Temporal trends in non-stricturing and non-penetrating behaviour at diagnosis of Crohn's disease in Örebro, Sweden: A population-based retrospective study

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KEYWORDS
Crohn's disease; Epidemiology; Incidence; Prevalence; Phenotype

Abstract

\textbf{Background and aim:} The incidence of Crohn's disease (CD) is continuing to rise in several countries and in others it appears to have already levelled off after a period of increase. We updated our previous population-based study, by re-extraction of all information on patients diagnosed with CD between 1963 and 2010. Our aim was to assess temporal trends in incidence, prevalence and disease phenotype at diagnosis.

\textbf{Methods:} Patients of all ages with a potential diagnosis of CD were identified retrospectively by evaluation of medical notes of all current and previous patients at the colitis clinic, Örebro University Hospital amended by computerised search in the inpatient, outpatient, primary care and histopathological records. Diagnosis was confirmed by subsequent evaluation of medical notes. Disease phenotype was defined according to the Montreal classification.

\textbf{Results:} The incidence increased over time, especially among Crohn's disease, A1 and A3. SaTScan model revealed a statistically significant high incidence during 1991–2010 ($p = 0.0001$). The median age at diagnosis increased from 28 (3–79) years to 37 (5–87) years ($p = 0.0002$). The point prevalence increased from $21/10^5$ (14–32) in 1965 to $267/10^5$ (244–291) in 2010. Non-stricturing and non-penetrating disease at diagnosis increased from 12.5% in 1963–1965 to 82.3% in 2006–2010 ($p < 0.0001$).

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Conclusion: The incidence of CD increased over time, although it seemed to be plateauing during the most recent decades. A striking increase in non-stricturing, non-penetrating disease at diagnosis was observed, suggesting earlier diagnosis or phenotypic change. The observed point prevalence in 2010 is among the highest reported.

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1. Introduction

An increasing incidence of Crohn's disease has been reported since the mid-1900s, especially in Northern Europe and North America. A recent meta-analysis points towards continuous increase in the incidence of Crohn's disease even beyond 1980 in the majority of studies throughout the world. However, a plateau or even declining incidence has been observed in some of the high-incidence cohorts. These observations suggest that the incidence may soon level off in some of the areas with early rising incidence rates.

Although clinically Crohn's disease is regarded as one diagnosis, the diagnostic entity comprises a broad clinical spectrum. Progression to complicated disease behaviour, i.e. stricturing and penetrating disease, has been reported in a high proportion of patients with non-stricturing, non-penetrating disease, and is associated with an increased need for surgical interventions and poor quality of life. Modern therapy algorithms aim to rapidly achieve and maintain clinical and endoscopic remission and in theory, this strategy can reduce progression to complicated disease behaviour and need of surgery. Diagnostic delay has also been associated with increased risk for progression to stricturing disease and surgery. However, longitudinal data regarding diagnostic delay in the diagnosis of Crohn's disease are sparse. Retrospective assessment of diagnostic delay is difficult, since self-reported data on onset of symptoms might be influenced by recall bias. Yet, non-stricturing, non-penetrating disease represents a plausible marker of early disease, since it most often represent a temporary disease status. However, if there has been a temporal trend in the proportion with non-stricturing, non-penetrating disease at diagnosis remains unknown.

In a previous study from our catchment area, Lindberg et al. reported incidence and prevalence rates over the period 1963–1987. We re-extracted all information on patients diagnosed with Crohn's disease between 1963 and 1987, and extracted data on patients diagnosed with Crohn's disease from 1st of January 1988 up to 31st of December 2010. Our aim was to study temporal trends over the almost five decades long observation period. More specifically, we wanted to assess trends in incidence, prevalence and disease phenotype at diagnosis.

2. Material and methods

2.1. Study area and population

The primary catchment area of Örebro University Hospital covers 3998 km² and includes five municipalities. The population lives in a mix of urban and rural settings. The number of inhabitants increased from 164 972 in 1987 to 189 603 in 2010, with an average of 51.1% of the population being women. In addition to Örebro University hospital there are 17 primary health care clinics, some private general practitioners but no private gastroenterologists within the area. Since the late 1970s cases with inflammatory bowel disease (IBD), suspected or verified, have been referred to the hospital. All colonoscopy procedures within the catchment area were performed at the Endoscopy unit, Örebro University Hospital and all histopathological examinations were performed by the Department of Pathology of the same hospital. Information about the age and sex distributions of the general population in the catchment area was obtained from Statistics Sweden.

The Uppsala Regional Ethics Committee approved the study (2010/304).

2.2. Patient population

Patients of all ages with a potential diagnosis of Crohn's disease were identified retrospectively by evaluation of medical notes of all present and previous patients at the Colitis Clinic, Department of internal medicine, Örebro University Hospital. In addition the ICD10 codes: K500-K509; Crohn's disease, K528-K529; colitis UNS, M074-M076, IBD associated arthropathy, M091-M092, IBD associated juvenile arthritis and the ICD9 codes: 555; regional enteritis, 556; ulcerative colitis, and 558, other and unspecified non-infectious gastroenteritis and colitis were searched for in the county council’s computerised inpatient, outpatient and primary care records, covering diagnoses since 2000, and Örebro University Hospital’s old local computerised records, covering inpatients and outpatients between 1988 and 2000. The old local computerised records were linked with the histopathological records at the Department of Pathology, Örebro University Hospital (search terms; Crohn’s disease, inflammation, fistula or ulcer in gastric, small bowel, large bowel or rectal mucosa).

2.3. Diagnostic criteria and measures

The medical notes of all patients with potential Crohn’s disease were reviewed by YZ to verify the diagnosis. Patients were included if they lived within the catchment area at any time during their disease course, were diagnosed between 1963 and 2010 and fulfilled the Lennard–Jones criteria for Crohn’s disease. Records for patients where diagnosis was uncertain were jointly reviewed by YZ, CT and JH.

Date of the diagnosis was defined as the date of the first examination consistent with Crohn’s disease. In patients where the diagnosis had been changed from ulcerative
colitis or IBD-unclassified to Crohn’s disease the date of the first IBD diagnosis was used. In any patient where precise date of diagnosis could not be obtained retrospectively, the date was approximated to the 15th of the month where possible, otherwise to the 30th of June of the year of diagnosis. Location and behaviour of the disease were defined in all patients according to the Montreal classification. Thus, data for patients diagnosed during the previously reported period, 1963–1987, were re-extracted for information on diagnosis and disease phenotype. We have previously reported patients diagnosed with IBD during 2010 as a part of the European Crohn’s and Colitis Organisation’s (ECCO) Epidemiological Committee (EpiCom) inception cohort. Patients with Crohn’s disease within this cohort were included among patients diagnosed 1988–2010 in the present study.

2.4. Statistical analysis

Age at diagnosis is presented as median and range. Incidence rates were calculated as crude (all ages) and age standardised aggregated over 5-year periods by the direct method to allow for a changing population age structure over time. The age and sex characteristics of the Örebro population for each year of the study period were used for standardisation, while the Örebro population for 1999 was used as the standard comparison population. The 95% confidence intervals (CI) of the incidence rates were computed assuming a Poisson distribution. Time-trends in incidence were assessed using Poisson regression models. Possible temporal clusters in incidence rates were prospectively analysed based on discrete Poisson model analysis with a time aggregation length of five years, adjusted for age and sex, using SaTScan v 9.3 for Windows (http://www.satscan.org). The chi-squared test was used to compare sex distributions as well as distribution of disease phenotypes within patient population in 5-year periods. Point prevalence was calculated for the end of each 5-year period. Stata version 12 SE for Windows (Stata Corporation, College Station, TX) was used for these analyses.

3. Results

One thousand and twenty-six potential cases of Crohn’s disease were identified by assessment of all current and previous patients at the Colitis clinic, department of internal medicine, Örebro University Hospital and by computerised search within the inpatient, outpatient and primary care records as well as histopathological records. In total, 786 of the 1026 potential cases fulfilled the diagnostic criteria, and of these 535 were diagnosed between 1963 and 2010 as incident cases, i.e. living within the catchment area of Örebro University Hospital at the time of Crohn’s disease diagnosis. The remaining 240 cases were excluded due to diagnoses other than Crohn’s disease (ulcerative colitis; n = 15, inflammatory bowel disease unclassified; n = 31, microscopic colitis; n = 1, non-IBD diagnoses; n = 193).

Of the 535 incident cases, 285 were female, yielding a female to male ratio of 1.1:1. The difference in sex distribution (adjusted for age) was not statistically significant (p = 0.7).

3.1. Incidence rates by 5-year periods over 1963–2010

Crude and age standardised incidence rates (IR) in 5 year study periods for the entire study period are shown in Table 1. Incidence rate ratios (IRR) increased with time, when comparing IR over the 5 year intervals (Supplement Table 2). Trend analysis, using Poisson regression models, revealed statistically significant linear and quadratic trends with increasing incidence rate estimates over time, although the estimates successively levelled off. A SaTScan model revealed a statistically significant high incidence during 1991–2010 (p = 0.0001). The sex distribution over the 5-year intervals did not vary within the patient population. However the age distribution varied significantly (p < 0.0001) and median age at diagnosis increased with time. Especially the incidence of Crohn’s disease, A1 and A3 appears to increase over time (Fig. 1).

3.2. Disease phenotypes at diagnosis

Information regarding disease location and behaviour at diagnosis was available in 534 (99.8%) and 532 (99.4%) patients, respectively. Disease characteristics at diagnosis according to the Montreal classification for patients diagnosed within each 5-year period are presented in Supplement Table 1. Age distribution varied significantly over time (Chi2 = 64.6, DF = 18, p < 0.0001). An increasing proportion of A3, i.e. patients diagnosed >40 years of age, was observed between 1963 and 2010 (Fig. 2, panel a). The proportion of patients in the A3 category increased from 0% in 1963–1965 to 32.3% in 2006–2010. Disease location at diagnosis in 5-year intervals appears rather stable during the 47-year period (p = 0.086), especially during the later decades (Fig. 2, panel b). Sex was not associated with disease location (data not shown). The proportion of patients with non-stricturing, non-penetrating disease (B1) at diagnosis increased from 12.5% in 1963–1965 to 82.3% in 2006–2010 (Fig. 2, panel c). That is a statistically significant increase by 69.8% (95% CI for the difference is 44.9% to 94.6%, p < 0.0001).

3.3. Point prevalence by 5-year periods

The point prevalence of Crohn’s disease gradually increased in the Örebro catchment area from 21/105 (95% CI, 14–32) on the 31st of December 1965 to 267/105 (244–291) on the 31st of December 2010. On 31 December 2010, 506 patients with Crohn’s disease lived in the area, and corresponding point prevalence figures for men and women were 236/105 (206–269) and 297/105 (263–333), respectively. Age standardised incidence rates in 5-year study periods and point prevalence at the end of each 5-year study period are shown in Fig. 3.

4. Discussion

This population based study revealed possible plateauing in the incidence of Crohn’s disease during the last decades following an initial increase. We also observed an increased proportion of patients diagnosed with non-stricturing and
Table 1. Crude and age-standardised incidence rate of Crohn’s disease per 100,000 inhabitants (with 95% CI) aggregated over 5-year periods by direct method.  

<table>
<thead>
<tr>
<th>Period</th>
<th>Males and females</th>
<th>Males</th>
<th>Females</th>
<th>Males and females</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of incident CD cases</td>
<td>No. of incident CD cases</td>
<td>Age-standardised IR (95% CI)</td>
<td>Age-standardised IR (95% CI)</td>
<td>Age-standardised IR (95% CI)</td>
<td>Age-standardised IR (95% CI)</td>
</tr>
<tr>
<td>1963-1965</td>
<td>20.5</td>
<td>2.4 (0.7-6.0)</td>
<td>2.1 (0.6-3.6)</td>
<td>23 (0.1-9.4)</td>
<td>2.4 (0.7-6.0)</td>
<td>2.1 (0.6-3.6)</td>
</tr>
<tr>
<td>1966-1970</td>
<td>23</td>
<td>4.6 (1.9-7.4)</td>
<td>4.3 (1.3-7.1)</td>
<td>36</td>
<td>4.6 (1.9-7.4)</td>
<td>4.3 (1.3-7.1)</td>
</tr>
<tr>
<td>1971-1975</td>
<td>25.5</td>
<td>4.8 (2.5-7.9)</td>
<td>4.6 (1.9-7.6)</td>
<td>35</td>
<td>4.8 (2.5-7.9)</td>
<td>4.6 (1.9-7.6)</td>
</tr>
<tr>
<td>1976-1980</td>
<td>27</td>
<td>5.1 (2.5-8.8)</td>
<td>4.9 (2.3-7.6)</td>
<td>37</td>
<td>5.1 (2.5-8.8)</td>
<td>4.9 (2.3-7.6)</td>
</tr>
<tr>
<td>1981-1985</td>
<td>28</td>
<td>5.3 (2.6-8.2)</td>
<td>5.1 (2.4-7.9)</td>
<td>32</td>
<td>5.3 (2.6-8.2)</td>
<td>5.1 (2.4-7.9)</td>
</tr>
<tr>
<td>1986-1990</td>
<td>37</td>
<td>6.4 (3.4-9.6)</td>
<td>6.2 (3.2-9.5)</td>
<td>39</td>
<td>6.4 (3.4-9.6)</td>
<td>6.2 (3.2-9.5)</td>
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<tr>
<td>1991-1995</td>
<td>38</td>
<td>6.9 (4.4-10.3)</td>
<td>6.6 (3.9-10.0)</td>
<td>32</td>
<td>6.9 (4.4-10.3)</td>
<td>6.6 (3.9-10.0)</td>
</tr>
<tr>
<td>1996-2000</td>
<td>41</td>
<td>7.2 (4.7-11.3)</td>
<td>6.9 (4.3-10.3)</td>
<td>34</td>
<td>7.2 (4.7-11.3)</td>
<td>6.9 (4.3-10.3)</td>
</tr>
<tr>
<td>2001-2005</td>
<td>42</td>
<td>7.5 (4.9-11.3)</td>
<td>7.3 (4.7-11.3)</td>
<td>34</td>
<td>7.5 (4.9-11.3)</td>
<td>7.3 (4.7-11.3)</td>
</tr>
<tr>
<td>2006-2010</td>
<td>43</td>
<td>7.8 (5.0-12.2)</td>
<td>7.5 (4.8-11.1)</td>
<td>35</td>
<td>7.8 (5.0-12.2)</td>
<td>7.5 (4.8-11.1)</td>
</tr>
</tbody>
</table>

**Note:** Örebro population in 1999 was used as standard population.  

**a** Median age at diagnosis of persons with Crohn’s disease.
progression to stricturing disease and increased need of surgery.\(^7\) In addition, the possibility to achieve endoscopic remission, and thereby improved long-term prognosis, seems to be greater in patients with shorter disease duration.\(^{20,21}\) However, information on date of onset of symptoms was incomplete, due to the retrospective design. The incomplete information was particularly pronounced in patients diagnosed in the earlier years of the study. This problem is illustrated by the limited amount of contemporaneous information on awareness of Crohn’s disease, including patient’s and doctor’s delay, in the literature.\(^{22-25}\) Non-stricturing, non-penetrating disease represents a plausible marker of early disease, although it may also present variation in disease phenotype. Interestingly, we observed a striking increase in non-stricturing, non-penetrating disease during the years 1963–2010. More than 80% of the patients had non-stricturing, non-penetrating disease at diagnosis during the last years of the observation period. This figure is consistent with a recently reported data from the Uppsala region of Sweden, as well as from the

![Figure 1: Age-specific incidence rate of Crohn’s disease, A1, A2 and A3, per 100,000 inhabitants, 1963–2010. A1; below ≤ 16 years old, A2; between 17 and 40 years old, A3; above ≥ 40 years old.](image)

![Figure 2: Disease phenotype at diagnosis 1963–2010. A1; below ≤ 16 years old, A2; between 17 and 40 years old, A3; above ≥ 40 years old, L1; ileal, L2; colonic, L3; ileocolonic, L4; isolated upper gastrointestinal, B1; non-stricturing non-penetrating, B2; stricturing, B3; penetrating.](image)
ECCO-EpiCom European inception cohort.12,26 This temporal trend suggests that patients are diagnosed earlier in their disease course today than in the past and it can be hypothesized that this could have improved treatment outcomes in the recent years. This is supported by the observed decreasing diagnostic delay in Denmark, a country with a health care system similar to Sweden.27,28 In contrast to some previous studies we did not observe an increase in the proportion of colonic disease at diagnosis over time.29,30 However, the literature is inconsistent and a stable phenotypic profile over time in terms of disease location at diagnosis has been reported.16 In addition, disease behaviour has not been included in several of the previous studies and it can be questioned if reported temporal trends in disease location at diagnosis reflect a shift in disease behaviour rather than a true change in disease location at diagnosis.

Another strength of our study is the inclusion of all patients with Crohn’s disease, irrespective of age at diagnosis. We observed an increasing incidence and proportion of patients diagnosed at age ≥ 40 years during the study period. These findings are supported by a recent data in other cohorts.31-33 Similarly, the incidence of Crohn’s disease, A1 (paediatric Crohn’s disease) rose over time, although the proportion of patients diagnosed at an age ≤ 16 years did not increase. The observed rise in incidence of paediatric Crohn’s disease is supported by several recent reports on paediatric Crohn’s disease,34,35 including data from Sweden,19,36 although the literature is inconsistent.31,37

The retrospective design is a potential limitation of the study. To limit the influence of possible information bias, assessment of all case notes at the Colitis clinic, Örebro University Hospital was amended by identification through computerised system. The histopathological records were included in this computerised search, as there was no single source of electronic records that covered the entire study period. Yet, the retrospective design might have introduced selection bias, since the computerised systems covered patients from 1988 only and early indolent cases with a single episode of inflammation might more easily have been overlooked. Furthermore, the improved diagnostic methods might have introduced a time dependent bias in terms of disease phenotype at diagnosis. Primarily this would influence assessment of location (temporal trends were not seen in our study) but less likely to influence assessment of non-stricturing, non-penetrating behaviour, which we observed to vary over time. The absence of information about immigrants is another potential limitation of the study. It is difficult to predict how migration would influence the results since an increased incidence of IBD has not been observed in first generation immigrants but there may be an increase among second-generation immigrants.38,39 It seems unlikely that immigrants without a previous diagnosis would have increased the proportion of Crohn’s disease, B1 over time. Conversely, a diagnostic delay would have increased the proportion of Crohn’s disease, B2 and B3, and could theoretically influence the age at diagnosis and contribute to the observed increasing proportion of Crohn’s disease, A3. The analyses of Crohn’s disease in one county only, and the limited number of inhabitants in our primary catchment area, are two further possible limitations of the study. Therefore, possible geographic variations within Sweden cannot be ruled out and some of the statistical analyses might lack power, due to the low number of patients with some Crohn’s disease characteristics within our catchment area. In line with current recommendations,40 we applied Lennard–Jones criteria for the diagnosis of Crohn’s disease in this study,10 in contrast to our previous study where Garland diagnostic criteria were used.8,41 In short, criteria of Garland classify patients into: definite, probable and possible Crohn’s disease, depending on findings for histology, endoscopy and radiology as well as the discharge diagnosis, where only
definite and probable diagnoses were included in our previous study. To our knowledge there are no direct comparisons between the criteria of Garland and the Lennard–Jones criteria. However, definite and probable Crohn's disease according to the criteria of Garland seem to depend more on histological and surgical findings and pay less attention to the overall clinical picture compared to that of Lennard–Jones criteria. We could not identify individual patients that were included in the previous study, since the raw data are no longer available. Therefore, all data from the previously reported study period (1963–1987) had to be re-extracted. The difference in patient identification procedures, diagnostic criteria, access to demographic information and length of the observation period influenced the observed point prevalence value. Lindberg et al. reported a point prevalence of 146 per 10⁵ individuals in 1987, which is somewhat lower than our figure for the same year.

In conclusion, we observed an increasing incidence of Crohn's disease in the Örebro catchment area, although the incidence rate seemed to be plateauing during the most recent decades. The incidence figures were notably higher among those aged 40 years and above as well as among paediatric Crohn's disease. An increasing proportion of patients were diagnosed with non-stricturing, non-penetrating disease over time, possibly suggesting that patients with Crohn's disease are diagnosed in an earlier point in the disease course than in previous years, alternatively it may reflect the change in disease phenotype. The observed point prevalence in 2010 is among the highest reported.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2014.07.006.

Conflict of interest
None.

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