Introduction

Ulcerative colitis (UC) and Crohn’s disease (CD) are two different disorders that constitute inflammatory bowel disease (IBD). Distinctive traits of this incurable condition of unknown aetiology include an unforeseeable and potentially devastating disease course with relapsing-remitting chronic inflammation of the gastrointestinal tract, which results in substantial costs at both an individual and societal level. Today it is widely recognised that the development of IBD is multifaceted and influenced by genetic susceptibility, an impaired immune response and environmental risk factors (1).

IBD is presently a global phenomenon due to an increasing incidence over the last decades. This increase has traditionally been confined to western industrialised countries, but these nations are currently experiencing a stabilising incidence resulting in high prevalence rates. On the other hand, newly industrialised countries, e.g., in Eastern Europe and Asia, have reported a drastically
The first disorder to be discovered and described as a disease was UC. In 1859, the British physician, Sir Samuel Wilks, described the autopsy of Miss Bankes, aged 42 years, who died after months of fever and diarrhoea with what he defined and named as UC (9). More than 100 years later, her death was attributed to CD rather than UC (10). In 1875, Wilks and Moxon further described the appearance of UC as inflammation and ulceration throughout the colon of a young woman who died of severe bloody diarrhoea (11). Sir William Hale White brought about the recognition of UC as an entity in the medical community with the publication of a series of cases in 1888, which comprehensively described UC. In 1909, a symposium was held at the Royal Society of Medicine in London, where more than 300 cases of UC from various hospitals in London were presented and debated. Not only cases were reported, also diagnostic procedures were described during this time. Furthermore, in 1909, Lockhart-Mummery determined the efficacy and safety of sigmoidoscopy (12). The recognition of UC in children was established in 1923 after a publication of UC in children aged 8–15 years (13). By the 1920s UC was a well-known medical condition (14), and in the 1930s and 1940s, surgical procedures were being standardized and fields like radiology, pathology and psychiatry got involved in the understanding and investigation of UC (12). In 1950, Sloan et al., published an important paper in the history of UC with detailed description of the clinical features of UC based on life stories of 2,000 patients (15) and in 1955, the first blinded, controlled trial of cortisone in UC patients was conducted by Truelove and Witts (16).

The distinction between CD and UC was made in 1932 by the American gastroenterologist, Burrill B. Crohn, and his colleagues Leon Ginzburg and Gordon D. Oppenheimer, who described the condition at a meeting at the American Medical Association. Five months later a paper followed in which the disease was recognized as a disease entity different from UC and named after Dr. Crohn (14,17). However, already in 1612, the German surgeon, Wilhelm Fabry, described a case resembling CD (18). In the intermediate time between Fabry and Crohn, several descriptions were made and labelled as “regional ileitis” or “regional enteritis”. These observations were made by e.g., Morgagni in 1769, describing an autopsy of a 20-year-old man. By Combe and Saunders in 1813, with a case report and Abercrombie in 1828, who described the disorder in a 13-year-old girl. Dalziel published a series of case reports in 1913, which led to the recognition of the efficiency of surgery in CD patients (14). In the years that followed, distinct features of CD were discovered, such as the occurrence of skip lesion, which was made by Wells, and the wide age range in patients suffering from the disorder. In 1956, the condition forced President Eisenhower to have acute surgery and this doubtlessly increased the awareness of CD. Although the diseases were discovered and named at various points in time, with the recognition of UC as a disease more than 70 years prior to CD, the two diseases presumably coincided. These diseases that used to be fatal, are in modern time chronic controllable disorders and despite the lengthy historical acknowledgement, IBD is not fully understood today (12).
Global incidence of IBD

The global incidence pattern of IBD is dominated by geographical variation in and between regions with the highest incidence rates reported in Europe, Oceania and North America. However, this reflects the fact that these high-incidence parts of the world have published the majority of studies. It is now evident that the traditional incidence pattern is shifting with a steep increasing incidence reported by recent population-based studies from e.g., Eastern Europe, Asia and South America, as these become industrialised and experience socioeconomic growth and demographic changes, e.g., increasing urbanisation (2). Furthermore, somewhat stabilizing or even decreasing incidence rates have been reported in North America and Europe (3).

Denmark has one of the highest incidences of IBD. An increasing trend was observed from 1980 to 2013, where the incidence of CD rose from 5.2 to 9.1 per 100,000 person-years and the incidence of UC increased from 10.7 to 18.6 per 100,000 person-years (19). Similar high numbers were found in a Swedish study from the Uppsala region for the period from 2005–2009 with a mean overall incidence at 20.0 cases per 100,000 inhabitants (20). The highest IBD incidence ever reported is found in the Faroe Islands at 74 per 100,000 person-years from 2010–2014 (21). The record high incidence in this archipelago is driven by UC of which the Faroe Islands have the highest incidence in the world (2). In the Netherlands, the annual incidence of CD and UC increased from 5.8 and 11.7, respectively, per 100,000 in 1991 to 17.5 and 21.5 in 2010, corresponding to an average annual increase of 6% and 3.8% (22). An example of the increasing incidence in the younger population segment has been reported in French adolescents, where the incidence of CD and UC rose from 4.2 and 1.6 per 100,000 to 9.5 and 4.1 from 1988–1990 to 2009–2011, respectively (23).

Within Europe, the incidence of IBD is characterized by a north-south and an east-west gradient, with an incidence of UC in Northern and Southern Europe at 11.4 and 8.0 per 100,000, respectively, and an incidence of CD at 6.3 per 100,000 in Northern Europe in comparison to only 3.6 per 100,000 in Southern Europe, respectively (6). During the last decade, a significant rise in IBD has also been observed in Eastern Europe. Data from Western Hungary reveal that the incidence of CD and UC has reached a value of 8.9 and 11.9 per 100,000, respectively, which is a level comparable to that of Western Europe (24). Similar trends in incidence are observed in North America with figures from US and Canada. In Olmsted County, the incidence of CD and UC increased from 8.7 and 10.7 per 100,000 person-years between 1970 and 2010, but when looking at the period from 2000-2010, the incidence of CD and UC increased from 10.7 and 12.2 per 100,000 (25). In Ontario, Canada, the incidence of both UC and CD increased significantly from 10.7 to 12.1 and 9.6 to 12.1, respectively, per 100,000 person-years between 1999 and 2008 (8). Although, other regions of Canada have found a decreasing incidence. In Nova Scotia, the annual incidence rate for both CD and UC declined from 27.4 to 17.7 and 21.4 to 16.7, respectively, per 100,000 persons in the period 1996–2009 (26). A similar trend has been observed in Québec, where the annual incidence rates of CD and UC significantly decreased from 18.1 to 16.8 and 12.5 to 9.8, respectively, per 100,000 person-years, between 2001 and 2008 (27).

In Asia, recent studies have shown an increasing incidence of IBD. In Korea, the incidence of CD rose from nearly 0 to 1.3 per 100,000 in the period 1986 to 2005, and UC rose from 0.3 to 3.1 per 100,000. By 2006–2012, the average annual incidence of CD had reached 3.2 and 4.6, per 100,000 (28). IBD was thus almost non-existent 30 years ago, but this rising incidence has entailed that IBD is now adding to the disease burden in Asia, presumably due to environmental, lifestyle and dietary changes, e.g., industrial pollution, vaccination, increased usage of antibiotics and improved housing equipment such as refrigeration (29). Likewise, in Taiwan, the crude incidence of CD increased from 0.17 in 2001 to 0.47 per 100,000 in 2015, whereas that of UC increased from 0.54 in 2001 to 0.95 per 100,000 in 2015 (30). Interestingly, a population-based study assessed the relationship between urbanization and incidence of IBD in the Asia-Pacific region on newly diagnosed IBD cases between 2011 and 2013. The study included 13 countries or regions in Asia-Pacific with a mean annual IBD incidence at 1.50 per 100,000 (95% CI, 1.43–1.57). The highest incidence was found in India at 9.3 (95% CI, 8.38–10.31) and China at 3.6 (95% CI, 2.97–4.42). The incidence of IBD was higher across different areas of Asia with a higher population density and interestingly a south-north disease gradient (IRR: 0.94; 95% CI, 0.91–0.98) reported for IBD incidence and a west-east gradient (IRR: 1.14; 95% CI, 1.05–1.24) for CD incidence in mainland China. IBD and population density, as an expression for urbanization, entails several risk factors, e.g., better access to health services, pollution, altered diet, improved housing and the absence of microbial exposures and infections in early childhood,
also known as the hygiene hypothesis (31). Of note, it seems that the incidence of CD in Asia increases more rapidly than UC, making the prevalence of the two diseases more uniform (29).

Global prevalence of IBD

The prevalence of IBD has a varying geographical distribution like the incidence pattern of IBD (2). IBD is inherently associated with increasing prevalence over time due to chronicity with a lack of cure, the young age of onset, and low mortality and it may rise exponentially due to increasing incidence and population ageing.

In Europe, the prevalence of CD ranges from 1.5 to 213 cases per 100,000, while that of UC ranges from 2.4 to 294 per 100,000 (32). Overall, 0.3% of the European population is estimated to have been diagnosed with IBD, corresponding to a total of 2.5–3 million people (32). In North America, the prevalence of IBD has already reached 0.5% of the population and is projected to affect approximately 4 million persons by 2030 (33). Population-based studies from Olmsted County have shown that the prevalence of CD increased from 174 to 247 per 100,000 persons from 2001 to 2011 with a likewise increase in the prevalence of UC from 214 to 286 (25). Data from Canada reported a prevalence of IBD at 725 per 100,000 in 2018, which is estimated to rise to 981 by 2030 (33).

In Asia, the prevalence of IBD is much lower compared to the West. However, due to the rising incidence the IBD population in Asia is growing rapidly. Between 2001 and 2015, the prevalence of CD and UC in Taiwan increased from 0.6 and 2.1 to 3.9 and 12.8, respectively, per 100,000 (35). In 2014, Hong Kong reported a prevalence of UC and CD at 24.5 and 18.6 per 100,000 (34). Studies from South Korea have shown similar increasing trend in the prevalence rate of UC, which rose from 7.6 per 100,000 in 1997 (35), to 30.9 in 2005 (36). In a survey study from Japan much higher prevalence rates were found for both UC and CD. The annual prevalence rates of UC and CD, per 100,000, were 172.9 and 55.6, respectively (37). Nearly a 10-fold increase compared to a previous survey performed 25 years earlier (38).

Possible explanations of the altering epidemiology

Numerous components have been suggested in the shifting epidemiology of IBD with the majority of these being associated with rapid socioeconomic development in countries undergoing industrialisation and urbanisation (4). Genetics is one such factor, however, the observed rise in the incidence and prevalence of IBD far outweighs what can be explained by genetics alone. Moreover, genetics cannot explain the varying incidence in both time trends and within regions with inhabitants of comparable genetic background (39). Genetics is accountable for a small part of the pathogenesis and occurrence of IBD. A proband concordance rate of 58% was found in monozygotic twins implying that genetics is important in CD susceptibility, while this was found to lesser degree for UC (40). In 2001, the NOD2 gene was the first susceptibility gene identified as a risk factor for CD (41). The finding of the NOD2 gene has been followed by the identification of 201 susceptibility genes/loci in genome-wide association studies (GWAS). Still, just 25% of IBD heritability has been explained by these genetic studies (42).

Therefore, the identification of environmental factors has received an increased focus. However, identifying elements of importance is challenging since it could be the sum of a plethora of crucial environmental factors with each factor possibly only conferring a modest risk to the development of IBD. Therefore, scrutinising epidemiological differences between countries or regions with high vs. low occurrence of IBD, e.g., East and West, might elucidate factors that become prominent as IBD emerges. The hygiene hypothesis has been proposed to explain the increasing incidence and changing epidemiology of IBD as well as the rise of autoimmune diseases and allergies. According to the hygiene hypothesis, growing up in an environment with limited exposure to microbes, due to e.g., improved housing and sanitation, vaccines, antibiotics and clear drinking water, results in an impaired immune response later in life (43). These factors are associated with socioeconomic status and case-control studies have previously found higher socioeconomic status in IBD patients. However, this association is not corroborated by most recent studies, as improved hygiene has become more ubiquitous, thus making socioeconomic status a less pronounced factor in the development of IBD (44).

The involvement of changeable environmental components in disease onset occurrence, especially in UC, has been supported by migration studies (45,46). This phenomenon was recognised in a study of South Asian immigrants to the UK in 1992, which showed that the IBD incidence among first-generation immigrants was much higher than that among South Asians within Asia (47). Subsequent follow-up indicated that second-generation
immigrants had an increased risk of extensive UC compared to first-generation (48).

A Canadian population-based study also reported a similar lower incidence of IBD in first-generation immigrants. On the other hand, the incidence of IBD in second-generation assumed that of non-immigrants, though with regional exceptions (49). Likewise, a nation-wide Swedish study of IBD in immigrant populations showed lower IBD rates in first-generation compared to the native population. By second-generation, this decreased incidence was no longer detectable in the majority of the immigrant groups, while some groups experienced an increase (50). Little is known as to whether migration from high- to low-incidence areas is protective. However, a recent study from the Faroe Islands of Faroese immigrants to Denmark showed that Faroese-born Danish residents had an excess risk of UC compared to Danes, which decreased by second-generation in men and over two generations in women. Thus, the incidence of UC in third-generation imitated that of Danes. These findings emphasise the gene-environment interaction alongside the importance of environmental risk factors in the development of UC in generations of Faroese origin (51). Overall, these observations point to the impact of the environment on IBD risk over time, as migrant studies have suggested that environmental exposures occurring early in life are important, indicating that the role of timing is crucial.

**Environmental factors**

The global rapid increase of IBD within the last century has taken IBD from being an uncommon disease to affecting millions of people today. Therefore, environmental factors are assumed to have accelerated this rise in IBD, as genetic risk factors have remained unchanged for hundreds or even thousands of years (52).

The impact of risk factors depends on phenotype. For CD, known risk factors of high to moderate epidemiological evidence include smoking, tonsillectomy, appendectomy and urban living, with the latter also being a risk factor for IBD. Furthermore, IBD development has been associated with oral contraceptives, vitamin D deficiency, non-Helicobacter pylori-like enterohepatic Helicobacter species and antibiotic usage. Consumption of soft drinks increased the risk of UC. Protective factors have also been identified. High levels of vitamin D, bed sharing and physical activity reduced the risk of CD. For IBD, these factors included high levels of folate, breastfeeding and Helicobacter pylori infection, which was also found beneficial against the onset of CD and UC. For UC, tea consumption was a protective factor. Although environmental factors have been linked to the development of IBD, the mechanisms behind are not yet fully understood (53).

The spread of IBD to newly industrialised countries is likely due to these environmental influences, such as changing diet, better hygiene practices and westernised lifestyle. However, we need to examine whether the environmental factors prevalent in the West are the same as in the East.

One of most well recognised environmental risk factors is smoking. The effect of smoking in IBD development has been extensively studied in the West, where smoking has been found to be a risk factor for CD onset and contributing to a more severe disease course. Conversely, smoking has a somewhat positive influence on the disease course of UC, and UC develops more frequently in former or non-smokers. However, the effect of smoking in CD patients has not been replicated in populations outside the West, possibly due to smoking being alterable by ethnicity and genetic factors (53,54). In Asia-Pacific, an increased risk of UC onset was found in former smokers of both Asian and Australian Caucasians, differing from findings in the West. Furthermore, smoking was not found to be a risk factor for CD in Asians (55). Interestingly, an Indian study of 4,006 IBD patients found the majority of both CD and UC patients to be never smokers (56). Smoking prevalence in Western IBD patients has decreased; while newly industrialised countries have experience reduced smoking prevalence in the general population. Thus, long-term implications on these IBD populations can be expected (54).

The occurrence of IBD in newly industrialised regions coincides with a Westernisation of dietary habits, thus potentially changing the gastrointestinal microbiota, which may impair the immune system leading to the onset of IBD. The Westernised diet consists of processed foods high on saturated fats, animal protein, refined sugar, food additives combined with a low intake of fruits and vegetables, fiber and raw foods (57). Similar dietary habits as reported in the West seem to increase the risk of IBD in China, such as consumption of refined sugar, meat, saturated fats, daily intake of egg and milk, while e.g., tap water was found to be protective against UC (58). Tea and coffee consumption has also been found to be a protective factor in both Asia and Australia (55).

Physical activity has been found to be protective against CD onset in highly active persons, and this association
exists in both Europe and Asia (53,55,59). However, a Chinese systematic review reported on Chinese studies that had found physical activity to be protective against CD and UC (58). Breast feeding in both European and Asian populations identified a dose-dependant protective effect against the onset of CD and UC, which seems to be more beneficial in Asian populations compared to Western (59). The most beneficial effect was observed at duration of 12 months or more (4,55). Another risk factor is antibiotic usage in childhood, which has been associated with an increased risk of CD in children (60,61). However, the Asia-Pacific Crohn's and Colitis Epidemiology study (ACCESS) found a protective effect of antibiotics usage before the age of 15 years on both CD and UC development (55).

**Eastern and Western disease manifestation**

In the West, IBD presents with a bimodal age distribution with a peak in the incidence at around 20–30 years for both CD and UC, and a second peak in the incidence of UC at 60–79 years. However, the average age at IBD onset ranged from 31–34 years as reported from North America, Oceania and Western Europe (59). In the ACCESS study, the median age of CD patients was 34, while it was 42 for UC patients (29). However, a study from Taiwan reported the mean age of CD patients to be 38 years and 45 for UC patients for the period of 2001–2015 (30). In India, the mean age at diagnosis was reported at 38 years for UC and 34 for CD (56). A Korean study found the mean age at diagnosis to be 35 years for UC and 22 for CD, thus similar age for UC patients in the East as in the West, but CD patients in Korea were younger compared to the West (36).

In Europe, the gender distribution in UC occurrence is generally equally distributed between the genders. However, some studies have found higher risk of UC among men after the age of 45 years. CD has been reported to occur more frequently in females, though not all studies agree on this female predominance (59). In Asia, males more often suffer from IBD, and especially of CD, than females. For UC, Asian countries have reported similar gender distributions as Western countries (30,37). The higher incidence of IBD in men compared to women is also found in Korea, India and in other Asian studies (28,62). In Japan, smoking has been proposed to explain the gender difference in CD occurrence, as males more frequently smoke than women (37). Smoking is also more frequent in Korean men than women, where this observed predominance in men also occurs, however, smoking alone is not likely to explain the CD prevalence between men and women (63).

Industrialised countries have firstly reported an increase in UC incidence, which later has been followed by an increase in CD incidence. This incidence pattern was replicated in Japan, Hong Kong, South Korea and Malaysia, in chronological order, with UC being the most common condition. Interestingly, a decrease in the UC-to-CD incidence ratio has been reported in Taiwan, Hong Kong, South Korea and Malaysia, while Western countries have reported a steady ratio (30). On the other hand, a more notable difference occurs in disease presentation between East and West, as CD in Asia presents with an overrepresentation of perianal fistulas. A lack of family history and less frequent extra-intestinal manifestations has been reported in Asian IBD patients (56,63). In India, also only few patients have reported a positive family history, but this may reflect the short time period of IBD occurrence in this part of the world, thus family history is likely to become more pronounced in future studies (56,62). In the West, family history is a well-recognised risk factor for IBD due to similar genetic predisposition mixed with same environmental exposures (64).

The natural disease course of IBD may also differ in Eastern and Western countries. The prognosis today in the Western world is different from that reported from the last century probably related to better treatment. The disease course of IBD has changed, with reduced surgery rates and decreasing colorectal cancer (CRC) rates. In a systematic review of 44 population-based cohorts, Tsai et al. reported cumulative risks of first major abdominal surgery in patients with UC and CD diagnosed in the 21st century. Cumulative 5-year risk of surgery of 7.0% in UC, and 17.8% in CD were reported, which is substantially lower than those reported in patients diagnosed in the 20th century, where surgery rates of 9.5% in UC and 35.7 in CD were reported (65). A decrease in the rate of CRC malignancy has also been found since the start of the twenty-first century in a Danish cohort. Patients with IBD, particularly CD, were at increased risk for gastrointestinal malignancies. However, the relative risk of gastrointestinal malignancy decreased since 1978, possibly also due to better treatment (66). Several studies from the West have found that patients with CD have an increased mortality compared to the general population. A meta-analysis found that the all-cause standardized mortality ratio (SMR) based on inception cohort studies alone was 1.34 (95% CI, 1.15–1.56) (67). This was also found in a nationwide registry study from Denmark with a 50% higher mortality among CD patients than among
the general population. This risk was unchanged during the study period of 1982 to 2010 (68). Contrary to CD, the overall mortality for patients with UC is not greater than that of the general population. An all-cause SMR in inception cohort studies of 1.08 (95% CI, 0.97–1.21) was found in a meta-analysis covering population based studies (68). In Asia, the clinical long-term course is not well established (63), however, the early course has been found to be comparable to that of the West according to the ACCESS study. Although, Asian CD patients were more likely to experience complications (69). In Korea, bowel resection rates are lower than in the West and previously reported in studies from Korea and Japan, with the rates being equally distributed by gender for UC, but higher for males with a CD diagnosis (28). Survival is also different between East and West, with survival reported in Korean IBD patients (28) being higher than found in the West (70).

The search for optimal therapies with minimal adverse effects for these incurable disorders is an on-going priority. Although several advances have been made in IBD therapeutics in recent time, some patients will lose response to conventional therapies or not respond at all. New medications such as small-molecule drugs like JAK inhibitors and S1P-receptor inhibitors are promising, alongside the development of advanced biological treatment including newer anti-TNF and anti-IL-12/IL-23 antibodies. Furthermore, faecal microbiota transplant and stem-cell transplant may be future options for patients who do not wish medical therapy (71).

Conclusion

The pattern of IBD in the East resembles that of the West, though 50 years ago, indicating that a balance between East and West is approaching.

Interestingly, Japan has reported the highest prevalence rate of IBD compared to any other Asian country. Reasons for this observed trend may be improved diagnostic tools and treatment, increased disease awareness among health care personnel or it may also reflect differences in epidemiological methodology and target populations. Although both differences and similarities exists in the Eastern and Western epidemiology of IBD, with differences possibly caused by accessibility of health care, level of disease awareness among researchers, health personnel and the general population, alongside improved diagnostic tools and treatment, use of standardised case definitions and the availability of high quality population-based studies.

At present perhaps the most important difference lies within methodological differences in e.g., the registration and reporting of IBD and establishment of long-term appropriate and validated databases and registries with collection of prospective data. With the establishment of databases, we can foresee an evolution of the IBD epidemiology influenced by the findings in Asia adding information on the epidemiology of IBD and possibly also on the environmental factors influencing the occurrence and course of IBD.

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