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# **Systematic Review: Psychological Morbidity in Young People with Inflammatory Bowel Disease - Risk Factors and Impacts**

Short title: Systematic Review: Psychological Morbidity in IBD

Keywords: inflammatory bowel disease, paediatric gastroenterology, psychiatric disorders, Crohn's disease, Ulcerative colitis

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## ABSTRACT

**Background:** Psychological morbidity in young people aged 10-24 years, with inflammatory bowel disease (IBD) is increased, but risk factors for and impact of this are unclear.

**Aim:** To undertake a systematic literature review of the risk factors for and impact of psychological morbidity in young people with IBD.

**Methods:** Electronic searches for English-language articles were performed with keywords relating to psychological morbidity according to DSM-IV and subsequent criteria; young people; and IBD in the MEDLINE, PsychInfo, Web of Science and CINAHL databases for studies published from 1994-September 2014.

**Results:** 1444 studies were identified, of which 30 met the inclusion criteria. The majority measured depression and anxiety symptoms, with a small proportion examining externalising behaviours. Identifiable risk factors for psychological morbidity included: increased disease severity ( $r^2=0.152$ ,  $P < 0.001$ ), lower socioeconomic status ( $r^2=0.046$ ,  $P < 0.001$ ), corticosteroids ( $P \leq 0.001$ ), parental stress ( $r=0.35$ ,  $P < 0.001$ ) and older age at diagnosis ( $r=0.28$ ,  $P=0.0006$ ). Impacts of psychological morbidity in young people with IBD were wide-ranging and included abdominal pain ( $r=0.33$ ;  $P < 0.001$ ), sleep dysfunction ( $P < 0.05$ ), psychotropic drug use (HR 4.16, 95% CI 2.76-6.27), non-adherence to medication (12.6% reduction), and negative illness perceptions ( $r= -0.43$ ).

**Conclusions:** Psychological morbidity affects young people with IBD in a range of ways, highlighting the need for psychological interventions to improve outcomes. Identified risk factors provide an opportunity to develop targeted therapies for a vulnerable group.

Further research is **required to examine** groups under-represented in this review, such as those with severe IBD and **those** from ethnic minorities.

## **INTRODUCTION**

Inflammatory Bowel Disease, including both Crohn's Disease and Ulcerative Colitis **affects an estimated 1.5million people in North America, 2.2 million people in Europe and several hundred thousand more worldwide** with a globally rising incidence in children and young people (1–3). Around 20-30% of **inflammatory bowel disease** presents in childhood (4) with a peak onset in adolescence (1) and with a younger age at presentation being a risk factor for poor disease prognosis (5). Young people living with **inflammatory bowel disease** face a range of issues and challenges that can represent a major psychosocial burden leading to a loss of self-esteem and self-confidence, poorer quality of life, and heightened levels of psychological distress (6). Adolescents with **inflammatory bowel disease** have been estimated to be **at 4.6 fold increased risk of** clinically significant symptoms of anxiety or depression than healthy peers (7). **Inflammatory bowel disease** has also been demonstrated to have a detrimental impact on young people's education, employment and relationships (8,9). Cognitive behavioural therapy has been demonstrated to improve mood and quality of life in adolescents with IBD and subsyndromal depression (10). **European guidelines recommend that patients with inflammatory bowel disease are screened for anxiety, depression and if indicated refer for psychotherapeutic interventions (11,12). A recent worldwide survey of health care professionals caring for inflammatory bowel disease**

patients perceive that mental health assessment should be standard IBD care (13).

However, a defined pathway for referral is available in only 12% of UK adult inflammatory bowel disease centres, to which young people transition from the age of 16, compared to two-thirds in paediatric care (14), and as a result psychological morbidity is frequently untreated in inflammatory bowel disease (15).

Two reviews have examined aspects of psychological functioning and adjustment in young people with inflammatory bowel disease. Greenley et al. (16) examined psychosocial adjustment of young people ( $\leq 18$  years) with inflammatory bowel disease. The review, which included only studies with a comparison group or those where published normative data was available, found that subjects with inflammatory bowel disease had higher rates of depressive disorders and internalising conditions compared to other chronic conditions such as cystic fibrosis, diabetes and malignancy. Ross et al. (17) found an increased incidence of psychiatric disorders (anxiety and depression) using standard diagnostic interviews in young people ( $\leq 18$  years) with IBD. However, identifying psychological morbidity in young people with inflammatory bowel disease is difficult due to the overlapping nature of symptoms which may be related to organic disease, adverse effects of medications or due to psychological morbidity (18).

Furthermore, difficulties arise because studies and reviews classify young people according to differing age groups, with studies examining paediatric populations (<16 years), 'youth' (<18 years) or 'adults' (>18 years). The World Health Organisation

defines adolescence as the developmental stage between 10-19 years, and youth as 15-24 years. In addition, classification, prevalence and incidence of psychological distress are difficult to define (16,19) due to lack of consistent use of diagnostic criteria of DSM-IV (20) in research settings. In line with **World Health Organisation** recommendations, this review treats two age groups (adolescence and youth) as a single group aged 10-24 years, referred to as young people throughout. This age group is a critical time for young people, when they are learning about their disease, transitioning from children's service provision through to adult care, and from parent-led care to self-management whilst at a life stage characterised by change, exploration, risk-taking and identity development.

Health care professionals managing young people with IBD need to be aware of the possible consequences of psychological morbidity and be adept at identifying those at risk of psychological morbidity. This systematic review therefore aims to synthesize the available evidence regarding the impact of psychological morbidity in young people with **inflammatory bowel disease** and associated risk factors and to make recommendations regarding future research and service development in this area.

## **REVIEW CRITERIA AND METHODOLOGY**

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

## **Data Sources and Search Strategy**

A systematic literature search was undertaken using four relevant databases, Medline (via Ovid), PsycInfo (via Ovid), Web of Science, and CINAHL aiming to capture all relevant studies across disciplines including psychology, psychiatry, paediatric and adult gastroenterology from 1994 (to correspond to the introduction of the DSM-IV criteria) to 24th of September 2014. Search terms relating to psychological morbidity (“mental disorder”, “psychological health”, “mental health”, “psychological distress”, “mood disorder”, “affective disorder”, “schizophren\*”, “psychosis”, “psychotic”, “somatoform disorder”, “eating disorder”, “depress\*”, “personality disorder”, “anxiety”), young people (“young people”, “young person”, “young adult”, “youth”, “adolescent”, “adolescence”, “teenager”, “paediatric”, “pediatric”, inflammatory bowel disease (“inflammatory bowel disease”, “IBD”, “Crohn’s”, “Ulcerative Colitis”, “colitis”) were entered and combined, and limited to ‘adolescent’ and ‘young adult’.

## **Study eligibility and selection criteria**

Three authors (A.J.B, G.R, A.J.L) determined study eligibility. Studies were initially screened by the first author; decisions about study inclusion were made independently by all three authors (A.J.B, G.R, A.J.L). Studies were included if (a) published in full and written in English (b) utilised standardized measures of psychological morbidity or defined psychiatric disease by psychotropic drug use (c) used established valid and reliable questionnaires. Studies were excluded if (a) psychological morbidity could not be extricated from the presented data (b) they were case studies or not empirical

studies (e.g. narrative reports, reviews), and (c) they were only published in abstract. Additional studies of interest were identified by hand searches of bibliographies and cited references and by consultation with clinical experts in the field.

### **Data extraction and Quality Assessment**

30 studies were included for review (Figure 1; (21)). Of these, 24 were conducted in North America and 6 in Europe. The median number of participants in the studies was 79 (range 20-2144), mean age 14.7 years (range 8-18years) with an **inflammatory bowel disease** type of 83% **Crohn's disease**; 16% **ulcerative colitis** and 1% **inflammatory bowel disease** unclassified. A formal assessment of study quality was conducted using the GRADE system (22) with 15 (50%) being graded as low and 15 as very low in quality. 28/30 studies reviewed were cohort, cross sectional designs investigating psychological morbidity, psychosocial burden and factors associated with these and related outcomes (see **Tables 1, 2 and Supplementary on-line Information: Full Summary of Studies Included**).

## **RESULTS**

### **RISK FACTORS FOR PSYCHOLOGICAL MORBIDITY**

*Age at Diagnosis.* Within this **inflammatory bowel disease** population, a later age of diagnosis may correlate with increased risk of psychological morbidity. Szigethy et al. (23) found that a diagnosis at an older age correlated with a greater number of depressive symptoms ( $r=0.28$ ,  $P=0.0006$ ), independent of **inflammatory bowel disease**

duration. Mackner et al. in 2006 (24) found that young people with **inflammatory bowel disease** diagnosed in adolescence had an increased report of somatic complaints ( $P < 0.05$ ) compared to those with childhood onset **inflammatory bowel disease**. Despite these findings, the use of psychotropic drugs in young people with **inflammatory bowel disease** were not found to correlate with age at diagnosis (25), nor in various depression subtypes (26).

*Socioeconomic Status.* Three studies have found a significant relationship between socioeconomic status and depression in young people with IBD (27–29), with two studies finding no association (30,31). Clark et al. (27) found in multivariate model analysis that **socioeconomic status** was one of the strongest predictors of depressive symptoms in young people with **Crohn's disease** ( $r^2 = 0.046$ ,  $P < 0.001$ ). Two further studies used family income as a **socioeconomic status** measure and found that a family income less than \$75000 had higher total **Children's Depression Inventory (32)** scores than those with  $> \$75000$  ( $P = 0.023$ ) (29), and higher depression scores came from lower income families ( $r = -0.028$ ) (28). However, from the latter study conclusions are limited as details of family income cut offs are not presented, and a control group of participants with functional gastrointestinal symptoms are included within the analysis of those with **inflammatory bowel disease**.

*Gender.* Four studies have examined whether there is a relationship between gender and psychological morbidity in young people with **inflammatory bowel disease**, with

three studies suggesting no association (25,26,33). However, in a larger study, Loftus and colleagues suggest gender may play a role in the young people of psychological morbidity young people with **inflammatory bowel disease** present with, and this is related to age of the young people with **inflammatory bowel disease**. Teenage girls (age not further specified) had a two-fold increased risk of anxiety disorders (HR=2.45; 95% CI=1.41-4.25), whereas boys aged <12 years had an increased risk of depression (HR=2.55. 95% CI 1.1.5-5.67) (34).

*Ethnicity.* The role ethnicity may play is uncertain. All studies in this review report a significant Caucasian predominance in their cohorts. However two studies, with small sample sizes of 50 and 56 participants, did not find an association between ethnicity and psychological morbidity in young people with IBD (30,35).

*Inflammatory Bowel Disease Activity and Severity.* Several studies have examined the relationship between **inflammatory bowel disease** severity and depression with a positive association observed in 6 studies (23,27,29,31,36) but no association in 3 (30,33,37). In the study of Clark et al. (27) a positive association was found between measures of disease activity (**Paediatric Crohn's Disease Activity Index (38) and erythrocyte sedimentation rate**) and depressive symptoms after controlling for predictors, in stepwise regression models ( $r^2=0.152$ ,  $P < 0.001$ ). Reed-Knight and colleagues found greater depressive symptoms in the 14% of the cohort with moderate/severe disease activity compared to those with mild or inactive disease

activity (36). Furthermore, this study evaluated the relationship between inflammatory markers and depressive symptoms and found a relationship with **erythrocyte sedimentation rate** ( $r = 0.30, p < 0.05$ ) but not **C - reactive protein** ( $r=0.11, p= 0.44$ ). In a small study, disease severity was a significant predictor of self-reported depressive symptoms ( $B= 0.122, SE B 0.044, P<0.01$ ), but not parent reported (29), although nearly 80% of participants in this study had inactive or mild disease. **Children's Depression Inventory** scores did not differ in those with inactive disease compared to those with moderate or severely active disease, nor between those following acute, chronic intermittent or chronic disease courses (23). No control groups was used for comparison however. A pooled measure of disease severity for **ulcerative colitis** (measured by Clinical Score of Kozarek (39)) and **Crohn's disease** (measured by **Paediatric Crohn's Disease Activity Index** (38)) showed significantly increased mean depressive symptoms in the moderate/severe group compared with the inactive group ( $F (2.88)=4.171, P=0.019$ ), and in those receiving systemic steroids ( $P=0.019$ ) (23). In a study based on both self-report and parent-report, young people with severe **inflammatory bowel disease** symptoms (measured only by self-report visual analogue scales) had greater internalising and externalising (behavioural) problems compared to those with mild disease activity ( $P < 0.01$ ) (31).

Of the studies reporting no relationship with disease severity and psychological morbidity one of these report that patients with mild **inflammatory bowel disease** diagnosed for  $\geq 1$  year have psychosocial functioning similar to that of controls, and

disease severity did not differ in those with or without depressive symptoms (40).

However, this study had a small sample size, a **Crohn's disease** predominant cohort and 93.6% of patients with mild or inactive disease). In a second small study examining predictors of depression in new onset **inflammatory bowel disease** ( $\leq 3$  months) Burke et al. (37) found that the depressed group had significantly less severe disease than the non-depressed group ( $P=0.006$ ). Finally, Herzog and colleagues examined **Children's Depression Inventory** scores and found no relationship with inflammatory markers (**C-reactive protein**) or disease scores (33).

***Inflammatory Bowel Disease Duration.*** No significant correlation has been demonstrated between duration of disease and psychological morbidity in a number of studies (23,30,31,33,41). However, all of these studies include participants with a well-established IBD diagnosis, with a mean duration of disease of 1.2- 5.4 years. Therefore determining the risk that a diagnosis of **inflammatory bowel disease** may have on psychological morbidity within the first year of diagnosis is uncertain from the studies available. Furthermore, details regarding **inflammatory bowel disease** diagnosis confirmation is frequently not provided.

***Inflammatory Bowel Disease Type.*** Difference between **inflammatory bowel disease type** and relationship to psychological morbidity is detailed in 6 studies, with no significant difference reported between **ulcerative colitis** and **Crohn's disease** in young people and depressive symptoms (23,30,31,33,42) nor with antidepressant use (25).

Difficulty exists in interpreting these findings as studies have not been designed or powered sufficiently to determine effect of **inflammatory bowel disease** type on depressive/anxiety symptoms, and with **Crohn's disease** predominant cohorts in 2 studies (23,40).

*Corticosteroids.* Five studies have examined corticosteroid use and anxiety/depressive symptoms, with four suggesting that corticosteroid use contributes to psychological morbidity (23,27,34,43). Mrakotsky et al. (2012) compared a group of young people receiving high-dose corticosteroids (>30mg/day or 1mg/kg/day for more than 5days) with controls with **inflammatory bowel disease** but in clinical remission and off systemic steroids for more than 6months. Parental-report of internalizing symptoms in **Crohn's disease** were greater in the steroid group ( $P \leq 0.001$ ) (43). A further study examining risk factors for depression in young people with **inflammatory bowel disease** found, after controlling for disease activity, that depressive symptoms were positively associated with steroid dose ( $P < 0.01$ ) (27). Szigethy et al. (23) also found that young people receiving steroids were more likely than those without steroids to have clinically significant depressive symptoms **with a Children's Depression Inventory** score of  $\geq 12$  ( $P = 0.019$ ). In addition when specific symptoms of depression (anhedonia, sleep disturbance, fatigue, decreased appetite) were removed from the **Children's Depression Inventory** score there was no change in the correlation, suggesting that this finding is not related to disease severity (23). Loftus et al. (34) who also considered anxiety related disorders found that the use of corticosteroids significantly increased the risk of

developing anxiety disorders (incidence of 3.04 per 100 patient years vs. 1.32 in controls), but not depression in young people with Crohn's disease. In contrast Reed-Knight and colleagues did not find a relationship between current, but lower oral steroid use (defined as budesonide >3 mg /day and/or prednisone >5mg/day) and Children's Depression Inventory score (36).

*Immunosuppressive Drugs.* The use of immunosuppressive drugs in young people with inflammatory bowel disease and psychological morbidity has been examined in three studies with no relationship found between the use of anti-TNF drugs, thiopurines and psychological morbidity. A recent study focused on investigating anti-TNF (infliximab) as a predictor of depression in young people with CD (27). Stepwise regression analysis indicated that infliximab use was not significantly associated with depressive symptoms (27). The study excluded those on concurrent antidepressant therapy, those with comorbid psychiatric disorders or being treated with other anti-TNF agents (40/550 excluded), which may limit the generalizability of the findings. In a further study investigating depression subtypes in young people with IBD, treatment with anti-TNF did not differ between the 3 subtypes of depression described (26). Depression in young people with inflammatory bowel disease was sub-divided by latent class analyses into the following subtypes: 1) mild depression, 2) somatic depression – with significant symptoms of depressed affect and motor hypoactivity, and 3) cognitive despair – with highest scores of suicidal ideation and hopelessness. Significant differences between subtypes 1 and 2 were found with biological markers and scores of

**inflammatory bowel disease** activity. Subgroup 3 was associated with a longer duration of IBD diagnosis and presence of a stoma. This study is limited by the small numbers (n=13) in subgroup 3 and heterogeneity in **inflammatory bowel disease** phenotypes. Virta & Kolho (25) in a Finnish case controlled study of antidepressant use in young people with **inflammatory bowel disease**, found no significant association between immunosuppressant medication e.g. azathioprine and antidepressant use.

*Parental Stress.* Four cross-sectional studies (29,37,44,45) and one longitudinal study (46) have found a significant relationship between parental stress or family factors and psychological morbidity. Burke et al. (37) found those whose mothers had depression were significantly more likely to have depressive symptoms compared to those without a history of maternal depression ( $P=0.03$ ). A larger more recent study found that self-report of internalizing symptoms was associated with parenting stress ( $r=0.35$ ,  $P<0.001$ ) and more frequent medically-related situations ( $r=0.26$ ,  $P<0.01$ ) as measured by The Paediatric Inventory for Parents (32), but a similar finding was not observed in those with externalising symptoms (45). Significant exclusion criteria were another chronic illness, high risk treatment-associated behavioural and psychiatric symptoms and high dose steroids. Family affective involvement (degree of family interest and involvement with one another) significantly predicted parent-report of young people depressive symptoms, but not self-report ( $B= 4.13$ ,  $P= 0.05$ ) as did family problem solving ( $B= 5.49$ ,  $P< 0.05$ ) (29). The only longitudinal study in this field examined young people receiving an amino-salicylate or thiopurine and depressive symptoms, with measures repeated at

6 months (46). Baseline parenting stress accounted for a significant amount of the variance in depressive symptoms at follow up ( $r$ -change=0.53,  $P<0.05$ ) suggesting that parenting stress impacts on young people depressive symptoms in **inflammatory bowel disease**.

## THE IMPACT OF PSYCHOLOGICAL MORBIDITY

*Medication Adherence.* Understanding factors relating to adherence to medication in young people with **inflammatory bowel disease** and its relationship to psychological morbidity may help to identify if and when young people with **inflammatory bowel disease** may benefit from therapeutic and psychological interventions. Of four cross-sectional studies - all without controls – that have examined the relationship between adherence to medication and depressive/anxiety symptoms, three suggest a relationship (47–49). Gray et al. (49) measured adherence by Medication Adherence Measure (50), and found that depression/anxiety symptoms moderated the relationship between **Medication Adherence Measure** endorsed barriers to adherence (e.g. forgot, refusal) and adherence. Specifically in young people with high levels of anxiety/depressive symptoms, adherence was reduced by 12.6% ( $B= 0.43$ ,  $P<0.001$ ) in contrast to those with lower levels of anxiety/depressive symptoms (**adherence reduction of 2%**) where increasing other **Medication Adherence Measure** endorsed barriers to adherence did not affect adherence (49). Hommel et al. (47) examined medication adherence by **Medication Adherence Measure**, pill counts and thiopurine active metabolite concentrations and found that depressive symptoms showed a weak

negative association with adherence measured by thiopurine active metabolite concentrations ( $r=-0.40$ ,  $P<0.05$ ) and amino-salicylate Medication Adherence Measure adherence ( $r=-0.56$ ,  $P<0.01$ ). However, pill count adherence scores for 6-mercaptopurine and aminosalicylate medications did not correlate with parent or self-report quality of life (47). Reed-Knight et al. (48) measured adherence with Medication Adherence Measure by self-report and parent-report with externalizing clinical scales measuring attention and conduct problems. Attention and conduct problems showed a negative association with parent and self-report adherence ( $B= -0.038$ ,  $SE= 0.0017$ ,  $P<0.05$ ). In contrast, Mackner & Wallace (30) found no association with adherence and psychological morbidity when using a standard interview schedule to measure adherence, but biases in this study include a selective outpatient cohort in remission (inactive or mild disease in 94%) and a low response rate.

*Physical Symptoms.* Abdominal pain may be a feature of both active disease and underlying psychological morbidity. Thus, Srinath et al. (51) found that in depressed young people, inflammatory bowel disease related factors such as weight loss ( $r= 0.33$ ,  $P= 0.001$ ), diarrhoea ( $r= 0.34$ ,  $P = 0.001$ ), erythrocyte sedimentation rate ( $r=0.22$ ;  $P=0.02$ ) were associated with abdominal pain (as measured by the self-report Abdominal Pain Index (52)), but so too were depressive symptoms ( $r=0.33$ ;  $P < 0.001$ ). Depression, weight loss, and abdominal tenderness (measured by Paediatric Crohn's Disease Activity Index) were the strongest predictors of pain for young people with Crohn's disease. In ulcerative colitis the role psychological morbidity plays in abdominal

pain may be clearer, with only depressive severity predicting pain (51). This suggests that psychological morbidity plays an important role in illness perceptions of young people with **inflammatory bowel disease**, which is, in turn, important when interpreting self-reported components of well-established disease activity measures.

*Health Care Utilization.* The relationship between health care contact and psychological morbidity in young people with **inflammatory bowel disease** has been investigated with conflicting results (35,53). Reigada et al. (53) found anxiety (measured with Screen for Child Anxiety-Related emotional Disorders (54)), and depressive symptoms (measured with Center for Epidemiological Studies depression Scale (55)) did not correlate with an increase in health-care contacts when controlled for current disease activity. In contrast **inflammatory bowel disease** specific anxiety (defined as worry about impact of symptoms of **inflammatory bowel disease** in the last two weeks, and an un-validated measure) was associated with greater utilization of medical services (including inpatient admissions) and decreased social functioning compared to those with lower levels of **inflammatory bowel disease** specific-anxiety. Ondersma et al. (35) found that depressive symptoms correlated with subjective symptoms and disability and also with an increased frequency of health care contact. Details regarding measurement and analysis in the latter study are not provided and limitations exist with the measurement of health care contacts by self-report.

*Psychotropic Drugs.* A clear, measurable manifestation of psychological morbidity is the use of pharmacological treatments for psychological indications. Two large studies based on national registries in Finland (25) and North America (34) have shown an increased use of antidepressants in young people with **inflammatory bowel disease**. The most recent of these, based on 3 national Finnish registries (25), examined the use of antidepressants in young people with recent onset **inflammatory bowel disease**, with a median follow up time from diagnosis of 2.1 years. The cumulative incidence of antidepressant initiations after diagnosis with IBD was 1.2% and 2.4% at 2 and 3 years respectively, compared to 0.9% and 1.0% in age, sex matched healthy controls, with an almost 3-times greater use of antidepressants in **inflammatory bowel disease** compared to controls up to 3 years from diagnosis (3.2% vs 1.2%,  $P=0.031$ ). Loftus et al. (34) performed a large population study based on medical claims, prescription drug claims, and enrolment data in which they compared the risks of developing psychological morbidity (anxiety and depression) with the incidences of psychotropic medication. After controlling for patient characteristics including comorbidity profiles, health plan types and geographical variation, young people with **Crohn's disease** were 2-times more likely to receive psychotropic drugs than **Crohn's disease**-free age, sex and health plan enrolment matched controls. The likelihood of receiving a tricyclic antidepressant in the **Crohn's disease** group was 4 times greater than controls (HR=4.16, 95% CI=2.76-6.27) (34). This increase in tricyclic antidepressant use may in part be explained by functional bowel symptoms following CD diagnosis, but this was not assessed by the investigators.

Of note patients with any mental health disorders or psychotropic medication use before the index date were excluded.

*Sleep.* The relationship between sleep and psychological morbidity in depressed young people with **Crohn's disease** has been examined in two recent cross-sectional studies (56,57). Benhayon and colleagues (56) assessed subjective sleep quality, daytime dysfunction, and sleep latency measured by Likert ratings in the Pittsburgh Sleep Quality Index (58). Although sleep disturbances were greater in depressed young people with **Crohn's disease** (compared to healthy controls without depression) the findings reveal a complex relationship between **inflammatory bowel disease** activity, psychological morbidity and various aspects of sleep. Multivariate modelling suggests that qualitative measures of sleep (including sleep disturbance, daytime dysfunction, subjective sleep quality, and sleep latency) was predicted by anxiety ( $r^2=11.0$ ,  $P=0.001$ ), disease activity ( $r^2=19.2$ ,  $P < 0.0001$ ) and abdominal pain ( $r^2=17.0$ ,  $P < 0.0001$ ) but not to biomarkers of inflammation (C - reactive protein). In contrast the quantitative measures of sleep disturbance (including sleep duration and habitual sleep efficiency) were predicted by disease activity only ( $r^2=18.3$ ,  $P < 0.0001$ ) (56). Pirinen et al. found that the 20% of an **inflammatory bowel disease** cohort classified as sleep-troubled, reported higher rates of anxiety/depression ( $P < 0.05$ ) and somatic complaints ( $P < 0.01$ ) than those without sleep-trouble (57). Mrakotsky et al. (43) reported greater sleep dysfunction in **inflammatory bowel disease** patients receiving corticosteroids and that this correlated

with depressive symptoms. However, the small sample sizes result in poor statistical power in both studies in this field.

*Illness Perception.* Subjective illness perception and its relationship with psychological morbidity has been investigated in two studies (28,35). In the first study (35), depressive symptoms were measured through negative affectivity and were compared to subjective illness severity (pain, behaviour, fatigue). **Negative affectivity** correlated significantly with subjective symptoms, and it was estimated that 34% of variance in subjective illness severity was accounted for by **negative affectivity**, whilst being unrelated to disease activity as measured by **erythrocyte sedimentation rate**. The more recent study examined illness perception and depressive symptoms in **inflammatory bowel disease** and a control group of young people with functional gastrointestinal complaints (28). In this study the only independent variable to predict depressive symptoms was whether young people “saw their illness as a problem” ( $r=-0.43$ ) on the subjective well-being score, suggesting the role illness perceptions may play in psychological morbidity. However, interpretation of these results is limited by the small sample size, the use of non-validated measures of illness perception and subsequent analysis which did not separate **inflammatory bowel disease** from **functional gastrointestinal complaints**.

*Cognitive Functioning.* Cognitive functioning and its relationship to psychological morbidity has been examined in two studies (59,60). Castaneda et al. (59) investigated

a small sample of young people with **inflammatory bowel disease** and compared them to a control group with Juvenile Idiopathic Arthritis, and found no major cognitive deficits in either group. Mild impairments in the verbal memory test were found in **inflammatory bowel disease** patients compared with controls, but depressive symptoms did not relate to the differences observed. Jones and colleagues (60) examined cognitive and emotional processing by measuring pupillary responses which reflect cognitive and emotional processing, in a small cohort young people with **inflammatory bowel disease**, with and without depression and compared to healthy controls with and without depression. Exaggerated initial pupillary responses to negative emotional words in young people with **inflammatory bowel disease** with and without depression were observed, but not associated with disease severity or corticosteroid use. These results suggest young people with **inflammatory bowel disease** experience more negative emotional stimuli compared to healthy controls.

*Family Functioning.* Family functioning (defined as problem solving, communication, roles, affective responsiveness, affective involvement, and behavior control) has been examined in young people with **inflammatory bowel disease** with psychological morbidity (measured by parent-report). Odell and colleagues (44) found that greater parent-reported externalizing behaviour in young people accounted for **26% of variance in family functioning**, more than parental stress associated with caring for a child with a medical illness (measured by Pediatric Inventory for Parents) (44). In contrast, internalising behaviours (depressive symptoms) in young people were not associated

with variance in family functioning. These findings suggesting that parents/care-givers perception of young people with externalising behaviour (behavioural problems) result in an increased disruption to family functioning. This may enable early identification of families in whom targeted psychological interventions may provide the greatest benefit.

*Spiritual Well-Being.* Spiritual well-being (existential and religious well-being measured by Spiritual Well-Being Scale (61)) and its relationship with psychological morbidity in young people with **inflammatory bowel disease** and healthy controls was investigated by Cotton et al. (42) with evidence of higher levels of existential well-being was associated with fewer depressive symptoms ( $r = -0.48, P < 0.01$ ). In a multivariate model of analysis, lower existential well-being contributed 11% of variance of depressive symptoms ( $r^2 = 0.18$ ), but religious well-being not found to predict depressive symptoms.

## CONCLUSIONS

This review has demonstrated evidence that abdominal pain perception, sleep dysfunction, **increased** use of psychotropic drugs, non-adherence to medication, and negative illness perceptions are likely manifestations of psychological morbidity in young people with IBD. Risk factors for psychological morbidity are likely to include increased disease severity, lower **socioeconomic status**, use of corticosteroids, family/parental factors and an older age at diagnosis of **inflammatory bowel disease**. By

contrast, there is currently insufficient data regarding gender, ethnicity, **inflammatory bowel disease** type or duration and psychological morbidity.

The evidence in this field is limited by key methodological and design inconsistencies. Nearly all studies thus far have examined only depression and anxiety, resulting in a significant gap in the literature with regards to other diagnosable psychological conditions. There is wide variation in the assessment methods used to measure and define psychological morbidity and **inflammatory bowel disease** severity. The studies included recruit predominantly paediatric populations, with none focusing specifically on young people aged between 16 and 24 years which is of importance due to the increasing prevalence of depression from pre-puberty to post puberty (62). Future studies need a longitudinal design with prospective follow-up to determine causality, with increased representation of young people with severe **inflammatory bowel disease** requiring surgical interventions, those from ethnic minorities, and extending age of recruitment to 24 years. To determine the full range of possible manifestations of psychological morbidity in young people with **inflammatory bowel disease** research is needed in health risk behaviours, educational/employment attainment and further work in the areas of illness perceptions, protective factors against psychological morbidity, cognitive functioning and health care utilisation. Such data would directly inform cost-benefit analysis to enable commissioning of psychological services with subsequent evidence with which to increase the availability of commissioned psychological services for young people within paediatric and adult services.

The findings of this review suggest that psychological morbidity in young people with **inflammatory bowel disease** may have significant implications for disease management, such as medication adherence, self-report of symptoms of abdominal pain, and illness perceptions. This may pose challenges for **inflammatory bowel disease** assessment and management in young people, for example with disease severity assessment tools, which assume a direct, causal link between disease activity and symptoms and which are used to guide clinical decisions regarding treatment escalation, continuation or the introduction of immunosuppressive medications. **Screening for psychological morbidity should be part of routine clinical practice for young people with inflammatory bowel disease. This is in line with European Crohn's and Colitis Organisation guidelines (11,12). Risk stratification in this vulnerable group might enable identification of subtypes of psychological morbidity and allow for development of individualised interventions.**

## **AUTHORSHIP STATEMENT**

Guarantor of the article: A.J.Brooks

Author contributions: AJB reviewed the literature and prepared the manuscript. AJL, AJB, GR, AR, EJP reviewed study eligibility and designed the study. AJB, GR, AJL, BMC prepared the final version of the manuscript.

All authors approved the final draft prior to submission.

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## Tables

Table 1. Summary of Risk Factors for Psychological Morbidity in Young People with Inflammatory Bowel Disease

Table 2. Summary of Impacts of Psychological Morbidity in Young People with Inflammatory Bowel Disease

Table 3. Supplementary Information: Full Summary of Studies Included

*(Table submitted as separate document)*

## Figures

Figure 1. Flow chart demonstrating the search strategy in accordance with PRISMA (21)

*(Figure submitted as separate document)*