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ORIGINAL ARTICLE—ALIMENTARY TRACT

Inflammatory bowel disease in children: epidemiological analysis of the nationwide IBD registry in Japan

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Abstract
Objective We analyzed the database of the Japanese nationwide inflammatory bowel disease (IBD) registry, which was started in 1975, to characterize basic epidemiological and clinical features of childhood IBD, comparing them to those in adults.
Study design We analyzed the age of disease onset, disease severity and anatomical distribution in patients that were newly registered between 2003 and 2006 ($n = 2{,}940$ for CD and 14,857 for UC). We also analyzed the current age, gender and family history of IBD of all patients filed in 2005, which included patients who were newly registered in 2005 and those who had been registered before 2005 and for whom an annual report had been received in 2005 (total number of subjects: 10,934 for CD and 37,846 for UC).
Results At the time of registration, 10.6% of CD and 5.9% of UC patients were ≤16 years old. In CD, the male to female ratio was 2.6 in adult- and 1.7 in childhood-onset patients ($P < 0.001$). In UC, the male to female ratio was close to 1 in both age groups. In comparison with adults, pediatric patients more commonly had a positive family history for CD and UC ($P < 0.001$), tended to have more severe disease at the time of registry ($P < 0.001$ for CD, $P < 0.05$ for UC) and more often had extensive colitis in UC ($P < 0.001$).
Conclusion The nationwide registry in Japan showed IBD in children has clinical features that are distinct from those in adults.

Keywords Crohn's disease · Incidence · Ulcerative colitis · Montreal classification · Child

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Introduction

Previous reports have suggested that childhood inflammatory bowel disease (IBD) has several clinical features that are distinct from those in adults [1–6]. The incidence of IBD in children is lower compared to that in adults. Pediatric ulcerative colitis (UC) patients are more likely to have total colitis than adults are [1, 6–8]. Growth failure is a serious clinical problem only in pediatric patients [5, 6, 9–11]. The above unique features of pediatric IBD have been described in relatively large prospective epidemiological studies and in recent registry data from the US [1, 12–14]. However, most of these studies did not include adult patients and therefore do not allow direct comparison between age groups. Epidemiological data for IBD vary widely with regard to time and place of collection [15]. For example, the prevalence of UC in Northern Europe is several times higher than that in Japan and other Eastern Asian countries [15]. The incidence of Crohn's disease (CD) has increased markedly in the last century [16–18] and may still be increasing in some countries [19].

Therefore, the proper way to characterize pediatric IBD without any significant bias is to obtain data from children and adults at the same place and time, and in the same manner.

Recognizing the social and economic impact of IBD and the need for epidemiological information, the Japanese government started a nationwide registry in 1975. Doctors are encouraged to file patient data at any one of the local offices of the Japanese Ministry of Health, Labor and Welfare (MHLW). Data are converted to electronic form and sent to the research committee of the MHLW. Data include clinical features, such as age, sex, family history and disease profile, and social factors, such as occupation and insurance status. If doctors send a report, patients receive all the medical cost for treatment of the disease from the government in return. Previous studies have shown that most patients agree to be registered, and 50–70% of new Japanese IBD patients are estimated to be registered every year [20]. Even though Japan's incidence of IBD is lower than that in Western countries, this nationwide database, which included more than 10,000 CD and 40,000 UC patients in 2005, provides valuable epidemiological information on IBD in Japan.

In this study, members of the working party of epidemiology in the IBD study group organized by the Japanese government analyzed the database to characterize basic clinical features of childhood IBD and compared them to those in adults.

Methods

In Japan, since 1975, when a definite diagnosis of UC or CD is made, the patient is asked if he or she wants to be registered in the national database. If the patient agrees, the doctors complete the questionnaire and file it with the local office of the MHLW. The questionnaire covers patient age, gender, address, time of onset, disease severity and distribution, complications, laboratory data, endoscopic and/or barium enema studies, histological findings, and family and social history, including place of birth, occupation and type of health insurance. Each patient must meet the diagnostic criteria for CD or UC published by the MHLW (http://www.nanbyou.or.jp: Japanese article). Members of local branches check the data in the questionnaire to confirm that it meets the diagnostic criteria. If it does, the data are then converted to electronic form and submitted to the MHLW.

Once the patient is registered, the doctor must send an annual report for the patient to the MHLW every year thereafter, until the disease is determined to be cured or the registration is cancelled by the patient, neither of which happens often. Therefore, the database contains two series of data; new registry data from patients newly registered each year and annual report data from all previously registered patients.

In this study, we analyzed the age of disease onset in patients that were newly registered between 2003 and 2006 ($n = 2{,}940$ for CD and 14,857 for UC). We also analyzed the current age, gender and family history of IBD of all patients filed in 2005, which included patients who were newly registered in 2005 and those who had been registered before 2005 and for whom an annual report was received in 2005 (total number of subjects: 10,934 for CD and 37,846 for UC).

Throughout this study, children were defined as individuals aged $\leq$16 years and adults as $>$16 years old, according to the Montreal classification. Family history was regarded as positive when a parent, brother or sister had IBD.

For disease severity and anatomical distribution, we used new registration data filed between 2003 and 2006. The International Organization of the Study of Inflammatory Bowel Disease (IOIBD) assessment score was used to assess severity of CD [21]. Severity of UC was on the report, which was determined according to Truelove's criteria [22].

Since this registry was started before the Montreal classification was published in 2006, it was not possible to analyze some data according to the Montreal classification [23]. To be more specific, disease behavior of CD was not analyzed.

Statistical analysis

Data were analyzed by chi-square test to compare categorical data between children and adults. Differences were considered statistically significant at $P < 0.01$. SPSS 15.0 (SPSS, Inc., Chicago, IL) was used for all analysis.

Ethical considerations

When the data were provided to us by the government, they were blinded (no names or initials) so that we could not identify the individuals. Data access was restricted to the authors T.I. and T. Tomomasa. This study was approved by the MHLW and the Ethical Committee in Gunma University, Department of Pediatrics.

Results

Age at diagnosis

Three hundred eleven (10.6%) of 2,940 CD patients newly registered between 2003 and 2006 were $\leq$16 years old. Among 10,934 CD patients in the whole registry in 2005,

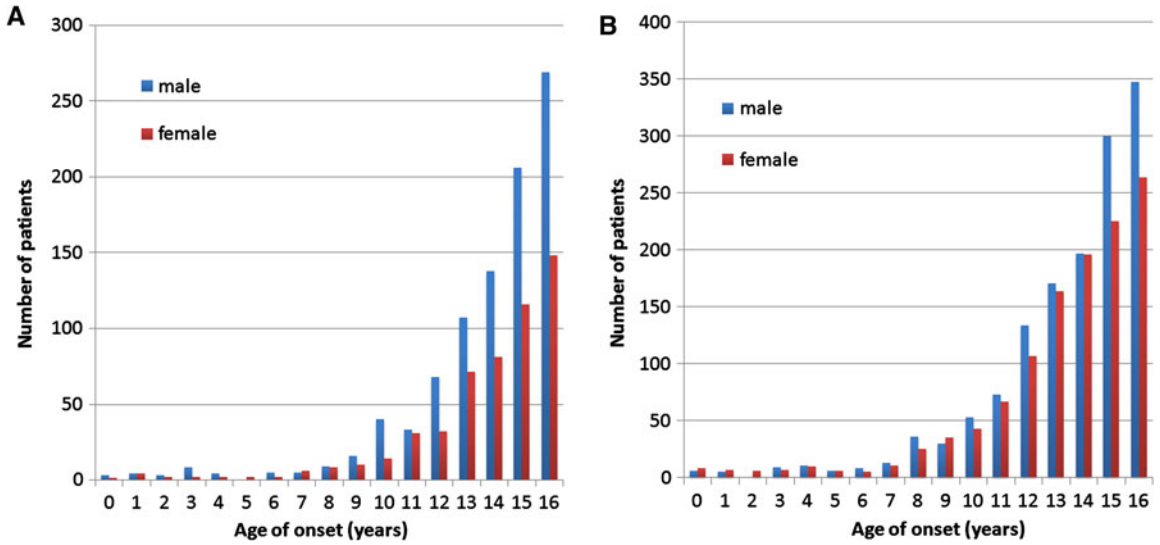

Fig. 1 **a** Age at onset of CD in Japanese patients registered in 2005 ($n = 1{,}450$); **b** age at onset of UC in Japanese patients registered in 2005 ($n = 2{,}355$)

1,450 (13.2%) were ≤16 years old (A1 in the Montreal classification) at the time of disease onset, and 219 (2.0%) were ≤16 years old at the time of the registration in 2005. The distribution of age at onset in these 1,450 patients is shown in Fig. 1a. There was an abrupt increase in the onset of CD after age 8–10 years old. Between 2003 and 2006, 14,857 UC patients were newly registered. Of these, 880 (5.9%) were ≤16 years old. Of 37,846 UC patients who were registered in 2005 (newly and previously registered), 2,355 (6.2%) had disease onset at ≤16 years old (A1), and 599 (1.6%) were ≤16 years old at the time of registration in 2005. The distribution of onset age in the 2,355 pediatric UC patients is shown in Fig. 1b. The age distribution of pediatric UC was similar to that of CD, having a trend to increase after 8–10 years of age.

Sex distribution (Table 1)

In CD, there was a significant difference in the sex distribution between adults and children. In adults, males were 2.6 times more likely to have CD than females, whereas in children, males were only 1.8 times more likely to have CD ($P < 0.001$, chi-square test). In UC patients, there were no significant differences in the male to female ratio compared between adults and children, as shown in Table 1. These trends did not alter after being adjusted by sex distribution for the whole Japanese population, which was 0.955 for adults and 1.049 for children [24].

Family history

For CD and UC, patients with a childhood onset had a positive family history more often than adults did. The percentage of those with childhood-onset CD with a family history for the same disease was 3.0%, while only 1.7% of adult-onset patients showed a positive family history of CD ($P < 0.001$, chi-square test). The percentage of CD patients with a positive family history of UC was 0.8% in childhood-onset and 0.6% in adult-onset patients (no significant difference). For UC, 4.1% of childhood-onset and 1.8% of adult-onset patients showed a positive family history for UC ($P < 0.001$, Fisher's exact test), while 0.2% of childhood and 0.2% of adult-onset patients showed a positive family history for CD (no significant difference).

Table 1 Sex distribution (male to female ratio) of IBD patients in Japanese children and adults

	Male	Female	Male-to-female ratio	P^b
CD ($n = 10{,}934$)				
Child (adjusted[a])	1,266	689	1.84	<0.001
			1.75	
Adult (adjusted[a])	6,391	2,588	2.58	
			2.58	
UC ($n = 37{,}846$)				
Child (adjusted[a])	1,791	1,512	1.05	0.183
			1.13	
Adult (adjusted[a])	18,307	16,236	1.18	
			1.18	

Analysis of patients who were newly registered in 2005 and those for whom the annual report was filed in 2005

[a] Adjusted by the male to female ratio in the Japanese population

[b] Chi-square test

Table 2 Disease severity at the time of first registry of CD and UC

	Child	Adult
IOIBD score for CD		
0–1	56 (18.1%)	473 (19.9%)
2–4	126 (40.6%)	1,203 (50.6%)
5–7	119 (38.4%)	653 (27.5%)
8–10	9 (2.9%)	48 (2.0%)
Total	310 (100.0%)	2,377 (100.0%)
P^a	<0.001	
Truelove's severity for UC		
Mild	291 (33.6%)	6,262 (45.7%)
Moderate	456 (52.7%)	6,162 (45.0%)
Severe	108 (12.5%)	1,188 (8.7%)
Fulminant	10 (1.2%)	87 (0.6%)
Total	865 (100.0%)	13,699 (100.0%)
P^a	<0.001	

Analysis of patients newly registered between 2003 and 2006

[a] Chi-square test

Table 3 Comparison of the disease location at diagnosis in childhood- and adult-onset CD and UC patients

	Child	Adult
CD		
L1 (terminal ileum)	83 (25.8%)	729 (28.7%)
L2 (colon)	62 (19.3%)	650 (25.6%)
L3 (ileocolon)	143 (44.4%)	1,004 (39.6%)
L4 (upper GI)	2 (0.6%)	0 (0.0%)
L1 + L4	12 (3.7%)	26 (1.0%)
L2 + L4	3 (0.9%)	26 (1.0%)
L3 + L4	17 (5.3%)	101 (4.0%)
Upper GI	34 (10.6%)	153 (6.0%)
Total	322 (100.0%)	2,536 (100.0%)
P^a	<0.001	
UC		
E1 (proctitis)	156 (14.0%)	3,001 (22.7%)
E2 (left sided)	360 (32.4%)	4521 (34.2%)
E3 (pancolitis)	596 (53.6%)	5,697 (43.1%)
Total	1,112 (100.0%)	13,219 (100.0%)
P^a	<0.001	

Analysis of patients newly registered between 2003 and 2006

[a] Chi-square test

Disease severity (Table 2)

As shown in Table 2, pediatric CD patients had higher IOIBD scores than adults did when they were first registered ($P < 0.001$, chi-square test). Percentage of patients with IOIBD score ≥ 5 was 41.3% in children and 29.5% in adults. Similarly, in children, moderate, severe and fulminant UCs were more frequent than in adult patients at the time of first registry (66.4 vs. 54.3%), while mild disease was less frequent (46.4 vs. 56.9%, respectively. $P < 0.001$, chi-square test).

Disease extent (Table 3)

Table 3 shows the affected site at the time of first registry in CD. Ileum and upper gastrointestinal (GI) involvement was observed more commonly in pediatric patients ($P < 0.001$, chi-square test). Extensive colitis (E3 in the Montreal classification) was more common in childhood-onset than in adult-onset UC (53.6 vs. 43.1%), whereas left-sided colitis (E2) and proctitis (E1) were more common in adult-onset than in childhood-onset patients (46.4 vs. 56.9%. $P < 0.001$, chi-square test).

Discussion

IBD is one of the most suffered chronic diseases to affect children and adolescents. Its etiology is unknown, and it is not easy to treat. Analysis of epidemiological data in the pediatric population should enable us to develop better understanding of the etiology of IBD and provide better clinical care for children with the disease [2, 6]. Using data from the nationwide registry of the Japanese government, which includes both adult and childhood data, we characterized pediatric IBD by comparing its clinical features with those in adults.

The database used in this study does not yet cover all IBD patients in Japan, and it is estimated that only 50–70% of patients are included. One major reason that not all patients have been filed is that some data are still in the process of being put into the computer at local MHLW offices. The delay in data handling results mainly from the shortage of office manpower, which is clearly independent of the age of the patients. Registration rates varied by prefecture from 0 to over 90%; 14 of 47 prefectures showed registration rates above 90%, whereas 13 prefectures did not register any patients in 2003. Therefore, there should not have been much bias in the conclusion obtained in this study that analyzed age-related changes. Another concern is that patients with mild symptoms tend not to register for this survey because of their low medical costs. However, our result regarding severity did not differ from previous studies without financial support [26]; furthermore, this sampling bias should be same in both children and adults so that it would not affect the results regarding differences in severity between children and adults.

As for IBD, a population-based study with a large enough number of patients to determine the proportion of

pediatric patients is lacking. The only data available to compare directly the incidence of IBD between adults and children are from a prospective study on the incidence of IBD in a restricted area in Denmark [1]. This study found that 6% with CD and 7% with UC had IBD onset before the age of 16 years.

In the present survey, the proportion of pediatric patients with newly registered CD and UC was 10.6 and 5.9%, respectively. In most cases, registration was done soon after diagnosis, and we assume that these numbers were close to the real incidence of the disease. The figures were, in fact, close to those of the Danish study [1]. The proportion of people who are ≤16 years old in the whole Japanese population is 13.8% [24]; therefore, the age-adjusted incidence of CD is 1.3 times greater in adults than that in children, and the incidence of UC in adults is estimated to be 2.3 times greater.

The proportion of patients below 16 years of age in 2005 was 2.6% for CD and 2.0% for UC. Therefore, the estimated prevalence of CD and UC in children adjusted by age was 5.3 and 6.9 times lower than in adults, respectively.

Incidence and prevalence of IBD vary considerably with country and race. It has been suggested that in Asian countries, incidence and prevalence of CD and UC are less than those in Western countries, especially in Northern Europe and North America. This geographic difference explains why the number of UC patients was twice that of CD in the present study. It has been reported that UC is more common than CD in Asian countries [15], which is distinct from Western countries where CD is more common than UC. The trend that UC is more common than CD in Japanese adults is also true in children. However, the ratio of UC to CD in children was 2.7, which is significantly lower than that in adults (5.1).

The age distribution of CD and UC in childhood in the present study was similar to that reported in Western countries [1, 8]. The number of patients increased abruptly after 8–10 years of age in those studies and in ours. The only exception is a recent analysis in the US in which an abrupt increase in the incidence after 8–10 years of age was obvious in CD, but not in UC. The reason for this discrepancy is not clear, and more data will be needed to reach a conclusion.

For CD in Western countries, it has been shown that women are more commonly affected than men, with a male to female ratio of 0.6–0.9 [25]. In children, boys are more likely to have CD than girls, with the male to female ratio being 1.3–1.6 [7, 8, 18]. In a recent study from Scotland, the male to female ratio was 0.6 in adult-onset patients and 1.5 in childhood-onset patients, which confirmed previous reports [28].

It has been recognized previously that, in Asian countries, CD is more common in males than in females, even in adults, although the reason for this is not known [15]. The gender distribution for CD in the present study was consistent with that previously reported in Asia, with a male-to-female ratio in adults of 2.4. Interestingly, the male to female ratio in childhood CD was significantly less (1.3) than in adults, and was close to that in Western countries. These facts suggest that some environmental, hormonal or lifestyle factors in Japanese adult male or female patients have some influence on the onset of CD.

In most studies from Western countries, male to female ratios for UC are close to 1 in adults [15, 25–28] and children [1, 12, 28, 29]. In the present study, we confirmed that there was no major difference in this ratio between children and adults, both being close to 1. One exception is a recent population-based study in Minnesota that showed a male predominance in incidence of UC, which was most obvious in childhood (male:female 3.4:1.3 for 0–19 years old) [19].

The present study showed that, in adults, 1.7% of CD and 1.8% of UC patients had a family member with the same disease. In children, the rates were higher: 3.0% for CD ($P < 0.001$) and 4.1% for UC ($P < 0.001$). However, these frequencies were still lower when compared to those in Western countries [12]. In a study by Kugathasan et al. [8], 11% of newly diagnosed pediatric IBD cases had first- or second-degree relatives with a history of IBD, and Feeney et al. [30] have reported that 30% of pediatric CD patients did so.

It has been shown that, in Japan, the first-degree relatives of UC patients have a 25-fold greater frequency of UC than in the general population, which is comparable to Western countries [27]. Therefore, as Yang et al. [15] have suggested, the lower rate of family history of UC is likely to reflect the relatively low prevalence of UC in Japan. Similarly, the lower familial occurrence of CD than UC can be explained by the lower prevalence of CD compared to UC in Japan.

In CD, age-related differences in anatomic distribution of the disease are controversial. Polito et al. [3] have reported that pediatric CD patients have the disease in the small intestines more often than older patients do. Others have reported that there are no definite differences in anatomic localization of the disease between children and adults [5, 7]. CD in very young children (≤5 years old) tends to have only colonic involvement [31]. The present study did not show any definite difference between pediatric-onset and adult-onset patients in the anatomical distribution of the disease.

Most adult studies with a large number of subjects have shown that 14–37% of patients with UC have total colitis, whereas 44–49% have proctosigmoiditis [25, 32]. In a recent large series of Finnish children, 61.2% of those with UC had total colitis [14]. Studies in the UK [7] and US [8]

have revealed that, in approximately 90% of pediatric UC patients, the entire colon or the portion beyond the splenic flexure was involved. These results suggest that children have more widespread colonic involvement in UC than adults do. In the study by Langholz et al. [1], in which pediatric and adult data were compared, although total colitis in children was less frequent (29%) than that described above, it was still significantly more frequent than that in adults (16%). Our data showed a similar trend that extensive colitis (E3) was more common in children than in adults, whereas left-sided colitis (E2) and proctitis (E1) were less common.

CD varies in its severity in adults and in children, although no studies have compared severity between age groups. In the present study, we found that the mean IOIBD score at initial diagnosis was slightly higher in children than in adults. It must also be noted that some problems specific to children, such as growth failure, are not included in the IOIBD score. Further prospective investigation that involves both adults and children is warranted.

In a small series of pediatric UC patients reported by Gryboski et al. [33], 11% had severe, 37% moderate and 53% mild disease. In 171 patients reported by Hyams et al. [34], 57% had moderate or severe, and 43% had moderate disease. These data were not compared with those of adult patients.

In the present study, moderate, severe and fulminant UC were more frequent among children, while mild disease was less frequent in children than in adults. These results were consistent with the fact that the disease severity in UC correlates with disease extent [25], and children with UC tend to have more extensive disease than adults.

Our data should be carefully interpreted regarding disease severity, which changes with time, either because of natural history or treatment. In this study, severity was determined based on the data at first registration. As mentioned above, most patients were registered soon after a diagnosis was made. However, diagnosis of IBD in children can be delayed because of the much lower incidence in that population, which might cause some increase in disease severity at the first registration.

In summary, incidence and prevalence of CD and UC are lower in children than in adults. The effect of gender on the incidence or prevalence of CD, but not of UC, differs with age. A family history for the disease in question is more common in children than in adults. Disease severity is greater in CD and UC in children than in adults. UC in childhood-onset patients results in more extensive disease than is the case for adult-onset patients. In conclusion, this nationwide surveillance in Japan showed that CD and UC in children have clinical features that are distinct from those in adults.

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Conflict of interest statement None.

References

1. Langholz E, Munkholm P, Krasilnikoff P, 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.
2. Hait E, Hait L, Bousvaros A, Grand R. Pediatric inflammatory bowel disease: what children can teach adults. Inflamm Bowel Dis. 2005;11(6):519–27.
3. Polito Jn, Childs B, Mellits E, Tokayer A, Harris M, Bayless T. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. Gastroenterology. 1996;111(3):580–6.
4. Washington K, Greenson J, Montgomery E, Shyr Y, Crissinger K, Polk D, et al. Histopathology of ulcerative colitis in initial rectal biopsy in children. Am J Surg Pathol. 2002;26(11):1441–9.
5. Griffiths A. Specificities of inflammatory bowel disease in childhood. Best Pract Res Clin Gastroenterol. 2004;18(3):509–23.
6. Mamula P, Markowitz J, Baldassano R. Inflammatory bowel disease in early childhood and adolescence: special considerations. Gastroenterol Clin North Am. 2003;32(3):967–95, viii.
7. Sawczenko A, Sandhu B. Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child. 2003;88(11):995–1000.
8. Kugathasan S, Judd R, Hoffmann R, Heikenen J, Telega G, Khan F, 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.
9. Motil K, Grand R, Davis-Kraft L, Ferlic L, Smith E. Growth failure in children with inflammatory bowel disease: a prospective study. Gastroenterology. 1993;105(3):681–91.
10. Heuschkel R, Salvestrini C, Beattie R, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. Inflamm Bowel Dis. 2008;14(6):839–49.
11. Taminiau J. Review article: The clinical importance of growth in children with inflammatory bowel disease: is it important to the gastroenterologist? Aliment Pharmacol Ther. 2007;26(Suppl 2):53–6.
12. Heyman M, Kirschner B, Gold B, Ferry G, Baldassano R, Cohen S, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. J Pediatr. 2005;146(1):35–40.
13. Weinstein T, Levine M, Pettei M, Gold D, Kessler B, Levine J. Age and family history at presentation of pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2003;37(5):609–13.
14. Turunen P, Kolho K, Auvinen A, Iltanen S, Huhtala H, Ashorn M. Incidence of inflammatory bowel disease in Finnish children, 1987–2003. Inflamm Bowel Dis. 2006;12(8):677–83.
15. Yang S, Loftus EJ, Sandborn W. Epidemiology of inflammatory bowel disease in Asia. Inflamm Bowel Dis. 2001;7(3):260–70.
16. Logan R. Inflammatory bowel disease incidence: up, down or unchanged? Gut. 1998;42(3):309–11.
17. Russel M, Stockbrügger R. Epidemiology of inflammatory bowel disease: an update. Scand J Gastroenterol. 1996;31(5):417–27.
18. Farmer R, Michener W. Prognosis of Crohn's disease with onset in childhood or adolescence. Dig Dis Sci. 1979;24(10):752–7.

19. Loftus C, Loftus EJ, Harmsen W, Zinsmeister A, Tremaine W, Melton Lr, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis. 2007;13(3):254–61.
20. Kinjo F. Epidemiological research on inflammatory bowel disease in Okinawa prefecture. Annual report of intractable inflammatory bowel disorders research, The Specified Disease Treatment Research Program 1999.
21. de Dombal F, Softley A. IOIBD report no 1: Observer variation in calculating indices of severity and activity in Crohn's disease. International Organisation for the Study of Inflammatory Bowel Disease. Gut. 1987;28(4):474–81.
22. Truelove S, Witts L. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041–8.
23. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749–53.
24. Data provided by the Statistics Bureau, Ministry of Internal Affairs and Communications; 2005.
25. Andres P, Friedman L. Epidemiology and the natural course of inflammatory bowel disease. Gastroenterol Clin North Am. 1999;28(2):255–81, vii.
26. Morita N, Toki S, Hirohashi T, Minoda T, Ogawa K, Kono S, et al. Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. J Gastroenterol. 1995;30(Suppl 8):1–4.
27. Calkins B, Lilienfeld A, Garland C, Mendeloff A. Trends in incidence rates of ulcerative colitis and Crohn's disease. Dig Dis Sci. 1984;29(10):913–20.
28. Van Limbergen J, Russell R, Drummond H, Aldhous M, Round N, Nimmo E, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135(4):1114–22.
29. Michener W, Farmer R, Mortimer E. Long-term prognosis of ulcerative colitis with onset in childhood or adolescence. J Clin Gastroenterol. 1979;1(4):301–5.
30. Feeney M, Murphy F, Clegg A, Trebble T, Sharer N, Snook J. A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2002;14(5):529–34.
31. Mamula P, Telega G, Markowitz J, Brown K, Russo P, Piccoli D, et al. Inflammatory bowel disease in children 5 years of age and younger. Am J Gastroenterol. 2002;97(8):2005–10.
32. Farmer R, Easley K, Rankin G. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. Dig Dis Sci. 1993;38(6):1137–46.
33. Gryboski J. Ulcerative colitis in children 10 years old or younger. J Pediatr Gastroenterol Nutr. 1993;17(1):24–31.
34. Hyams J, Davis P, Grancher K, Lerer T, Justinich C, Markowitz J. Clinical outcome of ulcerative colitis in children. J Pediatr. 1996;129(1):81–8.