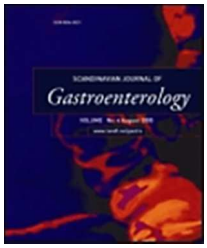

Incidence of Inflammatory Bowel Disease in Iceland 1995-2009.
A Nationwide Population based Study.

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Incidence of Inflammatory Bowel Disease in Iceland 1995-2009.

A Nationwide Population based Study.

Inflammatory Bowel Disease in Iceland.

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Abstract

Objective

We analysed the incidence of inflammatory bowel disease in Iceland for the period 1995-2009.

Material and Methods

New cases of ulcerative colitis and Crohn's disease were retrieved by thorough review of all small and large intestinal pathology reports with any type of inflammation from all the pathology departments in Iceland for the period 1995-2009. All suspicious new cases of inflammatory bowel disease were then scrutinized retrospectively by examination of their clinical records.

Results

A total of 1175 cases of inflammatory bowel disease were diagnosed, 884 ulcerative colitis, 279 Crohns disease and 12 inflammatory bowel disease unclassified. The crude annual incidence of ulcerative colitis was 20.5/100.000, increasing from 18.1 the first 5 year period to 22.1 the last 5 year period. The crude annual incidence of Crohns disease was 6.5/100.000, 6.7 the first 5 year period and 6.6 the last 5 year period.

Conclusions

This study shows statistically significant increase in the incidence of ulcerative colitis during the study period. The incidence of Crohns disease has however remained stable.

Key words: Crohns disease, epidemiology, incidence, inflammatory bowel disease, population based, ulcerative colitis.

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Introduction

The nationwide incidence of ulcerative colitis (UC) and Crohn's disease (CD) in Iceland was investigated in two retrospective studies during the periods 1950-1979 and 1980-1989 and prospectively for the period 1990-1994, spanning 45 years. (1,2,3). These studies demonstrated a continuous increase in incidence of both diseases during the study periods, the incidence of UC reaching 16.5 per 100.000 and that for CD 5.5 per 100.000 in 1990-1994. Iceland participated in the two-year EC IBD study (4) and the one-year ECCO Epicom study (5).

Globally the incidence of inflammatory bowel disease (IBD) has been increasing with time as indicated in a recent comprehensive review, where 75% of CD studies and 60% of UC studies in time-trend analysis showed increase with time in both high and low incidence areas. (6) There is a difference in incidence between the more effluent and less effluent parts of the world as well as within continents such as North America and Europe and in individual countries like Norway, France, Canada, Scotland, Italy, Spain and Portugal. (6,7).

We have extended our study of incidence of IBD in Iceland for an additional 15-year period 1995-2009 with the aim to find out, if the IBD incidence in Iceland has continued to increase and also looking at the extent, severity and behaviour of the disease at diagnosis. With this study, information on IBD incidence over a period of 60 years 1950-2009 in the whole Icelandic population has become available.

Materials and methods

This study is a retrospective nationwide population based register study, including all IBD patients diagnosed in Iceland during 1995-2009. Iceland is 103.000 km^2 in size, with a mean population increasing from 267.380 in 1995, the first year of the study, to 319.246 in 2009, the last year of the study. The state supported public health system is accessible to all inhabitants and all individuals are traceable with their social security numbers.

Our knowledge of IBD diagnosed in Iceland 1950-1994, ensured that only new cases were included in our present study.

The retrieval of new cases of UC and CD was based on a yearly scrutiny of all reports of all small and large intestinal biopsies and surgical specimens showing any type of inflammation submitted to all the pathology departments in Iceland during the study period 1995-2009, in direct continuation of earlier prospective study 1990-1994. (3) Totally, eighteen thousand and five hundred histology reports were examined.

All cases suspected to represent IBD were further followed up by reviewing their hospital and outpatient records. The clinical history of the patients was examined, endoscopy description, x-ray findings as well as other relevant findings from patients notes, supporting the IBD diagnosis was collected. Only cases fulfilling the accepted criteria of Lennard Jones (8) were included in this study. Initially 1563 cases were selected for further follow up. Of these, 388 cases were excluded due to other diseases such as infectious and self-limited colitis.

All cases found were verified by histology. The date of diagnosis was based on the first endoscopy with inflammatory changes or small bowel x-ray indicating Crohns disease. The extent of UC was classified into three types, proctitis reaching 15 cm (E1), left sided inflammation reaching left flexure (E2) and extensive colitis, where inflammation extended beyond left flexure into transverse or right colon (E3). The severity was classified as mild (S1), moderate (S2) and severe (S3). (9)

The classification of CD was based on the Montreal classification (9)

The severity of CD at time of diagnosis was recorded as mild, moderate and severe disease. (10)

Statistical methods

Information about the number of men and women for each year of the study period and for each year of age was obtained from the Statistics Iceland (Statistics Iceland: http://hagstofan.is/Hagtolur/Mannfjoldi/Yfirlit). Calculation of the crude annual incidence was based on the number of cases observed in the total population at risk for the whole period. In addition, the crude incidence for each of the three five year periods was calculated, based on the mean population of each five year period to find out, whether there was a significant change in incidence throughout the whole fifteen year period. It was assumed, that the number of cases followed Poisson distribution. Accordingly 95% confidence limits were calculated for the number of cases per 100000 inhabitants. A chi square trend test was used for trend analysis where a p value less than 0.05 was assumed significant. We also used Poisson regression to test the time-trend in age-adjusted incidence rates for UC in Iceland were the significance level was $p<0.05$.

To facilitate the comparison with populations with different age distribution we calculated the standardized incidence rate by using the standard European population (11). The National Bioethics Committee and The Data Protection Authority in Iceland approved this study.

Results

As shown in table I a total of 1175 cases were retrieved fulfilling the diagnosis of IBD, 884 UC and 279 CD. There were in addition 12 cases of inflammatory bowel disease unclassified (IBDU). Table I shows also the median age and the crude annual incidence per 100.000. Table II shows the standardized incidence rate using the Standard European Population.

Ulcerative colitis:

In table 2 we show the age-standardized incidence for UC for men and women in 3 time periods where we used the age distribution in the European standard population. In table 3 we show the crude incidence for UC for men and women in 3 time periods. These results in table 2 and table 3 are similar. We then used a trend test shown in table 3 to see if the increase in the crude incidence over time was significant. The increase in crude incidence of UC was significant for the whole population (p= 0.02) and for men separately (p=0.04) but not for women (p=0.2).

Poisson regression was used to calculate the p value for the trend in the age-adjusted incidence for UC in the population in 3 five-year periods. For the whole group (men and women) there was a significant trend (p=0.03), but not for men (p=0.08) and women (p=0.21) separately. After excluding the youngest age group (0-16 years) the trend increased significantly when analysing both men and women together (p=0.02) and for men separately (p= 0.03) but not for women (0.32).

The male/female ratio for UC was 1.18 (95% CI 1.03-1.35), ranging from 1.13 to 1.22 for the three 5-year periods.

Fig 1 depicts the highest age related incidence in the age group 30-39 years, 34.18, similar for males (33.39) and females (35.0). However in the age groups over 40 years the incidence for men was higher than for women.

Table IV shows the extent of inflammatory changes and severity of UC at the time of diagnosis. The incidence of proctitis was 7.6 per 100.000 with no sex difference.

There was a significant increase in extensive colitis during the three successive 5-year periods. There was no change in the severity of UC when we compare the three five year periods for mild and moderate disease, but the percentage of patients with severe disease increased during the three, five year periods, shown in table IV. Mild severity (S1) was most often seen in UC (63%). Gender did not affect the extension or the activity of UC.

Crohn´s disease:

The crude incidence of CD was stable throughout the period, shown in table V. The result is similar for the age-standardized incidence for CD shown in table 2.

In figure 2 we see that the highest age related incidence for both genders together was observed in the age group 60-69, 11.0. Both genders appear to have early and late peaks of their incidence. The early peak is more prominent among males in the age group 10-19 years, or 9.4 per 100.000 and the late peak is more prominent among females in the age group 60-69 or 14.8.

Looking at the age range, 10 % (28/279) were 16 years and younger (A1), 41% (114/279) were 17-39 years old (A2) and 49% (137/279) were 40 years and older (A3).

Perianal disease (p) was found in 7.5% (21/279) of the Crohns patients.

Male/female ratio for CD for the period 1995-2009 was 0.85 (95% CI 0.67-1.07).

Table VI shows the localization, behaviour and severity of CD at diagnosis in three five year periods, the most frequent involvement being colon only (L2) 53% and by behaviour non- stricturing, non-penetrating (B1) 66%.

Discussion

In this study it is evident that the incidence of UC is still increasing in Iceland. Extensive and severe disease increased throughout the study period. The incidence of CD was however, stable.

There is a difference in age distribution in different populations and therefore to facilitate comparison between populations we have calculated the age-standardized incidence rate for UC and CD using the European Standard Population.

The main strength of this study is that this is a population-based study of a whole nation with a combination of yearly scrutiny of pathology reports and retrospective collection of clinical data. There is high quality primary health care in Iceland with the possibilities of sophisticated diagnostic methods comparable to most other countries in the developed part of the world. All cases are diagnosed and confirmed with histology. All patient records were available for review.

The main limitations of the study are that it is retrospective and spans over 15 years and during this time the healthcare has been changing with a tripling of the number of colonoscopies done from 2000 to 2010 (Information from the State Insurance Company and the National University Hospital of Iceland) and improvement in the sensitivity of diagnostic methods such as CT and MRI. However the diagnostic strategy was the same throughout this study as was used in the EC-IBD study (4). The evaluation of severity and extension of both diseases is difficult due to the retrospective nature of the study, we used accepted criteria in our evaluation and we have used the same method for evaluating these criteria for the whole study period. With our methods we see more

patients with extensive and severe ulcerative colitis and we see more Crohns patients with mild disease.

Ulcerative colitis

The crude annual incidence was 20.4 per 100.000, increasing from 18.1 the first 5-year period to 22.1 the last 5-year period 2005-2009, which is one of the highest found so far. In a recent publication from Iceland (17) the incidence for the youngest age group (0-16 years) increased to year 2000 but has been stable from year 2000. We have therefore chosen to calculate the time trend for the age-adjusted incidence with poisson regression both in the whole population and after excluding patients younger than 17 years old. The M/F ratio was 1.18, ranging from 1.13 to 1.22 for the three 5-year periods, the incidence in the last 5-year period for males reaching 24.3 per 100.000 population and that for females 19.9. In older age groups it was observed, that the incidence for males was higher in all, the linear decreasing incidence for females with increasing age being similar to that seen in previous Icelandic studies. (2, 3)

We believe that our results show true increase in incidence of UC, evidenced by similar and stable distribution of extent and severity of the disease, the only difference being a modest increase in the number of extensive and severe disease during the study period.

The UC incidence in our study is similar to that found in recent studies from Uppsala County Sweden for the period 2005-2009, 20.0 and Finland for the period 2000-2007, 24.8, increasing from 22.1 2000-2001 to 27.4 2006-2007 per 100.000. (12, 13) In Copenhagen Denmark the UC incidence for the period 2003-2005 was found to be much lower or 13.4 per 100.000, increasing however from earlier studies. (14) In Faroe Islands for the period 2005-2009, a very high incidence was found, 26.8 per 100.000,

increasing from rather high incidence reported for the period 1981-1988 or 20.3 per 100.000. (15, 16)

The increase in incidence of UC in our present study is in general reflected in all three types of extent of disease indicating unchanged nature of the disease as is also concluded in a recent study from Uppsala County Sweden. (12).

Crohn´s disease

Our study shows a stable incidence of CD in contrast to UC throughout the 15-year period. The incidence of CD is low in Iceland compared to the other Nordic countries: In a recent incidence study from Finland the incidence of CD was 9.2 (13), and from Uppsala County, Sweden 9.9. (18). Incidence in Faroe Islands was found to be increasing from 3.6 in the period 1981-1988 to 8.7 per 100.000, 2005-2009. (15, 16) Incidence figure from Copenhagen was 8.6 per 100.000 (14)

Our results are important because they show an increase in the incidence of UC in a population with a known high incidence. The same effect is seen in the Uppsala County in Sweden, in Finland and Faroe Islands. (12, 13, 16) at the same time the incidence of Crohns disease is stable around 6.5 in Iceland compared to 9-10 in Sweden, Finland, Denmark and the Faroe Islands. Our results are comparable to the results from Iceland in the ECCO Epicom study. (5)

Smoking is a well-recognized risk factor for IBD (7) with a polarizing effect on UC vs CD. From the sixties smoking has been steadily decreasing in Iceland and presently about 14% of both men and women smoke. (19)

Is it possible, that the decreasing smoking in Iceland could contribute to the increase in the UC incidence and stable CD incidence?

In our study reliable information about smoking habits was obtained from 49% of the UC group, of which 11.1% were current smokers at diagnosis and 65% from the CD group, of which 41.9% were current smokers. Although our results are biased due to small numbers it draws again attention to the difference in smoking habits between UC and CD patients.

It can be concluded; that the incidence of UC in Iceland is high compared to the UC incidence in the other Nordic countries and is still rising in the age group over 16 years, whereas, the CD incidence is stable and relatively low compared to that in the other Nordic populations.

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The authors report no conflict of interest and the authors alone are responsible for writing the paper.

Figure legends:

Figure 1: Age related incidence per 100 000 inhabitants for all UC patients in Iceland 1995-2009 and for men and women separately.

Figure 2: Age related incidence per 100 000 inhabitants for all CD patients in Iceland 1995-2009 and for men and women separately.

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Table I

Number of IBD patients, number of men and women, crude annual incidence and median age (range) of patients with IBD, UC, CD and IBDU in Iceland 1995-2009.

	IBD	UC	CD	IBDU
All	1175	884	279	12
Men	618	481	129	8
Women	557	403	150	4
Crude annual incidence/100000	27.05	20.35	6.42	0.28
95% confidence interval	25.5-28.6	19.0-21.7	5.7-7.2	
Age, years				
Median	37	37	38	44.5
Range	3-91	8-91	3-86	24-79

Table II

Age-standardized incidence rates of UC and CD in Iceland in 3 time periods 1995-1999, 2000-2004 and 2005-2009 using the European standard population.

	UC		CD	
Period	Men	Women	Men	Women
1995-1999	20.2	17.7	5.9	8.5
2000-2004	24.1	18.8	5.2	7.7
2005-2009	25.1	20.1	6.6	7.0
1995-2009	23.3	18.8	5.9	7.7

Table III

Number (n) and crude Incidence (I) of Ulcerative Colitis in Iceland for 3 five-year periods in 1995-2009.

	All*		Men**		Women***	
Period	n	I	n	I	n	I
1995-1999	246	18.1	131	19.3	115	17.0
2000-2004	295	20.6	159	22.1	136	19.0
2005-2009	343	22.1	191	24.3	152	19.9

* Test for trend: Chi-square method. 1 df. $\chi^2 = 5.69$; $p<0.02$

**Test for trend: Chi-square method. 1 df. $\chi^2 = 4.19$; $p< 0.04$

***Test for trend: Chi-square method. 1 df. $\chi^2 = 1.63$; $p= 0.20$

Table IV

Extension and severity of ulcerative colitis (Based on the Montreal Classification (9)) at diagnosis in Iceland 1995-2009.

Extension. E1: Proctitis, E2: Left Colitis, E3: Extensive Colitis

	E1		E2		E3		
Period	n	%	n	%	n	%	Total
1995-1999	89	36	123	50	34	14*	246
2000-2004	108	37	135	46	52	18*	295
2005-2009	131	38	135	40	77	23*	343
Total	328	37	393	45	163	19	884

*Test for trend: Chi-square method. 1 df. $\chi^2 = 7.25$; $p<0.007$

Severity.

	Mild		Moderate		Severe		
Period	n	%	n	%	n	%	Total
1995-1999	161	65	77	31	8	3	246
2000-2004	180	61	98	33	17	6	295
2005-2009	218	64	101	29	24	7	343
Total	559	63	276	31	49	5.5	884

Table V

Number (n) and Crude incidence (I) of Crohns disease in Iceland in 3 five-year periods 1995-2009.

	All*		Men**		Women***	
Period	n	I	n	I	n	I
1995-1999	91	6.7	40	5.9	51	7.5
2000-2004	86	6.0	38	5.3	48	6.7
2005-2009	102	6.6	51	6.5	51	6.7

* Test for trend: Chi-square method. 1 df, $\chi^2 = 0.01$; p=0.92

** Test for trend: Chi-square method. 1 df, $\chi^2 = 0.26$ p=0.61

***Test for trend: Chi-square method. 1 df, $\chi^2 = 0.36$ p=0.55

Table VI

Distribution of Crohns disease in Crohns patients in Iceland 1995-2009. Localization of CD was grouped into four types, L1 ileal, L2 colonic, L3 ileocolonic and finally L4 isolated upper G.I. tract inflammation. Based on the Montreal Classification (9)

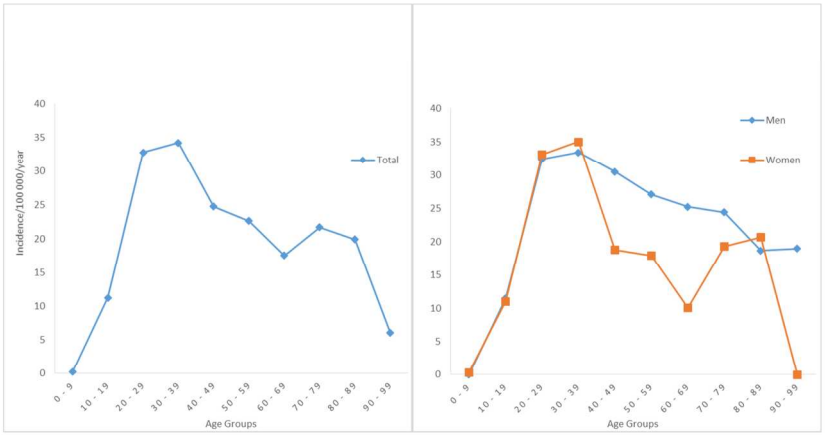
	L1		L2		L3		L4		Total
Period	n	%	n	%	n	%	n	%	
1995-1999	15	17	53	62	19	22	4	5	91
2000-2004	12	14	47	55	21	24	6	7	86
2005-2009	22	22	49	48	26	25	5	5	102
Total	49	17,6	149	53,4	66	23,7	15	5,4	279

Behaviour of Crohns disease in Crohns patients in Iceland 1995-2009. Behaviour was grouped into 3 categories: B1 non-stricturing non-penetrating, B2 stricturing and B3 penetrating. Based on the Montreal Classification (9)

	B1		B2		B3		Unknown		
Period	n	%	n	%	n	%	n	%	Total
1995-1999	52	57	7	8	14	15	18	20	91
2000-2004	59	69	4	5	14	16	9	10	86
2005-2009	72	71	10	10	10	10	10	10	102
Total	183	65.6	21	7.5	38	13.6	37	13	279

Severity of Crohns disease in Crohns patients in Iceland 1995-2009. The severity at time of diagnosis was recorded as mild S1, moderate S2 and severe S3. (10)

	Mild		Moderate		Severe		Unknown		
Period	N	%	N	%	N	%	N	%	Total
1995-1999	20	22	58	65	6	7	7	8	91
2000-2004	24	28	56	65	6	7	0	0	86
2005-2009	40	39	50	49	12	12	0	0	102
Total	84	30.1	164	58.8	24	8.6	7	2.5	279



Age related incidence per 100 000 inhabitants for all UC patients in Iceland 1995-2009 and for men and women separately.
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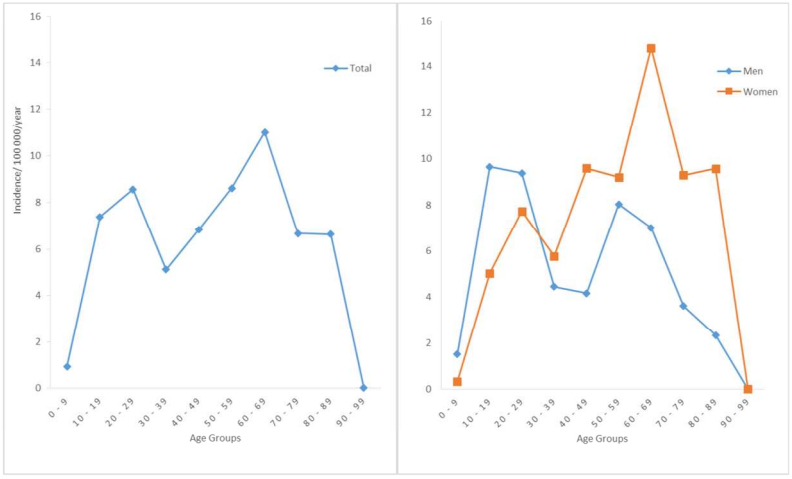

Age related incidence per 100 000 inhabitants for all CD patients in Iceland 1995-2009 and for men and women separately.
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