Navigating IBD: The Role of Environmental Stressors and Nutrition

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Abstract

IBD is an umbrella term to describe chronic inflammatory disorders that affect the GI tract. The primary disorders are Crohn's Disease (CD) and ulcerative colitis (UC). Broadly, differences between the two diseases depend on what part of the gut is inflamed; CD affects any segment of the GI tract, usually in the ileum, whereas ulcerative colitis inflammation is concentrated in the colon and rectum. Symptoms of both diseases include abdominal pain with diarrhea and systemic manifestations such as fatigue and fever. Although genetic predisposition is associated, environmental factors include diet and pollution. This article will discuss the symptoms, treatments, genetics, and environmental stressors related to IBD and what current therapeutic options are available to treat the diseases.

Introduction

Approximately 1.6 million Americans have Inflammatory Bowel Disease (IBD), accounting for 0.5% of the U.S. population. It affects all ages with approximately 80,000 children a year getting diagnosed alone (1). The disease can be broken down into two major types — Crohn's disease and ulcerative colitis — largely dependent on where in the intestine the inflammation is concentrated. Crohn's disease is an inflammatory condition that affects all parts of the intestine, but primarily the ileal portion of the small intestine; ulcerative colitis primarily impacts the colon (2). As a whole, both diseases are presumed to be caused by numerous factors including dietary & environmental exposures, autoimmune reactions, and individuals with certain genetic backgrounds. As a society, attention to these diseases is imperative because of their role in causing secondary complications such as colorectal cancer. Many doctors believe that remission can help with this issue, but flares can occur with no probable cause (3). This article will focus on the symptoms of IBD, how current research is focused on trying to understand what environmental stressors are present and their varying effects on the gut, the impact of microbes (such as *E. coli* bacteria) on overall gut health, and how diet can contribute or alleviate symptoms.

Introduction to IBD

What is our gastrointestinal system?

The gastrointestinal tract (GI) is a complex set of organs composed of the mouth, pharynx (throat), esophagus, stomach, small intestine, large intestine, rectum, and anus. These organs make up the pathway that food and liquids take as they are swallowed, digested, absorbed as nutrients, and finally exit the body (4). The vast majority of the GI tract is broken down into two major components: the small intestine (which is further segmented into three regions: duodenum, jejunum, and ileum) and the colon (consisting of the proximal and distal colon) (5).

On the most fundamental layer, the gut acts as a barrier between the outside (lumen) and the inside of our body. In certain parts of the intestine, the lumen is home to trillions of microbes (bacteria and fungi) that normally live in symbiosis with the gut, producing important nutrients for our benefit. To keep these microbes at equilibrium, the GI is also home to the majority of our immune system. These specialized immune cells help maintain a barrier between the microbes and the intestinal wall. They can sense what microbes are present and lead to the production of substances that maintain separation such as mucus, antimicrobial peptides, and/or antibodies

(NIH). Both microbes and the immune system maintain homeostasis with each other, but imbalances can lead to gut inflammation which can cause secondary metabolic diseases (6).

What is IBD and what are the major differences between the sub-diseases (Crohn's and ulcerative colitis)?

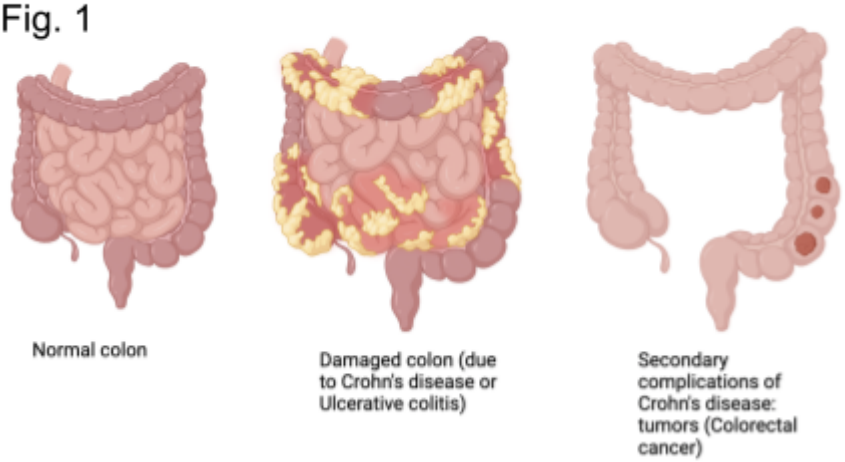
Inflammatory bowel disease (IBD) is an umbrella term that largely represents two primary diseases: Crohn's disease and ulcerative colitis. They are both diagnosed by observing chronic inflammation in the GI tract, and can largely be distinguished by what portion of the gut is inflamed. Crohn's disease can be observed at any portion of the GI tract, ranging from the mouth to the anus. In the majority of cases, it affects a distal segment of the small intestine, specifically, the ileum. Affected areas of Crohn's disease appear in patches next to healthy tissue (CDC). Ulcerative colitis, on the other hand, involves inflammation and sores (ulcers), and occurs in the large bowel and the rectum. Affected areas of this condition are usually sustained, beginning at the rectum and noticeable further up in the colon.

Both conditions can have severe consequences to the body if chronic inflammation is not addressed, leading to secondary complications such as cancer or excessive fibrosis (7).

What are the symptoms of the diseases?

IBD severity can widely range from being manageable (for example through changes to diet) to causing hospitalization and requiring lifelong medication. The symptoms a patient is met with can evaluate the extent to which IBD occurs in a person. Common symptoms depend on the severity and location of the inflammation, ranging from mild to severe (7). IBD symptoms can include abdominal pain, diarrhea, constipation, bowel urgency, gas and bloating, loss of appetite, unexplained weight loss, mucus or blood in the stool, and an upset stomach. In acute cases, symptoms can extend to stunted growth, fatigue, fever, itchy red eyes, joint pain, nausea, vomiting, skin rashes, and vision problems (8). These can occur in periods of active illness. Inflammation can subside during periods of "remission" (7).

Fig. 1



Comparisons between healthy and inflamed IBD guts
Secondary Complications such as colorectal cancer can occur when untreated

What are the secondary complications of the disease?

There are numerous secondary complications to IBD **(Figure 1)**. The National Institutes of Health report Crohn's disease diagnoses often turn into colorectal cancer with rates of 2.9% at 10 years of age, 5.6% at 20 years of age, and 8.3% at 30 years of age (9). Other complications can include fistulas, abscesses, fissures, strictures, bowel perforations, increased risk of cancer, organ complications (kidney stones and the liver), and toxic megacolon. IBD can cause a higher risk of infections and mouth sores (7).

Apart from complications in the bowel, IBD can induce other systemic damage such as anemia, malnutrition, and osteoporosis (7). Recent research into this field explores that while Crohn's disease causes numerous forms of physical damage, it can lead to stress and mental health disorders.

Stress has the ability to change gut microbiota as well as the way the nerves experience senses, resulting in IBD-like symptoms (10). Those with Crohn's and ulcerative colitis are more likely to experience a decrease in mental health, which stems from experiences in anxiety and depression (11). As described by the Crohn's & Colitis Foundation, these personality changes occur in IBD patients when the disease is active (60% to 80% of patients), as well as during remission (up to 30% of patients) (12).

What are the current treatments of IBD?

The primary goal in treating IBD is to reduce the inflammation found in the gut. Targeting the immune system not only reduces symptoms, but also allows for longer periods of remission and a lower risk of secondary complications. There are two primary approaches taken by doctors: drug therapy (external medication) and surgery (removing portions of the intestine).

To determine which treatment is necessary, a diagnostic test for anemia or possible infection is performed.. This can be done by a simple blood test or more commonly, a stool test which can show hidden blood (occult), excessive/reduced mucus, and/or parasites present in the stool. To confirm any findings, doctors will often perform invasive procedures such as endoscopies and colonoscopies to determine the severity of the condition. These exams allow gastroenterologists to view the entire colon by using a camera at the end. Less invasive exams can involve swallowing a capsule with a camera in it that sends images to the healthcare professional on the outside.

There are four main types of treatments used to manage IBD: anti-inflammatory drugs, steroids and other immune system suppressors such as biologics, and antibiotics. As a general rule, the medication prescribed depends on which area of the intestine is affected and the severity of the symptoms.

Anti-inflammatory drugs are usually the first option to treat mild-to-moderate ulcerative colitis. These include aminosalicylates such as mesalamine, balsalazide, and olsalazine. To speed up remission, short-term courses of corticosteroids may be used. These drugs are both anti-inflammatory and immunosuppressive.

Immunosuppressants work by lowering the immune response that triggers the chemicals which cause inflammation and injures the digestive tract lining. These include azathioprine and mercaptopurine, thiopurine, and methotrexate. Swallowable medications, known as "small molecules", have been recently developed, such as tofacitinib, upadacitinib, and ozanimod.

Biologics are a newer category of therapies that target the proteins that cause inflammation. These treatments can be utilized through the vein as infusions or subcutaneous

injections usually in the thigh. Commonly used biologics include infliximab, adalimumab, and golimumab, among others.

Antibiotics may be prescribed with other medications or with an active infection, including perianal Crohn's disease. Regularly used antibiotics include ciprofloxacin (Cipro) and metronidazole (Flagyl). Pain relievers, anti-diarrheal medications, enteral and parenteral nutrition, as well as vitamins and supplements can also help treat IBD.

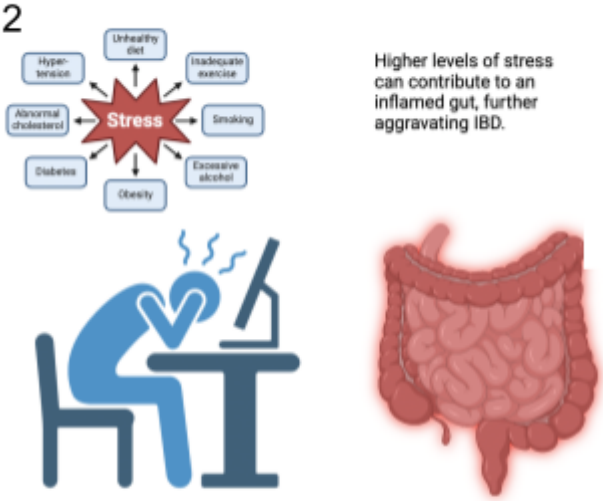
When treating ulcerative colitis with surgery, doctors remove the entire colon and rectum. Surgeons then create an internal pouch connected to the anus, which allows bowel movements in place of a bag. Sometimes when internal pouches cannot be used, a permanent opening in your abdomen is created, known as a ileal stoma, where stool passes into an attached bag to be collected (13).

How does stress contribute to IBD?

Stress, as the WHO defines it, is “a state of worry or mental tension caused by a difficult situation (14).” High stress levels can also indicate higher levels of cortisol in the body (15).

Depression can cause a person to progress into periods of feelings of self-harm and other negative sentiments (16). Those with depression have a negative link with their appetite, either eating too little or over-eating (17). However, these self-imposed eating disorders can cause less nutrients to be absorbed into the body, or increase the consumption of junk foods. These specific foods can further catalyze inflammation in the gut, accelerating IBD (18).

Fig. 2



High levels of stress can lead to negative health consequences including worsening levels of inflammation in the gut.

In a study conducted by the American Journal of Gastroenterology, researchers concluded that increased cortisol levels are present in those with Crohn’s disease and patients in surgery, which can be related to severe gut inflammation **(Figure 2)** (19). These increased levels correlate with a higher release of glucocorticoids which happens during severe and acute diseases (20).

Low stress levels have correlated with overall happier lifestyles (21). In a study by the NIH, they found out that repeated psychological stress speeds up severity of IBD by changing the neuroendocrine-immune network and microbiome homeostasis. IBD also causes anxiety and depression-like symptoms by over-activating brain immune regulation (22).

While there may not be a clear correlation between type A/B personalities and IBD, there have been studies relating other types of personalities with IBD. The NIH conducted another study in which they concluded there is a relation between psychosomatic elements on the onset of IBD, which contributes to the development and quality of life of patients with IBD. It showed that there were high rates of neuroticism, external thinking, and impulsive traits (23). However, a cause and effect relationship was not able to be established.

Is there a correlation between specific ages and IBD?

In a person's life, there are normally 5 distinct stages of development that they go through. These include children, adolescents, young adults, middle aged adults, and seniors. These different stages are associated with different goals and characteristics which create distinct levels of stress.

Children have lower levels of stress as they attempt to blend in with the people around them. Children in today's society have often been eating unhealthy foods which can be associated with the western diet. Nutritional factors such as a diet with increased glucose and trans fats have been correlated with IBD (24). The NIH states that this diet is associated with increased levels of proinflammatory cytokines, changed intestinal accessibility, and an altered intestinal microbiome makeup that creates inflammation in the gut (25).

As they take on more responsibilities and move through major life milestones, teenagers develop a moderate to high level of stress that can impact their gut health. For those with IBD-related diseases, the symptoms may worsen simply because following their medication schedules may be difficult for them. The NIH notes 48% of teenage patients took one IBD medication, 36% took two, and only 11% took three medications because teens simply do not want to take their medication (26). It presents differently in teenagers because IBD can lead to growth failure and delayed puberty (27). Their BMI is also affected.

Young adults also have the highest rates of developing IBD related mental health conditions, almost 15.2% developing conditions by age 18 (28). The disease is most active in this age group due to the high levels of stress they encounter. It can also be due to the unhealthy diet they follow from not having adequate food security, specifically due to income (29).

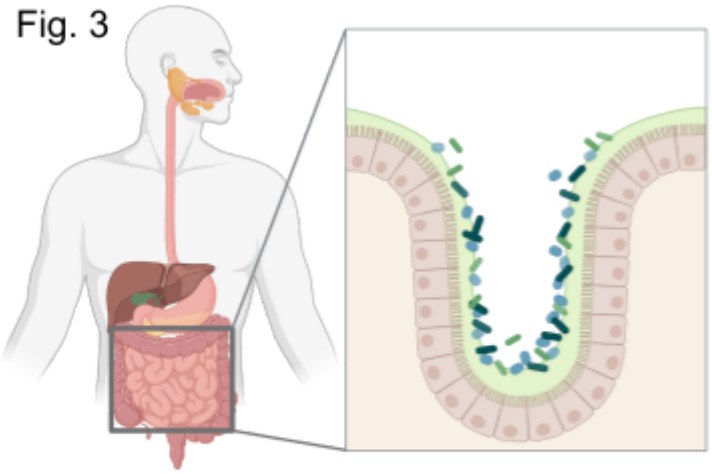
Middle aged adults and seniors have very similar likelihoods of being diagnosed with IBD. The TIME magazine states that more than a quarter of people with IBD are "elderly" , a percentage that is expected to increase to 30% by 2030. Doctors are beginning to notice a third spike in this age group (30). Surgery can be a less helpful approach for elderly patients at higher risk for complications (31). They often have to get parts of their bowels resected and receive ostomy pouches (32). There is also a higher percentage of patients with ulcerative colitis than Crohn's disease (33).

As individuals become older, chances of IBD increase as cells begin to break down and get weaker. They become more frail which can contribute to IBD (34). Additionally, there has been a noticeable overlap between the biology between IBD and aging. This can cause different outcomes in IBD as well.

Prevalence of Commensals and Pathogens in IBD

Microbes live on various surfaces of the body and are most concentrated in our intestinal tract **(Figure 3)** (35). In healthy contexts, the microbes are in a commensalistic relationship with the body and provide useful, beneficial functions for us (36). For example, in the intestine, they can fight against pathogens by stopping their growth and boost the host immune system (37). Additionally, these "commensals" are capable of providing the body with specific vitamins and other nutrients that cannot be produced by human cells (38). Three major phyla are seen in the gut: Firmicutes, Actinobacteria, and Bacteroides (39).

Fig. 3



The intestinal tract is home to a dense community of bacteria that live in the lumen of the gut.

Firmicutes are a phyla of bacteria responsible for fermenting dietary fiber and interacting with the intestinal mucosa (40). A high level of firmicutes causes an unequal distribution of microbes within the gut. This can be directly proportional to inflammation; as the number of firmicutes increases to dangerous levels, it can worsen inflammation within the intestines (41). Moderation of such bacteria helps keep the gut healthy.

Actinobacteria are gram positive, anaerobic bacteria. There are three main families of actinobacteria, but one most present in the human gut is Bifidobacteria (42). Actinobacteria make secondary metabolites which can prove to be useful to humans and numerous animals. These secondary metabolites have antibiotic, antifungal, and anticancer qualities (43). In the gut, actinobacteria are part of the gut microbiome made up of microbiota and keep the body safe from outside invasions from inflammatory chemicals. The actinobacteria help maintain gut homeostasis and help against intestine imbalances (44).

Bacteroides are anaerobic, gram-negative bacteria that make up almost 25% of the intestinal gut microbiome with many beneficial functions for human health. They can cross-communicate with intestinal cells, affecting the intestinal immune system, interact with the host, or produce molecules that can change the intestinal immune response SCFAs by fermenting numerous simple and complex sugars. They help digest food and keep a healthy microbiome, essential in dietary fiber metabolism and the interaction within the gut microbiota (45). They play two roles in gut inflammation and inflammatory bowel disease (IBD). While they generally help control immune responses and protect against inflammation, an inequality in Bacteroides can cause immune activation and worsen conditions like Crohn's disease and ulcerative colitis (37). Thus, Bacteroides are necessary for gut health, but can cause inflammation in imbalanced states. They suppress inflammation of IBD, and enterotoxigenic strains develop chances of colorectal cancer (46).

The microbiome influences different functions in the body including metabolic processes, regulation of immune system activity, or even defense against pathogenic microflora (37). The microbiome includes bacteria, archaea, fungi, and viruses; its balance is required to maintain

homeostasis (47). This microbial imbalance, or dysbiosis, has been linked to the pathogenesis of inflammatory bowel diseases, making up a group of chronic inflammatory gut conditions that include Crohn's disease and ulcerative colitis (48).

Role of the Gut Microbiome in IBD

When compared to healthy people, there are changes in the gut microbiota of patients with IBD. These include less variety of microbes and an inequality in the levels between beneficial and pathogenic bacteria, a condition known as dysbiosis (49). One important study showed that compared to controls, IBD patients usually have lower numbers of the beneficial bacteria *Faecalibacterium prausnitzii*, which are known for their anti-inflammatory properties (50). There is an increased load of potentially harmful bacteria, including Proteobacteria and Enterobacteriaceae, linked with inflammation and epithelial barrier disruption (51).

Dysbiosis can cause hyper-activation of the immune system (52). In a healthy state, good bacteria keep gut homeostasis by producing SCFAs, which provide food for colon cells and mimic immune functions (53). Lowering their counts reduces SCFA production, which harms the gut's ability to regulate inflammation (54). Additionally, the overgrowth of pathogenic bacteria could produce harmful metabolites such as LPS, which would activate the pro-inflammatory pathways through the stimulation of the TLRs of the immune system (55).

Imbalance can lead to gut permeability or "leaky gut," which can allow pathogenic bacteria and toxins to enter the intestinal lining and the bloodstream (56). This triggers a chronic immune response, causing sustained inflammation and tissue damage, a characteristic of IBD (57).

The changed microbiome in IBD patients affects several mechanisms which can cause inflammation (58). The dysbiotic microbiome communicates with the mucosal immune system and changes the microbiome (59). The communication can enable dendritic cells and macrophages to create pro-inflammatory cytokines, such as TNF-alpha and IL-6, which push the inflammatory response (60). The cytokines disrupt the intestinal barrier and progress the cycle of inflammation (61).

The production of virulence factors by the pathogenic gut bacteria can directly modulate the function of epithelial cells by damaging the epithelial barrier or through molecular mimicry of epithelial signaling pathways (62). Therefore, it augments the expression of the tissue inflammatory mediators, leading to further intensification of the inflammatory cascade in IBD (63).

Understanding of the relationship between the gut microbiota and IBD has opened avenues for treatment. Strategies aimed at restoring microbial balance are being researched. Some of these strategies include the use of probiotic treatment, prebiotics, and dietary modifications like an already modified food for medical purposes. A number of the many probiotics can be harnessed to repopulate beneficial bacteria to decrease inflammation, not only due to their use in the future but also because the present paper suggests. Consequently, the use of tailored probiotic treatment might also result in immune response modulation and gut barrier reinforcement (64).

High-fiber and fermented foods may modify the growth of beneficial bacteria and their metabolic effects to enhance SCFA production, thus modulating a normally functioning balance among immune responses and gut barrier function (65).

Several studies do support this type of treatment as an option to combine with other IBD therapies. Fecal microbiota transplantation is the process through which a fecal material from a healthy donor is transferred to a patient with IBD for the purpose of restoration of microbial balance (66). Early intervention has shown a potential effect of radical improvement in gut microbiota composition and inflammation reduction, even though more investigations are necessary not only to unravel its long-term effects but also to clearly explain its optimal application.

The interplay of the gut microbiome with the immune system is core in IBD pathogenesis (67). This dysbiosis iterates immune deregulation, increasing inflammation and decreasing the gut barrier's function (68). The fact that such targeted treatments for restoration of the microbial balance in IBD are already here points out to the enormous potential of microbiome-based therapy in improving patient outcomes.

Impact of the Genetic Makeup on IBD Presentation

Genetics plays a critical role in the development of IBD. Some major genes implicated in the development of the disease include the interleukin-23 receptor (IL-23R), the nucleotide-binding oligomerization domain-containing protein 2 (NOD2), and the human leukocyte antigen complex (69). Interestingly, all of these genes play a significant role in the body’s immune response and often give rise to proinflammatory pathways.

IL-23 is a cytokine involved in the modulation of mucosal immune response (70). It belongs to the IL-12 family of cytokines and induces or maintains Th17 cells, which subsequently produce additional cytokines such as IL-17 and IL-22 (71). While IL-17 and IL-22 provide host defense against infection by specific pathogens, their dysregulation can lead to autoimmune responses (72). IL-23R, the receptor for IL-23, is expressed on the surface of T cells, NK cells, and dendritic cells. Gene mutations and SNPs in the receptor have been shown to increase the activity of the receptor, giving an increased signal via the IL-23 pathway and consequently promoting chronic inflammation (73).

NOD2 serves as a pattern recognition receptor for muramyl dipeptide, which is the product of peptidoglycan of the bacterial cell wall, and initiates NF-κB activation, thereby initiating a host immune response (74). More importantly, it is involved at the core of recognizing intracellular pathogenic organisms and thus in keeping, at bay, immune responses against commensal microbiota in the intestines (75). Genetic variants of the NOD2 gene are strongly associated with Crohn's disease (76). The frameshift mutations, such as the 1007fs, and the missense mutations like R702W and G908R, result in defective NOD2 protein that affects cellular autophagy and the generation of antimicrobial peptides (77). This defect provokes excessive responses by immune cells against normally innocuous gut microbiota, leading to chronic inflammation (78).

HLAs, or Human Leukocyte Antigens, are proteins located on the surface of almost all cells of the human body (79). They perform a vital role in immunity by allowing the immune system to distinguish “self” protein from foreign proteins (like viruses and bacteria) (80). Mutations or variants of HLA genes consequently affect immune function and are involved in many autoimmune diseases (81). These mutations can alter the presentation of antigens, consequently leading immune cells to wrongly attack one's own body tissues (82). In terms of IBD, a class of HLA genes – HLA Class II – plays a major role in the development of the disease (83). Knowing these mutations and their consequences helps in the diagnosis of treatment against autoimmune diseases.

Much of the genetic basis of IBD is known and therapies targeted to direct personalized strategies are increasingly being developed. Second variants at IL-23R, NOD2, and HLA modified the host immune response and, through that, did influence the pathogenesis of IBD (69). Results provided a molecular basis for mechanisms driving IBD and opened ground for further research and therapeutic innovation.

Demographics of patients with IBD

In the case of IBD, there are prevalence rate differences among various ethnic groups around the world. It has been noted in several studies that the highest cases of IBD are found in Caucasians (84). The prevalence rate is approximately 0.3% to 0.5% in North America and Europe (85). Hispanics have the second highest prevalence, which has been calculated at 0.1% to 0.3% (86). Those with a family history of IBD are at much greater risk compared to others (87). First-degree relatives of IBD patients are at an increased risk, by 10 to 15-fold, of developing IBD compared to the general population (88). This familial risk is greater in Caucasians for whom individual genetics studies have identified many risk alleles, including those in the IL-23R and NOD2 genes, that explain some of the elevated risk for the disease (89).

There are also geographic and socioeconomic factors that influence diagnosis of IBD. It is more prevalent in urbanized and developed regions; the prevalence of IBD in North America is 0.25%-0.35%, while in Europe, it ranges between 0.3% and 0.5% (85). Because of the factors such as pollution, antibiotic use, and diet that lead to inflammation, citizens of urban areas in Western countries have a higher risk (90). The Hygiene Hypothesis, which suggests that lower exposure to microbes in childhood contributes to an increased risk for autoimmune disorders like IBD, is also associated with the higher hygiene standards of urban living (91).

More recent studies indicate an increasing incidence of IBD in previously low-risk areas, such as the eastern part of the world (92). In countries across Asia and Africa, there is a rising trend of IBD cases correlating with possible pollution and dietary changes (93). For instance, the prevalence of IBD in China and India have been increasing at about 10 to 15 percent yearly, showing the impact of urbanization and dietary influences from the west (94). Strikingly, one clear pattern shows, among other reasons, the big role that environmental and lifestyle changes play in the global spread of IBD (95). The rising prevalence in non-Western countries points out a clear need for public health strategies to regard IBD as a global health concern (96).

The Pollution, Hygiene, and IBD Link

Exposure to exogenous pollutants like sulfur dioxide and nitrogen dioxide has been linked to the course of IBD (97). Sulfate and nitrate particles contribute to acid rain, which, when falling on the plants we eat, may then damage the gastrointestinal system (98). Apart from the effects on crop yields, acid rain could also affect the quality of the diet (99). It introduces harmful substances into the diet that might upset the gut microbiota and hence be proinflammatory for the gut (100). Additionally, exposure to residential SO_2 and NO_2 can lead to an increased incidence of IBD, since these gasses are capable of creating oxidative stress and inflammation in the gut lining, an event which could trigger or worsen IBD symptoms (101).

The relationship between smoking, nicotine, and IBD is complex. Smoking, on the one hand, has been very well documented as a risk factor for the development of CD, while on the other hand, it seems to have a protective effect against UC (102). Smoking itself causes inflammation and oxidative stress, which aggravate symptoms in IBD patients and finally lead to

the development of disease (103). However, nicotine, a compound formed in tobacco composition, was shown to alleviate symptoms in some UC patients (104). Studies show that nicotine probably induces the receptors on some types of immune cells, thereby reducing the production of pro-inflammatory cytokines. Thus, inflammation in the colon is reduced in subjects with the condition (105). Even in the light of these findings, nicotine cannot be seen as a potential therapy for IBD in view of the overall toxic effects of nicotine and its addiction potential (106). Chronic exposure to nicotine may induce cardiovascular disease, dependence, and multiple systemic toxicities, which makes nicotine an unlikely therapeutic option for IBD (107). Therefore, while nicotine has transient beneficial effects on symptoms in UC, it is far outweighed by its negative effects, thus raising the need for safer treatment options.

The hygiene practices and use of antibiotics have a strong impact on the gut microbiome (108). Poor personal hygiene can contribute to frequent infections of pneumonia, urinary tract infections, and 'strep throat', each of which is normally treated with antibiotics (109). While such antibiotics might be effective against infections, they have an antagonistic effect on the gut microbiota by killing the beneficial bacteria (110). Such a disruption could make the gut more compromised and therefore open to the development of inflammatory conditions like IBD (48). Another theory is the hygiene hypothesis: the lingering creation of overly sterile environments, to which exposure in childhood can mean increased susceptibility to autoimmune diseases like IBD (91). The reduced exposure to microorganisms during early life might avert the development of a healthier immune system and lead to hazardous immune responses (111). What this theory does stress is the need for balanced exposure to microbes for the healthy development of the immune system, and it does caution against excessive cleanliness.

In terms of the interplay between genetic and environmental risk factors, environmental factors—such as pollution, lifestyle habits like smoking, and hygiene practices—play a very big role in the prevalence and development of IBD. While SO_2 and NO_2 pollutants affect gastrointestinal health directly through diet and by inducing oxidative stress (112), the complex role of smoking and nicotine in general has risks and benefits, mainly for UC (104). However, the health risks from nicotine make it unsuitable for treatment (113). The Hygiene Hypothesis and antibiotic use further underline this required balance in the gut microbiome to keep up good health (114)—this very balance that is important for preventing inflammatory conditions like IBD.

Diet and its link to IBD

Diet is a major determinant of risk and management of IBD (115). High intake of fruits, vegetables, and fiber-based diets reduces the risk of IBD through simple food elements and pro-health gut-related bioactive compounds provided by them (116). High intake of saturated fats, red meat, animal fats, and processed foods, on the other hand, can predispose an individual to IBD due to their high levels of linoleic acid and other fats that might have proinflammatory effects in case the body does not absorb them well (117). Refined foods have low satiety potential, and thus one can end up overeating. When they overeat, people can end up eating unhealthy foods or too much of one specific kind of harmful food leading to inflammation (118).

Fiber forms an integral part of gut health (119). Soluble fiber absorbs water in the intestines, making stool softer, while insoluble fiber gives bulk to the stool for its passage (120). While insoluble fiber may cause irritation of the intestines, inadequate fiber causes bowel

obstruction (121). Gut bacteria ferment fiber into SCFA, such as butyrate, which as mentioned above, can promote anti-inflammatory responses (122).

L-Carnitine is an amino acid rich in red meat. When ingested, the gut microbiota is capable of metabolizing L-carnitine into the metabolite TMAO, a molecule implicated in heightening cardiovascular disease risk (123). Studies have revealed that in IBD, choline levels are usually higher, but carnitine levels were similar. Additionally, decreased TMAO levels are seen in IBD compared to those without the disease, suggesting a new factor to diagnose patients effectively (124).

High sugar intake, typical of Western diets, instigates drastic changes in the gut microbiome (125). Based on a study conducted in mice, high-sugar diets thinned protective mucus in the intestines by reducing beneficial bacteria and increasing bad bacteria. These changes can lead to colitis and metabolic disorders by promoting inflammation and lowering the gut's ability to act against disease-causing pathogens (126). Additionally, glucose can induce loss of the beneficial Th17 immune cells (127).

Conclusion

IBD, both Crohn's and ulcerative colitis, is an important area of study because the prevalence of the diseases keeps increasing in people with significant deterioration in the quality of life. The estimation of approximately 1.6 million affected Americans and about 80,000 diagnosed children calls for a dire need to know means and ways of managing IBD (1). The condition has a complex etiology that incorporates dietary, environmental, autoimmune, and genetic aspects; hence, it requires continued research and public awareness.

The rising prevalence of IBD also points to a pressing need for research into environmental stressors and microbial influences on gut health. Indeed, current research is unraveling the contribution these elements make during the process of disease development and symptom severity. In addition, understanding the role that diet may play in either aggravating or relieving symptoms can help in devising more effective management strategies.

Bibliography

1. *THE FACTS ABOUT Inflammatory Bowel Diseases*. (2014, November). Crohn's & Colitis Foundation of America. https://www.crohnscolitisfoundation.org/sites/default/files/2019-02/Updated%20IBD%20Factbook.pdf
2. *Crohn's Disease*. (2023, January 13). PennMedicine. https://www.pennmedicine.org/for-patients-and-visitors/patient-information/conditions-treated-a-to-z/crohns-disease#:~:text=The%20exact%20cause%20of%20Crohn,body%20tissue%20(autoimmune%20disorder)
3. Brody, Barbara. (2022, May 19). *5 things we now know about Crohn's disease*. Johnson&Johnson. https://www.jnj.com/health-and-wellness/things-we-now-know-about-crohns-disease
4. *gastrointestinal tract*. (n.d.). National Cancer Institute. Retrieved August 7, 2024, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/gastrointestinal-tract
5. *Digestive System*. (2021). Cleveland Clinic. https://my.clevelandclinic.org/health/body/7041-digestive-system
6. di Vincenzo, F., del Gaudio, A., Petito, V., Lopetuso, L. R., & Scaldaferri, F. (2024). Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Internal and Emergency Medicine*, *19*(2), 275–293. https://doi.org/10.1007/s11739-023-03374-w
7. *Inflammatory Bowel Disease (Overview)*. (2024). Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/15587-inflammatory-bowel-disease-overview
8. *Inflammatory Bowel Disease (IBD) Basics*. (2024, June 21). CDC. https://www.cdc.gov/inflammatory-bowel-disease/about/index.html
9. Kim, E. R. (2014). Colorectal cancer in inflammatory bowel disease: The risk, pathogenesis, prevention and diagnosis. *World Journal of Gastroenterology*, *20*(29), 9872. https://doi.org/10.3748/wjg.v20.i29.9872
10. Chaudhry, T. S., Senapati, S. G., Gadam, S., Mannam, H. P. S. S., Voruganti, H. V., Abbasi, Z., Abhinav, T., Challa, A. B., Pallipamu, N., Bheemisetty, N., & Arunachalam, S. P. (2023). The Impact of Microbiota on the Gut–Brain Axis: Examining the Complex Interplay and Implications. *Journal of Clinical Medicine*, *12*(16), 5231. https://doi.org/10.3390/jcm12165231
11. *Mental health and wellbeing*. (2023). Crohn's & Colitis UK. https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/living-with-crohns-or-colitis/mental-health-and-wellbeing#:~:text=Research%20suggests%20that%20people%20living,mental%20health%20in%20some%20way
12. *Complications and Extraintestinal Manifestations*. (n.d.). Chron's and Colitis Canda. Retrieved August 7, 2024, from https://crohnsandcolitis.ca/About-Crohn-s-Colitis/IBD-Journey/Complications-and-Extraintestinal-Manifestations/Stress,-Anxiety,-and-Depression
13. Faubion, William. (2020). *Inflammatory bowel disease (IBD)*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/inflammatory-bowel-disease/diagnosis-treatment/drc-20353320

14. *Stress*. (2023, February 21). World Health Organization. https://www.who.int/news-room/questions-and-answers/item/stress
15. Tee-Melegrito, R. A. (2023, May 5). *Cortisol and stress: What is the connection?* MedicalNewsToday. https://www.medicalnewstoday.com/articles/cortisol-and-stress
16. *Depression*. (n.d.). National Institute of Mental Health. Retrieved August 7, 2024, from https://www.nimh.nih.gov/health/topics/depression#:~:text=Because%20depression%20tends%20to%20make,symptoms%20may%20benefit%20from%20treatment
17. Simmons, W. K., Burrows, K., Avery, J. A., Kerr, K. L., Bodurka, J., Savage, C. R., & Drevets, W. C. (2016). Depression-Related Increases and Decreases in Appetite: Dissociable Patterns of Aberrant Activity in Reward and Interoceptive Neurocircuitry. *American Journal of Psychiatry*, *173*(4), 418–428. https://doi.org/10.1176/appi.ajp.2015.15020162
18. Butler, M. J., Perrini, A. A., & Eckel, L. A. (2021). The Role of the Gut Microbiome, Immunity, and Neuroinflammation in the Pathophysiology of Eating Disorders. *Nutrients*, *13*(2), 500. https://doi.org/10.3390/nu13020500
19. Cardoso, H. M., Nunes, A. C. R. M., Cruz, A. M., Santos, C. C. M., & Veloso, F. T. P. (2006, September). *Importance of Serum Cortisol Levels in Inflammatory Bowel Disease*. American Journal of Gastroenterology. https://journals.lww.com/ajg/fulltext/2006/09001/importance_of_serum_cortisol_levels_in.1197.aspx#:~:text=Conclusions%3A%20In%20IBD%2C%20increased%20cortisol,related%20to%20more%20severe%20IBD
20. Thau, L., Gandhi, J., & Sharma, S. (2024). *Physiology, Cortisol*.
21. Bohn, K. (2021, March 22). *Living a stress-free life may have benefits, but also a downside*. PennState.
22. Ge, L., Liu, S., Li, S., Yang, J., Hu, G., Xu, C., & Song, W. (2022). Psychological stress in inflammatory bowel disease: Psychoneuroimmunological insights into bidirectional gut–brain communications. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.1016578
23. Eugenicos, M. P., & Ferreira, N. B. (2021). Psychological factors associated with inflammatory bowel disease. *British Medical Bulletin*, *138*(1), 16–28. https://doi.org/10.1093/bmb/ldab010
24. Bertani, L., Ribaldone, D. G., Bellini, M., Mumolo, M. G., & Costa, F. (2021). Inflammatory Bowel Diseases: Is There a Role for Nutritional Suggestions? *Nutrients*, *13*(4), 1387. https://doi.org/10.3390/nu13041387
25. Singh, R. K., Chang, H.-W., Yan, D., Lee, K. M., Ucmak, D., Wong, K., Abrouk, M., Farahnik, B., Nakamura, M., Zhu, T. H., Bhutani, T., & Liao, W. (2017). Influence of diet on the gut microbiome and implications for human health. *Journal of Translational Medicine*, *15*(1), 73. https://doi.org/10.1186/s12967-017-1175-y
26. Lu, Y. (2011). Inflammatory bowel disease in adolescents: What problems does it pose? *World Journal of Gastroenterology*, *17*(10), 2691. https://doi.org/10.3748/wjg.v17.i22.2691
27. Amaro, F., & Chiarelli, F. (2020). Growth and Puberty in Children with Inflammatory Bowel Diseases. *Biomedicines*, *8*(11), 458. https://doi.org/10.3390/biomedicines8110458
28. Cooney, R., Tang, D., Barrett, K., & Russell, R. K. (2024). Children and Young Adults With Inflammatory Bowel Disease Have an Increased Incidence and Risk of Developing

Mental Health Conditions: A UK Population-Based Cohort Study. *Inflammatory Bowel Diseases*, *30*(8), 1264–1273. https://doi.org/10.1093/ibd/izad169

29. Nguyen, N. H., Khera, R., Ohno-Machado, L., Sandborn, W. J., & Singh, S. (2021). Prevalence and Effects of Food Insecurity and Social Support on Financial Toxicity in and Healthcare Use by Patients With Inflammatory Bowel Diseases. *Clinical Gastroenterology and Hepatology*, *19*(7), 1377-1386.e5. https://doi.org/10.1016/j.cgh.2020.05.056
30. Courage, K. H. (2022, April 8). *The Connection Between IBD and Aging*. TIME. https://time.com/6165526/ibd-and-aging/
31. Axenfeld, E., Katz, S., & Faye, A. S. (2023). Management Considerations for the Older Adult With Inflammatory Bowel Disease. *Gastroenterology & Hepatology*, *19*(10), 592–599.
32. Chrobak-Bień, J., Marciniak, A., Kozicka, I., Lakoma Kuiken, A., Włodarczyk, M., Sobolewska-Włodarczyk, A., Ignaczak, A., & Borowiak, E. (2023). Quality of Life in Patients over Age 65 after Intestinal Ostomy Creation as Treatment of Large Intestine Disease. *International Journal of Environmental Research and Public Health*, *20*(3), 1749. https://doi.org/10.3390/ijerph20031749
33. Katz, S., & Feldstein, R. (2008). Inflammatory bowel disease of the elderly: a wake-up call. *Gastroenterology & Hepatology*, *4*(5), 337–347.
34. Ananthakrishnan, A. N. (2021). Frailty in Patients With Inflammatory Bowel Disease. *Gastroenterology & Hepatology*, *17*(6), 263–268.
35. DeBruyn, J. (2023, September 28). *Your microbes live on after you die − a microbiologist explains how your necrobiome recycles your body to nourish new life*. THE CONVERSATION.
36. *Commensalism*. (n.d.). ScienceDirect. Retrieved August 7, 2024, from https://www.sciencedirect.com/topics/medicine-and-dentistry/commensalism#:~:text=Commensalism%20is%20a%20long%2Dterm,the%20host%20in%20many%20ways
37. Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. *Cell Research*, *30*(6), 492–506. https://doi.org/10.1038/s41422-020-0332-7
38. Martín, R., Miquel, S., Ulmer, J., Kechaou, N., Langella, P., & Bermúdez-Humarán, L. G. (2013). Role of commensal and probiotic bacteria in human health: a focus on inflammatory bowel disease. *Microbial Cell Factories*, *12*(1), 71. https://doi.org/10.1186/1475-2859-12-71
39. Belizário, J. E., & Napolitano, M. (2015). Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches. *Frontiers in Microbiology*, *6*. https://doi.org/10.3389/fmicb.2015.01050
40. Sun, Y., Zhang, S., Nie, Q., He, H., Tan, H., Geng, F., Ji, H., Hu, J., & Nie, S. (2023). Gut firmicutes: Relationship with dietary fiber and role in host homeostasis. *Critical Reviews in Food Science and Nutrition*, *63*(33), 12073–12088. https://doi.org/10.1080/10408398.2022.2098249
41. Magne, F., Gotteland, M., Gauthier, L., Zazueta, A., Pesoa, S., Navarrete, P., & Balamurugan, R. (2020). The Firmicutes/Bacteroidetes Ratio: A Relevant Marker of Gut Dysbiosis in Obese Patients? *Nutrients*, *12*(5), 1474. https://doi.org/10.3390/nu12051474
42. *Actinobacteria*. (n.d.). ScienceDirect. Retrieved August 7, 2024, from https://www.sciencedirect.com/topics/medicine-and-dentistry/actinobacteria#:~:text=Actin

obacteria%20are%20gram%20positive%2C%20multiple,the%20human%20gut%20are%20Bifidobacteria
43. Lind, E. (2019, June). *Actinobacteria*. National Park Service. https://www.nps.gov/articles/actinobacteria.htm#:~:text=Actinobacteria%20produce%20secondary%20metabolites%E2%80%94organic,%2C%20antifungal%2C%20and%20anticancer%20qualities
44. Binda, C., Lopetuso, L. R., Rizzatti, G., Gibiino, G., Cennamo, V., & Gasbarrini, A. (2018). Actinobacteria: A relevant minority for the maintenance of gut homeostasis. *Digestive and Liver Disease*, *50*(5), 421–428. https://doi.org/10.1016/j.dld.2018.02.012
45. *Bacteroides*. (n.d.). Retrieved August 8, 2024, from https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/bacteroides#:~:text=Bacteroides%20is%20essential%20in%20dietary%20fiber%20metabolism%20and%20gut%20microbiota%20interaction.&text=The%20interplay%20between%20gut%20microbiota,biological%20benefits%20on%20host%20health.&text=Dietary%20fiber%20also%20affects%20host%20through%20gut%20microbiota%2Dindependent%20pathways
46. Zamani, S., Hesam Shariati, S., Zali, M. R., Asadzadeh Aghdaei, H., Sarabi Asiabar, A., Bokaie, S., Nomanpour, B., Sechi, L. A., & Feizabadi, M. M. (2017). Detection of enterotoxigenic Bacteroides fragilis in patients with ulcerative colitis. *Gut Pathogens*, *9*(1), 53. https://doi.org/10.1186/s13099-017-0202-0
47. Ogunrinola, G. A., Oyewale, J. O., Oshamika, O. O., & Olasehinde, G. I. (2020). The Human Microbiome and Its Impacts on Health. *International Journal of Microbiology*, *2020*, 1–7. https://doi.org/10.1155/2020/8045646
48. Shan, Y., Lee, M., & Chang, E. B. (2022). The Gut Microbiome and Inflammatory Bowel Diseases. *Annual Review of Medicine*, *73*(1), 455–468. https://doi.org/10.1146/annurev-med-042320-021020
49. Pandey, H., Jain, D., Tang, D. W. T., Wong, S. H., & Lal, D. (2024). Gut microbiota in pathophysiology, diagnosis, and therapeutics of inflammatory bowel disease. *Intestinal Research*, *22*(1), 15–43. https://doi.org/10.5217/ir.2023.00080
50. Martín, R., Rios-Covian, D., Huillet, E., Auger, S., Khazaal, S., Bermúdez-Humarán, L. G., Sokol, H., Chatel, J.-M., & Langella, P. (2023). *Faecalibacterium* : a bacterial genus with promising human health applications. *FEMS Microbiology Reviews*, *47*(4). https://doi.org/10.1093/femsre/fuad039
51. Zeng, M. Y., Inohara, N., & Nuñez, G. (2017). Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunology*, *10*(1), 18–26. https://doi.org/10.1038/mi.2016.75
52. Zhao, M., Chu, J., Feng, S., Guo, C., Xue, B., He, K., & Li, L. (2023). Immunological mechanisms of inflammatory diseases caused by gut microbiota dysbiosis: A review. *Biomedicine & Pharmacotherapy*, *164*, 114985. https://doi.org/10.1016/j.biopha.2023.114985
53. Fusco, W., Lorenzo, M. B., Cintoni, M., Porcari, S., Rinninella, E., Kaitsas, F., Lener, E., Mele, M. C., Gasbarrini, A., Collado, M. C., Cammarota, G., & Ianiro, G. (2023). Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. *Nutrients*, *15*(9), 2211. https://doi.org/10.3390/nu15092211
54. Ney, L.-M., Wipplinger, M., Grossmann, M., Engert, N., Wegner, V. D., & Mosig, A. S. (2023). Short chain fatty acids: key regulators of the local and systemic immune response

in inflammatory diseases and infections. *Open Biology*, *13*(3). https://doi.org/10.1098/rsob.230014

55. He, J., Li, H., Jia, J., Liu, Y., Zhang, N., Wang, R., Qu, W., Liu, Y., & Jia, L. (2023). Mechanisms by which the intestinal microbiota affects gastrointestinal tumours and therapeutic effects. *Molecular Biomedicine*, *4*(1), 45. https://doi.org/10.1186/s43556-023-00157-9

56. Chancharoenthana, W., Kamolratanakul, S., Schultz, M. J., & Leelahavanichkul, A. (2023). The leaky gut and the gut microbiome in sepsis – targets in research and treatment. *Clinical Science*, *137*(8), 645–662. https://doi.org/10.1042/CS20220777

57. Santana, P. T., Rosas, S. L. B., Ribeiro, B. E., Marinho, Y., & de Souza, H. S. P. (2022). Dysbiosis in Inflammatory Bowel Disease: Pathogenic Role and Potential Therapeutic Targets. *International Journal of Molecular Sciences*, *23*(7), 3464. https://doi.org/10.3390/ijms23073464

58. Gyriki, D., Nikolaidis, C., Stavropoulou, E., Bezirtzoglou, I., Tsigalou, C., Vradelis, S., & Bezirtzoglou, E. (2024). Exploring the Gut Microbiome's Role in Inflammatory Bowel Disease: Insights and Interventions. *Journal of Personalized Medicine*, *14*(5), 507. https://doi.org/10.3390/jpm14050507

59. Belkaid, Y., & Hand, T. W. (2014). Role of the Microbiota in Immunity and Inflammation. *Cell*, *157*(1), 121–141. https://doi.org/10.1016/j.cell.2014.03.011

60. Zhang, J.-M., & An, J. (2007). Cytokines, Inflammation, and Pain. *International Anesthesiology Clinics*, *45*(2), 27–37. https://doi.org/10.1097/AIA.0b013e318034194e

61. Lechuga, S., Braga-Neto, M. B., Naydenov, N. G., Rieder, F., & Ivanov, A. I. (2023). Understanding disruption of the gut barrier during inflammation: Should we abandon traditional epithelial cell lines and switch to intestinal organoids? *Frontiers in Immunology*, *14*. https://doi.org/10.3389/fimmu.2023.1108289

62. Liévin-Le Moal, V., & Servin, A. L. (2013). Pathogenesis of Human Enterovirulent Bacteria: Lessons from Cultured, Fully Differentiated Human Colon Cancer Cell Lines. *Microbiology and Molecular Biology Reviews*, *77*(3), 380–439. https://doi.org/10.1128/MMBR.00064-12

63. Saez, A., Herrero-Fernandez, B., Gomez-Bris, R., Sánchez-Martinez, H., & Gonzalez-Granado, J. M. (2023). Pathophysiology of Inflammatory Bowel Disease: Innate Immune System. *International Journal of Molecular Sciences*, *24*(2), 1526. https://doi.org/10.3390/ijms24021526

64. Ji, J., Jin, W., Liu, S., Jiao, Z., & Li, X. (2023). Probiotics, prebiotics, and postbiotics in health and disease. *MedComm*, *4*(6). https://doi.org/10.1002/mco2.420

65. Portincasa, P., Bonfrate, L., Vacca, M., de Angelis, M., Farella, I., Lanza, E., Khalil, M., Wang, D. Q.-H., Sperandio, M., & di Ciaula, A. (2022). Gut Microbiota and Short Chain Fatty Acids: Implications in Glucose Homeostasis. *International Journal of Molecular Sciences*, *23*(3), 1105. https://doi.org/10.3390/ijms23031105

66. Basson, A. R., Zhou, Y., Seo, B., Rodriguez-Palacios, A., & Cominelli, F. (2020). Autologous fecal microbiota transplantation for the treatment of inflammatory bowel disease. *Translational Research*, *226*, 1–11. https://doi.org/10.1016/j.trsl.2020.05.008

67. Qiu, P., Ishimoto, T., Fu, L., Zhang, J., Zhang, Z., & Liu, Y. (2022). The Gut Microbiota in Inflammatory Bowel Disease. *Frontiers in Cellular and Infection Microbiology*, *12*. https://doi.org/10.3389/fcimb.2022.733992

68. Fakharian, F., Thirugnanam, S., Welsh, D. A., Kim, W.-K., Rappaport, J., Bittinger, K., & Rout, N. (2023). The Role of Gut Dysbiosis in the Loss of Intestinal Immune Cell Functions and Viral Pathogenesis. *Microorganisms*, *11*(7), 1849. https://doi.org/10.3390/microorganisms11071849
69. el Hadad, J., Schreiner, P., Vavricka, S. R., & Greuter, T. (2024). The Genetics of Inflammatory Bowel Disease. *Molecular Diagnosis & Therapy*, *28*(1), 27–35. https://doi.org/10.1007/s40291-023-00678-7
70. Korta, A., Kula, J., & Gomułka, K. (2023). The Role of IL-23 in the Pathogenesis and Therapy of Inflammatory Bowel Disease. *International Journal of Molecular Sciences*, *24*(12), 10172. https://doi.org/10.3390/ijms241210172
71. McGeachy, M. J., Cua, D. J., & Gaffen, S. L. (2019). The IL-17 Family of Cytokines in Health and Disease. *Immunity*, *50*(4), 892–906. https://doi.org/10.1016/j.immuni.2019.03.021
72. Mills, K. H. G. (2023). IL-17 and IL-17-producing cells in protection versus pathology. *Nature Reviews Immunology*, *23*(1), 38–54. https://doi.org/10.1038/s41577-022-00746-9
73. Sewell, G. W., & Kaser, A. (2022). Interleukin-23 in the Pathogenesis of Inflammatory Bowel Disease and Implications for Therapeutic Intervention. *Journal of Crohn's and Colitis*, *16*(Supplement_2), ii3–ii19. https://doi.org/10.1093/ecco-jcc/jjac034
74. Keestra-Gounder, A. M., & Tsolis, R. M. (2017). NOD1 and NOD2: Beyond Peptidoglycan Sensing. *Trends in Immunology*, *38*(10), 758–767. https://doi.org/10.1016/j.it.2017.07.004
75. Balasubramanian, I., & Gao, N. (2017). From sensing to shaping microbiota: insights into the role of NOD2 in intestinal homeostasis and progression of Crohn's disease. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *313*(1), G7–G13. https://doi.org/10.1152/ajpgi.00330.2016
76. Ashton, J. J., Seaby, E. G., Beattie, R. M., & Ennis, S. (2023). *NOD2* in Crohn's Disease—Unfinished Business. *Journal of Crohn's and Colitis*, *17*(3), 450–458. https://doi.org/10.1093/ecco-jcc/jjac124
77. *NOD2 nucleotide binding oligomerization domain containing 2 [Homo sapiens (human)]*. (2024, July 29). National Library of Medicine. https://www.ncbi.nlm.nih.gov/gene/64127
78. Lauro, M. L., Burch, J. M., & Grimes, C. L. (2016). The effect of NOD2 on the microbiota in Crohn's disease. *Current Opinion in Biotechnology*, *40*, 97–102. https://doi.org/10.1016/j.copbio.2016.02.028
79. *Histocompatibility antigen test*. (2023). MedlinePlus. https://medlineplus.gov/ency/article/003550.htm#:~:text=These%20are%20found%20on%20the,not%20from%20your%20own%20body
80. *HLA-B gene*. (n.d.). MedlinePlus. Retrieved August 8, 2024, from https://medlineplus.gov/genetics/gene/hla-b/#references
81. Cruz-Tapias, P., Castiblanco, J., & Anaya, J.-M. (2013). *HLA Association with Autoimmune Diseases* (J. Anaya, Y. Schonfeld, & A. Rojas-Villarraga, Eds.). National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK459459/
82. Nordquist, H., & Jamil, R. T. (2024). *Biochemistry, HLA Antigens*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK546662/
83. Stokkers, P. C. F., Reitsma, P. H., Tytgat, G. N. J., & van Deventer, S. J. H. (1999). HLA-DR and -DQ phenotypes in inflammatory bowel disease: a meta-analysis. *Gut*, *45*(3), 395–401. https://doi.org/10.1136/gut.45.3.395

84. *Groundbreaking Study Led by the Crohn's & Colitis Foundation Estimates Nearly 1 in 100 Americans Has Inflammatory Bowel Disease (IBD)*. (2023, July 20). Chron's and Colitis Foundation. https://www.crohnscolitisfoundation.org/groundbreaking-study-led-the-crohns-colitis-foundation-estimates-nearly-1-100-americans-has#:~:text=Importantly%2C%20the%20study%20found%20significant,times%20higher%20than%20Asian%20Americans
85. Caviglia, G. P., Garrone, A., Bertolino, C., Vanni, R., Bretto, E., Poshnjari, A., Tribocco, E., Frara, S., Armandi, A., Astegiano, M., Saracco, G. M., Bertolusso, L., & Ribaldone, D. G. (2023). Epidemiology of Inflammatory Bowel Diseases: A Population Study in a Healthcare District of North-West Italy. *Journal of Clinical Medicine*, *12*(2), 641. https://doi.org/10.3390/jcm12020641
86. Aniwan, S., Harmsen, W. S., Tremaine, W. J., & Loftus, E. v. (2019). Incidence of inflammatory bowel disease by race and ethnicity in a population-based inception cohort from 1970 through 2010. *Therapeutic Advances in Gastroenterology*, *12*, 175628481982769. https://doi.org/10.1177/1756284819827692
87. *Family History is Biggest Risk for Crohn's and Colitis*. (n.d.). Boston Endoscopy Center. Retrieved August 8, 2024, from https://bostonendoscopycenter.com/news/family-history-is-biggest-risk-for-crohns-and-colitis#:~:text=If%20your%20mother%20and%20your,more%20relatives%20who%20are%20affected
88. Higgins, R. (2014). *ABDOMINAL PAIN - INFLAMMATORY BOWEL DISEASE*. ACS/ASE Medical Student Core Curriculum . https://www.facs.org/media/q3updyuk/abdominal_pain_inflammatory.pdf
89. Jarmakiewicz-Czaja, S., Zielińska, M., Sokal, A., & Filip, R. (2022). Genetic and Epigenetic Etiology of Inflammatory Bowel Disease: An Update. *Genes*, *13*(12), 2388. https://doi.org/10.3390/genes13122388
90. Vedamurthy, A., & Ananthakrishnan, A. N. (2019). Influence of Environmental Factors in the Development and Outcomes of Inflammatory Bowel Disease. *Gastroenterology & Hepatology*, *15*(2), 72–82.
91. Okada, H., Kuhn, C., Feillet, H., & Bach, J.-F. (2010). The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clinical and Experimental Immunology*, *160*(1), 1–9. https://doi.org/10.1111/j.1365-2249.2010.04139.x
92. Alatab, S., Sepanlou, S. G., Ikuta, K., Vahedi, H., Bisignano, C., Safiri, S., Sadeghi, A., Nixon, M. R., Abdoli, A., Abolhassani, H., Alipour, V., Almadi, M. A. H., Almasi-Hashiani, A., Anushiravani, A., Arabloo, J., Atique, S., Awasthi, A., Badawi, A., Baig, A. A. A., … Naghavi, M. (2020). The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology & Hepatology*, *5*(1), 17–30. https://doi.org/10.1016/S2468-1253(19)30333-4
93. Hodges, P., & Kelly, P. (2020). Inflammatory bowel disease in Africa: what is the current state of knowledge? *International Health*, *12*(3), 222–230. https://doi.org/10.1093/inthealth/ihaa005
94. Pandey, B., Reba, M., Joshi, P. K., & Seto, K. C. (2020). Urbanization and food consumption in India. *Scientific Reports*, *10*(1), 17241. https://doi.org/10.1038/s41598-020-73313-8

95. Abegunde, A. T., Muhammad, B. H., Bhatti, O., & Ali, T. (2016). Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. *World Journal of Gastroenterology*, *22*(27), 6296. https://doi.org/10.3748/wjg.v22.i27.6296
96. Kaplan, G. G., & Windsor, J. W. (2021). The four epidemiological stages in the global evolution of inflammatory bowel disease. *Nature Reviews Gastroenterology & Hepatology*, *18*(1), 56–66. https://doi.org/10.1038/s41575-020-00360-x
97. Zaltman, C., do Espírito Santo, P. A., & de Magalhães Costa, M. H. (2024). Ambient air pollution and inflammatory bowel disease—a narrative review. *Digestive Medicine Research*, *7*, 13–13. https://doi.org/10.21037/dmr-23-12
98. *Effects of Acid Rain*. (2024, May 7). United States Environmental Protection Agency. https://www.epa.gov/acidrain/effects-acid-rain
99. Fatma, K., & Ahmet, Ö. (2023). Negative effects of acid rains on agricultural areas. *Annals of Environmental Science and Toxicology*, *7*(1), 013–016. https://doi.org/10.17352/aest.000065
100. Hills, R., Pontefract, B., Mishcon, H., Black, C., Sutton, S., & Theberge, C. (2019). Gut Microbiome: Profound Implications for Diet and Disease. *Nutrients*, *11*(7), 1613. https://doi.org/10.3390/nu11071613
101. Kaplan, G. G., Hubbard, J., Korzenik, J., Sands, B. E., Panaccione, R., Ghosh, S., Wheeler, A. J., & Villeneuve, P. J. (2010). The Inflammatory Bowel Diseases and Ambient Air Pollution: A Novel Association. *American Journal of Gastroenterology*, *105*(11), 2412–2419. https://doi.org/10.1038/ajg.2010.252
102. Berkowitz, L., Schultz, B. M., Salazar, G. A., Pardo-Roa, C., Sebastián, V. P., Álvarez-Lobos, M. M., & Bueno, S. M. (2018). Impact of Cigarette Smoking on the Gastrointestinal Tract Inflammation: Opposing Effects in Crohn's Disease and Ulcerative Colitis. *Frontiers in Immunology*, *9*. https://doi.org/10.3389/fimmu.2018.00074
103. AlQasrawi, D., Qasem, A., & Naser, S. A. (2020). Divergent Effect of Cigarette Smoke on Innate Immunity in Inflammatory Bowel Disease: A Nicotine-Infection Interaction. *International Journal of Molecular Sciences*, *21*(16), 5801. https://doi.org/10.3390/ijms21165801
104. Felson, S. (2024, June 1). *Smoking and Ulcerative Colitis: What's the Link?* WebMD. https://www.webmd.com/ibd-crohns-disease/ulcerative-colitis/uc-smoking-the-link
105. Zhang, W., Lin, H., Zou, M., Yuan, Q., Huang, Z., Pan, X., & Zhang, W. (2022). Nicotine in Inflammatory Diseases: Anti-Inflammatory and Pro-Inflammatory Effects. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.826889
106. Guslandi. (1999). Nicotine treatment for ulcerative colitis. *British Journal of Clinical Pharmacology*, *48*(4), 481–484. https://doi.org/10.1046/j.1365-2125.1999.00039.x
107. Price, L. R., & Martinez, J. (2020). Cardiovascular, carcinogenic and reproductive effects of nicotine exposure: A narrative review of the scientific literature. *F1000Research*, *8*, 1586. https://doi.org/10.12688/f1000research.20062.2
108. Patangia, D. v., Anthony Ryan, C., Dempsey, E., Paul Ross, R., & Stanton, C. (2022). Impact of antibiotics on the human microbiome and consequences for host health. *MicrobiologyOpen*, *11*(1). https://doi.org/10.1002/mbo3.1260
109. Barrette, L. (2022, January 5). *Colds and Flu: Do You Need Antibiotics?* University of Rochester Medical Center. https://www.urmc.rochester.edu/news/publications/health-matters/%E2%80%98tis-the-season-colds-flu-and-superbugs

110. *Do antibiotics harm healthy gut bacteria?* (2024, April 12). MedicalNewsToday. https://www.medicalnewstoday.com/articles/common-antibiotics#summary
111. Stromberg, J. (2015, January 28). *The hygiene hypothesis: How being too clean might be making us sick*. Vox. https://www.vox.com/2014/6/25/5837892/is-being-too-clean-making-us-sick
112. Rio, P., Gasbarrini, A., Gambassi, G., & Cianci, R. (2024). Pollutants, microbiota and immune system: frenemies within the gut. *Frontiers in Public Health*, *12*. https://doi.org/10.3389/fpubh.2024.1285186
113. Mishra, A., Chaturvedi, P., Datta, S., Sinukumar, S., Joshi, P., & Garg, A. (2015). Harmful effects of nicotine. *Indian Journal of Medical and Paediatric Oncology*, *36*(01), 24–31. https://doi.org/10.4103/0971-5851.151771
114. Langdon, A., Crook, N., & Dantas, G. (2016). The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Medicine*, *8*(1), 39. https://doi.org/10.1186/s13073-016-0294-z
115. Hashash, J. G., Elkins, J., Lewis, J. D., & Binion, D. G. (2024). AGA Clinical Practice Update on Diet and Nutritional Therapies in Patients With Inflammatory Bowel Disease: Expert Review. *Gastroenterology*, *166*(3), 521–532. https://doi.org/10.1053/j.gastro.2023.11.303
116. Campmans-Kuijpers, M. J. E., & Dijkstra, G. (2021). Food and Food Groups in Inflammatory Bowel Disease (IBD): The Design of the Groningen Anti-Inflammatory Diet (GrAID). *Nutrients*, *13*(4), 1067. https://doi.org/10.3390/nu13041067
117. Limdi, J. K. (2018). Dietary practices and inflammatory bowel disease. *Indian Journal of Gastroenterology*, *37*(4), 284–292. https://doi.org/10.1007/s12664-018-0890-5
118. Shapira, N. (2019). The Metabolic Concept of Meal Sequence vs. Satiety: Glycemic and Oxidative Responses with Reference to Inflammation Risk, Protective Principles and Mediterranean Diet. *Nutrients*, *11*(10), 2373. https://doi.org/10.3390/nu11102373
119. Fu, J., Zheng, Y., Gao, Y., & Xu, W. (2022). Dietary Fiber Intake and Gut Microbiota in Human Health. *Microorganisms*, *10*(12), 2507. https://doi.org/10.3390/microorganisms10122507
120. Poulson, B. (2024, July 24). *Soluble vs. Insoluble Fiber: Benefits and Differences*. Verywellhealth. https://www.verywellhealth.com/soluble-vs-insoluble-fiber-7093262#:~:text=There%20are%20two%20main%20types,to%20keep%20bowel%20movements%20regular
121. Dresden, D. (2024, February 9). *How much fiber is too much?* MedicalNewsToday. https://www.medicalnewstoday.com/articles/321286
122. Ney, L.-M., Wipplinger, M., Grossmann, M., Engert, N., Wegner, V. D., & Mosig, A. S. (2023). Short chain fatty acids: key regulators of the local and systemic immune response in inflammatory diseases and infections. *Open Biology*, *13*(3). https://doi.org/10.1098/rsob.230014
123. Thurler, K. (2022, August 1). *Research Links Red Meat Intake, Gut Microbiome, and Cardiovascular Disease in Older Adults* . TuftsNow. https://now.tufts.edu/2022/08/01/research-links-red-meat-intake-gut-microbiome-and-cardiovascular-disease-older-adults
124. Wilson, A. M., Teft, W. P., Tirona, R. P., Woolsey, S., Morse, B. P., DeGorter, M. P., Hegele, R. M., Choi, Y.-H. P., & Kim, R. M. (2015, October). *Trimethylamine-N-oxide: A Novel Biomarker for the Identification of Inflammatory Bowel Disease*. American Journal

of Gastroenterology. https://journals.lww.com/ajg/fulltext/2015/10001/trimethylamine_n_oxide__a_novel_biomarker_for_the.1818.aspx#:~:text=Choline%20levels%20were%20higher%20in,to%20a%20non%2DIBD%20population

125. Satokari, R. (2020). High Intake of Sugar and the Balance between Pro- and Anti-Inflammatory Gut Bacteria. *Nutrients*, *12*(5), 1348. https://doi.org/10.3390/nu12051348

126. UT Southwestern Medical Center. (2020, October 29). *High-sugar diet can damage the gut, intensifying risk for colitis*. ScienceDaily. https://www.sciencedaily.com/releases/2020/10/201029142042.htm

127. Zhang, D., Jin, W., Wu, R., Li, J., Park, S.-A., Tu, E., Zanvit, P., Xu, J., Liu, O., Cain, A., & Chen, W. (2019). High Glucose Intake Exacerbates Autoimmunity through Reactive-Oxygen-Species-Mediated TGF-β Cytokine Activation. *Immunity*, *51*(4), 671-681.e5. https://doi.org/10.1016/j.immuni.2019.08.001