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Inflammatory Bowel Disease in South Limburg (the Netherlands) 1991–2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms

Mariëlle J.L. Romberg-Camps [a,*], Martine A.M. Hesselink-van de Kruijs [a], Leo J. Schouten [b], Pieter C. Dagnelie [b], Charles B. Limonard [c], Arnold D.M. Kester [d], Laurens P. Bos [e], Jelle Goedhard [f], Wim H.A. Hameeteman [a], Frank L. Wolters [g], Maurice G.V.M. Russel [h], Reinhold W. Stockbrügger [a]

[a] *Maastricht University Medical Center +, PO Box 5800, 6202 AZ Maastricht, The Netherlands*
[b] *Department of Epidemiology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands*
[c] *MEMIC, Centre for Data and Information Management, PO Box 616, 6200 MD Maastricht, The Netherlands*
[d] *Department of Methodology and Statistics, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands*
[e] *Department of Internal Medicine and Gastroenterology, Maasland Hospital, PO Box 5500, 6130 MB Sittard, The Netherlands*
[f] *Department of Internal Medicine and Gastroenterology, Atrium Medical Centre Heerlen, Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands*
[g] *Department of Gastroenterology, Vie-Curi Medical Centre Venlo, Tegelseweg 210, 5912 BL Venlo, The Netherlands*
[h] *Department of Gastroenterology, Medisch Spectrum Twente Enschede, PO Box 50000, 7500 KA Enschede, The Netherlands*

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Abstract

Background and aims: Increasing incidence in Inflammatory Bowel Disease (IBD) has been suggested. Recent data on population based incidence rates within Europe are however scarce. Primary aim was to investigate prospectively the incidence of IBD within a well-defined geographical and administrative area of the Netherlands, the South Limburg IBD registry.

Abbreviations: CD, Crohn's Disease; EAPC, Estimated Annual Percentage Change; EASR, European Age Standardized Rate; GP, general practitioner; IBD, Inflammatory Bowel Disease; IBD-SL, South Limburg IBD registry; IC, Indeterminate Colitis; UC, Ulcerative Colitis.

* Corresponding author. Department of Internal Medicine and Gastroenterology, Maasland Hospital Sittard, PO Box 5500, 6130 MB Sittard, The Netherlands. Tel.: +31 884597800; fax: +31 884597983.

E-mail addresses: m.camps@orbisconcern.nl (M.J.L. Romberg-Camps), Martine.Hesselink@INTMED.unimaas.nl (M.A.M. Hesselink-van de Kruijs), lj.schouten@epid.unimaas.nl (L.J. Schouten), Dagnelie@EPID.unimaas.nl (P.C. Dagnelie), Ch.Limonard@MEMIC.unimaas.nl (C.B. Limonard), arnold.kester@stat.unimaas.nl (A.D.M. Kester), r.bos@orbisconcern.nl (L.P. Bos), JGD01@atriummc.nl (J. Goedhard), w.hameeteman@mumc.nl (W.H.A. Hameeteman), fwolters@viecuri.nl (F.L. Wolters), m.russel@ziekenhuis-mst.nl (M.G.V.M. Russel), reinholdstockbrugger@gmail.com (R.W. Stockbrügger).

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Secondary aims were to study the duration of symptoms before diagnosis (lag time) and seasonal influences on the incidence of IBD.
Methods: The incidence was examined using standardized registration of all newly diagnosed IBD patients, between 1–1–1991 and 1–1–2003. Medical records were reviewed to verify the diagnosis. At inclusion, diagnostic lag time was registered in months.
Results: Age standardized incidence rates per 100,000 person-years (p-y) were: Crohn's Disease, male 4.84, female 7.58; Ulcerative Colitis, male 8.51, female 6.92; and Indeterminate Colitis, male 1.05, female 0.93. Incidence rates did not significantly changes over time in either Crohn's Disease, Ulcerative Colitis or Indeterminate Colitis. Lag time was 5 (0–360) months in Crohn's Disease, 3.0 (0–480) months in Ulcerative Colitis and 3.0 (0–180) months in Indeterminate Colitis. Lag time was not significantly different between the periods 1991–1993 and 2000–2002, and no statistical differences in the onset of symptoms per calendar month or season were found.
Conclusions: Our results, from the South Limburg region (the Netherlands), show no significant change in incidence rates of IBD. The incidence found is relatively high compared to other European countries. Lag time did not change during the study period, and seasonal influence of incidence rates could not be confirmed.

1. Introduction

Crohn's Disease (CD), Ulcerative Colitis (UC) and Indeterminate Colitis (IC) are chronic inflammatory disorders of the gastrointestinal tract. UC and IC affect the colon, whereas CD can involve any part of the gastrointestinal tract from the oral cavity to the anus. A patient is classified as having IC if, after careful investigation, the differential diagnosis between CD and UC remains uncertain.

Recent publications show that the incidence of Inflammatory Bowel Diseases (IBD) is still increasing in the adult population in Spain,[1] Greece,[2] Croatia[3] and Denmark.[4] Also higher rates of IBD are seen in northern, industrialized countries[5], however differences seem to get smaller.[1,3,6,7]

During recent years, diagnostic options in the field of IBD have significantly improved. This could possibly influence incidence rates by discovering sub-clinical disease and also the duration of time from first complaints until the diagnosis, i.e. the diagnostic lag time. Possibly also patients and doctors awareness with regard to IBD plays a role in earlier diagnosis.[4]

Although the cause of Inflammatory Bowel Diseases is still not elucidated, genetic and environmental factors are thought to play an important role in the aetiology.[8,9] Data increasingly implicate that there is a dysfunctional mucosal immune response to bacteria in the pathogenesis of IBD, especially in the case of CD.[10,11] Chronic inflammatory response is possibly triggered by infections with bacterial or viral pathogens and/or due to a defective mucosal barrier. The search for causative or modulating risk factors in the environmental field is ongoing, some of them possibly connected with public and personal hygienic circumstances.[12,13] The risk of infections might be subjected to climate, changes of biorhythm or other environmental events, secondarily influencing IBD onset. This could potentially result in seasonal variation of incidence rates. However, until now, published data on seasonal variation of incidence rates show conflicting results.[14–17]

Primary aim of the present study was to evaluate the incidence of IBD in a regional Dutch population (South Limburg), that has been followed continuously over a prolonged period of time, and to compare these data with the available literature. Secondary aims were to study the diagnostic lag time and the role of seasonality in the onset of disease in this uniformly defined population based inception cohort of IBD patients.

2. Materials and methods

2.1. Population and design

In 1991, a population-based IBD Registry was established through collaboration between the Department of Gastroenterology and Hepatology of the University Hospital Maastricht and the MEMIC (Centre for Data and Information Management, Maastricht University). Primary objective of the registry was to prospectively study the incidence of IBD and to investigate risk factors within a well-defined geographical and administrative area of the Netherlands, namely South Limburg (IBD-SL). Previous protocols were designed to study the development of clinical features and quality of life in IBD in a medium time prospect.[18] In the present analysis, incidence rates, pre-diagnostic duration of symptoms and seasonality are evaluated.

South Limburg is located in the South-East of the Netherlands, bordering Germany to the East and Belgium to the South and West; South Limburg's northern border with the rest of the Netherlands is very narrow. The region had an average population of 645,000 between 1991 and 2003, and migration in and out of the area is known to be low.[19] Population data for the region of South Limburg, regarding to age and sex, for the years 1991–2002 was obtained from the Central Statistics' Office in the Netherlands (CBS).[19]

All three hospitals in South Limburg, i.e. the University Hospital in Maastricht, the General District Hospitals of Heerlen (Atrium Medical Centre, with associated hospitals Kerkrade and Brunssum) and Sittard (Maasland Hospital) participated in this study. Apart from general practitioner (GP) practices, there are no other hospitals or outpatient clinics in this area. With regard to possible treatment of IBD

patients by GPs, completeness of case ascertainment was previously assessed and found to be high.[20] Inclusion of IBD patients was, after exclusion of infections and other recognized causes of bowel inflammation, based on endoscopic and/or radiological evidence, supported by mucosal biopsies and/or examination of surgical specimens. For case definition of CD, the criteria of Lennard Jones were applied.[21] Ulcerative Colitis was defined as continuous mucosal inflammation without granulomata, affecting the rectum and/or some or all of the colon in continuity with the rectum. Using the strict criteria mentioned above, patient recruitment for all diagnosed patients (hospitalized and outpatients) was performed by gastroenterologists, physicians, surgeons and paediatricians working in the IBD-SL area.[20] At inclusion, duration of symptoms before diagnosis (lag time) was registered in months, as were data with regard to smoking behaviour at diagnosis. Smoking status had been divided in three categories; "smoker at diagnosis"; "stopped smoking before diagnosis"; "never smoked before diagnosis".

If disease criteria were not completely met, patients could temporarily be classified as having "possible UC" or "possible CD". In the present study, all newly diagnosed patients (i.e. with no prior history on IBD), registered between January 1st, 1991 and January 1st, 2003, were included. The patients were followed from inclusion until data collection for the present analysis, from July 1st, 2005, until January 1st, 2006, or to a prior date in case of death or loss to follow-up (LTFU). At data collection, inclusion criteria were once again verified for all patients. The enrolment diagnosis was used for data analysis except for patients with a change of diagnosis within one month after enrolment; in these cases, the corrected diagnosis were used for analysis ($N=40$).

The Ethical Committees of all participating centres approved the protocol, and written informed consent was obtained from all patients. If patients were below 18 years of age, parents or a legal representative signed for informed consent.

2.2. Statistical analysis

Calculations were performed using the definite registered diagnosis according to the above criteria. Annual incidence rates were calculated based upon the number of patients diagnosed as numerator and the average number of inhabitants in each calendar year as denominator, for both genders, and in 10-year age strata. To adjust for changes in the age distribution of the population, age incidence rates were standardized using the European Standard Population, indicated as European Age Standardized Rate (EASR).[22]

The Estimated Annual Percentage Change (EAPC) was calculated by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable, i.e. $y=mx+b$ where $y=\ln$ (rate) and $x=$calendar year. Then the EAPC equals $100*(e^m-1)$. Testing the hypothesis that the EAPC is equal to zero is equivalent to testing the hypothesis that the slope of the line in the above equation is equal to zero. The latter hypothesis was tested using a t-test, with a number of degrees of freedom equal to the number of calendar years minus two. The standard error of mean was obtained from the fit of the regression line.[23,24] This calculation assumed that the rates increased/decreased at a constant rate over the entire period.

With regard to lag time, the median time with range was calculated and proportions of patients with different lag time intervals were statistically tested using chi square

Table 1 Crude and Standardized (EASR) Incidence Rates (per 100,000 person-years) 1991–2002.

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	1991–2002
CD													
Male													
Crude	6.66	9.48	4.73	4.08	3.44	5.31	2.81	4.38	3.44	5.33	4.40	4.78	4.90
Standardized	6.09	8.95	4.51	4.16	3.52	5.17	3.12	4.23	3.32	5.69	4.03	5.43	4.84
Female													
Crude	5.54	8.89	9.48	9.76	7.91	5.77	8.20	4.25	7.28	7.29	7.61	6.17	7.35
Standardized	5.61	8.38	9.63	9.43	7.67	5.47	8.95	4.54	7.70	7.91	8.94	6.34	7.58
UC													
Male													
Crude	9.83	14.22	10.08	9.42	9.70	10.00	11.25	8.75	6.26	7.83	6.91	5.73	9.17
Standardized	8.89	13.27	9.44	9.15	8.74	9.20	10.71	8.17	5.94	7.12	6.71	5.11	8.51
Female													
Crude	6.77	7.67	11.62	7.62	7.91	7.29	7.89	7.59	6.07	5.16	5.78	4.01	7.12
Standardized	6.49	7.04	11.49	7.10	7.52	7.40	7.35	7.46	6.10	5.32	5.71	3.61	6.92
IC													
Male													
Crude	1.90	2.21	1.58	1.26	0.63	1.25	0.62	1.25	0.31	1.25	0.63	0.64	1.13
Standardized	1.83	2.00	1.52	1.10	0.56	1.12	0.64	1.09	0.36	1.05	0.52	0.55	1.05
Female													
Crude	1.23	0.61	0.61	1.52	0.91	1.52	0.61	1.21	0.91	0.61	1.52	0.31	0.97
Standardized	1.09	0.68	0.57	1.45	0.86	1.38	0.60	1.16	0.85	0.67	1.49	0.29	0.93

CD = Crohn's Disease, UC = Ulcerative Colitis, IC = Indeterminate Colitis, EASR = European Age Standardized Rate.

analysis. The onset of symptoms for CD, UC and IC was calculated by subtracting lag time (months) from the date of diagnosis, the overall variation per month and season per diagnosis was subsequently analyzed using chi square analysis. Seasons were defined as Winter (December–February), Spring (March–May), Summer (June–August), Autumn (September–November). Data analyses were performed using the Statistical Package for the Social Sciences (SPSS 15.0 for Windows; SPSS Inc., Chicago, IL). *P*-values less than 0.05 were considered statistically significant.

3. Results

3.1. Patient population

Between 1–1–1991 and 1–1–2003, 1264 newly diagnosed patient were included in the IBD-SL registry. After reviewing medical records, ten patients where excluded who had no IBD (haemorrhoids: 1, diverticular disease: 1, ischemic colitis: 1, infectious gastro-enteritis: 1, irritable bowel syndrome: 3 and unknown diagnoses with no report of earlier IBD: 3).

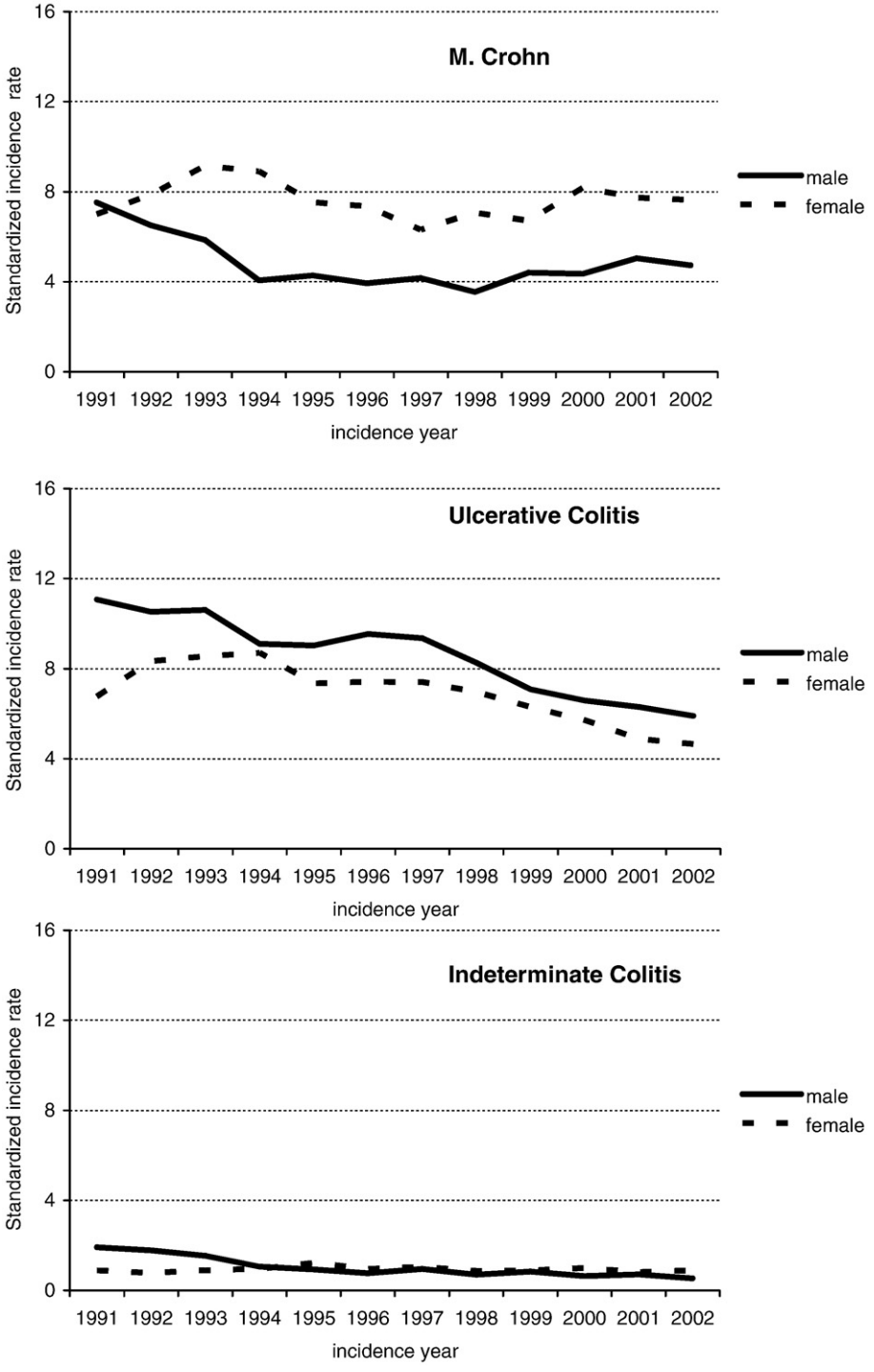

Figure 1 Standardized incidence rates per 100,000 person-years, 1991–2002, based on the 3-years moving average.

Of the 1254 remaining patients, 67 patients were excluded because medical records were unavailable and diagnosis could not be confirmed, leaving 1187 patients included. There was no significant difference in age, sex or diagnosis between included and excluded patients. Distribution of diagnoses for the included patients was 476 for CD, 630 for UC and 81 for IC. The sex distribution in CD was 187 males and 289 females. For UC there were 350 males and 280 females, and for IC 43 males and 38 females. Mean age (range) was 34 (5–79) years for CD, 42 (8–84) years for UC, and 42 (13–77) years for IC.

In CD, 53% smoked at diagnosis compared to 20% for UC and 30% for IC ($p<0.0001$). The percentage of patients having stopped smoking before diagnosis was 16% for CD, 44% for UC and 34% for IC ($p<0.0001$). Mean time from cessation of smoking to diagnosis was not significantly different between the diagnostic groups. The percentage of CD, UC and IC patients that had never smoked was 31%, 36% and 36% respectively.

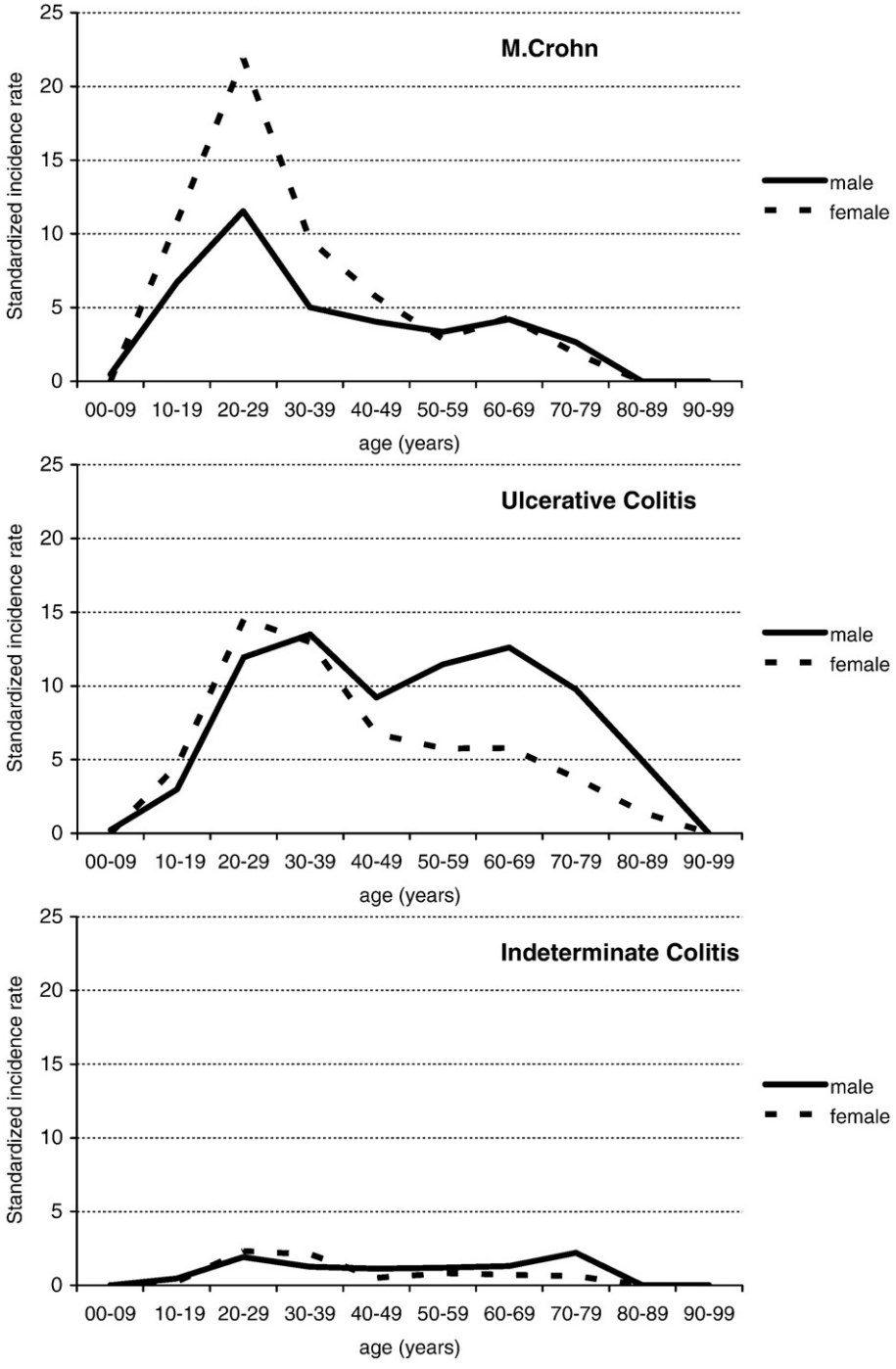

Figure 2 Age-specific standardized incidence rates per 100,000 person-years 1991–2002.

3.2. Incidence

In Table 1 data on crude and age standardized incidence rates per 100,000 person-years (p-y) over time are shown according to diagnosis and gender. Mean – EASR corrected – incidence values, per diagnosis were: for CD, male 4.84, female 7.58; for UC, male 8.51, female 6.92; and for IC, male 1.05, female 0.93 per 100,000 p-y. Overall incidence rates were for CD 6.2, UC 7.7 and IC 1.0 per 100,000 p-y.

Fig. 1 shows the standardized incidence rates for male and female patients over time (1991–2002) for CD, UC and IC in the IBD-SL region, based on the three years' moving average. The EAPC [95% Confidence Interval] during 1991–2002 was for CD male; −3.4% [−10.3%,4.1%], CD female; −0.6% [−6.4%,5.5%], UC male; −5.3% [−10.6%,0.2%], UC female; −4.6% [−10.4%,1.6%], IC male; −11% [−24.9%,5.4%] and IC female; −1.4% [−16.8%,17.0%]. None of these values was statistically significant.

In Fig. 2, age-specific incidence rates (per 100,000 person-years) in 1991–2002 are shown for CD, UC and IC for male and female patients. In CD, incidence peaked at 20 to 29 years of age, being markedly higher in females (21.9 per 100,000 p-y) than in males (11.6 per 100,000 p-y). In UC, peak incidence at young age was similar in males and females. However, the peak incidence for males was observed a decade later (30–39 years of age), with a second peak in incidence at 60–69 years of age. The incidence of IC was low, being only 1.0 per 100,000 p-y in male and 0.9 per 100,000 p-y in female patients.

3.3. Lag time

In 1122 out of 1187 patients (95%), patient reported data with regard to duration of symptoms before diagnosis (lag time) were available. Patients with and without information on lag time, did not significantly differ with regard to gender, diagnosis and overall mortality.

In the total study population, the median lag time was 3 (0–480) months.

The median lag time by diagnosis was 5 months (0–360) in CD, 3.0 (0–480) in UC and 3.0 (0–180) in IC.

In Table 2 the distribution of lag time is shown. The percentage of all patients reporting complaints less than one year before diagnosis was 83%, for less than two years this was 91%.

In order to investigate a possible change in lag time patients diagnosed in the 3-year period from 1991 to 1993 (N=338) were compared with patients diagnosed in the 3-year period from 2000 to 2002 (N=236). The percentages of patients having complaints for more than one year, more than two years, or even longer were not statistically different between the two time periods.

3.4. Seasonal variation

The distribution of onset of symptoms according to calendar month is shown in Fig. 3. No statistically significant difference was found by month either in the entire IBD cohort, or in CD, UC and IC. Neither was there a significant difference when the onset of symptoms was analyzed by season.

4. Discussion

4.1. Incidence

The present population based study in the IBD-SL region shows no significant increase in the total incidence of CD, UC and IC together. However, although not significant, a trend to a decline of the incidence of UC could be observed. Nevertheless, incidence rates in South Limburg are relatively high compared to reports from the central part of the Netherlands ten years earlier by Shivananda and co-workers, who used similar inclusion criteria.[25,26] No recent incidence figures from other regions of the Netherlands are available.

Age and sex distribution are similar to those reported by Russel et al. in 1998[20] and comparable to other studies.[4,27–31] A peak incidence for CD in earlier age and higher incidence rates in females than males were found. In UC, incidence peaks between twenty and forty years of age, with a second peak for men at more advanced age, that possibly reflects an exposure to extrinsic risk factors as previously suggested.[32–34]

An overview of published European incidence rates is given in Table 3.[1–7,20,25–33,35–57] A recent study from Germany also found a stable incidence of CD and UC.[57] However, our incidence results are in contrast to data from Sweden,[30,39] Denmark[4,5,29,32,40] and the United Kingdom[42–44] which all indicate an increasing IBD incidence. Recent publications from Copenhagen found an increasing incidence of CD rather than of UC for the time period 2003–2005.[4] And although IBD incidence rates are still very low in Greece, an increasing incidence of CD was also found there.[2] Moreover, the overview in Table 3 shows generally higher incidence rates in the North than in the South of Europe,

Table 2 Lag time: percentage of patients having complaints before diagnosis in different time periods.

Duration of complaints	CD (N=448)	UC (N=600)	IC (N=74)	Year of diagnosis 1991–1993 (N=338)	Year of diagnosis 2000–2002 (N=236)	Overall
Less than one year	77%	88%	89%	86%	81%	83%
Between one and two years	11%	6%	9%	7%	9%	8%
Between two and five years	6%	4%	0%	3%	5%	5%
Between five and ten years	5%	2%	1%	3%	3%	3%
More than ten years	1%	0%	1%	1%	2%	1%

CD = Crohn's Disease, UC = Ulcerative Colitis, IC = Indeterminate Colitis.

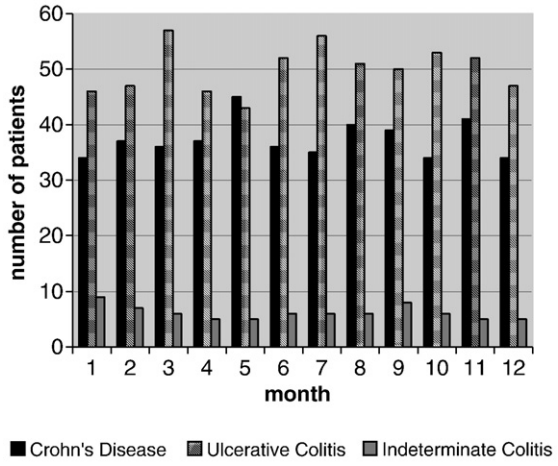

Figure 3 Overall variation per month in onset of symptoms for CD, UC and IC (n=1122).

earlier described in a large European cohort study (EC-IBD).[5] More recent studies from Croatia,[3] Malta[7] and Spain[1] show however incidence rates comparable to those in Northern Europe. The reported increase of IBD incidence over the last decades in different European countries supports the idea that environmental factors play an important role in the aetiology and pathogenesis of IBD. At inclusion, the possible influence of smoking as an extrinsic influencing factor was confirmed in our data, in CD smoking might be seen as an aetiologic factor whereas in UC significantly more patients stopped smoking before the start of there complaints.[58–60] However as we have no smoking results of non-IBD patients the above correlation is speculative. A change to westernized lifestyle[61] and improved hygienic circumstances[12,13] have also been implicated. Other factors with impact on incidence rates are the improvement of diagnostic facilities and a better access to health care facilities. The stable incidence rates in the South-Limburg cohort would suggest that such factors have been levelling out in the past 15 years in this area.

Incidence rates of diseases depend mainly on the completeness of case collection in a well-defined geographic or political area as well as on the accuracy of information about the background population. In this study, continuously updated background figures were provided by the Statistics Netherlands.[19] Completeness of case collection can also be assumed high, due to the small number of hospitals involved and the common practice in the Netherlands that patients with IBD are almost exclusively treated by medical specialists associated with the regional hospitals. One could argue that completeness of case ascertainment in our study could have been further improved by involving General Practitioners (GPs). For logistic reasons, the circa 300 GPs working in the IBD-SL region were not individually involved in the study but received recurrent requests to check whether their IBD patients had been registered in the cohort. In this context there is a risk that patients with mild disease, e.g. UC proctitis, could have been missed. However, in the present study, follow-up duration of patients with proctitis was not significantly shorter than that of left-sided or pancolitis (data not shown). In addition, 240 of the registered UC patients (38%) had at diagnosis proctitis as disease localization, resulting in a mean incidence of 3.1 per 100,000 inhabitants a year (1991–2001). This incidence is even higher than the one found by Russel et al. 1991 to 199420 supporting the assumption that few patients were missed for inclusion. The incidence of proctitis at diagnosis reported from other countries differs widely, ranging from 18% even up to 60%[4,16,27,31–33,47,62,63].

An important potential cause of differences in crude incidence rates between different studies is variation in age distribution of the populations assessed. Therefore, age standardization has to be applied when studying time trends, as age distributions can change over time. Also for incidence comparison between countries standardization is necessary. We found one study using incidence correction with the use of the World Standardized Population for age correction.[27] Some others did use EASR correction,[1–3,5–7,46,56] however, this is in the minority of European IBD incidence studies.

4.2. Lag time and seasonal influence

Median duration of symptoms before diagnosis was 5 months in CD, 3.0 in UC and 3.0 in IC. Overall, 83% of patients were diagnosed within one year after the start of their complaints. Despite the fact that health care organisation and diagnostic tools had improved over time, we found no significant difference in lag time during the total study period.

A recent study from Corsica[47] shows comparable results on lag time. However, shorter time periods are reported from Italy[14] and longer median intervals were reported from Denmark.[4] The percentage of patients having symptoms for less than one year before diagnosis reported was around 70% in two studies,[20,62] and 80% for patients diagnosed within two years in one.[14] In the present study diagnosis was made earlier as suggested by the high proportion of patients having complaints shorter than one or two years. Reason could be the easy access to health care, and the granted basic insurance for every inhabitant in the Netherlands. In older studies, lag time during ongoing inclusion over a prolonged period of time is reported as stable in UC39, decreasing in CD[4,29,62] and decreasing in UC.[62]

Seasonal influences on the temporal incidence of IBD could not be confirmed. IBD patients generally present with quite a long history of symptoms before diagnosis, making it difficult to retrospectively determine when symptoms began. As infections and/or a dysfunctional mucosal immune response to bacteria could play an important role in the pathogenesis of IBD (especially in the case of CD[10,11]), the frequent onset of symptoms in spring and summer in CD reported from Italy[14] is interesting. However, no conclusive evidence for one specific microbial agent is available. A cyclic pattern with regard to specific infections is commonly observed.[64] Such pattern has been described by some authors for UC[15,17] and denied by others for both CD15and UC.[14,16]

Although this study is population based in a well-defined geographical area and patient inclusion was prospective, recall bias on the timing of onset of symptoms is still a confounding factor. Investigating seasonality of disease onset is also difficult for other reasons: extrinsic pathogenic factors can act in the most different ways, as the time between environmental influences and the reaction of the patient can be highly variable (for example acute reaction to a triggering infection or slow alteration of the patients immune system by repeated exposition). Conditions useful and/or necessary for the study of seasonality in IBD have recently been discussed[65] but will also be difficult to be fulfilled in future research.

Table 3 Incidence rates of CD, UC and IC per 100,000 inhabitants and year in Europe from the North to the South European countries.

Publication year	Time period	Country area	First author, reference	CD	UC	IC
1988	1983–1984	Norway western	Haug[35]		14.8	
1990	1983–1986	Norway northern	Kildebo[36,37]	5.8	12.8	
1996	1990–1993	Norway Oslo	Moum[33,38]	5.8	13.6	
1991	1965–1983	Sweden Uppsala	Ekbom[30]	6.6	11.5	
1985	1955–1979	Sweden Stockholm	Nordenvall[39]		1.7/4.3	
1982	1962–1978	Denmark Copenhagen	Binder[40]	2.7	8.1	
1991	1962–1987	Denmark Copenhagen	Langholz[32]and Munkholm [29]	4.1	9.2	
1996	1991–1993	Denmark Copenhagen	Shivananda[5]	M/F 5.4/9.3	M/F 8.4/11.2	
2006	2003–2005	Denmark Copenhagen	Vind[4]	M/F 8.6/9.1	M/F 13.4/13.3	M/F 1.1/1.4
1996	1991–1993	Ireland Dublin[a]	Shivananda[5]	M/F 4.5/5.9	M/F 18.6/11.6	
1984	1968–1977	UK South Glamorgan	Morris[41]		7.2	
1988	1935–1954	UK Cardiff	Rose[42]	0.2		
1992	1968–1987	UK Cardiff	Srivastava[43]		6.4	
1995	1986–1990	UK Cardiff	Thomas[44]	5.9		
1987	1979–1983	Netherland Leiden	Shivananda [25,26]	M/F 3.8/4.0	6.8	
1998	1990–1994	Netherlands South Limburg	Russel [20]	6.9	10.0	
Present study	1991–2003	Netherlands South Limburg[a]	Romberg-Camps et al.	6.2 M/F 4.8/7.6	7.7 M/F 8.5/7.0	1.0 M/F 1.1/0.9
1994	1980–1984	Germany Ruhr area	Dirks[45]		2.9	
1994	1980–1984	Germany Ruhr area	Goebell[28]	4.0		
1999	1980–1995	Germany[a]	Timmer[46]		5.0	
2008	2004–2006	Germany[a]	Ott[57]	6.6	3.9	
1994	1988–1990	France Northern[b]	Gower Rousseau[27]	3.2	4.9	
2007	2002–2003	France Corsica	Abakar-Mahamat[47]	4.1	9.5	
2003	1997–2001	Hungary Western	Lakatos [48]	4.7	11.0	0.7
2004	2002–2003	Romania	Gheorghe[31]	0.5	1.0	
1991	1980–1989	Yugoslavia Zagreb	Vucelic[49,50]	0.7	1.5	
2006	2000–2004	Croatia, Primorsko-goranska[a]	Sincic[3]	7.0	4.3	
1996	1990–1993	Italy Northern	Ranzi[52]	3.4	7.0	
1991	1978–1992	Italy Florence	Trallori[51]	1.5	4.0	
1991	1987–1989	Sicily	Cottone[55]	2.7		
2001	Review article	Spain	Pajares[53]	1.9	3.8	
2003	1954–1997	Spain	Saro Gismera[54]	2.0	2.8	1.1
2004	2000–2002	Spain Northern[a]	Rodrigo[6]	7.5	9.1	
2008	2001–2003	Spain Navarre[a]	Arin Letamendia[1]	5.9	9.6	0.6
2008	1993–2005	Malta[a]	Cachia[7]	M/F: 1/1.6	M/F: 8.2/7.6	
1996	1990–1994	Greece Crete[a]	Manousos[56,66]	3.0	8.9	
2007	1983–2005	Greece North-Western	Economou[2]	0.9	2.7	

[a]Standardized incidence rates are presented using European Age Standardized Population (EASP) correction.
[b]Standardized incidence rates using the World Standardized Population for age correction.
M = male, F = female.

In conclusion, our results show a relatively high incidence of IBD in the South-Limburg region without significant change of incidence rates during the 11 years' study period. If any, the incidence of UC tended to decline during the investigated period. No seasonal influence was found, and despite the introduction of new diagnostic techniques, diagnostic lag time did not change. The stable incidence rates could mean, that the extrinsic influences which have modified the epidemiology of IBD in recent years (decline of UC and increase of CD) have slowed down to a near steady state in the study area. This may be different in other geographic and social environments. Therefore, continued studies with prospective and comparable registrations of IBD in an (inter-)national context will be extremely important for the understanding of factors contributing to onset and development of these disorders, but may also be helpful for well planned distribution of health care resources and – not in the least – for the invention of new therapeutic principles.

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Contribution to data analysis

Centre for Data and Information Management, University of Maastricht (MEMIC): J. Berben, A. Legtenberg; *Department of Epidemiology, Maastricht University*: J. Steevens.

Data collection

M. Cillissen, E. Heijnen, N. Koopman, E. Kuiper, G. Raven.

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Authors contribution

MR: research fellow gastro-enterology, writing and development protocol, performing study, data analysis, writing manuscript.

MH: protocol development, data collection, statistical analysis.

LS: protocol development, statistical analysis, co-writing manuscript.

PD: main investigator, data analysis, co-writing manuscript.

CL: protocol development, development data base for data gathering, data cleaning and analysis, co-writing manuscript.

AK: statistical analysis, co-writing manuscript.

LB: main member IBD South Limburg Study group, protocol development, patient inclusion, substantial input in final manuscript.

JG: main member IBD South Limburg Study group, protocol development, patient inclusion, substantial input in final manuscript.

WH: main member IBD South Limburg Study group, protocol development, patient inclusion, substantial input in final manuscript.

FW: former member IBD South Limburg Study group, protocol development, patient inclusion, substantial input in final manuscript.

MR: former member IBD South Limburg Study group, protocol development, patient inclusion, substantial input in final manuscript.

RS: chairman and main member IBD South Limburg Study group, main investigator, protocol development, patient inclusion, substantial input in final manuscript.

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