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Early life exposures and the microbiome: implications for inflammatory bowel disease prevention

Lin Zhang, PhD[1,2,3,*], **Manasi Agrawal, MD, MS**[4,5,*], **Siew C Ng, PhD**[1,2,3], **Tine Jess, MD, DMSci**[4,6]

[1]Microbiota I-Center (MagIC), Hong Kong SAR, China

[2]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China

[3]Li Ka Shing Institute of Health Sciences, State Key Laboratory of Digestive Disease, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong SAR, China

[4]Center for Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark

[5]The Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York NY

[6]Department of Gastroenterology & Hepatology, Aalborg University Hospital, Aalborg, Denmark

Abstract

The early life period is one of microbiome establishment and immune maturation. Early life exposures are increasingly being recognized to play an important role in inflammatory bowel disease (IBD) risk. The composition of functions of the gut microbiome in the prenatal, perinatal and postnatal period may be crucial towards development of health or disease, including IBD, later in life. We herein present a comprehensive summary of the interplay between early life factors and microbiome perturbations and their association with risk of IBD. In addition, we provide an overview of host and external factors in early life that are known to impact gut microbiome maturation and exposures implicated in IBD risk. Considering the emerging concept of IBD prevention, we propose strategies to minimize maternal and offspring exposure to potentially harmful variables and recommend protective measures during pregnancy and the postpartum period. This holistic view of early life factors and microbiome signatures amongst mothers

Corresponding author: Tine Jess, MD, DMSci, Center for Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Department of Clinical Medicine, Aalborg University, A. C. Meyers Vænge 15, 2450 København, Denmark.
*denotes equal contribution

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MA has served as a consultant for Douglas Pharmacoceuticals. LZ and SCN are named inventors of patent applications held by the CUHK and MagIC that cover the therapeutic and diagnostic use of microbiome. SCN has served as an advisory board member for Pfizer, Ferring, Janssen, and Abbvie and has received honoraria as a speaker for Ferring, Tillotts, Menarini, Janssen, Abbvie, and Takeda, research grants through her affiliated institutions from Olympus, Ferring, and Abbvie. SCN is also a scientific co-founder and shareholder of GenieBiome Ltd and she receives patent royalties through her affiliated institutions. TJ has served as a consultant for Ferring.

and their offspring will help frame our current understanding of their importance toward IBD pathogenesis and frame the roadmap for preventive strategies.

Keywords

early life; Crohn's disease; inflammatory bowel disease; microbiome; ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic gastrointestinal immune-mediated inflammatory disease, associated with substantial morbidity, disability, and complications.[1–3] Globally, IBD incidence and prevalence are on the rise, leading to an increase in individual-, healthcare- and societal-level burdens.[4–7] IBD prevention is an emerging concept; and while we have made strides in IBD diagnosis and treatment (secondary and tertiary prevention), we have to better understand environmental risk factors and downstream effects, particularly those that operate in early life, towards broader public health impact.[1, 8] The Developmental Origins of Health and Disease hypothesis suggests that the developing fetus and child, when exposed to harmful exposures, can develop microbiome perturbations, immune dysregulation, and increased risk of disease later in life, including IBD.[9] Hence, the early life period, which is considered to extend from the prenatal period to 3 years old, represents a critical window during which exposures pertaining to diet, medications, and personal and extended environment can modulate organs and immune development, confer long-lasting effects on the offspring, and influence risk for various diseases after a long latent period.[10] Other mechanisms, including epigenetic alterations, oxidative stress, and inflammation, may also contribute to health and disease later in life. [11] In this review, we summarize recent advances in our understanding of the relationships among early life risk factors, microbiome perturbations, and subsequent IBD risk. We highlight knowledge gaps and propose strategies in the early life period that may potentially contribute to reducing IBD risk later in life.

EARLY LIFE FACTORS KNOWN TO MODULATE GUT MICROBIOME ESTABLISHMENT

Gut microbiome development starts at birth, with the establishment of bacterial communities such as *Bifidobacterium longum*, *Escherichia coli*, and *Bacteroides fragilis*. These are acquired from the mother, with gradual diversification depending on variables such as diet, environment, and use of antibiotics. Introduction of external foods leads to exposure to new bacteria and emergence of adult-specific family like *Ruminococcaceae*.[12] By age 2 years, the microbiome starts to resemble an adult-like composition with increased Bacteroidetes, decreased Proteobacteria, and relatively stable Firmicutes.[12] This evolving microbial ecosystem plays a significantly dynamic role in early life, influencing immune development, metabolism, and potentially, the risk of disease development in later life.[12, 13]. The infant gut microbiome can be broadly divided into three types, namely F-type, P-type, and A-type, based on the relative abundance of phyla Firmicutes, Proteobacteria, or Actinobacteria, respectively.[14] The country of residence during the early life period plays

a critical role in determining these categories (Figure 1).[15, 16] Denmark and Spain are F-type, in which the infant microbial gut type contains higher levels of *Enterococcaceae*, *Streptococaceae* etc.[17, 18] The three East Asian countries, China, Japan, and Korea, are P-type, where *Enterobacteriaceae* predominates in the first month of life.[14, 19, 20] *Bifidobacterium*-dominated A-type cluster in Southeast Asia, Australia, parts of Europe, as well as in the African continent.[21–24] Genetic and environmental differences across geography are likely to account for these distinct microbiome types.

The early life period is characterized by specific temporal microorganism acquisition, colonization, and selection, with differential functional features over time. These are modulated by various exposures during the prenatal, perinatal and postnatal periods, as discussed below (Figure 2).[25–31] During pregnancy, host factors such as changes in hormone levels are associated with remodelling of the gut microbiome.[32, 33] Third trimester fecal microbiome analysis suggests a higher burden of inflammation and lower stool energy content, measured by constant volume calorimetry, when compared to the first trimester fecal microbiome analysis.[32]

The maternal microbiome plays a key role in shaping the infant microbiota. In a study of 135 mother-infant dyads, *Bifidobacterium adolescentis* and *B. longum* were transmitted from mothers to infants.[34] Further, the maternal-fetal transmission of several specific bacterial strains, including *Bifidobacterium lactis*, *Lactobacillus rhamnosus GG* (LGG), *Bacteroides spp.*, and *Lactobacillus* may impact the development and function of the neonatal immune system.[35] Importantly, while the mode of birth seems to dictate the initial transmission, the composition shifts towards a more adult-like configuration by around three years of age, with Firmicutes becoming more dominant.[36]

Numerous studies have highlighted a correlation between maternal microbiome and the development of immune-mediated diseases in their offspring. McCauley et al. demonstrated that vertical transmission of maternal bacteria influences fetal immune programming and subsequent allergy risk.[37] The microbial composition of maternal milk, including the more abundant *Bacteroides vulgatus*, may influence the risk of infant celiac disease through vertical transmission.[38] Based on these data, maternal microbial species such as Bacteroides, Bifidobacteria, and *Lactobacilli* may play a role in modulating the risk of immune-mediated diseases in the offspring.

Variables relating to lifestyle, weight changes during pregnancy, stress, and comorbid conditions, such as gestational diabetes and depression, are reported to influence the gut microbiome during pregnancy. Further, a high-fat diet during pregnancy can lead to *Enterococcus* enrichment and *Bacteroides* depletion in the neonatal gut.[39] Recent pre-clinical work suggested that a decline of gut microbial diversity and enrichment of Proteobacteria were observed in mice offspring when dams fed with low-fiber diets during lactation; these perturbations were not reversed with a high-fiber diet for the offspring.[40] Maternal smoking during pregnancy also influences the offspring's gut microbiome. In animal models, smoking-related nicotine exposure during pregnancy influenced maternal gut microbiota, which in turn alters fetal exposure levels to circulating short-chain fatty acids and leptin during in-utero development.[41] In a longitudinal study from Germany, maternal

smoking during pregnancy was associated with offspring microbiome perturbations in early life, which in turn may influence later outcomes such as cognitive function.[42]

Maternal factors during pregnancy like stress, obesity, diet, exercise, and sleep also can contribute to an infant's gut microbial development. In a study of risk factors on depressive symptoms, with maternal and obstetric information collected between birth and 11 years of age, maternal stress during pregnancy was linked to depression in children.[43] Compared to women with normal body weight, those who were overweight during pregnancy had a lower relative abundance of *Bifidobacterium* and *Bacteroides* and an increased relative abundance of *Staphylococcus*, *Enterobacteriaceae*, and *Escherichia coli*.[44] Maternal obesity has also been associated with altered infant gut microbiota, with potential implications towards offspring outcomes.[39, 44–46] Diet, especially maternal fiber intake[47–49] and alcohol consumption[50–52] show a significant impact on the gut microbiota compositions of both mother and offspring. Regular exercise and adequate sleep during pregnancy influence maternal health and the establishment of the offspring's gut microbiome.[53, 54]

Caesarean section delivery shapes an early life gut microbial signature that is distinct from that after vaginal delivery, with a higher level of dissimilarity in offspring, compared to the mother, in the former.[25, 55] Caesarean section can disturb the vertical transmission of specific species, such as maternal *Bacteroides strains,* and delay infant *Bifidobacterium* colonization.[25, 56–58] In most Caesarean section-delivered infants, *Bacteroides* species are depleted, and replaced by microbiota from breast milk, saliva, and skin, or even opportunistic pathogen colonization, including *Enterococcus*, *Enterobacter* and *Klebsiella* species.[25, 26, 56, 58–60] Maternal bacterial strains tend to colonize, while those from other sources are less stable in the neonate.[56] These differences can last up to 6–18 months of life and recover by 3–5 years of age.[25, 61] Although epidemiological data suggest that the risk of IBD may not be affected by the mode of delivery, further study of the long-term impact of above microbial perturbations is warranted.[62, 63]

Next, antibiotic exposure during early life is associated with microbiome homeostasis disruption.[64] In the Finnish Health and Early Life Microbiota (HELMi) study, intrapartum antibiotics were associated with a change in the composition and diversity of the infant gut microbiota, with a more disruptive effect of cephalosporins relative to penicillin.[65] Similarly, in a prospective study of infants from the New Hampshire Birth Cohort, intrapartum penicillin was associated with lower *Bacteroides*, *Bifidobacterium,* and *Blautia* colonization of infant gut microbiome; these alterations were persistent at 1 year of age.[30] Another Finnish study suggested that perinatal antibiotic exposure led to offspring microbial colonization of potentially pathogenic nosocomial species.[66] Finally, early life antibiotics may lead to the colonization of antibiotic-resistant microbiota.[67–69] Recovery of the microbiome following antibiotics exposure was inconsistent, and varied across offspring, with some having persistent perturbations at 12 months of age.[69] Downstream effects of microbiome perturbations can include metabolic alterations, including those in folate synthesis, glycerolipid metabolism, fatty acid biosynthesis, and glycolysis.[70]

Preterm birth leads to deviant and less diverse gut microbiome development, compared to at-term birth.[71] The nosocomial environmental microbiome has been detected in preterm

offspring.[72] Lower gestational age may also be associated with antibiotic-resistance genes.[73] For example, multi-drug resistant species of *Escherichia*, *Klebsiella* and *Enterobacter* dominate the gut microbiota of premature infants in a longitudinal preterm birth cohort.[67] According to a Canadian cohort study, differences in birth season may influence the beta diversity of fungal communities.[74]

Early life nutrition, primarily breastfeeding, influences sustained infant gut microbiome maturity.[75] Gut microbiome composition varies between breastfed and formula-fed infants; this difference persists at 6–24 months of age.[28] For example, in an observational case-control study, *Bifidobacterium* and *Lactobacillus* were the predominant species in breastfed infants.[26, 76] Weaning before 6 months of age was associated with an enrichment of several antibiotic-resistant genes and mobile genetic elements in infants, while longer duration of breastfeeding was associated with a lower Gammaproteobacteria prevalence and more stable gut ecology.[28] This may influence antibiotic resistance gene carriage by the infant gut microbiome.[77] Formula-fed infants have a higher prevalence of Bacteroidetes and Firmicutes and a higher abundance of *Ruminococcus gnavus*, *Lachnospiraceae bacterium*, and opportunistic pathogens.[28, 58, 60, 73] Further data are needed to understand the effects of specific breast milk constituents on offspring gut microbiome and long term outcomes.

Offspring living in the urban environment may have a less diverse gut microbiome compared to those more rural.[78] Living in an industrialized environment has been linked with increased gut Bacteroidetes and decreased Firmicutes.[79, 80] The impact of breastfeeding on the offspring gut microbiome is altered in an industrialized environment with a paucity of *Bifidobacterium infantis*.[78] Exposure to furry pets in early life may lead to enrichment of animal-specific species, such as *Bifidobacterium pseudolongum*.[81] Certainly, pets have been linked with reduced risk of childhood atopy and obesity.

During early life, the relationship between the gut microbiome and the host immune system plays a crucial role in health and disease. First, exposure to environmental bacteria in dust after birth has been shown to influence the microbiota and modulate host immune responses in mouse models, in which dominance of Proteobacteria and Firmicutes relative to Bacteroidetes is associated with enhanced Th2-mediated inflammation.[82] In studies of the lower respiratory tract and gut microbiome in children at risk for asthma, a decrease in *Veillonella*, *Faecalibacterium*, and *Rothia* species during early infancy was correlated with protection against asthma, and the increasing genus *Clostridium* was positively correlated with fecal IgE levels and immune regulation.[83, 84] A transitional period during early life, where the neonate's microbiome evolves towards an adult-like configuration could also be a critical period in the development of immune tolerance.[85]

Factors early in life have a significant impact on the incidence of diseases in infancy and childhood. However, the degree of impact on adulthood varies across diseases and individual-level variables.[86, 87] There is currently insufficient evidence that factors in early life can directly affect the incidence of diseases in the elderly. Diseases in the elderly are more likely to be the result of accumulated environmental exposures and immunosenescence, with significant heterogeneity across risk variables.

Overall, geographic location in early life, maternal factors, including stress, obesity, diet, gestational age at birth, mode of delivery, nutrition, antibiotic exposure, exercise, sleep, and the offspring environment can impact the colonization and maturation of the human gut microbiota during early life. The long-term implications of these features, including post-birth recovery of the microbiome, are yet to be established.

The microbial composition dynamics in patients with IBD bear striking resemblances to changes induced by early life disturbances. The dysbiosis or imbalance of gut microbiota in IBD is typically characterized by a reduction in commensal bacterial diversity, which is consistently observed in both stool and mucosal samples drawn from IBD patients and marked specifically by a decline in Bacteroidetes and a surge in *Enterobacteriaceae*.[88–92] Many other beneficial bacterial species are significantly reduced in IBD including *Bacteroides*, *Lactobacillus*, *Bifidobacterium adolescentis*, and *Clostridium*.[93–95] Contextually, the gut microbiota of infants also changes due to various factors, paralleling the dynamics seen in IBD. It is noteworthy that Bacteroidetes are unavailable to most infants born by Caesarean section until the late neonatal period.[96] Similar to microbial changes in IBD, antibiotic exposure, formula feeding, and prematurity are associated with a reduction in the abundance of *Bifidobacterium* and *Lactobacillus*, and an increase in *Enterobacteriaceae* abundance.[73, 97–100]

EARLY LIFE RISK FACTORS FOR IBD

Studies exploring the role of early life factors towards IBD risk fall broadly into one of two categories; first, traditional or clinical epidemiological data wherein exposure assessment is done through surveys, questionnaires and register data and second, molecular epidemiological data with measurement of exposures in biological samples leveraging omic techniques.[101] Each approach has strengths and limitations and putting data together from both categories of studies is most informative.

Numerous epidemiological studies have been conducted in the last few decades to explore the association of risk factors that operate in the early life period and the development of IBD. In a granular systematic review of 114 studies with meta-analyses of 39 studies, our group studied maternal health and prenatal exposures, perinatal exposures, birth month, breastfeeding, hygiene-related factors, social factors, immigration, antibiotics, offspring health, including infections, and passive smoking.[27] We reported that in utero exposure to antibiotics [odds ratio, OR 1.8; 95% confidence interval (CI) 1.2, 2.5] and early life otitis media (OR 2.1; 95% CI 1.2, 3.6) were associated with IBD. The association between postnatal exposure to antibiotics and IBD (OR: 1.7, 95% CI 0.97, 2.9) was less clear.[27] In a subsequent analysis of nationwide data with over 8 million person-years of follow up, we found that in utero exposure to ≥3 more courses of antibiotics, but not fewer courses, was associated with a 45% increase in ulcerative colitis risk [adjusted hazard ratio (aHR) 1.45, 95% CI 1.06, 2.00].[102] There was no increase in CD risk with antibiotic exposure during pregnancy (aHR 1.15, 95% CI 0.83, 1.60).[102] In another nationwide case-control study, Jawad et al reported that antibiotic exposure at <5 years of age was associated with increased pediatric-onset IBD risk, especially with an increasing number of antibiotic courses.[103] These data on antibiotics and IBD risk are consistent with the known disruption of gut

microbiome with increasing courses of antibiotics, which may then lead to downstream effects of mucosal immune dysregulation. The association between early-life infections and IBD may be direct, that is, infections may be causal towards IBD risk, or indirect, mediated via antibiotics, used for the treatment of infections. Mechanistic data lend weight to these observational studies; Miyoshi et al demonstrated that in the IL-10-deficient murine colitis model, maternal exposure to antibiotics during pregnancy led to persistent gut dysbiosis and increased the risk of spontaneous and chemically-induced colitis in the offspring.[104] Additional provocative data include a population-based cohort study demonstrating that exposure to mebendazole, a broad-spectrum anthelminthic agent, before 5 years of age, but not later in life, was associated with increased risk of UC in adulthood.[105] Certainly, parasitic infestation has been linked with immune tolerance, and early life eradication may inform later risk of disease.

There is a strong link between maternal IBD and subsequent risk of childhood IBD. IBD has a familial aggregation which is likely to be mediated, at least in part, by maternal IBD.[106] This is supported by the MECONIUM study, which demonstrated that offspring of women with IBD had a lower gut microbial diversity and elevated calprotectin, relative to those born of healthy controls. Of course, the clinical relevance of these findings is yet to be established.[109, 110] In a comprehensive Canadian epidemiological report, the incidence of IBD in children under five is rising rapidly.[107] In a nationwide study from Denmark, a consistent increase in IBD incidence was noted, particularly among children.[4] In a systematic review of 131 studies from 38 countries, the incidence of pediatric-onset IBD was found to be increasing across cohorts.[108]

Next, diet and nutrition play a key role in microbiome and immune development, and later health and disease. Breast milk contains indispensable micro- and macronutrients, and breastfeeding is associated with vast health benefits for the offspring. Breastfeeding has been linked with a protective effect against IBD in many, but not all, studies on the topic. In a systematic review and meta-analysis of 35 studies, breastfeeding was associated with a lower risk of CD (OR 0.71, 95% CI 0.59, 0.85) and UC (OR 0.78, 95% CI 0.67; 0.91).[111] The inverse association was stronger among Asian individuals and with 12 months as compared to 3 or 6 months of breastfeeding.[111] Others, however, have demonstrated a null association between breastfeeding and IBD risk.[112, 113] There is a biological basis for these observations as well; for example, human milk oligosaccharides are critical towards Bifidibacterium establishment in the offspring gut, which in turn, plays a key role in intestinal homeostasis and immune function.[114, 115] Early introduction of foods such as gluten, egg yolk, and peanuts have been linked with lower risk of celiac disease,[116] atopic dermatitis,[117] and allergies[118]. This may be mediated through the modulation of mucosal immune tolerance.[119] Studies on early life nutrition and IBD risk will be informative. The influence of maternal nutrition during pregnancy on offspring outcomes is being explored in the Modulating Early Life Microbiome through Dietary Intervention in Pregnancy (MELODY) trial.[120]

Exposure to tobacco smoke is an important risk factor for IBD; maternal smoking during pregnancy was associated with IBD in the offspring with an OR of 1.5 (95% CI 1.2, 1.9) in the meta-analysis described above.[27] Active smoking during childhood was also

associated with IBD risk; children who smoked regularly by the age of 10–15 years had higher odds of both CD and UC.[121] However, data on the impact of passive exposure to smoke during early life on IBD are conflicting.[121, 122] Relatedly, exposure to air pollution has also been linked with IBD risk. Elten et al, using geographic information system-based data, investigated the impact of nitrogen dioxide, fine particulate matter, ozone, and oxidant capacity on pediatric-onset IBD.[123] They found that exposure to the latter pollutant during early pregnancy was associated with an increase in IBD risk. Mechanistic data lend biological plausibility; smoking leads to epigenetic alterations, with downstream alterations in gene expression, and subsequent risk of disease.[124] While hyper- and hypomethylation signatures prior to IBD onset are yet to be explored, an altered epigenome is reported in multiple studies of post-diagnosis biological samples.[125, 126]

Early life exposure to chemical pollutants and toxins is increasingly being studied in the context of IBD. In a proof-of-concept analysis of deciduous teeth from 12 individuals with IBD and 16 healthy controls, Nair et al measured heavy metals and timing of exposure using a novel laser ablation-inductively coupled plasma-mass spectrometry analysis of deciduous teeth samples.[127] They reported that there were time-specific differences in lead, copper, zinc, and chromium uptake in teeth from individuals who later developed IBD, compared to those who did not. These pilot data denote a potential role for heavy metal exposure during the early life period and warrant further study. Certainly, heavy metals have been linked to gut microbiome perturbations and inflammatory responses. Other chemicals such as per- and polyfluoroalkyl substances (PFAS) have been linked with altered barrier function and immune dysregulation.[128] Microplastics, which are plastic particles <5 mm in size, are also implicated in microbiome perturbations and potentially, intestinal inflammation.[129, 130] Future studies exploring these chemical pollutants in early life biological samples will be highly informative.

Next, there are emerging data on the role of the natural environment in shaping immune tolerance. This is especially relevant in our modern environment, considering climate change and biodiversity loss at an alarming rate. Elten et al demonstrated that childhood residential green space, based on satellite-derived normalized difference vegetation index, was associated with a protective effect against pediatric-onset IBD in a dose-dependent manner.[131] Finally, considering a more ecological perspective, most of the above exposures are a function of shifts in the environment and culture with urbanization and industrialization, and these observations fit with the rise in IBD in parallel with industrialization as well as upon immigration from developing to developed countries.[132, 133]

EARLY LIFE PREVENTATIVE STRATEGIES

IBD is a heterogeneous disease; certainly, the two sub-types of CD and UC are distinct in phenotype, disease course and pathophysiology, albeit with overlaps.[2, 3] Therefore, we propose that there are likely to be multiple “hits” with progressive accumulation of susceptibility to IBD. Broadly, insults during the early life period are likely to lead to microbiome perturbations and immune dysregulation, creating a background for IBD susceptibility, whereas later exposures may lead to disease onset (Figure 3). Therefore, preventive strategies during the early life period (Figure 4) would be targeted toward

maintaining gut microbiome homeostasis, mucosal immune tolerance, and robust immunity and constitute primordial and primary prevention strategies.[1] We hypothesize that these strategies would be relevant towards protection against immune-mediated disease overall, in addition to IBD specifically.

Starting with the pregnant mother, we recommend antibiotic stewardship, and judicious use of antibiotics only when necessary and for the shortest possible duration. Avoidance of smoking and passive exposure to tobacco smoke is likely to be beneficial against IBD risk, as well as maternal-offspring health overall. A healthful, balanced diet, with avoidance of "pro-inflammatory" components such as processed foods, is also likely to be beneficial.[134] Avoiding exposure to chemical and air pollutants and increasing exposure to nature and greenspace, when feasible, will also be important.

With respect to the offspring, as above, antibiotic and antihelminth stewardship, and avoiding exposure to tobacco smoke, air, and chemical pollutants, would be relevant to promote a robust microbiome and mucosal immunity. In addition, breastfeeding is important towards a healthy microbiome; its benefits extend to all aspects of health. Early introduction of various foods is protective against food allergies, but its role in IBD is less clear.[135]

The feasibility of early intervention treatments in life has been demonstrated in reducing asthma risk. In a systematic review and meta-analysis study of 20 eligible trials including 4866 children, infants with lower gut microbiome diversity were more likely to develop asthma later in childhood, and supplementation of specific bacterial genera (*Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*) in the first 100 days of life was associated with lower asthma risk.[136] Future interventions may include dietary and microbial manipulation in IBD. For example, an anti-inflammatory diet during pregnancy could inform offspring health. The MELODY trial investigates the impact of an anti-inflammatory dietary intervention during pregnancy on the gut microbiome of pregnant women with Crohn's disease, relative to those on a regular diet and healthy controls, as well as on the gut microbiome and fecal calprotectin of their offspring. If the trial indicates a positive impact of the dietary intervention, this may become an important tool to modulate the gut microbiome and potentially intestinal inflammation.[120] Probiotic preparations that contain keystone microbial strains may be beneficial. In results from another study, early restitution of a single Bacteroides strain in mice models appear promising.[137] However, we recognize that the impact of these strategies to prevent IBD later in life will be challenging to measure and is likely to vary across geography, cultures, and age groups.

KNOWLEDGE GAPS AND DEBATES

While strides have been made in unraveling the impact of early life variables on the microbiome and IBD risk, many unanswered questions remain. The presence of placental bacterial colonization during pregnancy and its downstream effects are debated.[138] Current research is insufficient to definitively prove or reject the sterile womb hypothesis, according to which the in utero environment is completely microbiome-free.[139, 140] Should that be true, it raises questions about quick and successful postnatal adaptation of the neonate to a complex and unsterile environment. Conversely, if indeed a placental

microbiome exists, its function and impact remain unexplored. The role of fungi and viruses in early life and their role in intestinal inflammation remain to be established.[141, 142] A large majority of data on early life exposures and IBD risk are from Western countries.[27] While data from Asia on the impact of breastfeeding and smoking suggest a potentially differential impact on IBD risk relative to that in Western countries,[143] future studies are needed from diverse populations.

Gut microbial diversity loss has been demonstrated among immigrants to the United States and these differences are more substantial among second-generation immigrants.[144] An immigration study in Canada also demonstrated that early life migration results in gut communities similar to those among natives of country immigrated to.[145] Further studies are needed to explore potential underlying mechanisms. Interestingly, multigenerational inherited microbiome traits have been associated with immunological development and susceptibility to chronic diseases.[146–149] In this regard, the impact of maternal IBD on these transmission patterns and on the establishment of the fetal immune system is key to disentangle.

While clinical epidemiological studies are limited by confounding, systematic bias and error in causal inference, analyses of biological samples are limited by access to early life cohorts with long term follow up, availability of omic analytic techniques and associated costs. Therefore, putting data together from both categories of studies is most informative. Finally, while it is observed that early life risk factors lead to gut microbiome perturbations, the longevity and implications of such alterations remain unclear.

With respect to risk factors for IBD, the “black box” that is the molecular pathway from exposure to outcome, warrants further studies. For example, we need to understand the impact of cigarette smoking on intestinal mucosal function and homeostasis beyond the impact on the gut microbiota.[150] Certainly, cigarette smoking leads to hypermethylation alterations, but causal links between smoking, epigenetic modifications, further downstream effects, and IBD are yet to be explored.[151] Similarly, the effects of early life pollution, diet, medications, and stated broadly, the urban environment, on intestinal inflammation, immune function, and IBD risk warrant investigation.

Towards efforts to reduce IBD risk, study of potential early life preventive strategies is important but exceedingly difficult. We propose above “healthful” strategies that, based on indirect data, may be associated with a reduction in IBD risk while promoting overall health. However, we recognize that the impact of these strategies to prevent IBD later in life will be challenging to measure. In the future, interventions to modulate the gut microbiome may emerge. These could include dietary modulation, interventions to change breastfeeding practices, and potentially microbial manipulations.[120, 152]

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In summary, we highlight the relevance of the early life period in association with risk of IBD and discuss microbiome perturbations that may underlie these potential associations. Strategies to improve maternal and offspring health during pregnancy and postpartum will

help improve long-term outcomes. Several knowledge gaps remain, and ongoing and future research works will be highly informative.

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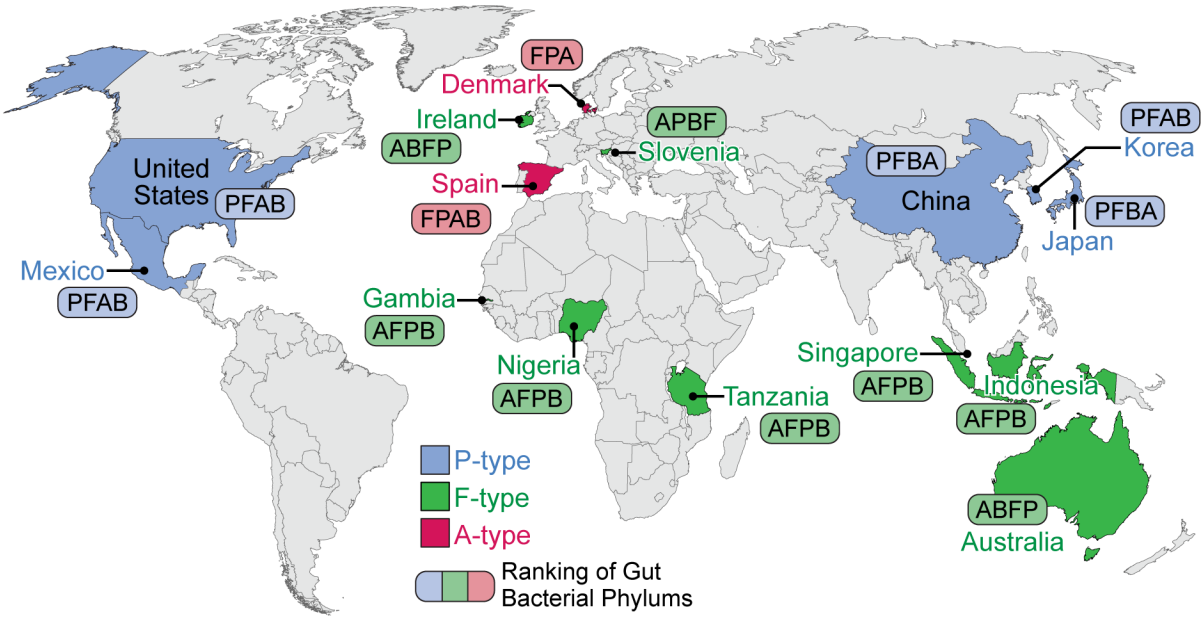
KEY MESSAGES

- Early life exposures can impact the colonization and maturation of the gut microbiome in the first few years of life.
- The early life period represents a window of opportunity for gut microbiome and immune function modulation with a potential impact on health and disease later in life.
- Early life interventions, such as antibiotic stewardship, avoidance of exposure to tobacco smoke, healthful diet, and encouragement of breastfeeding and greenspace exposure, when possible, may be beneficial towards microbiome maturation and reduced IBD risk.



Infant gut microbiome is classified into three types, based on the relative abundance of bacterial phyla as below:

Proteobacteria (P-type): Enterobacteriaceae is the most abundant bacterial family with important subclasses being *Enterobacter, Klebsiella*, and *Escherichia*

Firmicutes (F-type): Includes Firmicutes family bacteria such as *Enterococcus, Streptococcus, Lactobacillus, Veillonella,* and *Clostridium*

Actinobacteria (A-type): The major family is Bifidobacteriaceae, with *Bifidobacteria* being an important subclass

Figure 1.

Impact of geography on early life gut microbiome type: Among infants from 15 countries (China,[14] Japan,[20] Korea,[19] Mexico,[153] The US,[154] Denmark,[17] Spain,[18] Indonesia,[24], Singapore,[24] Australia,[23] Ireland,[21] Slovenia,[22] Gambia, [155] Nigeria,[156] Tanzania,[78]), the bacterial phyla in infant fecal samples showed significant differences in gut bacterial type by region of residence.

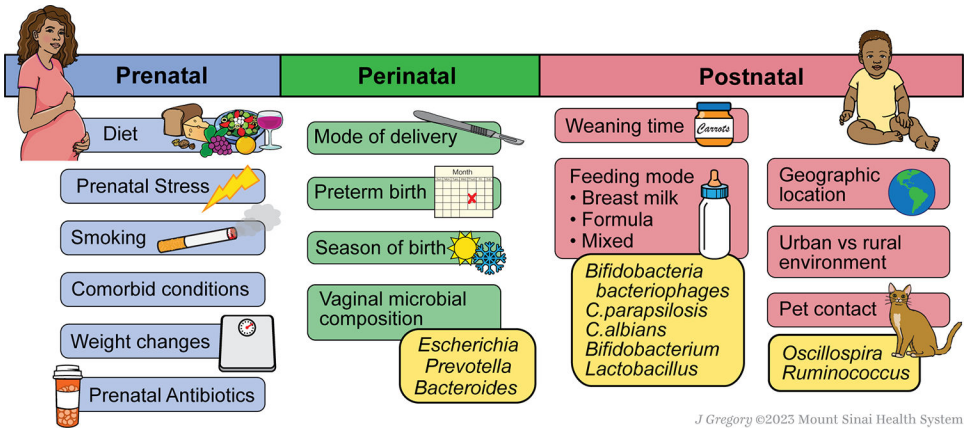


Figure 2.

An overview of relevant early life host and external factors on early life microbiome perturbations. The major influencing factors are summarized in this figure. These factors include those that operate during the prenatal, perinatal, and postnatal periods.

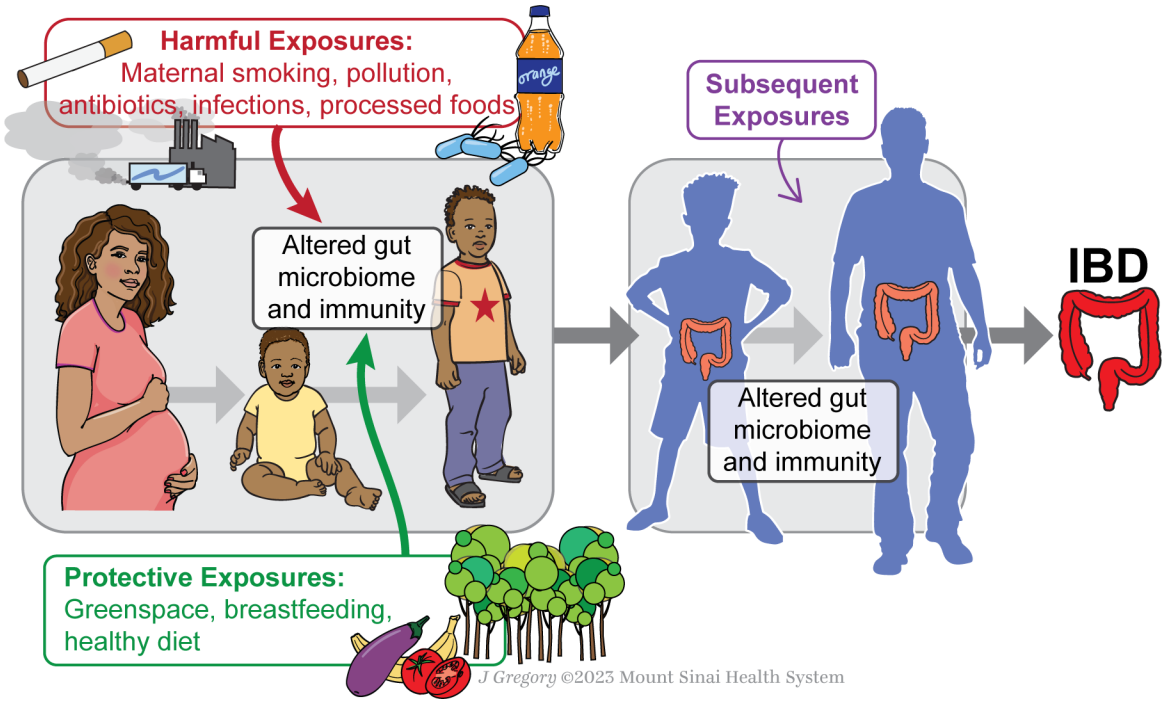


Figure 3.

Proposed "multiple hits" hypothesis in IBD pathogenesis, with early life variables leading to altered gut microbiome and immune function, leading to susceptibility to subsequent exposures and IBD risk.

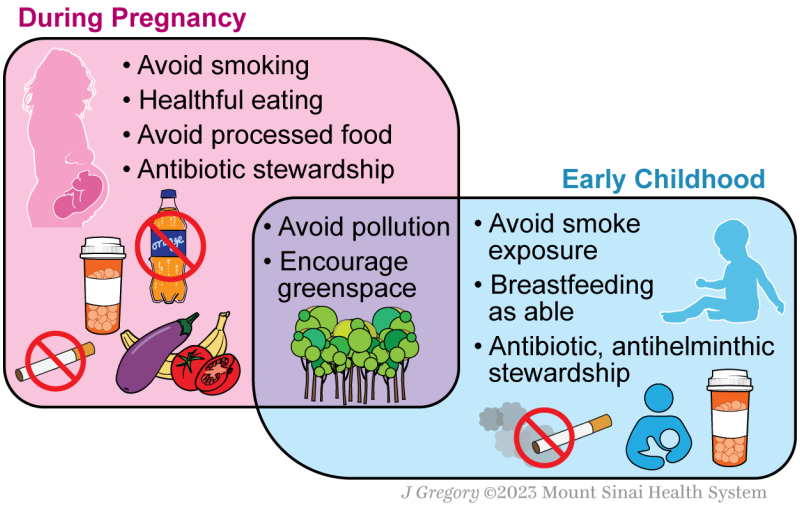


Figure 4.

Proposed interventions during pregnancy and in early childhood towards potential reduction in IBD risk later in life.