

REVIEW ARTICLE

Environmental risk factors for inflammatory bowel disease

Noreen Singh¹ | Charles N. Bernstein² 

¹Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

²University of Manitoba IBD Clinical and Research Centre, Winnipeg, Manitoba, Canada

Correspondence

Charles N. Bernstein, University of Manitoba, 804-715 McDermot Avenue, Winnipeg, MB R3E3P4, Canada.

Email: Charles.bernstein@umanitoba.ca

Abstract

Inflammatory bowel disease (IBD) is a chronic, progressive immune-mediated inflammatory condition of the gastrointestinal tract. Environmental risk factors play a role in developing either type of IBD, Crohn's disease and ulcerative colitis; although the exact mechanism is still unknown. Herein, we review environmental risks from early life exposures, lifestyle and hygiene, vaccinations, surgeries, exposure to drugs and gastrointestinal pathogens that may increase the risk of developing IBD.

KEYWORDS

Crohn's disease, environmental, inflammatory bowel disease, risk factors, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease characterized by inflammation of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are the two main types. Although the exact cause of IBD is unknown, it has been hypothesized that IBD may develop in persons with a genetic predisposition, who experience yet-to-be defined environmental factors, an altered gut microbiome and a dysregulated immune response.¹ The purpose of this review is to explore the environmental risk factors for developing IBD such as early life exposures, lifestyle and hygiene, vaccinations, surgeries, exposure to drugs and gastrointestinal pathogens that may increase the risk of developing IBD.

LIFESTYLE AND HYGIENE

There are many hypotheses suggesting that exposures during prenatal life to 5-years of age, described as "early life" is a period of susceptibility whereby events in this period increase the risk of IBD. A systematic review by Agrawal et al. found that prenatal exposure to

antibiotics within the first year of life (OR 1.8; 95% CI: 1.2–2.5), passive tobacco smoke (OR 1.5; 95% CI: 1.2–1.9) and early life otitis media (may be a proxy for antibiotic use) (OR 2.1; 95% CI: 1.2–3.6) were associated with a higher risk of IBD.² Chicken pox infection (OR 3.89; 95% CI: 1.61–9.4) was associated with a higher risk of CD.³ A meta-analysis from Xu et al. found that breastfeeding was protective for CD (OR 0.71; 95% CI: 0.59–0.85) and UC (OR 0.78 [95% CI: 0.67–0.91]).⁴ This protection was seen greater among Asians (OR 0.31; 95% CI: 0.20–0.48) than Caucasians (OR 0.78; 95% CI: 0.66–0.93; $p = 0.0001$).⁴ Furthermore, this meta-analysis showed a dose-dependent association with at least 12-months of breastfeeding for CD (OR 0.20; 95% CI: 0.008–0.50) and UC (OR 0.21, 95% CI: 0.10–0.43) compared to 3-or 6-months.⁴ On the other hand, Agrawal et al. found no association of IBD with mode of delivery, maternal age, perinatal factors, vaccinations, socioeconomic or hygiene-related factors (although the specifics of "hygiene-related factors" were left undefined).²

Urban living is a risk factor for developing CD and UC with an OR 1.17 (95% CI: 1.03, 1.32) and 1.42 (95% CI: 1.26, 1.60), respectively.⁵ There is a stronger association during childhood for the development of CD.⁶ In fact, a Canadian study found a protective effect of rural living in childhood onset IBD.⁷

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A retrospective study by Cholanpranee et al. found a protective association between IBD with lower environmental hygiene: bed sharing (OR 0.66; 95% CI: 0.46–0.87), exposure to farm animals (OR 0.45; 95% CI: 0.31–0.65) and pets (OR 0.76; 95% CI: 0.63–0.88).⁸ Having pets as a child was a protective effect in UC.³ The strength of association with farm animals was statistically stronger in non-white cohorts (OR 0.27; 95% CI: 0.02–0.53) than white cohorts (OR 0.55; 95% CI: 0.45–0.65) ($p = 0.028$).⁸ Paradoxically, access to toilet (OR 0.71; 95% CI: 0.56–0.85) and hot water (OR 0.67; 95% CI: 0.44–0.89) had a protective association with UC in non-white cohorts.⁸ Hence, poor hygiene may not be an issue but rather differential exposures, some considered less hygienic (like farm animal exposure) and some considered more hygienic (like flushed toilets).

Smoking has been described as an environmental risk factor since the 1980s. Moreover, smoking has a protective effect of developing UC with a meta-analysis showing that smokers have an OR of 0.58 (95% CI: 0.45–0.75) of developing UC compared to non-smokers.^{9–11} A meta-analysis showed increased risk of CD in smokers in non-Jewish Whites (RR 1.95; 95% CI: 1.69–2.24; moderate evidence).¹² Not only does smoking increase the risk of CD by 2-fold, it is associated with more severe, refractory disease.^{10,11} Multiple studies have shown that current smokers were more likely to have perianal (29.5% vs. 26.2%; $p < 0.05$) and stricturing disease (22.5% vs. 19.3%; $p < 0.05$) than non-smokers.^{11,13} The mechanism by which smoking impacts IBD is unclear. There are over 4500 components of cigarette smoke with 150 that are potentially carcinogenic. It is unclear which specific component is protective in UC and detrimental in CD. Further, assessing smoking is not just about cigarette smoking since there may be effects of e-cigarettes, vaping, and smokeless tobacco.

VACCINATIONS

A meta-analysis studying the risk of vaccination and IBD found seven childhood vaccines (BCG, diphtheria, tetanus, smallpox, poliomyelitis, measles-containing vaccines) had no association of developing IBD.¹⁴ However, a sub-group analysis established a risk of developing either CD (RR 2.28, 95% CI: 1.12–4.63) or UC (RR 3.48, 95% CI: 1.2–9.71) from the poliomyelitis vaccine but this should be cautiously considered due to study heterogeneity.¹⁴ There was also a trend of a risk of developing IBD with the H1N1 vaccine (RR 1.13; 95% CI: 0.97–1.32) but the authors emphasized that they do not support that childhood vaccinations or H1N1 increase the risk of developing IBD.¹⁴ A recent multivariate analysis of 70 Southeast Asian children found that being vaccinated for rotavirus reduced the odds of developing IBD (OR 0.1)¹⁵; however, this is contrary to the American study by Liles et al. of 333 cases of pediatric IBD (diagnosed before the age of 10), which found no association of rotavirus vaccine and IBD.¹⁶ Lastly, there was no increased risk of IBD within 2 years of receiving the human papillomavirus vaccination.¹⁷

EXPOSURE TO DRUGS

Antibiotics can potentially contribute to the dysbiosis and dysregulated immune response in IBD.¹⁸ A meta-analysis including 7208 patients found that antibiotic exposure increased the risk of CD (OR 1.74; 95% CI: 1.35–2.23) but not for UC (OR 1.08; 95% CI: 0.91–1.27).¹⁹ This association was strongly seen in children having an increased risk of CD (OR 2.75; 95% CI: 1.72–4.38).¹⁹ Furthermore, all antibiotics with the exception of narrow-spectrum penicillins increased the risk of IBD; with exposure to metronidazole (OR 5.01; 95% CI: 1.65–15.25) or fluoroquinolones (OR 1.79 95% CI: 1.03–3.12) being the most strongly associated with developing new IBD.¹⁹ The timing of antibiotic introduction may be important especially in the first year of life when the infants' gut microbiome and enteric immune system are maturing into a more permanent state.²⁰ Further, childhood antibiotic use has the strongest association with IBD onset at younger ages.²¹ Oral contraceptives (OCP) use has been shown to increase the risk of IBD by 30% (OR 1.32, 95% CI: 1.17–1.49, $p < 0.001$, $I^2 = 14\%$), CD by 24% (OR 1.24, 95% CI: 1.09–1.40, $p < 0.001$, $I^2 = 38\%$) and UC by 30% (OR 1.30, 95% CI: 1.13–1.49, $I^2 = 26\%$).^{22–24} Longer exposures to OCP were also associated with an increased risk with each additional month of OCP increasing the risk of CD by 6.4% (5.1%–7.7%) and UC by 3.3% (2.1%–4.4%).^{23,25} Progesterone-only pills had no risk of developing CD (OR 1.09; 95% CI: 0.84–1.40) but a modest association with UC (OR 1.35; 95% CI: 1.12–1.64).²⁵ Lastly, parenteral contraceptives were associated with a borderline increased risk of CD (OR 1.15; 95% CI: 0.99–1.47) and UC (OR 1.17; 95% CI: 0.98–1.39). These findings are consistent with the hypothesis that estrogen has immune-mediator properties.²⁶

SURGERIES

Surgical risk factors have been shown to have a relationship with IBD. A meta-analysis by Koutroubki et al. revealed that appendectomy offered a 69% reduction in developing UC (95% CI: 62%–75%).²⁷ This finding was consistent with a study by Deng and Wu by which an appendectomy had a protective effect on developing UC (OR 0.44; 95% CI: 0.30, 0.64).²⁸ On the other hand, an increase risk of developing CD (RR 1.61) was seen following an appendectomy.²⁹ Interestingly, a meta-analysis of 17 studies found that there was a positive effect of developing CD following a tonsillectomy (OR 1.37; 95% CI: 1.16–1.62) and no association of developing UC (OR 0.94; 95% CI: 0.84–1.05).³⁰ However, when adjusted for smoking, the risk of developing CD increased to 1.66 (95% CI: 1.03–2.68) while with UC it was still not significantly associated (OR = 1.03; 95% CI: 0.74–1.44), perhaps owing to the protective effect of smoking.³⁰ The tonsils, appendix and Peyer's patches belong to the mucosa-associated lymphoid tissues, which may be associated with IBD.³⁰ Interestingly, developing CD following a tonsillectomy or appendectomy has been shown but not with UC, unless smoking is involved. The risk related to appendectomy or tonsillectomy may be secondary to the use of antibiotics for treatment of appendicitis or tonsillitis as

opposed to any specific risk posed by appendiceal or tonsillar tissue. A possible explanation can be due to the interplay between genetic predisposition, gastrointestinal bacteria and gut immunity.³⁰

PSYCHOLOGICAL FACTORS

A prospective study of 95,000 European adults found that work-related stress is not a major risk factor for development for CD or UC, HR of 0.83 (95% CI: 0.48, 1.43) and 1.06 (95% CI: 0.76, 1.48), respectively.³¹ Two different studies from Manitoba reported that psychiatric disorders were significantly increased in persons with IBD for at least 5-years prior to diagnosis of IBD.^{32,33} This data suggests either shared risk factors for mood disorders and IBD or that the presence of mood disorders alters systemic immune response or gut microbiome or both.

DIETARY INTAKE AND NUTRIENTS

Over the last several years, IBD has increased in previously low incidence areas (i.e. Asia) and it has been hypothesized due to the Westernization of local diets including a high composition of proteins, saturated fats, sweets and additives.³⁴ An animal study by Laudis found that mice given food additives (emulsifiers carboxymethylcellulose, polysorbate 80, maldodextrin) induces stress and can increase the host susceptibility of developing colitis.³⁴ In fact, a prospective cohort study with 116,097 adults from 21 countries in seven geographical regions found that higher intake of ultra-processed food was associated with a higher risk of IBD for ≥ 5 servings/day (HR 1.82, 95% CI: 1.22–2.72) and 1–4 servings/day (HR 1.67, 95% CI: 1.18–2.37).³⁵

A review of nine studies with 966 UC cases and 171,589 controls did not find a dose-response between fat intake and UC risk with the relative risk for 30 g increment/day was 1.023 (95% CI: 0.963–1.087, $n = 6$) for total fat intake.³⁶ This finding is similar in patients with CD as a review of nine studies found a lack of association between total carbohydrate, fat and protein intake with the relative risks for every 10 g increment/day were 0.991 (95% CI: 0.978–1.004) for total carbohydrate intake, 1.018 (95% CI: 0.969–1.069) for total fat intake and 1.029 (95% CI: 0.955–1.109) for total protein intake.³⁷ Zeng et al. found an association that high sucrose might increase the risk of CD. These findings are inconsistent with the study by Racine et al. that found that there was no association of consuming “high sugar and soft drinks” and “animal fats, seafood, potatoes and alcohol” with CD risk with the relative risks of 1.48 (95% CI: 0.60–3.61) and 0.71, (95% CI: 0.29–1.73), respectively.³⁸ On the contrary, soft drink consumption was associated with a higher risk of UC (RR: 1.69, 95% CI: 1.24–2.30) and tea consumption with a lower risk (RR: 0.69, 95% CI: 0.58–0.83).³⁹ These findings remain controversial as it was widely believed that macronutrients contribute to the development of CD however, it is unknown as to when dietary ingestion over the lifespan would trigger the risk for IBD.

Vegetables and fruit are rich in nutrients including mono-unsaturated and polyunsaturated fatty acids, *n*-3 fatty acids, fiber, vitamins and minerals thus have a protective effect against cardiovascular disease and cancer.⁴⁰ A meta-analysis of 14-case controlled studies found that higher consumption of fruit was inversely associated with the risk of UC (OR 0.69; 95% CI: 0.49–0.96) and CD (OR 0.57; 95% CI: 0.44–0.74).⁴⁰ A higher consumption of vegetables had a protective effect with UC (OR 0.71; 95% CI: 0.58–0.88) but not a statistically significant effect in CD (OR 0.66; 95% CI: 0.40–1.09).⁴⁰ This finding was consistent with two studies. Firstly, a retrospective study by Niewiadomski et al. found high fruit intake to be protective in UC (OR 0.59; 95% CI: 0.4–0.88, $p = 0.003$).³ Secondly, a prospective cohort study of 116,087 patients found that white meat, red meat, dairy, starch, fruit, vegetables and legumes were not associated with IBD.³⁵ This protective effect is hypothesized because vegetables and fruit are abundant in fiber, micronutrients (Vitamin C and E, folate) and phytochemicals that have been shown to reduce mucosal inflammation and maintain intestinal barrier function.⁴⁰

Increasing fiber intake has been shown to have a protective effect in CD.³⁷ A meta-analysis by Liu et al. found that the intake of dietary fiber reduced the risk of CD by 13% ($p < 0.05$) for every 10 g/d increment.⁴⁰ Although, there have been no studies of statistical significance showing an association of fiber with UC.⁴¹ Fiber has been shown to have an influence on the gut microbiome and contains butyrate (an anti-inflammatory effect).⁴⁰

While IBD can lead to impaired nutritional absorption and post-diagnosis deficiencies, causation has not been made regarding nutrient deficiency as a risk factor for the development of IBD. Del Pinto et al. found that 64% of patients with IBD had a vitamin D deficiency when compared to controls (OR 1.64; 95% CI: 1.30, 2.08, $I^2 = 7\%$, $p < 0.0001$) and UC had double the odds of a vitamin D deficiency (OR 2.28; 95% CI: 1.18, 4.41, $I^2 = 41\%$, $p < 0.01$). Latitude did not have an influence ($p = 0.34$).⁴²

Dietary composition has been suggested to alter the microbiome composition therefore it can affect its inflammatory response.⁴³ Ninety percent of the gastrointestinal microbiota consist of four types: *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*.⁴⁴ Dietary changes, if drastic, can alter the intestinal microbiome in 24hours.⁴⁵ In fact, animal-based diet can have increased abundance of bile-tolerant bacteria, *Alistipes*, *Bilophila* and *Bacteroides* species and decrease in *Firmicutes*.⁴⁵ On the other hand, plant-based diets can lead to an increased abundance of *Firmicutes*.⁴⁵

GASTROINTESTINAL PATHOGENS

Development of IBD may be caused by a defective intestinal barrier causing increased intestinal gut permeability, allowing pathogenic microbes to trigger an aberrant immune response. A systematic review by Axelrad et al. studied the association of gastrointestinal infections and IBD (Table 1, reproduced with permission from the publishers).⁴⁶ Several bacteria have been found to have an increased risk of IBD.⁴⁶ *Helicobacter pylori* has been consistently shown in the

TABLE 1 Pathogens associated with Inflammatory Bowel Disease (IBD) (reproduced with permission from the publishers)

Risk of developing inflammatory bowel disease	Increased	Decreased
Bacteria	<ul style="list-style-type: none"> • <i>Campylobacter</i> species • <i>Clostridioides difficile</i> • <i>Citrobacter</i> species • <i>Enterohepatic Helicobacter</i> species • <i>Escherichia coli</i> • <i>Klebsiella pneumonia</i> • <i>Listeria monocytogenes</i> • <i>Mycobacterium avium paratuberculosis</i> • <i>Proteus mirabilis</i> • <i>Salmonella</i> species • <i>Yersinia enterocolitica</i> 	<ul style="list-style-type: none"> • <i>Helicobacter</i> species
Viruses	<ul style="list-style-type: none"> • Adenovirus • Cytomegalovirus • Epstein-Barr virus • Human herpes virus 3 • Human herpes virus 6 • Human herpes virus 8 • Measles virus • Mumps virus • Norovirus • Rotavirus • Rubella virus 	
Fungi	<ul style="list-style-type: none"> • <i>Aspergillus</i> species • <i>Candida</i> species • <i>Cryptococcus neoformans</i> 	
Parasites	<ul style="list-style-type: none"> • <i>Amoeba/Entamoeba histolytica</i> • <i>Toxoplasma gondii</i> 	<ul style="list-style-type: none"> • <i>Trichuris suis</i> • <i>Hymenolepis diminuta</i> • <i>Schistosoma</i> species • <i>Nector americanus</i>

literature to have a decreased risk in IBD and a recent meta-analysis by Castano-Rodriguez et al. found that *H.pylori* exposure has a 57% lower odds of developing IBD (pOR 0.43; 95% CI: 0.36–0.50).⁴⁷ Viruses and fungi increase the risk of IBD.⁴⁶ Lastly, amoeba/*Entamoeba histolytica* and *Toxoplasma gondii* have been associated with an increased risk of IBD whereas *Trichuris suis*, *Hymenolepis diminuta*, *Schistosoma* species and *Nector americanus* have been associated with a decreased risk of IBD.⁴⁶ The above species can be cultured however, only 30% of the microbial diversity in the gut can be cultured.⁴⁸ Kotlowski et al. studied 84 biopsies from the cecum, rectum, or right colon distal to ileocolonic anastomosis (if previous cecal resection) by

ribosomal intergenic spacer analysis to culture *Enterobacteriaceae*.⁴⁸ It was found that *Enterobacteriaceae* species were 3–4 logs higher in tissues with IBD and the B2+D phylogenetic groups are more prevalent in patients with UC and CD.⁴⁸

CONCLUSION

The exact mechanism by which IBD is developed remains unknown; however, there is an interaction between environmental risk factors that can either increase or act as protective in its development

TABLE 2 Potential risk and protective environmental factors for

	Crohn's disease	Ulcerative colitis	Inflammatory bowel disease
Risk factors	<i>Lifestyle and hygiene</i> <ul style="list-style-type: none"> • Chicken pox infection • Smoking 		<ul style="list-style-type: none"> • Antibiotics within the 1st year of life • Passive tobacco smoke • Early life otitis media • Urban living
	<i>Vaccinations I</i> <ul style="list-style-type: none"> • Poliomyelitis vaccine 		<ul style="list-style-type: none"> • H1N1 vaccine
	<i>Exposure to drugs</i> <ul style="list-style-type: none"> • Antibiotics 	<ul style="list-style-type: none"> • Progesterone-only pills 	<ul style="list-style-type: none"> • Antibiotics (metronidazole, fluoroquinolones) except for narrow-spectrum penicillins • Oral contraceptive pills • Parenteral contraception
	<i>Surgeries</i> <ul style="list-style-type: none"> • Appendectomy • Tonsillectomy 		
	<i>Psychological factors</i>		<ul style="list-style-type: none"> • Psychiatric disorders (mood disorders)
	<i>Dietary intake and nutrients</i> <ul style="list-style-type: none"> • High sucrose 	<ul style="list-style-type: none"> • Soft drink • Fruit 	<ul style="list-style-type: none"> • Ultra-processed food
	<i>Gastrointestinal pathogens</i>		See Table 1 for full details
Protective factors	<i>Lifestyle and hygiene</i>	<ul style="list-style-type: none"> • Pets as a child • Access to toilets • Smoking 	<ul style="list-style-type: none"> • Breastfeeding • Rural living • Bed sharing • Exposure to farm animals and pets
	<i>Surgeries</i>	<ul style="list-style-type: none"> • Appendectomy 	
	<i>Dietary intake and nutrients</i> <ul style="list-style-type: none"> • Fiber 	<ul style="list-style-type: none"> • Tea consumption • Vegetables 	
	<i>Gastrointestinal pathogens</i>		<ul style="list-style-type: none"> • <i>Helicobacter species</i>

(Table 2). Further studies will need to identify environmental triggers of IBD but also must define the timing in the lifecycle these risk factors may be operative.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

No data are available.

ORCID

Charles N. Bernstein  <https://orcid.org/0000-0001-8041-3574>

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