INCIDENCE AND PREVALENCE OF CROHN'S DISEASE AND ULCERATIVE COLITIS (2013–2017) BASED ON THE LATVIAN NATIONWIDE MEDICINES REIMBURSEMENT DATABASE

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Inflammatory bowel disease (IBD) is a chronic, relapsing–remitting, inflammatory condition of the gastrointestinal tract which consists of Crohn's disease (CD), ulcerative colitis (UC) and undifferentiated IBD. Epidemiology of IBD is changing worldwide, but a significant gap remains in the description of the IBD population in Latvia. The aim of the study was to determine the incidence and prevalence rates of IBD in Latvia in the period between 2013 and 2017. Retrospective analysis of reimbursed medicines claims for IBD diagnoses from the Latvian National Health Service database (NHS) was conducted for the period of 2012 to 2017. From CD patients, 53.7% were female and the area of residency strongly favoured urban areas vs rural districts of Latvia, 59.1% vs 40.9%, respectively. A similar demographic pattern was observed in UC patients, where 56.2% were female and 55.1% of the total UC population lived in urban areas. The overall age- and sex-adjusted incidence rates for CD and UC were 16.45 (CI95% [14.68, 18.21]) and 70.53 (CI95% [66.88, 74.19]) per 100 000 population, respectively, for the entire 2013–2017 period. The prevalence of CD and UC in 2012 was 12.4 and 54.8 cases per 100 000 persons, respectively, compared to 15.5 and 79.5 cases per 100 000 persons in CD and UC in 2017, resulting in a 25% increase in prevalence of CD and 41% increase in UC over the 5-year period. For the first time temporal trends in IBD incidence and prevalence as well as differences across age groups and gender over a five-year period are reported for Latvia.

Key words: Crohn's disease, epidemiology, National Health Services and Central Statistics Bureau databases, incidence, prevalence.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing–remitting, inflammatory condition of the gastrointestinal tract. It includes Crohn's disease (CD), ulcerative colitis (UC) and undifferentiated IBD (IBDU) (Ananthakrishnan, 2013). IBDU is diagnosed when the disease has features of both UC and CD (Geboes *et al.*, 2008). The aetiology of these illnesses remains unclear; however, evidence suggests a synergic effect of genetic, environmental and health-related factors (Mahid *et al.*, 2006; Baumgart *et al.*, 2011; Ruel *et al.*, 2014; Van Limbergen *et al.*, 2014).

IBD affects both genders at similar rates, with incidence peaking in younger adults (Molodecky *et al.*, 2012). Pa-

tients with IBD usually require life-long monitoring and therapy, which significantly impacts their quality of life and has considerable implications for the health system. IBD rates in regions with previously high incidence rates have been reported to be slightly decreasing or stabilising (Leddin *et al.*, 2014).

Incidence and prevalence of IBD is increasing worldwide with Western countries having the highest reported prevalence compared to Asian countries. However, a rapid increase in prevalence of IBD in Asia has been observed in the last years (Burisch *et al.*, 2014).

The incidence of IBD in Latvia remains unclear and lack of data was previously highlighted in a previous study (Krus-

tiņš and Pokrotnieks, 2014). Epidemiology of IBD is changing worldwide, but a significant gap remains in the description of the IBD population in Latvia. The aim of this study was to determine the incidence of IBD in Latvia between the years 2013 and 2017.

METHODS

In Latvia, patients have access to state reimbursed medicines for IBD if they have a documented diagnosis. The Latvian National Health Services (NHS) maintain a database of reimbursed medicines and manipulations, including consumption and utilisation data. The population of Latvia continued to decrease from 2 023 825 in 2013 to 1 950 116 in 2017 (Anonymous, 2019). The start date of 1 January 2012 for analysis was chosen as this was the time of digitalisation of reimbursed prescription medicines tracking. The study population included newly diagnosed patients with CD and UC in the study period of 2013–2017. The year 2012 data was used to distinguish between prevalence and incidence of CD and UC. The NHS database of reimbursed medicines includes information on patient sex, age, area of habitation, date of prescription, date of dispensing the medicine, name of dispensed medicine (including information on dosage form and dispensed quantity), as well as prescribing medical speciality. According to Latvian legislation on prescription of reimbursed medicines, prescription can be prescribed to cover a three-month therapy course, and a prescription as such is valid for 90 days (Anonymous, 2005). In addition, the database contains information about each physician's visit, medical procedure, hospitalisation, medication dispensed in the outpatient setting, date of service/prescription, number of days of medication supplied, and tests performed. The initial study population included all patients who were registered in NHS database as having received reimbursed prescription medicine for diagnosis of Crohn's disease and Ulcerative colitis for the period from 1 January 2012 till 30 November 2018. Data for 2018 were not included in incidence and prevalence analysis since whole year data was not available at the time of request.

In this study, patients were defined as having IBD if they received therapy for IBD at least twice with at least a 30-day interval. Diagnoses were identified using appropriate ICD codes for UC (ICD-9 556; ICD-10 K51) and CD (ICD-9 555; ICD-10 K50), through which patients were further classified as CD, UC or unclassified IBD patients. The date of IBD diagnosis was considered the date of first prescription by physician. The annual incidence rates for UC and CD for each gender were estimated as the number of incident patients divided by number of inhabitants in the same calendar year. Information of the size of population for each year was obtained from the Central Statistics Bureau database of Latvia (Anonymous, 2019). Some patients were registered with both UC and CD, and in order to compare changes in the incidence rates over time, patients with both diagnoses were included under the first disease registered. The incidence rates were directly standardised to the 2013 Latvian population using 10-year age groups and by using

the 2013 European Standard population. The 95% confidence intervals (CI) of the estimated incidence rates were based on a Gamma distribution (Tiwari *et al.*, 2006). Furthermore, the mean incidence rates for UC and CD were given within different age groups (< 10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and > 80), and according to gender.

Poisson regression was used to estimate effect of calendar year on the incidence of CD, UC and IBD for each sex by age groups and overall. Demographic characteristics included age, sex and area of residency (rural or urban). Patients were stratified according to the place of registration — urban (including people living in capital and eight regional size cities — Rīga, Daugavpils, Jēkabpils, Jelgava, Jūrmala, Liepāja, Rēzekne, Valmiera, Ventspils) and rural (rest). The analysis was conducted using MS Excel 2018 and SPSS version 23.0.

This study was approved by the Independent Research Ethics Committee of Rīga Stradiņš University, Rīga, Latvia, and was in compliance with Helsinki Declaration. Requested data were reviewed and approved by the NHS.

RESULTS

For the studied period of almost seven years (1 January 2012 till 30 November 2018), 4828 unique patients including paediatric were treated with reimbursed medications for CD and UC indications. From 4828 unique patients, 1311 patient received reimbursed medicine only once (Fig. 1). From those patients with only one prescription, there were 312 patients with diagnosis CD (306 adults), and with 999 patients with UC (985 adults) (Tables 1–3).

After removal of patients that received their prescription in 2011 and procured it in 2012, the number of unique patients fitting the criteria was 3089, from which 18.6% were CD and 81.4% were UC. From CD patients, 53.7% were female and the area of residency strongly favoured urban areas vs rural districts of Latvia, 59.1 vs 40.9%, respectively. A similar demographic pattern was observed in UC patients, where 56.2% were female and 55.1% of total UC population lived in urban areas (Table 4). The age of diagnosis of UC and CD differed significantly depending on sex, with the highest incidence rate in female CD patients peaking twice (in 20–39 and 60–69 age groups); for male CD patients the incidence peaked in 20–39 year age subgroup. For female UC patients the incidence was evenly distributed between 20–29 up to 40–49 age subgroups, and peaked in the 70–79 age subgroup, for male patients the UC incidence peaked in the 30–39 age group (Table 5).

The directly age-standardised rates of CD and UC allowed for comparisons across years with adjustment for age distribution over time and were calculated for both CD and UC (Table 6). The overall age- and sex-adjusted incidence rates for CD and UC were 16.45 (CI95% [14.68, 18.21]) and 70.53 (CI95% [66.88, 74.19]) per 100 000 population, re-

Fig. 1. Flowchart of ascertainment of inflammatory bowel disease (IBD) cases in Latvia from 2012 to 2017 CD, Crohn's disease; UC, ulcerative colitis.

Table 1. Diagnosis distribution of patients with only 1 prescription for inflammatory bowel disease diagnosis in the period of 2012–2018. Overview of patient demographic parameters

Diagnosis	2012	2013	2014	2015	2016	2017
K50	62	47	46	53	38	32
K51	136	107	106	113	143	146
Total	198	154	152	166	161	178

Table 2. Diagnosis distribution of patients with only 1 prescription for inflammatory bowel disease diagnosis in the period of 2012–2018

Diagnosis	Frequency, n	%
K50.0	187	14.3
K50.1	50	3.8
K50.8	24	1.8
K50.9	51	3.9
K51.0	407	31.0
K51.1	10	0.8
K51.2	136	10.4
K51.3	56	4.3
K51.4	47	3.6
K51.5	14	1.1
K51.8	96	7.3
K51.9	233	17.8
Total	1311	100.0

Table 3. Gender and area of habitation distribution of patients with only 1 prescription for inflammatory bowel disease diagnosis in the period of 2012–2018

Patient gender	Frequency, n (%)	Area of habitation	Frequency, n (%)
Male	486 (37.1)	Rural	751 (57.3)
Female	825 (62.9)	Urban	560 (42.7)

Table 4. Demographic data on patients with IBD in Latvia, 2012–2017

	IBD overall (total n = 3089)	CD (total n = 575)	UC (total n = 2514)
Gender			
Male	1366	266	1100
Female	1723	309	1414
Mean age, years (± SD)			
Male	45.1 ± 18.4	40.3 ± 18.5	46.3 ± 18.1
Female	54.0 ± 19.3	51.9 ± 19.3	54.4 ± 19.2
Place of living			
Urban	1724	340	1384
Rural	1365	235	1130

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

Table 5. Total number (%) of incident cases of CD and UC in Latvia, 2013–2017

Age group	CD		UC		Total
	n	%	n	%	
<10	1	0.6	3	0.4	4
10–19	5	2.8	35	4.4	40
20–29	28	15.8	90	11.4	118
30–39	29	16.4	104	13.2	133
40–49	19	10.7	97	12.3	116
50–59	22	12.4	119	15.1	141
60–69	35	19.8	123	15.6	158
70–79	28	15.8	156	19.7	184
>80	10	5.6	63	8.0	73
All women	177	100	790	100.0	967

Age group	CD		UC		Total
	N	%	N	%	
<10	2	1.3	5	0.8	8
10–19	18	11.3	32	4.9	81
20–29	32	20.0	96	14.8	271
30–39	37	23.1	148	22.8	337
40–49	21	13.1	107	16.5	250
50–59	22	13.8	93	14.3	214
60–69	13	8.1	91	14.0	196
70–79	11	6.9	63	9.7	162
>80	4	2.5	15	2.3	35
All men	160	100	650	100.0	810

CD, Crohn's disease; UC, ulcerative colitis

Table 6. Annual directly age-sex standardised incidence rates per 100 000 patients with CD and UC in Latvia in 2013–2017

Crohn's disease						
Year	Male	95% CI [LL, UL]	Female	95% CI [LL, UL]	Total	95% CI [LL, UL]
2013	4.18	2.87, 5.49	3.37	2.18, 4.3	3.71	2.87, 4.55
2014	3.71	2.37, 5.05	3.04	2.04, 4.04	3.38	2.54, 4.21
2015	3.09	1.92, 4.26	3.97	2.8, 5.14	3.53	2.71, 4.35
2016	2.51	1.52, 3.51	3.11	2.08, 4.13	2.81	2.1, 3.52
2017	3.6	2.36, 4.85	2.13	1.25, 3.01	2.87	2.11, 3.63
Ulcerative colitis						
Year	Male	95% CI [LL, UL]	Female	95% CI [LL, UL]	Total	95% CI [LL, UL]
2013	14.28	11.82, 16.75	14.15	11.96, 16.34	14.22	12.57, 15.86
2014	13.22	10.81, 15.63	12.66	10.6, 14.72	12.94	11.35, 14.52
2015	13.62	10.89, 15.63	17.05	14.63, 19.47	15.16	13.46, 16.85
2016	15.84	13.19, 18.49	11.77	9.76, 13.77	13.8	12.14, 15.47
2017	14.82	12.14, 17.5	12.93	10.82, 15.03	13.87	12.17, 15.58

CD, Crohn's disease; UC, ulcerative colitis

Table 7. Prevalence data by year 2012–2017 for IBD, UC and CD in Latvia

Year	Total population of Latvia	Total population with IBD, n	IBD prevalence per 100 000	Total population with CD, n	CD prevalence per 100 000	Total population with UC, n	UC prevalence per 100 000
2012	2 044 813	1374	67.2	253	12.4	1121	54.8
2013	2 023 825	1466	72.4	271	13.4	1195	59.0
2014	2 001 468	1516	75.7	283	14.1	1233	61.6
2015	1 986 096	1661	83.6	326	16.4	1335	67.2
2016	1 968 957	1775	90.1	308	15.6	1467	74.5
2017	1 950 116	1852	95.0	302	15.5	1550	79.5

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

Fig. 2. Directly age-standardised incidence rates of Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease (IBD) in Latvia, 2013–2017.

spectively, for the entire 2013–2017 period (Fig. 2). Age- and sex-adjusted incidence rates for CD decreased during the study period from 2013 to 2017. Poisson regression analysis showed that female sex was significantly associated with higher incidence rate of CD ($p < 0.001$), whereas area of habitation was not. Similar results were observed in UC patients with female sex being significantly associated with higher incidence rate of UC ($p < 0.001$).

The age- and sex-adjusted prevalence for CD and UC was calculated (Table 7). The prevalence of CD and UC in 2012

Fig. 3. Prevalence of IBD, UC and CD in Latvia in the period from 2012 to 2017.

was 12.4 and 54.8 cases per 100 000 persons, respectively, compared to 15.5 and 79.5 cases per 100 000 persons in CD and UC in 2017, resulting in a 25% increase in prevalence of CD and 41% increase in UC (Fig. 3).

DISCUSSION

This study of descriptive epidemiology of CD and UC in a population-based cohort of Latvian patients between 2013 and 2017 showed a decrease in the incidence rate but increase in prevalence. The increasing prevalence of CD and

UC may be due to the fact that patients are living longer with the disease and that the disease itself is better managed, leading to normal or near-normal life expectancy. Such a phenomenon is described in the literature as “compounding prevalence” (Kaplan, 2015). Incidence and prevalence of CD and UC have been extensively studied in various countries (Kiudelis *et al.*, 2012; Agnarsson *et al.*, 2013; Leddin *et al.*, 2014; Lucendo *et al.*, 2014; Nørgård *et al.*, 2014; Kim *et al.*, 2015). Compared to other countries, incidence of CD in Latvia is similar to that in countries with lower incidence, whereas for UC incidence is similar to that in Scandinavian countries (Lophaven *et al.*, 2017). Absolute prevalence of IBD, UC and CD seems relatively low (0.095%, 0.015% and 0.08%, respectively) but increasing through the five-year period, which is in consensus with global trends where the age-standardised prevalence rate increased from 79.5 (75.9–83.5) per 100 000 population in 1990 to 84.3 (79.2–89.9) per 100 000 population in 2017 (Alatab *et al.*, 2020). Recent prevalence estimates from Scandinavia, Western Europe and North America range from 0.21% to 0.44% for IBD, from 0.007% to 0.27% for Crohn’s disease (CD) and from 0.008% to 0.29% for ulcerative colitis (Green *et al.*, 2006; Juillerat *et al.*, 2008; Manninen *et al.*, 2010). However, a direct comparison of these estimates is complicated by differences in data sources and collection techniques, case ascertainment, diagnostic criteria used, study period and limited sample sizes.

Compared to other studies, the Latvian population seems to have later onset of UC and CD independently of sex, which might be explained by longer time till diagnosis, and epidemiologically is reflected as a shift towards a more adult population.

Study limitations include the case identification algorithm, since it was not validated previously in the Latvian patient cohort. It might be that having two prescriptions with at least a 30-day interval is not sufficient to distinguish a true IBD patient from a patient with IBD-like symptoms. Additionally, diagnosis could not be verified, as by endoscopies or radiological investigation that are deemed necessary to prove the diagnosis of IBD. Therefore, overestimation of the true IBD population in Latvia is possible.

Our study has several strengths. First and foremost, the data derive from a large, well-defined population with nationwide coverage. The use of nationwide data of all Latvian residents makes observations obtained in this retrospective study independent of regional differences in practice patterns, exposures, and genetic susceptibility. For the first time we have investigated temporal trends in IBD incidence as well as differences across age groups and gender over a five-year period, and studies covering a longer time period could complement the existing evidence and provide a comprehensive long-term picture of IBD in Latvia.

An important consideration when examining the data was the peak in age-standardised incidence rates in 2015, which can be explained by a change of medication reimbursement policy. Before 2015, medications for IBD were reimbursed

by the state in the amount of 50 or 75%, whereas starting from 2015 some important groups of medications were 100% reimbursed; this year was also highlighted by broader accessibility to biologic therapy (Anonymous, 2015). The peak might be attributed to changes in the reimbursement conditions, which shifted part of the patients that were previously paying for the therapy out-of-pocket to the reimbursed service sector.

Another important finding was the number of unique patients with IBD diagnosis that were lost on follow up or could be probably misdiagnosed, with the trend to increase over time. This highlights the need for more thorough patient monitoring and usage of other diagnoses, e.g. K52 (unspecified colitis), before a robust IBD diagnosis is made.

CONCLUSIONS

In conclusion, we report that the prevalence of UC and CD is increasing based on data from medically treated IBD patients. The evidence from this study indicates that incidence rates of both CD and UC are declining. This study highlights a large and progressively growing population of IBD patients who will require further study. Additional studies in the Latvian and Baltic populations are needed with more stringent validation and inclusion criteria, as well as prospective IBD registries. This has implications for both epidemiology and health planning.

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KRONA SLIMĪBAS UN ČŪLAINĀ KOLĪTA INCIDENCE UN PREVALENCE 2013.–2017. GADĀ, BALSTOTIES UZ LATVIJAS NACIONĀLO KOMPENSĒJAMO MEDIKAMENTU DATUBĀZI

Iekaisīgā zarnu slimība (IZS) ir hronisks, recidivējoši remitējošs kuņģa–zarnu trakta iekaisuma stāvoklis, kas iekļauj tādās slimības kā Krona slimība (KS), čūlainais kolīts (ČK) un nediferencēta IZS. IZS epidemioloģija mainās visā pasaulē, tomēr IZS populācijas raksturojums Latvijā līdz šim brīdim nav veikts. Pētījuma mērķis bija izpētīt IZS incidences un prevalences rādītājus Latvijā laikposmā no 2013. līdz 2017. gadam. Tika veikta Latvijas Nacionālā veselības dienesta (NVD) kompensējamo zāļu pieprasījumu IZS diagnozei retrospektīva analīze, ietverot laika posmu no 2012. gada līdz 2017. gadam. 2017. gadā no KS pacientiem 53,7% bija sievietes, un lielākā daļa pacientu dzīvoja pilsētās, nevis lauku reģionos, attiecīgi 59,1 pret 40,9%. Līdzīgs demogrāfiskais modelis tika novērots ČK pacientiem, kur 56,2% bija sievietes un 55,1% no visiem ČK iedzīvotājiem dzīvoja pilsētās. Kopējā vecuma un dzimuma koriģētā incidence KS un ČK bija attiecīgi 16,45 (CI95% [14,68; 18,21]) un 70,53 (CI95% [66,88; 74,19]) uz 100 000 iedzīvotājiem laikposmā no 2013. līdz 2017. gadam. KS un ČK prevalence 2012. gadā bija attiecīgi 12,4 un 54,8 gadījumi uz 100 000 iedzīvotājiem, salīdzinot ar 15,5 un 79,5 gadījumiem uz 100 000 iedzīvotājiem KS un ČK 2017. gadā, palielinot KS un ČK izplatību piecu gadu laikā attiecīgi par 25% un 41%. Šis ir pirmais pētījums, kurā tiek analizēti Latvijas IZS populācijas incidences un prevalences dati, kā arī atšķirības vecuma grupās un dzimumos piecu gadu periodā.