Journal of Crohn's and Colitis, 2021, 1824–1836
doi:10.1093/ecco-jcc/jjab039
Advance Access publication February 27, 2021
Original Article

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Association Between Inflammatory Bowel Disease and Psychiatric Morbidity and Suicide: A Swedish Nationwide Population-Based Cohort Study With Sibling Comparisons

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Abstract

Background and Aims: Inflammatory bowel disease [IBD] is linked to psychiatric morbidity, but few studies have assessed general population comparators. We aimed to investigate the risk of psychiatric morbidity and suicide in adult-onset IBD patients.

Methods: We used a nationwide population-based cohort study in Sweden [1973–2013]. We studied the risk of psychiatric disorders and suicide in 69,865 adult-onset IBD patients [ulcerative colitis, UC: *n* = 43,557; Crohn's disease, CD: *n* = 21,245; and IBD-unclassified: *n* = 5063] compared to 3,472,913 general population references and 66 292 siblings.

Results: During a median follow-up of 11 years, we found 7465 [10.7%] first psychiatric disorders in IBD [incidence rate, IR/1000 person-years 8.4] and 306 911 [9.9%] in the general population [IR 6.6], resulting in 1.8 extra psychiatric morbidity per 100 patients followed-up for 10 years and a hazard ratio [HR] of 1.3 [95% confidence interval, 95%CI = 1.2–1.3]. The highest risk of overall psychiatric morbidity was seen in the first year after IBD diagnosis [HR = 1.4, 95%CI = 1.2–1.6] and in patients with extraintestinal manifestations [HR = 1.6, 95%CI = 1.5–1.7]. Psychiatric morbidity was more common in all IBD subtypes [HR 1.3–1.5]. An increased risk of suicide attempts was observed among all IBD types [HR = 1.2–1.4], whereas completed suicide was explicitly associated with CD [HR = 1.5] and elderly-onset [diagnosed at the age of > 60 years] IBD [HR = 1.7].

Conclusion: Adult-onset IBD was associated with an increased risk of psychiatric disorders and suicide attempts. Psychological follow-up should be provided to patients with IBD, especially those

with extraintestinal manifestations and elderly-onset IBD. This follow-up should be within the first year after IBD diagnosis.

Key Words: Depression; eating disorders; IBD; inflammatory bowel disease; mood disorders; substance misuse.

1. Introduction

Inflammatory bowel disease [IBD] is characterized by chronic gastrointestinal inflammation and encompasses two predominant forms: Crohn's disease [CD] and ulcerative colitis [UC]. These relapsing–remitting diseases often need combined medical and surgical treatment and have been linked to substantial comorbidity.[1,2] IBD typically occurs in one in 300 individuals in the Western world.[3]

Several studies have observed a link between IBD and mental health problems such as suicide,[4–10] mood and anxiety disorders,[11–16] and psychotic disorders[17] [for a detailed literature review, see Supplementary Table S1]. Among the suggested explanations are a stigmatizing treatment that includes surgery and stomas, abdominal pain, malabsorption, vitamin deficiencies and chronic inflammation, potentially affecting the central nervous system and the gut–brain axis,[18] causing alterations in the gut microbiome,[19] and work-related issues.[20,21]

Despite the extensive literature, most studies lack the statistical power to examine psychiatric disorders according to IBD phenotype or beyond the first 10 years of follow-up. Furthermore, there are little data on completed suicide, with a recent meta-analysis summarizing the available data indicating an excess risk [1.36-fold increased risk in CD and 1.16-fold increased risk in UC, although none of these risk estimates were statistically significant].[22] A recent study from our group found that suicide *attempts* were more common in individuals with childhood-onset IBD,[23] but few outcome events prevented us from examining completed suicide.

Surprisingly, previous research on psychiatric disorders in IBD have not considered familial factors. Sibling data may shed light on the mechanisms underlying a possible association between IBD[24] and psychiatric disorders and suicide[25,26] while also taking unmeasured genetic and lifestyle or socioeconomic confounders into account.

A fuller understanding of the relationship between IBD and psychiatric disorders is crucial for an evidence-based recommendation in IBD management. It would be valuable, for instance, to identify high-risk groups who would benefit from further psychiatric screening and psychological intervention.

In a nationwide cohort study, we included adults with incident IBD diagnosed in 1973–2013. We then calculated the risk of future psychiatric disorders and suicide compared to age- and sex-matched reference individuals from the general population.

Additionally, to control for possible genetic and environmental confounding, IBD patients were compared to their non-IBD siblings. Finally, we performed a case-control study to explore the temporal relationship between IBD and psychiatric disorders before IBD diagnosis.

We hypothesized that adulthood-onset IBD is associated with psychiatric disorders and suicide.

2. Methods

2.1. Setting and data source

The Swedish National Patient Register [SNPR] began in 1964 and went nationwide in 1987.[27] Specialist outpatient data were added in 2001. The SNPR includes psychiatric diagnoses constituting the reasons for specialist mental health care, regardless of the type of treatment [pharmacological, psychotherapy or both], and has been available since 1973. This register also supplies information on IBD (including data on primary sclerosing cholangitis [PSC], other extraintestinal manifestations and IBD surgery) and psychiatric diagnoses.

Information on suicide was collected from the Cause of Death Register,[28] data on psychiatric medication from the Prescribed Drug Register,[29] data on education from the nationwide LISA database,[30] and data on country of birth from the Total Population Register.[31]

2.2. Study design

2.2.1. Study 1: Cohort study

In this cohort study we examined the association between IBD and later psychiatric disorders. For each individual with IBD, we retrieved ≤ 50 reference individuals from the Swedish Population Register.[31] Reference individuals were matched for age, sex, birth year and county of birth [individuals born outside of Sweden were matched with reference individuals born outside Sweden]. Finally, we excluded all study participants with a record of psychiatric diagnosis, intellectual disability or emigration before IBD diagnosis [Supplementary Figure 1].

We identified siblings through the Swedish Multi-generation Register.[32] This register contains data on all individuals born in 1932 or later and registered as Swedish residents in 1961 or later.[32] Siblings also had to be alive and living in Sweden on the date of IBD diagnosis in the index person. Finally, we restricted the sibling comparators to siblings who had never had a diagnosis of IBD.

2.2.2. IBD

For IBD diagnosis, we requested two or more diagnostic listings with IBD, the first of which had to occur when the person was ≥ 18 years of age (see Supplementary Table 2 for relevant international classification of disease [ICD] codes).[1] This IBD definition, used by us[2] and others,[33] has a high positive predictive value [93%].[34] CD was defined as having the first two IBD diagnostic listings with CD [and UC correspondingly]. Individuals with an ICD record of K52.3 [indeterminate colitis in ICD-10] or with one UC and one CD code [of the first two IBD diagnostic listings] were categorized as IBD-unclassified [IBD-U].

2.2.3. Psychiatric outcomes

Data on psychiatric diagnoses were retrieved from the National Patient Register. Psychiatric diagnoses have shown a validity of 81–95%.[35,36] One record of psychiatric disorders was regarded as a positive event [Supplementary Table 3]. We used the Cause of Death Register to ascertain suicide [see Supplementary Table 3 for relevant definitions]. More than 95% of suicides undergo a forensic autopsy to confirm the diagnosis.[28] Attention-deficit hyperactivity disorder [ADHD] was defined through an appropriate patient register diagnosis or record of ADHD medication in the Swedish Prescribed Drug Register [Supplementary Table 6].[37] Our primary outcome measures were overall psychiatric morbidity or completed suicide. Secondary

outcomes were psychotic disorders, mood disorders, anxiety disorders, eating disorders, substance misuse, behavioural disorders, ADHD, autism spectrum disorders, personality disorders and suicide attempts.

2.3. Study 2: Case-control study

In the case-control study, we explored the relationship between IBD and psychiatric disorders before IBD diagnosis. To ensure ≥ 5 years of exposure time we restricted our dataset to individuals diagnosed with IBD between 1978 and 2013 [psychiatric diagnoses are available since 1973] living in Sweden ≥ 5 years before IBD diagnosis. Each individual with IBD was matched with ≤ 50 reference individuals from the general population. Reference individuals were required to have lived in Sweden during the past 5 years before the first IBD diagnosis of matched IBD individuals.

2.4. Statistics

As noted, all analyses in study 1 were restricted to study participants with no prior record of psychiatric disorders. Follow-up time started on the first visit of patients with IBD [the corresponding date in the matched reference individuals] and ended with the first psychiatric diagnosis of interest [separate censoring date for each defined psychiatric outcome], emigration, death or December 31, 2013, whichever occurred first. Reference individuals had to be alive on the second listing for IBD in the index individuals. Conditional Cox regression, stratified by matching [each index individual and his/her reference individuals were analysed per stratum], was used to estimate hazard ratios [HRs] with 95% confidence intervals [CIs] adjusted for sex, year and place of birth [county of Sweden for Swedish-born and region of birth for foreign-born individuals]. Cumulative hazard functions and Schoenfeld's residuals against time were used to assess the proportional hazards assumption. In study 2, the association between IBD and prior psychiatric diagnoses was evaluated using conditional logistic regression adjusting for sex, birth year and county of birth. We also provided odds ratios [ORs], including and excluding the last year before IBD to decrease the risk of detection bias.

In secondary analyses, we used siblings as comparators to control for unmeasured familial [genetic and environmental] confounding. Sibling analyses were adjusted for age, sex, year and place of birth. Finally, the robust sandwich variance estimator was used to correct for familial clustering of data.

In an a priori defined analysis, we calculated stratum-specific HRs according to sex [male, female], country of birth [Sweden, other], education (compulsory, 2 years; upper secondary, 3 years, university [<3 years or ≥ 3 years]], age at diagnosis of IBD [18 to <40, 40 to <60, ≥60 years], ICD classification at the time of diagnosis [ICD-8, -9, -10], presence of complications during follow-up [extraintestinal manifestations, PSC], surgery [bowel surgery and perianal surgery], and psychiatric history in first-degree relatives [for relevant definitions, see Supplementary Tables 4 and 5]. We chose 2002 as the cut-off for the analysis of the year of diagnosis given that 2001 is likely to contain a mix of incident IBD and prevalent cases that had never required inpatient care.

2.4.1. Sensitivity analyses

We conducted two sensitivity analyses. First, we defined overall psychiatric morbidity as having a record of psychiatric medications in the Prescribed Drug Register. This analysis is likely to identify milder psychiatric disorders [e.g. mild anxiety and depression] cared for by general practitioners in an outpatient setting. Because the Prescribed Drug Register started on July 1, 2005, we restricted this analysis to IBD with onset on January 1, 2006 or later to allow for a 6-month exposure period. Such an approach ensures that any record of psychiatric medications reflected incident prescriptions.

Second, to increase our outcome's specificity and decrease misclassification, we restricted our outcome to two or more [later] psychiatric diagnoses with the date of the last listed diagnosis as the outcome date. SAS software [version 9.3] was used for statistical analysis.

2.5. Ethics approval

This study was approved by the Regional Ethical Review Board in Stockholm [Dnr 2013/862-31/5]. We obtained anonymized data from Statistics Sweden and the National Board of Health and Welfare. Because this was a register-based study, no participant was contacted and informed consent was waived.[38]

3. Results

3.1. Background data

This study was based on 69,865 patients with IBD diagnosed in adulthood [≥18 years] [UC: *n* = 43,557, CD: *n* = 21,245; and IBD-U: *n* = 5063], 3,472,913 matched general population reference individuals and 66,292 non-IBD siblings.

Sex distribution was equal. Nine of ten patients were born in Sweden, and one in three had attended university [Table 1]. Patients were followed for a median of 11 years [range 5–18]. The median age at the end of follow-up was 57 years [range 44–70]. During follow-up, 2.9% of the individuals received a PSC diagnosis, 12.6% other extraintestinal manifestations and 24.6% had bowel surgery. Almost 40% of the IBD patients had a first-degree relative with a psychiatric diagnosis at any time during the observation period [compared to 38% of the reference individuals] [Table 1].

3.2. Main results

3.2.1. Psychiatric disorders

There were 7465 [8.4/1000 person-years] first events of psychiatric disorders in individuals with IBD compared to 306 911 [6.6/1000 person-years] in general population reference individuals. These figures are equal to an adjusted HR of 1.3 [95% CI = 1.2–1.3], corresponding to 1.8 additional cases of first psychiatric disorder per 100 patients with IBD followed-up for 10 years.

Compared to reference individuals, patients with IBD were at a particularly increased risk of mood (incidence rate [IR] 3.9 vs 2.8; HR = 1.4, 95% CI = 1.4–1.5) and anxiety disorder [IR 4.0 vs 3.0; HR = 1.3, 95% CI = 1.3–1.4]. Associations between IBD and mood disorders were observed for bipolar disorder [IR 0.4 vs 0.3, HR = 1.1, 95% CI = 1.1–1.2], major depressive disorder [IR 3.6 vs 2.5; HR = 1.4, 95% CI = 1.4–1.5] and other mood disorders [IR 0.3 vs 0.2, HR = 1.4, 95% CI = 1.2–1.6]. Statistically significant differences of minor clinical significance [similar or comparable IR] were also observed for eating disorders [IR 0.1 vs 0.1; HR = 1.3, 95% CI = 1.1–1.7], substance misuse [IR 2.2 vs 2.0; HR = 1.1, 95% CI = 1.1–1.1] and personality disorders [0.4 vs 0.3; HR = 1.2, 95% CI = 1.1–1.3] [Table 2]. Further adjustment for education and family history of psychiatric disorders resulted in similar estimates [Supplementary Table 7]. The excess risk for overall psychiatric morbidity was seen in all IBD subtypes [HRs ranged from 1.3 to 1.5] [Table 3]. Major depressive disorder, other mood disorders and anxiety disorders were more prevalent in all IBD subtypes, whereas

Table 1. Baseline characteristics of patients with adult-onset [≥18 years of age] inflammatory bowel disease [IBD] diagnosed in 1973–2013, matched reference individuals, and siblings to patients with IBD

Characteristic	IBD	Ulcerative colitis	Crohn's disease	IBD-unclassified	Reference individuals	*P* value	Siblings of patients with IBD	*P* value
Total	69 865 [100%]	43 557 [100%]	21 245 [100%]	5063 [100%]	3 472 913 [100%]		66 292 [100%]	
Male sex	36 189 [51.8]	23 546 [54.1]	10 072 [47.4]	2571 [50.8]	1 795 908 [51.7]	0.6534	33 851 [51.1]	0.0489
Female sex	33 676 [48.2]	20 011 [45.9]	11 173 [52.6]	2492 [49.2]	1 677 005 [48.3]		32 441 [48.9]	
Country of birth								
Sweden	62 904 [90.0]	39 374 [90.4]	18 991 [89.4]	4539 [89.7]	3 124 892 [90.0]	0.6194	64 033 [96.6]	0.0003
Other	6961 [10.0]	4183 [9.6]	2254 [10.6]	524 [10.3]	348 021 [10.0]		2259 [3.4]	
Level of education								
Compulsory school	16 917 [24.2]	10 364 [23.8]	5288 [24.9]	1265 [25.0]	818 511 [23.6]	<0.0001	14 175 [21.4]	<0.0001
Upper secondary 2 years	18 596 [26.6]	11 435 [26.3]	5869 [27.6]	1292 [25.5]	872 127 [25.1]		19 187 [28.9]	
Upper secondary 3 years	12 151 [17.4]	7357 [16.9]	3829 [18.0]	965 [19.1]	598 713 [17.2]		12 241 [18.5]	
University < 3 years	8317 [11.9]	5235 [12.0]	2458 [11.6]	624 [12.3]	418 575 [12.1]		8399 [12.7]	
University ≥3 yearsd	12 148 [17.4]	8007 [18.4]	3321 [15.6]	820 [16.2]	649 727 [18.7]		11 730 [17.7]	
Missing	1736 [2.5]	1159 [2.7]	480 [2.3]	97 [1.9]	115 260 [3.3]		560 [0.8]	
Age at IBD diagnosis and/or cohort entry, years								
18 to < 40	33 861 [48.5]	20 109 [46.2]	11 306 [53.2]	2446 [48.3]	1 691 846 [48.7]	0.8811	37 895 [57.2]	<0.0001
40 to < 60	20 795 [29.8]	13 466 [30.9]	5915 [27.8]	1414 [27.9]	1 032 266 [29.7]		22 032 [33.2]	
≥ 60	15 209 [21.8]	9982 [22.9]	4024 [18.9]	1203 [23.8]	748 801 [21.6]		6365 [9.6]	
Mean [SD]	44.1 [17.9]	45.0 [17.8]	42.0 [17.8]	44.5 [18.9]	43.9 [17.9]	0.1660	38.3 [14.9]	<0.0001
Median [IQR]	40.8 [28.8–57.5]	42.1 [30.0–58.4]	38.2 [26.7–55.2]	41.0 [28.0–58.9]	40.7 [28.7–57.4]		36.8 [26.6–49.2]	
Start year of follow-up, years								
1973–1979	5657 [8.1]	3130 [7.2]	2190 [10.3]	337 [6.7]	282 643 [8.1]	0.8811	4396 [6.6]	<0.0001
1980–1989	11 353 [16.2]	6708 [15.4]	3970 [18.7]	675 [13.3]	566 599 [16.3]		10 843 [16.4]	
1990–1999	14 305 [20.5]	9013 [20.7]	4357 [20.5]	935 [18.5]	712 676 [20.5]		13 410 [20.2]	
2000–2013	38 550 [55.2]	24 706 [56.7]	10 728 [50.5]	3116 [61.5]	1 910 995 [55.0]		37 643 [56.8]	
Version of ICD classification at the time of cohort entry								
ICD-8 [1973–1986]	13 376 [19.1]	7753 [17.8]	4857 [22.9]	766 [15.1]	667 894 [19.2]	0.7608	11 635 [17.6]	<0.0001
ICD-9 [1987–1996]	11 975 [17.1]	6987 [16.0]	4124 [19.4]	864 [17.1]	596 975 [17.2]		11 225 [16.9]	
ICD-10 [1997–2013]	44 514 [63.7]	28 817 [66.2]	12 264 [57.7]	3433 [67.8]	2 208 044 [63.6]		43 432 [65.5]	
Source of data at the time of cohort entry								
Inpatient register [prior to 2002]	38 817 [55.6]	24 030 [55.2]	12 490 [58.8]	2297 [45.4]	1 935 238 [55.7]	0.3930	36 012 [54.3]	<0.0001
Inpatient and outpatient registers[since 2002]	31 048 [44.4]	19 527 [44.8]	8755 [41.2]	2766 [54.6]	1 537 675 [44.3]		30 280 [45.7]	
Age at the end of follow-up, years								
Mean [SD]	56.8 [17.9]	57.4 [17.7]	55.8 [17.9]	55.6 [18.5]	57.3 [18.2]	<0.0001	52.5 [15.6]	<0.0001
Median [IQR]	57.3 [42.6–70.3]	57.8 [43.3–70.8]	56.4 [41.7–69.4]	56.3 [40.6–69.5]	57.7 [42.8–70.8]		54.2 [41.2–65.1]	
Reasons for end of follow-up								
Psychiatric diagnosis	7465 [10.7]	4313 [9.9]	2605 [12.3]	547 [10.8]	306 911 [8.8]	<0.0001	5621 [8.5]	<0.0001
Death	10 718 [15.3]	6866 [15.8]	3190 [15.0]	662 [13.1]	440 866 [12.7]		2269 [3.4]	
Emigration	1038 [1.5]	630 [1.4]	339 [1.6]	69 [1.4]	60 077 [1.7]		1088 [1.6]	
End of study	50 644 [72.5]	31 748 [72.9]	15 111 [71.1]	3785 [74.8]	2 665 059 [76.7]		57 314 [86.5]	
Length of follow-up, years								
< 1	3743 [5.4]	2213 [5.1]	1137 [5.4]	393 [7.8]	127 881 [3.7]	<0.0001	2122 [3.2]	<0.0001
1 to < 5	14 159 [20.3]	8539 [19.6]	4123 [19.4]	1497 [29.6]	665 594 [19.2]		11 541 [17.4]	
5 to < 10	15 037 [21.5]	9779 [22.5]	4236 [19.9]	1022 [20.2]	750 449 [21.6]		13 521 [20.4]	
≥ 10	36,926 [52.9]	23 026 [52.9]	11 749 [55.3]	2151 [42.5]	1 928 989 [55.5]		39 108 [59.0]	

Table 1. Continued

Characteristic	IBD	Ulcerative colitis	Crohn's disease	IBD-unclassified	Reference individuals	*P* value	Siblings of patients with IBD	*P* value
Mean [SD]	12.7 [9.9]	12.4 [9.4]	13.8 [10.6]	11.1 [10.1]	13.3 [10.0]	0.0094	14.2 [10.2]	<0.0001
Median [IQR]	10.8 [4.9–17.9]	10.7 [5.1–16.7]	11.4 [5.1–20.9]	7.7 [3.2–16.6]	11.3 [5.4–19.0]		12.0 [6.0–20.6]	
Complications during follow-up								
Extraintestinal manifestations	8818 [12.6]	4984 [11.4]	3163 [14.9]	671 [13.3]				
Primary sclerosing cholangitis	2048 [2.9]	1537 [3.5]	355 [1.7]	156 [3.1]				
IBD surgery								
Bowel surgery	17 200 [24.6]	8621 [19.8]	7500 [35.3]	1079 [21.3]				
Perianal surgery	5691 [8.1]	2402 [5.5]	2854 [13.4]	435 [8.6]				
Psychiatric diagnoses in first degree relatives	27 672 [39.6]	16 947 [38.9]	8635 [40.6]	2090 [41.3]	1 322 730 [38.1]	<0.0001	33 409 [50.4]	<0.0001
Psychiatric diagnoses in parents	11 894 [17.0]	7260 [16.7]	3729 [17.6]	905 [17.9]	563 897 [16.2]	<0.0001	13 718 [20.7]	0.7981
Psychiatric diagnoses in siblings	10 181 [14.6]	6204 [14.2]	3219 [15.2]	758 [15.0]	479 241 [13.8]	<0.0001	18 798 [28.4]	<0.0001
Psychiatric diagnoses in children	12 050 [17.2]	7337 [16.8]	3804 [17.9]	909 [18.0]	575 561 [16.6]	<0.0001	11 150 [16.8]	0.4936

an increased risk of bipolar disorder was specifically associated with UC [IR 0.4 vs 0.3; HR = 1.2, 95% CI = 1.1–1.4]. Later substance misuse was specifically associated with CD [IR 2.7 vs 2.0; HR = 1.3, 95% CI = 1.3–1.4] and IBD-U [IR 2.6 vs 2.0; HR = 1.3, 95% CI = 1.1–1.5].

3.2.2. Suicide and suicide attempts

During follow-up, 211 patients with IBD and 9393 reference individuals committed suicide [IR 0.22 vs 0.19]. This figure was equal to an HR of 1.2 [95% CI = 1.1–1.4] [Table 2]. Suicide attempts were also more common in IBD. The increase in suicide was statistically significant only in individuals with CD [IR 0.29 vs 0.19; HR = 1.5, 95% CI = 1.2–1.9], whereas an increased risk of suicide attempts was observed in all types of IBD [HR 1.2–1.4] [Table 3]. Suicide was more prevalent in elderly-onset IBD [IR 0.32 vs 0.20; HR = 1.7, 95% CI = 1.3–2.4] [Table 4].

3.2.3. Vulnerable risk groups

The highest risk of overall psychiatric morbidity [HR = 1.4, 95% CI = 1.2–1.6] was observed during the first year after IBD diagnosis, but excess risk persisted even after 10 years of follow-up [HR = 1.2, 95% CI = 1.2–1.3]. Psychiatric disorders were pervasive in patients with extraintestinal manifestations [HR = 1.6, 95% CI = 1.5–1.7]. The relative risk of suicide was exceptionally high in older patients [diagnosed at age ≥ 60 years] [IR 0.3 vs 0.0; HR = 1.7, 95% CI = 1.3–2.4] [Table 4].

3.2.4. Sibling analyses

Sibling analyses confirmed an increased risk of psychiatric disorders [HR = 1.3, 95% CI = 1.3–1.4] and of committing suicide in IBD [HR = 1.4, 95% CI = 1.1–1.8] [Table 2].

3.3. Sensitivity analyses

The association with IBD remained [HR = 1.8, 95% CI = 1.7–1.9]] after defining any psychiatric morbidity as having a record of psychiatric medications. IBD was associated with an increased use of antidepressants [HR = 1.7, 95% CI = 1.6–1.7], anxiolytics [HR = 1.8, 95% CI = 1.8–1.9] and antipsychotics [HR = 1.5, 95% CI = 1.4–1.7] but not ADHD medication [HR = 0.9, 95% CI = 0.6–1.2] [Supplementary Table 8]. Similar results were obtained from the sibling comparison [Supplementary Table 7] and specifically for UC, CD and IBD-U [Supplementary Table 9].IBD was also associated with having two or more diagnoses of later psychiatric disorders [HR = 1.2, 95% CI = 1.2–1.3] [Supplementary Table 10].

3.4. Psychiatric disorders before the diagnosis of IBD

Prior psychiatric morbidity was associated with later IBD compared to the general population [OR = 1.2, 95% CI = 1.1–1.2] and siblings [OR = 1.1, 95% CI = 1.1–1.1]. The positive association was observed for all IBD types and remained significant when the first year before IBD diagnosis was excluded from the analysis [Supplementary Tables S11–14].

4. Discussion

4.1. Main findings

This nationwide population-based study of more than 69 000 patients with adult-onset IBD and psychiatric disorders confirms and

Table 2. Frequency, absolute incidence rates per 1000 person-years for psychiatric disorders in patients with adult-onset inflammatory bowel disease [IBD] compared with matched reference individuals and with their siblings without IBD

Outcomes	Population comparison				Siblings comparison			
	IBD	Reference individuals	Hazard ratio [95% CI]	*p* value	IBD	Non-IBD siblings	Hazard ratio [95% CI]	*p* value
	No. of outcomes/ person-years [incidence rate/1000 person-years]	No. of outcomes/ person-years [incidence rate/1000 person-years]			No. of outcomes/ person-years [incidence rate/1000 person-years]	No. of outcomes/ person-years [incidence rate/1000 person-years]		
Primary:								
Overall psychiatric disorders	7465/889 685 [8.4]	306 911/46 348 442 [6.6]	1.3 [1.2–1.3]	<0.0001	4060/508 658 [8.0]	5621/938 164 [6.0]	1.3 [1.3–1.4]	<0.0001
Suicide	211/940 405 [0.2]	9393/48 582 813 [0.2]	1.2 [1.1–1.4]	0.0167	103/537 406 [0.2]	139/977 856 [0.1]	1.4 [1.1–1.8]	0.0164
Secondary:								
Psychotic disorders	434/936 305 [0.5]	22 064/48 360 574 [0.5]	1.0 [0.9–1.1]	0.4744	185/535 250 [0.3]	316/974 489 [0.3]	1.1 [0.9–1.3]	0.3854
Schizophrenia	107/939 335 [0.1]	6 983/48 506 564 [0.1]	0.8 [0.6–1.0]	0.0131	71/536 690 [0.1]	105/976 590 [0.1]	1.2 [0.9–1.6]	0.2573
Other psychotic disorders	394/936 727 [0.4]	18 965/48 399 357 [0.4]	1.1 [1.0–1.2]	0.0735	163/535 491 [0.3]	281/974 989 [0.3]	1.1 [0.9–1.3]	0.4204
Mood disorders	3 580/917 179 [3.9]	132 878/47 680 664 [2.8]	1.4 [1.4–1.5]	<0.0001	1 829/524 726 [3.5]	2 323/962 027 [2.4]	1.4 [1.3–1.5]	<0.0001
Bipolar disorder	354/937 884 [0.4]	16 307/48 454 985 [0.3]	1.1 [1.1–1.2]	0.0423	192/535 983 [0.4]	310/975 561 [0.3]	1.1 [0.9–1.4]	0.1700
Major depressive disorder	3308/919 421 [3.6]	120 550/47 802 192 [2.5]	1.4 [1.4–1.5]	<0.0001	1 699/525 973 [3.2]	2 116/963 963 [2.2]	1.5 [1.4–1.6]	<0.0001
Other mood disorders	314/938 484 [0.3]	11 661/48 507 569 [0.2]	1.4 [1.2–1.6]	<0.0001	168/536 305 [0.3]	219/976 400 [0.2]	1.4 [1.1–1.7]	0.0031
Anxiety disorders	3705/917 537 [4.0]	145 124/47 635 285 [3.0]	1.3 [1.3–1.4]	<0.0001	2150/524 209 [4.1]	2 817/959 896 [2.9]	1.4 [1.3–1.5]	<0.0001
Eating disorders	93/939 848 [0.1]	3 495/48 559 732 [0.1]	1.3 [1.1–1.7]	0.0045	59/537 042 [0.1]	81/977 417 [0.1]	1.5 [1.1–2.1]	0.0276
Substance misuse	2065/925 841 [2.2]	97 232/47 852 723 [2.0]	1.1 [1.1–1.1]	0.0002	1202/528 668 [2.3]	1913/964 487 [2.0]	1.2 [1.1–1.3]	<0.0001
Personality disorders	345/937 524 [0.4]	15 086/48 448 465 [0.3]	1.2 [1.1–1.3]	0.0060	206/535 615 [0.4]	278/975 555 [0.3]	1.3 [1.1–1.6]	0.0018
Attention-deficit hyperactivity disorder	312/939 412 [0.3]	14 387/48 536 554 [0.3]	1.1 [1.0–1.2]	0.1188	195/536 777 [0.4]	315/976 928 [0.3]	1.3 [1.1–1.6]	0.0027
Autism spectrum disorders	73/940 172 [0.1]	4 047/48 565 623 [0.1]	0.9 [0.7–1.1]	0.4268	49/537 266 [0.1]	82/977 525 [0.1]	1.3 [0.9–1.9]	0.1872
Suicide attempts	537/936 549 [0.6]	21 123/48 430 867 [0.4]	1.3 [1.2–1.4]	<0.0001	264/535 353 [0.5]	386/975 103 [0.4]	1.2 [1.1–1.4]	0.0157

Table 3. Frequency, absolute incidence rates per 1000 person-years [95% confidence intervals, CI] and hazard ratio of primary and secondary psychiatric outcomes in patients with adult-onset inflammatory bowel disease [IBD] stratified by type of IBD diagnosis. IBD compared with matched general population reference individuals

Outcomes	Ulcerative colitis				Crohn's disease				IBD-unclassified			
	No. of outcomes/ person-years [incidence rate/1000 person-years]	No. of outcomes/ person-years [incidence rate/1000 person-years]	Hazard ratio [95% CI]	*p* Value	No. of outcomes/ person-years [incidence rate/1000 person-years]	No. of outcomes/ person-years [incidence rate/1000 person-years]	Hazard ratio [95% CI]	*p* value	No. of outcomes/ person-years [incidence rate/1000 person-years]	No. of outcomes/ person-years [incidence rate/1000 person-years]	Hazard ratio [95% CI]	*p* value
	Patients	Reference individuals			Patients	Reference individuals			Patients	Reference individuals		
Primary:												
Overall psychiatric morbidity	4313/540 177 [8.0]	187 365/28 077 044 [6.7]	1.2 [1.2-1.2]	<0.0001	2 605/293 143 [8.9]	99 749/15 321 321 [6.5]	1.4 [1.3–1.4]	<0.0001	547/56 364 [9.7]	19 797/2 950 077 [6.7]	1.4 [1.3–1.6]	<0.0001
Suicide	111/568 656 [0.2]	5 777/29 395 863 [0.2]	1.0 [0.8–1.2]	0.8599	89/311 773 [0.3]	3064/16 095 715 [0.2]	1.5 [1.2–1.9]	0.0001	11/59 976 [0.2]	552/3 091 235 [0.2]	1.0 [0.6–1.9]	0.8895
Secondary:												
Psychotic disorders	263/566 265 [0.5]	13 194/29 270 119 [0.5]	1.1 [0.9–1.2]	0.3479	145/310 277 [0.5]	7505/16 013 347 [0.5]	1.0 [0.9–1.2]	0.9700	26/59 764 [0.4]	1 365/3 077 108 [0.4]	1.0 [0.7–1.4]	0.8742
Schizophrenia	69/568 031 [0.1]	4 039/29 353 708 [0.1]	0.9 [0.7–1.1]	0.2913	35/311 337 [0.1]	2483/16 066 843 [0.2]	0.7 [0.5–1.0]	0.0531	3/59 967 [0.1]	461/3 086 013 [0.1]	0.3 [0.1–1.0]	0.0538
Other psychotic disorders	231/566 562 [0.4]	11 356/29 291 875 [0.4]	1.1 [1.0–1.2]	0.229	138/310 399 [0.4]	6427/16 027 818 [0.4]	1.1 [0.9–1.3]	0.1918	25/59 765 [0.4]	1182/3 079 664 [0.4]	1.1 [0.7–1.6]	0.6958
Mood disorders	2094/555 695 [3.8]	80 835/28 863 327 [2.8]	1.4 [1.3–1.4]	<0.0001	1223/303 293 [4.0]	43 493/15 782 869 [2.8]	1.5 [1.4–1.6]	<0.0001	263/58 190 [4.5]	8550/3 034 467 [2.8]	1.6 [1.4–1.8]	<0.0001
Bipolar disorder	232/567 128 [0.4]	9695/29 323 001 [0.3]	1.2 [1.1–1.4]	0.0015	103/310 896 [0.3]	5561/16 048 927 [0.3]	0.9 [0.8–1.1]	0.5677	19/59 860 [0.3]	1051/3 083 058 [0.3]	0.9 [0.6–1.5]	0.7588
Major depressive disorder	1920/556 972 [3.4]	73 413/28 933 445 [2.5]	1.4 [1.3–1.4]	<0.0001	1141/304 150 [3.8]	39 366/15 826 812 [2.5]	1.5 [1.4–1.6]	<0.0001	247/58 299 [4.2]	7771/3 041 935 [2.6]	1.7 [1.5–1.9]	<0.0001
Other mood disorders	187/567 595 [0.3]	7027/29 351 232 [0.2]	1.4 [1.2–1.6]	<0.0001	103/311 074 [0.3]	3875/16 069 796 [0.2]	1.4 [1.1–1.7]	0.0012	24/59 815 [0.4]	759/3 086 541 [0.2]	1.6 [1.1–2.4]	0.0257
Anxiety disorders	2118/555 901 [3.8]	87 563/28 837 946 [3.0]	1.2 [1.2–1.3]	<0.0001	1317/303 275 [4.3]	48 080/15 766 670 [3.0]	1.4 [1.3–1.5]	<0.0001	270/58 361 [4.6]	9481/3 030 670 [3.1]	1.5 [1.3–1.7]	<0.0001
Eating disorders	51/568 368 [0.1]	1905/29 383 989 [0.1]	1.4 [1.0–1.8]	0.0289	38/311 547 [0.1]	1343/16 086 222 [0.1]	1.4 [1.0–2.0]	0.0328	4/ 59 932 [0.1]	247/3 089 521 [0.1]	0.8 [0.3–2.2]	0.6979
Substance misuse	1092/560 845 [1.9]	59 843/28 961 322 [2.1]	0.9 [0.9–1.0]	0.0192	817/306 074 [2.7]	31 182/15 845 471 [2.0]	1.3 [1.3–1.4]	<0.0001	156/ 58 921 [2.6]	6207/3 045 930 [2.0]	1.3 [1.1–1.5]	0.0019
Personality disorders	197/567 039 [0.3]	8760/29 321 793 [0.3]	1.1 [1.0–1.3]	0.0643	122/310 704 [0.4]	5315/16 044 847 [0.3]	1.2 [1.0–1.4]	0.0980	26/ 59 781 [0.4]	1011/3 081 825 [0.3]	1.3 [0.9–1.9]	0.1711
Attention-deficit hyperactivity disorder	173/568 079 [0.3]	8724/29 367 910 [0.3]	1.0 [0.9–1.2]	1.000	101/311 454 [0.3]	4660/16 080 545 [0.3]	1.1 [0.9–1.3]	0.3835	38/59 879 [0.6]	1003/3 088 099 [0.3]	1.9 [1.4–2.6]	<0.0001
Autism spectrum disorders	39/568 521 [0.1]	2487/29 385 363 [0.1]	0.8 [0.6–1.1]	0.1460	24/311 694 [0.1]	1294/16 090 220 [0.1]	0.9 [0.6–1.4]	0.7642	10/59 956 [0.2]	266/3 090 040 [0.1]	1.9 [1.0–3.5]	0.0507
Suicide attempts	4 313/540 177 [8.0]	187 365/28 077 044 [6.7]	1.2 [1.2-1.2]	<.0001	2 605/293 143 [8.9]	99 749/15 321 321 [6.5]	1.4 [1.3–1.4]	<.0001	547/56 364 [9.7]	19 797/2 950 077 [6.7]	1.4 [1.3–1.6]	<0.0001

Table 4. Hazard ratio of the first ever event of overall psychiatric morbidity and suicides in a cohort of patients with adult-onset inflammatory bowel disease [IBD]. Individuals with IBD compared with matched general population reference individuals

Characteristic	Overall psychiatric morbidity				Suicide			
	No. of outcomes/person-years [incidence rate/1000 person-years]	No. of outcomes/person-years [incidence rate/1000 person-years]	Hazard ratio [95% CI]	*p* value	No. of outcomes/person-years [incidence rate/1000 person-years]	No. of outcomes/person-years [incidence rate/1000 person-years]	Hazard ratio [95% CI]	*p* value
	Patients	Reference individuals			Patients	Reference individuals		
Sex								
Male sex	3479/454 890 [7.6]	149 148/23 565 876 [6.3]	1.2 [1.2-1.2]	<0.0001	147/477 827 [0.3]	6891/24 651 152 [0.3]	1.1 [1.0–1.3]	0.1636
Female sex	3986/434 795 [9.2]	157 763/22 782 565 [6.9]	1.3 [1.3–1.4]	<0.0001	64/462 578 [0.1]	2502/23 931 661 [0.1]	1.3 [1.0–1.7]	0.0202
Country of birth								
Sweden	6623/820 438 [8.1]	276 377/42 803 832 [6.5]	1.3 [1.2–1.3]	<0.0001	200/866 252 [0.2]	8752/44 847 062 [0.2]	1.2 [1.0–1.4]	0.0090
Other	842/ 69 247 [12.2]	30 534/35 44 609 [8.6]	1.4 [1.3–1.5]	<0.0001	11/ 74 153 [0.1]	641/3 735 751 [0.2]	0.9 [0.5–1.6]	0.6398
Level of education								
Compulsory school	1984/225 743 [8.8]	84 823/11 702 559 [7.2]	1.2 [1.2–1.3]	<0.0001	87/239 817 [0.4]	3452/12 346 821 [0.3]	1.3 [1.0–1.6]	0.0319
Upper secondary 2 years	2222/265 434 [8.4]	89 190/12 925 614 [6.9]	1.2 [1.2–1.3]	<0.0001	58/282 280 [0.2]	2807/13 641 645 [0.2]	1.0 [0.8–1.4]	0.7788
Upper secondary 3 years	1255/133 963 [9.4]	48 434/6 806 445 [7.1]	1.3 [1.2–1.4]	<0.0001	26/141 879 [0.2]	1152/7 116 634 [0.2]	1.1 [0.7–1.6]	0.7639
University < 3 years	862/104 903 [8.2]	33 071/5 488 411 [6.0]	1.3 [1.2–1.4]	<0.0001	17/110 283 [0.2]	753/5 718 476 [0.1]	1.2 [0.7–2.1]	0.4601
University ≥3 years	1029/147 884 [7.0]	44 800/8 261 687 [5.4]	1.3 [1.2–1.4]	<0.0001	15/153 908 [0.1]	857/8 560 117 [0.1]	1.1 [0.6–1.9]	0.7058
Age at IBD diagnosis and/or cohort entry, years								
18 to < 40	4307/505 306 [8.5]	177 644/25 796 082 [6.9]	1.2 [1.2–1.3]	<0.0001	123/538 230 [0.2]	5314/27 271 285 [0.2]	1.2 [1.0–1.4]	0.0646
40 to < 60	2089/267 599 [7.8]	85 108/13 844 080 [6.1]	1.3 [1.2–1.3]	<0.0001	49/280 955 [0.2]	2720/14 418 763 [0.2]	0.9 [0.7–1.2]	0.6203
≥ 60	1069/116 780 [9.2]	44 159/6 708 280 [6.6]	1.4 [1.3–1.5]	<0.0001	39/121 220 [0.3]	1359/6 892 765 [0.2]	1.7 [1.3–2.4]	0.0008
Start year of follow-up, years								
1973–1979	826/155 868 [5.3]	38 601/8 295 298 [4.7]	1.2 [1.1–1.2]	<0.0001	54/165 731 [0.3]	2456/8 794 669 [0.3]	1.2 [0.9–1.6]	0.2188
1980–1989	1570/256 755 [6.1]	67 208/13 414 829 [5.0]	1.2 [1.2–1.3]	<0.0001	58/270 751 [0.2]	3138/14 060 847 [0.2]	1.0 [0.8–1.3]	0.8895
1990–1999	1847/214 613 [8.6]	74 595/11 297 818 [6.6]	1.3 [1.2–1.4]	<0.0001	50/227 408 [0.2]	2013/11 817 259 [0.2]	1.3 [1.0–1.7]	0.0742
2000–2013	3222/262 450 [12.3]	126 507/13 340 496 [9.5]	1.3 [1.2–1.3]	<0.0001	49/276 516 [0.2]	1786/13 910 038 [0.1]	1.4 [1.0–1.9]	0.0224
Version of ICD classification at the time of cohort entry								
ICD-8 [1973–1986]	1885/338 047 [5.6]	85 331/17 819 856 [4.8]	1.2 [1.1–1.2]	<0.0001	97/357 772 [0.3]	4790/18 787 797 [0.3]	1.1 [0.9–1.3]	0.4284
ICD-9 [1987–1996]	1633/210 139 [7.8]	64 848/11 121 097 [5.8]	1.3 [1.3–1.4]	<0.0001	54/222 402 [0.2]	2127/11 625 073 [0.2]	1.3 [1.0–1.8]	0.0306
ICD-10 [1997–2013]	3947/341 499 [11.6]	156 732/17 407 489 [9.0]	1.3 [1.2–1.3]	<0.0001	60/360 231 [0.2]	2476/18 169 944 [0.1]	1.2 [0.9–1.6]	0.1234
Source of data at the time of cohort entry								
Inpatient register [prior to 2002]	5116/711 748 [7.2]	217 847/37 293 662 [5.8]	1.2 [1.2–1.3]	<0.0001	180/753 521 [0.2]	8289/39 179 989 [0.2]	1.2 [1.0–1.3]	0.0636
Inpatient and outpatient registers [since 2002]	2349/177 937 [13.2]	89 064/9 054 780 [9.8]	1.3 [1.3–1.4]	<0.0001	31/186 884 [0.2]	1 104/9 402 824 [0.1]	1.4 [1.0–2.0]	0.0632
Length of follow-up, years								
< 1	806/1 876 [430]	23 378/ 73 151 [320]	1.4 [1.2–1.6]	<0.0001	25/8690 [2.9]	570/297 416 [1.9]	0.6 [0.2–1.7]	0.3073
1 to < 5	2 069/42 148 [49.1]	82 569/1 998 059 [41.3]	1.1 [1.0–1.2]	0.0024	70/58 070 [1.2]	2651/2 705 539 [1.0]	1.1 [0.8–1.5]	0.6274
5 to < 10	1700/111 537 [15.2]	75 096/5 565 126 [13.5]	1.0 [1.0–1.1]	0.2839	46/122 757 [0.4]	2417/6 107 664 [0.4]	1.0 [0.7–1.5]	0.8166
≥10	2890/734 123 [3.9]	125 868/38 712 105 [3.3]	1.2 [1.2–1.3]	<0.0001	70/750 888 [0.1]	3755/39 472 195 [0.1]	1.0 [0.8–1.3]	0.9153

Table 4. Continued

Characteristic	Overall psychiatric morbidity				Suicide			
	No. of outcomes/person-years [incidence rate/1000 person-years]	No. of outcomes/person-years [incidence rate/1000 person-years]	Hazard ratio [95% CI]	*p* value	No. of outcomes/person-years [incidence rate/1000 person-years]	No. of outcomes/person-years [incidence rate/1000 person-years]	Hazard ratio [95% CI]	*p* value
	Patients	Reference individuals			Patients	Reference individuals		
Complications during follow-up								
Extra intestinal manifestations	1302/122 889 [10.6]	40 842/6 179 148 [6.6]	1.6 [1.5–1.7]	<0.0001	19/132 126 [0.1]	1163/6 487 144 [0.2]	0.8 [0.5–1.3]	0.3284
Primary sclerosing cholangitis	221/30 034 [7.4]	10 146/1 643 385 [6.2]	1.2 [1.0–1.4]	0.0085	3/ 31 446 [0.1]	388/1 724 802 [0.2]	0.4 [0.1–1.3]	0.1306
IBD surgery								
Bowel surgery	2405/331 847 [7.2]	95 644/17 300 695 [5.5]	1.3 [1.3–1.4]	<0.0001	94/352 318 [0.3]	4296/18 191 669 [0.2]	1.1 [0.9–1.4]	0.2201
Perianal surgery	868/102 112 [8.5]	31 288/5 227 059 [6.0]	1.4 [1.3–1.5]	<0.0001	29/109 526 [0.3]	1299/5 506 498 [0.2]	1.1 [0.8–1.6]	0.5050
Psychiatric diagnoses in first degree relatives	3828/366 707 [10.4]	157 161/18 314 432 [8.6]	1.2 [1.2–1.3]	<0.0001	109/394 684 [0.3]	4731/19 536 671 [0.2]	1.2 [1.0–1.4]	0.0994
Psychiatric diagnoses in parents	1782/149 981 [11.9]	71 633/7 360 506 [9.7]	1.2 [1.2–1.3]	<0.0001	49/162 722 [0.3]	2085/7 913 820 [0.3]	1.3 [1.0–1.7]	0.0912
Psychiatric diagnoses in siblings	1434/135 207 [10.6]	60 476/6 559 666 [9.2]	1.2 [1.1–1.2]	<0.0001	41/146 465 [0.3]	1779/7 051 238 [0.3]	1.2 [0.8–1.6]	0.3975
Psychiatric diagnoses in children	1832/170 435 [10.7]	75 426/8 613 156 [8.8]	1.2 [1.2–1.3]	<0.0001	55/184 237 [0.3]	2405/9 215 917 [0.3]	1.1 [0.8–1.5]	0.4324

complements previous findings of a positive association between these conditions. This study employed a longer follow-up than other studies and provided precise risk estimates for subgroups of IBD patients and specific psychiatric outcomes. Although the highest relative risks for psychiatric disorders were seen in the first year of follow-up, persistent excess risks were observed even 10 years after IBD diagnosis. Moreover, we identified several risk groups [e.g. IBD patients with extraintestinal manifestations].

We found a 70% heightened risk of suicide in elderly-onset IBD. Elderly-onset IBD [≥ 60 years] has been linked to a lower use of biologics and immunomodulators but higher absolute risks of bowel surgery compared to IBD diagnosed at a younger age.[39] We speculate that IBD in the elderly may be undertreated. Sibling analyses generally confirmed the findings of the general population-based analyses.

4.2. Comparison to previous literature

4.2.1. Psychiatric disorders

Overall, our findings are similar to those recently presented by our research group for childhood-onset IBD.[23] Based on 6464 individuals diagnosed with childhood-onset IBD, that study reported an HR of 1.6 [95% CI, 1.5–1.7]. The incidence of psychiatric disorders in the current study was lower in IBD patients [8.4/1000 person-years in adulthood vs 17.1 in childhood] and matched reference individuals [6.6/1000 vs 11.2 in childhood], resulting in an HR of 1.3 in adulthood-onset IBD. Adulthood-onset IBD was associated with 1.8 extra cases of psychiatric disorders per 100 patients with IBD followed-up for 10 years.

An increased risk of overall psychiatric disorders [HR = 3.8] has recently been reported in young [aged 5–24 years] IBD patients.[40] However, because the authors did not report the age of IBD onset, it remains unclear how many of these represent adult-onset IBD.[40] In 2019, Bernstein *et al*.[41] followed 6199 incident cases of adult-onset IBD in Canada. While these researchers did not report an HR for overall psychiatric disorders or examine suicide, they examined depression [their incidence rate ratio: 1.6 vs an HR of 1.5 in our study], anxiety disorder [1.4 vs 1.4 in our study], bipolar disorder [1.8 vs 1.1 in our study] and schizophrenia [1.6 vs 0.8 in our study]. Given the wider 95% CIs in the Canadian study[41] [our study was ten times larger], our findings may be compatible. However, our study's overall HRs may be somewhat lower than those of Bernstein *et al*.[41] Because their study was part of a more extensive investigation on immune-mediated diseases, their reference group was filtered from individuals with demyelinating disease, rheumatoid arthritis and related disorders. Their reference group was healthier than the general population [it consists of a mixture of people with and without diseases]. Such a reference group may have inflated the HR in their exposed cohort [IBD]. A similar effect is the 'healthy-worker effect' described in the occupational cohorts. This phenomenon means that industry workers are less likely to experience adverse health and psychiatric outcomes than the population at large.[42]

Moreover, Bernstein *et al*. included a mixture of ICD diagnoses and psychiatric medication for their diagnosis of psychiatric disorders, including medications that may not have been prescribed for psychiatric symptoms and conditions [e.g. drugs often prescribed for situational anxiety, migraine, pain, impaired sleep, sexual problems]. In our study, patients with IBD were at a 1.8-fold increased risk of receiving any psychiatric medication compared to the general population. Of note, Bernstein *et al*. found the highest relative risks of depression in patients diagnosed aged ≥ 65 years[41]; however, the authors did not examine suicide.

As opposed to Bernstein *et al*.,[41] we found no association between IBD and increased risk of non-affective psychotic disorders. Individuals with IBD in our study were slightly less [statistically significant difference but with similar IRs] likely to be diagnosed with schizophrenia before or after IBD diagnosis. This discrepancy could be related to differences in diagnostic practices. For instance, despite a lack of significant results for psychotic disorders, our patients with IBD were more likely to receive antipsychotic medication after IBD diagnosis. Unfortunately, register data do not provide information on an indication to this prescription. Results from other epidemiological studies are also ambiguous. For example, in line with our results, a UK study found a lower prevalence of schizophrenia in IBD patients than in general population controls.[43] In a Danish study, the risk of schizophrenia was similar to the general population in UC but increased 5 years after CD diagnosis [relative risk 1.7].[17] A cohort study from Canada showed that females with IBD were slightly less likely to receive a diagnosis of postpartum psychotic disorders than the general population, despite being at increased risk of mood and anxiety disorders.[16]

In summary, these data indicate that there are differences in diagnostic practice across healthcare systems. The conversion between different diagnostic categories is a common phenomenon in psychiatry.[44] Diagnosing psychiatric morbidity, including psychotic disorders, could be particularly challenging in patients with IBD due to uncertain causal relationships between both conditions and social stigma. Depending on local clinical practice, psychiatrists in this situation might be more likely to assign the less stigmatizing diagnosis of affective psychosis [e.g. psychotic depression] rather than schizophrenia.

The positive association between IBD and concurrent bipolar disorders [relative risks 1.8 for CD and 1.9 for UC] was first reported in a Danish study.[17] However, those results were based on only 92 patients with both IBD and bipolar disorder [as compared to 354 in our study]. The Danish researchers did not point out that the association with bipolar disorder might be due to ascertainment bias.[17] Bipolar disorder in our cohort was explicitly associated with UC [IR 0.4 vs 0.3; HR 1.2], whereas Bernstein *et al*. observed a significant association with both CD and UC.[41]

Our study confirms previous US and Canadian observations of an association between IBD and common psychiatric disorders [e.g. major depressive disorder and anxiety disorders].[11,40,41] Those disorders were the most prevalent types of psychiatric morbidity in all IBD types, suggesting that depressive and anxiety disorders may constitute possible psychological screening targets in IBD patients. An increased risk of substance misuse in IBD has been noted in children and young adults [< 25 years][40] and in females after childbirth,[16] but not in nationwide cohorts. Although our study found a relatively low incidence rate of substance misuse in IBD, recent clinical observations suggest that the problem may be much more prevalent and underdiagnosed. Of 247 IBD participants interviewed by Carney *et al*., 41 [17%] met the criteria for a lifetime diagnosis of substance misuse.[45]

4.2.2. Suicide

In our study, more than 200 IBD patients committed suicide during follow-up [IR 0.22 in IBD vs 0.19 in our general population cohort], constituting a 1.2-fold increased risk. The increased incidence and risk of suicide was specifically associated with CD [IR 0.29 vs 0.19, HR = 1.5] and elderly-onset IBD [IR 0.32 vs 0.20, HR = 1.7]. Of the few studies examining completed suicide in IBD,[5,7,8,46,47] only one has demonstrated a positive association between IBD and suicide.[5] As part of the examination of mortality, Jess *et al*. reported a 1.3-fold increased risk of completed suicide in UC, but no association with CD[5] [based on 113 cases of suicide in IBD]. In contrast, Persson *et al*.

reported a 1.9-fold increased risk of suicide in CD [although the risk estimate just failed to attain statistical significance], but no increased risk in UC [relative risk 0.8].[46] When Zhang *et al*. performed a meta-analysis based on seven studies on suicide in IBD, they found a 1.36-fold increased risk in CD and a 1.16-fold increased risk in UC.[22] However, none of the risk estimates reached statistical significance, probably due to insufficient power. In our earlier study on childhood-onset IBD, we found a 1.4-fold increased risk of a suicide attempt[23] but abstained from any analysis of completed suicide because of the lack of statistical power [there were only 14 deaths from suicide in the paediatric IBD cohort]. We are unaware of any study examining IBD subgroups and suicide. We found no association with sex, education level or surgery. As opposed to, for example, cancer,[48] we found no increased risk of suicide immediately after diagnosis, but the most excess risk seemed to occur 1–5 years after IBD diagnosis.

4.2.3. Psychiatric disorders before IBD diagnosis

Our case-control study confirms previous findings showing that psychiatric morbidity was more prevalent in individuals who later in life developed IBD. For instance, an increased risk of CD in females with depressive symptoms has been reported in the Nurses' Health Study.[49] Similarly, data from observation based on psychiatric diagnostic interviews suggest that symptoms indicating depression, anxiety and substance misuse sometimes occur before IBD diagnosis.[11,45] Together, these findings suggest that psychiatric symptoms may be related to the preclinical manifestation of IBD.

4.2.4. Mechanisms

Several factors may contribute to the excess risk of psychiatric disorders in IBD: one factor is psychosocial impairment,[21,50] a fear of urgent faecal incontinence. A second factor is anxiety associated with the prognosis of the disease, including unexpected disease exacerbations. Other factors include the call for surgery, operation causing the need for an ostomy bag, an increased risk of cancer,[51,52] and a disruption of the gut–brain axis.[53] The association may also be due to IBD-related treatments [e.g. oral corticosteroids] linked to an increased risk of psychiatric morbidity.[54] However, it was beyond the scope of this study to examine the influence of medications on psychiatric health.

Of note, a recent US study of hospitalization data reported a positive association between substance misuse and suicide *ideation* in IBD patients.[55] We found a positive association between IBD and substance misuse, which may have contributed to the excess risk of suicide noted in our study. The US study reported lower risks of suicide ideation in elderly-onset IBD. However, the authors did not present any data pertaining directly to suicide [they did not distinguish between suicide and self-inflicted injury]. Furthermore, their analyses were restricted to healthcare data with a risk of omitting suicide cases before contact with a psychiatric service.[55]

Our sibling analyses also demonstrated a positive association between IBD and psychiatric disorders, suggesting that unmeasured genetic, socioeconomic, or lifestyle confounders are unlikely to explain the risk increase.

4.3. Strengths and limitations

One strength of this study is its statistical power that results from a nationwide approach [with more than 69 000 IBD patients] and the virtually complete follow-up because of the universal use of the personal identity number. During a median follow-up of 11 years, more than 7000 IBD patients developed psychiatric disorders. Long follow-up enabled us to calculate precise risk estimates with 95% CIs for overall psychiatric morbidity and several secondary outcomes [mood disorders: 1.4–1.5, anxiety disorders: 1.3–1.4]. Even for a rare outcome such as suicide, the power of our designed showed a statistically significant increased risk [95% CI = 1.1–1.4].

The high statistical power also allowed us to examine subgroups of IBD patients at an exceptionally high risk of psychiatric disorders, including patients with extraintestinal manifestations and elderly-onset IBD. In addition, the sibling comparison enabled the adjustment of unmeasured familial confounding from genetics, and early environmental factors shared between siblings neglected in previous studies.

Sweden has a tax-funded healthcare system with universal access. This setting is important because research has indicated that low socioeconomic status is linked to psychiatric disorders.[56]

Our study also had some limitations that may have influenced the results. We did not have data on disease intensity, laboratory markers or histopathology scores. Instead, we used IBD surgery and extraintestinal manifestations as markers for disease activity. The risk of psychiatric disorders, including suicide, may be related to disease intensity. Patients undergoing bowel surgery did not have a higher HR for psychiatric disorders than other IBD patients, suggesting that disease activity is not a decisive factor for comorbidity. It was beyond the scope of our study to explore the association between specific medications and IBD. A recent meta-analysis concluded that there were insufficient data to establish a link between biological therapy during IBD and adverse psychiatric events.[57]

Furthermore, we did not have data on body mass index, vitamin deficiencies or smoking, the last being associated with substance misuse.[45]

Moreover, because of the study's observational register-based nature, we evaluated only diagnosed psychiatric outcomes. This limitation may result in either over- or underestimation of the association between IBD and psychiatric disorders. We cannot rule out the possibility that IBD patients under psychological surveillance are more likely to receive a psychiatric diagnosis. On the other hand, people with chronic physical health conditions [such as IBD] and their physicians may attribute some psychiatric symptoms [e.g. insomnia, fatigue in the course of depression] to the physical condition itself [IBD] rather than the stress of coping with the disease and psychiatric comorbidity. Consequently, attribution bias to somatic conditions may prevent patients from seeking mental health professional services and receiving an appropriate psychiatric diagnosis.

4.4. Conclusions and clinical implications

Ours is one of the most extensive studies on psychiatric disorders in adulthood-onset IBD, and perhaps the first in its field to take advantage of sibling data adjusting for familial confounding.

In conclusion, in this large population-based study that included sibling data, adult-onset IBD was associated with an increased risk of later psychiatric disorders and suicide attempts.

The highest risk of overall psychiatric morbidity was observed in the first year after IBD diagnosis and in patients with extraintestinal manifestations. The risk of overall psychiatric morbidity was seen in all IBD subtypes, and major depressive and anxiety disorders were common in all IBD subtypes [including IBD-U]. An increased risk of bipolar disorder was specifically associated with UC. An increased risk of suicide attempts was observed in all IBD types, but completed suicide was explicitly associated with CD and elderly-onset [> 60 years] IBD.

The results from this study have important implications for clinicians and policy-makers working with IBD care. We were able to identify the risk groups who would benefit from further psychiatric screening and psychological intervention. The exceptionally high risk of psychiatric morbidity in the first year after IBD diagnosis suggests the need for psychological surveillance or even routine psychological care during this vulnerable period. Because major depression and anxiety disorders were the most prevalent psychiatric disorders and increased in all IBD types, we contend that possible mental health screening should focus primarily on those conditions. Psychological counselling and follow-up should be an integral part of the professional support offered to patients with IBD. Such an approach applies especially to individuals from high-risk groups [e.g. patients with extraintestinal manifestations and elderly-onset IBD].

Psychosocial and psychiatric interventions should be provided to IBD patients diagnosed with psychiatric morbidity, preferably in an interdisciplinary setting involving gastroenterologists and mental health professionals. The recent study by Lores *et al*. on psychological intervention for IBD patients observed six times greater engagement in psychological intervention integrated into IBD in-service than treatment offered externally by primary healthcare services.[58]

Further research is needed on the effectiveness of mental health screening and therapeutic strategies in patients with IBD and psychiatric morbidity. Importantly, future studies are required to evaluate the effect of preventive and early-stage interventions on long-term psychiatric morbidity in patients with IBD.

Funding

A.B. was supported by the Swedish Research Council [No. 2017-00788], Stockholm Region [No. 20180718] and Karolinska Institutet, Strategic Research Program in Neuroscience [StratNeuro], and the Fredrik O Ingrid Thurings Stiftelse [No. 2016-00254] while working on this project. O.O. was supported by grants from the Swedish Medical Society and the Young Scholar Award from the Strategic Research Area Epidemiology programme at Karolinska Institutet and through the regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Institutet [ALF]. Financial support was also provided from the Swedish Cancer Society, the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social And Medical Sciences [SIMSAM] framework grant [340-2013-5867], and the Swedish Foundation for Strategic Research. None of the funding providers have had any role in the design and conduct of the study; in the collection, management, and analysis of the data; or in the preparation, review, and approval of the manuscript.

Conflict of Interest

All authors have completed the Unified Competing Interest form and declare the following: H.L. has served as a speaker for Eli-Lilly and Shire and has received research grants from Shire; all outside the submitted work. J.H. received consulting/lecture fees from Abbvie, Celgene, Ferring, Hospira, Janssen, Medivir, MSD, Pfizer, Prometheus, RenapharmaVifor, Sandoz, Shire Takeda and Tillotts Pharma and research grants from Janssen, MSD and Takeda. O.O. has been the principal investigator for Karolinska Institutet projects partly financed by investigator-initiated grants and safety programmes from Janssen, Ferring and Pfizer. Karolinska Institutet has also received fees for lectures and participation on advisory boards by O.O. from Janssen, Ferring and Takeda. J.F.L. coordinates a study on behalf of the Swedish IBD quality register [SWIBREG]. This study has received funding from Janssen Corporation. The other authors have no financial relationships relevant to this article to disclose.

Author Contributions

Guarantor: A.B. had full access to all of the study data and takes responsibility for data integrity and data analysis accuracy. Study concept and design: A.B., J.F.L. and O.O. Analysis: A.B. Drafting of the manuscript: J.F.L., A.B. Critical revision of the manuscript for important intellectual content and approval of the final version: All. Transparency declaration: the lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned [and, if relevant, registered] have been explained.

Data sharing statement

No additional data are available because of Swedish regulations.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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