I: Clues to aetiology and pathogenesis

1: Global changes in incidence

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Introduction

Variation in disease occurrence is the essence of epidemiology. When this variation is between place or person, and standardised measures are available, measurement of such variation can be relatively accurate, albeit often expensive and laborious, as demonstrated by the European collaborative study on inflammatory bowel disease (EC-IBD) [1]. In contrast, measurement of variation over time is usually fraught with difficulty and any trends revealed, unless substantial, are often surrounded by uncertainty. With regard to inflammatory bowel disease (IBD), more sensitive diagnostic techniques, widening case definitions, increasing availability of specialist investigation and greater public and professional awareness of both diseases will all serve to increase the numbers of new diagnoses and have the potential to contribute to an apparent rise in incidence. In this chapter we will review recent data on the incidence of IBD worldwide and, at the risk of over generalising, assess what they imply as to the aetiology of IBD.

The rise in incidences of ulcerative colitis and later Crohn's disease that was seen in many Western countries during the past century, preceded the growth of modern gastroenterology and was evident in both individual studies and routine morbidity and mortality data [2–4]. Over the last few years, however, there have been a number of conflicting reports of the incidence of both diseases either continuing to increase, or being stable or even declining. For example, Bernstein *et al.*, using health insurance data for Manitoba, Canada, reported an overall incidence of Crohn's disease of 146/million/year, the highest yet reported, whereas a few hundred miles to the south in Olmsted County, Minnesota, Loftus *et al.* found an incidence over a similar period of 69/million/year [5, 6]. An almost two-fold variation has also been reported from the United Kingdom, with Kyle finding the incidence of Crohn's disease continuing to rise in north-east Scotland at 98/million/year in 1985–87, while in the Cardiff area incidence was declining with the figure for 1986–90 being 62/million/year and 56/million/year for 1991–95 [7, 8]. There have been fewer reports of the time trends in incidences of ulcerative colitis, which may reflect the additional challenge for epidemiological studies of distinguishing it from non-recurrent, mainly infective forms of colitis. Even so, in the (EC) IBD study the incidence of ulcerative colitis in parts of Europe as far apart as Iceland and Crete was higher than previously recorded [1].

Are these differences real or can the disparate findings of these studies be explained by differences in study design or imperfections of the methods used? One possible explanation is that the differences reported reflect sampling and study size. For many diseases, cancer in particular, this problem can be overcome by examining mortality or morbidity routinely collected at a national or regional level.

Evidence from trends in routinely collected morbidity data

For IBD, mortality data are of little value in assessing its incidence over time. Death from IBD is now rare,

with fewer than 400 deaths per year now being certified as due to IBD in the United Kingdom [9]. In addition, over 75% of these deaths occur in those over 70 years, whereas the incidence of IBD is greatest in those under age 40. Although mortality rates do show a broad correlation with incidence figures between countries, the relationship breaks down when comparing mortality and incidence within a country over time [10]. Thus, the rapid rise in incidence of Crohn's disease during the 1950s and 1960s in the United Kingdom and the United States was associated with a less than doubling of mortality rates [11]. At the same time, mortality from ulcerative colitis in these countries declined sharply when other data suggested incidence was unchanged or possibly increasing.

Routinely collected morbidity data has mainly consisted of data on hospital admissions, which has been collected over many years in several countries. Another source of data is that collected by health insurance or health maintenance organisations, typically from North America, which has the advantage of including data on outpatient (ambulatory) care as well as that for inpatient care. Using either source it is necessary to separate first admissions or contacts from repeat contacts. Hospital admission data are also affected by changing patterns of care, with patients being increasingly cared for as outpatients. With these considerations in mind it is notable that in Denmark the annual incidence of Crohn's disease, based on their national registry of inpatients, increased from 46 to 62/million/year in women between 1981–84 and 1989–92, and from 33 to 41/million/year in men over the same period [12]. The figures were similar to the overall crude incidence of 41/million/year reported elsewhere for Copenhagen County in 1979–87. In contrast, the incidence of ulcerative colitis over this period fell from 154 to 123/million/year in women and from 141 to 126/million/year in men.

Hospital admission data (now called hospital episode statistics) are collected in the United Kingdom, but except in the Oxford region and Scotland it is not possible to identify first admissions from repeat admissions [13, 14]. In England, hospital admission rates for Crohn's disease increased by approximately 4% annually during the period from 1970 to 1985, but when admissions in the Oxford region were linked to individuals, first admissions for men declined by 0.5% annually and for women rose by 0.1%, neither being statistically significant [13]. Over the same period hospital admission rates for ulcerative colitis in England showed no change, although first admission rates in the Oxford region showed a 1% average annual increase, which was not statistically significant [13].

Both these studies, like most studies on routinely collected data, relied on accurate coding of the discharge diagnosis. This is a particular problem for inflammatory bowel disease where there is often some uncertainty as to whether the diagnosis is Crohn's disease (CD) or ulcerative colitis (UC). To overcome this problem Bernstein *et al*. in their study using health insurance records for Manitoba, validated the diagnoses according to questionnaire responses obtained from a subset of patients directly approached [5]. They also ignored all cases with a first medical contact within the first 5 years of their study period to try to ensure that only incident cases were included. How successful they were is difficult to judge. Inclusion of a proportion of non-incident cases will disproportionately increase incidence in the older age groups. Their figures for the incidence of Crohn's disease are some of the highest reported at 169/million/year in women and 123/million/year in men. Incidence rates for ulcerative colitis were also high at 144/million/year in women and 143/million/year in men.

Thus, the routinely collected data give a mixed picture. The lack of increase in the figures from the Oxford region could reflect an increased proportion of patients having outpatient care only. The same restriction also applies to the Danish data, although a validation study on a subset showed the diagnostic accuracy to be high, and overall incidence was in keeping with a smaller hospital-based study [12]. The Canadian data are particularly remarkable, as generally the figures for IBD incidence reported from North America have tended to be lower than those from Europe. These three studies reflect some of the important limitations of routinely collected morbidity data – namely that it is usually difficult to make direct comparisons between data sets on account of differences in the health-care systems

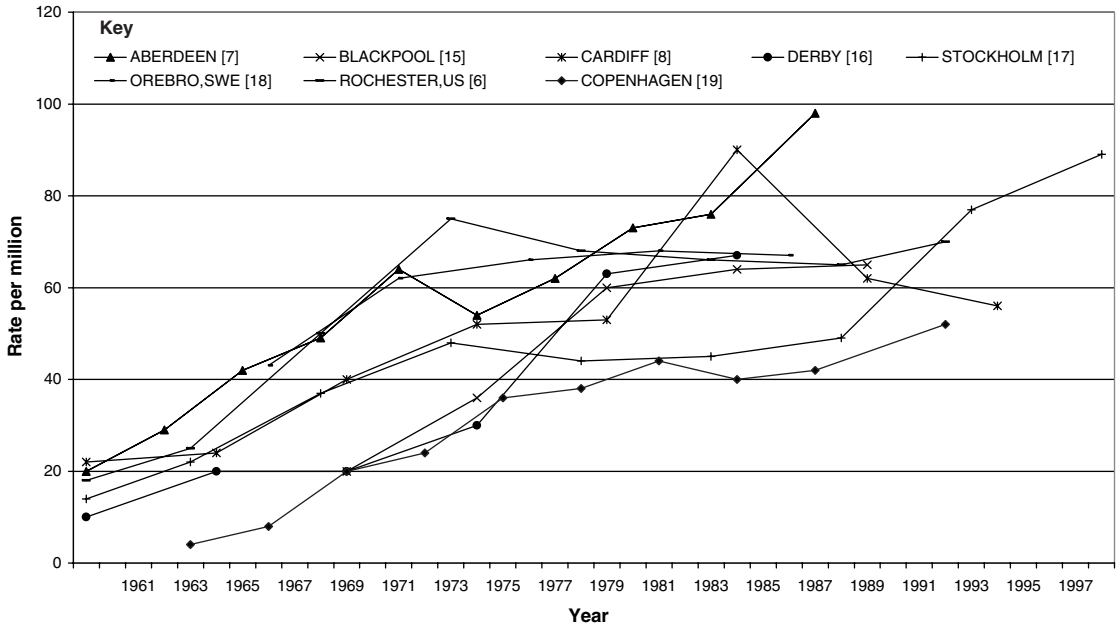

Fig 1.1 Recent time trends in incidence of Crohn's disease.

involved. Secondly, changes in how the data are collected often restrict analyses to time periods of less than 20 years. A third limitation is that it is usually not possible to validate the accuracy of diagnosis, which is of special importance when distinguishing Crohn's disease from ulcerative colitis.

Time trends in individual studies

The alternative to figures generated from routine data is to use the results of individual *ad hoc* studies. In many European countries with centralised state-funded health care, such studies appear deceptively straightforward. Population catchment areas are often well defined and specialist care is provided by a small number of gastroenterologists, who also usually provide whatever private care is available. However, IBD is relatively uncommon, and prospective studies need to be prolonged to provide reliable figures on time trends. Other issues that have not always been carefully addressed include the criteria for diagnosis, residence criteria and clear definitions for date of onset or diagnosis. In addition, as already mentioned, the effects of increasing awareness, better case ascertainment, greater use of more sensitive tests such as colonoscopy and evolving case definitions need to be considered.

Fortunately, in a few areas IBD incidence has been monitored either prospectively or by repeated retrospective studies over periods of more than 20 years, and these studies arguably provide the most reliable evidence on incidence trends (Figs 1.1 and 1.2). Rates have been plotted according to the last year of each time period reported and in most areas the rates have been age-standardised to correct for changes in their population age structures over time. Of the eight areas shown in Fig 1.1, only in the Aberdeen area and most recently in Stockholm has the incidence of Crohn's disease shown more than a small increase since 1980 [7, 25]. When the Aberdeen data are age-standardised there is some reduction in the rate of increase, although the final figure remains high at 88/million [26]. It is too soon to know whether this represents a sustained increase; a similar peak in incidence was previously found in Cardiff. Otherwise the remarkable feature is how little variation there is between places as different as Cardiff in the United Kingdom,

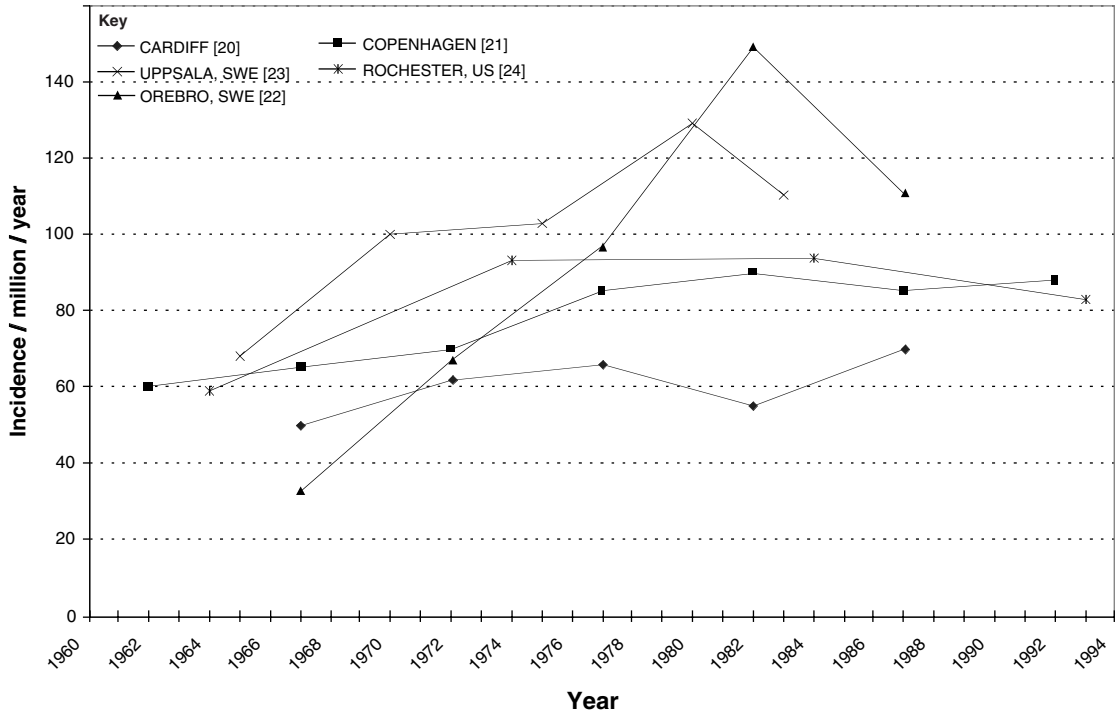

Fig 1.2 Recent time trends in incidence of ulcerative colitis.

Orebro in Sweden and Rochester in the United States.

These studies were all performed in an era when colonoscopy was not regarded as the standard investigation it has now become. For example, in northern France in the 1990s 92% of patients with Crohn's disease and 99% of those with ulcerative colitis had had a colonoscopy at diagnosis [17]. A recent updating of data from Stockholm found that 70% of Crohn's patients had a colonoscopy at diagnosis [25]. Equivalent figures for the 1980s and earlier have not been reported and it is unclear what proportion of IBD would have been labelled as ulcerative colitis in the absence of evidence, either macroscopic or microscopic, obtained at colonoscopy. Nevertheless, greater use of colonoscopy would account for the increasing proportion of patients found to have Crohn's disease affecting the colon, as reported in several recent studies [8, 17, 28].

There have been fewer studies of ulcerative colitis incidence. In the countries where IBD is common incidence rates for ulcerative colitis have tended to show more variation than those for Crohn's disease. Probably this reflects the additional problems posed by variable ascertainment of mildly symptomatic cases including those with proctitis only, and distinguishing single or transient episodes of colitis induced by infection or drugs. In Nottingham, the prevalence of previously undiagnosed ulcerative colitis in subjects offered faecal occult blood testing for colorectal cancer screening was 700/million [29]. Most were mildly symptomatic but had not sought medical advice. In the recent Norwegian study a diagnosis of ulcerative colitis could not be confirmed in 12% of patients when reinvestigated one year after diagnosis [30].

Given these considerations and the various changes in health care already mentioned, the increases in incidence over time (shown in Fig 1.2) are perhaps less than might have been expected. What does seem to have changed is the age-specific pattern, with an increase in incidence of ulcerative

colitis at older ages in men but not in women. Thus, in the EC-IBD study and in the recent data from northern France the expected peak in incidence in the younger age groups was present for women but not for men [1, 27].

Geographic trends in incidence

Over the past 30 years a large number of other *ad hoc* studies have been reported from diverse locations worldwide. Table 1.1 shows the incidence rates reported from recent European studies. The incidence of both diseases appears to show around a 10-fold variation across Europe, but in general, the incidence of both is highest in countries in northern latitudes. The north-south gradient in IBD incidence was first described in Europe and was based on observations from these individual studies. However, the conclusions reached by comparison of these studies are once again hampered by variations in study design, notably case definition, methods of case ascertainment and time period of investigation. In addition, many studies reported only crude rather than age-standardised or age-specific incidence rates for their populations and in others, case ascertainment in children and the elderly was less complete than at other ages. The European collaborative study on IBD incidence was set up to overcome these problems by standardising methods throughout all participating centres. It concluded that the 'magnitude of the observed excess in north is less than expected on the basis of previous studies . . . this may reflect increases in incidence of IBD in Southern Europe whilst north may have stabilised' [1]. Incidence rates from centres participating in EC-IBD are shown in Table 1.1 in bold.

In North America significant geographic variation also appears to exist, and generally populations

Table 1.1 European studies of inflammatory bowel disease incidence in the 1990s (Centres from EC- IBD in bold).

				Rates/100,000/year		
First author	Year	Area	Time period	UC (*n*)	CD (*n*)	Design
Shivananda EC-IBD [1]	**1996**	**8 Northern European cities**	**1991–93**	**11.8 (869)**	**7.0 (477)**	**Prospective**
Shivananda EC-IBD [1]	**1996**	**12 Southern European cities**	**1991–93**	**8.7 (510)**	**3.9 (229)**	**Prospective**
Bjornsson [28]	**2000**	**Iceland**	**1990–94**	**16.5 (215)**	**5.5 (72)**	**Prospective**
Moum [31, 32]	**1997**	**South-east Norway**	**1990–93**	**12.8 (496)**	**6 (232)**	**Prospective**
Salupere [33]	2001	Tartu, Estonia	1993–98	1.7 (16)	1.4 (13)	Prospective
Rubin [34]	2000	North Tees, UK	1990–94	13.9 (94)	8.3 (56)	Retrospective
Yapp [8]	2000	Cardiff, UK	1991–95		5.6 (84)	Retrospective
Russel [35]	**1998**	**Netherlands**	**1991–95**	**10 (257)**	**6.9 (176)**	**Prospective**
Latour [36]	1998	Leige, Belgium	1993–96	3.6 (111)	4.5 (137)	Prospective
Pagenault [37]	1997	Brittany, France	1994–95	2.9 (165)	2.8 (205)	Prospective
Flamenboum [38]	1997	Puy de Dome, France	1993–94	2.4 (29)	6.6 (79)	Prospective
Lakatos [39]	2004	Western Hungary	1977–01	5.8 (560)	2.2 (212)	Retrospective
Ranzi [40]	**1996**	**Cremona, Italy**	**1990–93**	**7.0 (82)**	**3.4 (40)**	**Prospective**
Trallori [41]	1996	Florence	1990–92	9.6	3.4	Retrospective
Tragnone [42]	1996	Italy (8 cities)	1989–92	5.2 (509)	2.3 (222)	Prospective
Manousos [43, 44]	**1996**	**Crete**	**1990–94**	**11.3 (116)**	**3.5 (36)**	**Prospective**
Tsianos [45]	**2003**	**N W Greece**	**1982–97**	**6.6 (357)**	**0.5 (43)**	**Retrospective**
Molinie [27]	**2004**	**Northern France**	**1988–99**	**4.0 (2665)**	**6.0 (4013)**	**Prospective**

UC: ulcerative colitis; CD: Crohn's disease.

with the highest incidence and prevalence rates have been located in northern latitudes [4, 5, 46, 47]. Once again, these findings are based on the results of individual studies and are therefore difficult to compare due to methodological differences. One study that overcomes these problems is a study in the United States of military veterans and Medicare beneficiaries, which shows that the incidence of IBD is higher in the north compared to the south [48, 49].

Further analysis of the large Scottish cohort of juvenile-onset IBD between 1981 and 1995 [50] has also found that northerly region of residence was an independent risk factor for developing CD but not UC [48]. The relative risk of CD in the south compared with the north was 0.73 (95% CI 0.58–0.92, $p < 0.001$), but UC did not show this north/south variation. This pattern has not been examined in other paediatric populations, but does support the hypothesis that CD incidence exhibits a latitudinal gradient with incidence increasing with more northern latitudes.

Rest of the world

Until the 1980s reports of IBD occurrence from outside Europe and North America consisted essentially of case reports or case series. The exception was South Africa where Wright *et al.* found the incidence of both diseases in the Cape Town area to be greatest in the Whites but with incidence less than half that found in equivalent European populations. Incidence of both diseases in the coloured population was lower again and lowest of all in the Blacks [51]. Recent well-researched studies from Japan and Korea have shown IBD to be much less common than in Europe with UC incidence being 10–20/million/year and CD less than 5/million/year [52–55].

In line with the data from Japan and the Far East, UC has traditionally been regarded as rare in the developing world. However, an impressive pair of population surveys in northern India has revealed an UC incidence of 60/million/year and a prevalence of symptomatic UC of 443/million – figures not much lower than those reported from several European countries [56]. It is unclear whether these figures reflect an increasing UC incidence, as this is the first formal study of IBD incidence from India.

Trends in incidence of juvenile-onset Crohn's disease

Incidence patterns for whole populations may conceal changes taking place in smaller subgroups of that population, such as children. Although Crohn's disease incidence may be stable overall, several groups have suggested that incidence in children is particularly increasing. The epidemiology of this subgroup is of particular importance because several current hypotheses as to the causes of CD and UC relate to events happening in infancy or childhood [57–61].

In assessing any increase in incidence in children, one needs to consider some additional factors that could account for a spurious increase (Table 1.2). Firstly, the steep increase in incidence at ages 15 and 16 coincides with the arbitrary division between childhood and adulthood. Thus, any reduction in the time between symptom onset and diagnosis could have a disproportionate effect on incidence in childhood. As Table 1.3 shows, researchers have been divided in choosing age 14, 15 or 16 as the upper limit of childhood. How this might affect the figures is difficult to gauge, but it is notable that in the study from Copenhagen where the low incidence below age 15 is based on only six cases, in a further 17 symptom onset was before age 15 but diagnosis occurred in adulthood. Secondly, time from symptom onset to diagnosis of Crohn's disease in children has shortened; in the United Kingdom this has gone from around 12 months in the early 1980s to around 5 months in the recent data collected [77]. Other factors include the increased intensity of investigation and changing criteria for diagnosis of Crohn's disease.

As noted above, diagnosis for all hospital admissions in Scotland are recorded in a linked fashion for the whole country in the 'Scottish Hospitals discharges linked database' [78]. The linkage of data allows the whole series of that patient's admissions to be identified at any one time, allowing identification of incident cases rather than just hospital admission episodes. Using this database Barton *et al.*

Table 1.2 Possible factors contributing to an increase in incidence of Crohn's disease in children.

Greater case ascertainment
Quicker diagnosis → diagnosis at age 15, not 16
Diagnostic transfer, atypical UC → CD
Widening case definitions e.g. inclusion of orofacial granulomatosis
Earlier onset in predisposed individuals
Real increase in incidence

UC: ulcerative colitis; CD: Crohn's disease.

looked at incidence rates for juvenile onset IBD from 1968 to 1983 [71]. They found a three-fold rise in incidence for CD, and a marginal fall in UC. The data for CD, after allowing for a short lag, would seem to parallel the increase seen in adults over the preceding few decades. Over the last decade with increasing interest in the aetiological role of perinatal and early childhood factors, other groups have now published comparable epidemiological studies of the juvenile-onset subgroup (Table 1.3).

The figures from the Scandinavian countries seem to show more variation, with the rates from Denmark and Finland being a half to a third of those from Sweden and Norway. In part, this reflects the different age bands used (Table 1.3). Nevertheless, the situation within Sweden is as varied, because the recent data from northern Stockholm (Table 1.4) suggests a doubling in incidence of Crohn's disease, predominantly accounted for by increasing colonic disease, and a decline in ulcerative colitis

Table 1.3 Recent incidence data for Crohn's disease (CD) and ulcerative colitis (UC) in childhood.

					CD		UC	
First author	Area	Period	Duration (years)	Age group	Rates per 100,000/year	*n*	Rates per 100,000/year	*n*
Europe								
Langholz [62]	Copenhagen	1962–87	15	0–14	0.2	6	2.0	63
Olafsdottir [63]	W Norway	1984–85	2	0–15	2.5	10	4.3	17
Bentsen [64]	SE Norway	1990–94	4	0–15	2.0	14	2.2	15
Lindberg [65]	SW Sweden	1984–86	3	0–15	1.9	211†	1.4	287†
		1993–95	3	0–15	2.0	–	3.2	–
Hildebrand [66]	N Stockholm	1990–01	12	0–15	4.9	102	2.4	50
Kolek [67]	Czech republic	1990–01	12	0–15	1.0	19	1.1	22
Van der Zaag-Loonen [68]	Netherlands	1999–01	2	0–17	2.1		1.6	
Tourtelier [69]	NW France	1994–97	4	0–16	1.6	43	0.6	14
UK								
Cosgrove [70]	S Wales	1983–93	11	0–15	2.2	21	0.7	7
Barton [71]	Scotland	1968	1	0–16	0.7	10	1.9*	18
		1983	1	0–16	2.3	28	1.6*	13
Armitage [72]	Scotland	1981–95	15	0–15	2.3	383	3.4	197
Hassan [73]	Wales	1995–97	1	0–16	1.4	20	0.8	11
Sawczenko [74]	UK	1998	1	0–15	3.1		1.4	
USA								
Kugathasan [75]	Wisconsin	2000–01	2	0–17	4.6	129	2.1	60
Australia								
Phavichitr [76]	Melbourne	1996–01	5	0–16	2.0	233	–	–

*Rate for 6–16 years.
†Numbers for both periods.

Table 1.4 Incidence of Crohn's disease in children – northern Stockholm [65].

	Rate per 100,000/year for ages 0–15 years (95% CI)	
	CD	UC
	$N = 102$	$N = 48$
1990–92	1.7 (0.7–3.3)	3.3 (1.9–5.4)
1993–95	3.5 (2.1–5.5)	1.8 (0.8–3.3)
1996–98	5.6 (3.8–8.1)	1.9 (0.9–3.5)
1999–01	8.4 (6.2–11.3)	1.8 (0.9–3.4)
Overall	4.9 (4.0–6.0)	2.2 (1.6–2.9)

UC: ulcerative colitis; CD: Crohn's disease.

in under 16-year-olds during the 1990s, while the larger study covering just over half the childhood population (< 16 years) of Sweden found no increase in Crohn's disease incidence but a two-fold rise in incidence of ulcerative colitis [65, 66].

In the paediatric age group, further research from Scotland has also shown a higher incidence of CD in the more affluent areas of Scotland, as defined by postcode sector [50]. This pattern was independent of temporal, gender or regional trends and was therefore not purely a reflection of the geographical distribution of deprivation. The relationship to affluence was seen in CD, but not in UC, thus it is unlikely that the association was simply due to a higher reporting of symptoms to primary care in affluent areas.

Conclusions

It would be a serious mistake to assume incidence trends should be similar even in developed countries. With these caveats, there is broad support for the following:

- In Westernised countries, where Crohn's disease is already common, there is no *consistent* evidence of a continuing rise with the most reliable data showing stable incidence since the 1980s.
- In areas reporting an increase in Crohn's disease (northern France and Stockholm) the increase has been predominantly in colorectal Crohn's disease.
- Overall incidence of ulcerative colitis in the same countries is not rising.
- In areas of Europe where historically IBD has been uncommon or rare the incidence of both diseases is rising, although some of the rise may reflect greater access to health care with the general pattern being of an increase in UC followed by Crohn's disease, within a generation or less.
- Both diseases are now appearing in Japan and the rest of Asia.
- The incidence of Crohn's disease in children is increasing but how much of the increase is accounted for by earlier diagnosis, varying definitions of childhood and changes in diagnostic criteria is still not clear.

Overall, this pattern is in keeping with some environmental factors associated with economic development or Westernised lifestyles. Focussing on the emergence of IBD in the developing world is likely to be a fruitful area for research.

References

1 Shivananda S, 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; 39:690–7.

2 Miller DS, Keighley AC, Langman MJ. Changing patterns in epidemiology of Crohn's disease. *Lancet* 1974;2(7882):691–3.

3 Calkins BM, Mendeloff AI. Epidemiology of inflammatory bowel disease. *Epidemiol Rev* 1986;8: 60–91.

4 Sandler RS. Epidemiology of inflammatory bowel disease. In: Targan SR, Shanahan F, eds. *Inflammatory Bowel Disease: From Bench to Bedside*. Baltimore: Williams and Wilkins; 1994:5–32.

5 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(10):916–24.

6 Loftus EV Jr, 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(6):1161–8.

7 Kyle J. Crohn's disease in the northeastern and northern Isles of Scotland: an epidemiological review. *Gastroenterology* 1992;103:392–9.

8 Yapp TR, Stenson R, Thomas GA, Lawrie BW, Williams GT, Hawthorne AB. Crohn's disease incidence in Cardiff from 1930: an update for 1991–1995. *Eur J Gastroenterol Hepatol* 2000;12(8):907–11.
9 Gordon FH, Montgomery SM, Hamilton MI, Pounder RE. Mortality in inflammatory bowel disease: the case for a national confidential enquiry. *Gut* 1997;40(Suppl 1):A21.
10 Sonnenberg A. Geographic variation in the incidence of and mortality from inflammatory bowel disease. *Dis Colon Rectum* 1986;29(12):854–61.
11 Sonnenberg A. Mortality from Crohn's disease and ulcerative colitis in England–Wales and the U.S. from 1950 to 1983. *Dis Colon Rectum* 1986;29(10):624–9.
12 Fonager K, Sorensen HT, Olsen J. Change in incidence of Crohn's disease and ulcerative colitis in Denmark. A study based on the National Registry of Patients, 1981–1992. *Int J Epidemiol* 1997;26(5):1003–8.
13 Primatesta P, Goldacre MJ. Crohn's disease and ulcerative colitis in England and the Oxford record linkage study area: a profile of hospitalized morbidity. *Int J Epidemiol* 1995;24(5):922–8.
14 Sonnenberg A. Hospital discharges for inflammatory bowel disease. Time trends from England and the United States. *Dig Dis Sci* 1990;35(3):375–81.
15 Lee FI, Nguyen-Van-Tam JS. Prospective study of incidence of Crohn's disease in northwest England: no increase since the late 1970's. *Eur J Gastroenterol Hepatol* 1994;6:27–31.
16 Fellows IW, Freeman JG, Holmes GKT. Crohn's disease in the city of Derby, 1951–85.*Gut* 1990; 31:1262–5.
17 Lapidus A, Bernell O, Hellers G, Persson P-G, Loftberg R. Incidence of Crohn's disease in Stockholm County 1955–89. *Gut* 1997;41:480–6.
18 Lindberg E, Jarnerot G. The incidence of Crohn's disease is not decreasing in Sweden. *Scand J Gastroenterol* 1991;26:495–500.
19 Munkholm P, Langholz E, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of Crohn's disease in the County of Copenhagen, 1962–87: a six-fold increase in incidence. *Scand J Gastroenterol* 1992; 27:609–14.
20 Srivastava ED, Mayberry JF, Morris TJ, *et al*. Incidence of ulcerative colitis in Cardiff over 20 years: 1968–87.*Gut* 1992;33:256–8.
21 Binder V. Epidemiology. In: *Inflammatory Bowel Disease*. Falk Symposium No. 96. Dordrecht: Kluwer Academic; 1998:39–43.
22 Tysk C, Jarnerot G. Ulcerative proctocolitis in Orebro, Sweden. A retrospective epidemiologic study, 1963–1987. *Scand J Gastroenterol* 1992;27:945–50.
23 Ekbom A, Helmick C, Zack M, Adami H-O. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden.*Gastroenterology* 1991;100:350–8.
24 Loftus EV Jr, 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.
25 Lapidus, A. Crohn's disease in Stockholm County – an epidemiological update 1990–2001. *Gut* 2004; 53(Suppl 1):A139.
26 Morris DL, Kyle J, Montgomery SM, Wakefield AJ, Pounder RE. Crohn's disease in North-East Scotland: a real rise in incidence. *Gut* 1999; 44(Suppl 1):A28.
27 Molinie F, Gower-Rosseau C, Yzet T, *et al*. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988–1999). *Gut* 2004;53:843–8.
28 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.
29 Howarth GF, Robinson MH, Jenkins D, Hardcastle JD, Logan RF. High prevalence of undetected ulcerative colitis: data from the Nottingham fecal occult blood screening trial. *Am J Gastroenterol* 2002;97(3):690–4.
30 Moum B, Ekbom A, Vatn MH, *et al*. Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective population based study in southeastern Norway. *Gut* 1997;40(3):328–32.
31 Moum B, Vatn MH, Ekbom A, *et al*. Incidence of Crohn's disease in four counties in southeastern Norway, 1990–93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol* 1996;31(4):355–61.
32 Moum B, Vatn MH, Ekbom A, *et al*. Incidence of ulcerative colitis and indeterminate colitis in four counties of southeastern Norway, 1990–93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol* 1996; 31(4):362–6.
33 Salupere R. Inflammatory bowel disease in Estonia: a prospective epidemiologic study 1993–1998. *World J Gastroenterol* 2001;7(3):387–8.
34 Rubin GP, Hungin AP, Kelly PJ, Ling J. Inflammatory bowel disease: epidemiology and management in an English general practice population. *Aliment Pharmacol Ther* 2000;14(12):1553–9.

35 Russel MG, Dorant E, Volovics A, *et al*. High incidence of inflammatory bowel disease in The Netherlands: results of a prospective study. The South Limburg IBD Study Group. *Dis Colon Rectum* 1998;41(1):33–40.
36 Latour P, Louis E, Belaiche J. Incidence of inflammatory bowel disease in the area of Liege: a 3 years prospective study (1993–1996). *Acta Gastroenterol Belg* 1998;61(4):410–3.
37 Pagenault M, Tron I, Alexandre JL, *et al*. Incidence of inflammatory bowel diseases in Bretagne (1994–1995). ABERMAD [Association Bertonne d'Etude et de Recherche des Maladies de l'Appareil Digesif]. *Gastroenterol Clin Biol* 1997;21(6–7): 483–90.
38 Flamenbaum M, Zenut M, Aublet-Cuvelier B, *et al*. Incidence of inflammatory bowel diseases in the department of Puy-de-Dome in 1993 and 1994. EPIMICI [Epidemiologie des Maladies Inflammatoires Cryptogenetiques de l'Intestin group]. *Gastroenterol Clin Biol* 1997;21(6–7):491–6.
39 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(3):404–9.
40 Ranzi T, Bodini P, Zambelli A, *et al*. Epidemiological aspects of inflammatory bowel disease in a north Italian population: a 4-year prospective study. *Eur J Gastroenterol Hepatol* 1996;8(7):657–61.
41 Trallori G, Palli D, Saieva C, *et al*. A population-based study of inflammatory bowel disease in Florence over 15 years (1978–92). *Scand J Gastroenterol* 1996; 31(9):892–9.
42 Tragnone A, Corrao G, Miglio F, Caprilli R, Lanfranchi GA. Incidence of inflammatory bowel disease in Italy: a nationwide population-based study. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). *Int J Epidemiol* 1996;25(5):1044–52.
43 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(9):893–8.
44 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(6):599–603.
45 Tsianos EV, Katsanos KH, Christodoulou D, Dimoliatis I, Kogevinas A, Logan RF, on behalf of Northwest Greece Inflammatory Bowel Disease Study Group. Continuing low incidence of Crohn's disease in Northwest Greece. *Dig Liver Dis* 2003;35: 99–103.
46 Loftus EV Jr, 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(3): 336–43.
47 Pinchbeck BR, Kirdeikis J, Thomson AB. Inflammatory bowel disease in northern Alberta: an epidemiologic study. *J Clin Gastroenterol* 1988;10(5): 505–15.
48 Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation of inflammatory bowel disease within the United States. *Gastroenterology* 1991;100:143–9.
49 Sonnenberg A, Wasserman IH. Epidemiology of inflammatory bowel disease among U.S. military veterans. *Gastroenterology* 1991;101(1):122–30.
50 Armitage EL, Aldhous MC, Anderson N, *et al*. Incidence of juvenile-onset Crohn's disease in Scotland: association with northern latitude and affluence. *Gastroenterolgy* 2004;127:1051–7.
51 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;70:10–15.
52 Lee YM, Fock KM, See SJ, Ng TM, Khor C, Teo EK. Racial differences in the prevalence of ulcerative colitis and Crohn's disease in Singapore. *J Gastroenterol Hepatol* 2000;15:622–5.
53 Morita N, Toki S, Hirohashi T, *et al*. Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. *J Gastroenterol* 1995;30:1–4.
54 Yang SK, Loftus EV Jr, Sandborn WJ. Epidemiology of inflammatory bowel disease in Asia. *Inflamm Bowel Dis* 1001;7:260–70.
55 Yang SK, Hong WS, Min YI, *et al*. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong District, Seoul, Korea, 1986–1997. *J Gastroenterol Hepatol* 2000;15:1037–42.
56 Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut* 2003;52:1587–90.
57 Gent AE, Hellier MD, Grace RH, Swarbrick ET, Coggon D. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet* 1994;343(8900): 766–7.
58 Montgomery SM, Pounder RE, Wakefield AJ. Infant mortality and the incidence of inflammatory bowel disease. *Lancet* 1997;349:472–3.
59 Bernstein CN, Kraut A, Blanchard JF, Rawsthorne P, Yu N, Walld R. The relationship between inflammatory bowel disease and socioeconomic variables. *Am J Gastroenterol* 2001;96:2117–25.

60 Gilat T, Hacohen D, Lilos P, Langman MJ. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. *Scand J Gastroenterol* 1987;22(8):1009–24.

61 Ekbom A, Adami HO, Helmick CG, Jonzon A, Zack MM. Perinatal risk factors for inflammatory bowel disease: a case-control study. *Am J Epidemiol* 1990;132(6):1111–19.

62 Langholz E, Munkholm P, Krasilnikoff PA, Binder V. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. *Scand J Gastroenterol* 1997;32(2): 139–47.

63 Olafsdottir EJ, Fluge G, Haug K. Chronic inflammatory bowel disease in children in western Norway. *J Pediatr Gastroenterol Nutr* 1989;8(4): 454–8.

64 Bentsen BS, Moum B, Ekbom A. Incidence of inflammatory bowel disease in children in southeastern Norway: a prospective population-based study 1990–94. *Scand J Gastroenterol* 2002;37(5): 540–5.

65 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(3):259–64.

66 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(10):1432–4.

67 Kolek A, Janout V, Tichy M, Grepl M. The incidence of inflammatory bowel disease is increasing among children 15 years old and younger in the Czech Republic. *J Pediatr Gastroenterol Nutr* 2004; 38(3):362–3.

68 van der Zaag-Loonen HJ, Casparie M, Taminiau JA, Escher JC, Pereira RR, Derkx HH. The incidence of pediatric inflammatory bowel disease in the Netherlands: 1999–2001. *J Pediatr Gastroenterol Nutr* 2004;38(3):302–7.

69 Tourtelier Y, Dabadie A, Tron I, *et al*. Incidence of inflammatory bowel disease in children in Brittany (1994–1997). Breton association of study and research on digestive system diseases (Abermad). *Arch Pediatr* 2000;7(4):377–84.

70 Cosgrove M, Al Atia RF, Jenkins HR. The epidemiology of paediatric inflammatory bowel disease. *Arch Dis Child* 1996;74(5):460–1.

71 Barton JR, Gillon S, Ferguson A. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983; marginal fall in ulcerative colitis, three-fold rise in Crohn's disease. *Gut* 1989;30(5):618–22.

72 Armitage E, Drummond H, Ghosh S, Ferguson A. Incidence of juvenile-onset Crohn's disease in Scotland. *Lancet* 1999;353:1496–7.

73 Hassan K, Cowan FJ, Jenkins HR. The incidence of childhood inflammatory bowel disease in Wales. *Eur J Pediatr* 2000;159(4):261–3.

74 Sawczenko A, Sandhu BK, Logan RF, *et al*. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet* 2001;357:1093–4.

75 Kugathasan S, Judd RH, Hoffmann RG, *et al*. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study.*J Pediatr* 2003;143(4):525–31.

76 Phavichitr N, Cameron DJ, Catto-Smith AG. Increasing incidence of Crohn's disease in Victorian children. *J Gastroenterol Hepatol* 2003;18(3):329–32.

77 Sawczenko A, Lynn R, Sandhu BK. Variations in initial assessment and management of inflammatory bowel disease across Great Britain and Ireland. *Arch Dis Child* 2003;88:990–4.

78 Heasman MA, Clarke JA. Medical record linkage in Scotland. *Health Bull (Edinb)* 1979;37:97–103.