

Chapter 2

IBD in the New World, Old World, and Your World

Stephanie Coward and Gilaad G. Kaplan

Abbreviations

CAD	Canadian dollar
CD	Crohn's disease
IBD	Inflammatory bowel disease
NSAID	Nonsteroidal antiinflammatory drugs
UC	Ulcerative colitis
USD	United States dollar

Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD) or ulcerative colitis (UC), was recorded in medical documents in the nineteenth century before coming to the forefront as an entrenched chronic disease in the 1900s [1–3]. Over the past century, the incidence and prevalence of IBD have significantly increased in the Western world, with the highest rates recorded in highly industrialized nations [4]. Toward the end of the twentieth century, the incidence of IBD began to rise in newly industrialized countries in Asia, South America, and the Middle East. Exploring these epidemiologic trends may provide clues to IBD's etiology.

S. Coward, MSc • G.G. Kaplan, MD, MPH, FRCPC (✉)
Department of Medicine and Community Health Sciences, University of Calgary,
3280 Hospital Drive NW, 6D56, Calgary, AB T2N 4N1, Canada
e-mail: ggkaplan@ucalgary.ca

The pathogenesis of IBD remains elusive; however, our understanding suggests that IBD's cause and progression are driven by multifactorial interactions of genetic loci [5, 6], environmental factors [7], and the gut microbiome [8, 9]. Metaanalyses of genetic studies suggest that over 200 different genetic risk loci are associated with the development of IBD, with some specific to Crohn's disease or ulcerative colitis but many are shared [10, 11]. Most of these genes are responsible for the interplay between the gut's immune system and the microbiome. Nonetheless, genetic factors alone are not sufficient to explain the global increase in the incidence of IBD. Environmental determinants are key to understanding the global patterns of IBD incidence. Several environmental factors have been found to be associated with IBD such as smoking, hygiene, antibiotics, stress, and diet [7].

Historically, the incidence and prevalence of IBD have been the highest in the highly industrialized countries of the Western world, but now newly industrialized nations are reporting steadily increasing incidence and prevalence [12]. Historical trends that were initially apparent within the Western world have now been mimicked by newly industrialized countries [2, 13]. Comparing the highly industrialized countries to the newly industrialized countries may provide clues to the etiology of IBD. The differences currently seen within epidemiologic comparisons between the highly and newly industrialized countries may be explained through genetics and environmental factors [7].

IBD is most commonly diagnosed in young individuals between the ages of 18 and 35 years [14], although IBD can be diagnosed at any age [15]. IBD is a chronic and incurable disease that alternates between active and inactive periods. Due to low mortality, IBD exhibits compounding prevalence or an exponential increase in prevalence over time where new incident patients are added every year and few patients die [12]. The combination of high cost of disease treatment and compounding prevalence requires mitigation strategies or IBD will become unmanageable in countries throughout the world.

The high incidence and prevalence seen within the West have led to high annual costs to the healthcare system. In 2004, the estimated cost of IBD in the United States was nearly \$6 billion United States Dollars (USD) in direct costs, while Canada's estimated cost in 2012 was \$1.2 billion Canadian dollars (CAD) [16, 17]. Although the prevalence of IBD is low in newly industrialized countries, the combination of rising incidence and large base-populations will dramatically escalate the cost of managing IBD across the world. Accordingly, addressing the impending global burden of IBD must include mitigation in newly industrialized nations.

This chapter will introduce the historical epidemiology of IBD and then describe the current landscape of IBD. Further, in order to provide an overview of the impending burden, this chapter will align the past landscapes of IBD seen within highly industrialized countries with what is now happening in newly industrialized nations. The purpose of this chapter is to provide rationale for the need to mitigate the impending burden of IBD throughout the world.

IBD in Highly Industrialized Countries of the Western World

Historical and Current Perspective

While IBD is entrenched within Western society, it is a relatively new disease [1–3]. Dr. Samuel Wilks published the first case report in 1859 in England [18]. He described an autopsy of a woman who was thought by individuals in the medical community to have died of dysentery; however, Dr. Wilks reported on an inflammatory process seen within the terminal end of the ileum, extending throughout the large intestine [18]. He specifically noted that her autopsy was unique and bore no resemblance to previous bowel diseases that he was accustomed to [18]. Nearly 20 years later, in 1875, Dr. Wilks introduced the diagnosis of “ulcerative colitis” to the medical community [18, 19]. Following this raised awareness, more cases of ulcerative colitis were recognized in England, leading to the 1909 publication including over 300 patients with ulcerative colitis admitted to five hospitals throughout London.

In 1932, the term “regional ileitis,” a preliminary term for Crohn’s disease, was reported which led to the differentiation of IBD into two distinct diseases. Crohn et al. described a disease in patients that had similar clinical features to ulcerative colitis, yet involving the terminal ileum [20]. By the middle of the twentieth century, ulcerative colitis and Crohn’s disease were established diseases of the West with consistent reporting of rising incidence.

Incidence and Prevalence

Numerous epidemiological studies were published on the incidence and prevalence of Crohn’s disease and ulcerative colitis throughout the twentieth century [4]. The earliest studies, which led to rising reported incidence, may have been influenced by a diagnostic bias caused by increased awareness of IBD and advances in endoscopic modalities to diagnose IBD [12]. Some of the first studies on incidence and prevalence of IBD came from Europe and North America, with countries in more northern latitudes reporting the highest incidence.

Current Landscape

In 2002, 1.3 million people with IBD were estimated to live in North America. IBD has become an immense burden on the individual and on the healthcare system. While IBD can be diagnosed at any age, most individuals are diagnosed in the prime of their lives during adolescence and early adulthood [21]. Initially, IBD was thought of as a disease of Caucasian individuals; more recent studies have shown

that the disease can be diagnosed in virtually all ethnicities [4]. Immigration studies suggest that first-degree offspring of immigrants from regions with low prevalence of IBD to countries of high prevalence have similar risk of IBD as individuals who were born in and remained in Western countries [22].

Multidecade longitudinal epidemiologic studies in Cardiff (UK) and Olmsted County (United States) demonstrate consistently increasing incidence rates throughout the twentieth century and into the twenty-first century [4]. A recent global meta-analysis of incidence and prevalence of IBD found that, as of 2010, the highest incidence of UC was seen in Europe (24.3 per 100,000 person-years) and the highest incidence of CD was seen in North America (20.2 per 100,000 person-years). Many of the studies that reported longitudinal data suggest that the incidence of CD and UC was significantly increasing [4]. More recent epidemiologic studies from Canada highlight that the incidence of pediatric-onset IBD, particularly very early onset IBD (below the age of 6 years), is rising [23]. In contrast, adult-onset IBD is starting to stabilize and, in some regions, even declining [24, 25].

The highest prevalence for UC and CD is in Western countries of Europe, North America, and Australia [4]. In Canada alone it is estimated that over 233,000 individuals have IBD, equating to 0.67% of the population [16]. Over one million individuals are estimated to be living with IBD in the United States, with over \$6 billion USD spent on direct healthcare costs [17, 26]. In Europe, approximately 2.5–3 million residents are estimated to live with IBD, with direct healthcare costs exceeding €4.5 billion annually.

Due to the high prevalence of IBD, healthcare systems have been faced with substantial burdens. Individuals with IBD utilize healthcare resources more frequently than their non-IBD counterparts. This includes hospitalizations, emergency department visits, doctor office visits, and endoscopic procedures [27]. Initially, the hospitalization rates for CD and UC were significantly increasing by 4.3% and 3.0%, respectively [28]. However, a metaanalysis of the cumulative risk of surgery has demonstrated that the risk of surgery for CD and UC has significantly decreased over the past generation [29]. The risks of surgery have been decreasing primarily due to the advent, and increased prescription, of antitumor necrosis factor (anti-TNF) therapies. Unfortunately, these agents come with a substantial tradeoff from high drug costs [30].

Environmental Risk Factors in the Western World

Several environmental risk factors have been shown to affect the diagnosis and prognosis of IBD [7, 9]. Environmental determinates that have been consistently demonstrated in Western countries include smoking, appendectomy, early-life exposures, diet, vitamin D, and medications such as nonsteroidal antiinflammatory drugs (NSAIDs) and antibiotics (Fig. 2.1).

Smoking is one of the most studied and consistently associated environmental factors. Smoking has a deleterious effect on the development and prognosis of CD,

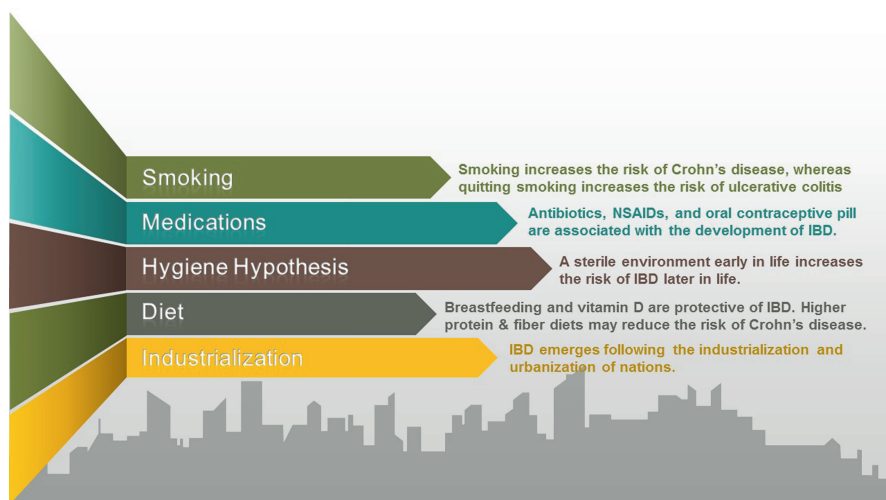


Fig. 2.1 Environmental factors associated with development of IBD in industrialized countries (Image provided by Presenter Media)

with current smokers at two times increased risk of disease development. Compared to never smokers, current smokers experience more flares after diagnosis and are more likely to require early surgery, and then experience postoperative relapse, while current smokers who quit after diagnosis experience rates of flares similar to never smokers [31–35]. Contrary to this is smoking's effect on UC whereby both never smokers and former smokers are more likely than current smokers to be diagnosed with UC. Further, former smokers are more likely to need an early colectomy as compared to never smokers [31]. The mechanism of smoking's effect on IBD is unclear, but recent studies suggest that smoking may modulate the intestinal microbiome [36].

Appendicitis, particularly in those under the age of 10, is protective in the diagnosis of UC [37]. Initially it appeared that appendectomy led to an increased risk of CD [38]. A population-based study and subsequent metaanalysis took a more in-depth look at this association, discovering that the association between appendectomy and the diagnosis of CD was dependent on time, where the highest risk of CD occurred within 6 months of the appendectomy, which was likely indicative of misclassification bias regarding the diagnosis of appendicitis [39, 40].

Medications have been correlated with IBD. Antibiotics during childhood are linked to an increased risk of pediatric-onset IBD; in particular, CD [41]. A dose-response relationship was noted with individuals who had more than one course of antibiotics also having increased odds of developing IBD [41]. Use of nonsteroidal antiinflammatory drugs led to increased risk of disease development and worsened disease activity [42, 43]. As well, a metaanalysis on the effect of oral contraceptives on IBD found an increased risk for both CD and UC [44].

Various aspects of diet have been associated with IBD. However, many dietary studies need to be interpreted cautiously because earlier studies were case-control studies subject to recall bias as well as diagnostic bias whereby change in dietary behavior was influenced by the symptoms of IBD. More recent prospective cohort studies have overcome limitations of these earlier studies by using validated food frequency questionnaires collected prior to the diagnosis of IBD. These cohort studies suggest that consumption of animal protein leads to increased risk of development of IBD and increased dietary fiber intake reduces the risk of CD [45, 46]. However, the cohorts were conducted in adults and which meant the majority of IBD patients were diagnosed in middle age. While these studies provide insight into the effect of diet on adult-onset IBD, few have evaluated diets in early life. This is a major gap in the literature as most scientists speculate that exposures early in life are likely to have the strongest effect on the development of IBD.

Breastfeeding is the most widely studied early-life exposure among patients with IBD. Metaanalysis studies have consistently demonstrated that breastfeeding has a protective effect on the development of IBD [47, 48]. The hygiene hypothesis postulates that IBD emerged in urban areas due to increased sanitation that reduced childhood exposure to enteric pathogens. Metaanalysis studies have demonstrated that CD occurs more commonly in urban areas than in rural areas [49, 50]. Additional evidence supporting the hygiene hypothesis includes a decreased risk of CD associated with living on a farm, drinking unpasteurized milk, early exposure to cats, lower birth order, and larger housing density due to larger families [51–53].

Several other environmental risk factors have been explored in IBD. Young individuals living in regions exposed to high concentrations of traffic-related pollutants (i.e., nitrogen dioxide) were at increased risk of developing CD [54]. A north-south gradient, whereby higher incidence of IBD was seen in northern countries as compared to southern countries, has been long reported. In part, the difference in incidence across geographic latitudes has been postulated to be secondary to differential sun exposure with lower levels of Vitamin D in the North.

Each of these environmental risk factors is prevalent within Western countries. As a country becomes industrialized, there is higher utilization of medications, a movement toward Western diets, and greater urbanization of the population.

IBD in Newly Industrialized Countries Outside the Western World

Historical and Current Perspective

As IBD grew in epidemic proportions in Western countries during the twentieth century, the prevalence of IBD in newly industrialized countries outside the West was extremely low. However, during the latter part of the twentieth century, numerous countries in Asia, South America, and the Middle East transitioned from

developing countries to newly industrialized countries. Through this economic and societal transition, UC appeared followed closely by CD. Although well-designed population-based studies are absent for many industrializing and newly industrialized countries, the epidemiologic studies that have been published reveal an escalation in the incidence of IBD. The evolution of IBD in newly industrialized countries appears to mimic the early days of Western countries [4]. Together, these studies paint a dim picture of the future where IBD is evolving from a rare disease of the Western world into a global phenomenon.

Incidence and Prevalence

Epidemiologic studies from newly industrialized countries are limited because surveillance healthcare tracking systems, which are the hallmark of many Western countries, are lacking. Moreover, differential access to healthcare, technology, and diagnostic modalities differs between countries as well as within countries by socioeconomic status. The disparity of healthcare is magnified when comparing rural areas to urban areas of newly industrialized countries. Additionally, misdiagnosis of IBD as an infectious disease may be a common occurrence until physicians in newly industrialized countries gain awareness of IBD as an emerging problem. Collectively, these factors translate to either sparse published data or early studies reporting very low incidence and prevalence. Fortunately, over the past generation, many of these challenges have been overcome in newly industrialized countries of Asia, South America, and the Middle East, painting a clearer picture of the rising incidence of IBD outside the Western world.

The emergence of IBD in Asia is now established. One-hundred years after Dr. Wilks published a case report of IBD in 1859, the first case of UC was reported in China [55, 56]. From this single case, the incidence of UC expanded rapidly in China. A systematic analysis of over 1500 studies published in the Chinese literature documented a steady rise in incidence, with over 10,000 cases of UC diagnosed in China by the year 2000 [56]. A follow-up study suggested that the number of cases of UC rose dramatically to over 260,000 by the year 2010 [57]. Similar to Western countries, the appearance and rise in incidence of CD lagged behind UC in Asia. Accordingly, over the past 30 years, the ratio of diagnosis of UC versus CD in Asia has dropped from 8:1 to nearly 1:1 [58]. The rapid rise in the incidence of IBD in Asia has been documented in several temporal trend analyses. The temporal trends seen within Asia in the last generation have outpaced all the data arising from Western countries during the same time period. For example, in South Korea the annual percentage changes in the incidence of IBD were 21% and 18% for CD and UC, respectively, from 1986 to 1997 [59, 60].

The most profound description of the epidemiology of IBD in Asia has been documented by the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) cohort study, which includes 21 medical centers from 8 countries in Asia (and Australia as a control Western country). Within the ACCESS cohort, a population-based

inception cohort of newly diagnosed patients with IBD from 2011 to 2012 was identified, reporting that the incidence of ulcerative colitis and Crohn's disease in Asia ranged from 0.24 to 2.05 and 0.05 to 1.25 per 100,000 persons, respectively [61]. The variability in incidence between regions and countries in Asia was explained by several factors including surveillance methodology, urban versus rural residence, economic advancement, and Westernization of diet and lifestyle. While incidence and prevalence in Asia are still not as high as what is observed in Western countries, the rising incidence rates in conjunction with large population sizes act as a prelude to Asia matching and, possibly exceeding, the burden of IBD seen in Western countries.

Epidemiologic studies arising from South America are not as rich as those published in Asia. However, several studies have shed light on the emergence of IBD. From 1987 to 1993, clinicians from Panama recorded that the incidence of UC was 1.2 per 100,000 person-years, whereas no cases of CD were classified [62]. In contrast, a study from Brazil recorded a similar incidence of CD (2.5 per 100,000 person-years) and UC (2.4 per 100,000 person-years) from 1980 to 1999 [63]. Temporal trend analyses showed that the annual percentage changes in the incidence of CD and UC were 4.0% and 0.2% per year during this time period, respectively [63]. Victoria et al. subsequently determined that the estimated prevalence of CD and UC in 2009 were 15.0 and 76.1 per 100,000, respectively [64]. The data from South America is sparse; however, the increasing incidence over time and the current high prevalence are both indicative of a historical progression similar to that seen in Western countries.

The Middle East shows similar trends at the end of the twentieth century to those seen in South America, even approximating the incidence and prevalence reported in Western countries. The incidence for CD ranged from 1.1 to 4.2 per 100,000 person-years, with marginally higher rates observed for UC, ranging from 2.3 to 6.3 per 100,000 person-years [65–68]. The highest significant annual percentage changes recorded in the Middle East were 14.3% and 7.5% for CD and UC, respectively [4]. Similar to what was seen in the Western world in the 1960s, the prevalence estimates in the 1970s in the Middle East were 12.3 per 100,000 persons for CD and 37.4 per 100,000 persons for UC [69, 70]. In the latter part of the twentieth century, these estimates were similar to Western countries: 67.9 per 100,000 persons for CD and 168.3 per 100,000 persons for UC [71, 72]. While the CD estimates in the Middle East are approximately a third of the Western world, the UC estimates are now aligned [4]. This rapid rise in incidence of IBD in the Middle East implies that, in the next generation, prevalence estimates of newly industrialized countries may match those in highly industrialized countries.

South America, the Middle East, and Asia had relatively low prevalence during the twentieth century, but are now experiencing a rapid rise in incidence. While their prevalence estimates are still a fraction of those recorded in Western countries, prevalence of IBD in newly industrialized countries is steadily climbing. Moreover, the large population sizes of many newly industrialized countries (e.g., there are over two billion people in China and India) mean that even marginal elevation in prevalence translates to large absolute numbers of patients. Consequently, the challenges

faced by countries in the Western world will soon be faced by newly industrialized countries throughout the world. Thus, the implementation of strategies to mitigate the impending global burden of IBD is essential. The primary way to address the global rise of IBD is to understand the environmental factors that drive the development of IBD, using that information to develop preventative strategies.

Environmental Risk Factors in Contrast to the Western World

Nonindustrialized countries favor rural living and agriculture. Countries that sustain themselves through these means have a lower prevalence of IBD than their industrialized counterparts [4]. As countries become industrialized they undergo a transition from their prior culture to one that mirrors what is seen in highly industrialized countries. Individuals move from rural cites to urban centers where manufacturing is favored over agriculture. There are also changes to lifestyle behaviors prevalent within Western countries such as environmental factors associated with IBD: smoking, hygiene, medications, diet, and air pollution [12]. Specifically, people are more likely to take up smoking, environments become cleaner and therefore the microbes people are exposed to have changed, there is greater access to Western medicine [73], breastfeeding decreases, intake of dietary fiber decreases, and air pollution levels increase due to increased motor vehicle usage and increased development of industries [73].

IBD in Your World: Importance of the Global Rise of IBD

Burden of IBD Today

Within newly industrialized countries, it is estimated that over four million people have IBD with this estimate rising annually [4, 16, 74, 75]. A chronic disease imparts a substantial burden on both the individual and the healthcare system. As each year passes an increased number of people are diagnosed with IBD. Given the low mortality of the disease coupled with the young age of diagnosis, the number of individuals affected by IBD rises, causing the effect known as compound prevalence. This is a relatively new epidemiologic phenomenon seen with chronic diseases, but as IBD is commonly diagnosed earlier in life, compound prevalence of IBD impacts highly industrialized countries while, at the same time, is presently in its infancy in newly industrialized countries. Gradually, incidence and prevalence in the industrializing and newly industrializing countries are increasing, yet they are still much lower than what is seen in highly industrialized countries [4, 76]. So far, the newly industrialized countries have not yet experienced the substantial burden felt in the highly industrialized countries. However, given similar temporal trends, newly industrialized

countries need to capitalize on the lessons learned in the West. The result of increasing incidence and prevalence is an inevitable increase in the already substantial costs on the healthcare system. The question that arises is, what will that burden be? In order to prepare, it is necessary to predict what will happen.

Predicting the Future in Highly Industrialized Countries

Preliminary analysis of the temporal trends and predictive models suggests that within North America the prevalence of IBD may rise from 0.5% of the population in 2015 to 0.7% in 2025. In Canada the final percentage affected in 2025 is even higher at approximately 0.9% ([77]; Canadian Digestive Disease Week; Montreal, Canada). While the annual percentage change and overall prevalence is lower within the United States, the burden is higher due to the larger at-risk population. The financial burden on the healthcare system will be over ten times the cost in the United States than in Canada. If something is not done to mitigate this burden, each country's respective healthcare system may be overwhelmed (Fig. 2.2).

Within the Western world there are various factors that will impact the future incidence, prevalence, and costs of IBD. An aging IBD population in Western countries will complicate clinical practice due to managing comorbidities. These factors are indicative of an increasing burden that will be felt by Western countries.

As the burden increases, the healthcare system may be overwhelmed. While surgical rates for IBD are decreasing, the increasing prevalence of the disease, as a function of the increasing population and incidence, along with the increased utilization of biologics, the Western world will experience a significant rise in costs. The overall burden of the disease, the costs, and total affected population, will keep rising. By 2030 the current approach for dealing with IBD maybe unsustainable.

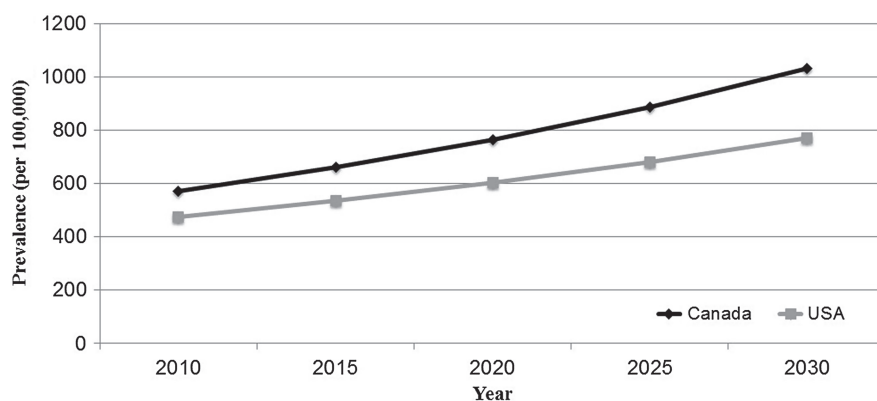


Fig. 2.2 Predictive trends showing the rise in prevalence of IBD in Canada and the United States from 2010 to 2030 (Adapted from Coward et al. [77]; Canadian Digestive Disease Week; Montreal, Canada. Images provided by Presenter Media)

Predicating the Future in Newly Industrialized Countries

With rapidly rising incidence rates seen in newly industrialized countries, these countries are at risk of matching the prevalence of Western nations overtime. Unfortunately, a Western-level prevalence may have a greater impact on some of these newly industrialized countries (e.g., China and India) than what is seen in Western countries due to high population size [78]. Given that newly industrialized countries will have higher absolute population numbers affected by IBD, the overall burden and costs could be higher. Moreover, disparity of care for IBD may exist within newly industrialized countries whereby patients with higher socioeconomic status may have greater access to management (e.g., biologics) than impoverished patients. In order for these newly industrialized countries to handle the impending burden, various methodologies need to be employed with restructuring of health-care delivery models to adapt to the rising burden of IBD.

Mitigating the Rising Burden of IBD

While there are developments regarding the etiology of IBD, we have not yet fully discovered it. The origins and mechanisms of IBD are aspects of the disease that we could use to address the impending burden. By looking closer at environmental factors that interact with genetic loci and gut microbiota, we can better understand the origins, then pathogenesis, of IBD. We can utilize this information to develop alternative strategies that involve manipulating our environment to prevent disease development and mitigate the rising global prevalence of IBD.

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