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Inflammatory Bowel Disease and Risk of More than 1,500 Comorbidities: A Disease-wide Prediagnostic and Postdiagnostic Phenomic Association Study

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INTRODUCTION: Inflammatory bowel disease (IBD) is associated with various extraintestinal manifestations. We aimed to identify comorbidities in IBD and the timing of their development to provide potentially useful insight into the associations with IBD.

METHODS: We conducted a population and disease-wide phenomic association study in IBD, using >6 million *International Classification of Diseases, Tenth Revision* coded healthcare contacts from 10 years before and up to 17 years after IBD diagnosis to investigate associations with 1,583 comorbidities. To explore diseases with potential etiological significance, we compared association in the prediagnostic and the postdiagnostic periods. We corrected also for multiple-testing. These estimates were validated with publicly available data from Finland.

RESULTS: We identified 312 significant associations with 125 appearing before diagnosis. Risk of extraintestinal manifestations was increased up to 10 years before IBD diagnosis, such as psoriasis (OR_{CD}: 2.58 95% confidence interval: [2.00–3.31]; OR_{UC}: 1.54 [1.26–1.88]) and reactive arthropathies (OR_{CD}: 2.07 [1.42–2.96]; OR_{UC}: 1.42 [1.08–1.84]). Risk of cardiometabolic and neuropsychological disorders was increased both prediagnostically and postdiagnostically. Potential treatment sequelae, such as osteoporosis (HR_{CD}: 2.56 [2.30–2.86]; HR_{UC}: 1.92 [1.79–2.07]) were primarily seen postdiagnostically. In only 15.7% (44/281) and 11.4% (35/301) of comorbidities in Crohn's disease and ulcerative colitis, respectively, did we observe heterogeneity between Denmark and Finland.

DISCUSSION: Findings demonstrate that IBD is a multisystemic disease, particularly manifesting with metabolic, immune, and neuropsychological disorders, up to 10 years before diagnosis. We find evidence for the generality of these findings with an international comparison. Diseases of etiological interest warrant further investigation.

KEYWORDS: inflammatory bowel disease; Crohn's disease; ulcerative colitis; prediagnosis; comorbid diseases

ABBREVIATIONS: CD, Crohn's disease; CI, confidence interval; EIMS, extraintestinal manifestations; IBD, inflammatory bowel disease; *ICD-10*, *International Classification of Diseases, Tenth Revision*; IMID, immune mediated inflammatory diseases; LPR, Danish National Patient Register; UC, ulcerative colitis

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/D736>, <http://links.lww.com/AJG/D737>

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INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic intestinal conditions with a multifactorial etiology. Identified genetic risk loci (1,2) may—in combination with environmental factors, such as diet, smoking, exercise, and exposure to infectious agents—be implicated in disease development (3) through multiple mechanisms, including epigenetic modifications, alterations in the gut microbiota, and immune dysregulation (4). To complicate the etiological understanding of IBD further, between 6% and 50% of patients develop extraintestinal manifestations (EIMs), including erythema nodosum, uveitis, primary sclerosing cholangitis, and ankylosing spondylitis (5), which may share common inflammatory pathways, genetic associations (6), and response to anti-inflammatory therapies including those targeting tumor necrosis factor (TNF), interleukin (IL)-12/23, and Janus kinase (JAK) inhibition. Emerging evidence also suggests that neuropsychiatric diseases (7) and cardiovascular diseases occur with increased frequency in IBD (8), and additional diseases may occur either due to chronic inflammation, altered immunity, and/or treatment with corticosteroids and immunosuppression (9).

Hence, our understanding of IBD as a single-organ disease is challenged, whereas evidence of the involvement of other organs is still fragmented. This creates limitations for our etiological understanding of IBD and the ability to optimize disease phenotyping and tailor treatment (10). In other immune mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis and psoriasis, there is increasing systematic investigation into associated comorbidities, primarily those manifesting after IMID diagnosis. This has not only enhanced the understanding of disease etiology of diseases such as rheumatoid arthritis and psoriasis but has also revealed that comorbidities lead to increased cost of care, poorer medical outcomes (11,12), and reduced emotional functioning (13). With a compounding prevalence of IBD worldwide and an increasing average age of patients with IBD (14), the comorbid burden is only expected to increase further, and a greater understanding of the interrelationship of IBD and comorbid diseases is urgently needed.

Using Danish nationwide healthcare data on all disease categories, as defined by the *International Classification of Diseases, Tenth Revision (ICD-10)*, we aimed to undertake the first population and disease-wide association study in IBD exploring all prediagnostic comorbidities from 10 to 1 year before IBD, as well as all postdiagnostic comorbidities observed from date of IBD diagnosis and up to 17 years after.

METHODS

Data and study population

The Danish National Patient Register (LPR) covers the entire population of Denmark with comprehensive data from 1977 (15). These data record hospital contacts with associated diagnostic codes including outpatient contacts from 1995 and contacts from private hospitals from 2002. IBD and all other diseases are defined with reference to the World Health Organization's *ICD-10* (16). The LPR data are linked to the Danish Civil Registration System (CPR) (17) by a unique personal identification number to verify and obtain data on age, sex, vital statistics, and residence.

The study cohort comprises all Danish residents with a new IBD diagnosis in the period from January 1, 2005 to December 31, 2021. IBD cases were identified with reference to the LPR with the

following criteria, as established in a previous study (18), at least 2 inpatient or outpatient contacts within a 2-year period, with associated (primary or secondary) IBD diagnostic codes (CD: *ICD-10*: K50; UC: *ICD-10* codes K51). To make sure that patients are truly incident at the time of inclusion in the study, patients with an earlier inpatient or out-patient contact with an IBD diagnostic code (CD: *ICD-8* 563.01, 563.02, 563.08, 563.09 and *ICD-10*: K50; UC: *ICD-8* 563.19, 569.04 and *ICD-10* codes K51) were excluded. A case is defined as either UC or CD based on the most recent diagnostic code and the date of first recorded diagnosis is termed the index-date. To allow adequate time to identify prediagnostic comorbidities and to improve identification of only newly diagnosed IBD cases, the patients with IBD must reside in Denmark continuously for at least 10 years before their index-date to be included as a case in the study. Demographic and residency data for cases and controls were retrieved from the CPR.

At the index date, each case was matched to 6 controls from the general Danish population by sex, date of birth, and municipality of residence. Each control must also have been a resident in Denmark continuously for at least 10 years before the index-date. In addition, the controls must reside in Denmark until the second inpatient or outpatient contact of their case to avoid immortality bias. Finally, the control must be free of IBD diagnoses before the index-date. The study population was followed until a censoring event including emigration, death, December 31, 2021 (end of study), or any diagnosis of IBD (for matched controls).

Comorbidities

We defined comorbidities as all 1,583 diseases recorded at the 3-character level in Chapters (I–XIX) of *ICD-10* (e.g., M72 Fibroblastic disorders). Hence, known EIMs, such as erythema nodosum, pyoderma gangrenosum, iridocyclitis, arthritis, and ankylosing spondylitis, and IMIDs, such as psoriasis and rheumatoid arthritis, were a subgroup of all comorbidities.

All analyses were conducted on the same group of patients, with each patient potentially contributing with multiple comorbidities or EIMs. Each disease was analyzed independently; however we did adjust for multiple testing, as described in the statistical analysis subsection below.

Statistical analysis

We analyzed the association between IBD and the 1,583 comorbidities. The analysis was split into 2 diagnostic windows (prediagnosis and postdiagnosis) for each 3-character disease category. First, we calculated the cumulative incidence spanning from 10 years prior up to 10 years after the IBD diagnosis date for the first appearance of any diagnosis by disease category within each chapter. We then calculated prediagnosis and postdiagnosis risk of *ICD-10* disease category diagnosis and finally, calculated risk of prediagnosis association compared with postdiagnosis association of statistically significant disease categories with large effect size.

The IBD prediagnostic period is defined as the 9-year period from 10 years prior to 1 year before the index-date. We excluded the most recent year before diagnosis from the prediagnostic period to avoid capturing sequelae of IBD management after diagnosis in the prediagnostic period. For each disease category, we recorded the number of cases and controls with that diagnosis in the prediagnostic period, performed the Fisher exact test to compute the *P* value, and calculated an odds ratio estimate (OR) with a confidence interval (CI).

Table 1. Demographic baseline characteristics (age (yr), year of diagnosis, sex at birth) of patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) and sex and age-matched controls

	Crohn's disease		Ulcerative colitis	
	N = 11,298	Controls, N = 67,788	N = 23,067	Controls, N = 138,402
Age of IBD onset (index date), y				
17–39	5,749 (50.9%)	34,458 (50.8%)	9,306 (40.3%)	55,817 (40.3%)
40–59	3,144 (27.8%)	18,934 (27.9%)	7,401 (32.1%)	44,375 (32.1%)
60+	2,405 (21.3%)	14,396 (21.2%)	6,360 (27.6%)	38,210 (27.6%)
Calendar year of birth				
1905–1939	740 (6.5%)	4,440 (6.5%)	2,501 (10.8%)	15,006 (10.8%)
1940–1959	2,508 (22.2%)	15,048 (22.2%)	6,230 (27.0%)	37,380 (27.0%)
1960–1979	3,506 (31.0%)	21,036 (31.0%)	7,740 (33.6%)	46,440 (33.6%)
1980–2003	4,544 (40.2%)	27,264 (40.2%)	6,596 (28.6%)	39,576 (28.6%)
Calendar year of IBD diagnosis (index date)				
2005–2009	2,724 (24.1%)	16,344 (24.1%)	6,977 (30.2%)	41,862 (30.2%)
2010–2014	3,261 (28.9%)	19,566 (28.9%)	7,265 (31.5%)	43,590 (31.5%)
2015–2018	3,134 (27.7%)	18,804 (27.7%)	5,494 (23.8%)	32,964 (23.8%)
2019–2021	2,179 (19.3%)	13,074 (19.3%)	3,331 (14.4%)	19,986 (14.4%)
Sex				
Female	6,368 (56.4%)	38,208 (56.4%)	11,916 (51.7%)	71,496 (51.7%)
Male	4,930 (43.6%)	29,580 (43.6%)	11,151 (48.3%)	66,906 (48.3%)

IBD, Inflammatory bowel disease.

The postdiagnostic period is defined as the period immediately after diagnosis and ends at the point of censoring or *ICD-10* disease category diagnosis. For each disease category, the study population comprises all IBD cases and controls without a previous diagnosis of the disease category in question. Therefore, all diagnoses within a disease category are the first for the case or the match. We performed Cox proportional regression analysis for *ICD-10* disease category diagnosis to compute a hazard ratio (HR), 95% confidence interval and *P* value.

To correct for multiple testing, we adjusted our significance threshold (from $P < 0.05$) with the Bonferroni correction (19). We tested 6,332 disease associations (1,583 disease categories for both CD and UC, in the prediagnostic and postdiagnostic windows) resulting in a Bonferroni adjusted *P* value of 7.90×10^{-6} , which we refer to as the threshold for disease-wide statistical significance.

In the interest of identifying potential disease associations, comorbidities with disease-wide statistical significance (in either the prediagnostic or postdiagnostic period) were further screened for prevalence threshold of at least 0.2% for assessment. Certain estimates could not be reported due to anonymity requirements and low case numbers; in these cases, the intervals are left blank in the figures.

Finally, we identified comorbidities with strong prediagnostic effects, relative to their postdiagnostic effects. This analysis included only highly significant prediagnostic ($P < 0.001$) disease categories, where the ratio of prediagnostic to postdiagnostic effect is greater than 1.2-fold.

To understand the generalizability of our findings based on Denmark's registries, we compared effect sizes for IBD-associated comorbidities with those available through the Finnish electronic registry system (FinRegistry) (20). The effect estimates that we could obtain

through this resource did not distinguish between the prediagnostic and postdiagnostic windows, which is an important limitation, but it does allow us to validate estimates. For the purposes of computing comparable estimates, we did not distinguish between prediagnostic and postdiagnostic windows in the validation subanalysis.

To identify heterogeneity in relationships between IBD and comorbidities in FinRegistry relative to the Danish registries, we used the Breslow-Day test with the Tarone correction (21) as implemented by the R package metafor (22). Some FinRegistry estimates did not include counts for privacy reasons, so for these diseases we could not assess heterogeneity. To identify systematic biases of the registries as to the size of ORs, we conducted a paired Wilcoxon signed rank test (23).

RESULTS

We identified 11,298 patients with CD and 23,067 patients with UC diagnosed with IBD in Denmark in the period from January 1, 2005 to December 31, 2021. Each patient was matched to 6 individuals from the general Danish population by sex, date of birth, and municipality ($n = 206,190$) using the date of diagnosis as index date (see Supplementary Figure S1, <http://links.lww.com/AJG/D736>). Among patients with IBD, 56.4% of patients with CD and 51.7% of patients with UC were women, 50.9% of patients with CD and 40.3% of patients with UC were diagnosed before age 40 (Table 1).

Cumulative incidence of comorbidities pre-IBD and post-IBD

We observed an overall pattern of multimorbidity across organ systems, beginning up to 10 years before diagnosis and being increasingly pronounced over time. We particularly observed a significantly increased risk of cardiometabolic,

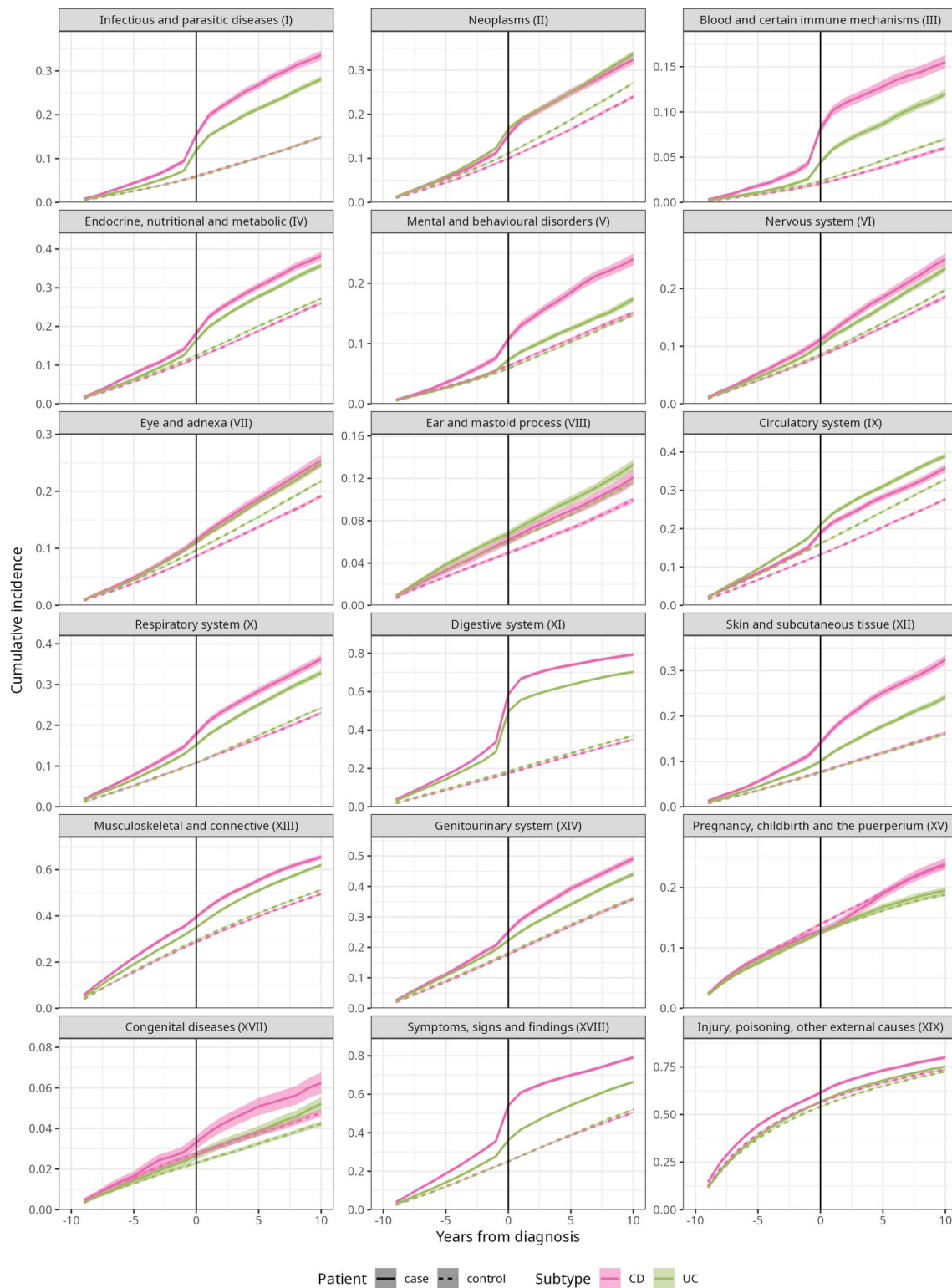


Figure 1. Cumulative incidence of ICD-10 diagnoses presented by chapter for CD, Crohn's disease and UC, ulcerative colitis and age, sex, and municipality-matched controls from -10 to 10 years from IBD, inflammatory bowel disease diagnosis. CD, Crohn's disease; IBD, Inflammatory bowel disease; ICD-10, *International Classification of Diseases, Tenth Revision*; UC, ulcerative colitis.

neuropsychological, and skin and musculoskeletal disorders present up to a decade before IBD diagnosis (Figure 1). For most organ systems, the excess occurrence of diseases both

prediagnostically and postdiagnostically was more pronounced in CD than in UC (Figure 1, see Supplementary Figure S2, <http://links.lww.com/AJG/D736>).

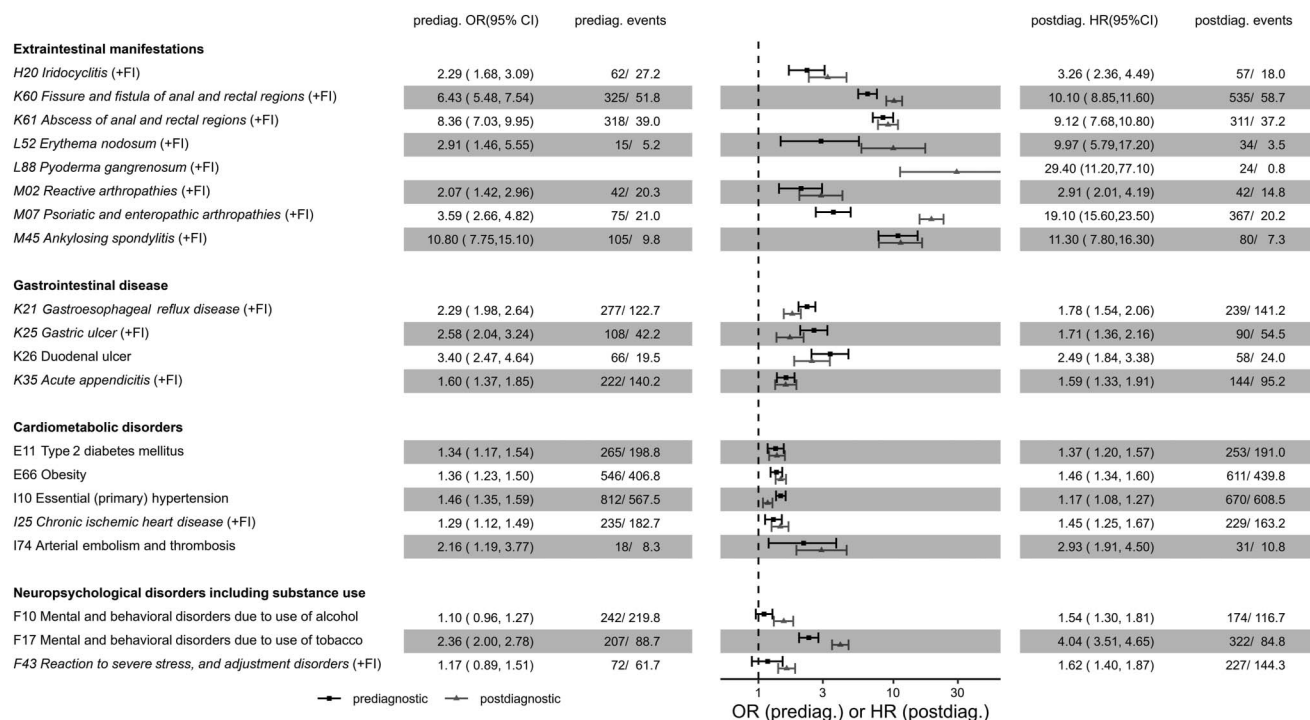


Figure 2. Prediagnostic and postdiagnostic risks of selected extraintestinal manifestations, gastrointestinal diseases, cardiometabolic, and neuropsychological disorders in CD. Prediagnostic OR and 95% CI and postdiagnostic HR and 95% CI estimates compared with age, sex and municipality-matched controls. Diagnoses meeting the prevalence threshold ($\geq 0.2\%$) with disease-wide significance (Bonferroni correction: $P < 7.90 \times 10^{-6}$) are included. The (+FI) symbol indicates that this effect is also significant in the Finnish registry. See Supplementary Figure S3a and Figure S3b, <http://links.lww.com/AJG/D736> for a comprehensive list of CD associated diagnoses. CD, Crohn's disease; CI, confidence intervals; HR, hazard ratio; OR, odds ratio.

Figures 2 and 3 illustrate the prediagnostic and postdiagnostic risks of selected EIMs, gastrointestinal diseases, cardiometabolic, and neuropsychological disorders for patients with CD and UC, respectively.

We confirmed an increased risk of psoriasis and rheumatoid arthritis in patients with IBD vs the matched control population, and further showed that the increased risk was present up to 10 years before IBD diagnosis, as illustrated by estimates for psoriasis (OR_{CD}: 2.58 [2.00–3.31]; OR_{UC}: 1.54 [1.26–1.88]) and rheumatoid arthritis in CD (OR: 2.18 [1.69–2.80]).

Prediagnostic and postdiagnostic EIMs

We confirmed the occurrence of a series of EIMs after IBD diagnosis and were able to show that most of these EIMs already occurred in excess up to 10 years before IBD diagnosis, including diseases of the joints, eyes, skin, and respiratory tract. Joint and musculoskeletal disorders, such as reactive arthropathies, were seen at increased rates in both CD (OR: 2.07 95% CI: [1.42–2.96]) and UC (OR: 1.42 [1.08–1.84]) before IBD diagnosis, and even more pronounced after IBD diagnosis. Pyoderma gangrenosum was only increased before diagnosis in UC (OR_{UC}: 4.80 [1.65–13.50]), despite a markedly excess risk in CD after diagnosis (HR_{CD}: 29.40 [11.20–77.10]).

Prediagnostic gastrointestinal diseases

Several gastrointestinal and liver disorders, which were expected postdiagnostically, were already observed in excess in the prediagnostic period for both CD and UC. Diagnoses of chronic gastrointestinal diseases associated with IBD, including

gastroesophageal reflux disease (OR_{CD}: 2.29 [1.98–2.64]; OR_{UC}: 1.65 [1.48–1.84]), gastric (OR_{CD}: 2.58 [2.04–3.24]; OR_{UC}: 1.68 [1.42–1.99]) and duodenal ulcers (OR_{CD}: 3.40 [2.47–4.64]; OR_{UC}: 0.98 [0.76–1.26]) showed stronger prediagnostic association with CD than UC. As expected, acute appendicitis before IBD diagnosis was associated with increased risk of CD (OR_{CD}: 1.60 [1.37–1.85]) and decreased risk of UC (OR_{UC}: 0.77 [0.66–0.90]).

Prediagnostic and postdiagnostic cardiometabolic disorders

We observed an increased risk of cardiovascular diseases in the prediagnostic period, including hypertension (OR_{CD}: 1.46 [1.35–1.59]; OR_{UC}: 1.24 [1.17–1.31]) and ischemic heart disease (OR_{CD}: 1.29 [1.12–1.49]; OR_{UC}: 1.31 [1.20–1.42]) for both CD and UC, and arterial embolism and thrombosis (OR_{CD}: 2.16 [1.19–3.77]) in CD, which increased over time in the postdiagnostic period. We furthermore observed an increased risk of type 2 diabetes mellitus both before (OR_{CD}: 1.34 [1.17–1.54]; OR_{UC}: 1.14 [1.04–1.24]) and after IBD diagnosis, as well as an increased risk of obesity, particularly in the postdiagnostic period (HR_{CD}: 1.46 [1.34–1.6]; HR_{UC}: 1.23 [1.15–1.32]).

Prediagnostic and postdiagnostic neuropsychological disorders including substance use

Excess risk of several mental and behavioral disorders, including depression, anxiety, and substance use disorders was observed in the prediagnostic and postdiagnostic periods for patients with CD in particular, who had a markedly increased risk of alcohol (HR: 1.54 [1.30–1.81]), tobacco use disorders (HR: 4.04 [3.51–4.65]), and stress and adjustment disorders (HR: 1.62 [1.40–1.87]) postdiagnostically.

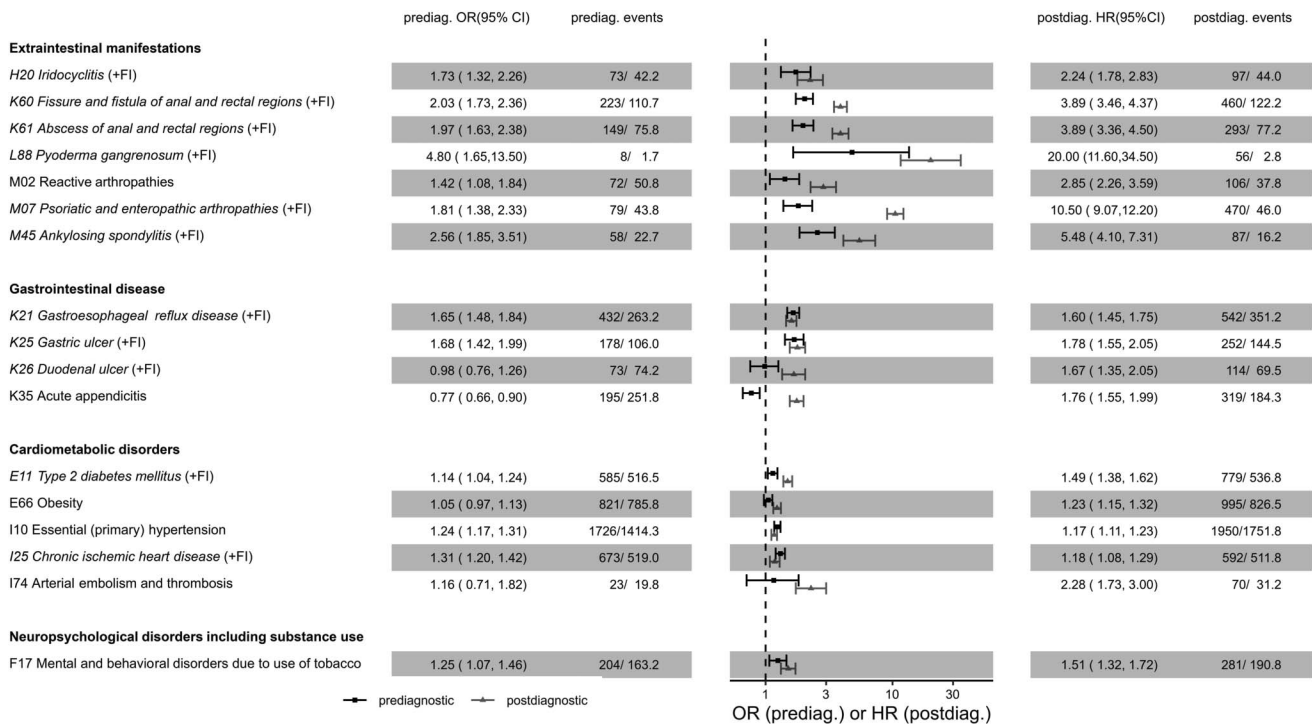


Figure 3. Prediagnostic and postdiagnostic risks of selected extraintestinal manifestations, gastrointestinal diseases, cardiometabolic, and neuropsychological disorders in ulcerative colitis. Prediagnostic OR and 95% CI and postdiagnostic HR and 95% CI estimates compared with age, sex and municipality-matched controls. Diagnoses meeting the prevalence threshold ($\geq 0.2\%$) with disease-wide significance (Bonferroni correction: $P < 7.90 \times 10^{-6}$) are included. The (+FI) symbol indicates that this effect is also significant in the Finnish registry. See Figure S4a and Figure S4b, <http://links.lww.com/AJG/D736> for a comprehensive list of UC associated diagnoses. CI, confidence intervals; HR, hazard ratio; OR, odds ratio; UC, ulcerative colitis.

All effect sizes calculated for comorbidities associated with CD and UC in the prediagnostic and postdiagnostic periods are presented in Supplementary Digital Content (see Table S1, <http://links.lww.com/AJG/D737>). All these effect sizes, except diseases with vague or catch-all descriptions, are visualized in Supplementary Digital Content (see Figures S3 and S4, <http://links.lww.com/AJG/D736>).

Disease risk in prediagnostic relative to postdiagnostic phase

Finally, we assessed which diseases were more prominent in the prediagnostic relative to the postdiagnostic period (Figure 4). Overall, there were more diseases occurring predominantly pre-diagnostically, compared with the postdiagnostically in patients with CD (14 diseases) than in patients with UC (10 diseases), confirming the more pronounced systemic prodromal development of CD and include expected diagnoses, such as hemorrhoids (OR: 2.59 [2.28–2.94]; HR: 1.81 [1.60–2.04]), as well as unexpected diagnoses, such as hypertension which was more prominent before diagnosis (OR: 1.46 [1.35–1.59]; HR: 1.17 [1.08–1.27]). Finally, patients with UC were at higher risk of being diagnosed with stress before compared with after UC diagnosis (OR: 1.41 [1.17–1.70]; HR: 1.08 [0.95–1.22]), potentially reflecting delayed diagnosis of IBD reflected by increased symptoms of deterioration.

Meta-analysis

To test our findings, we looked up all codes in the Finnish data (with the limitation that the Finnish estimates did not distinguish between the prediagnostic and postdiagnostic periods) and

marked all estimates presented in Figures 2–4 with (+FI) if our associations were confirmed in the Finnish data. Furthermore, direct comparison of Danish and Finnish effect sizes is shown in Figure 5, where we also indicate where there is evidence of inconsistency between Finland and Denmark when corrected for multiple testing. Effects which were stronger in Denmark appear above the line, and effects which were stronger in Finland appear below the line.

There was evidence of heterogeneity of ORs between the 2 countries in only 15.7% (44/281) and 11.4% (35/301) of diseases in CD and UC respectively. In every disease except one, the directions of the effect size were consistent. The one exception was E78.0 Pure hypercholesterolemia, where the Finnish data indicated a protective effect for IBD (OR_{CD}: 0.67 [0.60–0.67]; OR_{UC}: 0.82 [0.76–0.88]), whereas IBD was a risk factor in Denmark (OR_{CD}: 1.30 [1.18–1.42]; OR_{UC}: 1.25 [1.18–1.32]). We conducted a paired Wilcoxon signed rank test between the registry systems. Crohn's disease ORs were systematically higher in Denmark relative to Finland ($P < 1 \times 10^{-6}$), whereas there was no significant difference between effect sizes for Danish and Finnish patients with UC ($P = 0.203$).

DISCUSSION

This comprehensive population-based disease-wide association study examining >1,500 diseases among >35,000 patients with IBD and >200,000 controls revealed that a diagnosis of IBD was associated with 312 other diseases, of which 125 diseases were present up to 10 years before diagnosis. Based on these observations, we created an interactive resource to explore IBD

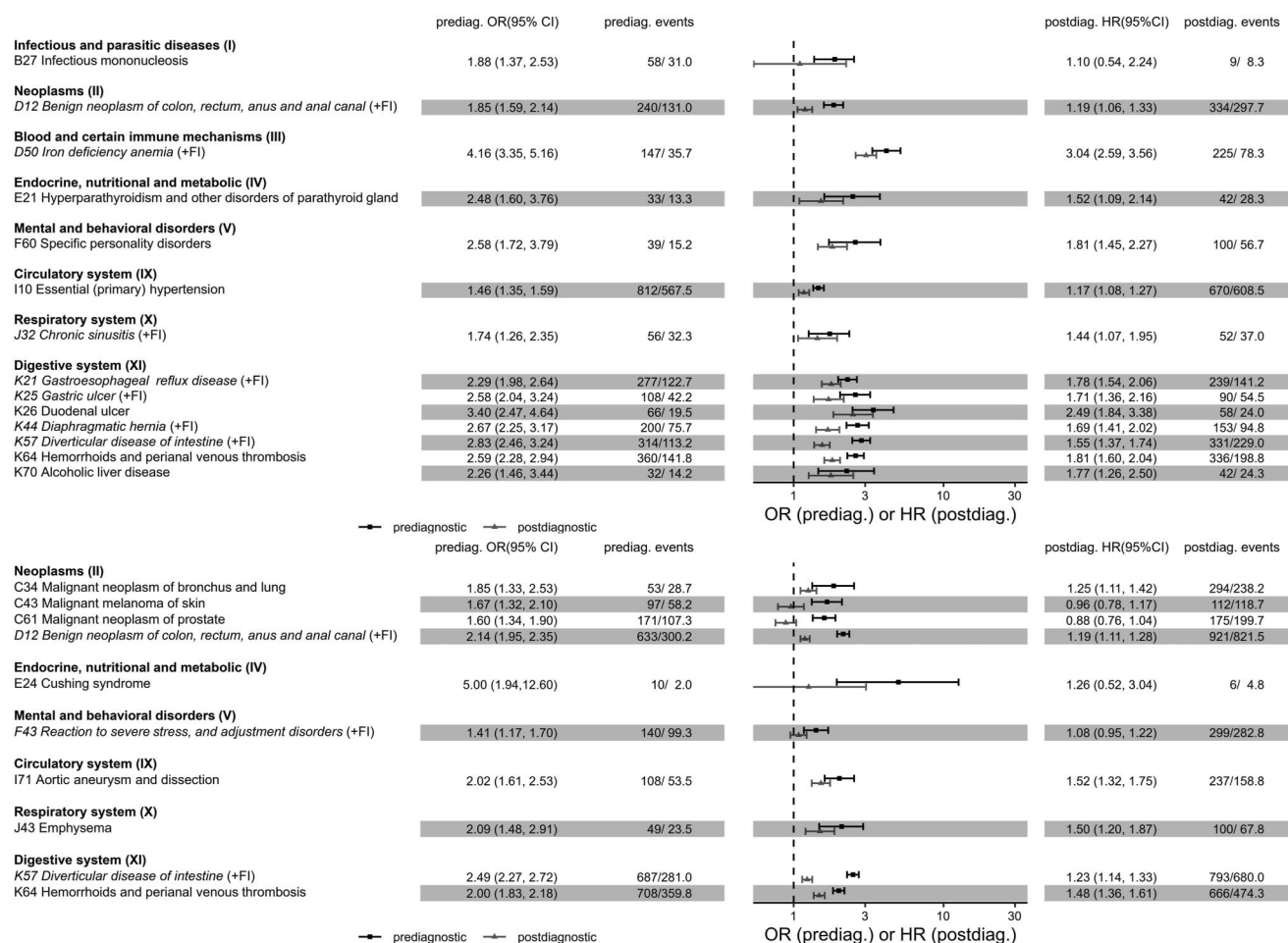


Figure 4. Diagnoses associated with CD and UC before IBD. Prediagnostic OR compared with postdiagnostic HR of diagnoses of disease-wide significance for Crohn's disease and ulcerative colitis. Highly statistically significant diagnoses ($P < 0.001$), with prediagnostic effect estimates (OR) at least 1.2 of the postdiagnostic effect estimates (HR) are included. The (+FI) symbol indicates that this effect is also significant in the Finnish registry. CD, Crohn's disease; HR, hazard ratio; IBD, inflammatory bowel disease; OR, odds ratio; UC, ulcerative colitis.

comorbidities across organ systems (see Supplementary Table S1, <http://links.lww.com/AJG/D737>). In addition to identifying expected diseases associated with IBD, including known EIMs, we identified multisystem comorbidities up to a decade before the incident IBD diagnosis, including cardiometabolic, neuropsychological, and immune and infectious diseases associated with both CD and UC. Most of the prediagnostic comorbidities appeared with larger effect sizes and earlier in CD than patients with UC. Results were validated and confirmed with respect to publicly available (albeit cruder) Finnish estimates.

The validity of our findings is further confirmed by observation of an expected increased risk of EIMs in patients with IBD, including erythema nodosum, pyoderma gangrenosum, and iridocyclitis, ankylosing spondylitis, as well as psoriasis, and coeliac disease (24). In addition to showing the exact magnitude of these risks at a population level representing the true spectrum of IBD (from the mildest to the most severe case), hence providing estimates that can be used for information of newly diagnosed patients with a yet unknown disease course, we also show that these disorders are present at significantly increased frequency several years before diagnosis, pointing toward a long prodromal phase of IBD with multiorgan involvement. We observe that the

risk of EIMs, psoriasis, and rheumatoid arthritis in the post-diagnostic period is larger in CD than in UC, again highlighting CD particularly as a multisystem disease. Our findings may have implications for screening and therapeutic considerations and raises the question, whether EIM and other autoimmune diagnoses should prompt practitioner investigation for IBD in the context of gastrointestinal symptoms.

In addition to EIMs, psoriasis, and rheumatoid arthritis, we observe an increased risk of cardiometabolic disorders after IBD diagnosis in accordance with former observational studies (25,26). We show that these diseases may be present up to a decade before IBD diagnosis, which may have both etiological and treatment implications. The pre-IBD presence of cardiometabolic diseases indicates that not only chronic systemic inflammation, but also shared underlying mechanisms for development of cardiometabolic disease and IBD may exist, potentially reflecting shared environmental factors such as smoking and diet, which may act through microbiome dysfunction (3). The increased risk of cardiometabolic disease in the prediagnostic period may also have clinical implications. The risk of ischemic heart disease is increased markedly before IBD diagnosis and warrants clinical awareness after an IBD diagnosis. As JAK inhibitors—a class of

associations with IBD can be regarded as confirmatory. Delay in IBD diagnosis may affect some of the prediagnostic results, however Vind et al (2006) (34) find that median delay in IBD diagnosis is 8.3 months for CD and 4.5 months for UC. For this reason, we excluded the year before diagnosis from the prediagnostic period. The observation of comorbidities occurring >1 year before IBD diagnosis is therefore likely to reflect variation in whether comorbidities occur before or after IBD onset. We matched for calendar period but did not stratify for this as this was out of scope in the already extensive assessment of prediagnostic and postdiagnostic occurrence of all comorbidities. However, due to changes in treatment possibilities over calendar time, it would be of interest in future studies to examine the effect of treatment changes on the occurrence of specific comorbidities to IBD. The study also contains risk of ascertainment bias, but this is diminished by use of population-representative, nationwide diagnostic data, where cases are additionally matched to controls within municipality of residence. This is particularly the case for our findings in analyses from the prediagnostic period, where patients with IBD would not be subject to the same level of clinical follow-up as following diagnosis. Postdiagnostic effects ought to be interpreted in light of possible treatment effects, these relationships may be counterintuitive. For example, there is evidence to suggest that, counterintuitively, anti-TNFs increase the risk of other IMIDs in patients with IBD (35).

In conclusion, in this population-based disease-wide study of almost 35,000 patients with IBD followed for >300,000 prediagnostic and >250,000 postdiagnostic person-years (average 7.68 person-years per case), we observed an overall pattern of multimorbidity beginning from 10 years before diagnosis, with a more pronounced effect in CD relative to UC. Findings indicate the presence of multisystem pathology, which is increasing in frequency throughout the disease course. This underscores the need for multidisciplinary care, including cardiometabolic measurements and neuropsychological support, and increased attention to the management of a broad range of co-occurring disorders already present at the time of IBD diagnosis.

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CONFLICTS OF INTEREST

Guarantor of the article: Anthony C. Ebert, MPhil, PhD.

Specific author contributions: A.C.E., G.P., M.B., and T.J. conceptualized the paper. All authors were involved in the developing the methodology, and validation of findings. A.C.E. and G.P. developed the code for and undertook the analysis. A.C.E., G.P., and M.B. provided the formal statistical methodology input. A.S. and A.C.E. developed the Finnish validation analysis. The original draft was written by A.C.E., M.B., C.W.L., and T.J. All authors contributed to review and editing of the manuscript. A.C.E., M.B., B.V., C.W.L., L.L., A.S. and T.J. contributed to the visualization of findings.

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Data sharing: The study was 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) is strongly associated with other diseases.
- ✓ IBD has a complex etiology.

WHAT IS NEW HERE

- ✓ IBD seems to be a multiorgan systemic disease not confined to the gut.
- ✓ Associations between IBD and nondigestive disorders are present up to 10 years before diagnosis either reflecting a prolonged prediagnostic phase or common etiologies.
- ✓ Postdiagnostic extraintestinal manifestations are more pronounced in Crohn's disease relative to ulcerative colitis.
- ✓ These findings are validated in an international comparison.

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