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Review Article

The epidemiology and risk factors of inflammatory bowel disease

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Abstract: This review aimed to summarize the epidemiology (incidence, prevalence and morality) and risk factors of inflammatory bowel disease (IBD). IBD is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract and includes Crohn's Disease (CD) and ulcerative colitis (UC). IBD has increasing incidence and prevalence in most of countries and becomes a global emerging disease. A westernized lifestyle or habits and some environmental factors have been found to contribute to the pathogenesis of IBD. The relevant risk factors include Smoking, hygiene hypothesis, microorganisms, appendectomy, medication, nutrition, and stress have all been found to be associated with the modality of IBD, but results are inconsistent on this issue in available studies. Therefore, more studies are required to identify and understand the environmental determinants of IBD.

Keywords: Incidence, prevalence, morality, inflammatory bowel disease, environmental factors

Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract and includes ulcerative colitis (UC) and Crohn's disease (CD), which shows differences in the pathology and clinical characteristics. Currently, the etiology and pathogenesis of IBD are still poorly understood. It is widely accepted that the pathogenesis of IBD has involvement of genetic factors and environmental factors [1]. More than 100 genes have been identified by genome-wide association scan to increase the susceptibility to IBD [2]. However, genetic susceptibility can not completely explain the high incidence and prevalence of IBD observed in the developed and developing countries [3].

IBD was first recognized in European countries during the industrial revolution. The incidence and prevalence of IBD significantly increase in the 20th century [4]. In the review, we summarized the epidemiology of IBD and evaluated the relationship between environmental exposures and IBD.

Epidemiology of IBD

Incidence/prevalence of IBD in adolescents

Around 25 percent of patients with IBD are diagnosed in the first 2 decades of their life [5, 6]. Of them, most are diagnosed in childhood (about 13-18 years) and its incidence is increasing in the early second decade of life [7]. Moreover, studies from a variety of countries demonstrate that the incidence of IBD in increasing, especially in adolescence [4, 8]. Currently, the highest annual incidence of IBD in Europe was 24.3 per 100,000 person-years for UC, and 12.7 per 100,000 person-years for CD, that in North America was 19.2 per 100,000 person-years for UC and 20.2 per 100,000 person-years for CD and that in Asia and Middle East was 6.3 per 100,000 person-years for UC and 5.0 per 100,000 person-years for CD. The highest prevalence for UC was 505 per 100,000 persons in Europe, and 249 per 100,000 persons in North America. The annual prevalence of CD was 322 per 100,000 persons in Europe, and 319 per 100,000 persons in North America. A time-trend analysis showed that 75% of stud-

ies on CD and 60% of studies on UC displayed an increasing incidence with statistical significance ($P < 0.05$) [9].

Molodecky et al [4, 10] conducted a systematic review in which the incidence and prevalence of UC and CD were compared across different regions and over time. Their results showed the incidence and prevalence of IBD were the highest in western countries, specifically in Northern Europe and Canada. However, in Nova Scotia, a city with the highest incidence of IBD in Canada, the incidence and prevalence of IBD are decreasing [11]. De Wals calculated the incidence of IBD from 1996 to 2009, and their results revealed that the annual age standardized incidence declined from 27.4/100,000 population to 17.7/100,000 population for CD and from 21.4/100,000 population to 16.7/100,000 for UC [11]. The reduced incidence of IBD may be explained by the environmental factors. Folic acid fortification has been found to be associated with a dramatic reduction in the incidence of neural-tube defects, and the greatest reduction is reported in Canada [11].

The incidence and prevalence of IBD in Africa are also increasing [12-19]. Wright et al investigated the incidence of IBD in the GI Clinic of Groote Schuur Hospital of Cape Town, a city of South Africa (SA), from 1975 to 1980. Results showed the incidence in different races was 1.2, 1.6 and 2.1 per 100,000 person-years during 1975-1980, and 0.4, 1.3 and 2.4 per 100,000 person-years during 1970-1974, respectively, showing the significant reduction in its incidence in SA ($P < 0.05$). Despite the incidence of IBD shows an increased trend in the Africa [12, 15-18], data are insufficient for the calculation of overall incidence of IBD in the entire African population.

Increasing incidence and prevalence of IBD across Asia-pacific parts was observed in a 1-year period (2011-2012) [20]. Siew et al showed the annual overall incidence was 1.37 per 100,000 individuals in Asia (95% confidence interval [CI]: 1.25-1.51; 0.54 for CD, 0.76 for UC, and 0.07 for IBD-undetermined) and 23.67 per 100,000 individuals in Australia (95% CI: 18.46-29.85; 14.00 for CD, 7.33 for UC, and 2.33 for IBD-undetermined). In Asia, the highest incidence was found in China (3.44/100,000). The ratio of UC to CD was 0.5 in Australia and 2.0 in Asia. Complicated CD (stricturing, perianal or penetrating) was more common in Asia than in Australia ($P = 0.001$), but the familial transmissibility of IBD was less common in Asia ($P < 0.001$).

The increased incidence of IBD in developing countries may be ascribed to the lack of medical resource, especially in some severely ill patients. The limited availability of treatments in these countries is still lacking, but how this affects the clinical accessibility is still unknown.

Pediatric IBD

The incidence of IBD in children is increasing worldwide [21, 22]. North America and Europe have the highest incidence of pediatric IBD. In developing countries, its incidence is rising due to the popularization of westernized lifestyle. IBD in adolescents and children accounts for approximately 30% of total IBD [23-26]. Kugathasan et al reported the incidence of IBD in a city of the United States was 5 per 100,000 to 11 per 100,000 children (4.56 per 100,000 for CD and 2.14 per 100,000 for UC), indicating that CD predominates over UC in children. Especially, the incidence of CD rises dramatically, while a steady increase is found in the incidence of pediatric UC [27].

A Canadian study [8] revealed that the incidence of pediatric IBD increased from 9.5/100,000 in 1994 to 11.4/100,000 in 2005. The highest increase was found in young children, with the incidence increasing by 5% annually in children younger than 4 years and by 7.6% in children aged 6-9 years [8]. In Scotland, a study conducted by Herderson et al [28] reported the incidence of IBD was 7.82 per 100,000 person per years in subjects younger than 16 years. In northern Stockholm (1990-2001), Hildebrand et al [29] found in the incidence of pediatric IBD changed over time, and a significant increase was observed in the overall incidence of pediatric IBD (7.4 per 100,000 person per year). Perminow et al [30] investigated the incidence of IBD in adolescents by comparing prospective data with retrospective data (1993-2004) in a Norwegian population. Their results showed the overall incidence of pediatric IBD did not alter over time, but a reduced trend was found in UC and an increased trend in CD. A study from the Sydney Children's Hospital, Randwick (SCHR) catchment area

showed the incidence of IBD in 2006 for the Middle Eastern pediatrics (0-16 years) was higher (33.1 per 100000 children per year) as compared to control group (4.3 per 100000 children per year). However, the prevalence of IBD in the Middle Eastern pediatrics was significantly higher (165.4 per 100000 children) as compared to control group (28.7 per 100000 children) [31].

Regional variation in the incidence of pediatric IBD provides an additional support for hypothesis that environmental risk factors may influence the occurrence of IBD in adolescents and children.

Migration IBD

Studies on the migrant populations investigate the characteristics of IBD patients in their original countries, and then follow up these patients by several generations in the new areas to evaluate the relationship between environmental risk factors and IBD. It has been confirmed that studies on the epidemiology of IBD in migrant populations are helpful to elucidate the etiology of IBD [32].

UK over two study periods: 1972-1980 and 1981-1989. Probert *et al* [33] found that the incidence of UC in the first and second-generation migrant Indians was comparable to that in native UK population, while higher than that in India, but the incidence of CD was much lower [34]. In Leicestershire, a prospective, hospital-based study showed a higher UC incidence in immigrants of the first and second generation in South Asians and Europeans (17.2 per 10^5 and 7.0 per 10^5, respectively). Crucially, second generation South Asians suffered more extensive colitis than the first generation immigrants. It was similar to that in the Europeans [35]. Subsequent studies from Sweden and UK also revealed an increasing risk for IBD in the second generation immigrants, but the first-generation immigrants had a lower risk as compared to original inhabitants [36]. Pinsk et al indicated that the incidence of pediatric IBD among immigrant South Asians in Canada was higher than in the native population [37]. In a largest study exploring the impact of immigration on the risk for IBD in Canada, Benchimol *et al* [38] found a lower risk for IBD in immigrants, especially those from East Asia, than in the general population. Older age groups at immigration had a greater reduction in the risk for IBD, meanwhile, the decreased risk continued in children from Central Asia, East Asia and Latin America but not from South Asia, Middle East, Western Europe and Africa.

A population-based cohort study by Eric et al showed that the incidence of IBD in immigrants from South Asia was lower than in non-immigrants (IRR 0.32, 95% CI 0.22-0.49), as did the other immigrants of regions (IRR 0.29, 95% CI 0.20-0.42). The adult-onset (1999-2008) IBD and pediatric-onset (1994-2008) showed lower incidence in South Asian immigrants than in non-immigrants. Early-life environmental exposures may trigger a genetic predisposition to the development and progression of IBD in South Asian immigrants and their Canada-born children [39].

Mortality of IBD

An overview of mortality risk among IBD patients has been captured [40, 41]. Duricova et al conducted a meta-analysis of population-based studies on overall mortality of CD (1965-2008). Their results showed the overall risk for death in CD patients was dramatically higher than in control groups, and the pooled standardized mortality was nearly 1.39 [40]. Meanwhile, the overall mortality in UC patients was comparable to that of controls, and the overall pooled standardized mortality estimated was 1.1 [41]. The discrepancy in the mortality of IBD is still unclear, and smoking may play a vital role because smoking is more common among patients with CD.

Treatments for IBD are changing, and their influence on the prognosis of IBD is still unclear. A Danish cohort study on the mortality of IBD patients was conducted by Jess et al [42] from 1982 to 2010 (36,080 UC patients and 15,361 CD patients). Their results showed that, in the first year after the diagnosis of IBD, the mortality of IBD patients increased dramatically; intermediate-term (1990-2000) and long-term (1990-2010) mortalities increased by 10% for UC and 50% for CD. However, the mortality of UC decreased over time during 1982-2010. Recently, a meta-analysis [43] of all-cause mortality SMRs was reported. The all-cause mortality summary SMR was 1.19 (95% CI, 1.06-1.35) for UC patients and 1.38 (95% CI, 1.23-1.55) for CD patients, which were consistent with previous findings.

Evidence on the cause-specific mortality of IBD is conflicting. Duricova et al reported the cause-specific mortality of CD between 1965 and 2008, the risk for death due to cancers dramatically increased (SMR 1.50, 95% CI: 1.18-1.92), which was similar to that due to chronic obstructive pulmonary disease (SMR 2.55, 95% CI: 1.19-5.47), pulmonary cancer (SMR 2.72, 95% CI: 1.35-5.45), genitourinary diseases (SMR 3.28, 95% CI: 1.69-6.35) and gastrointestinal diseases (SMR 6.76, 95% CI: 4.37-10.45). However, the risk for death due to colorectal cancer became stable between 1965 and 2008 [40]. Jess et al found, in UC patients, the mortality related to nonalcoholic liver diseases, gastrointestinal diseases, respiratory diseases and pulmonary embolism increased, but the pulmonary cancer mortality decreased [41]. Jess et al also revealed that the mortality of UC reduced largely ascribed to the decreased mortality from colorectal cancer and gastrointestinal disorders (1982-2010) [42]. However, a conflicting conclusion was made by Bewtra et al. He found the mortality from pulmonary disease, colorectal cancer, and nonalcoholic liver disease in IBD patients increased, but the cardiovascular disease mortality declined [43].

A recent report conducted by Ananthakrishnan et al [44] investigated the impact of primary sclerosing cholangitis (PSC) on the mortality of IBD. In a multicenter cohort study, a total of 10028 patients with IBD were recruited, 2% of them were diagnosed with IBD-PSC and the mortality in these patients was much higher than in patients with IBD alone (95% CI, 2.30-5.36) [44]. This might be related to the excess risk for digestive tract cancer, pancreatic disease, colorectal cancer and cholangiocarcinoma.

Although both CD and UC share causes of death, it is likely that there are differences in cause-specific mortality between them. Kassam et al showed that colorectal cancer-associated mortality of IBD remained controversial. The mortality of CD is likely to be attributable to the gastrointestinal diseases, respiratory diseases and infection, and that of UC to the infection and gastrointestinal diseases. The incidence of clostridium difficile infection as a cause of death in IBD is increasing. Both UC and CD patients have an increased risk for thromboembolic disease. The treatment-associated mortality should be assessed continuously due to the advancements in the medical and surgical interventions [45].

Smoking has been known as a factor influencing the incidence of IBD and has an association with the increased mortality from pulmonary diseases, cardiovascular disease, and malignancies. Previous findings on the mortality of IBD have been challenged. Although traditional causes of death such as digestion tract carcinoma are still the main causes of UC or CD-associated mortality, emerging threats are likely to have a larger impact on the IBD patients.

Smoking

Smoking is known to affect IBD. Harries *et al* first described the association between smoking and UC [46]. They identified a decreased frequency of smoking in UC patients as compared to healthy controls. A meta-analysis conducted by Mahid et al demonstrated that smoking increased the risk for CD by two folds [47]. A recent study revealed the proportion of CD patients with smoking is strikingly high with persistent increase as compared to the general population in Swiss, particularly in females [48]. Of interest, smoking is a protective factor for UC but a risk factor for CD [49]. For CD patients, smoking cessation is a crucial therapeutic strategy for IBD [50]. On the contrary, smoking appears to decrease the risk for UC, with a majority of UC patients being non-smokers or exsmokers [51]. A prospective cohort study conducted by Higuchi et al revealed that, after smoking cessation, the risk for UC still increased within 2-5 years and remained rising for nearly 20 years [52]. However, not all cohorts draw a consistent conclusion on the effect of smoking on UC and CD. Cosnes et al found current smoking had an association with later age at onset of UC and decreased the risk of need for immunosuppression among men, not women. On the contrary, smoking has association with younger age at onset and increases the frequent need for immunosuppression in CD in women, not men [53].

Convincing reasons for the divergent influence of smoking on UC and CD have not been identified, but several mechanisms have been presented for the explanation of relationship between smoking and IBD [54, 55]. Smoking

may affect the development of IBD by acting on nicotinic acetylcholine receptors, which are present in bowel mucosal epithelial cells [56], and on intracellular calcium (Ca^{2+}) in T cells [57]. For UC patients, clinical trials on nicotine replacement therapy show inconsistent findings. Thus, other factors of smoking may impact the development of IBD [58]. There is evidence showing that chemicals in cigarette smoke may modulate the cytokines [59], regulate the immunity of cells [60], modify the mucus renewing of the intestine [61], alter the blood flow, and promote the progression of microvascular thrombi [62]. Smoking also has an important impact on the microbiota. Smoking cessation has been found to be associated with a vital change in the microbiome, and the immune response may explain the impact of smoking cessation on the UC [63, 64].

Although smoking plays a vital role in the pathogenesis of IBD, the incidence of CD is still high in some countries (such as Canada) with a low prevalence of smoking [65, 66]. On the contrary, a low incidence of CD occurs in South Korea where the smoking prevalence is significantly higher than in Canada [67]. Thus, the association between smoking and IBD is multifactorial.

Hygiene hypothesis

The hygiene hypothesis has been proposed that reduced exposure to enteric bacteria and improved sanitation during early life may give rise to inappropriate immunological responses in later life [68]. A majority of factors, such as sibship, family size, urban upbringing, birth order, and pet exposure, have been explored as markers of environmental exposures in childhood [69-72].

Living with more siblings has more exposure to enteric organisms in early life, which may decrease the risk for IBD in later life [68, 73]. Bernstein et al demonstrated that CD patients are much more likely to have fewer siblings and live in smaller house-holds. However, this is not improved in UC [72]. Baron et al found that IBD patients were raised with a greater number of older siblings as compared to controls [73] and that the number of older siblings was associated with an increased risk for UC [74]. Lower birth rank increases the risk for both UC and CD [75].

Differences in the environmental exposures and lifestyles between urban and rural areas may explain the higher incidence of IBD in urban [76]. Carpio et al showed UC was more frequently found in inland municipalities and CD in urban and coastal areas. The place of residence may also influence the clinical course and phenotype of IBD as patients living on the coast more likely develop extensive UC, ileocolonic CD, and need immunosuppressive therapy [77]. However, a population-based case-control study conducted by Malekzadeh et al [78] showed no association between urban environment and IBD. However, a case-control study conducted by Declercq et al in France revealed that CD was more frequently found in rural and peri-urban areas [79].

Additionally, Amre et al found that patients with adult-onset CD were less likely to live with cats before age 5 [71]. In addition, there is evidence showing that exposure to cats in early life is associated with the pediatric-onset CD [72].

Microorganisms

Several microorganisms have been confirmed as possible causes of IBD. Some candidate organisms have been proved to be associated with the pathogenesis of IBD.

The possibility of an infectious origin in IBD has been postulated since Dalziel et al for the first time described CD in 1913. He compared CD with Johne's disease in cattle, caused by *Mycobacterium Avium Paratuberculosis* (MAP) [3]. Feller [80] reported a positive association between MAP (detected by ELISA or polymerase chain reaction) and CD after a meta-analysis of case-control studies. However, the relationship between MAP and CD is still not conclusive.

In recent years, increasing studies focus on the role of a specific type of *E. coli*, adherent-invasive *E. coli* [*Adherent-invasive escherichia coli* (AIEC)]. The first study on the role of *Escherichia coli* in IBD reported that mirorganisms isolated from CD patients had more adherent properties to human cells as compared to those from control patients, and previously unrecognized invasive *E. coli* were present in Crohn's mucous tissues [80-82]. Higher *E. coli* antigens and *E. coli* antibody titers have been found in the blood or resected specimens of CD patients [83, 84]. Glasser et al [85] found that AIEC was

able to survive and replicate in macrophages, without inducing host cells response and stimulating the infected cells to release tumor necrosis factor (TNF)-α. Recently, AIEC infection was proven to up-regulate microRNAs to reduce the expression of proteins required for the autophagy and autophagy response in the intestinal epithelial cells. In ileal samples from CD patients, these microRNAs are augmented, but ATG5 and ATG16L1 expressions diminish [86].

Nazareth et al evaluated the prevalence of MAP and *E. coli* (EC) DNA in the peripheral blood of 202 patients with IBD. Their results showed patients with active CD showed the highest MAP DNA prevalence among IBD patients (68%), and the EC DNA prevalence was 80%. In addition, co-infection of MAP and AIEC was common and persistent in CD patients. Nevertheless, facilitative mechanisms between a susceptible host and these two potential human pathogens may allow their implication in the pathogenesis of CD [87].

Several studies have postulated that *Helicobacter pylori* (HP) infection has a protective role against chronic inflammatory diseases, including IBD. Luther et al and Wu et al found that HP infection decreased the risk for IBD [88, 89]. HP infection protects against the development of IBD through increasing the expression of *FOXP3* a protein involved in the T-regulatory cell function [88].

Pathogenic bacteria [89], such as Campylobacter, Salmonella, and other bacteria in the intestine have been implicated in the pathogenesis of IBD. Colonization of parasitic worms, such as helminths, also has an association with a reduced prevalence of IBD.

The role of different viruses in the IBD pathogenesis is still not completely understood. However, the role of measles virus has been explored in the pathogenesis of IBD [69]. Other viruses, such as Mumps (parotiditis) [90], Citomegalovirus [91], Virus de Epstein-Barr (VEB) [92], are also found to be associated with IBD.

Appendectomy

Appendectomy demonstrates a divergent influence on IBD. Kaplan et al found that appendectomy increased the risk for the development of CD [93]. However, the risk for CD decreased, while patients were operated before 10 years of age [94]. The relationship between appendectomy and CD is still not conclusive. Studies reveal a later diagnosis of CD for those who experienced an appendectomy previously [95, 96]. The reason for appendectomy is likely to be a more important factor determining the outcome of IBD. Andersson et al found that appendectomy due to perforating appendicitis may increase the risk for subsequent intestinal resection, while appendectomy due to other reasons reduced the risk for CD [94].

On the contrary, appendicitis has been demonstrated to protect against the UC development in a majority of meta-analyses, especially among children undergoing appendicitis before 10 years of age [97-99]. Frequency of appendectomy was found to be the lowest in UC patients, suggesting that appendectomy decreases the risk for UC, which was consistent with previous findings [100]. The reason why appendicitis protects against the development of UC is still unknown and the appendix may play a physiological role in regulating the immunological response to the intestinal microflora [101].

Medication

Medications have an association with IBD including non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, antibiotics and others. Disruption of the intestinal barrier by agents (such as NSAIDs) or alteration of commensal flora by agents (such as antibiotic) has been found to be associated with the increased risk for IBD. A case-control study conducted by Felder et al found a positive association between NSAIDs and IBD [102]. Conventional NSAIDs may cause clinical relapse in about 20% of patients with quiescent IBD, which may attribute to the dual inhibition of the cyclo-oxygenase (COX). Several COX-2-selective NSAIDs appear to be safe [103], but the non-selective inhibition of COX might be harmful because it may reduce the prostaglandin [104]. Reduced prostaglandin has been found in IBD patients [104], which may regulate the immune function, especially through the induction of interleukin (IL)-10, one of anti-inflammatory cytokines, and the inhibition of TNF [104].

Meanwhile, the use of oral contraceptives (OCPs) has been found to have a positive association with CD and UC [105]. Timner et al [106] found that, in women who continued to take OCPs, the risk for the development of CD relapse increased by three folds; this influence was amplified in women who took OCPs and smoked at the same time. The mechanism underlying the association between OCPs and increased risk for IBD is still unclear.

Several studies have demonstrated that the use of antibiotics is associated with the IBD pathogenesis [107]. However, this association is difficult to determine because antibiotics may be prescribed in undiagnosed IBD patients in order to treat the symptoms of IBD which are misdiagnosed as a gastrointestinal infection [108]. Although the reason for the association between use of antibiotics and IBD is unknown, Hilderbrand et al. found that exposure to antibiotics in childhood influenced the development of IBD by interfering with the normal development of tolerance to enteric bacteria [107].

Nutrition

The association between nutrition and IBD has been extensively studied. Dietary fat has been found to play a role in the IBD pathogenesis [109, 110]. Patients with western lifestyle, such as intake of more fast food, higher sugar diet, and lower fiber diet, exhibit a higher incidence of IBD. [111] Amre et al [112] showed that a greater consumption of total fats and saturated and monounsaturated fats was associated with the increased risk for CD in Canadians, and similar relationship has been demonstrated between UC and polyunsaturated and monounsaturated fat consumption [113]. Low consumption of n-3 polyunsaturated fatty acid (PUFA) and high consumption of n-6 PUFA are associated with an increased risk for both CD and UC. Saturated and unsaturated fats might play an important role in the inflammatory response by modulating the gut microbiome and Toll-like receptors in macrophages [114, 115].

High intake of dietary fibers, particularly soluble fibers (such as fruits and vegetables) has been found to protect against CD and UC [113, 116]. A prospective cohort study conducted by Annathakrishan et al found that high and long-term intake of dietary fiber might have a 40% reduction in the risk for CD, particularly intake of fibers from fruits and vegetables [117] A recent meta-analysis also identified that consumption of fruits and vegetables had a negative association with the risk for IBD [118]. This may be explained as that soluble fibers are metabolized by the intestinal microbiota into short-chain fatty acids that are able to inhibit the transcription of pro-inflammatory mediators [119].

Emerging evidence shows that vitamin D may also take part in the occurrence of IBD [120-122]. Vitamin D deficiency is common in newly diagnosed IBD patients and much more common in IBD patients as compared to healthy controls [123, 124]. Knockout of vitamin D receptor has been shown to increase the risk for colitis [123]. Vitamin D might be protective against IBD.

Stress

Stress may also have an important role in the pathogenesis of IBD. It has been proposed that stress may initiate or reactivate the gastrointestinal inflammation leading to the deterioration of clinical symptoms of IBD [125, 126]. Neural pathways from the hypothalamus to the sympathetic systems and parasympathetic nervous systems are activated by stress. Meanwhile, stress is associated with the enteric nervous system which controls the endocrine and the gastrointestinal tract motility [127, 128]. Animal studies, observational studies and epidemiological evidence in IBD demonstrate that stress may aggravate the symptoms of IBD and has an association with the exacerbations of CD and UC [129-131]. Bitton et al found that CD patients with poor coping strategies and perceived stress tended to undergo a relapse of IBD early [129]. However, a recent study conducted by Heikkila et al suggested that job strain was less likely to have an association with the development of IBD. This findins suggest IBD patients may not concern the job strain [132].

Conclusion

IBD is a chronic, relapsing and remitting diseases and its etiology is still unclear. The incidence of IBD worldwide differs between regions and at distinct times. Although the incidence of IBD has increased in the developed and developing

countries since the 19th century, it begins to decline in some regions. The high incidence and prevalence of IBD have been attributed to the westernized lifestyle. Meanwhile, studies on migrant population reveal that immigrant settlers from the low prevalence regions to the high prevalence regions have an increased risk for IBD development. Thus, environmental exposures are considered to contribute to the IBD development.

Some environmental risk factors are associated with IBD, such as smoking, hygiene hypothesis, microorganisms, appendectomy, medication, nutrition and stress. However, the specific mechanism underlying the association between environmental factors and IBD is still poorly understood, and increasing risk factors are identified in studies. The genetic susceptibility and phenotypes of IBD arouse clinicians that more attention should be paid to the investigation of environmental risk factors of IBD.

Disclosure of conflict of interest

None.

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