocrine*. 2019; 64(2), 254–264.
191. Wang J, Zheng J, Shi W, *et al*. Dysbiosis of maternal and neonatal microbiota associated with gestational diabetes mellitus. *Gut*. 2018; 67(9), 1614–1625. doi: 10.1136/gutjnl-2018–315988
192. Hu J, Nomura Y, Bashir A, *et al*. Diversified microbiota of meconium is affected by maternal diabetes status. *PLoS ONE*. 2013; 8(11), e78257.
193. Hasan S, Aho V, Pereira P, *et al*. Gut microbiome in gestational diabetes: a cross-sectional study of mothers and offspring 5 years postpartum. *Acta Obstet Gynecol Scand*. 2018; 97(1), 38–46.
194. Lynch SV, Wood RA, Boushey H, *et al*. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol*. 2014; 134(3), 593–601.e2.
195. Fujimura KE, Johnson CC, Ownby DR, *et al*. Man's best friend? The effect of pet ownership on house dust microbial communities. *J Allergy Clin Immunol*. 2010; 126(2), 410–412, 412 e411–413.
196. Fujimura KE, Demoor T, Rauch M, *et al*. House dust exposure mediates gut microbiome lactobacillus enrichment and airway immune defense against allergens and virus infection. *Proc Natl Acad Sci USA*. 2014; 111(2), 805–810.
197. Laursen MF, Zachariassen G, Bahl MI, *et al*. Having older siblings is associated with gut microbiota development during early childhood. *BMC Microbiol*. 2015; 15, 154.
198. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy*. 1999; 29(5), 611–617.
199. Gereda JE, Leung DY, Thatayatikom A, *et al*. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet*. 2000; 355(9216), 1680–1683.
200. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA*. 2002; 288(8), 963–972.