Depression in individuals who subsequently develop Inflammatory Bowel Disease: a population-based nested case-control study

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Contributorship

The POP-IBD study group is a collaboration between St George's, University of London, Imperial College London, University College London and King's College London, conducting population based studies in the field of Inflammatory Bowel Disease. JB, SS, RP, CA, IP & MH conceived and designed this study. JB prepared the data and carried out statistical analysis

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Abstract

Objective

Depression is a potential risk factor for developing inflammatory bowel disease (IBD). This association may be related to gastrointestinal (GI) symptoms occurring before diagnosis. We aimed to determine whether depression, adjusted for pre-existing GI symptoms, is associated with subsequent IBD.

Design

We conducted a nested case-control study using the Clinical Practice Research Datalink identifying incident cases of ulcerative colitis (UC) and Crohn's Disease (CD) from 1998-2016. Controls without IBD were matched for age and sex. We measured exposure to prevalent depression 4.5-5.5 years before IBD diagnosis. We created 2 sub-groups with prevalent depression based on whether individuals had reported GI symptoms before the onset of depression. We used conditional logistic regression to derive odds ratios for the risk of IBD depending on depression status.

Results

We identified 10,829 UC cases, 4,531 CD cases and 15,360 controls.

There was an excess of prevalent depression five years before IBD diagnosis relative to controls (UC: 3.7% vs 2.7%, CD 3.7% vs 2.9%).

Individuals with GI symptoms prior to the diagnosis of depression had increased adjusted risks of developing UC and CD compared to those without depression (UC: OR 1.47, 95% CI 1.21-1.79, CD: OR 1.41, 95% CI 1.04-1.92). Individuals with depression alone had similar risks of UC and CD to those without depression (UC: OR 1.13, 95% CI 0.99-1.29, CD: OR 1.12, 95% CI 0.91-1.38).

Conclusions

Depression, in the absence of prior GI symptoms, is not associated with subsequent development of IBD. However, depression with GI symptoms should prompt investigation for IBD.

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Summary Box

What is already known about this subject?

Depression has been associated with a two-fold risk of developing inflammatory bowel diseases (IBD). However, Individuals often experience gastrointestinal (GI) symptoms for many years before receiving a diagnosis of IBD. It is unclear whether the apparent association between prior depression and subsequent IBD potentially represents reverse causation, where undiagnosed symptoms of IBD result in depression.

What are the new findings?

Individuals with IBD have a higher prevalence of depression than matched controls as early as nine years before diagnosis. Depression in the absence of prior GI symptoms, is not associated with a future diagnosis of either UC or CD. However, those with depression diagnosed after already experiencing GI symptoms are at increased risk of later being diagnosed with UC and CD. The excess prevalence of depression prior to a diagnosis of IBD may be a consequence of diagnostic delay and untreated GI symptoms.

How might it impact on clinical practice in the foreseeable future?

Depression in combination with persistent GI symptoms may represent undiagnosed IBD. NICE and BSG guidelines recommend the use of the faecal calprotectin test, a non-invasive biomarker of gastrointestinal inflammation, to evaluate such patients in primary care to determine whether onward specialist referral is appropriate.

Introduction

Patients with Inflammatory Bowel Diseases (IBD), comprising Crohn's Disease (CD) and ulcerative colitis (UC), are more likely to be diagnosed with depression in the years following diagnosis.[1–3] Studies of the association between IBD and depression show a bi-directional relationship.[4,5] This has led to a hypothesis that depression is a risk factor for developing IBD and that treating it may reduce this risk.[6,7] Possible biological mechanisms for this are that persistent stress manifesting as depression drives a neuro-enteric pathway through chronic activation of the hypothalamic-pituitary-adrenal axis inducing systemic pro-inflammatory cytokines, which has been demonstrated in experimental models.[8–11]

The lifetime risk of depression amongst individuals with IBD is twice that of matched controls.[12] Similarly, in the opposite direction, there is a two-fold risk of IBD developing amongst people with depression.[7] The time between onset of gastrointestinal (GI) symptoms and diagnosis of IBD is frequently prolonged.[13] These symptoms, often characterised by pain and changes of bowel habit, may cause distress and, potentially, depression. Furthermore, immune-dysregulation and the inflammatory burden of IBD may be associated with the onset of depression, which can occur in a range of immune-mediated inflammatory diseases.[2,14,15] This indicates the apparent association between prior depression and subsequent IBD potentially represents reverse causation, whereby symptoms of IBD result in depression rather than the other way around.[16] Previous studies have not accounted for the ordering of such 'prodromal' GI symptoms, common in the years leading up to the diagnosis of IBD, in relation to the emergence of depression.[7,16,17] Thus, it remains uncertain whether the higher rates of depression prior to IBD diagnosis reflect the effect of symptoms of undiagnosed IBD.

Using a nationally representative population-based nested case-control study design we aimed to test the hypothesis that the diagnosis of depression is associated with subsequent onset of IBD after accounting for prior GI symptoms.

Methods

Data source and Ethical approval

We identified cases and controls from a previously defined population-based incident cohort using the Clinical Practice Research Datalink (CPRD), one of the largest validated primary care research databases in the world. It contains longitudinal, patient-level, anonymised electronic health records of 18 million patients from more than 700 general practices and is broadly representative of the United Kingdom (UK) population.[18] Primary care physicians use Read codes to record symptoms, diagnoses and prescriptions. Data are audited to ensure accuracy and completeness. The database has been extensively validated and used for research of long term conditions including IBD and depression.[19–24] We obtained ethical and scientific approval for our study from the Independent Scientific Advisory Committee (ISAC Protocol number: 15_018R).

Study Part 1: Depression before the diagnosis of IBD

We conducted a case-control study to determine the prevalence of depression in the 10 years before the diagnosis of IBD compared to individuals without IBD.

Incident case definition

We defined incident IBD cases as individuals with a first ever diagnosis Read code for either CD or UC at least one year after registering with an 'Up To Standard' practice for the period January 1st 1998 to May 1st 2016 using a published and validated methodology by Lewis et al.[19] We excluded individuals if they had records indicating both CD and UC, or indeterminate codes. Cases contributed time to the study from their date of registration on the database until the date of their IBD diagnosis, which was used as their index date.

Control Groups

Each case of CD and UC was individually matched on age and sex to four controls without a recorded diagnosis of either CD or UC at any stage of their follow-up. After stratification by age and sex, the members of the control groups were selected at random. By definition, members of the control groups

had no date for a diagnosis of IBD so each was assigned the IBD diagnosis date of their matched IBD case as their index date.[25]

Statistical Analysis

Baseline characteristics of the cases and controls were summarised using frequencies and percentages. We determined the prevalence of depression in the year of IBD diagnosis and each of the ten years before it. Individuals were included in the denominator for each year examined, provided their follow-back covered that entire year. We defined prevalent depression as any individual with a code for a diagnosis or symptoms of depression in that year, or a prescription for antidepressant medication in that year and a previous code for depression in their clinical record. We estimated the risk differences (95% CI) of prevalent depression between cases and controls (i.e. the absolute difference in the prevalence of depression between these two groups).

Study Part 2: Prior depression and the risk of IBD

We conducted a nested case-control study to determine the risk of IBD based on exposure to depression 4.5-5.5 years before the index date.

Selection of cases and controls

We identified all cases and controls from part 1 of the study that were registered in CPRD for a minimum of 5.5 years before their index date. Cases were matched to one control of the same age and sex. Where there was more than one potential match the control was selected at random. Cases who could not be matched to a control with follow-up covering the 5.5 years before their index date were excluded from the study (Appendix A – Selection of cases and controls).

Exposure to Depression

We defined exposure to depression as prevalent depression five years (4.5-5.5 years, Appendix B) prior to the index date. We defined prevalent depression as any individual with a code for a diagnosis or symptoms of depression in that year, or a prescription for antidepressant medication in that year

and a previous code for depression in their clinical record (Appendix C – code list).[22,26] An initial analysis revealed amitriptyline was used at a dose of 30mg or less per day in a large majority, below the dose recommended for the treatment of depression, we therefore excluded tricyclic antidepressants from the analysis.[27] We included codes for depressive symptoms, as well as diagnostic codes for depression, since this has been shown to improve accuracy of depression estimation compared with the use of diagnostic depression codes alone and accounts for a shift in temporal trends in coding for depression.[28,29]

Since some individuals report GI symptoms many years before IBD is diagnosed,[13] some cases of depression could develop after the onset of IBD-associated GI symptoms, but before their diagnosis.[16] We therefore created 2 sub-groups among individuals with prevalent depression: i) those who had already reported GI symptoms before the onset of their depression and ii) those who had not. We defined individuals as having reported GI symptoms before the onset of their depression if they had codes for relevant GI symptoms: abdominal pain, diarrhoea and per rectal bleeding (Appendix D), at any time before their first code for depression or antidepressant medication prescription.

Covariates

We adjusted for the covariates of smoking and socio-economic status. Smoking status has been linked to both depression and also the risk of developing IBD.[30,31] We defined individuals as `smokers', `ex-smokers' or `non-smokers' based on codes for smoking status in the five years before the end of the exposure period (4.5 to 9.5 years before the index date). Individuals whose most recent code indicated active smoking were classed as `smokers' and those with codes indicating previous but not current smoking were classed as `ex-smokers'. Individuals who had only `non-smoker' codes were classified as `non-smokers'. Individuals without data on smoking have been shown to likely be either never-smokers or non-recent smokers and were therefore classed as `non-smokers'.[32] We used the Index of Multiple Deprivation (IMD), a postcode-linked measure of socio-economic deprivation, to assign individuals to 1 of 5 groups using IMD quintiles, from IMD group 1 (least deprived) to 5 (most deprived).

Statistical Analysis

We used conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals for the risk of CD and UC according to depression status. All models were conditional on matching of age and sex.

We assigned patients with depression 4.5-5.5 years before the index date to 2 sub-groups, i) those who had already reported GI symptoms before the onset of their depression and ii) those who had not.

Model 1: We calculated the risk of CD and UC in the two sub-groups relative to individuals without depression.

Model 2: We calculated the risk of CD and UC in the two sub-groups described above relative to individuals without depression, adjusting for smoking and socio-economic status. In a sensitivity analysis we replicated model 2 but altered the exposure period for depression to between two and four years prior to the index date.

Model 3: Since coding for depression and depressive symptoms may underestimate the prevalence of depression, and a tenth of our study sample were prescribed antidepressant medication without a code for depression (Figure 1), we conducted a further analysis, adjusting for smoking and socio-economic status but applying a broader definition of prevalent depression. In this model individuals with antidepressant medication prescriptions but no code for depression or depressive symptoms were also categorised as having prevalent depression.

All analyses were performed using STATA 16 (Statacorp LP, USA).

Results

Between 1st January 1998 and 1st May 2016, we identified 5,874 incident cases of CD, 13,681 incident cases of UC and two control groups of 23,496 and 54,724 individuals without IBD respectively. Median follow-back before the diagnosis date was 7.4 years.

Depression before the diagnosis of IBD – Study Part 1

The prevalence of depression in cases who developed UC and CD was similar to that of the control groups 10 years before diagnosis (cases vs. controls UC: 1.7% vs. 1.5%, CD: 1.7% vs. 1.6%).

However, as early as nine years before diagnosis, UC cases had a higher prevalence of depression compared with the control group, increasing to 5.9% of UC cases vs. 4.7% of controls in the year before diagnosis (Risk difference: 1.2%, 95% CI 0.7%-1.7%). In CD, a similar divergence was seen from seven years before diagnosis, eventually increasing to 6.1% of CD cases having prevalent depression compared with 4.5% of controls in the year before diagnosis (Risk difference: 1.6%, 95% CI 0.8%-2.3%, see Figure 2 and Appendix E).

Prior depression and the risk of ulcerative colitis and Crohn's Disease – Study Part 2

We identified 10,829 cases of UC and 4531 cases of CD with follow-up covering the exposure period 5 years (4.5 – 5.5 years) before their diagnosis date and matched 1:1 to controls without IBD. Cases of UC and CD were more likely to have prevalent depression during the exposure period than their respective control groups (Table 1).

Model 1: Relative to those without depression, individuals with depression alone had an increased risk of developing UC (OR 1.25, 95%CI 1.03-1.52). We found a similar pattern for CD (OR 1.21, 95%CI 0.90-1.63). The risk estimates were higher for those with depression and previous GI symptoms (UC: OR 1.58, 95%CI 1.24-2.02; CD: OR 1.36, 95%CI 0.94-1.99, Appendix F).

Model 2: After additionally adjusting for smoking status and socio-economic status, individuals with depression alone had a similar risk of developing UC and CD relative to those without depression (UC: OR 1.21, 95% CI 0.99-1.47, CD: OR 1.05, 95% CI 0.78-1.42). The risk estimates were higher for those with depression and previous GI symptoms (UC: OR 1.52, 95% CI 1.19-1.94, CD: OR 1.21, 95% CI 0.82-1.77, Table 2).

A sensitivity analysis replicated model 2 but changed the exposure period for depression to between two and four years prior to the index date. Individuals with depression alone had an increased risk of developing UC but not CD relative to those without depression (UC: OR 1.23, 95% CI 1.05-1.45, CD: OR 1.08, 95% CI 0.84-1.39). Individuals with depression and previous GI symptoms had higher risk estimates for developing UC and CD (UC: OR 1.29, 95% CI 1.08-1.53, CD: OR 1.29, 95% CI 0.98-1.71).

Model 3: Using a broader definition of prevalent depression to account for under reporting in primary care we found, after adjustment for all covariates, individuals with depression alone without prior GI symptoms, had a similar risk of UC and CD compared with individuals without depression (UC: OR 1.13, 95% CI 0.99-1.29, CD: OR 1.12, 95% CI 0.91-1.38). Individuals with depression and previous GI symptoms were at increased risk of both UC and CD compared with those who were not depressed (UC: OR 1.47, 95% CI 1.21-1.79, CD: OR 1.41, 95% CI 1.04-1.92, Table 2).

Discussion

Main findings

We found individuals with UC and CD had a higher prevalence of depression than their matched control groups in the years prior to IBD diagnosis. Depression rates diverged, as early as nine years before diagnosis, with the largest excess in the year before diagnosis. After adjusting for relevant covariates, individuals diagnosed with depression after already experiencing GI symptoms were at increased risk of later being diagnosed with UC and CD. However, depression alone was not associated with a future diagnosis of either UC or CD.

Findings in relation to previous studies

We found individuals with IBD had an excess of prevalent depression five years before diagnosis relative to controls. This supports a recent study, using the Danish national registries, which demonstrated mood disorders as a whole, including depression and bipolar affective disorder, were associated with subsequent diagnoses of IBD.[33]

However, after accounting for GI symptoms that pre-dated the onset of depression we found that depression alone was not associated with developing UC or CD. Our findings differ from two previous studies that attempted to account for diagnostic delay of IBD.[34,35] Ananthakrishnan et al. (2013) found women with depressive symptoms were more likely to develop CD (HR 2.36, 1.40-3.99) but not UC (HR 1.14, 0.68-1.92).[35] Frolkis et al. (2018) found individuals with depression were at increased risk of developing both CD (HR=2.11; 95% CI 1.65 to 2.70) and UC (HR 2.23, 95% CI 1.92 to 2.60).[34] However, neither study was able to determine whether GI symptoms were already present before the onset of depression. This may have confounded their results as one in ten individuals with IBD present to their doctor with GI symptoms 5 years before diagnosis and these symptoms could lead to depression.[36]

The importance of determining the temporality between the onset of depression and GI symptoms in establishing the associated risk of premorbid depression on subsequently developing IBD has been highlighted.[16] To address this issue, we identified all individuals with depression 4.5-5.5 years before the index date who had previously visited their primary care physician for GI symptoms before the onset of their depression. We found these individuals were at increased risk of later being diagnosed with UC and CD but not those who had depression alone. We found similar results when a broader definition of depression was used to account for under-reporting of depression in primary care. We also carried out a sensitivity analysis using an exposure period closer to the index date, two to four years before IBD diagnosis, which indicated no increased risk in CD amongst individuals with depression alone and a small increase in the risk of UC. This contrasts with the findings of

Ananthakrishnan et al. (2013) who found an increased risk in CD but not UC using a similar time frame, though the reason for this difference is unclear.[35]

Both depression and IBD often have a gradual and subtle onset making it difficult to determine which condition developed first. This may mean that, therefore, previously described associations between depression and subsequent IBD may, at least in part, be the consequence of reverse causation with undiagnosed GI symptoms of IBD resulting in depression.

Strengths and Limitations

To our knowledge this is the first population-based study to examine the association of premorbid depression with the later development of IBD while also accounting for pre-existing GI symptoms. Data were drawn from a large nationally representative validated research database, free of referral centre bias. Data were recorded at the time of consultation and are therefore not subject to recall bias.

In common with all observational studies using routinely collected data, inaccuracies in coding and completeness may occur. Previous studies suggest up to 50% of depression is not detected in primary care.[37] This may explain why the prevalence of depression in our study population was lower than in national surveys, however most missed cases of depression are mild.[24,38] As with previous studies, we were unable to determine the severity of depression using a standardised psychiatric tool since these are not routinely used by UK primary care health professionals.[34,39] While our findings suggest depression, in the absence of GI symptoms, is not associated with subsequent development of IBD, formal testing of directionality and causality between depression and IBD was not possible in this study. We acknowledge GI symptoms are not specific to IBD and may have been due to other conditions. We adjusted for socio-economic status, using the index of multiple deprivation data from 2015, this is a cross-sectional marker of socio-economic status which we acknowledge is dynamic and may have changed during our study period. Finally, given cases were not matched to controls from the same primary care practice it is possible different practice patterns may have affected our results.

Implications

Our findings suggest depression, in the absence of GI symptoms, is not associated with the subsequent development of either UC or CD. However, our findings of an excess of depression in the years before IBD diagnosis support a holistic approach when individuals present with GI symptoms, including screening for depression.

We found individuals who experienced GI symptoms before the recorded onset of depression were at an increased risk of eventually receiving a diagnosis of IBD. This suggests depression may arise secondary to GI symptoms experienced during the period prior to the diagnosis of IBD. Our findings may relate to diagnostic delay in IBD and further research is needed to ascertain the burden of such delays and their relationship with other co-morbidities including poor mental health.

Conclusions

Individuals with UC and CD have a higher prevalence of depression than matched control groups in the years prior to IBD diagnosis. Depression rates diverge, as early as nine years before diagnosis, with the largest excess in the year before diagnosis. Depression, in the absence of prior GI symptoms, is not associated with subsequent development of IBD. However, depression with GI symptoms should prompt investigation for IBD.

Table 1: Baseline characteristics of cases and controls in study part 2

IBD Status	Crohn's Disease	Control Group (CD)	Ulcerative Colitis	Control Group (UC)
n=	4,531	4,531	10,829	10,829
Demographics				
Male (%)	2,137 (47)	2,137 (47)	5,832 (54)	5,832 (54)
Age at diagnosis (%)				
<17	406 (8)	406 (8)	266 (2)	266 (2)
17-39	1,640 (36)	1,640 (36)	2,812 (26)	2,812 (26)
>39	2,485 (55)	2,485 (55)	7,751 (72)	7,751 (72)
Social deprivation (%)				
IMD 1-3	1,632 (36)	1,674 (37)	4,428 (41)	4,135 (38)
IMD 4-5	957 (21)	871 (19)	1,868 (17)	2,071 (19)
Unknown	1,942 (43)	1,986 (44)	4,533 (42)	4,623 (43)
Smoking Status (%)				
Non Smoker	3,413 (75)	3,769 (83)	8,063 (74)	8,581 (79)
Smoker	644 (14)	440 (10)	1,142 (11)	1,073 (10)
Ex-Smoker	474 (10)	322 (7)	1,624 (15)	1,175 (11)
Depression Status (%)				
No Depression	4,365 (96)	4,399 (97)	10,431 (96)	10,533 (97)
Depression Alone	101 (2.2)	84 (1.9)	230 (2.1)	188 (1.7)
Depression & GI symptoms	65 (1.4)	48 (1.1)	168 (1.6)	108 (1.0)

Smoking and depression status refer to the period 5 years before the index date

IMD – Index of Multiple Deprivation. IMD 1 represents the least deprived and IMD 5 the most deprived. Index of multiple deprivation data are available only in England.

Table 2: Risk of Crohn's Disease and ulcerative colitis by depression status

Conditional Logistic Regression	Crohn's Disease				Ulcerative colitis			
	Model 2 n=9,062		Model 3 n=9,062		Model 2 n=21,658		Model 3 n=21,658	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Depression Status								
No Depression	1	-	1	-	1	-	1	-
Depression Alone	1.05	0.78-1.42	1.12	0.91-1.38	1.21	0.99-1.47	1.13	0.99-1.29
Depression with previous GI symptoms	1.21	0.82-1.77	**1.41**	1.04-1.92	**1.52**	1.19-1.94	**1.47**	1.21-1.79
Smoking Status								
Non-Smoker	1	-	1	-	1	-	1	-
Smoker	**1.67**	1.46-1.91	**1.65**	1.44-1.89	**1.13**	1.04-1.24	**1.14**	1.04-1.25
Ex-Smoker	**1.69**	1.44-1.97	**1.68**	1.44-1.96	**1.48**	1.36-1.61	**1.49**	1.37-1.61
Social deprivation (%)								
IMD 1-3	1	-	1	-	1	-	1	-
IMD 4-5	1.08	0.96-1.21	1.08	0.96-1.21	**0.83**	0.77-0.90	**0.83**	0.77-0.90
Unknown	1.03	0.90-1.08	0.99	0.90-1.09	**0.91**	0.86-0.97	**0.91**	0.86-0.97

Cases and controls were matched by age and sex and therefore conditional logistic regression was used. Statistically significant results highlighted in bold.

Model 2 - We calculated the risk of CD or UC adjusting for all variables in the table conditional on matching for age and sex.

Model 3 - We calculated the risk of CD or UC adjusting for all variables in the table conditional on matching for age and sex. In this model individuals with antidepressant medication prescriptions but no code for depression or depressive symptoms were also categorised as having prevalent depression.

No Depression - No depression in the exposure period

Depression Alone - Prevalent depression in the exposure period but no gastrointestinal symptoms preceding the onset of depression

Depression with previous GI symptoms – Prevalent depression in the exposure period with gastrointestinal symptoms preceding the onset of depression

IMD – Index of Multiple Deprivation, 1 represents the least deprived and 5 represents the most deprived. Index of multiple deprivation data are only available in England.

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