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TITLE PAGE

Title: Effect of Psychological Therapy on Disease Activity, Psychological Co-morbidity, and Quality of Life in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis

Short running head: Psychological therapy has limited effects in IBD

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Abbreviations:	CBT	cognitive behavioural therapy
	CD	Crohn's disease
	CI	confidence interval
	GI	gastrointestinal
	IBD	inflammatory bowel disease
	MeSH	medical subject heading
	NNT	number needed to treat

RR	relative risk
SD	standard deviation
SMD	standardised mean difference
UC	ulcerative colitis

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SUMMARY

Background: Inflammatory bowel disease (IBD) may be associated with psychological co-morbidity and impaired quality of life. Psychological co-morbidity could have an impact on the natural history of IBD. Psychological therapies may therefore have beneficial effects on disease activity, mood, and quality of life in patients with IBD. We conducted a systematic review and meta-analysis examining these issues.

Methods: MEDLINE, EMBASE, EMBASE Classic, PsychINFO and the Cochrane central register of controlled trials were searched through September 2016. Randomised controlled trials (RCTs) recruiting patients ≥ 16 years with IBD that compared psychological therapy with a control intervention or treatment as usual were eligible. Dichotomous data were pooled to obtain relative risks (RR) of inducing remission in active disease, or preventing relapse of quiescent disease, with 95% confidence intervals (CI). Continuous data were pooled to estimate standardised mean differences (SMD) in disease activity indices, anxiety, depression, perceived stress, and quality of life scores with 95% CIs.

Findings: The search identified 1,824 citations. Fourteen RCTs were eligible for inclusion. The RR of relapse of quiescent IBD with psychological therapy vs. control was 0.98 (95% CI 0.77-1.24). A significant difference in depression scores (SMD -0.17; 95% CI -0.33 to -0.01) and quality of life (SMD 0.30; 95% CI 0.07 to 0.52) were observed with psychological therapy vs. control at the end of therapy. However, these beneficial effects were lost at final point of follow-up. There was no effect on disease activity indices or other psychological wellbeing scores when compared with control.

Interpretation: Psychological therapies, and CBT in particular, may have limited short-term beneficial effects on depression scores and quality of life in patients with IBD. Further RCTs of these interventions in patients with co-existent psychological distress is required.

Funding: None.

RESEARCH IN CONTEXT

Evidence before this study

- There is increasing evidence to suggest that poor psychological health may have negative effects on the natural history of inflammatory bowel disease (IBD).
- Psychological therapies are effective in the treatment of mood disorders.
- Evidence supports the use of psychological therapies in some gastrointestinal diseases, including irritable bowel syndrome.
- A previous systematic review and meta-analysis of randomised controlled trials (RCTs) suggested psychological therapies may have beneficial effects on quality of life in IBD but data were limited, and different modalities of therapy were not discussed.

Added value of this study

- We have conducted a contemporaneous systematic review and meta-analysis of RCTs reporting the effect of psychological therapies in IBD.
- Sub-group analysis based on the effects of different modalities of psychological therapy was conducted.

Implications of all the available evidence

- Psychological therapies, particularly cognitive behavioural therapy, improved depression scores and quality of life in patients with IBD in the short-term.
- Psychological therapies did not appear to have any effect on disease activity or other measures of psychological wellbeing in IBD patients.

- Further investigation of the effect of psychological therapies in IBD patients at risk of psychological distress is warranted.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as the inflammatory bowel diseases (IBD), are chronic inflammatory conditions of the gastrointestinal (GI) tract without cure. Throughout a lifetime of disease, the typical natural history is that of quiescence, interspersed with episodic flare-ups of disease activity. Although the aetiology of IBD remains uncertain, several factors are implicated in its development, including a pro-inflammatory dysbiosis, impaired intestinal barrier function, and dysfunction of the enteric immune system. The increased prevalence of depression and anxiety observed among patients with IBD^{1,2} has led to suggestions that the co-existence of mood disorders may influence the natural history,³⁻⁵ although whether this affects the development of disease is less certain.^{6,7}

In IBD, psychological co-morbidity, including anxiety, depression, somatisation, and perceived stress, is not only associated with active disease, but also ongoing symptoms in the absence of inflammation.⁸⁻¹² Although a temporal relationship between the presence of psychological co-morbidity and the onset of IBD activity has been suggested,¹³ a causal relationship remains unproven. If this association is genuine, activation of the brain-gut axis, involving autonomic nervous system-mediated catecholamine release and hypothalamic-pituitary-adrenal axis secretion of stress hormones, and the GI response to this, may contribute.¹⁴⁻¹⁶ These brain-gut interactions have been studied in other chronic GI disorders, including irritable bowel syndrome, where the relationship between GI symptoms and psychological co-morbidity is well-established,¹⁷ and where the direction of effect may be bi-directional.^{18,19}

Randomised controlled trials (RCTs) of psychological therapies, such as cognitive behavioural therapy or hypnotherapy, have been conducted in irritable bowel syndrome and meta-analyses of these studies have demonstrated that they are effective treatments.^{20,21}

However, whether these therapies are also effective in IBD remains uncertain. A previous systematic review and meta-analysis published in 2011 suggested that these were possibly of benefit in adolescents with IBD, but not adults.²² However, the authors included quasi-randomised and non-randomised studies in their analysis and there have been numerous additional studies published in the intervening years.²³⁻³³ We therefore aimed to re-examine the efficacy of psychological therapies in IBD, with particular emphasis on their effects on disease activity indices, psychological wellbeing, including anxiety, depression, and perceived stress, and quality of life.

METHODS

Search Strategy and Study Selection

A literature search of MEDLINE, EMBASE, EMBASE Classic, PsychINFO and the Cochrane central register of controlled trials (from 1947 to September 2016) was carried out to identify studies investigating the effects of psychological therapies in IBD. Eligible studies had to include patients (≥ 16 years of age) with an endoscopic, histological, or radiologically confirmed diagnosis of IBD, and report the effect of psychological therapy of any modality, when compared with control or treatment as usual, on outcomes including disease activity, depression, anxiety, perceived stress, or quality of life. Only RCTs were eligible for inclusion. The eligibility criteria, which were defined a priori, are summarised in Box 1.

The literature search was performed using the terms: cognitive therapy, psychotherapy, behaviour therapy, relaxation techniques, mindfulness, meditation, or hypnosis (both as medical subject headings (MeSH) and free text terms), and the following free text terms: behavioural therapy, relaxation therapy, mindfulness meditation, or hypnotherapy. These terms were combined using the Boolean set operator AND with studies identified using the terms: Crohn disease, inflammatory bowel disease, colitis, ileitis, or ulcerative colitis (both as MeSH and free text terms), and Crohn\$ disease or regional enteritis (as free text terms). There were no language restrictions applied to the search and any foreign articles were translated. All titles and abstracts identified by the search were assessed for inclusion, and a recursive search of the bibliographies of selected articles was carried out. Two investigators judged eligibility on the selected articles independently, using pre-designed eligibility forms, and a third investigator resolved any disagreements.

Outcome Assessment

Dichotomous outcomes assessed were the efficacy of psychological therapy versus control in terms of failure to achieve remission in active IBD, or to prevent relapse of disease activity in quiescent IBD. We extracted data for these endpoints at the final point of trial follow-up, in order to maximise the number of events in the analysis. Continuous outcomes assessed included the efficacy of psychological therapies versus control in terms of effect on clinical disease activity indices, anxiety scores, depression scores, perceived stress scores, or quality of life scores. Trials were analysed separately according to whether they recruited patients with IBD with clinically active disease at the time of randomisation, or patients whose disease was quiescent. As the effect of psychological therapies on mood and quality of life may be greatest immediately after completion of therapy, we extracted data for these endpoints both at completion of therapy, and at the final point of follow-up. Where studies did not report these types of data, but were otherwise eligible for inclusion in the meta-analysis, we attempted to contact the original investigators in order to obtain supplementary dichotomous or continuous data. In six of these trials we were successful.^{23,25,28,29,32,33}

Data Extraction

Data extraction was carried out by two investigators independently, using a Microsoft excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, US) as dichotomous outcomes (remission or failure of remission in active IBD, and relapse or no relapse of disease activity in quiescent IBD), or mean disease activity scores, mean psychological wellbeing scores, or mean quality of life scores, along with a standard deviation (SD). As most RCTs recruited patients with IBD, rather than only patients with CD, or only patients with UC, we pooled studies to examine the overall effect of psychological therapies in IBD overall, rather than according to disease type. For dichotomous outcomes, data were extracted as an intention-to-treat analysis, wherever trial reporting allowed this, with all drop-outs

assumed to be treatment failures (i.e. failed to achieve remission in active IBD trials, or disease activity relapsed in quiescent IBD trials). However, due to high drop-out rates in some trials we performed a sensitivity analysis using a per protocol analysis. For the secondary outcomes, mean scores and SDs after psychological therapy or control were recorded only for those who provided complete data, in order not to overestimate the efficacy of psychological therapies in IBD.

In addition, the following data were recorded for each trial: type of psychological therapy used, country, setting (primary, secondary, or tertiary care-based), number of centres, number of sessions of psychological therapy administered, duration of therapy, and duration of follow-up. We also recorded the handling of the control arm in each trial.

The evidence base for psychological interventions in the management of depression and anxiety is greatest for cognitive behavioural therapy (CBT).³⁴ We therefore conducted a subgroup analysis including only trials using CBT, to assess whether the effect was stronger for this treatment modality.

Assessment of Risk of Bias

This was conducted by two investigators in accordance with guidance published in the Cochrane handbook.³⁵ Any disagreement was resolved by discussion. Risk of bias was assessed by recording the methods used to generate the randomisation schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, what proportion of subjects completed follow-up, whether an intention-to-treat analysis was extractable, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

The degree of agreement between the two investigators, in terms of judging study eligibility, was measured using a Kappa statistic. For dichotomous outcomes the impact of psychological therapies was expressed as a relative risk (RR) of failure to achieve remission with 95% confidence intervals (CI) with intervention versus control in trials of therapy for active IBD, or RR of relapse of disease activity in trials of therapy for quiescent IBD. Where psychological therapies appeared more effective than control in IBD, we planned to calculate the number needed to treat (NNT), along with 95% CIs, using the formula $NNT = 1 / (\text{control event rate} \times (1 - RR))$. For continuous data, including effect on disease activity indices, psychological wellbeing scores, and quality of life scores, the impact of psychological therapies was summarised using a standardised mean difference (SMD) and 95% CIs.

Heterogeneity between studies was assessed using the I^2 statistic with a cut off of 50%,³⁶ and the χ^2 test with a P value <0.10 , as the threshold to define a statistically significant degree of heterogeneity. All data were pooled using a random effects model,³⁷ in order to give a more conservative estimate of the effect of psychological therapies on disease outcomes in IBD. We used Review Manager version 5.3 (RevMan for Windows 2014, the Nordic Cochrane Centre, Copenhagen, Denmark) to generate Forest plots of pooled RRs and SMDs with 95% CIs, as well as funnel plots. These were assessed, if there were a sufficient number (≥ 10) of studies included in the meta-analysis,³⁸ for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test.³⁹

Role of the funding source

No funding received. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

The literature search identified a total of 1,824 citations of which, after title and abstract review, 46 were deemed potentially relevant and were assessed further for eligibility (Figure 1). Of these, a further 32 were excluded for various reasons leaving 14 studies eligible for data extraction.^{23-33,40-42} Agreement between reviewers for eligibility assessment was excellent (Kappa statistic = 0.91). Detailed study characteristics are provided in Table 1, and risk of bias across all studies is reported in page 1 of the webappendix.

Effect of Psychological Therapy on Disease Activity, Psychological Wellbeing, and Quality of Life in Patients with Active IBD

Only two of the 14 RCTs eligible for inclusion included patients with IBD with ongoing active disease.^{30,31} Only one of these studies reported dichotomous data concerning the efficacy of psychological therapy in the induction of remission of active IBD.³⁰ In total, 12 (21.1%) of 57 patients undergoing psychological therapy entered clinical remission, compared with 2 (3.5%) of 57 patients in the control group, after 18 months of follow-up.

In terms of effect on other outcomes, including change in clinical disease activity indices,³⁰ depression,³¹ anxiety,³¹ and perceived stress scores,³¹ each of these were only reported in one RCT, and therefore formal meta-analysis was not possible. Psychological therapy was not associated with an improvement in any of these outcomes, when compared with control, in patients with active IBD. Both studies assessed the effect of psychological therapy on quality of life in a total of 153 patients with IBD. Here, the SMD in quality of life score at the final point of follow-up was not significantly different (0.27; 95% CI -0.05 to 0.59).

Effect of Psychological Therapy on Disease Activity, Psychological Wellbeing, and Quality of Life in Patients with Quiescent IBD

Twelve of the 14 eligible RCTs assessed these outcomes in patients with IBD who had quiescent disease at randomisation.^{23-29,32,33,40-42} Four of these presented data in patients with CD,^{25,32,40,42} four in patients with UC,^{27,28,40,41} and five in patients with IBD.^{23,24,26,29,33} Results from all analyses in patients with quiescent IBD are summarised in Table 2.

Effect of Psychological Therapy in Preventing Relapse of Quiescent IBD

In total, there were six RCTs reporting dichotomous data concerning the effect of psychological therapy on relapse rates in quiescent IBD. One study included CD patients,⁴² three studies included UC patients,^{27,28,41} and two included patients with IBD.^{24,29} Overall, 159 (57.4%) of 277 patients treated with psychological therapy experienced a relapse of disease activity, compared with 127 (52.7%) of 241 patients in the control group. Compared with control, the RR of relapse of disease activity in all patients with IBD treated with psychological therapy was 0.98 (95% CI 0.77 to 1.24) (Figure 2). There was significant heterogeneity between studies ($I^2 = 50\%$, $P = 0.07$), but too few studies to assess for publication bias. When the effect of psychological therapies on relapse of disease activity was studied according to whether trials recruited patients with CD, patients with UC, or patients with IBD there remained no effect of psychological therapies at final point of follow-up (Figure 2). Per protocol analysis did not reveal any beneficial effect of psychological therapies on disease relapse (RR = 0.86; 95% CI 0.71 to 1.05), but there was no heterogeneity between studies ($I^2 = 0\%$, $P = 0.46$).

Effect of Psychological Therapy on Clinical Disease Activity Indices in IBD

Eight RCTs reported data on the effect of psychological therapy on disease activity indices in patients with IBD at the final point of follow-up. Six RCTs assessed impact on disease activity indices in CD,^{23,24,26,32,33,40} and seven in UC.^{23,24,26,27,33,40,41} There was no significant difference in disease activity indices among those treated with psychological therapy, compared with those in the control group, at the final point of follow-up (SMD = -0.03; 95% CI -0.20 to 0.14) (Figure 3), with no evidence of heterogeneity between studies ($I^2 = 0\%$, $P = 0.87$). Again, there were too few studies to assess for publication bias. There was also no effect of psychological therapies on disease activity indices among only patients with CD, or only patients with UC (Figure 3).

Effect of Psychological Therapy on Anxiety Scores in IBD

Five studies provided data on the effect of psychological therapy on anxiety scores in IBD at the end of therapy,^{23,24,33,40,41} and five at the final point of follow-up.^{23,24,32,33,40} At completion of therapy, when data were pooled from a total of 504 patients, there was no effect of psychological therapies on anxiety scores (SMD = -0.14; 95% CI -0.33 to 0.04) (webappendix pg. 2). There was no heterogeneity between the included RCTs ($I^2 = 7\%$, $P = 0.37$), and too few studies to assess for publication bias. At the last point of follow-up, there was still no effect of psychological therapies on anxiety scores in 437 patients (SMD = -0.18; 95% CI = -0.39 to 0.04) (webappendix pg. 3). There was also no effect of psychological therapies on state^{13,26,42} or trait^{13,26,27} anxiety scores in three trials at either completion of therapy, or at final point of follow-up (webappendix pgs. 4-7).

Effect of Psychological Therapy on Depression Scores in IBD

Seven studies examined the effect of psychological therapy on depression scores in IBD at end of therapy,^{23,24,26,27,33,40,42} and eight at the final point of follow-up.^{23,24,26,27,32,33,40,42} Data were available for 605 patients at completion of therapy, with a SMD in depression scores for those treated with psychological therapy compared with control of -0.17 (95% CI -0.33 to -0.01, $P = 0.04$) (webappendix pg. 8), with no heterogeneity between studies ($I^2 = 0\%$, $P = 0.76$). Again there were too few studies to assess for publication bias. This beneficial effect on depression scores was only seen in RCTs that recruited patients with IBD (webappendix pg. 8). At the final point of follow-up, when data were pooled from 593 patients, the effect on depression scores was no longer evident (SMD = -0.11; 95% CI -0.27 to 0.05), with no heterogeneity ($I^2 = 0\%$, $P = 0.93$) (webappendix pg. 9). There were too few studies to assess for publication bias.

Effect of Psychological Therapy on Perceived Stress Scores in IBD

Six RCTs reported data on the effect of psychological therapy on perceived stress score in IBD, when compared with control.^{23-25,27-29} When data were pooled at the end of therapy, psychological therapy had no effect on perceived stress scores in 434 patients (SMD = -0.07; 95% CI -0.31 to 0.18) (webappendix pg. 10), with no heterogeneity between studies ($I^2 = 34\%$, $P = 0.18$). At the final point of follow-up, when data were available for 401 patients, there was still no beneficial effect of psychological therapies compared with control (SMD in perceived stress scores = -0.10; 95% CI -0.33 to 0.13) (webappendix pg. 11), again with no heterogeneity noted between included studies ($I^2 = 22\%$, $P = 0.27$). There were too few studies to assess for publication bias in both these analyses. Again, there were no effects noted according to whether studies recruited patients with CD only, patients with UC only, or patients with IBD.

Effect of Psychological Therapy on Quality of Life in IBD

Eleven studies reported data on the effect of psychological therapy on quality of life in IBD.^{23-29,32,33,41,42} Nine of these RCTs assessed effects on IBD-specific quality of life at end of therapy,^{23,25-29,33,41,42} and 10 at the final point of follow-up.^{23,25-29,32,33,41,42} In addition, four trials examined effect on physical quality of life or mental quality of life separately,^{23,24,28,33} both at end of therapy and at the final point of follow-up. There was a significant improvement in IBD-specific quality of life at the end of therapy, when data were pooled from 578 patients (SMD 0.30; 95% CI = 0.07 to 0.52, P = 0.01) (Figure 4). There was borderline heterogeneity observed between the included studies ($I^2 = 42\%$, P = 0.09), but too few studies to assess for publication bias. When the effect of psychological therapies on IBD-specific quality of life was studied according to whether trials recruited patients with CD, patients with UC, or patients with IBD there was only a benefit observed among patients with IBD at the end of therapy (SMD = 0.37; 95% CI 0.15 to 0.59, P = 0.001) (Figure 4). Any beneficial effect of psychological therapy on IBD-specific quality of life at completion of therapy was lost by the final point of follow-up. When data were pooled from 577 patients there were no differences in IBD-specific quality of life (SMD = 0.15; 95% CI -0.05 to 0.34) (Supplementary Figure 6). There was no heterogeneity between studies ($I^2 = 22\%$, P = 0.24), and no evidence of publication bias (Egger test, P = 0.44).

When compared with control, psychological therapy had no effect on physical quality of life or mental quality of life at completion of therapy in 399 patients (SMD = 0.17; 95% CI -0.03 to 0.37 and SMD = 0.15; 95% CI -0.05 to 0.34, respectively). There was no evidence of heterogeneity between studies in these analyses although with only four RCTs, power to detect this would be limited. At final point of follow-up in 363 patients there was no difference in physical (SMD = 0.02; 95% CI = -0.19 to 0.23) or mental quality of life (SMD = 0.05; 95% CI = -0.22 to 0.32) when those receiving psychological therapy were compared

with control, with no heterogeneity noted for either outcome. There were too few studies to assess for publication bias in all these analyses.

Effect of CBT in Preventing Relapse of Quiescent IBD, and Effect on Clinical Disease Activity Indices, Anxiety Scores, Depression Scores, Perceived Stress Scores, and Quality of Life in IBD

Five studies^{23-26,29}, including 511 patients with IBD, reported data on the effect of CBT on one or more of these endpoints. There was a significant improvement in quality of life at the end of therapy, when data were pooled from 254 patients (SMD = 0.37; 95% CI 0.02 to 0.72; webappendix pg. 11), although this beneficial effect was lost at the final point of follow-up. There was no other significant effect of CBT on disease activity indices, anxiety or depression scores, or perceived stress scores when compared with control therapy.

DISCUSSION

This systematic review and meta-analysis has demonstrated that psychological therapies may provide a limited, short-term improvement in depression scores and quality life in patients with clinically quiescent IBD, but that these effects appear to be lost over time. The beneficial effect on quality of life was greater when only RCTs that used CBT, which is thought to have the best evidence for efficacy in the management of anxiety and depression,³⁴ were included in the analysis. Otherwise, psychological therapies did not appear to improve either clinical disease indices or psychological outcomes in IBD. There did not appear to be any benefits of psychological therapies according to type of IBD. Furthermore, there was no significant effect on most measurements of mood, either at the point where psychological therapy had just been completed, or during extended follow-up. Part of this lack of benefit may have arisen from a lack of sensitivity or specificity of the instruments used to detect changes in mood, as well as failure by the majority of trials to recruit only patients who had abnormal levels of psychological health when compared with the general population.

Strengths of this study include the rigorous methodology adopted. Several of the studies included in the 2011 Cochrane review²² addressing this issue did not fulfil our inclusion criteria for various reasons. These included a lack of randomisation,^{43,44} recruitment of patients with both active and quiescent disease, with no reporting of data separately for these distinct groups of patients,⁴⁵ being conducted in an adolescent population,⁴⁶ redundant publication,⁴⁷ or providing no extractable data.⁴⁸ In addition, we made every effort to contact the authors of potentially eligible studies, where dichotomous or continuous data of interest were not available in the published manuscript. We used an intention-to-treat analysis, with all patients lost to follow-up assumed to be treatment failures, for dichotomous endpoints such as remission or relapse of disease activity, in order to avoid

overestimation of the effect of the active intervention. We also pooled all data using a random effects model, in order to give a more conservative estimate of the effect of psychological therapies in IBD. A further strength of this study is the number of participants included. This systematic review and meta-analysis included an additional 11 contemporaneous studies,^{23,24,28-30,32,33} and almost three times more participants than were included in the Cochrane review published by Timmer et al. in 2011.²² We performed analyses according to type of IBD, in order to assess whether there was any benefit of psychological therapy in either CD or UC. Lastly, we conducted a subgroup analysis to investigate the effect of CBT alone, as this has the best evidence for use in anxiety and depression.³⁴

There are limitations to this meta-analysis, which arise mainly from the relatively small number of studies available for analysis, and their risk of bias. Although there was no significant heterogeneity seen in the majority of the endpoints studied, there was significant heterogeneity between RCTs reporting on the effect of psychological therapies on relapse of disease activity in quiescent IBD. In addition, all the trials we identified were at high risk of bias, due to the lack of adequate blinding, with only one trial employing a double-blind design.²⁷ This is often a problem with studies of psychological therapies, although there is the potential to blind assessors to therapy. However, only four of the studies we identified performed this.^{28,30,33,42} The included studies employed various methods of handling the control arms, which may mean that pooling the data from them could be viewed as inappropriate. The fact that duration of follow-up was not uniform between eligible studies may also mean that a significant benefit of psychological therapies, which is perhaps time-dependent, has been overlooked. Individual trials also used differing types, formats, durations, and intensities of psychological therapy, which may have led to a lack of benefit when all studies were pooled together. However, when only the five RCTs that used CBT were considered in the analysis, there was still no effect on disease activity indices, anxiety or

depression scores, or perceived stress scores. Finally, the trials we identified span an 18-year period, during which the management of IBD has been revolutionised by the advent of biological therapies. We cannot exclude the fact that increasing use of these drugs in more recent studies may have had an impact on the findings of this meta-analysis.

Our findings are in keeping with those previously published in adult IBD populations.²² Other than a significant improvement in depression and quality of life scores immediately following the cessation of therapy, we failed to detect a statistically significant benefit of these interventions in IBD. Despite this, psychological therapy has been shown to be effective in the treatment of other chronic GI disorders, including irritable bowel syndrome, functional dyspepsia, and non-cardiac chest pain.^{21,49,50} The majority of the RCTs included in this meta-analysis were conducted in patients in clinical remission. Only two studies examined the effect of psychological therapy in active disease.^{30,31} However, observational studies in IBD populations demonstrate that often the greatest psychological burden is seen in patients with active disease, or those with quiescent disease with ongoing GI symptoms in the absence of inflammation,^{8,10} suggesting it is these subgroups of patients who may benefit most from these types of treatment. Only one RCT performed a subgroup analysis in patients with “functional” symptoms, which met criteria for irritable bowel syndrome, in patients with quiescent disease.²⁹ In this study, quality of life scores in those receiving mindfulness-based therapy were significantly improved when compared with control after 4 months of follow-up, and remained higher during the entire 12 months of the study, although this difference was no longer statistically significant. In addition, symptom scores were generally lower among those assigned to psychological therapy throughout the entire 12 months of the study. Finally, none of the included RCTs investigated the effect of psychological interventions in patients with IBD with pre-existing depression or anxiety, despite there being evidence for a benefit in this distinct group of patients, particularly in paediatric populations.^{46,51,52}

In addition to the outcomes addressed in this systematic review and meta-analysis, fatigue is now recognised as an increasing problem in people with IBD, and is more prevalent than in the general population, affecting up to 40% of patients.^{53,54} Furthermore, fatigue may be associated with depression and reduced quality of life, independent of disease activity.^{55,56} To date, only two of the studies we identified have sought to investigate the effect of psychological therapies in this particular subgroup of patients with IBD,^{32,33} randomising patients in clinical remission with raised fatigue scores to receive solution focused therapy, problem solving therapy, or treatment as usual. In the larger of these two studies,³³ significant improvements in fatigue scores and quality of life were observed after 3 months of follow-up in the intervention group, suggesting psychological therapy may be beneficial in this particular population.

In summary, the results of this systematic review and meta-analysis suggest that psychological therapy, and CBT in particular, may be of limited short-term benefit in terms of improvements in depression and quality of life in patients with IBD. However, despite several hundred patients in most of the analyses we conducted, we could not detect any beneficial effect of psychological therapies on disease activity, or other measures of psychological health, including anxiety or stress. Despite this, there remains a need for further investigation of the utility of these interventions, particularly in those patients who are more likely to suffer from co-existent psychological distress or fatigue. In addition, with the increasing use of faecal biomarkers of intestinal inflammation, such as calprotectin, as a means of assessing disease activity objectively, it is likely that increasing numbers of patients with IBD with ongoing GI symptoms in the absence of inflammation will be identified. This distinct cohort of patients also have unmet needs, in terms of therapy, and are often difficult to manage. Trials assessing the effects of psychological therapies, which use an adequate number of therapy sessions, have a sufficient duration of follow-up, use blinded assessors for

endpoint assessment, and focus on the efficacy of CBT in these patients would therefore also be welcome.

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AUTHORS CONTRIBUTIONS

DJG, AI, RS, AMW, PJH, and ACF conceived and drafted the study. DJG, AI and RS collected all data. DJG, AMW, PJH and ACF analysed and interpreted the data. DJG, AMW, PJH, and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

DECLARATION OF INTERESTS

DJG: none, AI: none, RS: none, AMW: none, PJH: none, ACF: none.

ETHICS COMMITTEE APPROVAL

Not required.

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Box 1. Eligibility Criteria for Study Inclusion.

Randomised controlled trials.

Patients aged ≥ 16 years with a confirmed diagnosis of IBD, according to endoscopic, histological, or radiological criteria.

Compared psychological therapies with a control, including a physician's "usual management", symptom monitoring, or supportive therapy.

Reported a dichotomous assessment of failure of remission in active disease or relapse of disease activity in quiescent disease, or a continuous assessment of clinical disease activity, psychological co-morbidity*, or quality of life.

* Eligible studies could assess psychological co-morbidity via measurement of anxiety (including state and trait anxiety), depression, or perceived stress.

Table 1. Characteristics of Included Studies.

Study	Participants and Setting	Active Intervention	Handling of the Control Arm	Duration of Follow-up	Outcomes Studied (% of Patients Providing Complete Data)
Jantschek 1998 ⁴²	108 patients with CD from 4 tertiary care centres in Germany	10 sessions of psychodynamic psychotherapy over 12 months	Standardised drug therapy including tapered prednisolone and sulfasalazine	24 months	Relapse of disease activity: Crohn's disease activity index, but no threshold specified (100) Psychological wellbeing: Beck depression inventory and state-trait anxiety (75.0) Quality of life: IBD-Q (73.1)
Smith 2002 ^{40*}	100 patients (50 with CD, 50 with UC) from 1 tertiary care centre in the UK	3 to 6-monthly sessions of stress management and attention control therapy over 12 months	Routine clinical follow-up	12 months	Clinical disease activity indices: modified Crohn's disease activity index (100) Psychological wellbeing: hospital anxiety and depression scale (100)

Langhorst 2007 ⁴¹	60 patients with UC recruited via public advertisement in Germany	Weekly sessions of stress reduction, stress management, dietary recommendations, and mindfulness over 10 weeks	Usual medical care	12 months	<p>Relapse of disease activity: Rachmilewitz clinical activity index >5 (100)</p> <p>Clinical disease activity indices: Rachmilewitz clinical activity index (93.3)</p> <p>Psychological wellbeing: brief symptom inventory for anxiety (93.3)</p> <p>Quality of life: IBD-Q (93.3)</p>
Boye 2011 ³⁰	114 patients with IBD from 4 tertiary care centres in Norway and Germany	3 group sessions, followed by weekly individual sessions for 6 to 9 weeks, and up to 3 booster sessions of psychoeducation and relaxation, with cognitive behavioural therapy-based sessions, over 12 months	Treatment as usual	18 months	<p>Remission of disease activity: Harvey-Bradshaw index or Rachmilewitz clinical activity index ≤ 1 (100)</p> <p>Clinical disease activity indices: Harvey-Bradshaw index or Rachmilewitz clinical activity index (100)</p> <p>Quality of life: IBD-Q (100)</p>

Vogelaar 2011 ^{32,†}	40 patients with CD from 1 tertiary care centre in the Netherlands	5 sessions of solution focused therapy, or 10 sessions of problem solving therapy, over 3 months	Treatment as usual	6 months	Clinical disease activity indices: Crohn's disease activity index (57.5) Psychological wellbeing: hospital anxiety and depression scale (57.5) Quality of life: IBD-Q (57.5)
Kefer 2012 ²⁵	28 patients with CD from 1 tertiary care centre in the USA	Weekly sessions of project-management, including cognitive behavioural therapy and social learning theory, over 6 weeks	Treatment as usual	8 weeks	Psychological wellbeing: perceived stress questionnaire (100) Quality of life: IBD-Q (100)
Mizrahi 2012 ³¹	56 patients with IBD from 1 tertiary care centre in Israel	3 sessions of relaxation training and guided imagery over 5 weeks	Waiting list control	5 weeks	Psychological wellbeing: state-trait anxiety, and visual analogue scales for depression and stress (69.6) Quality of life: IBD-Q (69.6)

Keefe 2013 ²⁸	54 patients with UC from 1 tertiary care centre in the USA	Weekly sessions of gut-directed hypnotherapy over 7 weeks	Attention control	12 months	Relapse of disease activity: Self-report, Mayo score >2, or escalation of therapy (100) Psychological wellbeing: perceived stress questionnaire (92.6) Quality of life: IBD-Q and short-form-12 (92.6)
Berrill 2014 ²⁹	66 patients with IBD from 2 tertiary care centres in the UK	6 sessions of multi-convergent therapy, including mindfulness meditation and cognitive behavioural therapy, over 16 weeks	Standard medical therapy	12 months	Relapse of disease activity: Harvey-Bradshaw index ≥ 5 or simple clinical colitis activity index ≥ 3 (100) Psychological wellbeing: perceived stress questionnaire (77.3) Quality of life: IBD-Q (89.4)

Jedel 2014 ²⁷	55 patients with UC from 1 tertiary care centre, and the greater Chicago area, in the USA	Weekly sessions of mindfulness-based stress reduction, including sitting meditation, body scans, yoga postures, and awareness of personal reactions to everyday events, over 8 weeks	Attention control	12 months	Relapse of disease activity: ulcerative colitis disease activity index >2 (100) Clinical disease activity indices: ulcerative colitis disease activity index (92.7) Psychological wellbeing: Beck depression inventory, state-trait anxiety, and perceived stress questionnaire (92.7) Quality of life: IBD-Q (92.7)
Vogelaar 2014 ³³	98 patients with IBD from 2 tertiary care centres in the Netherlands	6 sessions of solution focused therapy over 3 months, with a booster session at month 6	Treatment as usual	9 months	Clinical disease activity indices: Crohn's disease activity index or Rachmilewitz clinical activity index (91.8) Psychological wellbeing: hospital anxiety and depression scale (91.8) Quality of life: IBD-Q and short-form-36 (91.8)

<p>Mikocka-Walus 2015 ²⁴</p>	<p>174 patients with IBD from 2 tertiary care centres in Australia</p>	<p>Weekly sessions of face-to-face or internet-delivered cognitive behavioural therapy over 10 weeks</p>	<p>Standard care</p>	<p>12 months</p>	<p>Relapse of disease activity: Crohn's disease activity index ≥ 150 or simple clinical colitis activity index ≥ 3 (100)</p> <p>Clinical disease activity indices: Crohn's disease activity index or simple clinical colitis activity index (40.8)</p> <p>Psychological wellbeing: hospital anxiety and depression scale, state-trait anxiety, and COPE questionnaire (60.9)</p> <p>Quality of life: short-form-36 (60.9)</p>
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Schoultz 2015 ²⁶	44 patients with IBD from outpatient gastroenterology clinics in two national health boards in Scotland, UK	Weekly sessions of mindfulness-based cognitive therapy, including body scan, sitting and walking meditation, mindful stretching, and cognitive behavioural exercises, over 8 weeks	Waiting list control	6 months	Clinical disease activity indices: Crohn's disease activity index or simple clinical colitis activity index (52.3) Psychological wellbeing: Beck depression inventory and state-trait anxiety (54.5) Quality of life: IBD-Q (54.5)
McCombie 2016 ²³	199 patients with IBD from secondary and tertiary care centres, as well as support groups, in New Zealand	8 sessions of computerised cognitive behavioural therapy over 12 weeks	Treatment as usual	6 months	Clinical disease activity indices: Harvey-Bradshaw index or simple clinical colitis activity index (55.3) Psychological wellbeing: hospital anxiety and depression scale and perceived stress questionnaire (58.8) Quality of life: IBD-Q and short-form-12 (58.8)

*Smith 2002 ⁴⁰ provided all outcomes data for those with CD (Smith 2002a) and those with UC (Smith 2002b) separately.

†Vogelaar 2011 ³² compared solution focused therapy (Vogelaar 2011a) and problem solving therapy (Vogelaar 2011b) with treatment as usual.

Table 2. Effect of Psychological Therapy on Disease Activity, Psychological Wellbeing, and Quality of Life in Patients with Quiescent IBD.

	Number of trials	Number of patients	Summary Statistic for Effect of Psychological Therapies (95% confidence interval)	P value for the difference	I ² (P value)
Preventing relapse of IBD (RR)	6	518	0.98 (0.77 to 1.24)	0.87	50% (0.07)
Clinical disease activity indices (SMD)	8	534	-0.03 (-0.20 to 0.14)	0.73	0% (0.87)
Anxiety scores (SMD)					
At completion of therapy	5	504	-0.14 (-0.33 to 0.04)	0.13	7% (0.37)
At final point of follow-up	5	437	-0.18 (-0.39 to 0.04)	0.10	17% (0.30)
State anxiety scores (SMD)					
At completion of therapy	3	217	-0.14 (-0.41 to 0.14)	0.33	0% (0.66)
At final point of follow-up	3	207	-0.04 (-0.32 to 0.24)	0.76	0% (0.62)
Trait anxiety scores (SMD)					
At completion of therapy	3	191	-0.16 (-0.44 to 0.13)	0.28	0% (0.80)
At final point of follow-up	3	181	0.05 (-0.25 to 0.34)	0.75	0% (0.48)
Depression scores (SMD)					
At completion of therapy	7	605	-0.17 (-0.33 to -0.01)	0.04	0% (0.76)
At final point of follow-up	8	593	-0.11 (-0.27 to 0.05)	0.17	0% (0.93)

Perceived stress scores (SMD)					
At completion of therapy	6	434	-0.07 (-0.31 to 0.18)	0.59	34% (0.18)
At final point of follow-up	6	401	-0.10 (-0.33 to 0.13)	0.40	22% (0.27)
Quality of life scores (SMD)					
At completion of therapy	9	578	0.30 (0.07 to 0.52)	0.01	42% (0.09)
At final point of follow-up	10	577	0.15 (-0.05 to 0.34)	0.14	22% (0.24)

RR; relative risk, SMD; standardised mean difference

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review and Meta-analysis.

Figure 2. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control in Preventing Relapse of Quiescent IBD at the Final Point of Follow-up.

Figure 3. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Disease Activity Indices in Quiescent IBD at the Final Point of Follow-up.

Figure 4. Forest Plot of RCTs Reporting the Effect of Psychological Therapies vs. Control on Quality of Life Scores in Quiescent IBD at the Completion of Therapy.