Introduction

Crohn’s disease (CD) is a progressive disease characterised by chronic transmural inflammation in the gastrointestinal tract that may cause chronic diarrhoea, strictures and abscesses. The disease course is heterogeneous and varies from an indolent disease with a few flares to a severe course with repeated surgery.

Previous studies suggest that CD mortality rates may range from 30% lower [1] to 70% higher [2,3] than in the general population and that CD survival may have improved over time [4–10]. Few studies, however, have examined temporal trends in CD survival in the ‘modern era’ of targeted therapies. A recent study by Olen et al. found that inflammatory bowel disease (IBD) related deaths have declined over time [11]. However, given that patients with Crohn’s disease were identified from the International Classification of Diseases (ICD) codes, it is unknown if the study findings are applicable to all phenotypes of Crohn’s disease.

We conducted a regional, population-based study with the aim to assess the 10-year survival in patients diagnosed with Crohn’s disease during 1963–2010 compared with the general population of the same demographic structure and to identify factors associated with excess mortality. We estimated all-cause mortality and Crohn’s disease-specific mortality and also examined whether Crohn’s disease-specific survival had changed over three predefined diagnostic periods.
Materials and methods

Study population and setting

We identified all incident patients diagnosed with CD between January 1, 1963, and December 31, 2010 within the Örebro University Hospital primary catchment area, [12] comprising 189603 inhabitants in the year 2010. The diagnosis was confirmed by evaluation of medical notes. The cohort and the study region have been described in detail previously [12,13]. Briefly, information about sex, date of birth, date of diagnosis, disease location, and clinical characteristics according to the Montreal classification [14] were extracted from the IBD cohort database of Örebro University Hospital and from medical records. A total of 494 patients with CD were identified, of whom two were excluded from the current study due to missing information on disease behaviour.

Mortality and follow-up

Information on the date and the underlying cause of death was obtained from the Cause of Death Register [15] using each patient’s unique personal identity number. Patients were followed from the date of diagnosis until death, emigration, or end of follow-up on December 31, 2011, whichever occurred first.

Statistical analysis

Patient characteristics were tabulated by calendar period of diagnosis and compared using the \( \chi^2 \) test, Fisher exact test, or median test as appropriate based on measurement type and distribution. The calendar periods were chosen in order to obtain a more even patient distribution and to facilitate detection of effects on survival resulting from changes in diagnostic criteria and treatment of CD.

The investigated measures of survival and mortality included: overall survival, net survival, relative survival ratio (RSR), and crude mortality due to Crohn’s disease as well as due to other causes.

Since survival strongly depends on age, Kaplan–Meier estimates of overall survival (the probability that a patient is still alive at a certain time point after CD diagnosis) were computed by age groups (<17, 17–39, 40–59, 60–69, and ≥70 years at diagnosis). Net survival, the probability of survival where CD is the only possible cause of death, was estimated using the Pohar Perme estimator of net survival [16]. Crude probabilities of dying of CD or other causes, which take competing risk of death into account, were estimated using the Cronin and Feuer method [17]. While crude probabilities of death could be more informative for patients and clinicians, net survival (or net mortality, which is 1 minus net survival) was used to compare the Crohn’s disease-specific survival across the three diagnostic periods. As it is unaffected by hazard due to other causes, net-survival is the recommended measure for comparing disease-specific survival of different populations defined according to time period, geography, or other characteristics. Since net survival generally depends on age at diagnosis, we computed age-stratified and age-standardised estimates.

Relative survival ratio (RSR), a measure of total excess mortality associated with a diagnosis of CD, compares the overall survival of the CD patients to the expected overall survival in a disease-free but otherwise comparable general population [17]. Cumulative expected survival was estimated using Swedish general population life-tables matched to the CD cohort by age, sex, and calendar year applying the Ederer I method [16,17]. Relative survival analysis was stratified by sex due to inherent sex-based differences in death rates. An RSR of 1.00 implies that the survival of CD patients is just as good or as poor as that of the reference population. An RSR <1.00, indicates a worse survival than expected, and it is assumed that the excess mortality is due to the disease under the study. An RSR >1.00 is observed if the patient group has a lower mortality rate than that expected. A generalised linear model with a Poisson error structure [17,18] was used to model the effect of age at diagnosis, sex, calendar year at diagnosis, as well as disease location and behaviour on the excess mortality rate ratio (EMRR). The analysis was restricted to patients aged ≥40 at diagnosis.

All calculations were performed using STATA software version 14SE (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The study was approved by the Uppsala Regional Ethics Committee (2010/304 and 2010/304/1).

Results

Characteristics of the patients with Crohn’s disease

Basic demographics and clinical characteristics of the patients with Crohn’s disease (n = 492: 226 men and 266 women) are shown in Table 1. Compared with patients diagnosed during the earlier calendar period of 1963–1985, patients diagnosed between 1986–2010 had a higher median age at diagnosis and were more likely to have inflammatory (B1) disease behaviour.

Survival and mortality estimates

In over 4,075 person-years of follow-up, 30 patients (13 men and 17 women: 6.1%) with Crohn’s disease died. The leading cause of death was cardiovascular disease followed by complications of Crohn’s disease (Supplementary Table 5). The observed 10-year overall survival was 100% for patients aged <17 years at diagnosis, 99% for patients aged 17–39 years, 94% for patients aged 40–59 years and 76% for patients aged 60–69 (Figure 1). Patients aged 70 or above at diagnosis (Figure 1) had the lowest overall survival (35%) with a median survival of 7.9 years. Ten-year overall survival improved over the three calendar periods for both younger and older male and female patients (Table 2).

The 10-year net survival tended to decline with increasing age, and women had higher net and crude probabilities of dying of CD than men (Figure 2, Table 2).
Temporal trends of Crohn’s disease-specific survival

The ten-year net survival estimate was worse for patients diagnosed during 1963–1985 compared with patients diagnosed during 1986–1999 or 2000–2010 (Table 2, Figure 3), indicating that Crohn’s disease-specific survival improved over time.

Relative survival ratio and excess mortality

The overall survival of CD patients was almost equal to that in the general population during the first 10 years of follow-up (RSR = 0.98; 95% CI: (0.95–1.00)). However, the survival of female patients aged ≥60 years at diagnosis was lower than expected, particularly during the first calendar period (1963–1985) (Table 3).
Table 2. Crude and net probability of death by sex and age for patients diagnosed with Crohn’s disease in 1963 to 2010 in Örebro, Sweden.

| Calendar period of diagnosis | Sex and age of the patients | Net probability of death | Crude probability of death due to CD | Crude probability of death due to other causes |
|-----------------------------|-----------------------------|--------------------------|--------------------------------------|-----------------------------------------------|
| 1963–2010                   | All, aged 40–59              | 0.012                    | 0.011                                | 0.050                                         |
|                             | All, aged 60–69              | 0.061                    | 0.059                                | 0.180                                         |
|                             | All, aged ≥70                | 0.380                    | 0.292                                | 0.362                                         |
|                             | Men, aged 40–59              | −0.013                   | −0.014                               | 0.060                                         |
|                             | Women, aged 40–59            | 0.034                    | 0.034                                | 0.031                                         |
|                             | Men, aged 60–69              | −0.069                   | −0.068                               | 0.248                                         |
|                             | Women, aged 60–69            | 0.191                    | 0.183                                | 0.111                                         |
|                             | Men, aged 70+                | 0.230                    | 0.227                                | 0.374                                         |
|                             | Women, aged 70+              | 0.476                    | 0.339                                | 0.354                                         |
| 1963–1985                   | All, aged 40–59              | 0.061                    | 0.054                                | 0.059                                         |
|                             | All, aged 60+                | 0.462                    | 0.405                                | 0.195                                         |
|                             | Men, aged 40–59              | 0.031                    | 0.023                                | 0.082                                         |
|                             | Women, aged 40–59            | 0.091                    | 0.087                                | 0.032                                         |
|                             | Men, aged 60+                | 0.336                    | 0.246                                | 0.254                                         |
|                             | Women, aged 60+              | 0.545                    | 0.512                                | 0.155                                         |
| 1986–1999                   | All, aged 40–59              | −0.011                   | −0.010                               | 0.048                                         |
|                             | All, aged 60+                | 0.121                    | 0.084                                | 0.298                                         |
|                             | Men, aged 40–59              | −0.026                   | −0.024                               | 0.062                                         |
|                             | Women, aged 40–59            | 0.004                    | 0.005                                | 0.034                                         |
|                             | Men, aged 60+                | 0.085                    | 0.088                                | 0.296                                         |
|                             | Women, aged 60+              | 0.176                    | 0.086                                | 0.301                                         |
| 2000–2010                   | All, aged 40–59              | −0.017                   | −0.015                               | 0.041                                         |
|                             | All, aged 60+                | 0.073                    | 0.070                                | 0.202                                         |
|                             | Men, aged 40–59              | −0.066                   | −0.063                               | 0.063                                         |
|                             | Women, aged 40–59            | 0.014                    | 0.015                                | 0.027                                         |
|                             | Men, aged 60+                | −0.177                   | −0.133                               | 0.276                                         |
|                             | Women, aged 60+              | 0.331                    | 0.282                                | 0.129                                         |

The estimates are for patients diagnosed after 40 years of age at 10-year follow-up time. The age groups 60–69 and 70+ have been pooled together due to sparsity of patients aged 70+ in the earlier diagnostic period. Negative values may happen when the reference mortality rates are from a population with worse general mortality than the cohort of patients under study. Ten-year all-cause mortality was split into the probability of dying from Crohn’s disease and from other causes.

Figure 2. Overall, net and crude probability of death at 10 years from diagnosis with respect to sex and age for patients diagnosed with Crohn’s disease in 1963 to 2010 in Örebro, Sweden.
After adjusting for age, sex, disease location and behaviour, as well as years of follow-up, there is some evidence that patients diagnosed during 1986–1999 and 2000–2010 experienced 60% and 64% lower excess mortality respectively compared with patients diagnosed during 1963–1985 (Table 4). Older age, female sex, colonic localisation compared with ileal localisation, and stricturing/penetrating disease behaviour compared with inflammatory disease behaviour seemed to be associated with excess mortality. However, statistical significance was reached only for age at diagnosis. The estimated excess mortality rate for patients aged 60 years or above at diagnosis was 8.0 times higher than that of patients aged 40–59 years at diagnosis.

**Discussion**

In this population-based, regional cohort, we found that both overall and Crohn’s disease-specific survival was worse for patients diagnosed with CD during the earlier (1963–1985) calendar period than for patients diagnosed later. Crohn’s disease-specific survival declined with increasing age at diagnosis and was poorer for female patients. The 10-year overall survival of CD patients was largely similar to that in the general population but was reduced in older female patients, particularly in those diagnosed during the 1963–1985 calendar period. The multivariable-adjusted Poisson regression model suggested that earlier diagnostic period, older age, female sex, colonic location, and stricturing/penetrating disease behaviour may be associated with excess mortality, although statistical significance was reached only for older age.

Mortality has been examined in numerous studies of Crohn’s disease, but the findings regarding Crohn’s disease mortality are inconsistent in the existing literature [19]. Inconsistent findings may in part be explained by
Table 4. Excess mortality ratios during the first 10 years after Crohn's disease diagnosis stratified by calendar period of diagnosis, age group, sex, disease location and behaviour.

| Variable                          | Excess Mortality Rate Ratio (95% CI) | p Value |
|-----------------------------------|-------------------------------------|---------|
| **Diagnostic period**             |                                     |         |
| 1963–1985                         | Reference                           |         |
| 1986–1999                         | 0.40 [0.07-2.14]                    | .285    |
| 2000–2010                         | 0.36 [0.07-1.96]                    | .236    |
| **Sex**                           |                                     |         |
| Male                              | Reference                           |         |
| Female                            | 4.16 [0.62-27.85]                   | .142    |
| **Age at diagnosis, years**       |                                     |         |
| ≥60                               | Reference                           |         |
| 40–59                             | 7.99 [1.64-39.00]                   | .010    |
| **Disease location**              |                                     |         |
| Ileal (L1)                        | Reference                           |         |
| Colonic (L2)                      | 4.20 [0.81-21.88]                   | .088    |
| **Disease behaviour**             |                                     |         |
| Inflammatory (B1)                 | Reference                           |         |
| Strictures or penetrating (B2, B3)| 2.56 [0.52-12.58]                   | .248    |

Analysis was limited to patients aged 40 or above at diagnosis. Disease location and behaviour are classified according to Montreal classification system. Estimates are not available for ileocolonic (L3) and for isolated upper gastrointestinal (L4). CI: confidence interval.

methodological differences, differences in diagnostic criteria [20], variations in degree of selection bias, and possible temporal changes in disease severity and survival.

The overall survival observed in our study population was comparable to that reported from similar population-based cohorts of CD patients [2,5,7,21]. We found that, compared with the 1963–1985 diagnostic period, disease-specific survival improved during the 1986–1999 and 2000–2010 calendar periods. The Swedish nationwide population-based cohort study also suggested that IBD-related deaths have declined over time [11]. The early period is known for the extensive use of surgical resections [22], and excess mortality early after diagnosis [23]. Advances in medical and surgical therapies probably contributed to these findings [24]. Changes in disease severity [12] and diagnostic criteria [20], as well as decreasing proportion of patients progressing to complications [25] could all contribute to the improvement of disease-specific survival over time.

Some previous studies suggested lower [1], while others found higher than expected [2,3] mortality rates in CD patients as compared with the general population. A study by Munkholm [26] did not show excess mortality during the first 10 years after diagnosis. However, an excess mortality was noted over a longer follow-up time. In a study by Olen et al., Crohn’s disease patients diagnosed between 1964–2014 and identified from the national patient register using ICD codes had a higher mortality rate compared with the general population controls [11]. While we confirmed all cases with Crohn’s disease by a review of medical records, some cases in the nationwide Swedish study may not have fulfilled the diagnostic criteria for Crohn’s disease since a previous validation study reported a positive predictive value of 97% when defining Crohn’s disease from ICD codes [27]. Overall, the survival of CD patients in our study was similar to that in the general population during the first 10 years of follow-up, which could partly be due to a high proportion of patients diagnosed under the age of 60 years. Our further analysis; stratified by calendar period of diagnosis, age, and sex; suggested lower than expected survival for female patients aged ≥60 years at diagnosis, particularly if diagnosed during the 1963–1985 calendar period. Estimates from our multivariable-adjusted regression model also suggested that the earlier diagnostic period (1963–1985), older age at diagnosis, female sex, and potentially colonic location and stricturing/penetrating disease behaviour may be independently associated with disease-related excess mortality. Some previous studies have also linked female sex [7,28] and colonic disease at diagnosis [7,21] with poorer survival, while existing data on disease behaviour is more ambiguous. Some studies found that inflammatory disease behaviour was associated with increased mortality risks [7], and that stricturing/penetrating disease was not associated with decreased survival [29]. Others found no difference in disease behaviour between deceased CD patients and survivors [8].

This study has several strengths but also some weaknesses. The strengths of this study include the use of prospectively collected data from medical records, which ensured the inclusion of all patients diagnosed with CD in the specified period and the availability of clinically relevant information. We followed patients using national registers, which enabled a virtually complete follow-up. We applied various measures of survival, which provided different but complementary information and thus a complete picture of CD survival in a given population. Since the cause of death can be misattributed in death certificates, we estimated CD-related survival using relative survival methodology, which does not depend on the cause of death information (the information on underlying cause of death was included only for descriptive purposes). Our study, however, was limited by the small number of patients. Small sample size may increase the impact of unmeasured confounding factors. Due to the low number of events in the predominantly young patient population, statistical power was limited for some analyses, and we could not formally assess statistical significance of possible interaction effects in the regression model. As CD patients are more often smokers compared to general population, the difference between all-cause mortality between CD patients and the general population could be inflated by deaths caused by smoking (cardiovascular disease, cancers, etc). Disease location and behaviour were assessed at diagnosis using medical notes, and changes over time were not taken into account, as this would create even more subgroups with fewer cases.

In conclusion, we found that Crohn’s disease-specific survival improved over time. Overall, the 10-year survival of patients diagnosed with Crohn’s disease during 1963–2010 was almost equal to that of the comparable general population. However, older female patients, particularly women diagnosed in the 1963–1985 calendar period, had worse than expected survival. Earlier diagnostic period, older age, female sex, colonic disease, and complicated disease behaviour at diagnosis seemed to be associated with excess CD-related mortality in the multivariable-adjusted regression model.
Acknowledgements
The authors thank David Anderson for language editing.

Ethics approval
The study was approved by the Uppsala Regional Ethics Committee (2010/304 and 2010/304/1).

Authorship statement
Guarantor of the article
Yaroslava Zhulina.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Financial disclosures
Jonas Halfvarson served as speaker and/or advisory board member for AbbVie, Celgene, Celltrion, Dr. Falk Pharma and the Falk Foundation, Ferring, Hospira, Janssen, MEDA, Medivir, MSD, Olink Proteomics, Pfizer, Prometheus Laboratories, Sandoz/Novartis, Shire, Takeda, Thermo Fisher Scientific, Tillotts Pharma, Vifor Pharma, UCB and received grant support from Janssen, MSD, and Takeda.

Funding
This work was supported by Örebro University Hospital Research Foundation [grant number OLL-762471].

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