Increased Burden of Psychiatric Disorders in Inflammatory Bowel Disease

*Charles N. Bernstein, MD,[*] Carol A. Hitchon, MD, MSc,[*] Randy Walld, BSc,[†] James M. Bolton, MD,[‡] Jitender Sareen, MD,[‡] John R. Walker, PhD,[§] Lesley A. Graff, PhD,[§] Scott B. Patten, MD, PhD,[¶] Alexander Singer, MB BAO BCh,[‖] Lisa M. Lix, PhD,[†,**] Renée El-Gabalawy, PhD,[¶,††] Alan Katz, MB ChB MSc,[†,‖,**] John D. Fisk, PhD,[††,‡‡] and Ruth Ann Marrie, MD, PhD[*,‖]; for the CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease*

Background: Psychiatric comorbidity in inflammatory bowel disease (IBD) is well known; however, data from a truly representative sample are sparse. We aimed to estimate the incidence and prevalence of psychiatric disorders in an IBD cohort compared with a matched cohort without IBD.

Methods: Using population-based administrative health data from Manitoba, Canada, we identified all persons with incident IBD from 1989 to 2012 and a general population matched cohort (5:1). We applied validated algorithms for IBD, depression, anxiety disorders, bipolar disorder, and schizophrenia to determine the annual incidence of these conditions post–IBD diagnosis and their lifetime and current prevalence.

Results: There were 6119 incident cases of IBD and 30,573 matched individuals. After adjustment for age, sex, socioeconomic status, region of residence, and year, there was a higher incidence in the IBD cohort compared with controls for depression (incidence rate ratio [IRR], 1.58; 95% confidence interval [CI], 1.41–1.76), anxiety disorder (IRR, 1.39; 95% CI, 1.26–1.53), bipolar disorder (IRR, 1.82; 95% CI, 1.44–2.30), and schizophrenia (IRR, 1.64; 95% CI, 0.95–2.84). Incidence rate ratios were similar for Crohn's disease and ulcerative colitis between males and females and were stable over time. However, within the IBD cohort, the incidence rates of depression, anxiety, and bipolar disorders were higher among females, those aged 18–24 years vs those older than 44 years, urbanites, and those of lower socioeconomic status. The lifetime and current prevalence rates of psychiatric disorders were also higher in the IBD than the matched cohort.

Conclusions: The incidence and prevalence of psychiatric disorders are elevated in the IBD population.

Key Words: mental health; psychiatric disorders; population based; inflammatory bowel disease; chronic immunoinflammatory disease.

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From the *Department of Internal Medicine, †Manitoba Centre for Health Policy, ‡Department of Psychiatry, §Department of Clinical Health Psychology, ‖Department of Family Medicine, **Department of Community Health Sciences, and ††Department of Anesthesia and Perioperative Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada; ¶Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; ‡‡Departments of Psychiatry, Psychology and Neuroscience, and Medicine, Dalhousie University, Halifax, NS, Canada

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Address correspondence to: Charles N. Bernstein, MD, 804F-715 McDermot Avenue, University of Manitoba, Winnipeg, MB R3E3P4 (charles.bernstein@umanitoba.ca).

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INTRODUCTION

Psychiatric disorders adversely affect a broad range of outcomes in inflammatory bowel disease (IBD). Depression is associated with an increased risk of disease relapse and poorer response to treatment.[1–4] Anxiety is associated with an increased risk for surgery, lower adherence to medication, and poorer quality of life.[1, 5, 6] In a multi-institution cohort study, after adjusting for confounders, comorbid depression and/or anxiety was associated with a 28% increased risk of surgery in Crohn's disease (CD), more colonoscopies, and an increased likelihood of using immunomodulators.[7] No studies have used a prospective method in a population-representative cohort to examine these associations. Fatigue is a troubling symptom in persons with IBD, and depression may contribute to fatigue in some persons.[8, 9]

Although psychiatric disorders have been shown to emerge after a diagnosis of IBD,[10] they may also antedate the diagnosis of IBD by some years.[11, 12] Most studies reporting these findings have focused on depression or anxiety and have emphasized the prevalence rather than incidence of psychiatric disorders, although the latter is critical for understanding etiology. Considering the adverse effects of comorbid psychiatric disorders on the course of IBD, it is important to comprehensively define the burden of psychiatric comorbidity in IBD. Hence, we pursued a population-based study to determine the incidence and prevalence of depression, anxiety, bipolar disorder, and schizophrenia after a diagnosis of IBD. We compared findings from the IBD cohort with matched controls from the general population without IBD.

METHODS

Setting and Data Sources

Manitoba is a central Canadian province with a population of 1.3 million and universal, publicly funded health care. We utilized databases in the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy. These administrative (health claims) databases cover more than 98% of the population and can be linked at an individual level using an encrypted unique personal health identification number (PHIN). The University of Manitoba Health Research Ethics Board approved the study, and the Manitoba Health Information Privacy Committee approved data access.

We used the following databases (and data): the Population Registry (sex, dates of birth and death, dates of health care coverage, postal code of residence), Discharge Abstract Database (hospitalizations, including admission and separation dates, and up to 25 diagnoses recorded using International Classification of Disease [ICD] codes, including ICD-9-CM codes until 2004 and ICD-10-CA codes thereafter), Medical Services (ie, physician claims, including date of service and a single ICD-9-CM physician-assigned diagnosis), and the Drug Program Information Network (DPIN; all prescriptions dispensed including drug name, dispensation date, and drug identification number [DIN]). The DIN is linked to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System.[13] DPIN became available in 1995, whereas the other databases were available from April 1, 1984, through March 31, 2012.

Study Populations

We conducted a retrospective, matched cohort study. As reported elsewhere,[14] we identified all Manitoba residents with IBD during the study period by applying a validated case definition.[15] These IBD cases were further classified as CD and ulcerative colitis (UC). The date of diagnosis (index date) was the date of the first health claim for IBD. We restricted the analysis to incident cases of IBD. An incident case was one in which there were no claims for IBD contacts for 5 years before the index date; 1989 was the index year for the earliest incident cases. There is no ICD code for IBD type unclassified or indeterminate colitis, and based on our experience, these subjects are grouped with those identified as UC. If subjects had health system contacts for both CD and UC, they were identified by the majority of their most recent 9 contacts. Next, we created a cohort without IBD, which was matched 5:1 on sex, year of birth ± 5 years, and the first 3 digits of their postal code. The postal code provided detailed information on region of residence within the province. As this was part of a larger study involving other immune-mediated diseases, IBD, demyelinating disease, rheumatoid arthritis, and related disorders was excluded from this cohort. We assigned each control the index date of its matched case.

Psychiatric Disorders

To identify individuals affected by psychiatric disorders in each cohort, we applied case definitions for identifying depression, anxiety, bipolar disorder, and schizophrenia (Supplementary Table 1).[16, 17] The case definitions for depression and anxiety have been validated in IBD and multiple sclerosis (MS) populations.[16, 17] The case definition for schizophrenia has been validated in the MS population and the United States Medicaid population; in the latter population, it has a positive predictive value of 86.8%.[18] Prescription claims were only available since 1995 and were included in the case definition for depression and anxiety disorder, so we included a binary model covariate indicating whether the disorder occurred before or after these data were available. To estimate incidence of these psychiatric disorders post–IBD diagnosis, the first psychiatric disorder claim had to occur post–index date for IBD and had to be preceded by a 5-year period with no claims for that psychiatric disorder.[19] Therefore, we report incidence for April 1, 1989, through March 31, 2012.

We estimated lifetime prevalence by assuming that once a person met the case definition for the selected disorder, he or she was considered affected thereafter if alive and residing in Manitoba. Because some of the individuals identified using this approach could experience remission of the psychiatric disorder, we also approximated the current prevalence of these conditions

TABLE 1: Characteristics of Incident Disease Cohorts at the Time of Diagnosis and Matched Cohorts at the Matched Index Date

Characteristic	CD (n = 2389)	CD Matches (n = 11,938)	UC (n = 2957)	UC Matches (n = 14,778)	IBD (n = 5346)	IBD Matches (n = 26,716)
Female, No. (%)	1408 (58.9)	7040 (59.0)	1500 (50.7)	7500 (50.8)	2908 (54.4)	14,540 (54.4)
Age at diagnosis, mean (SD), y	40.3 (16.8)	40.3 (16.8)	44.7 (17.7)	44.7 (17.7)	42.8 (17.4)	42.7 (17.4)
Duration of follow-up from the index date, median (IQR), y	11.0 (5.5–16.6)	10.2 (4.7–16.3)	10.0 (4.7–16.2)	9.3 (4.1–15.5)	10.4 (5.0–16.4)	9.6 (4.3–15.9)
Region of residence, No. (%)						
Urban	1611 (67.4)	8051 (67.4)	1929 (65.2)	9642 (65.2)	3540 (66.2)	17,693 (66.2)
Rural	778 (32.6)	3887 (32.6)	1028 (34.8)	5136 (34.8)	1806 (33.8)	9023 (33.8)
Socioeconomic status	–0.23 (0.89)	–0.19 (0.87)	–0.28 (0.92)	–0.22 (0.89)	–0.26 (0.91)	–0.21 (0.88)

requiring ongoing care each year. Once the case definition was met, the subject would be counted as a current prevalent case if there was at least 1 hospitalization or 2 physician claims for the disorder in that year. Prior work has shown that when application of this approach is used in the general Manitoba population, the prevalence estimates for depression and anxiety disorder are comparable to those obtained in the Canadian Community Health Survey–Mental Health.[20] The incidence and prevalence estimates were age- and sex-standardized to the 2010 Canadian population. Average annual sex- and age-specific incidence and prevalence estimates using the age groups 18–24, 25–44, 45–64, and ≥65 years, commonly applied to the annual Canadian Community Health Survey (CCHS), were reported.

Covariates

Sex (male as reference group), age (18–24 [reference group], 25–44, 45–64, ≥65 years), socioeconomic status (SES) in quintiles (lowest quintile as reference group), region (urban or rural [reference group]), and fiscal year were included as covariates. Postal codes were linked to dissemination area–level census data by postal code to determine SES. Socioeconomic status was defined by the Socioeconomic Factor Index, version 2 (SEFI-2), which is a factor score that incorporates information regarding average household income, percentage of single parent households, unemployment rate, and high school education rate; scores of less than 0 indicate higher SES.[18] The mean SEFI2 score in the province is 0, with mean scores in neighborhoods in the largest city in the province varying from –1.3 to +1.2. Urban regions included the cities of Winnipeg (population >600,000) and Brandon (population >47,000). To account for possible surveillance bias due to increased health system encounters, we counted the annual number of physician visits.

Analysis

To compare the incidence rates and prevalence between the IBD and matched cohorts, and the CD and UC cohorts and their matched cohorts, we used negative binomial regression models, for which we report prevalence ratios (PRs), incidence rate ratios (IRRs), and 95% confidence intervals (CIs). To account for variable duration of follow-up, we included the natural logarithm of person-years as a model offset. Models also included the covariates defined above. The models of prevalence used generalized estimating equations with an exchangeable correlation structure to account for dependence of repeated measures within individuals. Additional adjusted models contained the 2-way interaction of cohort*year to test whether temporal trends differed between the IBD and matched cohorts.

Statistical analyses were performed using SAS V9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

There were 6119 incident cases with IBD, of whom 44.7% had CD and 55.3% had ulcerative colitis (UC), and 30,573 matched controls. Nearly 55% were women, with a mean (SD) age at the index date of 42.8 (17.4) years, and 66.2% were urbanites (Table 1).

Incidence

In 2011, the crude annual incidence of depression in the IBD cohort per 1000 was 18.6 (95% CI, 14.2–24.3) vs 10.8 (95% CI, 9.26–12.5) in the matched cohort; of anxiety disorders, it was 25.0 (95% CI, 19.6–32.0) vs 16.3 (95% CI, 14.3–18.6) in the matched cohort; of bipolar disorder, it was 3.80 (95% CI, 2.29–6.30) vs 1.56 (95% CI, 1.09–2.23) in the matched cohort. The average annual incidence (reported due to small cell sizes instead of crude annual incidence) of schizophrenia was 4.62 (95% CI, 3.12–6.84) in the IBD cohort vs 3.15 (95% CI, 2.53–3.92) in the matched cohort.

The average annual age-specific incidence rates of the psychiatric disorders varied by age in the IBD cohort, and in the CD and UC subgroups (Fig. 1). The incidence of psychiatric

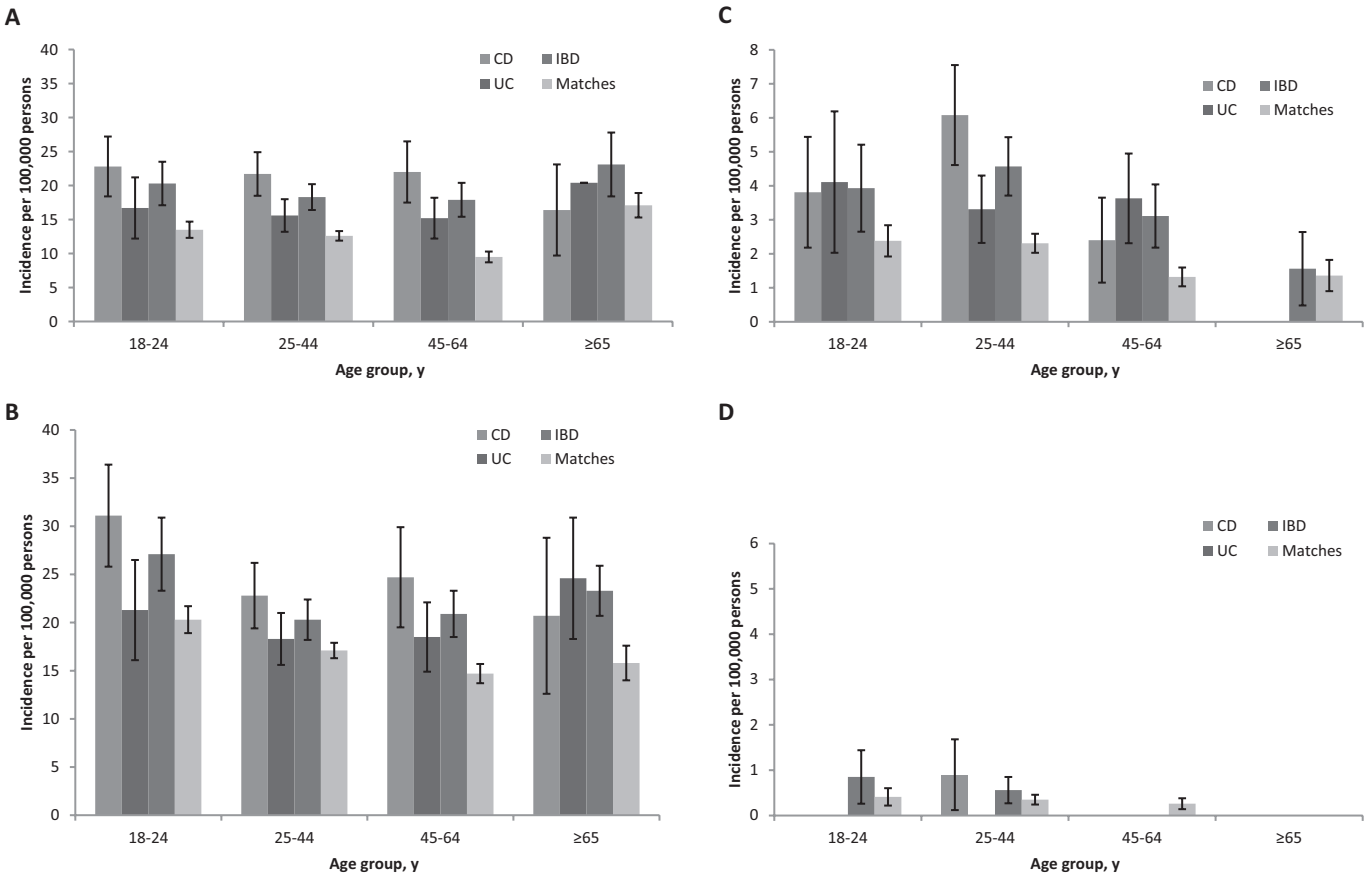

FIGURE 1. Average annual age-specific incidence of psychiatric disorders. Error bars represent 95% confidence intervals. A, Depression. B, Anxiety disorder. C, Bipolar disorder. D, Schizophrenia.

disorders also varied by sex. Within sexes, the incidence rates of depression (IRR, 1.72; 95% CI, 1.51–1.96 for males; and IRR, 1.47; 95% CI, 1.33–1.63 for females), anxiety disorder (IRR, 1.27; 95% CI, 1.12–1.43 for males; and IRR 1.35; 95% CI, 1.22–1.48 for females), and bipolar disorder (IRR, 1.96; 95% CI, 1.48–2.60 for males; and IRR 1.92; 95% CI, 1.57–2.36 for females) were higher in the IBD cohort as compared with the matched cohort. The average annual incidence of schizophrenia did not significantly differ between IBD groups and controls (IRR, 1.80; 95% CI, 0.95–3.42 for males; and IRR, 1.22; 95% CI, 0.65–2.30 for females). The IRRs were similar in CD compared with matched controls and UC compared with matched controls, and they were similar between the sexes for all psychiatric disorders except for depression, where the IRR was higher in males with CD (IRR, 2.02; 95% CI, 1.67–2.45) than females with CD (IRR, 1.53; 95% CI, 1.33–1.76) or than males with UC (IRR, 1.34; 95% CI, 1.17–1.54) (Table 2).

Over the entire study period, the incidence of depression was higher in the IBD cohort than in the matched population (IRR, 1.58; 95% CI, 1.41–1.76), as was the incidence of anxiety disorders (IRR, 1.39; 95% CI, 1.26–1.53) and bipolar disorder (IRR, 1.82; 95% CI, 1.44–2.30) (Table 3). The incidence of schizophrenia was elevated in the IBD cohort as compared with the matched cohort, but this failed to reach statistical significance (IRR, 1.64; 95% CI, 0.95–2.84). Women, those aged 18–24 years, those of lower SES, and those living in urban settings had an increased incidence of depression, anxiety disorder, and bipolar disorder (Table 3). Persons aged 65 years and older had an increased incidence of depression. The incidence of all disorders did not change over time.

When we conducted these analyses stratified by type of IBD, the findings were similar. After adjustment, the CD cohort had a higher incidence of depression (IRR, 1.76; 95% CI, 1.51–2.05), anxiety disorder (IRR, 1.56; 95% CI, 1.35–1.79), and bipolar disorder (IRR, 1.73; 95% CI, 1.25–2.40) than their matched cohort (Supplementary Table 2). The incidence of schizophrenia was also elevated in the CD cohort but did not reach statistical significance (IRR, 1.83; 95% CI, 0.85–3.97). After adjustment, the UC cohort had a higher incidence of depression (IRR, 1.43; 95% CI, 1.24–1.64), anxiety disorder (IRR, 1.27; 95% CI, 1.11–1.44), and bipolar disorder (IRR, 1.82; 95% CI, 1.33–2.50) than their matched cohort (Supplementary Table 3). The incidence of schizophrenia did not differ between the UC cohort and its matched cohort (IRR, 1.53; 95% CI, 0.71–3.30).

TABLE 2: Sex-Specific Average Annual Incidence of Psychiatric Disorders per 1000 Person-Years

Sex	CD	CD Matches	IRR (95% CI)	UC	UC Matches	IRR (95% CI)
Depression						
Male	17.6 (14.8–20.5)	8.7 (7.8–9.6)	**2.02 (1.67–2.45)**	13.2 (11.2–15.3)	8.8 (8.0–9.5)	**1.51 (1.26–1.80)**
Female	24.8 (21.8–27.9)	16.2 (15.2–17.3)	**1.53 (1.33–1.76)**	21.1 (18.3–23.9)	14.9 (13.9–15.9)	**1.41 (1.22–1.64)**
Anxiety disorder						
Male	20.2 (17.0–23.4)	13.3 (12.1–14.4)	**1.52 (1.27–1.82)**	15.4 (12.2–16.6)	13.2 (12.2–14.1)	1.09 (0.92–1.30)
Female	29.4 (25.8–32.9)	21.3 (20.0–22.6)	**1.38 (1.21–1.58)**	25.7 (22.5–29.0)	19.6 (18.4–20.8)	**1.31 (1.14–1.51)**
Bipolar disorder						
Male	2.6 (1.6–3.6)	1.5 (1.2–1.9)	**1.74 (1.11–2.73)**	3.0 (2.1–3.9)	1.4 (1.1–1.7)	**2.13 (1.48–3.07)**
Female	5.6 (4.3–6.8)	2.6 (2.2–3.0)	**2.13 (1.63–2.77)**	3.5 (2.6–4.5)	2.1 (1.8–2.5)	**1.67 (1.21–2.31)**
Schizophrenia						
Male	0.60 (0.12–1.07)	0.27 (0.13–0.42)	2.17 (0.83–5.72)	0.49 (0.13–0.86)	0.31 (0.18–0.45)	1.57 (0.67–3.70)
Female	0.53 (0.16–0.90)	0.33 (0.20–0.47)	1.60 (0.72–3.57)	s	0.33 (0.19–0.46)	0.83 (0.29–2.40)

Abbreviation: s, suppressed for privacy and confidentiality.

TABLE 3: Adjusted[a] Rate Ratios and 95% Confidence Intervals for the Association Between Inflammatory Bowel Disease and Incidence of Psychiatric Disorders

Variable	Depression	Anxiety Disorder	Bipolar Disorder	Schizophrenia
Cohort				
Matches	1.0	1.0	1.0	1.0
IBD	**1.58 (1.41–1.76)**	**1.39 (1.26–1.53)**	**1.82 (1.44–2.30)**	1.64 (0.95–2.84)
Sex				
Male	1.0	1.0	1.0	1.0
Female	**1.68 (1.55–1.81)**	**1.54 (1.45–1.65)**	**1.65 (1.38–1.98)**	0.92 (0.61–1.41)
Age, y[b]				
18–24	1.0	1.0	1.0	1.0
25–44	0.93 (0.83–1.04)	**0.79 (0.71–0.87)**	1.11 (0.86–1.43)	0.60 (0.33–1.10)
45–64	**0.77 (0.68–0.87)**	**0.72 (0.65–0.80)**	**0.68 (0.52–0.89)**	
≥65	**1.21 (1.07–1.37)**	**0.76 (0.68–0.86)**	**0.51 (0.36–0.73)**	
Socioeconomic status				
Quintile 1 (lowest)	**1.26 (1.11–1.42)**	**1.30 (1.16–1.45)**	**1.45 (1.11–1.89)**	**2.96 (1.45–6.03)**
Quintile 2	**1.18 (1.05–1.32)**	1.08 (0.98–1.20)	**1.45 (1.13–1.87)**	**3.11 (1.60–6.07)**
Quintile 3	**1.14 (1.02–1.28)**	1.08 (0.97–1.19)	**1.38 (1.08–1.78)**	1.50 (0.72–3.17)
Quintile 4	**1.03 (0.92–1.15)**	**1.11 (1.01–1.22)**	1.11 (0.86–1.42)	1.75 (0.89–3.46)
Quintile 5 (highest)	1.0	1.0	1.0	1.0
Region				
Rural	1.0	1.0	1.0	1.0
Urban	**1.20 (1.10–1.31)**	**1.24 (1.15–1.34)**	**1.78 (1.46–2.18)**	1.43 (0.90–2.28)
No. physician visits	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**
Year[c]	0.993 (0.984–1.001)	1.005 (0.997–1.012)	1.008 (0.989–1.027)	0.957 (0.915–1.001)

[a]Models for depression and anxiety disorders also include term to adjust for whether prescription claims were used in the case definition.
[b]Schizophrenia age groups collapsed to 18–24 and ≥25 years due to small cell sizes.
[c]Year refers to annual change; bolding indicates associations that are statistically significant.

Prevalence

The age-specific lifetime and crude prevalence rates for each psychiatric disorder within CD, UC, all IBD, and the IBD matched cohorts for 2011 are shown in Figure 2. The lifetime and crude prevalence rates of depression, anxiety, and bipolar disorder were consistently higher in the IBD cohorts than in the matched cohorts.

After adjustment for age, sex, SES, region of residence and year, the lifetime prevalence rates of depression (PR, 1.42; 95% CI, 1.32–1.52), anxiety disorder (1.24; 95% CI, 1.17–1.31), and bipolar disorder (IRR, 1.45; 95% CI, 1.19–1.77) were higher in the IBD cohort than the matched cohort over the entire study period (Table 4). The lifetime prevalence of schizophrenia did not differ between the IBD and matched cohorts (PR, 1.11; 95% CI, 0.76–1.60). As observed for incidence, female sex, lower SES, and urban residence were associated with an increased lifetime prevalence of depression, anxiety disorders, and bipolar disorder (Table 4). In contrast to the findings for incidence, older age was associated with an increased lifetime prevalence of psychiatric disorders, and lifetime prevalence increased slightly over time in both populations, except for schizophrenia. Temporal trends were similar in both populations (data not shown). Findings were similar for current prevalence (data not shown). When we repeated the analyses stratified by type of IBD, most of the findings were consistent with those observed in the IBD cohort overall, with only 1 exception, that of schizophrenia in CD (Supplementary Tables 4 and 5).

DISCUSSION

We found that the incidence and prevalence of multiple psychiatric disorders, including depression, anxiety, and bipolar disorder, were higher in the IBD population than in a matched cohort from the general population. This study is the largest to date to evaluate the incidence and prevalence of psychiatric disorders in persons with IBD and one of few studies to report estimates by age, sex, and changes over time. Further, it is one of the few studies to address the incidence and prevalence of bipolar disorder or schizophrenia in persons with IBD.[21, 22] We found a suggestion of an increased risk of schizophrenia after being diagnosed with CD but not UC. Elsewhere, it has been reported that there is no increased risk of schizophrenia in IBD.[23] There is no known mechanism that could explain this; however, we report it here to facilitate future efforts at replication.

Several demographic factors were associated with the risk of psychiatric disorder. As compared with men, women with IBD had a higher incidence and prevalence of depression, anxiety, and bipolar disorder, which mirrors the sex differential in the general population.[24] The increased IRR in males and females with CD and UC compared with controls was similar for anxiety disorders, bipolar disorder, and depression. However, males

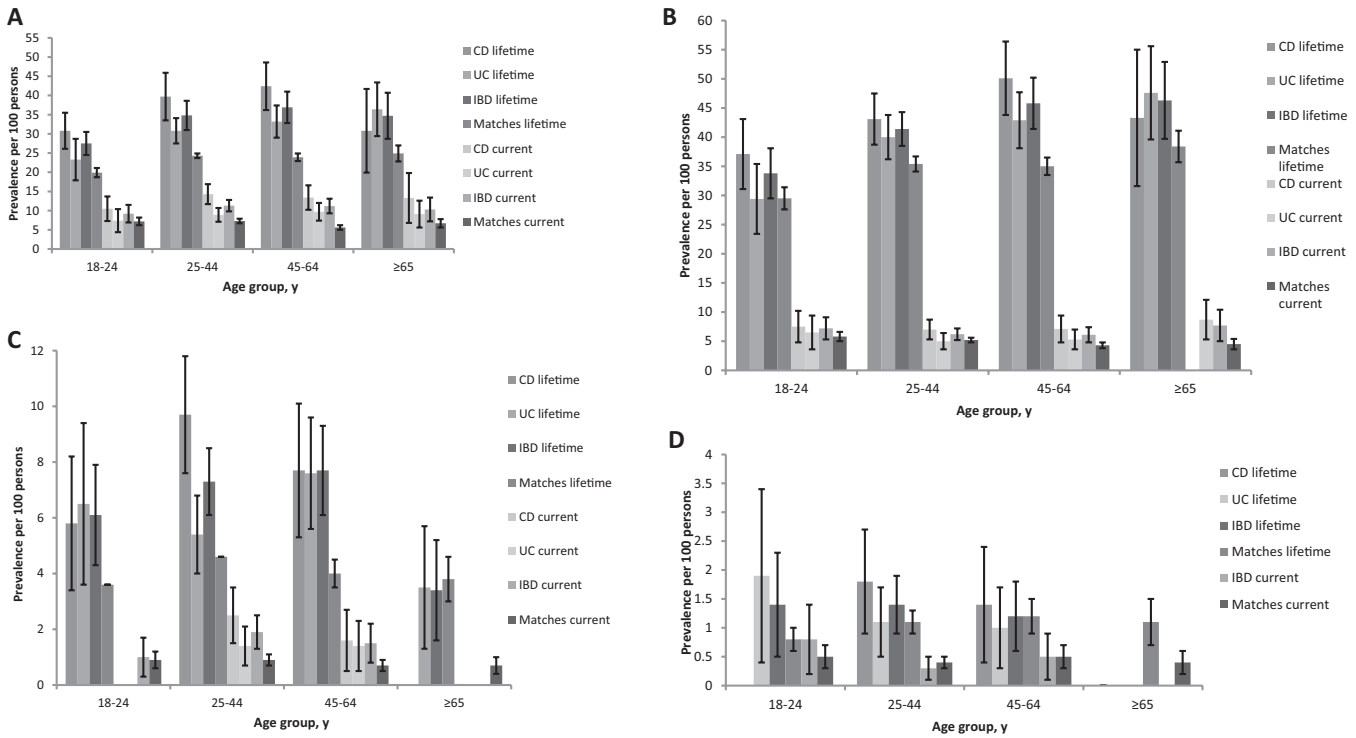

FIGURE 2. Age-specific lifetime and current prevalence of psychiatric disorders in 2011. Error bars represent 95% confidence intervals. A, Depression. B, Anxiety disorder. C, Bipolar disorder. D, Schizophrenia.

TABLE 4: Adjusted[a] Rate Ratios and 95% Confidence Intervals for the Association Between Inflammatory Bowel Disease and Lifetime Prevalence of Psychiatric Disorders

Variable	Depression	Anxiety Disorder	Bipolar Disorder	Schizophrenia
Cohort				
Matches	1.0	1.0	1.0	1.0
IBD	**1.42 (1.32–1.52)**	**1.24 (1.17–1.31)**	**1.45 (1.19–1.77)**	1.11 (0.76–1.60)
Sex				
Male	1.0	1.0	1.0	1.0
Female	**1.76 (1.64–1.90)**	**1.54 (1.48–1.62)**	**1.58 (1.34–1.87)**	0.75 (0.55–1.02)
Age, y				
18–24	1.0	1.0	1.0	1.0
25–44	**1.95 (1.66–2.30)**	**1.95 (1.70–2.23)**	**1.74 (1.18–2.57)**	0.96 (0.57–1.62)
45–64	**2.34 (1.98–2.76)**	**2.15 (1.87–2.47)**	**2.06 (1.38–3.08)**	1.51 (0.89–2.58)
≥65	**1.99 (1.68–2.36)**	**2.05 (1.78–2.37)**	**1.24 (0.81–1.91)**	0.97 (0.56–1.67)
Socioeconomic status				
Quintile 1 (lowest)	1.22 (1.09–1.36)	**1.27 (1.18–1.36)**	1.24 (0.92–1.66)	**3.25 (1.92–5.51)**
Quintile 2	1.12 (1.04–1.21)	**1.08 (1.02–1.14)**	**1.26 (1.02–1.57)**	**2.73 (1.73–4.31)**
Quintile 3	1.09 (0.99–1.19)	**1.10 (1.03–1.18)**	1.21 (0.99–1.46)	0.86 (0.40–1.87)
Quintile 4	1.03 (0.95–1.11)	**1.07 (1.02–1.13)**	0.99 (0.79–1.24)	1.14 (0.59–2.21)
Quintile 5 (highest)	1.0	1.0	1.0	1.0
Region				
Rural	1.0	1.0	1.0	1.0
Urban	**1.28 (1.19–1.37)**	**1.26 (1.20–1.32)**	**1.88 (1.50–2.35)**	2.28 (1.66–3.12)
No. physician visits	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**
Year[b]	**1.04[c] (1.04–1.05)**	**1.035[d] (1.03–1.04)**	**1.055[e] (1.04–1.07)**	**1.025 (1.01–1.05)**

[a]Models for depression and anxiety disorders also include term to adjust for whether prescription claims were used in the case definition.
[b]Year refers to annual change; bolding indicates associations that are statistically significant.
[c]Year effect in cases 1.036 (95% CI, 1.031–1.042), year effect in controls 1.046 (95% CI, 1.041–1.051).
[d]Year effect in cases 1.025 (95% CI, 1.02–1.03), year effect in controls 1.039 (95% CI, 1.036–1.043).
[e]Year effect in cases 1.045 (95% CI, 1.029–1.062), year effect in controls 1.061 (95% CI, 1.046–1.076).

with CD had a higher IRR for depression compared with population controls than females with CD, suggesting that the relative increase in the incidence of depression conferred by CD is greater for men than for women. Similar findings have been reported in other chronic immune-mediated inflammatory diseases such as MS and may reflect biological or social factors.[25] The incidence of these psychiatric diagnoses was higher in the youngest age group studied (those aged 18–24 years); however, the prevalence of depression and bipolar disorder was higher in the older age groups, as the period for possible development of the disorders increases over the years, and is likely to exceed the increased mortality associated with these disorders. Hence, clinicians should be mindful of considering new diagnoses of psychiatric disorders in young persons with IBD and the increased likelihood of these comorbidities across the age spectrum. Efforts at earlier detection may be both feasible[24] and useful.

We also found increased rates of these psychiatric disorders in urbanites and those of lower SES. The literature addressing whether rates of depression are higher in urban vs rural residents in the general population has been inconclusive,[27–30] with findings varying by country. Prior reports have attributed differences in urban vs rural rates to SES and education, and another attributed differences to race.[31–33] Canadian studies have reported on a protective effect against developing mental health disorders of rural living.[34, 35] Another Canadian study reported no differences in access to mental health services in rural vs urban living,[36] which is different than what has been reported in the United States[37] and may reflect differences in the health systems in the 2 countries.

Previously we have shown that the risk of incident depression, anxiety disorders, and bipolar disorder increases as the number of comorbid physical disorders increases.[38] Cancer, hypertension, chronic lung disease, and ischemic heart disease were associated with an increased incidence of depression. Chronic lung disease and ischemic heart disease were associated with an increased risk of anxiety disorder as well. Chronic lung disease

and psoriasis were associated with an increased risk of bipolar disorder. However, the presence of these comorbidities did not account for the increased risk of psychiatric disorders in IBD.

The peak age of onset for CD is in the third decade, and UC incidence starts to rise in the third decade, with more consistent incidence rates across the age spectrum in UC. Nonetheless, IBD typically affects most individuals during their prime social and career development period.[39] With an increased incidence of psychiatric disorders after the diagnosis of IBD, there is the potential for a prolonged burden of mental health disorders in persons with IBD. There has been limited research on management of mental health disorders specifically in persons with IBD.[40] As the brain–gut axis is potentially critical in the pathobiology of IBD,[41] there is potential for the inflammatory state of the gut to impact the brain and mental health. Therefore, it should not be assumed that treatments of psychiatric disorders in the general population will have the same effectiveness in persons with IBD. There are well-known mental health effects of corticosteroids but little information on the potential for harm or benefit in terms of mental health of the various biological therapies that are known to be effective in IBD. Hence, there is much research to be undertaken to optimize therapy for persons with IBD who develop a psychiatric disorder.

The strengths of this study include the large size of the study population and the use of population-based data sources. There are also some limitations. Administrative data may have limited the accuracy of the diagnostic codes reported. However, we employed a validated case definition for IBD, and the case definitions used to identify psychiatric comorbidity have been validated in IBD.[17] The case definitions used to identify depression and anxiety disorder have been validated in IBD,[17] and when employed in a matched cohort, they produce similar current prevalence estimates for depression to those reported in the CCHS based on the Composite International Diagnostic Interview.[20] Estimates for anxiety disorder are slightly higher than in the CCHS, likely reflecting that the CCHS is limited to generalized anxiety disorder and our case definition is broader. Although the case definition for schizophrenia has not been validated in the IBD population, it performs well in the US Medicaid population and in the MS population, another immune-mediated inflammatory disease. The lifetime prevalence of schizophrenia in Canada as estimated using sources other than administrative data ranges from 0.6% to 0.86% in Canada, similar to our findings.[42] The case definition employed for bipolar disorder has been validated only in an MS population. However, the prevalence of bipolar disorder of 4.2% among controls in 2011 is very consistent with the reported lifetime prevalence of bipolar disorder in the national comorbidity replication survey (US) and other publications.[43, 44] We included the most common psychiatric disorders but not all psychiatric disorders, as adequate administrative definitions of other disorders (such as substance use disorders) were not available in the administrative data. Further, our administrative data lack clinical details, so we could not evaluate the associations between disease phenotype and risk of psychiatric disorders. We were also unable to examine the role of health behaviors or factors such as vitamin D insufficiency. Administrative data will capture diagnoses for which care is sought from a physician and will not capture psychiatric disorders that are not diagnosed or those managed by nonphysician providers such as psychologists. Therefore, our estimates of incidence are likely underestimates, but this is likely to be a nondifferential effect across the IBD and matched populations. Individuals with IBD may have more frequent contact with the health care system, potentially increasing the likelihood of diagnosis of psychiatric disorders; however, our findings regarding the increased risk of these disorders were largely the same after accounting for the annual number of physician visits. This suggests that our findings are not due to surveillance bias.

In conclusion, we found that persons diagnosed with IBD are at increased risk of being diagnosed with depression, anxiety disorder, or bipolar disorder, and there may be an increased risk for being diagnosed with schizophrenia in persons with CD. Having a chronic immune-mediated inflammatory disease may predispose to the development of depression or anxiety either because of shared predisposing genes, the impact of immune factors on triggering depression, anxiety, or bipolar disorder, or merely the stress of the chronic disease predisposing to a psychiatric disorder.[41, 45–50] As collaborative care models of IBD have been recently promoted as a gold standard,[51] it is critical to understand the burden of psychiatric comorbidity in IBD so that these care models can be adequately resourced. More research is required to determine the causes of these associations and to optimize treatment of mental disorders in persons with IBD. Clinicians should be very aware of the associations and vigilant in treating them. This will benefit persons with IBD from a mental health perspective but also potentially with respect to the course of their disease.

SUPPLEMENTARY DATA

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

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