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Abstract

Background and aims: The incidence of ulcerative colitis (UC) and Crohn's disease (CD) has increased during the 20th century in North America and Western Europe. However, there are conflicting reports whether the incidence has declined, stabilized or even continued to increase. No nationwide Danish data on the incidence of UC and CD exist after 1992, and therefore we studied the incidence of UC (1995 through 2011) and CD (1995 through 2012).

Methods: Based on data from the Danish National Patient Registry we identified patients recorded with a first time diagnosis of UC or CD in the study periods. Among these — patients

Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; NPR, Danish National Patient Registry; ICD, International Classification of Diseases; IRR, incidence rate ratio.

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1. Introduction

The incidence of ulcerative colitis (UC) and Crohn’s disease (CD) is subject to considerable variation between geographic regions and time, and the incidence has increased during the past half century in the populations of Western Europe and North America. The highest occurrence of UC and CD is found in Canada\textsuperscript{1–3} and Europe\textsuperscript{3,4}, and within Europe the highest incidence rates are found in Scandinavia\textsuperscript{5–18} and the United Kingdom.\textsuperscript{19–22}

During the last decades it has been discussed whether the incidence has continued to increase, has stabilized or has even declined.\textsuperscript{21–26} There are, however, some indications of a continuing increase of the incidence of UC and CD,\textsuperscript{3,23,27,28} and a recent Swedish study showed one of the highest incidences of UC in the world.\textsuperscript{23} No nationwide Danish data on the incidence of UC and CD have been reported since 1992 (with reported mean incidence for UC of 13.2 per 100,000 person-years and for CD 4.6 per 100,000 person-years).\textsuperscript{12} Later reported local data from the Northern Jutland and Copenhagen County in Denmark have indicated a continuous increase in the incidence rates of UC and CD.\textsuperscript{7,8}

UC and CD are relatively rare diseases and it is both extremely time consuming and expensive to estimate incidence rates based on prospective registration. Furthermore, surveillance bias may be a problem if disease registration varies between regions and over time. For these reasons it is valuable if existing public health registers can provide valid surveillance data according to incidence rates over longer time periods.

Based on nationwide data from the Danish National Patient Registry (NPR), we aimed to examine the incidence rates of UC and CD from 1995.

2. Materials and methods

2.1. Study population and setting

In Denmark, all citizens have free access to a tax supported health care system throughout the study period. Its uniform organization allowed us to use a population-based setting using nationwide data. Since 1977, all patients are registered in the NPR when they are discharged from Danish hospitals, and the NPR also includes all outpatient visits since 1995.\textsuperscript{29,30} The population of Denmark was approximately 5.2 million (in 1995) increasing to 5.6 million (in 2012). The start of the period, 1 January 1995, was chosen since this was the time for inclusion of also outpatient visits in the NPR. The study population included new diagnosed patients with CD in the study period of 1995 through 2012, while the study population of UC patients included new diagnosed patients from 1995 through 2011. Thus, data from 2012 on UC patients were excluded because of a reclassification from the World Health Organization of the International Classification of Diseases (ICD) 10 diagnostic codes for UC (implemented in Denmark by 1 January 2012).

2.2. Identification of UC and CD patients

Information in the NPR includes patients’ unique civil registration numbers, hospital, departments, dates of admission and discharge, procedures performed and up to 20 discharge diagnoses based on the ICD, 8th revision before 1994 and ICD, 10th revision from 1994 onward (ICD-9 has never been used in Denmark). All patients with a valid civil registration number, who were discharged with affirmative UC (ICD-8 codes: 563.19, 569.04; ICD-10 codes: DK51.0, DK51.1, DK51.2, DK51.3) or affirmative CD (ICD-8 codes: 563.01; ICD-10 codes: DK50.0, DK50.1, DK50.8) from any hospital in Denmark were included in the NPR from 1 January 1977, and all patients diagnosed for the first time with UC from 1995 through 2011 and CD from 1995 through 2012 were identified. Among these — patients were only included in the study as incident cases if they had at least one more discharge diagnosis of UC/CD or at least three subsequent outpatient visits.

2.3. Statistical analysis

The annual incidence rates for UC and CD and for each gender were estimated as the number of incident patients, divided by the number of inhabitants in the middle of the same calendar year. Information on the size of population for each year was obtained from the National Central Statistical Register.\textsuperscript{31} Some patients were registered with both UC and CD in the NPR and in order to compare changes in the incidence rate over time, patients with both diagnoses were included under the first disease registration. The incidence rates for UC were directly standardized to the 2011 Danish population using 15-year age groups, and similarly the incidence rates for CD were standardized to the 2012 population. Age-adjusted incidence rates were also summarized within four calendar periods of time (1995–
1998, 1999–2003, 2004–2008, and 2009–2011/2012). The 95% confidence intervals (CI) of the estimated incidence rates were based on the assumption of Gamma distribution. Furthermore, the mean incidence rates for UC and CD were given within different age groups (<15, 15–29, 30–44, 45–59, 60–74, >75) and according to gender.

Poisson regression models were used to estimate the incidence rate ratio (IRR) for the annual change in the incidence, adjusted for gender and age (using the above-mentioned age categories).

All analyses were conducted using Stata 13 software (StataCorp LP, College Station, TX, USA).

2.4. Ethical approvals and permissions

According to Danish law there are no ethical approvals of register-based studies. The study was approved by the Danish Data Protection Agency (J.nr. 2013-41-1670).

3. Results

There were 17,500 patients fulfilling our criteria for incident cases of UC from 1995 through 2011, and 7863 patients of CD from 1995 through 2012.

3.1. Incidence rate of UC

Fig. 1 shows the age-standardized incidence rates for UC according to gender and each calendar year in the study period. In 1995 the estimated rate was 13.6 (95% CI: 11.9–14.8) per 100,000 person years for men and 13.9 (95% CI: 12.1–15.0) per 100,000 person years for women. In the period from 1995 throughout 2011 the rate for both men and women increased, and in 2011 reaching 23.5 (95% CI: 22.7–25.5) for men and 22.4 (95% CI: 20.6–24.2) for women.

The mean age-adjusted incidence rate for UC in four time periods is summarized in Table 1 and shows the increasing incidence, reaching a mean incidence from 2009 through 2011 of 23.2 per 100,000 per year for women and 23.4 per 100,000 per year for men. Table 2 shows the mean incidence rates per year for UC within different age groups and according to gender. In women the highest incidence rates were found in age groups 15–29 years and 30–44 years, and in men the highest incidence rates were found in the same age groups.

The result from the Poisson regression model showed an IRR of 1.035 (95% CI: 1.030–1.040), corresponding to an annual increase of the incidence rate of 3.5% adjusted for age and gender. The IRR also corresponds to a doubling in the incidence rate of UC during a period of 20.4 years (95% CI: 17.6–23.2).

3.2. Incidence rate of CD

Fig. 2 shows the age-standardized incidence rates for CD according to gender and each calendar year in the study period. In 1995 the estimated rate was 6.8 (95% CI: 5.6–7.7) per 100,000 person years for women and 4.6 (95% CI: 3.6–5.3) per 100,000 person years for men. In the period of 1995 through 2012 the incidence rates increased, and in 2012 reaching 9.5 (95% CI: 8.3–10.7) per 100,000 person years for women and 8.8 (95% CI: 7.2–10.1) per 100,000 person years for men.

The mean age-adjusted incidence rate for CD in four time periods is summarized in Table 3 and shows the increasing incidence, reaching a mean incidence from 2009 through 2012 of 10.3 per 100,000 per year for women and 8.9 per 100,000 per year for men.

Table 4 shows the mean incidence rates per year for CD within different age groups and according to gender. For both men and women the highest incidence rate was found in the age group 15–29 years.

The Poisson regression model estimated an IRR of 1.024 (95% CI: 1.019–1.030), corresponding to an annual increase of the incidence rate of 2.4% adjusted for age and gender — and to a doubling in the incidence rate of CD during a period of 28.7 years (95% CI: 22.0–35.5).

4. Discussion

In this population based study, using nationwide Danish data from the last two decades, we found increasing trends in the incidence rates of UC and CD. In the study periods, the mean incidence rate for UC increased from approximately 14 to 23 per 100,000 per year for both men and women; and the mean incidence rate for CD increased from 7.8 to 10.3 per 100,000 per year for women and from 5.6 to 8.9 per 100,000 per year for men.

Our study has several strengths. Data were obtained independently of the study question, and a population-based approach is possible in Denmark due to a unique availability of nationwide registries. Internationally, the NPR is considered to be the most comprehensive of its kind, and the NPR records more than 99% of all hospital discharges for somatic diseases. We thus had access to the obligatory registration from Danish hospitals since 1977 and all outpatient visits since 1995. We used the NPR to identify patients with diagnoses of UC and CD, and the completeness and the validity of UC and CD diagnoses in the NPR are of high quality. The completeness of diagnoses of UC and CD has been examined in a Danish study using the pathology system.
The completeness of UC and CD registration in the confirmed diagnosis of UC or CD, 94% were included in the sample. This approach is not surprising that the incidence curves for UC and CD flatten out/even decrease at the end of the study periods. This is most probably due to our methodological approach and our strict criteria for counting first outpatient visits. Therefore, we might in fact have underestimated the true incidence rates of UC and CD. As a reference standard — showing that of all patients with a confirmed diagnosis of UC or CD, 94% were included in the NPR. The completeness of UC and CD registration in the NPR is most probably even higher in our study period as UC and CD diagnoses given in outpatient visits are now also registered. Furthermore, the overall positive predictive values (i.e., the percentage of patients registered under the disease code fulfilling the criteria of CD and UC) were 97% and 90% for CD and UC, respectively. The positive predictive value of UC diagnoses increased further (to 94%) when the diagnosis was given at a specialized department of gastroenterology. The validity of diagnostic coding for UC and CD in the NPR is essential. Based on the results of the validity study of UC and CD, and because we have been very strict in our criteria of incident cases we believe that our results are valid. First of all we have included only affirmative codes for UC and CD, and thus not included unspecified UC and CD codes in our study. Furthermore, we have been very strict in our criteria of incident cases, i.e., included patients had at least two discharge diagnoses of UC/CD or one discharge diagnosis with at least three subsequent outpatient visits. Therefore, we might in fact have underestimated the true incidence rates of UC and CD.

The figures showing the incidence trends for UC and CD indicate a decrease in the rates at the end of the study periods. This is most probably due to our methodological approach. Thus, it is not surprising that the incidence curves for UC and CD flatten out/even decrease at the end of the study periods since a patient with first time diagnosis at the end of the study period has a lesser chance of fulfilling the criteria for being included as incident case (i.e., having a second UC/CD diagnosis in the NPR at least three visits as outpatients) compared to a patient with a first UC/CD diagnosis several years ago. Thus, for 25% of UC patients, the distance between the first and the second diagnoses in the NPR was more than 2.3 years and the corresponding figure for CD patients was 1.2 years. The advantage of our methodological approach and our strict criteria for counting a patient as an incident case is, however, that it provides insurance on the validity of our results.

Our study also has limitations. The continuous increasing incidence rates found in our study might be influenced by an improved classification system and improved diagnostic tools (e.g., capsule endoscopies). Furthermore, it is also possible that greater awareness, either by physicians or by patients, may result in the diagnosis of mild cases which might have been previously unnoticed. However, the increasing incidence of UC and CD found in this study is a continuation of the incidence trend reported in the former Danish study using nationwide registry data based on ICD-8 codes, and we do not see sudden dramatic peaks in the incidence during the recent years reflecting a sudden greater awareness of the disease, introduction of new diagnostic tools, or sudden peaks according to the shift to ICD-10 codes. One might speculate whether the increasing incidence of UC and CD reflects an increasing tendency to refer patients from the general practitioner to hospitals, but it is our experience that only very few UC and CD patients are handled in the primary health care or the very small private sector, and for decades it has been a common practice in Denmark to refer these patients to public hospital units for diagnosis and treatment. A recent study from our neighbor country, Sweden, also reported an increasing incidence and showed that the proportion of severe cases was similar to historical data — indicating a true increase and not attributing to better diagnostics. Despite a theoretical influence of the abovementioned factors, such as change in classification system and greater awareness, we thus believe that our study indicates a real increase in the incidence rates of UC and CD during the last two decades.

Former Danish studies from two specific counties have reported incidence rates for early periods also included in this study. In the study by Jacobsen et al. the incidence rates for CD and UC at the end of their study period (2002) are in accordance with our results. In the period of 2003–2005, our results on CD

Incidence rates were also in line with the study by Vind et al.7, whereas we find higher incidence rate for UC. The study from Vind et al. was not based on the NPR but on specific county hospital departments/private gastroenterological surgeons where not all were participating, and thus the results of Vind et al. might have been underestimated. An alternative explanation is that county specific results are not in all aspects easily compared to nationwide data due to possible interregional differences in the incidence of UC and CD across Denmark. The existence of such differences in the incidence rates is recently underlined in the paper from the ECCO-EpiCom cohort showing that the incidence rates in 2010 varied considerably across Danish participating centers (for UC between 7.4 and 20.1 per 100,000 and for CD between 4.8 and 11.4 per 100,000).34

There have been reports of a stabilization of the incidence rates in Western Europe countries and North America.25,26 However, continuously increasing incidence rates have also been reported7,16,28 and a comprehensive review from 2012 concludes that the incidence of UC and CD is increasing with time and in different regions around the world, indicating its emergence as a global disease.3 Our estimated incidence rates of UC and CD correspond with recent results from two Swedish studies from Uppsala County.23,35 Our study indicates that the incidence rate of UC in Denmark is among the highest in the world and in the same level as reported rates from Canada (19.2 per 100,000 per year), Iceland (24.3 per 100,000 per year), and Sweden (20.0 per 100,000 per year).1,3,23,36 Also, our estimated incidence rate of CD is among the highest in Northern Europe and in line with reported rates from the United Kingdom (10.6 per 100,000 per year) and Sweden (9.9 per 100,000 per year).3,22,35 Studies of variations of the incidence of UC and CD across demographic factors, such as age and gender, are important because they yield clues to the etiology of disease. Furthermore, studies of incidence provide valuable information about the burden of illness for policy makers and resource planners in the health care system. As UC and CD affect individuals in the most formidable and productive years of life the diseases result in long-term cost to the patient, health care system, and society.37

Many studies have been published to understand the underlying reasons for the increased incidence of UC and CD, but so far without great success.3,38 The emergence of UC and CD in traditionally low prevalent regions suggests that the development of diseases may be influenced by environmental risk factors and studies have indicated that environmental factors, not genetics (with ethnicity a proxy), are the major driving force for the increase in incidence over time.3,38 It is, however, still unclear what the main component of “environmental factors” is.3,27 In conclusion, based on nationwide Danish data from the last two decades, the incidence rates of UC and CD have continued to increase.

**Conflict of interest**

The authors have no conflict of interest.

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The specific author contributions: BMN and KF have contributed to the conception and design, the analysis and interpretation of data, drafting the article for intellectual content, and finally approved the version to be published. JN has contributed to the design, carried out the data
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