



Evolving Epidemiology of IBD

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Abstract

Purpose of Review Once thought a disease of Western civilizations, the inflammatory bowel diseases (IBD) impose a global burden, now penetrating populations in Asia, Africa, and South America. We summarize similarities and differences in the epidemiology of IBD globally, highlighting gaps in knowledge where future study is needed.

Recent Findings While incidence of IBD is stabilizing (or even decreasing) in many westernized regions, prevalence continues to grow due to a young age of onset and low mortality. In newly westernized regions, IBD is beginning to penetrate populations comparable to the rapid increases seen in North America, Europe, and Oceania in the last century.

Summary IBD imposes a significant fiscal and resource burden on healthcare systems. As global prevalence of these diseases continues to increase, we desperately need to anticipate the future burden to proactively prepare our healthcare systems for the challenges of increased patient load and aging populations with comorbid conditions and longer disease course.

Keywords Inflammatory bowel disease · Epidemiology · Global health · Burden of disease · Crohn's disease · Ulcerative colitis

Introduction

Crohn's disease and ulcerative colitis, together inflammatory bowel disease (IBD), are chronic relapsing and remitting afflictions that impose a life-long burden on an increasingly large portion of the population—to the individual, to caregivers, and to society as well. Today, it is estimated that more than two million North Americans live with IBD, and that population is forecasted to be approaching four million by 2030 [1, 2, 3•]. The burden of these diseases encompasses aspects such as the direct cost of medications, hospitalizations, and surgeries; indirect

societal costs such as lost productivity, premature retirement, or premature death; and out-of-pocket personal costs to those afflicted and their caregivers attributable to travel to healthcare encounters, time off from work, and non-recoverable (i.e., from insurance or other third-party billing) costs of treatment [4•]. In 2018, the direct medical costs in Canada are conservatively estimated at \$1.28 billion, roughly \$4371 per person per year; attributable indirect costs impart a further burden of \$1.29 billion, or \$4781 per person per year; and, extrapolating from a US study [5], those with IBD are cumulatively faced with an additional \$541 million burden in out-of-pocket costs each year related to their disease [6]. By comparison, a recent study on the financial burden of gastrointestinal disorders in the USA ranked IBD as the fifth most costly gastrointestinal condition in annual healthcare expenditures, costing \$7.2 billion USD in 2015 [7].

Further to the tangible monetary costs of these illnesses are the intangible personal costs that they extoll. IBD is typically diagnosed in individuals between 18 and 35 years of age (although the rate of pediatric diagnosis has steadily been increasing over recent years) [8, 9] and has been shown to negatively impact general health, mental health, and social functioning at a time when many individuals are beginning to start families or careers [10–16].

Considering the burden of IBD, a source of particular concern is the fact that the prevalent population of IBD continues to grow. A systematic review of 119 studies investigating the

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incidence of IBD around the world finds that the incidence of IBD is steadily increasing in newly industrialized regions in Africa, Asia, and South America, but has become stable or even displays decreasing trends in parts of North America and Europe [17••]. Despite declining incidence trends in some regions, based on a further 69 prevalence studies also included in that systematic review, the prevalence of IBD continues to increase worldwide [17••]. Table 1 demonstrates the evolving incidence of IBD in the last generation [8, 18–49].

IBD in Westernized Nations

One of the previously held beliefs about the epidemiology of IBD was that it is a disease of the Western world, affecting primarily those of Caucasian descent in industrialized countries within Europe, North America, and Oceania. This idea has now been dismissed as we observe trends in newly westernized nations in Asia, the Middle East, and South America that are comparable to what was observed in the last century for the Western world [17••, 48••, 49–54].

In the Western world, IBD was heralded by the industrial revolution in the 1700s: manufacturing, increased air pollutants, dietary changes such as less plant-based fibers, and societal shifts from rural to urban living. Abercrombie's 1828 book describes several cases in the UK that, retrospectively, are thought to have been some of the earliest recorded cases of IBD [52, 55]; the term *ulcerative colitis* was ushered into medical vernacular by Sir Samuel Wilks in 1875 [56]; and the recognition of Crohn's disease as a distinct condition from ulcerative colitis was made by Crohn et al. in 1932 [57]. From those first few confirmed cases of IBD in the UK, the diseases exploded through the population during the latter half of the twentieth century [58]. However, at the turn of the twenty-first century, temporal trend studies are documenting that many countries in the Western world have incidence that is stabilizing and, in some regions, decreasing (Table 1).

Despite the stabilization in incidence, the Western world is experiencing compounding prevalence, which is observed in diseases with low mortality, a young age of onset, and no current-known cure; with a steady influx of new cases and relatively few annual deaths in the afflicted population, prevalence continues to grow—even if disease penetration through the population reaches a ceiling effect [3••, 53]. For example, numerous papers report stable or decreasing incidence rates in most regions of Canada [4••, 17••, 20, 58, 59]; despite this fact, historical trends have been analyzed for a forecasted growth from the current 270,000 Canadians living with IBD to 406,000 by 2030 [2, 60].

The rising prevalence of IBD over the last century and a half is a substantial concern for medical practitioners: namely, an aging population presents unique challenges for disease management due to the longer disease duration and a greater risk of

comorbid conditions [61–63]. Seniors (those aged 65+) are the fastest growing subpopulation of people with IBD due to both an aging population of previously diagnosed cases and newly diagnosed elderly-onset cases [4••]. Of particular concern for the care of this population is the risk of comorbid conditions and medication interactions: a 2015 cohort study found that elderly IBD patients have an average of nine prescribed medications, and 40% of those participants had an interaction with one of their IBD medications [63, 64]. Further, due to an increased risk of infection among seniors, there are higher concerns with prescribing immunosuppressants. A multi-center European study found that 11% of seniors in their cohort prescribed anti-TNF therapy developed a severe infection as compared to only 0.5% of senior controls (not on anti-TNF therapy) and 2.6% of controls aged under 65 years on anti-TNF therapy [63, 65]. As the population of IBD patients continues to age, clinicians will find an increasing need to work in multi-disciplinary teams to effectively manage comorbid conditions, positively influence patient adherence to management plans, and improve overall quality of life [62, 63].

IBD in Newly Westernized Nations

At the turn of the twenty-first century, the incidence of IBD is rising in many newly industrialized countries in Asia and Latin America (Table 1). The rise in incidence is believed to be secondary to westernization of cultures and societies in these regions. In the mid-to-late twentieth century, the typical Chinese diet had begun to resemble a Western diet: increased amounts of animal and dairy products, refined sugars, processed foods, and less plant-based fibers. China underwent an industrial revolution in the 1950s. Not coincidentally, the first documented case of ulcerative colitis in China was in 1956 [52]. As westernization of China continued into the new millennium, the incidence of IBD accelerated, leading to a growing prevalence: by 2000, there were approximately 2000 people in China with Crohn's disease and 10,000 people with ulcerative colitis; by 2010, 266,394 people in China were estimated to have IBD [52].

Similar to the trends now observed in China, we are finding familiar patterns of disease penetration in other westernizing nations around the world. The data provided in Abdulla et al.'s study documenting IBD in Bahrain, a Middle Eastern nation with an average population under $\frac{3}{4}$ of a million people from 1984 to 2014, reported an increase in IBD incidence from approximately 0.42/100,000 between 1984 and 2001 to 1.68/100,000 between 2002 and 2014 [54]. During almost the same period, the incidence in Hong Kong rapidly increased from 0.1/100,000 in 1985 to 3.1/100,000 in 2014 [51], but Hong Kong had begun the process of westernization decades before Bahrain. A similar trend is also described for Malaysia, which, as of 2013, still has a low prevalence of IBD:

Table 1 Evolving incidence of IBD over the past generation throughout the world. The average annual percentage change (AAPC) reflects the percent change in incidence across the study periods: 95% confidence

intervals (CI) that cross 0 are stable, below 0 are significantly decreasing, and above 0 are significantly increasing. Amalgamated data from Ng et al.'s systematic review, most recent study periods only [17••]

Country (region)	Time period	Average annual percent change (95% CI)	
		Crohn's disease	Ulcerative colitis
Canada (Manitoba) [18]	1990–2001	−0.4 (−2.4, 1.7)	−2.1 (−4.5, 0.5)
Canada (Ontario) [8]	1999–2008	1.7 (0.4, 2.9)	1.8 (0.5, 3.2)
Canada (Québec) [19]	2001–2008	−1.2 (−1.7, −0.7)	−3.6 (−5.3, −1.8)
Canada (Nova Scotia) [20]	1996–2009	−3.0 (−4.1, −1.9)	−1.2 (−2.4, −0.1)
Brazil (Piauí) [21]	1988–2012	11.1 (4.8, 17.8)	14.9 (10.4, 19.6)
Barbados (nationwide) [22]	2000–2004	−5.3 (−25.3, 20.1)	−2.6 (−21.5, 20.7)
China (Hong Kong) [23, 24]	1991–2006	4.4 (−0.7, 9.7)	1.8 (−10.0, 15.1)
Taiwan (nationwide) [25]	1998–2008	4.0 (1.0, 7.1)	4.8 (1.8, 8.0)
South Korea (Songpa) [26]	1991–2005	13.8 (8.7, 19.0)	9.5 (2.7, 16.7)
South Korea (nationwide) [27]	2006–2012	−2.4 (−4.7, 0.0)	−2.2 (−4.6, 0.2)
Malaysia (Kinta Valley) [28]	1990–2013	12.0 (−31.9, 84.0)	8.5 (1.8, 15.7)
Kuwait (nationwide) [29]	1990–1999	–	−1.7 (−8.9, 6.1)
Hungary (Veszprém) [30]	2002–2006	9.9 (−2.3, 23.6)	−6.2 (−20.2, 10.2)
Denmark (North Jutland) [31]	1988–2002	3.3 (−8.4, 16.6)	–
United Kingdom (Cardiff) [32]	2001–2005	1.1 (−0.8, 3.1)	–
Iceland (nationwide) [33]	1995–2009	−0.1 (−10.3, 11.3)	1.4 (−1.7, 4.6)
Sweden (Stockholm) [34]	1990–2001	2.2 (−2.2, 6.7)	–
Sweden (Uppsala) [35]	2005–2009	13.8 (2.4, 26.4)	5.3 (−1.5, 12.6)
Faroe Island (nationwide) [36]	2010–2014	2.3 (−9.5, 15.5)	2.0 (−15.8, 23.6)
Spain (Caceres) [37]	2000–2009	−3.8 (−18.7, 13.8)	2.4 (−10.0, 16.4)
Spain (Ciudad Real) [38]	2000–2012	7.2 (2.8, 11.8)	3.8 (−0.2, 7.9)
Croatia (Rijeka and Istria) [39]	1990–1994	7.8 (−1.4, 17.9)	–
Croatia (Zadar) [40]	2000–2010	13.5 (5.6, 21.9)	4.6 (−3.2, 13.1)
Croatia (Vukovarsko-Srijemska) [41]	1991–2010	4.5 (−0.3, 9.5)	12.3 (8.9, 15.8)
Malta (nationwide) [42]	1993–2005	0.8 (−6.5, 8.7)	4.6 (−0.8, 10.3)
Bosnia and Herzegovina (Tuzla) [43, 44]	1995–2006	34.4 (22.1, 47.9)	24.8 (11.0, 40.3)
France (Northern France) [45]	2006–2007	0.9 (−0.3, 2.2)	−1.3 (−2.8, 0.3)
Austria (Styria) [46]	1997–2007	2.7 (0.6, 4.8)	2.7 (0.0, 5.5)
Netherlands (South Limburg) [47]	1991–2002	−1.5 (−4.6, 1.6)	−5.4 (−8.1, −2.6)

9.24/100,000; however, there is a sharp increase in incidence from approximately 0.1/100,000 in the 1990–1994 period to 0.68/100,000 in the 2005–2009 period [66]. The Malaysian study reports significant variation between observed ethnic groups within the population, suggesting that the prevalence of IBD is much higher in the ethnic Indian population (24.91/100,000) than the Malay (7.0/100,000) or Chinese (6.9/100,000) populations [66]. The similarity in prevalence between ethnic Indians in Malaysia to westernized populations has been found in several studies and may in part be due to susceptibility genes (e.g., NOD2 and CARD15), which are reported to occur more frequently in the Indian population as compared to other Asian populations [66–69].

Environmental factors associated with westernization have a major impact on the incidence of IBD. The Asia-pacific Crohn's and Colitis Epidemiology Study (ACCESS) is a multi-national, population-based, prospective cohort study gathering data from China, Hong Kong, Indonesia, Sri Lanka, Macau, Malaysia, Singapore, Thailand, and Australia. Ng et al. matched IBD patients in the ACCESS cohort with healthy controls (matched on age [± 3 years], gender, ethnicity, and geographic region) to examine possible environmental factors for IBD in a largely Asian cohort (84%) [28]. Selected environmental risk factors for developing IBD among Asian participants are compared to the Western world in Table 2. These data

show some similarities—for example, breastfeeding is universally protective of IBD in Asia and the Western world. In contrast, dissimilarities also exist with the most interesting being the lack of association between current smokers and the diagnosis of Crohn's disease in Asia; smoking and Crohn's disease are well-established and reproducible risk factors throughout the Western world. Consequently, regional environmental risk factor studies are needed to explore the similarities and differences in IBD around the world (Table 2).

Looking to westernizing nations on the other side of the world, we do not yet have an accurate understanding of the incidence of IBD in most South American nations due in part to a lack of population-based studies from those regions; however, several epidemiologic studies of hospitalizations in Chile and other South American countries show similar trends to what is seen in China, Bahrain, Malaysia, and other newly westernized nations, suggesting that trends in incidence are likely to be quite similar in those regions as well [49, 50]. A systematic review of IBD in Latin America suggests that the incidence of Crohn's disease in Brazil has dramatically risen in the last 40 years from 0.08/100,000 in 1988 [21], to 0.68/100,000 between 1991 and 1995 [74], to 3.5/100,000 between 2001 and 2005 [74], and to 5.48/100,000 in 2015 [75, 76]. Similarly, the incidence of ulcerative colitis increased from 3.86/100,000 between 1991 and 1995 [74], to 5.3/100,000 in 2001–2005 [77] and to 8/100,000 as of 2015 [75]. That systematic review finds similar increases in several other South American regions as well (e.g., Puerto Rico and Barbados) [76].

At this point, very few epidemiologic studies are available on African populations. Molodecky et al.'s systematic

review of incidence and prevalence of IBD around the world includes five South African studies published 1975–1992 [58, 78–82]. An update of that systematic review in 2017 found only one additional study from North Africa (Algeria) [17••, 83]. In the Algerian study, although not enough data were provided to calculate an AAPC for inclusion in Table 1, the incidence of ulcerative colitis was found to have nearly doubled in only 5 years: in 2003, the incidence of ulcerative colitis in people ≥ 15 years of age was analyzed at 2.76/100,000; by 2007, the incidence had increased to 5.12/100,000.

The lack of epidemiologic studies concerning populations in newly westernized nations represents a major gap in current knowledge. A systematic review of world-wide incidence and prevalence studies on IBD published between Jan. 1, 1990, and Dec. 31, 2016, found 119 studies on incidence and 69 studies on prevalence [17••]; Fig. 1 displays the geographic distribution of populations studied, by region, to highlight the need for further study in newly westernized regions. The lack of epidemiologic data on incidence and prevalence in many countries (Fig. 1) is a limitation on defining the global burden of IBD. Hospitalization rates provide an indirect measure of disease penetration in a population that lacks data on incidence and prevalence. This is particularly relevant for newly westernized nations.

A global study evaluated hospitalization patterns from 1990 to 2016 among 34 countries belonging to the Organization for Economic Cooperation and Development (OECD) [85••]. This international study shows that countries with high hospitalizations for IBD are predominantly in the Western world and that most of these countries reported decreasing hospitalization rates over time. The reduction in

Table 2 Comparing selected environmental risk factors for developing IBD between Asia and the Western world. Legend: positive association (+), negative association (–), no significant association (null)

Selected environmental risk factors	Western nations [†]		Asian nations [‡]	
	Crohn's disease	Ulcerative colitis	Crohn's disease	Ulcerative colitis
Breast feeding > 12 months	–	–	–	–
Appendectomy	+/null	–	Null	Null
Antibiotic use ≤ 15 years of age	+	+	–	–
Flush toilet	+/null	Null	Null	–
Smoking: current vs. never-smoker	+	–	Null	Null
Smoking: ex vs. never-smoker	+	+	Null	+
Coffee (daily)	Null	Null	Null	–
Tea (daily)	Null	Null	–	–
Physical activity (daily vs. less often)	–	Null	–	Null

[†] Derived from a compilation of observational studies of environmental risk factors for IBD in Western nations [70–73] in the Ng et al. ACCESS case-control study [28]

[‡] Derived from a compilation of observational studies of environmental risk factors for IBD in Asia-only participants in the Ng et al. ACCESS case-control study [28]

average annual hospitalizations was postulated to be due to better disease management through better medications [54, 86, 87], better disease understanding and diagnostic skills and tools [43, 88], and through greater awareness of IBD [88].

In contrast, newly industrialized countries in Asia and Latin America have much lower rates of hospitalization for IBD; however, their rates are accelerating over time. For example, South Korea and Chile have among the fewest hospitalizations for IBD among OECD countries (15.4 and 9.0 per 100,000, respectively) [85••], but the rate of hospitalizations is accelerating by 5% per year (1996–2015) in South Korea and 6% per year (2001–2014) in Chile. The rising hospitalization rates in newly westernized nations are correlated with the rising incidence and prevalence of IBD in these regions. Consequently, newly industrialized countries in Asia and Latin America must expand their clinical infrastructure and resources to prepare for rising demands on their healthcare systems.

Conclusion

IBD is a global disease. However, the impact of IBD to society is regionally diverse. In the Western world, countries in North America, Europe, and Oceania are experiencing a stabilization in incidence, but a steadily rising prevalence. Throughout the Western world, the penetration of hospitalization and surgical costs continues to represent a significant portion of the direct healthcare costs of IBD; however, hospitalization and surgical rates are declining through these regions. Currently, the largest contributor to fiscal burden is medications—in particular, the rising penetrance of biologics [4••, 5, 89–91]. Modern disease management is creating better outcomes for IBD patients as these therapies are working. However, due to the high cost of biologics, we need to be able to anticipate the future burden of IBD more than ever in order to prepare healthcare systems for a growing number of patients and increased associated costs in the Western world.

Based on historical patterns, Coward et al. project that the prevalent population of IBD patients in North America will nearly double in the next 12 years, from approximately 2 million to almost 4 million [92••]. Additionally, IBD is expected to cost healthcare systems in Canada and the USA almost \$10 billion in 2018 (\$7.2 billion USD annual cost for the USA as of 2015 [7] and a conservative estimate of \$2.57 billion CAD annual cost for Canada as of 2018) [4••]. Beyond the almost doubling of the prevalent population, healthcare systems will need to manage the complications of the fastest growing subpopulation of IBD patients—an aging population with complications from longer disease duration and a greater risk of comorbid conditions [61–63]. Further, the rate of early-onset IBD, affecting people < 18 years old, has been rapidly increasing throughout the twenty-first century: a Canadian study found that between 1999 and 2010, the number of pediatric IBD patients increased by 50% [9, 93]. Similar to our aging IBD population, as we look into the future, those with early-onset IBD will also present more complex cases due to longer disease duration as they transition to adult and, eventually, senior IBD care.

In contrast, the prevalence of IBD in newly westernized societies remains low, but the incidence of IBD is accelerating rapidly. The incidence of IBD has yet to peak in these regions, and only time will tell if the incidence of IBD in Asia and Latin America will eventually approximate the values observed in the Western world. Nonetheless, the prevalence of IBD will steadily climb over the next generation in newly westernized societies—analogueous to the rising prevalence of the Western world during the twentieth century. Consequently, the international IBD community will need to work together and learn from each other to face the global burden of IBD. Based on the growing population of people afflicted with IBD, we must act quickly to prepare our healthcare systems for this mounting burden that they will have to endure so that the necessary care may still be provided to those who need it.

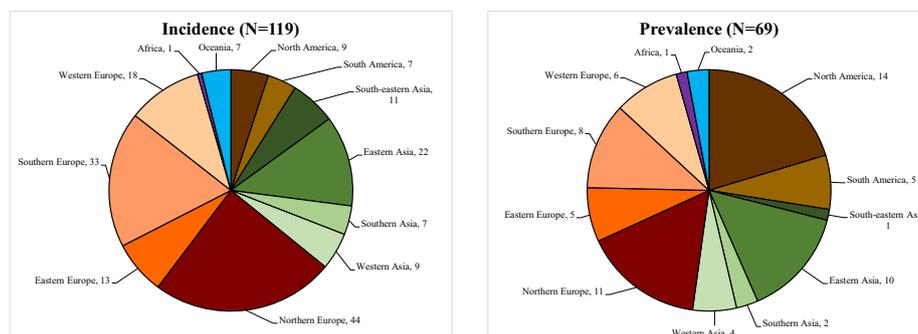


Fig. 1 Number of population studies investigating the incidence or prevalence of IBD 1990–2016 by geographic region. Some incidence studies report data for multiple regions; the incidence graph represents

119 studies covering 181 regional populations [17••]. The geographic regions were defined by the United Nations Statistics Division [84]

Compliance with Ethical Standards

Conflict of Interest Joseph Windsor declares no conflict of interest.

Gilaad Kaplan reports personal fees from Pfizer, Janssen, Abbvie, and Takeda, outside the submitted work. Dr. Kaplan has a patent issued (Treatment of Inflammatory Disorders, Autoimmune Disease, and PBC, UTI Limited Partnership, assignee. Patent 62/555,397. 7 Sept. 2017).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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