

# Influence of Environmental Factors in the Development and Outcomes of Inflammatory Bowel Disease

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**Abstract:** Inflammatory bowel disease (IBD), which mainly comprises Crohn's disease (CD) and ulcerative colitis (UC), is a term for chronic inflammatory diseases of the gut arising due to a dysregulated immune response to a dysbiotic gut microbiome on a background of genetic predisposition. However, genetics explains a small fraction of risk, and the external environment plays a large and important role in disease pathogenesis and natural history. Cigarette smoking, one of the earliest- and most-studied risk factors, increases the risk of CD onset and is associated with severe disease. In contrast, although smoking cessation increases the risk of UC onset and relapse, current smoking appears to be protective. Appendectomy is inversely associated with the risk of UC. Various dietary factors may influence risk of IBD, including an inverse association with dietary fiber. Exclusion diets have anecdotal reports of efficacy but lack evidence from rigorous clinical trials. Psychosocial factors such as depression, stress, and sleep disturbance play a role in onset as well as in determining natural history. There is an important need for rigorous studies robustly informing the association and mechanism(s) of influence of the external environment on IBD risk and for clinical trials examining the efficacy of alteration of the environment in ameliorating the course of IBD.

Inflammatory bowel disease (IBD), a term for chronic inflammatory disorders that primarily affect the gut, mainly comprises Crohn's disease (CD) and ulcerative colitis (UC). The course of IBD has a relapsing and remitting pattern that often requires the use of immunomodulators or immunosuppressive medications to control disease activity.<sup>1,2</sup> IBD frequently has its onset during young adulthood, but onset at an older age is not uncommon.<sup>3</sup> The key underlying mechanism that has been postulated is a dysregulated immune response to microbial flora in conjunction with environmental factors interacting in a genetically susceptible host.<sup>4,5</sup> IBD has a complex genetic architecture with more than 200 gene variants associated with the disease. However, genetics explains less than 25% of heritability of either CD or UC.<sup>5</sup> Traditionally, IBD was

## Keywords

Inflammatory bowel disease, environment, diet, smoking, microbiome

considered to be predominantly a disease of white individuals in the Western Hemisphere.<sup>6</sup> The rapid increase in incidence over the last 4 decades—including in countries in Asia, where it was previously rare—suggests that westernization of lifestyle and urbanization are key influences on disease risk.<sup>7</sup> Epidemiologic data over the past decade have provided evidence for a prominent role for the environment in the pathogenesis of IBD.<sup>7,8</sup> Environmental factors can be behaviors that increase risk at an individual level (such as diet), or they may modify the risk of populations of an entire region (such as with urbanization, air pollution, and ultraviolet light exposure). External environmental exposures from the time of birth to adulthood influence the gut microbiome, increase gut permeability, and modulate immune responses such as increasing the expression of proinflammatory cytokines, which, in turn, alters the risk and natural history of the disease throughout life.<sup>9-11</sup> This article reviews the literature on various environmental factors in IBD that influence the development of disease as well as affect outcomes. Identification of environmental influences could lead to pathways for disease prevention as well as identification of new treatment strategies.

## Cigarette Smoking

Smoking is one of the earliest- and most-studied environmental influences on the risk of IBD. It modulates both immune responses and the diversity and composition of the gut microbiome through which it may exert its influence on disease risk.<sup>12,13</sup> In addition, chronic smoke exposure can also alter the composition and integrity of the epithelial mucous membrane, which, in turn, can predispose patients to intestinal inflammation (Table).<sup>14</sup>

Current smoking is inversely associated with the risk of UC.<sup>15-17</sup> In addition, current smokers have a milder disease course and better prognosis compared to nonsmokers, and have a lower risk of colectomy.<sup>15</sup> In contrast, smoking cessation in UC is frequently associated with relapse. A prospective cohort study of female nurses confirmed an increase in the risk of UC in former smokers (hazard ratio [HR], 1.56; 95% CI, 1.26-1.93), with the risk remaining elevated for at least 2 to 5 years after cessation (HR, 3.06; 95% CI, 2.00-4.67).<sup>16</sup> In a meta-analysis by Mahid and colleagues, former smokers had an increased risk of UC (odds ratio [OR], 1.79; 95% CI, 1.37-2.34) and current smokers had a decreased risk compared to nonsmoking controls (OR, 0.58; 95% CI, 0.45-0.75).<sup>18</sup> However, trials of nicotine preparations in patients with UC have had variable and mostly null effects, suggesting that at least some of the effect of current smoking on UC risk may be from nonnicotine components of smoke.<sup>19</sup>

In contrast to UC, both current and former smokers have an elevated risk for CD.<sup>16,17</sup> Current smokers

have a worse prognosis, with an increased need for corticosteroids, immunosuppressants, and IBD-related surgeries.<sup>20,21</sup> Interestingly, in a study by Cosnes and colleagues, the adverse effects of smoking were more prominent in women than in men.<sup>20</sup> In a prospective study of 622 patients with CD, more current smokers (46%) had a disease flare compared to nonsmokers (30%) and former smokers (23%).<sup>22</sup> This effect was significant in heavy smokers (>15 cigarettes/day). A prospective cohort study has shown current smokers to be at a 2-fold elevated risk for CD (HR, 1.90; 95% CI, 1.42-2.53) with some reduction in magnitude but a persistent increase in risk in former smokers (HR, 1.35; 95% CI, 1.05-1.73).<sup>16</sup> In a prospective study of 474 patients with CD who were smokers, those who stopped smoking (n=59; 12%) for more than 1 year had a risk of relapse and need for corticosteroids and immunosuppressants similar to nonsmokers, whereas those who continued smoking had an elevated risk.<sup>23</sup> Another prospective cohort study, by Nunes and colleagues, showed that patients with CD who were smokers had frequent relapses regardless of maintenance immunosuppression.<sup>24</sup> In a meta-analysis by To and colleagues, patients with CD who were smokers had increased odds of flare of disease activity (OR, 1.56; 95% CI, 1.21-2.01), flare after surgery (OR, 1.97; 95% CI, 1.36-2.85), need for first surgery (OR, 1.68; 95% CI, 1.33-2.12), and need for second surgery (OR, 2.17; 95% CI, 1.63-2.89) compared to nonsmokers.<sup>25</sup>

However, there may be ethnic or geographic variation in the effect of smoking on CD risk. Retrospective analysis of patients with CD in India showed no effect of oral tobacco use or smoking on medical or surgical therapy.<sup>26</sup> Smoking was also not a risk factor for CD in ACCESS (Asia-Pacific Crohn's and Colitis Epidemiologic Study), which was conducted in Asia and Australia,<sup>27</sup> although former smoking was associated with UC in both regions.

## Appendectomy

Appendectomy has been reported to be inversely associated with the risk of UC. It has been postulated that the increased CD4/CD8 ratio and infiltration of CD4+ and CD69+ T cells in the appendix of patients with UC may act as a priming site in the pathogenesis of UC.<sup>28</sup> One of the first studies to propose this association was a large, population-based study from Sweden in which individuals who underwent appendectomy for appendicitis or mesenteric lymphadenitis before the age of 20 years had a lower risk of UC (relative risk [RR], 0.76; 95% CI, 0.65-0.90).<sup>29</sup> The association did not hold true if the appendectomy was performed for nonspecific abdominal pain. The same population-based cohort, as well as

**Table.** Environmental Factors and Their Potential Mechanisms of Action and Impact on Incident and Established CD and UC

<b>Environmental Factors and Mechanisms of Action</b>	<b>Disease Onset</b>	<b>Disease Course</b>	<b>Intervention Study Findings</b>
<b>Cigarette smoking</b> <ul style="list-style-type: none"> <li>• Disruption of epithelial barrier</li> <li>• Intestinal inflammation</li> <li>• Gut microbiome</li> </ul>	<b>UC</b> <i>Current:</i> ↓ Risk <i>Former:</i> ↑ Risk <b>CD</b> <i>Current:</i> ↑ Risk <i>Former:</i> ↑ Risk	<b>UC</b> <i>Current:</i> Milder disease ↓ Risk of colectomy <i>Former:</i> ↑ Risk of relapse <b>CD</b> <i>Current:</i> ↑ Need for corticosteroids, immunosuppressants ↑ Risk of IBD-related surgery <i>Former:</i> ↑ Risk	<ul style="list-style-type: none"> <li>• Smoking cessation in CD ↓ risk of flare compared to active smokers</li> <li>• Nicotine preparations variably effective in UC</li> </ul>
<b>Appendectomy</b> <ul style="list-style-type: none"> <li>• CD4/CD8 infiltration</li> <li>• ↑ CD4+ and CD69+ T cells</li> <li>• Effect on microbiome</li> </ul>	<b>UC</b> ↓ Risk <b>CD</b> ↑ Possible risk	<b>UC</b> ↓ Risk of relapse, immunosuppression, colectomy <b>CD</b> ↑ Risk	<ul style="list-style-type: none"> <li>• ACCURE trial (ongoing) examining the effect of appendectomy on UC course</li> </ul>
<b>Diet</b> <ul style="list-style-type: none"> <li>• Intestinal permeability</li> <li>• Intestinal microbiome</li> <li>• Disruption of mucus layer</li> </ul>	<b>UC</b> ↑ Risk: Animal fats, n-6 PUFAs <b>CD</b> ↓ Risk: n-3 PUFAs, vegetables, fruits, fiber, dietary zinc, potassium	Variable and inconsistent association between diet and risk of relapse	<ul style="list-style-type: none"> <li>• Exclusive enteral nutrition is effective for induction of remission in CD</li> <li>• Exclusionary diets (SCD, autoimmune protocol diet) achieve clinical remission in a subset of patients with IBD</li> </ul>
<b>Antibiotics</b> <ul style="list-style-type: none"> <li>• Dysbiosis</li> </ul>	↑ Risk of UC and CD: in Western studies/whites ↓ Risk of UC and CD: in Asian studies		<ul style="list-style-type: none"> <li>• Ciprofloxacin + biologic agents are effective for perianal fistula closure in CD</li> <li>• ↓ Postoperative recurrence with nitroimidazole</li> <li>• Fecal microbiota transplantation is moderately effective in UC in randomized, controlled trials</li> </ul>
<b>Vitamin D</b> <ul style="list-style-type: none"> <li>• Decrease in intestinal inflammation</li> <li>• Upregulation of cathelicidin</li> </ul>	↑ Risk of UC and CD	↑ Risk of flares, treatment refractoriness ↓ Quality of life	<ul style="list-style-type: none"> <li>• Vitamin D3 supplementation reduces clinical disease activity and markers of inflammation and results in a trend toward lower rates of relapse</li> </ul>
<b>Depression/stress/sleep</b> <ul style="list-style-type: none"> <li>• Vagus nerve inhibition</li> <li>• Proinflammatory cytokine production</li> <li>• Gut microbiome modification</li> <li>• Increase in intestinal permeability</li> </ul>	↑ Risk of UC and CD	↑ Risk of relapse and failure of immunosuppressive therapy	<ul style="list-style-type: none"> <li>• Mind-body interventions and antidepressants improve quality of life in patients with IBD with variable effect on risk of relapse</li> </ul>
<b>NSAIDs</b> <ul style="list-style-type: none"> <li>• Disruption of epithelial barrier</li> </ul>	↑ Risk of UC and CD	↑ Risk of relapse	<ul style="list-style-type: none"> <li>• A pilot study showed no increased risk of relapse with selective COX-2 inhibitors such as celecoxib in patients with UC in remission</li> </ul>

(Table continued on the following page)

**Table.** (Continued) Environmental Factors and Their Potential Mechanisms of Action and Impact on Incident and Established CD and UC

Environmental Factors and Mechanisms of Action	Disease Onset	Disease Course	Intervention Study Findings
<b>Exercise</b> • Unknown	↓ Risk of UC (with at least 27 MET hours/week)	Regular exercise: ↑ Quality of life ↓ Stress ↓ Disease activity in UC and CD	None
<b>Breastfeeding</b> • Gut microbiome	↓ Risk of CD and UC		None
<b>Urban environment</b> • Hygiene hypothesis • Air pollution	↑ Risk of CD and UC	↑ Risk of IBD-related hospitalizations	None

ACCURE, The Effect of Appendectomy on the Clinical Course of Ulcerative Colitis; CD, Crohn's disease; COX-2, cyclooxygenase-2; IBD, inflammatory bowel disease; MET, metabolic equivalent of task; NSAIDs, nonsteroidal anti-inflammatory drugs; PUFAs, polyunsaturated fatty acids; SCD, Specific Carbohydrate Diet; UC, ulcerative colitis.

others,<sup>30,31</sup> demonstrated an increased risk of CD after an appendectomy, although it is less clear if this is causal or merely represents appendectomy due to involvement from CD (Table).

The effect of appendectomy on the course of UC remains uncertain. A study by Naganuma and colleagues found a lower relapse rate for patients with UC who had appendectomy prior to diagnosis (57% vs 79%).<sup>32</sup> Two other studies found a lower requirement for immunosuppression in patients with UC who underwent an appendectomy compared to controls.<sup>33,34</sup> Studies by Selby and colleagues and Hallas and colleagues found no difference in colectomy rates between patients who had an appendectomy prior to or after the onset of UC compared to the control group.<sup>35,36</sup> A Swedish cohort study conducted by Myrelid and colleagues, which included 63,711 patients with UC, demonstrated a lower risk of colectomy (HR, 0.44; 95% CI, 0.27-0.72) and UC-related hospital admission if appendectomy was performed early in life and prior to UC diagnosis and an increased risk of colectomy if appendectomy was performed after UC diagnosis (HR, 1.56; 95% CI, 1.20-2.03).<sup>37</sup> Recent research has found that the vermiform appendix has a direct interaction with the intestinal microbiome, which regulates the intestinal biofilm. The intestinal biofilm has been found to play a major role in the recovery and recolonization of colonic commensal flora after diarrheal illness.<sup>38</sup>

## Diet

Among all of the environmental factors, diet is thought to play the predominant role in the etiopathogenesis

of IBD. It exerts its effect by modulating the intestinal microbiome,<sup>39</sup> predisposing patients to proinflammatory substrate production, disruption of mucus layer, and the increase of intestinal permeability.<sup>40,41</sup> In a prospective cohort study, higher intake of dietary fiber was associated with a decreased risk of CD (HR, 0.64; 95% CI, 0.41-0.99). Fiber intake, if obtained from vegetables or fruits, had the greatest reduction in risk compared to fiber obtained from cereals or whole grains.<sup>42</sup> Higher intake of dietary n-3 polyunsaturated fatty acids (PUFAs; eg, fish oil), eicosapentaenoic acid, and docosahexaenoic acid was associated with a lower incidence of UC in middle-aged adults; in contrast, a diet rich in n-6 PUFAs (which, in turn, is metabolized to arachidonic acid) was associated with an increased risk of UC due to proinflammatory properties.<sup>43,44</sup> A case-control study of children across Canada examining dietary consumption 1 year prior to CD diagnosis found that a higher ratio of omega-3/omega-6 fatty acids was associated with a lower risk of CD.<sup>45</sup> In a French study, high intake of animal protein (meat or fish) was associated with an increased incidence of IBD.<sup>46</sup> Westernization of diet (eg, diet high in certain saturated fats, processed meats, and refined sugars) is associated with promoting human dysbiosis, which may increase the proinflammatory state in the colon.<sup>47,48</sup> Dietary influence at an early age may modify the risk of disease during adulthood durably. In the Nurses' Health Study II, there was an increase in the incidence of CD among subjects who had a lower intake of fruits, vegetables, and fish during their adolescence.<sup>49</sup> Dietary zinc intake was associated with a reduced risk of CD. However, prospective research with dietary zinc or supplementation did not modify the risk of UC.<sup>50</sup> In a prospective study of

women, dietary potassium was inversely associated with the risk of CD and UC (Table).<sup>51</sup>

Prospective studies have revealed that patients with IBD who are zinc deficient have worse IBD-related outcomes, which eventually improve with replacement,<sup>52,53</sup> although the directionality of this association warrants more investigation. Experimental studies<sup>54,55</sup> have supported the argument that zinc deficiency contributes to the worsening of intestinal inflammation, although disease activity itself can contribute to zinc deficiency. High sulfur- or high sulfate-containing foods were associated with relapse in UC.<sup>56-58</sup> Sulfur-containing food items, such as preserved meat, alcoholic beverages, milk, dietary supplements such as chondroitin sulfate, or food additives such as carrageenan, are common with the westernization of diet.<sup>40</sup> Sulfate-reducing bacteria produce toxic hydrogen sulfide as a result of oxidative metabolism.

Various diets have been used by patients with IBD in an attempt to attenuate intestinal inflammation.<sup>40</sup> The most consistent benefit has been for an exclusive enteral nutrition with complete elimination of normal diet.<sup>59</sup> Other diets are yet to be validated in rigorous clinical trials for anti-inflammatory effects. After diagnosis, the majority of patients with IBD believe that diet plays a role in their disease.<sup>60,61</sup> Certain exclusionary diets—such as the Specific Carbohydrate Diet; the low-fermentable oligo-, di-, and monosaccharide and polyol diet; and the Paleolithic diet—are commonly used by patients with IBD; however, these diets are yet to be validated by intervention studies.<sup>40</sup> Diets that combine partial enteral nutrition with specific foods that are thought to have potential anti-inflammatory effects, such as n-3 PUFAs and soluble fiber, have shown benefit in an open-label study with the resolution of intestinal inflammatory markers.<sup>62</sup> However, partial enteral nutrition is not recommended in active CD<sup>63</sup> and remains to be established as efficacious in randomized, controlled trials.

Curcumin is a phytochemical derived from the herb turmeric (*Curcuma longa*), a commonly used spice in Asian cuisine and medicine known to have antioxidant and anti-inflammatory properties.<sup>64,65</sup> Research has shown that it is effective in the inhibition of the tumor necrosis factor pathway as well as in CD4 T-cell proliferation.<sup>66</sup> In a randomized, placebo-controlled trial, Hanai and colleagues showed that curcumin may be beneficial to maintain remission in UC.<sup>67</sup> In a randomized, controlled clinical trial of patients with active mild to moderate UC, Lang and colleagues showed that high-dose curcumin in combination with mesalamine was superior to mesalamine alone.<sup>68</sup> Clinical response was achieved by 17 patients (65.3%) in the curcumin group compared to 3 patients (12.5%) in the placebo group ( $P < .001$ ; OR, 13.2; 95% CI, 3.1-56.6).<sup>68</sup>

## Antibiotics

The gut microbiome plays an important role in the development of IBD. It is a complex environment within a human that harbors up to 100 trillion cells of microbes.<sup>69</sup> Research has shown that patients with IBD exhibit a decrease in diversity of the gut microbiota and have an average of 25% fewer microbial genes than healthy persons.<sup>70</sup> In a study by Ott and colleagues, the diversity of microflora in CD and UC was reduced to 50% and 30%, respectively, predominantly among anaerobic bacteria.<sup>71</sup> Although it remains unclear whether dysbiosis is causal or a consequence of inflammation in the gut,<sup>72</sup> several environmental factors implicated in the pathogenesis of IBD mediate their effect through altering the gut microbiome (Table). Important among these is exposure to antibiotics. In population-based research, exposure to antibiotics within the first year of life was associated with an increased risk of IBD, particularly CD.<sup>73</sup> A meta-analysis of 11 observational studies showed a marked increase in the risk of CD in children with exposure to most antibiotic groups.<sup>74</sup> A nested case-control study conducted in Manitoba, Canada<sup>75</sup> demonstrated that adults with incident IBD were more likely to have been prescribed antibiotics 2 to 5 years prior to diagnosis compared to controls. Antibiotic exposure in treatment-naïve patients with CD amplifies the microbial dysbiosis.<sup>76</sup> Contrary to numerous studies of the Western population, a questionnaire-based study in Asia-Pacific showed a decreased risk of IBD with antibiotic exposure.<sup>27</sup> Similarly, a prospective case-control study showed that antibiotic use reduced the incidence of CD (OR, 0.27; 95% CI, 0.11-0.67) and UC (OR, 0.38; 95% CI, 0.18-0.80) in Middle Eastern migrants in Australia but not in the white Australian control population.<sup>77</sup>

Microbiome manipulation using antibiotics or fecal microbiota transplantation (FMT) has become a new avenue of therapeutics in IBD. A single randomized, controlled trial showed enteric release-formulated rifaximin to be superior to placebo in inducing clinical remission.<sup>78</sup> A randomized, controlled trial showed that ciprofloxacin in combination with biologic therapy was superior to adalimumab (Humira, AbbVie) monotherapy in perianal fistula closure in CD.<sup>79</sup> Nitroimidazole antibiotics along with immunosuppressive therapy were associated with a reduced risk of postoperative recurrence of CD (RR, 0.64; 95% CI, 0.44-0.92; number needed to treat, 4).<sup>80</sup> FMT has emerged as a novel approach for altering the gut microbiota. This approach has been remarkably effective for *Clostridium difficile* colitis, where the lack of microbial diversity is the key factor contributing to the pathogenesis of the disease.<sup>81</sup> Four published randomized clinical trials evaluating FMT for inducing remission of active UC have shown promising results (28% in the FMT group vs



9% in the placebo group; OR, 3.67; 95% CI, 1.82-7.39;  $P=.64$ ) based on a meta-analysis.<sup>82-86</sup> At present, however, the primary data are inadequate to support routine use of antibiotics or FMT as primary therapy for either UC or CD.

## Breastfeeding

The microbiome of an infant is directly correlated with events such as the mode of delivery, intrapartum antibiotics, and breastfeeding.<sup>87,88</sup> Many studies in both Asian populations and the Western Hemisphere have found an inverse association between breastfeeding and the risk of CD and UC.<sup>89,90</sup> In the largest meta-analysis thus far, comprising 7536 individuals, breastfeeding was inversely associated with the risk of CD (OR, 0.71; 95% CI, 0.59-0.85) and UC (OR, 0.78; 95% CI, 0.67-0.91). This effect was greater in Asians compared to whites for the risk of CD.<sup>91</sup> There was also a dose-dependent association, with the greatest protective effect for CD occurring when being breastfed for at least 12 months (Table).

## Depression, Stress, and Sleep Disturbance

Depression and psychosocial stress may play a role in the pathogenesis of CD and UC.<sup>92</sup> There are several pathways through which stress may exert this effect, including vagus nerve inhibition, proinflammatory cytokine production, modification of the gut microbiome, and increase in intestinal permeability.<sup>93</sup> Prospective cohorts have shown that women with depressive symptoms had a greater risk of incident CD.<sup>94</sup> However, not all studies have found this association, and in one study, major life stress was not associated with an increase in the risk of IBD.<sup>95</sup> Stress has also been more frequently associated with disease relapse in IBD, although evidence has been mixed whether this is due to objective worsening of inflammation or stress-induced gastrointestinal symptoms. In a multi-institutional cohort study of 5405 patients with CD, depressive disorder and anxiety were associated with an increased risk of surgery (OR, 1.28; 95% CI, 1.03-1.57) and health care utilization.<sup>96</sup> A study by Bernstein and colleagues found that high perceived stress was associated with IBD flares.<sup>97</sup> Interventions such as antidepressants and psychological counseling were associated with a reduction in IBD flares and health care utilization, as well as an improvement in quality of life in some, but not all,<sup>98</sup> studies.<sup>99</sup> Patients with low stress and good coping mechanisms had fewer relapses than those with avoidant coping and high perceived stress.<sup>100</sup> Major depressive disorder has also been associated with failure of infliximab (Remicade, Janssen) therapy (OR, 0.166; 95% CI, 0.049-0.567) and decreased time to retreatment ( $P=.001$ ).<sup>101</sup> Mindfulness, mind-body

intervention programs, and yoga did not substantially and durably impact disease activity in patients with IBD.<sup>102</sup> Stress management psychotherapy was studied in a randomized, controlled trial of 114 patients with IBD and did not show any significant change in disease course or rate of relapse, although it showed some improvement in quality of life in UC (Table).<sup>103</sup>

Along with an impaired psychological state and high rate of perceived stress, the quality and duration of sleep are reduced in IBD. An Internet-based questionnaire found that sleep impairment was common in IBD even during remission.<sup>104</sup> Sleep disturbance at baseline during remission was associated with a 2-fold increase in the risk of active disease in patients with CD at 6 months (OR, 2.00; 95% CI, 1.45-2.76).<sup>104</sup> Another prospective cohort study demonstrated that both having fewer than 6 hours of sleep per day and having more than 9 hours of sleep per day were associated with an increase in the risk of UC.<sup>105</sup>

## Nonsteroidal Anti-Inflammatory Drug Use

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used and available over the counter. There has been a growing amount of evidence implicating them in the development, as well as relapse, of IBD.<sup>106-108</sup> Women who used NSAIDs for at least 15 days per month had an increased risk of both CD and UC. Aspirin did not have any significant effect on IBD.<sup>106</sup> Among patients with established CD, NSAID use at least 5 times per month had a higher risk of active disease at follow-up (RR, 1.65; 95% CI, 1.12-2.44).<sup>108</sup> In a prospective trial by Takeuchi and colleagues, patients with quiescent CD and UC were assigned to receive paracetamol ( $n=26$ ) and the nonselective NSAIDs naproxen ( $n=32$ ), diclofenac ( $n=29$ ), and indomethacin ( $n=22$ ) for 4 weeks.<sup>100</sup> Nonselective NSAIDs were associated with a 17% to 28% relapse rate within 9 days of ingestion and an increase in intestinal inflammation.<sup>109</sup> A pilot study on therapy with celecoxib in UC patients in remission did not find an increase in the relapse rate compared to placebo, suggesting that this target may likely be safer than nonselective NSAIDs in patients with IBD (Table).<sup>110</sup>

## Geography and Urban Living

The greater incidence of IBD in Western countries compared to Eastern countries suggests that geography-related factors may modify disease risk. Even in North America, the incidence is higher in whites compared to African Americans, Asians, and Hispanics.<sup>111,112</sup> The increase in incidence in Japan, China, India, and Korea has been largely attributed to urbanization, westernization of diet, and improvement in hygiene.<sup>113,114</sup> A Canadian study

revealed that people living in rural areas had a lower incidence of IBD compared to urban residents (30/100,000 vs 33/100,000, respectively).<sup>115</sup> This association was strongest for childhood exposures to rural environment. A meta-analysis of 25 and 30 observational studies in UC and CD, respectively, similarly demonstrated an association of urban environment or residence with a higher incidence of UC and CD, respectively.<sup>116</sup> In a Swiss study, living in an urban zone was associated with both CD and UC (RR, 1.49 and 1.63, respectively).<sup>117</sup> Supporting a role for geography and the macroenvironment is the finding that migration from a low-incidence to high-incidence region is associated with an increase in disease risk, particularly in the offspring.<sup>118</sup> Two initial key studies from the United Kingdom demonstrated the increased incidence of UC and CD in children of South Asian migrants, with a risk similar to that of the native white population. The children of migrants matched the incidence rates of the natives of higher incidence regions (Table).<sup>119,120</sup>

One hypothesis for the difference in incidence of IBD between urban and rural areas is that greater environmental hygiene in an urban setting has fewer protective influences, such as exposure to animals and pets, which may contribute to an immune response that is skewed toward autoimmunity and atopy. Dog ownership is associated with increased exposure to a distinct house dust-related microbe such as *Lactobacillus johnsonii*.<sup>121</sup> Supplementation of wild mice with *L. johnsonii* influenced adaptive immunity and conferred protection from allergy and viral infections. Consistent with this, a systematic review of 29 studies showed that exposure to pets and farm animals was associated with a reduced risk of IBD, and this association was stronger in nonwhites than in whites.<sup>122</sup> Hafner and colleagues demonstrated an inverse association between the prevalence of prior hepatitis A virus infection and prior worm infestation and the risk of IBD.<sup>123</sup> An Israeli study on surrogate markers of the hygiene hypothesis showed an association with living in an urban environment, a small number of siblings, and a high birth order with an increased incidence of IBD.<sup>124</sup> Areas with high prevalence of *Helicobacter pylori* infection have a lower incidence of IBD, suggesting that poor environmental hygiene (facilitating *H. pylori* transmission) is protective against IBD.<sup>125,126</sup>

### Latitude of Residence and Role of Vitamin D

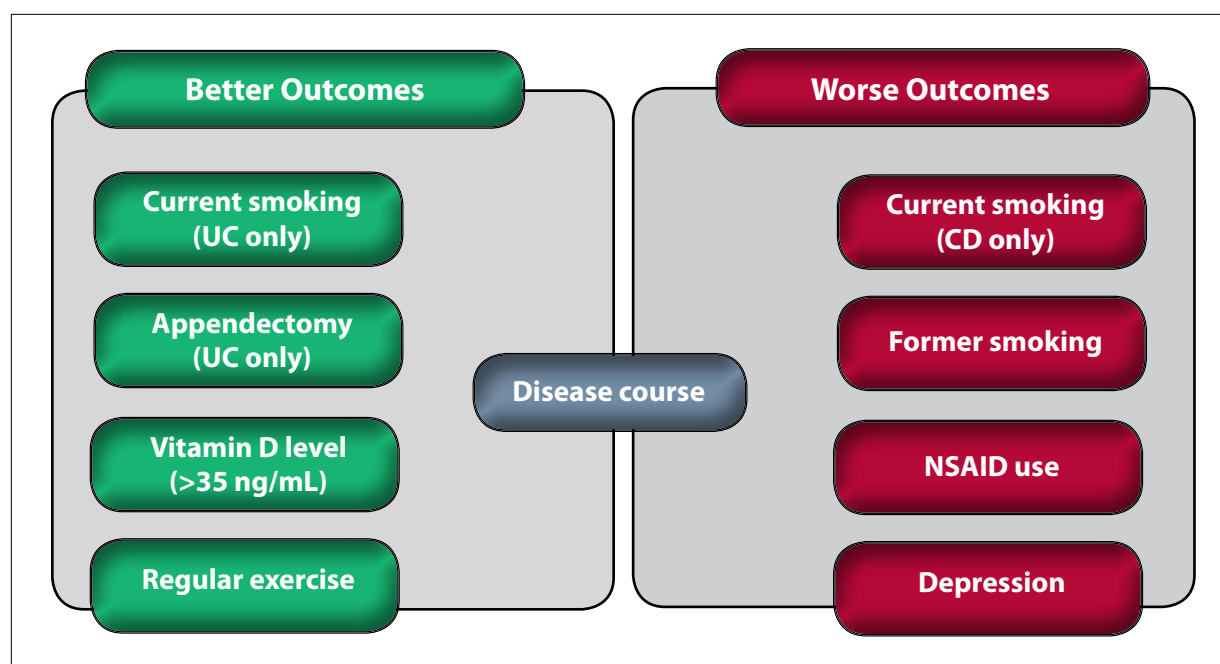
Vitamin D is known to modulate intestinal inflammation through several mechanisms.<sup>127</sup> It has been implicated as playing a role in the pathogenesis as well as the natural history of IBD, although not all literature has been consistent on this association.<sup>127,128</sup> In the prospective

Nurses' Health Study I and II cohorts, southern latitude of residence was associated with a reduced risk of IBD, particularly for residence during early adulthood. The adjusted HR for women residing at southern compared to northern latitudes at 30 years of age was 0.48 (95% CI, 0.30-0.77) for CD and 0.62 (95% CI, 0.42-0.90) for UC.<sup>129</sup> A similar north-south gradient was noted in a French study.<sup>130</sup> One implication of the association with northern latitudes is that such regions are associated with low ultraviolet sunlight exposure, resulting in vitamin D deficiency.<sup>131</sup> An analysis of predicted serum vitamin D status using a model incorporating various sources of vitamin D related to lifestyle, diet, and geography similarly demonstrated an inverse association between predicted plasma levels of 25-hydroxy vitamin D and the risk of CD (HR for fourth quartile compared to lowest quartile, 0.54; 95% CI, 0.30-0.99; Table).<sup>132</sup>

Vitamin D deficiency occurs more frequently in IBD patients than in the general population. Vitamin D deficiency in IBD patients is not entirely a consequence of active disease and may be due to poor dietary intake and reduced sunlight exposure, physical activity, and absorption of vitamin D.<sup>127,128,131</sup> Patients with IBD who have vitamin D deficiency have a higher risk of flares and treatment refractoriness and a lower health-related quality of life.<sup>133</sup> A Norwegian study showed a high prevalence of vitamin D deficiency in patients with CD as opposed to UC (53% vs 44%), and vitamin D-deficient patients had increased disease activity, frequent relapses, and high fecal calprotectin levels.<sup>134</sup> A prospective study of patients with UC in remission demonstrated that serum levels of vitamin D lower than 35 ng/mL were associated with an increased risk of relapse, suggesting that there might be a higher threshold of vitamin D adequacy in chronic inflammatory diseases.<sup>135</sup> A pilot study by Jorgensen and colleagues to replace vitamin D3 in patients with CD significantly improved serum vitamin D levels with a trend toward reduced risk of relapse in those receiving supplementation.<sup>136</sup> Small studies have also shown vitamin D supplementation to reduce circulating markers of inflammation and clinical disease activity, although these studies have had small sample sizes and have lacked control groups.<sup>137,138</sup>

### Air Pollution

Prior to the implementation of environmental regulations, between 1940 and 1980, the increase in incidence of UC and CD paralleled growing air pollution.<sup>113</sup> The link between environmental air pollution and IBD has been described suggesting several biologically plausible mechanisms, notably through the effect of both particulate and chemical pollutants on immune response and



**Figure.** A proposed list of environmental influences associated with better and worse outcomes in inflammatory bowel disease. CD, Crohn's disease; NSAID, nonsteroidal anti-inflammatory drug; UC, ulcerative colitis.

induction of systemic inflammation.<sup>139</sup> Another postulated mechanism is through the alteration of the gut microbiome, as found in a study using a murine model, in which ingestion of airborne particulate matter induced inflammatory changes in the intestine modulated through alteration of the gut microbiome.<sup>140</sup> Epidemiologic studies associating IBD risk with air pollution exposure have yielded conflicting results. Individuals younger than 25 years of age living in areas with higher sulfur dioxide and nitrogen dioxide levels had an increased risk of UC and CD, respectively.<sup>141</sup> In a study in Wisconsin, the total criteria pollutant emissions were associated with IBD-related hospitalization in adults for both UC (incidence rate ratio [IRR], 1.48; 95% CI, 1.27-1.73) and CD (IRR, 1.39; 95% CI, 1.26-1.52).<sup>142</sup> The association between particulate matter and disease risk has interestingly revealed an inverse association between exposure to particulate matter 2.5  $\mu\text{m}$  or less in diameter and the risk of IBD in 2 separate cohorts. In contrast, exposure to heavily trafficked roads was associated with an increase in the risk of disease.<sup>143,144</sup>

## Exercise

An analysis of the Nurses' Health Study I and II cohorts demonstrated that physical activity of at least 27 metabolic equivalent of task (MET) hours per week was

associated with a 44% reduction in the risk of developing CD compared to sedentary women (MET <3 hours/week).<sup>145</sup> Regular exercise has shown benefit in improving quality of life and stress in CD patients. In a large prospective study of 1857 patients with UC or CD, an increase in the level of exercise was associated with a decrease in the risk of active disease by 32% in patients with CD and 24% in patients with UC at 6 months (Table).<sup>146</sup>

## Summary

Environmental influences exert important roles on the pathogenesis and natural history of IBD. The environmental factors that influence outcomes after diagnosis are summarized in the Figure. Growing epidemiologic data support many of the anecdotal observations that have transpired in patients with IBD. In addition, recent experiments have provided key mechanistic insights into how such environmental and lifestyle influences may modify susceptibility to IBD. However, there exists a paucity of interventional studies aiming to modify disease course through modification of the environmental factors. There is an important need for collaborative translational research in this area to provide novel and safe routes of disease prevention and treatment and to improve patient outcomes.



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