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

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ABSTRACT

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

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

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

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

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

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

Keywords: inflammatory bowel disease, psychological morbidity, prediction

INTRODUCTION

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

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

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

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

REVIEW CRITERIA AND METHODOLOGY

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

Data Sources and Search Strategy

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

Study Eligibility and Selection Criteria

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

Abstracts were screened to assess whether they met the following inclusion criteria: (i) published in full, in a peer-reviewed journal and written in English (ii) included outcome measures pertaining to psychological distress at baseline and follow-up and (iii) included extractable data on participants/patients with IBD diagnoses. Exclusion

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

Table 1. Search Terms for Systematic Review

Psychological morbidity terms	**AND**	**Prediction terms**	**AND**	**IBD terms**
"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"
Search limited to English-language articles				

Data Extraction

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

Quality Assessment

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

RESULTS

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

Table 2. Factors examined for their value in predicting the development of psychological morbidity in people with IBD.

Study (reference)	**Ananthakrishnan 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)
Active Disease		✓			✓		
Severe Disease	✓ 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				✓		
Gender	✓ female			✓ male	✓ female		
Age	✓ for anxiety in UC X for depression in UC and anxiety/depression in CD			✓	X		
Comorbidity	✓						
Gratitude						✓	
Parenting Stress			✓				
Symptom Burden							✓
✓ = Examined and found to be a significant predictor							

X = Examined but found not to be a significant predictor

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Table 3a. Physical Factors predictive of the development of psychological morbidity in people with inflammatory bowel disease

Identified predictive factor	Study (reference), Country	Follow up duration	Significant outcomes	Non-significant outcomes
Active Disease	Gracie et al (23), Germany	2 year minimum	Harvey Bradshaw Index or Simple Clinical Colitis Activity Index ≥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
Severe Disease	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 ≤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] ≤2 Surgeries: Crohn's disease anxiety [OR = 1.79, 95% CI = 1.09 – 2.93]	Immunmodulator use: Ulcerative colits 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 ≤3 years diagnosis: Ulcerative colitis depression Ulcerative colitis anxiety ≤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]
Age	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]
Comorbidity	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
Gender	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
Gratitude	Sirois and Wood (27), USA and Canada	6 months	Depression [r = -0.43, p < 0.01]	N/A
Parenting Stress	Guilfoyle et al (24), USA	6 months	Depression [R-change = 0.03, F(1,58) = 35.6, p < 0.05]	N/A
Symptomatology	Trindade et al (28), Portugal	18 months	Symptomatology: r = 0.25, p < 0.01	N/A

Study Characteristics

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

Assessment of Psychological Morbidity

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

Statistical Analysis

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

GRADE Assessment

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

Physical Factors Predicting Psychological Morbidity

Active Disease

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

Severe Disease

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

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

Age

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

Gender

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

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

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

Comorbidity

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

Psychological Factors

Gratitude

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

Parenting Stress

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

Symptom Burden

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

DISCUSSION

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

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

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

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

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

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

Conflicts of Interest

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

Dr Alenka Brooks: Speaker fees, Janssen.

For the remaining authors no conflicts of interest are declared.

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