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1 **Title:** Systematic Review: Predicting the Development of Psychological  
2 Morbidity in Inflammatory Bowel Disease

3

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## 22 **ABSTRACT**

23 **Background:** Psychological morbidity in inflammatory bowel disease is common  
24 with significant impact on quality of life and health outcomes, but factors which  
25 predict the development of psychological morbidity are unclear.

26

27 **Aim:** To undertake a systematic literature review of the predictors of psychological  
28 morbidity in patients with inflammatory bowel disease.

29

30 **Methods:** Electronic searches for English-language articles were performed with  
31 keywords relating to psychological morbidity according to the Diagnostic and  
32 Statistical Manual of Mental Disorders IV and subsequent criteria, and inflammatory  
33 bowel disease; in MEDLINE, PsychInfo, Web of Science and EMBASE for studies  
34 published from January 1997 to the 25<sup>th</sup> January 2019.

35

36 **Results:** Of 660 studies identified, seven met the inclusion criteria. All measured  
37 depression, with three also measuring anxiety. Follow-up duration was variable  
38 (median of 18 months range 6 – 96 months). Risk factors identified for development  
39 of psychological morbidity included physical factors: aggressive disease [HR 5.77,  
40 95% CI = 1.89 – 17.7] and greater comorbidity burden [OR 4.31, 95% CI = 2.83 –  
41 6.57] and psychological risk factors: degree of gratitude [ $r = -0.43$ ,  $p < 0.01$ ] and  
42 parenting stress [ $R$ -change = 0.03,  $F(1,58) = 35.6$ ,  $p < 0.05$ ]. Age-specific risk were  
43 identified with young people (13 – 17 years) at increased risk.

44 **Conclusions:** Identifiable risks for the development of psychological morbidity in  
45 inflammatory bowel disease include physical and psychological factors. Further

46 research is required from large prospective studies to enable early interventions in  
47 those at risk and reduce the impact of psychological morbidity.

48

49 **Keywords:** inflammatory bowel disease, psychological morbidity, prediction

## 50 **INTRODUCTION**

51 Inflammatory bowel disease (IBD), encompassing both Crohn's disease (CD) and  
52 ulcerative colitis (UC) can present at any age but is most frequently diagnosed

53 during the second and third decades of life (1). Psychological morbidity is widely  
54 reported in patients with IBD (2–4) with prevalence rates as high as 50% (2), and is  
55 associated with failure to gain work and loss of employment (5,6), increased rates of  
56 sick leave (7), reduced work productivity (8) and increased utilisation of health  
57 services (9) including early rehospitalisation (10) thereby increasing the economic  
58 burden of IBD (11). Further data shows that patients with IBD and psychological  
59 morbidity such as depression, are at an increased risk for reduced treatment  
60 adherence (12) and poorer self-management behaviours including diet, exercise and  
61 smoking (13).

62

63 Systematic reviews (14–18) have highlighted the increased levels of psychological  
64 morbidity in IBD, but limited research exists to identify risk factors for future  
65 development of psychological morbidity in IBD. Those risk factors identified, such as  
66 increased disease severity (17,18), younger age at diagnosis and lower  
67 socioeconomic status (16) are derived predominantly from cross-sectional studies  
68 within the systematic reviews (range 89-93%) (14–16). Longitudinal studies are  
69 necessary to identify factors that are able to predict the development of  
70 psychological morbidity.

71

72 Prediction of future psychological morbidity in IBD patients is of importance to enable  
73 early intervention and improve patient outcomes. The aim of this systematic review is  
74 to examine the available evidence regarding factors which predict the development  
75 of psychological morbidity in people with IBD.

## 76 **REVIEW CRITERIA AND METHODOLOGY**

77 This systematic review was conducted according to the Preferred Reporting Items  
78 for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (19).

79

### 80 **Data Sources and Search Strategy**

81 A systematic literature search was undertaken using four relevant databases:  
82 Medline (via Ovid), EMBASE, Web of Science and PsychInfo (Scopus) aiming to  
83 capture all relevant studies across disciplines including psychology, psychiatry,  
84 paediatric and adult gastroenterology over a 20 year period. The date of the  
85 literature search was 25<sup>th</sup> of January 2019, with the search conducted from the 1<sup>st</sup>  
86 January 1997. Table 1 shows title, abstract and keyword search terms relating to  
87 “prediction”, “inflammatory bowel disease” and “psychological morbidity” as defined  
88 by the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition (20).  
89 Duplicate abstracts were eliminated.

90

### 91 **Study Eligibility and Selection Criteria**

92 Three authors (A.B.H, A.J.B, A.J.L) determined study eligibility to ensure reliability of  
93 the selection process. Studies were initially screened by the first author and  
94 decisions about study inclusion were made independently by all three authors.  
95 Concerns and disagreements were discussed and a final agreement was reached.

96

97 Abstracts were screened to assess whether they met the following inclusion criteria:

98 (i) published in full, in a peer-reviewed journal and written in English (ii) included

99 outcome measures pertaining to psychological distress at baseline and follow-up and

100 (iii) included extractable data on participants/patients with IBD diagnoses. Exclusion

101 criteria were (i) case studies or non-empirical studies (e.g. narrative reports, reviews)  
 102 (ii) studies showing associations at one time point rather than predicting the  
 103 development of psychological morbidity using follow-up data (iii) reviews, editorials  
 104 and conference abstracts (iv) intervention studies. Additional studies of interest were  
 105 searched for by hand in bibliographies and cited references of identified papers and  
 106 by consultation with clinical experts in the field. The flow chart of study selection can  
 107 be seen in Figure 1.

<b>Psychological morbidity terms</b>	<b>AND</b>	<b>Prediction terms</b>	<b>AND</b>	<b>IBD terms</b>
"Affective disorder" OR "Anxiety" OR "Depression" OR "Depressive" OR "Eating Disorder" OR "Mental disorder" OR "Mental health" OR "Mood disorder" OR "Personality disorder" OR "Psychological distress" OR "Psychotic" OR "Schizophren*" Or "Somatoform disorder"		"Forecast" OR "Forecasting" OR "Predict*" OR "Predictive method" OR "Projection" OR "Risk"		"Colitis" OR "Crohn's disease" OR "IBD" OR "Inflammatory bowel disease" OR "Ulcerative Colitis"
<i>Search limited to English-language articles</i>				

108

109

## 110 **Data Extraction**

111 Data extracted from the studies is outlined in the supplementary data and in Tables  
 112 2, 3a and 3b. Data included country of study, participant gender, age and diagnosis,  
 113 length of study follow up and study design, type of assessment for psychological  
 114 morbidity and type of analysis conducted. Retention rate was included where  
 115 relevant, and significant outcomes were recorded.

116

## 117 Quality Assessment

118 Both ABH and AJB conducted a formal assessment of study quality using the  
 119 GRADE system (21). Assessments were conducted individually and discrepancies  
 120 between coders were resolved through discussion.

121

## 122 RESULTS

123 Factors which predicted the development of psychological morbidity in patients with  
 124 IBD were categorised as: physical and psychological factors. Factors included in the  
 125 studies examined are summarised in Table 2, and the outcomes in Table 3a and 3b.

126

Study (reference)	Ananthkrishnan et al (22)	Gracie et al (23)	Guilfoyle et al (24)	Loftus et al (25)	Panara et al (26)	Sirois and Wood (27)	Trindade et al (28)
<b>Active Disease</b>		✓			✓		
<b>Severe Disease</b>	✓ for depression in CD (surgery within 3 years, immunomodulator use, stoma surgery, perianal disease)  ✓ for anxiety in UC (surgery within 3 years, stoma surgery, ≥ 2 surgeries)  X for UC				✓		
<b>Gender</b>	✓ female			✓ male	✓ female		
<b>Age</b>	✓ for anxiety in UC X for depression in UC and anxiety/depression in CD			✓	X		
<b>Comorbidity</b>	✓						
<b>Gratitude</b>						✓	
<b>Parenting Stress</b>			✓				
<b>Symptom Burden</b>							✓
✓ = Examined and found to be a significant predictor							

X = Examined but found not to be a significant predictor

127

<b>Table 3a. Physical Factors predictive of the development of psychological morbidity in people with inflammatory bowel disease</b>				
<b>Identified predictive factor</b>	<b>Study (reference), Country</b>	<b>Follow up duration</b>	<b>Significant outcomes</b>	<b>Non-significant outcomes</b>
<b>Active Disease</b>	Gracie et al (23), Germany	2 year minimum	Harvey Bradshaw Index or Simple Clinical Colitis Activity Index $\geq 5$ : Anxiety [HR = 5.77, 95% CI = 1.89 – 17.7, p = 0.03]	Baseline disease activity and development of depression p = 0.89
	Panara et al (26), USA	8 years (S.D 3.8)	Endoscopic and radiological assessment: Depression [HR = 1.5, 95% CI = 1.1 – 2.0, p = 0.04]	N/A
<b>Severe Disease</b>	Ananthakrishnan et al (22), USA	1, 2 and 5 years	Immunomodulator use: Crohn's disease depression [OR = 1.5, 95% CI = 1.03 – 2.38]  Perianal Disease: Crohn's disease depression [OR = 1.64, 95% CI = 1.01 – 2.69]  Stoma surgery: Crohn's disease anxiety [OR = 1.73, 95% CI = 1.05 – 2.85]  Crohn's disease depression [OR = 1.90, 95% CI = 1.15 – 3.13]  Surgery $\leq 3$ years of diagnosis: Crohn's disease anxiety [OR = 2.19, 95% CI = 1.44 – 3.33] Crohn's disease depression [OR = 1.54, 95% CI = 1.01 – 2.37]  $\leq 2$ Surgeries: Crohn's disease anxiety [OR = 1.79, 95% CI = 1.09 – 2.93]	Immunomodulator use: Ulcerative colitis depression Ulcerative colitis anxiety Crohn's disease anxiety  Perianal disease: Ulcerative colitis depression Ulcerative colitis anxiety Crohn's disease anxiety  Stoma surgery: Ulcerative colitis depression Ulcerative colitis anxiety  Surgery $\leq 3$ years diagnosis: Ulcerative colitis depression Ulcerative colitis anxiety  $\leq 2$ Surgeries: Ulcerative colitis depression Ulcerative colitis anxiety Crohn's disease depression
	Panara et al (26), USA	8 years (S.D 3.8)	Aggressive disease: Depression [HR = 1.4, 95% CI = 1.02 – 1.9, p = 0.03]	Use of mesalazine: Depression [HR 0.83, 95% CI = 0.64 – 1.07, p = 0.16]  Perianal disease: Depression [HR 1.2, 95% CI 0.89 – 1.62, p = 0.24]  History of IBD surgery: Depression [HR 1.3, 95% CI = 0.92 – 1.76, p = 0.13]
<b>Age</b>	Ananthakrishnan et al (22), USA	1, 2 and 5 years	Age per 1 year: Ulcerative colitis anxiety [OR = 0.98, 95% CI = 0.91 – 1.00]	Age per 1 year: Ulcerative colitis depression Crohn's disease anxiety Crohn's disease depression

	Loftus et al (25), USA	≥6 months	Girls 13 – 17: Anxiety [HR = 2.45, 95% CI = 1.41 – 4.25, p = 0.0014]  Boys 0 – 12: Depression [HR = 2.55, 95% CI = 1.15 – 5.67, p = 0.0216]  Boys 13 – 17: Depression [HR = 1.99, 95% CI = 1.32 – 3.02, p = 0.0011] Anxiety [HR = 3.01, 95% CI = 1.73 – 5.24, p < 0.0001]	Girls 0 – 12: Depression [HR 2.24, 95% CI = 0.95 – 5.31, p = 0.0665] Anxiety [HR 1.48, 95% CI = 0.56 – 3.88, p = 0.427]  Girls 13 – 17: Depression [HR 1.30, 95% CI = 0.87 – 1.95, p = 0.2028]  Boys 0 -12: Anxiety [HR 1.60, 95% CI = 0.68 – 3.75, p = 0.2776]
	Panara et al (26), USA	8 years (S.D 3.8)	N/A	Age ≥40 years: Depression [HR = 1.3, 95% CI = 0.88 – 1.82, p = 0.18]
<b>Comorbidity</b>	Ananthakrishnan (22), USA	1,2 and 5 years	Charlson Score ≥3: Crohn's disease anxiety [OR = 1.84, 95% CI = 1.44 – 3.33] Ulcerative colitis anxiety [OR = 3.26, 95% CI = 1.98 – 5.38] Crohn's disease depression [OR = 4.31, 95% CI = 2.82 – 6.57] Ulcerative colitis depression [OR = 3.73, 95% CI = 2.33 – 5.97]	N/A
<b>Gender</b>	Ananthakrishnan et al (22), USA	1,2 and 5 years	Female Gender: Crohn's disease depression [OR = 1.77, 95% CI = 1.16 – 2.71] Ulcerative colitis depression [OR = 2.92, 95% CI = 1.80 – 4.76] Crohn's disease anxiety [OR = 2.07, 95% CI = 1.35 – 3.19] Ulcerative colitis anxiety [OR = 1.84, 95% CI = 1.18 – 2.87]	N/A
	Loftus et al (25), USA	≥6 months	Girls 13 – 17: Anxiety [HR = 2.45, 95% CI = 1.41 – 4.25]  Boys 0 – 12: Depression [HR = 2.55, 95% CI = 1.15 – 5.67]  Boys 13 – 17: Depression [HR = 1.99, 95% CI = 1.32 – 3.02] Anxiety [HR = 3.01, 95% CI = 1.73 – 5.24]	Girls 0 – 12: Depression [HR 2.24, 95% CI = 0.95 – 5.31, p = 0.0665] Anxiety [HR 1.48, 95% CI = 0.56 – 3.88, p = 0.427]  Girls 13 – 17: Depression [HR 1.30, 95% CI = 0.87 – 1.95, p = 0.2028]  Boys 0 -12: Anxiety [HR 1.60, 95% CI = 0.68 – 3.75, p = 0.2776]
	Panara et al (26), USA	8 years (S.D 3.8)	Female Gender: Depression [HR = 1.3, 95% CI = 1.1 – 1.7, p = 0.01]	N/A

**Table 3b.** Psychological factors predictive of the development of psychosocial morbidity in people with inflammatory bowel disease

Identified predictive factor	Study (reference), Country	Follow up duration	Significant outcomes	Non-significant outcomes
<b>Gratitude</b>	Sirois and Wood (27), USA and Canada	6 months	Depression [ $r = -0.43$ , $p < 0.01$ ]	N/A
<b>Parenting Stress</b>	Guilfoyle et al (24), USA	6 months	Depression [R-change = 0.03, $F(1,58) = 35.6$ , $p < 0.05$ ]	N/A
<b>Symptomatology</b>	Trindade et al (28), Portugal	18 months	Symptomatology: $r = 0.25$ , $p < 0.01$	N/A

129

### 130 Study Characteristics

131 Seven studies were identified (see Fig 1), five in adult cohorts and two in paediatric  
 132 cohorts, specifically 13 – 17 years (24) and <18 years (25). Of these, five were  
 133 undertaken in the United States (22,24–27), of which one also recruited from  
 134 Canada (27). Two studies were undertaken in Europe (23,28). The median number  
 135 of participants was 427 (range 93 – 12864), female predominance (median 57.2%,  
 136 range 43.0% - 88.1%), median age 43 years (range 15.5 – 48 years), with an IBD  
 137 type of 30.2% UC and 68.8% CD was evident. The median longitudinal follow-up  
 138 was 18 months (range 6 – 96 months), with a median reported retention rate at  
 139 follow-up of 55.8% (range 33.7 – 69.8%).

140

### 141 Assessment of Psychological Morbidity

142 Three studies assessed the development of both anxiety and depression. Two of  
 143 these used the International Classification of Diseases (ICD-9) (22,25) and one used  
 144 the Hospital Anxiety and Depression Scale (HADS) (23). The remaining studies  
 145 assessed the development of depression only, with all applying different measures  
 146 (24,26–28).

147

## 148 **Statistical Analysis**

149 Regression models were the most commonly utilised statistical method (n = 6) (22–  
150 27), one study used a cross-lagged panel analysis (28).

151

## 152 **GRADE Assessment**

153 Of the seven studies, three were graded as low, three moderate and one as high  
154 quality.

155

## 156 **Physical Factors Predicting Psychological Morbidity**

### 157 **Active Disease**

158 Physical factors shown to be predictive of psychological morbidity include disease  
159 activity (23,26). Gracie et al found that higher disease activity at baseline was  
160 predictive of the development of anxiety after a two-year follow-up period [HR 5.77,  
161 95% CI = 1.89 – 17.7, p = 0.03] (23). This study defined active disease using a  
162 Harvey-Bradshaw Index or Simple Clinical Colitis Activity Index of  $\geq 5$  for CD and UC  
163 respectively (23). The prevalence of depression in this study was too low to allow  
164 conclusions to be drawn regarding the factors predicting its development. Panara et  
165 al identified that depression was predicted by endoscopic and radiological disease  
166 activity [HR 1.5, 95% CI = 1.1– 2.0, p = 0.04] (26) Endoscopic disease activity was  
167 defined as the presence of any inflammatory changes in the GI mucosa due to the  
168 patient's IBD (26). Radiological disease activity was defined as the presence of any  
169 abnormal findings in cross-sectional imaging secondary to the patient's IBD,  
170 including strictures, tract inflammation and pelvic collections (26).

171

**172 Severe Disease**

173 Panara et al defined aggressive disease as prior or current surgery for IBD, the use  
174 of one or more biologic drugs at any time during the disease course or perianal  
175 involvement and/or fistulating disease (26). They identified patients with this  
176 composite endpoint as being at increased risk of developing depression [HR 1.4,  
177 95% CI = 1.02 – 1.9, p = 0.03] at a mean follow-up of 8 years. Importantly none of  
178 the individual factors were independently predictive of development of depression  
179 after multivariate analysis.

180

181 Ananthakrishnan et al examined factors predicting psychological morbidity in  
182 patients who had undergone bowel resection or required hospitalisation, rather than  
183 in the general IBD population (22). CD patients who underwent stoma surgery were  
184 at approximately twofold increased risk of developing depression [adjusted OR 1.90,  
185 95% CI = 1.15 – 3.13]. In terms of potential markers of disease severity,  
186 immunomodulator use was associated with an increased risk of developing  
187 depression [adjusted OR 1.56, 95% CI 1.03 – 2.38] for CD. UC patients who  
188 underwent surgery within 3 years from initial diagnosis had more than a twofold  
189 increased risk of developing anxiety [adjusted OR 2.19, 95% CI = 1.44 – 3.33], with  
190 stoma surgery associated with an adjusted OR of 1.73, 95% CI = 1.05 – 2.85.  
191 However, these factors were not significantly predictive of the development of  
192 psychological morbidity in ulcerative colitis when multivariate analysis was performed  
193 (22).

194

**195 Age**

196 The relationship between age and development of psychological morbidity is  
197 complex. Two studies identified age as a potential predictive factor for the  
198 development of psychological morbidity (22,25), whilst another did not find a  
199 significant relationship (26). Ananthakrishnan et al found that older age at time of  
200 surgery was predictive of developing anxiety in UC [OR 0.98, 95% CI = 0.97 - 1.00]  
201 (22). However, the authors also found that older age was not significantly predictive  
202 of the development of depression in UC, nor was it significantly predictive of either  
203 anxiety or depression in CD (22). In a study of patients <18 years old, Loftus et al  
204 found when age and sex stratified subgroups were studied, patients with current CD  
205 were at increased risk of developing psychological morbidity at follow up (at least 6  
206 months) compared to non-CD controls (25).

207

## 208 **Gender**

209 Two studies concluded that female gender was predictive of the development of  
210 psychological morbidity (22,26) and one found male gender to be more predictive  
211 (25). Ananthakrishnan et al found that female gender was predictive of depression in  
212 both CD [OR = 1.77; 95% CI = 1.16 – 2.71] and UC [OR = 2.29; 95% CI 1.80 – 4.76]  
213 following IBD surgery (22). Female gender was also identified as predictive of  
214 depression in a general IBD cohort [HR 1.3, 95% CI: 1.1 – 1.7] in a study by Panara  
215 et al (26).

216

217 In a study of young patients, Loftus et al stratified according to age and  
218 demonstrated that males with CD have greater risk of psychological morbidity than  
219 their female contemporaries (25). Although adolescent (age range 13 - 17 years)  
220 females were at a twofold increased risk of anxiety disorders [HR 2.45; 95% CI: 1.41

221 – 4.25] compared to non-CD controls, adolescent males were at even higher risk  
222 [HR 3.01, 95% CI = 1.73 – 5.24] compared to their peers (25). Within the same  
223 adolescent age group, females were significantly more likely to develop depression  
224 than their peers [HR = 1.74, 95% CI = 1.35 – 2.25] but were slightly less likely to do  
225 so than males of the same age as compared to controls [HR = 1.99, 95% CI = 1.32 –  
226 3.02] (25).

## 227 **Comorbidity**

228 Comorbidity, defined as the presence of one or more additional disorders or  
229 diseases occurring alongside the primary disease, is predictive of the development  
230 of psychological morbidity after IBD-related surgery (22). Comorbidity was quantified  
231 using the Charlson Index which gives a score based on the number of coexisting  
232 medical conditions, identified using the International Classification of Diseases IX  
233 definitions for any non-IBD medical condition (29). A score of  $\geq 3$  was predictive of  
234 developing both anxiety and depression across IBD. Patients with CD and a  
235 Charlson Score  $\geq 3$  had greater than a fourfold increased risk of developing  
236 depression after surgery for IBD [OR 4.31, 95% CI = 2.83 – 6.57] and almost a  
237 twofold increased incidence of developing anxiety [OR 1.84, 95% CI = 1.19 – 2.84]  
238 (22). Similarly, patients with UC and comorbidities were at more than a threefold  
239 increased risk of developing both depression [OR 3.37, 95% CI = 2.33 – 5.97] and  
240 anxiety [OR 3.26, 95% CI = 1.98 – 5.38] (22).

241

## 242 **Psychological Factors**

### 243 **Gratitude**

244 Sirois and Wood showed that IBD patients with higher levels of gratitude at baseline  
245 were less likely to develop depressive symptoms after 6 months than those with  
246 lower levels at baseline [ $r = -0.43$ ,  $p < 0.01$ ] (27). Gratitude was defined as 'a life  
247 orientation toward noticing the positive in life, including both thankfulness to others  
248 and a wider sense of appreciation for what one has' (27,30).

249

### 250 **Parenting Stress**

251 Guilfoyle et al identified parenting stress as predictive of the development of  
252 depressive symptoms in adolescents with IBD after a 6 month follow-up period [R-  
253 change = 0.03,  $F(1,58) = 35.6$ ,  $p < 0.05$ ] (24). Baseline parenting stress was  
254 quantified by the frequency and severity of illness-related parenting stress across  
255 four factors (communication, medical care, role functioning and emotional  
256 functioning) (24).

257

### 258 **Symptom Burden**

259 Trindade et al reported that a higher burden of IBD symptomatology predicted the  
260 development of depressed mood [ $r = 0.25$ ,  $p < 0.01$ ] (28). After an 18-month follow  
261 up, the relationship between symptomatology and development of depressed mood  
262 appeared to be regulated by two factors: 'cognitive fusion' (a maladaptive process  
263 that refers to the relationship a person has with his/her own cognitive events); and  
264 'brooding' (a passive comparison of one's current situation with some unachieved  
265 standard) (28).

## 266 DISCUSSION

267 This review has identified a range of physical and psychological factors - including  
268 active or severe disease, medical comorbidity, gratitude and parenting stress - that  
269 may predict the development of psychological morbidity in patients with IBD. Age  
270 and gender specific risks have also been identified, but the relationship is more  
271 complex.

272

273 The ability to identify risk of future development of psychological morbidity in patients  
274 with IBD is important but the evidence in this field is limited. Data is limited by  
275 methodological and design inconsistencies including duration of follow-up and  
276 definitions of psychological morbidity as well as over-representation of patients from  
277 developed countries. The majority of data in the current studies relates to potential  
278 predictive factors derived from cross-sectional studies for which there is a strong  
279 literature base e.g. gender, age, treatment related factors and previous surgery (14–  
280 18). Such factors are reported individually rather than as a set of factors that might  
281 have complex relationships and interact to create different levels of risk for the  
282 development of psychological morbidity. Two studies in this review have attempted  
283 to combine factors to create a composite end-point of severe disease, but use  
284 different factors in their analysis (22,26). Future longitudinal multi-centre studies are  
285 needed to enable modelling of multiple factors in to an algorithm to enable a  
286 psychological morbidity risk score to be obtained.

287

288 The age of patients with IBD may be important in the prediction of psychological  
289 morbidity, with young people identified as at increased risk in this review, supporting  
290 findings in previous research (31). Despite American and European guidelines (32–

291 34), only 12% of adult IBD services (35), compared to 67% of paediatric centres (36)  
292 provide access to a specialist psychologist. Failing to employ a preventative, rather  
293 than reactive, approach to psychological well-being in adult IBD populations (37) is  
294 likely to impact negatively on health risk behaviours and self-management  
295 behaviours, with subsequent costs including from work impairment (38). Young  
296 people transitioning to adult care are also an at-risk group and may require further  
297 psychological assessment and screening of psychological morbidity with the known  
298 increased prevalence of depression through puberty (16). Furthermore, gender-  
299 specific risks observed are in line with cross-sectional studies that identify adverse  
300 mental health outcomes in a general population of females (39–41).

301

302 This review has highlighted the important relationship between physical and mental  
303 health. More aggressive disease behaviour, comorbidities, and disease activity all  
304 increase the risk of developing psychological morbidity in IBD cohorts (22–27). The  
305 definition of aggressive disease behaviour in the paper by Panara included use of  
306 biologics medication. It is likely that the threshold for such treatment may vary across  
307 centres or over time but – together with the other measures used (need for surgery  
308 and perianal disease) – would reasonably be regarded as a marker of a more  
309 aggressive disease course. The relationship between psychological morbidity,  
310 particularly depression, and IBD is complex, but it is imperative that clinicians  
311 recognise the bidirectional relationship between the two (23). Rates of adherence to  
312 medication are lower in patients with depression (12) and mood can also impact on  
313 response to treatment, with the presence of major depressive disorder at baseline  
314 lowering remission rates significantly (42). Targeting these at risk patients, before  
315 they develop psychological morbidity, would help clinicians deliver the most effective

316 care as well as avoiding complications encountered from lack of adherence to  
317 medication.

318

319 Psychological factors are also important when predicting the development of  
320 psychological morbidity with higher levels of gratitude protecting against developing  
321 psychological morbidity (27). Those with lower levels of gratitude might benefit from  
322 a psychological intervention, such as a mindfulness based stress reduction or a  
323 positive psychology gratitude intervention (43), when diagnosed with IBD. Parenting  
324 stress has been noted in other situations including in parents of children with  
325 paediatric cancer (44). Interventions including Cognitive Behavioural Therapy or  
326 Mindful Parenting (45) may help parents with methods of coping and reduce their  
327 distress (44,46,47).

328

329 In conclusion, this systematic review demonstrates psychological morbidity in IBD  
330 may be predicted by both physical and psychological factors. However, disease  
331 activity and behaviour may be the only factor with a consistent relationship to the  
332 development of future anxiety and depression. Further longitudinal data from large  
333 IBD cohorts are required to determine whether other well-described associations are  
334 predictive factors. Development of a valid predictive tool for psychological morbidity  
335 in IBD would benefit patients and health care professionals and could improve  
336 efficiency and reduce the cost of health care for patients with IBD.

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339

### 340 **Author Contributions**

341 ABH reviewed the literature and prepared the manuscript. AJL, AJB, ABH reviewed  
342 study eligibility and designed the study. ABH, AJL, AJB, GR prepared the final  
343 version of the manuscript. All authors approved the final version of the manuscript.

344

### 345 **Conflicts of Interest**

346 Professor Alan Lobo: Speaker fees, Consultancy or Advisory Board member for  
347 MSD, Abbvie, Pfizer, Janssen, Takeda UK, Vifor Pharma, Shield Therapeutics and  
348 Medtronic.

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350 Dr Alenka Brooks: Speaker fees, Janssen.

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352 For the remaining authors no conflicts of interest are declared.

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