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INFLAMMATORY BOWEL DISEASE (S HANAUER, SECTION EDITOR)

What Can We Learn From Inflammatory Bowel Disease in Developing Countries?

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Abstract Inflammatory bowel diseases occur due to an aberrant immune response to luminal antigens in genetically predisposed individuals. Although specific genetic loci have been identified underlying the predisposition, they have not fully explained the disease etiology. Striking epidemiological observations implicate the critical role of environmental influences on disease penetrance. The emergence of disease consistently observed as a society becomes modernized or developed may be attributed to westernization of diet, changing antibiotic use, or improved hygiene status. These factors are linked with changes in the gastrointestinal microbiota which, in turn, may affect development of the immune system and influence the risk of disease occurrence. Geographic variations within developing countries suggest that the strength of influence by risk factors in a society varies greatly. Studies of IBD in populations of developing countries where there are opportunities to prospectively collect changing exposure data over time may provide clues to the disease etiology.

Keywords Inflammatory bowel disease · Epidemiology · Environment · Diet · Microbiota

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Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease affecting the gastrointestinal tract, and includes ulcerative colitis and Crohn's disease. While the exact etiology of the disease is unknown, it is thought to arise from a dysregulated immune system resulting in chronic mucosal inflammation. This is contributed by both genetic and environmental factors. The heritability of Crohn's disease is thought to be around 50 % [1], with a lower estimate for ulcerative colitis [2]. Recent genome-wide association studies (GWAS) have identified numerous genetic variants associated with ulcerative colitis [3•, 4] and Crohn's disease [5•, 6]. These genetic factors together can only explain a small proportion of the heritability and disease susceptibility [7]. Genetic mutations of IBD in non-Caucasians differ from that of Caucasians [8•]. While more genetic variants remain to be identified, it is likely that environmental factors play an important role in the pathogenesis of IBD. In support of this hypothesis is the striking observation that IBD emerges when a society makes the transition from a 'developing' to a 'developed' status. This epidemiologic change cannot be explained by genetic changes alone, particularly in the absence of a large background genetic shift, and is likely to be contributed by changes in the environment. Some may regard IBD as a "disorder of modern lifestyle" or even a "disease of the affluence". The present paper aims to describe important observations in developing countries that provide clues to our understanding of IBD. Developing nations have two-thirds of the world's population. Major changes over the past two decades in these populations, including but not limited to changes in dietary patterns, improved socioeconomic status, improved sanitation and altered microbial exposures, have been implicated as potential environmental risk factors for IBD.

Epidemiology

Incidence and Prevalence

The incidence and prevalence of IBD varies greatly around the globe. Traditionally, higher rates are seen in developed countries in the west. The estimated incidence and prevalence for IBD are up to 15 per 10^5 and 200 per 10^5 person-years, respectively in some populations [9•]; with the highest rates reported in northern Europe and North America.

Despite a lower incidence and prevalence, epidemiological studies showed that IBD is not uncommon among non-Caucasians. In East Asia, the prevalence of ulcerative colitis ranges between 7.0 per 10^5 persons in Hong Kong [10] to 30.9 per 10^5 persons in South Korea [11], whereas for Crohn's disease it is between 2.9 per 10^5 persons in Singapore [12] to 13.5 per 10^5 persons in Japan [13]. The age- and sex-adjusted incidence rate for IBD ranges between 0.4 per 10^5 person-years in Hong Kong [10] and 3.6 per 10^5 person-years in South Korea [11].

Higher prevalence and incidence rates were observed in other parts of Asia. In a house-to-house survey in north India [14], the prevalence and incidence rate of ulcerative colitis among the Punjabi population were 44.3 per 10^5 and 6.0 per 10^5 person-years. This incidence rate is one of the highest reported in Asia. As for the Middle East, the prevalence of ulcerative colitis ranges between 41.7 per 10^5 persons in Kuwait [15] and 167.2 per 10^5 persons in Israel [16], while for Crohn's disease it is between 53.1 per 10^5 persons in Lebanon [17] and 65.1 per 10^5 persons in Israel [18]. The incidence rate here ranges between 1.4 and 5.0 per 10^5 person-years; these figures appear higher than that of data from East Asia.

There is a paucity of descriptive population-based epidemiological data from developing countries. Two studies, conducted in different regions of Puerto Rico, have reported a greatly divergent prevalence of 12.5 per 10^5 persons in rural area [19] versus 62.2 per 10^5 persons in urban area [20] for ulcerative colitis. The prevalence of Crohn's disease is 5.9 per 105 persons in rural areas and 41.4 per 10^5 persons in urban areas. Within Asia, Japan is only country that has a national IBD registry. The total number of affected persons with IBD is thought to be more than 100,000 from data from the Japanese Ministry of Health, Labor and Welfare. Data from other countries in Asia were derived mostly from hospital cohorts or physician-based surveys. Accurate epidemiologic data in some developing countries are affected by limited access to health-care, poor physician awareness, and lack of diagnostic equipments. Thus, data available in the literature may have only captured the tip of the iceberg of the population with the best healthcare access, and is unlikely to reflect the true disease burden, especially in developing countries in Asia, Africa and South America.

Temporal Trends

Despite the lack of national registries or population-wide epidemiological studies in developing countries, time-trend studies have suggested that IBD is not uncommon and is on a rising trend among many non-Caucasian populations. The prevalence of ulcerative colitis rose from 7.6 per 10^5 in 1997 to 30.9 per 10^5 persons in 2005 in South Korea [11], and from 2.3 per 10^5 to 6.3 per 10^5 persons in Hong Kong within a decade [10]. A review from a national registry published in 2008 revealed a greater than threefold rise of Crohn's disease in Japan, from a prevalence of 2.9 per 10^5 in 1986 to 13.6 per 10^5 persons in 1998 [13]. A collective analysis on 10,218 ulcerative colitis patients in China also showed a threefold rise in disease diagnosis from the 1980s to 1990s [21]. Although this article is not a formal epidemiological study and hence cannot infer a true temporal increase in incidence, it suggests that ulcerative colitis is not uncommon and may be on the rise in many developing countries. In support of this is the observation that, when IBD emerges in a country, ulcerative colitis appears first, followed after a variable interval by Crohn's disease. This worldwide trend is evident in developing countries, in under-developed sectors of society such as aboriginals living in New Zealand and Canada, and also amongst migrants from developing to developed countries. It could well be that changes in life-style factors including diet affect ulcerative colitis risk more than Crohn's disease, as reflected in increased incidence occurring some years before Crohn's disease risk is affected.

An increasing disease trend has also been reported in other countries outside East Asia. A study based on a community survey of physicians in Israel in the period 1987−1997 reported an incidence rate of 5.0 per 10^5 person-years for Crohn's disease, with a greater than two-fold increase from 2–3 per 10^5 person-years in an earlier period of 1967−1986 [16]. Although the incidence rate of ulcerative colitis appeared relatively stable at about 5.0 per 10^5 person-years [18], the authors reported a rise in prevalence of both ulcerative colitis and Crohn's disease, from 121.0 per 10^5 and 25.5 per 10^5 persons in 1987 to 167.2 per 10^5 and 65.1 per 10^5 persons in 1997, respectively. In Puerto Rico, the incidence of ulcerative colitis rose from 1.96 to 3.32 per 10^5 person-years from 1996 to 2000 [19]. A four-fold rise in incidence rate of Crohn's disease from 0.49 to 1.96 per 10^5 person-years was observed. In a recent systematic review consisting of more than 100 studies, the incidence and prevalence of IBD are increasing with time and in different regions around the world, indicating its emergence as a global disease [22].

Clinical Characteristics

The distribution of IBD is characterized by a bimodal distribution in many western countries. The diagnosis of

Crohn's disease and ulcerative colitis usually peaks at age 20−30 and age 30−40 years, respectively, both followed by a smaller peak at an older age of 60−70 [23]. Although previous studies in Asia have reported a similar peak age of onset for both diseases, they have not consistently observed the second smaller peak at the older age [11, 14–16, 18, 21, 24–26].

Previous studies suggest a slight female preponderance for Crohn's disease, and an equal or slight male preponderance for ulcerative colitis in western populations [27, 28]. Most Asian studies suggest a similar gender distribution for ulcerative colitis, whereas for Crohn's disease, in contrast to western populations, there appeared to be a male predominance, with a male-to-female ratio ranging between 1.67 and 2.9 to 1 [11, 13, 24, 29]. A slight female preponderance was seen in the Hispanic population for IBD [19, 20, 30, 31].

The clinical course of ulcerative colitis in Asia is generally regarded as similar to the western populations [32, 33], although isolated studies suggest a milder disease severity [15, 26]. Fulminant disease appeared to be rare in the Chinese population [21, 26]. Previous data from a western population suggest that 37 % of patients have pan-colitis at diagnosis [34], and in Asia, 21−45 % of patients have pan-colitis at diagnosis [10, 26, 29, 35•, 36–42]. The two hospital-based studies in Puerto Rico showed largely divergent results of 15 versus 80 % [30, 31].

In contrast to ileal disease, which is more common in the west, several studies from East Asia showed ileo-colonic predominance for Crohn's disease, with 66.7 % in South Korea [11], 65.8 % in Japan [43] and 50.5 % in Hong Kong [44], similar to the finding of 52.3 % in the Hispanic population [31]. More heterogeneous results have been obtained in other parts of Asia [26, 38, 45] and the Middle East [17, 18, 46, 47] with ileo-colonic involvement ranging between 12.5 and 40.9 %. Such heterogeneity has also been observed in western studies [48–50], with an evidence of phenotypic evolution over time [44, 51–53].

The frequencies of extraintestinal manifestation for both types of IBDs in developing countries appeared to be lower than the reported figures of 21−41 % for the Caucasian populations [54–56]. The frequency appeared to be lowest for ulcerative colitis in East or Southeast Asia, ranging between 5.7 and 13.6 % [29, 41, 57], whereas the frequency for Crohn's disease ranges around 6.4−23 % [26, 29, 38, 41, 58]. Higher rates ranging up to 40.0 % have been reported in studies from the Middle East and South Asia [36, 46].

The incidence of colorectal cancer among ulcerative colitis patients in Asia [17, 29, 46, 57, 59, 60••] appeared to be lower than those in the west [61]. A study from India estimated the colorectal cancer risk in ulcerative colitis patients to be 2.3 % at 10 years [62], lower than the estimate of 8.3 % for western populations [63]. However, this is likely to be a reflection of the low disease prevalence, and colorectal cancer may increase over time as the disease become more prevalent in developing countries.

Migrant Populations

Studies of migrant populations can potentially help dissect the etiologic importance of genetic and environmental factors in causing a disease. Studies in first- and second-generation South Asians in Leicester in the United Kingdom showed a high rate of ulcerative colitis compared with the local populations, suggesting that the disease pattern follows that of the indigenous population after only one generation [64, 65, 66••]. Given the relative constant genetic composition within a few decades, such drastic changes in disease epidemiology in the migrant populations are likely to be accounted for by environmental factors. Together with other migrant studies in North America [67–69], this suggests that environmental factors may be more important than genetic factors in the etiology of IBD. This is also consistent with findings from twin studies [2, 70, 71, 72••]. In monozygotic twins, the concordance rates for Crohn's disease range between 20 and 50 %, whereas the concordance rates for ulcerative colitis are even lower. Several lessons can be learnt from migration studies. It is clear that immigrants have a genetic predisposition, and that there must be an environmental factor triggering disease expression, and it seems that environmental exposure during childhood is critical.

In the following section, we discuss what we perceive as the most important environmental factors in developing countries that may account for the changing epidemiology of IBD. These factors include an adoption of a western diet [73], improved hygiene and sanitation [74•] and socioeconomic growth. Although no single agent has been found to be causative, some of these factors, together or in isolation, have been shown to influence the disease risk and natural course of IBD.

Environmental Factors

Diet

Global variation in dietary habits is by far one of the most likely explanations for the differences in risk of IBD across different geography and the increase in disease incidence in migrant and developing populations. The rising rates of IBD in Asia coincide with the introduction and expansion of packaged food, fast food chains, and increased use of antibiotics and aluminum foils. Rapid industrialization in developing countries has been accompanied by westernization of diet, such as increased consumption of refined sugar, fatty acids, cereals, and meat and reduced consumption of fruit

and vegetables [75, 76]. In China, meat, edible oil, and fat intake have increased in both rural and urban areas over the last 20 years [77]. In Japan, the consumption of sugar, animal protein, and ω-6 fatty acid correlates with the rising incidence of ulcerative colitis and Crohn's disease [78, 79]. Increased intake of dairy products and meat has also paralleled the rising trend of ulcerative colitis in Japan [37]. Children with Crohn's disease in Canada were found to have lower dietary fiber and ω-3 fatty acid [80].

The largest population-based dietary study, conducted by the European Prospective Investigation into Cancer and Nutrition (EPIC) group, has reported a correlation between increased intake of linoleic acid, a ω-6 fatty acid, and the risk of ulcerative colitis. Linoleic acid is present in many food substances including red meat, cooking oils, and certain margarines, and represents a major ingredient in the diet in developing countries. Linoleic acid undergoes metabolic conversion to arachidonic acid and can be converted to eicosanoids which are present in excess in mucosa of ulcerative colitis patients and inhibited by 5-aminosalicylic acid [81, 82].

Based on epidemiological data and case−control series, the relationships between changes in food consumption would fit, in a timely manner, with changes in intestinal microbiota associated with IBD. Population-based and prospective data assessing dietary risk factors in IBD may benefit from investigations of the interactions between the gut microbiota and any confirmed dietary factors. This is particularly important in developing nations in which westernization of diet is evident. The observation that the timing of introduction of certain foods or chemicals to infants affects the risk of developing celiac disease and diabetic autoimmunity is also likely to be relevant to IBD.

Gut Microbiota

The human gut is colonized by up to 10^{14} bacterial cells and constitutes the largest microbial community within the human body [83]. In normal individuals, the intestinal microbiota have a symbiotic relationship with the host to carry out important metabolic and immunomodulatory function. Recent studies have found a different microbial composition in IBD patients, with decreased prevalence of commensal bacteria and a concomitant increase in others, leading to the hypothesis that IBD may have resulted from immune dysregulation secondary to a host−microbiota symbiosis breakdown. The importance of such a mutualistic relationship is also supported by recent GWAS which implicate genes involved in immunity and autophagy in the susceptibility to IBD. These biological pathways are important in sensing and mounting immune response against different microorganisms.

Several studies have shown that IBD patients have a reduced abundance of dominant commensal bacteria in the gut. Mucosal biopsies taken from IBD patients were found to be depleted in commensal bacteria, notably *Bacteroidetes* and *Firmicutes*, with a concomitant over-representation of *Actinobacteria* and *Proteobacteria* [84••]. These findings are consistent with several other studies, which also observed a decreased *Clostridium* abundance [85, 86]. Such a distinct microbiota composition was confirmed in a subsequent metagenomic sequencing experiment [87••]. The different microbiota composition exists not only between healthy individuals and IBD patients but also between different ethnic groups. A recent study showed remarkable differences in the gut microbiota composition between Malawian and Finnish infants, with a greater proportion of *Bifidobacterium*, *Bacteroides-Prevotella* and *Clostridium* [88]. Nonetheless, it is unknown how this difference may alter the intestinal physiology in the disease process. Despite speculations that several micro-organisms are the culprits in Crohn's disease, such as *Mycobacterium avium paracellulare* [89, 90], *Listeria* [91] or the measles virus [92, 93]; these findings have not been consistently replicated [94]. There is no concrete evidence that a single pathogen is the cause of the disease. Many of the features of a modern lifestyle observed in developing countries, including changes in domestic hygiene, smaller family size, antibiotic usage, crowding, and reduced parasitism may be proxy markers of microbial exposure during childhood [95]. Alterations in the gut microbiota could also be linked with many features of developing societies including westernization of diet, increased stress level, and obesity [96].

Recent observational studies have demonstrated an association between antibiotic use either taken in childhood or at any time before IBD diagnosis and the subsequent diagnosis of IBD [97, 98]. Although these studies have methodological limitations, and causality or biological mechanisms cannot be inferred, antibiotic use can rapidly change the spectrum of the intestinal bacterial composition and thus explain rapid changes in disease incidence in the pediatric population or in developing nations. Studies investigating antibiotic use in developing countries are important to explore whether this is a contributing factor to the increasing incidence.

Hygiene Theory

The hygiene hypothesis suggests that the rise of certain allergic and autoimmune diseases is related to the improvement in sanitation and hygiene, which has led to a decrease of infectious diseases. This hypothesis was first proposed by Strachan, who observed an inverse correlation between hay fever and the number of older sibling when following more than 17,000 British children in the 1958 birth cohort [99••].

This hypothesis gained support from epidemiological studies showing increased incidence of atopic [100–102] and other autoimmune diseases in developed countries [103–106]. Such an increase parallels improvements in socioeconomic status and gross national product of the countries, along with industrialization and urbanization, with concomitant falls in family size and incidence of infectious diseases [106]. It has been hypothesized that exposure to certain infectious agents early in life induces tolerance and immune-regulation to protect against allergic and autoimmune diseases.

The global epidemiology of IBD is consistent with the hygiene hypothesis. In China, the increase in IBD appears to parallel a reduction in the incidence of several infectious diseases as the government implements nationwide vaccination programmes and vigilant control measures [107]. Although Canada has one of the highest rates of IBD in the world, the low rates of IBD among First Nations Manitobans and British Columbians could also be explained by the hygiene hypothesis. Many of the Manitoban First Nations live in crowded and poor conditions, and are infected with hepatitis A, *Helicobacter pylori*, and pinworms. A population-based study from Israel showed that surrogate markers of enhanced childhood hygiene were associated with the risk for IBD, including living in an urban environment (OR 1.38), small number of siblings in the family (for 1 sibling vs. 5 or more, OR 2.63), and higher birth order (for birth order of 5 or higher vs. 1, OR 2.35) [108]. A case−control study from South India showed that urban residence (OR 1.70) and piped water (OR 1.59), which were indicators of better hygiene, increased the risk of Crohn's disease, whereas exposure to cattle (OR 0.57) was protective for Crohn's disease [109]. While one might speculate that better sanitary conditions is responsible for reduced microbial diversity, industrial pollution in a society might serve as another explanation for a changed environment. It is unlikely that the exogenous predisposition for IBD can be explained by one single environmental factor.

Smoking

Smoking is one of the most thoroughly studied environmental factors, and has been consistently shown to be associated with the risk, the natural course, and outcome of both ulcerative colitis and Crohn’s disease. It has been well recognized that smoking decreases the risk of ulcerative colitis [odds ratio(OR), 0.58; 95 % CI=0.45−0.67) but increases that of Crohn’s disease (OR, 1.76; 95 % CI= 1.40−2.22) [110••]. The effect of smoking in ulcerative colitis is consistent in other populations, including Japan [111], China [112], and Iran [113], although the effect on Crohn’s disease in the west has not been replicated in South Korea, Hong Kong, and Israel [24, 114–117].

The association between smoking and IBD, however, may not be applicable to all geographic areas or ethnic groups. Smoking alone cannot account for the worldwide trends of IBD incidence and is unlikely to be the cause of the rising incidence in developing countries. Countries with some of the lowest current smoking rates among adult male populations, such as Sweden and Canada, have among the highest incidence rates of Crohn's disease, whereas in Asia and South Africa where more than 50 % of the adult male populations smokes, the incidence of Crohn's disease remains low. It is likely that smoking does not cause Crohn's disease but modulates the disease once present.

Summary

The epidemiology of a disease often gives clues to etiologic agents. Although our understanding of the etiology of IBD is far from complete, important information and clues can be derived from emerging data in developing countries. It stands to reason that the driving forces behind the rise of IBD in developing nations are environmental factors, as these nations have undergone enormous social and economic growth over the past two decades. The two most well-established risk factors for IBD, smoking and appendectomy, cannot fully account for all variations in IBD incidence and prevalence. By far the most topical and likely factors that may explain geographic variability and the rising incidence in developing countries and urban areas are changes in diet and improved hygiene with downstream effects on the intestinal microbiota. Nevertheless, given the myriad of lifestyle changes associated with industrialization, it is difficult to dissect independent risk factors as likely etiologic agents. It is likely that these environmental factors act both independently and synergistically to affect the disease risk. There is evidence that gene−environment interactions are important in IBD [118].

Further support for the importance of environmental factors is obtained from the migrant studies of the South Asian populations [64, 65, 66••]. The fact that the disease pattern follows that of the indigenous population after only one generation points to something that happens early in life. The major event that differentiates the first and the second generation of migrant is the life experience during infancy, childhood, or early adolescence. The hygiene theory that early infections in life protect against allergy or autoimmune disease fits perfectly into this observation.

Moreover, it is possible that the weights of genetic and environmental factors differ between ethnic groups. For example, some *NOD2* variants have not been detected in the Han Chinese [119, 120], Japanese [121, 122], Korean [123], Indian [124], and Malaysian [125] populations. Genetic mutations of IBD in Asians have also been found

to be different from Caucasians, with a lack of significant association with *ATG16L1* in East Asians [8•]. These findings suggest that genetics may play a different role in the pathogenesis of IBD in non-Caucasian populations. The highly variable allele frequencies of *NOD2* and other variants are not unexpected, given that disease modifying variants are commonly under the pressure of natural selection and show high degree of population differentiation [126, 127]. Such genetic heterogeneity may also explain the considerable lower rates of familial aggregation [21, 24, 26, 45, 69, 128–131] and the male predominance in Crohn's disease in Asia [11, 13, 24, 29].

Recent advances in sequencing technologies have allowed the gut microbiota to be studied using a metagenomic approach. While it may not identify a single etiologic agent, it would undoubtedly inform us, with an unprecedented depth, on the relationship between the microbial composition, the disease status, and the host genetics which is largely related to the ethnic origin, as in the recent metagenome-wide association study of gut microbiota in type 2 diabetes [132].

Lastly, epidemiological studies in developing countries are limited by the lack of population-wide registries. An ideal study should be conducted in an area with universal access to health care, standardized case definition, and a well-maintained registry. This is often difficult, given limitations in resources in many developing countries. Large collaborative efforts should be encouraged to build a platform for research in this field, which will not only inform the scale of disease burden but also help dissect the etiology of this impending IBD epidemic.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sofaer J. Crohn's disease: the genetic contribution. Gut. 1993;34 (7):869–71.
2. Tysk C et al. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut. 1988;29(7):990–6.
3. • Anderson CA et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet. 2011;43(3):246–52. *This meta-analysis identified numerous genetic variants that are associated with susceptibility to ulcerative colitis*.
4. Barrett JC et al. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nat Genet. 2009;41(12):1330–4.
5. • Barrett JC et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet. 2008;40 (8):955–62. *This meta-analysis identified numerous genetic variants that are associated with susceptibility to Crohn's disease*.
6. Franke A et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet. 2010;42(12):1118–25.
7. Gibson G. Hints of hidden heritability in GWAS. Nat Genet. 2010;42(7):558–60.
8. • Ng SC et al. Genetics of inflammatory bowel disease in Asia: systematic review and meta-analysis. Inflamm Bowel Dis. 2012;18(6):1164–76. *This study showed that genetic factors contributing to IBD in non-Caucasian are different to Caucasians*.
9. • Cosnes J et al. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785–1794.e4. *This review described the global epidemiology of IBD*.
10. Lok KH, Hung HG, Ng CH. Epidemiology and clinical characteristics of ulcerative colitis in Chinese population: experience from a single center in Hong Kong. J Gastroenterol Hepatol. 2008;23:406–10.
11. Yang SK et al. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986–2005: a KASID study. Inflamm Bowel Dis. 2008;14(4):542–9.
12. Lee YM, Fock K, See SJ. Racial differences in the prevalence of ulcerative colitis and Crohn's disease in Singapore. J Gastroenterol Hepatol. 2000;15:622–5.
13. Yao T, Matsui T, Hiwatashi N. Crohn's Disease in Japan: diagnostic criteria and epidemiology. Dis Colon Rectum. 2000;43:S85–93.
14. Sood A, Midha V, Sood N. Incidence and prevalence of ulcerative colitis in Punjab, North India. Gut. 2003;52:1587–90.
15. Al-Shamali MA, Kalaoui M, Patty I. Ulcerative colitis in Kuwait: a review of 90 cases. Digestion. 2003;67:218–24.
16. Niv Y, Abuksis G, Fraser GM. Epidemiology of ulcerative colitis in Israel: a survey of Israeli kibbutz settlements. Am J Gastroenterol. 2000;95:693–8.
17. Abdul-Baki H, ElHajj I, El-Zahabi LM. Clinical epidemiology of inflammatory bowel disease in Lebanon. Inflamm Bowel Dis. 2007;13:475–80.
18. Niv Y, Abuksis G, Fraser GM. Epidemiology of Crohn's disease in Israel: a survey of Israeli kibbutz settlements. Am J Gastroenterol. 1999;94:2961–5.
19. Appleyard CB, Hernandez G, Rios-Bedoya CF. Basic epidemiology of inflammatory bowel disease in Puerto Rico. Inflamm Bowel Dis. 2004;10:106–11.
20. Torres EA, De Jesus R, Perez CM. Prevalence of inflammatory bowel disease in an insured population in Puerto Rico during 1996. P R Health Sci J. 2003;22:253–8.
21. Jiang XL, Cui HF. An analysis of 10218 ulcerative colitis cases in China. World J Gastroenterol. 2002;8:158–61.
22. Molodecky NA et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54 e42. quiz e30.
23. Loftus Jr EV, Sandborn WJ. Epidemiology of inflammatory bowel disease. Gastroenterol Clin N Am. 2002;31(1):1–20.
24. Leong RW, Lau JY, Sung JJ. The epidemiology and phenotype of Crohn's disease in the Chinese population. Inflamm Bowel Dis. 2004;10:646–51.
25. Yang SK, Hong WS, Min YI. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong District, Seoul, Korea, 1986–1997. J Gastroenterol Hepatol. 2000;15:1037–42.
26. Wang YF, Zhang H, Ouyang Q. Clinical manifestations of inflammatory bowel disease: East and West differences. J Dig Dis. 2007;8:121–7.

27. Vind I et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol. 2006;101:1274–82.
28. Bernstein CN, Wajda A, Svenson LW. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol. 2006;101:1559–68.
29. Jiang L, Xia B, Li J. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. Inflamm Bowel Dis. 2006;12:212–7.
30. Moreno JM, Rubio CE, Torres EA. Inflammatory disease of the gastrointestinal tract at the University Hospital, Medical Center, Puerto Rico. 1980–1987. Bol Asoc Med PR. 1989;81:214–8.
31. Nguyen GC, Torres EA, Regueiro M. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. Am J Gastroenterol. 2006;101:1012–23.
32. Langholz E, Munkholm P, Davidsen M. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology. 1994;107:3–11.
33. Stewenius J, Adnerhill I, Ekelund GR. Risk of relapse in new cases of ulcerative colitis and indeterminate colitis. Dis Colon Rectum. 1996;39:1019–25.
34. Farmer RG, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. Dig Dis Sci. 1993;38:1137–46.
35. • Hou JK, El-Serag H, Thirumurthi S. Distribution and manifestations of inflammatory bowel disease in Asians, Hispanics, and African Americans: a systematic review. Am J Gastroenterol. 2009;104(8):2100–9. *This systematic review described the epidemiology of IBD among different ethnic populations*.
36. Kochhar R, Mehta SK, Nagi B. Extraintestinal manifestations of idiopathic ulcerative colitis. Indian J Gastroenterol. 1991;10:88–9.
37. Kitahora T, Utsunomiya T, Yokota A. Epidemiological study of ulcerative colitis in Japan: incidence and familial occurrence. The Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan. J Gastroenterol. 1995;30:5–8.
38. Cao Q, Si JM, Gao M. Clinical presentation of inflammatory bowel disease: a hospital based retrospective study of 379 patients in eastern China. Chin Med J (Engl). 2005;118:747–52.
39. Fujimoto T et al. Change of clinical characteristics of ulcerative colitis in Japan: analysis of 844 hospital-based patients from 1981 to 2000. Eur J Gastroenterol Hepatol. 2007;19:229–35.
40. Lawrance IC, Murray K, Hall A. A prospective comparative study of ASCA and pANCA in Chinese and Caucasian IBD patients. Am J Gastroenterol. 2004;99:2186–94.
41. Ling KL, Ooi CJ, Luman W. Clinical characteristics of ulcerative colitis in Singapore, a multiracial city-state. J Clin Gastroenterol. 2002;35:144–8.
42. Park SH, Kim YM, Yang SK. Clinical features and natural history of ulcerative colitis in Korea. Inflamm Bowel Dis. 2007;13:278–83.
43. Oriuchi T, Hiwatashi N, Kinouchi Y. Clinical course and long-term prognosis of Japanese patients with Crohn's disease: predictive factors, rates of operation, and mortality. J Gastroenterol. 2003;38:942–53.
44. Chow DK, Leong RW, Lai LH. Changes in Crohn's disease phenotype over time in the Chinese population: validation of the Montreal classification system. Inflamm Bowel Dis. 2008;14:536–41.
45. Thia KT, Luman W, Jin OC. Crohn's disease runs a more aggressive course in young Asian patients. Inflamm Bowel Dis. 2006;12:57–61.
46. Aghazadeh R, Zali MR, Bahari A. Inflammatory bowel disease in Iran: a review of 457 cases. J Gastroenterol Hepatol. 2005;20:1691–5.
47. Fidder HH, Avidan B, Lahav M. Clinical and demographic characterization of Jewish Crohn's disease patients in Israel. J Clin Gastroenterol. 2003;36:8–12.
48. Bjornsson S, Johannsson JH. Inflammatory bowel disease in Iceland, 1990–1994: a prospective, nationwide, epidemiological study. Eur J Gastroenterol Hepatol. 2000;12(1):31–8.
49. Lapidus A. Crohn's disease in Stockholm County during 1990–2001: an epidemiological update. World J Gastroenterol. 2006;12:75–81.
50. Mekhjian HS et al. Clinical features and natural history of Crohn's disease. Gastroenterology. 1979;77(4 Pt 2):898–906.
51. Freeman HJ. Natural history and clinical behavior of Crohn's disease extending beyond two decades. J Clin Gastroenterol. 2003;37:216–9.
52. Louis E, Collard A, Oger AF. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. Gut. 2001;49:777–82.
53. Papi C et al. Evolution of clinical behaviour in Crohn's disease: predictive factors of penetrating complications. Dig Liver Dis. 2005;37(4):247–53.
54. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Med (Baltimore). 1976;55:401–12.
55. Monsen U, Sorstad J, Hellers G. Extracolonic diagnoses in ulcerative colitis: an epidemiological study. Am J Gastroenterol. 1990;85:711–6.
56. Rankin GB, Watts HD, Melnyk CS. National cooperative Crohn's disease study: extraintestinal manifestations and perianal complications. Gastroenterology. 1979;77:914–20.
57. Wang Y, Ouyang Q. Ulcerative colitis in China: retrospective analysis of 3100 hospitalized patients. J Gastroenterol Hepatol. 2007;22:1450–5.
58. Park JB, Yang SK, Myung SJ. Clinical characteristics at diagnosis and course of Korean patients with Crohn's disease. Korean J Gastroenterol. 2004;43:8–17.
59. Chang DK, Kim YH, Byeon JS. The current status of ulcerative colitis-associated colorectal cancer in Korea: a KASID study. Korean J Gastroenterol. 2005;46:276–82.
60. •• Thia KT et al. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol. 2008;103(12):3167–82. *A comprehensive review on the epidemiology of IBD in various Asian countries*.
61. Dobbins 3rd WO. Dysplasia and malignancy in inflammatory bowel disease. Annu Rev Med. 1984;35:33–48.
62. Venkataraman S, Mohan V, Ramakrishna BS. Risk of colorectal cancer in ulcerative colitis in India. J Gastroenterol Hepatol. 2005;20:705–9.
63. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48:526–35.
64. Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among europeans and first- and second-generation South Asians in Leicester (1991–1994). Am J Gastroenterol. 1999;94:2918–22.
65. Jayanthi V, Probert CS, Pinder D. Epidemiology of Crohn's disease in Indian migrants and the indigenous population in Leicestershire. Q J Med. 1992;82:125–38.
66. •• Probert CS, Jayanthi V, Pinder D. Epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. Gut. 1992;33:687–93. *This migrant study described the epidemiology of ulcerative colitis among South Asians settling in the United Kingdom. It also demonstrated the importance of environmental factors in the etiology of ulcerative colitis*.
67. Grossman A, Fireman Z, Lilos P. Epidemiology of ulcerative colitis in the Jewish population of central Israel 1970–1980. Hepato-Gastroenterology. 1989;36:193–7.

68. Niv Y, Abukasis G. Prevalence of ulcerative colitis in the Israeli kibbutz population. J Clin Gastroenterol. 1991;13:98–101.
69. Yang H, McElree C, Roth MP. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. Gut. 1993;34:517–24.
70. Halfvarson J, Jess T, Magnuson A. Environmental factors in inflammatory bowel disease: a co-twin control study of a Swedish-Danish twin population. Inflamm Bowel Dis. 2006;12:925–33.
71. Orholm M et al. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. Scand J Gastroenterol. 2000;35(10):1075–81.
72. •• Thompson NP et al. Genetics versus environment in inflammatory bowel disease: results of a British twin study. BMJ. 1996;312(7023):95–6. *This twin study described the low concordance rate of IBD even among idential twins, suggesting that the environmental factors may be more important in the development of IBD*.
73. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. Am J Gastroenterol. 2011;106(4):563–73.
74. • Gent AE et al. Inflammatory bowel disease and domestic hygiene in infancy. Lancet. 1994;343(8900):766–7. *This case−control study showed a higher rate of Crohn's disease among individuals with better domestic hygiene in infancy.*
75. Frangos CC. Inflammatory bowel disease: reviewing an old study under a new perspective. Gut. 2007;56(11):1638–9.
76. Jowett SL et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut. 2004;53 (10):1479–84.
77. Yang G et al. Emergence of chronic non-communicable diseases in China. Lancet. 2008;372(9650):1697–705.
78. Sakamoto N, Kono S, Wakai K. Dietary risk factors for inflammatory bowel disease: a multicenter case–control study in Japan. Inflamm Bowel Dis. 2005;11:154–63.
79. Shoda R, Matsueda K, Yamato S. Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan. Am J Clin Nutr. 1996;63:741–5.
80. Amre DK, D'Souza S, Morgan K. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn/'s disease in children. Am J Gastroenterol. 2007;102:2016–25.
81. Nishida T et al. Increased arachidonic acid composition of phospholipids in colonic mucosa from patients with active ulcerative colitis. Gut. 1987;28(8):1002–7.
82. Sharon P et al. Role of prostaglandins in ulcerative colitis. Enhanced production during active disease and inhibition by sulfasalazine. Gastroenterology. 1978;75(4):638–40.
83. Eckburg PB et al. Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635–8.
84. •• Frank DN et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A. 2007;104(34):13780–5. *This study was one of the first to demonstrate a different microbial composition in the gut among IBD patients and normal individuals*.
85. Gophna U et al. Differences between tissue-associated intestinal microfloras of patients with Crohn's disease and ulcerative colitis. J Clin Microbiol. 2006;44(11):4136–41.
86. Manichanh C et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut. 2006;55(2):205–11.
87. •• Qin J et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59–65. *This study was the first to use massive parallel sequencing to catalogue the gut microbiota, and confirmed different gut microbial composition among IBD patients*.
88. Grzeskowiak L et al. Distinct gut microbiota in southeastern African and northern European infants. J Pediatr Gastroenterol Nutr. 2012;54(6):812–6.
89. Feller M et al. Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. Lancet Infect Dis. 2007;7(9):607–13.
90. Greenstein RJ. Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease. Lancet Infect Dis. 2003;3(8):507–14.
91. Liu Y et al. Immunocytochemical evidence of Listeria, Escherichia coli, and Streptococcus antigens in Crohn's disease. Gastroenterology. 1995;108(5):1396–404.
92. Ekbom A et al. Crohn's disease after in-utero measles virus exposure. Lancet. 1996;348(9026):515–7.
93. Ekbom A et al. Perinatal measles infection and subsequent Crohn's disease. Lancet. 1994;344(8921):508–10.
94. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012.
95. Koloski NA, Bret L, Radford-Smith G. Hygiene hypothesis in inflammatory bowel disease: a critical review of the literature. World J Gastroenterol. 2008;14(2):165–73.
96. Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. Gut. 2008;57(9):1185–91.
97. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am J Gastroenterol. 2010;105(12):2687–92.
98. Hildebrand H et al. Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. Scand J Gastroenterol. 2008;43(8):961–6.
99. •• Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259–60. *This study was the first to propose the 'hygiene theory' in the etiology of allergic and autoimmune diseases*.
100. Masoli M et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59 (5):469–78.
101. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351(9111):1225–32.
102. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med. 2006;355(21):2226–35.
103. Harjutsalo V, Sjoberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet. 2008;371(9626):1777–82.
104. Gale EA. The rise of childhood type 1 diabetes in the 20th century. Diabetes. 2002;51(12):3353–61.
105. Rautiainen H et al. Prevalence and incidence of primary biliary cirrhosis are increasing in Finland. Scand J Gastroenterol. 2007;42(11):1347–53.
106. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. 2002;347(12):911–20.
107. Wang L et al. Emergence and control of infectious diseases in China. Lancet. 2008;372(9649):1598–605.
108. Klement E et al. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2008;103(7):1775–82.
109. Pugazhendhi S et al. Environmental factors associated with Crohn's disease in India. Indian J Gastroenterol. 2011;30 (6):264–9.
110. •• Mahid SS, Minor KS, Soto RE. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006;81:1462–71. *This meta-analysis showed the effect and magnitude of smoking on IBD*.

111. Morita N, Toki S, Hirohashi T. Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. J Gastroenterol. 1995;30:1–4.
112. Jiang L, Xia B, Li J. Risk factors for ulcerative colitis in a Chinese population: an age-matched and sex-matched case–control study. J Clin Gastroenterol. 2007;41:280–4.
113. Firouzi F, Bahari A, Aghazadeh R. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: a case control study in Iran. Int J Color Dis. 2006;21:155–9.
114. Fich A, Eliakim R, Sperber AD. The association between smoking and inflammatory bowel disease among Israeli jewish patients. Inflamm Bowel Dis. 1997;3:6–9.
115. Reif S, Klein I, Arber N. Lack of association between smoking and inflammatory bowel disease in Jewish patients in Israel. Gastroenterology. 1995;108:1683–7.
116. Reif S, Lavy A, Keter D. Lack of association between smoking and Crohn's disease but the usual association with ulcerative colitis in Jewish patients in Israel: a multicenter study. Am J Gastroenterol. 2000;95:474–8.
117. Jang JY, Kim HJ, Jung JH. The role of smoking as a risk factor in inflammatory bowel diseases: single center study in Korea. Korean J Gastroenterol. 2006;47:198–204.
118. Quigley EM. Epigenetics: filling in the 'heritability gap' and identifying gene-environment interactions in ulcerative colitis. Genome Med. 2012;4(9):72.
119. Leong RW et al. NOD2/CARD15 gene polymorphisms and Crohn's disease in the Chinese population. Aliment Pharmacol Ther. 2003;17(12):1465–70.
120. Guo QS et al. NOD2 3020insC frameshift mutation is not associated with inflammatory bowel disease in Chinese patients of Han nationality. World J Gastroenterol. 2004;10(7):1069–71.
121. Yamazaki K et al. Absence of mutation in the NOD2/CARD15 gene among 483 Japanese patients with Crohn's disease. J Hum Genet. 2002;47(9):469–72.
122. Inoue N et al. Lack of common NOD2 variants in Japanese patients with Crohn's disease. Gastroenterology. 2002;123 (1):86–91.
123. Croucher PJ et al. Haplotype structure and association to Crohn's disease of CARD15 mutations in two ethnically divergent populations. Eur J Hum Genet. 2003;11(1):6–16.
124. Pugazhendhi S et al. Common NOD2 mutations are absent in patients with Crohn's disease in India. Indian J Gastroenterol. 2008;27(5):201–3.
125. Chua KH et al. Identification of NOD2/CARD15 mutations in Malaysian patients with Crohn's disease. J Dig Dis. 2009;10 (2):124–30.
126. Barreiro LB et al. Natural selection has driven population differentiation in modern humans. Nat Genet. 2008;40(3):340–5.
127. Sabeti PC et al. Positive natural selection in the human lineage. Science. 2006;312(5780):1614–20.
128. Monsen U, Brostrom O, Nordenvall B. Prevalence of inflammatory bowel disease among relatives of patients with ulcerative colitis. Scand J Gastroenterol. 1987;22:214–8.
129. Park JB, Yang SK, Byeon JS. Familial occurrence of inflammatory bowel disease in Korea. Inflamm Bowel Dis. 2006;12:1146–51.
130. Yang SK, Loftus Jr EV, Sandborn WJ. Epidemiology of inflammatory bowel disease in Asia. Inflamm Bowel Dis. 2001;7:260–70.
131. Yoshida Y, Murata Y. Inflammatory bowel disease in Japan: studies of epidemiology and etiopathogenesis. Med Clin N Am. 1990;74:67–90.
132. Qin J et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55–60.