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A 20-Year Temporal Change Analysis in Incidence, Presenting Phenotype and Mortality, in the Dutch IBDSL Cohort—Can Diagnostic Factors Explain the Increase in IBD Incidence?

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Abstract

Background: The aim was to study temporal changes in incidence, disease phenotype at diagnosis, and mortality of adult inflammatory bowel disease [IBD] patients in South Limburg, The Netherlands, diagnosed between 1991 and 2010. In addition, the 2010 IBD prevalence was estimated.

Methods: A multi-faceted approach including hospital administrations, the national pathology registry [PALGA], and general practitioners led to the identification of 1162 patients with Crohn's disease [CD], 1663 with ulcerative colitis [UC], and 84 with unclassified IBD [IBD-U]. Temporal changes in incidence, disease phenotype, and mortality were studied using linear, multinomial regression analyses, and standardised mortality rates [SMR], respectively.

Results: The annual incidences increased from 17.90/100 000 in 1991 to 40.36/100 000 in 2010 for IBD, from 5.84/100 000 to 17.49/100 000 for CD, and from 11.67/100 000 to 21.47/100 000 for UC [$p < 0.01$ for all]. A shift towards milder disease at diagnosis was observed over time [eg decrease of complicated disease in CD, increase of proctitis in UC]. IBD mortality was similar to that in the general population (SMR 0.92; 95% confidence interval [CI] 0.81–1.05), and did not change over time. The estimated IBD prevalence was 830/100 000.

Conclusions: The IBD incidence in South Limburg increased significantly between 1991 and 2010.

The shift towards milder disease at diagnosis in parallel with the improved diagnostics and ability to detect low-grade inflammation was suggestive of an important role of diagnostic factors in this increase. Environmental factors probably played a role as well. The mortality was low and, together with the increasing incidence, led to the high prevalence of IBD in South Limburg.

Key Words: Inflammatory bowel disease; epidemiology; time trend.

1. Introduction

Inflammatory bowel disease [IBD] is a chronic inflammatory condition of the intestine, encompassing the subtypes Crohn's disease [CD], ulcerative colitis [UC], and unclassified IBD [IBD-U]. IBD is characterised by sequences of exacerbation and remission, and is considered to arise from complex interactions between an altered intestinal immune response, the intestinal microbiota, and environmental exposures in a genetically susceptible host.[1,2] This complex background contributes to the heterogeneous clinical presentation and disease course.[3,4] IBD may have severe impact on a patient's [quality of] life,[5] but also society endures trough high health care costs [eg due to loss of productivity or work absenteeism].[6] In 2013, the European prevalence was estimated at 0.3% [equalling 2.5–3 million persons].[6]

For local health planning, but also for allocation of funding money and patient communication, it is important to understand the current and future [societal] burden of IBD. Temporal change analyses in IBD epidemiology show that the prevalence is expected to further increase in future,[7] as IBD incidences are rising in virtually every region of the world,[7] and mortality in IBD is only marginally increased compared with the general population.[8] Considering the widespread use of epidemiologic data, their validity is of utmost importance. Many data on [temporal changes in] IBD epidemiology, however, are derived from selected populations or administrative databases that are not designed for research purposes. Both may introduce methodological problems. The former can be characterised by an under-representation of mildly diseased cases,[9] and the latter are sensitive for suboptimal case ascertainment [misclassifying prevalent cases as incident, or overclassifying non-IBD cases as IBD] and/or for changes in inclusion criteria over time.[10,11] In addition, most studies lack detail on diagnostic factors or presenting disease phenotype over time, whereas such data can be useful for interpreting any observed temporal changes. A verification of temporal changes in epidemiological data in a stable, detailed, longstanding, population-based cohort of IBD patients is, therefore, warranted.

Here, we report on temporal changes in incidence, disease phenotype at diagnosis, and mortality, in adult IBD patients from the Dutch population-based IBD South Limburg [IBDSL] cohort, diagnosed between 1991 and 2010. In addition, we estimated the 2010 prevalence of adult IBD patients in South Limburg.

2. Materials and Methods

2.1. Source population

South Limburg is a geographical region in the south of The Netherlands, the greater part enclosed by Belgium and Germany [Figure 1]. In 1991, South Limburg comprised 638781 inhabitants, and the population size declined to 607784 in 2010.[12] The vast majority of inhabitants are Caucasian [exact numbers were not retrievable for ethical reasons] and 59% live in urban areas [defined as > 1000 inhabitants per km^2].[12] Hospital care in South Limburg is provided by three hospitals including one university hospital [Maastricht University Medical Centre+] and two general hospitals [Zuyderland Medical Centres, locations Heerlen and Sittard-Geleen]. Cross-border health care is limited and migration rates are rather low,[12] favouring population-based research in this region.

2.2. Study population

All IBD patients from the population-based IBDSL cohort were eligible for the current study. For details on this cohort, we refer to the cohort profile.[13] In brief, patients diagnosed with IBD between 1 January 1 1991 and 31 December 31 2010, while living in South Limburg and being over 18 years of age at diagnosis, were prospectively included and followed. A multi-faceted identification strategy, including the three regional hospitals, PALGA [the nationwide Dutch pathology database covering all pathology reports generated in the Netherlands since 1991][14] and general practitioners, resulted in over 93% completeness. The remaining 7% was not likely to be associated with a specific IBD phenotype.[13] IBDSL has been approved by the Ethics Committee of the Maastricht University Medical Centre [NL31636.068.10], is registered in ClinicalTrial.gov [NCT02130349], and meets the ethical standards of the revised version of the Declaration of Helsinki.[15]

2.3. Study endpoints and definitions

Endpoints of the present study were temporal changes in incidence [1], disease phenotype at diagnosis [2], and mortality of adult IBD patients between 1991 and 2010 [3], and the IBD point prevalence in 2010 [4]. Endpoints were calculated for IBD [ie combination of CD, UC, and IBD-U], and for CD and UC separately.

IBD was diagnosed according to the Lennard-Jones criteria[16] and was confirmed by endoscopic, radiological, and/or histological findings. The date of endoscopic or radiological examination with first evidence of IBD was set as time of diagnosis. In case of a change in diagnosis over time, the latest diagnosis was used. For this reason endpoints were not calculated separately for IBD-U, as most of these patients had a CD or UC diagnosis at a later stage.

Disease phenotype at diagnosis was characterised by age, disease location, and disease behaviour, according to the Montreal consensus.[17] CD disease location groups were ileal [L1], colonic [L2], ileocolonic [L3], and isolated upper gastrointestinal [GI] disease [L4]. The presence of any upper GI disease, either isolated or with concomitant lower GI involvement, was also noted [L4 + L4 modifier]. CD disease behaviour groups were non-stricturing and non-penetrating [B1], stricturing [B2], or penetrating [B3]. The presence of perianal disease at diagnosis was also noted [P]. UC disease location groups were rectal disease [E1], left-sided disease [E2], and extensive disease [E3].

2.4. Design and analyses

2.4.1. Temporal changes in incidence

The IBD incidence was expressed as the number of new IBD cases per 100000 adult South Limburg inhabitants. All IBDSL cases were stratified by calendar year of diagnosis, age at diagnosis, and gender, and divided by calendar year-, age-, and gender-specific population rates from South Limburg. The latter were derived from Statistics Netherlands [CBS],[12] responsible for official Dutch statistics.

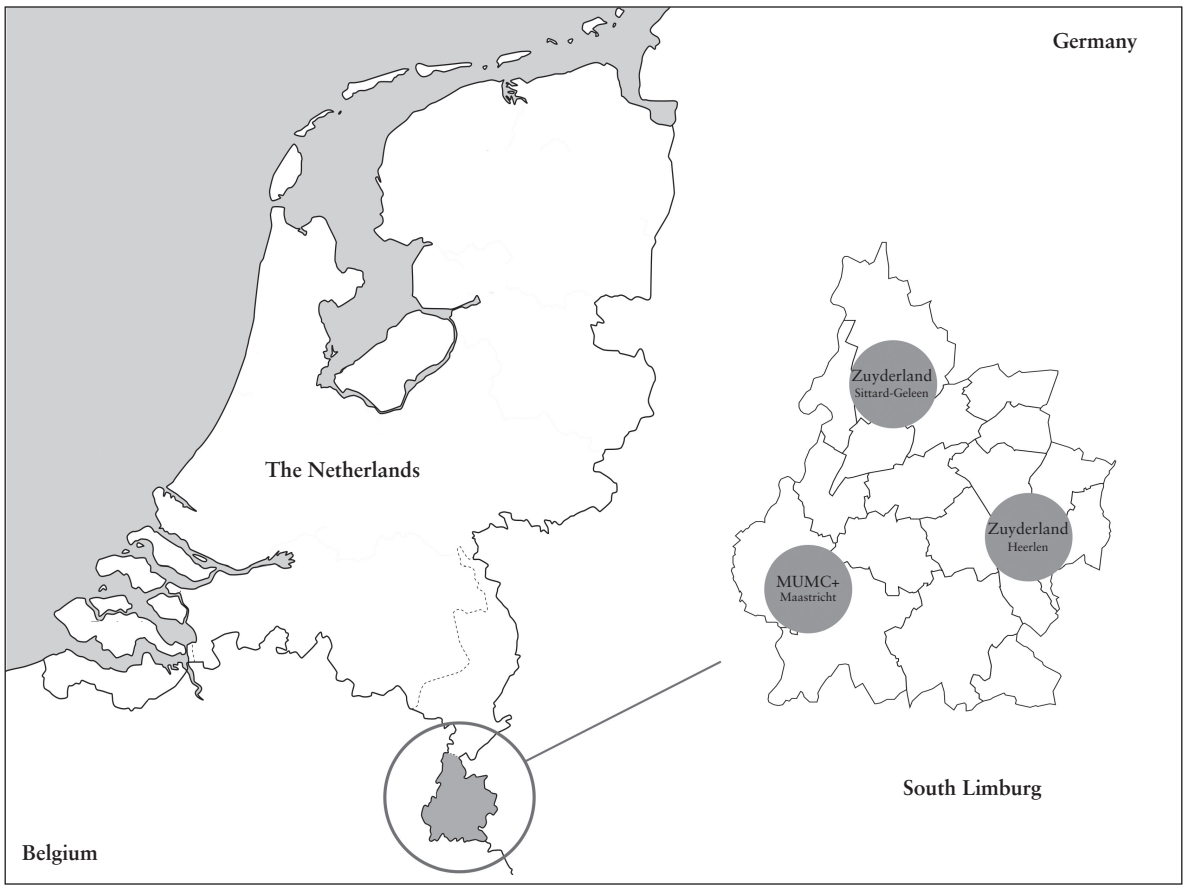

Figure 1. Geographical location of South Limburg, and the hospitals: Maastricht University Medical Centre+ [MUMC+], Zuyderland Medical Centre Heerlen, and Zuyderland Medical Centre Sittard-Geleen. Adapted from van den Heuvel *et al.*[13]

Incidence rates were calculated for every year between 1991 and 2010. Temporal changes in incidence were determined by linear regression analysis [$\alpha = 0.05$]. Subsequently, Joinpoint regression analysis was conducted [post hoc],[18] to identify multiple time trends within the study period. The average annual percentage changes [APC] were calculated for the total study period and for every observed Joinpoint trend.[19] Differences in trends between males and females, and between CD and UC, were tested for trend parallelism [$\alpha = 0.05$].[20] To facilitate international comparisons, incidence rates were also standardised to the European standard population, using European Age Standardized Rates [EASR].[21]

2.4.2. Temporal changes in disease phenotype at diagnosis

Age was expressed as mean, and IBD location and IBD behaviour as the proportion of patients per location or behaviour group, respectively. The mean age at IBD diagnosis was calculated for every year between 1991 and 2010, and temporal changes were determined by linear regression analysis [$\alpha = 0.05$]. The proportions of patients per location or behaviour group were calculated for every year between 1991 and 2010, and temporal changes in distribution of the groups were determined by multinomial logistic regression analyses [$\alpha = 0.05$]. In case the distribution changed over time, a post hoc binary logistic regression analysis [$\alpha = 0.05$] was performed to study in which group[s] the proportion changed.

2.4.3. Temporal changes in mortality

For the mortality analyses, patients were followed until 31 December 2012, or until lost to follow-up [ie death or permanent migration outside the region]. The IBD mortality was expressed as standardised mortality ratio [SMR], which is the ratio between observed [O] and expected [E] deaths. Data on observed deaths and migration were obtained through linkage to the national resident registration,[22] which is the official government database continuously updated on the vital status and addresses of all Dutch inhabitants. Expected deaths for the South Limburg region were based on data of Statistics Netherlands [CBS].[12] Calendar year-, age-, and gender-specific mortality rates were used to calculate the expected number of deaths for every patient year at risk, which were then accumulated into the overall expected number of deaths. Patient-years were recorded from the year of IBD diagnosis up to and including the year follow-up ends [ie loss to follow-up or end of study]. Patient-years in which the patient was not at risk were censored. Incomplete patient-years [ie years in which diagnosis, loss to follow-up or censoring occurred] were corrected for by considering them as having contributed half-person-years, in order to prevent overestimation. SMRs were calculated for the total cohort, and in order to study temporal changes, SMRs were also determined in two subcohorts based on the era of diagnosis [ie one subcohort of patients diagnosed between 1991 and 2000, and one subcohort of patients diagnosed between 2001 and 2010; follow-up ended 2 years after each era]. Confidence intervals were determined by Byar's approximation [$\alpha = 0.05$]. Subanalyses were performed in each cohort for gender, location at diagnosis, and behaviour at diagnosis. Only IBD patients aged ≥ 20 years at diagnosis were included, as mortality rates of younger persons were not readily available.

2.4.4. Point prevalence

The IBD prevalence was expressed as the number of prevalent IBD cases per 100 000 adult South Limburg inhabitants. Prevalence was determined by using cases from the IBDSL population [alive in 2010], completed with an estimation of alive prevalent South Limburg adult cases who did not fulfil the IBDSL inclusion criteria [eg IBD diagnosis before 1991 and patients diagnosed elsewhere but migrated into South Limburg]. The latter was done by a stepwise approach. First, current and historic [since 1991] registries of the participating IBDSL hospitals were used to identify every IBD patient not fulfilling IBDSL inclusion criteria. Second, corrections were applied for: [a] patients not having IBD; [b] deceased patients; and [c] patients migrated inside and outside the region. Correction factors were derived from a case-ascertainment check reviewing the medical files of 2000 random IBD patients from the participating hospitals. Then, the total number of prevalent IBD patients in 2010 was divided by the South Limburg adult population for that year. Additionally, the South Limburg prevalence was extrapolated in order to estimate IBD prevalence in The Netherlands [nationwide]. Therefore, the ratio of newly diagnosed IBD patients living in South Limburg to all newly diagnosed patients in The Netherlands was used. This ratio was determined by reviewing postal codes from a random sample of 5000 newly diagnosed IBD patients [diagnosed between 1991 and 2011], derived from PALGA.[14]

3. Results

In total, 2909 IBD patients [1162 CD, 1663 UC, and 84 IBD-U] were diagnosed between 1 January 1 1991 and 31 December 2010, and were included in the IBDSL cohort. Baseline characteristics are presented in Table 1.

3.1. Incidence

In the total IBD group, the mean incidence rate was 27.49 per 100 000. Between 1991 and 2010, the IBD incidence increased significantly from 17.90 to 40.36 per 100 000, corresponding to an average APC of 4.35% [95% CI 2.70–6.01][Table 2, Figure 2]. A two-trend Joinpoint regression model showed the best fit. Between 1991 and 1999, the IBD incidence was found to be rather stable with an average APC of 0.39% [95% CI -2.95–3.84]. Since 1999, an increase has been observed with an average APC of 7.32% [95% CI 5.53–9.15].

For CD, the mean incidence rate was 10.94 per 100 000. Between 1991 and 2010, the CD incidence increased significantly from 5.84 to 17.49 per 100 000, corresponding to an average APC of 5.97% [95% CI 4.68–7.28][Table 2, Figure 2]. No differences in temporal changes were observed between genders [males: average APC 5.87%, 95% CI 3.73–8.06, females: average APC 5.88%, 95% CI 4.51–7.26, $p = 0.99$]. Also for CD, a two-trend Joinpoint regression model showed the best fit. Between 1991 and 1998, the CD incidence was rather stable [average APC 1.12%, 95% CI -5.21–7.88], followed by an increase [average APC: 7.79%, 95% CI 5.44–10.19].

For UC, the mean incidence rate was 15.75 per 100 000. Between 1991 and 2010, the UC incidence increased significantly from 11.67 to 21.47 per 100 000, corresponding to an average APC of 3.79% [95% CI 2.39–5.21][Table 2, Figure 2]. No differences in temporal changes were observed between genders [males: average APC 2.60%, 95% CI 1.11–4.11, females: average APC 5.07%, 95% CI 3.27–6.90, $p = 0.06$]. Also for UC, a two-trend Joinpoint regression model showed the best fit. The UC incidence was stable between 1991 and 1999 [average APC -0.75%, 95% CI -6.04–4.83], followed by an increase [average APC 6.42%, 95% CI 3.30–9.65].

Overall, the incidence of CD showed a stronger increase over time than the incidence of UC [$p = 0.04$], resulting in a decrease in UC:CD ratio from 1.76 in patients diagnosed between 1991 and 1995 to 1.39 in those diagnosed between 2006 and 2010 [average APC -2.01%, 95% CI -3.68 to -0.30].

3.2. Disease phenotype at diagnosis

For CD, the mean age at diagnosis increased from 35.0 years (standard deviation [SD] 14.8) to 36.9 years [SD 15.5], between 1991 and 2010 [$p < 0.01$]. L1 was the most common location at diagnosis

Table 1. Baseline characteristics at diagnosis of South Limburg IBD, CD, UC, and IBD-U patients.

Characteristic	IBD [*N* = 2909]	CD [*N* = 1162]	UC [*N* = 1663]	IBD-U [*N* = 84]
Age [in years], mean [SD]	42.6 [16.9]	37.7 [15.9]	45.8 [16.7]	48.4 [17.1]
Male, *N* [%]	1360 [46.8]	434 [37.3]	886 [53.3]	40 [47.6]
Location, *N* [%][a,b]				
L1	—	500 [43.0]	—	—
L2	—	371 [31.9]	—	—
L3	—	267 [23.0]	—	—
L4	—	24 [2.1]	—	—
L4 + L4 modifier	—	124 [10.7]	—	—
E1	—	—	565 [34.2]	—
E2	—	—	789 [47.8]	—
E3	—	—	296 [17.9]	—
Behaviour, *N* [%][a]				
B1	—	900 [77.5]	—	—
B2	—	177 [15.2]	—	—
B3	—	85 [7.3]	—	—
P	—	94 [8.1]	—	—

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, IBD-undefined; *N*, number of patients; SD, standard deviation.

[a]Phenotype according to Montreal Classification. Disease location of CD was defined as ileal disease [L1], colonic disease [L2], ileocolonic disease [L3], isolated upper gastrointestinal disease [L4], and any upper disease [regardless of whether disease is isolated or not] [L4 + L4 modifier]. Disease behaviour of CD was defined as non-stricturing non-penetrating [B1], stricturing [B2], or penetrating [B3], and perianal disease [P]. Disease location of UC was defined as ulcerative proctitis [E1], left-sided UC [E2], and extensive UC [E3].

[b]Disease location for UC could not be retrieved in 11 cases.

Table 2. Temporal changes in the incidence rates of South Limburg IBD, CD, and UC patients.

		1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Avg
IBD	Male																					
	SL	21.54	28.97	16.24	16.19	21.25	23.98	20.01	20.80	19.24	21.61	24.79	21.68	31.08	26.68	29.22	35.04	37.65	39.41	43.39	32.23	26.44
	EASR	21.35	28.24	15.76	16.24	21.10	23.74	20.60	20.55	19.62	21.54	25.02	22.42	31.84	27.45	30.01	35.22	38.70	40.71	45.79	36.26	26.72
	Female																					
	SL	14.43	18.51	23.72	23.29	19.86	22.84	24.29	17.54	22.02	22.00	23.16	25.85	27.99	33.05	36.22	41.72	42.26	38.08	47.37	48.08	28.48
	EASR	14.23	18.92	24.16	23.87	20.30	23.44	25.78	18.61	24.32	24.24	26.88	28.11	31.13	35.05	41.40	43.80	45.58	42.94	55.10	55.83	30.69
	Total																					
	SL	17.90	23.61	20.08	19.83	20.54	23.40	22.20	19.13	20.66	21.81	23.95	23.82	29.50	29.95	32.81	38.47	40.02	38.73	45.43	40.36	27.49
	EASR	17.68	23.32	19.95	19.95	20.75	23.54	23.17	19.64	21.97	22.78	25.82	25.28	31.43	31.30	35.60	39.89	42.14	41.89	50.34	46.12	28.67
CD	Male																					
	SL	5.19	8.34	3.56	5.53	5.12	8.65	5.10	6.28	5.10	7.07	7.48	7.49	10.49	6.06	10.96	12.22	10.23	16.83	15.96	11.83	8.43
	EASR	5.06	8.06	3.40	5.53	5.37	8.72	5.48	6.20	5.43	7.64	7.68	8.95	11.01	6.47	11.92	13.26	11.61	18.21	17.86	14.58	8.81
	Female																					
	SL	6.46	8.69	9.79	12.02	8.99	8.24	11.58	7.47	11.94	11.93	11.58	14.24	12.27	13.84	18.88	16.22	14.73	22.93	22.91	22.88	13.32
	EASR	6.45	8.78	9.79	12.34	9.34	8.49	12.84	8.27	13.39	13.50	14.22	16.52	14.55	15.68	22.61	19.30	16.53	27.19	27.84	27.99	14.93
	Total																					
	SL	5.84	8.52	6.76	8.86	7.10	8.44	8.42	6.89	8.61	9.57	9.58	10.95	11.40	10.05	15.02	14.28	12.54	19.96	19.53	17.49	10.94
	EASR	5.63	8.33	6.67	8.90	7.39	8.58	9.21	7.22	9.45	10.55	10.95	12.74	12.68	11.13	17.20	16.28	14.10	22.62	22.82	21.27	11.86
UC	Male																					
	SL	15.56	20.24	12.68	10.66	16.13	14.94	14.52	14.52	13.35	13.75	16.53	14.19	19.78	19.81	16.23	21.59	26.19	20.11	25.38	19.18	17.21
	EASR	15.57	19.80	12.36	10.71	15.73	14.63	14.76	14.35	13.45	13.18	16.60	13.47	19.90	20.19	16.11	20.91	25.79	20.24	25.76	20.35	17.12
	Female																					
	SL	7.98	9.82	13.56	10.89	10.49	13.86	12.70	9.70	10.07	10.07	10.83	10.49	14.95	18.06	15.80	23.18	25.59	15.15	21.75	23.65	14.36
	EASR	7.77	10.14	14.00	11.15	10.55	14.14	12.94	9.96	10.93	10.74	11.77	10.57	15.65	18.34	17.57	22.66	27.38	15.75	23.69	26.21	14.98
	Total																					
	SL	11.67	14.90	13.13	10.78	13.24	14.38	13.59	12.05	11.67	11.86	13.61	12.29	17.30	18.91	16.01	22.41	25.88	17.57	23.51	21.47	15.75
	EASR	11.68	14.78	13.10	10.86	13.16	14.38	13.77	12.23	12.18	11.86	14.06	12.02	17.81	19.24	16.77	21.78	26.50	18.14	24.63	23.37	16.02

Incidences are expressed as cases per 100 000 persons.

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; SL, incidence rates as observed in South Limburg; EASR, incidence rate standardised to the European standard population; Avg, average incidence rate over the years 1991–2010.

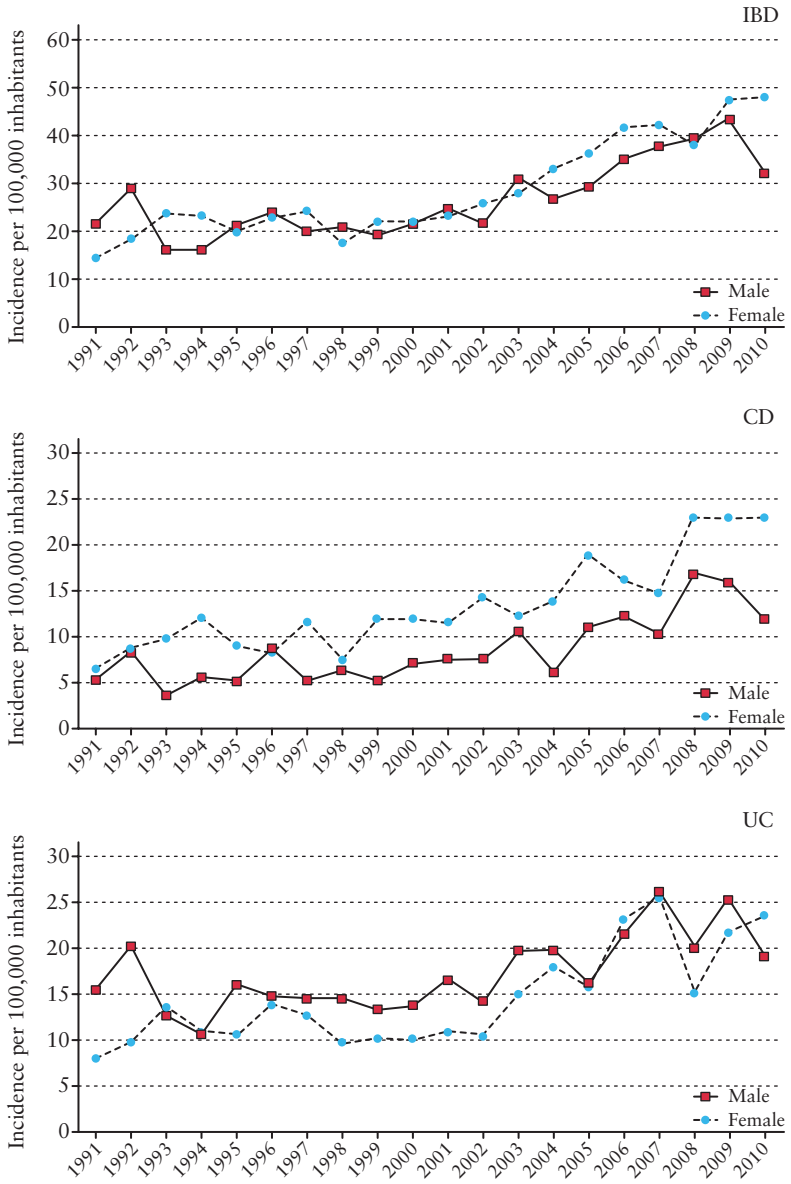

Figure 2. Temporal changes in incidence rates of South Limburg IBD, CD, and UC patients. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

[43.0%][Table 1]. Over time, a shift in the distribution of disease location was observed in the multinomial logistic regression analysis [p = 0.03], and post hoc analyses showed a decrease in L1 [average APC -1.87%, 95% CI -2.75 to -0.98][Figure 3]. Upper GI disease, either isolated or with concomitant lower GI involvement [L4 + L4 modifier], was diagnosed in 10.7% of the total CD population, and increased over time [average APC 4.01%, 95% CI 0.64–7.49]. B1 disease was the most common behaviour at diagnosis [77.5%][Table 1]. Over time, a shift in the distribution of disease behaviour was observed in the multinomial logistic regression analysis [p = 0.01], and post hoc analyses showed a decrease in complicated disease [B2 + B3 combined, average APC -2.41, 95% CI -4.56 to -0.22], and a decrease in B3 alone [average APC -5.44%, 95% CI -8.71 to -2.06] [Figure 3]. Perianal disease [P] was present in 8.1%, and did not change over time [average APC -1.55%, 95% CI -3.81–0.77].

For UC, the mean age at diagnosis increased from 42.5 years [SD 17.0] to 45.9 years [SD 16.6] between 1991 and 2010 [p < 0.01]. E2 disease was the most common location at diagnosis [47.8%] [Table 1]. Over time, a shift in the distribution of disease location was observed in the multinomial logistic regression analysis [p < 0.01], with the post hoc analyses showing an increase in E1 [average APC 1.87, 95% CI 0.28–3.48] and a decrease in E2 [average APC -2.14%, 95% CI -3.00 to -1.28][Figure 3].

3.3. Mortality

Of the 2909 IBD patients, 2804 IBD patients were included in the mortality analysis [27 405 patient-years] and 105 IBD patients were excluded for previously mentioned reasons. Of the included patients, 1117 patients had CD [10 599.5 patient-years], 1603 had UC [16 139 patient-years], and 83 had IBD-U [666.5 patient-years].

For the total IBD group, mortality did not differ from that in the the background population, either in the total cohort [SMR 0.92, 95% CI 0.81–1.05] in the 1991–2000 subcohort [SMR 0.89,

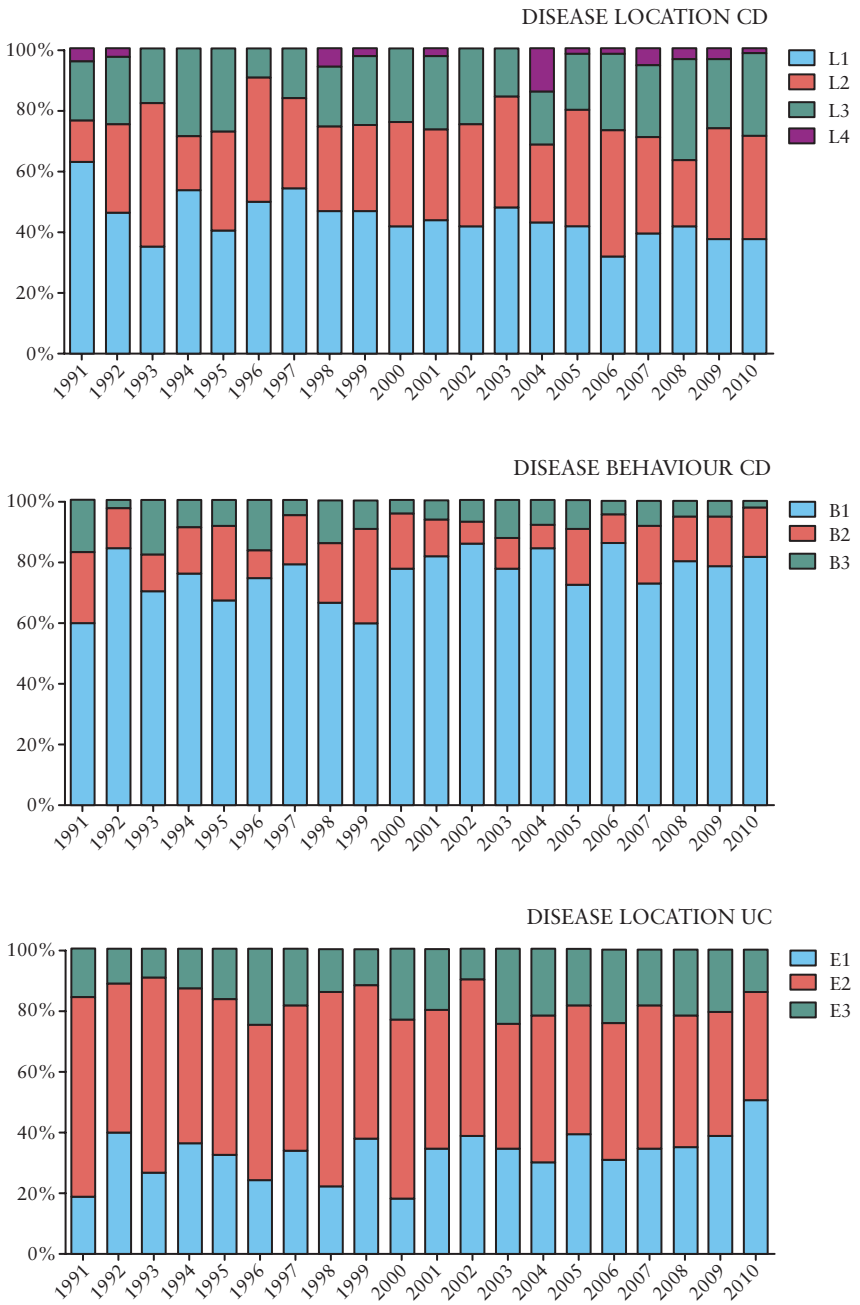

Figure 3. Temporal changes in phenotype distribution at diagnosis of South Limburg CD and UC patients. CD, Crohn's disease; UC, ulcerative colitis; phenotype was set at diagnosis, according to Montreal Classification. Disease location of CD was defined as ileal disease [L1], colonic disease [L2], ileocolonic disease [L3], or isolated upper gastrointestinal disease [L4]. Disease behaviour of CD was defined as non-stricturing non-penetrating [B1], stricturing [B2], or penetrating [B3]. Disease location of UC was defined as ulcerative proctitis [E1], left sided UC [E2], and extensive UC [E3].

95% CI 0.66–1.16], or in the 2001–10 subcohort [SMR 0.81, 95% CI 0.64–1.01][Table 3]. Results were similar in the gender-specific analyses.

For CD and UC separately, mortality did not differ from that in the background population, either in the total cohort or in the era-specific subcohorts [Table 3]. The gender-specific analyses revealed an increased mortality risk for female CD patients in the total cohort [SMR 1.54, 95% CI 1.09–2.13]. In the phenotype-specific analyses, an increased mortality risk was observed for CD patients with colonic disease at diagnosis [L2] in the total CD cohort [SMR 1.84, 95% CI 1.22–2.66] and in the 1991–2000 CD subcohort [SMR 3.01, 95% CI 1.37–5.70][Table 3]. In contrast, a decreased mortality risk was observed for UC patients with proctitis at diagnosis [E1] in the total cohort [SMR 0.69, 95% CI 0.48–0.96], and for left-sided UC patients in the 1991–2000 subcohort [SMR 0.59, 95% CI 0.35–0.95][Table 3].

3.4. Prevalence

In 2010, the IBD prevalence in South Limburg was estimated at 830 per 100 000 for IBD [4186 prevalent cases in South Limburg], at 331 per 100 000 for CD [1670 cases], at 475 per 100 000 for UC

Table 3. Temporal changes in standardised mortality ratios of South Limburg IBD, CD, and UC patients.

		Total cohort					1991–2000 cohort[b]					2001–2010 cohort[b]				
		N/PYAR	O	E	SMR	[95% CI]	N/PYAR	O	E	SMR	[95% CI]	N/PYAR	O	E	SMR	[95% CI]
IBD	Total	2804/27 405	235	254.6	0.92	[0.81–1.05]	1108/7348	54	61.0	0.89	[0.66–1.16]	1696/10 430	76	93.8	0.81	[0.64–1.01]
	Gender															
	Male	1325/13 180	137	159.3	0.86	[0.72–1.02]	654/3692	31	43.0	0.72	[0.49–1.02]	778/4823.5	44	51.0	0.86	[0.63–1.16]
	Female	1479/14 233	98	95.2	1.03	[0.84–1.25]	454/3656	23	18.1	1.27	[0.81–1.91]	918/5606.5	34	42.9	0.79	[0.55–1.11]
CD	Total	1117/10 599.5	62	54.0	1.15	[0.88–1.47]	407/2650.5	17	13.4	1.27	[0.74–2.03]	710/4335	22	21.5	1.02	[0.64–1.54]
	Gender															
	Male	417/3980	25	29.9	0.84	[0.54–1.23]	257/1004	8	7.9	1.01	[0.44–2.00]	267/1642.5	10	11.0	0.91	[0.44–1.67]
	Female	700/6619.5	37	24.0	**1.54**	**[1.09–2.13]**	150/1646.5	9	5.5	1.64	[0.75–3.11]	443/2692.5	12	10.6	1.13	[0.58–1.98]
	Location[a]															
	L1	480/4876	24	31.8	0.75	[0.48–1.12]	194/1305	4	8.6	0.47	[0.13–1.19]	286/1818	7	10.2	0.69	[0.27–1.41]
	L2	358/3209	28	15.2	**1.84**	**[1.22–2.66]**	125/762	9	3.0	**3.01**	**[1.37–5.70]**	233/1384.5	12	8.9	1.35	[0.70–2.36]
	L3	256/2321	9	4.6	1.98	[0.90–3.76]	82/551.5	2	0.8	2.50	[0.28–9.03]	172/1011	3	1.9	1.58	[0.32–4.61]
	Behaviour[a]															
	B1	862/7988	50	42.0	1.19	[0.88–1.57]	296/1927	14	11	1.27	[0.70–2.14]	566/3453	17	16.6	1.02	[0.60–1.64]
	B2	172/1700	5	7.6	0.66	[0.21–1.54]	72/456	1	1.1	0.91	[0.01–5.06]	100/572.5	3	3.4	0.88	[0.18–2.58]
	B3	84/913	7	4.4	1.59	[0.64–3.28]	39/267.5	2	1.2	1.67	[0.19–6.02]	44/309.5	2	1.6	1.25	[0.14–4.51]
UC	Total	1603/16 139	170	193.5	0.88	[0.75–1.02]	684/4592	37	47.0	0.79	[0.55–1.09]	919/5688	54	67.5	0.80	[0.60–1.04]
	Gender															
	Male	868/8873.5	111	125.9	0.88	[0.73–1.06]	388/2630.5	23	34.5	0.67	[0.42–1.00]	480/2998	34	38.6	0.88	[0.61–1.23]
	Female	735/7265.5	59	67.6	0.87	[0.66–1.13]	296/1961.5	14	12.5	1.12	[0.61–1.88]	439/2690	20	28.9	0.69	[0.42–1.07]
	Location[a]															
	E1	536/5216.5	35	50.7	**0.69**	**[0.48–0.96]**	200/1382	9	11.6	0.78	[0.35–1.47]	336/2025	12	19.2	0.62	[0.32–1.09]
	E2	764/8038.5	98	112.3	0.87	[0.71–1.06]	362/2440.5	17	28.6	**0.59**	**[0.35–0.95]**	402/2590	29	37.1	0.78	[0.52–1.12]
	E3	288/2761.5	32	28.1	1.14	[0.78–1.61]	108/667	8	5.6	1.43	[0.62–2.82]	180/1063.5	13	11.2	1.16	[0.62–1.98]

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; *N*, number of patients; PYAR, person-years at risk; O, observed deaths; E, expected deaths; SMR, standardised mortality ratio; 95% CI, 95% confidence interval by Byar's approximation.

[a]Phenotype at diagnosis, according to Montreal Classification. Disease location of CD was defined as ileal disease [L1], colonic disease [L2], or ileocolonic disease [L3]. Disease behaviour of CD was defined as non-stricturing non-penetrating [B1], stricturing [B2], or penetrating [B3]. Disease location of UC was defined as ulcerative proctitis [E1], left-sided UC [E2], and extensive UC [E3].

[b]Follow-up ends 2 years after this period.

[2395 prevalent cases], and at 24 per 100 000 for IBD-U [121 cases]. According to the national pathology registry PALGA, 5.2% of newly diagnosed Dutch IBD cases lived in South Limburg. The nationwide Dutch IBD prevalence was therefore estimated to be 613 per 100 000 [approximately 80 627 prevalent cases].

4. Discussion

In this study, we reported on temporal changes in incidence, disease phenotype at diagnosis, and mortality in adult IBD patients from South Limburg, diagnosed between 1991 and 2010. The following key findings were observed: the incidences of IBD, and its subtypes CD and UC, have increased significantly over time. The proportion of CD patients with ileal disease at diagnosis [L1] and those with complicated disease at diagnosis [B2 + B3] decreased over time, whereas the proportion of UC patients with ulcerative proctitis at diagnosis [E1] was found to increase. IBD mortality rates were similar to background population mortality, but an increased risk was observed for female CD patients and CD patients with colonic disease at diagnosis [L2]. A decreased mortality risk was found for UC patients with ulcerative proctitis at diagnosis [E1]. Finally, the 2010 IBD prevalence was estimated at 830 per 100 000 for South Limburg and at 613 per 100 000 for The Netherlands [nationwide].

The observed IBD incidence rates in the region of South Limburg are among the highest in literature, and are in line with Molodecky *et al.*'s landmark review that showed higher incidences in Western countries when compared with the rest of the world.[7] The high IBD incidence in South Limburg may be explained by several factors that have previously been associated with IBD, for instance easy health care access, the high levels of diagnostics and administration, a Western lifestyle, and the relatively high grade of urbanisation.[12,23–26] In addition, South Limburg and neighbouring regions in Belgium and Germany had intensive mining and coal industries in the 20th century, and still are rather heavily industrialised. Subsequent air pollution may have contributed to the high IBD incidence.[25,27,28]

The South Limburg IBD incidence has increased significantly between 1991 and 2010, which is in keeping with epidemiological studies from other West European countries [Denmark,[29] Sweden,[30,31] and France[32]]. In South Limburg, methodological factors are unlikely to play a role in this increase because identification methods have been stable throughout the entire study period. Also genetic influences are limited due to the restricted study length. The incidence increase can, therefore, best be explained by diagnostic and environmental factors, as elucidated below.

Several important diagnostic changes have been introduced during the study period, which most probably contribute to a part of the increase in IBD incidence. First, imaging techniques have advanced over the years; the quality of the endoscopes has improved[33] and sensitive imaging techniques have been introduced in the participating hospitals, such as computed tomography [CT, introduced in 1994], video capsule endoscopy [VCE, in 2002] and magnetic resonance imaging [MRI, in 2006]. Second, the mode of diagnosis has shifted over the years. In CD, for instance, the most frequently used diagnostic tool between 1991 and 1995 was small bowel follow-through [in 56% of all CD diagnoses, SBFT], followed by endoscopic procedures [49%]. This gradually shifted towards 6% and 89% between 2006 and 2010, respectively. In the latter period CT was used in 15% of CD diagnoses, MRI in 13%, and VCE in 5%. Third, referral routines of general practitioners [GP] to secondary/tertiary care have been optimised in the catchment area, including direct referrals for endoscopic procedures by GPs. Finally, awareness of the disease has probably increased among patients, GPs, and specialists [eg easier access to information, regular IBD training for GPs, and the transition of gastroenterology care from specialists in internal medicine to trained gastroenterologists]. Altogether, these diagnostic changes point towards an under-diagnosis of mild IBD cases in the early years of the cohort as well as a relative late detection of IBD at that time, both contributing to the current increase in diagnosed IBD incidence. This hypothesis was supported by several observations in the IBDSL cohort. The proportion of CD patients with complicated disease at diagnosis [B2 + B3], for instance, decreased over time, and the proportion of UC patients with ulcerative proctitis [E1] increased. In addition, upper GI disease at diagnosis [L4 + L4 modifier] increased over time as well, which suggests that at least some of such cases were missed in the period preceding the diagnostic changes. Finally, previous IBDSL studies on the same study period have shown a significant attenuation of surgery at diagnosis, both in CD and in UC.[34,35] To what extent the diagnostic changes contributed to the increased IBD incidence remains speculative.

Despite the fact that only circumstancial evidence is available, part of the increase in IBD incidence in South Limburg is most probably attributable to environmental factors. The rapid rise in IBD incidence worldwide,[7] the low concordance levels in IBD twin studies,[36–39] the increasing IBD risk in immigrants migrating from low- to high-prevalence areas,[40–42] and the spatial differences in IBD incidence within regions,[7,43] have indicated the important role of environmental factors in the aetiology IBD. In addition, genome-wide association studies [GWAS] have found that genetic susceptibility is only responsible for approximately 30% of the IBD incidence, and the remaining contribution is mainly driven by the environment.[7,44,45] Several environmental risk factors have already been associated with IBD [eg smoking, diet, childhood hygiene, socioeconomic factors, and many others].[46] Altogether, this gives reason to believe that the observed increase in South Limburg IBD incidence is also partly driven by environmental factors, but elaborating on specific local factors remains speculation. The most profound environmental changes in South Limburg over the past decades are the attenuating socioeconomic status and increasing urbanisation, both associated with IBD.[26,43,47] Further research on IBD-related environmental exposures in South Limburg is important, but is beyond the scope of this study.

Several temporal changes in phenotype characteristics at diagnosis have been observed. First, the proportion of CD patients with ileal disease at diagnosis [L1] has decreased over time. In the early 90s, sigmoidoscopies and SBFT were commonly performed in the diagnostic workup for abdominal complaints in South Limburg, whereas colonoscopies, CT, and MRI are currently preferred. It may be possible that proximal colonic involvement was occasionally missed in the early years, resulting in an L1 rather than an L3 classification. This temporal change must be taken into account when interpreting studies that use the Montreal classification. Second, the mean age at diagnosis for both CD and UC patients has increased over time. Increases, however, were subtle [1.9 years in CD and 3.4 years in UC between 1991 and 2010] and may very well be an effect of population ageing.[12,48]

The overall mortality rates in the South Limburg CD and UC populations were similar to the background population mortality, and have not changed over time. In a recent meta-analysis by Bewtra *et al.*, the mortality risk in inception cohorts was increased in CD [SMR 1.34, 95% CI 1.15–1.56] but not in UC [SMR 1.08, 95% CI 0.97–1.21].[8] Our results seem beneficial, but we must take into

consideration that inception cohorts, and thus the IBDSL cohort, have a somewhat short duration to adequately study IBD-related death. Furthermore, the risk profile of some specific patients groups did differ from the background population. Female CD patients, for instance, had an increased risk for death. Of the 37 observed deaths, four were CD-related [stenosis-based ileus, euthanasia, complications after IBD surgery, and palliative care in a case of penetrating disease], six were possibly CD-related [colorectal carcinoma in five cases, and pneumonia within 1 month after IBD surgery], 10 were not CD-related, and 17 causes of death could not be retrieved from the patient files [and therefore a relation with CD is not likely]. The reason for this increase is unclear, although we cannot exclude that it [in part] may be affected by the high percentage of female smokers at diagnosis [53% vs 44% in men].[49] CD patients with colonic disease at diagnosis [L2] were also at increased risk for death. Of the 28 observed deaths, four were CD-related [euthanasia, complications after IBD surgery in two patients, and palliative care in a case of penetrating disease], three were possibly CD-related [colorectal carcinoma, cholangiocarcinoma, and pneumonia within 1 month after IBD surgery], eight were not CD-related, and 13 causes of death could not be retrieved. UC patients with ulcerative proctitis at diagnosis [E1] were at decreased risk for death.

The increasing incidence and low mortality, together with the chronic nature of IBD, and the often young age of onset,[1,2] have contributed to the high IBD prevalence estimate in South Limburg [830 per 100 000]. The IBDSL cohort does not include paediatric IBD patients, and true prevalence rates may therefore even be [slightly] higher. The estimated nationwide IBD prevalence in The Netherlands is high as well [613 per 100 000, equivalent of 80 627 prevalent IBD cases in 2010], but lower when compared with South Limburg. This is in line with the overall lower health status in the South Limburg region [eg relative high prevalences of other chronic diseases, cancer, and depression, and a lower life expectation].[50,51] As preventive measures are not available yet, the observed findings give reason to believe that IBD prevalence will even further increase in future, and subsequently the burden for health care and society is expected to increase as well. The need for preventive measures is thus high, and their modifiable character make environmental factors an important target for interventions. More extensive research on [specific] environmental exposure is therefore warranted. This research should follow a more holistic approach, not only focusing on single exposures, but looking at the totality of environmental exposure from conception onwards [also known as exposomics].[45,52]

In conclusion, this population-based study in the Dutch South Limburg region showed marked increases in the incidences of adult IBD, CD, and UC between 1991 and 2010. The shift towards milder disease at diagnosis, in parallel with improved diagnostics and ability to detect low-grade inflammation, was suggestive of an important role of diagnostic factors in this increase. Environmental factors probably played a role as well. The mortality was low and, together with the increasing incidence, led to the high prevalence of IBD in South Limburg.

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Conflict of Interest

Authors have no conflicts of interest to disclose.

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