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Modifiable environmental factors in inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (Crohn's disease, ulcerative colitis) are believed to arise as a result of a dysregulated immune response to commensal gut microbial flora in a genetically susceptible host. Several environmental factors may influence predisposition to disease or its natural history by modification of both the host immune response and intestinal microbial composition. Proposed environmental influences include tobacco use, diet, antibiotics, vitamin D deficiency, stress, appendectomy, and use of oral contraceptive use. Emerging epidemiologic evidence has confirmed the association of many of these factors with incident disease using prospective data. In addition, laboratory data has supported their mechanistic plausibility and relevance to intestinal inflammation. However, fewer studies have examined their impact on natural history. This article will focus on translating such evidence into clinical practice by a focus on interventional studies that have modified such environmental influences to improve disease outcomes.

Keywords

Crohn's disease; ulcerative colitis; environment; diet; smoking

INTRODUCTION

Inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)), are chronic immune-mediated inflammation diseases hypothesized to occur due to the confluence of external environmental influences, intestinal dysbiosis, and genetic predisposition.¹⁻³ An important role for environmental factors in the pathogenesis of IBD is supported by low rates of disease concordance even in monozygotic twins (10–15% in UC, 30–35% in CD)³ and relatively rapid temporal changes in disease incidence over time and with migration from low incidence to high incidence regions.^{4-67, 8} Over the past few years, the evidence base for the role of environmental factors in IBD has expanded significantly both with epidemiologic studies from rigorous prospective cohorts, and translational research highlighting the interplay between such factors, the gut microbiome, and intestinal inflammation. Consequently, there is considerable interest from both patients and physicians on modulation of such environmental factors to improve disease course or reduce incidence

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of inflammatory bowel disease. Here, we review some of the recent literature on environmental factors associated with IBD, focusing on those where there is evidence supporting that modifying the exposure can improve disease outcomes.

TOBACCO USE

Smoking is a well described environmental factor affecting both incident and established IBD. Several mechanisms have been proposed to explain its effect. Smoking may impair autophagy^{9, 10} and modify gut microbial composition, thereby resulting in intestinal inflammation.^{11–13} The exact reason for its discordant effect on CD and UC is unclear; one hypothesis is differential functional impairment of peripheral blood mononuclear cells responses in CD but not UC.¹⁴ Clinically, in established CD, tobacco use is associated with greater disease activity,^{15, 16} increased requirement for immunosuppressants,^{17–21} a higher risk of stricturing and fistulizing disease,^{20, 22–24} and early post-operative recurrence.^{15, 17, 25} A recent meta-analysis of 33 studies found that compared to non-smokers, active smokers had an increased odds of disease flare (OR 1.56; 95% CI 1.21 – 2.01)¹⁵. However, the odds of disease relapse in ex-smokers was similar to non-smokers (OR 0. 0.90; 95% CI 0.59 – 1.39), demonstrating that smoking cessation may be a beneficial environmental influence in CD. The comparability of outcomes in former smokers and non-smokers was also confirmed by a recent multi-center prospective cohort study where only current smoking (OR 1.58) but not former smoking was associated with increased disease activity.¹⁶ An elegant study by Cosnes *et al.* of 474 smokers with CD evaluated the impact of smoking cessation on disease outcomes.²⁶ Over a median follow-up of 29 months, those who quit had a significantly decreased risk of flare as compared to active smokers ($p < 0.0001$).²⁶ Several trials have also evaluated smoking cessation strategies in IBD.²⁷ In the recent Tabacron study, a multicenter prospective interventional smoking cessation study, 408 actively smoking CD patients were enrolled across 14 centers in Spain.²⁷ Smokers were verbally counseled by their gastroenterologists regarding the adverse effects of smoking on CD and were given a graphic handout summarizing the information. Over 18 months, 62% of patients attempted to quit smoking, 31% successfully quit and an additional 8% relapse on their smoking prior to the end of the follow-up period.²⁷

In contrast to CD, current tobacco use is associated with a decreased incidence and risk of disease exacerbations of UC while smoking cessation may trigger both disease onset and relapses. A large prospective cohort study utilizing the Nurses' Health Study demonstrated increased UC onset in the 2–5 years following tobacco cessation (HR, 3.06; 95% CI, 2.00–4.67)²⁸. This increased risk persisted for 15 years after tobacco cessation. In patients with established UC, current tobacco use is associated with a decreased risk of disease flares, colectomy,²⁹ and hospitalizations.^{30, 31} Consequently, several studies have examined whether nicotine replacement therapy may be beneficial in established UC. A 2004 Cochrane Review of 7 studies of transdermal nicotine for UC suggested higher rates of clinical remission at 4–6 weeks among patients who received transdermal nicotine compared to placebo (OR 2.56; 95% CI 1.02, 6.45).³² However, nicotine provided no benefit when compared to standard medical therapy and was associated with three-fold increase in adverse events.³² One small interventional study of smoking resumption in ex-smokers with refractory UC demonstrated that 14/15 patients who resumed smoking (average 8.6

cigarettes per day) were able to achieve steroid-free remission over a median of 23 months.³³ However, given the numerous deleterious consequences of tobacco use, initiation or resumption of cigarette smoking cannot be recommended in patients with UC.

DIET

Diet is one of the most common patient-reported triggers of disease activity. The evidence-base for its effect on disease risk and established disease has grown over the past few years with data from prospective cohorts demonstrating a correlation between long-term adult dietary macro- and micronutrients and incident IBD. Further support for its role comes from the growing understanding of the role of gut microbial dysbiosis in the pathogenesis of IBD and the influence of both long-term adult diet and short-term changes on gut microbial diversity and composition, which are key to the pathogenesis of IBD.^{34, 35,36–39}

Enteral Nutrition

The most robust evidence in support of a dietary intervention that modifies outcome in CD is with enteral nutrition. The study of enteral feeding therapy for induction of remission in pediatric CD goes back more than three decades,^{40, 41} with several recent meta-analyses summarizing their efficacy. Most studies are in a pediatric CD population with few studies in adults or among those with UC. Exclusive enteral nutrition (EEN) may achieve remission in 50–70% of patients by 6–8 weeks, an efficacy that is comparable to or slightly inferior to systemic corticosteroid therapy.^{42–44} The type of enteral formula used does not influence rates of clinical remission; a randomized controlled trial comparing elemental formula (EF) to a polymeric formula (PF) in pediatric CD demonstrated remission rates of 93% and 79% with EF and PF respectively, without a statistically significant difference between the two. One third of the children maintained remission at two years.⁴⁵ Exclusive enteral nutrition may synergize with other systemic therapies; response rates were higher for a combination of infliximab and enteral nutrition in comparison to infliximab alone.⁴⁶ Partial enteral nutrition (PEN) is not as effective as EEN suggesting that in addition to the potential changes induced by the enteral formula, complete or near-complete exclusion of table foods is an important determinant of clinical response with this therapy. A recent prospective study compared clinical and mucosal outcomes with EEN and PEN to anti-TNF therapy in pediatric CD. In a study of 90 children with active disease, clinical remission rates were comparable with EEN (88%) and anti-TNF therapy (84%), both of which were significantly superior to PEN (64%). Normalization of fecal calprotectin was infrequent with PEN and similarly high with EEN and anti-TNF therapy. Maintaining response induced by enteral nutrition remains a challenge as exclusive enteral nutrition is poorly tolerated with high rates of drop off with continued therapy.⁴⁷ A single center retrospective study evaluating PEN after inducing remission with EEN in pediatric patients revealed that among 58 patients (out of 66) who were continued on PEN, only forty-three patients were adherent and cumulative remission rates at 1 and 2 years were 67% and 52% respectively.⁴⁸

Exclusion diets

Several exclusion diets have been examined in IBD, however most such reports are anecdotal case series. One of the most popular exclusion diets is the specific carbohydrate

diet (SCD), developed initially by Hass in the 1930s for treatment of celiac disease. A case report of improvement of UC with the SCD triggered popularity of this diet in the management of IBD.^{49, 50} The SCD consists of excluding all complex carbohydrates, grains, and refined sugars except for honey and milk. A prospective study of the efficacy of the SCD by Cohen *et al.* enrolled 10 patients, among whom 9 completed 12 weeks and 7 completed 52 weeks of the SCD.⁵¹ Statistically significant reductions in the Harvey Bradshaw index (3.3 to 0.6), Pediatric Crohn's disease activity index (21.1 to 7.8) and endoscopic severity on capsule endoscopy using the Lewis score were observed. Among patients who persisted with the diet, the improvement in clinical disease activity remained at 1 year. A larger retrospective review of 26 pediatric IBD patients on SCD in conjunction with conventional therapy demonstrated an improvement in disease activity in both pediatric Crohn's disease (32.8 at baseline to 8.8 at 6 months) and ulcerative colitis (28.3 at baseline to 18.3 at 6 months), CRP, sedimentation rate, and fecal calprotectin for a majority of the patients.⁵² While small uncontrolled observational studies demonstrate benefit in resolution of symptoms and perhaps improvement in mucosal inflammation, rigorous randomized trials examining efficacy compared to standard dietary advice are essential before robust conclusions can be drawn about the role of SCD.

Other exclusion diets including a gluten-free diet, low FODMAP diet, and paleolithic diet have not been well studied in IBD. Sigall-Boneh *et al.* proposed a novel dietary intervention consisting of a combination between polymeric formula and a diet that excluded processed meats and other packaged goods, gluten, dairy, animal fat, breads, canned goods, and products containing emulsifiers⁵³. Clinical response (defined as Harvey-Bradshaw index ≤ 3 for all patients and pediatric Crohn's disease activity index <7.5 in children) was seen in 37 (78.7%) and 33 (70.2%) patients, respectively, after 6 weeks period of treatment. Remission was observed in 70% of children and 69% of adults.⁵³ Rajendran *et al.* evaluated an IgG4-guided exclusion diet for 4 weeks in 29 patients.⁵⁴ Patients were tested for IgG4 to 14 food antigens and the four most reactive foods were excluded for each subject.⁵⁴ Nearly all (90%) patients reported symptomatic improvement. The same group performed a larger trial evaluating this diet of excluding the four most reactive patients compared to a sham diet in 96 patients, where four foods with the lowest antibody titers were excluded.⁵⁵ Modest improvements in quality of life and disease activity measured by the CDAI were noted with the exclusion diet in comparison to the sham diet controls.

Supplementation of dietary fiber and fat

Patients with CD have been traditionally advised a low-fiber diet due to concerns about symptomatic and subclinical strictures.⁵⁶ However, emerging evidence suggests that certain types of fiber may be beneficial in some patients with IBD. Fiber may theoretically help maintain disease remission through increased production of short chain fatty acids that play an immunomodulatory role in the gut and favor the blooming of beneficial bacteria.⁵⁷ In addition, food rich in dietary fiber may also contain other components such as aryl hydrocarbon ligands that may ameliorate intestinal inflammation.^{58–60} In experimental models, soluble fiber-enriched media demonstrate reduced translocation of bacteria across the intestinal epithelium.⁶¹ Both prospective cohort and case-control studies demonstrate an inverse association between fiber intake, particularly from fruits and vegetables, and risk of

CD.^{62, 63} In a prospective follow up of the CCFA Partners cohort, patients with CD consuming the highest quartile of dietary fiber intake at baseline had lower risk of disease relapse at 6 months.⁶⁴ A small pilot study evaluating the role Germinated Barley Foodstuff (GBF) (a water-insoluble dietary fiber) in patients with UC showed a reduction in symptoms (abdominal pain and cramping) and C-reactive protein in GBF group compared to controls ($P=0.016$).⁶⁵ In a large systematic review of controlled trials of fiber supplementation in IBD, fiber was noted to have a beneficial effect on disease outcomes in some patients with UC (in 3 out of 10 studies) or pouchitis (1 trial).⁶⁶ However, the trials included were heterogenous and small. A recent experimental study showed that supplementation of polyphenols in dried apple peel powder to mice with dextran sulfate sodium (DSS) induced intestinal inflammation resulted in a normalization of inflammatory cytokines by regulating cellular signaling pathways and changes in microbiota composition.⁶⁷ Thus, further research is needed on whether there is a potential beneficial effect of dietary fiber, particularly soluble fiber from fruits and vegetables, in individuals with established disease. At the same time, patients with symptomatic or suspected stricture should continue to be advised a low residue diet to prevent mechanical complications of bowel obstruction.

Epidemiologic studies have shown a protective effect of long chain n-3 polyunsaturated fatty acids (PUFAs) in patients with UC through inhibition of inflammatory cytokine production and favoring generation of anti-inflammatory eicosanoids.^{68, 69, 70} Few controlled trials have examined the efficacy of n-3 PUFA in IBD and results have been mixed. A systematic review of 9 randomized trials showed that while n-3 PUFA may increase rates of remission in CD (relative risk [RR] 0.77; 95% confidence interval [CI] 0.61–0.98), there was considerable heterogeneity between the studies and there was no effect when analyzing only high quality studies.⁷¹ In the EPIC trial, n-3 PUFA supplementation was not effective in maintaining remission in CD.⁷² The literature on n-3 PUFA supplementation is more sparse in UC despite stronger epidemiologic evidence in support of a role of n-3 and n-6 PUFA in this disease.^{69, 73} Many initial studies were small and lacked sufficient power to demonstrate an effect.^{74–77}

Other dietary supplements

Other dietary supplements have also been explored in IBD in small studies. Glutamine and whey protein improved intestinal permeability and morphology in patients with CD in remission.⁷⁸ A randomized controlled trial of curcumin capsules (3g/day) and mesalamine was superior over mesalamine alone in inducing remission (54% vs. 0%, $p=0.01$).^{79–85} Clinical response (reduction of 3 points in SCCAI) and endoscopic remission was seen 65.3% and 38% of the curcumin group respectively vs. 12.5% and 0 % in the placebo group ($P < .001$).⁸¹

VITAMINS AND OTHER MICRONUTRIENTS

Active intestinal inflammation and poor oral intake during acute illness are associated with myriad vitamin and micronutrient deficiencies including iron, vitamin D, zinc, and vitamin B12.^{86, 87} Though most micronutrient deficiencies are caused by active disease and do not impact disease pathogenesis, zinc and vitamin D in particular have been proposed to have

key immunologic roles leading to the hypothesis that repletion may also be of therapeutic benefit.

Vitamin D

Several studies have established an association between vitamin D deficiency and active IBD.^{88–90} Vitamin D deficiency has also been associated epidemiologically with increased risk of surgery, hospitalizations, and *C. difficile* infection in patients with UC or CD.^{91, 92} A 2013 cohort study of 3,217 IBD patients demonstrated an increased risk of surgery with progressively lower levels of vitamin D in patients with CD, with a 50% and 75% increased odds of surgery, respectively, in patients who had insufficient (20–29 ng/ml) or deficient (< 30ng/mL) plasma 25(OH)D when compared to patients with vitamin D ≥ 30 ng/ml.⁹¹ Vitamin D deficiency was also associated with a 2 fold increase in risk of surgery in UC.⁹¹ Notably, subsequent normalization of vitamin D resulted in reduced odds of surgery when compared to individuals who remained persistently deficient (odds ratio 0.56; 95% CI 0.32 – 0.98).⁹¹ A more recent prospective study of 70 UC patients in remission demonstrated that a vitamin D level ≥ 35 ng/mL was associated with an increased risk of relapse at 12 months (OR 1.25; 95% CI 1.01 – 1.56).⁹³ Vitamin D may exert a modulating role on intestinal inflammation through several mechanisms. It increases apoptosis of activated T helper type-1 cells thereby decreasing the release of pro-inflammatory mediators (TNF-alpha, interferon-gamma, ICAM-1 expression) in active IBD.^{94–99} Vitamin D also has direct effects on the innate immune response through interaction with toll-like receptors and upregulation of cathelicidin antimicrobial peptide to enhance intracellular bacterial killing.^{100, 101}

Three recent clinical trials have examined the role of vitamin D supplementation on disease activity in IBD. A Scandinavian trial of 108 CD patients in remission suggested a possible lower rate of relapse in the supplementation group (13%) compared to placebo (29%) (p=0.06).¹⁰² A recent randomized double-blind controlled pilot study of high-dose vitamin D3 (10,000 IU daily) versus low-dose vitamin D3 supplementation (1000 IU daily) for 12 months in 34 patients with CD in remission demonstrated no significant difference in outcomes on intention-to-treat analysis.¹⁰³ However, per protocol analysis demonstrated a decreased risk of 12-month relapse in the high-dose vitamin D as compared to the low-dose vitamin D group (0/12 versus 3/8; p=0.049).¹⁰³ A randomized controlled trial of 90 patients comparing high dose vitamin D (300,000 IU intramuscular vitamin D) to placebo demonstrated a significant decrease in ESR and CRP in the vitamin D group as compared to placebo.¹⁰⁴ Thus, while further studies are needed, vitamin D appears to have a promising role in ameliorating intestinal inflammation.

Zinc

Zinc sensing receptors on colonocytes play an important role in regulating colonic permeability and downstream inflammation through impact on occludin, an essential component of intercellular tight junctions.¹⁰⁵ Animal models of colitis and cell culture experiments demonstrate an improvement in pro-inflammatory cytokines with zinc supplementation.^{106, 107} In healthy elderly subjects, a randomized controlled trial of 6-months of zinc supplementation (dose 45 mg zinc gluconate per day) versus placebo demonstrated a significant decrease in several pro-inflammatory markers including high-

sensitivity C-reactive protein, interleukin-6, macrophage chemoattractant protein 1, and vascular cell adhesion molecule 1.¹⁰⁶ Analysis of a large prospectively enrolled cohort with a follow-up of over 3,317,550 person-years revealed that higher intake of daily zinc intake divided into quintiles was inversely associated with risk of CD but not UC.¹⁰⁸ A recent cohort study utilizing the clinical data of a large registry of inflammatory bowel disease patients (773 Crohn's disease, 223 ulcerative colitis) demonstrated an independent association of zinc deficiency with subsequent hospitalizations, surgery, and disease related complications, with reduction in that risk in individuals who normalized zinc levels prior to the outcome.¹⁰⁹ Uncontrolled observational data in 12 patients demonstrated resolution of intestinal permeability alternations in quiescent CD with zinc supplementation.¹¹⁰ However, no randomized clinical trial has been performed to evaluate the effect of zinc supplementation in patients with IBD.

STRESS

Anxiety and depression are more common in patients with IBD. However, research has also suggested that such psychological comorbidity could themselves increase risk of incident IBD and lead to a more severe course, thereby rendering them as possible behavioral targets for modification.^{111, 112} In a prospective cohort study, women with the greatest degree of depressive symptoms had a two-fold increase in risk of incident CD¹¹¹. Further, experimental support for this hypothesis comes from animal models where induction of depression in mice was associated with development of colitis which could be ameliorated by treatment with antidepressants.¹¹³ The effect of depression on intestinal inflammation may be mediated through its effect on the microbiota, increasing circulating inflammatory cytokines by disrupting bacterial populations in the intestine.^{114,115} In experimental work, treatment of mice with antibiotics prevented this inflammatory response to stress. The data on the impact of stress and depression in established disease is more heterogeneous. While some studies have demonstrated increased risk of clinical flares^{116, 117}, non-response to therapy¹¹⁸, and IBD-related surgery, others have suggested an association primarily with symptomatic worsening of symptoms but not intestinal inflammation measured by fecal calprotectin levels^{116, 119}.

While treatment of active IBD improves symptoms of depression and anxiety, whether improvement in IBD clinical status can be achieved with treatment of stress and depression is unknown.¹²⁰ In an elegant summary of the literature by Timmer *et al.* that included 21 studies and 1,745 participants, among adult IBD patients, there was no benefit with psychotherapy in induction of clinical remission. In contrast, in adolescents, psychotherapy resulted in a short-term improvement in quality of life.¹²¹ In a trial of 161 youth with CD and depression randomized to cognitive behavioral therapy (CBT) or supportive listening, patients in the intervention group demonstrated significant improvement in both the severity of depression and Crohn's disease activity measured using the Pediatric Crohn's Disease Activity Index (PCDAI) ($z = 1.97$, $P = 0.05$)¹²², supporting the results of a previous randomized controlled trial where CBT was associated with a greater reduction in IBD activity compared to supportive listening.¹²³ In a randomized trial of 29 patients with IBD assigned to the Breath-Body-Mind Workshop (BBMW) (breathing, movement, and meditation) or an educational seminar, participation in the workshop was associated with

improvements in psychological and physical symptoms, quality of life, and C-reactive protein levels.¹²⁴ Other studies have used guided imagery with relaxation training and solution-focused therapy (SFT) to demonstrate improvements in fatigue and quality of life in patients with IBD.^{125–130} IBD patients with high levels of perceived stress may benefit more from this therapy than those without, as demonstrated in a trial by Jedel *et al.* where only the increased- perceived stress subgroup demonstrated a reduction in flares of UC with mindfulness-based therapy.^{131, 132} Fewer studies have examined the effect of antidepressants on disease activity. A small trial demonstrated an improvement in physical, psychological, and social dimensions of quality of life in IBD patients treated with Duloxetine.¹³³ An observational case-control study of 29 patients who were started on antidepressants for mood disorders demonstrated a lower rate of relapse (1 vs. 0, $P=0.002$) and steroid use (1 [0–3] vs. 0 [0–4], $P<0.001$) in the year after starting treatment compared to the year before.¹³⁴ In conclusion, emerging data supports that psychological interventions improve quality of life in patients with IBD. However, there is need for rigorous interventional studies of both behavioral and pharmacologic interventions with objective markers of disease activity and inflammation as an endpoint to truly determine if amelioration of stress, anxiety, and depression can modify natural history in patients with IBD.

SLEEP

Patients with IBD commonly have disturbed sleep, particularly when their disease is active with nocturnal symptoms. However, sleep disruption may be common even in patients with inactive disease and indeed precede the development of IBD as evidenced by a prospective study where sleep duration less than 6 hours or greater than 9 hours per day was associated with an increased risk of ulcerative colitis.¹³⁵ Poor sleep quality during remission at baseline is associated with increased risk of disease relapse at 6 months.¹³⁶ Sleep impairment is predictive of subclinical inflammation and histologic disease activity.¹³⁷ However, many questions remain unanswered and none have examined the effect of interventions improving sleep on disease activity in IBD. In a murine model of colitis, application of intra-colonic melatonin gel formulation resulted in reduced intestinal inflammation.^{138–140} There are no clinical trials examining if behavioral or pharmacological improvement of sleep quality in IBD is associated with improved disease outcomes, but with growing epidemiologic evidence, there is a need for such studies.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most commonly used analgesics. While their effects in inducing gastric and small bowel ulceration has been widely documented, their intake, particularly at high doses and over a prolonged period of time, may also be associated with risk of incident IBD and trigger relapses.¹¹⁶ In a prospective study of 76,795 U.S. women from Nurses' Health study, women who used NSAIDs at least 15 days per month were found to have increased risk for both CD and UC. This effect was not seen with aspirin use.¹⁴¹ CD patients who reported regular NSAID use 5 times/month were at higher risk of active disease at 6 months.¹⁴² A randomized controlled trial of NSAIDs in quiescent IBD demonstrated that one-third of patients relapsed

within 7–10 days of initiating therapy¹⁴³ while selective COX-2 inhibitors like celecoxib did not have a similar deleterious effect.¹⁴⁴

APPENDECTOMY

Appendectomy has contrasting effects on CD and UC. Appendectomy may be associated with an increased risk of CD.^{145, 146} Conversely, the appendix may be a priming site for the development of UC,¹⁴⁷ and epidemiologically, early appendectomy has been inversely associated with development of UC.^{148, 149} Mechanistic hypotheses for this phenomenon include alteration of activated T-cell populations following appendectomy to favor regulatory T cells,¹⁵⁰ and changes in the CD4/CD8 ratio.^{147, 151} However, the use of therapeutic appendectomy to mitigate disease severity and colectomy in patients with existing UC is unclear. Some studies suggested an inverse relationship between appendectomy and risk of colectomy in patients with UC¹⁵² though other large studies have not identified this effect. A subgroup of patients who underwent appendectomy after diagnosis of UC had a two-fold increase in risk of colectomy.¹⁵³ A small case series of 6 patients with refractory UC demonstrated that appendectomy was associated with achievement of remission with maintenance therapy in only 1 patient, while the other 5 relapsed subsequently after initial improvement.¹⁵⁴ The results of an ongoing multicenter trial examining the benefits of appendectomy in combination with mesalamine in UC are awaited.¹⁵⁵

OBESITY

The prevalence of IBD has risen concordantly with the prevalence of obesity.¹⁵⁶ In prospective cohorts, a higher body mass index was associated with the development of CD but not UC.^{157, 158} The pro-inflammatory state promoted by obesity may contribute to a skewed CD4+ T-cell population leading to expansion of Th17 T-cells, inflammatory mediators associated with IBD.¹⁵⁹ There is conflicting data about whether obesity impacts disease outcomes in established IBD with interpretation of results further challenged by the fact that weight loss is a marker of disease severity. Analysis of 482 prospective-registry patients with Crohn's disease with 3D computed-tomography visceral adipose volume measurements demonstrated increased odds of surgery in the highest quintile of visceral adipose as compared to the lowest quintile (multivariable-adjusted OR 2.02; p-trend = 0.06).¹⁶⁰ Higher quintiles of visceral adipose volume also correlated with risk of penetrating disease (Ptrend = 0.02).¹⁶⁰ Conversely, in a recent large, retrospective cohort study of 1494 patient with IBD, obesity was not associated with corticosteroid use, emergency department visits, hospitalizations, or surgery.¹⁶¹ There are no studies of the impact of changes in central fat or targeted weight loss therapy on disease activity in IBD.

ORAL CONTRACEPTIVE USE

Oral contraceptive pills (OCP) have been associated with an increased risk of CD.^{162–164} A few studies have examined the effect of hormonal contraceptives on disease course. In a nationwide study, Khalili *et al.*¹⁶⁵ found that the use of OCP in UC patients was not associated with a higher risk of disease progression, need for surgery, or anti-TNF therapy.

However, in established CD, use of combination of estrogen and progestin oral contraceptives was associated with a higher likelihood of surgery, particularly with long-term use.¹⁶⁶ It is difficult to infer causality from observational studies where additional confounding factors may influence the effect of the association, and individualized decision-making is essential based on the availability of other options.

CONCLUSION

Numerous epidemiologic risk factors for the development and exacerbation of IBD have been identified recently with high quality epidemiologic and laboratory data supporting biologic plausibility and mechanisms of effect (Table 1). While they provide insight into the pathogenesis of disease, they also offer numerous attractive options to modify to improve disease outcomes in patients with IBD. High quality data to inform us about the role of these interventions, the appropriate patient population, and expected disease outcomes are lacking for most of the environmental factors. There is an important need for further study in this area to facilitate an active role for patients in the management of their disease through such modifications and further improve their outcomes.

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Table 1

Summary of evidence of the role of modifiable environmental factors in IBD

Environmental Factor	Epidemiologic evidence of association with incident disease	Evidence of effect on disease activity in established disease	Interventional studies examining effect of modification on disease outcomes
Cigarette Smoking	CD: ↑ disease incidence. UC: ↓ disease incidence.	CD: ↑ disease activity, immunosuppressant requirements, risk of stricturing and fistulizing disease. ↓ time to post-operative recurrence. UC: Decreased risk of disease exacerbations.	2001 Cosnes et al. – Smoking cessation in CD patients associated with significantly decreased risk of flare compared to active smokers.
Diet			
Enteral Nutrition			2007 Dziechciarz et al. – No significant difference in the remission rates between Enteral nutrition and steroid therapy from pooled analysis of 4 randomized trials. One trial revealed significant increase in the percentage of patients achieving remission in the total EN group compared with the partial EN group. 2014 Grovez wt al. - Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn's disease.
Specific Carbohydrate Diet (SCD)			2014 Cohen et al. - Clinical and mucosal improvements were seen in children with CD who used SCD for 12 and 52 weeks. 2016 Obih et al. - Specific carbohydrate diet improves clinical and laboratory parameters for pediatric patients with nonstricturing, nonpenetrating CD as well as UC.
IgG4 Exclusion Diet			2016 Gunasekera et al. - Treatment of CD with an IgG4-Guided Exclusion Diet as an adjunct, can improve quality of life and symptoms in patients with CD.
Fiber supplementation	CD: Long-term intake of dietary fiber, particularly from fruit, is associated with lower risk of CD but not UC	CD: ↓ risk of disease relapse at 6 months with high fiber diet	2016 Brotherton et al. – Avoidance of Fiber Is Associated With Greater Risk of Crohn's Disease Flare in a 6-Month Period. 2014 Faghfoori et al. - The consumption of Germinated Barley Foodstuff may be efficient in attenuating the inflammation and clinical signs in patients with Ulcerative Colitis.
Fat supplementation	UC: ↓ disease incidence with greater consumption of long chain n-3 polyunsaturated fatty acids (PUFAs).		2014 Lev-Tzion et al. - Evidence from two large high quality studies suggests that omega 3 fatty acids are probably ineffective for maintenance of remission in CD. 1992 Hawthorne et al. -Fish oil supplementation produces a modest corticosteroid sparing effect in active disease, but there is no benefit in maintenance therapy in patients with UC.
Micronutrients and vitamins			

Environmental Factor	Epidemiologic evidence of association with incident disease	Evidence of effect on disease activity in established disease	Interventional studies examining effect of modification on disease outcomes
Vitamin D	Low predicted vitamin D levels were associated with ↑ incidence of CD. CD is more common in genographic regions with low ultraviolet light exposure.	Vitamin D deficiency associated with ↑ relapse rate, surgery risk, hospitalization in CD and UC.	2010 Jorgensen et al. - No decrease in 12-month relapse in CD patients receiving 1200 IU vitamin D3 vs. placebo. 2016 Narula et al. - No difference in 12-month relapse with supplementation of 10,000 IU daily vitamin D3 vs. 1000 IU daily vitamin D3 in CD patients on intention-to-treat analysis. Per protocol analysis did demonstrate a significant improvement in patients on 10,000 IU vitamin D (p=0.04). 2016 Sharifi et al. - Significant decrease in ESR and CRP in patients on 300,000 IU intramuscular vitamin D vs. placebo.
Zinc	Deficiency associated with ↑ incidence of CD.	Deficiency associated with ↑ hospitalization risk, surgery risk, and disease-related complications.	2001 Sturniolo GC et al. - Zinc supplementation in 12 patients with quiescent CD resulted in normal intestinal permeability in 10/12.
Stress	CD: ↑ disease incidence. UC: ↑ disease incidence.	CD: cognitive behavioral therapy (CBT) improvement in both the severity of depression and Crohn's disease activity CD and UC: Duloxetine associated with improvement in physical, psychological, and social dimensions of quality of life and ↓ symptom severity	2015 Szigethy et al. - Effect of 2 psychotherapies on depression and disease activity in pediatric Crohn's disease. 2015 Daghighzadeh et al. - Efficacy of duloxetine add on in treatment of inflammatory bowel disease patients: A double-blind controlled study.
Sleep	UC: Prolonged or shortened sleep duration was associated with an increased risk of UC.	CD: Poor sleep quality during remission associated with ↑ risk of disease relapse UC: ↑ risk of disease relapse during remission	None
Non-steroidal anti-inflammatory agents	CD: ↑ disease incidence. UC: ↑ disease incidence.	CD: ↑ risk of relapse UC: ↑ risk of relapse.	2006 Takeuchi et al. - non-selective NSAIDs were associated with a 17–28% risk of relapse within 9 days in patients with IBD. 2006 Sandborn et al. - Celecoxib was not associated with increased risk of relapse compared to placebo in patients with UC in remission.
Appendectomy	CD: ↑ disease incidence. UC: ↓ disease incidence.	UC: Conflicting data on whether appendectomy reduces risk of colectomy in UC.	ACCURE trial - Ongoing multicenter Netherlands and UK trial comparing mesalamine maintenance vs. mesalamine + appendectomy on rate of 1-year UC relapse.
Obesity	↑ risk of Crohn's disease but not UC.	CD: Data demonstrating either increased risk of surgery or no effect of greater BMI in CD.	None
Oral Contraceptive Use	CD: ↑ disease incidence UC: No association	CD: long-term use of combined OCP associated with higher likelihood of surgery. UC: OCP use was not associated with risk of colectomy.	None