

Chapter 2

The Changing Epidemiology of IBD

Anders Ekblom

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Key Points

- Incidence rates of IBD are increasing in areas of the world previously unaffected by these diseases.
- Among children, the incidence of Crohn's disease (but not ulcerative colitis) has greatly increased.
- Age-specific incidence rates are highest for patients aged 20–40 years old.
- Specific population incidence rates first increase for ulcerative colitis, with an increase in Crohn's disease seen 15–20 years later.
- Environmental factors associated with a decreased incidence of ulcerative colitis include smoking and appendicitis.
- Smoking is associated with a greater incidence of Crohn's disease. A putative “North–South” in Northern America and Europe has been challenged by more recent studies.

Introduction

It has been possible in any given year during the last hundred years to write a review article or a book chapter titled “The changing epidemiology of IBD” which could make the case that what was written last year at least to some extent

A. Ekblom (✉)

Department of Medicine, Clinical epidemiology unit M9:01,
Karolinska Institute, 17176 Stockholm, Sweden
e-mail: anders.ekblom@ki.se

was obsolete. The reason for this is better methodology on how to deal with observational data but foremost is that the disease entities ulcerative colitis (UC) and Crohn's disease (CD) during the last century have affected new populations or new segments of populations. Why should we be interested in such changes? There are at least three different reasons:

1. In order to fulfill our goal of finding primary prevention measures for inflammatory bowel disease (IBD), changes in the descriptive epidemiology could provide hints of the underlying causes of these diseases.
2. These changes should serve as benchmarks when new hypothesis of the etiology are presented.
3. The numbers are of interest for providers of healthcare in order to assure that there is clinical expertise available for these patient groups.

IBD up to 1950

During the nineteenth century, there are scattered cases of UC described especially in the British literature. Already in 1909 there was a symposia held at the Royal Society of Medicine in London, where 317 patients from different hospitals were presented [1]. In 1913, Kenneth Dalziel, a Scottish surgeon, reported nine patients with a new disease entity described as "chronic intestinal enteritis and not tuberculosis" [2]. These nine patients are the first bona fide cases of CD although other patients have been described during the same time period both from Scandinavia and Ireland [3]. However, it was not until 1932 when Dr Burrill B Crohn introduced the term "regional ileitis" [4] and CD as a defined clinical entity was established.

Different case series were presented during the first half of the twentieth century, but they have in most instances one common feature; the lack of a denominator making it impossible to assess any prevalence or incidence figures. It is therefore impossible to describe any temporal trends during this time period. To use only the number of patients as a proxy is also without meaning as it is impossible to disentangle if the increasing number of IBD patients is due to a better awareness among clinicians or reflects a real increase in incidence.

However, there are two retrospective studies in defined populations from 1935 and onward, which have tried to assess the incidence. In one study from Rochester Minnesota, the authors were able to demonstrate an annual incidence for UC of 6.0/100,000 for the period 1934–1944 and an annual incidence for CD of 1.9/100,000 for the period 1935–1954 [5, 6]. In another study from Cardiff, UK, there was an annual incidence of 0.2/100,000 for CD during the period 1935–1945 [7]. Finally, there is one study of data from the US Army where the risk of discharge for an underlying cause of UC was assessed, where Jewish ethnicity was associated with an increased risk of such discharge compared to other ethnic groups [8].

Thus, in 1950 there was a growing understanding of a correlation between UC and CD (see below), the hypothesis of a Jewish ethnicity as risk factor had been formulated, and that IBD at least in some populations constituted a clinical problem of some magnitude.

1950–1975

During this period, there were an abundance of retrospective studies published from different populations, especially in Western Europe [9–12] but also in Northern America [13]. There were some common patterns with regards to the descriptive epidemiology in all these studies; there was a strong correlation between UC and CD, i.e., populations with a high incidence or mortality of UC had also a high incidence of mortality of CD and vice versa [14]. There are at least three possible partly overlapping explanations for these correlations.

1. Misclassification of either UC or CD which would lead to a false high incidence of either one of the disease entities.
2. There are shared genetic or other environmental risk factors for the two diseases.
3. It is the same disease and UC and CD represent opposite ends of a continuous spectra.

Later studies have shown an association between family occurrence of UC and CD, i.e., individuals with a family history of CD are at an increased risk for CD and vice versa [15]. However, such an association is not sufficient to explain the temporal trends for these diseases when they emerge. An increase in UC precludes an increase in CD with around 15–20 years [16]. During this transition period, the increase in incidence and the age distribution will change. Populations with a low annual incidence have an almost flat age-specific incidence, but during the transition from low incidence to high the increase is most pronounced in the age group of 20–40 years both for UC and CD [9, 17]. Although there have been quite a few reports about a second peak in older ages (60+), the existence of such peak remains controversial, and it has been argued that this second peak represents a delayed diagnosis made when the disease relapses [7].

There were also rather small variations in the incidence figures after the transition period 4.0–8.0/100,000 for CD and 15–20/100,000 for UC [16]. Moreover, the age-specific incidence was similar in most populations, such as Sweden and Olmsted County, USA [16, 18, 19]. It is also worth pointing out that due to the differences in the start of the transition period, the prevalence figures could vary substantially in different populations although they had the same annual incidence. This means that prevalence figures are highly unreliable tools to compare the occurrence of IBD in different populations or over time.

Other features which changed during this period were the phenotypes, such as the extent of the disease and localization. In the 1960s, ulcerative proctitis or distal colitis emerged as a specific phenotype [20] as common as pancolitis in patients with UC [16]. In the case of CD, distal ileitis had been the normal feature, but during the 1960s a new phenotype + Crohn's colitis was described [21]. This disease entity had probably to some extent previously been categorized as UC, but it was obvious that this clinical phenotype became more frequent during the second part of the twentieth century.

During this period, the first reports were published of cigarette smoking as a protective factor against UC [22, 23]. Many exposures, especially dietary, such as

refined sugar, margarine, etc., was proposed as etiological exposures, but the results from analytical studies did not show consistent results [24]. Jewish ethnicity and high socioeconomic status were repeatedly shown to be associated with an increased risk of IBD [11, 25]. However, these studies were in most instances small and with a study design, which was not always optimal.

1975–2000

During this time period, an ever increasing number of retrospective studies were published with descriptive data from different parts of the world although mainly Western Europe and Northern America. It then became obvious that some new characteristics of IBD had emerged as follows;

1. There were reports of a North–South gradient in the occurrence of IBD both from Northern America and Europe [26] in the first half of the period an observation which was challenged in the later part of the period [27] and a “new” hypothesis emerged speculating in a West–East gradient.
2. The incidence of IBD seems to respect national borders [28, 29] although there are exceptions such as in Greece where Crete has higher incidence than the rest of the country [30, 31].
3. In some populations, a birth-cohort effect could be demonstrated [16, 32] indicating that early exposures are of importance in the etiology of IBD.
4. In line with this good hygiene during childhood was repeatedly implicated as a risk factor both directly and indirectly [33, 34].
5. Previous findings of high socioeconomic status as a risk factor for IBD was contradicted in studies from this period and even a reverse association was found [35].
6. Incidence studies from Israel did challenge the notion of Jewish ethnicity as an independent risk factor as the incidence of IBD in Israel did not differ from populations in Western Europe and Northern America [27].
7. Immigration studies especially from the UK also showed that second generation immigrants from the West Indies [36] and the Indian subcontinent [37, 38] had the same or even higher incidence of IBD as the background population casting doubts of a special vulnerability among Caucasians.
8. Minorities often with a lower socioeconomic status, such as Maoris in New Zealand [39], Bedouins in Israel [40], and Aborigines in Canada [41] were found to be at a substantially lower risk for IBD.
9. The pattern of a higher incidence in UC compared to CD turned out not to be a generalized phenomena when studies from France [27] and some parts of Canada [42] were able to demonstrate the opposite.

During this period, the first prospective studies of the incidence in IBD were published [27, 43], highlighting the problem of indeterminate colitis [44] something which can be downplayed in retrospective studies. Indeterminate colitis

turned out to be much more common than previously thought [45] and it still remains to be established if it is an entity of its own. The most prominent prospective study was a collaborative effort from 20 European centers 1991–1993. The study was able to demonstrate that the North–South gradient seemingly was history and that the incidences of IBD in different populations throughout Europe were remarkably uniform [27].

Smoking remained the only environmental factor which consistently was associated with IBD; as a protective factor for UC and a risk factor for CD [46, 47], in the latter case smoking also seems to aggravate the disease course [48]. Ex-smoking status, on the other hand, seems to increase the risk of UC [49]. Oral contraceptive use was also implicated as a risk factor for CD [50], especially in the USA [51], but a female predominance of CD in high incidence areas was already present before the introduction of oral contraceptives in the 1960s. *Mycobacterium paratuberculosis*, already hypothesized as an etiological factor by Dalziel in 1913 [2], was proposed repeatedly [52, 53] and studied extensively during this period but no causal association could be established [54]. A new association was also identified for UC as appendectomy was shown to be protective against UC [55, 56]. However, in-depth studies seemingly revealed that it was the underlying appendicitis at a younger age that was protective not the appendectomy as such [57]. This is of great interest as the change for the incidence for appendicitis also remains an enigma similar to that of IBD and interestingly early hygiene exposures has been hypothesized to be an underlying cause [58].

Thus, in the end of the last century, we were facing an epidemic of IBD so far mainly affecting Western Europe and Northern America, where it had become one of the most common patient groups for gastroenterologists. The scientific community had failed to identify any primary preventative measures as the underlying etiology remained elusive. Smoking, as a protective factor for UC, identified already in the 1950s was the only environmental factor, where a casual association had been established.

2000 and Onward

The beginning of the twenty-first century meant that some of the established facts of the descriptive epidemiology of IBD were challenged again. The notion that the maximum annual incidence for CD in high incidence population was below 10.0/100,000 was contradicted by findings from Canada, where incidence figures as high as 20/100,000 were reported [59]. However, the data source can be questioned, but incidence figures from Norway [60] and New Zealand [39] also yielded higher numbers than previously experienced. IBD in children had, during the twentieth century, been seen as a rarity [61], but reports starting in Scotland [62] and later from Sweden [63, 64] could show a remarkable increase in incidence in CD in children but a stable incidence for UC.

Outside Western Europe and Northern America, we can now follow a pattern in the incidence of IBD similar to that we experienced around 1950:

1. Eastern Europe: Incidence figures from Hungary [65] clearly indicates that the transition period is over and that Hungary now has a pattern similar to Western Europe, while Croatia seems to be in the transition period [66]. This is contrast to the neighboring countries, such as Poland [67], Romania [68], and Slovakia [69], all of which still have a low incidence.
2. Southern America and Caribbean: Puerto Rico [70] and Barbados [71] have started to show an increase in incidence, and there are indications that a similar phenomenon is under way in Chile [72] and Brazil [73].
3. Africa: With the exception of South Africa, where those with a Caucasian background have an incidence similar to that of Western Europe [25], information is scarce but there are no indications of a rise in incidence.
4. Middle East with the exception of Israel: Although there is still a low incidence, there are signs of an increase in Lebanon [74], Saudi Arabia [75], and Iran [76].
5. India: In a very thorough cross-sectional study in Punjab, the authors could report an incidence figure for UC of 6.0/100,000 [77] perhaps indicating a start of a transition to a higher incidence.
6. China: There is almost a total lack of descriptive epidemiologic data, but there are indications of an emerging raise in the urban population for UC [78] and the consensus at the 2004 Asian Pacific Week in Beijing, China was: "A progressive rise in the prevalence of IBD is discernable in most Asian Pacific countries, more so for UC than CD" [79].
7. Korea and Japan: Incidence and prevalence figures of IBD during the twentieth century indicated a low incidence [80, 81], but the number of patients which have been presented especially from Japan [82] indicates that the incidence is substantially higher than previously thought.
8. Australia and New Zealand: The incidence figures and temporal trends seem to be same as in Western Europe and Northern America [39].

The analytical studies which have been done in these low incidence populations have not yielded any new information; smoking, family history of IBD, oral contraceptive use, and appendectomy have emerged as risk or protective factors with risk estimates similar to those reported from high incidence populations [82–84]. The only exception is high socioeconomic standard which is associated with an increased risk similar to that in Western Europe and Northern America 25–50 years ago.

Conclusions

The last hundred years have taught us a lot of the descriptive epidemiology of IBD, and we can now with some certainty postulate what will happen in the next 20 years in what is at present low incidence population. There will be an increase and there

will be reasons to believe that IBD patients will, in the future, constitute a major part of the patients for gastroenterologists in Asia, Southern America, as well as East Europe. Hopefully, the access to these patient groups will enable the research community to find the underlying etiology in order to find strategies for primary prevention, but such an endeavor urgently needs new hypothesis. We do not need etiological studies of smoking, oral contraceptives without better characterization of the underlying phenotype and potential interactions with different genotypes.

References

1. Hawkins HP. Natural history of ulcerative colitis and its bearing on treatment. *Br Med J*. 1909; 1:765–70.
2. Dalziel TK. Chronic interstitial enteritis. *BMJ*. 1913;2:1068–70.
3. Walker JF, Fielding JF. Crohn's disease in Dublin in the latter half of the nineteenth century. *Ir J Med Sci*. 1988;157:235–7.
4. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathological and clinical entity. *J Am Med Assoc*. 1932;99:1323–9.
5. Stonnington CM, Philips SF, Melton III LJ, Zinsmeister AR. Chronic ulcerative colitis: incidence and prevalence in a community. *Gut*. 1987;28:402–9.
6. Sedlack RE, Nobrega FT, Kurland LT, Sauer WG. Inflammatory colon disease in Rochester, Minnesota, 1935–1964. *Gastroenterology*. 1972;62:935–41.
7. Rose JD, Roberts GM, Williams G, Mayberry JF, Rhodes J. Cardiff Crohn's disease jubilee: the incidence over 50 years. *Gut*. 1988;29:346–51.
8. Acheson ED. The distribution of ulcerative colitis and regional enteritis in United States veterans with particular reference to Jewish religion. *Gut*. 1960;1:291–3.
9. Samuelsson, S.M. (1976) *Ulcerös colit och proctit*. Thesis. Uppsala: Department of Social Medicine, University of Uppsala.
10. Norlén BJ, Krause U, Bergman L. An epidemiologic study of Crohn's disease. *Scand J Gastroenterol*. 1970;5:385–90.
11. Hellers G. Crohn's disease in Stockholm County, 1955–1974. *Acta Chir Scand*. 1979;490 (Suppl1):1–84.
12. Evand JG, Acheson ED. An epidemiological study of ulcerative colitis and regional enteritis in the Oxford area. *Gut*. 1965;6:311–24.
13. Monk M, Mendeloff AI, Siegel CI, Lilienfeld A. An epidemiological study of ulcerative colitis and regional enteritis among adults in Baltimore. I Hospital incidence and prevalence, 1960 to 1963. *Gastroenterology*. 1968;54(Suppl):822–4.
14. Sonnenberg A. Geographic variation in the incidence of and mortality from inflammatory bowel disease. *Dis Colon Rectum*. 1986;29:854–61.
15. Orholm M, Munkholm P, Langholz E, Haagen Nielsen O, Sørensen TIA, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med*. 1991;324:84–8.
16. Ekblom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology*. 1991;100:350–8.
17. Bergman L, Krause U. The incidence of Crohn's disease in central Sweden. *Scand J Gastroenterol*. 1975;10:725–9.
18. Loftus Jr EV, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Crohn's disease in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gastroenterology*. 1998;114:1161–8.
19. Loftus Jr EV, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gut*. 2000;46:336–43.

20. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative proctitis in central Sweden 1965–1983. A population-based epidemiological study. *Dig Dis Sci*. 1991;36:97–102.
21. Lockhart-Mummery HE, Morson BC. Crohn's disease (regional enteritis) of the large intestine and its distribution from ulcerative colitis. *Gut*. 1960;1:87–105.
22. Boller R. Erfahrungen und 89 Colitis-ulcerosa-Fällen der Abteilung Boller im allgemeinen Krankenhaus Wien. *Gastroenterologia*. 1956;86:693–6.
23. Samuelsson SM, Ekbom A, Zack M, Helmick CG, Adami HO. Risk factors for extensive ulcerative colitis and ulcerative proctitis: a population based case-control study. *Gut*. 1991;32:156–30.
24. Persson PG, Ahlbom A, Hellers G. Crohn's disease and ulcerative colitis. A review of dietary studies with emphasis on methodologic aspects. *Scand J Gastroenterol*. 1987;22:385–9.
25. Wright JP, Froggatt J, O'Keefe EA, et al. The epidemiology of inflammatory bowel disease in Cape Town 1980–1984. *S Afr Med J*. 1986;70:10–5.
26. Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation in inflammatory bowel disease within the United States. *Gastroenterology*. 1991;100:143–9.
27. Shivananda L, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European collaborative study on inflammatory bowel disease (EC-IBD). *Gut*. 1996;39(5):690–7.
28. Brahme F, Lindstrom C, Wenckert A.. An epidemiological study of incidence, prevalence, mortality, and secular trends in the city of Malmö, Sweden. *Gastroenterology*. 1975;69:342–51.
29. Binder V, Both H, Hansen PK, Hendriksen C, Kreiner S, Torp-Pedersen K. Incidence and prevalence of ulcerative colitis and Crohn's disease in the County of Copenhagen 1962–1978. *Gastroenterology*. 1982;83:563–8.
30. Manousos ON, Koutroubakis I, Potamianos S, Roussomoustakaki M, Gourtsoyiannis N, Vlachonikolis IG. A prospective epidemiologic study of Crohn's disease in Heraklion, Crete. Incidence over a 5-year period. *Scand J Gastroenterol*. 1996;31:599–603.
31. Manousos ON, Giannadaki E, Mouzas IA, et al. Ulcerative colitis is as common in Crete as in northern Europe: a 5-year prospective study. *Eur J Gastroenterol Hepatol*. 1996;8:893–8.
32. Sonnenberg A, Koch TR. Period and generation effects on mortality from idiopathic inflammatory bowel disease. *Dig Dis Sci*. 1989;34:1720–9.
33. Gent AE, Helliler MD, Grace RH, Swarbrick ET, Coggon D. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet*. 1994;343:766–7.
34. Montgomery SM, Pounder RE, Wakefield AJ. Infant mortality and the incidence of inflammatory bowel disease. *Lancet*. 1997;349:472–3.
35. Ekbom A, Adami HO, Helmick CG, Jonzon A, Zack M. Perinatal risk factors for inflammatory bowel disease: a case-control study. *Am J Epidemiol*. 1990;132:1111–19.
36. Bartholomew C, Butler A. Inflammatory bowel disease in the West Indies. *Br Med J*. 1979;2:824–5.
37. Jayanthi V, Probert CSJ, Pinder D, Wicks ACB, Mayberry JF. Epidemiology of Crohn's disease in Indian migrants and the indigenous population in Leicestershire. *Q J Med*. 1992;298:125–38.
38. 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.
39. Geary RB, Richardson A, Frampton CM, Collett JA, Burt MJ, Chapman BA, et al. High incidence of Chron's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis*. 2006;12:936–43.
40. Odes HS, Fraser D, Fenyves D, Fraser GM, Sperber AD. Inflammatory bowel disease in the Bedouin Arabs of southern Israel: rarity of diagnosis and clinical features. *Gut*. 1991;32:1024–6.
41. Blanchard JF, Bernstein CN, Wajda A, Rawsthorne P. Small-area variations and socioepidemiographic correlates for the incidence of Crohn's disease and ulcerative colitis. *Am J Epidemiol*. 2001;154:328–35.

42. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol*. 1999;149:916–24.
43. Moum B, Vatn MH, Ekbom A, et al. Incidence of ulcerative colitis and indeterminate colitis in four counties in southeastern Norway, 1990–1993. *Scand J Gastroenterol*. 1996;31:362–6.
44. Price AB. Overlap in the spectrum of non-spectrum inflammatory bowel disease – 'colitis-indeterminate'. *J Clin Pathol*. 1978;31:567–77.
45. Moun B, Ekbom A, Vatn MH, et al. Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective population based study in south eastern Norway. *Gut*. 1997;40:328–32.
46. Harries AD, Baird A, Rhodes J. Non-smoking: a feature of ulcerative colitis. *Br Med J (Clin Res Ed)*. 1982;284:706.
47. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Br Med J (Clin Res Ed)*. 1989;34:1841–54.
48. Cottone M, Roselli M, Orlando A, Oliva L, Cappello M, Traina M, et al. Smoking habits and recurrence in Crohn's disease. *Gastroenterology*. 1994;106:643–8.
49. Tysk C, Järnerot G. Has smoking changed the epidemiology of ulcerative colitis? *Scand J Gastroenterol*. 1992;27:508–12.
50. Rhodes JM, Cockel R, Allan RN, Hawker PC, Dawson J, Elias E. Colonic Crohn's disease and use of oral contraception. *Br Med J*. 1984;1:595–96.
51. Boyko EJ, Theis MK, Vaughan TL, Nicol-Blades B. Increased risk of inflammatory bowel disease associated with oral contraceptive use. *Am J Epidemiol*. 1994;140:268–78.
52. Morgan KL. John's and Crohn's. Chronic inflammatory bowel disease of infectious aetiology? *Lancet*. 1987;1(8540):1017–9.
53. Hermon-Taylor J. Causation of Crohn's disease: the impact of clusters. *Gastroenterology*. 1993;104:643–6.
54. Sartor RB. Does *Mycobacterium avium* subspecies paratuberculosis cause Crohn's disease? *Gut*. 2005;54:896–8.
55. Gilat T, Hachon D, Lilos P, Langman MJS. Childhood factors in ulcerative colitis and Crohn's disease. *Scand J Gastroenterol*. 1987;22:1009–24.
56. Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. Appendectomy protects against ulcerative colitis. *Gastroenterology*. 1994;106:1251–3.
57. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. *N Engl J Med*. 2001;344:808–14.
58. Barker DJP, Morris JA. Acute appendicitis, bathrooms, and diet in Britain and Ireland. *Br Med J*. 1988;296:953–8.
59. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol*. 2006;101:1559–68.
60. Moum B, Vatn MH, Ekbom A, et al. Incidence of Crohn's disease in four countries in south-eastern Norway 1990–93. A prospective population-based study. *Scand J Gastroenterol*. 1996;31:355–61.
61. Lindberg E, Lindquist B, Holmquist L, Hildebrand H. Inflammatory bowel disease in children and adolescents in Sweden, 1984–1995. *J Pediatr Gastroenterol Nutr*. 2000;30:259–64.
62. Armitage E, Drummond H, Ghosh S, Ferguson A. Incidence of juvenile-onset Crohn's disease in Scotland. *Lancet*. 1999;353:1496–7.
63. Askling J, Grahnquist L, Ekbom A, Finkel Y. Incidence of paediatric Crohn's disease in Stockholm, Sweden. *Lancet*. 1999;354:1179.
64. Hildebrand H, Finkel Y, Grahnquist L, Lindholm J, Ekbom A, Askling J. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990–2001. *Gut*. 2003;52:1432–4.
65. Lakatos L, Mester G, Erdelyi Z, et al. Striking elevation in incidence and prevalence of inflammatory bowel disease in a province of Western Hungary between 1977–2001. *World J Gastroenterol*. 2004;10:404–9.

66. Sincić BM, Vucelić B, Persić M, Brncić N, Erzen DJ, Radaković B, et al. Incidence of inflammatory bowel disease in Primorsko-goranska County, Croatia, 2000–2004: A prospective population-based study. *Scand J Gastroenterol*. 2006;41(4):437–44.
67. Wiercinska-Drapalo A, Jaroszewicz J, Flisiak R, et al. Epidemiological characteristics of inflammatory bowel disease in north-eastern Poland. *World J Gastroenterol*. 2005;11:2630–3.
68. Gheorghe C, Pascu O, Gheorghe L, et al. Epidemiol inflammatory bowel disease adults who refer gastroenterology care Romania multicentre study. *Eur J Gastroenterol Hepatol*. 2004;16:1153–9.
69. Prikazka M, Letkovicova M, Natejikova V. Crohn's disease in Slovakia: prevalence, socioeconomic and psychological analysis. *Eur J Epidemiol*. 1998;14:49–53.
70. Appleyard CB, Hernandez G, Rios-Bedoya CF. Basic epidemiology of inflammatory bowel disease in Puerto Rico. *Inflamm Bowel Dis*. 2004;10:106–11.
71. Edwards CN, Griffith SG, Hennis AJ, Hambleton IR. Inflammatory bowel disease: Incidence, prevalence, and disease characteristics in Barbados, West Indies. *Inflamm Bowel Dis*. 2008;14(10):1419–24.
72. Figueroa CC, Quera PR, Valenzuela EJ, et al. Inflammatory bowel disease: experience of two Chilea centers. *Rev Med Chil*. 2005;133:1295–304.
73. Souza MH, Troncon LE, Rodrigues CM, et al. Trends in the occurrence (1980–1999) and clinical features of Crohn's disease and ulcerative colitis in a university hospital in southeastern Brazil. *Arq Gastroenterol*. 2002;39:98–105.
74. Abdul-Baki H, ElHajj I, El-Zahabi LM, et al. Clinical epidemiology of inflammatory bowel disease in Lebanon. *Inflamm Bowel Dis*. 2007;13:475–80.
75. Al-Ghamdi AS, Al-Mofleh IA, Al-Rashed RS, et al. Epidemiology and outcome of Crohn's disease in a teaching hospital in Riyadh *World J Gastroenterol*. 2004;10:1341–4.
76. Aghazadeh R, Zali MR, Bahari A, et al. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol*. 2005;20:1691–5.
77. Sood A, Midha V, Sood N, et al. Incidence prevalence ulcerative colitis Punjab north India. *Gut*. 2003;52:1587–90.
78. Jian L, Xia B, Li J, Ye M, Yan W, Deng Y, et al. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. *Inflamm Bowel Dis*. 2006;12:212–17.
79. Quyan Q, Tandon R, Goh KL, et al. The emergence of inflammatory bowel disease in the Asian Pacific region. *Curr Opin Gastroenterol*. 2005;21:408–13.
80. Yoon CM, Kim SB, Park IJ, et al. Clinical features of Crohn's disease in Korea. *Gastroenterol Jpn*. 1988;23:576–81.
81. Morita N, Toki S, Hirohashi T, et al. Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. *Gastroenterology*. 1995;30 Suppl 8:1–4.
82. Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. *Inflamm Bowel Dis*. 2005;11:154–63.
83. Gheorghe C, Pascu O, Cheorghe L, et al. Epidemiology of inflammatory bowel disease in adults who refer to gastroenterology care in Romania: a multicentre study. *Eur J Gastroenterol Hepatol*. 2004;16:1153–9.
84. Firouzi F, Bahari A, Aghazadeh R, et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: a case control study in Iran. *Int J Colorectal Dis*. 2006;21:155–9.



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