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ORIGINAL ARTICLE

Environmental Factors in the Relapse and Recurrence of Inflammatory Bowel Disease: A Review of the Literature

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Abstract
Introduction The causes of relapse in patients with Crohn's disease (CD) and ulcerative colitis (UC) are largely unknown. This paper reviews the epidemiological and clinical data on how medications (non-steroidal anti-inflammatory drugs, estrogens and antibiotics), lifestyle factors (smoking, psychological stress, diet and air pollution) may precipitate clinical relapses and recurrence. Potential biological mechanisms include: increasing thrombotic tendency, imbalances in prostaglandin synthesis, alterations in the composition of gut microbiota, and mucosal damage causing increased permeability.
Results The clinical epidemiological data consistently reports positive associations between smoking and relapses in CD, and inverse ones with UC. For NSAIDs and estrogens, the epidemiological findings are inconsistent, although general antibiotic use was associated with a reduced risk of relapse in CD. High levels of stress were positively associated with relapse, although psychological interventions did not have therapeutic benefits. The limited work on diet has reported sulphur-containing foods are positively associated with relapse in UC, but there is no work in CD. Ecological data reported positive correlations between air pollution levels and IBD hospitalisations.
Conclusions In the future, to clarify this area, more clinical epidemiological work is required where detailed drug types and doses, and complete dietary intakes are measured, in specific forms of IBD. Such work could provide guidance to both patients and doctors to help maintain remission.

Keywords Relapse · Recurrence · Inflammatory bowel disease · Precipitating factors

Introduction

The inflammatory bowel diseases (IBD) are a heterogeneous group of disorders affecting the gastrointestinal tract, of which the commonest are Crohn's disease (CD) and ulcerative colitis (UC). The prevalence of IBD in Western countries has increased in the last 50 years and, although the etiology is largely unknown, probably involves a complex interaction between genetic, immunological and environmental factors, which culminates in an aberrant response to luminal antigens [1]. Although genetic loci have been found for predicting the nature of the disease [2], the rapid increase in the prevalence of IBD suggests that environmental factors are responsible. Patients with IBD have an impaired quality of life [3, 4]; require lifelong treatments, including medications and surgery [5]; have an increased risk of colorectal carcinoma [6] and may suffer from extra-intestinal complications [7, 8]. Clinically, IBD has a relapsing and remitting course, so the aims of therapy are to both induce and maintain remission. Exacerbating factors which precipitate clinical relapses should therefore be avoided, but currently these are poorly understood.

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This article reviews the evidence on whether certain environmental factors influence the development of clinical relapses and recurrences (further disease postsurgery). These include the medications: nonsteroidal anti-inflammatory drugs, estrogens and antibiotics; and aspects of lifestyles: smoking, alcohol, stress, air pollution and diet. Plausibly, there may be interactions between these exposures, possibly through interaction with the microbiota which may alter the disease course. Clarifying whether these exposures are involved is important in attempts to reduce relapse rates and improve clinical outcomes and patients' quality of life. This paper will discuss possible biological mechanisms on how each of these factors may influence clinical outcomes and whether these mechanisms are supported by the clinical and epidemiological studies (summarized in Table 1).

Known Clinical Factors for Relapse

The relapse rate in IBD is currently difficult to predict in individual patients. However, certain clinicopathological features are associated with both a worse prognosis and a more severe disease course. Patients younger than 40 years at diagnosis are more likely to have a severe CD course [9]. Furthermore, this also applies to those requiring either steroids at their first presentation, two or more courses of steroids annually, patients with perianal involvement and those with penetrating/stricturing complications [9–11]. For UC, younger patients, those with multiple relapses and patients with basal plasmocytosis in histological biopsies are more likely to relapse [12].

Smoking

Chemicals in cigarette smoke have pathophysiological effects on the vasculature which affect vessel patency, vascular tone, inflammatory activity and thrombotic tendency. Smoking decreases both nitric oxide synthesis and endothelium-dependent vasodilatation resulting in vessel narrowing and a pro-thrombotic, pro-inflammatory state, which is reversible upon cessation [13–15]. This thrombotic tendency is exacerbated by smoking which increases platelet adhesion and aggregation [16]. Such a role of thrombosis seems plausible as individuals with an inborn error of coagulation, such as hemophilia, have a lower incidence of CD [17]. The pathogenesis of CD is a complex multistaged process not yet fully understood, although thrombosis may be involved through a process initiated by focal arteritis. The latter leads to fibrin-deposition, arterial occlusion, and subsequent microinfarction or neovascularization [18]. This possible mechanism is supported by both experimental work, which demonstrated thrombosis in capillaries of rectal biopsies of patients with UC and CD [19]. Furthermore, angiographic studies have reported reduced density and caliber of vessels resulting in a lower mesenteric blood flow in segments of affected bowel [20, 21]. Whether these pathological changes are directly involved in the pathogenesis of CD, or are a secondary consequence, is unknown. Thrombotic events leading to downstream ischemia and the production of reactive oxygen species [22] may exacerbate CD firstly by causing the inducible transcription factor NF-κB (nuclear factor κB) to bind to DNA [23]. This promotes inflammation mediated through up-regulating cytokines and chemokines [24, 25]. Previous studies have identified activated NF-κB in the epithelial cells of patients with IBD [26]. Secondly, reactive oxygen species may also precipitate relapses by increasing the permeability of the mucosal and vascular epithelium, mediated through superoxide and hydrogen peroxide [22, 27]. This increased permeability may lead to a greater exposure of antigens exacerbating CD.

The experimental mechanisms for how smoking may precipitate clinical relapse of CD are supported by the epidemiological data. A meta-analysis of 16 observational studies of 2,962 CD patients (48 % smokers) reported that smokers were more likely to develop clinical recurrence after disease-modifying surgery than non-smokers (OR 2.07, 95 % CI 1.25–3.44, $p < 0.005$) [28]. A retrospective cohort study in France of 400 patients with CD reported that smokers were more likely to require glucocorticoids and immunosuppressive therapy—markers of disease severity—during follow-up [29]. For patients smoking between 10 and 20 cigarettes per day, there was a greater risk of requiring glucocorticoids (RR 1.15, 95 % CI 1.05–1.25) and immunosuppressive therapy (RR 1.58, 95 % CI 1.09–2.29). A prospective cohort study, nested in the placebo arm of a Canadian multicenter randomized controlled trial, studied 152 CD patients. In total, 40 % relapsed, which was significantly higher in smokers (HR 2.1, 95 % CI 1.1–4.2) [30]. A cohort study of 622 French patients with CD reported that smokers (of greater than 16 cigarettes per day) were more likely to relapse (adjusted RR 1.35, 95 % CI 1.03–1.76, $p = 0.03$) [31]. There was evidence of a dose–response, which has been reported in other work in both relapse and recurrence [32–35].

For UC, a number of investigations have documented that perhaps, surprisingly, smoking is inversely associated with disease severity. A French cohort study of 96 patients reported that, following smoking cessation, there was a statistically significant increase ($p < 0.01$) in years with active disease, years of hospitalization and years with medical therapy (oral steroids, IV steroids and azathioprine) [36]. An Australian prospective cohort study of 101 UC patients, all with a functioning ileal pouch-anal anastomosis, were followed up for 2 years, during which time non-smokers were more likely to develop episodes of pouchitis than smokers,

Table 1 Summary of potential exposures for relapse

Exposure	State of the evidence	What needs to be done?
Smoking	Plausible biological mechanisms including decreased blood vessel patency and increased thrombotic tendency. Clinical data report that smoking increases the risk of relapses of CD, but reduces that of UC	Clarify the underlying biological mechanisms to support the consistent observational data
NSAIDs	Plausible biological mechanisms involving increased intestinal permeability and altered production. Conflicting epidemiological data reporting positive or no associations	Cohort studies comparing relapse rates in patients with IBD according to prior NSAID use, adjusting for all covariates, including maintenance therapies
Estrogen-containing medications	Possible effects in increasing the thrombotic tendency. For the OCP, studies document positive, or no, associations. For HRT, data showing inverse or no associations	Detailed prospective studies of patients investigating CD and UC individually, the varying clinical scenarios and the dose and duration of estrogen use
Antibiotics	Plausible mechanisms involving antibiotics inducing changes in the proportions of pathogenic and commensal gut bacteria. Epidemiological work for CD documenting inverse associations between general antibiotic use and relapse, but not for UC	Clarification of the mechanisms of individual microorganisms in the pathogenesis of relapse. Prospective cohort studies measuring antibiotics, including their dose and duration of use for different clinical manifestations of IBD. Importantly, consistency is required between the mechanistic and epidemiological data
Stress	Mechanisms unknown, although possible effects on decreasing mucous secretion and increasing gut permeability. Most observational work shows positive associations between stress and relapse, but no proven beneficial psychological interventions	Assessment of psychological interventions, in randomized controlled clinical trials, to lower stress and reduce relapse rates
Diet	Laboratory and observational work that excess dietary sulfur may precipitate relapse	Detailed cohort studies in patients with IBD recording their dietary intake and correlating with clinical relapse. Randomized controlled clinical trials of dietary interventions, including a low-sulfur diet in UC
Pollution	Laboratory work reports detrimental effects of air pollutants on the intestinal mucosa. Ecological work reporting associations with density of air pollutants and IBD hospitalizations	Analytical epidemiological studies comparing exposure to pollutants and risk of clinical relapse

IBD inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *NSAID* nonsteroidal anti-inflammatory drugs, *HRT* hormone replacement therapy

although this did not quite reach statistical significance (25 vs. 6 %, $p = 0.054$) [37]. The mean number of episodes of pouchitis per group over follow-up of approximately 3.5 years was higher in non-smokers compared to smokers (0.639 vs. 0.059, $p = 0.005$, range of number of episodes = 0–6). Why smoking may prevent relapse of UC is uncertain, but nicotine does decrease the expression of pro-inflammatory cytokines, such as IL-1β and IL-8 [38], increase anti-inflammatory ones, such as IL-4 [39], and modulates the innate immune response through a Toll-like receptor-4-dependent pathway [40].

In summary, the biological mechanisms for why smoking may affect CD and UC in opposing ways are unknown. Tobacco smoke contains approximately 3 500 compounds [41], some of which may have multiple effects on intestinal mucosal cells. However, the consistent data from both experimental and epidemiological studies, including the dose–response effects, suggest smoking is a causative factor for CD relapse. The inverse association with UC requires clarification by understanding the possible underlying mechanisms. However, smoking cessation should be encouraged in all IBD patients for its general health benefits, but particularly in those with CD.

NSAIDs

There are plausible biological mechanisms for how non-steroidal anti-inflammatory drugs (NSAIDs), including

aspirin, may exacerbate inflammatory bowel disease [42]. NSAIDs enter the hydrophobic channel of cyclooxygenase enzymes (COX) and form a hydrogen bond with arginine [43, 44], whereas aspirin irreversibly binds to a serine residue [45]. Consequently, there is steric blockage of the COX channel preventing the n-6 polyunsaturated fatty acid arachidonic acid entering [45]. Subsequently, prostaglandin production from arachidonic acid is reduced, including prostacyclin (PGI_2), prostaglandin E_2 and thromboxane (TXA_2) [46]. Prostaglandin E_2 (PGE_2) has anti-inflammatory effects mediated by inhibiting TNF-α, IL-1, 5-lipoxygenase and leukotrienes [47, 48]. Plausibly, decreasing PGE_2 levels by NSAID use may have pro-inflammatory consequences. Secondly, NSAIDs increase the permeability of cell membranes by interacting with and disrupting phospholipids [49]. This may result in an increased exposure to luminal antigens, the recognition and processing of which are disturbed in IBD [2, 50]. Finally, NSAIDs may decrease COX-mediated vasorelaxation within the gastrointestinal vasculature resulting in impaired healing and exacerbating inflammation [51].

The findings from epidemiological studies investigating relapse and NSAID use are conflicting. The ideal study design would compare relapse rates in patients with IBD according to NSAID use or not. To the best of our knowledge, there is only one such study: A retrospective investigation of 60 patients treated in a tertiary referral center (68 % CD, 20 % UC and 12 % indeterminate colitis) which reported that patients were more likely to be taking a daily dose of any NSAIDs the month before relapse than those with IBD who were not (adjusted OR 6.31, 95 % CI 1.16–34.38, $p = 0.03$) [52]. The analysis was performed with CD and UC as a combined group and importantly neither smoking status, maintenance therapy nor compliance were included due to incomplete data collection. A case–control study of 60 IBD in-patients (36 CD and 24 UC) from the USA, which used irritable bowel syndrome patients as the control group, also reported NSAIDs were positively associated with relapse (OR 20.3, 95 % CI 2.6–159.7, $p < 0.0001$) [53]. A Scottish study of 200 IBD patients compared with general population controls found no association between current NSAID use and emergency admissions for IBD colitis (CD: OR 1.12, 95 % CI 0.48–2.59; UC: OR 1.72, 95 % CI 0.62–4.79) [54]. A retrospective record review of 192 IBD patients (58 % CD) in a US hospital reported no association for relapses of CD (OR 0.34, 95 % CI 0.07–1.39, $p = 0.16$) or UC (OR 0.65, 95 % CI 0.15–3.31, $p = 0.50$) [55]. A retrospective cohort study used a computerized record system of 1940 IBD patients (45 % CD) registered in one US health maintenance organization, with follow-up for at least 6 months, and reported no association between NSAID use and IBD relapse (HR 0.93, 95 % CI 0.68–1.27) [56].

In summary, the laboratory data suggest several mechanisms for NSAIDs inducing relapses, with some supportive, but not consistent, clinical epidemiological data. Further work is required investigating NSAID use specifically in CD and UC patients with and without clinical relapses, adjusting for all covariates and with detailed information on the prescription of maintenance therapies. However, the current evidence would suggest using NSAIDs with caution in IBD patients, and the guidance from the British Society of Gastroenterology (BSG) recommends this approach [57].

Estrogen-Containing Medications

Medications containing estrogen include the oral contraceptive pill (OCP) and hormone replacement therapy (HRT). In UK, it is estimated that 28 % of women younger than 50 years use the OCP [58]. HRT was used by approximately 20 million women worldwide in the late 1990s [59]. Estrogens are generally safe medications, although they may cause the uncommon, but serious side effect of venous thromboembolism (VTE) [60]. The hormone increases the activity of clotting factors of both the intrinsic and extrinsic pathways, and raises fibrinogen concentrations, which predisposes to thrombosis [61]. Therefore, it is likely that estrogens may precipitate relapses and recurrences of CD due to similar mechanisms to those described for smoking. Estrogens, which increase thrombogenicity, may plausibly promote microinfarction, thus contributing to the downstream effects of ischemia, exacerbating inflammation, and therefore clinical relapses. Estrogen receptors are present in the human colon [62, 63], although their physiological role, and whether they are involved in the pathogenesis of IBD is unknown.

The results of clinical epidemiological studies investigating estrogen use and relapse are conflicting. A prospective cohort study from Paris followed 331 women with a Crohn's disease activity index of less than 200 at enrollment for 12–18 months [64]. At baseline, oral contraceptive users (10 % using the progesterone-only pill) were more likely to have active colonic disease than nonusers (59 vs. 47 %, $p = 0.03$), but there were no subsequent associations between the OCP and relapses during follow-up (HR 1.11, 95 % CI 0.80–1.55). A further prospective investigation, nested in the placebo arm of a randomized controlled trial [30], followed 152 CD patients (52 % female), many of whom were eligible to take the OCP for up to 48 weeks. Current and previous OCP users were significantly more likely to relapse than nonusers (HR 3.0, 95 % CI 1.5–5.9, $p < 0.001$). In a study of 97 women who underwent primary surgical resection for CD, the recurrence rates at 5 and 10 years were compared between

participants who were users and nonusers of the OCP in the year following surgery [65]. There were no statistically significant differences at both 5 years (25 vs. 28.4 %) and 10 years (40.7 vs. 64.0 %). The small number of patients studied, particularly at 10 years, would have made true differences hard to detect. The effect of estrogens on UC relapse was investigated in a prospective cohort study in the USA and Canada in 74 participants (57 % women) taking the OCP, but reported no statistically significant difference in relapse rates between users and nonusers (26.5 vs. 40 %) [12].

HRT use was investigated in a US case–control of 65 postmenopausal women with CD ($n = 40$) and UC ($n = 25$) and reported an inverse association with disease activity in IBD as a whole (HR 0.18, 95 % CI 0.04–0.72, $p = 0.001$) [66]. More than 1 year's use of HRT was associated with a greater reduction in relapse than use for just 1 year. A prospective record review of 192 IBD patients (58 % CD), seen by a single gastroenterologist, detailed information on HRT use (obtained from a general information chart) [55]. Relapse of IBD was recorded, and there were no associations with either CD (OR 0.34, 95 % CI 0.07–1.39) or UC (OR 1.00, 95 % CI 0.16–7.63).

In summary, differences in the results of epidemiological studies investigating exogenous estrogen imply its influence on IBD is unknown. These inconsistencies may be explained by the differences in patient ages, the type of disease and the doses of estrogen studied. Further detailed clinical epidemiological observational studies documenting the precise clinical scenarios and estrogen preparations are required to clarify whether estrogens do precipitate relapses and recurrences.

Antibiotics

The human gastrointestinal system contains approximately 100 trillion (10^{14}) microorganisms, predominantly in the colon, consisting mainly of species of *Streptococci*, *Staphylococci* and *Lactobacilli* [67]. Indeed, the commonest locations for IBD, the terminal ileum and colon [67], contain bacteria which influence fermentation and immunoregulation [68, 69]. The use of antibiotics, which affect the composition of the gut microbiota, may therefore influence clinical disease activity if there is an imbalance between commensal and/or potentially pathogenic bacteria. A role for bacteria is supported by the association between CD and mutations of the NOD2/CARD15 gene, which is involved in the immunological response to bacteria [70]. Antibiotics could plausibly increase or decrease the risk of relapse according to the way they influence the composition of the microbiota. Demonstrating antibiotics affect relapse would be supported by, firstly, beneficial evidence for antibiotics as a treatment for IBD and, secondly, investigating whether antibiotics used for other indications influence relapse and recurrence.

For antibiotic use for non-IBD indications, an epidemiological case-crossover study of 3,435 UK participants (35 % CD) in the UK General Practice Research Database reported an inverse association for use of any antibiotics prescribed 60 days before relapse in CD (OR 0.78, 95 % CI 0.64–0.96, $p < 0.019$), but not UC (OR 0.96, 95 % CI 0.82–1.12, $p = 0.58$) [71]. There was also a significant effect of the timing of antibiotics, with participants prescribed antibiotics 0–15 days before relapse least likely to relapse (OR 0.60, 95 % CI 0.43–0.83, test for trend, $p = 0.001$). The treatment of moderately active IBD with antibiotics was documented in a systematic review and meta-analysis of 23 RCTs (14 CD) in adults [72]. This compared the effectiveness of numerous singular and combination antibiotic regimens versus placebo for inducing remission. For CD, 1,160 patients were treated for between 4 and 16 weeks with antibiotics to induce remission, and a beneficial effect was reported both for inducing remission (RR 0.85, 95 % CI 0.73–0.99, $p = 0.03$) and in a sub-cohort of 186 patients for maintaining remission (RR 0.62, 95 % CI 0.46–0.84, $p = 0.002$). For UC, 662 patients were treated for between 1 and 12 weeks, and a beneficial effect was observed (RR 0.64, 95 % CI 0.43–0.96, $p = 0.03$). A diverse number of antibiotics were studied including anti-tuberculosis drugs, macrolides, fluoroquinolones, 5-nitroimidazoles and rifaximin, either alone or in combination.

In summary, antibiotic therapy in active IBD may have clinically beneficial effects, although epidemiologically; the type of antibiotic, dose and clinical setting needs to be clarified. Currently, antibiotics have therapeutic uses in IBD for the treatment of complications [57]. More studies are required in different populations to see whether general antibiotic use affects relapse, which may subsequently inform prescribing practice in IBD patients.

Stress

Stress may be defined as "a threat to homeostasis" [73], provoked by stressors [74], which may be either physical or psychological [74]. Stressors initiate both central and peripheral responses to alleviate the "threat" and maintain homeostasis through behavioral and physical adaptations [75]. In rats with quiescent colonic inflammation, disease re-activation occurred after restrainment [76], and in murine work, stress reduced mucous secretion and increased colonic permeability [77], both features of IBD.

The consequences of stress can be investigated in either follow-up observational work, or randomized controlled

trials of psychological interventions designed to alleviate stress. A Canadian observational cohort study recruited 101 CD patients in clinical remission with follow-up for 1 year [78]. At baseline, and 3-month intervals, psychosocial questionnaires measuring stress, psychosocial distress and coping strategies were administered. Relapse was positively associated with both stress (HR 4.5, 95 % CI 1.9–10.7, $p < 0.001$) and coping strategies (HR 1.9, 95 % CI 1.2–2.8, $p = 0.004$) measured using a validated tool. A prospective cohort study of 62 Italian UC patients monitored symptoms at 6-month intervals [79], in participants completing a perceived stress and depression questionnaire. Patients in the highest tertile of perceived stress were more likely to relapse (OR 6.5, 95 % CI 1.2–34, $p < 0.05$), although there were no associations with depression. In Canada, 704 patients with known IBD (61 % CD) were sent surveys at 3-month intervals, for 1 year to measure disease activity, perceived stress and exposure to "major life events" [80]. High perceived stress levels were associated with increased exacerbations (OR 2.40, 95 % CI 1.35–4.26), but not major life events. In a further prospective investigation of 85 consecutive IBD patients, participants completed monthly questionnaires, of which 32 patients (75 % CD) relapsed [81]. There were no significant associations reported between stress levels and the risk of relapse and non-relapse (47 vs. 50 %, $p =$ NS). A Cochrane review of 21 psychological studies (1,745 participants) assessed interventions in IBD and reported no difference in remission rates between the intervention and the control groups at 12 months (OR 0.85, 95 % CI 0.48–1.48) [82]. In a European multicentered randomized controlled trial of 114 IBD patients (49 % CD) who had relapsed, or had "enduring disease" in the last 18 months, participants were randomized to receive either "treatment as usual," or stress management psychotherapy [83]. There were no statistically significant differences between relapse rates during the course of the study between groups (23 vs. 30 %, $p > 0.05$). Therefore, most evidence suggests associations between higher stress levels and clinical relapses, although to date there are no psychological interventions to prevent these.

Diet

Dietary factors may influence relapse, as the pathophysiology of IBD may be an exaggerated reaction to luminal antigens. In pediatric CD patients, enteral diets, both elemental and polymeric [84, 85], are used to induce remission, although symptoms do recur when patients restart their normal diet [86]. Food contains a combination of macro- and micronutrients (including vitamins and minerals), and many food additives. Although there is evidence that diet may affect the development of new IBD, there is minimal work on food items that may precipitate relapse. One mineral for which there are plausible biological mechanisms for inducing relapse is sulfur. Dietary sulfur is present as sulfated amino acids, inorganic sulfur and a preservative food additive [87, 88]. Sulfur may be toxic to human colonocytes following its metabolism by colonic bacteria to hydrogen sulfide (H_2S) [89]. This mechanism was demonstrated in the colonocytes of anaesthetized rats which were perfused with either H_2S or control buffer. In the former, there was superficial mucosal ulceration, dose-dependent apoptosis, and loss or shrinkage of goblet cells and crypts [89, 90]. Furthermore, sulfides inhibited the butyrate-dependent energy metabolism of colonocytes [91], which may have a pathophysiological effect on such cells. In a clinical study investigating dietary sulfur, a UK prospective cohort of 183 UC patients in remission completed weekly food frequency questionnaires [92]. The authors derived an index of sulfur intake using information from the Royal Society of Chemistry food classification. The highest tertile of total dietary sulfur intake was positively associated with relapse (OR 2.76, 95 % CI 1.19–6.40), as was sulfate (OR 2.61, 95 % CI 1.08–6.30). A high consumption of red and processed meat was positively associated with relapse (OR 5.19, 95 % CI 2.09–12.9), and meat protein is an important source of sulfide generation in the gut [93]. Furthermore, a high alcohol intake was also positively associated with UC (OR 2.42, 95 % CI 1.04–5.62), which may be relevant as sulfides are added to alcohol for both flavor and a preservative [94]. A cross-sectional study in 81 patients with UC reported a significant correlation ($p < 0.001$) between foods containing high levels of sulfite with higher sigmoidoscopy scores, representative of more active disease [95]. Clinical trials investigating whether a low-sulfur intake may prevent relapse of UC are required. To the best of our knowledge, there are no similar studies investigating sulfur in CD, although work has reported interactions between genetic polymorphisms and fat intake on CD activity [96]. A high intake of total, saturated, and monounsaturated fats, and a higher ratio of n-6/n-3 polyunsaturated fatty acids with active disease are associated with a more active disease phenotype, mainly in patients carrying the variant alleles of TNF-alpha (857 C/T polymorphism) and IL6 (174 G/C polymorphism). More clinical studies are needed in both UC and CD investigating the effects of many nutrients on relapse, remission and disease activity.

Air Pollution

Air pollution may plausibly increase the risk of relapse of IBD through several mechanisms. Pollutants increase the

secretion of TNF-α, which is elevated in healthy human participants who inhaled diesel exhausts [97]. Furthermore, animal studies suggested that air pollutants may damage the colonic mucosa [98], and work in the respiratory system showed an increased susceptibility to bacterial infection mediated by an impairment of the microbial defense mechanism [99]. To date, only one study has investigated air pollution and relapse rates of inflammatory bowel disease [100]. Here, an ecological investigation of IBD patients in different counties in Wisconsin, USA (65 % CD), compared the average total annual emission density of air pollutants with IBD-related hospitalizations. This reported that a 1-log increase in the density of total emission pollutants resulted in increased hospitalization for both CD (IRR 1.39, 95 % CI 1.26–1.52) and UC alike (IRR 1.48, 95 % CI 1.27–1.73) [100]. Furthermore, hospitalization rates for the individual pollutants, such as carbon monoxide, nitrous oxide, sulfur dioxide, volatile organic chemicals and particulate matter <2.5 μm, were all increased. To study the effects of pollutants, further analytical studies are required comparing exposure to pollutants in the air between IBD patients with and without relapse.

Conclusions

The mechanisms for disease relapses in CD and UC are largely unknown, although probably involve a complex interaction of immunological, environmental, pharmacological, psychological and dietary factors. To date, the evidence strongly suggests that smoking adversely affects CD and may alleviate UC. NSAIDs and estrogens may aggravate the disease course, although the epidemiological evidence is conflicting. Furthermore, antibiotics may have a benefit in CD, but more studies investigating general and specific antibiotics in different populations are required to clarify further our understanding of the mechanisms involved and what work needs to be done. Psychological stress appears to precipitate IBD exacerbations. Work investigating the effect of diet on relapse is in its infancy, and it is preferable that diet is investigated in cohort studies, including confirming whether sulfur may be involved in UC. The effect of air pollutants is currently limited, and possible links need to be investigated in etiological studies. In the future, observational work is required to clarify associations, as clinical trials of possible exposures such as medications would be impossible due to both ethical and pragmatic reasons. Observational studies should investigate several aspects including the type of disease; its site; detailed medication records, including doses and durations; all known covariates (including smoking and family history) and using controls who are IBD patients in remission. Furthermore, many dietary factors need to be studied and assessed for potential clinical benefits in randomized controlled trials. Such work on factors which affect relapse and recurrence may improve patients' quality of life through preventive measures.

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Conflict of interest None.

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