Published in final edited form as:

Curr Gastroenterol Rep. 2013 January ; 15(1): 302. doi:10.1007/s11894-012-0302-4.

Environmental Triggers for Inflammatory Bowel Disease

Ashwin N. Ananthakrishnan

Division of Gastroenterology, Massachusetts General Hospital and, Harvard Medical School, Boston, MA, USA

Abstract

Inflammatory bowel diseases [IBD; Crohn's disease (CD), ulcerative colitis (UC)] are chronic immunologically mediated diseases that are due to a dysregulated immune response to intestinal flora in a genetically susceptible host. Despite advances in genetics, the likelihood of occurrence of disease remains incompletely explained and there appears to be a strong role for the environment in mediating risk of disease. Smoking remains the most widely studied and replicated risk factor, contributing to increased risk and severity of CD while conferring protection against UC. Recent data has suggested novel risk factors. Lower plasma vitamin D is associated with an increased risk of Crohn's disease, and vitamin D supplementation may prevent relapse of disease. Several medications including oral contraceptives, post-menopausal hormone replacement, aspirin, NSAIDs, and antibiotics may increase risk of CD or UC with the mechanisms of effect remaining inadequately defined. There is continuing evidence that depression and psychosocial stress may play a role in the pathogenesis of both CD and UC, while at the same time also increasing risk for disease flares. There is also a growing understanding of the role of diet on IBD, in particular through its effect on the microbiome. Animal protein intake and n-6 fatty acids may increase risk of UC while n-3 fatty acids and dietary fiber may confer protection. The effect of diet on established disease remains poorly studied. There is need for routine measurement of a spectrum of environmental exposures in prospective studies to further our understanding.

Keywords

Crohn's disease; Ulcerative colitis; Environment; Smoking; Diet; Vitamin D

Introduction

The past decade has seen a tremendous increase in our understanding of the pathogenesis of inflammatory bowel disease^{1, 2}. Advances in genetics and computational methods have led to the identification of 163 loci that modify risk of Crohn's disease (CD) or ulcerative colitis (UC)³. A total of 30 and 23 single nucleotide polymorphisms (SNPs) appear to be distinctly associated with CD and UC, respectively, while another 110 loci are common to both diseases. Nevertheless, known risk loci convey less than a third of the risk for either disease². Indeed, epidemiologic data suggest a strong role for the environment⁴⁻⁶. Disease concordance in monozygotic twins approaches 50 % at best, with many studies suggesting that the estimates may be lower. The risk of IBD in the immigrant population resembles that of country of residence rather than the country of origin⁷. Also, countries that have witnessed a rapidly changing environment and lifestyle have seen an increase in the incidence

Correspondence: Ashwin N Ananthakrishnan, Massachusetts General Hospital Crohn's and Colitis center, 165 Cambridge Street, 9th Floor, Boston, MA 02114, USA, Phone: 617-726-0267, Fax: 617-726-3080, aananthakrishnan@partners.org.

Disclosure

A. Ananthakrishnan has served on a one-time scientific advisory board for Prometheus.

of IBD over the past few decades at a rate of change that outpaces what could be attributed solely to genetics⁸. This review summarizes some of the recent literature on traditionally recognized risk factors as well as highlighting the data regarding novel environmental triggers for IBD.

SMOKING

Smoking remains the most widely studied and replicated environmental trigger for Crohn's disease and ulcerative colitis. Since the first described inverse association between UC and smoking in 1982, subsequent studies confirmed the protective effect of current smoking on the development of UC, lower rate of relapse, and reduced need for colectomy in current smokers^{9–12}. However, cessation of smoking is associated with an increase in risk of UC within 2–5 years of cessation, and a recent cohort study by Higuchi et al. highlighted that this risk could remain elevated over 20 years¹³. Contrary to its effect on UC, smoking increases the risk of developing CD two-fold^{10, 13, 14}, increases risk of disease flares and need for steroids, and is associated with a higher rate of post-operative disease recurrence^{9–11, 14–16}. Despite strong epidemiologic data, the mechanism how smoking impacts IBD remains unclear as does the reason for its protective effect in UC but deleterious impact on CD^{4, 14}. One component of cigarette smoke hypothesized to be responsible for its action is nicotine; animal models demonstrated an amelioration of colitis by administration of nicotine⁴. However, clinical trials of nicotine in UC have yielded equivocal results¹⁷. More recent studies suggest that the effect of smoking may instead be mediated through oxidative stress¹⁸. Bergeron et al. demonstrated that mononuclear cells from current smokers with CD secreted lower amounts of interleukin-8 (IL-8), IL-10, and IL-23 compared to non-smokers. This susceptibility to the effect of smoking was not seen in healthy controls and UC patients. In addition, CD patients also synthesized lower levels of the cytoprotective heat shock protein 70 (Hsp70). These findings in conjunction with previous studies suggest that the differential effect of smoking on anti-inflammatory (IL-10) and pro-inflammatory cytokines, and on defenses against oxidative stress, may contribute to its clinical effect on UC and CD. However, mechanisms for the differential effect on both diseases given the strong overlapping genetic component require further study.

VITAMIN D

Traditionally recognized for its role in calcium metabolism and bone health, there has been increasing recognition of the immunologic role of vitamin D^{19–23}. Indeed, recent literature suggests that the role of vitamin D is fairly varied and associated with a diverse spectrum of diseases. A deficiency of vitamin D could be a consequence of IBD itself with reduced physical activity, sunlight exposure, malnutrition, inadequate dietary intake of vitamin D, or lower bioavailability, all contributing to the deficiency^{22–24}. However, that vitamin D deficiency is common even in newly diagnosed IBD patients suggests that low vitamin D itself can contribute to increased risk of IBD²⁵.

The Nurses Health Study I and II are two large, prospective cohorts of female nurses, initiated in 1976 and 1989, respectively, by the Harvard School of Public Health, to examine environmental influences on chronic disease. Through detailed biennial questionnaires, participants provide information on a spectrum of dietary and lifestyle factors along with information on health status. Two recent studies from these cohorts highlight the role of vitamin D in IBD pathogenesis. Khalili et al. examined the variation in IBD incidence by geography of residence at the time of birth, and at ages 15 and 30 years²⁶. Residence at age 30 had a greater impact on disease incidence than that at birth. Women who resided in southern latitudes had a lower risk of CD (Hazard ratio (HR) 0.48, 95 % confidence interval (CI) 0.30–0.77) and UC (HR 0.62, 95 % CI 0.42–0.90) than those residing in northern

latitudes. These findings are consistent with data suggesting a similar north south gradient in disease incidence²⁷, mimicking exposure to ultraviolet light, a major determinant of vitamin D status. Indeed, a French study modeling surface UV radiation intensity using satellite data found an increased incidence of CD in areas with low sunlight exposure²⁸. To more specifically examine the effect of vitamin D, Ananthakrishnan et al. used the NHS cohort and a validated model of predicted plasma 25-hydroxy vitamin D incorporating dietary and lifestyle variables²⁹. The mean predicted plasma vitamin D ranged from 22 ng/mL in the lowest quartile to 32 ng/mL in the highest quartile. On multivariate analysis, compared to the lowest quartile, women in the highest quartile had half the incidence of CD (HR 0.54, 95 % CI 0.30–0.99); no effect on UC risk was observed. Dietary vitamin D intake had a more modest effect and attained statistical significance for UC but not CD, likely owing to the weaker contribution of diet to overall vitamin D status.

Studies have also examined the association between vitamin D status and disease activity. In a retrospective study of 504 IBD patients, Ulitsky et al. found that lower vitamin D was associated with a modest increase in disease activity and a lower health-related quality of life in CD³⁰. In mice models, vitamin D deficiency is associated with an increased susceptibility to dextran sodium sulfate (DSS)-induced colitis^{21, 31}. An improvement in the severity of intestinal inflammation was noted within 2 weeks of supplementation with 1,25(OH)₂D₃³¹. Using microarray analysis on colonic biopsy tissue, Zhu et al. found that several of TNF- α related genes in colonic tissue were down-regulated by administration of 1,25(OH)₂D₃³². Jorgensen et al. performed a randomized, double-blind placebo-controlled trial administering a daily dose of 1,200 IU vitamin D3 or placebo to 94 CD patients in remission³³. At the end of 1 year, 6/46 patients (13 %) in the vitamin D arm had relapsed compared to 14/48 patients treated with placebo ($p = 0.06$). The prior mechanistic studies and the Jorgensen clinical trial suggest the need for larger studies of vitamin D as a therapeutic agent in the treatment of IBD, particularly CD, either as monotherapy or in conjunction with existing treatments.

MEDICATIONS

Aspirin, NSAIDs

The gastrointestinal adverse effects of aspirin and non-steroidal anti-inflammatory factors are well recognized. However, while their potential effect in triggering onset or relapse of IBD has been clinically suspected, limited high quality evidence was available to support this. Prior literature were mostly from case control studies where exclusion of confounding by indication, identifying use of aspirin or non-steroidal anti-inflammatory drugs to treat pre-diagnosis symptoms of CD and UC, and differentiating NSAID enteritis or colitis from true idiopathic IBD have been difficult to achieve. The European Prospective Investigation into cancer and Nutrition Study (EPIC) is a large, international prospective cohort to examine diet and lifestyle factors in cancer and chronic disease. The EPIC cohort recruited men and women between the ages of 30–74 from several participating sites across the UK, France, Denmark, Italy, Spain, Greece, Norway, and Sweden, and recently published results have furthered our understanding of environmental factors. Chan et al. identified a six-fold increase in risk of CD among regular users of aspirin but no such association with UC³⁴. The effect was more prominent in non-smokers. In contrast, Ananthakrishnan et al. using a detailed and time varying assessment of aspirin and NSAID use, found no association between dose, duration, or frequency of aspirin use and risk of either CD or UC³⁵. However, high dose, prolonged duration, and frequent use of NSAIDs was associated with an increased risk of CD and UC³⁵. While neither study sheds light on the relative safety of these agents in the setting of established disease, data on frequency of flares triggered by aspirin or NSAIDs has been conflicting, as recently reviewed³⁶. There was no association between NSAID intake and symptomatic flares in the Manitoba IBD cohort³⁷. However, a

prospective trial of acetaminophen, diclofenac, and indomethacin in IBD patients in remission demonstrated an increase in fecal calprotectin and a symptomatic flare in up to a third of patients within 28 days of use, primarily occurring within 7 days of initiation³⁸.

Hormone Use

Confirming prior studies and meta-analyses³⁹, Khalili et al. demonstrated an association between ever-use of oral contraceptives and increased risk of CD⁴⁰. In UC, an effect was noted only among those with a past history of smoking suggesting a potential interaction. In contrast, among post-menopausal women, hormone replacement therapy was associated with an increased risk of UC with a greater effect with longer duration of use⁴¹. Estrogen alone, and combined estrogen + progestin therapy had similar effects. In contrast, a case control study using General Practice Research Database (GPRD) demonstrated an association between hormone use and CD but not UC⁴². Finally, a study by Kane et al. identified a lower risk of IBD flare among hormone users⁴³. Given the divergent results, further studies addressing these hypotheses are essential to determinate the accurate effects both on incident disease and on the risk of flare in those with established disease.

Antibiotics

Given the established central role of intestinal flora in the pathogenesis of IBD, it is possible that environmental factors such as antibiotics influence risk of development of disease through their effect on the microbiome. Less is understood about the temporal relationship between the microbiome and disease development, whether early life flora acquired during birth and infancy is critical, or whether an individual at-risk for IBD remains susceptible to dynamic changes in flora associated with dietary patterns or other lifestyle factors. Shaw et al. explored both these hypotheses using the Manitoba population-based IBD registry. Antibiotic use within the first year of life was more common among pediatric IBD cases (mean age at diagnosis 8.4 years) compared to matched controls (58 vs. 39 %, adjusted odds ratio 2.9, 95 % CI 1.2–7.0)⁴⁴. A similar analysis among adult IBD subjects revealed that individuals receiving 3 antibiotic dispensations 2 or more years prior to diagnosis had a modestly greater odds of being an IBD case (OR 1.5, 95 % CI 1.3–1.8)⁴⁵.

STRESS

Stress has long been purported to play a role in the pathogenesis of CD and UC, and to mediate a role in disease flares^{46–48}. An elegant prospective study by Bitton et al. suggested that individuals with lower levels of stress and better coping mechanisms had a reduced risk of disease flare⁴⁹. Mood components of perceived stress including depression and anxiety may play a strong role in mediating this exacerbation of disease related to stress⁵⁰. Much of the literature on the role of stress or depression on disease incidence has been restricted to major life events or retrospective ascertainment of exposures, susceptible to the possibility of recall bias or reverse causality. A prospective study using the Nurses Health Study found that both recent and remote depressive symptoms ascertained using the mental health inventory (MHI-5), were associated with increased risk of CD but not UC⁵¹. The effect of recent depressive symptoms within 4 years of diagnosis was more prominent than that of remote depression. There is limited high-quality data on whether interventions to treat depression or stress can modify its effect on disease. A retrospective observational study by Goodhand et al. found a reduction in the number of symptomatic relapses and need for steroids if the year following initiation of anti-depressant therapy than in the year prior⁵². However, a Cochrane review found no benefit of psychological interventions on IBD⁵³.

AIR POLLUTION

Several lines of ecological and epidemiologic evidence suggest that ambient air pollution may contribute to risk of CD and UC. U.S. population-based studies demonstrate an increase in the incidence of CD and UC between 1940 and 1980, which correlates with the era of rising ambient air pollution prior to widespread implementation of environmental regulations. Also, the rising incidence of CD and UC in developing countries parallels industrialization⁸. Several biological mechanisms plausibly mediate association between environmental air pollution and IBD^{54, 55}. Elevated atmospheric particulate matter is associated with an increase in circulating polymorphonuclear leukocytes and plasma cytokines including TNF- α and may impair vascular function^{54, 55}. In support of this hypothesis, Kaplan et al. using The Health Improvement Network database in the United Kingdom found that residence in an area with the highest tertile of NO₂ was associated with an increased risk of CD while higher SO₂ exposure was associated with increased risk of early (<25 years) UC⁵⁶. Similarly, in another study, total criteria pollutant emission was associated with increased rate of hospitalizations for both CD and UC, suggesting that ambient air pollution may also influence established disease⁵⁷. However, further studies from different geographic regions and using more detailed temporal measures of exposure to air pollution are essential to examine if air quality affects intestinal inflammation.

DIET

One of the environmental triggers most commonly reported by patients, but yet one where there is a significant gap in data is diet^{58, 59}. A majority of prior studies have been limited by factors including retrospective ascertainment of diet, allowing for both recall bias as well as modifications in diet that may have occurred since the onset of disease symptoms, and the small number of incident cases limiting power. Recent data from the EPIC cohort and the Nurses Health Study have attempted to prospectively examine the role of dietary factors on IBD pathogenesis.

Much of the work has centered on dietary macronutrient intake. A nested case control study by Hart and colleagues found that participants in the highest quartile of intake of linoleic acid had a two-fold increase in risk of UC (OR 2.49, 95 % CI 1.23–5.07)⁶⁰. A subsequent study by de Silva et al. also identified an association between tissue arachidonic acid concentrations (which was strongly influenced by dietary arachidonic acid intake) and a four-fold increase in risk of UC⁶¹. In contrast, dietary n-3 PUFA conferred protection from UC⁶². Several n-3 PUFA including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and total n-3 intake were inversely associated with risk of UC. Other dietary macronutrients have been explored in less detail but are supported by plausible biologic mechanisms. Prior studies by Amre et al. had demonstrated an inverse association between intake of fruits and vegetables and risk of IBD⁶³. In an analysis of the Nurses Health Study, total dietary fiber intake was associated with a reduced incidence of CD but not UC⁶⁴. In addition, the source of dietary factor was also a determinant of disease risk. Fiber intake from fruits, vegetables, and, in particular, cruciferous vegetables, reduced the risk of CD but not insoluble fiber from whole grain or bran diet did not. A subgroup of the EPIC study, the French E3N cohort, examined the association between dietary protein intake and found a direct association between higher animal protein intake (in particular fish and meat) and risk of IBD⁶⁵. The role of dietary micronutrients, particularly those supported by plausible biological mechanisms including iron and zinc, have not been examined in association with disease risk in the prospective studies.

There are far fewer data examining the role of diet in triggering disease flare with no prospective studies examining this question using validated measures of dietary intake. In a

survey of 244 IBD patients in France, over half the participants reported belief that diet played a role in disease relapse⁶⁶. However, the spectrum of foods that patients reported excluding to prevent relapse was distributed among the different food groups, suggesting that there may not be uniform dietary triggers to relapses.

Conclusions

Limitations of prior research on environmental risk factors stem from the lack of large cohorts with detailed prospectively collected information on a spectrum of environmental exposures with adequate power to detect weaker effects. Some of these limitations have been addressed through recent analyses of large prospective cohorts designed to examine the role of the environment in chronic disease. As advances in genetics and immunology further our understanding of disease pathogenesis, this knowledge needs to be coupled with high quality data on environmental risks to construct a more comprehensive model of disease development. Given the heterogeneity in effect of many environmental influences, it is likely that there exists an interaction between genetics and environment such that some individuals are more susceptible to the effect of specific environmental factors. In addition, the relative contribution of genetics and environment needs to be defined to understand the role of the environment in those at high-risk of disease. This is important because, given the relative rarity of IBD, a population-based preventive measure is unlikely to have a substantial impact. However, high-risk groups may have a better yield in preventive interventions. Equally, and of more perhaps concern to patients, is the effect of environment on established disease. Unfortunately, other than the effect of smoking, the impact of other environmental factors on established disease remain poorly studied with a lack of high-quality data to guide our practice. To provide the answers, there is a need for the integration of environment questionnaires into prospective IBD registries. This would not only provide a more complete view of the disease itself but also practical answers that will be of value to providers and patients alike.

Acknowledgments

This work was supported by a Research Scholars Award from the American Gastroenterological Association

References

1. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature*. 2011; 474:307–17. [PubMed: 21677747]
2. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009; 361:2066–78. [PubMed: 19923578]
- **3. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern D, Hun KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amineinejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Cohain A, Cichon S, D'Amato M, De Jong DJ, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Gieger C, Karlsen J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro MD, Rotter JJ, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor K, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJSZ, Zhang B, Zhang CK, Zhao H, Consortium TIIG, Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly M, Franke A, Parkes M, Vermeire S, Barret JC, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory

- bowel disease. *Nature*. 2012 (in press). Most updated analysis of genetic risk for Crohn's disease and ulcerative colitis that expands our current knowledge to 163 risk alleles.
4. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011; 140:1785–94. [PubMed: 21530745]
 5. Danese S, Fiocchi C. Etiopathogenesis of inflammatory bowel diseases. *World J Gastroenterol*. 2006; 12:4807–12. [PubMed: 16937461]
 6. Lakatos PL. Environmental factors affecting inflammatory bowel disease: have we made progress? *Dig Dis*. 2009; 27:215–25. [PubMed: 19786744]
 7. Williams CN. Does the incidence of IBD increase when persons move from a low- to a high-risk area? *Inflamm Bowel Dis*. 2008; 14 (Suppl 2):S41–2. [PubMed: 18816730]
 8. Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol*. 2008; 103:3167–82. [PubMed: 19086963]
 9. Cosnes J. Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice. *Best Pract Res Clin Gastroenterol*. 2004; 18:481–96. [PubMed: 15157822]
 10. Cosnes J. What is the link between the use of tobacco and IBD? *Inflamm Bowel Dis*. 2008; 14 (Suppl 2):S14–5. [PubMed: 18816683]
 11. Lakatos PL, Szamosi T, Lakatos L. Smoking in inflammatory bowel diseases: good, bad or ugly? *World J Gastroenterol*. 2007; 13:6134–9. [PubMed: 18069751]
 12. Odes HS, Fich A, Reif S, Halak A, Lavy A, Keter D, Eliakim R, Paz J, Broide E, Niv Y, Ron Y, Villa Y, Arber N, Gilat T. Effects of current cigarette smoking on clinical course of Crohn's disease and ulcerative colitis. *Dig Dis Sci*. 2001; 46:1717–21. [PubMed: 11508673]
 13. Higuchi LM, Khalili H, Chan AT, Richter JM, Bousvaros A, Fuchs CS. A Prospective Study of Cigarette Smoking and the Risk of Inflammatory Bowel Disease in Women. *American Journal of Gastroenterology*. 2012 (in press).
 14. Birrenbach T, Bocker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. *Inflamm Bowel Dis*. 2004; 10:848–59. [PubMed: 15626903]
 15. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology*. 2001; 120:1093–9. [PubMed: 11266373]
 16. Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre JP. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology*. 1996; 110:424–31. [PubMed: 8566589]
 17. Nikfar S, Ehteshami-Ashar S, Rahimi R, Abdollahi M. Systematic review and meta-analysis of the efficacy and tolerability of nicotine preparations in active ulcerative colitis. *Clin Ther*. 32:2304–15. [PubMed: 21353102]
 18. Bergeron V, Grondin V, Rajca S, Maubert MA, Pigneur B, Thomas G, Trugnan G, Beaugerie L, Cosnes J, Masliah J, Sokol H, Seksik P, Bachelet M. Current smoking differentially affects blood mononuclear cells from patients with Crohn's disease and ulcerative colitis: relevance to its adverse role in the disease. *Inflamm Bowel Dis*. 2012; 18:1101–11. [PubMed: 21987436]
 19. Cantorna MT, Mahon BD. D-hormone and the immune system. *J Rheumatol Suppl*. 2005; 76:11–20. [PubMed: 16142846]
 20. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med (Maywood)*. 2004; 229:1136–42. [PubMed: 15564440]
 21. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr*. 2004; 80:1717S–20S. [PubMed: 15585793]
 22. Garg M, Lubel JS, Sparrow MP, Holt SG, Gibson PR. Review article: vitamin D and inflammatory bowel disease - established concepts and future directions. *Aliment Pharmacol Ther*. 2012; 36:324–44. [PubMed: 22686333]
 23. Lim WC, Hanauer SB, Li YC. Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol*. 2005; 2:308–15. [PubMed: 16265284]
 24. Farraye FA, Nimitphong H, Stucchi A, Dendrinos K, Boulanger AB, Vijjeswarapu A, Tanenbaum A, Biancuzzo R, Chen TC, Holick MF. Use of a novel vitamin D bioavailability test demonstrates

- that vitamin D absorption is decreased in patients with quiescent Crohn's disease. *Inflamm Bowel Dis.* 2011; 17:2116–21. [PubMed: 21910173]
25. Leslie WD, Miller N, Rogala L, Bernstein CN. Vitamin D status and bone density in recently diagnosed inflammatory bowel disease: the Manitoba IBD Cohort Study. *Am J Gastroenterol.* 2008; 103:1451–9. [PubMed: 18422819]
 26. Khalili H, Huang ES, Ananthakrishnan AN, Higuchi L, Richter JM, Fuchs CS, Chan AT. Geographical variation and incidence of inflammatory bowel disease among US women. *Gut.* 2012
 27. Nerich V, Monnet E, Weill A, Vallier N, Vanbockstael V, Auleley GR, Balaire C, Dubost P, Rican S, Allemand H, Carbonnel F. Fine-scale geographic variations of inflammatory bowel disease in France: correlation with socioeconomic and house equipment variables. *Inflamm Bowel Dis.* 2010; 16:813–21. [PubMed: 19902547]
 28. Nerich V, Jantchou P, Boutron-Ruault MC, Monnet E, Weill A, Vanbockstael V, Auleley GR, Balaire C, Dubost P, Rican S, Allemand H, Carbonnel F. Low exposure to sunlight is a risk factor for Crohn's disease. *Aliment Pharmacol Ther.* 2011; 33:940–5. [PubMed: 21332762]
 - **29. Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, Richter JM, Fuchs CS, Chan AT. Higher predicted vitamin d status is associated with reduced risk of Crohn's disease. *Gastroenterology.* 2012; 142:482–9. First study to demonstrate an association between pre-diagnosis lower vitamin D levels and risk for Crohn's disease in a large prospective cohort. [PubMed: 22155183]
 30. Ulitsky A, Ananthakrishnan AN, Naik A, Skaros S, Zadvornova Y, Binion DG, Issa M. Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. *JPEN J Parenter Enteral Nutr.* 2011; 35:308–16. [PubMed: 21527593]
 31. Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25-Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. *J Nutr.* 2000; 130:2648–52. [PubMed: 11053501]
 32. Zhu Y, Mahon BD, Froicu M, Cantorna MT. Calcium and 1 alpha,25-dihydroxyvitamin D3 target the TNF-alpha pathway to suppress experimental inflammatory bowel disease. *Eur J Immunol.* 2005; 35:217–24. [PubMed: 15593122]
 33. Jorgensen SP, Agnholt J, Glerup H, Lyhne S, Villadsen GE, Hvas CL, Bartels LE, Kelsen J, Christensen LA, Dahlerup JF. Clinical trial: vitamin D3 treatment in Crohn's disease - a randomized double-blind placebo-controlled study. *Aliment Pharmacol Ther.* 2010; 32:377–83. [PubMed: 20491740]
 34. Chan SS, Luben R, Bergmann MM, Boeing H, Olsen A, Tjonneland A, Overvad K, Kaaks R, Kennedy H, Khaw KT, Riboli E, Hart AR. Aspirin in the aetiology of Crohn's disease and ulcerative colitis: a European prospective cohort study. *Aliment Pharmacol Ther.* 2011; 34:649–55. [PubMed: 21790683]
 35. Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS, Chan AT. Aspirin, Nonsteroidal Anti-inflammatory Drug Use, and Risk for Crohn Disease and Ulcerative Colitis: A Cohort Study. *Ann Intern Med.* 2012; 156:350–9. [PubMed: 22393130]
 - *36. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? *Am J Gastroenterol.* 2009; 104:1298–313. quiz 1314. Comprehensive review of the role of several environmental triggers in IBD. [PubMed: 19337242]
 37. Bernstein CN, Singh S, Graff LA, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol.* 2010; 105:1994–2002. [PubMed: 20372115]
 38. Takeuchi K, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B, Bjornsson E, Bjarnason I. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2006; 4:196–202. [PubMed: 16469680]
 39. Cornish JA, Tan E, Simillis C, Clark SK, Teare J, Tekkis PP. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol.* 2008; 103:2394–400. [PubMed: 18684177]

40. Khalili H, Higuchi LM, Ananthakrishnan AN, Richter JM, Feskanich D, Fuchs CS, Chan AT. Oral Contraceptives, Reproductive Factors, and Risk of Inflammatory Bowel Disease. *Digestive Disease Week*. 2012
41. Khalili H, Higuchi LM, Ananthakrishnan AN, Manson JE, Feskanich D, Richter JM, Fuchs CS, Chan AT. Hormone Therapy Increases Risk of Ulcerative Colitis but not Crohn's Disease. *Gastroenterology*. 2012
42. Garcia Rodriguez LA, Gonzalez-Perez A, Johansson S, Wallander MA. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther*. 2005; 22:309–15. [PubMed: 16097997]
43. Kane SV, Reddy D. Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease. *Am J Gastroenterol*. 2008; 103:1193–6. [PubMed: 18177456]
44. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol*. 2010; 105:2687–92. [PubMed: 20940708]
45. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics and new diagnoses of Crohn's disease and ulcerative colitis. *Am J Gastroenterol*. 2011; 106:2133–42. [PubMed: 21912437]
46. Maunder RG. Evidence that stress contributes to inflammatory bowel disease: evaluation, synthesis, and future directions. *Inflamm Bowel Dis*. 2005; 11:600–8. [PubMed: 15905709]
47. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*. 2005; 54:1481–91. [PubMed: 16162953]
48. Mawdsley JE, Rampton DS. The role of psychological stress in inflammatory bowel disease. *Neuroimmunomodulation*. 2006; 13:327–36. [PubMed: 17709955]
49. Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, Cohen A, Vermeire S, Dufresne L, Franchimont D, Wild GE. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut*. 2008; 57:1386–92. [PubMed: 18390994]
50. Camara RJ, Schoepfer AM, Pittet V, Begre S, von Kanel R. Mood and nonmood components of perceived stress and exacerbation of Crohn's disease. *Inflamm Bowel Dis*. 2011; 17:2358–65. [PubMed: 21287671]
51. Ananthakrishnan AN, Khalili H, Pan A, Higuchi LM, PSds, Richter JM, Fuchs CS, Chan AT. Association Between Depressive Symptoms and Incidence of Crohn's Disease and Ulcerative Colitis—Results from the Nurses' Health Study. *Clin Gastroenterol Hepatol*. 2012
52. Goodhand JR, Greig FI, Koodun Y, McDermott A, Wahed M, Langmead L, Rampton DS. Do antidepressants influence the disease course in inflammatory bowel disease? A retrospective case-matched observational study. *Inflamm Bowel Dis*. 18:1232–9. [PubMed: 22234954]
53. Timmer A, Preiss JC, Motschall E, Rucker G, Jantschek G, Moser G. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev*. :CD006913.
54. Tan WC, Qiu D, Liam BL, Ng TP, Lee SH, van Eeden SF, D'Yachkova Y, Hogg JC. The human bone marrow response to acute air pollution caused by forest fires. *Am J Respir Crit Care Med*. 2000; 161:1213–7. [PubMed: 10764314]
55. van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T, Qui D, Vincent R, Hogg JC. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). *Am J Respir Crit Care Med*. 2001; 164:826–30. [PubMed: 11549540]
56. Kaplan GG, Hubbard J, Korzenik J, Sands BE, Panaccione R, Ghosh S, Wheeler AJ, Villeneuve PJ. The inflammatory bowel diseases and ambient air pollution: a novel association. *Am J Gastroenterol*. 2010; 105:2412–9. [PubMed: 20588264]
57. Ananthakrishnan AN, McGinley EL, Binion DG, Saeian K. Ambient air pollution correlates with hospitalizations for inflammatory bowel disease: an ecologic analysis. *Inflamm Bowel Dis*. 2011; 17:1138–45. [PubMed: 20806342]
58. Chapman-Kiddell CA, Davies PS, Gillen L, Radford-Smith GL. Role of diet in the development of inflammatory bowel disease. *Inflamm Bowel Dis*. 2010; 16:137–51. [PubMed: 19462428]

- *59. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol*. 2011; 106:563–73. Comprehensive review of the role of diet in the pathogenesis of inflammatory bowel diseases. [PubMed: 21468064]
60. Tjonneland A, Overvad K, Bergmann MM, Nagel G, Linseisen J, Hallmans G, Palmqvist R, Sjodin H, Hagglund G, Berglund G, Lindgren S, Grip O, Palli D, Day NE, Khaw KT, Bingham S, Riboli E, Kennedy H, Hart A. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. *Gut*. 2009; 58:1606–11. [PubMed: 19628674]
61. de Silva PS, Olsen A, Christensen J, Schmidt EB, Overvad K, Tjonneland A, Hart AR. An association between dietary arachidonic acid, measured in adipose tissue, and ulcerative colitis. *Gastroenterology*. 2010; 139:1912–7. [PubMed: 20950616]
62. John S, Luben R, Shrestha SS, Welch A, Khaw KT, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. *Eur J Gastroenterol Hepatol*. 2010; 22:602–6. [PubMed: 20216220]
63. Amre DK, D'Souza S, Morgan K, Seidman G, Lambrette P, Grimard G, Israel D, Mack D, Ghadirian P, Deslandres C, Chotard V, Budai B, Law L, Levy E, Seidman EG. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. *Am J Gastroenterol*. 2007; 102:2016–25. [PubMed: 17617201]
64. Ananthakrishnan AN, Khalili H, De Silva PS, Korzenik J, Higuchi L, Richter JM, Fuchs CS, Chan AT. Higher Dietary Fiber Intake Is Associated With Lower Risk of Crohn's Disease but Not Ulcerative Colitis - a Prospective Study *Gastroenterology* 2012. Digestive Disease Week Abstract #: 863.
65. Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. *Am J Gastroenterol*. 2010; 105:2195–201. [PubMed: 20461067]
66. Zallot C, Quilliot D, Chevaux JB, Peyrin-Biroulet C, Gueant-Rodriguez RM, Freling E, Collet-Fenetrier B, Williet N, Ziegler O, Bigard MA, Gueant JL, Peyrin-Biroulet L. Dietary beliefs and behavior among inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2012

Table 1

Environmental risk factors for Crohn's disease and ulcerative colitis

Environmental factor	Effect on disease onset	Effect on disease course	Intervention studies
Smoking–Crohn's disease	+	+	Smoking cessation is beneficial in CD
Smoking–ulcerative colitis	–	–	Equivocal results from trials of nicotine replacement therapy
Appendectomy–CD	?+	None	None
Appendectomy–UC	–	?–	None
Low vitamin D	?+ (CD)	?+ (CD)	Vitamin D supplementation may reduce risk of relapse in CD
Oral contraceptive	+ (CD)	No data	None
Post-menopausal hormone use	?+ (UC)	?–	None
NSAIDs	?+ (CD, UC)	+ (CD, UC)	None
Antibiotics	?+ (both early childhood and adult exposure)	No data	Trials of antibiotics for the treatment of CD and UC have been mostly null. Antibiotics are effective in preventing post-operative recurrence in CD.
Depression and psychosocial stress	?+ CD. Equivocal in UC	Equivocal. May trigger relapses.	Antidepressant use reduced need for steroids and symptomatic relapse in one study. Other psychological interventions have not been shown to be effective.
Air pollution	?	?	None
Dietary fiber	? (CD; particularly fruits and vegetables)	No data	None
Dietary fat	?+ (UC) (n-6 fatty acids increase risk. n-3 fatty acids may confer protection)	No data	None
Dietary protein	?+ (UC) (particularly animal protein)	No data	None