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Supplement Article

Early life factors, diet and microbiome, and risk of inflammatory bowel disease

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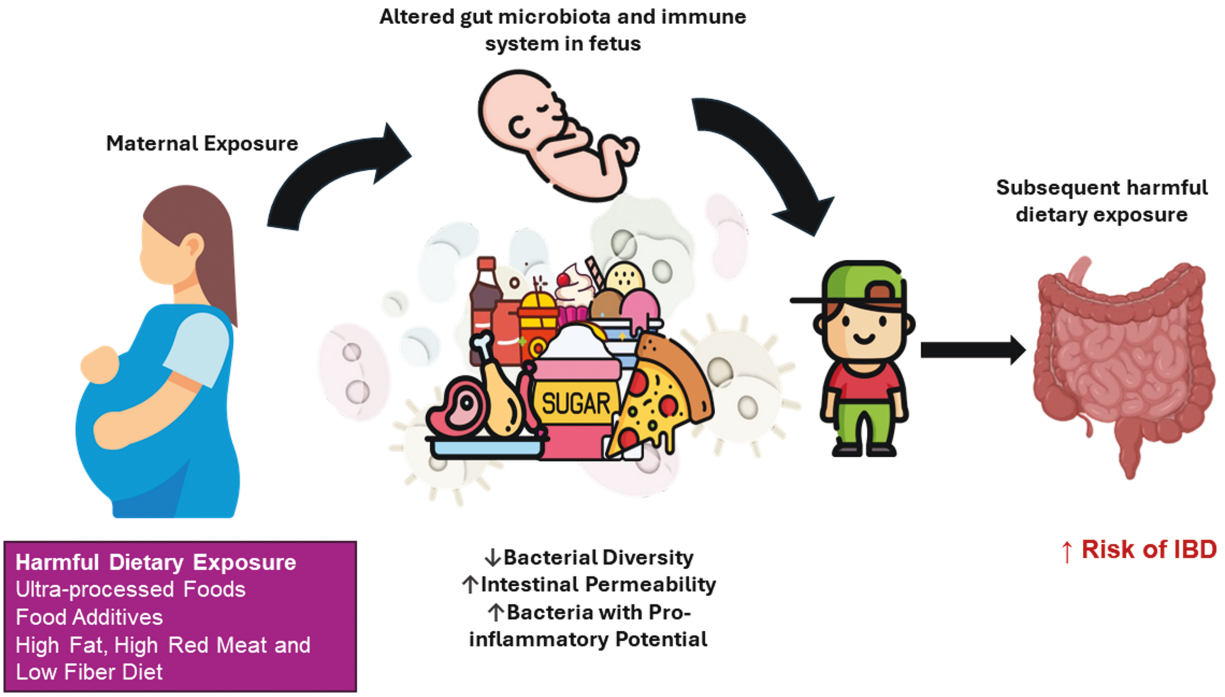
Abstract

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), result from a loss of immune tolerance to gut microbiota, leading to inflammation. Their incidence is increasing, especially in newly industrialized countries. The etiology is multifactorial, involving genetic, immune, microbiota, and environmental factors. Maternal microbiome changes during pregnancy can elevate IBD risk in offspring, influenced by diet, smoking, and antibiotic exposure. Early life microbiota manipulation shows promise for preventing IBD. Epidemiological and pre-clinical studies highlight diet's significant role in IBD development. High-inflammatory dietary patterns correlate with increased CD risk, while Mediterranean-like diets promote beneficial gut microbiome changes and reduce inflammation. Certain food additives, such as emulsifiers and artificial sweeteners, may exacerbate IBD by altering gut microbiota. A systematic review indicates that higher ultra-processed food consumption significantly increases CD risk. Lifestyle modifications, including healthy dietary adherence, could substantially reduce IBD risk, with studies showing that favorable choices can halve the risk in genetically predisposed individuals. Additionally, maternal diet impacts offspring IBD risk, as seen in mouse models where high-fat diets led to increased inflammation. Evidence suggests that maternal probiotics and specific dietary patterns may mitigate these risks. Overall, these findings emphasize the potential for dietary interventions to modulate gut microbiota and immune responses, offering promising avenues for IBD prevention and management. Further large-scale studies are needed to explore the impact of dietary strategies on IBD risk and gut health.

Graphical Abstract



Key words: Inflammatory Bowel Disease; Diet; Microbiome; Environmental risk factors.

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Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are caused by loss of mucosal immune tolerance towards commensal gut microbiota resulting in uncontrolled inflammatory responses. Both CD and UC can be difficult to manage clinically, and their incidences are increasing worldwide especially in newly industrialized countries.[1] The aetiology of these disorders is multifactorial, influenced by the complex interactions of genes, the immune system, intestinal microbiota, and external environmental factors such as diet, lifestyle, and exposure to antibiotics. A healthy gut microbiota community typically exhibits a high level of taxonomic diversity, abundant microbial gene richness, and a stable core microbiota.

In healthy individuals, 99% of gut bacterial phyla consist of Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Firmicutes and Bacteroidetes together make up about 90% of the overall microbiome composition. These phyla play a crucial role in maintaining gut homeostasis and are responsible for the production of short-chain fatty acids. It is well-established in pre-clinical and clinical studies that IBD is associated with perturbations of gut microbiota composition, characterized by a decrease in alpha diversity, with a decrease in abundance of Bacteroidetes and Firmicutes and an increase in that of *Gamma-proteobacteria*, especially AIEC. Even though it has long been suspected that most of the microbiome was shaped by the 'bugs' inherited from mothers during birth and genetics, recent work has identified that the human microbiome is shaped primarily by the environment and cohabitation and only around 6.6% of taxa were heritable, whereas almost 50% were significantly explained by cohabitation. These data suggest that lifestyle factors that are generally considered to be healthy, such as adhering to a healthy diet, not smoking, and living in a green and unpolluted area, are linked to microbiota patterns associated with good health.[2]

Early life microbiome and IBD

The early childhood period, when the microbiota is less mature and more malleable, represents a unique window of opportunity for microbial manipulation. Studying microbiota at this golden age will allow us to dissect the development of a faulty microbiota and identify therapeutic targets to reverse dysbiosis associated with diseases leading to prevention and this is of paramount importance in IBD. For example, in a preclinical model, maternal antibiotic-induced gut dysbiosis vertically transmitted to offspring increased colitis risk in ($IL10^{-/-}$) mice and engraftment of Bacteroides restored development of the early-life gut microbiome and decreased colitis risk later in life.[3] In addition, a proof-of-concept study showed that the intestinal microbiota of infants born by caesarean section can be restored postnatally by maternal faecal microbiota transplantation. Although the long-term implications of such an approach on risk of IBD remain unclear, it highlighted the potential of microbiota manipulation in early life as a potential therapeutic approach. However, this should only be done after careful clinical and microbiological screening.[4]

Accumulating data suggest that the gastrointestinal tract of newborns becomes colonized with bacteria while in the womb,[5] with the presence of different microbes reported in amniotic fluid,[6,7] umbilical cord blood,[8] as well as placental and foetal membranes.[9,10] The source of these microbes is of continued interest, because initial intestinal colonization is believed to play a crucial role in priming of the mucosal immune system and an impaired response may predispose subjects to the development of immune mediated diseases such as IBD later in life.[11] A recent study has identified a novel mechanism of vertically transmitted protection of the newborn. It was found that bacteria in the mother's intestine during gestation can drive later innate maturation of the neonatal gut in the absence of colonization, through the transfer of specific bacterial metabolites to the foetus and via mother's milk.[12] It was also reported that the effects of the gut microbiota on postnatal immune maturation were not simply due to colonization of the new-born after birth.[13] Given the complexity of microbes present in the gestational gut, it will be exciting to understand whether there are other modules of priming induced by distinct microbes and their metabolites. Along these lines, it is tempting to speculate that this transgenerational effect represents a predictive adaptive response whereby mothers prepare the neonates for specific challenges that they are likely to encounter based on gestational environmental cues, not only by microbial colonization but also by metabolite transfer.

Impact of maternal microbiota and maternal lifestyle on risk of IBD in offspring

Alterations in the maternal microbiome during pregnancy may be associated with an increased risk of adverse pregnancy outcomes.[14] Disruptions in the microbiome can lead to inflammation and immune dysregulation,[15] which are believed to be involved in the development of pregnancy complications. However, to date there are limited data on how this impacts risk of IBD in offspring. A human study showed that abnormal gut microbiota composition persisted in mothers with IBD during pregnancy and was associated with changes in bacterial diversity and abundance of bacteria species in the infant's stool.[16] In germ-free mice, a dysbiotic microbiota triggered abnormal imprinting of the intestinal immune system.[16] Additionally, a preclinical study reported that an antibiotic-perturbed maternal microbiota could be transferred to their offspring and resulted in worsened colitis in susceptible mice,[17] which supports the role of the maternal microbiome in the development of IBD in offspring. Several prevention studies have been reported that aimed to target the maternal microbiome to alleviate intestinal inflammation in offsprings. An animal study reported that maternal *Lactobacillus reuteri* supplementation altered the gut microbiome in offspring mice and further protected female offspring from experimental colitis.[18] Though human studies are limited, there is an ongoing dietary intervention clinical trial MELODY (Modulating Early Life Microbiome through Dietary Intervention in Pregnancy), which aims to improve the microbiome composition of pregnant women with Crohn's disease to determine the effectiveness of dietary intervention in restoring the microbiome during early life in the offspring, thereby promoting priming of a healthy immune system.[19] The diet provided consists of beneficial *probiotic* foods such as yogurt and fermented cabbage or *prebiotic* foods such as legumes and artichokes.[19] Such an approach is promising but longer follow-up will be needed to confirm if dietary intervention in early life can reduce the risk of IBD.

Other maternal factors such as smoking and exposure to antibiotics are also known to affect the risk of IBD and these factors are modifiable. A meta-analysis, including nine studies, has reported an association between tobacco smoking during pregnancy and diagnosis of IBD in the offsprings (OR 1.49; 95% CI 1.17-1.90).[20] However, there was no significant association after considering the IBD subtype [Crohn's disease (CD): pOR 1.21, 95% CI 0.75-1.96, and ulcerative colitis (UC): pOR 1.51, 95% CI 0.99-2.31][20]. In a subsequent population-based cohort study, offsprings of mothers who smoked were found to have an increased risk for IBD compared with those born to non-smoking mothers (OR = 1.48, 95 % CI 1.2–1.8, $P < 0.01$).[21]

Pre-clinical studies have reported that prenatal antibiotic exposure led to increased risk of IBD in infants.[17,22,23] Animal studies reported that administering antibiotics during pregnancy had major effects on the offspring's gut microbiome leading to reduced bacterial diversity[23] and gut dysbiosis.[22] This has been shown to influence the immune response of the offspring and increase their susceptibility to developing intestinal inflammation in chemical-induced murine models of colitis[23] or a genetically prone murine models.[22] In addition, an animal study showed that elevated risk of IBD in infants following prenatal antibiotics may be attributed to the transmission of an antibiotic-perturbed microbiota from mothers to their children.[17] Epidemiological data have repeatedly shown that prenatal antibiotic use was associated with an increased risk of IBD.[24] Meta-analysis of cohort and case-control studies have reported an association between antibiotic exposure during pregnancy and subsequent diagnosis of IBD in the offsprings (OR 1.75; 95% CI 1.22-2.51).[20,25] In a population-based study, intra-uterine antibiotic exposure was associated with an increased risk of very early onset (VOE)-IBD (adjusted HR (aHR) 1.93; 95% CI 1.06-3.50), this risk was increased for Crohn's disease (CD, aHR 2.48, 95% CI 1.01-6.08), but not for ulcerative colitis (UC, HR 1.25, 95% CI 0.47-3.26).[25] The highest risk of VEO-IBD was seen in mothers exposed to antibiotics in the third trimester of pregnancy (aHR 2.57, 95% CI 1.10-6.01).[25] In a recent population-based study, exposure to three or more courses of antibiotics was associated with an increased risk of IBD (aHR 1.29, 95% CI 1.03-1.62),[26] which was driven by UC (aHR 1.45, 95% CI 1.06-2.00) but not CD (aHR 1.15, 95% CI 0.83-1.60) risk.[26] Although a population study showed maternal antibiotic exposure during pregnancy was not associated with IBD onset in the offsprings,[27] the cohort focused on an at-risk population who also had a family history of IBD which may have overshadowed the effects of prenatal antibiotics.

Diet and its role in IBD development

Epidemiological and preclinical studies have highlighted the importance of diet in IBD risk. In an analysis of 3 large prospective cohorts, it was found that dietary patterns with high inflammatory potential was associated with an increased risk of CD but not UC.[28] As part of the Genetic, Environmental, Microbial (GEM) Project, Mediterranean-Like dietary patterns were associated with changes in gut microbiome composition and lowered subclinical gastrointestinal inflammation.[29] Furthermore, there is a potential link between certain food additives and development or exacerbation of IBD due to their impact on gut microbiota and immune responses. Emulsifiers have been shown to cause inflammation in germ free mice via altered gut microbiome.[30] Artificial sweeteners and maltodextrin induced alterations in the gut microbiota with an increased relative abundance of *Bacteroides and* decreased *Firmicutes*, which are similar to those observed in IBD in mice models.[31,32] Oral intake of nanoparticles, titanium and aluminium, could lead to impaired intestinal barrier function and enhance intestinal inflammation in animal model.[33,34] A systematic review and meta-analysis consisting of 1 068 425 individuals from 5 cohort studies showed that individuals who consumed higher amounts of ultra-processed foods had an increased risk of developing CD (HR, 1.71; 95% CI, 1.37-2.14), but not UC (Hazard Ratio, 0.84; 95% CI, 0.68-1.02).[35] These data may help guide future dietary strategies that influence microbial composition and host gut inflammation to prevent risk of immune diseases.[29]

Interestingly, understanding gene microbial interactions may have a role in disease mitigation. Across 6 cohorts from the United States and Europe, a substantial burden of IBD risk may be preventable through lifestyle modification. In a prospective cohort study of US adults with 5 117 021 person-years of follow-up, including 346 cases of CD and 456 cases of UC,modifiable risk scores (MRS) for CD and UC and healthy lifestyle scores were developed. It was found that adherence to a low MRS and healthy lifestyle could have respectively prevented 42.9% (95% CI, 12.2-66.1%) and 61.1% (95% CI 16.8-84.9%) of CD, and 44.4% (95% CI, 9.0-69.8%) and 42.2% (95% CI, 1.7-70.9%) of UC. Their findings were also externally validated in 3 European cohorts.[36] In a large-scale cohort study, 502 490 participants were recruited across the UK from 2006 to 2010 and recorded in the UK Biobank. This recruitment led to 707 cases with CD and 1576 cases with UC after a 12-year follow-up. The hazard ratios (HR) of individuals with a high genetic risk but a favourable lifestyle (2.33, 95% CI, 1.58-3.44 for CD, and 2.05, 95% CI, 1.58-2.66 for UC) were reduced nearly by half, compared with those with a high genetic risk but an unfavourable lifestyle (4.40, 95% CI, 2.91-6.66 for CD and 4.44, 95% CI, 3.34-5.91 for UC).[37] Therefore, adherence to a healthy lifestyle was associated with a nearly 50% reduced risk of CD and UC in individuals with a high genetic risk.

Diet modulates the gut microbiome, which in turn can impact the immune system but the subsequent response may be personalized depending on the type of diet. For instance, a high-fibre diet was shown to alter microbiome functions and elicited personalized immune responses whereas fermented-food diet was associated with increased microbiome diversity and decreased markers of inflammation.[38] Consumption of a diet high in red meat increased colitis in DSS-induced colitis mice model as evidenced by higher disease activity and histopathological scores.[39] In genetically susceptible mice, feeding a high fat diet promoted taurine conjugation of hepatic bile acids, leading to the expansion of a low-abundance, sulphite-reducing pathobiont, *Bilophila wadsworthia* and development of colitis.[40] According to data from the Nurses' Health Study Cohort consisting of 170 805 women, women who had a high long-term intake of trans-unsaturated fatty acid had a higher risk of developing UC (HR 1.34, 95% CI, 0.94-1.92).[41] In the E3N prospective study involving 67 581 French women, a strong association was observed between high animal protein intake and an increased risk of IBD (OR 3.03, 95% CI, 1.45-6.34). This association was especially pronounced in UC (OR 3.29; 95% CI, 1.34-8.04).[42] From the EPIC cohort which included 413 593 participants from 8 European countries, higher meat and red meat consumption were associated with

higher odds of developing UC, but not CD.[43] A meta-analysis by Koelman et al showed that patients on Mediterranean diet have significant reduction in serum levels of IL-6 and IL-1β.[44] A prospective cohort study of 83 147 participants revealed that participants who were adhering to Mediterranean diet had a lower risk of CD (adjusted HR 0.42; 95% CI, 0.22-0.80).[45] These data highlighted how coupling dietary intervention can shape our gut microbiota and immune system and potentially modulate the risk of developing IBD. A few dietary interventions have been studied in IBD, including whole food anti-inflammatory diet (IBD anti-inflammatory diet, CD-TREAT, autoimmune protocol) and CD exclusion diet. All showed promising clinical responses, but a majority of studies were limited by sample size.[46–53] Large-scale dietary intervention studies are needed to explore its role on gut microbiota modulation and in reducing inflammation in IBD.

Influence of maternal diet to offsprings

To date, most of the data that altering diet in mothers affects risk of IBD in offsprings have been derived from mouse models and thus are difficult to extrapolate clinically. In a mouse model of IBD, Winnie$^{-/-}$ mice (point mutation in the Muc2 gene) had accumulation of aberrant MUC2 within the intestinal goblet cells leading to activation of endoplasmic reticulum stress.[54] Investigators supplemented the mother's diet before conception and up to 6 months after with tomatoes enriched in bioactive polyphenols compared with normal tomatoes and found that Winnie$^{-/-}$ mice born and nursed by mothers consuming more polyphenols had less dysbiosis and a slight reduction in inflammation. These studies allow careful control over the effect of diet on the maternal and offspring microbiome.[55] In mouse models, mothers fed a western diet (high fat, and sugar) had offsprings with a higher risk for severe inflammation. Mice born of dams fed a western diet (high-fat/high-sugar (60% high-fat diet supplemented with 12% (w/vol) glucose water, HF/HS) compared to a normal diet had more severe TNBS colitis.[56] A maternal high fat diet (48% of calories from fat) accelerated severe ileitis in offspring of TNFΔARE mice.[57] Maternal high fat diet worsened DSS colitis in adult offspring of C57BL/6 mice. The microbiota of the offspring remains changed even after feeding the same diet as control mice.[58] The mechanism by which a maternal high fat diet may result in increased susceptibility to IBD includes the finding that offspring of mothers exposed to a HFD (60%) developed a microbiota that was distinct from the maternal microbiome and was characterized by expansion of Firmicutes and a decrease in Gammaproteobacteria (primarily *Escherichia*). The offspring also had an increase in IL-17-producing type 3 innate lymphoid cells (ILC3s); these are the innate counterpart to Th17 cells. In this model, administration of LPS/PAF results in small intestinal inflammation that was more severe in the offspring of HFD-fed mothers.[59] Thus, at least in mice, there is compelling evidence that the diet of the mother can impact risk of IBD or severity of IBD in offspring, some through the shaping of the microbiota.

The notion that maternal diet may shape the risk of disease in offspring has been examined in intervention studies of allergic conditions. Probiotic intake in late pregnancy and during lactation reduced the risk of eczema in children.[60] Women with IBD are more likely to have children with IBD than fathers with IBD and the risk is highest if the mother already had IBD at the time the children are born.[61] Data demonstrate that there is bacterial imprinting in the newborn through meconium.[16] In North America, mothers of patients with UC and CD took

Table 1. Summary on important early life intervention, diet, and microbiome in IBD development

Critical early interventions 	**Early childhood interventions can shape microbiota and help prevent dysbiosis, reducing IBD risk based on preclinical findings.**
Maternal influence on offspring 	Changes in the maternal microbiome during pregnancy can affect foetal gut development and immunity, with factors like smoking and antibiotic use linked to higher IBD risk in children
Dietary impact on IBD 	High-fibre and Mediterranean diets may help manage IBD, whereas diets high in red meat and transfats are associated with increased disease risk.
Processed foods and IBD 	Emulsifiers and artificial sweeteners can trigger gut inflammation and alter microbiota, with high ultra-processed food intake correlating to increased risk of Crohn's disease
Role of maternal diet 	Maternal high-fat diets negatively impact offspring microbiota, raising their IBD susceptibility.
Prevention strategies 	Emphasis on a diet low in emulsifiers and high in fibre, along with reduced antibiotic use in mothers and infants, is crucial for mitigating IBD risk.

vitamin, mineral, and iron preparations during pregnancy significantly less frequently than mothers of controls.[62] The Norwegian Mother and Child Cohort Study (MoBa) includes about 95 000 pregnant women recruited throughout Norway from 1999 to 2008 and includes a subset of women with IBD. Pregnant women with CD or UC who ate higher levels of a traditional Norwegian diet (high consumption of lean fish, fish products, potatoes, rice porridge, cooked vegetables, and gravy) were less likely to have offspring that were small for gestational age. There was however no follow up on whether there was a reduced risk of IBD in the children.[63] The same study found that women with IBD consumed less dairy protein during pregnancy; compared to those that consumed higher levels, their children were less likely to be small for gestational age.[64] Diet may have an impact on the microbiome or on breast milk. The microbiome can also impact breast milk composition.[65] Data support that maternal consumption of probiotics and lactation protects against eczema and that fish oil supplementation during pregnancy and lactation may reduce risk of egg allergies. These data support the idea that diet during pregnancy of a mother with IBD may change the risk of these conditions in their offspring.[60]

Conclusion

In summary, diet and host immune responses determine microbial composition and functions and dietary pattern high in processed food is associated with a greater likelihood of Crohn's disease development. Emulsifiers are associated with intestinal inflammation in preclinical and clinical models and the gut microbiota serves as the link between diet and inflammation. Maternal IBD is a major risk factor for IBD in offspring and early-life events impacting microbiota development such as maternal diet, feeding behaviour, antibiotics exposure has been linked to risk of developing IBD and future studies should target these factors for disease prevention. Table 1 summarised the key early life intervention, diet and microbiome in IBD development. Until more data are available, current prevention strategies include a heathy diet low in emulsifiers and high in fibre or fermented food and reduced intake of antibiotics in mothers and infants unless indicated.

Supplementary material

Supplementary material is available at *Journal of the Canadian Association of Gastroenterology* online.

Author contributions

Joyce Wing Yan Mak and Aaron Tsz Wang Lo are responsible for conceptualization, drafting and review of the article. Siew Chien Ng is responsible for conceptualization, drafting and revising the article critically for important intellectual content and final approval of the version to be submitted. All authors agreed with the final version submitted.

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Conflicts of interest

J.W.Y.M. and A.T.W.L. have no conflicts of interests to declare. S.C.N. has served as an advisory board member for Pfizer, Ferring, Janssen, and Abbvie and received honoraria as a speaker for Ferring, Tillotts, Menarini, Janssen, Abbvie, and Takeda. S.C.N. has received research grants through her affiliated institutions from Olympus, Ferring, and Abbvie. S.C.N is a founder member, non-executive director, non-executive scientific advisor, and shareholder of GenieBiome Ltd. S.C.N. receives patent royalties through her affiliated institutions. S.C.N. is named inventors of patent applications held by The Chinese University of Hong Kong and Microbiota I-Center that cover the therapeutic and diagnostic use of microbiome.

In addition to this COI statement, ICMJE disclosure forms have been collected for all co-authors and can be accessed as Supplementary material here.

Data availability

There is no data associated with this manuscript.

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