

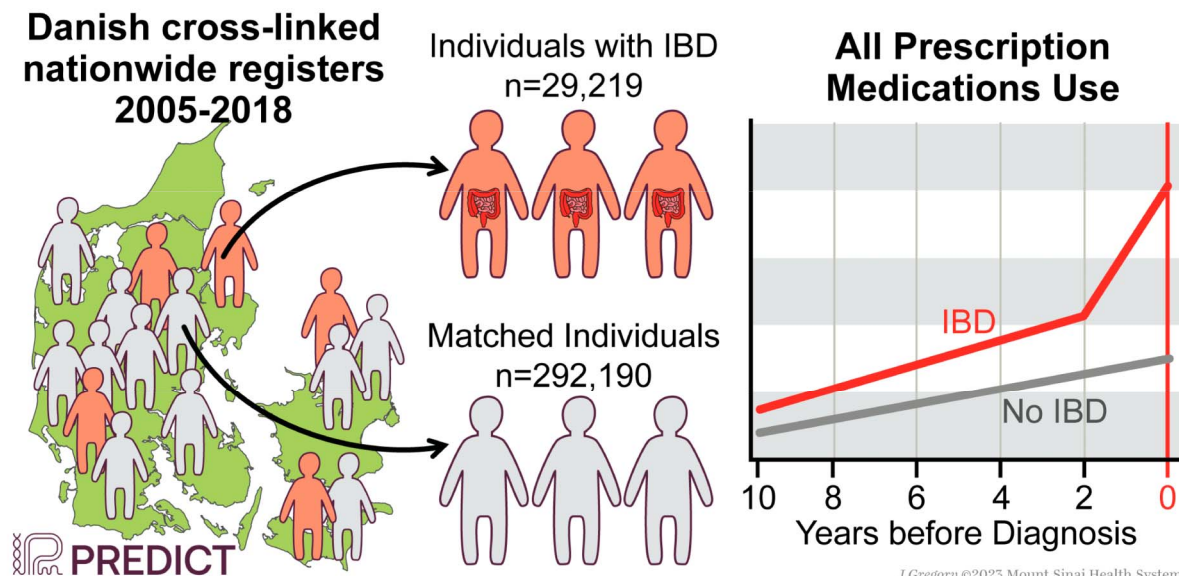
Medication-Wide Study: Exploring Medication Use 10 Years Before a Diagnosis of Inflammatory Bowel Disease

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INTRODUCTION: There is growing interest in the prediagnostic phase of inflammatory bowel disease (IBD) and in the overlap of IBD with other diseases. We described and compared use of any prescription medication between individuals with and without IBD in a 10-year period preceding diagnosis.

METHODS: Based on cross-linked nationwide registers, we identified 29,219 individuals diagnosed with IBD in Denmark between 2005 and 2018 and matched to 292,190 IBD-free individuals. The primary outcome was use of any prescription medication in years 1–10 before IBD diagnosis/matching date. Participants were considered as medication users if they redeemed ≥ 1 prescription for any medication in the World Health Organization Anatomical Therapeutic Chemical (ATC) main groups or subgroups before diagnosis/matching.

Medication-wide study: Exploring medication use ten years prior to IBD



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RESULTS: The IBD population had a universally increased use of medications compared with the matched population before IBD diagnosis. At 10 years before diagnosis, the proportion of users was 1.1-fold to 1.8-fold higher in the IBD population in 12 of 14 ATC main groups of medication (P -value < 0.0001). This applied across age, sex, and IBD subtypes, although it was the most pronounced for Crohn's disease (CD). Two years before diagnosis, the IBD population had a steep increase in medication use for several organ systems. When analyzing therapeutic subgroups of medication, the CD population exhibited 2.7, 2.3, 1.9, and 1.9 times more users of immunosuppressants, antianemic preparations, analgesics, and psycholeptics, respectively, than the matched population 10 years before diagnosis (P -value < 0.0001).

DISCUSSION: Our findings demonstrate universally increased medication use years before IBD, especially CD, diagnosis and indicates multiorgan involvement in IBD.

KEYWORDS: Crohn's disease; epidemiology; ulcerative colitis; pharmacoepidemiology; prediagnosis

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/C985>

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INTRODUCTION

Inflammatory bowel disease (IBD) is a complex immune-mediated inflammatory disease (IMID) of the gastrointestinal tract, with 2 main subtypes, Crohn's disease (CD) and ulcerative colitis (UC) (1,2). IBD is a progressive disease leading to complications, disability, and significant healthcare costs, and it has no cure (1–6). IBD is also associated with extraintestinal manifestations and with other IMIDs (7–9). Timely diagnosis and intervention can mitigate the worse outcomes seen in patients with longer time to diagnosis as demonstrated in a recent meta-analysis (10). There is increasing evidence that IBD diagnosis is preceded by a long prediagnostic phase characterized by increased intestinal permeability, higher fecal calprotectin, and distinct proteomic and antibody biomarkers in serum that can go back up to 10 years before diagnosis as demonstrated in the GEM and PREDICTS cohorts (11–16). From a clinical standpoint, increased healthcare utilization such as primary care visits for gastrointestinal symptoms, altered laboratory parameters pertaining to inflammation, and use of gastrointestinal medications have been reported in the 5-year period preceding CD, but not UC, diagnosis in recent studies (17,18). A population-based study demonstrated increased gastrointestinal symptoms for both patients with CD and patients with UC in a 5-year period before diagnosis (19). However, data on gastrointestinal and all other organ prescription medications over a longer period preceding IBD diagnosis are lacking.

In this observational study, we examine the use of gastrointestinal and all other organ prescription medications among individuals with IBD in each of the 10 years preceding diagnosis and compare with the medication use among a matched population of individuals without IBD. We hypothesized that IBD diagnosis is preceded by a prediagnostic phase characterized by involvement of organ systems beyond the gastrointestinal tract, reflected by increased use of medications across all organ systems.

METHODS

Patterns of prescription medication were examined by identifying all individuals with incident IBD in Denmark in 2005–2018. Individuals with IBD were matched 1:10 to individuals without IBD from the Danish population on age, sex, municipality of

residence, and quarter of year of IBD diagnosis. Their prescription histories were compared for each year of the preceding 10 years.

Data sources

The data sources for this study included the Danish National Prescription Registry (DNPR), the Danish National Patient Register (NPR), and the Danish Civil Registration System (20–22). The DNPR contains detailed individual-level information on all prescriptions redeemed at Danish pharmacies since 1995 (20). Prescriptions in DNPR are coded according to the Anatomical Therapeutic Chemical (ATC) classification system (23). The NPR contains data on all somatic hospital admissions in Denmark since 1977 and outpatient, psychiatric, and emergency department visits since 1995. In NPR, hospital contacts are coded using International Classification of Diseases (ICD), 8th and 10th revisions (22). Linkage between the DNPR and NPR is possible through a unique personal identification number assigned to all Danish residents since 1968. The Danish Civil Registration System contains data on vital status, address, and migration to and from Denmark, which allows complete follow-up of study participants (21).

Ethical considerations

Research based on register-based data does not require ethical permission in Denmark.

IBD population

The IBD population included individuals 18 years or older diagnosed with IBD between January 1, 2005, and December 31, 2018, who lived in Denmark 10 years before IBD diagnosis (with an allowed absence from Denmark of up to 1 year in total during that period). We further excluded all individuals with an IBD registration before 2005 (ICD-8: CD: 563.01–09; UC: 563.19 and 569.04 and ICD-10: CD: K50; UC: K51). We considered a patient's registration dates to define incident IBD cases. Registration dates referred to either the date of an outpatient visit or the start of an inpatient contact. Any outpatient visit registered under an outpatient contact and any inpatient contact associated with a primary or secondary IBD diagnosis (ICD-10 codes K50 and K51

for CD and UC, respectively) were considered an IBD-related registration. We included individuals with at least 2 IBD-related registrations within 2 years. If the registrations were coded as the same IBD subtype (either UC or CD), then the case was classified accordingly. If both CD and UC diagnosis codes were registered, we considered it unclassified IBD. Unclassified IBD was not included in subtype analyses. The date of the first IBD-related registration was considered as the date of IBD diagnosis. The date of the second IBD-related registration was used as the date for matching to mitigate immortal time bias.

Matched population

The matched population was the Danish population, 18 years or older in 2005–2018, living in Denmark 10 years before the matching date (with an allowed absence of up to 1 year in total during that period), and with no registrations of IBD before the matching date. Individuals without IBD were matched 10:1 to the IBD population for age at diagnosis (in 1-year intervals), sex, calendar period of IBD diagnosis (in quarter-of-year intervals), and municipality of residence at the date of matching.

Statistical analysis

We divided time before the IBD diagnosis/matching date into 1 year intervals. For each interval, we defined the number of medication users as the number of individuals who had at least one redeemed prescription of a drug. We divided prescriptions according to the World Health Organization classification of medication at the anatomical main group and therapeutic subgroup levels (23,24). An overview of ATC anatomical main groups and therapeutic subgroups is provided in Supplementary Table 1 (Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). Next, we calculated the proportion of medication users per 1,000 persons. We reported this proportion for the whole IBD population and further stratified by subtype of IBD (CD, UC), sex (female, male), and age of IBD onset (18–39 years, 40–59 years, and 60 years and older). The proportion of medication users in the IBD population compared with the proportion of medication users in the matched population was presented by a ratio. A ratio above 1 thus signified a larger proportion of users in the IBD population (in the following referred to as “more users” or “more abundant use”). We examined statistical significance of differences between the IBD and matched populations using χ^2 tests. We based the significance level on Bonferroni-corrected P -values: $P < 0.004$ for main groups of medication (0.05/14 [number of tests]) and $P < 0.0006$ for subgroups of medication (0.05/82 [number of tests]).

In addition, we conducted 2 sensitivity analyses: (1) analysis of a subpopulation with medication data spanning 15 years before IBD diagnosis/matching date and (2) analysis where individuals with IMIDs before the date of IBD diagnosis/matching date were excluded. IMIDs were defined as explained in detail previously (Supplementary Table 2, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>) (25).

RESULTS

Study population

We included 29,219 individuals with IBD and 292,190 matched individuals (Figure 1). The median age at IBD diagnosis/matching date was 43 (interquartile range [IQR] 29–60) years, and 15,626 (53.5%) were women. Of the individuals who had IBD, 8,766 individuals (30.0%) were diagnosed with CD and

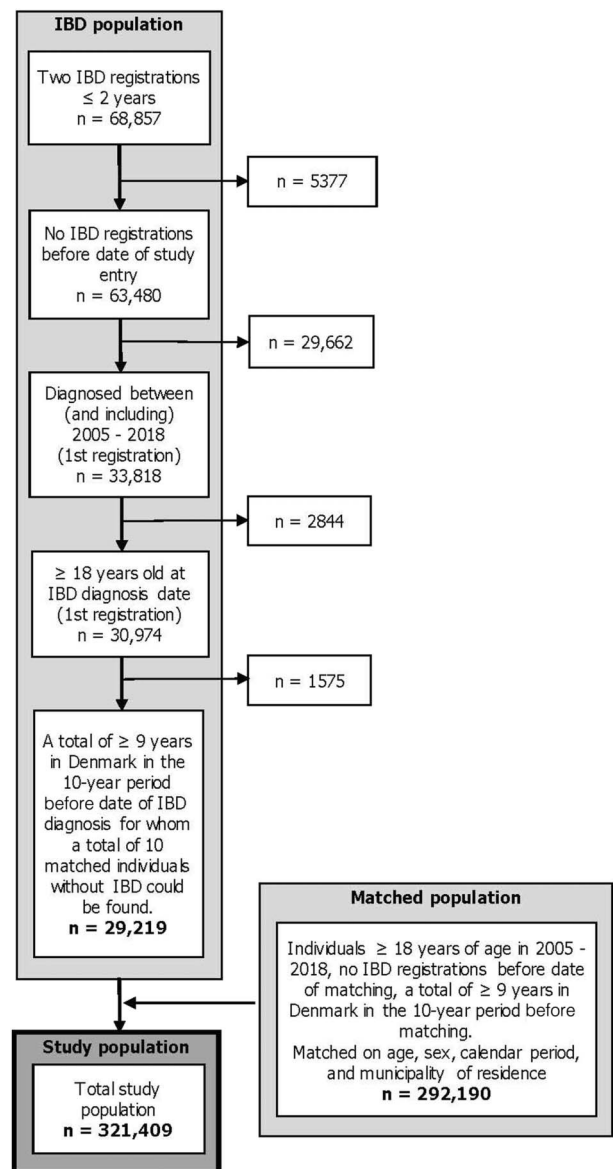


Figure 1. Flowchart of the population. IBD, inflammatory bowel disease.

19,582 individuals (67.0%) were diagnosed with UC (Table 1). The median age at diagnosis of CD and UC was 39 (IQR 25–56) years and 45 (IQR 31–61) years, respectively (Supplementary Table 3, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>).

Medication use in the 10 years before IBD diagnosis

In the 10th year before IBD diagnosis/matching date, the IBD population had more users than the matched population in 12 of the 14 main groups of medication (P -value < 0.0001) (Figures 2 and 3, Supplementary Table 4, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). In the IBD population vs the matched population, the largest difference in users was found for IBD-related medications, including medications used to treat immunological diseases (1.8 times more users than the matched population) and gastrointestinal conditions (1.4 times more users than the matched population). When we examined all other

Table 1. Study population characteristics

	IBD	Non-IBD	Total
Total	29,219	292,190	321,409 (100.0)
Sex			
Female	15,626 (53.5)	156,260 (53.5)	171,886 (53.5)
Male	13,593 (46.5)	135,930 (46.5)	149,523 (46.5)
IBD subtype			
CD	8,766 (30.0)	.	8,766 (30.0)
UC	19,582 (67.0)	.	19,582 (67.0)
Unclassified	871 (3.0)	.	871 (3.0)
Age at diagnosis/matching date (yr)			
18–39	12,802 (43.8)	128,020 (43.8)	140,822 (43.8)
40–59	8,975 (30.7)	89,750 (30.7)	98,725 (30.7)
≥60	7,442 (25.5)	74,420 (25.5)	81,862 (25.5)
Median age at diagnosis/matching date, yr (IQR)	43 (29–60)	43 (29–60)	.
CD	39 (25–56)	.	.
UC	45 (31–61)	.	.
Calendar year of diagnosis/matching			
2005–2009	9,569 (32.8)	95,690 (32.8)	105,259 (32.8)
2010–2014	10,818 (37.0)	108,180 (37.0)	118,998 (37.0)
2015–2018	8,832 (30.2)	88,320 (30.2)	97,152 (30.2)

Numbers are N (%), unless otherwise specified.
CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; UC, ulcerative colitis.

medications, the IBD population also had more users. The IBD population had 1.2 times more users of medication used to treat cardiovascular diseases, dermatological diseases, endocrinological diseases, neurological and psychiatric diseases, musculoskeletal diseases, respiratory diseases, and blood-forming organ diseases, compared with the matched population. For medication used to treat gynecological and urological diseases, infectious diseases, and sensory organ diseases, the IBD population had 1.1 times more users than the matched population.

When we evaluated temporal trends across the 10 years preceding IBD diagnosis/matching date, the proportion of users increased consistently for both the IBD and matched populations. For medication for musculoskeletal, nervous system, and blood disorders, both the IBD and matched populations exhibited a steady rise in use during the 10-year period, with the IBD population consistently having more users than the matched population. Two years before diagnosis, the IBD population exhibited a steep increase in use of medications for gastrointestinal and metabolic diseases but also for cardiovascular, endocrinological, infectious, neoplastic and immunological, and parasitic diseases (Figure 2).

Medication use in the 10 years before IBD diagnosis according to IBD subtype, sex, and age at diagnosis

In general, the temporal trends in medication use among individuals with CD and UC were similar to the use described for the overall IBD population. Yet, the CD population had more users than the UC population in most of the main medication groups

(Figure 3 and Supplementary Figure 1, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). When we stratified by sex, we observed more users among women compared with men regardless of IBD status (Figure 3 and Supplementary Figure 2, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). When we stratified by age at IBD diagnosis (18–39 years, 40–59 years, and 60 years and older), the IBD population had more medication use than the matched population in all 3 age groups (Figure 3 and Supplementary Figure 3, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>).

Medication use at the 10 years before IBD diagnosis time point by therapeutic subgroup of medication

At the 10th year before diagnosis, the IBD population had a more abundant use of medications for most organ systems compared with the matched population (Supplementary Figure 4, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). This finding persisted when we divided the IBD population into CD and UC populations (Figure 4). The CD population exhibited statistically significantly more users than the matched population for 32 of 82 subgroups at the 10 years before IBD diagnosis time point, covering medication in nearly all organ systems (Figure 4, left panel). For the UC population, this number was 26 of 82 (Figure 4, right panel). No subgroups of medication showed statistically significantly lower use by the IBD population (CD, UC, respectively) compared with the matched population.

In the CD population, the largest statistically significant difference in medication users was found for IBD-related

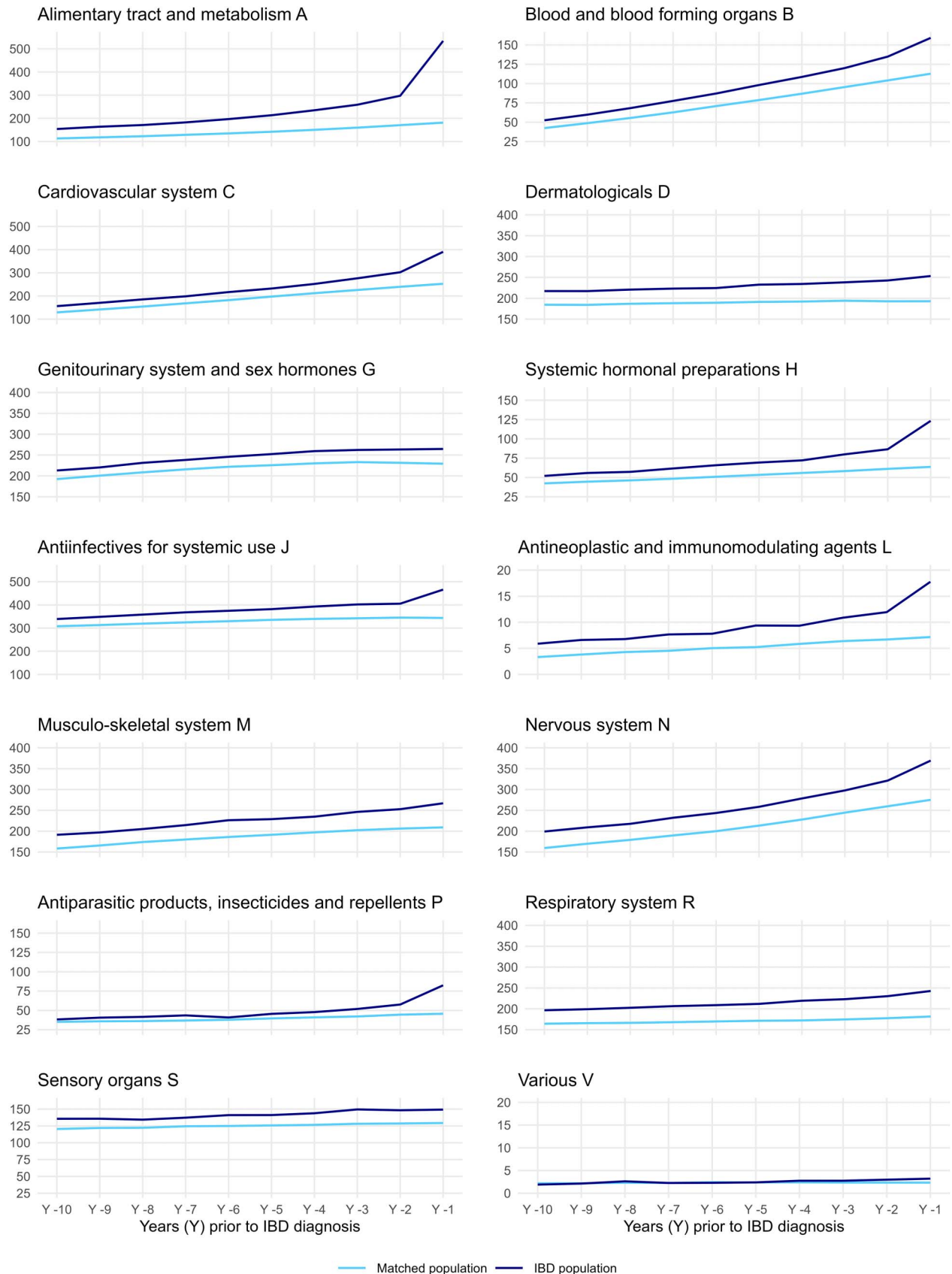


Figure 2. Medication users by anatomical main group of medication. The number of medication users per 1,000 persons by anatomical main group of medication in a period of 10 years before IBD diagnosis/matching date. IBD, inflammatory bowel disease.

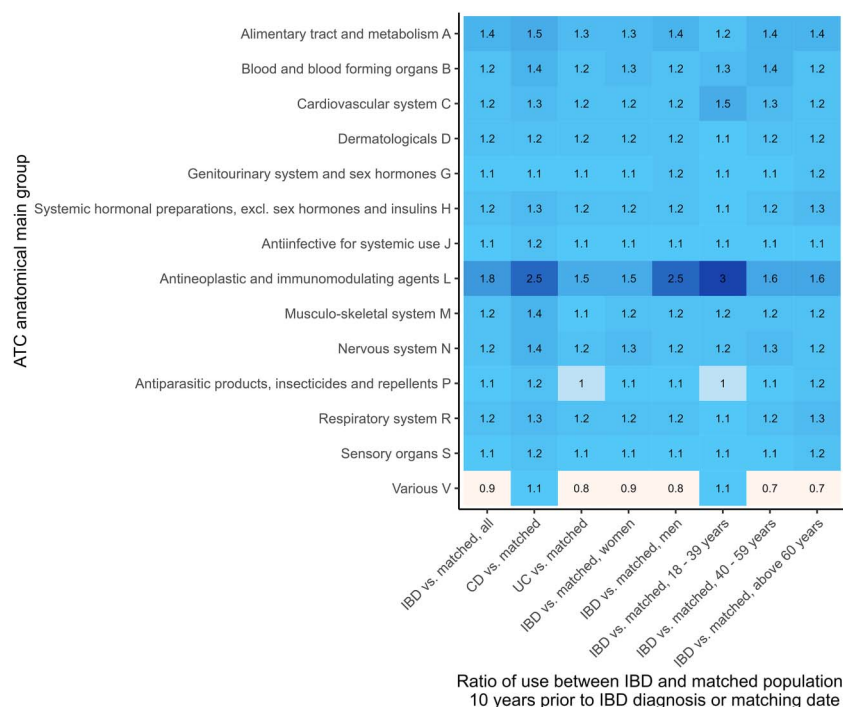


Figure 3. Ratio of medication use between the IBD population and the matched population at the 10 years before IBD diagnosis/matching date time point. The ratio of the standardized medication use between the IBD population and the matched population by anatomical main group of medication at the 10 years before IBD diagnosis/matching date time point. IBD vs matched: P -value < 0.0001 for all anatomical main groups, except *Antiparasitic products, insecticides, and repellents*, P -value = 0.006; and *Various*, P -value = 0.31. CD vs matched: P -value < 0.0001 for all anatomical main groups, except *Various*, P = 0.62. UC vs matched: P -value < 0.0001 for all anatomical main groups, except *Antineoplastic agents and immunosuppressants*, P -value = 0.0006; *Antiparasitic products, insecticides, and repellents*, P -value = 0.46; and *Various*, P -value = 0.18. IBD vs matched, women: P -value < 0.0001 for all anatomical main groups, except *Antiparasitic products, insecticides, and repellents*, P -value = 0.02, and *Various*, P -value = 0.68. IBD vs matched, men: P -value < 0.0001 for all anatomical main groups, except *Genitourinary system and sex hormones*, P -value = 0.005; *Antiparasitic products, insecticides, and repellents*, P -value = 0.18; and *Various*, P -value = 0.30. IBD vs matched, 18–39 years: P -value 0.0001 for all anatomical main groups, except *Blood and blood-forming organs*, P -value = 0.06; *Systemic hormonal preparations, excl. sex hormones and insulins*, P -value = 0.09; *Antiparasitic products, insecticides, and repellents*, P -value = 0.53; *Sensory organs*, P -value = 0.0017; and *Various*, P -value = 0.74. IBD vs matched, 40–59 years: P -value < 0.0001 for all anatomical main groups, except *Antineoplastic and immunomodulating agents*, P -value = 0.0008; *Antiparasitic products, insecticides, and repellents*, P -value = 0.095; and *Various*, P -value = 0.15. IBD vs matched, 60 years and older: P -value < 0.0001 for all anatomical main groups, except *Antineoplastic and immunomodulating agents*, P -value = 0.0004; *Antiparasitic products, insecticides, and repellents*, P -value = 0.007; and *Various*, P -value = 0.31. ATC, Anatomical Therapeutic Chemical classification system; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

medications, such as immunosuppressants, which showed 2.7 times more users in the CD population vs the matched population (*Immunosuppressants L04*, P -value < 0.0001). Medication used to suppress immune reactions is classified into several different subgroups in the ATC system, and other groups with immune-suppressing and anti-inflammatory medications also had more users in the CD population vs the matched population (*Corticosteroids for systemic use H02*, *Corticosteroids, dermatological preparations D07*, *Drugs for obstructive airway diseases R03*, all P -value < 0.0001). Likewise, medication used to treat intestinal infection and inflammation showed 2.6 times more users in the CD population vs the matched population (*Antidiarrheals, intestinal anti-inflammatory/anti-infective agents A07*, P -value < 0.0001). However, a broad range of medications for blood disorders, cardiovascular diseases, some infections, respiratory diseases, nervous system disorders, and some sensory conditions were also found to be used by 1.1 to 1.8 times more users in the CD population vs the matched population (Figure 4, left panel). For the UC population, we also found more medication users compared with the matched population both in IBD-related and

other organ medications. However, effect sizes were generally lower (Figure 4, right panel).

Sensitivity analyses

To examine the length of the prediagnostic phase of IBD, we performed a sensitivity analysis of individuals who had medication data from 15 years before IBD diagnosis/matching date. A total of 213,704 individuals (19,486 individuals with IBD and 194,218 matched individuals) corresponding to 66% of the original study population were included. At the 15 years before the date of IBD diagnosis/matching date time point, the IBD population had a larger proportion of users in 10 of 14 main medication groups, although differences were slightly diminished compared with what was observed at the 10 years before diagnosis time point. In accordance with the finding at 10 years before diagnosis, the CD population generally had a more abundant medication use compared with the matched population than the UC population (Supplementary Figure 5, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>).

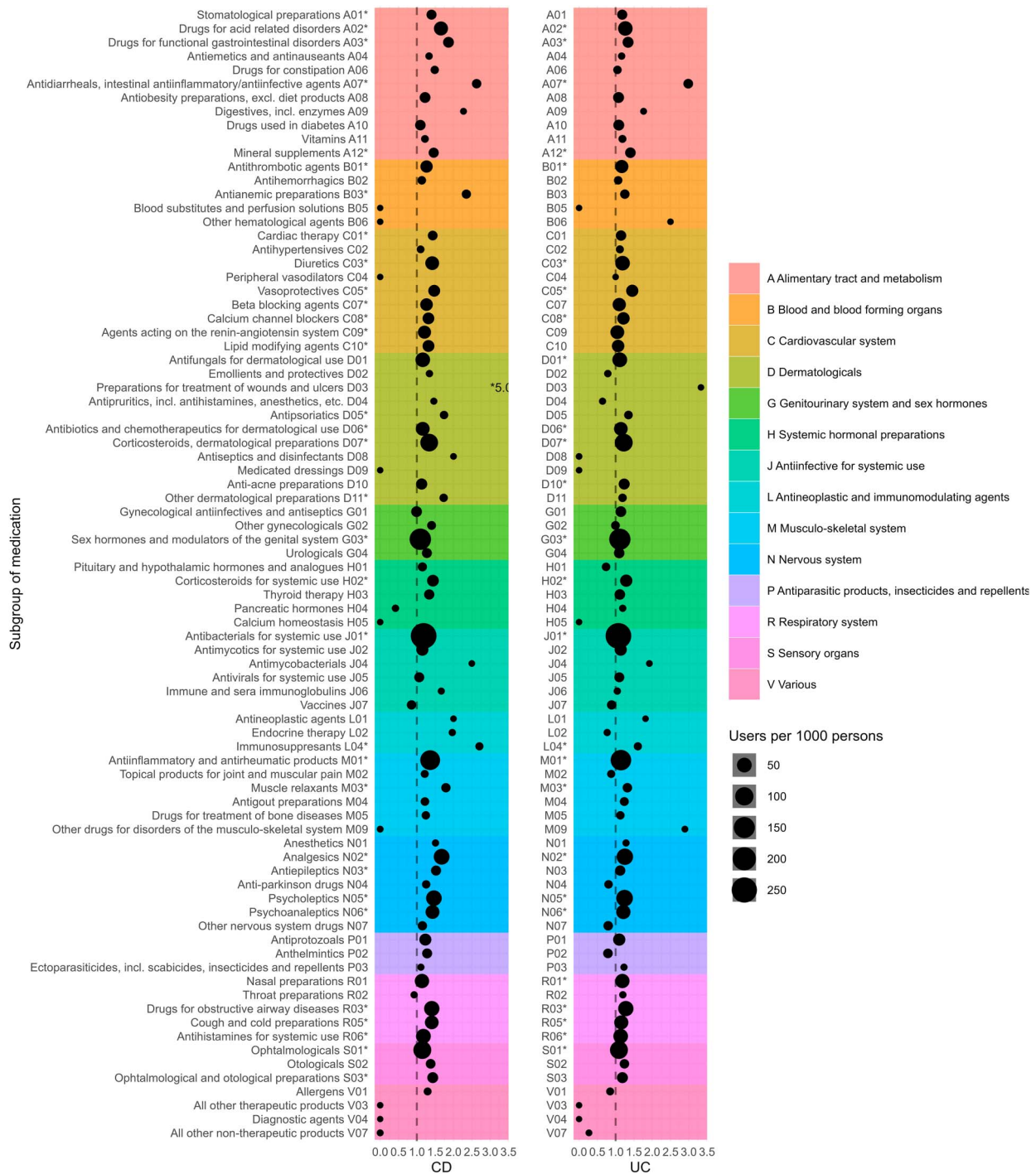


Figure 4. Ratio of medication use between the IBD population (divided into CD and UC, respectively) and the matched population at the 10 years before IBD diagnosis/matching date time point, by therapeutic subgroup of medication. The ratio of the standardized medication use between the IBD population (divided into CD and UC, respectively) and the matched population by therapeutic subgroup of medication at the 10 years before IBD diagnosis/matching date time point. “*” after the therapeutic subgroup name indicates statistical significance after Bonferroni correction (P -value < 0.0006). Remaining P -values are reported in Supplementary Table 4 (Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). The bubble placement indicates the ratio. The bubble size reflects the number of users per 1,000 persons for the study population and thus represents how widely medication in the subgroup is used. The number of users per 1,000 persons (bubble size) is not shown for *Preparations for wounds and ulcers D03* in the panel showing CD (left) (0.02 users per 1,000 persons). The ratio of standardized medication use between the CD and matched populations for this subgroup is 5.0. Subgroups with number of medication users <0.03 per 1,000 persons are not presented. CD, Crohn’s disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

To examine the role of preexisting IMIDs, we performed a sensitivity analysis where individuals with prior IMIDs were excluded. A total of 63,636 individuals (19.8%) had a diagnosis of one or more IMIDs before IBD diagnosis/matching date. Among the IBD population, 26.3% had a diagnosis of one or more IMIDs before IBD diagnosis while 19.1% of the matched population had a diagnosis of one or more IMIDs before the matching date. The ratio of 1:10 between the IBD population and the matched population remained almost intact (deviation < 1%). The characteristics of the population with no prior IMIDs were similar to those of the initial study population with slightly fewer women and older individuals compared with the initial population (Supplementary Table 5, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). After exclusion of individuals with prior IMIDs, results were similar to the main findings, although differences between the IBD population and the matched population were slightly diminished. This was especially prominent for immunomodulating medications (Supplementary Figure 6, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>). Yet, at the 10 years before diagnosis time point, the IBD population without prior IMIDs had more users of medication in 11 of 14 main groups of medications (Supplementary Figure 7, Supplementary Digital Content 1, <http://links.lww.com/AJG/C985>).

DISCUSSION

Based on an unselected population of 29,219 individuals with incident IBD and 292,190 matched individuals without IBD, we described that the IBD population had more abundant use of a broad range of medications up to 10 years preceding IBD diagnosis, with a steep increase for several medication groups in the 2 years preceding IBD diagnosis. This pattern was present across age, sex, and IBD subtypes, although more pronounced for CD than UC.

A previous register-based study has demonstrated increased costs of medication for 10 years before a diagnosis of IBD, although not reporting which types of medications (6). Yet, to our knowledge, ours is the first study to report on all medication uses in a 10-year period preceding IBD diagnosis where use is reported in specified medication groups. Consistent with a commonly observed long unrecognized prediagnostic phase of IBD characterized by nonspecific gastrointestinal symptoms, we found that medications to treat diarrhea and gastrointestinal infections as well as pain, anemia, and inflammation were used more in the IBD population than the matched population before diagnosis. Furthermore, we found a steep increase in the use of those medications in the past 2 years preceding diagnosis which likely reflects undiagnosed IBD in this period of time. This also supports previous data on delay between symptom onset and IBD diagnosis (10,26). While administrative diagnostic delay is possible, available data indicate that waiting time from referral by general practitioners to examination by a gastroenterologist in most cases does not exceed 12 weeks in Denmark (27). Our findings comply with previous reports of higher use of proton pump inhibitors, antibiotics, and nonsteroidal anti-inflammatory drugs in the 2 years before IBD diagnosis (28); higher use of antispasmodic medications in the 5 years before IBD diagnosis (29); higher use of antidepressants 9 years before diagnosis (30); and a study showing that individuals with IBD are more likely to have gastrointestinal symptoms 18 months before diagnosis (19). More unexpected was the finding of an increased use of almost all types

of medications for up to 10 years before diagnosis. While the increased medication use in the 2 to 3 years immediately before diagnosis may reflect a delay in diagnosis of IBD, it is unlikely that a patient and/or administrative diagnostic delay would happen over a 10-year period.

Strikingly, the increased use of medications up to 10 years before IBD diagnosis was not limited to gastrointestinal specialties. The more abundant use of medications for neoplastic and immunological diseases may reflect treatment of preexisting extraintestinal manifestations of IBD and/or symptoms of other IMIDs among individuals who later develop IBD (31). However, exclusion of individuals with a diagnosis of an IMID before IBD did not eliminate our findings suggesting that the increased medication use was not solely explained by the presence of IMIDs before IBD diagnosis. While IMIDs have traditionally been siloed into organ-specific classifications, emerging data points to several shared pathophysiological processes across IMIDs. Furthermore, the presence of an IMID increases the risk of other IMIDs. This has led to a call to redefine IMIDs based on their molecular profile, instead of organ localization (8,9).

Our observation of increased use of cardiovascular medications; medications used to treat psychiatric diseases, anxiety, insomnia, and depression; and medications for obstructive airway diseases supports the previously reported associations between IBD and these diseases (32–37). However, increased use of medications for these diseases 10 years before IBD diagnosis is a salient finding and warrants further investigation.

The CD population generally had a more abundant medication use compared with matched controls than the UC population. This is in accordance with previous data reporting the occurrence of a prodromal period of several years in CD but not in UC and another study reporting that a panel of antibodies and protein biomarkers predicted development of CD but not UC 5 years before diagnosis (17,38). Finally, a previous study found that in the 5-year period before diagnosis, patients with CD had higher use of antibiotics, proton pump inhibitors, and etanercept than patients with UC. The same study also found that patients with CD, but not UC, had increased use of nonsteroidal anti-inflammatory drugs, antibiotics, and steroids in the 2 years before diagnosis (18). Interestingly, in a sensitivity analysis including 66% of our study population, we found increased medication use, especially in the CD population, 15 years before a diagnosis of IBD.

Another possible explanation for our findings is that treatment with certain medications could be an independent risk factor for the development of IBD. Medications such as isotretinoin, antibiotics, nonsteroidal anti-inflammatory drugs, oral contraceptives, mycophenolate mofetil, etanercept, ipilimumab, and rituximab have been linked to causing or worsening IBD (28,39). All of these medications belong to subgroups more used by the IBD population. However, our observation was not restricted to those medications.

Our study has several strengths. In contrast to previous studies that focused on medications and symptoms related to the gastrointestinal tract up to 5 years preceding IBD diagnosis, we agnostically examined longitudinal prediagnostic use of all prescription medications across all organ systems and up to 10 years preceding IBD diagnosis. Data were drawn from nationwide registries providing a large and unselected study population. Moreover, we were able to follow all individuals for 10 years before a diagnosis of IBD/matching date with no loss to follow-

up. Information on medication use was retrieved from the DNPR, which includes individual-level information on all prescriptions redeemed at Danish pharmacies, implying that results were not influenced by recall bias. A recent study reported high validity of CD and UC ICD-10 codes in the NPR (40). Using 2 diagnosis codes for either CD or UC, the positive predictive value was 0.96 (95% confidence interval, 0.95–0.97) and 0.95 (95% confidence interval, 0.94–0.96), respectively, suggesting that misclassification of IBD is not likely. Using the first IBD-related registration as the date of diagnosis and the second IBD-related registration as the date of matching prevented immortal time bias. However, our study also has limitations. We examined redemptions of prescription medication; those bought over the counter or administered during hospitalization could not be ascertained in this study. Moreover, we did not have complete information on indication for medical treatment precluding direct evaluation of reasons for prescriptions. In addition, confounding may be at play. As our aim was not to make causal inferences, we did not adjust for risk factors of IBD such as familial history of IBD or tobacco smoking. A tobacco user may be more likely to have various conditions warranting medical treatment such as chronic obstructive pulmonary disease and cardiovascular disease and be more likely to develop IBD.

Overall, our aim was to characterize prediagnostic medication use rather than to make causal inferences. Some medications may be risk-bearing for IBD development; some conditions requiring medical treatment may predispose to IBD such as gastrointestinal infections (treated with antibiotics) or depression (treated with antidepressants); the IBD disease process may start several years before patients and doctors suspect it; or IBD may be a multiorgan disease to a much larger extent than hitherto established. The results presented in this article describe the time before diagnosis among all patients with IBD in Denmark, which could spark investigations of specific medications as risk-bearing for IBD development, investigations into the systemic nature of IBD (especially CD) and possibly earlier diagnosis of IBD.

In conclusion, in this nationwide study of 29,219 individuals with IBD and 292,190 matched individuals without IBD, we found that the IBD population had an increased use of a broad range of medications through 10 years before diagnosis, with a steep increase in use for several medication groups in the past 2 years before diagnosis. Collectively, our findings further suggest that IBD, and especially CD, could be a multiorgan disease to a much larger extent than hitherto established. The long prediagnostic period represents a window of opportunity for earlier detection and intervention as well as toward prediction and prevention strategies of IBD.

CONFLICTS OF INTEREST

Guarantor of the article: Linéa Bonfils, MD.

Specific author contributions: Conceptualization: L.B., T.J., and K.H.A. Planning and conducting the study: L.B., A.K.S., and K.H.A. Interpreting data: L.B., A.K.S., G.J.P., M.A., D.J.W., J.-F.C., T.J., and K.H.A. Drafting the manuscript: L.B. and K.H.A.

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Data Transparency Statement: This study is based on data from the Danish National Health registers (<https://sundhedsdatastyrelsen.dk>). The register data are protected by the Danish Act on Processing of Personal Data and are accessed through application to and approval from the Danish Data Protection Agency and the Danish Health Data Authority.

Study Highlights

WHAT IS KNOWN

- ✓ Inflammatory bowel disease (IBD) has a prodromal phase, but data describing it are scarce.

WHAT IS NEW HERE

- ✓ We conducted a population-based nationwide and medication-wide explorative study to describe medication use preceding a diagnosis of IBD.
- ✓ Patients with IBD have higher use of almost every medication already 10 years before IBD diagnosis.

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