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REVIEW

Role of environmental factors in the pathogenesis of Crohn's disease: a critical review

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Abstract

Purpose To review role of environmental factors in the pathogenesis of Crohn's disease.

Methods We systematically reviewed trials and systematic reviews using PubMed and Web of science databases. Here, we review the current information on the causative factors and mechanisms of CD, including smoking, exercise, diet, animal protein, breastfeeding, history of childhood infection and vaccination, oral contraceptives, and antibiotics of CD. We also highlight important knowledge gaps that need to be filled in order to advance the field of CD research.

Results Epidemiological studies have indicated the significance of environmental factors in the disease behavior and outcome of Crohn's disease (CD). There are a few recognized environmental factors, such as cigarette smoking, exercise, dietary habits, and breastfeeding, which are associated with the pathogenesis of CD. These factors are hypothesized to change the epithelial barrier function, which disturbs both the innate and adaptive immune systems and the intestinal flora. However, the effect of several risk factors, such as appendectomy and pharmaceutical use, differs across several studies, indicating the need for more rigorous research. Furthermore, few studies have examined effective interventions based on environmental factors that can improve disease outcomes. Recent studies have indicated that the pathogenesis of CD is related to environmental and genetic factors.

Conclusion We review the current information on the causative factors and mechanisms of CD, including smoking, exercise, diet, animal protein, breastfeeding, history of childhood infection and vaccination, oral contraceptives, and antibiotics of CD. However, further studies are needed to understand knowledge gaps in the field of CD.

Keywords Crohn's disease · Environmental factors · Diet · Intestinal microbiota · Intestinal epithelial cells · Immune system

Introduction

Crohn's disease (CD) is a chronic, recurrent, intestinal inflammatory disease which affects the entire gastrointestinal tract and is associated with extraintestinal manifestations. The incidence and prevalence of CD has gradually increased worldwide [1, 2]. In the last 50 years, the morbidity of CD has increased from 6–15/100,000 persons to 50–200/100,000 persons in the West [3]. In North America, the incidence of CD ranges from 3.1 to 14.6/100,000 persons, and the Asia-Pacific Crohn's and Colitis Epidemiology Study(ACCESS) has revealed that the incidence of CD per 100,000 was 0.54 in Asia and 14.00 in Australia. This study also found that the incidence was increasing rapidly, and that it was becoming a socioeconomic burden [4, 5]. The disease onset is during young adulthood, and is characterized by long periods of remission with relapse which require hospitalization and therapeutic interventions [6]. Current etiological evidence suggests that CD may arise from a complex interplay between genetic predisposition, defects in the intestinal immune system, and environmental factors, including smoking, exercise, diet, appendectomy, breastfeeding, medicine, and sanitation [7]. Genetic variants indicate that the metabolism of the intestinal microbiome in individuals with CD differs from the metabolism of healthy individuals [8–10], which may explain why CD patients present with intestinal dysbiosis and have a less diverse gut microbiome than healthy individuals [10].

Some epidemiologic studies have shown that environmental factors play essential roles in the development of CD. First,

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this is evidenced by the consistent increase in the incidence of CD across different geographic regions around the world that have adopted a Westernized lifestyle, including dietary habit changes, better sanitation, and industrialization [11]. Second, studies have shown that the incidence of CD increases in immigrants who migrate from regions with a low prevalence of CD to regions with a high prevalence of CD within one or two generations, which further indicates the role of environmental factors in the pathogenesis of CD [12]. Finally, data from epidemiological surveys and medical research indicate that the external environment is involved in mediating the risk of CD. External factors may affect enteral permeability, in addition to the intestinal immune system, and gut microbiota, and the resulting series of changes in the gut may create a predisposition to CD [13].

Although there are plenty of epidemiological studies, clinicopathological data, genetic experiments, and laboratory evidence indicating the impact of environmental factors on the pathogenesis of CD, the underlying pathogenic mechanism remains unclear. This review provides an overview of the environmental risk factors, including lifestyle factors, childhood influences, appendectomy, and antibiotic use, associated with the incidence and natural history of CD. Here, we analyzed recent available data regarding CD in order to evaluate the known environmental factors related to CD, and summarize their roles in the pathogenesis of CD (Table 1).

Lifestyle factors

Smoking

Cigarette smoking, which is one of the well-established risk factors for CD, increases susceptibility to CD and aggravates its clinical course. Among CD patients, smokers have more clinical relapses, more intestinal complications, higher surgery rates, poorer responses to treatment, and greater requirements for rescue therapy than non-smokers [44–47]. With regard to the influence of gender, one study has shown that the association between CD and smoking is stronger in women [48]. A survey in France that included about 3000 patients with CD showed that those who never smoked were less likely to develop active disease compared with light smokers (33% vs. 38%), and heavy smokers were likely to suffer from more active disease compared with light smokers (41% vs. 38%) [49].

Aside from increasing the risk of CD, smoking also seems to influence the progression of CD. A study involving 3224 patients with CD conducted by the Spanish National Inflammatory Bowel Disease (IBD) database (ENEIDA) revealed that continuous smoking resulted in the progression of CD from a simple "inflammatory" disease (Montreal classification B1) to stricturing or penetrating disease (Montreal classification B2/B3, respectively) [50]. One study examined 506 patients with CD and found that the odds ratio (OR) for progression to B2/B3 disease in smokers with stage B1 disease was 2.02 [51].

Smoking can also cause histological changes in the intestine. Fricker et al. verified that smoking accounted for the changes observed in the intestinal tissue of patients with CD, including an increased number of lymphocytes and an increase in the levels of proinflammatory cytokines TNF-α, IFN-γ, and TGF-β. This study also found that smoking increased the level of vascular endothelial growth factor (VEGF), which was elevated in patients with CD, and induced cellular turnover. Furthermore, mucosal vasculature resulted in gastrointestinal immune dysfunction [52].

People who smoke actively develop CD more easily [53]. Numerous studies have assessed the impact of smoking on the long-term clinical outcomes of CD. One study reported that harmful effects are observed even in light smokers with CD, such that the clinical outcomes may not be positive even if smokers with CD reduce their frequency of smoking [49]. However, Cosnes et al. found that smoking cessation for over 1 year presented with a milder disease course than continuous smoking over a median follow-up of 29 months [54]. Moreover, smoking cessation is related to a decrease in the risk of relapse [55]. Recently, Fricker et al. revealed that smoking cessation could resolve inflammatory and pathological features in the ileum; however, it had no efficacy in the colon [52]. Most studies strongly suggest that patients with CD reduce or discontinue their smoking habit.

Although there is evidence in support of the link between smoking and CD, the mechanisms are still unclear. One probable mechanism may be related to changes in the host gastrointestinal microbiota and immune system caused by smoking. A previous study found that there was a significant decrease in the bacterial diversity of the small intestine in smokers compared with non-smokers [56]. With the recent advances in molecular microbiology, it is now possible to comprehensively assess the enteric microbiota of patients with CD. One study used fluorescence in situ hybridization (FISH) to detect the luminal microbiota in 101 patients with active CD [14]. A multivariate analysis showed that *Bacteroides–Prevotella* species were found more often in smokers compared with non-smokers (38.8% vs. 28.3%) [14]. Another study analyzed inflamed mucosal tissue from 15 patients with active CD and found that the *Faecalibacterium prausnitzii* fraction in smokers was smaller compared with that in non-smokers [57]. *F. prausnitzii* was found to be reduced in patients with CD compared with healthy controls. The smaller *F. prausnitzii* fraction may be associated with the higher CD risk in smokers [2]. Smoking may also modulate humoral and cellular immunity, including innate and adaptive responses [58]. The effects of smoking on the human immune system are complex, which may explain the dichotomous influence of smoking on CD.

Table 1 Studies on environmental factors and its role in CVD

Environmental factors	Mechanism	Increase (+)/decrease (−) the risk of CD	References
Smoking	Increases lymphocytes and proinflammatory cytokines; changes the host gastrointestinal microbiota and immune system	+	Shanahan, E.R., et al. [14–17]
Exercise	Promotes autophagy to protect IECs from cell death and regulate intestinal homeostasis; promotes the release of anti-inflammatory cytokines and decreases the expression of proinflammatory cytokines; relieves pain and decreases the risk of the complications of CD; prevents auto-immune diseases, such as CD, via reducing stress	−	He C, B.M., Moresi V, et al. [18–21]
Diet			Ananthakrishnan, A.N., et al. [22–25]
Vegetable or fruit, tea, and coffee	Dietary fiber is beneficial to the intestinal flora and it can cause inhibition of NF-κβ, transcription of pro-inflammatory mediators, and protects against environmental antigens; antioxidants present in tea and coffee have a protective effect	−	
High sugar, fat, and protein	Irritates the mucosal immune system and suppresses the intestinal microbiota	+	
Animal protein	Polyunsaturated fatty acid correlates with different proinflammatory cytokines; animal protein intake may alter the colonic protein metabolism	+?	Scoville, E.A., et al. [26–28]
Breastfeeding	Optimizes the infants' gut microflora, facilitates mucosal immunity and the intestinal mucosa	−	Jeurink, P.V., et al. [29–36]
History of childhood infection and vaccination	Upregulates the Th2 response and inhibits the expression of proinflammatory cytokines by Th1	−	Basson, A., et al. [37, 38]
Oral contraceptives	Exogenous estrogen decreases the colonic paracellular permeability; estrogens enhance the cell proliferation and immune system; testosterone suppresses the expression of Toll-like receptor 4 on macrophages, which participates in pathogen recognition and innate immunity	+	Braniste, V., et al. [39–42]
Antibiotics	Leads to an imbalance in the normal intestinal microbiota and may have a continuous influence on gastrointestinal immune tolerance and sensitivity to pathogens	+	Shaw, S.Y., J.F. Blanchard, and C.N. Bernstein [43]

Mice passively exposed to smoke show a series of biochemical alterations, such as an increase in epithelial cell apoptosis, dendritic cells, chemokine expression, and T lymphocyte recruitment [15]. Further, it has been shown that nicotine acts on stimulated macrophages and leads to the direct inhibition of TNF-α secretion. Interestingly, TNF-α has been identified to play a role in intestinal epithelial barrier dysfunction [16, 59]. A previous study cultured mononuclear cells from smokers with CD and found that the levels of cytokines secreted were lower in these patients compared with that in non-smokers with CD, which indicates impairment of the mononuclear cell function [16]. Another study examined the change in IL-10 and IL-12 expression in human peripheral blood mononuclear cells (PBMCs) from patients with CD and found that the IL-10/IL-12 ratio was significantly decreased in smokers with CD than that in non-smokers with CD [17]. IL-10 has been confirmed to be a protective factor in CD patients because it facilitates maintenance of intestinal integrity and controls gut inflammation. However, as a proinflammatory cytokine, the level of IL-12 was increased in patients with CD [60, 61]. Moreover, an in vitro study involving cells from smokers with CD exposed to cigarette smoke extract suggested that the sensitivity of the cells to anti-inflammatory or antioxidant factors was significantly impaired [17]. Recently, data from a Denmark cohort found that smoking led to impaired gastrointestinal barrier function and increased permeability of the intestinal epithelium, as well as the lower levels of IGF-1 (insulin-like growth factor 1) [62]. All of these findings imply that smoking is associated with CD via its effects on immune factors.

With regard to the interaction of smoking with genetic factors, a study from the USA revealed that PTPN2 (protein tyrosine phosphatase non-receptor type-2), a CD-associated single-nucleotide polymorphism (SNP), was found in smokers with CD, not in non-smokers with CD [63]. A group of investigators who studied a prospectively recruited cohort showed that smoking was linked to the genetic variants in the glutathione transferase enzymes (GSTP1) and cytochrome CYP2A6/EGLN 2 locus. These variants have been shown to play a role in the risk of developing CD [64]. A subsequent study indicated that smoking could modify interleukin 23 receptor (IL23R), thereby increasing the risk of CD [65].

Exercise

Previous reports have shown that people in white-collar occupations who have a higher social position are more likely to develop CD [66]. Sonnenberg and colleagues discovered that CD was associated with sedentary occupations, such as administrative jobs, sales jobs, and health professions [67]. Recent studies have shown that moderate exercise can reduce the risk of CD. For example, a study by Persson et al. indicated that the relative risk (RR) of CD was inversely related to physical activity. The estimated RR associated with weekly and daily exercise was 0.6 and 0.5, respectively [68]. Further, studies on two large prospective cohorts of females in the USA demonstrated that females who exercised less than 3 metabolic equivalent task (MET) hours per week had a 44% higher risk of developing CD compared with physically active women (> 27 MET h/week) [69].

As suggested by several in vivo studies, exercise may promote autophagy, which is responsible for the prevention of diseases, such as inflammatory disorders, infections, and even cancers [18]. Studies have suggested that autophagy protects intestinal epithelial cells (IECs) from cell death and regulates intestinal homeostasis as well as prevents infection by pathogens. However, dysfunctional autophagy can lead to the pathogenesis of IBD [19]. Coupled with these studies, susceptibility loci, such as NOD2, for CD have been verified by genome-wide association studies (GWAS) to be located within autophagy pathways. Thus, autophagy pathways may be involved in the mechanism by which exercise influences the risk of CD. Recently, it was proposed that exercise-induced contraction of skeletal muscles could promote the release of IL-15 and IL-6, which have been demonstrated to be anti-inflammatory cytokines. Additionally, exercise reduced mesenteric white adipose tissue (mWAT), which is composed of macrophages and T lymphocytes, and decreased the expression of proinflammatory cytokines. Moreover, physical exercise was shown to relieve the pain associated with the complications of CD, such as ankylosing spondylitis, and decrease the risk of osteoporosis [19, 20]. It has also been suggested that exercise prevents autoimmune diseases, such as CD, via reducing stress [21]. Further studies on genes, autophagy, and innate immune pathways will be useful in understanding the relationship between exercise and CD.

Diet

Diet strongly affects the constituents of the intestinal microbiome [70]. Several dietary risk factors are associated with CD, including high sugar, fat, and protein content. Insufficient amounts of vegetables or fruits in the diet and consumption of fast food are also risk factors [71].

The lifestyle of Asian people has become more Westernized in the last 20 years. The main characteristic of this change is that fiber consumption has reduced, and the consumption of processed foods and high-fat foods has increased [72]. Research has indicated that dietary fiber is beneficial to the intestinal flora. Intestinal bacteria metabolize the fiber from fruits into short-chain fatty acids, which inhibit NF-κβ and the transcription of proinflammatory mediators. In addition, the effects of fiber were shown to be mediated through the aryl hydrocarbon receptor (AhR) and play a role in protecting against environmental antigens [22]. It has been demonstrated that animal protein and fat are associated with *Bacteroides*, while sugar was related to *Prevotella*. The compositions of these two intestinal bacteria have been shown to be disrupted in patients with CD [23]. With a Westernized diet, the intestine is continuously exposed to a considerable number of antigens, which may irritate the mucosal immune system, suppress the intestinal microbiota, and influence the progression of CD [71]. Total parenteral nutrition has proven to be an efficacious therapy for CD, as it gives the bowel a chance to rest [24]. Additionally, the antioxidants present in tea and coffee seem to have a protective effect with regard to the development of CD [25].

Animal protein

It is still unclear how protein intake is associated with the development of CD, although several studies have shown such an association. A recent meta-analysis has shown a positive correlation between protein intake and CD [73]. Furthermore, a large prospective cohort study on middle-aged French women (E3N) investigated the association between the composition of pre-illness diet and the risk of CD [74]. The study found that a high intake of animal protein (both fish and meat) and a high risk for CD were closely related (HR, 3.03) [74]. Furthermore, this study also indicated that n-3 polyunsaturated fatty acid increased whereas n-6 decreased in CD patients. These two fatty acids correlated with different proinflammatory cytokines; for example, n-3 directly correlated with IFN-γ and L-5, whereas n-6 correlated with IL-8 and TNF-am[26]. In addition, a recent case-control study in Japan demonstrated that higher oil and animal protein consumption increased the risk of CD [75]. The positive relationship between animal protein and CD can be explained by the inability of the small intestine to absorb heme and certain amino acids of animal proteins. Instead, the heme and amino acids are metabolized by the microflora when they reach the colonic lumen [27]. Based on the elevation of fecal ammonia, fecal volatile sulfur substances, and urinary p-cresol, studies have shown that an increase in animal protein intake may alter the colonic protein metabolism [28]. The colonic microflora can produce metabolic byproducts, and the accumulation of which may explain why high animal protein consumption increases the risk of CD.

Childhood factors

Breastfeeding

CD is associated with the breastfeeding period, according to one multivariate analysis, which showed that being breastfed for less than 6 months was related to the incidence of CD [76]. According to a Danish study, the risk of developing CD was decreased in people who were breastfed for more than 6 months [77]. Similar results were observed in another meta-analysis, which reported that the OR for the protective effect of breastfeeding was 0.67 [78]. Ashwin et al. presented a review with a meta-analysis revealing that the OR for the association between CD and breastfeeding was 0.71 on questionnaires and almost the same on medical record reviews (OR, 0.68). This study also found differences by ethnicity, where the effect of breastfeeding on CD was greater in Asian (OR, 0.31) than Caucasian populations (OR, 0.78) [79].

With regard to the ideal duration of breastfeeding, scientists from different areas have different opinions. An Asia-Pacific region population-based case-control study indicated that being breastfed for more than 50 weeks had a protective effect in Asians (OR, 0.10) against CD [80]. In North America and Europe, leading pediatric societies recommend that for the first 24 weeks of life, the primary form of nutrition should be breast milk [81]. Ashwin et al. found that the function of breastfeeding in reducing the risk of CD should last at least 12 months [79].

It is still unclear how breastfeeding influences disease activity in female patients with CD during the postpartum period. European investigators conducted a study on 154 female patients with CD who gave birth over a 6-year period and found that relapse often occurs in non-breastfeeding women compared with breastfeeding women [82]. A recent North American population-based study discovered that women with CD can breastfeed their infants without increasing the risk of CD worsening (OR of CD flare for breastfeeding women vs. non-breastfeeding women, 0.84) [83]. Another study from the USA clarified that the relationship between breastfeeding and disease activity may more likely be a result of stopping CD treatment [84].

Based on recent studies, breast milk contains components that enhance immune tolerance and bacterial colonization of the intestine in terms of neonates [81]. The benefits of breast milk may include optimization of the infant's gut microflora, facilitation of the mucosal immunity, and intestinal mucosa [85].

Jiménez et al. examined the umbilical cord for pre-birth microbiota and showed that the infant gut may have prenatal colonization [86]. Poroyko and Marques reported that the piglet and human intestinal microbiota could be influenced by diet by showing how breastfed piglets differ from formula-fed ones [87, 88]. The intestinal microbiome of 1-year-old infants matures rapidly and may change dynamically according to the delivery type, hygiene, and diet [88]. It has been demonstrated that the type of feeding (breast and/or formula feeding) can influence the structure and function of the microbiome. Breast milk supplies the infant with varied microbial consortia and plenty of oligosaccharides and prebiotics, which ensures that the gut remains colonized by microbes that are useful for metabolism and the development of the immune system [29]. With regard to the gut microbiota, non-breastfed infants exhibit more diverse colonization and reduced amounts of *Bifidobacterium* and *Lactobacillus* species compared with breastfed infants. Tannock et al. examined the fecal microbiota in stool samples from breastfed babies and found that the most abundant bacterial families were *Bifidobacteriaceae* (61%), *Enterobacteriaceae* (8%), and *Coriobacteriaceae* (6%), and the most abundant families in the stool of formula-fed infants were *Bifidobacteriaceae* (on average about 43%), *Lachnospiraceae* (on average about 17%), and *Erysipelotrichaceae* (on average about 10%) [30]. Formula-fed infants showed greater diversity in their gut microbiota [31]. A recent study showed that *Peptostreptococci*, such as *Clostridioides difficile*, was increased in infants that were not breastfed. *C. difficile* has been linked to gastrointestinal diseases [31, 89, 90]. Human milk has different effects on the intestinal microbiome than formula, and this may partly explain the documented differences in autoimmune disease morbidity between breastfed and formula-fed infants [91].

In terms of its immune benefits, breast milk has been proven to prevent infections, promote intestinal barrier function, and confer protection against inflammation [32]. A previous study demonstrated that breast milk contains lysozyme, lactoferrin, and immunoglobulins, such as secretory IgA (sIgA), which protects babies from infections [33]. It has been verified that sIgA provides the gastrointestinal tract of suckling mammals with their first antigen-specific immune protection [34]. Moreover, early maternal sIgA exposure inhibited the translocation of aerobic bacteria from the intestine into draining lymph nodes in newborns [35]. Early sIgA exposure has long-term benefits for IECs, as it helps maintain a healthy intestinal microbiota and regulate gene expression [35]. Several studies have illustrated that adiponectin, leptin, and epidermal growth factor, as well as insulin-like growth factor, in breast milk play a role in regulating inflammatory responses and maintaining the integrity of intestinal epithelium [36]. Epidemiological studies have also demonstrated that early breast milk exposure has a significant protective effect with regard to the development of CD [92].

History of childhood infection and vaccination

Non-invasive markers are useful for detecting disease activity in children with CD. Anti-*Saccharomyces cerevisiae* antibody (ASCA) is one such serological marker that has been highly

useful in diagnosing CD. The sensitivity and specificity of this antibody are 40–70% and 82–89%, respectively [93]. In 2015, a study analyzed simultaneous repeated measures of ASCA IgA and IgG titers and pediatric CD activity index (PCDAI) in 57 children with CD in order to evaluate how disease activity and quantitative serum ASCA were related. In a univariate linear regression model, both the ASCA IgA and IgG titers were shown to have an obvious relationship with PCDAI [94]. This study also found that infrequent contact with animals increased the risk of CD in children [94]. Another study showed that frequent contact with animals in early life was a protective factor for CD in Germany (OR, 0.5), which was consistent with a similar study in Canada (OR, 0.66) [76]. Childhood exposure to animal-associated microorganisms and lower vaccination rates seem to modulate the immune system and protect the body from CD.

With regard to vaccination during childhood, the relationship between Bacillus Calmette–Guerin (BCG) vaccination, a vaccine for tuberculosis disease, and increasing CD risk is compelling [95]. In addition, in a retrospective study from Croatia, investigators studied the incidence of measles virus infection and vaccination, both of which are traditionally considered risk factors for CD [96]. A cohort of 1560 unselected IBD patients from 31 countries revealed that Western European CD patients had fewer vaccinations and suffered from more infections in childhood than Eastern European patients [97]. A case-control study revealed physician-diagnosed infections in early life played a role in the increase of CD [98]. Thus, the increasing incidence of CD in Eastern Europe may also result from more vaccinations and fewer infections during childhood. A study conducted in the Asia-Pacific region found that having dogs as pets at an early age significantly decreased the risk of CD [80]. Another study found that having cats before 5 years of age protected children from development of CD later in life [99]. A South African research study demonstrated that exposure to various microorganisms during childhood decreased the risk of CD. The mechanism could be that a helminth infection, such as *Acinetobacter lwoffii* and *Lactococcus lactis*, upregulates a Th2 response and inhibits the expression of proinflammatory cytokines by Th1-associated immune-mediated diseases, such as CD [37, 38].

Medicine

Oral contraceptives

Endometriosis is associated with CD, and the risk of CD is high even in patients who were diagnosed with endometriosis more than 20 years ago [100]. This indicates that oral contraceptives used to treat endometriosis may influence the risk of CD [100]. Females with CD are commonly found to have cyclical IBD symptoms, such as abdominal pain, fever, and diarrhea, that correlate with their menstrual cycle [101]. In two large prospective cohorts studied in the USA, the multivariate-adjusted HR of CD for women who currently used contraceptives was 2.82, and that for non-users and past users was 1.39 [102]. This cohort study also found that the risk of CD was enhanced in past and current users of oral contraceptives compared with non-users [102]. In a meta-analysis of 14 studies, women who were using oral contraceptives were found to have a pooled RR of 1.51 for CD. The pooled relative risk was 1.46 after adjusting for smoking, and it increased proportionately with the length of exposure to oral contraception [103]. Furthermore, a Swedish research study showed that oral contraceptives increased the risk of surgery in CD patients and the risk of steroid prescription could be enhanced by contraceptives. This research also found a combination of oral contraceptives had a much more significant effect on the risk of surgery as compared with other types of contraceptives [104]. Several studies have identified that oral contraceptives are linked to CD through different ways. First, exogenous estrogen decreased the colonic paracellular permeability and enhanced the proinflammatory response [39, 40]. Second, estrogen plays a role in enhancing cell proliferation and the immune system, which could regulate the disease progression [41]. Third, it has been shown that the level of testosterone is affected by oral contraceptives, and some studies have demonstrated that testosterone might be linked to a lower risk of CD plausibly via suppressing the expression of Toll-like receptor 4 on macrophages which participates in pathogen recognition and innate immunity [42, 105]. However, other influential factors, such as genetic factors, were not considered in this study.

Antibiotics

It is a widely accepted hypothesis that the inflammation triggered by bacterial community alterations in the intestine, by either a growth in the population of pathogenic bacteria or a reduction in the protective bacteria population, is responsible for the pathogenesis of CD [106]. Consistent with this hypothesis, studies have indicated correlations between infections of the gut and the onset of CD [107, 108]. Compared with healthy controls, the diversity of the gut microbiota (specifically, anaerobic bacteria) in patients with CD is reduced, but the causal relationship is unclear [109]. Another study showed that there were alterations in the gut microbiota of patients with CD, with a decrease in *Actinobacteria*, and some families of *Firmicutes* and an increase in *Bacteroidetes*, *Enterococcaceae*, and *Proteobacteria* [110]. Furthermore, several observational studies have demonstrated that antibiotic use is related to a subsequent diagnosis of CD [111, 112]. Some studies have also demonstrated that the risk of CD is associated with previous or cumulative antibiotic use [43,

111]. A meta-analysis of 11 observational studies (8 case-controls and 3 cohorts) found that antibiotic exposure was obviously correlated with the odds of a primary CD diagnosis (OR, 1.74) and that the risk was significantly increased in pediatric CD patients (OR, 2.75) [113]. A previous study reported that 71% of patients with CD were administered antibiotics before their diagnosis compared with only 58% of controls. Moreover, those who had ≥ 1 and ≥ 2 antibiotic dispensations before diagnosis showed 1.27- and 1.48-fold increased risks for CD, respectively, compared with patients who never used antibiotics [114]. A study from Canada showed that metronidazole had a 3-fold increased risk for IBD, and the adjusted odds ratios (AORs) of all types of antibiotics, except clindamycin, were 1.12–2.86 [114, 115]. Furthermore, tetracycline was shown to be linked to the development of CD [116]. Abuse of antibiotics has led to an imbalance in the normal intestinal microbiota and may have a continuous influence on the gastrointestinal immune tolerance and sensitivity to pathogens [43]. This influence could depend on the type, duration, and time point of antibiotic use. Moreover, if specific gut colonization with certain microorganisms can protect against CD, antibiotic exposure could lead to the loss of these protective microorganisms [117]. However, another systematic review summarized 23 studies on the postoperative recurrence of CD and indicated that the risk of recurrence could be reduced by nitroimidazole antibiotics, immunosuppressive therapy, azathioprine/6-MP or infliximab, and mesalamine [118].

Conclusion

The increasing incidence of CD also indicates gene–environment interactions, although further studies are needed to confirm these interactions. Not all individuals are uniformly susceptible to the external environment. It is conceivable that the relationship between environmental triggers and CD may be affected by genetic polymorphisms, which could influence biological processes by altering the activity of the enzymes involved. Interestingly, CD has been found to occur predominantly in males (male:female ratio, 1.86) [119]. Furthermore, the susceptibility of patients with CD to smoking, ethnicity, and gender exhibits remarkable heterogeneity [120]. The potential role of gene–environment interactions in CD pathogenesis may provide insights regarding the exact mechanisms underlying the influence of the external environment. Continued examination of gene–environment interactions may expand our understanding of unexplained variance in the risk of CD.

This review has confirmed several associations between CD and environmental factors, such as smoking, exercise, medicines, and diet. However, a major limitation of this review is that only a few studies have observed how these environmental factors affect the natural history of CD, and even fewer have studied whether the outcomes of patients can be improved by interventions that focus on these factors. The findings of this review indicate that future studies should focus on providing recommendations for lifestyle and behavioral modifications, which when combined with therapy, will ensure the maintenance of remission, prevention of complications, and improvement of outcomes. There are still some knowledge gaps in identifying the role of environmental factors in CD which have beneficial effects on patients and healthcare professionals, and these require in-depth research in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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