Efficacy of psychological therapies in people with inflammatory bowel disease: a systematic review and meta-analysis

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Summary

Background There is increasing evidence for an influence of the gut–brain axis on the natural history of inflammatory bowel disease (IBD). Psychological therapies could, therefore, have beneficial effects in individuals with IBD, but data are conflicting. We aimed to update our previous systematic review and meta-analysis to assess whether the inclusion of more randomised controlled trials (RCTs) showed any beneficial effects and whether these effects varied by treatment modality.

Methods In this systematic review and meta-analysis, we searched MEDLINE, Embase, Embase Classic, PsychINFO, and the Cochrane Central Register of Controlled Trials from Jan 1, 2016, to April 30, 2023, for RCTs published in any language recruiting individuals aged 16 years or older with IBD that compared psychological therapy with a control intervention or treatment as usual. We pooled dichotomous data to obtain relative risks (RR) with 95% CIs of inducing remission in people with active disease or of relapse in people with quiescent disease at final follow-up. We pooled continuous data to estimate standardised mean differences (SMD) with 95% CIs in disease activity indices, anxiety scores, depression scores, stress scores, and quality-of-life scores at completion of therapy and at final follow-up. We pooled all data using a random-effects model. Trials were analysed separately according to whether they recruited people with clinically active IBD or predominantly individuals whose disease was quiescent. We conducted subgroup analyses by mode of therapy and according to whether trials recruited selected groups of people with IBD. We used the Cochrane risk of bias tool to assess bias at the study level and assessed funnel plots using the Egger test. We assessed heterogeneity using the I^2 statistic.

Findings The updated literature search identified a total of 469 new records, 11 of which met eligibility criteria. 14 studies were included from our previous meta-analysis published in 2017. In total, 25 RCTs were eligible for this meta-analysis, all of which were at high risk of bias. Only four RCTs recruited patients with active IBD; there were insufficient data for meta-analysis of remission, disease activity indices, depression scores, and stress scores. In patients with active IBD, psychological therapy had no benefit compared with control for anxiety scores at completion of therapy (two RCTs; 79 people; SMD –1·04, 95% CI –2·46 to 0·39), but did have significant benefit for quality-of-life scores at completion of therapy (four RCTs; 309 people; 0·68, 0·09 to 1·26), although heterogeneity between studies was high (I^2=82%). In individuals with quiescent IBD, RR of relapse of disease activity was not reduced with psychological therapy (ten RCTs; 861 people; RR 0·83, 95% CI 0·62 to 1·12), with moderate heterogeneity (I^2=60%), and the funnel plot suggested evidence of publication bias or other small study effects (Egger test p=0·046). For people with quiescent IBD at completion of therapy, there was no difference in disease activity indices between psychological therapy and control (13 RCTs; 1015 people; SMD –0·01, 95% CI –0·13 to 0·12; I^2=0%). Anxiety scores (13 RCTs; 1088 people; –0·23, –0·36 to –0·09; 18%), depression scores (15 RCTs; 1189 people; –0·26, –0·38 to –0·15; 2%), and stress scores (11 RCTs; 813 people; –0·22, –0·42 to –0·03; 47%) were significantly lower, and quality-of-life scores (16 RCTs; 1080 people; 0·31, 0·16 to 0·46; 30%) were significantly higher, with psychological therapy versus control at treatment completion. Statistically significant benefits persisted up to final follow-up for depression scores (12 RCTs; 856 people; –0·16, –0·30 to –0·03; 0%). Effects were strongest in RCTs of third-wave therapies and in RCTs that recruited people with impaired psychological health, fatigue, or reduced quality of life at baseline.

Interpretation Psychological therapies have beneficial, short-term effects on anxiety, depression, stress, and quality-of-life scores, but not on disease activity. Further RCTs in selected groups are needed to establish the place for such therapies in IBD care.

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Research in context

Evidence before this study

There is increasing evidence that the gut–brain axis exerts effects on both psychological health and disease activity in inflammatory bowel disease (IBD). However, whether treatments targeting the gut–brain axis, such as psychological therapies, have any beneficial effects in people with IBD is less clear. Our previous meta-analysis examining this issue was published in 2017; it showed no long-term benefits of psychological therapies on disease activity, psychological health, or quality of life. A comprehensive search of the medical literature in MEDLINE, Embase, Embase Classic, PsychINFO, and the Cochrane Central Register of Controlled Trials from Jan 1, 2016, to April 30, 2023, without any language restrictions, identified multiple new randomised controlled trials (RCTs) of psychological therapies in people with IBD, providing a rationale for this updated systematic review and meta-analysis. We aimed to assess whether the inclusion of more trials showed any beneficial effects of psychological therapies in individuals with IBD and to examine whether these effects varied by treatment modality.

Added value of this study

We conducted a systematic review and meta-analysis of RCTs of psychological therapies in adults (aged ≥16 years) with IBD. Of 25 eligible RCTs, only four recruited patients with active disease. The increased number of RCTs in this updated meta-analysis enabled, for the first time, subgroup analyses examining the effects of psychological therapies in selected groups and highlighted people for whom psychological therapies might have a more beneficial role in IBD. We were also able to compare the effects of cognitive behavioural therapy and third-wave therapies, which could inform researchers of which therapies to trial in selected groups. Incomplete and inconsistent reporting of data meant that the effect of psychological therapies on remission, disease activity indices, depression scores, and stress scores in people with active IBD could not be estimated, but quality-of-life scores were significantly higher with active therapy versus control at completion of treatment in four RCTs (standardised mean difference 0·68, 95% CI 0·09 to 1·26); anxiety scores were not different. In RCTs conducted in individuals with quiescent IBD, the relative risk (RR) of relapse of disease activity was not reduced after psychological therapy versus control (RR 0·83, 95% CI 0·62 to 1·12). There was also no difference in disease activity indices between groups at completion of therapy. However, compared with control, psychological therapies led to significantly lower anxiety scores, depression scores, and stress scores, and significantly higher quality-of-life scores at treatment completion. This benefit continued until final follow-up for depression scores. The effect appeared to be strongest in RCTs of third-wave therapies (ie, acceptance, mindfulness, and value-focused approaches) and in RCTs that recruited people with impaired psychological health, fatigue, or reduced quality of life at baseline who could be expected to derive the most benefit from psychological therapies.

Implications of all the available evidence

Although psychological therapies targeting the gut–brain axis do not appear to reduce the risk of relapse in individuals with quiescent IBD, they appear to improve short-term quality of life in people with active IBD and in those with quiescent IBD. There was also a beneficial effect on psychological health in individuals with quiescent IBD, with significant improvements in anxiety, depression, and stress scores compared with control at completion of therapy and in depression scores until final follow-up. Our findings suggest that psychological therapies have benefits on measures of psychological health in people with IBD, and that such therapies could be important as adjunctive treatments in clinical practice. Further RCTs trialling these therapies in selected groups are needed to enable appropriate guidelines to be developed for their use in clinical practice.

Introduction

Inflammatory bowel disease (IBD), consisting of Crohn's disease and ulcerative colitis, is a chronic gastrointestinal condition with increasing prevalence across North America and Europe.[1] The course of IBD typically consists of flares of disease activity interspersed with periods of disease quiescence. Several factors are implicated in its development, including dysbiosis, reduced integrity of the intestinal barrier, and immune dysfunction within the gut. The gut and brain communicate through the gut–brain axis, and this bi-directional communication system is being increasingly recognised as having a crucial role in both the psychological health[2] and prognosis of individuals with IBD.[3] Individuals with ongoing disease activity are more likely to develop new-onset symptoms of depression or anxiety than those whose disease is quiescent,[4,5] and those with coexistent symptoms of anxiety or depression appear to be more likely to have adverse disease outcomes than those without these symptoms.[4–6] Once psychological symptoms develop, they appear to be persistent or fluctuating, with as few as one in ten people with IBD having complete resolution of these symptoms.[7]

However, whether treatments directed at the gut–brain axis, such as psychological therapies, can influence disease activity or psychological health in individuals with IBD is unclear. Although there have been multiple randomised controlled trials (RCTs) examining the effects of interventions, including cognitive behavioural therapy (CBT) and gut-directed hypnotherapy, in people with IBD, many of these RCTs are small and underpowered, have high rates of loss to follow-up, study different outcomes (eg, anxiety, depression, stress, or quality of life), and show conflicting results. We previously assessed this issue via a systematic review and meta-analysis,[8] identifying all RCTs published up to 2016.

The meta-analysis of these RCTs did not show any long-term benefit of psychological therapies for either IBD activity or psychological health. However, only 14 RCTs of 1196 people with IBD were included in this previous systematic review and meta-analysis.

Since that previous meta-analysis, multiple RCTs have been conducted. Therefore, we aimed to update our previous systematic review and meta-analysis of psychological therapies in individuals with IBD. We aimed to assess whether psychological therapy had any effect on disease activity, psychological symptoms (ie, anxiety, depression, or stress scores), or health-related quality of life.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched MEDLINE, Embase, Embase Classic, PsychINFO, and the Cochrane Central Register of Controlled Trials for RCTs published between Jan 1, 2016, and April 30, 2023, without any language restrictions to update our previous systematic review and meta-analysis.[8] We also hand-searched conference proceedings (ie, Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and Asian Pacific Digestive Week) between Jan 1, 2016, and April 30, 2023, to identify trials published only in abstract form. We did not search trial registries. We also conducted a recursive search of the bibliographies of all eligible articles.

We defined eligible studies as those including adults (ie, aged ≥16 years) with an endoscopically, histologically, or radiologically confirmed diagnosis of IBD that reported the effect of psychological therapy of any modality compared with a control intervention or treatment as usual on inducing remission for individuals with active disease; on preventing relapse for individuals with quiescent disease; or on disease activity, depression, anxiety, perceived stress, or quality of life. Only RCTs were eligible for inclusion. The eligibility criteria were defined a priori (appendix p 1).

The literature search was conducted by two investigators (CR and ACF) using the terms "cognitive therapy", "psychotherapy", "behaviour therapy", "relaxation techniques", "mindfulness", "meditation", or "hypnosis" as both MeSH terms and free-text terms and the terms "behavioural therapy", "relaxation therapy", "mindfulness meditation", "psychotherapy", or "hypnotherapy" as free-text terms. These terms were combined, via the set operator "AND", with studies identified with the terms "Crohn disease", "inflammatory bowel disease", "colitis", "ileitis", or "ulcerative colitis" as MeSH terms and with the free-text terms "Crohn$ disease" or "regional enteritis". We applied no language restrictions to the search. Two investigators (CR and ACF) independently evaluated all abstracts identified. We obtained potentially relevant papers, which were then evaluated in more detail using predesigned forms to independently assess eligibility according to the predefined criteria. We planned to translate papers not published in English, but translation was not required. We resolved disagreements between investigators by discussion. If studies did not report all data on our dichotomous or continuous outcomes but were otherwise eligible for inclusion in the meta-analysis, we attempted to contact the original investigators via email to obtain additional data. For duplicate RCTs, we included the publication with the most extractable data and excluded all other publications.

Data analysis

The dichotomous outcomes we assessed were the effect of psychological therapy versus control intervention or treatment as usual in inducing remission in people with active IBD or in preventing relapse of disease activity in people with quiescent IBD. We extracted data for these outcomes assessed at final follow-up of each trial to maximise the number of events in the analysis. The continuous outcomes we assessed were the effects of psychological therapies versus control intervention or treatment as usual on clinical disease activity indices, anxiety scores, depression scores, stress scores, and quality-of-life scores. Trials were analysed separately according to whether they recruited people with clinically active IBD or predominantly those whose disease was quiescent at the time of randomisation (ie, more people included in the RCT had quiescent IBD than had active IBD). We excluded trials recruiting mixed populations of individuals with active or quiescent IBD in prespecified sensitivity analyses. As the effect of psychological therapies on mood and quality of life might be greatest immediately after completion of therapy, we extracted data for these outcomes at completion of therapy and at final follow-up for each trial. We analysed outcomes by IBD type if data were available.

Data extraction was independently conducted by two investigators (CR and ACF) using a Microsoft Excel spreadsheet (XP Professional Edition version 2306) for dichotomous outcomes (remission or no remission in people with active IBD; relapse or no relapse of disease activity in individuals with quiescent IBD) and mean disease activity indices, anxiety scores, depression scores, stress scores, and quality-of-life scores with SDs (continuous outcomes). For dichotomous outcomes, we extracted data as intention-to-treat (ITT) analyses if trial reporting allowed, with all individuals who dropped out assumed to have done so as a result of ineffective treatment (in trials of active IBD) or disease relapse (in trials of quiescent IBD). For the continous outcomes, mean scores and SDs after psychological therapy or control intervention or treatment as usual could only be obtained for people for whom complete data were available. Furthermore, the type of psychological therapy used, country, setting (ie, based in primary, secondary, or tertiary care), number of centres, number of sessions of psychological therapy administered, duration of therapy,

See Online for appendix

and duration of follow-up were recorded for each trial. We also recorded the handling of the control group in each trial.

We used the Cochrane risk of bias tool to assess bias at the study level.[12] Two investigators (CR and ACF) independently conducted this assessment and recorded the methods used to generate the randomisation schedule and conceal treatment allocation; whether masking was implemented for participants, personnel, and outcomes assessors; whether there was evidence of incomplete outcome data for any of the outcomes of interest; and whether there was evidence of selective reporting of outcomes. We resolved disagreements by discussion.

We measured the degree of agreement between the two investigators (CR and ACF) in terms of judging study eligibility using the κ statistic. We pooled all data using a random-effects model[13] to provide a conservative estimate of the effect of psychological therapies on disease outcomes in people with IBD. For dichotomous outcomes, we expressed the effects of psychological therapies as the relative risk (RR) with 95% CI of not achieving remission with intervention versus control in trials of therapy for individuals with active IBD or the RR with 95% CI of relapse of disease activity in trials of therapy for individuals with quiescent IBD. If psychological therapies appeared more efficacious than control, we planned to calculate the number needed to treat (NNT), along with the 95% CI, using the formula NNT=1/(control event rate×[1−RR]); however, this calculation was not required. For continuous data, including effects on disease activity indices; anxiety, depression, and stress scores; and quality-of-life scores, we summarised the effect of psychological therapies using standardised mean difference (SMD) and 95% CIs. An SMD of 0·2 can be considered to represent a small effect, 0·5 a moderate effect, and 0·8 a large effect.[14]

We conducted subgroup analyses including only trials of the same modality of psychological therapy, if sufficient RCTs existed, to assess whether the effect was stronger for any specific treatment modality for all outcomes, if data were available. These subgroup analyses were only possible for CBT (ie, therapy emphasising thoughts and beliefs in understanding and changing behaviour and emotional responses) and so-called third-wave psychological approaches. Third-wave psychological approaches have evolved from CBT and focus on the process of change and how a person relates to internal experiences (ie, false self-beliefs). They include acceptance, mindfulness, and value-focused approaches.[15] We also conducted subgroup analyses for all outcomes, if data were available, according to whether trials recruited selected groups of individuals with IBD, such as those with anxiety, depression, stress, fatigue, or reduced quality of life, as we hypothesised that these people might be more likely to benefit from psychological therapy than unselected individuals.

We assessed heterogeneity between studies using the χ^2 test, with a p value of <0·1 used to define a significant degree of heterogeneity, and the I^2 statistic. I^2 ranges between 0% and 100%, with values of 0–24% indicating no heterogeneity, 25–49% considered low, 50–74% considered moderate, and 75% or more considered high heterogeneity.[16] We used Review Manager version 5.4.1 to generate forest plots of pooled RRs and SMDs with 95% CIs and funnel plots. We assessed these funnel plots for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test if there was a sufficient number of studies (ie, ten or more) included in the meta-analysis.[17,18]

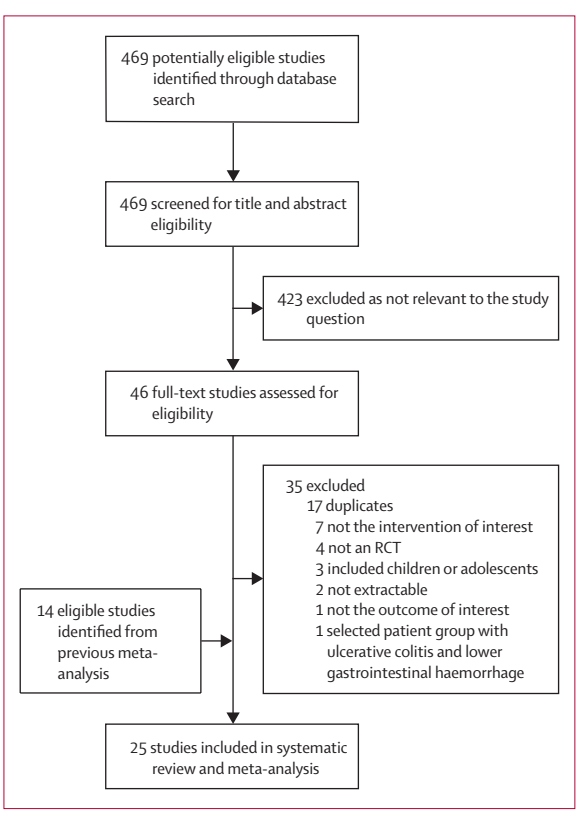

Figure 1: **Study selection**
RCT=randomised controlled trial.

Role of the funding source
There was no funding source for this study.

Results

The updated literature search identified a total of 469 new records, of which, after title and abstract review, we deemed 46 potentially relevant and assessed them further for eligibility (figure 1). We were able to obtain supplementary data for three RCTs,[9–11] enabling their inclusion. 35 citations were subsequently excluded, leaving 11 new eligible studies[9–11,19–26] to be pooled with the existing 14 studies found eligible for inclusion in the previous systematic review and meta-analysis.[27–40] Two RCTs[22,33] reported that they recruited individuals

with quiescent IBD and functional symptoms that met the criteria for irritable bowel syndrome. Agreement between reviewers for eligibility assessment was excellent (κ 0·83). Detailed characteristics of the 25 eligible RCTs are provided in the appendix (pp 2, 11). All of the trials were considered at high risk of bias (appendix p 2). Four of the RCTs were conducted only in individuals with active IBD,[9,25,30,31] 18 were conducted only in those with quiescent IBD,[10,11,19,23,24,26–29,32–40] and three were conducted in mixed populations (these three were excluded from sensitivity analyses).[20–22] For individual analyses, trials were pooled according to type of data reported (ie, people with quiescent IBD *vs* people with active IBD).

Ten trials used third-wave therapies, such as mindfulness or acceptance and commitment therapy,[9–11,20,23–26,34,37] eight trials used CBT,[19,21,22,30,32,33,35,36] two trials used solution-focused therapy,[39,40] one trial used psychodynamic therapy,[29] one trial used gut-directed hypnotherapy,[38] one trial used guided imagery,[31] one trial used stress management,[27] and one trial used a combination of multiple therapies.[28] Only nine RCTs recruited specific populations of people, rather than unselected individuals with IBD. Four RCTs recruited people with fatigue,[19,26,39,40] two recruited individuals with increased stress,[20,24] one recruited those with depression,[10] one recruited people with reduced quality-of-life scores,[21] and one recruited those with either increased stress or reduced quality-of-life scores.[11]

Of the four trials including individuals with IBD with ongoing active disease,[9,25,30,31] only one reported dichotomous data concerning the effect of psychological therapy in inducing the remission of active IBD.[30] In total, 12 (21%) of 57 patients with active IBD undergoing stress-management psychotherapy entered clinical remission compared with two (4%) of 57 patients in the control group (treatment as usual) after 18 months of follow-up. Only one of these four trials reported the effect of psychological therapy on disease activity indices in patients with active disease (n=116),[9] with significantly lower disease activity indices at completion of therapy when comparing the reduction from baseline for intervention with the reduction from baseline for control in people assigned to CBT and mindfulness-based stress reduction (median 4·0, IQR 2·0–5·0, p<0·001) versus those allocated to the waiting list (7·0, 4·5–9·0, p=0·005).

In total, ten RCTs reported dichotomous data concerning the effect of psychological therapy on relapse rates in individuals with quiescent IBD only. One RCT included people with Crohn's disease,[29] four RCTs included people with ulcerative colitis,[23,28,34,38] and five RCTs included individuals with IBD.[11,20,24,33,35] Overall,

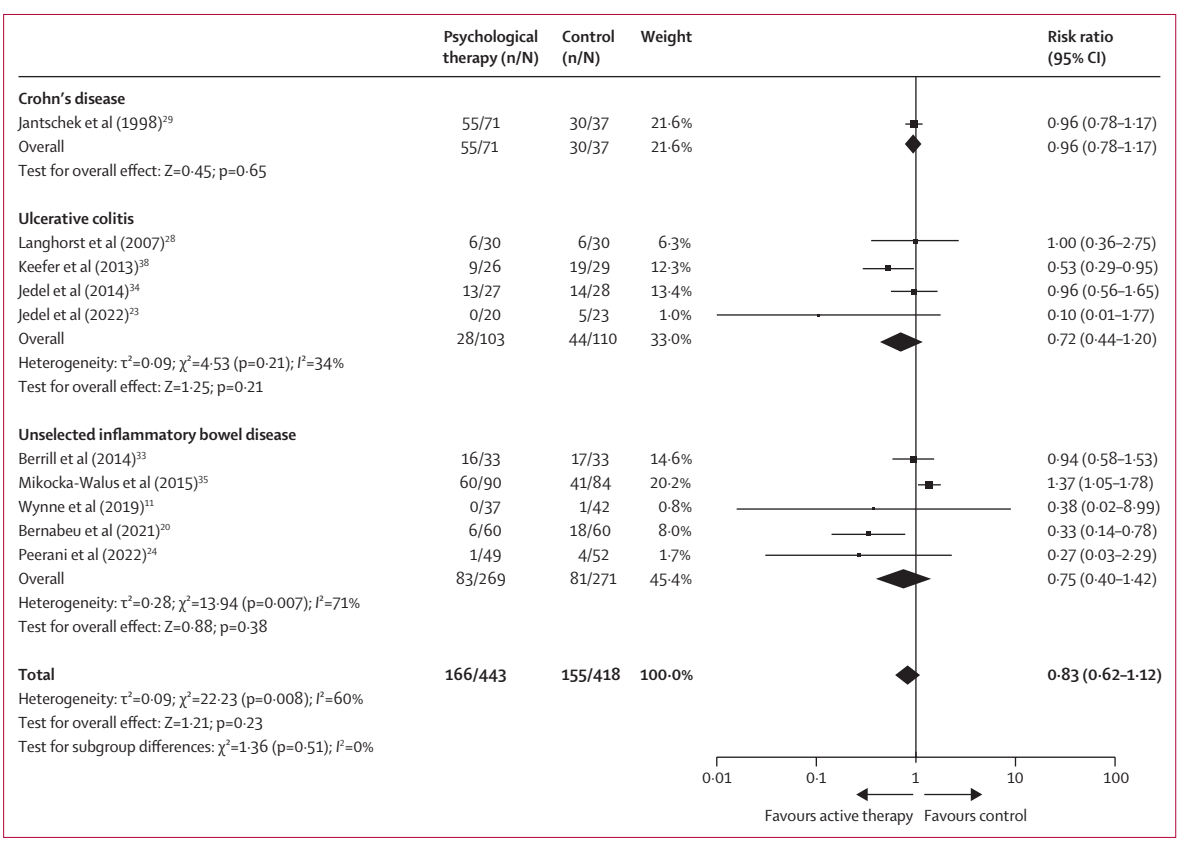

Figure 2: **Forest plot of randomised controlled trials reporting the effect of psychological therapy versus control in preventing relapse in individuals with quiescent inflammatory bowel disease at final follow-up**

166 (38%) of 443 individuals assigned to psychological therapy had a relapse of disease activity compared with 155 (37%) of 418 in the control groups. Compared with control intervention or treatment as usual, the RR of relapse of disease activity in all individuals with quiescent IBD assigned to psychological therapy was 0·83 (95% CI 0·62–1·12; figure 2). There was moderate heterogeneity between studies (I^2=60%) and the funnel plot (appendix p 24) suggested evidence of publication bias or other small study effects (Egger test p=0·046). There was also no effect according to the type of IBD (figure 2). Relapse rates by CBT versus third-wave therapy or for selected populations versus unselected populations were not assessed.

13 RCTs reported data on the effect of psychological therapy on disease activity indices at completion of therapy in 1015 individuals with quiescent IBD.[11,19,20,22–24,27,28,34–37,40] Nine RCTs assessed effect on disease activity indices in people with Crohn's disease,[11,19,20,24,27,35–37,40] 12 assessed effect in those with ulcerative colitis,[11,19,20,23,24,27,28,34–37,40] and one assessed effect in individuals with IBD;[22] some studies assessed more than one of these groups. There was no significant difference in disease activity indices among participants assigned to psychological therapy compared with those in the control groups at completion of therapy (SMD –0·01, 95% CI –0·13 to 0·12; table 1; appendix p 4) and no evidence of heterogeneity between studies (I^2=0%; Egger test p=0·14). There was also no effect of psychological therapies on disease activity indices according to IBD type (appendix p 4). Excluding two trials that included a mixed population of people with quiescent IBD and people with active IBD did not affect the significance of the pooled result (847 people; SMD –0·08, 95% CI –0·22 to 0·05, p=0·23; I^2=0%, p=1·00).[20,22] Results were similar when the 11 trials (n=663) reporting effect on disease activity indices at the last point of follow-up were pooled (Egger test p=0·66; table 1; appendix p 5).[11,19,23,27,28,34–37,39,40] None of the studies recruiting mixed populations reported data from final follow-up, only at completion of therapy. There were sufficient data to pool trials of CBT and third-wave therapies; neither had a significant effect on disease activity indices (table 2). Similarly, there was no effect in trials that recruited selected or unselected groups of people (table 3).

Two RCTs reported on the effect of psychological therapy on anxiety scores in 79 individuals with active IBD.[25,31] There was no benefit in favour of active therapy at completion of therapy (SMD –1·04, 95% CI –2·46 to 0·39). Only one RCT reported on the effect of psychological therapy on depression scores or stress scores in individuals with active IBD,[31] meaning formal meta-analysis was not possible. In this trial, there was a significant improvement in stress scores (mean 2·83, SD 2·43 in the therapy group; 4·10, 1·99 in the control group; p<0·01) but no improvement in depression scores compared with the control group (1·39, 2·23 in the therapy group; 1·90, 1·99 in the control group; no p value). All four RCTs including people with active IBD reported the effect of psychological therapy on quality-of-life scores in 309 individuals.[9,25,30,31] Overall, quality-of-life scores were significantly higher after completion of therapy in those assigned to active treatment versus control (SMD 0·68, 95% CI 0·09 to 1·26; p=0·02; appendix p 3), but with high heterogeneity between studies (I^2=82%). There were no data for people with active disease at final follow-up for these outcomes.

13 RCTs provided data on the effect of psychological therapy on anxiety scores at completion of therapy in individuals with quiescent IBD[10,11,19–24,27,28,35,36,40] and nine provided data at final follow-up.[10,11,23,26,27,35,36,39,40] At completion of therapy, when data were pooled from a total of 1088 individuals, anxiety scores were significantly lower in those assigned to a psychological therapy than those assigned to a control group (table 1; figure 3). There was no heterogeneity between the included RCTs (I^2=18%; Egger test p=0·96). The effect was similar when the three trials that recruited a mixed population of individuals were excluded from the analysis (784 people; SMD –0·20, 95% CI –0·36 to –0·05; p=0·008; I^2=10%, p=0·35).[20–22] In the 700 people analysed, the significant difference in anxiety scores did not persist at final follow-up (table 1; appendix p 6). Subgroup analysis in trials of CBT or third-wave therapies showed that third-wave therapies had a beneficial effect on anxiety scores, but this effect was only significant at completion of therapy (table 2). In the subgroup analysis between selected and unselected populations, this beneficial effect on anxiety scores was only seen at completion of therapy in trials recruiting selected individuals (table 3).

	Number of trials	Number of participants	SMD (95% CI) for effect of psychological therapy	p value for the difference	I^2 (p value for χ^2)
Disease activity indices					
At completion of therapy	13	1015	–0·01 (–0·13 to 0·12)	0·91	0% (0·93)
At final follow-up	11	663	–0·03 (–0·18 to 0·12)	0·71	0% (0·91)
Anxiety scores					
At completion of therapy	13	1088	–0·23 (–0·36 to –0·09)	0·0009	18% (0·26)
At final follow-up	9	700	–0·17 (–0·34 to 0·01)	0·06	20% (0·25)
Depression scores					
At completion of therapy	15	1189	–0·26 (–0·38 to –0·15)	<0·0001	2% (0·43)
At final follow-up	12	856	–0·16 (–0·30 to –0·03)	0·02	0% (0·94)
Stress scores					
At completion of therapy	11	813	–0·22 (–0·42 to –0·03)	0·03	47% (0·04)
At final follow-up	9	551	–0·18 (–0·40 to 0·04)	0·11	38% (0·12)
Quality-of-life scores					
At completion of therapy	16	1080	0·31 (0·16 to 0·46)	<0·0001	30% (0·13)
At final follow-up	14	773	0·13 (–0·02 to 0·29)	0·08	8% (0·36)

SMD=standardised mean difference.

Table 1: **Effect of psychological therapy versus control on clinical disease activity indices and anxiety, depression, stress, and quality-of-life scores in people with quiescent inflammatory bowel disease**

15 RCTs examined the effect of psychological therapy on depression scores at completion of therapy in individuals with quiescent IBD[10,11,19–24,27,29,34–37,40] and 12 examined the effect at final follow-up.[10,11,23,26,27,29,34–37,39,40] Data were available for 1189 individuals at completion of therapy, with a significant reduction in depression scores for those assigned to psychological therapy compared with control (table 1; figure 4) and no heterogeneity between studies (Egger test p=0·39). Removing the three studies with a mixed population had no effect on the pooled result (885 people; SMD –0·28, 95% CI –0·41 to –0·15; p<0·001; I^2=0%, p=0·57).[20–22] At final follow-up, when data were pooled from 856 individuals, the significant effect on depression scores persisted, with no heterogeneity (Egger test p=0·77; table 1; appendix p 7). Subgroup analysis showed that both CBT and third-wave therapies significantly improved depression scores versus control at completion of therapy, but this finding was only present at final follow-up for third-wave therapies (table 2). The effect on depression scores was only seen at completion of therapy in trials recruiting selected individuals (table 3).

11 RCTs reported data on the effect of psychological therapy on stress scores in individuals with quiescent IBD compared with control at completion of therapy[10,11,20,23,24,32–36,38] and nine reported data at final follow-up.[10,11,23,32–36,38] When data were pooled at the completion of therapy (in 813 participants across both groups), psychological therapy led to a significant reduction in stress scores compared with control intervention (table 1; appendix p 8), with low heterogeneity between studies (Egger test p=0·93). At final follow-up, when data were available for 551 individuals, there was no beneficial effect of psychological therapies compared with control (table 1; appendix p 9). A significant effect on stress scores was only shown in trials of third-wave therapies, which persisted to final follow-up (table 2). The effect on stress scores was only seen in trials recruiting selected individuals, which persisted to final follow-up (table 3). Sensitivity analysis removing mixed populations for stress outcome was not possible because no mixed-population studies reported stress scores at final follow-up.

16 RCTs reported data on the effect of psychological therapy on quality of life in individuals with quiescent IBD at completion of therapy[10,19–24,28,29,32–34,36–38,40] and 14 reported data at final follow-up.[10,19,23,26,28,29,32–34,36–40] There was a significant improvement in IBD-specific quality of life at completion of therapy when data were pooled from 1080 people (table 1; figure 5), with low heterogeneity

	Number of trials	Number of participants	SMD (95% CI) for effect of psychological therapy	p value for the difference	I^2 (p value for χ^2)
Disease activity indices					
At completion of CBT	4	360	0·07 (–0·14 to 0·18)	0·50	0% (0·60)
At final follow-up with CBT	3	203	–0·05 (–0·34 to 0·23)	0·72	0% (0·98)
At completion of third-wave therapy	6	412	–0·04 (–0·24 to 0·15)	0·66	0% (0·79)
At final follow-up with third-wave therapy	4	168	–0·07 (–0·39 to 0·24)	0·64	11% (0·35)
Anxiety scores					
At completion of CBT	5	465	–0·17 (–0·42 to 0·09)	0·20	43% (0·13)
At final follow-up with CBT	2	204	–0·10 (–0·45 to 0·26)	0·59	44% (0·18)
At completion of third-wave therapy	5	379	–0·27 (–0·50 to –0·04)	0·02	16% (0·31)
At final follow-up with third-wave therapy	4	263	–0·15 (–0·48 to 0·19)	0·40	43% (0·16)
Depression scores					
At completion of CBT	5	466	–0·24 (–0·45 to –0·03)	0·03	21% (0·28)
At final follow-up with CBT	2	204	–0·20 (–0·46 to 0·07)	0·15	0% (0·47)
At completion of third-wave therapy	7	454	–0·36 (–0·55 to –0·17)	0·0002	0% (0·59)
At final follow-up with third-wave therapy	6	338	–0·26 (–0·47 to –0·04)	0·02	0% (0·90)
Stress scores					
At completion of CBT	4	333	–0·01 (–0·35 to 0·34)	0·98	54% (0·09)
At final follow-up with CBT	4	300	–0·13 (–0·39 to 0·14)	0·35	20% (0·29)
At completion of third-wave therapy	6	430	–0·39 (–0·61 to –0·17)	0·0004	18% (0·29)
At final follow-up with third-wave therapy	4	201	–0·39 (–0·71 to –0·06)	0·02	23% (0·27)
Quality-of-life scores					
At completion of CBT	6	435	0·34 (0·08 to 0·60)	0·009	37% (0·16)
At final follow-up with CBT	4	216	0·33 (–0·08 to 0·73)	0·11	41% (0·17)
At completion of third-wave therapy	6	372	0·37 (0·16 to 0·57)	0·0005	0% (0·45)
At final follow-up with third-wave therapy	5	259	0·20 (–0·06 to 0·46)	0·13	6% (0·37)

CBT=cognitive behavioural therapy. SMD=standardised mean difference.

Table 2: **Effect of CBT or third-wave therapy versus control on clinical disease activity indices and anxiety, depression, stress, and quality-of-life scores in people with quiescent inflammatory bowel disease**

	Number of trials	Number of participants	SMD (95% CI) for effect of psychological therapy	p value for the difference	I^2 (p value for χ^2)
Disease activity indices					
At completion of therapy in selected groups	5	409	−0·06 (−0·26 to 0·14)	0·55	0% (0·79)
At final follow-up in selected groups	4	204	0·05 (−0·23 to 0·33)	0·71	0% (0·68)
At completion of therapy in unselected groups	8	606	0·03 (−0·13 to 0·19)	0·73	0% (0·84)
At final follow-up in unselected groups	7	459	−0·07 (−0·25 to 0·12)	0·49	0% (0·86)
Anxiety scores					
At completion of therapy in selected groups	7	546	−0·37 (−0·54 to −0·21)	<0·0001	0% (0·55)
At final follow-up in selected groups	5	338	−0·21 (−0·44 to 0·01)	0·06	6% (0·38)
At completion of therapy in unselected groups	6	542	−0·07 (−0·24 to 0·09)	0·39	0% (0·56)
At final follow-up in unselected groups	4	362	−0·11 (−0·39 to 0·17)	0·44	41% (0·15)
Depression scores					
At completion of therapy in selected groups	7	546	−0·43 (−0·60 to −0·26)	<0·0001	0% (0·50)
At final follow-up in selected groups	5	338	−0·18 (−0·39 to 0·03)	0·10	0% (0·79)
At completion of therapy in unselected groups	8	643	−0·12 (−0·28 to 0·03)	0·12	0% (0·92)
At final follow-up in unselected groups	7	518	−0·15 (−0·33 to 0·02)	0·09	0% (0·82)
Stress scores					
At completion of therapy in selected groups	4	341	−0·45 (−0·74 to −0·17)	0·002	39% (0·18)
At final follow-up in selected groups	2	112	−0·62 (−1·00 to −0·24)	0·002	0% (0·69)
At completion of therapy in unselected groups	7	472	−0·07 (−0·28 to 0·14)	0·54	21% (0·27)
At final follow-up in unselected groups	7	439	−0·08 (−0·29 to 0·12)	0·43	12% (0·34)
Quality-of-life scores					
At completion of therapy in selected groups	6	464	0·44 (0·26 to 0·63)	<0·0001	0% (0·57)
At final follow-up in selected groups	5	271	0·08 (−0·16 to 0·31)	0·52	0% (0·95)
At completion of therapy in unselected groups	10	616	0·21 (0·01 to 0·42)	0·04	35% (0·13)
At final follow-up in unselected groups	9	502	0·18 (−0·06 to 0·43)	0·14	42% (0·09)

SMD=standardised mean difference.

Table 3: **Effect of psychological therapy versus control on clinical disease activity indices and anxiety, depression, stress, and quality-of-life scores in selected and unselected people with quiescent inflammatory bowel disease**

between studies (Egger test p=0·80). Exclusion of the three studies that recruited a mixed population of participants had no effect on the pooled result (776 people; SMD 0·34, 95% CI 0·17 to 0·52; p<0·001; I^2=25%, p=0·20).[20–22] However, at final follow-up in 773 individuals, the effect of psychological therapies on quality of life was not significant (Egger test p=0·41; table 1; appendix p 10). A significant improvement in quality-of-life scores was seen in trials of both CBT and third-wave therapies at completion of therapy, but this improvement did not persist to final follow-up (table 2). An improvement in quality-of-life scores was seen in trials recruiting both selected and unselected individuals, but was strongest in selected groups and did not persist to final follow-up with either therapy (table 3).

Discussion

We present findings from an updated systematic review and meta-analysis examining the effects of psychological therapies on disease activity indices, disease relapse, psychological health, and quality of life in individuals with IBD. To date, only one study has examined the effect of psychological therapy in people with clinically active IBD,[9] preventing any formal meta-analysis or conclusions as to their effect in terms of inducing remission. The small number of trials in people with active IBD also precluded formal meta-analysis to examine the effects of psychological therapy on psychological health, except for anxiety scores for which no benefit was shown. There was no effect of psychological therapies on the risk of relapse of disease activity or clinical disease activity indices in individuals with quiescent IBD. In terms of other outcomes, however, psychological therapies, when considered together, led to short-term improvements in anxiety, depression, and stress scores in individuals with quiescent IBD; this improvement persisted to final follow-up for depression scores, but not for anxiety or stress scores. Most of the effect sizes observed were small, but some were more moderate. When we conducted subgroup analysis, only third-wave therapies were associated with significant effects on anxiety and stress scores at completion of therapy, but both CBT and third-wave therapies led to improvements in depression scores at completion of therapy. Third-wave therapies were also associated with improvements in depression and stress scores at final follow-up. Anxiety, depression, and stress scores only improved in trials recruiting selected groups of people with IBD in whom psychological therapy might be expected to have the most benefit. Quality-of-life scores

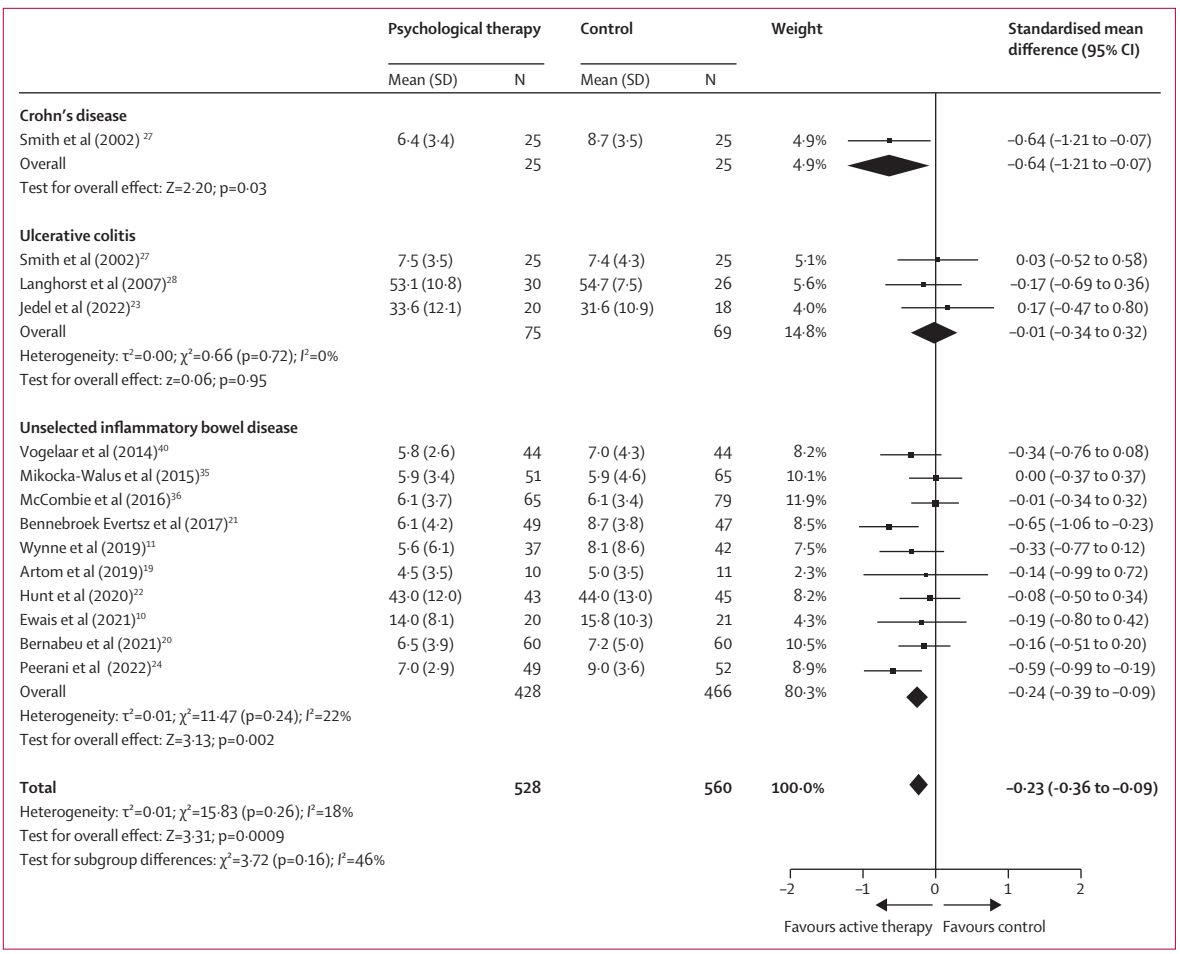

Figure 3: **Forest plot of randomised controlled trials reporting the effect of psychological therapy versus control on anxiety scores in individuals with quiescent inflammatory bowel disease at completion of therapy**

improved with psychological therapies at completion of treatment both for individuals with active and those with quiescent IBD, with CBT and third-wave therapies, and in selected and unselected people, although these improvements were not significant at final follow-up. Overall, we found no significant differences regarding the effects of psychological therapies between individuals with Crohn's disease and those with ulcerative colitis.

The number of eligible RCTs since the previous version of this systematic review and meta-analysis has increased considerably, with data from an additional 11 studies available.[8] Other strengths of this updated meta-analysis include the independent eligibility assessment and data extraction done in duplicate, use of a random-effects model to provide a conservative estimate of the effect of psychological therapies in individuals with IBD, and the subgroup analyses according to modality of psychological treatment and whether selected groups of individuals who could be expected to be more likely to respond to psychological therapy, rather than unselected patients with IBD, were recruited. We used an ITT analysis for dichotomous outcomes, with all individuals lost to follow-up presumed to have no response to treatment. We also extracted data separately, wherever possible, according to type of IBD and conducted analyses separately according to disease activity at the time of recruitment, which enabled accurate interpretation of the effects of psychological therapies in these separate populations. Furthermore, we contacted the authors of the original studies to obtain supplementary data, maximising the number of studies eligible for inclusion.

Limitations of our meta-analysis occur particularly in the subgroup of patients with clinically active IBD, for whom the small number of studies precluded, for the most part, any meaningful conclusions from being made. Furthermore, there was substantial heterogeneity between trials of effect on quality-of-life scores. None of the trials were at low risk of bias, largely because masking in trials of psychological therapy is logistically difficult. Of the 24 studies included, only two trials were reported as being double-blind.[23,34] Furthermore, only seven trials that reported continuous data provided results for all individuals who completed the treatment course, which might mean that the benefit of psychological therapies in

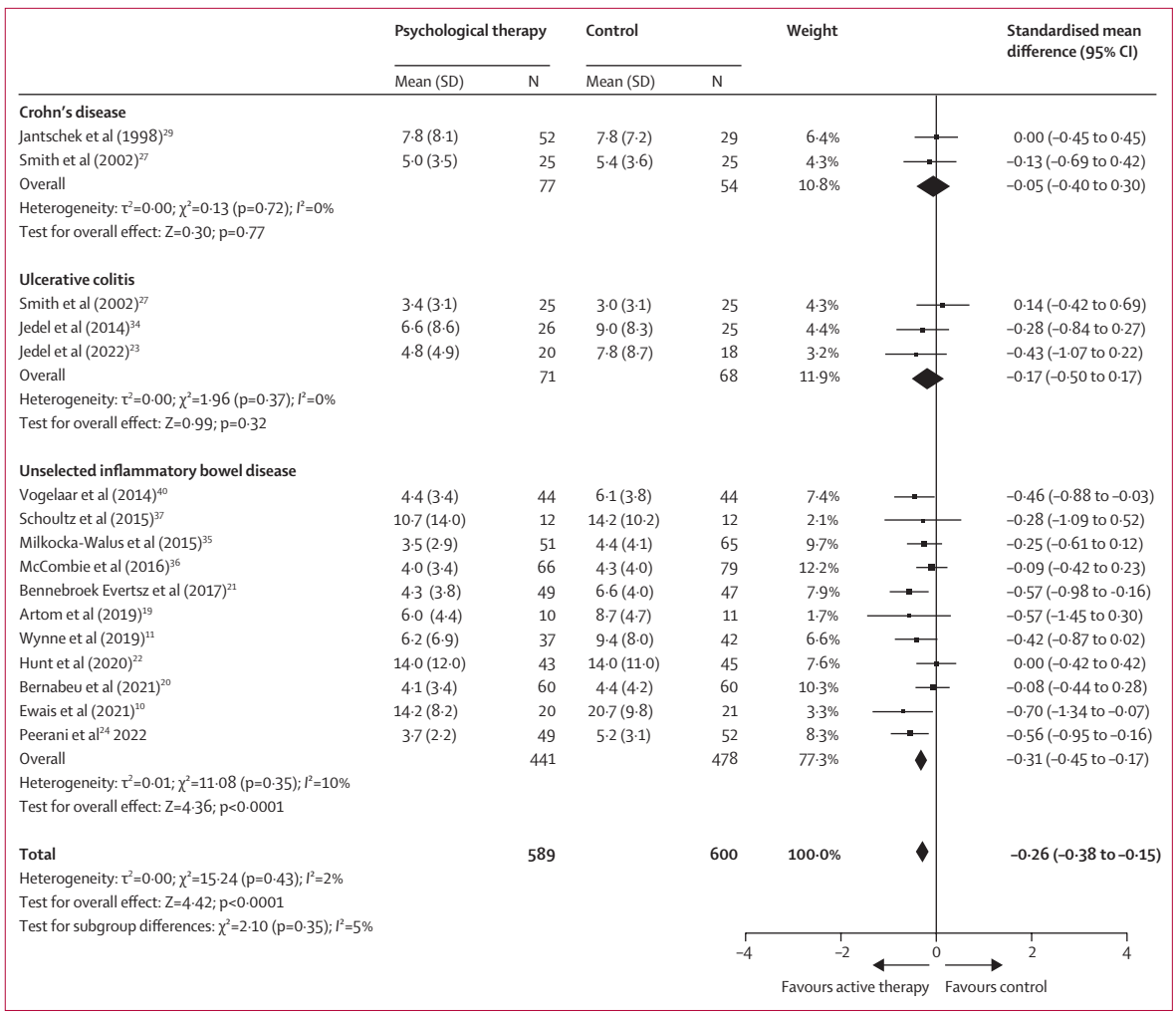

Figure 4: **Forest plot of randomised controlled trials reporting the effect of psychological therapies versus control on depression scores in individuals with quiescent inflammatory bowel disease at completion of therapy**

people with IBD has been overestimated. Our pooling of individual RCTs to consider the effects of psychological therapy as one entity, despite studies recruiting different patient groups and using different protocols (eg, the type of psychological intervention administered, method of delivery, duration of treatment, and frequency of sessions), could be criticised. However, we attempted to address this limitation to some extent by conducting separate analyses for CBT and third-wave therapies and for different patient groups. Nevertheless, there are limitations in comparing CBT with third-wave therapies as third-wave therapies are derived from CBT (although they include some new constructs, such as acceptance or mindfulness).[41] Moreover, CBT studies tend to be older, whereas third-wave therapy could be considered to be the newer and improved CBT. We were unable to compare CBT with any other therapies as too few trials were available. To know whether there are any differences in efficacy between traditional (and longer) approaches, such as psychodynamic therapy, and briefer therapies, such as CBT, would be of great practical interest to gastropsychologists. In addition, the multitude of pharmacological treatments with established efficacy to treat individuals with IBD and the fact that few studies detailed alterations in medication or treatment escalation throughout the study period could be substantial confounding factors when considering the efficacy of psychological therapies, particularly in patients with active IBD. Finally, most RCTs included in this systematic review and meta-analysis were conducted in high-income countries, so whether there is any benefit of these therapies in other populations is unclear.

For functional gastrointestinal disorders, in which gut–brain axis communication is considered to be a fundamental driver of symptom burden, psychological therapies have an established contribution in reducing symptoms of anxiety and depression and physical-symptom burden.[42–44] Symptoms compatible with functional bowel disorders are reported by up to a third of

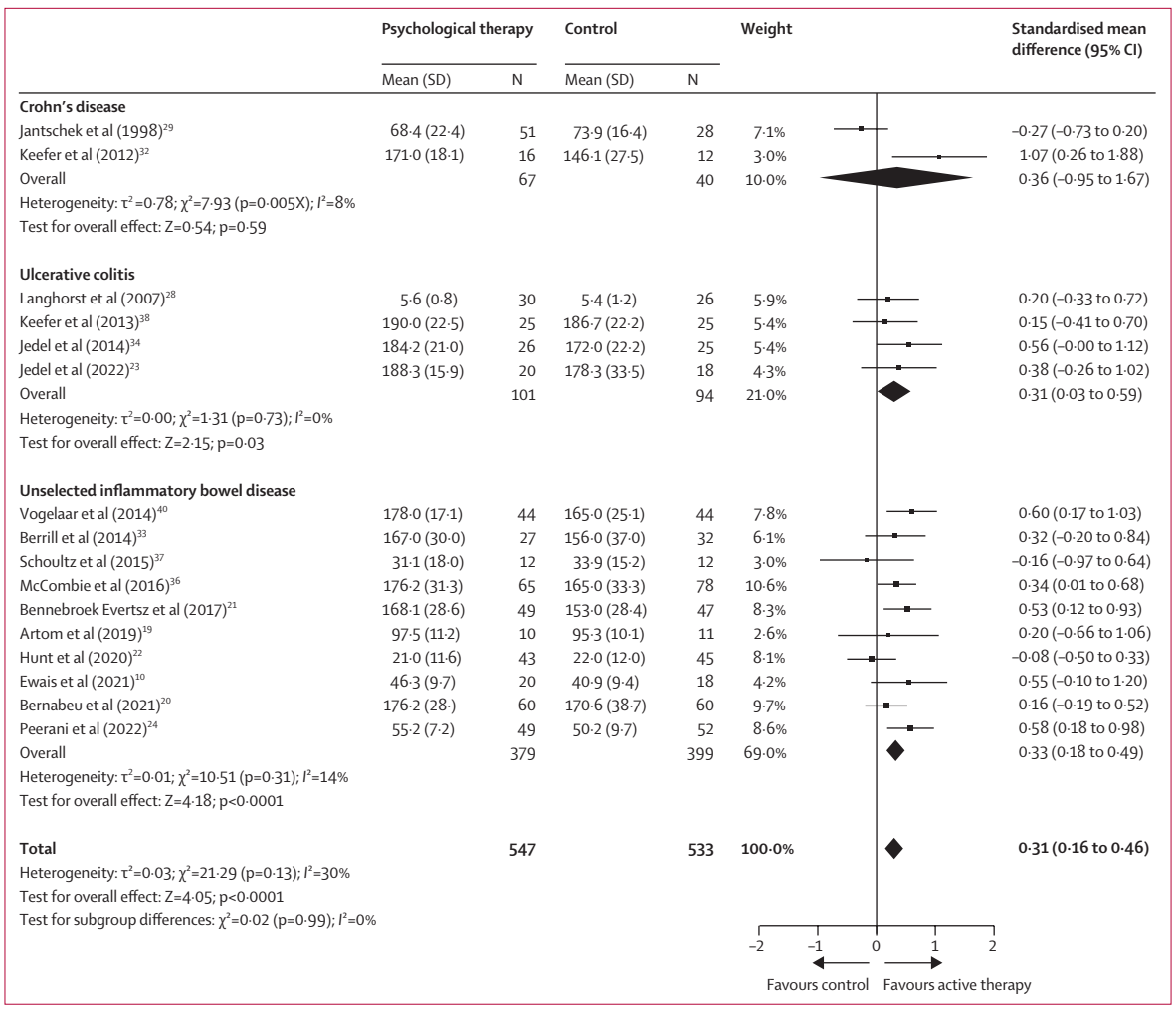

Figure 5: **Forest plot of randomised controlled trials reporting the effect of psychological therapies versus control on quality-of-life scores in individuals with quiescent inflammatory bowel disease at completion of therapy**

individuals with quiescent IBD[45–47] and evidence from a meta-analysis of 9192 individuals highlighted that gut–brain axis interactions also contribute to the natural history of IBD.[5] However, only two RCTs eligible for inclusion in this systematic review and meta-analysis reported that they recruited participants with quiescent IBD and what the authors defined as functional symptoms that met the criteria for irritable bowel syndrome,[22,33] and only one RCT reported a subgroup analysis examining this issue.[33] Furthermore, the presence of psychological comorbidity in individuals with IBD contributes to both adverse disease outcomes and increased health-care use,[3–7] which is particularly relevant considering the prevalence of psychological comorbidity in people with IBD compared with the general population.[2] Studies have previously shown that screening for psychological comorbidity is feasible in clinical practice[48] and national guidelines acknowledge that psychological therapies have a role in IBD management,[49] but there is no official guidance as to whom to refer for psychological therapies and when. The absence of official guidance might be due, in part, to uncertainty regarding the efficacy of psychological therapies in individuals with IBD, with individual studies having promising results but previous meta-analyses failing to show more than non-sustained improvements in quality-of-life and depression scores.[8,50] The findings from this systematic review and meta-analysis reveal, however, that some psychological therapies, particularly third-wave therapies, might be associated with improvements in psychological health and quality of life in individuals with IBD, particularly in people with impaired psychological health, fatigue, or reduced quality of life at baseline. These findings support the use of such therapies in clinical practice.

Despite the fact that psychological comorbidity in individuals with IBD is most prevalent during periods of disease activity[2,7] or in those with quiescent disease who have co-existing symptoms compatible with a functional

bowel disorder,[45,46] there were few RCTs examining the effects of psychological therapies in these populations. Furthermore, most trials assessing psychological therapies in individuals with quiescent IBD have been conducted in unselected populations irrespective of psychological health, despite there being evidence for a benefit in groups with impaired psychological health (particularly in paediatric populations).[48,51,52] Using unselected populations means a major benefit is unlikely to be shown, which was supported by the results of our subgroup analyses. Even if psychological therapies were of benefit in unselected populations, IBD services do not have the funding or the resources to provide access to such therapies for everyone with IBD. Future RCTs should therefore focus on assessing the effects of psychological therapies in individuals who have high levels of psychological symptoms at study entry, in those with irritable bowel-type symptoms in the presence of biochemical or mucosal remission, and in other individuals at risk of poor outcomes (eg, those reporting substantial pain or fatigue) who are more likely to benefit.

The findings of this systematic review and meta-analysis show the potential efficacy of psychological therapies in providing short-term improvements in anxiety, depression, stress, and quality-of-life scores in individuals with quiescent IBD, but not in improving disease activity indices or in preventing relapse of disease activity. Few studies of patients with active IBD were available for meta-analysis. Third-wave therapies appeared to exert a stronger effect than CBT in individuals with quiescent IBD, and the benefit of third-wave therapies persisted until final follow-up for depression and stress scores. However, further prospective trials assessing the efficacy of these therapies in individuals who are most likely to benefit from them are needed to enable formal guidelines to be developed to aid clinicians in the selection of individuals for psychological therapy in clinical settings.

Contributors

All authors conceptualised and drafted the study. CR and ACF collected, accessed, verified, analysed, and interpreted all data and drafted the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Trial-level data are already in the public domain, but reasonable requests for access to the trial-level data we extracted, and to supplemental data provided by individual original investigators, will be considered. No other data are available.

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