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TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

Influence of environmental factors on the onset and course of inflammatory bowel disease

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Abstract

Numerous environmental factors have been linked with inflammatory bowel disease. These include smoking, diet, hygiene, drugs, geographical and psychosocial factors. These factors may either increase the risk of or protect against developing this condition and can also affect the course of illness in a positive or negative manner. A number of studies have examined the influence of environmental factors on inflammatory bowel diseases as a whole as well as on ulcerative colitis and Crohn's disease separately. As there are differences in the pathogenesis of ulcerative colitis and Crohn's disease, the effect of environmental factors on their onset and course is not always similar. Some factors have shown a consistent association, while reports on others have been conflicting. In this article we discuss the current evidence on the roles of these factors on inflammatory bowel disease, both as causative/protective agents and as modifiers of disease course.

Key words: Environmental factors; Crohn's disease; Ulcerative colitis; Etiology; Outcome

Core tip: Environmental factors have an important influence on the onset and course of inflammatory bowel disease. Multiple factors have been implicated with some showing a consistent effect, while the roles of others have been variable. The current evidence on their role in inflammatory bowel disease is discussed. A better understanding of these factors may help plan future preventive strategies.

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INTRODUCTION

The latter half of the twentieth century witnessed a steep increase in the prevalence of inflammatory bowel disease (IBD) in developed nations of North America and Europe. During the last three decades, populations previously considered to have low risk such as in Asia and eastern Europe are witnessing a substantial increase in this disease[1]. This may be explained by changes in environmental factors in these regions. Environmental factors that have been proposed to play a role in the emergence of IBD are smoking, diet, drugs, major life stressors, hygiene and lifestyle[1,2]. In this paper we review the role of environmental risk factors on the onset and course of ulcerative colitis (UC) and Crohn's disease (CD), the two main types of IBD.

ENVIRONMENTAL FACTORS IN THE PATHOGENESIS OF IBD

IBD is a complex disorder where interplay between host genetics, gut microbiota and environmental factors are regarded as drivers of chronic inflammation in the gut[3]. Genetic factors play an important role with more than 150 IBD susceptibility gene loci identified to date. However, approximately two-thirds of patients with IBD have no identifiable genetic defect, which suggests that gut microbiota and environmental factors play an important role[4]. Studies on individuals migrating from countries with low prevalence of IBD to regions with high prevalence have shown an increased risk of IBD among migrants further supporting the role for environmental factors[5-8]. These factors include smoking, diet, drugs, psychosocial factors, climate, pollution and hygiene[9]. The composition of gut microbiota, currently considered a key factor in the pathogenesis of IBD, is affected by environmental factors such as breast feeding, antibiotics, smoking, obesity and diet[10,11]. For example, breast fed and formula fed infants showed a difference in the quantity of *Bifidobacteria* in the gut[12]. Smoking cessation changes the gut flora by increasing the proportion of *Firmicutes,* reducing *Proteobacteria* and increasing microbial diversity making the flora different from gut microbiota in IBD where there is an abundance of *Proteobacteria* and *Actinobacteria*, reduced *Firmicutes* along with reduced microbial diversity[10,13]. These data suggest that an alteration in microbial composition of the intestine by environmental factors is one mechanism by which environmental factors increase susceptibility to IBD.

Environmental factors may also directly act on the intestinal mucosa and alter immune function and gene expression. This can be due to a change in intestinal permeability or an alteration in host gene expression by epigenetic modification or other mechanisms[14-16]. The end result is an abnormal host immune function and chronic inflammation in the gut. An interesting example of how environmental factors affect gut immune function is provided by studies on transcription factor aryl hydrocarbon receptor (AhR)[17]. This transcription factor which is altered by dietary and environmental factors affects innate immunity in gut and immune cells (T cells and natural killer cells). Intestinal T cells and natural killer cells isolated from Crohn's disease patients have shown low levels of AhR expression and these receptors respond to AhR ligands by upregulating interleukin-22 and downregulating inflammatory cytokines[17]. Therefore, it is plausible that environmental factors that downregulate AhR alter immune function and predispose to CD[17]. Smoking has also been shown to affect gene expression and immune function in the gut[18]. The complex interaction between host genes and environmental factors works both ways[19]. While the above examples demonstrate the effect of the environment on host gene expression, host genes can also influence the composition of microbiota which forms the local gut environment. *NOD2* gene mutation predisposes to the development of IBD. A possible mechanism may be an alteration in gut microbiota in *NOD2* gene mutation as shown in animal studies[20]. Mutation in autophagy-related 16-like 1 gene (*ATG16L1*) has also been found to increase the risk of IBD and it is possible that defective autophagy may alter the gut microbiome[19]. Further insights into the gene-environment interaction will lead to a better understanding of the pathogenesis of IBD.

The "hygiene hypothesis" has been commonly cited as the reason for the difference in IBD prevalence in different regions[21]. Better hygiene in developed regions leads to reduced microbial exposure in childhood which may affect development of the gut immune system and immune tolerance. Helminth infestation in animal models has been shown to upregulate Th2 cytokines and attenuate the Th1 pathway in the intestinal mucosa leading to suppression of inflammation and enhancement of the mucosal barrier[22,23]. Reduced exposure to helminths in developed societies has been suggested to be a risk factor for CD. Other factors such as stress, linked to exacerbation of IBD, may affect immune function by altering gut permeability and non-steroidal anti-inflammatory drugs (NSAIDs) by non-selective inhibition of cyclo-oxygenase[24,25].

Dietary factors may affect gut immune function directly in addition to their effect on microbiota[26]. There has been a recent increase in interest in the role of vitamin D in CD[27]. Our group and others have shown that vitamin D levels are reduced in patients with CD and levels correlate negatively with disease activity[28]. Data obtained mainly from animal studies have shown that vitamin D has immune regulating properties[29]. This includes maintenance of $CD8^+$ T

cells in the quiescent stage, shifting the cytokine profile to anti-inflammatory type and inhibition of epithelial cell apoptosis mediated by the vitamin D receptor[29]. Chen *et al*[30] have shown that TNF-α downregulates the vitamin D receptor, which in turn may promote inflammation. A high fibre diet protects against IBD by promoting the formation of short chain fatty acids like butyrate, which are a source of energy for colonocytes and by regulating T cell function[31]. The Nurses Health Study showed that soluble dietary fiber (fruits and vegetables) was associated with a reduced risk of CD[31]. The protective effect of fruits and vegetables may be through their antioxidant properties and clearing of reactive oxygen species[32]. Red meat has been associated with increased risk of IBD. Linoleic acid (long-chain omega-6 fatty acid) found in red meat and food oils is metabolized to arachidonic acid metabolites which are involved in the production of inflammatory mediators such as leukotrienes and prostaglandins[33]. Higher consumption of fish oils made up of omega-3 fatty acids (higher omega-3 to omega-6 fatty acid ratio) has been shown to be protective in children with CD[32]. There is some evidence that phytochemicals, such as curcumin found in turmeric, have antioxidant and free radical scavenging properties which may limit inflammation and help maintain remission in IBD[34,35]. These data suggest that environmental factors play a role in the pathogenesis of IBD by altering gut microbiota and affecting gut immunity by numerous mechanisms.

INTERPRETING THE AVAILABLE EVIDENCE

There are a large number of publications exploring the link between environmental factors and IBD. With the exception of smoking and appendectomy, the roles of other risk factors have been inconsistent and it is important to understand the type of study design when interpreting the results of these studies. Many of these are case-control studies which are relatively easy to perform and require few resources. However, an important limitation is the recall bias which affects the accuracy of ascertaining risk factors. Several prospective cohort studies have been carried out and data obtained from them are more robust. An important cohort study of note in this regard is the Nurses Health Study (NHS) Ⅰ and Ⅱ from the United States[31]. NHS Ⅰ was initiated in 1976 and included 121700 subjects and NHS Ⅱ was initiated in 1989 and included 116000 subjects. Periodic assessment of factors such as smoking, oral contraceptive pills (OCPs), alcohol and diet were carried out prospectively and occurrence of disease was noted. While this was mainly initiated for the outcomes of cardiovascular illness and cancer, a number of studies have been published on the role of these factors and IBD. The main limitation is that the subjects were women and most were white and generalisability across race, gender and various socioeconomic strata was difficult. Some of the studies have made use of a population-based registry to minimise referral bias and reflect population characteristics[36]. Finally, a number of meta-analyses have been published on various risk factors and IBD and these represent a higher quality of evidence. One must be cautious in interpreting the results of a meta-analysis as inclusion of low quality studies and heterogeneity among studies may affect the outcome.

ENVIRONMENTAL FACTORS AND ONSET OF IBD

A large number of environmental factors have been proposed to have a causative or protective effect on the onset of both CD and UC. Available evidence from many of these studies is summarised in Tables 1, 2 and 3. These tables have been grouped according to the study design to keep the quality of evidence in perspective. Table 1 includes meta-analysis, Table 2 cohort studies and Table 3 summarises data from case-control studies.

Smoking

There is adequate evidence linking smoking with IBD. It has opposing effects on CD and UC. The meta-analysis by Mahid *et al*[37] showed that current smoking increases the risk of CD, but has a protective effect on the onset of UC. Interestingly, former smokers had an increased risk of developing UC. Data from the NHS cohort showed that both current and former smoking was associated with increased risk of CD[38]. Unlike the result from meta-analysis, the study showed current smoking was not protective against UC, but former smoking was a risk factor. Population-based case-control studies from New Zealand, Hungary and Sweden have also shown increased risk of CD and decreased risk of UC with smoking[39-41]. The strong data linking smoking to IBD suggests that prenatal and childhood exposure to passive smoking may predispose to CD. However, a meta-analysis which included 13 studies did not show any significant impact of prenatal and childhood exposure to smoking on the occurrence of CD or protection against UC[42]. Based on these data, there is a strong case to recommend smoking cessation to reduce the risk of CD.

Diet, vitamin D and breast feeding

Western diet which is high in refined sugar and low in fibre has been proposed as a risk factor for IBD[26]. Increasing consumption of western diet is considered a reason for the rising incidence of IBD in Asia. The NHS data on 170776 subjects showed that intake of a median of 24.3 g of fibre per day reduced the risk of CD by about 40%[31]. Further analysis showed that this benefit was highest for soluble fibre in fruits, while

Table 1 Environmental factors and onset of inflammatory bowel disease - meta-analyses

Author	Study setting	Effect on CD	Effect on UC	Effect on IBD overall
Soon *et al*[63], 2012	Urban living and risk of CD and UC	IR (incident rate ratio, 1.42; 95%CI: 1.26-1.6)	IR (incident rate ratio, 1.17; 95%CI: 1.03-1.32)	
Luther *et al*[70], 2010	*H. pylori* infection and risk of IBD, (23 studies)			DR (RR = 0.64; 95%CI: 0.54-0.75)
Barclay *et al*[50], 2009	Breast feeding and early onset IBD (7 studies)	NA	NA	DR (OR = 0.69; 95%CI: 0.51-0.94)
Jones *et al*[42], 2008	Prenatal or childhood passive smoking and risk of IBD (13 studies)	NA	NA	
Cornish *et al*[54], 2008	OCP and risk of IBD (14 studies)	IR (RR = 1.46 ; 95%CI: 1.26-1.70)	IR (RR = 1.28 ; 95%CI: 1.06-1.54)	
Mahid *et al*[37], 2007	Smoking and risk of IBD (13 studies related to UC and 9 related to CD)	IR with current smoking (OR = 1.76; 95%CI: 1.40-2.22)	DR with current smoking (OR = 0.58; 95%CI: 0.45-0.75) IR with former smoking (OR = 1.79; 95%CI: 1.37-2.34)	

IR: Increased risk; DR: Decreased risk; NA: No association; CD: Crohn's disease; UC: Ulcerative colitis; RR: Relative risk; IBD: Inflammatory bowel disease; OCP: Oral contraceptive pill.

Table 2 Environmental factors and onset of inflammatory bowel disease - cohort studies

Author	Study subjects	Effect on CD	Effect on UC
Timm *et al*[76], 2014, Europe	Population-based cohort 10864 subjects from ECRHS[1] cohort Outcome - place of upbringing and risk of IBD	DR with being born and living on livestock farm for first 5 yr of life	
Khalili *et al*[53], 2013, United States	146681 subjects from NHS Ⅰ and Ⅱ 3373726 person-years of follow-up Outcome - risk of IBD in adulthood	NA - Breastfeeding, low or high birth weight, preterm birth	NA - Breastfeeding, low or high birth weight, preterm birth
Ananthakrishnan *et al*[31], 2013, United States	170776 subjects from NHS Ⅰ and Ⅱ 3317425 person-years of follow-up Outcome - diet and risk of IBD in adulthood	DR - Long term intake of higher dietary fibre especially from fruit	NA with dietary fibre
Ananthakrishnan *et al*[84], 2013, United States	152461 subjects from NHS Ⅰ and Ⅱ 1787070 person-years of follow-up Outcome - Depressive symptoms and risk of IBD	IR with recent and baseline depressive symptoms	NA with recent and baseline depressive symptoms
Levi *et al*[75], 2013, Israel	Cohort of 953684 Jewish adolescents Outcome - sociodemographic factors and risk of IBD	IR with high socioeconomic status, western origin, male sex DR with four or more children in childhood	
Higuchi *et al*[38], 2012, United States	229111 subjects from NHS Ⅰ and Ⅱ Outcome - Smoking and risk of IBD	IR - Current smoker, former smoker	NA - Current smoker IR - Former smoker
Ananthakrishnan *et al*[56], 2012, United States	76795 subjects from NHS Ⅰ 1295317 person-years of follow-up Outcome - NSAID and aspirin exposure and risk of IBD	IR - frequent use of NSAID NA - Aspirin	IR - frequent use of NSAID NA - Aspirin
Ananthakrishnan *et al*[48], 2012, United States	72719 subjects from NHS 1492811 person-years of follow-up Outcome - Vitamin D and risk of IBD	DR - Higher predicted level of plasma Vitamin D	NA - Vitamin D level in plasma

[1]European Community Respiratory Health Survey. IR: Increased risk; DR: Decreased risk; NA: No association; CD: Crohn's disease; UC: Ulcerative colitis; RR: Relative risk; IBD: Inflammatory bowel disease; NSAID: Nonsteroidal anti-inflammatory drug; NHS: Nurses Health Study.

insoluble fibre from legumes, whole grains and cereals did not affect the risk. Interestingly the amount and type of fibre had no significant impact on the risk of UC[31]. A case-control study from Canada exploring dietary pattern and risk of CD among subjects up to 20 years of age found a diet containing vegetables, fish, olive oil, fruit, grain and nuts was negatively associated with CD[43]. Another case-control study from Denmark showed an increased risk of both CD and UC in patients on a diet containing low fibre and high sugar[44]. A study from our center showed that regular fish consumption reduces the risk of CD[45]. Tjonneland *et al*[46] performed a nested case-control study, which included participants in the EPIC (European Prospective Investigation into Cancer and Nutrition) study, to assess the link between dietary linoleic acid (source of arachidonic acid whose metabolites encourage inflammation) and UC. Dietary linoleic acid was found to be associated with an increased risk of developing UC and the effect was greater with higher intake[46].

There has been increasing reports of vitamin D deficiency among patients with IBD, especially CD[27]. While this may be a consequence of the disease, vitamin D may also play a role in modulating gut immune function and have an effect on the onset of IBD[47]. A prospective study of 72719 subjects in

Table 3 Environmental factors and onset of inflammatory bowel disease - case control studies

Author	Study setting	Effect on CD	Effect on UC
Ng *et al*[51], 2014, Asia Pacific	CD - 186 UC - 256 Controls - 940 Outcome - environmental risk factors and IBD	DR with breast feeding for > 12 mo, antibiotic use, having dogs, daily tea intake, daily physical activity	DR with breast feeding for > 12 mo, antibiotic use, daily tea and coffee intake, presence of hot water tap, flushing toilet in childhood IR with smoking
Sood *et al*[64], 2014, India	UC- 518 Controls - 188 Outcome - environmental risk factors and UC		IR with owning a pet and stressful events DR with better toilet facilities and having private bed
Chu *et al*[62], 2013, South Africa	CD - 88 UC - 63 Control - 219 Outcome - childhood risk factors and IBD	DR - Helminth infection, shared housing, raw beef consumption IR - Urban dwelling, parental tertiary education	DR - Helminth infection, mixed race, smoking, shared housing, raw beef consumption IR -parental tertiary education
Jakobsen *et al*[114], 2013, Denmark	CD - 59 UC - 56 Controls - 477 Outcome - environmental risk factors and pediatric IBD	IR with bedroom sharing, prior hospitalisation with gastrointestinal infection, family history DR with wholemeal bread consumption	IR with prior hospitalisation with gastrointestinal infection, family history DR with daily vegetable consumption
Hlavaty *et al*[52], 2013, Slovakia	CD - 190 UC - 148 Controls - 355 Outcome - environmental risk factors and IBD	IR with short duration of breast feeding, infrequent childhood sports activity, smoking, infrequent contact with animals in childhood	IR with short duration of breast feeding, infrequent childhood sports activity, smaller family size in childhood
Pugazhendhi *et al*[45], 2012, India	CD - 200 Controls - 200 Outcome - environmental risk factors and CD	IR with safe drinking water DR with regular fish consumption and presence of cattle in house	
Castiglione *et al*[115], 2012, Italy	CD - 468 UC - 527 Controls - 562 Outcome - environmental risk factors and CD	NA with any factors except IR with smoking and appendectomy	NA with any factors except DR with smoking and appendectomy
Hansen *et al*[44], 2011, Denmark	CD - 123 UC - 144 Controls - 267 Outcome - environmental risk factors and IBD	DR with breast feeding, tonsillectomy, IR with pertussis and polio vaccine, measles infection, smoking, low fibre and high sugar	DR with breast feeding, tonsillectomy, appendectomy, smoking IR with pertussis and polio vaccine, measles infection, low fibre and high sugar
López-Serrano *et al*[61], 2010, Spain	124 CD and 235 controls 146 UC and 278 controls Outcome - onset of IBD	IR - Living in urban area, high educational level, social status DR - Childhood respiratory infection and gastroenteritis	IR - Living in urban area, high educational level, social status DR - Childhood respiratory infection and gastroenteritis, appendectomy, current smoking
Gearry *et al*[39], 2010, New Zealand	Population-based case-control study CD - 638, UC - 653, Controls - 600 Outcome - risk factors and IBD	IR with smoking, high social class at birth, Caucasian ethnicity DR with breastfeeding and childhood vegetable garden	IR with high social class at birth, Caucasian ethnicity, migrant DR with smoking, breast feeding and childhood vegetable garden
Joseph *et al*[28], 2009, India	CD - 34 Controls - 34 Outcome - vitamin D and CD	IR - lower levels of Vitamin D	
Amre *et al*[32], 2007, Canada	CD - 130 Controls - 202 Outcome - diet and pediatric CD	DR - higher consumption of vegetables, fruit, fibre, fish, long chain omega three fatty acid	

Baron *et al*[116], 2005, France	CD - 222 UC - 60 Matched controls Outcome - pediatric onset IBD	IR - Family history, Breast feeding, BCG vaccination, history of eczema DR - Regular drinking of tap water	IR - Family history, disease during pregnancy, bedroom sharing DR- Appendectomy

IR: Increased risk; DR: Decreased risk; NA: No association; CD: Crohn's disease; UC: Ulcerative colitis; RR: Relative risk; IBD: Inflammatory bowel disease.

the NHS cohort showed a protective role for a higher predicted vitamin D level against the development of CD[48]. A case-control study by our group in India, which included 34 patients with CD and 34 controls found significantly lower levels of serum 25(OH) vitamin D in patients compared with controls (16.3 ± 10.8 ng/mL *vs* 22.8 ± 11.9 ng/mL, $P < 0.05$)[28]. Disease severity was negatively correlated with vitamin D levels. Lower duration of sunlight exposure with consequent vitamin D deficiency in northern latitudes might be a factor contributing to the north-south gradient of IBD, but this needs to be confirmed. In contrast to the above positive studies, a case-control study from the United States failed to show a significant difference in the vitamin D levels between IBD subjects and controls[49].

The data on breast feeding and onset of IBD are conflicting. The meta-analysis by Barclay *et al*[50] showed that breast feeding reduced the overall risk of early onset IBD, but had no impact on the onset of CD or UC separately. The recently published case-control study from the Asia Pacific region which included subjects from different Asian countries and Australia showed that breast feeding for more than a year reduced the risk of both CD and UC[51]. The case-control studies from Slovakia in 2013 and Denmark in 2011 also suggested that breast feeding may be protective[44,52]. In contrast, data from 146681 subjects in the NHS cohort did not show any association between breast feeding and onset of CD or UC[53]. Interestingly, a study from France showed that breast feeding may increase the risk of CD.

The evidence for benefits of high fibre and low fat diet, longer period of breast feeding and correcting vitamin D deficiency in preventing IBD is not conclusive. However, as some studies show that they may be beneficial and as they also have other health benefits, it may be reasonable to encourage these interventions.

Drugs

Among the drugs available, OCPs, NSAIDs and antibiotics have often been linked to the onset and course of IBD. The meta-analysis by Cornish *et al*[54], which included 14 studies with a total of 75815 subjects showed an increased risk of CD with the use of OCPs and risk increased with longer duration of use. There was also an increased risk of developing UC, but the effect was less than in CD. A large prospective cohort study involving 232452 women (NHS 1 and 2) also showed that oral contraceptive use was associated with CD. The association between OCPs and UC was restricted to women with a history of smoking[55]. Although current evidence suggests that there is a moderate association between exposure to OCPs and the development of CD, no conclusions can be made regarding the use of OCPs and the risk of developing IBD.

A study which explored the risk of IBD with NSAIDs and aspirin intake among 76795 subjects from the NHS Ⅰ cohort found an increased risk of developing CD and UC among those who used NSAIDs for at least 15 d every month. No association between aspirin use and IBD was found[56]. Antibiotics, by affecting gut microbiota, may modulate gut immune response and might be a risk factor for IBD. A nested case-control study from Canada (2234 patients and 22346 controls) which assessed the risk of IBD with antibiotic use (2-5 years pre-diagnosis) found a positive association between antibiotic use and the risk of both CD and UC[57]. In a case-control study involving 587 patients with CD, antibiotic use 2-5 years pre-diagnosis was found more often in patients than controls[58]. Virta *et al*[36], from Finland used the National Register to explore the link between antibiotics and risk of UC and CD. They found an increased risk of pediatric CD, but no added risk for pediatric UC with the use of antibiotics. The study also showed a stronger association of CD in boys and with the use of cephalosporins[36]. Interestingly, a study from Asia Pacific showed a decreased risk of CD and UC with antibiotic usage[51]. Data on the association between IBD and specific antibiotics are limited to the pediatric literature. Penicillins, cephalosporins, and tetracyclines have been linked with the development of CD, but the exact mechanism is not well understood[59,60]. Although studies support a link between antibiotic exposure and the onset of CD, causality has not been firmly established. However, prudent use of antibiotics is good clinical practice. Interpreting the association of drugs with IBD is challenging due to the wide variety of antibiotics, NSAIDs and OCPs available as well as the difficulty in determining the magnitude, type of exposure and duration of use of the drugs.

Hygiene

A number of studies have explored surrogate factors associated with the "hygiene hypothesis" and the risk of IBD. These include urban living, family size, toilet facilities, helminth infestation, drinking water facilities, *etc*[21]. Most were case-control studies, and the results

from some of these studies are summarised in Table 3. While the results are quite variable, some studies showed urban living, high social status, high social class and safe drinking water to be associated with an increased the risk of IBD[39,45,61,62]. A meta-analysis which included 40 studies also showed a positive association between urban living and both CD and UC[63]. Pugazhendhi *et al*[45] from our center showed a positive association between safe drinking water and CD, but not with urban living. Various studies have found that childhood respiratory and gastrointestinal infection, childhood helminth infestation, pet exposure and shared housing reduce the risk[61,62]. In contrast, the Asia Pacific study which showed reduced association of UC with the presence of a hot water tap and flushing toilet in childhood and the recent study from Northern India which showed reduced risk of UC with better toilet facilities and a private bed refute the hygiene hypothesis[51,64]. Evidence for the hygiene hypothesis is conflicting. The reasons may be the inclusion of a wide variety of factors under this category, lack of large prospective cohort studies, presence of confounders or a true lack of association.

Other factors

Several other factors such as appendectomy, infections, air pollution, seasonal variation, physical activity, vaccination, and psychological factors have been implicated in the etiology of IBD. A large Swedish study showed reduced risk of UC in patients whose appendix was removed for inflammatory pathology before the age of 20 years[65]. Other studies have also shown that appendectomy was associated with decreased risk of UC[66,67]. Unlike in UC, some studies including a meta-analysis showed that appendectomy increases the risk of CD up to 5 years after surgery and thereafter the risk falls to that seen in the general population[68,69]. As clinical symptoms of CD may be similar to acute appendicitis, some of the association seen during the initial time period after appendectomy may be related to an erroneous diagnosis. *Helicobacter pylori* (*H. pylori*) infection was shown to have a protective association with IBD in a meta-analysis of 23 studies[70]. It is unclear whether this is a reflection of overcrowding and low socioeconomic status associated with *H. pylori* infection or an effect of this bacterium on gut immunity[71]. On the other hand, a population-based cohort study from Denmark showed that past infection with *Salmonella* and *Campylobacter* was associated with an increased risk of both UC and CD[72]. In the past, *Mycobacterium avium* subspecies paratuberculosis was considered an etiological agent for CD, but recent data does not support this[73,74]. Large cohort studies have also shown a reduced incidence of IBD in subjects with more siblings and those who lived on a farm with livestock in childhood[75,76]. In a study from the United Kingdom, air pollution did not affect the overall onset of IBD; however, subset analysis showed that there was an increased risk of early onset CD with exposure to nitrogen dioxide and early onset UC after exposure to sulphur dioxide[77]. The north-south gradient of IBD observed in some regions may be related to differences in climate. In a Norwegian cohort, Aamodt *et al*[78] studied the influence of temperature, altitude and precipitation to assess the impact of latitude on the incidence of UC. Temperature had a negative association with UC, while the other factors had no significant effect. Others have shown an association between IBD and both childhood vaccines and physical activity[44,52,79]. Thompson and colleagues were the first to suggest that measles vaccination was associated with a 3-fold increased risk of CD and UC compared to unvaccinated controls[80]. Subsequent studies have not confirmed these findings[81,82]. Available data provide no firm evidence to suggest that routine vaccinations have an effect on the development of CD. Psychological factors have also been linked with the onset and course of IBD[83,84]. Data from 152461 subjects in the NHS cohort showed an increased risk of CD with recent and baseline depression, but no significant impact on UC[84]. Although a number of factors have been suggested to influence the onset of IBD, the data are inconsistent and conflicting.

ENVIRONMENTAL FACTORS AND THE COURSE OF IBD

The usual reasons for disease exacerbation in IBD are natural history of the disease, non-compliance with drugs and gastrointestinal infections; environmental factors may also influence the course of disease. Table 4 summarises data from some of the studies evaluating environmental factors and the course of IBD.

Smoking seems to have a definite, detrimental effect on the course of CD. Several studies have shown an increased risk of flares, more active disease, increased hospitalisation rates, increased risk of surgery and post-operative recurrence in patients with CD who are smokers compared with non-smokers[85-87]. Smoking also affects disease behaviour and is associated with a higher risk of penetrating disease and extra-intestinal manifestations[88,89]. There is a strong case for smoking cessation in CD as shown in an interventional study from France where patients who quit smoking had a reduced rate of disease exacerbations compared to smokers[90]. Based on these findings, smoking cessation should be strongly encouraged in CD. A recent meta-analysis of 20 studies on UC showed lower colectomy rates in active smokers[91]. Another population-based cohort study which included 771 patients with UC from seven European countries and Israel found lower relapse rates in current smokers[92]. The reason for the differential effect of smoking on CD and UC is unclear.

Psychological factors have been proposed to have

Table 4 Environmental factors and course of inflammatory bowel disease

Author	Study setting	Effect on CD	Effect on UC
Ott *et al*[89], 2014, Germany	Cohort study CD - 161 UC - 96 Outcome - Smoking and EIM	IR of EIM	NA
Feagins *et al*[101], 2014, United States	Case-control study Active IBD - 166 IBD in remission - 68 Outcome - triggers for flare of IBD	NA with NSAID, antibiotics, stress, smoking, infection and travel in past 3 mo	
Ananthakrishnan *et al*[97], 2013, United States	Multi-institutional cohort study, CD - 5405, UC - 5429 Outcome - psychiatric comorbidity and surgery and hospitalisation in CD and UC	IR of surgery with psychiatric comorbidity	NA of surgery with psychiatric comorbidity
Bernstein *et al*[93], 2010, Canada	Population-based cohort IBD - 704 Outcome - risk factors for flare Follow-up - 1 yr	IR of flare - High perceived stress NA with flare - NSAID, antibiotics, non-enteric infection	
Packer *et al*[110], 2010	Systematic review, 7 studies Outcome - Physical activity and course of IBD	Physical activity significantly increased quality of life and decreased disease activity	
Bitton *et al*[95], 2008, Canada	Cohort study, 101 patients with CD in remission Outcome - biopsychosocial factors and relapse Follow-up - 1 yr	IR with stress/avoidance coping, higher CRP, fistulising disease behaviour, disease confined to the colon	
Takeuchi *et al*[25], 2006, United Kingdom	Case series IBD - 209 Outcome - risk of flare with NSAID	IR of flare with non-selective NSAID	
Sandborn *et al*[100], 2006, United States	RCT - Celecoxib *vs* placebo for 2 wk UC - 222 Outcome - exacerbation during 2 wk		No significant difference between celecoxib (3%) and placebo group (4%)
Persoons *et al*[96], 2005, Belgium	Cohort study CD - 100 Outcome - major depressive disorder and response to infliximab	Major depressive disorder associated with reduced response to infliximab	
Cosnes *et al*[103], 1999, France	Cohort study CD - 331 Outcome - OCP and flare of CD Follow-up -12 to 18 mo	NA between OCP use and disease flare	
Cosnes *et al*[87], 1999, France	Cohort study CD - 622 Outcome - risk factors for flare of CD Follow-up -12 to 18 mo	IR of flare - Current smokers NA with flare - Obesity, dyslipidemia and alcohol consumption	
Boyko *et al*[117], 1998, United States	UC - 209, compared smokers with non-smokers Outcome: Smoking and course of UC		DR of hospitalisation NA with colectomy rates

IR: Increased risk; DR: Decreased risk; NA: No association; CD: Crohn's disease; EIM: Extraintestinal manifestation; IBD: Inflammatory bowel disease; NSAID: Nonsteroidal anti-inflammatory drug; RCT: Randomised controlled trial, CRP: C reactive protein, OCP: Oral contraceptive pill.

a greater role in influencing the course of IBD as compared to their etiological role. A large population-based cohort study from Canada showed an increased risk of flare in IBD patients with high perceived stress at one year follow-up[93]. A couple of other cohort studies, one of which included patients with CD and the other with UC, also showed that stress was associated with increased disease exacerbation[94,95]. A prospective observational study from Belgium showed that major depressive disorder was a risk factor for failure to achieve remission with infliximab and for earlier relapse in patients with active CD[96]. In addition to flares, psychiatric comorbidity may also affect the risk of surgery. A multi-institutional cohort study showed that psychiatric comorbidity increased the risk of surgery in patients with CD, but no association was observed with UC[97]. In contrast, a systematic review which included 12 studies showed a lack of convincing evidence that therapy of depression and anxiety alters the disease course of IBD[98]. Although the evidence for psychological factors influencing the course of IBD is not robust, it may be prudent to treat these patients to improve their quality of life.

Drugs may also influence the course of IBD. Data on NSAIDs as a trigger for disease relapse in IBD is conflicting. Case reports and small series suggest that nonselective NSAIDS trigger disease relapse[99]. In an uncontrolled study, Takeuchi *et al*[25], found an increased risk of flares in IBD patients taking non-selective NSAIDs, but not with selective COX-1 or COX-2 inhibitors. A randomised controlled trial of celecoxib and placebo in UC did not show a significant

difference in relapse rates between the two groups[100]. The Canadian population-based cohort study and a recent study from the United States also showed no impact of NSAIDs on disease flare[93,101]. Although the evidence is weak, the American College of Gastroenterology practice guidelines currently recognize NSAID use, including the use of COX-2 inhibitors, as a potential exacerbating factor for relapse of CD[102]. The role of antibiotics and OCPs in modulating disease activity in IBD is unclear[93,101,103]. A systematic review of 10 RCTs involving 1160 patients showed that antibiotics were more effective than placebo in inducing remission in active CD[104]. Shortcomings of the study were moderate heterogeneity between studies and multiple antibiotics used either alone or in combination. As multiple antibiotics were used in different studies, the data are difficult to interpret, and additional studies are required to address the role of antibiotics in influencing the course of IBD. A systematic review that included 10 studies suggested that there is no risk of disease exacerbation in women with IBD who use oral contraceptives[105].

Dietary factors have been suggested as triggers for disease flares. Data on this subject are limited and confusing as patient surveys show heterogeneity regarding trigger foods[106,107]. Fish oil which has omega-3 fatty acid with anti-inflammatory properties may be beneficial in maintaining remission in IBD. They may be of some utility in managing UC, but have not proven to be a substitute for conventional drugs[108]. A prospective study of 191 *patients with UC, who were followed-up for one year, to determine the effects of dietary* factors on relapse, showed that higher meat and alcohol consumption was associated with an increased risk of relapse[109]. The sulphur content in the food was proposed to be the likely trigger.

Other factors such as air pollution, exposure to ultraviolet light and physical activity have also been linked to the course of IBD. A systematic review of seven studies found physical activity to be associated with increased quality of life and decreased disease activity among patients with IBD[110]. Cucino *et al*[111], found the manual work and farming were associated with decreased mortality in IBD. Low exposure to ultraviolet light has been associated with an increased risk of hospitalisation and surgery among IBD patients[112]. Exposure to pollutants in air was also shown to increase hospitalisation rates[113]. Although the environmental factors have not been as extensively evaluated with respect to their role on the course of IBD compared to their etiological role, there is modest evidence that some of these factors may influence the course of illness.

CONCLUSION

Data suggest that environmental factors play a significant role in the etiology of IBD and probably on the disease course. While the evidence for some factors is strong, many factors require further supportive data. Interventional studies assessing the effects of modifying these risk factors on natural history and patient outcomes are an important unmet need.

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