

Psychiatric co-morbidity is associated with increased risk of surgery in Crohn's disease

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Publication data

Submitted 8 October 2012
First decision 24 October 2012
Resubmitted 9 December 2012
Accepted 10 December 2012
EV Pub Online 7 January 2013

SUMMARY

Background

Psychiatric co-morbidity, in particular major depression and anxiety, is common in patients with Crohn's disease (CD) and ulcerative colitis (UC). Prior studies examining this may be confounded by the co-existence of functional bowel symptoms. Limited data exist examining an association between depression or anxiety and disease-specific endpoints such as bowel surgery.

Aims

To examine the frequency of depression and anxiety (prior to surgery or hospitalisation) in a large multi-institution electronic medical record (EMR)-based cohort of CD and UC patients; to define the independent effect of psychiatric co-morbidity on risk of subsequent surgery or hospitalisation in CD and UC, and to identify the effects of depression and anxiety on healthcare utilisation in our cohort.

Methods

Using a multi-institution cohort of patients with CD and UC, we identified those who also had co-existing psychiatric co-morbidity (major depressive disorder or generalised anxiety). After excluding those diagnosed with such co-morbidity for the first time following surgery, we used multivariate logistic regression to examine the independent effect of psychiatric co-morbidity on IBD-related surgery and hospitalisation. To account for confounding by disease severity, we adjusted for a propensity score estimating likelihood of psychiatric co-morbidity influenced by severity of disease in our models.

Results

A total of 5405 CD and 5429 UC patients were included in this study; one-fifth had either major depressive disorder or generalised anxiety. In multivariate analysis, adjusting for potential confounders and the propensity score, presence of mood or anxiety co-morbidity was associated with a 28% increase in risk of surgery in CD (OR: 1.28, 95% CI: 1.03–1.57), but not UC (OR: 1.01, 95% CI: 0.80–1.28). Psychiatric co-morbidity was associated with increased healthcare utilisation.

Conclusions

Depressive disorder or generalised anxiety is associated with a modestly increased risk of surgery in patients with Crohn's disease. Interventions addressing this may improve patient outcomes.

Aliment Pharmacol Ther 2013; **37**: 445–454

INTRODUCTION

Depression and anxiety are common in patients with inflammatory bowel disease (IBD).^{1–3} Perceived stress, major life events and severity of depressive symptoms increase risk of Crohn's disease (CD) and ulcerative colitis (UC).^{4–6} While active disease itself is associated with both depression and anxiety, evidence supports a potential independent effect of stress on influencing risk of relapse.^{5–12} As well, the effect of perceived stress appears to be mainly exerted through the mood components, suggesting that psychiatric co-morbidity may influence natural history of CD and UC.¹³ In mouse models of dextran sodium sulphate (DSS)-induced colitis, induction of depression through intraventricular injection of reserpine resulted in reactivation of quiescent colitis, which could be prevented by administering desmethylimipramine, an antidepressant.¹⁴

Psychiatric co-morbidity has been mostly examined in the context of its effect on health-related quality of life in CD and UC.^{15, 16} However, the few studies that have previously examined the effect of psychiatric co-morbidity on disease activity, in particular, on the subsequent course of CD and UC, have several limitations including reliance on symptom-based disease activity indices that often correlate poorly with objective disease activity and short duration of follow-up.^{2, 6, 7, 17–20} In addition, while a wealth of literature exists regarding the healthcare costs associated with anxiety and depression in a primary-care population or in other chronic diseases including asthma, congestive heart failure and chronic obstructive pulmonary disease, limited data exist for IBD patients.^{11, 21–28}

The aims of our study were as follows: (i) to examine the frequency of depression and anxiety (prior to surgery or hospitalisation) in a large multi-institution electronic medical record (EMR)-based cohort of CD and UC patients, (ii) to define the independent effect of psychiatric co-morbidity on risk of subsequent surgery or hospitalisation in CD and UC, and (iii) to identify the effect of depression and anxiety on healthcare utilisation in our cohort. We hypothesise that psychiatric co-morbidity is an independent risk factor for more aggressive disease behaviour in CD and UC.

METHODS

Study population

Our study consisted of an EMR-based cohort of patients with CD or UC seen at two large tertiary referral hospitals in metropolitan Boston serving over 4 million

patients. The details regarding the creation of our cohort have been described previously.²⁹ In brief, we first captured all patients with at least one International Classification of Diseases, 9th edition (ICD-9) diagnosis code for CD or UC ($n = 24\,182$) (dates ranging from March 1988 to June 2010). From this cohort, using a combination of ICD-9 codes and free text terms identified through natural language processing, we developed an algorithm with a 97% positive predictive value (PPV) in accurately identifying patients with CD or UC. The PPV of this algorithm was confirmed through further chart review by a board certified gastroenterologist (A.N.A) and resulted in a cohort of 5506 patients with CD and 5522 patients with UC.

For this study, we first identified patients with co-existing diagnosis codes for depressive disorders (ICD-9 296.2x, 296.3x, 298.0x, 311) or generalised anxiety (ICD-9 293.84, 300.0x, 313.0x) using both the presence of such codes as well as the date of first occurrence of the above codes.^{1, 30} To validate the accuracy of the ICD-9 codes for depression and anxiety in our cohort, we selected a random subset of 100 patients with each of these codes and reviewed the medical records. We found the PPV for a diagnosis of depression or anxiety to be 92% and 90% respectively. Next, we identified patients who had undergone any bowel resection identified using appropriate ICD-9 codes (Table S1), and the date of occurrence of such resections ($n = 1334$). We excluded patients who had their first date of diagnosis code for anxiety or depression following the date of first surgery resulting in 2040 patients (19%) with CD or UC who had either anxiety or depression prior to their surgery. Our primary predictor variable was a composite of the presence of either depression or anxiety prior to surgery for CD or UC.¹³ In addition, we analysed depression and anxiety separately.

Variables and outcomes

Information was obtained on patient's age, age at first diagnosis code for CD or UC, gender, non-IBD co-morbidity measured using the Deyo modification of the Charlson score based on ICD-9 codes³¹ (excluding variables related to psychiatric co-morbidity) and duration of follow-up within our healthcare system. Information was also obtained on the presence of disease-related complications prior to surgery including fistulising or stricturing disease, and perianal disease using ICD-9 codes (Table S1). Use of medications including immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), antitumour necrosis factor α (anti-TNF) therapies

(infliximab, adalimumab) and corticosteroids (prednisone, budesonide) was ascertained as codified data using the electronic prescription function of our EMR. Similar to disease complication, medication use was ascertained prior to surgery. To adjust for intensity of healthcare utilisation, we summed the 'number of facts' with each 'fact' representing a distinct medical encounter that may include office visits, laboratory test, radiology studies and in-patient or out-patient procedures. Dividing this by duration of follow-up yielded a 'fact density', which served as a measure of healthcare utilisation per unit time of follow-up. As increased healthcare utilisation prior to surgery in those with severe disease could result in a greater number of diagnosis codes overall, our multivariate models adjusted for fact density.

Our primary outcome variables were occurrence of one or more IBD-related surgeries, IBD-related hospitalisations (primary discharge diagnosis of CD or UC) and all-cause hospitalisations. IBD-related surgeries were identified through the appropriate ICD-9 codes (Table S1) while IBD-related hospitalisations were those with a primary discharge diagnosis of CD or UC. For examination of the association of pre-existing depression and anxiety on hospitalisations, we excluded patients who were noted to have the above co-morbidities after their date of first hospitalisation. Our secondary outcomes included number of out-patient visits, number of visits to gastroenterologists, number of abdominal computed tomography (CT) scans and lower gastrointestinal (GI) endoscopies. Radiologic and endoscopic studies were identified using the relevant current procedural terminology (CPT) codes.

Statistical analysis

All data were analysed using STATA 11.0 (StataCorp, College Station, TX, USA). Continuous variables were summarised using means and standard deviations while categorical variables were expressed as percentages. The *t*-test was used to compare continuous variables with the Chi-squared test being used for comparison of categorical variables. To address confounding by disease severity, we developed a propensity score. Propensity scores are used to adjust for nonrandom distribution of variable of interest in observational studies to reduce the effect of known potential confounders that may be associated both with the exposure and outcome. As disease severity could be an important risk factor for both psychiatric co-morbidity (exposure) and surgery or hospitalisations (outcome), we developed a propensity score to estimate an individual's likelihood

of developing depression or anxiety given known or potential risk factors for such psychiatric co-morbidity. These was developed using a logistic regression model with the predictors being demographic (age, gender, Charlson co-morbidity), disease (IBD type, presence of fistulae, stricture, perianal disease) and treatment (need for antitumour necrosis factor α (anti-TNF) or immunomodulator therapies) factors. We further confirmed that our propensity score was adequately able to predict psychiatric co-morbidity, such that the difference between the propensity scores between patients with and without depression or anxiety was significantly different statistically at $P < 0.0001$ for both the CD and UC. We adjusted for this propensity score in all our multivariate models to account for nonrandom occurrence of anxiety and depression, to arrive at a more accurate estimate of the independent effect of psychiatric co-morbidity on our outcome of interest. Univariate and multivariate logistic regression was used to examine the independent effect of psychiatric co-morbidity on likelihood of subsequently undergoing IBD-related surgery, all-cause or IBD-related hospitalisations while controlling for potential confounders. For outcomes that were on the continuous scale, multivariate linear regression analysis was used. A two-sided P -value < 0.05 was indicative of statistical significance. Our study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Study population

There were 5405 patients with CD included in the study among whom 997 (18%) were noted to have diagnosis codes for depression or anxiety prior to their first surgery (Figure 1). Similarly, 1050 (19%) of 5429 UC patients had depression or anxiety prior to their first surgery. Approximately, 40% of patients with a diagnosis of depression also had a diagnosis of anxiety disorders. The mean interval between the date of first diagnosis code for anxiety or depression and surgery among CD patients was 19 months while that for UC was 17 months. CD patients with psychiatric co-morbidity were likely to be older at the time of their first encounter for CD (42 vs. 39 years), had a greater modified Charlson score (2.7 vs. 1.1) and were more likely to be women (62% vs. 52%) than those without such psychiatric co-morbidity ($P < 0.001$ for all comparisons) (Table 1). As well as in the UC cohort, patients with psychiatric co-morbidity were more likely to be older, female, and

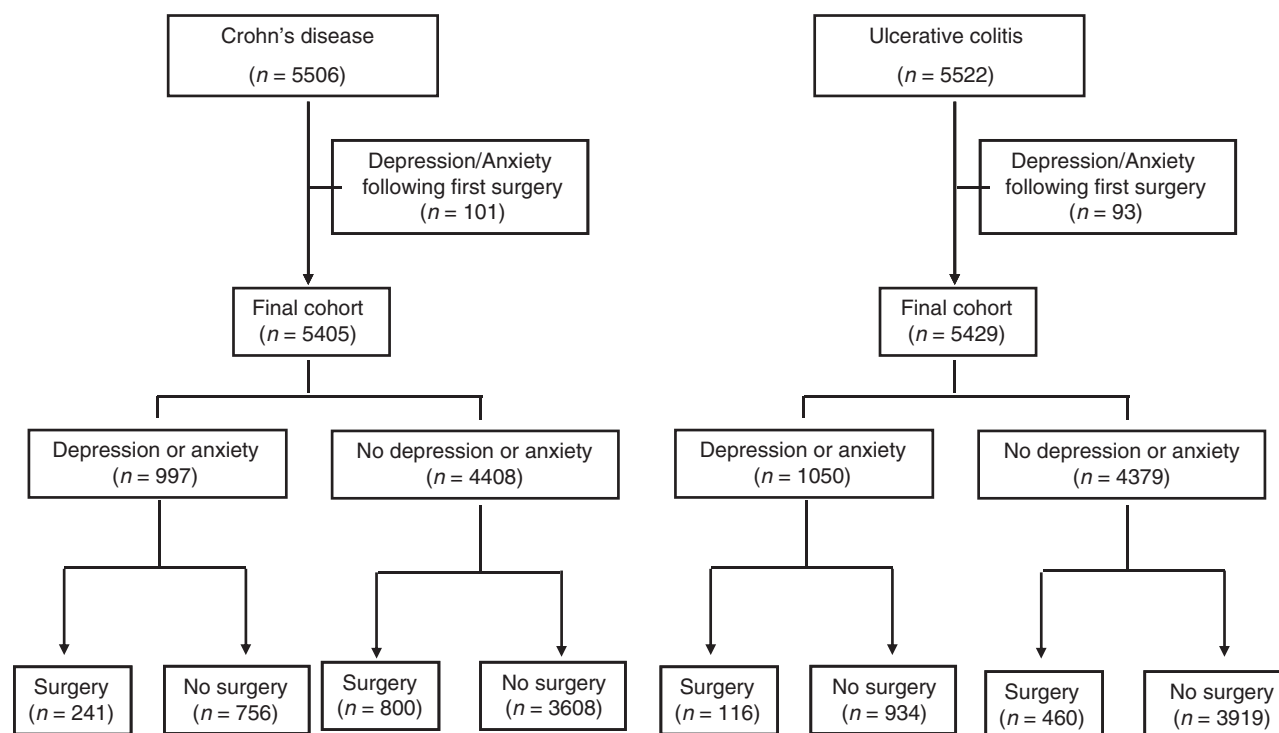


Figure 1 | Flowchart demonstrating development of Crohn's disease and ulcerative colitis cohorts.

have a greater non-IBD co-morbidity burden than those without psychiatric diagnoses.

Risk of surgery

CD patients with a pre-existing diagnosis of depression or anxiety were significantly more likely to require surgery than those without such co-morbidity (24% vs. 18%, $P < 0.001$, univariate OR: 1.43, 95% CI: 1.22–1.69) (Table 2). On multivariate analysis, adjusting for current age, age at first diagnosis code for IBD, gender, Charlson co-morbidity score, duration of follow-up, propensity score and presence of psychiatric co-morbidity prior to surgery was associated with a 28% increase in risk of surgery [Adjusted odds ratio (OR): 1.28, 95% confidence interval (CI): 1.03–1.57] (Table 2). Further adjustment for use of anti-TNF or immunomodulator therapy prior to surgery did not attenuate the effect of psychiatric co-morbidity (OR: 1.22, 95% CI: 1.01–1.47). In contrast, there was no effect of psychiatric co-morbidity on risk of surgery in UC (OR: 1.01, 95% CI: 0.80–1.28). Stratifying by gender, the effect of depression or anxiety on CD-related surgery was more prominent in women (OR: 1.28, 95% CI: 1.02–1.62) than men (OR: 1.12, 95% CI: 0.85–1.47), and in those who were older than the median of 44 years at first encounter for IBD (OR: 1.41, 95% CI: 1.08–1.85)

than those younger than this age (OR: 1.01, 95% CI: 0.80–1.29). The effect of anxiety on risk of surgery in CD (OR: 1.36, 95% CI: 1.05–1.75) was numerically greater than that of depression (OR: 1.20, 95% CI: 0.95–1.53), but this difference was not statistically significant. Neither diagnosis individually affected risk of surgery in UC. Adjusting for the occurrence of out-patient or gastroenterologist office visits did not alter the odds ratios.

Hospitalisations and medication use

Depression or anxiety did not increase likelihood of IBD-related hospitalisations in CD (OR: 1.05, 95% CI: 0.88–1.26) and indeed modestly reduced likelihood of UC-related hospitalisations (OR: 0.77, 95% CI: 0.63–0.93). However, all-cause hospitalisations were increased in the presence of psychiatric co-morbidity for both CD (OR: 1.48, 95% CI: 1.19–1.83) and UC (OR: 1.28, 95% CI: 1.07–1.52). In CD, presence of depression or anxiety was associated with an increased likelihood of anti-TNF therapy (OR: 1.17, 95% CI: 0.96–1.43), immunomodulators (OR: 1.43, 95% CI: 1.21–1.67) and corticosteroids (OR: 1.83, 95% CI: 1.58–2.13). In UC, psychiatric co-morbidity was associated with steroid use (OR: 1.42, 95% CI: 1.22–1.64), but not immunomodulators (OR: 1.16, 95% CI: 0.97–1.39) or anti-TNF agents (OR: 1.15, 95% CI: 0.87–1.53).

Table 1 | Characteristics of the study cohort

Characteristics	With psychiatric co-morbidity	Without psychiatric co-morbidity	P-value
Crohn's disease	(n = 997)	(n = 4408)	
Age in years [mean (s.d.)]	49.5 (17.7)	44.7 (19.1)	<0.001
Age at first IBD diagnosis code [mean (s.d.)]	42.0 (17.7)	38.5 (18.8)	<0.001
Female (%)	62	52	<0.001
Modified Charlson score [mean (s.d.)]	2.8 (2.5)	1.1 (1.8)	<0.001
Duration of follow-up in years [mean (s.d.)]	11.5 (6.8)	7.7 (6.5)	<0.001
Penetrating disease	7%	6%	0.10
Stricturing disease	12%	8%	<0.001
Perianal disease	16%	12%	0.001
Ulcerative colitis	(n = 1050)	(n = 4379)	
Age in years [mean (s.d.)]	52.7 (18.3)	47.9 (18.5)	<0.001
Age at first IBD diagnosis code [mean (s.d.)]	45.2 (17.8)	41.1 (18.1)	<0.001
Female (%)	66	50	<0.001
Modified Charlson score [mean (s.d.)]	2.8 (2.5)	1.1 (1.7)	<0.001
Duration of follow-up in years [mean (s.d.)]	12.5 (6.7)	9.1 (6.8)	<0.001

IBD, inflammatory bowel diseases; s.d., standard deviation.

Table 2 | Effect of psychological co-morbidity on outcomes of patients with Crohn's disease and ulcerative colitis

Outcome	With psychiatric co-morbidity %	Without psychiatric co-morbidity %	Adjusted odds ratio* (95% CI)
Crohn's disease			
Surgery	24	18	1.27 (1.03–1.58)
IBD-related hospitalisation	54	33	1.05 (0.88–1.26)
All-cause hospitalisation	83	54	1.48 (1.19–1.83)
Corticosteroids use	56	34	1.83 (1.57–2.13)
Immunomodulator use	37	28	1.43 (1.21–1.67)
Anti-TNF agent use	19	16	1.17 (0.96–1.43)
Ulcerative colitis			
Surgery	11	10	1.01 (0.80–1.29)
IBD-related hospitalisation	28	22	0.77 (0.63–0.93)
All-cause hospitalisation	74	49	1.28 (1.07–1.52)
Corticosteroids use	44	31	1.42 (1.22–1.64)
Immunomodulator use	20	18	1.16 (0.97–1.39)
Anti-TNF agent use	7	6	1.15 (0.86–1.53)

IBD, inflammatory bowel diseases; TNF, tumour necrosis factor.

* Adjusted for age, age at first diagnosis code for IBD, gender, modified Charlson co-morbidity index, duration of follow-up and propensity score.

Healthcare utilisation

A greater proportion of CD patients with underlying anxiety and depression underwent an abdominal CT scan (66% vs. 41%, $P < 0.001$) or colonoscopic evaluation (58% vs. 47%, $P < 0.001$) than those without psychiatric co-morbidity. The mean number of CT scans per patient was greater in those with depression or anxiety than those without (2.1 vs. 0.9, $P < 0.001$) as were the mean number of colonoscopies (2.5 vs. 1.9, $P < 0.001$) (Table 3), a difference that persisted after adjusting for duration of follow-up. Patients

with psychiatric co-morbidity also had significantly greater number of total out-patient visits with an IBD diagnosis, as well as visits to gastroenterologists compared with those without psychiatric co-morbidity (Table 3).

DISCUSSION

Depression and anxiety occur in a significant proportion of patients with CD and UC.^{1–3} Prior studies have mostly examined the effect of such psychiatric co-morbidity on symptom-based activity indices and health-

related quality of life,^{15, 16} both of which may be confounded by the co-existence of functional symptoms.^{32–34} Using disease-specific hard endpoints, we demonstrate that co-existing psychiatric co-morbidity was independently associated with a modestly increased risk of surgery in CD with a stronger effect for anxiety. In addition, such psychiatric co-morbidity was also associated with several measures of increased healthcare utilisation.

The prevalence of psychiatric co-morbidity in our cohort was greater than that identified among younger CD patients, and was only slightly lower than that identified through structured questionnaires in two Canadian studies.^{1, 2, 35} However, studies utilising detailed psychiatric interview have found the prevalence to be as high as 60% reflecting variations in methods used to ascertain these diagnoses, populations studied (tertiary referral centre vs. population-based cohorts), severity of disease in the underlying population and time frame of study.

There is considerable interest in the role of stress and psychiatric co-morbidity in triggering relapses in CD and UC.^{5–8, 10, 11, 36, 37} In mice models of colitis, induction of depression is associated with reactivation of quiescent inflammation.¹⁴ Epidemiologically, this hypothesis has been examined using cross-sectional and prospective studies. However, there exists significant heterogeneity in ascertainment of exposure and outcomes. In a prospective study of 101 CD patients with a 1-year follow-up, Bitton *et al.* demonstrated that patients with lower stress and lower scores on avoidance coping were less likely to

relapse than those with higher perceived stress.¹⁷ As subsequently demonstrated by Camara *et al.*, the association between perceived stress and exacerbation of CD may be influenced more by mood (depression and anxiety) than nonmood components, making it important to examine whether depression and anxiety are independent risk factors for more severe disease.¹³

In this study, we demonstrate that a diagnosis of depression or anxiety prior to surgery was independently associated with a modestly increased risk for subsequent surgery in CD after adjusting for potential confounders in a propensity-score adjusted model. By excluding patients who had their first diagnosis code for depression or anxiety following their surgery, we minimised the possibility of 'reverse causality' whereby having surgery or hospitalisation increases risk of depression or anxiety. In addition, adjusting for medication use prior to surgery as a marker of disease severity, we found that our estimates of the association between psychiatric co-morbidity and surgery remained unchanged, further supporting the independent effect of such factors. Finally, consistent with this direction of effect, we also found an association with increased use of corticosteroids, immunosuppressive or anti-TNF biological therapy in CD patients with co-existing depression or anxiety and corticosteroid use in UC patients.

There have been only a few prior studies that have examined the effect of depression on disease course prospectively. Mardini *et al.* demonstrated that depressive symptoms at baseline were associated with increased disease activity in CD over a 2-year follow-up.³⁸ Similarly,

Table 3 | Effect of psychological co-morbidity on healthcare utilisation of patients with Crohn's disease and ulcerative colitis

Outcome	With psychiatric co-morbidity [mean (s.d.)]	Without psychiatric co-morbidity [mean (s.d.)]	Adjusted regression co-efficient*(95% confidence interval)
Crohn's disease			
Number of out-patient visits with CD diagnosis	19 (25)	11 (18)	2.80 (1.54–4.06)
Number of gastroenterologist visits with CD diagnosis	9 (14)	6 (10)	1.54 (0.84–2.25)
Number of abdominal CT or MRI scans	4 (6)	2 (4)	1.06 (0.77–1.34)
Number of lower GI endoscopies	3 (4)	2 (3)	0.56 (0.33–0.79)
Ulcerative colitis			
Number of out-patient visits with UC diagnosis	10 (13)	7 (10)	1.43 (0.73–2.14)
Number of gastroenterologist visits with UC diagnosis	5 (8)	4 (7)	0.72 (0.24–1.20)
Number of abdominal CT or MRI scans	2 (4)	1 (3)	0.69 (0.40–0.90)
Number of lower GI endoscopies	3 (4)	2 (3)	0.50 (0.24–0.75)

CD, Crohn's disease; UCM, ulcerative colitis; CT, computed tomography; MRI, magnetic resonance imaging.

* Adjusted for age, age at first diagnosis code for IBD, gender, modified Charlson co-morbidity index, duration of follow-up, and propensity score.

Mittermaier *et al.*, in a mixed cohort of UC and CD patients identified a correlation between depression scores at baseline and number of relapses over an 18-month follow-up.³⁹ Thus, our findings are consistent with this prior literature. In contrast, in a cohort comprising 59 IBD patients (32 CD) followed over 1 year, baseline depression or anxiety was not associated with number of relapses, although arguably the power to detect a significant association in such a small sample is limited.⁴⁰ One challenge in interpreting prior studies has been the reliance on symptom-based measures of disease activity, which may correlate poorly with objective markers of inflammation and could be influenced by the co-existence of functional symptoms.^{32–34} Indeed, disorders such as irritable bowel syndrome (IBS) may be common in patients with CD and UC, and could influence interpretation of symptom-based disease activity scores, particularly in the setting of depression. Thus, facilitated by our longer duration of follow-up, our findings extend the results of the prior studies that were restricted to symptomatic flares to include disease-specific hard endpoints such as the need for IBD-related surgery.

We also observed some potential heterogeneity in effects with a stronger effect among women and older patients, although neither interaction met statistical significance. The gender difference could relate to genetic susceptibility to depression among women including oestrogen receptor polymorphisms, impact of fluctuating hormone levels and differences in coping. Older patients tend to have greater co-morbidity, an increased risk of depression and lower reserve with respect to changes in their health status and its impact on functioning. The reason behind the difference in effect between CD and UC remains unclear. Despite a majority of the risk loci being shared between CD and UC, considerable differences exist in the effect of environmental factors on the two diseases. Although most notably observed are the divergent effects of smoking and appendectomy on disease risk, prior work including ours examining the effect of depressive symptoms on disease risk has demonstrated a stronger effect on CD. Whether this is because of different dominant pathways of influence in CD (innate immunity, autophagy) compared with UC (epithelial barrier function) merits further exploration, as depressive and psychosocial stress may not have a uniform impact on all components of the immune system.

The second key aspect of our study is the examination of healthcare utilisation among the cohort of IBD patients with psychiatric co-morbidity. Adjusting for potential confounders and duration of follow-up, we

identified that depression or anxiety is associated with significantly greater rates of all-cause hospitalisation and out-patient visits including to gastroenterologists. Also concerning is our finding of the independent effect of psychiatric co-morbidity on undergoing abdominal imaging studies, primarily CT scans. We were not able to ascertain whether the imaging studies obtained were appropriate, but several recent studies have highlighted the high frequency of radiographic studies in CD patients.^{41–43} Thus, it is important for treating physicians to recognise that underlying psychiatric co-morbidity could be a potential risk factor for multiple radiologic studies, to practise judicious use of imaging studies and use alternate imaging modalities such as magnetic resonance imaging (MRI) studies wherever indicated and possible in such patients. Although the excess healthcare utilisation associated with depression or anxiety has not been specifically examined in the context of IBD, our findings are consistent with studies in the primary-care population⁴⁴ and other chronic diseases where depression and anxiety are associated with increased healthcare utilisation.^{23, 24, 28} Specifically, the higher odds ratios we identified for all-cause hospitalisation (compared with primary IBD-related hospitalisations) and overall out-patient visits (compared with visits to gastroenterologists) highlight that in addition to its effect on IBD itself, the impact of depression or anxiety on overall healthcare utilisation may be greater for non-IBD-related measures as has been demonstrated previously for asthma.²⁶

In addition to its effect on healthcare utilisation, we also found that psychiatric co-morbidity was associated with an increase in use of corticosteroids in both CD and UC, and immunomodulator use in UC. There are a few potential reasons for this association. First, it is possible that, as noted by prior studies, co-existing anxiety or depression may be associated with increased symptoms, which may lead to initiation of systemic steroids. Secondly, use of systemic steroids itself is associated with significant neuropsychiatric side effects – euphoria and mania in the acute setting, and depression with long-term use.^{45–47} As the timing of initiation or cessation of such episodic therapy is often incompletely captured in the EMR, we were not able to establish causal association between medication use and psychiatric co-morbidity, but this association is consistent with that identified with other disease-specific measures such as office visits and need for surgery.

Our study has several implications. To our knowledge, ours is the first study examining the effect of co-existing

depression or anxiety on IBD-related surgery over a prolonged follow-up. By excluding those who had first reported a diagnosis of psychiatric co-morbidity following surgery or hospitalisation, and using propensity score adjustment, we minimised the possibility of reverse causality or residual confounding by disease severity, and increased the robustness of our findings. Although the strength of association remains fairly modest when adjusted for other potential confounders, depression or anxiety forms a potentially modifiable risk factor for subsequent disease relapses or surgical morbidity. In addition, both depression and anxiety are also associated with impairment in disease-specific as well as overall health-related quality of life and psychosocial functioning. Thus, our results, in conjunction with prior studies in the literature, suggest a potential need for routine screening for psychiatric co-morbidity in IBD patients. In addition, there is continued need for research on interventions addressing depression and anxiety in IBD patients as the literature so far has been limited and conflicting.^{22, 48, 49} Such interventions may improve mood and health-related quality of life as well as natural history of disease and IBD-related healthcare costs. There is also need for continued basic research on the identification of the mechanisms how stress and psychological factors influence IBD course, and whether there are genetic, environmental or psycho-behavioural risk factors that increase susceptibility to the effect of stress.

There are a few limitations of our study. We relied on the use of administrative codes to identify the presence and date of diagnosis of depression and anxiety in our IBD cohort. Thus, there is the possibility of misclassification. However, this would likely bias the results towards the null, and would result in the true effect being larger than in our study. We also validated the accuracy of these codes in our data. However, we acknowledge that there may exist differences between studies that rely on established diagnoses compared with those using a structured psychiatric interview for cross-sectional assessment. We also accounted for the fact that the diagnosis code of depression or anxiety may be secondary to increased frequency of healthcare utilisation by adjusting for the density of such utilisation in our analysis and found no difference in our odds ratios. We acknowledge the possibility of residual confounding by disease severity or unmeasured confounders as exists in all observational studies. To minimise the effect of this, we used propensity score adjustment. However, propensity scores incorporate only known confounders and fail to completely account for unknown confounders including psycho-

socioeconomic variables. Given the retrospective design of the study, we also did not have detailed information regarding the severity of psychological co-morbidity or the impact of treatment for anxiety or depression on healthcare utilisation and need for surgery in IBD. In particular, the use of antidepressants or antianxiety medications is inadequately captured within our electronic medical record system; thus, the impact of such interventions on disease course merit exploration in future studies. We also did not have prospectively collected disease activity indices, endoscopic or other biomarkers of ongoing inflammation. Finally, because ours are referral institutions, we may not have identified exposures or outcomes that were predominantly documented outside our healthcare system. However, the consistency of our results adjusting for healthcare utilisation density (as a measure of comprehensiveness of care within our health system) increases our confidence in our findings. We were also not able to examine the effect of psychiatric co-morbidity on medication non-adherence.

In conclusion, using a large multi-institution cohort of IBD patients, we demonstrate that the presence of depression or anxiety is associated with a modestly increased risk of surgery in patients with CD. We did not identify a similar association in UC patients. In addition, psychiatric co-morbidity was associated with significantly greater disease- and nondisease-related healthcare utilisation in both CD and UC, suggesting a need for routine screening for depression and anxiety in IBD patients. Further establishment of the effectiveness of interventions to address this component of IBD care is important to improve patient outcomes.

AUTHORSHIP

Guarantor of the article: Dr Ananthakrishnan.

Author contributions: Study concept – Ananthakrishnan; Study design – Ananthakrishnan, Cai, Karlson, Liao; Data Collection – Ananthakrishnan, Gainer, Guzman Perez, Cai, Cheng, Savova, Chen, Churchill, Kohane, Shaw, Xia, De Jager, Plenge, Liao, Szolovits, Murphy; Analysis – Ananthakrishnan, Cai, Cheng, Perlis; Preliminary draft of the manuscript – Ananthakrishnan. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENT

Declaration of personal interests: None.

Declaration of funding interests: The study was supported by NIH U54-LM008748. A.N.A is supported by funding from the American Gastroenterological Association and

from the US National Institutes of Health (K23 DK097142). K.P.L. is supported by NIH K08 AR060257 and the Katherine Swan Ginsburg Fund. R.M.P. is supported by grants from the US National Institutes of Health (NIH) (R01-AR056768, U01-GM092691 and R01-AR059648) and holds a Career Award for Medical Scientists from the Burroughs Wellcome Fund. E.W.K. is supported by grants from the NIH (K24 AR052403, P60 AR047782, R01 AR049880).

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. List of International Classification of Diseases, 9th Edition (ICD-9) codes used in defining variables of interest.

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