Cost Burden of Crohn's Disease and Ulcerative Colitis in the 10-Year Period Before Diagnosis—A Danish Register-Based Study From 2003–2015

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Background: The diagnostic delay in inflammatory bowel disease (IBD) is well known, yet the costs associated with diagnoses before IBD diagnosis have not yet been reported. This study explored societal costs and disease diagnoses 10 years before Crohn's disease (CD) and ulcerative colitis (UC) diagnosis in Denmark.

Methods: This national register study included patients diagnosed between 2003 and 2015 identified in the Danish National Patient Registry (NPR) and controls who were individually matched on age and sex from the general population. Societal costs included health care services, prescription medicine, home care services, and labor productivity loss. Prediagnostic hospital contact occurring before CD or UC diagnosis was identified using the NPR. Average annual costs per individual were calculated before the patient's first CD or UC diagnosis. A 1-sample *t* test was then applied to determine significance in differences between cases and controls.

Results: Among CD (n = 9019) and UC patients (n = 20,913) the average societal costs were higher throughout the entire 10-year period before the diagnosis date compared with the general population. The difference increased over time and equaled €404 for CD patients and €516 for UC patients 10 years before diagnosis and €3377 and €2960, respectively, in the year before diagnosis. Crohn's disease and UC patients had significantly more diagnoses before their CD and UC diagnosis compared with the general population.

Conclusions: Compared with the general population, the societal costs and number of additional diagnoses among CD and UC patients were substantially higher in the 10-year period before diagnosis.

Key Words: societal costs, inflammatory bowel disease, registry study

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), the 2 main inflammatory bowel diseases (IBDs), are immunologically mediated, debilitating conditions resulting from destructive inflammation of the gastrointestinal tract. The pathogenesis of IBD is not completely understood but is believed to be a result of certain environmental factors, like smoking and diet, in combination with genetic prepositions, infiltration of microbiotic entities, and an abnormal immune response.[1, 2] Inflammatory bowel disease can lead to the development of severe symptoms, requiring hospitalization and/or surgery, and is also associated with a low health-related quality of life (HRQoL).[3] Comorbidities in the form of extraintestinal manifestations (EIMs) are diagnosed frequently in patients

both before and after diagnosis. Extraintestinal manifestations are also believed to impact the HRQoL of patients with IBD, as specific treatment is required, depending on the affected organ(s). Extraintestinal manifestations most frequently affect the joints, skin, hepatobiliary tract, and eyes.[4]

With IBD, a diagnostic delay is common and well known to increase the risk of developing complications such as strictures and a need for surgery.[5–7] The multifactorial reasons for this delay include the initial uncharacteristic symptoms and clinical presentation.[5] Consequently, patients may undergo extensive diagnostic testing with the risk of receiving the wrong diagnosis, thus creating additional costs and impacting society in various ways. A decrease in time from onset of symptoms to CD diagnosis has been reported in previous Danish database cohort studies, with onset to diagnosis being 8.3 months compared with a previous diagnostic time of 2.2 years.[8–11] However, the costs before IBD diagnosis have not yet been evaluated.

The aim of the present study was to investigate the prediagnostic burden of the societal costs of patients diagnosed with IBD. This study further explores the occurrence and the types of diagnoses in pre-IBD-diagnosed patients.

METHODS

Study Population and Study Design

A retrospective population-based study was designed to analyze the costs of Crohn's disease (CD) and ulcerative colitis (UC), respectively, before the patients' first CD/UC diagnosis. Data on all Danish residents were retrieved from the Danish Civil Registration System (CRS),[12] which includes all citizens and residents with a civil personal registration number, enabling an identity-secure linkage of information between the national registries. Patient-specific data were collected from the Danish National Patient Registry (NPR),[13, 14] and data on employment were collected from the Danish Longitudinal Database on Employment (DREAM).[15, 16] As the private health care system constitutes <1% of all the health care provided in Denmark, only residents treated within the public health care system were included.

To include all adult incident CD and UC cases between 2003 and 2015, the following selection criteria were applied: (1) Individuals had to be age >18, with at least 2 hospital contacts (admission, outpatient, or emergency room visit) collected from the NPR during the period 2003–2015, with a primary or secondary diagnosis of CD or UC using the International Classification of Diseases, 10th edition (ICD-10), codes K50 and K51, and at least 1 of the registrations had to be defined as the primary diagnosis. (2) The patient had to have no hospital contacts related to CD or UC during 1994–2002 (wash-out period). (3) Index date was defined as the first hospital contact—admission, outpatient, or emergency room visit—with CD or UC during 2003–2015. (4) Patients initially diagnosed with UC followed by a diagnosis with CD at a later stage were classified as diagnosed with CD. Because UC is more localized than CD,

an initial discovery of inflammation of the large intestine may be diagnosed as UC and followed by a later discovery of inflammation other places in the intestinal tract, thus making the correct diagnosis CD.

One control for each case was randomly selected from the general population via the CRS, matched on age and sex on January 1 of the year of IBD diagnosis. The NPR was then used to ensure that all controls were unexposed to CD or UC. To reduce the risk of introducing bias, we limited the matching criteria to only age and sex. Study participants were followed for up to 10 years before their index date; the earliest was from January 1, 2002.

Costs

Societal costs, including health care services, home care services, prescription medicine, and labor productivity, were all considered. Additionally, telephone consultations and tests ordered via the telephone and their resulting costs were also included whenever they were registered in the patient file.

The Danish National Health Service Register for Primary Care (NHSR) has information on the activities of health professionals contracted with the tax-funded public health care system including general practitioners, practicing medical specialists, physiotherapists, dentists, psychologists, chiropractors, and chiropodists.[15, 17, 18] The NPR contains information on all contacts with the hospital sector, including admissions, outpatient visits, and emergency room visits.[15, 17]

The NPR, including the Danish outpatient (DAGS) and the Diagnosis-Related Group (DRG), contains information on charges and cost estimates at each hospital contact.[17]

Prescription medicine costs were collected from the Register of Medicinal Product Statistics,[15, 17] where all acquisitions from Danish pharmacies are available. Acquisition and unit cost estimates were based on the market price, including patient co-payment and public reimbursement.

Data on municipal services, including individual-level information about weekly allocated home care of home nursing and other services for all age groups, were collected from the Database on Elderly Documentation,[15] available from 2008 onwards. Weekly home service was converted into cost estimates using Statistics Denmark's listed hourly costs for social and health care work in private homes.[19]

Labor productivity value was estimated using weekly employment data from the DREAM database. The DREAM database is owned by the Danish Ministry of Employment and includes information on weekly labor market public transfer payments, for example, unemployment benefits or disability payments for all Danish citizens since 1991.[16] Individuals receiving such a payment are included in the database for the corresponding year, whereas the remaining work force is not included. Individual yearly employment rates were collected from the DREAM database and presented as the annual percentage the individual was working and not working, where working was defined as not receiving transfer payments from the government. The individual

labor productivity value was defined as a product of the share of the year the individual was working and the sex-specific gross average yearly wage, adjusted by the number of effective weekly working hours.[20, 21] The labor productivity value estimations included only individuals considered to constitute the work force between the ages of 18 and 65.

All costs were set to the 2016 price level, and charges in the NHSR, DAGS, and DRG were inflated using the combined price and wage index for health care services by Danish region.[22] Prescription medicine prices were not inflated, as they fluctuate, making price indices difficult to interpret. In 2016, the estimated annual average labor productivity value was €72,411 for men and €54,778 for women. In the present study, all costs are reported in Euros with the following exchange rate: €1 = DKK 7.5.

Statistical Analyses

Average costs for each of the 5 cost types and labor productivity value per individual were calculated on a yearly basis for up to 10 years before the patient's first CD or UC diagnosis. Due to the large number of observations in all categories, a 1-sample *t* test was applied to determine significance in differences between cases and controls. The total difference in the costs between cases and controls was stratified by the 5 contributing types of independent cost components—primary sector, outpatient, hospital admission, prescription medicine, and home care—to explore the contribution of each cost.

The diagnostic codes in the comorbidity analysis, before UC or CD diagnosis, were collected from the NPR and divided into the 21 WHO disease classification groups (ICD10 chapters).[23] Comorbidity before IBD diagnosis was explored using a crude logistic regression analysis to estimate odds ratios (ORs) between cases and controls, with 95% confidence intervals (CIs) for each of the 21 ICD10 disease groups.

All statistical analyses were conducted in SAS, version 9.4 (SAS Institute Inc, Cary, NC, USA), on Statistics Denmark's research computers via a remote server.

ETHICAL CONSIDERATION

The study was register-based and complied with the regulations and instructions set up by the Danish Data Protection Agency (J. nr. 2014-54-0664). We only used anonymized data, we only present data in aggregate and in an anonymous form, and we neither contacted any study participants nor required any active participation from them.

RESULTS

Between 2003 and 2015, 10,302 incident cases of CD and 22,144 incident cases of UC were identified (Fig. 1). In 2015, the number of prevalent cases of CD was 16,737, whereas the number of prevalent cases for UC was 31,337.

As presented in the flowchart, 1283 CD and 1231 UC patients were excluded due to either being younger than 18 at the time of diagnosis or because their identified control died before diagnosis, resulting in a study population
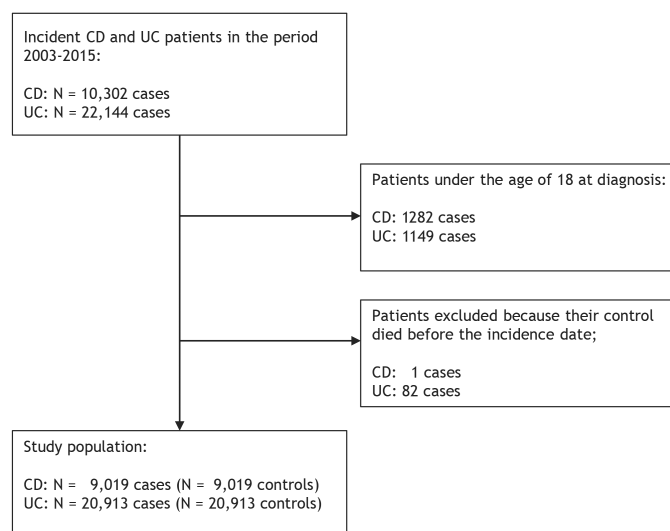
FIGURE 1. Flowchart of study population.

TABLE 1. Characteristics of the Study Populations

	Crohn's Disease	Ulcerative Colitis
Study population, No. cases	9019	20,913
Sex, No. (%)		
Male	3925 (43.5)	9961 (47.6)
Female	5094 (56.5)	10,952 (52.4)
Age at diagnosis, mean (SD), y	42.2 (18.3)	47.5 (18.4)
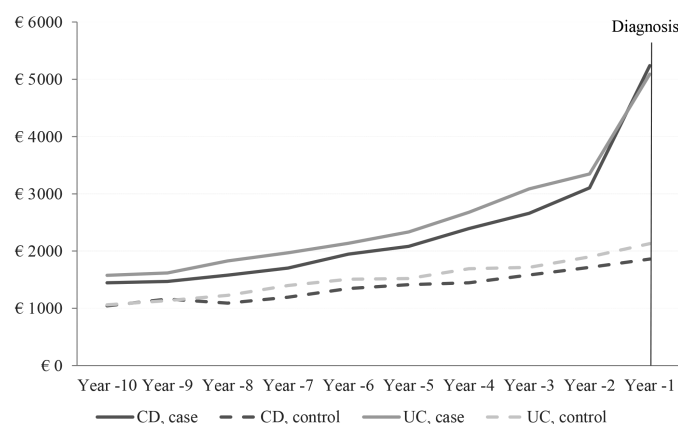
FIGURE 2. Average individual costs during the 10-year period before CD/UC diagnosis.

of 9019 incident CD and 20,913 incident UC cases. Basic study characteristics are shown in Table 1. Overall, 3925 men and 5094 women were included in the CD study population, and 9961 men and 10,952 women were included in the UC study population, with at least 1 day of observation between January 1, 2003, and December 31, 2015. The

average individual health care costs for CD and UC cases were statistically significantly higher compared with controls throughout the entire 10-year period before diagnosis (Fig. 2; Supplementary Tables 1 and 2).

Ten years before the date of diagnosis, average costs of CD patients were 1.4 times higher than those of controls, with the total difference in costs being €405. For UC patients, the costs were 1.5 times higher, with a difference of €516 compared with controls. A peak in costs was observed 1 year before diagnosis, where the average costs of CD patients were 2.8 times higher than in controls, resulting in a difference of €3377. For UC patients, the average costs were 2.4 times higher than controls, with a difference of €2960.

The average annual individual production value for CD controls was higher than that of CD cases during the entire 10-year period preceding diagnosis (Fig. 3). The same was found for UC cases, implying a production loss for both patient groups. For both CD and UC cases, production was at its lowest the year before diagnosis.

The individual annual differences in labor production value and health care costs separated by cost category are presented in Supplementary Tables 1 and 2, spanning 10 years before diagnosis. There was no statistically significant difference in home care costs over time. A statistically significant difference was found overall in the remaining health care cost categories for nearly the entire 10 years before diagnosis. However, this was not the case for CD in hospital admission years 9 and 10 before diagnosis or for labor production value in year 10 before UC patients' diagnosis.

Ten years before diagnosis, 30% of the difference in costs was due to higher hospital costs for CD cases, and 60% for the year before diagnosis (Fig. 4). For UC cases, the values were 51% and 58%, respectively (Fig. 5).

In the comorbidity analysis, CD cases were significantly overrepresented in most disease groups, apart from groups 15–17 and 20, which include pregnancy and birth-related outcomes
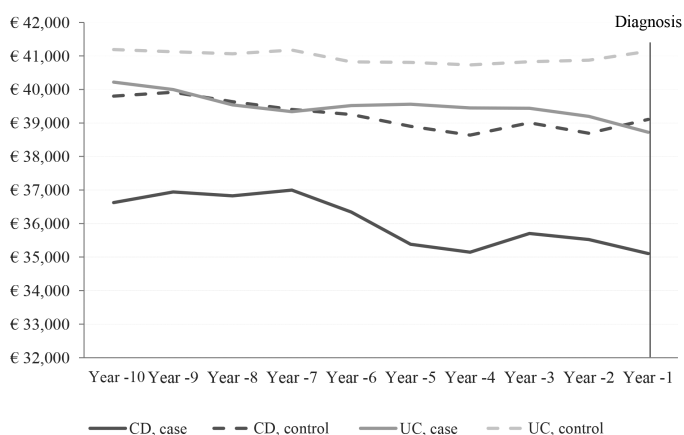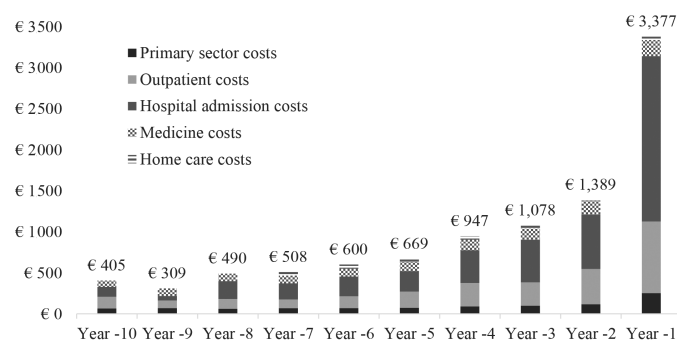
FIGURE 4. Difference in average individual costs between cases and controls by cost type, CD. Prices in Euros 2016.
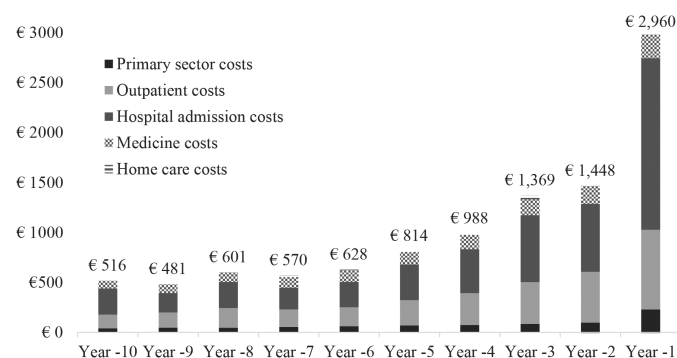
FIGURE 5. Difference in average individual costs between cases and controls by cost type, UC. Prices in Euros 2016.

and external causes of morbidity and mortality (Supplementary Tables 3, 5, and 7). Similar results were found before UC diagnosis, presented in Supplementary Tables 4, 6, and 8.

During the 10 years before CD diagnosis, these patients were almost 6 times more likely than controls to be diagnosed with a digestion-related disease (OR, 5.72; 95% CI, 5.32–6.15). This was also true before UC diagnosis (OR, 5.50; 95% CI, 5.25–5.76). Looking at a shorter time span before diagnosis (2 years or 5 years), the results of overrepresentation of comorbidities among CD and UC patients were confirmed. However, there was generally an increase in the ORs toward the diagnosing point.

DISCUSSION

In the present study, we evaluated the societal cost burden and prior diagnoses patients incurred up to 10 years before IBD diagnosis. The study discovered significantly higher health care costs among CD and UC patients compared with the general population during the entire 10-year period leading up to the date of diagnosis. Additionally, the average labor production values, based on average employment rates, were lower for CD and UC cases. Differences in labor productivity were highly related to sex and average yearly wage, where men tended to have higher gross wages and more women were on benefits.[20, 24] In Figure 3, we see that the average individual labor production values, for both

FIGURE 3. Average individual labor production value before CD/UC diagnosis. Prices in Euros 2016.

cases and controls, were higher in the UC groups compared with the CD groups. Further, patients diagnosed with CD or UC were more likely to have a previous diagnosis related to the digestive system. This could be explained by a diagnostic delay. Previous reports show a diagnostic delay among IBD patients, with the delay being up to 18 months of symptom onset for CD patients and up to 4 months for UC patients.[6, 7] Interestingly, in our study we found that there may in fact be a longer diagnostic delay than what has previously been reported.

The increased number of registered comorbidities in CD and UC patients is difficult to interpret. It is possible that some comorbidity diagnoses are misclassified retrospectively due to the complexity in diagnosing IBD, which our study is not able to evaluate. However, it is most likely that the misclassification of comorbidities, if true, is related to diseases in the gastrointestinal tract. Another explanation is that comorbidity could be more common, due to IBD being a more generalized disease.[25] Of note, due to registration of diagnosis codes at each hospital visit, we were able to identify which diseases were overrepresented in the patient groups compared with controls, providing an indication of hospital cost drivers between cases and controls. These findings also show that EIMs can in fact be common before the diagnosis of IBD and that they may not be due to IBD. This may explain the increased costs seen before diagnosis. Previous reports have also found EIMs up to 25 months before diagnosis.[26]

Several studies have previously explored the direct and indirect costs of CD and UC postdiagnosis.[27, 28] Among patients in 8 European countries, the mean total cost of inflammatory bowel disease care in the first year after diagnosis was €4.404/patient, decreasing to €1.792/patient in the second year.[27] However, cost patterns before diagnosis have still not been explored. The present study showed that hospital sector costs were the main driver of the differences in costs between cases and controls before diagnosis, especially 1 year before diagnosis. Further, CD and UC patients had more contact with the hospital sector, for reasons related to most of the 21 ICD10 disease groups; they also had higher health care costs and a longer absence from work compared with the general population.

The strengths of the present study are the long follow-up period and the large sample size. Additionally, using comprehensive individual-level data enabled us to identify and follow all individuals of interest in this study. The health care registers and employment databases allowed us to assemble a nationwide cohort with accurate longitudinal information. In Denmark, all individuals have equal access to health care and social security services, and most of the health care sector is publicly funded. There are no co-payments in the hospital, but some co-payments are required for certain services in the primary health care sector (eg, psychologists and dental services). The universal health care system diminishes the likelihood of incompleteness of data in the health registries and/or confounding by socioeconomic factors. Furthermore, by using a wash-out period of 9 years, we ensured that the selected population of CD and UC patients were in fact

incident cases. As CD and UC are severe chronic diseases, patients will be in contact with hospitals for the rest of their life, at varying frequencies. If the disease is well treated or in remission, the patient may not be in contact with the hospital for a certain period. Therefore, we used a wash-out period of 9 years to ensure that we found only incident patients in the study period.

There are limitations worth mentioning. The identification of CD and UC patients relied on the accuracy of the ICD-10 coding in the NPR. In general, the reliability and validity of the diagnosis registration have been assessed to be good.[16, 29, 30] However, there were no studies explicitly validating the registration of CD and UC diagnosis codes. Further, patients were included for up to 10 years before the index date, from January 1, 2002, at the earliest, not accounting for migration to and from Denmark at any point during the study period. For example, costs after emigration would reduce average cost estimates, and information on earlier health status would likely not be available among patients who recently migrated to Denmark before an IBD diagnosis. Additionally, individual costs related to acquisition of nonprescription medicine and informal care costs (ie, relatives' care of the patient) were not analyzed in this study.

Further, the results from the comorbidity analyses only provide an indication of what drives the difference in hospital costs. The analyses only provide results on the number of individuals within each disease group; they cannot evaluate which disease drives the hospital costs of CD and UC patients before diagnosis. Another key issue in observational studies is the possibility of unmeasured confounding.

CONCLUSIONS

The findings of this study suggest substantial societal costs in the 10-year period leading up to CD or UC diagnosis compared with the general population. During the 10-year period, CD and UC patients had significantly higher health care costs, including hospital admissions, outpatient visits, primary sector visits, prescription medicine, and a lower labor production value. Most significantly, CD and UC patients were more frequently in contact with the hospital sector regarding diseases of the digestive system before diagnosis, possibly implying a diagnostic delay.

Future studies should explore the cost patterns and symptoms before IBD diagnosis to identify disease markers that could provide earlier treatment to patients and lower the societal costs of the disease-burdened patient.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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