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Systematic Review and Meta-analysis: The impact of a depressive state on disease course in adult inflammatory bowel disease

Christopher Alexakis*

Shankar Kumar*

Sonia Saxena**

Richard Pollok*

Affiliations

*Department of Gastroenterology, St George's University Hospital NHS Trust, London, SW17 0QT

**Department of Primary Care and Public Health, Charing Cross Campus, Imperial College London, W6 8RF

Corresponding author:

Richard Pollok, Consultant Physician and Honorary Senior Lecturer, Department of Gastroenterology, St George's University Hospital NHS Trust, London, SW17 0QT

Email: richard.pollok@nhs.net Tel: +44 208 725 1206

Running title: depression on IBD disease course

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Abstract

Background: Despite a higher prevalence of psychosocial morbidity in Inflammatory Bowel Disease (IBD), the association between depressive state and disease course in IBD is poorly understood.

Aims: Investigate the impact of depressive state on disease course in IBD.

Methods: We conducted a systematic review in MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and PsychINFO for prospective studies evaluating the impact of baseline depressive state on subsequent disease course in adult IBD.

Results: Eleven studies matched our entry criteria, representing 3194 patients with IBD. Three reported on patients with ulcerative colitis (UC), four included patients with Crohn's disease (CD) exclusively, and 4 studies included both UC and CD. Five studies reported an association between depressive state and disease course. None of the UC-specific studies found any association. In 3 of 4 CD-specific studies, a relationship between depressive state and worsening disease course was found. In 4 of 5 studies including patients in remission at baseline, no association between depressive state and disease course was found. Pooled analysis of IBD studies with patients in clinical remission at baseline identified no association between depressive state and disease course (HR 1.04, 95%CI 0.97-1.12).

Conclusion: There is limited evidence to support an association between depressive state and subsequent deterioration in disease course in IBD, but what data exists is more supportive of an association with CD than UC. Baseline disease activity may be an important factor in this relationship. Further studies are needed to understand the relationship between mental health and outcomes in IBD.

Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), causes chronic inflammation predominantly affecting the gastrointestinal tract. There is considerable morbidity with a requirement for surgical intervention in up to 16% and 47% at 10 years in UC and CD respectively.[1] As a result, patients with IBD experience substantially reduced health-related quality of life compared with healthy adults of similar age.[2,3] Furthermore, depression is almost twice as common amongst patients with IBD when compared with healthy controls.[4] The causality of the link between psychological wellbeing and disease course in IBD is poorly understood. There is emerging literature that a depressive state may impact adversely on disease course in IBD, but this has not been systematically reviewed.

The underlying causes of IBD remain unknown but the higher prevalence of depression in patients with IBD has led to the suggestion that neuropsychiatric distress may significantly modify disease course.[5] There is some evidence to suggest that psychological stress may impact upon neuro-enteric pathways, mediating and enhancing gastrointestinal inflammation.[6,7] In animal studies, chemical induction of depression in a rodent model for IBD was associated with colitis reactivation.[8] In humans, the influence of a variety psychological states on disease course in IBD, including anxiety, acute experimental stress, life-event stress and perceived stress have been previously reported.[9,10,11,12,13,14] The results from these studies are conflicting, perhaps as a consequence of the marked heterogeneity in study design, varied definition of psychological exposure and wide-ranging quantification of disease outcomes. Data from retrospective population-based studies has indicated a possible association between the presence of depression and an increased risk of surgery in

CD, although difficulties arise when interpreting the potential confounding effect of disease severity on the risk of developing a depressive illness.[15] Cross-sectional studies have reported a varied correlation between a depressive state and disease outcomes, but these are limited by their inability to assess this relationship temporally.[9,16] Additionally, it remains difficult to distinguish whether psychological stress worsens disease course, or in fact worsening disease course alters psychological wellbeing.[17] This is an important question to resolve since it has significant implications for how we treat IBD patients with medical and psychological therapies. Previous systematic reviews have evaluated the relationship between IBD and anxiety and/or depression.[4,18] A small review by Maunder *et al*. that summarised the available literature characterising the longitudinal relationship between a variety of psychological stressors and disease activity, included only 4 studies describing the impact of a baseline depressive state on subsequent clinical outcomes.[19] To our knowledge, no systematic reviews currently exist specifically focusing on the evidence base of prospective studies addressing the impact of baseline depressive state on subsequent disease course in IBD.

We hypothesised that a depressive state could impact adversely on subsequent disease course in IBD. We therefore aimed to systematically summarise and review the existing literature on the impact of a depressive state on subsequent disease course in adult patients with IBD, restricting our searches to prospective studies to enable analysis of any temporal association between the two variables. We further aimed to perform a meta-analysis of UC and CD studies, where suitable publications were available, to quantify the direction and size of any effect in this potential relationship.

Methods

We used the PRISMA statement (see supplementary files), an internationally agreed peer-approved 27-point check list for reporting systematic reviews, to develop our own protocol and also consulted the methodology of a broader review of psychological factors in IBD.[20,21]

Search terms and data sources

We searched multiple electronic databases including MEDLINE (1946 to September 2016), EMBASE (1974 to September 2016), Cochrane Library and PsychINFO (1967 to September 2016). Additionally, we conducted hand searches of the reference lists of relevant review articles.

A combination of Medical Subject Headings (MeSH) terms and free text were used to generate the following search algorithm: (inflammatory bowel disease OR Crohn's disease OR ulcerative colitis) AND (depression OR depressive illness OR low mood OR depressive disorder OR depression symptoms) AND (disease activity OR disease flares OR disease symptoms). This was entered into the database search engines to generate the initial list of publications to be searched (EndNote™, Thompson Reuters, Toronto)

Study inclusion and exclusion criteria

Studies were selected for inclusion if they attempted to characterise the impact of a depressive state at study entry on subsequent disease course in adult patients with IBD. Only prospective cohort studies were included as we hypothesised a causal relationship between exposure to a depressive state and outcome. We only included studies reported in the English language.

Research including children or adolescents up to the age of 18 years were excluded as paediatric IBD is often considered as a separate entity in both clinical and research fields, particularly as it has a different, usually more aggressive disease course.[22] Secondly, it is likely that the psychological profile of children and adolescents with IBD is different from their adult counterparts. Current evidence suggests depression is less prevalent in younger patients with IBD.[23,24]

All studies included patients with IBD based on established clinical, histological and radiographic criteria. These included studies with solely CD or UC patients, or both, accepting that patients with CD may experience more depression than UC patients.[4] We included studies irrespective of baseline disease activity at entry into the study, but sub-categorised our results by whether study entrants were in remission, had active disease or were unselected for disease activity at study enrolment.

We included studies that measured a depressive state (including symptoms of depression) of participants at entry into the study using a recognised diagnostic instrument. These included the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Score (HADS) and the Patient Health Questionnaire 9 (PHQ-9), Global Severity Index symptom checklist 90R (GSI), or where depressive symptoms were screened for as part of a broader assessment of psychological state. We did not exclude patients on anti-depressant medications as it remains largely unclear if these medications impact on IBD course independently, but we documented it when they were used.

Our primary outcome was disease course. Acknowledging that there is a limited amount of research in this field, and thus not wanting to restrict the scope of the review, we have used this term to include a range of measures of disease outcomes, including recognised clinical,

blood and endoscopic surrogate markers of disease activity. Under the umbrella term of disease course, we included studies that quantified disease outcomes with clinical scoring tools such as the Crohn's Disease Activity Index (CDAI) or Harvey Bradshaw Index in CD, and Mayo Score or Colitis Activity Index (CAI) in ulcerative colitis. We also considered any research that defined outcomes using objective markers of inflammation including blood and faecal markers (including calprotectin), and/or endoscopic or histological findings. We also accepted studies reporting increased medication requirements as a surrogate marker for worsening disease course, for example the need for steroids, requirement for rescue therapy (the use of agents such as ciclosporin or biologic therapies to avoid imminent surgery) or IBD-related surgery. Finally, we excluded any study that exclusively used patient-reported symptoms to quantify disease activity, for example survey-based studies. This was to minimise the potential confounding from gastrointestinal symptoms originating from co-existing functional bowel disorders that can occur in the absence of active intestinal inflammation.[25] This did not eliminate certain commonly used clinical scoring systems such as the CDAI, that contain a component of patient-reported symptoms in the score. Where available we noted whether the scoring systems were patient or physician reported.

Data extraction and synthesis

Two reviewers (CA and SK) independently screened the complete list of publications between September and December 2015. Subsequently, searches were updated to include additional relevant publications up to September 2016. Duplicate publications were removed and the remaining titles and abstracts were screened for inclusion into the review, against pre-determined criteria: 1) human study including patients with IBD; 2) English

154 language; 3) addressing psychological symptoms in patients with IBD and; 4) assessment of
155 disease course.

156 Relevant data from each study were extracted, including study design, population size and
157 characteristics, IBD disease type, measures of depressive state, IBD disease course measures
158 and time frame. After scrutinising each potential paper against our inclusion/exclusion
159 criteria detailed above, the final list of included research papers was generated. A third
160 reviewer (RP) was used to resolve any discrepancies by discussion. Each of the final papers
161 were appraised for quality and bias using the Critical Appraisal Skills Program (CASP)
162 checklist for cohort studies.[26] We adapted a scoring system based on the 6 quality criteria
163 questions in section A of the CASP checklist: 1) Did the study address a clearly focused
164 question? 2) Was the cohort recruited in an acceptable fashion and was there any issue with
165 selection bias? 3) Was exposure measured using a validated tool? 4) Was the outcome
166 measured using a validated tool? 5) Have the authors identified and adjusted for
167 confounding factors appropriately? 6) Was follow up of and study completion of entrants
168 adequate? All papers were graded by both reviewers against each of the quality indicators
169 and scored accordingly giving a maximum of 6 points and a minimum of zero points per
170 paper (one point per criteria achieved). We set a score of 0-2 as poor in quality, 3-4 as
171 moderate in quality, and 5-6 as good in quality.

172 **Statistical analysis**

173 We subsequently performed a meta-analysis to quantify the direction and effect size of the
174 impact of a depressive state on disease progress. We only included studies with UC or CD
175 patients who were in remission at study entry, and reported outcomes as Hazard Ratios
176 (HR). HR estimating the impact of a depressive state on subsequent disease progress were

177 extracted from each of the relevant studies. The pooled HR with 95 % confidence intervals
178 (CIs) was calculated using the log hazards ratio and standard error. We used the most
179 adjusted HR published in the respective studies. Where appropriate, if depression scores
180 were stratified by severity, we included data for the most severe depression cohort in the
181 quantitative analysis.

182 Initially, we analysed UC and CD studies separately, and then pooled all appropriate IBD
183 studies in a further sub-analysis. The Dersimonian-Laird random effects model was used to
184 calculate the pooled HR as it is unclear if there is a single true effect that underpins all of the
185 studies.[27] The Cochrane test and the I^2 statistic were calculated to quantify heterogeneity
186 between included studies within the analysis. A p-value of less than 0.10 was considered as
187 the cut-off for presence of statistical heterogeneity. For the I^2 statistic, a threshold of 50% or
188 above was considered to represent substantial heterogeneity. All calculations for the
189 quantitative analysis were performed on Review Manager (RevMan) Version 5.3.
190 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Summary of searches

Our electronic searches identified 1097 potentially eligible studies for screening after removal of duplicates and addition from the manual searches (Figure 1). Thirty-four texts were considered for full evaluation and data extraction. Eleven papers met our inclusion criteria representing a total of 3194 patients with IBD, with 4840 person years of follow-up (calculated as number of persons per study multiplied by the mean follow-up time contributed per study). Six papers originated from Europe, 4 from North America, and one from Australasia. In total, 3 studies examined patients with UC (see supplementary Table 1) and 4 studies analysed only patients with CD (supplementary Table 2). A further 4 studies included patients with UC and CD together (supplementary Table 3). Bubble charts were subsequently generated to graphically present study year, effect direction and study size. The bubble charts were further sub-categorised by disease sub-type and baseline disease activity (Figure 2/Figure 3).

Studies addressing the impact of a depressive state on subsequent disease course in UC

We identified three prospective studies that attempted to define the association between a depressive state and disease course in UC.[28,29,30] All three studies included patients who were deemed to be in steroid-free clinical remission at study entry. Depressive state was assessed in each of the studies alongside a number of other psychological characteristics; perceived stress[28,29,30], stressful life experiences [28,29] and anxiety.[30] All three studies used different tools to categorise a depressive state; the Centre for Epidemiological Studies Depression Scale (CES-D)[28], the Symptom checklist 90R (SCL-90R)[29], and the Hospital Anxiety and Depression Score (HADS)[30]. All three used disease exacerbation/relapse as the primary

outcome, however, each used separate instruments to define disease exacerbation/relapse: scoring systems based on clinical and endoscopic findings developed for the study[28,29] and the Colitis Activity Index.[30] Relapse rate was similar in all three studies (between 37%-44%). None of the authors found a significant association between baseline depressive state and subsequent deterioration in disease course in patients with UC (see supplementary Table 1).

Studies addressing the impact of a depressive state on subsequent disease course in CD

We identified four studies that specifically investigated the impact of a depressive state on disease course in patients with CD (see supplementary Table 2).[31,32,33,34] There was considerable heterogeneity in the disease status of patients at entry to study; two studies enrolled patients who were unselected for disease activity at baseline[31,34], one study included only patients in clinical remission at baseline[33], and one study specifically included patients with active disease as defined by the Crohn's disease activity index (CDAI)[32]. All four studies used different tools to categorise a depressive state; the Beck Depression Inventory (BDI)[31], the Patient Health Questionnaire 9 (PHQ-9)[32], the SCL-90R [33], and HADS [34]. All four studies used the CDAI to quantify disease activity in patients, although one study used response to infliximab as the primary outcome.[32] Relapse rates, where identifiable, were 22-37%. Three of the papers identified a significant association between a depressed state and subsequent disease activity. Mardini *et al* found a strong positive association between BDI scores and disease activity at both current and next 2 clinic visits (week 8 and week 12). Each unit increase in BDI correlated to a 6 unit increase in CDAI at next visit ($p=0.0004$). Persoons *et al* reported a significantly lower 4 week response rate to infliximab in patients with CD diagnosed with a major depressive disorder (MDD) at baseline compared patients without MDD(29% vs 70%, $p<0.001$). In the multivariate analysis, MDD was also

237 associated with failure to achieve remission (OR 0.17, 95% CI 0.05-0.57, p=0.004) and an
238 increased risk of subsequent retreatment with infliximab in long-term (HR 2.27, 95% CI 1.36-
239 3.79, p=0.002). Lastly, Camara *et al*, demonstrated that the depressive component of
240 perceived stress was significantly associated with a subsequent deterioration in disease
241 course (OR for flare of disease - 1.78 95% CI 1.38-2.28, p<0.001).

242 **Studies addressing the impact of a depressive state on subsequent disease course in IBD**
243 **(either UC or CD)**

244 We identified four studies that included both patients with UC and CD (see supplementary
245 Table 3). [35,36,37,38] Three of the studies entered patients with UC or CD at enrolment
246 unselected for baseline disease activity.[35,37,38] The fourth study only considered patients in
247 clinical remission.[36] Two studies characterised depressive state with BDI, and two studies
248 used the HADS.[37,38] The CDAI for CD patients, and the CAI/SCCAI in UC were used to
249 measure disease course in two of the papers[36,37]. A disease assessment tool developed by
250 the authors was used in the third study.[35] The final study constructed a disease assessment
251 tool that combined surrogate clinical parameters of disease course (increased medication
252 use, development of complicated disease, requirement for surgery) and disease activity
253 scores (CDAI in CD and Modified Truelove and Witts Activity Index (MTWAI) in UC).[38] With
254 respect to analysing the impact of a depressive state on disease course, two of the studies
255 published combined results for patients with IBD (CD and UC). The other two studies
256 analysed CD and UC separately, and in combination.[35,38] Two of the studies found no
257 association between a depressive state and subsequent risk of disease exacerbation.[35,37]
258 However, Mittermaier *et al* reported that higher BDI scores at baseline was associated with
259 the development of a flare, the number of flares, and inversely with time to flare

(independent of baseline disease activity scores).[36] As CD and UC patients were not analysed separately, no comment could be made about this finding with respect to the disease subgroups, a point made by the authors in their discussion. However, it is also noted that almost 80% of the participants had CD in this study. Mikocka-Walus *et al* also reported that depression was associated with a shorter time to disease relapse in patients with IBD, compared to patients without depression (log rank test for trend p<0.0001).[38] These findings were maintained in the sub-analysis of patients with CD and UC, although the effect was more pronounced in patients with CD (log rank test for trend p=0.0007 in CD, p=0.005 in UC).

Results of the pooled analysis

Four studies qualified for entry into the pooled analysis (Figure 4). Three studies were included in the subgroup analysis for patients with UC in remission at baseline.[28,29,30] Pooled analysis of HR showed no significant impact of baseline depressive state on subsequent disease course in these patients (pooled HR 1.02, 95%CI: 0.97-1.08). Heterogeneity of included studies was low (Cochrane Q test = 1, p=0.61, I^2 = 0%). There were too few studies to assess for publication bias using funnel plots. Only one study was suitable for analysis in the subgroup analysis of patients with CD in remission at baseline.[33] Again, there was no effect of baseline depression on subsequent disease course in these patients (HR 1.60, 95% CI: 0.92-2.77). A combined analysis of all suitable studies also did not indicate any significant effect between depressive state and disease course (HR1.04, 95% CI: 0.97-1.12).

Quality and validity of studies

A detailed breakdown of the Oxford CASP quality assessment scores for all eleven studies is provided (see supplementary table 4). Only one of the 11 studies met all 6 criteria for quality.[36] Six studies were scored as good quality, and 5 studies as moderate quality. No studies were scored as low quality using the CASP appraisal tool.

Although all the studies addressed the impact of a depressive status on a measurement of disease course, ten of the 11 studies assessed depressive state alongside multiple other clinical and psychological parameters. Only one paper examined depressive state as the unique exposure.[32]

All the studies would have been prone to referral centre bias, with the probable exception of Camara *et al* and Mikocka-Walus *et al*, who recruited study patients from multiple hospitals and clinics nationally, and together enrolled more patients than all the other nine studies combined.[34,38] Although there was marked heterogeneity in the instruments used to assess a depressive state, all 11 studies used validated tools for this purpose. Eight of the eleven studies used accepted tools for measuring disease course such as CDAI or CAI. Although the three oldest studies didn't use such tools, which may reflect the era of these studies, all three used detailed and robust methods including clinical and/or endoscopic parameters as surrogate markers of disease activity.[28,29,35] Only four studies included endoscopic parameters in the assessment of outcomes. [28,29,30,35] Three papers did not take in to account IBD-specific medication use at study enrolment which may be considered a confounding factor with regards to subsequent disease course.[35,37,38]

Furthermore, three studies included patients on concurrent antidepressant medication (ADM).[29,31,32] Although the impact of ADM is yet to be determined in subsequent disease course in IBD, the inclusion of patients on psychotropic medication into a study where

304 depression is a defining exposure, may be confounding. In fact, only the one study by
305 Mittermaier *et al*, actively excluded such patients from study entry.[36]

306 Study follow-up length was varied, but all the studies bar Persoons *et al* had follow up for at
307 least a year.[32] We considered a follow up period of at least a year as a satisfactory time
308 period for capturing subsequent changes in disease course, given the appreciable risk of a
309 disease flare over this time period for both UC and CD.[39,40] However, it is still difficult to
310 draw true conclusions on the time lag of any potential effect of a depressive state on
311 subsequent disease course. By contrast, Persoons *et al* used 4 weeks as the time span to
312 assess disease course in response to a baseline depressive state (using the surrogate marker
313 of response to infliximab treatment). Although this is a short follow up in comparison to the
314 other studies, it should not be discounted, as arguably the patients in this study had a more
315 severe disease phenotype with active inflammation at entry and most having previously
316 used biologic therapy.

317

Discussion

To our knowledge this is the first systematic review to examine the association between a depressive state and its subsequent impact on disease course in adult IBD. Of the 11 studies included, five suggested an association between a baseline depressive state and worsening disease course[31,32,34,36,38], but six failed to show association.[28,29,30,33,35,37]

In this review, we found greater evidence to suggest that a depressive state in CD may be associated with a subsequent deterioration in disease course than in UC. Three of the four studies that included only patients with Crohn's disease, and five of the eight studies (63%) that included patients with CD suggested an association between a depressive state and worsening disease course, manifest as either increased CDAI, poorer response to biologic therapy, or risk of flare. By contrast, only two of seven studies that included patients with UC reported an association between depression and disease activity in UC. None of the three studies that considered only patients with UC showed any association between a depressive state and disease course. Furthermore, in four out of 5 studies in which patients at study entry were in disease remission, no association between baseline depressive state and subsequent worsening of disease course was found.

By contrast, two thirds of the studies that included patients with active IBD at baseline reported an association between baseline depressive state and disease course deterioration. In the pooled meta-analysis of studies, including UC and CD patients in remission, no significant association was identified (HR 1.04 95% CI: 0.97-1.12). Further analysis of sub-groups found no significant association patients with UC, and in the one study of patients with CD suitable for inclusion also found no significant association.

It is difficult to draw concrete conclusions on the time frame for a worsening of IBD among patients with depression as all the studies were of different lengths and had different follow-up times. Hence the time frame may be a reflection on the duration of the study rather than the true time frame between depression and worsening of IBD.

The findings of this review suggest that there may be a differential effect of depression on outcomes between IBD subtypes. Other researchers have observed similar associations with poor mental health. Ananthakrishnan *et al* reported in a retrospective population-based study that the risk of surgery was significantly increased in patients with CD and a co-morbid diagnosis of major depressive disorder, whereas UC patients with major depressive disorder had no increased risk of colectomy.[15]

Although there was a lack of randomised controlled or empirical studies in this review, the quality of the individual prospective studies included was moderate to good (CASP validity score range 3-6). Despite this, we identified several limitations in the available literature. Firstly, as most of the studies recruited patients from a single clinic or hospital, the probability of selection and referral centre bias is increased. The relatively small number of patients in most of the studies made it more difficult to draw firm conclusions, particularly as only two studies (Mikocka-Walus *et al* (2008) and Camara *et al*) included appropriate power calculations in their methodology. Secondly there was a heavy reliance on using symptom scores for depression, which may not accurately reflect the true presence of clinical depression. For example, the HADS has a sensitivity and specificity of only 80% for predicting depression.[41] The use of more than one depression screening tool, or a formal clinical psychiatric evaluation of patients selected for studies, may improve the identification of patients with true depressive illness. Furthermore, there was considerable

variation between the studies as to the accepted cut-off values used to define cases of depression. Mikocka-Walus *et al* used a HADS >7 to define cases, whereas Langhorst *et al* used a cut-off of HADS>10. The use of non-validated tools for measuring disease activity may have been an issue in some of the earlier studies, but the current availability of clinical, biochemical, endoscopic and histological markers of disease activity means that this should not be a problem in future prospective studies.

The strengths of this review include the comprehensive and systematic approach to evaluating the available research in this field. Also, by including only prospective studies, it enabled a more robust approach in addressing the true impact of a depressive state on subsequent disease course, without the limitations encountered in retrospective and cross-sectional studies. There are limitations to this review that require discussion. We excluded texts that were not published in English, and thus relevant non-English studies may have been left out. This might also mean that certain populations were not represented appropriately, although we did identify studies from three separate continents. We also acknowledge that our search algorithm, although detailed, may not be fully comprehensive for all relevant studies. Of note, we only included the three terms 'disease activity', 'disease flares' and 'disease symptoms' in our search, and perhaps including additional terms for outcomes such as 'disease course', 'IBD course' and 'disease outcomes' would have added a further level of confidence in the search. Furthermore, we excluded findings reported only in abstract, which may have removed relevant studies. We have attempted to minimize the potential confounding effect of functional gastrointestinal symptoms by accepting into the review recognised and validated tools to measure disease activity. Whereas clinical scoring systems such as the CDAI are relatively easy to administer and are frequently used in clinical

studies, we appreciate that some of these tools may overestimate the true burden of active IBD, as they rely in some part on subjective patient-reported symptomology, which may be functional in origin. The CDAI has a reasonable reliability and validity,[42] but against the emerging gold standard of mucosal assessment as a measure of assessing disease activity, it does not correlate well.[43] Interestingly, the studies that did include endoscopic assessment failed to find an association between baseline depressive state and subsequent deterioration in disease course. Future studies addressing this research question may need to consider focusing on harder objective endpoints given the potential limitation of patient-reported symptoms.

We also acknowledge that our definition of a depressive state is broad, and that true depression is not a dichotomous entity. In this review, a variety of assessment methods and screening tools were utilised in the included studies. As with the IBD clinical-based activity scores, screening tools for depression are advantageous because of their simplicity, low cost and acceptable sensitivity. However, research on depression screening tools in other chronic illness have highlighted issues with overall validity and reliability.[44] Ideally, the diagnosis of depression for the purposes of this research question would be made following objective assessment by a mental health specialist.

Because of the heterogeneity of the studies included, the subsequent meta-analysis was limited to only three studies in patients with UC in remission at study entry, and one including patients with CD. Although in the UC sub-analysis heterogeneity amongst the included studies was low, the analysis only included 213 patients, from a total of 3194 patients in all studies (~6%). Therefore, it is difficult to draw more general conclusions regarding the impact of a depressive state on disease course in IBD. However, amongst

409 patients with UC who are in remission at baseline, depressive state appears not to influence
410 subsequent disease course.

411 The idea that a depressive state may impact on clinical outcomes in IBD taps into the
412 complex inter-relationship between psychological stressors and systemic inflammation.[6]
413 There is some biological plausibility given that acute psychological stress has been
414 demonstrated to lead to changes in inflammatory constituents at a cellular level in both
415 animal and human models of IBD.[8,10] Conversely, inflammation may also promote
416 depression through the up-regulation of inflammatory cytokines and intermediates.[45]
417 Whether small changes at a cellular level in response to psychological stress actually
418 translate to an objective increase in clinical markers of disease activity is more difficult to
419 establish. Of the eleven prospective studies identified in this review, five provided evidence
420 for an association between a depressive state and worsening disease course. Research from
421 cross-sectional studies generally conclude a correlation between depression and worsening
422 disease activity but cannot account for any temporal association between the exposure and
423 outcome.[9,46,47] A large prospective survey-based study also reported that depressive
424 symptoms were associated with an increased risk of patient-reported disease activity.[48]
425 Patients who experience an improvement in disease activity also suffer less from depressive
426 symptoms.[17] Furthermore, a link between a depressive state in human subjects and
427 deteriorating disease activity has been postulated in various non-gastrointestinal
428 inflammatory conditions including rheumatoid arthritis and ankylosing spondylitis,[49,50] but
429 not in others such as systemic lupus erythematosus.[51]

430 Depression is estimated to affect between 7-59% of patients suffering with IBD,[4] and may
431 independently worsen health related quality of life irrespective of disease severity.[52] The

finding that a depressive state may potentially alter disease course opens up the possibility of a variety of new treatment options in IBD. Depression is readily treatable with antidepressant medications (ADM). In a rodent model of IBD, chemically-induced depression treated with desipramine was associated with an improvement of the colitis.[8] Using ADMs to treat inflammatory conditions may not be limited to just IBD. Research in rheumatoid arthritis indicated both fluoxetine and citalopram improved disease activity in rodent models.[53] However, the role of such medications as therapeutic agents in patients with IBD remains to be fully evaluated. A small retrospective study has suggested a possible therapeutic benefit of ADMs in IBD reporting that patients treated with ADMs had fewer steroid courses in follow up.[54] Conversely, a systematic review including 12 non-randomised studies that assessed the efficacy of ADMs in IBD was inconclusive.[55] However, a recent systematic review by Macer *et al.,* incorporating a broad range of study designs including both prospective and retrospective studies, reported evidence of a positive effect of ADMs in 12 of the fifteen studies included.[56] A recent meta-analysis of 14 randomised controlled trials by Gracie *et al.* assessed the impact of psychological therapies on disease activity, mood and quality of life in patients with IBD.[57] Interestingly, although psychological therapies appeared to improve depression and quality of life in the short term, no effect on disease activity indices was found when compared to controls with inactive disease.

In light of the unclear impact of ADMs on the course of IBD, there have been calls to address this knowledge gap in the field and the first randomised controlled trials on the subject are currently being undertaken.[58] A recently reported placebo controlled pilot study in 26 patients with CD failed to show an impact of low dose fluoxetine on disease outcomes including CDAI scores and faecal calprotectin levels, although the results are difficult to

interpret due to small study numbers, relatively short follow-up time, and the inclusion of only patients in clinical remission at baseline.[59] Further studies investigating this potential association are warranted.

Irrespective of these findings, it may be advisable that patients with IBD are screened for depression (and other psychological disturbances) both at diagnosis and at subsequent follow-up. The link between psychological stressors and disease activity in IBD has been recognised in a number of national and international disease guidelines, of which many now recommend screening for concurrent psychological disorders in these patients.[60] This strategy may be particularly pertinent for patients with CD, who are more likely to suffer from depression than those with UC, and possibly experience a worse disease course in the presence of a depressive state. Screening for psychological disorders can also highlight patients who require additional psychological support with cognitive therapy and/or specific psychological medications, which may enhance compliance with medications.

In conclusion, this review has found limited evidence to support an association between depressive state and subsequent deterioration in disease course in IBD. But what data exits is more supportive of an association in patients with CD than UC. Baseline disease activity may be an important factor in this relationship. Study quality was variable and further studies are needed to understand the relationship between mental health and outcomes in IBD.

Authorship

CA will act as the guarantor for the article. All four authors contributed equally to the concept and design of the review. CA and SK performed the initial electronic searches and

the quality scoring. RP acted a third reviewer where required. All four authors contributed equally to the final manuscript. All four authors have approved submission of the final manuscript.

Statement of interest

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References

1. Frolkis AD, Dykeman J, Negrón ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2013;145(5):996-1006. doi:10.1053/j.gastro.2013.07.041.

2. Irvine EJ. Quality of life of patients with ulcerative colitis: Past, present, and future. *Inflamm Bowel Dis*. 2008;14(4):554-565. doi:10.1002/ibd.20301.

3. Cohen RD. The quality of life in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2002;16(9):1603-1609. doi:10.1046/j.1365-2036.2002.01323.x.

4. Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: Systematic review of the comorbidity of depression and anxiety with IBD. *Inflamm Bowel Dis*. 2016;22(3):752-762. doi:10.1097/MIB.0000000000000620.

5. Ananthakrishnan AN. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2013;9(6):367-374. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3736793&tool=pmcentrez&rendertype=abstract.

6. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*. 2005;54(10):1481-1491. doi:10.1136/gut.2005.064261.

7. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front Cell Neurosci*. 2015;9(October):392. doi:10.3389/fncel.2015.00392.

8. Ghia J-E, Blennerhassett P, Deng Y, Verdu EF, Khan WI, Collins SM. Reactivation of inflammatory bowel disease in a mouse model of depression. *Gastroenterology*. 2009;136(7):2280-2288.e1-e4. doi:10.1053/j.gastro.2009.02.069.

9. Gracie DJ, Williams CJM, Sood R, et al. Poor Correlation Between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in Inflammatory Bowel Disease. *Am J Gastroenterol*. 2016:1-11. doi:10.1038/ajg.2016.59.

10. Mawdsley JE, Macey MG, Feakins RM, Langmead L, Rampton DS. The Effect of Acute Psychologic Stress on Systemic and Rectal Mucosal Measures of Inflammation in Ulcerative Colitis. *Gastroenterology*. 2006:410-419. doi:10.1053/j.gastro.2006.05.017.

11. Targownik LE, Sexton K a, Bernstein MT, et al. The Relationship Among Perceived Stress, Symptoms, and Inflammation in Persons With Inflammatory Bowel Disease. *Am J Gastroenterol*. 2015;110(7):1001-1012. doi:10.1038/ajg.2015.147.

12. Shiga H, Miyazawa T, Kinouchi Y, et al. Life-event stress induced by the Great East Japan Earthquake was associated with relapse in ulcerative colitis but not Crohn's disease: a retrospective cohort study. *BMJ Open*. 2013;3(2):10.1136/bmjopen - 2012-002294. Print 2013. doi:10.1136/bmjopen-2012-002294; 10.1136/bmjopen-2012-002294.

13. Bernstein CN, Singh S, Graff L a, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol*. 2010;105(9):1994-2002. doi:10.1038/ajg.2010.140.

14. Sexton K a., Walker JR, Graff L a., et al. Evidence of Bidirectional Associations Between Perceived Stress and Symptom Activity. *Inflamm Bowel Dis*. 2017;23(3):473-483. doi:10.1097/MIB.0000000000001040.

15. Ananthakrishnan a N, Gainer VS, Perez RG, et al. Psychiatric co-morbidity is associated with increased risk of surgery in Crohn's disease. *Aliment Pharmacol Ther*. 2013;37(4):445-454. doi:10.1111/apt.12195.

16. Faust AH, Halpern LF, Danoff-Burg S, Cross RK. Psychosocial factors contributing to inflammatory bowel disease activity and health-related quality of life. *Gastroenterol Hepatol (N Y)*. 2012;8(3):173-181. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3365520&tool=pmcentrez&rendertype=abstract.

17. Porcelli P, Leoci C, Guerra V. A prospective study of the relationship between disease activity and psychological distress in patients with inflammatory bowel disease. *Scand J Gastroenterol*. 1996;Aug;31(8):792-796.

18. Mikocka-Walus A a., Turnbull D a., Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: A literature review. *Inflamm Bowel Dis*. 2007;13(2):225-234. doi:10.1002/ibd.20062.

19. Maunder RG, Levenstein S. The role of stress in the development and clinical course of inflammatory bowel disease: Epidemiological evidence. *Curr Mol Med*. 2008;8(May 2017):247-252. doi:10.2174/156652408784533832.

20. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Reprinted from Annals of Internal Medicine). *PLOS Med*. 2009;July 21;6(9). doi:10.1371/journal.pmed.1000097.

21. Schoultz M, Atherton I, Hubbard G, Watson AJ. Assessment of causal link between psychological factors and symptom exacerbation in inflammatory bowel disease: a protocol for systematic review of prospective cohort studies. *Syst Rev*. 2013;2(1):8. doi:10.1186/2046-4053-2-8.

22. Vernier–Massouille G, Balde M, Salleron J, et al. Natural History of Pediatric Crohn's Disease: A Population-Based Cohort Study. *Gastroenterology*. 2008;135(4):1106-1113. doi:10.1053/j.gastro.2008.06.079.

23. Walter JG, Kahn S a., Noe JD, Schurman J V., Miller S a., Greenley RN. Feeling Fine: Anxiety and depressive symptoms in youth with established IBD. *Inflamm Bowel Dis*. 2016;22(2):402-408. doi:10.1097/MIB.0000000000000657.

24. Reed-Knight B, Lobato D, Hagin S, et al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. *Inflamm Bowel Dis*. 2014;20(4):614-621. doi:10.1097/01.MIB.0000442678.62674.b7.

562 25. Teruel C, Garrido E, Mesonero F. Diagnosis and management of functional symptoms in
563 inflammatory bowel disease in remission. *World J Gastrointest Pharmacol Ther*. 2016;Feb
564 6;7(1):78-90. doi:10.4292/wjgpt.v7.i1.78.

565 26. Critical Appraisals Skills Program (CASP) - making sense of evidence: CASP tools and
566 checklists. http://www.casp-uk.net/#!checklists/cb36.

567 27. DerSimonian R, Laird N. Meta-Analysis in Clinical Trials. *Contemp Clin Trials*.
568 2015;45((00)):139-145.

569 28. Levenstein S, Prantera C, Varvo V, et al. Stress and exacerbation in ulcerative colitis: a
570 prospective study of patients enrolled in remission. *Am J Gastroenterol*. 2000;95(5):1213-
571 1220. doi:10.1111/j.1572-0241.2000.02012.x.

572 29. Bitton A, Sewitch MJ, Peppercorn MA, et al. Psychosocial determinants of relapse in
573 ulcerative colitis: a longitudinal study. *Am J Gastroenterol*. 2003;98(10):2203-2208.
574 doi:10.1016/S0002-9270(03)00750-0.

575 30. Langhorst J, Hofstetter A, Wolfe F, Häuser W. Short-term stress, but not mucosal healing nor
576 depression was predictive for the risk of relapse in patients with ulcerative colitis: a
577 prospective 12-month follow-up study. *Inflamm Bowel Dis*. 2013;19(11):2380-2386.
578 doi:10.1097/MIB.0b013e3182a192ba.

579 31. Mardini HE, Kip KE, Wilson JW. Crohn's Disease : A Two-Year Prospective Study of the
580 Association Between Psychological Distress and Disease Activity. *Dig Dis Sci*. 2004;49:492-
581 497.

582 32. Persoons P, Vermeire S, Demyttenaere K, et al. The impact of major depressive disorder on
583 the short- and long-term outcome of Crohn's disease treatment with infliximab. *Aliment*
584 *Pharmacol Ther*. 2005;22(2):101-110. doi:10.1111/j.1365-2036.2005.02535.x.

585 33. Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a
586 biopsychosocial model. *Gut*. 2008;57(10):1386-1392. doi:10.1136/gut.2007.134817.

587 34. Cámara RJ a, Schoepfer AM, Pittet V, Begré S, Von Känel R. Mood and nonmood components
588 of perceived stress and exacerbation of Crohn's disease. *Inflamm Bowel Dis*.
589 2011;17(11):2358-2365. doi:10.1002/ibd.21623.

590 35. North CS, Alpers DH, Helzer JE, Spitznagel EL, Clouse RE. Do life events or depression
591 exacerbate inflammatory bowel disease. *Ann Intern Med*. 1991;114:381-386.

592 36. Mittermaier C, Dejaco C, Waldhoer T, et al. Impact of Depressive Mood on Relapse in Patients
593 With Inflammatory Bowel Disease: A Prospective 18-Month Follow-Up Study. *Psychosom*
594 *Med*. 2004;66(1):79-84. doi:10.1097/01.PSY.0000106907.24881.F2.

595 37. Mikocka-Walus A a, Turnbull D a, Moulding NT, Wilson IG, Holtmann GJ, Andrews JM. Does
596 psychological status influence clinical outcomes in patients with inflammatory bowel disease
597 (IBD) and other chronic gastroenterological diseases: an observational cohort prospective
598 study. *Biopsychosoc Med*. 2008;2:11. doi:10.1186/1751-0759-2-11.

38. Mikocka-Walus A, Pittet V, Rossel J, von Känel R. Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2016;January(25):1542-3565. doi:10.1016/j.cgh.2015.12.045.

39. Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology*. 1994;July (107)(1):3-11.

40. Papi C, Festa V, Leandro G, et al. Long-term outcome of Crohn's disease following corticosteroid-induced remission. *Am J Gastroenterol*. 2007;102(4):814-819. doi:10.1111/j.1572-0241.2007.01055.x.

41. Bjelland I, Dahl A a, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. *J Psychosom Res*. 2002;52(2):69-77. doi:10.1016/S0022-3999(01)00296-3.

42. Yoshida EM. The Crohn's Disease Activity Index, its derivatives and the Inflammatory Bowel Disease Questionnaire: A review of instruments to assess Crohn's disease. *Can J Gastroenterol*. 1999;13(1):65-73.

43. Regueiro M, Kip KE, Schraut W, et al. Crohn's disease activity index does not correlate with endoscopic recurrence one year after ileocolonic resection. *Inflamm Bowel Dis*. 2011;17(1):118-126. doi:10.1002/ibd.21355.

44. Roy T, Lloyd CE, Pouwer F, Holt RIG, Sartorius N. Screening tools used for measuring depression among people with Type 1 and Type 2 diabetes: A systematic review. *Diabet Med*. 2012;29(2):164-175. doi:10.1111/j.1464-5491.2011.03401.x.

45. Remus JL, Dantzer R. Inflammation models of depression in rodents: relevance to psychotropic drug discovery. *Int J Neuropsychopharmacol*. 2016:pyw028. doi:10.1093/ijnp/pyw028.

46. Goodhand JR, Wahed M, Mawdsley JE, Farmer a D, Aziz Q, Rampton DS. Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. *Inflamm Bowel Dis*. 2012;18(12):2301-2309. doi:10.1002/ibd.22916.

47. Häuser W, Schmidt C, Stallmach A. Depression and mucosal proinflammatory cytokines are associated in patients with ulcerative colitis and pouchitis - A pilot study. *J Crohns Colitis*. 2011;5(4):350-353. doi:10.1016/j.crohns.2011.03.001.

48. Gaines LS, Slaughter JC, Horst SN, et al. Association Between Affective-Cognitive Symptoms of Depression and Exacerbation of Crohn's Disease. *Am J Gastroenterol*. 2016;111(6):864-870. doi:10.1038/ajg.2016.98.

49. Rathbun AM, Reed GW, Harrold LR. The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: A systematic review. *Rheumatol (United Kingdom)*. 2013;52(10):1785-1794. doi:10.1093/rheumatology/kes356.

50. Martindale J, Smith J, Sutton CJ, Grennan D, Goodacre L, Goodacre J a. Disease and psychological status in ankylosing spondylitis. *Rheumatology*. 2006;45(10):1288-1293. doi:10.1093/rheumatology/kel115.

637 51. Ward MM, Marx a S, Barry NN. Psychological distress and changes in the activity of systemic
638 lupus erythematosus. *Rheumatology*. 2002;41(2):184-188.

639 52. Guthrie E. Psychological disorder and severity of inflammatory bowel disease predict health-
640 related quality of life in ulcerative colitis and Crohn's disease. *Am J Gastroenterol*.
641 2002;97(8):1994-1999. doi:10.1016/S0002-9270(02)04198-9.

642 53. Sacre S, Medghalchi M, Gregory B, Brennan F, Williams R. Fluoxetine and citalopram exhibit
643 potent antiinflammatory activity in human and murine models of rheumatoid arthritis and
644 inhibit toll-like receptors. *Arthritis Rheum*. 2010;62(3):683-693. doi:10.1002/art.27304.

645 54. Goodhand JR, Greig FIS, Koodun Y, et al. Do antidepressants influence the disease course in
646 inflammatory bowel disease? A retrospective case-matched observational study. *Inflamm*
647 *Bowel Dis*. 2012;18(7):1232-1239. doi:10.1002/ibd.21846.

648 55. Mikocka-Walus A, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ.
649 Antidepressant and inflammatory bowel disease: a systematic review. *Clin Pract Epidemiol*
650 *Ment Heal*. 2006;2(15):1-8. doi:10.1186/1745-0179-2-Received.

651 56. Macer BJD, Prady SL, Mikocka-Walus A. Antidepressants in Inflammatory Bowel Disease.
652 *Inflamm Bowel Dis*. 2017;23(4):1. doi:10.1097/MIB.0000000000001059.

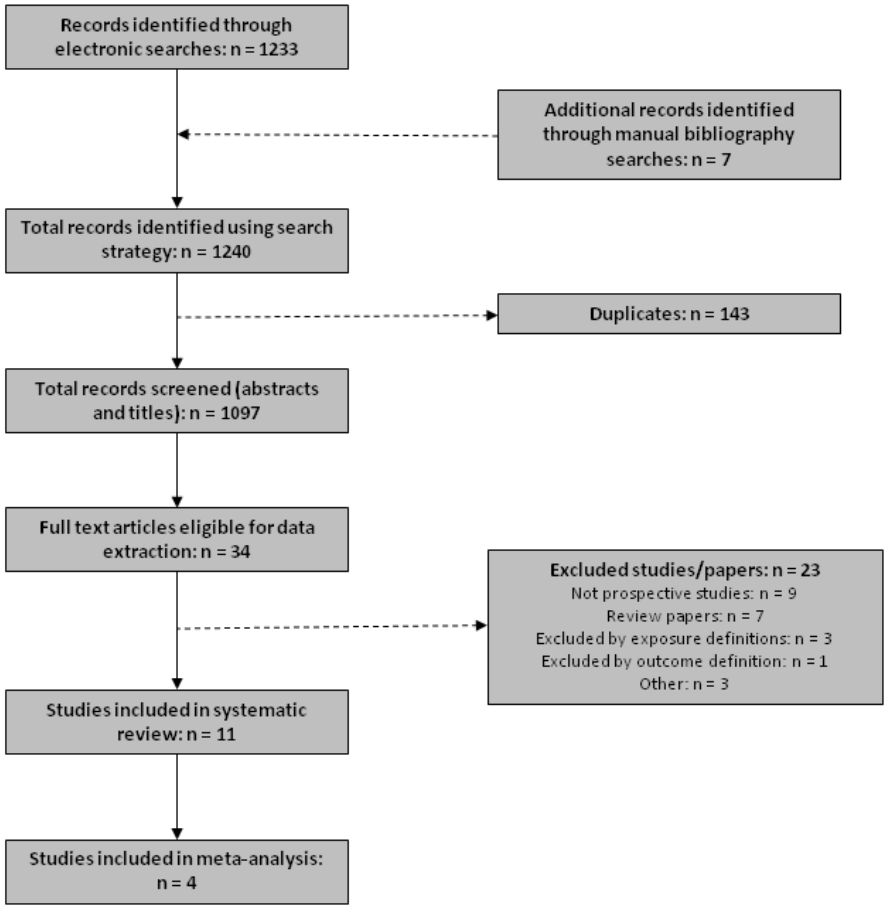
653 57. Gracie D, Irvine A, Sood R, Mikocka-Walus A, Hamlin P, Ford A. Effect of psychological therapy
654 on disease activity, psychological comorbidity, and quality of life in inflammatory bowel
655 disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(3):189-
656 199.

657 58. Andrews JM, Mikocka-Walus A. Antidepressants to maintain remission and improve quality of
658 like and mental health inCrohn's disease (CD) patients: a pilot randomized controlled trial The
659 Broad Medical Research Program; 2013.
660 http://www.broadmedical.org/funding/funded_grants/2013/SA_IBD-0352_Andrews.html.
661 Accessed October 14, 2014.

662 59. Mikocka-Walus A, Hughes P, Bampton P, et al. Fluoxetine for Maintenance of Remission and
663 to Improve Quality of Life in Patients with Crohn's Disease: a Pilot Randomized Placebo-
664 Controlled Trial. *J Crohns Colitis*. 2016;9(E-published ahead of print):TBA.

665 60. Häuser W, Moser G, Klose P, Mikocka-Walus A. Psychosocial issues in evidence-based
666 guidelines on inflammatory bowel diseases: A review. *World J Gastroenterol*.
667 2014;20(13):3663-3671. doi:10.3748/wjg.v20.i13.3663.

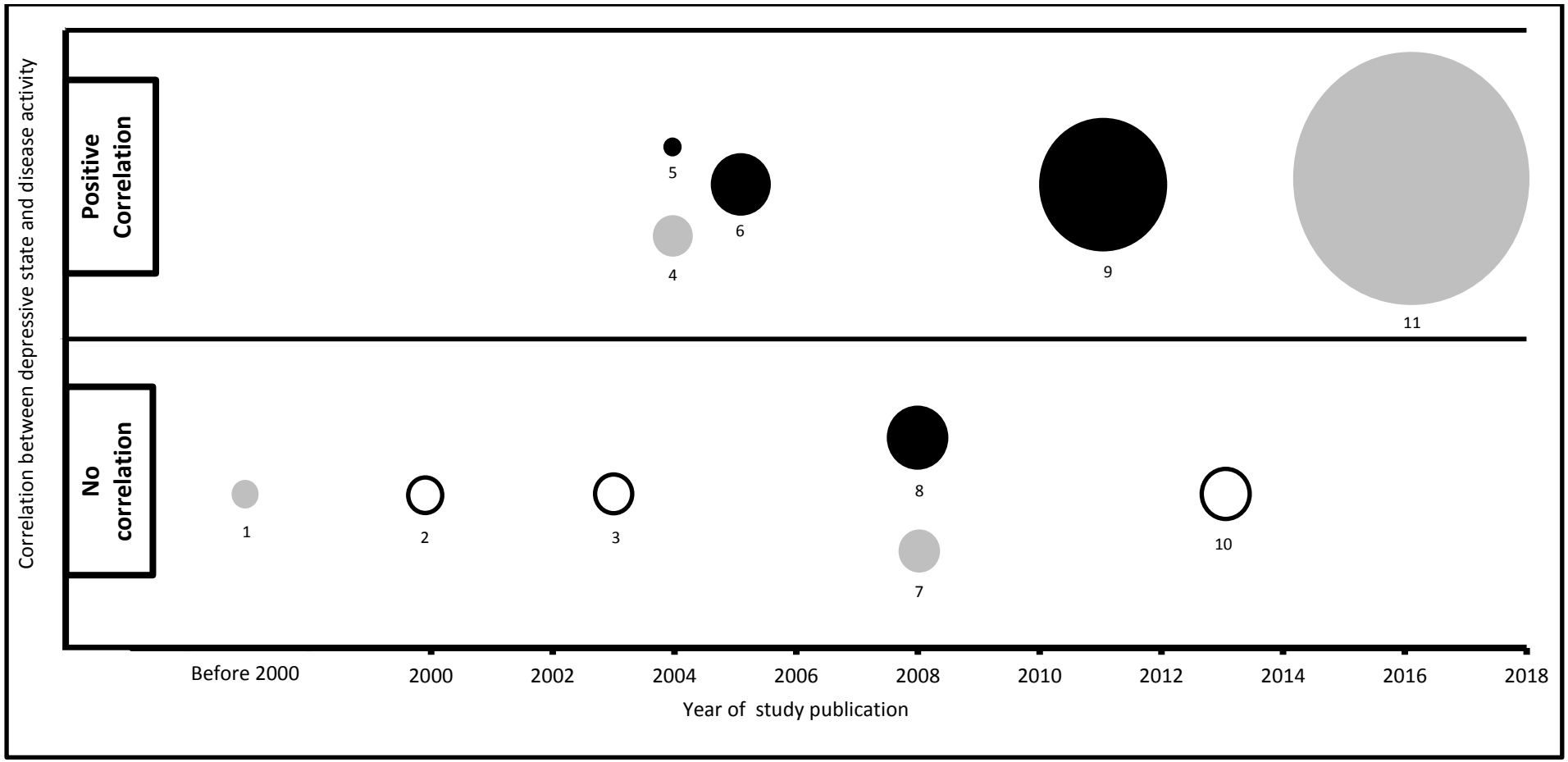
668



669

670 **Figure 1: schematic of systematic review methodology and study inclusion for qualitative and**
671 **quantitative analysis**

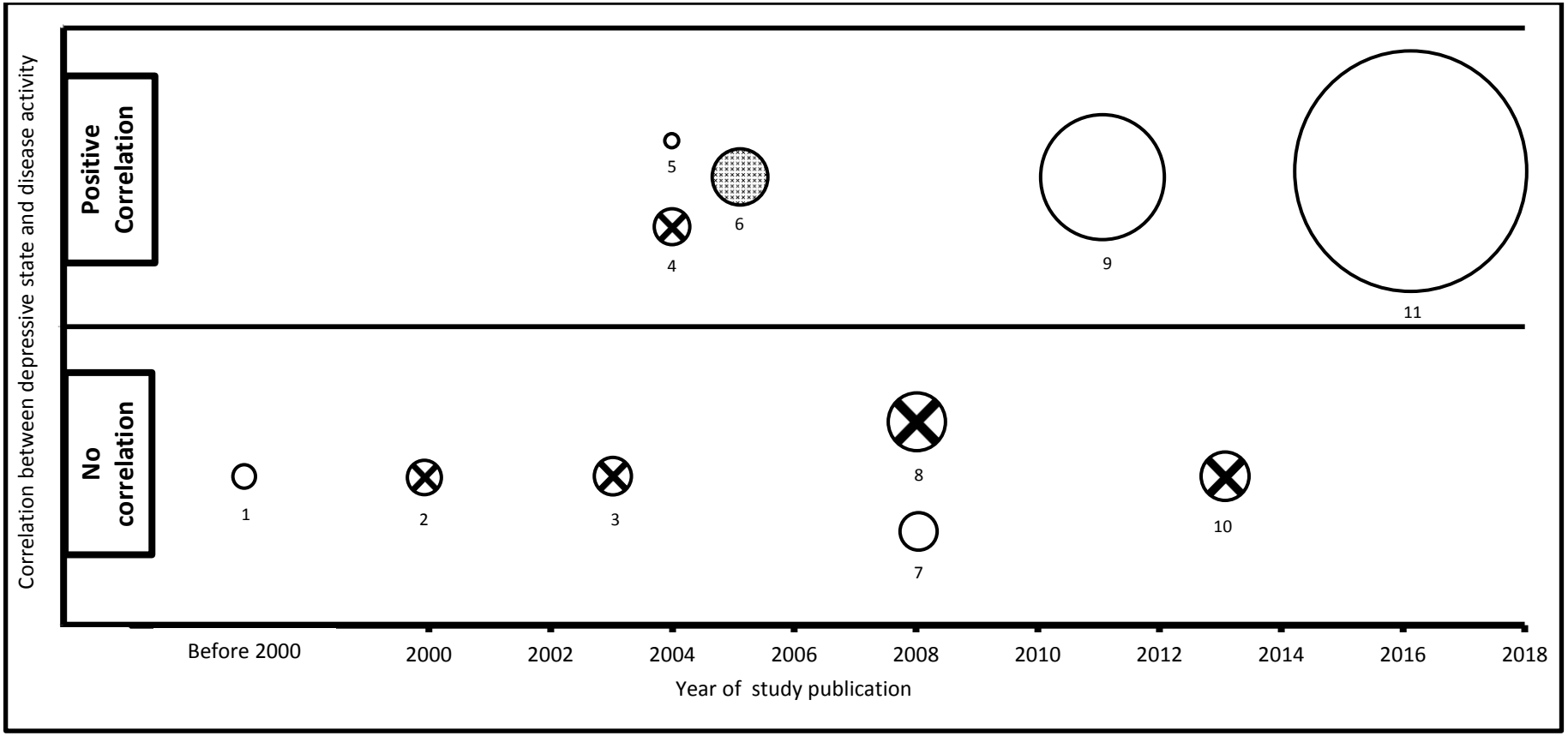
Figure 2: Bubble chart demonstrating studies and study size stratified by IBD disease sub-type dichotomising if they support or refute a correlation between depressive state and subsequent disease course in IBD



White circle - study including patients with ulcerative colitis (UC) only. Black circle - study including patients with Crohn's disease (CD) only. Grey circle - study including patients with UC and CD. Diameter of circles representative of study size. Exact study size given below:

1 - North *et al* 1991 (n=32), **2** - Levenstein *et al* 2000 (n=62), **3** - Bitton *et al* 2003 (n=60), **4** - Mittermeier *et al* 2004 (n=60), **5** - Mardini *et al* 2004 (n=18), **6** - Persoons *et al* 2005 (n=100), **7** - Mikocka-Walus *et al* 2008 (n=66), **8** - Bitton *et al* 2008 (n=101), **9** - Camara *et al* 2011 (n=597), **10** - Langhorst *et al* 2013 (n=91), **11** - Mikocka-Walus *et al* 2016(n=2007)

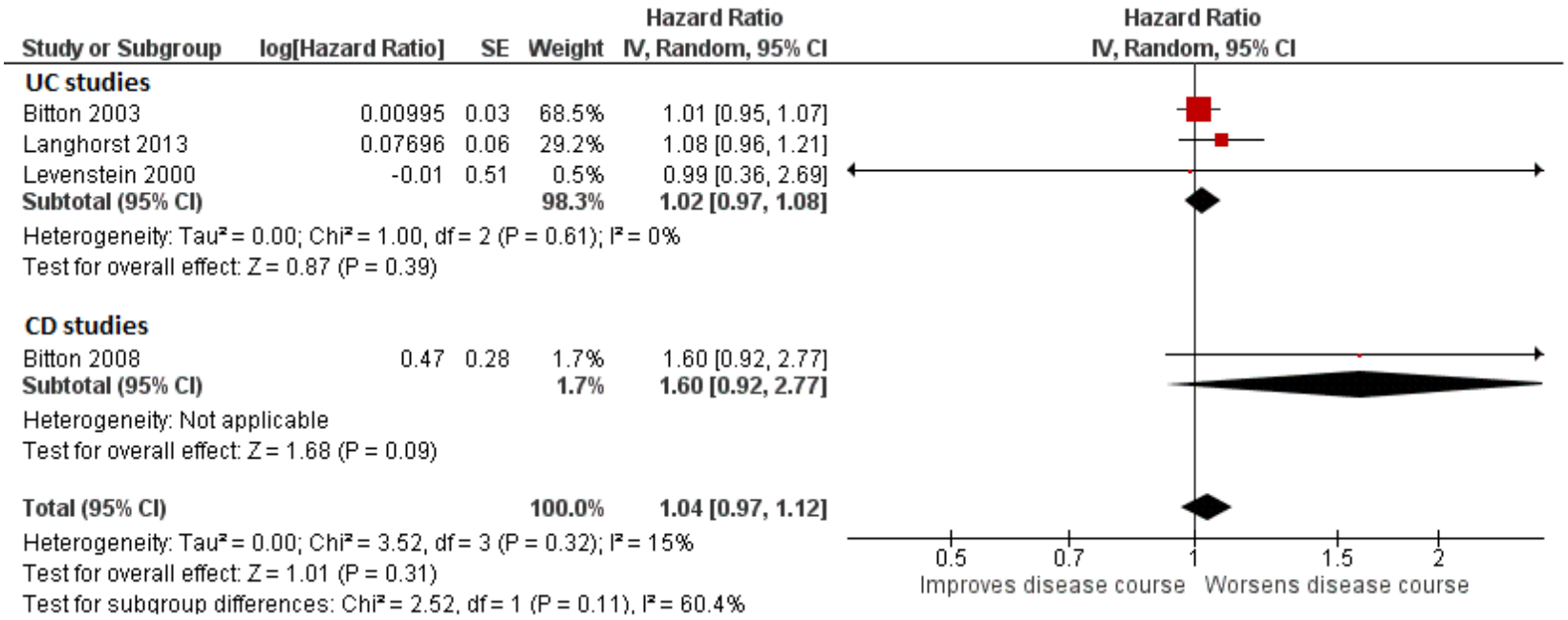
Figure 3: Bubble chart demonstrating studies and study size stratified by disease activity at study entry dichotomising if they support or refute a correlation between depressive state and subsequent disease course in IBD



Crossed circle - study including patients with IBD in remission at study entry. Empty circle - study including patients unselected for disease activity at study entry. Checked circle - study including patients with active disease at study entry. Diameter of circles representative of study size. Exact study size given below:

1 - North *et al* 1991 (n=32), **2** - Levenstein *et al* 2000 (n=62), **3** - Bitton *et al* 2003 (n=60), **4** - Mittermeier *et al* 2004 (n=60), **5** - Mardini *et al* 2004 (n=18), **6** - Persoons *et al* 2005 (n=100), **7** - Mikocka-Walus *et al* 2008 (n=66), **8** - Bitton *et al* 2008 (n=101), **9** - Camara *et al* 2011 (n=597), **10** - Langhorst *et al* 2013 (n=91), **11** - Mikocka-Walus *et al* 2016(n=2007)

Figure 4: quantitative analysis of the impact of a depressive state on disease course in patients with IBD who are in remission at baseline



Legend:

UC - ulcerative colitis

CD - Crohn's disease

SE - standard error

Section/topic	#	PRISMA 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.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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).	5,6,7
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.	7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,7,8
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.	7,8

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8, 9
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.	8, 9

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).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9,10
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.	29
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.	Supplementary tables 1-3
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).	Supplementary table 4
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.	32
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	32
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	32
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).	16,17
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).	18, 19

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-22
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.	23

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(7): e1000097. doi:10.1371/journal.pmed1000097