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AALBORG UNIVERSITY
DENMARK

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CV

I grew up in Frederiksberg, Copenhagen and graduated high school in 2006 with a diploma reflecting my interests in language, philosophy, and history. I always knew that I wanted to work with people, and though the science of the natural word was new to me, it drew me in. I applied to medical school and started my degree at the University of Copenhagen in 2009. I used my years at university not only to learn and fall in love with the field of medicine, but also exploring different roles within the field. I worked in GP offices and at hospitals, did volunteer teaching in primary schools, spent a semester in Uganda studying tropical medicine and another semester exploring the circadian rhythm research.

After graduating medical school in 2017, I worked in cardiology and in general medicine, and I started preparing for expat life as I relocated with my family to Seattle, USA for three years for my husband's postdoctoral work. I ventured to find a research project to invest my time in and was lucky to meet Professor Tine Jess and Associate professor Kristine Allin, who not only were involved in exciting research into inflammatory bowel disease, but who were also willing to work with me across 9 time zones to accomplish a PhD project. During the following years, we developed the idea for the project, achieved funding for it, and have now completed the three studies that form the basis for this thesis.

I am married to Christoffer Norn and have two sons, Viggo and Otto.

PAPERS INCLUDED IN THIS THESIS

This thesis is based on three published papers, which are referred to in the text by their roman numerals. The papers and associated supplementary materials are reprinted as appendices to this thesis with permission from the publishers.

PAPER I
Bisgaard TH, Allin KH, Keefer L, Ananthakrishnan AN, Jess T. Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment. Nature Reviews Gastroenterology & Hepatology **19**, 717-726 (2022)

PAPER II
Bisgaard TH, Allin KH, Elmahdi R, Jess T. The bidirectional risk of inflammatory bowel disease and anxiety or depression: A systematic review and meta-analysis. General Hospital Psychiatry **83**, 109-116 (2023)

PAPER III
Bisgaard TH, Poulsen G, Allin KH, Keefer, L, Ananthakrishnan AN, Jess T. Longitudinal trajectories of anxiety, depression, and bipolar disorder in inflammatory bowel disease: a population-based cohort study.
eClinical Medicine **59**, 101986 (2023)

PREFACE

A large part of the work going into the three studies that make up this thesis was undertaken from my home office in Seattle, Washington with late night group and supervisor meetings connecting me to the research group in Copenhagen. It was a daunting task to begin a PhD fellowship working remotely, and I would not have succeeded had it not been for the great support from my supervisors, co-workers, and my friends and family. I was privileged to finish the last 15 months of my fellowship working in office at PREDICT at Aalborg University in Copenhagen surrounded by inspiring and highly skilled colleagues. I would like to convey my deep appreciation and gratitude to all my colleagues at PREDICT, to all the co-authors, to the students I got to supervise, and to everyone who contributed to this thesis.

First, I would like to express my gratitude to my supervisors, Tine Jess and Kristine Allin. Kristine as my primary supervisor, thank you for the support. You always have an open door to discuss both science and personal concerns, and I have learned so much from your great knowledge and attention to detail during these years. Tine, even as you have established and directed a national research center during our time working together, you have always managed to be a present and active supervisor. I admire you as a researcher, a leader, and a strong role model, and I am grateful to have had the opportunity to learn from you. Thank you both for believing in me to succeed in this endeavor even with the added challenge of starting out remotely.

To my wonderful colleagues at PREDICT, thank you for making my time there enjoyable, for the stimulating lunch conversations, and for your ever-ready support and assistance. Thank you Gry Poulsen for fantastic statistical and analytical work. You have an inspiring flair and passion for your work, which makes learning from you a joy. My gratitude extends to the whole statistical powerhouse at PREDICT, Anastasia Karachalia Sandri, Anthony Ebert, Anne Vinkel Hansen, for always generously sharing your wisdom. Rahma Elmahdi, thank you for the great collaboration, and for enriching discussion on both science and life. To my office mates Linéa Bonfils and Camilla Engel Lemser, thank you for all the laughs, for making daily life in the office fun and inspiring, and for the MS Word support. Thank you Annemette Bønneland Kristensen and Jane Due Jensen for your invaluable help and for keeping the group running.

Finally, I thank my friends and family for their unwavering support. Parents Palle and Merete, brothers Simon and Mathias, in-laws Elizabeth and Claus, and cherished friends Anna, Camilla, Nicoline, Louise, your encouragement has meant the world to me. Jisun and Emily, your friendship and support were lifelines when home felt far away. Lastly, my deepest thanks to Christoffer, Viggo and Otto for enriching my life with love and joy.

I acknowledge the Danish National Research Foundation, the Lundbeck Foundation, and Aage og Johanne Louis-Hansens Fond, whose funding made this work possible.

ENGLISH SUMMARY

Background: Inflammatory bowel disease (IBD) has long been associated with depression and anxiety and more recently also with bipolar disorder. Evidence suggests that the psychiatric comorbidities can exacerbate the IBD disease course in addition to deteriorate the patients' quality of life. However, the current knowledge is fragmented, and it is unclear to which extent psychiatric diseases affect patients with IBD, and how the diseases interact and affect each other.

Aims: The aims of the three studies comprised in this thesis were to create a comprehensive overview of the epidemiology, mechanisms, and treatment impact on the co-occurrence of IBD with depression and anxiety; to understand the temporal relationship between IBD, depression and anxiety; and to investigate the longitudinal burden of depression, anxiety, and bipolar disorder in patients with IBD.

Methods: We first performed a narrative review covering multiple questions to create a general overview of the field. Next, we performed a systematic review with meta-analysis following PRISMA guidelines to specifically investigate the risk of IBD in patients with depression or anxiety and conversely the risk of depression or anxiety in patients with IBD. We systematically searched MEDLINE and Embase and used random effect model meta-analysis to calculate pooled risk estimates. Finally, we used the nationwide Danish registers to investigate the longitudinal trajectories of depression, anxiety, and bipolar disorder from five years before until ten years after IBD diagnosis. We used logistic regression to determine prevalence odds ratios for each outcome in the years before IBD diagnosis and we calculated the risk of developing new outcomes after IBD diagnosis using logistic Cox regression.

Results: The narrative review and the systematic review clearly showed that depression and anxiety are frequent and clinically important comorbidities to IBD. The association between the diseases appears to be bidirectional, and there are multiple biological mechanisms that contribute to explaining how the diseases interact. It is still unclear how treatment can impact the co-occurrence of the diseases. The cohort study of more than 22,000 Danish patients with IBD showed a 40% higher risk of depression and anxiety compared with the background population in the years prior to IBD diagnosis, and a 30% increased risk of anxiety and 50% increased risk of depression following IBD diagnosis. We found no clear association to bipolar disorder.

Conclusions: Psychiatric comorbidities, particularly depression and anxiety, constitute a significant burden in the lives of patients with IBD and should be managed as part of a holistic approach to care for these patients. Future research should focus on furthering our understanding of risk factors, connecting mechanisms and treatment.

DANSK RESUME

Baggrund: Inflammatorisk tarmsygdom (IBD) har længe været associeret med depression og angst og de seneste år også med bipolær sygdom. Tidligere studier tyder på, at de psykiatriske komorbiditeter kan forværre sygdomsforløbet af IBD, og de kan være ødelæggende for patienternes livskvalitet. Den eksisterende viden er dog fragmenteret, og det er uklart i hvor høj grad psykiske sygdomme påvirker patienter med IBD, og hvordan sygdommene interagerer og påvirker hinanden.

Formål: Formålet denne afhandlings tre studier var at danne et omfattende overblik over epidemiologien, mekanismerne og effekten af behandling på sammenhængen mellem IBD, depression og angst; at forstå den tidsmæssige forbindelse mellem IBD, depression og angst; og at undersøge byrden over tid af depression, angst og bipolær sygdom hos patienter med IBD.

Metoder: Vi udførte først et narrativt oversigtsstudie, der dækkede flere emner for at danne et generelt overblik over feltet. Dernæst udførte vi et systematisk litteraturstudie med en metaanalyse efter PRISMAs retningslinjer for specifikt at undersøge risikoen for IBD hos patienter med depression eller angst og omvendt risikoen for depression eller angst hos patienter med IBD. Vi søgte litteratur systematisk på MEDLINE og Embase, og vi brugte random effect model metaanalyse til at udregne samlede risikoestimater. Slutteligt brugte vi de nationale danske registre til at undersøge den tidsmæssige forekomst af depression, angst og bipolær sygdom fra fem år før indtil ti år efter IBD-diagnose. Vi brugte logistisk regression til at beregne prævalens odds ratio for hvert udfald i årene før IBD-diagnose, og vi brugte Cox regression til at beregne risikoen for at udvikle nye udfald efter IBD-diagnosen.

Resultater: Det narrative oversigtsstudie og det systematiske litteraturstudie viste klart, at depression og angst er hyppige og klinisk vigtige komorbiditeter til IBD. Associationen mellem sygdommene lader til at gå begge veje, og der er flere biologiske mekanismer, der bidrager til at forklare, hvordan sygdommene interagerer. Det er stadig uklart, hvordan behandling kan påvirke sygdommenes sammenfald. Kohortestudiet med flere end 22.000 danske patienter med IBD viste en 40% forøget risiko for depression og angst sammenlignet med baggrundsbefolkningen i årene før IBD-diagnose og en 30% forøget risiko for angst og 50% forøget risiko for depression efter IBD-diagnose. Vi fandt ingen klar association til bipolær sygdom.

Konklusioner: Psykiske sygdomme, særligt depression og angst, udgør en signifikant byrde gennem livet for patienter med IBD og bør behandles som en del af en helhedsorienteret tilgang til behandling af disse patienter. Fremtidig forskning bør

fokusere på at øge vores forståelse af risikofaktorer, forbindende mekanismer og behandling.

ABBRIVIATIONS

ATC	Anatomical Therapeutic Chemical
CD	Crohn's disease
CI	Confidence interval
CPR	Central Personal Register
DNPR	Danish National Patient Register
DSM	Diagnostic and Statistical manual of mental disorders
GABA	Gamma-aminobutyric acid
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
iNOS	Inducible nitric oxide synthase
IRR	Incidence rate ratio
NO	Nitric oxide
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PY	Person years
TNF-alfa	Tumor necrosis factor-alfa
UC	Ulcerative colitis

CONTENTS

BACKGROUND

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic condition of the gastrointestinal tract characterized by a relapsing disease course with periods of flares and remissions. IBD comprises two main subtypes; Crohn's disease (CD) and ulcerative colitis (UC), which differ in terms of location, extent, and histological features of inflammation. Both subtypes can present with diarrhea, abdominal pain, and weight loss. CD can affect the entire gastrointestinal tract with a discontinuous distribution of lesions and a predilection for the distal ileum and colon. CD is characterized by transmural inflammation creating a cobblestone pattern and in many cases resulting in strictures, fistulas, and fissures (1). UC exclusively affects the colon, starting distally with the potential to extend continually, in severe cases to the entire colon. The inflammation in UC is constricted to the mucosal layer of the colon resulting in endoscopically visible edema, loss of vascular patterns, erythema, erosions, and ulcerations, explaining why patients with UC often experience rectal bleeding and fecal urgency along with the other described symptoms (2).

Industrialized countries in Europe, North America, and Oceania have historically had higher prevalence of IBD than other parts of the world, estimated to approximately 0.3% in a 2018 study, but the incidence is now stable or even decreasing, whereas the incidence is rising in countries in Asia, Africa, and South America (3). In Denmark, the prevalence of IBD doubled in the time period from 1995 (0.27%) to 2015 (0.88%), and the incidence was rising between 1995 and 2016, when incidence reached 17.8/100,000 person years (PY) for CD and 28.4/100,000 PY for UC (4). A recent study found decreasing incidence from 2014 to 2020 suggesting that incidence in Denmark might have peaked and could be stabilizing (5). IBD is most typically diagnosed between the ages of 20-40, and some studies suggest at second smaller peak in incidence in the age groups between 60 and 70 years (6).

Pathophysiology

The exact etiology of IBD is unknown, but the disease is thought to result from a complex interplay between genetics, environmental and immunological factors, and the gut microbiome. Among environmental risk factors are lack of breastfeeding, antibiotic exposure in early life, smoking (risk factor for CD but protective for UC), major life stressors, diet containing a high intake of animal fat and protein as well as sugar, lack of vitamin D, reduced levels of physical activity, several medications, lack of sleep, and hygiene (6). Genome-wide association studies have identified several hundred risk loci that are statistically associated with development of IBD, and many implicated genes variants are involved in inflammatory pathways (7), still it is unclear to what degree genetics dispose to IBD. Genetic and environmental factors are

considered initiating triggers that can alter the intestinal barrier function. This can lead to translocation of intestinal microbiota and microbial products into the bowel wall leading to activation of immune cells following by production of pro-inflammatory cytokines. In patients where the immune system's regulatory mechanisms fail, this can lead to chronic inflammation of the bowel (8).

Impact on quality of life, fertility, and work ability

IBD causes substantial disruptions to many aspects of the patients' daily life. Periods with disease flares can require absences from education and work and patients with IBD have an increased risk of work disability. In a Norwegian study, the relative risk of disability pension was 1.8 (95% CI 1.4-2.3) for patients with UC and 2.0 (95% CI 1.4-2.7) for patients with CD compared with the general population (9). The symptoms of IBD and the associated stigma can cause patients to avoid social interactions and result in feeling isolated. Many patients with IBD experience sexual dysfunction, such as reduced desire or satisfaction, pain, or erectile dysfunction, and while patients with IBD have similar fertility rates as the background population, on average they have fewer children due to worry about pregnancy or about passing on the disease to their offspring (10). These disruptions to daily life along with the symptoms of IBD and the work required to manag the disease, including regular doctor's visits, taking medication, and undergoing surgery, lead to a reduced quality of life in patients with IBD compared with healthy individuals, which is found both in questionnaires focusing on mental and physical aspects of quality of life (11).

Psychiatric comorbidity

Psychiatric diseases are diagnosed using criteria defined by the Diagnostic and Statistical manual of mental disorders (DSM) (12) or the International Classification of Diseases (ICD) (13).

Depression

Depression is a common psychiatric disease, which affect women almost twice as often as men. The occurrence of depression varies considerably by country, with an overall rate of approximately 6% within a 12-month period, and a lifetime risk of depression estimated to be between 15% and 18% (14). Key symptoms include persistent low mood, loss of interest or pleasure, and low energy persisting for more than two weeks. Associated symptoms include sleep disturbance, changes in appetite, poor concentration, reduced self-esteem, loss of energy, feeling of guilt or worthlessness, and suicidal ideation or attempt.

Depression is typically diagnosed as either a depressive episode or recurrent depression, and it is divided into mild, moderate, or severe degrees, which informs treatment choices (12,13). In cases of mild depression, watchful monitoring is

recommended, while moderate depression should be treated with psychotherapy, antidepressants, or both. Severe depression should always be treated with antidepressants, occasionally during admission to a psychiatric hospital (15). In Denmark, most patients with depression are treated by general practitioners, while mainly patients with severe depression are referred to a psychiatrist. One study has demonstrated that 87% of prescriptions for antidepressants to patients who had not previously received antidepressants were prescribed by a general practitioner (16).

The pathophysiology of depression is not fully understood, but several contributing mechanisms have been identified, which include lack of monoamines (serotonin, noradrenalin, and dopamine), hypothalamic-pituitary-adrenal axis hyperactivity, inflammation that directly and indirectly affects brain circuits, changes in neuroplasticity, and genetic susceptibility. Environmental factors can further increase the risk of developing or having more severe depression. Such factors include absence of a life partner, recent negative life events, early childhood trauma, low socioeconomic status, and low social support (17).

Anxiety

Anxiety is a debilitating condition that can lead to significant disruptions in daily life, such as frequent absences from education or work, numerous visits to healthcare providers, and an elevated risk of disability pension (18,19). The anxiety conditions that are included in Paper III in this thesis are coded in the ICD-10 as F41, which mainly includes panic anxiety disorder and generalized anxiety disorder. Both are characterized by anxiety being the main symptom, and not being limited to specific situations. Patients with panic anxiety experience recurrent episodes of sudden, extreme anxiety often accompanied by symptoms such as palpitations, dizziness, dyspnea or sense of being choked, sweating, and a sense of derealization or depersonalization (13). Generalized anxiety is characterized by persistent and excessive anxiety and worry over a period of more than six months. Patients can experience many of the autonomous symptoms described for panic anxiety in addition to feelings of fatigue, muscle aches or soreness, restlessness, and difficulty in concentration and sleeping (13).

Studies from Europe have found a lifetime prevalence of generalized anxiety of 4.3%-5.9%, while the 12-month prevalence was estimated to be between 1.2%-1.9% (20). Those numbers likely reflect the more severe cases of anxiety that are referred to secondary sector treatment. In Denmark, the majority of patients with anxiety are diagnosed and treated in the primary sector, by general practitioners, psychiatrists, or psychologists, which is not registered in the national registers (19). Anxiety, like depression, is about twice as common in women compared with men, and the two conditions often occur together.

Psychological interventions are effective in treating anxiety, with cognitive behavioral therapy having the most evidence of efficacy. Additional medical therapy can be necessary in patients with moderate or severe anxiety. The drug of choice is antidepressant therapy, but also anti-epileptic medication can be effective. Benzodiazepines are good at treating acute anxiety and at managing the autonomous symptoms but can cause dependence (20).

The pathophysiology of anxiety is unclear but involves a combination of genetic, environmental, and neurobiological factors. A key factor in generalized anxiety is an imbalance in neurotransmitter levels such as gamma-aminobutyric acid (GABA), serotonin, and noradrenaline (20), and as in depression, imaging studies have found increased activity in the amygdala in patients with anxiety. Environmental factors that can contribute to development of anxiety disorders include childhood trauma, chronic stress, and other traumatic life experiences (21).

Bipolar disorder

Bipolar disorder is a recurrent mood disorder that is characterized by alternating mania and depressive episodes. It usually debuts early in life but with a significant diagnostic delay of 5-10 years. The disorder is associated with a great loss of quality of life, comorbidity with other psychiatric diseases, and a 20 times increased risk of suicide (22). Patients experience depressive episodes with similar symptoms to those described above and periods with manic symptoms such as elevated mood and increased energy and activity, loss of social inhibitions, pressure of speech, inflated self-esteem with feelings of grandeur and over-optimism, and a reduced need for sleep (13). Bipolar disorder can be divided into type 1, where the patient experiences mania in the classical sense, and type 2, where the patient has smaller variations in mood, alternating between depression and hypomania. Both types have a lifetime prevalence of approximately 1%, resulting in an overall lifetime prevalence for bipolar disorder of 2%, with variations between countries. The risk is similar in men and women (23).

Treatment of bipolar disorder can be difficult, and patients are usually referred to a specialist. Lithium is considered a first line treatment both in the acute phase and in maintenance therapy, but it entails a risk of toxicity, and the dose needs to be closely monitored. Other therapeutic options include anticonvulsants, antipsychotics, and antidepressants. Psychotherapy is helpful in depressive periods and for psychoeducation in manic periods (23).

Despite the serious impact on patients' lives, the pathophysiology of bipolar disorder is not well understood, but it is partly heritable, as having a first degree relative with the disorder is the strongest individual risk factor. Additionally, neuroimaging studies have found morphological changes in the brain in patients with bipolar disorder in areas such as the thalamus, the hippocampus, the amygdala, and the lateral ventricles,

which are involved in emotional and cognitive processing (24). Further, environmental risk factors such as traumatic life events likely play a role in the development of the disorder (23).

Associations between the diseases

Associations between IBD and several psychiatric diseases have been observed and described in the literature. Whereas patients with IBD were once considered of neurotic characters and thus stigmatized (25), we now have an increased yet still limited understanding of how IBD co-occurs with psychiatric diseases, and we are beginning to understand the possible interplay and mechanisms that could underly the co-occurrence. IBD has in particular been linked to depression and anxiety, with studies describing high prevalences of both symptoms of and diagnoses of the diseases (26–28). This field of study has received increasing interest in recent years and more high-quality studies have started to come out. There has been less attention on the relation of other psychiatric diseases to IBD, but a few studies have indicated a higher risk of bipolar disorder in patients with IBD (26,29,30).

Apart from the increased burden of dealing with more morbidity accompanied by increased health care utilization (31,32), evidence is emerging that the psychiatric comorbidities might contribute to exacerbations in the IBD disease course. A recent meta-analysis showed that patients with IBD and concurrent symptoms of anxiety or depression were at increased risk of more active IBD, escalation of therapy, hospitalization for IBD, and IBD related surgery (33). Management of co-occurring anxiety or depression might conversely benefit patients with IBD in several ways. Antidepressants work through regulating neurotransmitters leading to reduction in symptoms of anxiety and depression, and through similar mechanisms in the enteric nervous system leading to improvements to gastrointestinal symptoms through changes in motility and sensation in the gut. Further, antidepressants can help reduce pain and improve sleep quality, all of which can contribute to enhance patients' quality of life (34). Animal studies additionally suggest that antidepressants can directly work to reduce inflammation (35–37), and could thus possibly be a beneficial adjuvant therapy in the treatment of IBD, if the same mechanisms were shown to take place in humans. These effects suggest an interplay between IBD and anxiety and depression – and possibly other psychiatric diseases – that extent beyond the understandable strain and stress of suffering from a chronic disease such as IBD.

Gut-brain axis

The gut-brain axis is a bidirectional communication network between the gastrointestinal system and the central nervous system that enables the exchange of information, signals, and molecules, helping to maintain homeostasis, influencing

behavior, and affecting overall health. Extensive research in recent years has explored the components of the gut-brain axis, which include the autonomic nervous system, the enteric nervous system, the immune system, and the endocrine system. In addition, the gut microbiota plays a crucial role in the gut-brain axis (38). Numerous signaling mechanisms facilitate the communication between the gut and the brain. The gut microbiota can modulate the immune response and produce metabolites such as short-chain fatty acids and neurotransmitters such as GABA and serotonin that can influence the enteric and autonomic nervous systems. Afferent vagal nerve fibers carry signals from the gut to the brain, and circulating cytokines released from the gut can enter the brain or activate receptors that can modulate brain function (39,40). Conversely, efferent vagal nerve signaling from the brain to the gut and activation of the hypothalamic-pituitary-adrenal axis can affect bowel functions such as motility, intestinal permeability, and mucus production (40). The gut-brain axis has been implicated in various health conditions and diseases, including depression and anxiety, and while most research so far has been performed in animal models, bidirectional effects of the gut-brain axis are playing out in humans as well, implicating the gut-brain axis in facilitating the mutual interaction of diseases of the brain and the gut.

Knowledge gaps

At the inception of this PhD project, we had a strong presumption that IBD is associated with psychiatric diseases, particularly anxiety and depression, which was reflected in a growing number of studies on the topic. However, there was a clear lack of a comprehensive overview of the very fragmented existing knowledge in the field. Additionally, we lacked a better understanding of how the diseases occur together, when they arise in time relative to each other, and we lacked a proper quantification of the comorbidity burden caused by psychiatric diseases over the lifespan of patients with IBD.

AIMS

To address this lack of knowledge, we designed three studies with the following aims:

Study I

To comprehensively review the literature on the co-occurrence of IBD with anxiety and depression, including the epidemiology, the temporal relationship, the role of stress, the possible biological mechanisms linking the diseases, and the effects of treatment on the comorbidity.

Study II

To systematically review all unselected, population-based studies examining the bi-directional risk of IBD, anxiety, and depression.

Study III

To examine the risk of anxiety, depression, bipolar disorder, and use of antidepressants longitudinally leading up to and after IBD diagnosis compared with the general population.

METHODS

In this chapter, I outline the methods used for each study and I critically evaluate the reasoning behind the chosen methods. The methods are described in detail in each included article in the appendix.

Study I

Search strategy

To understand the state of knowledge in the field, we first carried out a comprehensive state-of-the-art review that covered the topic of anxiety and depression in patients with IBD broadly. We performed an extensive literature search to map out the epidemiology, mechanisms, and effect of treatment on the co-occurrence of IBD and anxiety and depression.

We searched MEDLINE using the terms: “inflammatory bowel disease” OR “Crohn’s disease” OR “ulcerative colitis” AND “depression” OR “anxiety” combined with “epidemiology”, “incidence”, “prevalence”, “antidepressants”, “microbiome”, “microbiota”, “gut-brain axis”, and “genetics”. Along with my experienced co-authors, I critically assessed the content and searched reference lists from identified studies to ensure a high-quality overview of the subject. When possible, we aimed to include studies of the highest evidence strength such as systematic reviews, meta-analyses, and randomized controlled trials.

Methodology considerations

We conducted this narrative review with the goal of creating a state-of-the-art and comprehensive overview of the current understanding of depression and anxiety in patients with IBD. The methodology employed was not limited to specific guidelines due to the extensive scope of the reviewed questions, but instead involved a broad and meticulous search of relevant literature with thorough evaluation of all identified studies. The review presents the most validated and reliable findings to date. With this method, we risk imposing our own bias, as we did not employ stringent, pre-defined inclusion- and exclusion criteria. This is the trade off to doing such a comprehensive review covering a wide topic. We tried to counter this risk of bias by having all coauthors critically evaluate the work, and we searched reference lists to identify primary articles in order to properly be able to present the findings.

Study II

Study design

We performed an extensive systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (41), which is a guideline developed to ensure use of appropriate methods containing a checklist of 27 items for transparency and completeness in reporting the results of the systematic review and meta-analysis. The guideline specifies how to present the results of the literature search, including the justifications for exclusions of identified articles, and it provides a detailed formula for what information should go into each section of the finished review. In the methods section, this includes specification of the study protocol, the eligibility criteria, the information sources and applied search terms, study and data collection process, and description of methods for evaluation of bias and for choice of analyses to combine the data from individual studies.

Search strategy and eligibility criteria

We searched MEDLINE and Embase for all English language articles published between 1991 and July 2022 using the search terms in Box 1 as both exploded subject headings and as key words.

Box 1. Search terms

1. inflammatory bowel disease
2. ulcerative colitis
3. Crohn disease
4. IBD
5. 1 OR 2 OR 3 OR 4
6. depression
7. anxiety
8. 6 OR 7
9. 5 AND 8

We included only studies that contained a risk estimate of anxiety or depression in patients with IBD or a risk estimate of IBD in patients with anxiety or depression. Included studies had to be unselected, defined as either being population-based or covering more than 50,000 individuals. We excluded studies that did not have a reference-group, if the outcomes were not clearly defined, or if the cohort was in some way selected, i.e., by treatment or disease severity. We included only the most recent study if several studies were based on the same cohort. In accordance with the PRISMA guidelines, the screening of search results was performed by two independent researchers to ensure that we identified all articles that fulfilled the pre-defined inclusion criteria.

Primary outcomes:

- Risk of anxiety or depression in patients with IBD
- Risk of IBD in patients with anxiety or depression

Secondary outcomes:

- Risk of anxiety or depression in patients with Crohn's disease or ulcerative colitis
- Risk of Crohn's disease or ulcerative colitis in patients with anxiety or depression

Statistical analyses

Due to an a priori assumption of both inter and intra study variance, we performed a random effects-model meta-analysis of extracted adjusted risk estimates from each study included in the meta-analysis with weighting based on the standard error of each study resulting in pooled hazard ratios (HR) of depression and anxiety in patients with IBD. We used the Sidik-Jonkman estimator for τ^2, which is a conservative estimator, in an effort to not overestimate the precision of our pooled result, as the analysis was based on few studies with assumed variance between populations. We evaluated for publication bias using Egger's regression test (42) of the funnel plot of included studies, as the visual inspection of the funnel plot was challenging due to few studies. We assessed study quality using the Newcastle-Ottawa Scale (43).

We undertook subgroup meta-analyses by IBD subtype (CD and UC) and sex, where the data were available. Additionally, we performed separate meta-analyses for adult-onset and pediatric-onset IBD.

We did not undertake a meta-analysis for risk of IBD following anxiety or depression, as we only identified two articles that fulfilled the inclusion criteria on that question.

Study III

Data sources

Danish Civil Registration System

The Danish Civil Registration System was created in 1968 and contains information on all individuals residing in Denmark since then. Among many other factors, it records vital status, migration, address of residence, and civil status. All persons are assigned a unique ten-digit Central Personal Register (CPR) number either at birth or upon immigration. The CPR number enables linkage across registers in Denmark. It is not possible to have data in this register deleted, and the register is updated daily, and thus holds complete information on the entire unselected population (44).

Danish National Patient Registry

Since its establishment in 1977, The Danish National Patient Register (DNPR) has contained data on all in-patient somatic hospital contacts. Since 1995, the register has also recorded somatic outpatient and emergency department contacts as well as psychiatric in- and out-patient and psychiatric emergency department contacts. The psychiatric contacts were until 1995 recorded in the Danish Psychiatric Central

Register, which is now a part of the DNPR. Diagnoses in the DNPR are indexed by the International Classification of Diseases (ICD)-8 and ICD-10 in the periods 1977-1994 and 1995-present respectively. The Danish public hospitals are tax funded, and a large proportion of activities at Danish private hospitals are likewise publicly funded under the rule of "free hospital choice" (45). Therefore, the register contains complete information on the entire population with only very minor exceptions for a small proportion of the privately paid services at private hospitals.

Danish National Prescription Registry

The Danish National Prescription Registry was established in 1994 and collects data on all prescriptions dispensed at retail pharmacies in Denmark by Danish residents. Each prescription is linked to the CPR-number, and the register contains data on medication type registered by Anatomical Therapeutic Chemical (ATC) code, dose, quantity, date of collection, indication (if filled by prescriber), and more (46).

Cohort construction

Informed by our comprehensive review of the current knowledge in the field, we decided to perform a study to characterize the longitudinal burden of psychiatric diseases in the lifespan of patients with IBD in Denmark. We used the data sources described above to construct a nationwide, unselected cohort of patients with IBD diagnosed after the age of 18 that we matched on age, sex, calendar time, and municipality of residence to individuals from the background population. Patients with IBD were identified using ICD-8 codes (1977-1994; CD: 563.01, 563.02, 563.08, 563.09; UC: 563.19, 569.04) and ICD-10 codes (1995-present; CD: K50; UC: K51), and we required two IBD contacts within a two-year period to avoid including misclassified patients. In order to increase time of diagnosis precision, the two contacts had to be the first ever contacts for IBD for each patient, and they had to be in the time interval between January 1st 2003 and December 31st 2013 allowing us data on from five years before until five to ten years after diagnosis.

Study outcomes

Data on study outcomes were retrieved from the DNPR and the Danish National Prescription Registry. We defined an outcome as at least one hospital contact (in- or outpatient) for anxiety, depression, or bipolar disorder (ICD-10 codes: depression: F32, F33; anxiety: F41; bipolar disorder: F31) or at least one dispensed prescription for antidepressants (ATC code N06A except for the subgroup N06AX12) in a year.

Statistical analyses

We wanted to thoroughly illustrate and analyze the longitudinal burden of psychiatric comorbidity in patients with IBD. Therefore, we first calculated the annual prevalence of each outcome for both patients with IBD and their matched references.

We then used logistic regression to calculate the prevalence odds ratio (OR) with 95% confidence intervals (CI) for each outcome in the five years before IBD diagnosis for patients with IBD compared with references. This study part can be considered a case-control study nested in the cohort study with a sufficient number of matched controls to limit introduction of bias. We divided the analysis to look at the periods 0-2 years and 3-5 years before IBD diagnosis separately to account for possible diagnostic delay that might influence especially the last year before IBD diagnosis. We also stratified the analysis by IBD subtype, sex, and age at IBD diagnosis.

Finally, we analyzed the period after IBD diagnosis using Cox regression to generate HRs with 95% CIs of each outcome as a measure of the relative risk. The model uses survival analysis to investigate time to event data and thus produces risk estimates with person years at risk as the denominator. We calculated both the overall risk of each outcome and the risk each year after IBD diagnosis, and we stratified the analyses by IBD subtype, sex, and age at IBD diagnosis. We restricted the analyses to patients with IBD and reference individuals with no history of the outcomes of interest in the five years before diagnosis or index date to ensure capture of incident psychiatric outcomes. As the matching was no longer applicable after restriction, we adjusted the analyses for age and year at diagnosis, sex, and municipality of residence.

SAS version 9.4 TS Level 1M7 was applied for all analyses.

RESULTS

In this chapter, I briefly summarize the main findings of each of the three studies. Each individual paper in the appendix contains detailed presentations of all results.

Study I

This comprehensive review summarized the state of knowledge about IBD, depression and anxiety structured around three main themes, which are condensed here.

Epidemiology

Many studies have investigated the prevalence of symptoms or diagnoses of depression and anxiety in patients with IBD with widely varying sample sizes and study designs resulting in a large variation in estimates. However, it is clear that depression and anxiety are common comorbidities to IBD. In meta-analyses (28,47,48), the pooled prevalence of symptoms of depression and anxiety varied between 21%-25.2% and 19.1%-35.1% respectively, while one meta-analysis (48) found a pooled prevalence of diagnoses of depression and anxiety of 15.2% and 20.7% respectively. In pediatric populations, the prevalence was lower with pooled prevalence of depression diagnoses and symptoms of 3.4% and 15% and pooled prevalence of anxiety diagnoses and symptoms of 4.2% and 16.4%, respectively (49).

The timing of the diseases relative to each other has been less thoroughly examined, but the available population-based studies (26,30,50–55) point to a bidirectional relationship with depression and anxiety being more prevalent in patients with IBD as early as five to ten years before diagnosis and for at least ten years after IBD diagnosis, as illustrated in Figure 1. This bidirectionality also seems to exist with regards to disease activity. Studies have found increased symptoms of depression and anxiety being associated with more active IBD disease course, and conversely increased IBD activity leading to more symptoms of depression and anxiety (56).

The role of stress in the onset and disease course of IBD is uncertain. Some studies suggest a connection between the occurrence of a stressful life event (57,58) or high levels of perceived stress (59) and a worsening in IBD disease activity, while other studies have found no such connection (60,61). The available studies on stress and IBD vary greatly both in design and in definitions of stress, and prospective studies with accurate measures of stress would be crucial in unraveling the role of stress as a factor in IBD and possibly as a mediator in the co-occurrence of IBD and psychiatric diseases.

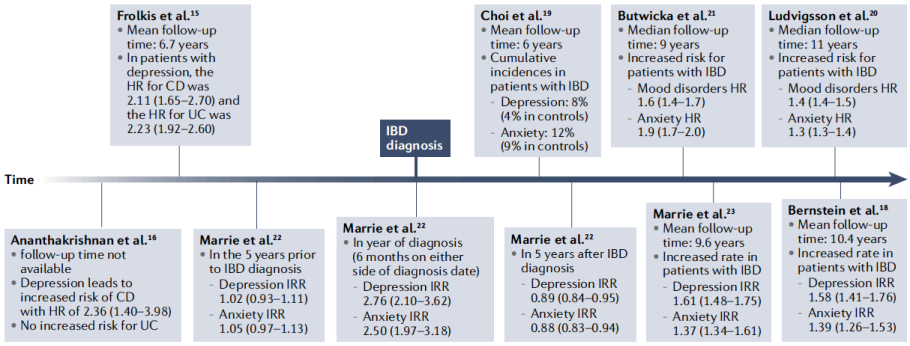

Figure 1. Population-based studies illustrating the temporal relationship between inflammatory bowel disease and depression and anxiety. The studies are ordered along the timeline in accordance with study period relative to IBD diagnosis; that is, how long before IBD diagnosis the studies started or how long after IBD diagnosis the studies followed up. 95% confidence intervals are provided in brackets. CD, Crohn's disease; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; UC, ulcerative colitis. *Reproduced from Paper I* (62) *with permission from Springer Nature.*

Mechanisms

The mechanistic evidence underlying the co-occurrence of IBD, depression, and anxiety stems both from studies in animals and from studies in humans. In mice with induced inflammation of the bowel, changes in the hippocampus of the brain have been observed, including increases in nitric oxide and tumor necrosis factor-alfa (TNF-alfa) and induction of P21, a protein related to proliferation of nerve cells (39,63–66). The hippocampus is involved in memory and emotional regulation, and a study has linked induced colitis in mice with behaviors indicative of depression (64). In humans as well, studies have demonstrated changes in brain morphology in areas pertaining to emotional processing, though these studies were limited by small sample sizes (67–69). Conversely, a few studies have shown increased susceptibility to gut inflammation in animals with induced depression, attributed at least in part to vagal nerve dysfunction and release of pro-inflammatory cytokines from intestinal macrophages (70–74). Additionally, studies in both animals and humans indicate that gut microbiome dysbiosis plays a role in the association of IBD and depression (75–79), and in humans, genetic correlation has been suggested to play a role in the co-occurrence of the diseases (80,81). Figure 2 summarizes the possible biological mechanisms that link IBD with depression and anxiety.

Effect of treatment

Studies in animals have demonstrated an anti-inflammatory effect of several antidepressants as well as direct improvements to gut inflammation following

treatment with antidepressants (35–37,82). In humans, results have been more conflicting with some studies indicating improvements to IBD activity in patients treated with antidepressants (50,83–85) and others findings no effects (86,87). Psychological interventions have also been investigated for effects on IBD disease course but with mixed results (88–90). Conversely, in the context of IBD, a few studies have linked the reduction of systemic inflammation after initiation of TNF-alfa inhibitors (91–93) or the anti-integrin drug Vedolizumab (94) to a decrease in symptoms of depression and anxiety.

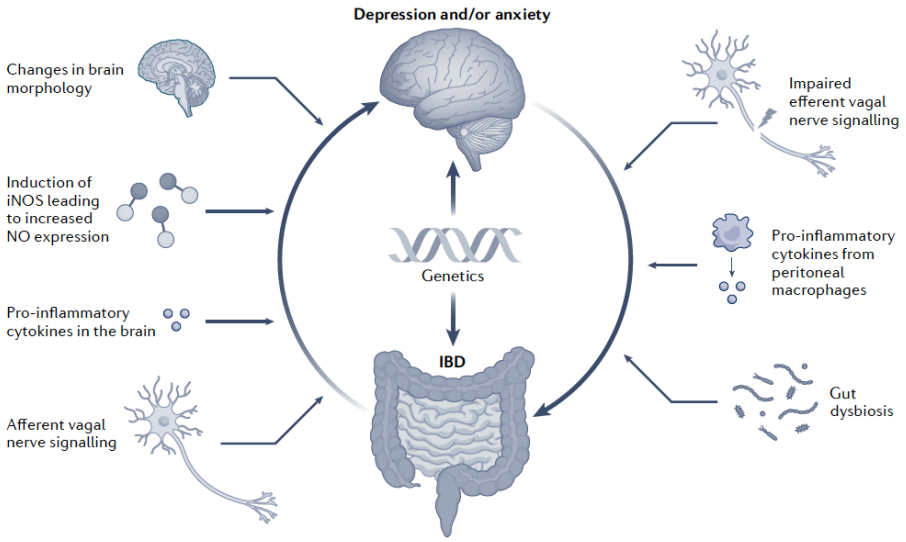

Figure 2. Potential mechanisms linking inflammatory bowel disease, depression and anxiety. Studies show changes in the brain in both humans and animals with gut inflammation, possibly mediated through vagal nerve signaling from the inflamed gut. In the brain, induction of inducible nitric oxide synthase (iNOS) followed by high levels of nitric oxide (NO), increases in pro-inflammatory cytokines and changes in brain morphology are among the factors that might lead to psychiatric diseases in patients with inflammatory bowel disease (IBD). In patients with depression, gut dysbiosis, impaired efferent signaling through the vagus nerve and increasing levels of pro-inflammatory cytokines from peritoneal macrophages are among the possible mechanisms contributing to onset or exacerbation of IBD. *Reproduced from Paper I* (62) *with permission from Springer Nature*.

Study II

The literature search yielded 6,853 results, and after title and abstract screening, we assessed 28 full-text articles and included nine articles in the review. Two (50,51) of the nine articles investigated the risk of IBD in depression cohorts with a total of 420,651 patients with depression and 5,356,934 reference individuals. Seven articles (26,30,53,54,95–97) investigated the risk of anxiety or depression in patients with IBD, six of which we included in the meta-analysis with one article only included in the sub-analysis on risk divided by IBD subtype. One article (97) could not be included in the meta-analysis, as the psychiatric outcomes were pooled, so we could not extract anxiety and depression numbers separately. The included articles are listed in Table 1 and Table 2. We evaluated all nine included studies using the Newcastle-Ottawa scale, which is a tool for assessing quality of non-randomized studies in meta-analyses. One study scored five out of nine, while the remaining eight studies scored eight or nine, indicating a general high study quality. The main analyses showed a high study heterogeneity, with I^2 ranging between 80%-95% in the main analyses, reflecting the percentage of variability that is not attributed to sampling error (see Figure 3 and Paper II, Figure 2), Neither the funnel plot (see Paper II, Supplementary Figure 4) nor the Egger's regression test indicated presence of publication bias (intercept 2.14, p=0.55).

Study	Country	Source population	Follow up time	IBD cohort size	Reference cohort size	Crude incidence rate / 1,000 person years		Adjusted risk estimate depression (95% CI)		Adjusted risk estimate anxiety (95% CI)		Adjustment variables	Method for measuring anxiety or depression
						IBD	References	CD	UC	CD	UC		
Bernstein et al., 2019 [20]	Canada	Regional adult population-based cohort, 55% female	Mean follow up time 10.4 years	IBD: 5,346 CD: 2,389 UC: 2,957	26,716	Depression: 18.6 Anxiety: 25.0	Depression: 10.8 Anxiety: 16.3	IRR 1.76 (1.51-2.05)	IRR 1.43 (1.24-1.64)	IRR 1.56 (1.35-1.79)	IRR 1.27 (1.11-1.44)	Age, sex, socioeconomic status, region (urban/rural), fiscal year	ICD-9 and ICD-10 diagnostic codes
Butwicka et al., 2019 [23]	Sweden	Swedish National Patient register, pediatric population, 44% female	Median follow up time 9 years	IBD: 6,464 CD: 2,536 UC: 3,228	323,200	Depression: 6.1 Anxiety: 9.8	Depression: 4.0 Anxiety: 5.3	HR 1.6 (1.4-1.9)	HR 1.4 (1.4-1.7)	HR 2.2 (1.9-2.4)	HR 1.6 (1.4-1.8)	Year of birth, sex	ICD-8, ICD-9, and ICD-10 diagnostic codes
Choi et al., 2019 [19]	South Korea	The National Healthcare Insurance Service, 27% female	Mean follow up time 6 years	IBD: 15,569 CD: 6,396 UC: 9,173	46,707	Depression: CD: 14.99 UC: 19.63 Anxiety: CD:20.88, UC: 31.19	Depression: CD-references: 7.75 UC-references: 11.18 Anxiety: CD-references: 14.31, UC-references: 21.55	HR 2.06 (1.74-2.44)	HR 1.93 (1.7-2.18)	HR 1.58 (1.38-1.82)	HR 1.58 (1.43-1.74)	Age, sex, residence, income, comorbidities	ICD-10 diagnostic codes
Loftus et al., 2011 [24]	USA	Health service database cohort (Market Scan), 46% female	Not available	CD: 2,144	10,720	Depression: 26.9 Anxiety: 18.1	Depression: 12.2 Anxiety: 5.7	1.74 (1.35-2.25)	Not assessed	2.28 (1.65-3.17)	Not assessed	Age, sex, Charlson comorbidity index score, region, type of health care plan	ICD-9 diagnostic codes
Ludvigsson et al., 2021 [18]	Sweden	Swedish National Patient Register, adult population, 48% female	Median follow up time 11 years	IBD: 69,865 CD: 21,245 UC: 43,557	3,472,913	Depression: 3.6 Anxiety: 4.0	Depression: 2.5 Anxiety: 3.0	HR 1.5 (1.4-1.6)	HR 1.4 (1.3-1.4)	HR 1.4 (1.3-1.5)	HR 1.2 (1.2-1.3)	Age, sex, year, and place of birth	ICD-8, ICD-9 and ICD-10 diagnostic codes
Umar et al., 2022 [22]	UK	National representative cohort from electronic medical database (IMRD), 48.3% female	Not available	IBD: 48,799 CD: 20,447 UC: 28,352	190,075	Depression: 10.75 Anxiety: 5.48	Depression: 7.9 Anxiety: 4.67	HR 1.36 (1.26-1.47)	HR 1.24 (1.16-1.33)	HR 1.38 (1.16-1.65)	HR 1.26 (1.07-1.47)	Age, sex, Townsend deprivation score, ethnicity, smoking status, Charlson comorbidity score	READ codes (coding system with information on symptoms, examinations, and diagnoses)
Vigod et al., 2019 [21]	Canada	Regional cohort (Manitoba), all pregnant and post-partum women	Follow up from conception to 1-year post-partum (~1 year and 9 months)	IBD: 3,721	798,908	150.17 (number only available for overall mental illness)	132.76 (number only available for overall mental illness)	HR for any new onset mood or anxiety disorder 1.13 (1.05-1.22)				Maternal age, neighborhood income quintile, rural/urban residence, medical comorbidity, prenatal care type, maternal and neonatal health conditions	ICD-9 and ICD-10 diagnostic codes

Table 1. Characteristics of included cohort studies on risk of depression or anxiety in patients with inflammatory bowel disease. CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; IRR, incidence rate ratio; UC, ulcerative colitis *Reproduced from Paper II* (97) *with permission from Elsevier*.

Study	Country	Source population	Follow up time	Depression cohort size	Reference cohort size	Crude incidence		Adjusted risk estimate (95% CI)	Adjustment variables	Method for measuring anxiety or depression
						Depression	References			
Ananthakrishnan, 2013 [25]	USA	Cohort from Nurses' Health Study, 100% female	Not available	16,986	32,948	CD: 0.15 /1000 person years UC: 0.13 /1000 person years	CD: 0.07 /1000 person years UC: 0.10 /1000 person years	HR for CD: 1.62 (0.95-2.77) HR for UC: 1.07 (0.63-1.83)	Race, ethnicity, cigarette smoking, menopause status, BMI, use of oral contraceptives, postmenopausal hormones, aspirin and NSAID	5-question Mental Health Index (MHI-5)
Frolkis, 2019 [26]	UK	National representative cohort from electronic medical database (THIN), 65% female	Median follow up time 6.7 years	403,665	5,323,986	CD: 203 (0.05%) UC: 539 (1.13%) *	CD: 1589 (0.03%) UC: 4675 (0.09%) *	HR for CD: 2.11 (1.65-2.7) HR for UC: 2.23 (1.92-2.6)	Age, sex, socioeconomic status, comorbid conditions, smoking status, anxiety, antidepressant use	READ codes (coding system with information on symptoms, examinations, and diagnoses)

*crude incidence numbers per person years not available

Table 2. Characteristics of included studies on risk of inflammatory bowel disease in patients with depression. CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis. *Reproduced from Paper II* (98) *with permission from Elsevier.*

As illustrated in Figure 3, the meta-analysis showed an increased risk of both anxiety (HR 1.48, 95% CI 1.29-1.70) and depression (HR 1.55, 95% CI 1.35-1.78) following a diagnosis of IBD. There were no differences in risk by sex.

On subgroup meta-analysis, risk of anxiety and depression was increased in both IBD subtypes, though patients with CD had higher increased risk (HR 1.67, 95% CI 1.41-1.98 and HR 1.63, 95% CI 1.45-1.83 respectively) than patients with UC (HR 1.37, 95% CI 1.21-1.55 and HR 1.46, 95% CI 1.26-1.68 respectively) (See Paper II, Figure 2).

When dividing the analyses into adult and pediatric populations, the risk of depression remained increased in both age groups. In the pediatric cohorts, the risk of anxiety was particularly elevated in pediatric patients with CD (HR 2.21, 95% CI 1.98-2.47), while the risk in pediatric patients with IBD overall did not have a significantly increased risk of anxiety (HR 1.47, 95% CI 0.66-2.37) (see Paper II, Supplementary figure 3).

The two available population-based cohorts of patients with depression both found an increased risk of IBD compared with the depression-free reference individuals. In one study from the Nurses' Health Study (51), only the risk of CD (HR 2.36, 95% CI 1.40-3.99) but not the risk of UC (HR 1.14, 95% CI 0.68-1.92) was increased in those with depressive symptoms. The population-based study from the UK (50) found that the risk of both CD (HR 2.11, 95% CI 1.65-2.70) and UC (HR 2.23, 95% CI 1.92-2.60) was increased following a physician-diagnosed depression.

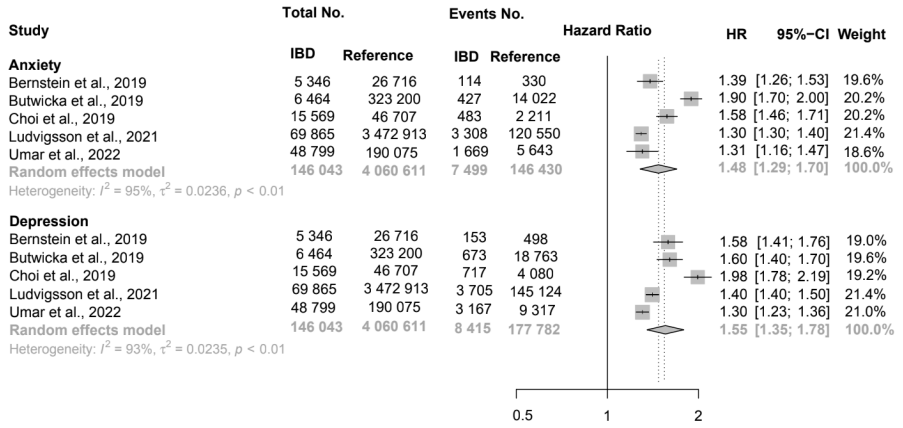

Figure 3. Risk of anxiety and depression in patients with inflammatory bowel disease. Squares represent the HR from each study, and the horizontal lines represent 95% confidence intervals. The vertical lines represent the pooled HR of anxiety and depression, respectively, and the diamonds represent the confidence intervals of the pooled HRs of anxiety and depression, respectively. CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease. *Reproduced from Paper II* (98) *with permission from Elsevier*.

Study III

We included 22,103 patients with IBD and a matched reference population of 110,515 individuals. Figure 4 illustrates the cohort construction and criteria for exclusion. 30.5% had CD and 69.5% had UC, there were slightly more females than males, and the mean age at IBD diagnosis was 45.9 years, see Paper III, Table 1.

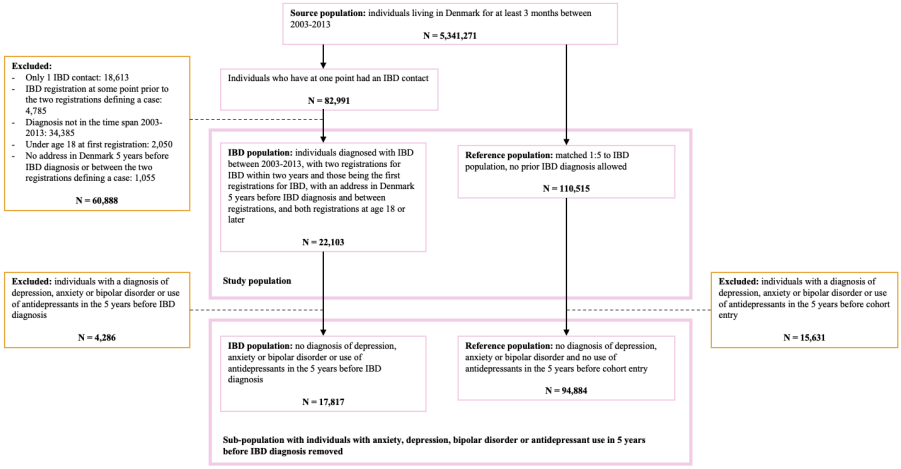

Figure 4. Flow chart describing formation of the IBD and matched reference cohorts. IBD, inflammatory bowel disease. *Reproduced from Paper III* (99) *with permission from Elsevier*.

Figure 5 illustrates the yearly prevalence of each outcome in the IBD and reference populations from five years before until ten years after IBD diagnosis/index date. Depression and use of antidepressants was more frequent in patients with IBD in the entire time period with a peak difference in the year of IBD diagnosis. Hospital contacts for anxiety is a relatively rare outcome, as it is mostly treated in the primary care sector. The numbers behind Figure 5 (Paper III, Supplementary table 1) reveal that also anxiety was more frequent in patients with IBD throughout the study period, though because of smaller numbers it is not as visually evident from the figure. The prevalence of bipolar disorder was consistently similar in patients with IBD and references.

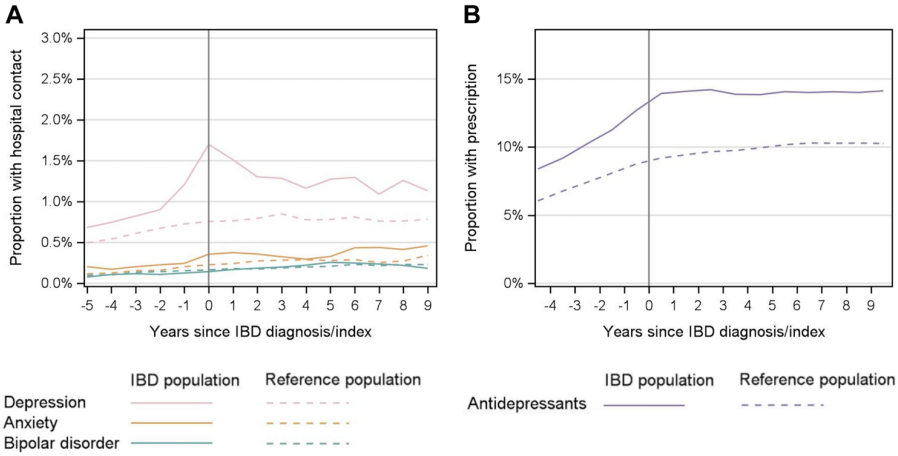

Figure 5. Yearly prevalence of (A) hospital contacts for depression, anxiety, bipolar disorder, and (B) dispensed prescriptions for antidepressants in the five years before and ten years after IBD diagnosis in patients with IBD and matched individuals from the reference population. IBD, inflammatory bowel disease. *Reproduced from Paper III* (99) *with permission from Elsevier*.

The odds of anxiety and depression were increased in patients with IBD compared with the reference population in the five years before IBD diagnosis, with an OR of 1.4 (95% CI 1.2-1.7) for anxiety and 1.4 (95% CI 1.3-1.6) for depression (see Paper III, Table 2). Similarly, patients with IBD had more dispensed prescriptions for antidepressants in the five years before diagnosis with an OR of 1.5 (95% CI 1.4-1.5). The odds were increased both 0-2 years and 3-5 years before IBD diagnosis. There was no association between IBD and bipolar disorder in the five years before IBD diagnosis. When analyzing CD and UC separately, the increased odds of anxiety were only statistically significant for patients with UC, whereas the odds for depression and antidepressant use were increased in both patients with CD and UC, but numerically higher for patients with CD.

In the analyses of risk of psychiatric diseases after IBD diagnosis, we excluded all patients with IBD and reference individuals with a hospital contact for one of the outcomes or with a dispensed prescription for antidepressants in the five years before IBD diagnosis/index date. During a mean follow-up time of 9-10 years depending on outcome, we found that patients with IBD had an increased risk of anxiety (HR 1.3, 95% CI 1.1-1.5), depression (HR 1.5, 95% CI 1.4-1.7), and for having a dispensed prescription for antidepressants (HR 1.4, 95% CI 1.3-1.4) compared with the background population. The risk was highest in the first year after diagnosis as illustrated in Figure 6.

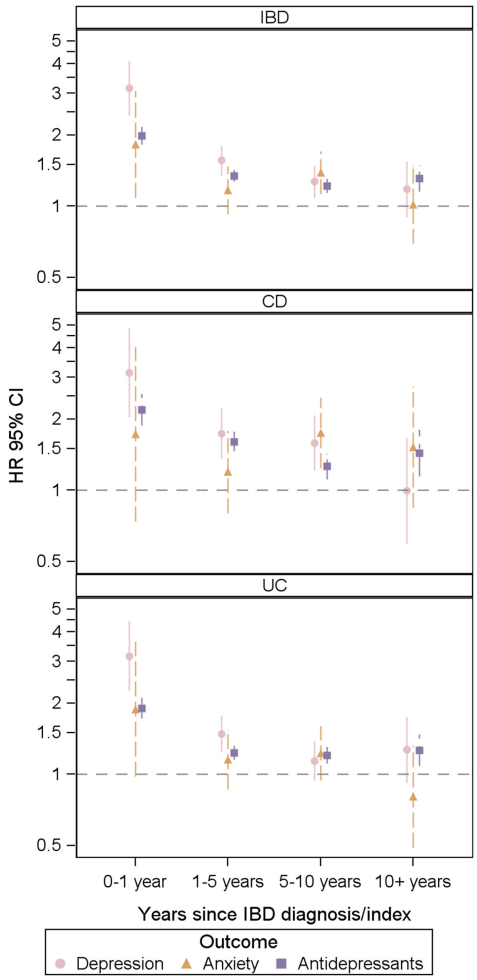

Figure 6. Risk of a hospital contact for depression and anxiety, and risk of having a dispensed prescription for antidepressants in patients with IBD, CD and UC compared with the reference population in the years after IBD diagnosis/index date. CD, Crohn's disease; CI, confidence interval; HR, Hazard Ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis. Symbols represent the estimate for each outcome and vertical lines represent the confidence interval. Bipolar disorder not represented because of too few cases. *Reproduced from Paper III* (99) *with permission from Elsevier*.

While both patients with CD and UC had increased risk of depression and use of antidepressants following IBD diagnosis, the risk was higher in patients with CD and

only patients with CD had an increased risk of anxiety (see Paper III, Table 3). Overall, patients with IBD were not generally at increased risk of developing bipolar disorder after IBD diagnosis, but the risk was increased in those with CD (HR 1.9, 95% CI 1.2-3.1).

Both before and after IBD diagnosis, the risk of depression and use of antidepressant use was increased more in those diagnosed after the age of 40 compared with patients with IBD diagnosed between the ages of 18-39. There were no differences in risk between females and males for any outcome (Paper III, Supplementary table 2 and Supplementary table 4).

DISCUSSION

The aim of this thesis was to create a comprehensive overview over and further our understanding of how IBD is connected to certain psychiatric diseases. The initial review article outlined the epidemiology, the possible connecting mechanisms, and the effects of treatment, thus creating an overview and highlighting gaps in knowledge. This gave rise to the question of temporal association of IBD, depression, and anxiety that led to us to perform a systematic review and meta-analysis, which clearly showed a bidirectional pattern of association between the diseases but also revealed a lack of unselected, population-based studies investigating the magnitude of association over time. Thus, for the last part of the thesis, we used the Danish national registers to investigate the burden posed over time of certain psychiatric diseases over the lifespan of patients with IBD, both years before and following up for years after IBD diagnosis.

Each study in this thesis used different methodologies that carry different strengths and limitations. In the following, I discuss the results, methods, strengths, and limitations for each study.

Study I

Summary of findings

With the increasing focus on and research into the gut-brain axis and how it connects gastrointestinal diseases with psychiatric and neurological diseases, understanding the role of depression and anxiety in IBD is important in the bigger picture of unraveling the causes behind and the disease course and prognosis of IBD. However, the knowledge about the connection between the diseases was scattered and disorganized, so the aim of our comprehensive review was to collect and synthesize the current state of knowledge on the epidemiology, the connecting mechanisms, and the impact of treatment. While outlining how IBD is connected with depression and anxiety as described in the results section, we identified several gaps of knowledge that should be considered in future research. In epidemiology, we suggest further explorations into the actual magnitude of risk as well as the temporal relationship and possible contributing factors; regarding mechanisms, we suggest studies in humans of the role of genetics and the gut microbiome, and how the different mechanisms interplay; and with regards to the treatment impact, we recommend interventional studies of effect of IBD medication on development of and improvement to depression and anxiety, and vice versa the effect of antidepressants and psychological interventions on IBD onset and disease course.

Strengths

We performed a rigorous literature search with the aim to include a balanced representation of all available research for each section of the review. While we did not follow systematic review methodology, we did present our search strategy in the published paper in an effort of transparency. We were also meticulous in presenting the results of included papers in a balanced manner with details not only about the findings but also about study design, numbers of included patients and reference or control groups, and limitations to studies' generalizability or applicability to the different sections.

The author group consisted of several researchers with different backgrounds, including clinical gastroenterology, epidemiology, and psychology. All authors assessed the included literature and critically evaluated the conclusions based on that literature. Additionally, the review went through several rounds of extensive external peer review by three acknowledged experts in the field, which prompted us to reconsider some choices and to make statements and conclusions clearer.

Limitations

Unlike systematic reviews, which are characterized by stringent criteria defined for instance in the PRISMA statement (41), there are no standardized guidelines for narrative reviews (100). Systematic reviews are designed to foster objectivity and prevent bias, but the strict criteria force a limited scope of the research question. Thus, there is a trade off when deciding on the scope, and in this case, the aim to create a comprehensive overview over this research field precluded the use of systematic review methods. When no predefined stringent criteria are employed, the search and inclusion process risks being biased towards selecting studies that confirm pre-existing knowledge or hypotheses. Such confirmation bias can be difficult to avoid, as it is not a deliberate process but rather something most individuals are unaware of (101). In this review, we attempted to limit this bias by including studies of the highest possible evidence strength. If available, we based the review sections on meta-analyses, systematic reviews, randomized controlled trials, and prospective cohort studies. Subsequently, large, well-designed observational studies such as case-control studies were preferred over smaller studies and case reports. In some sections, only smaller studies with designs lower in the evidence hierarchy (102) were available, in which case we made it clear in our summary that the evidence was weaker and made suggestions for future studies.

Study II

Summary of findings

This was the first systematic review to investigate the temporal risk of anxiety or depression in patients with IBD and risk of IBD in patients with depression or anxiety

including only unselected cohort studies. Our results underscored that anxiety and depression is consistently more frequent in patients with IBD across population-representative cohorts. The meta-analyses showed that patients with IBD had a 50% increased risk both of developing depression and of developing anxiety following their IBD diagnosis, and the risk of both outcomes was higher in patients with CD than in patients with UC. The systematic search found just two studies reporting risk of IBD in patients with depression and none in patients with anxiety. Thus, the study confirmed a bidirectional association between IBD and depression and elucidated a lack of unselected population-based studies, particularly a lack of studies on risk of IBD following depression or anxiety.

The pooled risk estimates for men and women did not differ based on the two studies that reported their results by sex, reflecting higher incidence rates for women both with and without IBD and thus resulting in comparable relative risks. In patients with pediatric-onset IBD, risk of depression was also increased, particularly in those with CD, while risk of anxiety was elevated for patients with CD but not patients with IBD overall. The analyses of pediatric populations were based on just three studies with some conflicting results, and additional studies from other population are needed to understand the risk of anxiety and depression in patients with pediatric-onset IBD.

The included studies were based on cohorts that represented all patients with IBD in a certain area or that covered more than 50,000 individuals, allowing us to reasonably assume that the cohorts represented the average patient with IBD, depression, or anxiety, respectively. Further, we only included studies with clearly defined outcomes and general population reference groups. We made the decision to impose such strict inclusion criteria in order to be able to generalize our findings to all patients with IBD. Many previous studies have included smaller samples of patients with IBD, often recruited from tertiary clinics (103–108) or through a self-selected process (61,109). These approaches have different limitations. Studies with IBD populations selected based on disease severity or treatment might find greater differences between the patients with IBD and the background population resulting in inflated risk estimates that are not generalizable to other IBD populations. Studies including patients with IBD through self-selection carry the same limitation of not being generalizable to other IBD populations, and they further entail a risk of selection bias, as patients with more severe IBD or with comorbid depression or anxiety could be more motivated to take part in a study resulting again in higher risk estimates. Conversely, patients with depression or anxiety could also be less likely to participate in research projects because of the added disease burden, which would lead to lower risk estimates. Previous meta-analyses (47,48) have included a wide range of studies precluding the results from being generalizable to the average patient with IBD.

Strengths

When performed in accordance with standardized guidelines and in adherence to predefined inclusion and exclusion criteria, a systematic review with meta-analysis is a strong evidence-based summary of the current knowledge about a specific and clearly defined question (110). However, the resulting meta-analysis is only as good as allowed by the quality of the studies going into it. By only including unselected cohort studies, this meta-analysis provides the best possible evidence for decision making in healthcare and for pointing to future research needs.

The literature search for this study went back more than 30 years and was comprehensive with broad search terms, yielding more than 6,000 search results. The search was designed this way to ensure identification of all eligible studies.

We used the Newcastle-Ottawa Scale (43) to assess the quality of all included studies. The scale is a validated (111), standardized tool for assessing non-randomized studies in meta-analyses, which awards included studies 0-9 points for cohort selection (up to four points), comparability (up to two points), and outcome assessment (up to three points). All but one study scored either eight or nine points, and the last study had a moderate score of five points, which confirmed a very good overall quality of included studies that ensured a high quality of our final analyses.

Limitations

This work caries some limitations that are specific to this study and some limitations that are more general to systematic reviews.

The studies included in this systematic review were all reporting on populations from high-income countries, and apart from one study from South Korea, all were Western populations from UK, Sweden, USA, and Canada. Access to health care in general and to mental health care in particular in these countries is probably higher than in many lower-income countries. While this does not necessarily mean that the co-occurrence pattern would look different, it is unknown if the findings of this systematic review are generalizable across the populations of the world.

We did not identify any cohorts following patients with anxiety for risk of IBD, and we found only two cohorts of patients with depression. Therefore, we cannot draw definite conclusions about the risk of IBD in these patients. We chose MEDLINE and Embase as our sources of information, as they are large databases of biomedical research. According to an exploratory study of database combinations for literature searches, MEDLINE and Embase are the databases that yield the largest number of results for searches (112). Despite the more than 6,000 results yielded from our literature search, we cannot be certain that there are no missed studies that fit the inclusion criteria. In hindsight, this systematic review could have been even stronger,

had we included more databases in our literature search. In particular, PsychInfo would have been a suitable option given our research question.

Detection bias is a type of bias that can be present in measurement of an outcome (113). The studies included in the systematic review were all observational and used the same definitions for outcomes regardless of exposure status. However, patients with chronic diseases such as IBD are likely more frequently in contact with a health care provider, which can lead them to have other diseases such as depression or anxiety detected and diagnosed, causing a bias toward higher risk estimates for patients with IBD compared with the background population. However, survey-based studies (114–116) have also found increased risk of depression and anxiety in patients with IBD compared with individuals without IBD, suggesting that our findings are not merely a result of bias.

The heterogeneity was high in the main analyses with values of I^2 above 80%. Values above 75% are considered high, while values over 50% are moderate, and values under 25% are low (117). This indicates that there was true variance between studies, but it is also a product of our cautious approach in choosing to use a random effects regression model and a conservative τ^2 estimator.

Reporting bias is an important limitation to consider in meta-analyses. It can occur when articles showing null-findings or less statistically or clinically significant results are less likely to be published, might take longer to be published, or might be less likely to be translated to English (118). I this study, we included only published studies in English for feasibility reasons, which led to a risk of biasing the meta-analysis results towards a larger pooled risk estimate. However, upon visual inspection of the funnel plot, no asymmetry was evident, though the interpretation was made difficult by a small number of studies. The formal Egger's test for bias did not indicate any significant asymmetry either, meaning there was no indication of reporting bias (119), though the test should be interpreted with caution in cases such as this with less than ten studies included in the analysis, as the power might have been too low to distinguish between bias and chance (120).

Study III

Summary of findings

We designed this register-based study to fill parts of the research gaps identified in our first two studies. We leveraged the national Danish registers to investigate the longitudinal burden of depression, anxiety, and bipolar disorder in all Danish patients with IBD diagnosed between 2003-2013, resulting in an IBD cohort of more than 22,000 individuals, who were matched to more than 110,000 individuals from the background population. This was to our knowledge the first study to investigate the

occurrence of depression, anxiety, and bipolar disorder starting five years before and continuing for ten years after IBD diagnosis in the same cohort of patients with IBD.

We found higher rates of both anxiety, depression and use of antidepressants both before and after IBD diagnosis, with a particularly high peak around the time of diagnosis, possibly reflecting an especially high stress from a recent diagnosis, or high impact of bowel symptoms or systemic inflammation. The frequency of anxiety and depression was increased in patients with IBD not only just before but also in the time period 3-5 years before IBD diagnosis. This is noteworthy, as it indicates either inflammatory processes already present long before IBD development – keeping in mind that the median diagnostic delay for IBD is less than a year (121) – or shared biological pathways between the diseases. This finding emphasizes the need to further our understanding of possible shared genetic and environmental factors. Following IBD-diagnosis, the risk of incident anxiety, depression, and use of antidepressants remained persistently increased for more than ten years, a pattern that matches that found in other populations (30,52), though the temporal pattern has not previously been investigated as thoroughly, as we did in this study.

The similar pattern for hospital contacts for depression and for use of antidepressants shows that patients with IBD are vulnerable to both severe but also more moderate depression, as a hospital contact for depression reflects a patient with depression so severe that they are treated in an outpatient clinic or under admission to a psychiatric ward, while a filled prescription for antidepressants reflects treatment for depression undertaken either at a hospital, by a psychiatrist in private practice, or by a general practitioner. By investigating both hospital contacts for depression and use dispensed prescriptions for antidepressants, the two outcome measures also serve to internally validate our results and increase our confidence in our findings.

In the main analysis, bipolar disorder was not associated with IBD neither before nor after IBD diagnosis. We did find a statistically significantly increased risk of bipolar disorder following a diagnosis of CD. This risk estimate was based on just 23 events in the CD population, and 64 events in the reference population, so this result should be interpreted with caution, but it does indicate an association that should be further explored.

Our subgroup analyses showed several interesting findings. Patients with CD had higher increased risk of depression and use of antidepressants both in the time before and after IBD diagnosis, which aligns with the findings from our systematic review and meta-analysis (Paper II). Our finding that anxiety risk was only elevated in patients with UC before diagnosis and only elevated in patients with CD in the years following diagnosis might reflect the relatively low event numbers, as most cases of anxiety in Denmark is treated in primary care or by privately practicing psychiatrists

or psychologists, which does not lead to registration in the National registers (19). Our stratified analyses revealed that patients diagnosed with IBD after the age of 40 had a particularly high risk of depression and of having a filled prescription for antidepressants compared with those diagnosed between the ages of 18-39. These statistically significant differences cannot be attributed to varying background frequencies, which were similar across the groups for depression and even higher in the older age groups for use of antidepressants. The relatively higher risk in patients with IBD onset after the age of 40 is remarkable given the tendency for more severe and extensive disease in those with early onset IBD (122). One possible explanation could be that IBD diagnosed later in life can be attributed to environmental factors to a greater extent than IBD diagnosed early in life, and that those environmental factors might also affect susceptibility to depression development. We found higher rates of all outcomes in females compared with males, both in those with IBD and in the references, but there was no difference in relative risk between the sexes. This is in line with our findings in Paper II and indicates that the risk conferred by IBD of developing depression or anxiety or using antidepressants was not sex dependent.

Choice of outcomes

We chose as outcomes the psychiatric diseases that most likely pose a significant burden in the life of patients with IBD. Depression and anxiety are clearly connected to IBD, as demonstrated in the two first studies, and while bipolar disorder has not received the same level of attention in the context of IBD, a few previous studies have suggested that patients with IBD might also be at increased risk of bipolar disorder (26,29,30). The outcomes in this study were defined as a hospital contact, which can be either an in- or out-patient visit. A hospital contact is only registered and available in the DNPR if the patient has been diagnosed or treated for the disease in question by a doctor in a hospital. It follows that the individuals in the study, who have an outcome of depression or anxiety, likely suffer from moderate or severe depression or anxiety, as most mild and many moderate cases of the diseases in Denmark are treated by either a general practitioner or by a psychiatrist in a private practice. We included dispensed prescriptions for antidepressants as an outcome in the study in order to also understand the burden of a broader range of depression and anxiety severities. This outcome captures all prescriptions that are filled at a Danish pharmacy in the study period, regardless of the prescriber. We deemed it a useful measure of a broader range of depression and anxiety, even though antidepressants are used for other indications, as data showed that the vast majority of prescriptions that contained data on indications were prescribed for depression (78%) or anxiety (11%), while 9% were prescribed vaguely for “diseases of the mind”, and just 1.2% prescribed for pain. Treatment of bipolar disorder is considered a specialist task and is usually not managed by general practitioners, why the data on bipolar disorder are likely more complete in the patient register.

Strengths

The strength of this study lies in the data sources and the rigorous methods that we employed to utilize that data. As described above under data sources, the Danish Civil Registration System contains complete and up-to-date information on all Danish residents, which coupled with the DNPR and the Danish National Prescription Registry through each person's unique CPR-number allowed us to form an unselected cohort of patients with IBD that is representative for Denmark and presumably generalizable to other populations. We were able to follow this cohort and the matched references longitudinally both back in time and with a long duration of follow-up time after IBD diagnosis. The prospective data collection in the registers removes the risk for recall or interviewer bias, which can cause significant issues in observational studies, if data are collected retrospectively.

As we aimed to investigate the longitudinal burden of psychiatric disease development, validity of diagnosis and precision of time of diagnosis was important. We achieved this by requiring cases to have at least two hospital contacts for IBD within a two-year period, thus reducing risk of including misclassified patients. This approach has been previously validated with a study showing a positive predictive value for a true IBD diagnosis of 95% (123). We further restricted the cohort to individuals with an address in Denmark for at least five years before IBD diagnosis and who did not have any registrations for IBD prior to fulfilling the requirement of two registrations within a two-year period, increasing the likelihood that we captured the true time of diagnosis.

Limitations

Some limitations inherent to this study should also be addressed. If either exposure or outcome diagnoses are misclassified in the register, it can lead to information bias. If the misclassification of one variable is unrelated to other study variables, it is non-differential, whereas differential misclassification is associated with other study variables (124). If some IBD diagnoses were misclassified, it is likely not associated to the study outcomes and can thus be considered non-differential, which can bias the risk estimates toward the null. However, since the IBD diagnoses were well-validated, this is likely not a concern in this study. Conversely, it is possible that patients with IBD could be more likely to receive a diagnosis of depression, anxiety, or bipolar disorder as a result of having more frequent contacts to health care providers compared with the reference individuals. This would be differential misclassification that could result in detection bias potentially resulting in inflated risk estimates, though this risk of bias is likely reduced by the long follow-up time in this study.

Confounding happens when a variable is both associated with the exposure and the outcome without being a mediator between the two (125). We limited the confusion of effects potentially caused by confounding by matching the patients with IBD on age, sex, calendar time, and municipality of residence. The matching of the

continuous variables – age at diagnosis and calendar time – was done in short time intervals to limit residual confounding from those factors. The analyses of the cohort that was restricted to individuals without any outcomes in the five years before IBD diagnosis were adjusted for the same variables used for matching to control for confounding. However, unmeasured confounding cannot be ruled out. We were not able to adjust for factors such as early life experiences, environmental factors such as diet or smoking, or socioeconomic factors beyond municipality of residence. These factors could all potentially confound the results of the study, but that would not change the fact that psychiatric diseases pose a great burden in the lives of patients with IBD.

CONCLUSION AND CLINICAL IMPLICATIONS

The three studies that form the basis of this thesis each add significantly to the understanding of how IBD is connected to and influenced by psychiatric diseases, particularly anxiety and depression.

The first study created an important, comprehensive overview over the current state of knowledge in the field. It showed that depression and anxiety are common comorbidities to IBD, that depression and anxiety might worsen the IBD disease course, and that the relationship between the diseases is likely bidirectional. It outlined the biological mechanisms that have so far been implicated in connecting the diseases, and it summarized the available evidence of impact of treatment on the disease occurrence and disease course.

The second study more systematically investigated the question of the temporal relationship between IBD, depression and anxiety and quantified the bidirectional risk. It showed that the risk of depression and anxiety is 50% increased in patients with IBD, and that patients with depression have an approximately two-fold increased risk of IBD, while underscoring a lack of high-quality population-based studies.

The third study illustrated and quantified the longitudinal burden of depression, anxiety, and bipolar disorder in Danish patients with IBD. It found that the risk of depression, anxiety, and use of antidepressants is persistently increased starting five years before and continuing at least ten years after IBD diagnosis. The risk was particularly high around the time of IBD diagnosis and in patients diagnosed with IBD after the age of 40.

The collected new knowledge gathered in this thesis underscores the importance of awareness of these psychiatric comorbidities to IBD, both among the patients and their relatives and among the health care providers in charge of treating the patients. Psychiatric comorbidity, especially anxiety and depression, should be a focus point in the evaluation and management of patients with IBD, particularly in the time around diagnosis but also consistently at follow up appointments. While it is widely accepted that living with a chronic disease such as IBD could lead to sadness and isolation in most individuals, the observation of a significant association with psychiatric diseases prior to IBD diagnosis and the biological mechanisms explored in this thesis contribute to explaining the complex interplay of IBD and psychiatric diseases beyond the strain of coping with a chronic disease. Due to this interplay of mechanisms and the evidence indicating that the psychiatric diseases can adversely affect the development and disease course of IBD, management of the psychiatric

comorbidities to IBD might not only serve to improve the patients' quality of life but also the course of their bowel disease.

In many countries and indeed in Denmark, health care is divided into medical specialties and subspecialties with limited capacity or tradition for cooperation. Patients suffering from more than one condition can experience fragmented care and are often left responsible for acquiring the care that they need for their psychiatric comorbidities. I believe that we could improve patient outcome with a more holistic approach to evaluation and management and with improved facilitation of support across specialties.

FUTURE PERSPECTIVES

While underscoring the clinical importance of awareness and treatment of comorbid psychiatric diseases in IBD, the present thesis also identified several gaps in knowledge that can help direct future research.

Though our understanding of the epidemiology of the co-occurrence has improved considerably, many aspects remain unclear. We lack data on the pre-diagnostic period of IBD, which could be examined in prospective studies with cohorts of patients with psychiatric diseases followed for development of IBD. This design could help elucidate the brain-to-gut side of the comorbidity. Both in the pre- and post-diagnostic period of IBD, there is a lack of data on which factors might contribute to the increased risk of psychiatric diseases, such as steroid use, socioeconomic factors, diet, IBD severity, and clinical markers of inflammation. Investigations into mediating or confounding effects of these factors could help identify new treatments and help in clinical guidance of patients with IBD. While some studies, including Paper III of this thesis, have found some associations to bipolar disorder, we need larger prospective population-based studies to discern any real connection with IBD. IBD is most commonly diagnosed early in adult life, but a significant proportion of patients are diagnosed in childhood. This population is understudied with regards to risk of psychiatric diseases, and nationwide register-based studies with a long duration of follow-up time would help identify the risk and burden of psychiatric diseases in this patient group.

Many of the studies into the connecting mechanisms have been performed in animals with attempts to correlate results to disease outcomes in humans. While we cannot perform the same type of studies in humans for obvious ethical reasons, some avenues for research are accessible. Both IBD and many psychiatric diseases are complex diseases with some degree of genetic components. Considering the observed bidirectional pattern of association between IBD and psychiatric diseases, genetic correlation studies could increase our understanding of the interplay of the diseases, and studies on genetic overlap coupled with family pedigree data could help elucidate how much of the heritability can be attributed to genetics and to shared environment, respectively. Another promising avenue for research is the ongoing attempt to characterize the gut microbiome and its impact on disease development. In the context of IBD and psychiatric diseases, interventional studies on modulation of the gut microbiome and the gut-brain axis might contribute importantly to future treatment options.

We have many treatment options for IBD and for psychiatric diseases separately, but we lack knowledge on the effects of treatment for IBD on psychiatric diseases and

vice versa. Management of patients with IBD would greatly benefit from randomized, interventional studies on both the effects of antidepressants as well as psychological interventions on IBD onset and disease course. Conversely, effects of common IBD therapies on development and severity of psychiatric diseases are unclear, and observational and interventional studies would help unravel these effects.

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APPENDICES

PAPER I

Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment

Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment

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Abstract | Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is a chronic, relapsing immune-mediated disease with a varying and sometimes severe disease course. IBD is often diagnosed in early adulthood and can lead to a substantial decline in quality of life. It has been suggested that patients with IBD are at increased risk of depression and anxiety, but it is still unclear to what extent these diseases co-occur and in what sequence they arise. This Review summarizes the literature on the degree of co-occurrence of IBD with depression and anxiety and the temporal relationship between these diseases. We also discuss the effect of psychological stress on the onset and course of IBD. In addition, we outline the possible mechanisms underlying the co-occurrence of IBD and depression and anxiety, which include changes in brain signalling and morphology, increases in peripheral and intracerebral pro-inflammatory cytokines, impairment of the nitric oxide pathway, changes in vagal nerve signalling, gut dysbiosis and genetics. Finally, we examine the possible effects of treatment of depression and anxiety on the risk and course of IBD, the influence of psychological interventions on IBD, and the effects of IBD treatment on psychiatric comorbidity.

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Inflammatory bowel disease (IBD) is a chronic and debilitating intestinal disease. Patients are usually diagnosed in early adulthood and have lifelong symptoms due to chronic inflammation, with variable severity and treatment response[1–4]. Patients with IBD might be at increased risk of depression and anxiety compared with the general population[5,6]. Development of depression or anxiety in this patient group can contribute to a loss in quality of life, complicate the clinical management of IBD[7,8] and even increase the frequency of active disease[9]. Although studies have suggested an increased risk of depression and anxiety in many chronic diseases due to their protracted disease course, the intricate communication between the gut and the brain, termed the 'gut–brain axis' or the 'gut–microbiota–brain axis', might render patients with IBD particularly susceptible to the development of psychiatric diseases. However, estimates of the magnitude of the co-occurrence of IBD and depression and anxiety vary greatly across studies, and the direction of the association remains uncertain, as do the causal mechanisms behind this association. The link between IBD and depression or anxiety might be unidirectional, bidirectional or caused by common external risk factors. In favour of a bidirectional relationship is the known bidirectional signalling between the gastrointestinal tract, including its microbiota, and the central nervous system (CNS), involving signalling through the autonomic nervous system, the immune system, the neuroendocrine system, the hypothalamic–pituitary–adrenal axis and metabolites[10]. Here, we review the current evidence for the relationship between IBD and depression and anxiety. We summarize the epidemiology of the co-occurrence of the diseases, including their temporal relationship and the influence of psychological stress. Furthermore, we discuss the possible mechanisms behind the co-occurrence of IBD and depression and anxiety, including the effects of antidepressants and psychological interventions on IBD and the effects of IBD medications on psychiatric comorbidity. On the basis of the evidence gathered in this Review, we suggest future directions for research into the co-occurrence of IBD and depression and anxiety.

Epidemiology

Estimates of the magnitude of the co-occurrence of IBD and psychiatric diseases vary greatly. Robustly defining the epidemiology could help inform patients and

Key points

- Depression and anxiety are common comorbidities in inflammatory bowel disease (IBD), but the prevalence varies across studies owing to heterogeneity in study populations and assessment tools for depression and anxiety.
- The relationship between IBD and depression and anxiety seems to be bidirectional.
- The mechanisms behind the relationship between IBD and depression and anxiety include increased pro-inflammatory cytokines, vagal nerve signalling, gut dysbiosis and changes in brain signalling and morphology.
- Antidepressants and behavioural therapies show not only effectiveness in the treatment of depression and anxiety but might also alleviate IBD symptoms or decrease the risk of relapse, although evidence is still limited.

clinicians and guide future research on the pathogenesis of the co-occurrence.

Prevalence of depression and anxiety in IBD

The prevalence of depression and anxiety in IBD has been examined in multiple studies of varying designs, sizes, populations and definitions of depression and anxiety. Some studies have used International Classification of Diseases 9 (ICD-9) or ICD-10 codes to assess depression and anxiety, while the majority have used various questionnaires to either assess diagnoses or quantify symptoms of the diseases, the most common one of which is the Hospital Anxiety and Depression Scale (HADS). Even between studies using HADS, cut-offs vary markedly, hence complicating comparisons across studies.

Three systematic reviews with meta-analyses on the prevalence of depression and anxiety in adult patients with IBD have been published, but were based on a heterogeneous sample of the available literature[11–13]. The pooled prevalence of symptoms of depression from the three reviews was, respectively, 21%[11], 21.6%[12] and 25.2%[13], while the pooled prevalence of symptoms of anxiety was 19.1%[11], 35.1%[12] and 32.1%[13], respectively. One of the three studies also summarized data from a subset of studies reporting diagnosis rather than symptoms of psychiatric disease and found a pooled prevalence of depression of 15.2% and a pooled prevalence of anxiety of 20.7%[12]. Only one systematic review has examined the prevalence of depression and anxiety in paediatric patients with IBD, reporting pooled 'symptom' prevalences of depression and anxiety of 15% and 16.4%, respectively, while the pooled prevalences of 'diagnoses' of depression and anxiety were 3.4% and 4.2%, respectively[14].

Despite pronounced heterogeneity in the studies underlying the previously mentioned systematic reviews and meta-analyses, most of which were smaller cross-sectional studies of selected IBD populations that used various tools to evaluate symptoms of depression and anxiety, the prevalence of depression and anxiety was clearly increased in patients with IBD and tended to be higher in adults than in children. The marked differences in reported pooled prevalence of symptoms versus diagnosis of depression and anxiety indicate that the majority of patients with IBD with psychiatric disorders remain undiagnosed, potentially owing to lack of appropriate psychological evaluations, limited awareness among gastroenterologists, social stigma and other factors.

Temporal relationship

Studies that investigate the temporal relationship between IBD and depression and anxiety are limited in number, but the picture emerging is that of a bidirectional relationship. A study comparing patients with new-onset depression to individuals without depression with a mean follow-up time of 6.7 years found an increased risk of both Crohn's disease (HR 2.11; 95% CI 1.65–2.70) and ulcerative colitis (HR 2.23; 95% CI 1.92–2.60) in the group with depression[15]. Likewise, analysis of data from 152,461 women in the American Nurses' Health Study showed an increased risk of developing Crohn's disease in women with depression (HR 2.36; 95% CI 1.40–3.98) compared with women without depression, although no increased risk was found for development of ulcerative colitis[16]. A large nested case–control study comparing patients with IBD to matched control individuals without IBD found similar prevalences of depression in the two groups 10 years before IBD diagnosis[17]. However, starting from 9 years before diagnosis, patients with ulcerative colitis had a higher prevalence of depression than control individuals and patients with Crohn's disease had a higher prevalence of depression starting 7 years before diagnosis than control individuals[17].

Other studies have investigated the occurrence of depression and anxiety following IBD. In a population-based study from Canada of patients with newly diagnosed IBD ($n = 6,119$) compared with matched control individuals ($n = 30,573$), increased incidences during 10 years of follow-up of both depression (incidence rate ratio (IRR) 1.58; 95% CI 1.41–1.76) and anxiety (IRR 1.39; 95% CI 1.26–1.53) subsequent to IBD diagnosis were observed[18]. Similarly, a South Korean population-based cohort study of patients with newly diagnosed IBD showed cumulative incidences of depression and anxiety of 8% (versus 4% in matched reference individuals) and 12% (versus 9% in matched reference individuals) after 6 years of follow-up[19]. Two studies from a nationwide Swedish cohort also showed increased risks of depression and anxiety following a diagnosis of IBD, both in patients with adult-onset IBD[20] and in patients with childhood-onset IBD[21] compared with matched reference individuals from the general Swedish population. In both groups, the highest risk of overall psychiatric morbidity was seen in the first year after IBD diagnosis and in patients with extra-intestinal manifestations. Another cohort study of patients with IBD and matched control individuals examined the occurrence of depression both before and after IBD diagnosis[22]. While the risks of both anxiety and depression were increased in the year of IBD diagnosis, this was not the case 5 years prior to IBD diagnosis or 5 years after IBD diagnosis. This observation contrasted with the findings of a previous study from the same research group that suggested an increased risk of depression (IRR 1.61; 95% CI 1.48–1.75) and anxiety (IRR 1.37; 95% CI 1.34–1.61) up to 10 years after IBD diagnosis[23].

Collectively, the studies suggest increased risks of depression and anxiety both before and after IBD diagnosis (FIG. 1). However, the observed direction of the association might also depend on the predisposition

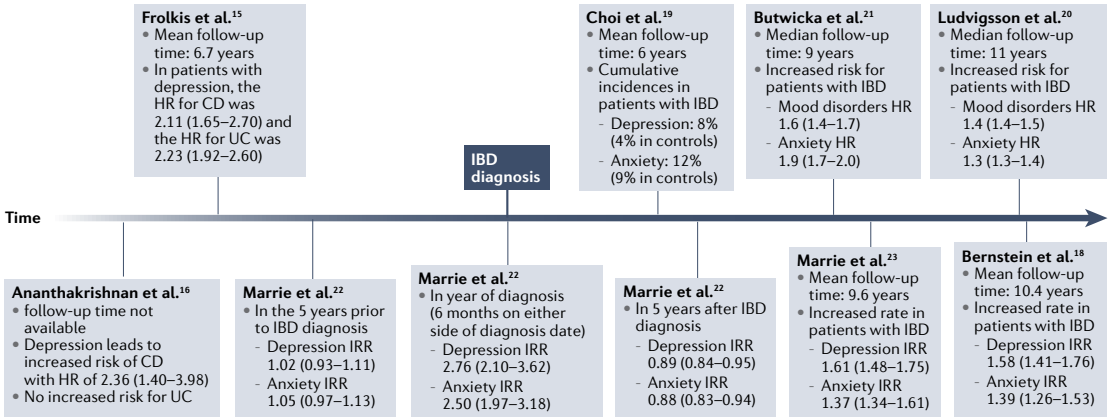

Fig. 1 | **Population-based studies illustrating the temporal relationship between inflammatory bowel disease and depression and anxiety.** The studies are ordered along the timeline in accordance with study period relative to inflammatory bowel disease (IBD) diagnosis; that is, how long before IBD diagnosis the studies started or how long after IBD diagnosis the studies followed up. 95% confidence intervals are provided in brackets. CD, Crohn's disease; HR, hazard ratio; IRR, incidence rate ratio; UC, ulcerative colitis.

of medical professionals to make a diagnosis of IBD or depression/anxiety, and the possibility of one diagnosis leading to either reduced or increased focus on the other. Definite conclusions cannot be drawn based on the small number of available studies.

With regard to IBD disease course, there also seems to be a bidirectional connection to mental health. This has been extensively reviewed in a systematic review and meta-analysis[24]. The researchers identified 12 longitudinal follow-up studies that examined the effect of symptoms of depression or anxiety on IBD disease course (12 studies) or the effect of IBD disease course on development of symptoms of depression or anxiety (3 studies). The meta-analysis showed that patients with IBD with symptoms of depression were at increased risk of flare, escalation of therapy, hospitalization, emergency department attendance and surgery, whereas patients with IBD with symptoms of anxiety were at increased risk of escalation of therapy, hospitalization and emergency department attendance. When focusing on the gut-to-brain direction, the meta-analysis showed that active IBD at baseline was associated with the development of symptoms of depression and anxiety. These results contrast with the finding of a previous systematic review and meta-analysis, which did not demonstrate an association between depressive state and IBD disease course in the pooled analysis[25]. This discrepancy is likely due to more studies being available for the later systematic review[24], enabling longer follow-up of a much higher number of patients. The results from the later meta-analysis[24] add to the results relating to IBD onset and support the understanding of a bidirectional relationship between IBD and depression and anxiety.

Stress and psychological factors in IBD

The potential bidirectional association between IBD and depression and anxiety leads to the question of whether psychological factors such as stress have an effect on IBD onset and disease course. Attempts have been made to answer this question using differing approaches, such as questionnaires on perceived stress or the experience of a traumatic or stressful life event, and the conclusions are inconsistent.

In a prospective study of IBD activity after stressful life events (death of a spouse or a close family member or friend, change of residence or job status, birth of a child, personal health, illness in a family member, marriage or divorce) including 124 patients with IBD, Duffy et al. found that patients who had undergone one or more of these events had a higher risk of active disease within the follow-up period of 6 months compared with patients with IBD who had not undergone these stressful life events (RR 2.56; 95% CI 1.34–4.86)[26]. The study found the highest risk of active disease among patients exposed to health-related stress. It is not clear, however, whether the health-related stress was related to their IBD or whether it was related to other health concerns. Another prospective study found that perceived stress increased the risk of exacerbation in patients with ulcerative colitis[27]. The hazard ratio was 2.8 (95% CI 1.1–7.2) comparing the tertile of patients with highest stress to the tertile with lowest stress. In a national population-based cohort study, a Swedish group measured the stress resilience of a large population and found an increased risk of ulcerative colitis (HR 1.19; 95% CI 1.03–1.37) and Crohn's disease (HR 1.39; 95% CI 1.13–1.71) in men with low stress resilience compared with men with high stress resilience[28]. In a smaller cross-sectional study of asymptomatic patients with ulcerative colitis ($n = 62$), patients who developed mucosal abnormalities visible by endoscopy reported higher levels of perceived stress in the past than patients without visible mucosal abnormalities, but the relationship was found to be greater with stress in the past 2 years than with stress in the past month[29]. In a population-based cohort study of 677 patients with IBD, disease activity was recorded

for up to 2 years after the Great East Japan Earthquake of 2011 (REF.[30]). The researchers found an increase in relapses in patients with ulcerative colitis but not in patients with Crohn's disease in the first 2 months after the earthquake compared with the relapse rates 1–2 years after the earthquake.

Conversely, some studies did not find a link between stress and IBD disease course. One large prospective cohort study based on the national patient register in Denmark found no association between the stressful life event of losing a child and first hospitalization or re-admission for IBD[31]. Similarly, a French population-based case–control study found no association between stressful life events and the risk of developing IBD[32].

A few studies have found weak associations between stress and IBD disease course. A population-based cross-sectional study ($n = 478$ patients with IBD) from Manitoba, Canada, found an association between perceived stress and symptomatic disease activity[33]. However, they did not find a connection between perceived stress and intestinal inflammation in patients with IBD as measured by faecal calprotectin levels. A prospective study of 60 patients with ulcerative colitis found an association between number of stressful events and time to relapse of ulcerative colitis (HR 1.26; 95% CI 1.04–1.53) but no association between ulcerative colitis relapse and perceived stress[34], and a small case-crossover study of 50 patients with IBD found an increased risk of relapse if the patient had felt stress the day before the relapse[35].

In summary, the role of stress in IBD onset and disease course remains unknown. The evidence points to some connection, but determining the importance and the direction of causality requires more studies. Previous studies either have used registers to examine the effects of single stressors rather than the actual stress felt by an individual, or have been based on questionnaires susceptible to recall bias. Future studies should be conducted prospectively with accurate measures of stress. Certainly, chronic or early-life stress increases vulnerability to psychiatric disorders, including depression and anxiety, and therefore could be an important factor in the relationship between IBD and psychiatric comorbidity[36]. Considering the high rates of depression and anxiety in patients with IBD, knowing the possible mechanisms behind this link would enable us to better understand the possible shared pathophysiology.

Mechanisms

Understanding the mechanisms that link IBD to depression and anxiety is important in the development of treatment and prevention strategies and to be able to better determine prognosis in patients with IBD. Much of the current mechanistic knowledge originates from animal models.

Evidence from animal studies

Induced colitis leads to changes in the brain. The CNS was previously thought of as completely immunologically privileged, protected by the blood–brain barrier from both infectious organisms and immune cells, but evidence now shows that the immune system does affect the brain[37,38]. There are several mechanisms by which this can happen, as discussed in detail in two previous reviews[39,40]. One mechanism is signalling through vagal nerve afferents. Evidence for this route includes the fact that sickness behaviour, including fatigue, social withdrawal, cognitive dysfunction and loss of motivation, was prevented by vagotomy prior to lipopolysaccharide (LPS)-induced peripheral inflammation in rodents[40]. Other mechanisms include circulating cytokines that signal via cerebral endothelial cells, causing cerebral production of prostaglandins and nitric oxide (NO); circulating cytokines and leukocytes that enter the brain through the circumventricular organs; and activation of Toll-like receptors on macrophages in the circumventricular organs, resulting in production of pro-inflammatory cytokines that diffuse into the brain[40]. In addition, a study published in 2021 observed closure of the brain choroid plexus in response to systemic inflammation, a potential defence strategy, which might explain behavioural changes in mice following induced colitis[41].

Induced colitis in animals leads to an increase in circulating pro-inflammatory cytokines, which affect several brain regions, most importantly the hippocampus[42–44]. The hippocampus is an area of the brain involved in memory and a part of the limbic system, which controls emotions. In a study of induced colitis in mice (via intrarectal injection of dinitrobenzene sulfonic acid), the mice showed behaviour consistent with depression and anxiety[42]. Examination of their brain revealed increased expression of genes related to inflammation and NO overproduction in the hippocampus. Another study found higher levels of tumour necrosis factor (TNF), as well as higher NO concentrations and inducible nitric oxide synthase (NOS) expression, an enzyme that catalyses the production of NO, in the hippocampus of mice with induced colitis[43]. Furthermore, intraperitoneal injection with a NOS inhibitor resulted in decreased concentrations of TNF and NO in the hippocampus and a reversal in behavioural despair, although no effect on colonic inflammation was observed. A possible effect of the increased levels of pro-inflammatory cytokines seen in the hippocampus is a reduction in hippocampal neurogenesis. In another study in mice with induced colitis, inflammation led to induction of the protein p21 in the hippocampus[44]. This protein arrests early neuronal progenitor proliferation. The researchers suggested that the decreased hippocampal neurogenesis could cause behavioural changes such as depression and cognitive impairment. In another study examining inflammation more broadly, the researchers induced inflammation in mice using intraperitoneal LPS injection[38]. This inflammation led to increased transcription of interferon-stimulated genes in the brain, suggesting interferon-mediated CNS inflammation. Behavioural changes in the mice were not examined, but other evidence links interferon therapy to the development of psychiatric symptoms. In an examination of 104 patients with chronic hepatitis C infection, the group treated with interferon therapy experienced a higher frequency of depression, anxiety and anger or hostility symptoms than the group that received no treatment[45].

Taken together, studies in rodents suggest that the behavioural changes seen after induced colitis could

result from an impaired central NO pathway, an increase in cerebral pro-inflammatory cytokine production, an increase in hippocampal neurodegeneration, vascular changes in the brain or a combination of these mechanisms.

Induced depression can lead to gut inflammation. In animals, depression can be induced by olfactory bulbectomy, intracerebrovascular injection of reserpine[46] and chronic unpredictable mild stress[47]. In several studies, Ghia and colleagues have used animal models of depression to study the effects on colitis. In 2008, they reported impaired vagal function in mice following induced depression, which led to gut inflammation[46]. Administration of the tricyclic antidepressant (TCA) desmethylimipramine protected against gut inflammation through restoration of parasympathetic function. In another study, Ghia et al. found that quiescent colitis in mice was reactivated after induction of depression[48]. This reactivation could likewise be prevented by the administration of a TCA. In 2011, Ghia et al. showed an increased release of pro-inflammatory cytokines from peritoneal macrophages in mice with induced depression[49]. They further showed that vagotomy reactivated inflammation in mice with chronic colitis. The role of the vagal nerve was also emphasized in a study in which colitis was induced in rats; the colitis improved after vagal nerve stimulation[50]. Accordingly, acetylcholine from the vagal nerve has been shown to cause a decrease in pro-inflammatory cytokines from intestinal macrophages[51].

The role of the gut microbiome. There are increasing data demonstrating a connection between the gut and the brain through the gut–brain axis. In a study of dextran sulfate sodium (DSS)-induced colitis in mice, both behaviour and the gut microbiota were examined[52]. The results showed impaired recognition memory and anxiety-like behaviour in mice with gut inflammation compared with controls. In addition, shifts in the gut microbiota were observed during active inflammation with substantial decreases in lactobacilli and segmented filamentous bacteria, which was reversed upon resolution of the gut inflammation. Some mice were treated with probiotics before induced colitis, which prevented the behavioural defects, improved the histological damage to the gut and prevented some of the shifts in the gut microbiota. Other studies have also shown links between colitis, the gut microbiota and behavioural changes. In one study, mice were subjected to 1 month of continuous stress followed by administration of DSS to induce colitis[53]. The colitis was severely enhanced in the stressed mice compared with mice that had not been stressed before DSS administration. The composition of the gut microbiota changed in the stressed mice, with an expansion of inflammation-promoting bacteria such as *Helicobacter* and *Streptococcus* species, which was further increased in stressed mice treated with DSS. Following faecal microbiota transplantation (FMT) from stressed mice to control mice, the control mice developed an enhanced response to the DSS, resulting in worse colitis. When the stressed mice were co-housed with control mice with a normal gut microbiota, the differences in colitis severity disappeared, further underscoring the probable role of the gut microbiota in the increased susceptibility to colitis in stressed mice. Two other studies also found behavioural changes consistent with depression following FMT from stressed mice to control mice[54,55]. Li et al. found that these behavioural changes were accompanied by an increase in neuroinflammation, with elevations in TNF and interferon-γ[54]. Marcondes Ávila et al. further showed that FMT from healthy donors to stressed mice led to an improvement in brain dysfunction, and vagotomy reduced the benefits from the healthy microbiota in the stressed mice[55], suggesting that at least part of the beneficial effects of FMT are mediated by the vagal nerve.

Although it is not possible to extrapolate directly from animal models to biological processes in humans as animal models of colitis do not completely match the morphological and immunological features of human IBD, the mechanisms described offer some possible links between IBD and depression or anxiety that merit investigation in humans. In the following section, we review current evidence from human studies.

Evidence from human studies

Changes in brain morphology. We describe above the microscopic brain changes seen in rodent studies of induced colitis. A few studies of humans with IBD have also shown changes in key areas of the brain relevant to psychiatric symptoms. In a study of patients with ulcerative colitis in remission, patients received different types of stimuli during an MRI scan[56]. Compared with healthy control individuals, patients with ulcerative colitis showed a reduction in blood oxygen-dependent signals in the amygdala and areas in the thalamus and cerebellum when presented with positive emotional stimuli, which could indicate an emotional dysfunction. In another study, MRI scans in patients with Crohn's disease revealed decreased grey matter volume in a portion of the frontal cortex and in the anterior midcingulate cortex compared with healthy control individuals[57]. These areas are involved in nociception, and emotional and cognitive processes[58]. The researchers further found that disease duration is negatively correlated with grey matter volume. Another study also found differences in structural brain measures between patients with IBD and healthy control individuals[59]. Patients with Crohn's disease in remission were compared with healthy matched control individuals, and MRI scans were carried out, as were measures of cognitive tasks and questionnaires about depression and personality. In this study, the researchers found cortical thickening in the left superior frontal region. This area is involved in affective processing and monitoring regarding punishment and reward, and in working memory processes and executive functions[59]. The decrease in grey matter volume is possibly due to exotoxicity and apoptosis as a result of increased cytokine release[57]. Cortical thickening can be the result of increased myelination and alterations in cell size[59]. Taken together, these findings indicate altered brain morphology in patients with IBD. However, all three studies included small sample sizes

(10–19 patients), which precludes definite conclusions. Larger studies are clearly warranted to elucidate the effects of IBD on brain structures and function.

The role of the gut microbiome. Dysbiosis is a common feature in patients with IBD. Patients often have decreased complexity in their gut microbiome, with lower diversity but higher density of colonization on the surface of the intestinal mucosa[60,61]. Similarly, studies on the gut microbiome in people with depression have found that depression is associated with changes in the gut microbiome, such as reduced richness and diversity, but the direction of effect is unclear[62–64]. Changes in the gut microbiome could affect the brain, resulting in psychiatric symptoms, or the gut microbiome could be affected by psychiatric diseases or their treatment. Although FMT is not used as a standard therapy for IBD, one small study examined the effect of FMT from healthy donors on psychiatric symptoms of depression, anxiety and obsessive–compulsive disorder in adults with moderate-to-severe IBD[65]. After 1 month, there were significant improvements in these parameters as well as improvements in gastrointestinal symptoms. Although this study only included ten patients and had no control group, it points to an interesting direction for research in the future.

Genetics. Both IBD and several psychiatric diseases, including depression and anxiety, have strong genetic and hereditary correlates[66–68]. Genome-wide association studies (GWAS) have revealed a highly polygenic and heterogeneous nature of psychiatric diseases such as mood disorders[66,67,69], and have further highlighted issues in powering studies to detect significant gene associations in mental disorders, such as major depressive disorder. These studies must include very large numbers of participants, because the effect of each genetic variant is very small[67]. In a 2021 study that combined GWAS from several databases and thus achieved information from 71,466 individuals with depression and 36,507 individuals with IBD, a genetic predisposition to depression was found to increase the risk of IBD, but no association was found between a genetic predisposition to IBD and the risk of depression[70]. GWAS have identified >200 loci associated with the development of IBD, contributing to 13.6% of Crohn's disease variance and 7.5% of ulcerative colitis variance, respectively[71]. We know that both IBD and psychiatric diseases are complex, and the genetic factors in these disorders are themselves complex. A study of 97 patients with IBD with psychiatric comorbidity, including depression and anxiety, and 146 patients with IBD without psychiatric comorbidity showed a higher burden of medium-sized copy number variations in the group with psychiatric comorbidity[72]. Moreover, the researchers found an enrichment of gene sets related to cytokine signalling pathways in patients with IBD with psychiatric comorbidity. More statistically well-powered investigations of genetic correlation could bring us closer to understanding to what degree the link between IBD and psychiatric disorders can be attributed to shared genetics.

As summarized in FIG. 2, the connection between IBD and psychiatric diseases probably arises from

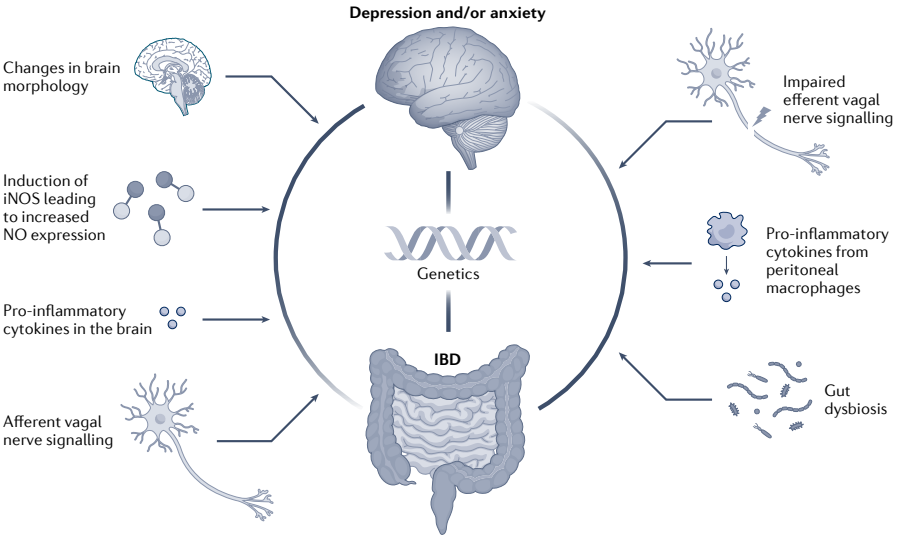

Fig. 2 | **Potential mechanisms linking inflammatory bowel disease, depression and anxiety.** Studies show changes in the brain in both humans and animals with gut inflammation, possibly mediated through vagal nerve signalling from the inflamed gut. In the brain, induction of inducible nitric oxide synthase (iNOS) followed by high levels of nitric oxide (NO), increases in pro-inflammatory cytokines and changes in brain morphology are among the factors that might lead to psychiatric diseases in patients with inflammatory bowel disease (IBD). In patients with depression, gut dysbiosis, impaired efferent signalling through the vagus nerve and increasing levels of pro-inflammatory cytokines from peritoneal macrophages are among the possible mechanisms contributing to onset or exacerbation of IBD.

several contributing factors, including increased levels of pro-inflammatory cytokines, vagal nerve signalling, changes in brain signalling and brain morphology, an impaired NO pathway and gut dysbiosis. These factors might interact and be influenced by underlying genetic predispositions.

Effect of treatment

It is generally accepted that immune dysregulation has a role in the pathogenesis of depression, and studies have found that several classes of antidepressants are capable of modulating the immune system and exerting anti-inflammatory effects[73].

Antidepressants in animal studies

Some studies have examined the effects of different antidepressants in a rat model of induced colitis. Four studies examined the effects of fluvoxamine (a selective serotonin reuptake inhibitor (SSRI))[74], venlafaxine (a serotonin and noradrenaline reuptake inhibitor (SNRI))[75], amitriptyline (a TCA)[76] and doxepin (a TCA)[77]. In all four studies, colitis was induced in rats using acetic acid, and the effect of the antidepressant was compared with the anti-inflammatory effect of dexamethasone. In three studies[74–76], reserpine was used to induce depression in a subset of animals, enabling comparison between depressed and non-depressed groups. Fluvoxamine, venlafaxine and amitriptyline all led to improvement in macroscopic and histopathological damage in the colon of both depressed and non-depressed rats and caused a decrease in colonic myeloperoxidase (MPO) (a marker of neutrophil infiltration) activity. The effects were comparable to that of dexamethasone[74–76]. In the study examining doxepin, depression was not induced, but the drug was administered either intraperitoneally or intracerebrovascularly[77]. The researchers found a decrease in colitis severity on both macroscopic and histopathological parameters, a decrease in MPO activity in colonic tissue and a decrease in pro-inflammatory cytokines, all of which were comparable to the effects of dexamethasone. Together, these studies suggest an anti-inflammatory effect of fluvoxamine, venlafaxine, amitriptyline and doxepin, and an improvement in colitis, but further confirmatory experiments are needed to validate the results.

Antidepressants in human IBD

Human studies on the effect of antidepressants on the course of IBD suggest some benefit, but the findings are mixed[78]. Literature reviews on the topic suggest that the effect might be attributed to the management of psychological and intestinal comorbidities, improved quality of sleep and reduced inflammation and pain[79]. In a cohort study that found an increased risk of developing IBD in people with depression compared with people without depression, the use of several antidepressants was found to be inversely associated with developing both Crohn's disease and ulcerative colitis[15]. In a small study, a review of electronic health records showed that patients with IBD and mood disorders had fewer relapses, and thus fewer courses of steroids, in the year following initiation of antidepressant treatment compared with the year before[80], and in a placebo-controlled trial of 35 patients with IBD, the SNRI duloxetine was found to decrease the severity of IBD symptoms in patients not diagnosed with depression or anxiety, although the size of the effect was very modest[81]. In a study comparing patients with IBD who had persistent symptoms (despite mild or inactive disease) to patients with irritable bowel syndrome, 59% of the patients with IBD experienced moderate improvement as a result of TCA treatment (amitriptyline, nortriptyline, desipramine or doxepin), which was comparable to the effect in patients with irritable bowel syndrome, of whom 46% experienced improvement[82]. A longitudinal study following patients with IBD for 2 years ($n = 331$) showed lower rates of steroid use, escalation of medical therapy, hospitalization and intestinal resection in the group of patients taking antidepressants at study entry compared with patients with IBD who did not take antidepressants; however, the differences were not statistically significant when controlling for potential confounders[83]. One randomized, double-blind study of 26 patients with IBD found no superiority of the SSRI fluoxetine compared with placebo on the course of IBD[84].

Most of the studies of antidepressants in patients with IBD, as well as in rodent models of induced colitis, showed improvement in IBD symptoms and disease course in patients exposed to antidepressants, not only in individuals with depression but also in individuals without depression. The studies were generally small, and larger studies could further inform future treatment strategies with antidepressants as a more readily used therapy in IBD.

Psychological interventions and IBD

Given the relationship between IBD and depression, anxiety and stress, and considering the previously described effects of antidepressants, psychological interventions might, in addition to having benefits for psychiatric diseases and quality of life, affect the disease course of IBD itself. For example, psychological interventions could affect the disease course by improving disease-interfering behaviours, such as treatment adherence, disease acceptance and pain catastrophizing[85], or they might work by addressing psychiatric comorbidities such as depression and anxiety, which in turn affect IBD disease course. This question has been addressed in two systematic reviews with meta-analyses[86,87]. A 2011 Cochrane review found, on the basis of five controlled trials with varying degrees of randomization, no significant difference between the proportions of patients with IBD in remission when comparing patients receiving psychotherapy with patients not receiving psychotherapy (OR 0.85, 95% CI 0.48–1.48)[86]. However, the researchers identified a high risk of bias in all the included studies. In a 2017 systematic review based on 14 randomized controlled trials, 6 trials assessed the effect of psychological therapy on prevention of IBD relapse and found no effect (RR 0.98, 95% CI 0.77–1.24), and eight trials assessed the effect of psychological therapy on improvement in clinical IBD activity indices and found no effect either (standardized mean difference −0.03, 95% CI −0.20 to 0.14)[87]. However, as the investigators noted in both the

2011 Cochrane review and in the 2017 systematic review, in most of the included studies the patients with IBD were not selected on the basis of symptoms of depression or anxiety. This fact could be one reason that an effect of interventions designed to ameliorate effects of poor emotional health was not detected. Furthermore, the meta-analyses pooled data from trials with varying psychological interventions, such as cognitive behavioural therapy, mindfulness, hypnotherapy and many more. That approach could have masked the effect of some therapies, but there are not yet enough studies to pool data on individual therapies. A prospective study published in 2021 did find that patients with IBD who were at risk of mental health disorders and who accepted psychological intervention had fewer visits to the emergency department for any reason in the 12 months following intervention compared with the preceding 12 months[88]. Larger, high-powered studies are needed to determine whether psychological interventions have ameliorating effects on IBD disease course, which patients are most likely to benefit from such interventions, and potential mechanisms of action.

IBD medication and depression and anxiety

A small number of studies have examined the effects of IBD medication, mainly TNF inhibitors, on depression and anxiety. Two studies found a decrease in symptoms of depression[89] and depression and anxiety[90] as well as an improvement in IBD disease activity after initiation of anti-TNF therapy in patients with IBD with active disease. Also, in one study the biologic IBD therapy vedolizumab improved symptoms of depression and anxiety to the same extent as TNF inhibitor therapy[91]; however, it was not clear whether the effects were linked to improvements in IBD activity. The benefits of IBD medication on psychiatric comorbidity seem to be linked to a reduction in systemic inflammation. In a randomized study of 60 patients with major depression, there was no overall difference in depression scores as measured by the Quick Inventory of Depressive Symptomatology–Self Report between patients treated with the anti-TNF therapy infliximab and those who received placebo[92]. However, in patients with baseline C-reactive protein (a marker of inflammation) >5 mg/l, there was a greater reduction in depression scores in the infliximab group. Although another study did not find a reduction in depressive symptoms in young patients with Crohn's disease treated with infliximab[93], the sparse data suggest that IBD medication might to some extent reduce symptoms of depression and anxiety via a reduction in systemic inflammation. However, a French cohort study including 100,054 patients with IBD found an increased risk of depression in patients with IBD who had been treated with infliximab compared with patients who had not received infliximab[94]. The study was not able to adjust for disease severity, which might be a risk factor for both depression and anxiety as well as for initiating infliximab treatment, but it underscores the fact that there is insufficient knowledge of the effect of IBD medication on psychiatric comorbidity and of whether IBD medication might have a direct effect on depression and anxiety or only works indirectly through the improvement in IBD.

Box 1 | **Knowledge gaps and research opportunities**

Epidemiology

- What is the temporal relationship between inflammatory bowel disease (IBD), depression and anxiety?
- What are the magnitudes of risks?
- Which factors contribute to risks?
- Do age, gender, disease subtypes, severity of IBD and/or severity of depression and anxiety have a role?
- Opportunities: large prospective unselected cohort studies with clear timing of diseases, patient characteristics and disease severity are needed.

Mechanisms

- What is the genetic correlation between IBD and psychiatric diseases?
- How large a role does the gut–brain axis have in the interplay between IBD, depression and anxiety?
- How do the different proposed mechanisms behind the co-occurrence interact?
- Opportunities: studies in humans of shared genetic factors, mechanistic interplay, brain imaging and effect of therapies directed at the gut microbiome are needed.

Treatment implications

- Are antidepressants and psychological interventions beneficial to IBD disease severity?
- How do IBD therapies affect the occurrence of depression and anxiety?
- Opportunities: interventional studies with well-defined treatment protocols and clearly defined quantifiable outcome measures are needed.

Clinical implications and future directions

This Review demonstrates that depression and anxiety are common comorbidities in IBD, but also highlights a lack of large, high-quality, prospective, population-based cohort studies that elucidate the actual magnitude and temporal relationship of these diseases. The mechanisms that link IBD to depression and anxiety are multifaceted, but might present opportunities for earlier, more effective interventions or prevention. The vagal nerve has a central role in mediating signals from the depressed brain to the gastrointestinal tract, and the occurrence of depression after induced colitis and occurrence of colitis after induced depression in animal models underscores the possibility of a bidirectional association between the diseases. Evidence pointing to an effect, albeit moderate, of antidepressants and behavioural therapies on the disease course of IBD also underscores the need for further research in this area. This Review emphasizes the need for awareness on how to prevent and manage depression and anxiety in patients with IBD.

There are still knowledge gaps and an evident potential for future research into the co-occurrence of depression and anxiety in patients with IBD (BOX 1). Going forwards, population-based cohort studies with clear assessment of psychiatric disorders are warranted to elucidate the true prevalence of symptoms and diagnoses of depression and anxiety among patients with IBD, the temporal relationship of the diseases, the time to depression and anxiety by year after IBD diagnosis and vice versa and the influence of patient demographics, IBD phenotype and IBD severity on the risk of psychiatric comorbidity. In addition, mechanisms of stress-induced inflammation should be examined in

prospective studies rather than cross-sectional studies, and functional studies in humans rather than in mice are needed in this area.

Clinically, it is essential for physicians not only to acknowledge that depression and anxiety are common consequences of IBD, but that these comorbidities must be considered as part of the context in which patients with IBD present. It is critical to clinical outcomes to no longer separate physical and mental health when caring for patients with IBD. As much of the literature that supports a bidirectional association is from observational studies, with a paucity of interventional data, there is a clear need for interventional trials of behavioural as well as pharmacological treatment of mood and psychiatric diseases in patients with IBD. Clearly defined outcome measures in such studies are essential. Most studies examining the association between stress and disease relapse in patients with established IBD have relied on symptom-based disease activity scores. The discordance between quantitative inflammation markers and symptoms is particularly striking in the presence of psychological comorbidity. Thus, it is important that future studies objectively examine the effect of parameters such as mood and resilience not just on symptoms but on quantitative markers of inflammation, such as faecal calprotectin or endoscopic evaluation. In addition, it is important to examine whether the benefit of interventions is sustained beyond the intervention period and whether interventions can be incorporated in the self-management of patients with IBD. Such studies should be based on well-characterized interventions with predefined protocols for treatment. Furthermore, attention to preclinical personality characteristics (resilience), attitudes (disease acceptance), beliefs (hope or optimism, self-confidence) and behaviours (self-regulation, social support) among patients with IBD could enable more scalable interventions that empower patients to self-manage their disease as it unfolds over their lifespan. All in all, there is a need for better guidelines on the conduct of clinical trials that aim to assess the efficacy and sustainability of psychological interventions in unselected patient populations.

In addition to intervention studies, future studies might also include population-based observational post-marketing studies that evaluate the real-world effect of antidepressants on the disease course of IBD as well as the effect of novel interventions, such as therapies directed at the gut microbiome, on the risk of psychiatric disease in patients with IBD.

In conclusion, given the frequent intersection of psychiatric comorbidity and IBD, recognition of their co-occurrence through systematic evaluation of patients with IBD, and appropriate management of such comorbidities, is important to ensure optimal patient outcomes. Further translational studies could outline the mechanism of the bidirectional association and suggest novel avenues for intervention.

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Author contributions

T.J., K.H.A., L.K. and A.N.A. made a substantial contribution to discussion of content and reviewed/edited the manuscript before submission. T.H.B. researched data for the article, made a substantial contribution to discussion of content, wrote the article and reviewed/edited the manuscript before submission.

Competing interests

A.N.A. served on scientific advisory boards for Gilead and Abbvie. L.K. is a consultant to Abbvie and Pfizer and has equity ownership in Trellus Health, Inc. The other authors declare no competing interests.

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Review criteria

The manuscript is based on a MEDLINE search using the terms: "inflammatory bowel disease" OR "Crohn's diseases" OR "ulcerative colitis" AND "depression" OR "anxiety" combined with "epidemiology", "incidence", "prevalence", "antidepressants", "microbiome", "microbiota", "gut-brain axis", "genetics". The initial search yielded 529 results, and 132 articles were included for full article screening. Additional articles were identified through search of reference lists.

PAPER II

The bidirectional risk of inflammatory bowel disease and anxiety or depression: A systematic review and meta-analysis

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Review article

The bidirectional risk of inflammatory bowel disease and anxiety or depression: A systematic review and meta-analysis

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is associated with anxiety and depression, but the magnitude and directionality of risk remains uncertain. This study quantifies the risk of anxiety or depression following a diagnosis of IBD, and the risk of IBD in individuals with anxiety or depression, using population representative data.

Method: We performed a systematic literature search using MEDLINE and Embase and included unselected cohort studies reporting risk of anxiety or depression in patients with IBD or risk of IBD in patients with anxiety or depression. We undertook Random Effect Model meta-analysis to calculate pooled Hazard Ratios (HR) for the risk of anxiety and depression in IBD and subgroup meta-analysis to calculate risk by IBD subtype and in pediatric-onset IBD.

Results: Nine studies were included; seven of which examined incidence of anxiety or depression among a total of >150,000 IBD patients. Meta-analysis showed an increased risk of both anxiety (HR: 1.48, 95% CI: 1.29–1.70) and depression (HR: 1.55, 95% CI: 1.35–1.78) following IBD diagnosis. Two studies investigating >400,000 individuals with depression showed a 2-fold increased risk of IBD.

Conclusions: The bidirectional association between IBD and anxiety and depression is clinically relevant and could indicate shared or mutually dependent disease mechanisms.

1. Introduction

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic and relapsing intestinal diseases, which are usually diagnosed in early adulthood. Patients suffer life-long symptoms due to chronic inflammation of the gastrointestinal tract, and the disease course and treatment response can be unpredictable [1]. Anxiety and depression frequently affect patients with IBD, one recent meta-analysis found a pooled prevalence of anxiety of 31.1% and pooled prevalence of depression symptoms of 25.2% [2]. The psychiatric comorbidities can have detrimental impact on quality of life [3]. While IBD in itself can be difficult to manage, studies suggest that patients with co-occurring anxiety and depression could be at greater risk of severe disease course [4,5]. While anxiety and depression might result from the strain of coping with chronic illness and are common comorbidities in many chronic diseases such as heart disease [6] and multiple sclerosis [7], bidirectional signaling between the gastrointestinal system and the central nervous system through the gut-brain axis could increase the risk of developing these psychiatric comorbidities in patients with IBD. Mechanisms at play include neurological signaling through the vagal nerve, humoral signaling through pro-inflammatory cytokines [8] and changes in gut microbiome [9]. Despite the reported co-occurrence of IBD and anxiety and depression, it is not well understood how the diseases impact one another, in which order they occur, or what the magnitude of risk is. This, in turn, limits our ability to understand the etiology of these diseases, accurately inform patients of their risk, and

Abbreviations: CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; REM, random effects model; UC, ulcerative colitis.

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hinders optimal clinical management. Several systematic reviews have investigated the prevalence of anxiety and depression and patients with IBD with very broad inclusion criteria resulting in inclusion of many studies with selective patient groups, e.g. representing only patients with severe IBD [10,11]. We aimed to conduct a systematic review with meta-analysis of all available unselected cohort studies examining the risk of anxiety or depression following a diagnosis of IBD and, conversely, the risk of IBD after a diagnosis of anxiety or depression. By only including unselected cohort studies, meaning cohorts that represent all patients with IBD in a given area, we aim to accurately depict the bidirectional risk of anxiety and depression that is generalizable to all patients with IBD.

2. Materials and methods

2.1. Literature search

We used PRISMA reporting guidelines [12] to conduct a systematic literature search for studies assessing the risk of anxiety or depression in IBD patients and, conversely, the risk of IBD in patients with anxiety or depression. Medline and Embase were searched for all relevant English language articles published from 1991 until July 2022. Both the following subject headings and search terms were used: (inflammatory bowel disease OR ulcerative colitis OR crohn$ disease OR IBD) AND (depression OR anxiety), all terms were searched both as exploded subject headings and as key words. We did a manual reference list search of all articles selected for final inclusion and any relevant reviews identified.

2.2. Inclusion and exclusion criteria

We defined the inclusion and exclusion criteria before performing the literature search. We included published, unselected cohort studies defined as being either population-based (i.e., including all patients with the disease under study in a geographical area over a given calendar period) or covering >50,000 individuals (hence assumed to be representative for the average patient with the disease). We chose to include only unselected cohorts to be able to calculate the pooled risk across all types of patients with IBD and not only selected groups, e.g. those ill enough to be included from a tertiary referral center. Studies had to report risk estimates of anxiety or depression in IBD patients or risk estimates of IBD in patients with anxiety or depression. Studies were excluded if the outcome was not clearly reported, if there was no non-IBD or non-anxiety or -depression reference group or if the cohort was selected by treatment or disease severity. When several studies were found to use the same cohort, only the most recent study was included to avoid duplication of data.

2.3. Data collection

Two authors (TB and RE) independently performed initial title and abstract screening and any discrepancies were discussed before consensus was reached. From all included studies, we collected data on outcomes as well as other data. The primary outcome was a risk estimate of anxiety or depression in patients with IBD or IBD in patients with anxiety or depression. In studies where risk estimates of anxiety or depression were not reported for IBD overall, we assumed that CD and UC patients together represented the IBD population and used the risk estimates presented for anxiety and depression in CD and UC, along with their respective standard errors to calculate a pooled IBD risk estimate. The secondary outcome was risk estimate of anxiety or depression by disease subtype (CD and UC) and risk estimate of CD or UC in patients with anxiety or depression. Other extracted data included publication year, start and end date of cohort follow-up, average age at inclusion, country, sex, tool for IBD diagnosis, screening tool for anxiety or depression diagnosis, follow-up time in either person-years or mean/median number of years, number of IBD, anxiety or depression patients and reference population, and number of patients with a given outcome (either IBD or anxiety or depression). Overall incidence rates of IBD and non-IBD populations, as reported by each study included, were also extracted and compared.

2.4. Risk of bias assessment

Included studies were assessed using the Newcastle-Ottawa Scale, which is a tool for assessing the quality of non-randomized studies in meta-analyses [13], which is a widely used and valid tool that has been previously evaluated [14]. Each study was awarded 0–9 points, where up to four points could be allocated for selection (exposed and non-exposed cohorts, ascertainment of exposure, and demonstration that outcome of interest was not present at start of study), two points could be allocated for comparability, and three points could be allocated for outcome (how it was assessed, sufficiency of follow-up time, and adequacy of follow-up), see Supplementary Box 1 for criteria behind the score. Scores were allocated by authors TB and reviewed by RE.

2.5. Statistical analysis

We extracted reported adjusted overall hazard ratios (HR) or analogous risk estimates and accompanying 95% CI to calculate standard errors and undertake random effects model (REM) meta-analyses using the inverse-variance method with Sidik-Jonkman estimator for τ^2, a measure of study variance. We chose REM due to a priori assumption of the presence of both intra- and inter- study heterogeneity. Subgroup meta-analyses were undertaken for risk of anxiety or depression by disease subtype separately and sex, where this data was available. Separate meta-analysis was undertaken to assess the risk of anxiety and depression in pediatric-onset IBD. Publication bias was evaluated using Egger's regression test [15] to assess asymmetry of funnel plot of included studies. Analyses were performed in R, using the "metagen" and "metabin" functions in "meta" [16] and "metaphor" [17] packages.

3. Results

3.1. Search results and study selection

Out of 6853 articles identified in the literature search, nine articles were included (Supplementary fig. 1). Of the nine included articles, seven investigated the risk of anxiety or depression following IBD diagnosis. Of those seven articles, five examined adult populations or populations of all ages [18–22] and two articles examined pediatric populations [23,24]. The seven studies were based on cohorts from Canada, USA, Sweden, UK, and South Korea; published between 2011 and 2022, and comprised a total 151,908 IBD patients and 4,869,239 reference individuals (Table 1). Six of the studies were eligible for meta-analysis, five of which included both CD and UC patients [18–20,23] and one included only CD patients [24]. Vigod et al. [21] was not included in the meta-analyses as depression and anxiety diagnoses were grouped as one outcome. Two articles investigated the risk of developing IBD following depression [25,26]. These two studies were based on cohorts from the USA and the UK, were published in 2013 and 2019, and comprised a total of 420,651 depression patients and 5,356,934 reference individuals (Table 2). As we only identified two studies investigating patients with depression and none with anxiety, we did not undertake meta-analysis of those studies.

Measurement of anxiety and depression was in most included studies done as diagnoses using ICD-codes [18–21,23,24], while two studies used READ codes [22,26] and one study used the 5-question Mental Health Index [25] (Table 1 and Table 2).

Table 1
Characteristics of included cohort studies on risk of depression and anxiety in inflammatory bowel disease.

Study	Country	Source population	Follow up time	IBD cohort size	Reference cohort size	Crude incidence rate / 1000 person years		Adjusted risk estimate depression (95% CI)		Adjusted risk estimate anxiety (95% CI)		Adjustment variables	Method for measuring anxiety or depression
						IBD	References	CD	UC	CD	UC		
Bernstein et al., 2019 [20]	Canada	Regional adult population-based cohort, 55% female	Mean follow up time 10.4 years	IBD: 5346 CD: 2389 UC: 2957	26,716	Depression: 18.6 Anxiety: 25.0	Depression: 10.8 Anxiety: 16.3	IRR 1.76 (1.51–2.05)	IRR 1.43 (1.24–1.64)	IRR 1.56 (1.35–1.79)	IRR 1.27 (1.11–1.44)	Age, sex, socioeconomic status, region (urban/rural), fiscal year	ICD-9 and ICD-10 diagnostic codes
Butwicka et al., 2019 [23]	Sweden	Swedish National Patient register, pediatric population, 44% female	Median follow up time 9 years	IBD: 6464 CD: 2536 UC: 3228	323,200	Depression: 6.1 Anxiety: 9.8	Depression: 4.0 Anxiety: 5.3	HR 1.6 (1.4–1.9)	HR 1.4 (1.4–1.7)	HR 2.2 (1.9–2.4)	HR 1.6 (1.4–1.8)	Year of birth, sex	ICD-8, ICD-9 and ICD-10 diagnostic codes
Choi et al., 2019 [19]	South Korea	The National Healthcare Insurance Service, 27% female	Mean follow up time 6 years	IBD: 15,569 CD: 6396 UC: 9173	46,707	Depression: CD: 14.99 UC: 19.63 Anxiety: CD:20.88, UC: 31.19	Depression: CD-references: 7.75 UC-references: 11.18 Anxiety: CD-references: 14.31, UC-references: 21.55	HR 2.06 (1.74–2.44)	HR 1.93 (1.7–2.18)	HR 1.58 (1.38–1.82)	HR 1.58 (1.43–1.74)	Age, sex, residence, income, comorbidities	ICD-10 diagnostic codes
Loftus et al., 2011 [24]	USA	Health service database cohort (Market Scan), 46% female	Not available	CD: 2144	10,720	Depression: 26.9 Anxiety: 18.1	Depression: 12.2 Anxiety: 5.7	1.74 (1.35–2.25)	Not assessed	2.28 (1.65–3.17)	Not assessed	Age, sex, Charlson comorbidity index score, region, type of health care plan	ICD-9 diagnostic codes
Ludvigsson et al., 2021 [18]	Sweden	Swedish National Patient Register, adult population, 48% female	Median follow up time 11 years	IBD: 69,865 CD: 21,245 UC: 43,557	3,472,913	Depression: 3.6 Anxiety: 4.0	Depression: 2.5 Anxiety: 3.0	HR 1.5 (1.4–1.6)	HR 1.4 (1.3–1.4)	HR 1.4 (1.3–1.5)	HR 1.2 (1.2–1.3)	Age, sex, year, and place of birth	ICD-8, ICD-9 and ICD-10 diagnostic codes
Umar et al., 2022 [22]	UK	National representative cohort from electronic medical database (IMRD), 48.3% female	Not available	IBD: 48,799 CD: 20,447 UC: 28,352	190,075	Depression: 10.75 Anxiety: 5.48	Depression: 7.9 Anxiety: 4.67	HR 1.36 (1.26–1.47)	HR 1.24 (1.16–1.33)	HR 1.38 (1.16–1.65)	HR 1.26 (1.07–1.47)	Age, sex, Townsend deprivation score, ethnicity, smoking status, Charlson comorbidity score	READ codes (coding system with information on symptoms, examinations, and diagnoses)
Vigod et al., 2019 [21]	Canada	Regional cohort (Manitoba), all pregnant and post-partum women	Follow up from conception to 1 year post-partum (~1 year and 9 months)	IBD: 3721	798,908	150.17 (number only available for overall mental illness)	132.76 (number only available for overall mental illness)	HR for any new onset mood or anxiety disorder 1.13 (1.05–1.22)				Maternal age, neighborhood income quintile, rural/urban residence, medical comorbidity, prenatal care type, maternal and neonatal health conditions	ICD-9 and ICD-10 diagnostic codes

Table 2
Characteristics of included studies on risk of inflammatory bowel disease in patients with depression.

Study	Country	Source population	Follow up time	Depression cohort size	Reference cohort size	Crude incidence		Adjusted risk estimate (95% CI)	Adjustment variables	Method for measuring anxiety or depression
						Depression	References			
Ananthakrishnan, 2013 [25]	USA	Cohort from Nurses' Health Study, 100% female	Not available	16,986	32,948	CD: 0.15 /1000 person years UC: 0.13 /1000 person years	CD: 0.07 /1000 person years UC: 0.10 /1000 person years	HR for CD: 1.62 (0.95–2.77) HR for UC: 1.07 (0.63–1.83)	Race, ethnicity, cigarette smoking, menopause status, BMI, use of oral contraceptives, postmenopausal hormones, aspirin and NSAID	5-question Mental Health Index (MHI-5)
Frolkis, 2019 [26]	UK	National representative cohort from electronic medical database (THIN), 65% female	Median follow up time 6.7 years	403,665	5,323,986	CD: 203 (0.05%) UC: 539 (1.13%) *	CD: 1589 (0.03%) UC: 4675 (0.09%) *	HR for CD: 2.11 (1.65–2.7) HR for UC: 2.23 (1.92–2.6)	Age, sex, socioeconomic status, comorbid conditions, smoking status, anxiety, antidepressant use	READ codes (coding system with information on symptoms, examinations, and diagnoses)

* crude incidence numbers per person years not available.

3.2. Incidence and risk of anxiety and depression following IBD

Seven studies addressing the risk of anxiety and depression in IBD patients (Table 1) reported the crude incidence of depression as 3.6–26.9/1000 person-years among patients with IBD compared with 2.5–12.2/1000 person-years in the reference populations. The crude incidence of anxiety was 4.0–25.0/1000 person-years among patients with IBD compared with 3.0–16.3/1000 person-years in the reference populations (Table 1).

Five studies reported data on the primary end point: risk of anxiety or depression in patients with IBD compared with the reference population [18–20,22,23], while Loftus et al. reported this only for CD [24]. Risk estimates were similar for depression in the four adult (HR 1.4, 95% CI 1.4–1.5 [18]; HR 1.98, 95% CI 1.78–2.19 [19]; incidence rate ratio (IRR) 1.58, 95% CI 1.41–1.76 [20]; HR 1.3, 95% CI 1.23–1.36 [22]) and one pediatric (HR 1.6, 95% CI 1.4–1.7) [23] population. There was a numerically lower risk of anxiety in adult populations (HR 1.3, 95% CI 1.3–1.4 [18]; 1.58, 95% CI 1.52–1.64 [19]; IRR 1.39, 95% CI 1.26–1.53 [20]; HR 1.31, 95% CI 1.16–1.47 [22]) than in the pediatric population (HR 1.9, 1.7–2.0) [23]. In one study, the sub-analysis of patients with pediatric-onset IBD (age 10–18 years) showed no increased risk of anxiety, IRR 0.96, 95% CI 0.72–1.15 [22].

Meta-analysis of the five studies reporting on the risk of anxiety or depression following an IBD diagnosis showed that patients with IBD were at increased risk of both anxiety (HR 1.48, 95% CI 1.29–1.70) and depression (HR 1.55, 95% CI 1.35–1.78) (Fig. 1).

Only two studies reported risk estimates by sex [19,20]. Subgroup meta-analysis showed no significant difference in risk of anxiety (female: HR 1.56, 95% CI 1.14–2.13, male: HR 1.56, 95% CI 1.04–2.32) or depression (female: HR 1.51, 95% CI 1.39–1.64, male: HR 1.73, 95% CI 1.59–1.88).

Six studies reported data on the secondary outcome: risk of anxiety or depression by IBD subtype. Five of these studies included both CD and UC patients [18–20,22,23], the last study included only CD patients

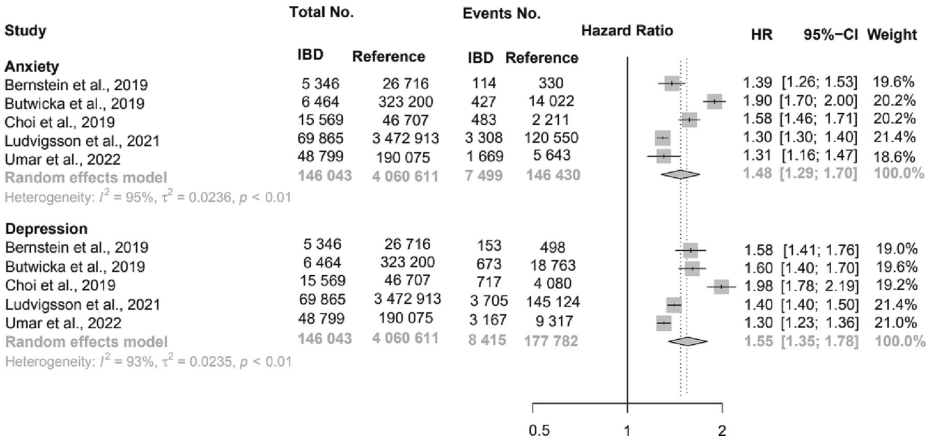

Fig. 1. Risk of anxiety and depression in patients with inflammatory bowel disease (IBD). Squares represent the hazard ratios (HR) from each study, and the horizontal lines represent 95% confidence intervals. The vertical lines represent the pooled HR of anxiety and depression, respectively, and the diamonds represent the confidence intervals of the pooled HRs of anxiety and depression, respectively.

[24]. The reported HRs for depression ranged from 1.36 (95% CI 1.26–1.47) to 2.06 (95% CI 1.74–2.44) for patients with CD and from 1.24 (95% CI 1.16–1.33) to 1.93 (95% CI 1.7–2.18) in patients with UC. The HRs for anxiety ranged from 1.38 (95% CI 1.16–1.65) to 2.28 (95% CI 1.65–3.17) for CD patients and from 1.2 (95% CI 1.2–1.3) to 1.6 (95% CI 1.4–1.8) for UC patients (Table 1).

Meta-analyses showed an increased risk of depression both among patients with CD (HR 1.63, 95% CI 1.45–1.83) and UC (HR 1.46, 95% CI 1.26–1.68) compared with non-IBD individuals (Fig. 2). Following exclusion of studies only including pediatric patients, the risk of depression remained increased both in patients with CD (HR 1.63, 95% CI 1.37–1.94) and UC (HR 1.47, 95% CI 1.23–1.76) (Supplementary fig. 2).

Likewise, meta-analyses showed an increased risk of anxiety both in patients with CD (HR 1.67, 95% CI 1.41–1.98) and UC (HR 1.37, 95% CI 1.21–1.55) compared with non-IBD individuals (Fig. 2). Removing the two pediatric cohorts resulted in a slightly lower, although still significantly increased estimate for the risk of anxiety among patients with CD (HR 1.47, 95% CI 1.36–1.58) but did not change the estimate for patients with UC (HR 1.32, 95% CI 1.17–1.49). Meta-analysis of two studies on pediatric-onset CD patients showed a particularly elevated risk of anxiety (HR 2.21, 95% CI 1.98–2.47), but meta-analysis of two studies with estimates for anxiety in pediatric IBD overall did not show an elevated risk of anxiety (HR 1.47, 95% CI 0.66–3.27) (Supplementary fig. 3).

The seventh study by Vigod et al., based on a cohort of perinatal women [21], did not report separate risk estimates for depression and anxiety, so was therefore not eligible for meta-analysis. This study did however show that perinatal women with a pre-pregnancy IBD diagnosis were at increased risk for mood and anxiety disorders (HR 1.13, 95% CI

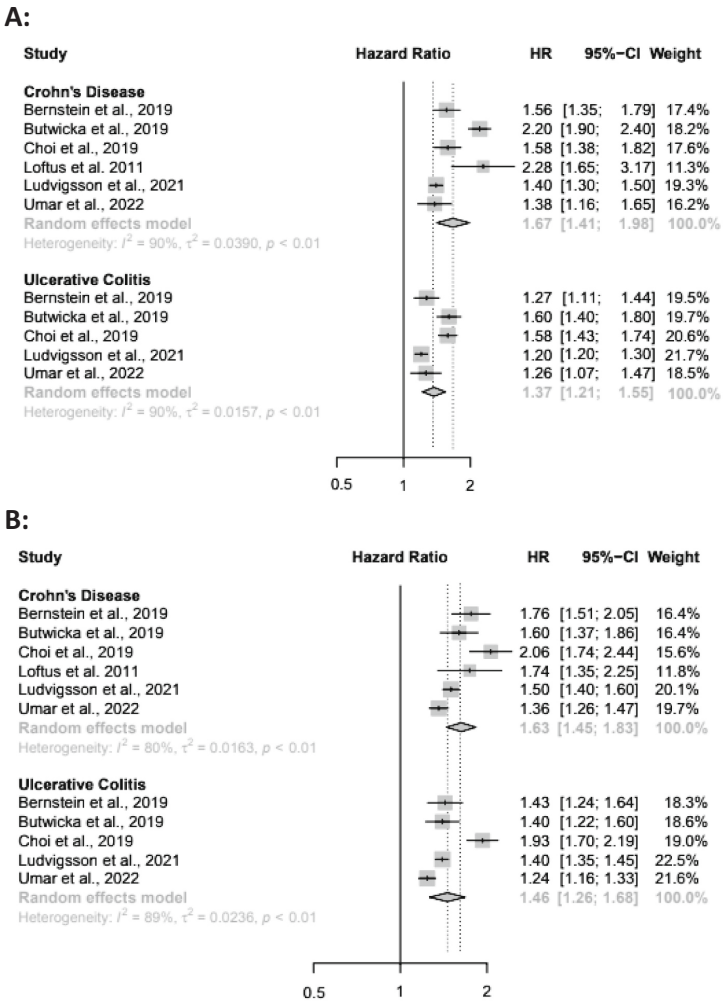

Fig. 2. Risk of anxiety (A) and depression (B) among patients with Crohn's disease and ulcerative colitis. Squares represent the hazard ratios (HR) from each study, and the horizontal lines represent 95% confidence intervals. The vertical lines represent the pooled HR of anxiety (A) and depression (B) in Crohn's disease and ulcerative colitis, respectively, and the diamonds represent the confidence intervals of the pooled HRs of anxiety and depression, respectively.

1.05–1.22).

3.3. Risk of IBD following depression or anxiety

Only two studies on IBD following anxiety or depression [25,26] fulfilled the inclusion criteria (Table 2). Both studies examined depression, not anxiety, as exposure. In a study of 152,371 female nurses [25] with recent depressive symptoms, risk of CD was significantly increased (HR 2.36, 95% CI 1.40–3.99), whereas risk of UC was not (HR 1.14, 95% CI 0.68–1.92) compared with female nurses without depressive symptoms. In a second study of 403,665 individuals with a physician-diagnosed clinical depression and 5,323,986 individuals without depression [26], risk of both CD (HR 2.11, 95% CI 1.65–2.70) and UC (HR 2.23, 95% CI 1.92–2.6) was increased following depression. A meta-analysis was not performed.

3.4. Study quality assessment and risk of bias assessment

Quality assessment using the Newcastle-Ottawa scale showed a high quality of included studies with all but one scoring 8 or 9 (Supplemental table 1). One study had a score of 5 [25] due to inclusion of only nurses in the cohort, self-reporting of exposure and outcome, and unclear follow-up time. Two studies received 8 points due to short or unclear follow up time for the outcome (less than two years or not stated) [21,24].

The systematic review was performed in accordance with PRISMA guidelines, see the PRISMA checklist in Supplementary table 2.

Studies appeared symmetrically distributed in the funnel plot of included studies on visual inspection (Supplementary fig. 4). However, potential asymmetry was identified when assessed with Egger's regression test (intercept 2.14, $p = 0.55$;), indicating potential publication bias.

The heterogeneity ranged between 80% and 95% in the main analyses and 0% to 97% in the supplementary analyses indicating that study populations differed substantially (Figs. 1-2 and Supplementary Figs. 2–3).

4. Discussion

In this systematic review for bidirectional risk of anxiety and depression in IBD, we identified nine studies for inclusion. Seven population-based studies all reported an increased risk of anxiety and depression following IBD diagnosis. Only two population-based cohort studies investigated risk of IBD in patients with depression and none in patients with anxiety. The two studies showed an approximately 2-fold increased risk of IBD following depression.

Meta-analysis of six of these unselected cohort studies included 151,908 IBD patients and 4,869,239 reference individuals and revealed a 1.5-fold increased risk of anxiety and depression among patients with IBD. The increased risk was present in both pediatric and adult populations and both in patients with CD and UC, with no difference in risk between men and women.

Our findings support the existence of a bidirectional relationship between IBD and depression. While previous reviews have focused on the prevalence of depression and anxiety in patients with IBD [2,10], to our knowledge, this is the first systematic review and meta-analysis that focuses on the temporal occurrence of incident anxiety, depression, and IBD. In a 2016 review on anxiety and depression in IBD of both selected and unselected study populations [11], only two studies were included for assessment of the temporal relationship, and only one of these was population-based. The interplay between IBD and anxiety and depression has also been examined in the context of IBD disease course. Two recent systematic reviews found aggressive IBD [27] and active IBD [28] to be associated with increased risk of depression and anxiety. When looking at brain-to-gut effects, a 2017 systematic review did not see a significant association between depressive state and worsening in IBD disease course [29]. However, two more recent systematic reviews both found associations between anxiety and depression and several indicators of worsening outcomes in IBD patients such as flares, escalation of therapy, and hospitalization [28,30]. This is further supported by the two studies presented in this meta-analysis examining the risk of IBD in individuals with depression or depressive symptoms, which both point to an increased risk of IBD following depression. It is also in line with a recent large case-control study from the UK showing depression to be more prevalent among IBD patients five years prior to diagnosis compared with matched controls [31]. Whether the increased risk of IBD attributed to depression could be an indication of a delayed diagnosis of IBD or if depression could be an independent causative risk factor for IBD merits further investigation.

The risk of anxiety among patients with CD decreased when removing pediatric patients from the meta-analysis. This could be because anxiety often debuts in childhood or early adulthood [32], and so this may be a product of timing of diagnosis of the two conditions. However, we did not see the same pattern in UC patients, where the risk of anxiety was comparable in both adult and pediatric populations. This underscores the notion that IBD might interplay with anxiety and depression and that the diseases might mutually exacerbate each other, either by directly affecting each other or through shared disease processes.

The study by Umar et al. [22] found no increased risk of anxiety in pediatric patients with IBD overall, while the two studies with data on anxiety by IBD subtype did find and increased risk, particularly in pediatric patients with CD [23,24]· The estimate found by Umar et al. thus contrasts that of the other estimates from pediatric populations. Although data from Umar et al. use a population representative English cohort, derived from a country-wide primary healthcare database, the Townsend score of the populations included, indicate an underrepresentation of lower socioeconomic groups, which might contribute to the lack of association between pediatric-onset IBD and anxiety identified in this study. These conflicting results underscore the particular need for further research into these outcomes in pediatric populations.

It is well-known that both anxiety and depression are almost twice as common in females [33,34], but we found no differences in risk between males and females. This reflects that the incidence rates for anxiety and depression were higher in both women with and without IBD compared with their male counterparts, resulting in similar relative risks. Thus, the increased risk of anxiety and depression associated with IBD does not appear to be sex dependent.

Living with a chronic and debilitating disease can lead to the development of anxiety and depression, but in addition to this strain, several biological mechanisms pertaining to the gut-brain axis might contribute further. Via the bidirectional communication through the gut-brain axis diseases of the gastrointestinal tract and the brain can interact and possibly exacerbate each other. Among suggested mechanisms, which are summarized in a recent review [3] are increases in pro-inflammatory cytokines in the brain and in the periphery, changes in brain morphology, impaired vagal nerve signaling, changes to the gut microbiome, and shared genetics.

The primary strength of the present study is the comprehensive literature search covering >30 years of research. The review is designed to include only unselected cohort studies to ensure generalizability of results. The broad search for literature yielded >6000 results which indicates that search terms were sufficiently broad. In terms of study quality, all but one included study – and all studies included in the meta-analysis – received 8 or 9 out of 9 points possible on the Newcastle-Ottawa Scale, where a score <5 indicates high risk of bias [14]. Despite criticism regarding validity of this scale [35], the Newcastle-Ottawa Scale remains a useful tool for evaluating study quality. It is well-known, each index is adaptable based on the research topic, it is validated for longitudinal studies [14], and it can be easily interpreted by clinicians and researchers.

There are possible limitations to the present study. Patients with IBD

could be more likely to receive a diagnosis of anxiety or depression, as they are more often seen by a doctor, potentially leading to detection bias. However, studies using survey-based design for symptoms of anxiety and depression also find an increased occurrence of anxiety and depression in patients with IBD [36–38], which speaks against such bias. The included studies differed somewhat with regards to exposure and outcome definitions. As the definitions were the same for the at risk and reference group in each study, however, this likely did not result in any systematic error in estimation of relative risk. Since all included studies are from high income countries (USA, UK, South Korea, Sweden, Canada), results are primarily representative for such populations and cannot be directly extrapolated to populations from other countries. As the Egger's regression test did not significantly show a symmetrical distribution of included studies on the funnel plot, we cannot rule out publication bias. We identified only two eligible studies on risk of IBD in patients with depression and no studies on patients with anxiety, which prevents us from drawing definite conclusions about the risk of IBD in these patient groups. This was partly due to our strict inclusion criteria, and it highlight the lack of high-quality population-based studies. Lastly, we assumed separate censoring for anxiety and depression in all included studies, although it was only explicitly stated in three of six studies included [18,23,24]. However, in all studies, there is a potential challenge in separating anxiety and depression, as symptoms can overlap, and the two diseases often co-exist.

This systematic review and meta-analysis shows that patients with IBD are at increased risk of developing anxiety and depression compared with non-IBD individuals, and that individuals with depression may also be at increased risk of developing IBD following their depression. These findings point towards a mutual relationship between IBD and depression, which has several potential biological explanations involving the gut-brain-axis. Future research should focus on the etiology of this bidirectional relationship, the temporal relationship between anxiety, depression and IBD *within* the same population, and on the burden of psychiatric diseases throughout the lifespan of IBD patients.

Author contributions

Conceptualization: all authors; literature search and review: TB, RE; statistical analyses: RE; drafting of manuscript: TB, interpretation of data and revision of manuscript: all authors. All authors have approved the final manuscript for publication.

Conference presentation

This work was presented at United European Gastroenterology (UEG) Week in Vienna October 8th–11th 2022.

Declaration of Competing Interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2023.05.002.

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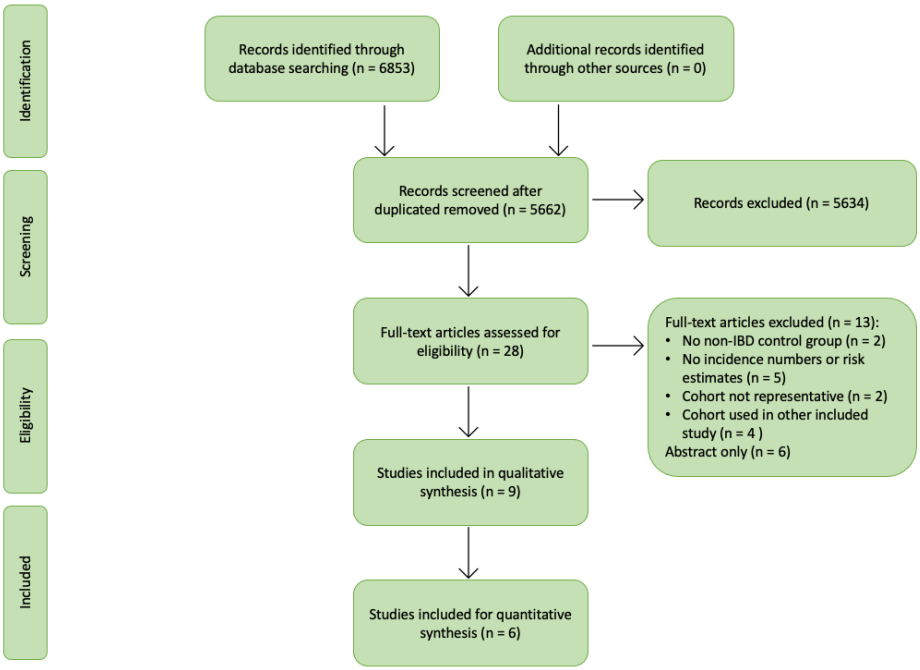
PAPER II supplementary appendices



Supplementary figure 1. PRISMA flow chart

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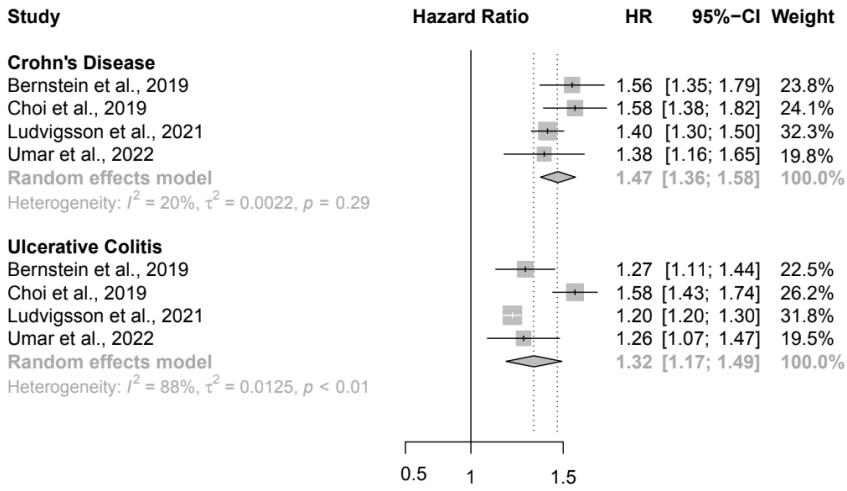

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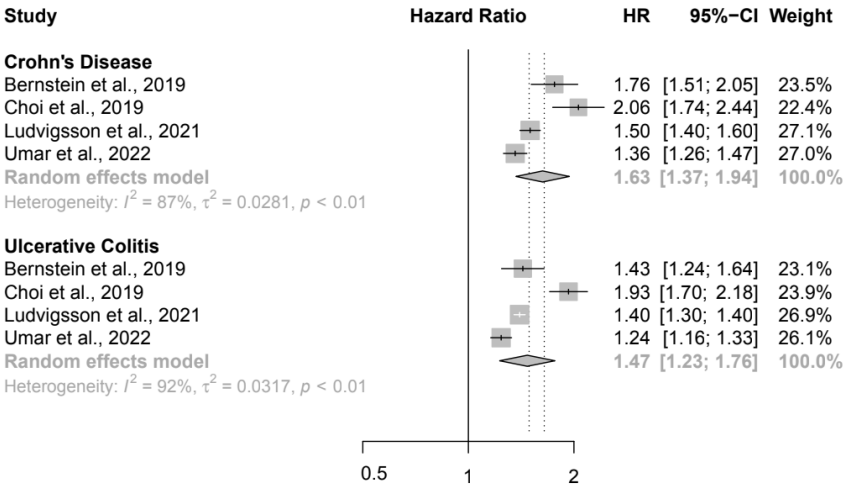
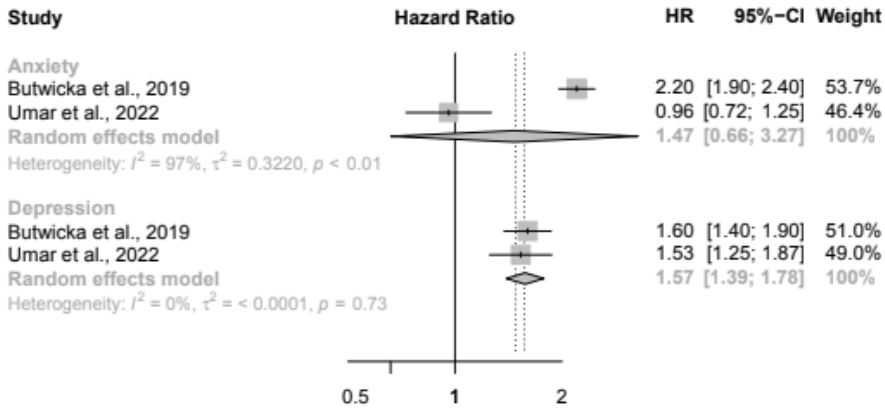


Supplementary figure 2. Risk of anxiety (A) and depression (B) among patients with Crohn's disease and ulcerative colitis upon exclusion of studies only including pediatric patients. Squares represent the hazard ratios (HR) from each study, and the horizontal lines represent 95% confidence intervals. The vertical lines represent the pooled HR of anxiety (A) and depression (B) in Crohn's disease and ulcerative colitis, respectively, and

the diamonds represent the confidence intervals of the pooled HRs of anxiety and depression, respectively.

A:



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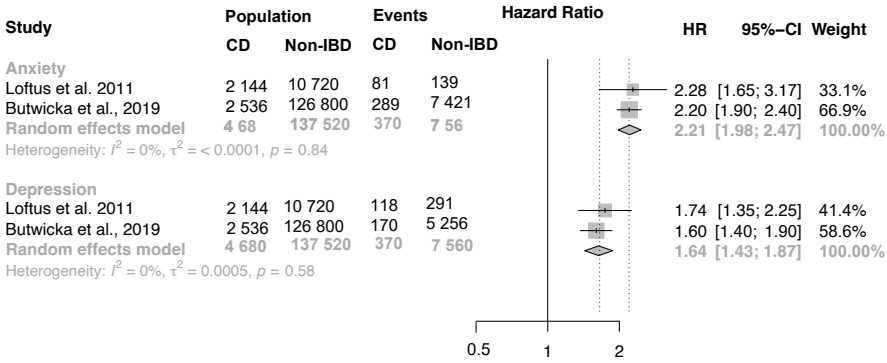
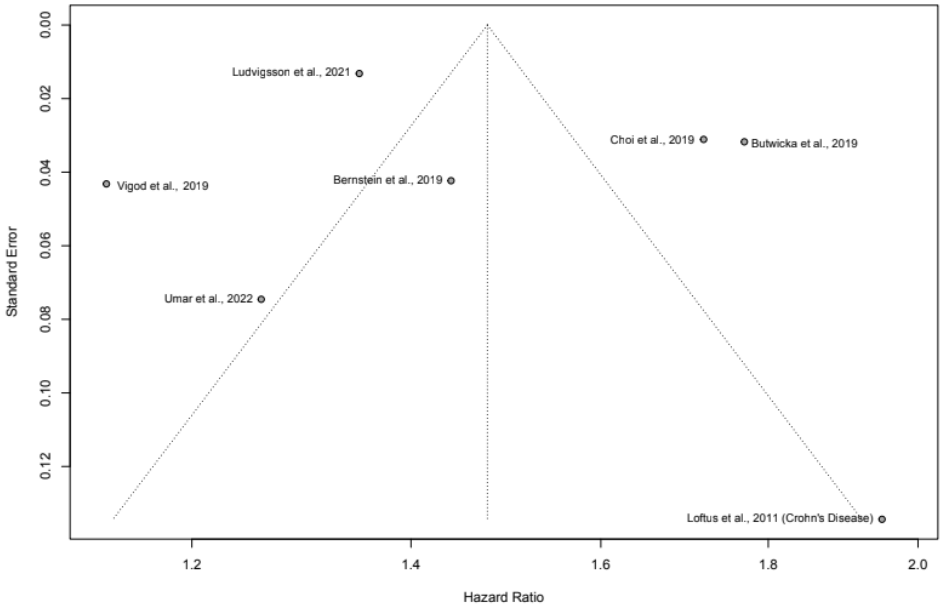


Supplementary figure 3. Risk of anxiety and depression in pediatric IBD populations (A) and in pediatric Crohn's disease (CD) populations (B). Squares represent the hazard ratios (HR) from each study, and the horizontal lines represent 95% confidence intervals. The vertical lines represent the pooled HR of anxiety and depression, respectively, and the diamonds represent the confidence intervals of the pooled HRs of anxiety and depression, respectively.



Supplementary figure 4. Funnel plot of included studies evaluating risk of anxiety or depression in patients with IBD**.**

Study	Assessment of quality of a cohort study – Newcastle Ottawa Scale Domain										
	Selection					Comparability	Outcome				
	1. Representativeness of the exposed cohort	**2. Selection of the non-exposed cohort**	**3. Ascertainment of exposure**	**4. Demonstration that outcome of interest was not present at start of study**	**Total (max 4)**	**Comparability of cohorts based on the design or analysis (max 2)**	**1. Assessment of outcome**	**2. Was follow-up long enough for outcomes to occur? (≥ 6 months)**	**3. Adequacy of follow-up of cohorts**	**Total (max 3)**	**Total NOS Score (max. 9; AHRQ standard)**
Ananthakrishnan et al. 2013 (18)	c) selected group of nurses in the Nurse's Health Study cohorts I and II	★ a) references drawn from same community as exposed cohort	c) written self-report	★ a) participants with prior history of IBD exluded from cohort	**2**	Study controls for ★ age and ★ comorbidities	c) Self-report followed up by medical records review.	★ a) Mean follow up time not noted, but median time to outcome	d) no statement	**1**	**5**

								was 6 yeas rs, so assume sufficient follow up time			
Bernstein et al. 2019 (13)	★ a) all Manitoba residence with incident IBD in study period	★ a) references drawn from same community as exposed cohort	★ a) ICD-9/ICD-10 codes in Manitoba Population Research Data Repository	★ a) outcome had to be preceded by 5 years with no records for that outcome.	**4**	Study controls for ★ sex and ★ age	★ b) linkage to Discharge Abstract Database, Medical Services, and Drug Program Information Network	★ a) yes, median follow up time 10.4 yeas rs	★ a) complete follow up	**3**	**9**
Butwicka et al. 2019 (16)	★ a) all persons in SNPR diagnosed with IBD before	★ a) references drawn from sam	★ a) ICD-8/ICD-9/ICD-10 codes in SNPR	★ a) all analyses were restricted to partici	**4**	Study controls for ★ sex and ★ age	★ b) linkage in SNPR	★ a) yes, mean follow up	★ a) complete follow up	**3**	**9**

	the age of 18	e community as exposed cohort		pants with no prior record of psychiatric disease				time 10 years			
Choi et al. 2019 (12)	★ a) all persons diagnosed with IBD in The National Healthcare Insurance Service (NHIS) database	★ a) references drawn from same community as exposed cohort	★ a) ICD-10 in NHIS database and V codes (special code registered in separate database)	★ a) all IBD patients with past history of anxiety or depression were excluded	**4**	Study controls for ★ sex and ★ age	★ b) linkage in NHIS database	★ a) yes, median follow up time 6 years	★ a) complete follow up	**3**	**9**
Frolkis et al. 2019 (19)	★ b) persons in The Health Improvement Network (THIN) with physician diagnosed depression	★ a) references drawn from same community as exposed cohort	★ a) at least 1 code for depressive disorder in THIN	★ a) participants with prior history of IBD excluded from cohort	**4**	Study controls for ★ sex and ★ age	★ b) linkage in THIN	★ a) yes, up to 26 years follow up, median follow up 6.7	★ a) complete follow up	**3**	**9**

								years			
Loftus et al. 2011 (17)	★ b) all CD patients under the age of 18 covered by the MarketScan database	★ a) references drawn from same community as exposed cohort	★ a) medical claim with a CD diagnosis based on ICD-9	★ a) all analyses were restricted to participants with no prior record of psychiatric disease	**4**	Study controls for ★ sex and ★ age	★ b) linkage in MarketScan database	b) no, mean follow up time not stated, minimum follow up time required in study only 6 months	★ a) complete follow up	**2**	**8**
Ludvigsson et al. 2021 (11)	★ a) all persons in The Swedish National Patient Register (SNPR) diagnosed with IBD at or after the age of 18	★ a) references drawn from same community as expo	★ a) ICD-8/ICD-9/ICD-10 codes in SNPR	★ a) all analyses were restricted to participants with no prior record of	**4**	Study controls for ★ sex and ★ age	★ b) linkage in SNPR	★ a) yes, median follow up time 12.7 years	★ a) complete follow up	**3**	**9**

		sed coh ort		psychi atric diseas e							
Umar et al. 2022 (15)	★ b) persons in The IQVIA medical research databas e (IMRD) with Read codes for sympto ms, examina tions or diagnosi s	★ a) refe renc es dra wn from sam e com mun ity as expo sed coh ort	★ a) at least 1 Read code for IBD in IMRD	★ a) all analys es were restric ted to partici pants with no prior record of psychi atric diseas e	**4**	Study contr ols for ★ sex and ★ age	★ b) linkag e in IMDR	★ a) Me an foll ow up tim e not not ed, but stu dy peri od 26 yea rs, so ass um e suffi cien t foll ow up tim e	★ a) com plet e foll ow up	**3**	**9**
Vigod et al. 2019 (14)	★ a) all Ontario women with a pre-pregnan cy diagnosi s of IBD and	★ a) refe renc es dra wn from sam e com	★ a) expos ure deter mined by valida ted algorit hms	★ a) partici pants with a histor y of a psychi atric disord er	**4**	Study contr ols for ★ age and ★ anten atal	★ b) linkag e to physic ian billing codes or codes from	b) no, less tha n 2 yea rs foll ow up	★ a) com plet e foll ow up	**2**	**8**

	with an in-hospital delivery of a singleton infant	mun ity as expo sed coh ort	based on admin istrati ve data	were exclud ed		factor s	emerg ency depart ment visits or hospit alizati ons				

Supplementary table 1. Quality assessment of included studies on anxiety, depression, and inflammatory bowel disease.

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ✸

b) somewhat representative of the average _____ in the community ✸

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ✸

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) ✸

b) structured interview ✸

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ✸

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) ✸

b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment ✸
b) record linkage ✸
c) self report
d) no description

2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) ✸
b) no

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for ✸
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

Supplementary Box 1. Questions for allocating points on the Newcastle-Ottawa scale.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 + supp. fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 + table 1+2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9 + fig 1-2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9 + fig 1-2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, supp. fig 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9, fig 2, supp fig 2-3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Supplementary table 2. PRISMA checklist.

PAPER III

Longitudinal trajectories of anxiety, depression, and bipolar disorder in inflammatory bowel disease: a population-based cohort study

Longitudinal trajectories of anxiety, depression, and bipolar disorder in inflammatory bowel disease: a population-based cohort study

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Summary

Background Inflammatory bowel disease (IBD) is associated with psychiatric diseases, but it is unclear to what degree patients with IBD are affected over their lifetime. We aimed to longitudinally investigate the risk of anxiety, depression, and bipolar disorder before and after IBD diagnosis to understand the full burden of these diseases in patients with IBD.

Methods In this population based cohort study, we identified 22,103 patients diagnosed with IBD between January 1, 2003 and December 31, 2013 in the Danish National registers and 110,515 matched reference individuals from the general population. We calculated yearly prevalence of hospital contacts for anxiety, depression, and bipolar disorder and dispensed prescriptions for antidepressants from five years before to ten years after IBD diagnosis. We used logistic regression to calculate prevalence odds ratios (OR) for each outcome prior to IBD diagnosis, and Cox regression to calculate hazard ratios (HR) of new outcomes after IBD diagnosis.

Findings During >150,000 person years follow-up, patients with IBD had higher risk of anxiety (OR 1.4; 95% confidence interval (CI) 1.2–1.7) and depression (OR 1.4; 95% CI 1.3–1.6) starting at least five years before and continuing until at least ten years after IBD diagnosis (HR 1.3; 95% CI 1.1–1.5 for anxiety and HR 1.5; 95% CI 1.4–1.7 for depression). The risk was particularly high around IBD diagnosis and in patients diagnosed with IBD after the age of 40 years. We found no association between IBD and bipolar disorder.

Interpretation This population-based study suggests that anxiety and depression are clinically significant comorbidities of IBD both before and after IBD diagnosis, which warrant thorough evaluation and management, particularly around the time of IBD diagnosis.

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Keywords: Inflammatory bowel disease; IBD; Gut-brain axis; Depression; Anxiety; Bipolar disorder

Introduction

Inflammatory bowel disease (IBD)—with its two subtypes Crohn's disease (CD) and ulcerative colitis (UC)—is a chronic, immune-mediated disease of the gastrointestinal tract. IBD can be diagnosed in all phases of life with a peak incidence in early adulthood.[1] The disease course is unpredictable, and patients face periods with flares, medical therapy, and often surgery. Many patients are impacted by their IBD for a large portion of their life, which often leads to absence from work or education[2,3] and reduced quality of life.[4]

Patients with IBD are more likely to experience anxiety, depression, and possibly bipolar disorder than the general population.[5–7] A recent meta-analysis found

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Translation: for the Danish translation of the abstract see Supplementary Materials section.

Research in context

Evidence before this study

We searched MEDLINE and Embase from January 1st 1991 to July 26th 2022 with the search terms (inflammatory bowel disease OR ulcerative colitis OR crohn's disease OR IBD) AND (depression OR anxiety OR bipolar disorder), and we did a manual reference list search of identified studies. Previous research has shown that inflammatory bowel disease (IBD) is associated with anxiety and depression and has indicated that the relationship between the diseases is bidirectional, but there is a lack of population-based studies of the association over time. Bipolar disorder has not been well examined in IBD, but some previous studies have suggested an association.

Added value of this study

This study quantifies and illustrates the burden of psychiatric diseases over time in more than 22,000 patients with IBD and confirms a bidirectional pattern in the co-occurrence of IBD, anxiety and depression, but not bipolar disorder, with increased occurrence of anxiety and depression from five years before until at least ten years after IBD diagnosis. We detected a particularly high risk of anxiety and depression in the first year after IBD diagnosis, and a higher risk in those diagnosed with IBD after the age of 40.

Implications of all the available evidence

Our findings emphasise the need for concurrent management of anxiety and depression in the care for patients with IBD, with a particular focus around the time of diagnosis. Future research should focus on mechanisms linking the diseases and on improving the holistic treatment of patients with IBD.

a pooled prevalence of anxiety symptoms of 31.3% and a pooled prevalence of depression symptoms of 25.2% in patients with IBD,[6] and a study found that patients with IBD had an increased risk of anxiety (HR 1.3, 95% CI 1.3–1.4) and of mood disorders (HR 1.4, 95% CI 1.4–1.5).[5] Another study found an increased incidence rate ratio (IRR) of bipolar disorder in patients with IBD (IRR 1.82, 95% CI 1.44–2.30).[8] The psychiatric comorbidities increases healthcare utilization and costs in patients with IBD,[9,10] and anxiety and depression might exacerbate the disease course of IBD,[11] while treatment of anxiety and depression has been linked to improvements in IBD symptoms along with enhanced quality of life.[12] Research indicates that the relationship between IBD, anxiety, and depression is bidirectional,[11] meaning that the risk of these diseases is higher both before and after IBD diagnosis. The hypothesized causes for this bidirectional relationship include shared diseases pathways, communication through the gut-brain axis, and shared genetic factors.[12]

While research into the connection between IBD and psychiatric diseases has increased, it remains unclear to which degree patients with IBD are impacted over their lifetime, and when the psychiatric comorbidities arise. Most previous studies have examined prevalence at a specific time point either before or after IBD diagnosis[8,13,14] without considering the development longitudinally year by year both before and after IBD diagnosis.

We aimed to examine the burden of anxiety, depression, and bipolar disorder longitudinally leading up to and following IBD diagnosis. We will quantify the prevalence of these diseases in the five years before IBD diagnosis and estimate the incidence of these outcomes in the ten years after IBD diagnosis. Using hospital, outpatient clinic and prescription data, we characterize the longitudinal trajectories of both severe and more moderate expressions of psychiatric comorbidity over time in patients with IBD in the Danish population.

Methods

Study population

The source population was identified through the Danish Civil Registration System as all individuals over the age of 18 years with an address in Denmark in the period 01.01.2003–12.31.2013 and was linked to other national registers using the unique personal identification number issued to all persons at birth or upon immigration. The Danish Civil Registration System is complete with regards to follow-up on all individuals and contains daily updated data on vital status, immigration and emigration.[15]

Case definition

IBD cases were identified through the Danish National Patient Registry (NPR), which contains information on all inpatient hospital contacts since 1977 as well as on all outpatient, emergency department and psychiatric hospital contacts since 1995. Details about the NPR data quality and research potential is described by Schmidt and colleagues.[16] We used ICD-8 (CD: 563.01, 563.02, 563.08, 563.09; UC: 563.19, 569.04) and ICD-10 codes (CD: K50; UC: K51). To limit inclusion of individuals with a misdiagnosis, cases had to have at least two hospital contacts (in- or outpatient) for IBD within a two-year period. This case definition has been shown to lead to a positive predictive value (PPV) of the IBD diagnosis of 95%.[17] The two contacts had to be the first registrations for IBD for that patient, meaning, patients with an initial IBD contact who only later fulfilled the two-contact criteria were not included in order to increase the precision of time of diagnosis. The study period was 1998–2018. Both of the two IBD contacts had to be

between January 1st 2003 and December 31st 2013 to allow for data on five years before and five to ten years after IBD diagnosis. The IBD patients had to have an address in a municipality in Denmark in the period between five years before first IBD contact and in the period between the two IBD contacts. IBD subtype was determined by ICD codes associated with the two contacts. If both CD and UC were registered, the IBD subtype was classified as CD. For each six-month interval of the inclusion period, all new IBD cases in the period were matched 1:5 on age, sex, municipality of residence, and calendar time (by year and semester) to individuals from the general population without IBD who were still living in Denmark at the end of the interval using frequency matching. We used the second of the two IBD contacts as time of matching. Each reference individual was assigned an index date, which was the first of the two IBD contacts of the corresponding IBD case.

Outcomes

Outcomes of psychiatric diseases were defined as at least one hospital contact for one of the psychiatric diseases obtained from the NPR and from the Danish Psychiatric Central Research Register, which contains information on psychiatric inpatient hospital contacts since 1970 and on psychiatric outpatient and emergency department contacts since 1995[18] (ICD-10 codes: depression: F32, F33; anxiety: F41; bipolar disorder: F31). The two registers were combined in 1995. These codes have not been systematically validated in scientific studies, but there is a data validation process at the Danish National Patient Register and at Centre for Psychiatric research, where electronic data from the registers and lists reported from individual departments are compared.[16,18] Data on prescriptions for antidepressants and indications for those prescriptions were obtained from the Danish National Prescription Registry, which contains information on all dispensed prescriptions since 1994,[19] using the ATC code N06A except for the subgroup N06AX12, and the outcome was defined as at least one dispensed prescription in a given year.

Statistical analysis

In order to have reliable data for the entire study period, we constricted the study to the years 1998–2018. We wanted to have ten years follow up time after IBD diagnosis for most individuals, and we chose to investigate the five years before IBD diagnosis so that we could reasonably assume that we included the time before the potential diagnostic delay, where the patients had developed IBD but had not yet been diagnosed.

We reported the annual prevalence of hospital contacts for anxiety depression, and bipolar disorder and dispensed prescriptions for antidepressants for the patients with IBD and the matched reference individuals. The annual prevalence of hospital contacts for a given was year was defined as the proportion of individuals with either a new contact starting that year or an ongoing contact continuing into that year. The annual prevalence of dispensed prescriptions for antidepressants was defined as the proportion with at least one dispensed prescription in that year.

We used logistic regression to analyse the prevalence odds ratio for anxiety, depression, bipolar disorder, and dispensed prescriptions for antidepressants five years before IBD diagnosis/index date in patients with IBD compared with reference individuals. We further analysed the prevalence odds ratio 0–2 years and 3–5 years before IBD diagnosis/index date, and we stratified analyses by IBD subtype, age at IBD diagnosis and sex.

We used Cox regression to analyse the risk of incident anxiety, depression, bipolar disorder, and dispensed prescriptions for antidepressants after IBD diagnosis/index date. This analysis was restricted to individuals with no contacts for anxiety, depression, or bipolar disorder or a dispensed prescription for antidepressants in the five years before IBD diagnosis/index date. The analysis was adjusted for age at diagnosis, sex, year of diagnosis, and municipality of residence since reference individuals were no longer matched after exclusion of individuals with a history of psychiatric disease or use of antidepressants. We further analysed the risk each year after IBD diagnosis, and we stratified analyses by IBD subtype, age at IBD diagnosis and sex.

All analyses were carried out using SAS 9.4 TS Level 1M7.

Ethical approval and informed consent

This study has approval from the Danish Data Protection Agency. In Denmark, ethical approval and informed consent is not required for register-based studies.

Role of the funding source

The funding sources had no role in study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the paper for publication. All authors had full access to the data in this study and accept responsibility for the decision to submit the manuscript for publication.

Results

From the source population of 5,341,271 individuals, we included 22,103 individuals with IBD (Supplementary Figure S1). The cohort consisted of 54.2% females and 45.8% males, 30.5% had CD, and 69.5% had UC. The mean age at IBD diagnosis was 45.9 years (Table 1). The 1:5 matched reference population contained 110,515 individuals.

	IBD (n = 22,103)	Crohn's disease (n = 6738)	Ulcerative colitis (n = 15,365)	References (n = 110,515)
Mean age at IBD diagnosis or index date	45.9 years	42.5 years	47.3 years	45.9 years
Age at diagnosis or index date				
18–39	9394 (42.5%)	3381 (50.2%)	6013 (39.1%)	46,970 (42.5%)
40–59	6830 (30.9%)	1916 (28.4%)	4914 (32.0%)	34,150 (30.9%)
60+	5879 (26.6%)	1441 (21.4%)	4438 (28.9%)	29,395 (26.6%)
Sex				
Female	11,985 (54.2%)	3873 (57.5%)	8112 (52.8%)	59,925 (54.2%)
Male	10,118 (45.8%)	2865 (42.5%)	7253 (47.2%)	50,590 (45.8%)
Year of IBD diagnosis or index date				
2003–2006	7733 (35.0%)	2254 (33.5%)	5479 (35.7%)	38,665 (35.0%)
2007–2010	8283 (37.5%)	2474 (36.7%)	5809 (37.8%)	41,415 (37.5%)
2011–2013	6087 (27.5%)	2010 (29.8%)	4077 (26.5%)	30,435 (27.5%)

IBD, Inflammatory bowel disease.

Table 1: **Baseline characteristics of all patients diagnosed with IBD at age 18 or later in Denmark between 2003 and 2013 and matched reference individuals.**

In the Danish National Prescription Registry, 56% of prescriptions for antidepressants included indications. Of these, 78% were given for depression, 11% for anxiety, and 9% for the non-specific indication "psychiatric disease". Less than 2% were given for pain, obsessive-compulsive disorder, and other rarer indications (Supplementary Table S5).

While 80%–90% of those with a hospital contact for depression received a prescription for antidepression, only 6%–11% of those with a prescription for antidepressants had a hospital contact for depression, indicating that antidepressants are prescribed for both severe and more moderate degrees of anxiety and depression, while only severe anxiety and depression is treated in the hospital sector (Supplementary Table S6).

Yearly prevalence of anxiety, depression, and bipolar disorder before, around, and after IBD diagnosis

Fig. 1 shows the yearly percentage of patients with IBD and reference individuals that had a hospital contact for anxiety, depression, or bipolar disorder or a dispensed prescription for antidepressants in the 5 years before and 10 years after IBD diagnosis/index date. Depression was consistently more frequent in the patients with IBD with a peak prevalence in the year of diagnosis of 1.7% compared with 0.8% in the reference population. Anxiety was also more frequent in patients with IBD from five years before and through ten years after IBD diagnosis. Patients with IBD had prescriptions for antidepressants more frequently than the reference individuals consistently from 5 years before until at least ten years after IBD diagnosis, with a yearly prevalence ranging between 8.4% and 14.3% vs. 6.1%–10.3% in the reference group. The prevalence of bipolar disorder was similar in the IBD and reference populations (Supplementary Table S1 for numbers behind the figure).

Odds of anxiety, depression, and bipolar disorder in the five years before IBD diagnosis

During the five years before IBD diagnosis/index date, 161 of the 22,103 IBD patients (0.7%) and 572 of the 110,515 reference individuals (0.5%) had a hospital contact for anxiety, resulting in an OR of 1.4 (95% CI 1.2–1.7) for anxiety in patients with IBD compared with the reference population (Table 2). The odds were increased both 0–2 years (OR 1.3; 95% CI 1.0–1.7) before and 3–5 years (OR 1.5; 1.2–1.8) before IBD diagnosis. Similarly, five years prior to diagnosis, 559 IBD patients (2.5%) and 1984 reference individuals (1.8%) had a hospital contact for depression, resulting in an increased OR of 1.4 (95% CI 1.3–1.6) for depression prior to IBD diagnosis. We found no association between IBD and bipolar disorder in the five years before IBD diagnosis. When we examined anxiety and depression in a broader perspective, i.e., also including cases treated outside hospitals, 4215 (19.1%) of the patients with IBD had at least one dispensed prescription for antidepressants in the 5 years before IBD diagnosis, compared with 15,309 (13.9%) of the reference population (OR 1.5; 95% CI 1.4–1.5).

On analysis of UC and CD separately, the increased odds of anxiety were only statistically significant for patients with UC (OR 1.6; 95% CI 1.3–1.9), whereas the odds for depression and antidepressant use were increased in both patients with CD (OR 1.6; 95% CI 1.4–1.9 for depression and OR 1.6; 95% CI 1.5–1.7 for antidepressants) and UC (OR 1.3; 95% CI 1.2–1.5 for depression and OR 1.4; 95% CI 1.3–1.5 for antidepressants). There were no differences based on sex, but patients with IBD diagnosed in the youngest age group (18–39 years) had lower odds of both a hospital contact for depression and for having a dispensed prescription for antidepressants compared with the older-onset groups (40–59 years and 60+ years) (Supplementary Table S2).

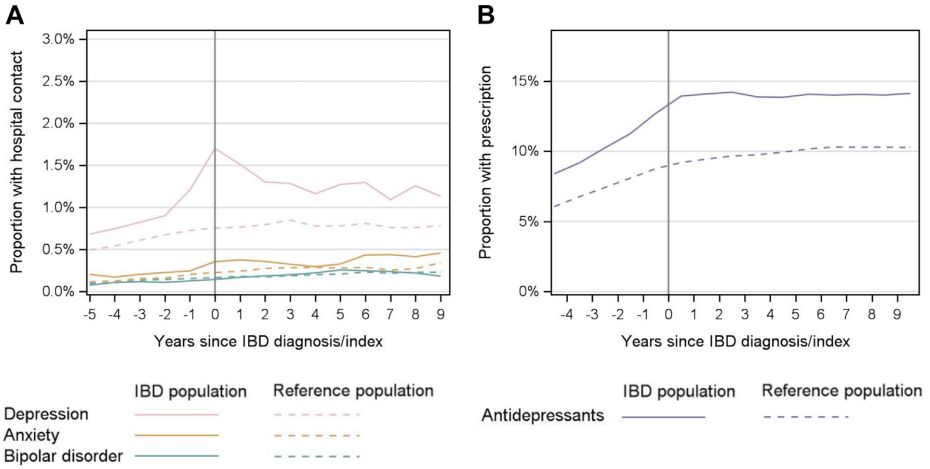

Fig. 1: **Yearly prevalence of (A) hospital contacts for depression, anxiety, bipolar disorder, and (B) dispensed prescriptions for antidepressants in the five years before and ten years after IBD diagnosis in patients with IBD and matched individuals from the reference population.** IBD, Inflammatory bowel disease.

Risk of anxiety, depression, and bipolar disorder in the ten years after IBD diagnosis

To study the risk of psychiatric disease after IBD diagnosis, we included 17,817 patients with IBD and 94,884 reference individuals with no contacts for anxiety, depression, bipolar disorder, or use of antidepressants in the five years before IBD diagnosis/index date (Supplementary Table S3). The mean follow-up time for patients with IBD and references was 9.8 years for the outcome of anxiety, 9.7 years for depression, 9.8 years for bipolar disorder, and 8.9 years for use of antidepressants.

	IBD			Crohn's disease			Ulcerative colitis		
	Patients	References	OR (95% CI)	Patients	References	OR (95% CI)	Patients	References	OR (95% CI)
Total	22,103	110,515		6738	33,690		15,365	76,825	
Anxiety									
0–5 years	161 (0.7%)	572 (0.5%)	1.4 (1.2–1.7)	44 (0.7%)	195 (0.6%)	1.1 (0.8–1.6)	117 (0.8%)	377 (0.5%)	1.6 (1.3–1.9)
0–2 years	85 (0.4%)	321 (0.3%)	1.3 (1.0–1.7)	26 (0.4%)	108 (0.3%)	1.2 (0.8–1.8)	59 (0.4%)	213 (0.3%)	1.4 (1.0–1.9)
3–5 years	98 (0.4%)	337 (0.3%)	1.5 (1.2–1.8)	28 (0.4%)	114 (0.3%)	1.2 (0.8–1.9)	70 (0.5%)	223 (0.3%)	1.6 (1.2–2.1)
Depression									
0–5 years	559 (2.5%)	1984 (1.8%)	1.4 (1.3–1.6)	191 (2.8%)	595 (1.8%)	1.6 (1.4–1.9)	368 (2.4%)	1388 (1.8%)	1.3 (1.2–1.5)
0–2 years	368 (1.7%)	1192 (1.1%)	1.6 (1.4–1.7)	128 (1.9%)	365 (1.1%)	1.8 (1.4–2.2)	240 (1.6%)	827 (1.1%)	1.5 (1.3–1.7)
3–5 years	327 (1.5%)	1219 (1.1%)	1.3 (1.2–1.5)	107 (1.6%)	354 (1.1%)	1.5 (1.2–1.9)	220 (1.4%)	865 (1.1%)	1.3 (1.1–1.5)
Bipolar disorder									
0–5 years	46 (0.2%)	268 (0.2%)	0.9 (0.6–1.2)	15 (0.2%)	69 (0.2%)	1.1 (0.6–1.9)	31 (0.2%)	199 (0.3%)	0.8 (0.5–1.1)
0–2 years	34 (0.2%)	203 (0.2%)	0.8 (0.6–1.2)	12 (0.2%)	52 (0.2%)	1.2 (0.6–2.2)	22 (0.1%)	151 (0.2%)	0.7 (0.5–1.1)
3–5 years	34 (0.2%)	199 (0.2%)	0.9 (0.6–1.2)	12 (0.2%)	52 (0.2%)	1.2 (0.6–2.2)	22 (0.1%)	147 (0.2%)	0.7 (0.5–1.2)
Use of antidepressants									
0–5 years	4215 (19.1%)	15,309 (13.9%)	1.5 (1.4–1.5)	1340 (19.9%)	4535 (13.5%)	1.6 (1.5–1.7)	2875 (18.7%)	10,774 (14.0%)	1.4 (1.3–1.5)
0–2 years	3308 (15.0%)	11,605 (10.5%)	1.5 (1.4–1.6)	1050 (15.6%)	3462 (10.3%)	1.6 (1.5–1.7)	2258 (14.7%)	8143 (10.6%)	1.5 (1.4–1.5)
3–5 years	3012 (13.6%)	11,167 (10.1%)	1.4 (1.3–1.5)	962 (14.3%)	3267 (9.7%)	1.6 (1.4–1.7)	2050 (13.3%)	7900 (10.3%)	1.3 (1.3–1.4)

IBD, Inflammatory bowel disease; OR, Odds ratio; CI, Confidence interval.

Table 2: **Frequency and odds of having a hospital contact for anxiety, depression, or bipolar disorders or having used antidepressants in the 0–5 years, 0–2 years and 3–5 years leading up to IBD diagnosis/index date.**

Cox-regression analyses showed that patients with IBD had an increased risk of hospital contacts for anxiety (HR 1.3 95% CI 1.1–1.5) and depression (HR 1.5; 95% CI 1.4–1.7), and an increased risk of having a dispensed prescription for antidepressants (HR 1.4; 95% CI 1.3–1.4) (Table 3) compared with reference individuals. The risk of depression (HR 3.2; 95% 2.4–4.1) and use of antidepressants (HR 2.0; 95% CI 1.8–2.2) was highest in the first year after IBD diagnosis, and the risk remained significantly increased for ten years after IBD diagnosis (Fig. 2). On subgroup-analysis, the risk of anxiety was statistically significantly increased for patients with CD (HR 1.5; 95% CI 1.2–1.9), but not for UC (HR 1.2; 95% CI 1.0–1.4). Patients with IBD did not overall have an increased risk of developing bipolar disorder after IBD diagnosis, but the risk was increased in patients with CD (HR 1.9; 1.2–3.1). Patients with IBD diagnosed between age 18 and 39 had a lower risk of depression (HR 1.2; 95% CI 1.0–1.4) or antidepressant use (HR 1.2; 95% CI 1.2–1.3) than those diagnosed after age 40. There were no differences in risk between females and males (Supplementary Table S4).

Discussion

In this nationwide cohort study including more than 22,000 patients with IBD, we characterised the psychiatric comorbidity longitudinally year by year from before to around and after IBD diagnosis to further the understanding of the burden presented by these diseases over the lifetime of patients with IBD. We found that patients with IBD consistently have a higher occurrence of anxiety and depression starting at least five years before IBD diagnosis and continuing for at least ten years following IBD diagnosis compared with individuals from the general population. The pattern was present both for severe anxiety and depression as measured by hospital contacts and for a broader range of cases as measured by dispensed prescriptions for antidepressants. The increased risk of psychiatric disease and treatment hereof both pre- and postdiagnosis was observed in both UC and CD patients and in women and men.

Unlike most previous population-based studies on this topic,[13,14,20–22] we examined the occurrence of psychiatric diseases in the same population over time both before and after IBD diagnosis. Our findings of an increased frequency of anxiety and depression as well as antidepressant use even 3–5 years before IBD diagnosis are in line with a 2019 study from Canada, where patients with IBD had increased incidence of depression five years before and of anxiety three years before IBD diagnosis.[23] It is unlikely that this is merely due to diagnostic delay of IBD, which is usually less than a year in Denmark.[24] It is possible that it could be due to subclinical inflammation present in the years before IBD development, or the diseases may share biological pathways that cause susceptibilities in individuals to both IBD, anxiety and depression. The increased levels of anxiety and depression and antidepressant use indicate that people are struggling even before getting an IBD diagnosis, and the stress could trigger onset of IBD, as has been previously suggested,[25] though it remains to be robustly established how much perceived stress affects symptoms of IBD and bowel inflammation measured objectively.[12,26]

We also observed increased risk of new-onset anxiety and depression at least ten years after IBD diagnosis both for severe and for more moderate expressions of anxiety and depression. The risk was particularly high in the first year after diagnosis, which is in line with findings from a Swedish population-based study.[5] The high diagnostic frequency of psychiatric comorbidity

	IBD (n = 17,817)				Crohn's disease (n = 5378)				Ulcerative colitis (n = 12,439)			
	Events	Person-years	IR/1000 PY	HR (95% CI)	Events	Person-years	IR/1000 PY	HR (95% CI)	Events	Person-years	IR/1000 PY	HR (95% CI)
Anxiety												
References	1062	931,400	1.14	1 (ref)	344	284,800	1.21	1 (ref)	718	646,600	1.11	1 (ref)
IBD	247	171,100	1.44	1.3 (1.1–1.5)	93	51,100	1.82	1.5 (1.2–1.9)	154	120,000	1.28	1.2 (1.0–1.4)
Depression												
References	2119	925,100	2.29	1 (ref)	672	282,800	2.38	1 (ref)	1447	642,400	2.25	1 (ref)
IBD	577	169,200	3.41	1.5 (1.4–1.7)	202	50,400	4.01	1.7 (1.5–2.0)	375	118,800	3.16	1.4 (1.3–1.6)
Bipolar disorder												
References	198	934,500	0.21	1 (ref)	64	285,900	0.22	1 (ref)	134	648,600	0.21	1 (ref)
IBD	46	171,100	0.27	1.2 (0.9–1.7)	23	51,400	0.45	1.9 (1.2–3.1)	23	120,500	0.19	0.9 (0.6–1.4)
Use of antidepressants												
References	14,719	850,800	17.30	1 (ref)	4412	260,200	16.95	1 (ref)	10,307	590,500	17.45	1 (ref)
IBD	3565	150,800	23.65	1.4 (1.3–1.4)	1160	44,300	26.16	1.6 (1.5–1.7)	2405	106,400	22.60	1.3 (1.3–1.4)

IBD, Inflammatory bowel disease; IR, Incidence rate; PY, Person years; HR, Hazard ration; CI, Confidence interval.

Table 3: **Frequency and risk of having anxiety, depression or bipolar disorders or receiving antidepressants in the ten years following IBD diagnosis or cohort entry in individuals who had not had psychiatric disorders or received antidepressants in the 5 years prior.**

around the time of IBD-diagnosis indicates a particularly high strain from the bowel-symptoms and from dealing with being diagnosed with a chronic illness. It could also point to an early window of opportunity for managing the psychiatric comorbidities while potentially also improving the course of IBD, since psychiatric comorbidity has been suggested to increase risk of active IBD.[11]

Depression was more frequent than anxiety in both the IBD and the reference population. The connection between IBD and depression has been partly explained by several mechanisms, including impaired vagal nerve signalling, changes in brain morphology, nitric oxide overproduction in the brain, and circulating pro-inflammatory cytokines in the periphery and in the brain.[12] However, it is important to note that anxiety is predominantly treated in general practice and specialist private practice, which means that it is much more frequent than what is reflected in data on hospital contacts.

The use of antidepressants in the Danish population rose during the study period and peeked around the year 2010, since when it slightly decreased,[27] which we took into account in our study design by time-dependent matching. Throughout the study period, patients with IBD had a higher use of antidepressants than individuals from the general population, particularly around the time of and in the first years after IBD diagnosis. While antidepressants are used for multiple conditions such as stress, PTSD, and chronic pain, the vast majority of prescriptions are given for depression. In the Danish National Prescription Registry, 78% of prescriptions for antidepressants that contained indications were given for depression and 11% for anxiety. It is thus appropriate to view the increased use of antidepressants in the IBD population as a measure of a broader spectrum of anxiety and depression disease that is possibly more indicative of mental health struggles than hospital contacts alone, as the hospital contacts represent only patients with severe anxiety and depression.

In the stratified analyses, the youngest age group (18–39 years) had increased risk of a hospital contact for depression and of antidepressant use, but their risk was lower than that of the older age groups both before and after IBD diagnosis. The differences were statistically significant despite similar background frequencies of depression in the groups and despite higher background frequencies of antidepressant use in the older groups compared with the group aged 18–39. This could reflect a particular vulnerability in older patients with IBD as a result of a longer delay in diagnosis, which could lead to worse mental health, or it could be because of environmental factors that likely have a stronger influence on IBD development in the older relative to genetics that are probably more important for IBD development in the young.

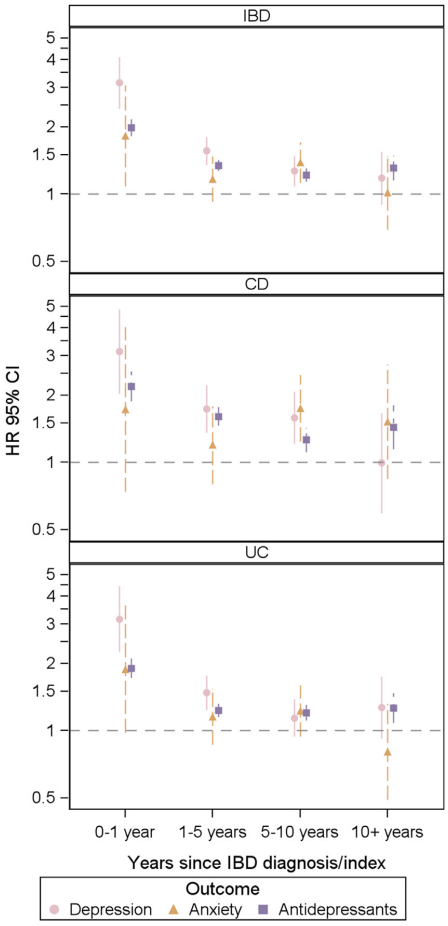

Fig. 2: **Risk of a hospital contact for depression and anxiety, and risk of having a dispensed prescription for antidepressants in patients with IBD, CD, and UC compared with the reference population in the years after IBD diagnosis/index date.** HR, Hazard Ratio; CI, Confidence interval; IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis. Symbols represent the estimate for each outcome and vertical lines represent the confidence interval. Bipolar disorder not represented because of too few cases.

Patients with CD and UC differed slightly in our analyses. Patients with CD had slightly higher increased risk of a hospital contact for depression and for having a prescription for antidepressants both in the years before and in the years following IBD diagnosis. This is in line with previous studies suggesting that patients with CD

are more vulnerable to psychiatric comorbidity than patients with UC.[14,20]

We found no differences in relative risk between males and females, which is consistent with a 2019 study from South Korea.[20] The rates of all outcomes were higher in both females with IBD and those from the background population, reflecting higher absolute rates of anxiety, depression, and bipolar disorder in females.

Bipolar disorder was not associated with IBD, except for patients with CD who had an increased risk of having a hospital contact for bipolar disorder in the years following IBD diagnosis. This could be an incidental finding, or it may be an effect of steroids given for CD that can lead to hypomania. The possible impact of steroid use on the association of IBD with anxiety, depression, and bipolar disorder merits further investigation, as steroids are well known to cause psychiatric adverse effects.[28]

A major strength of this work lies in the National Danish Registers, which contain complete information on all included individuals. We were able to include a large sample of patients with IBD that was unselected and represented all IBD patients in Denmark during the study period, and by using time-dependent matching, we were able to account for period effects. The cohort is thus representative for Denmark, and we believe that it is generalizable to other populations as well. We used well-validated criteria for identifying patients with IBD ensuring a high validity (PPV 95%).[17] We ensured precision in time of diagnosis by restricting the population to individuals who lived in Denmark in the five years before IBD diagnosis and who had the two IBD contacts as their first registrations for IBD. While the patient registers contain information from in- and out-patient hospital contacts and thus capture those with severe psychiatric disease, the prescription register contains information on all those treated not only in hospital settings but also in General practice and specialist private practice. We used both hospital contacts for anxiety, depression, and bipolar disorder as well as dispensed prescriptions for antidepressants as outcomes, which allowed us to capture a large spectrum of outcome severity. Uniquely, we were able to follow the cohort longitudinally both back in time and year by year after IBD diagnosis, rather than focusing on just one timepoint either before or after IBD diagnosis. This enabled us to assess the longitudinal burden of psychiatric comorbidity in patients with IBD.

This study also carries potential limitations. While our national registers contain large amounts of information, we cannot obtain granular data on disease activity, which would have been useful to include in the analyses. Antidepressants are used for several indications, but as mentioned above, 89% of prescriptions were indicated for depression or anxiety, and less than 2% of prescriptions were for pain. Misclassification of outcomes cannot be completely ruled out, but as there is an ongoing data validation process in the Danish registers,[16] this is likely a minor issue. Patients with IBD could be more frequently diagnosed with psychiatric diseases as an effect of more often being seen by a doctor resulting in surveillance bias. One way to try to account for surveillance bias is to adjust for number of hospital contacts. In this study, however, we compared the risk of psychiatric diseases in patients with IBD to that of individuals from the background population. Adjustment for hospital contacts would have resulted in a comparison between patients with IBD and patients with other chronic diseases. Still, surveillance bias is unlikely to be the only explanation for the continually increased risk of anxiety and depression in patients with IBD. The mean age of diagnosis for patients with IBD in this study was relatively high (45.9 years), in part because we excluded all those diagnosed before age 18, yet it matches another recent study which found that age of onset for UC has increased in Denmark.[29] We did not adjust for other comorbidities, as our goal was to investigate the increased burden of the outcomes over time in patients with IBD compared with the general population. It would be interesting for future investigations to adjust for comorbidities, for instance using the Charlson comorbidity index, to attempt to deduct how much of the co-occurrence that can be directly attributed to IBD.

In conclusion, our nationwide population-based study with access to both pre- and post-diagnostic data from both hospitals, out-patient clinics, and pharmacies, showed a clinically significant burden of anxiety and depression in patients with IBD continually from at least five years before diagnosis to at least ten years following IBD diagnosis. The risk of depression was particularly high around the time of diagnosis and was highest in those diagnosed with IBD after the age of 40. These results demonstrate that patients with IBD are vulnerable to mental health struggles and could benefit from comprehensive care that include evaluation and management of psychiatric comorbidity, with special attention at the time of IBD diagnosis. Future research should focus on understanding the mechanisms underlying the co-occurrence of the diseases and on improving the detection and management of concurrent anxiety and depression.

Contributors

TB, GP, KA, and TJ conceived of and designed the study and collected and analysed the data. TB drafted the manuscript. TB, KA, GP, and TJ verified the data. All authors had access to and interpreted the data, revised the manuscript, and approved the final manuscript. All authors accept responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Data for this study are drawn from the Danish national registers (https://sundhedsdatastyrelsen.dk) that cannot be made publicly available, as they are protected by the Danish Act on Processing of Personal Data. Access to the register data is achieved through application to and

approval from the Danish Data Protection Agency and the Danish Health Data Authority.

Declaration of interests

TB: None. GP: None. KA: Board member, the Epidemiological Committee of the European Crohn's and Colitis Organization and the Danish Society for Pharmacoepidemiology. LK: LK is co-founder, consultant, and equity owner of Trellus Health. LK is a consultant to AbbVie, Pfizer, Takeda, and Eli Lilly. LK is on the Board of directors at the Rome Foundation. AA: AA has received payment or honoraria from Takeda and Pfizer. TJ: TJ has received support for the present manuscript from the Danish National Research Foundation, the Lundbeck Foundation, and the Aage og Johanne Louis-Hansen Fond. TJ is a member of the Board of the Danish medical society Selskab for Teoretisk og Anvendt Terapi.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101986.

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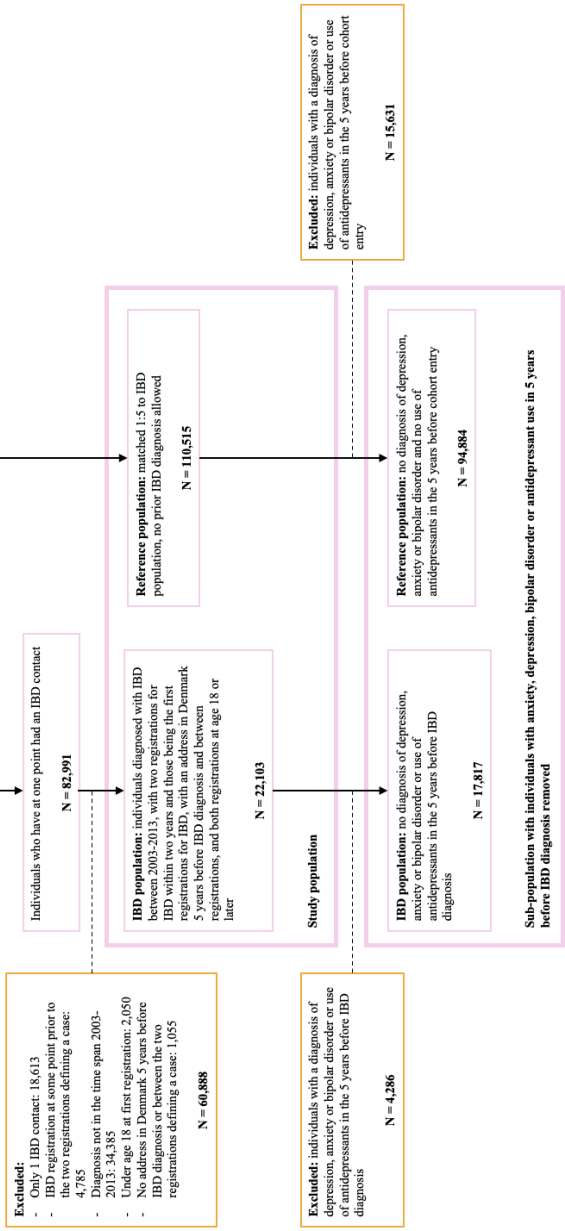
PAPER III supplementary materials

Contents



Supplementary figure 1. Flow chart describing formation of the IBD and reference cohorts. IBD, inflammatory bowel disease.

	IBD					References				
Time	**N**	**Anxiety (%)**	**Depression (%)**	**Bipolar disorder (%)**	**Antidepressants (%)**	**N**	**Anxiety (%)**	**Depression (%)**	**Bipolar disorder (%)**	**Antidepressants (%)**
-5	22,103	45 (0·2)	151 (0·7)	17 (0·1)	1,856 (8·4)	110,515	130 (0·1)	547 (0·5)	109 (0·1)	6,695 (6·1)
-4	22,103	38 (0·2)	165 (0·7)	24 (0·1)	2,029 (9·2)	110,515	139 (0·1)	598 (0·5)	114 (0·1)	7,483 (6·8)
-3	22,103	45 (0·2)	182 (0·8)	26 (0·1)	2,264 (10·2)	110,515	172 (0·2)	675 (0·6)	150 (0·1)	8,201 (7·4)
-2	22,103	50 (0·2)	199 (0·9)	24 (0·1)	2,489 (11·3)	110,515	176 (0·2)	744 (0·7)	158 (0·1)	8,938 (8·1)
-1	22,103	54 (0·2)	267 (1·2)	28 (0·1)	2,809 (12·7)	110,515	226 (0·2)	803 (0·7)	171 (0·2)	9,693 (8·8)
0	21,657	77 (0·4)	368 (1·7)	31 (0·1)	3,018 (13·9)	109,699	248 (0·2)	830 (0·8)	181 (0·2)	10,087 (9·2)
1	21,304	80 (0·4)	322 (1·5)	36 (0·2)	3,002 (14·1)	108,305	262 (0·2)	828 (0·8)	196 (0·2)	10,221 (9·4)
2	20,958	75 (0·4)	273 (1·3)	39 (0·2)	2,979 (14·2)	106,894	293 (0·3)	850 (0·8)	186 (0·2)	10,327 (9·7)
3	20,618	67 (0·3)	265 (1·3)	41 (0·2)	2,861 (13·9)	105,543	299 (0·3)	897 (0·8)	199 (0·2)	10,287 (9·7)
4	20,296	60 (0·3)	236 (1·2)	45 (0·2)	2,811 (13·9)	104,117	300 (0·3)	810 (0·8)	208 (0·2)	10,346 (9·9)
5	18,296	60 (0·3)	233 (1·3)	47 (0·3)	2,573 (14·1)	94,154	263 (0·3)	734 (0·8)	196 (0·2)	9,574 (10·2)
6	16,112	70 (0·4)	209 (1·3)	40 (0·2)	2,257 (14·0)	83,276	240 (0·3)	675 (0·8)	193 (0·2)	8,575 (10·3)
7	13,920	61 (0·4)	152 (1·1)	33 (0·2)	1,957 (14·1)	72,078	184 (0·3)	549 (0·8)	156 (0·2)	7,411 (10·3)
8	11,835	49 (0·4)	149 (1·3)	26 (0·2)	1,658 (14·0)	61,294	167 (0·3)	467 (0·8)	141 (0·2)	6,308 (10·3)
9	9,802	45 (0·5)	111 (1·1)	18 (0·2)	1,385 (14·1)	50,800	174 (0·3)	397 (0·8)	117 (0·2)	5,214 (10·3)
10	7,922	30 (0·4)	103 (1·3)	19 (0·2)	1,130 (14·3)	41,103	121 (0·3)	293 (0·7)	91 (0·2)	4,194 (10·2)

Supplementary table 1. Yearly prevalence of hospital contacts for anxiety, depression, and bipolar disorder and of dispensed prescriptions for antidepressants in patients with IBD and reference individuals. Time is indicated relative to time of IBD diagnosis/index date. IBD, inflammatory bowel disease.

	Age group/sex	IBD (n=22,103)		References (n=110,515)		OR (95% CI)	P-value
		Cases	%	Cases	%		
Anxiety	**18-39 years**	80	0·9	294	0·6	1·4 (1·1-1·7)	0·7993
	40-59 years	53	0·8	191	0·6	1·4 (1·0-1·9)	
	60+ years	28	0·5	87	0·3	1·5 (1·2-1·8)	
	Female	107	0·9	410	0·7	1·3 (1·1-1·6)	0·2047
	Male	54	0·5	162	0·3	1·5 (1·2-1·8)	
Depression	**18-39 years**	191	2·0	835	1·8	1·1 (1·0-1·3)	0·0022
	40-59 years	185	2·7	555	1·6	1·7 (1·4-2·0)	
	60+ years	183	3·1	594	2·0	1·4 (1·3-1·6)	
	Female	385	3·2	1,389	2·3	1·4 (1·2-1·6)	0·6343
	Male	174	1·7	595	1·2	1·4 (1·3-1·6)	
Bipolar disorder	**18-39 years**	16	0·2	67	0·1	1·2 (0·7-2·1)	0·2252
	40-59 years	13	0·2	108	0·3	0·6 (0·3-1·1)	
	60+ years	17	0·3	93	0·3	0·9 (0·6-1·2)	
	Female	33	0·3	169	0·3	1·0 (0·7-1·4)	0·2488
	Male	13	0·1	99	0·2	0·8 (0·6-1·1)	
Use of antidepressants	**18-39 years**	1,214	12·9	5,014	10·7	1·2 (1·2-1·3)	<·0001
	40-59 years	1,461	21·4	5,002	14·6	1·6 (1·5-1·7)	
	60+ years	1,540	26·2	5,293	18·0	1·5 (1·4-1·5)	
	Female	2,862	23·9	10,200	17·0	1·5 (1·5-1·6)	0·0082
	Male	1,353	13·4	5,109	10·1	1·4 (1·4-1·5)	

Supplementary table 2. Risk divided by age of diagnosis and sex of having a hospital contact for anxiety, depression, or bipolar disorder or having a dispensed prescription for antidepressants in the five years before IBD diagnosis/index date. IBD, inflammatory bowel disease; PY, person-years; OR, odds ratio.

	IBD (n=17,817)	Crohn's disease (n=5,378)	Ulcerative colitis (n=12,439)	References (n=94,916)
Mean age at IBD diagnosis or index date	44·5 years	41·2 years	46·0 years	45·1 years
Age at diagnosis or index date				
18-39	8,137 (45·7%)	2,864 (53·3%)	5,273 (42·4%)	41,805 (44·0%)
40-59	5,354 (30·0%)	1,485 (27·6%)	3,869 (31·1%)	29,058 (30·6%)
60 +	4,326 (24·3%)	1,029 (19·1%)	3,297 (26·5%)	24,053 (25·3%)
Sex				
Female	9,084 (51·0%)	2,945 (54·8%)	6,139 (49·4%)	49.533 (52·2%)
Male	8,733 (49·0%)	2,433 (45·2%)	6,300 (50·6%)	45,383 (47·8%)
Year of IBD diagnosis or index date				
2003-2006	6,401 (35·9%)	1,862 (34·6%)	4.539 (36·5%)	33,892 (35·7%)
2007-2010	6,630 (37·2%)	1,952 (36·3%)	4,678 (37·6%)	35,447 (37·3%)
2011-2013	4,786 (26·9%)	1,564 (29·1%)	3.222 (25·9%)	25,577 (26·9%)

Supplementary table 3. Baseline characteristics of all patients diagnosed with IBD at age 18 or later and reference individuals in Denmark between 2003-2013 with no history of psychiatric disease in the five years before cohort entry. IBD, inflammatory bowel disease.

		IBD (n=17,817)		References (n=94,884)		HR (95% CI)	P-value
	Age group/sex	Cases	IR/1000 PY	Cases	IR/1000 PY		
Anxiety	**18-39 years**	125	1·50	577	1·35	1·1(0·9-1·4)	0·1089
	40-59 years	62	1·15	229	0·77	1·5 (1·1-2·0)	
	60+ years	60	1·76	256	1·23	1·5 (1·1-2·0)	
	Female	154	1·75	667	1·36	1·3 (1·1-1·5)	0·8282
	Male	93	1·12	395	0·90	1·3 (1·0-1·6)	
Depression	**18-39 years**	249	3·02	1,090	2·57	1·2 (1·0-1·4)	<·0001
	40-59 years	137	2·57	429	1·46	1·8 (1·5-2·2)	
	60+ years	191	5·70	600	2·91	2·0 (1·7-2·3)	
	Female	327	3·76	1,303	2·67	1·4 (1·3-1·6)	0·1252
	Male	250	3·04	816	1·87	1·6 (1·4-1·9)	
Bipolar disorder	**18-39 years**	26	0·31	135	0·31	1·0 (0·7-1·5)	0·0549
	40-59 years	11	0·20	44	0·15	1·4 (0·7-2·7)	
	60+ years	9	0·26	19	0·09	3·0 (1·3-6·6)	
	Female	27	0·30	113	0·23	1·3 (0·9-2·0)	0·7482
	Male	19	0·23	85	0·19	1·2 (0·7-1·9)	
Use of antidepressants	**18-39 years**	1,447	19·49	6,130	15·73	1·2 (1·2-1·3)	<·0001
	40-59 years	1,015	21·48	3,871	14·21	1·5 (1·4-1·6)	
	60+ years	1,103	37·68	4,718	25·00	1·5 (1·4-1·6)	
	Female	2,058	27·09	8,888	20·13	1·3 (1·3-1·4)	0·2261
	Male	1,507	20·15	5,831	14·25	1·4 (1·3-1·5)	

Supplementary table 4. Risk divided by age of diagnosis and sex of having a hospital contact for anxiety, depression, or bipolar disorder or having a dispensed prescription for antidepressants in the ten years following IBD diagnosis/index date in patients with IBD and reference individuals with no prior contacts for those diseases or prescriptions for antidepressants in the five years before IBD diagnosis/index date. IBD, inflammatory bowel disease; IR, incidence rate; PY, person-years; HR, hazard ratio.

Indication	Total	Total without" No indication"
Depression	43·4%	77·8%
Anxiety	6·2%	11·2%
Bipolar disorder	0·001%	0·003%
Obsessive-compulsive disorder	0·3%	0·5%
Pain	0·7%	1·2%
For diseases of the mind	5·0%	8·9%
Other	0·2%	0·4%
No indication	44·2%	NA

Supplementary table 5. Indications for dispensed prescriptions for antidepressants. NA, not applicable.

	Percentage of those with a contact for depression who also had a prescription		Percentage of those with a prescription who also had a contact for depression	
Year	**IBD**	**References**	**IBD**	**References**
-5	89%	84%	7%	7%
-4	87%	85%	7%	7%
-3	86%	85%	7%	7%
-2	86%	86%	7%	7%
-1	90%	86%	9%	7%
0	89%	87%	11%	7%
1	88%	84%	9%	7%
2	88%	85%	8%	7%
3	85%	84%	8%	7%
4	87%	86%	7%	7%
5	87%	84%	8%	6%
6	87%	82%	8%	6%
7	83%	84%	6%	6%
8	87%	80%	8%	6%
9	85%	84%	7%	6%
10	85%	86%	8%	6%

Supplementary table 6. Comparison between having hospital contacts for depression and having dispensed prescriptions for antidepressants by year in patients with IBD and in reference individuals. IBD, inflammatory bowel disease.

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