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Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: A systematic review and meta-analysis

Kelsey T. Laird [a,*], Emily E. Tanner-Smith [b,c], Alexandra C. Russell [d], Steven D. Hollon [e], Lynn S. Walker [d]

[a] Department of Psychology and Human Development, Vanderbilt University, Nashville, TN, USA
[b] Peabody Research Institute, Vanderbilt University, Nashville, TN, USA
[c] Department of Human and Organizational Development, Vanderbilt University, Nashville, TN, USA
[d] Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt University, TN, USA
[e] Department of Psychology, Vanderbilt University, Nashville, TN, USA

HIGHLIGHTS

- A meta-analysis of 31 RCTs of psychotherapy for adults with IBS was conducted.
- Psychotherapy significantly improved both mental health and daily functioning.
- Several therapy modalities were similarly effective for improving mental health.
- Cognitive behavior therapy was most effective at improving daily functioning.

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ABSTRACT

Previous meta-analyses have shown that psychotherapy improves gastrointestinal symptoms in adults with irritable bowel syndrome (IBS); however, the impact on functioning in daily activities is unknown. Meta-analysis was used to estimate the effect of psychotherapy on mental health and daily functioning in adults with IBS. An extensive literature search located 28 eligible randomized controlled trials (RCTs) providing outcome data for mental health and 18 RCTs providing data for daily functioning. Compared to a mixed group of control conditions, psychotherapy produced significantly greater improvements to mental health ($\bar{d} = 0.41$) and daily functioning ($\bar{d} = 0.43$). Cognitive behavior therapy (CBT) was evaluated in the largest number of trials (21 trials), followed by hypnosis (4 trials), psychodynamic (3 trials), and relaxation (2 trials). The psychotherapeutic modalities were comparable with respect to their effect on mental health. CBT produced the greatest improvements to daily functioning, and this effect was significantly larger than that produced by relaxation therapy. These results have important clinical implications for treatment of adults with IBS.

Contents

Abbreviations: GI, gastrointestinal; IBS, irritable bowel syndrome; ITT, intent-to-treat; RCT, randomized controlled trial; SMD, standardized mean difference; TAU, treatment as usual.

* Corresponding author at: Vanderbilt University, 2146 Belcourt Ave., Nashville, TN 37212, USA.
E-mail address: kelsey.t.laird@vanderbilt.edu (K.T. Laird).

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1. Introduction

Irritable Bowel Syndrome (IBS) is a common and often debilitating functional gastrointestinal disorder (FGID) characterized by abdominal pain and altered bowel habits. Like other FGIDs, IBS is thought to result from reciprocal interactions between biological, psychological, and social factors, and has no universally effective medical treatment (Van Oudenhove et al., 2016). Individuals with IBS report difficulties with a broad range of daily activities compared to healthy controls (Hungin et al., 2003). A systematic review of eleven studies found that the average cost of IBS to an individual's productivity ranges from $335 to $748 per year, with the total annual indirect cost estimated to be $205 million in the United States (Inadomi et al., 2003). This sizable impact of IBS on daily functioning likely results not only from gastrointestinal discomfort but also from emotional distress (Bass, 2009). Psychological disorders affect 50% to 94% of IBS patients (Lydiard, 2001; Whitehead et al., 2002), and number of psychiatric diagnoses has been shown to predict both degree of physical role limitations and number of days of restricted activity 15 months later. The degree of distress was so great in one sample of tertiary care patients that 38% reported seriously contemplating suicide as a result of their symptoms (Miller et al., 2004).

The lack of satisfactory medical treatment for IBS has led to the development of a variety of psychological therapies. The rationale for such therapies is grounded in the biopsychosocial model described by Engel (Engel, 1980; Engel, 1977) and applied to FGIDs by Drossman and colleagues (Drossman, 1998; Halpert & Drossman, 2005; Tanaka et al., 2011). As it applies to IBS, this model states that thoughts, emotions, and behaviors are bidirectionally related to gut physiology and symptom manifestations. The model delineates several pathways through which psychological factors may affect clinical outcomes (e.g., gastrointestinal symptoms, emotional wellbeing, and daily functioning) in IBS.

Although several meta-analyses have evaluated the effect of psychological therapies on gastrointestinal symptoms in IBS (Ford et al., 2014; Ford et al., 2009; Lackner et al., 2004; Laird et al., 2016), effects on other important patient-reported outcomes remain largely unexamined. Specifically, no meta-analysis to date has investigated the effect of psychotherapies on functioning in daily activities, and only one meta-analysis (published more than a decade ago) has evaluated the effect of psychotherapies on mental health among individuals with IBS (Lackner et al., 2004). Furthermore, no meta-analysis to date has investigated whether therapeutic modality moderates these effects. Our previous meta-analysis reported that cognitive behavior therapy (CBT),[1] relaxation therapy, and hypnosis therapy were similar in the magnitudes of their effects on gastrointestinal symptoms (Laird et al., 2016); however, whether these therapeutic modalities are comparable in their effects on mental health and functioning is unknown. Because CBT is more likely to promote behavior change, it is possible that CBT will be associated with greater improvements to functioning compared to other therapeutic modalities.

Whether delivery method (online vs. in-person) or format of therapy (group vs. individual) moderate improvements to mental health and daily functioning is another important question to explore, as this may promote more effective or efficient delivery of psychotherapy in this population. Our previous meta-analysis reported that therapies delivered online were no less effective for reducing gastrointestinal symptoms than therapies delivered in person (Laird et al., 2016). This could be good news for individuals living in geographically remote areas; however, whether online therapies are as effective at improving mental health and daily functioning is unknown. Similarly, our previous meta-analysis found that format of therapy (group vs. individual) did not significantly moderate the efficacy of psychotherapy for improving gastrointestinal symptoms. If therapy delivered in a group format is as effective as individual therapy for improving mental health and daily functioning, this could be a cost-effective method of delivery.

How the dose of therapy is related to therapeutic outcomes is another important question. A recent meta-regression of psychotherapy for depression found that more sessions, greater total contact time between therapist and patient, and greater number of sessions per week each correlated with greater symptom improvement (Cuijpers et al., 2013). However, these authors also found that a longer duration of therapy in weeks was associated with *less* reduction of depressive symptoms. In our previous meta-analysis, the effect of psychotherapy on gastrointestinal symptoms was not significantly moderated by any of the dosage variables coded (number of sessions, session duration, therapy duration in weeks, session frequency (Laird et al., 2016)). What effect such dosage characteristics have on improvements to mental health and daily functioning in IBS is unknown.

Conclusions about the efficacy of psychotherapy for IBS also may be premature without adequate consideration of the type of control condition used. Unlike medication trials, in which placebo controls are the gold standard, control conditions utilized in psychotherapy trials vary widely (Huang et al., 2015). In our previous meta-analysis, gastrointestinal symptom improvement was similar for trials using active ($\bar{d} = 0.66$) vs. non-active controls ($\bar{d} = 0.68$) (Laird et al., 2016). How control condition type influences improvements to mental health and daily functioning has yet to be investigated. Country in which the study was conducted was another moderator of interest. In our previous analysis, we found that studies conducted in Sweden produced significantly greater reductions in gastrointestinal symptoms compared to studies conducted in the US and the UK (Laird et al., 2016). Of the five Swedish trials included, the two providing exposure-based CBT had especially large effect sizes and likely at least partially account for the greater average effect size found in Swedish trials. Whether Swedish studies also demonstrate a greater improvement to mental health and daily functioning is unknown.

[1] Despite its name, cognitive therapy is a cognitive behavioral intervention that often incorporates behavioral strategies in the service of testing beliefs. Therefore we included interventions labeled "cognitive therapy" within the larger category of "cognitive behavior therapy".

Finally, determining what participant characteristics are associated with larger differential effects will be useful information to clinicians, researchers, and patients because it will help identify which individuals are most likely to benefit from psychotherapy. IBS is two-to-three times more common in women compared to men (Drossman et al., 1993; Longstreth & Wolde-Tsadik, 1993), and among individuals with IBS, women may exhibit higher degrees of psychological distress (Fock et al., 2001; Corney & Stanton, 1990). Although the reason for this is not entirely clear, gender role socialization likely plays some part (Chang et al., 2006). However, sex did not significantly moderate the efficacy of psychotherapy for improving gastrointestinal symptoms in our previous meta-analysis (Laird et al., 2016). The current analysis is the first to assess whether sex moderates the effect of psychotherapy on mental health and daily functioning in adults with IBS.

The primary aims of this review were to 1) examine the efficacy of psychotherapy for improving mental health and daily functioning, and 2) investigate whether efficacy is moderated by therapeutic modality (i.e., CBT, hypnosis, psychodynamic, and relaxation therapy). Our secondary aim was to explore additional potential moderators of treatment effects. We evaluated several characteristics of the therapy as potential moderators: delivery method (online, in-person), format (group, individual), and dose (number of sessions, session duration, therapy duration in weeks, session frequency). We also evaluated trial characteristics: type of control condition (active, non-active) and country in which the trial was conducted. Finally, we evaluated the percent of female participants as a potential moderator of treatment effects. As in our previous meta-analysis (Laird et al., 2016), in order to synthesize the highest quality of research evidence available, we made the a priori decision to include only randomized controlled trials.

2. Methods

This study was conducted in accordance with the PRISMA statement, which provides a detailed guideline of preferred reporting style for systematic reviews and meta-analyses (Liberati et al., 2009; Moher et al., 2009).

2.1. Search strategy

We searched PubMed, PsycINFO, Science Direct, and ProQuest Dissertations and Theses through August 15th 2015. We used terms related to IBS, psychotherapy, and controlled trials (see Appendix A for full search details).

2.2. Selection criteria

Eligible studies were (a) randomized controlled trials (RCTs) of (b) psychological intervention(s) for (c) individuals with IBS aged 18 years or older that (d) assessed mental health or daily functioning pre- and post-treatment using a continuous measure and were (e) written in English. To be as conservative and as consistent in the application of our eligibility criteria as possible, trials that used quasi-random methods of allocation assignment (e.g., assignment based on order of entry into the trial or social security number) were excluded to the extent that this could be determined (Hunt et al., 2009; Mahvi-Shirazi et al., 2012; Lowen et al., 2013; van Dulmen et al., 1996; Siegel, 2003). Cluster randomization was considered acceptable for trials evaluating therapies administered in a group format. We judged an intervention to be psychological if it was based on a psychological model or framework. Studies in which the only psychological intervention was a support group were not included due to the frequent use of support groups as a control condition.

Eligible control conditions were supportive therapy or support groups, education controls, "sham" treatments (for trials of biofeedback and hypnosis), online discussion forums, enhanced medical care (defined as any medical care not received by the intervention group), 'treatment as usual' (TAU), symptom monitoring, and wait-list. Enhanced medical care was only eligible to serve as a control condition if no antidepressant was administered to all participants.

Published and unpublished trials were eligible, including refereed journals, non-refereed journals, and dissertations. Although some researchers have argued that it is legitimate to exclude unpublished trials from meta-analyses (Weisz et al., 1995), it is not clear that published trials are always of high quality, nor that unpublished trials are always of poor quality. To limit publication bias, we therefore attempted to identify all relevant trials, including those in gray/unpublished literature, following recent recommendations (Borenstein et al., 2011). Details of our screening and coding procedures are provided in Appendix B.

2.3. Outcome assessment

Only mental health outcome data using validated measures were eligible for inclusion. Because validated measures of daily functioning have only recently become available, data from non-validated questionnaires were permitted for this outcome.

Mental health outcomes (in order of preference, based on availability) were 1) an overall index of mental health, 2) frequency or severity of anxiety symptoms, and 3) frequency or severity of depressive symptoms. Our decision to prioritize measures of anxiety over those of depression was informed by evidence that symptoms of anxiety may be more prevalent than depressive symptoms in individuals with IBS (Janssens et al., 2015; Mykletun et al., 2010). Within a fear-avoidance framework (Lethem et al., 1983; Vlaeyen & Linton, 2000), even subclinical levels of anxiety are thought to influence the course of IBS – a hypothesis supported by longitudinal research (El-Serag et al., 2004). If prevention or early treatment is the goal, it may be especially important that psychological interventions for individuals with IBS reduce symptoms of anxiety. We anticipated that our approach would be a conservative one, as a previous meta-analysis showed slightly larger mean effects of psychological therapies on depressive symptoms compared to symptoms of anxiety (Lackner et al., 2004). Usable mental health outcome data were provided in 28 trials. We also calculated effect sizes for anxiety and depressive symptoms separately to test for potential differences in the efficacy of psychotherapy for reducing these psychological symptoms in adults with IBS.

We operationalized daily functioning as the degree to which an individual can engage in daily activities regardless of any physical symptoms that may or may not be present. Daily functioning outcomes (in order of preference, based on availability) were 1) an overall measure of life functioning, activity impairment (reverse scored), or disability (reverse scored) (Leon et al., 1997; Mundt et al., 2002), 2) role physical functioning (ability to work and engage in other daily activities regardless of physical health (Ware et al., 1993; Drossman et al., 2000; Patrick et al., 1998)), and 3) social functioning (ability to participate in social activities regardless of physical health (Lahmann et al., 2010)). Eighteen trials provided usable outcome data for daily functioning.

When a trial reported outcome data using multiple measures of a particular outcome (for example, both the SF-36 Mental Health scale and the SCL-90 Global Severity Index as indicators of mental health), data were extracted for the measure that was most frequently used for that outcome within the remaining sample of eligible studies. The SF-36 Mental Health scale was the most frequently used measure of mental health and the SF-36 Role Physical scale was the most frequently used measure of daily functioning. Self-reported outcomes were used in all trials except two that provided only physician-reported measures (Lahmann et al., 2010; Svedlund et al., 1983).

2.4. Data extraction

Data were extracted as intent-to-treat (ITT; i.e., analyzed as randomized, using all available follow-up data) when possible. Data were extracted with imputation of missing data when possible, if the method

was appropriate (i.e., multiple imputation, full information maximum likelihood, expectation maximization, or last observation carried forward if none of the former were available).

We coded several aspects of the included studies, including the following intervention characteristics: 1) therapeutic modality (CBT, psychodynamic, hypnosis, and relaxation therapy); 2) delivery method (online, in-person, telephone, or self-help); 3) format (group, individual); and 4) dose (number of in-person sessions, average session duration, therapy duration in weeks, and session frequency). We assessed the following trial characteristics: 1) type of control condition (active vs. non-active), and 2) country in which the trial took place. Control groups were classified as either active or non-active. Active controls included supportive therapy, online discussion forums, education, "sham" treatments, enhanced medical care, and TAU. Non-active controls included wait-list or symptom monitoring. Controls containing both active and non-active components were coded as active (Ljótsson et al., 2011; Ljótsson et al., 2010). Finally, we assessed the following participant characteristics: 1) diagnostic criteria (Rome criteria, Manning criteria, physician diagnosed); 2) sex ratio of participants (percent female); 3) racial diversity of participants (percent Caucasian); 4) mean duration of gastrointestinal symptoms in years (or years since diagnosis, if the former was not available).

2.5. Missing data

Authors were contacted when reports provided insufficient data for effect size computation and when selective reporting was suspected. When a trial included both eligible and ineligible participants (Schröder et al., 2012), data were requested for those participants meeting our inclusion criteria.

2.6. Data synthesis and statistical analysis

Standardized mean differences (SMDs) were computed as a measure of effect size. The SMDs were computed as the difference between the two groups' mean change scores divided by their pooled standard deviation.[2] To calculate pooled mean effect sizes, we used the Comprehensive Meta-Analysis software (version 3.3.070). Effect sizes were weighted by the inverse of their variances. Following recommendations that random effects-models be used when different measures are used across trials (Higgins et al., 2003), we made an a priori decision to use this model. A random-effects model assumes measurement error beyond subject sampling error is randomly distributed across studies. In random effects moderator analysis, the between-study variance (tau-squared) is not assumed to be the same for all subgroups. This value is computed separately for the two subgroups and not pooled across subgroups. In addition to the SMD, 95% confidence intervals were calculated; confidence intervals not including zero were considered statistically significant.

Six trials [five providing data for mental health [49–53] and four providing data for daily functioning (Boyce et al., 2003; Deechakawan et al., 2013; Heitkemper et al., 2004; Craske et al., 2011)] had two psychological treatments that were compared to the same control condition. Given that this standard random-effects meta-analysis model assumes uncorrelated error terms, we used a set of selection criteria to ensure the statistical independence of effect sizes included in each synthesis. Namely, to avoid statistical dependencies in the data, we included outcome data for only the treatment arm hypothesized by the authors to be most effective (due to either greater number of sessions, in-person delivery method, or particular format/treatment modality) in any given analysis. When a trial had more than one control arm, we only included outcome data for the less active control in any given analysis. This was to facilitate comparisons to past meta-analyses in which the majority of included studies had non-active control arms (Lackner et al., 2004). We then conducted sensitivity analyses to determine the impact of these two decisions on effect size estimates.

We tested whether there were genuine differences underlying the differences in effect sizes between studies (heterogeneity) or whether these were likely a result of chance (homogeneity) (Higgins et al., 2003). As an indicator of homogeneity, we calculated the *Q*-statistic (a measure of weighted squared deviations around the mean). A significant *Q* rejects the null hypothesis of homogeneity and indicates that the observed variability in effect sizes is unlikely to be a result of subject-level sampling error alone. We also calculated the between-studies variance (τ^2) and the ratio of true heterogeneity to total observed variation (I^2).

2.7. Assessment of publication bias and risk of study bias

Publication bias occurs when studies with large effects are more likely to be published and therefore are more easily located for inclusion in meta-analyses. Publication bias is more likely to affect small trials; thus, plots of trial effect size by degree of precision (e.g., variability or sample size) are usually asymmetrical (with a deficit of small studies with weak effects) in the presence of publication bias (Sterne & Egger, 2001). We conducted two statistical tests to determine whether study effect size was significantly related to study precision – the rank correlation test (which uses Kendall's rank correlation coefficient) and Egger's test (which regresses the effect size on the standard error of the effect size). A *p*-value of <0.05 indicates a significant association between the effect size and precision, and therefore signifies the possibility of publication bias.

We used the risk of bias assessment tool developed by the Cochrane Collaboration for RCTs (Higgins & Altman, 2008) to assess the following possible sources of bias in included trials: 1) adequate generation of allocation sequence; 2) concealment of allocation to conditions; 3) blinding of participants and personnel, 4) handling of incomplete outcome data, and 5) selective outcome reporting. The tool allows for 'high', 'low', and 'unclear' risk of bias ratings. Appendix C describes our criteria for assessing risk of bias.

3. Results

A study flow diagram (Fig. 1) shows the steps of identifying eligible trials. Of the 1162 records identified in the search, 31 unique trials were determined to be eligible for the meta-analysis and are presented in Table 1. Most reports included only one trial, but two reports (Lindfors et al., 2012; Blanchard et al., 1992) presented data on two studies and are therefore listed in two rows. Trials that contained multiple eligible psychotherapy conditions also span multiple rows.

3.1. Main effects

Mean effects of psychological therapies on mental health and daily functioning compared to a mixed group of control conditions using the first post-treatment assessment are shown in Figs. 2 and 3, respectively. The range of the first post-treatment assessment was 0–5 months post-treatment for mental health and 0–2 months post-treatment for daily functioning. Positive mean effect sizes indicate that the designated treatment group demonstrated greater average improvement compared to the control group; negative mean effect sizes indicate the reverse. Compared to a mixed group of (active and non-active) control conditions, psychological therapies were effective at improving both mental health ($\bar{d} = 0.41$, $p < 0.001$, 95%CI [0.29,0.54]) and daily

[2] The variance of this effect size requires information on the pretest-posttest correlation, which was rarely reported by trial authors. We therefore calculated the average of all provided pretest-posttest correlations, and used this value (0.629 for mental health and 0.614 for functioning) when no pretest-posttest correlation was provided.

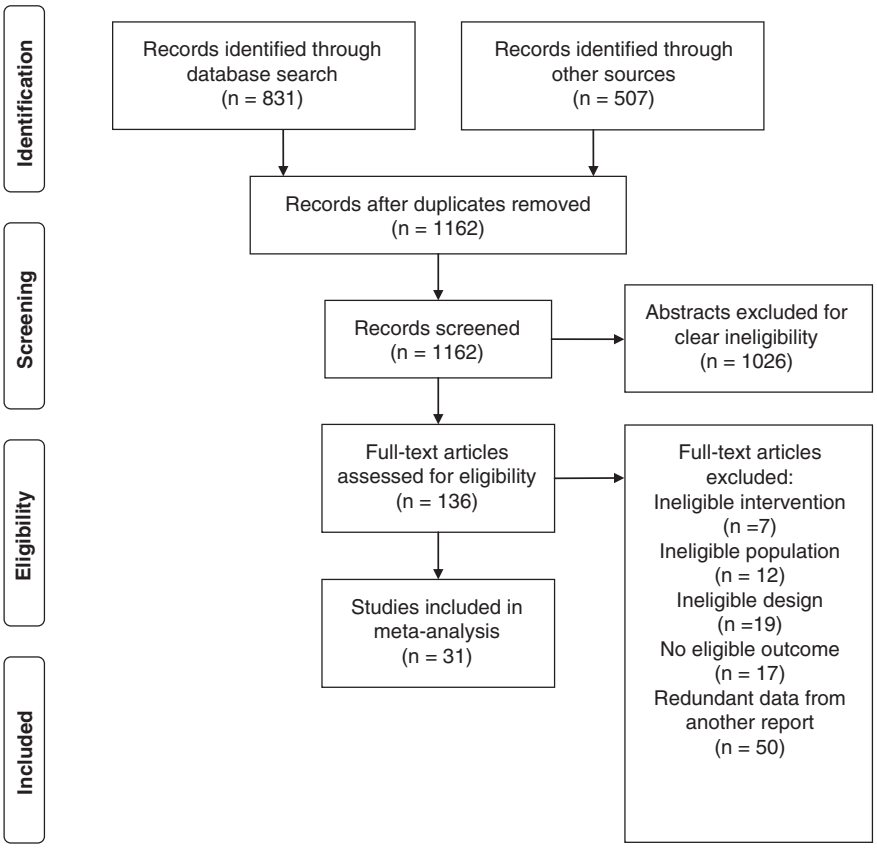

Fig. 1. Flow diagram summarizing trial identification and selection.

functioning ($\bar{d} = 0.43$, $p < 0.001$, 95%CI [0.30,0.55]).[3] There was a non-significant degree of heterogeneity in the effect of psychotherapy on mental health ($Q = 37.78$, $p = 0.081$, $I^2 = 28.54$) and daily functioning ($Q = 20.87$, $p = 0.232$, $I^2 = 18.54$).

3.1.1. Impact of publication bias and study risk of bias

There was no evidence of publication bias for the outcome of mental health, as indicated by Egger's test ($b = -0.16$, $p = 0.833$) and the rank correlation test ($\tau = -0.11$, $p = 0.418$). There was also no evidence of publication bias for the outcome of daily functioning, as indicated by Egger's test ($b = -0.71$, $p = 0.590$) and the rank correlation test ($\tau = -0.13$, $p = 0.449$). Funnel plots of main effects for both outcomes are provided in Appendix D. Thus, there was no evidence of significant publication or small study bias in the meta-analysis results.

Table 2 presents the risk of bias ratings. The number of trials meeting criteria for low risk of bias due to (1) allocation sequence, (2) concealment of allocation sequence, (3) blinding, (4) incomplete outcome data, and (5) selective reporting were: 17, 15, 2, 17, and 30, respectively. In a series of pre-specified analyses, we investigated whether risk of bias ratings were associated with effect size. Risk of bias categories containing fewer than two studies were omitted from the analyses. No risk of bias domain was significantly associated with the magnitude of the effect of psychotherapy on mental health or daily functioning. Thus, the overall mean effects were robust to the quality or risk of bias of the included studies.

3.2. Moderator analyses

3.2.1. Intervention characteristics

3.2.1.1. Therapeutic modality. Of the trials providing outcome data for mental health, CBT was the most frequent treatment modality (19 trials), followed by hypnosis (3 trials) psychodynamic (3 trials), and relaxation (2 trials). Similarly, of the trials providing outcome data for daily functioning, CBT was the most frequent treatment modality (9 trials), followed by hypnosis (4 trials) psychodynamic (2 trials), and relaxation (2 trials). These therapy types were evaluated to determine their relative efficacy compared to mixed control conditions. The therapy types were comparable in the magnitude of their effects on mental health ($Q_b = 1.85$, $p = 0.603$), but less so with respect to their effects on daily functioning (CBT $\bar{d} = 0.55$, $p < 0.001$, 95%CI [0.38, 0.71]; psychodynamic $\bar{d} = 0.53$, $p < 0.001$, 95%CI [0.26,0.79]; hypnosis $\bar{d} = 0.29$, $p = 0.013$, 95% CI [0.06, 0.53]); relaxation $\bar{d} = -0.09$, $p = 0.670$, 95%CI [−0.48, 0.31]; $Q_b = 10.35$, $p = 0.016$). Specifically, CBT produced significantly greater improvements to daily functioning compared to relaxation therapy ($Q_b = 8.44$, $p = 0.004$). Psychodynamic therapies also had significantly larger effects on daily functioning than relaxation therapy ($Q_b = 6.35$, $p = 0.012$). CBT was not significantly more effective at improving daily functioning compared to hypnosis, although this effect approached significance ($Q_b = 3.069$, $p = 0.080$). No other effect size comparisons between therapy types approached significance. Average effects on daily functioning by therapy type are presented in Fig. 4.

3.2.1.2. Online vs. In-person delivery method. We were unable to compare the effects on mental health of therapies delivered online vs. in-person because only one online trial provided outcome data for mental health (Ljótsson et al., 2010). Improvements to daily functioning were

[3] Sensitivity analyses were conducted in which effect size data from the most active control arms and the intervention arms hypothesized by the authors to be least effective were selected. As expected, using these data, average effects were only slightly smaller for mental health ($\bar{d} = 0.39$, $p < 0.001$, 95%CI [0.26,0.52]) and daily functioning ($\bar{d} = 0.38$, $p < 0.001$, 95%CI [0.24,0.52]).

Table 1
Descriptive statistics for characteristics of included studies.

First author	Year	Country	N	Race	Sex	Recruitment	Years	Criteria	Therapy	Delivery	Format	Sessions
Blanchard - S1	1992	US	20		77	Local; clinic	16	Phys +	Cognitive	In person	Individual	12
Blanchard - S2	1992	US	76		66	Local; clinic	13	Phys +	Cognitive	In person	Individual	12
Boyce	2003	AU	69		81	Local; clinic		RI	Cognitive	In person	Individual	8
Boyce	"	"	"	"	"	"	"	"	Relaxation	"	"	"
Corney	1991	UK	42		74	Clinic		Phys +	Behavioral	In person	Individual	10.5[a]
Craske	2011	US	69	72	74	Local; clinic		RII; phys +	Cognitive	In person	Individual	10
Creed	2003	UK	171	98	79	Clinic		RI	Dynamic	In person	Individual	8
Deechakawan	2013	US	118	91	86	Local; clinic		RII; phys	Cognitive	In person	Individual	9
Deechakawan	"	"	"	"	"	"	"	"	"	In person; phone	"	9
Gaylord	2011	US	75	76	100	Online; local; clinic		RII; phys	Cognitive	In person	Group	9
Greene	1994	US	20	100	75	Local; clinic	15	Phys	Cognitive	In person	Individual	10
Guthrie	1991	UK	102		77	Clinic	4	Phys +	Dynamic	In person	Individual	7
Haghayegh	2010	Iran	32		50	Clinic		RII	Cognitive	In person	Individual	8
Heitkemper	2004	US	95	87	100	Local; clinic		RI; phys	Cognitive	In person	Individual	8
Heitkemper	"	"	"	"	"	"		"	"	"	"	1
Heymann-Monnikes	2000	Germany	26		88	Clinic		RI	Cognitive	In person	Individual	10
Labus	2013	US	69	84	72	Clinic		RII; phys +	Cognitive	In person	Group	5
Lackner	2008	US	50	95	86	Local; clinic	17	RII; phys +	Cognitive	In person	Individual	10
Lackner	"	"	"	"	"	"	"	"	"	"	"	4
Lahmann	2010	Germany	80		66	Clinic		RII; phys +	relaxation	In person	Group	10
Lindfors - S1	2012	Sweden	90		79	Clinic		RII; phys +	Hypnosis	In person	Individual	12
Lindfors - S2	2012	Sweden	48		81	Clinic		RII	Hypnosis	In person	Individual	12
Ljotsson	2011	Sweden	61		74	Clinic	12	RIII	Cognitive	Online	Individual	0
Ljotsson	2010	Sweden	86		85	Online; local; clinic		RIII; phys	Cognitive	Online	Individual	0
Moser	2013	Austria	12		79	Clinic		RIII	Hypnosis	In person	Group	10
Moss-Morris	2010	AU	63	90	73	Clinic		RI or RII; phys +	Cognitive	In Person; phone	Individual	3
Payne	1995	US	34		85	Not reported	<1	RI; phys +	Cognitive	In person	Individual	10
Roberts	2006	UK	73		85	Clinic		phys +	Hypnosis	In person	Individual	5
Sanders	2007	US	28	100	78	Local; clinic	16	RII; phys	Cognitive	Self-help	Individual	0
Schroeder	2012	Denmark	37		79	Clinic	8	Phys +	Cognitive	In person	Group	9
Shinozaki	2010	Japan	101		52	Not reported		Phys +	Relaxation	In person	Individual	8
Svedlund	1983	Sweden	22		69	Clinic	13	RII	Dynamic	In person	Individual	10
Tkachuk	2003	US	44		96	Clinic	9	RII; phys +	Cognitive	In person	Group	10
Vollmer	1998	US	21		78	Local; clinic	13	RI	Cognitive	In person	Group	10
Vollmer	"	"	"	"	"	"	"	"	Cognitive	"	Individual	"
Zernicke	2013	Canada	25		90	Local		Phys	Cognitive	In person	Group	9

Note: S1 = Study 1; S2 = Study 2. Country denotes the country in which the study was conducted: AU = Australia. N denotes the number of participants who completed baseline study measures. Race denotes the percentage of the post-treatment sample that was Caucasian. Sex denotes the percent of the post-treatment sample that was female (if not available, baseline demographic data were used). Recruitment denotes the method used to recruit participants: Local = local advertisement; clinic = in clinic or through physician referral. Years denotes the average number of years since diagnosis or symptom onset. Sessions denotes the number of in person sessions offered to participants in the intervention group. Therapy denotes the active intervention evaluated. Criteria denotes the diagnostic criteria used to define IBS: RI, RII, and RIII denote Rome I–III criteria, respectively; phys = physician diagnosed; phys + = physician diagnosed including a physical exam.

[a] The treatment protocol for this study did not specify a standard number of sessions; participants were "mostly seen at weekly intervals for 6–15 one-hourly sessions".

significantly higher for therapies delivered online ($\bar{d} = 0.80$, $p < 0.001$, 95% CI [0.44, 1.16]) compared to those delivered in-person ($\bar{d} = 0.39$, $p < 0.001$, 95% CI [0.27, 0.51]; $Q_b = 4.62$, $p = 0.032$), although only two online therapy trials were included in this analysis (Ljótsson et al., 2011; Ljótsson et al., 2010).

3.2.1.3. Individual vs. group format. We tested whether effect sizes differed for therapies administered individually vs. in a group. For this analysis, as well as for all analyses investigating therapy "dose" (number, duration, and frequency of sessions), interventions that were primarily online or self-help were excluded (Ljótsson et al., 2011; Ljótsson et al., 2010; Moss-Morris et al., 2010; Sanders et al., 2007). There was no difference in the effect of therapies delivered in a group vs. individual format for mental health ($Q_b = 0.03$, $p = 0.863$) or daily functioning $Q_b = 0.22$, $p = 0.638$).

3.2.1.4. Number of sessions. We tested whether a greater number of talk therapy sessions (including in-person sessions and sessions conducted over the phone) was associated with greater improvements to mental health or daily functioning (primarily online or self-help interventions excluded). Among therapies whose primary delivery method was talk therapy, the number of sessions ranged from five to twelve. A meta-regression revealed no significant relation between number of sessions and effect on mental health ($b = -0.07$, $p = 0.073$) or daily functioning ($b = -0.06$, $p = 0.090$).

3.2.1.5. Therapy duration. We tested whether the average duration of sessions in minutes or total duration of therapy in weeks was associated with greater improvements to mental health or daily functioning (primarily online or self-help interventions excluded). Session duration ranged from 30 min to 210 min and had no significant effect on improvements to mental health ($b < -0.01$, $p = 0.103$) or daily functioning ($b < 0.01$, $p = 0.790$). Therapy duration ranged from five to sixteen weeks, and had a very small but significant negative effect on mental health ($b = -0.06$, $p = 0.019$) and no effect on daily functioning ($b = 0.03$, $p = 0.223$). However, once the single trial with the longest therapy duration (Schröder et al., 2012) was removed, the effect of therapy duration on mental health was no longer significant ($b = -0.03$, $p = 0.266$). The next longest duration of therapy of any trial was 13 weeks (Deechakawan et al., 2013).

3.2.1.6. Frequency of sessions. We investigated whether session frequency (which ranged from 0.6 (Schröder et al., 2012) to 2.0 (Lahmann et al., 2010) sessions per week) was significantly associated with effects on mental health and daily functioning. Again, interventions that were primarily online or self-help were excluded from these analyses. Session frequency was not significantly associated with improvement to mental health ($b = 0.25$, $p = 0.201$). Reduced session frequency was associated with greater improvement to daily functioning ($b = -0.44$, $p = 0.014$). However, when the single trial with the greatest weekly session frequency was removed (Lahmann et al., 2010), this effect was no longer

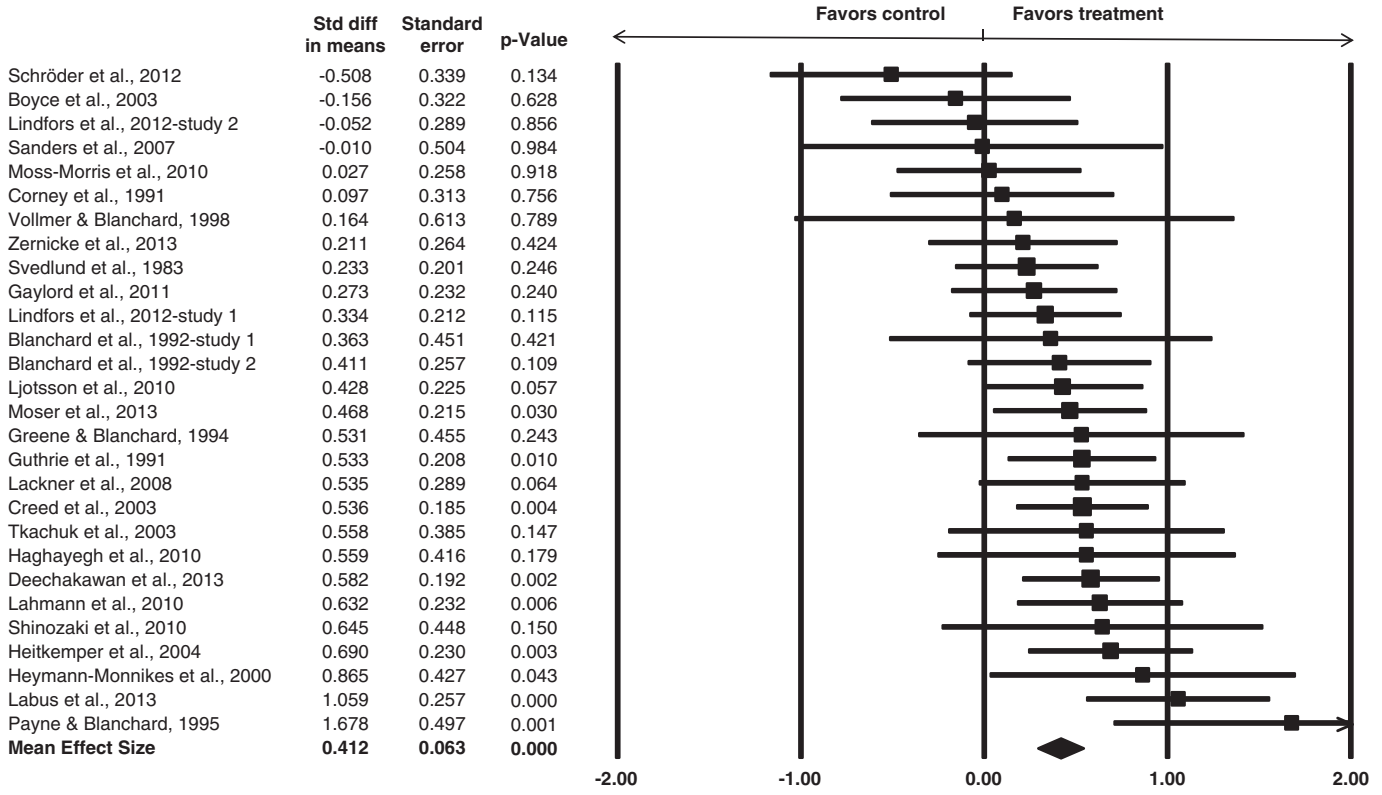

Fig. 2. Mean effects of psychological therapies on mental health symptoms compared to a mixed group of control conditions at the first post-treatment assessment.

statistically significant ($b = -0.46, p = 0.198$). The next highest session frequency of any trial was 1.125 sessions per week (Gaylord et al., 2011).

3.2.2. Trial characteristics

3.2.2.1. Active vs. non-active control condition. Degree of improvement to mental health among trials using active controls ($\bar{d} = 0.38$, $p < 0.001$, 95% CI [0.24, 0.52]) compared to those using non-active controls ($\bar{d} = 0.49$, $p < 0.001$, 95% CI [0.24, 0.74]) was not significantly different ($Q_b = 0.55$, $p = 0.458$). Similarly, degree of improvement to daily functioning among trials using active controls ($\bar{d} = 0.42$, $p < 0.001$, 95% CI [0.29, 0.56]) compared to those using non-active controls ($\bar{d} = 0.45$, $p < 0.090$, 95% CI [−0.07, 0.97]) was not significantly different ($Q = 0.01$, $p = 0.921$).

3.2.2.2. Country. Most trials providing mental health outcome data were conducted in the US (12 trials), followed by Sweden (4 trials) and the UK (3 trials). These countries did not significantly differ in the magnitude of their effects on mental health ($Q = 4.50$, $p = 0.105$). An equal number of trials providing outcome data for daily functioning were conducted in the US, Sweden, and the UK (4 trials each). There was no

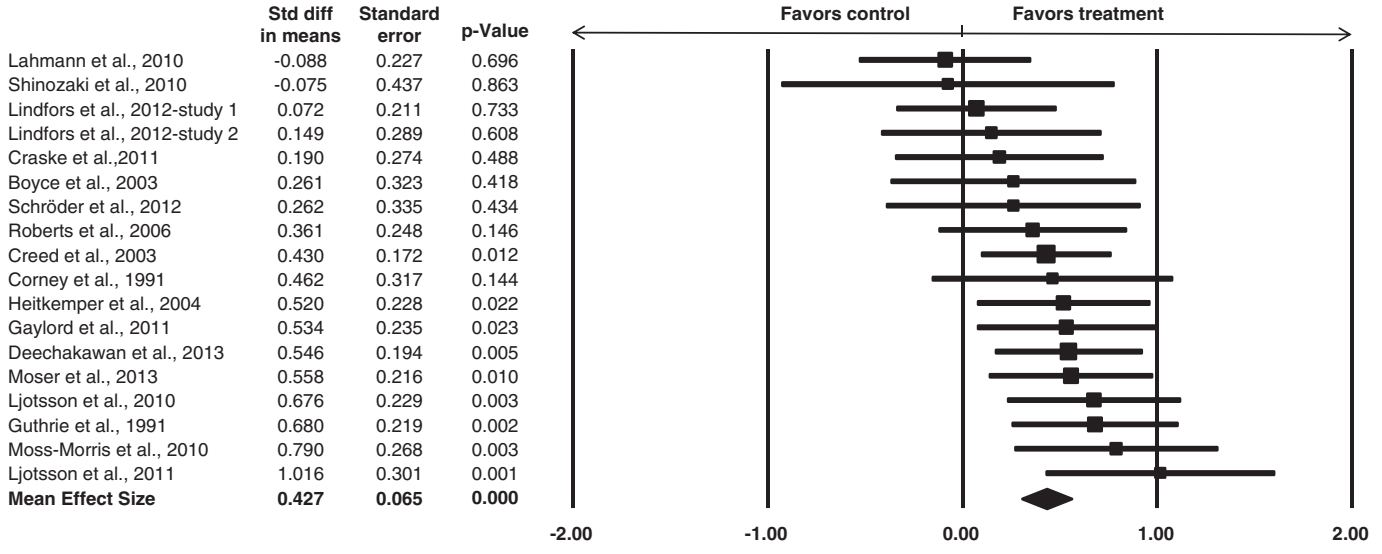

Fig. 3. Mean effects of psychological therapies on daily functioning compared to a mixed group of control conditions at the first post-treatment assessment.

Table 2
Risk of bias ratings for all studies.

First author	Year	Sequence generation	Allocation concealment	Blinding	% Dropout	ITT	Attrition	Selective reporting
Blanchard - S1	1992	Unclear	Unclear	High (Unclear)	0.00	Y	Low	Low
Blanchard - S2	1992	Unclear	Unclear	High (Low)	20.00	N	Unclear	Low
Boyce	2003	Low	Low	High	49.52	N	High	Low
Corney	1991	Unclear	Unclear	(High)	2.38	Y	Low	Low
Craske	2011	Low	Low	(Unclear)	21.81	Y	Unclear	Low
Creed	2003	Low	Low	High	10.53	Y	Low	Low
Deechakawan	2013	Low	Low	High	18.62	Y	Low	Low
Gaylord	2011	Low	Low	(Unclear)	31.96	Y	Unclear	High
Greene	1994	Unclear	Unclear	High	10.00	N	Unclear	Low
Guthrie	1991	Unclear	Unclear	High	12.75	N	Unclear	Low
Haghayegh	2010	Unclear	Unclear	(High)	25.00	N	High	Low
Heitkemper	2004	Low	Low	High	8.33	Y	Low	Low
Heymann-Monnikes	2000	Low	Unclear	Unclear	7.69	N	Unclear	Low
Labus	2013	Unclear	High	High	0.00	Y	Low	Low
Lackner	2008	Low	Low	High	20.00	Y	Low	Low
Lahmann	2010	Unclear	Unclear	(High)	2.50	Y	Low	Low
Lindfors - S1	2012	Low	Low	(High)	3.33	Y	Low	Low
Lindfors - S2	2012	Low	Low	High	6.25	Y	Low	Low
Ljotsson	2011	Low	Low	(High)	18.03	Y	Low	Low
Ljotsson	2010	Low	Low	(High)	5.81	N	Unclear	Low
Moser	2013	Low	Low	(Unclear)	4.87	Y	Low	Low
Moss-Morris	2010	Low	Low	(High)	6.25	Y	Low	Low
Payne	1995	Unclear	Unclear	High (Low)	8.33	N	Unclear	Low
Roberts	2006	Unclear	Unclear	High	18.00	Y	Low	Low
Sanders	2007	Low	Low	High	42.86	N	High	Low
Schröder	2012	Low	Low	(High)	16.28	Y	Low	Low
Shinozaki	2010	Unclear	Unclear	(High)	0.00	Y	Low	Low
Svedlund	1983	Unclear	Unclear	(High)	1.98	N	Low	Low
Tkachuk	2003	Unclear	Unclear	(High)	34.88	N	High	Low
Vollmer	1998	Unclear	Unclear	High	6.25	N	Unclear	Low
Zernicke	2013	Low	Unclear	High	33.33	Y	Unclear	Low

Possible ratings were low, high, or unclear risk of bias. Studies with two control groups were rated twice for risk of bias resulting from lack of blinding (ratings for active control groups appear in parentheses). ITT indicates whether the analyses were intent-to-treat (analyzed as randomized). S1 = Study 1; S2 = Study 2.

significant difference in the magnitude of these countries' effects on daily functioning ($Q = 0.01$, $p = 0.995$).

3.2.3. Participant characteristics

3.2.3.1. Sex. Meta-regression analysis revealed no relation between percentage of female participants degree of improvement to mental health ($b < 0.01$, $p = 0.943$) or daily functioning ($b < 0.01$, $p = 0.157$). These null findings should be interpreted with caution, however, as limited variability in this variable may have masked an effect. In all but one trial that reported this variable, the majority of participants were women (range: 50%–100%).

3.2.3.2. Other participant characteristics. We were unable to test whether race or duration of gastrointestinal symptoms moderate the efficacy of psychotherapy on mental health or functioning because too few studies reported these variables. Among studies that did report race, the majority of participants were Caucasian (range: 72%–100%).

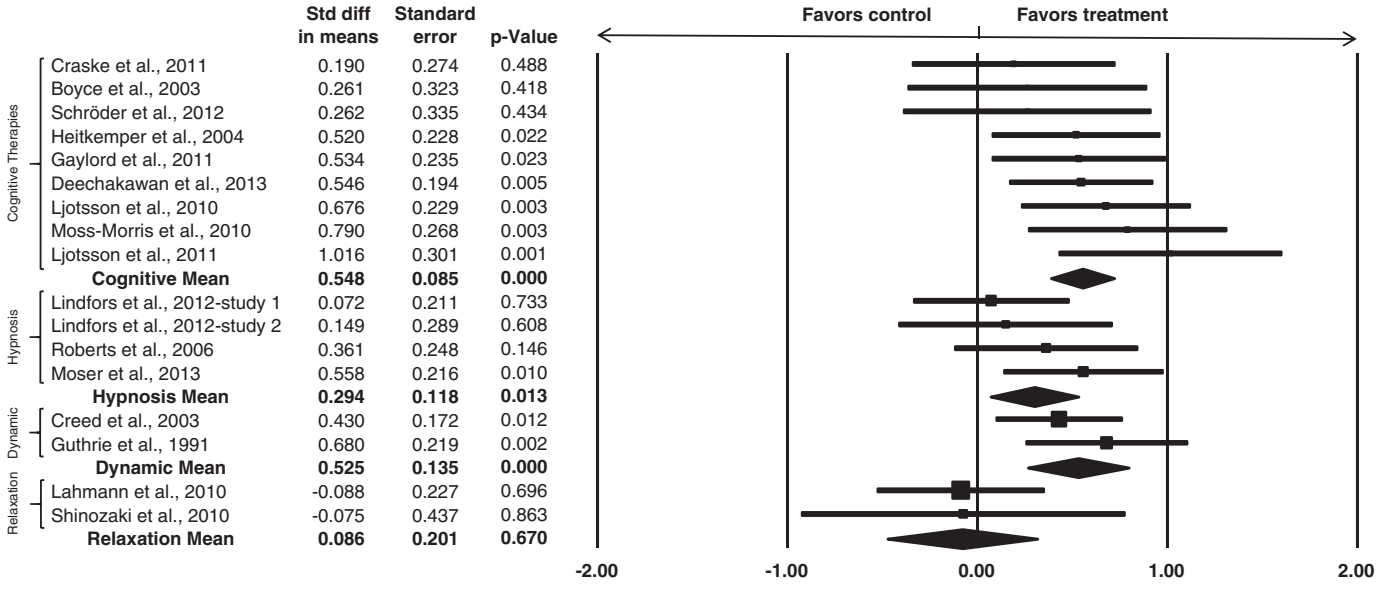

Fig. 4. Mean effects of psychotherapy on daily functioning, by treatment modality.

3.2.4. Follow-up interval

To test whether effect size was significantly moderated by length of follow-up interval, we computed effect sizes separately for assessments less than one month post-treatment, one-to-five months post-treatment, and six-to-twelve months post-treatment. For mental health, effect sizes were similar at less than one month ($\overline{d} = 0.42$, $p < 0.001$, 95% CI [0.30,0.55]), one-to-five months ($\overline{d} = 0.39$, $p < 0.001$, 95%CI [0.22,0.56]) and six-to-twelve months post-treatment ($\overline{d} = 0.33$, $p = 0.012$, 95%CI [0.07,0.58]). Similarly, for daily functioning, effect sizes were similar at less than one month ($\overline{d} = 0.43$, $p < 0.001$, 95%CI [0.30,0.57]), one-to-five months ($\overline{d} = 0.49$, $p < 0.001$, 95% CI [0.24, 0.75]) and six-to-twelve months post-treatment ($\overline{d} = 0.42$, $p < 0.001$, 95% CI [0.23, 0.61]).

3.2.5. Type of mental health outcome

To explore potential differences in the efficacy of psychotherapy for reducing symptoms of anxiety vs. depression in IBS, we also estimated effect sizes for anxiety and depression separately. An analysis including data from 20 studies revealed a significant effect of psychotherapy on symptoms of anxiety ($\overline{d} = 0.37$, $p < 0.001$, 95% CI [0.19, 0.55]). An analysis including data from 21 studies revealed a significant effect of psychotherapy on symptoms of depression ($\overline{d} = 0.29$, $p < 0.001$, 95%CI [0.14,0.45]). There was a significant degree of heterogeneity in the effect on both anxiety ($Q = 37.43$, $p = 0.007$, $I^2 = 49.24$) and depression ($Q = 32.93$, $p = 0.034$, $I^2 = 39.26$).

4. Discussion

The psychological interventions included in this meta-analysis were effective at improving mental health and (with the exception of relaxation therapy) daily functioning in adults with IBS. CBT was evaluated in the largest number of trials (21 trials), followed by hypnosis (4 trials), psychodynamic (3 trials), and relaxation therapy (2 trials). CBT produced the greatest improvement to daily functioning. The magnitude of this effect was significantly greater than that of relaxation therapy, which did not significantly improve functioning in our sample of eligible trials. There were no significant differences between treatment modalities with respect to mental health. These findings should be interpreted cautiously, however, given the small number of included studies using each of these therapeutic modalities and hence our limited statistical power to detect differences in effects across modalities. Our effect size estimates largely replicate those by Lackner and colleagues for mental health (Lackner et al., 2004) (being virtually identical for anxiety although a little lower for depression) and go beyond to estimate the effect of psychotherapy on daily functioning.

The estimated effects of psychotherapy on mental health and functioning were considerably lower than that recently calculated for gastrointestinal symptoms (Cohen's ds ranging from 0.69 to 0.76 depending on the follow up interval) (Laird et al., 2016). As others have proposed, this suggests that psychological therapies are currently more effective at reducing somatic symptoms compared to psychological ones (Lackner et al., 2004). Effects on mental health were the smallest of the three outcomes (mental health, daily functioning, and gastrointestinal symptoms) assessed in this and our previous meta-analysis (Laird et al., 2016). Future research should identify methods of increasing the efficacy of psychotherapy for improving mental health in IBS.

The current meta-analysis extended beyond other recent meta-analyses on this subject (Ford et al., 2014; Laird et al., 2016) to investigate the efficacy of psychological therapies on mental health and daily functioning. A meta-analysis of the effect of psychotherapy on mental health in IBS has not been conducted in over a decade (Lackner et al., 2004), and to our knowledge, no prior meta-analysis of the effect of psychotherapy on functioning has been conducted in this population. As others have argued (Kazdin & Wilson, 1978), multiple criteria should be used whenever evaluating the efficacy of psychotherapy. Mental health and daily functioning are bidirectionally related to physical health outcomes, and are important outcomes to assess when evaluating the efficacy of psychotherapy for individuals with IBS. Moreover, to the extent that brain-gut interactions contribute to IBS, psychological processes constitute an important target for therapeutic intervention.

The current study further extends previous work (Ford et al., 2014) by allowing for inclusion of 1) continuous outcome data, 2) short-term (less than seven day duration) therapies, and 3) trials with less than a seven day follow-up post-treatment assessment. Finally, and perhaps most relevant to intervention research, policy, and practice, this is the first meta-analysis to 1) directly compare the efficacy of different treatment modalities for improving mental health and functioning in IBS, and 2) test for other treatment, control condition, participant, and trial characteristics that might moderate the efficacy of psychotherapy on these outcomes.

While it is impossible to know what led to a relatively greater improvement in daily functioning in CBT compared to relaxation therapy, the former is more likely to encourage clients to confront uncomfortable situations than the latter. Others have observed that CBT incorporates enactive procedures like exposure (often, but not exclusively, in the context of running "behavioral experiments" to test the accuracy of beliefs) and differs from the more purely behavioral interventions more in terms of their proposed mechanisms (belief change vs extinction) than the procedures they use (Olatunji et al., 2010). Exposure may more directly increase daily functioning compared to other therapeutic modalities by giving individuals the opportunity to practice engaging in their daily routines despite their physical symptoms. Exposure may also reduce hypervigilance to visceral sensations, a characteristic of IBS thought to exacerbate symptoms (Craske et al., 2011; Naliboff et al., 1997; Verne et al., 2001). A recent dismantling study of 309 adults with IBS found that CBT with systematic exposure led to greater reduction in gastrointestinal symptoms relative to the same CBT protocol without an exposure component (Ljótsson et al., 2014). Two other studies of exposure-based CBT conducted by the same research team produced the largest and fourth-largest effects of the 41 trials included in our meta-analysis of the effect of psychotherapies on gastrointestinal symptoms (Ljótsson et al., 2010; Ljótsson et al., 2011). Taken together, this is suggestive evidence that systematic exposure may be particularly effective for improving gastrointestinal symptoms and daily functioning in individuals with IBS.

Somewhat surprisingly, improvements to daily functioning were slightly but significantly larger for interventions delivered online compared to those delivered in-person. This could be good news for efforts to enhance dissemination of treatment. However, only two online trials were available for this analysis, and both were trials of CBT with exposure, which may account for this effect (as noted previously, systematic exposure may more directly increase daily functioning compared to other therapeutic modalities). In addition to therapy type, there are likely individual characteristics such as computer literacy that may influence the efficacy of online trials. This will be important to assess in future work.

We found no significant effect of therapy format (group vs. individual) on effect size for either mental health or daily functioning. Our results suggest that a group format may be an effective and economical method of delivering psychological therapies to adults with IBS. As no trial to our knowledge has investigated the efficacy of CBT with exposure for IBS in a group setting, this could be a fruitful area for future research.

Meta-regression analyses revealed no significant effect of number of therapy sessions on effect size for either mental health or daily functioning. This finding, although in contrast to the implicit assumption that more is "better", is consistent with our recent finding that greater number of sessions did not predict greater improvements to gastrointestinal symptoms (Laird et al., 2016). Our results indicate that the type of therapy likely has a greater impact on outcomes than the number of talk therapy sessions received. Surprisingly, greater session frequency was

associated with smaller improvements to daily functioning in our sample of eligible trials. This result is in contrast to findings from a recent meta-analysis of the efficacy of psychotherapy for depression (Cuijpers et al., 2013), in which greater session frequency was associated with greater improvement in depressive symptoms. When we removed the trial with the highest session frequency from this analysis, this result was no longer significant. Thus, this finding should be interpreted cautiously. Future trials are needed to explore the effect of therapy session frequency on intervention efficacy.

A strength of this systematic review and meta-analysis is our use of rigorous methodology. Unlike prior meta-analyses in this field, we included a search of the "gray" literature. Also, two authors independently assessed eligibility and performed the data extraction, and ITT data were used wherever possible. Authors of potentially eligible studies were contacted to obtain unreported data or to exclude ineligible participants. This inclusive approach allowed us to analyze data from 31 trials providing outcome data for 1747 individuals (861 of whom were assigned to psychotherapy and 886 of whom were assigned to an active or non-active control). Eighteen of these trials provided data on daily functioning, which to our knowledge is an outcome that no previous meta-analysis of psychotherapy for IBS has evaluated.

Nonetheless, there are several limitations of the current study that should be acknowledged. First, there was variability between trials that could not be entirely explained by the trial characteristics examined in the moderator analyses. Although we collected data on a large number of characteristics associated with the trial quality, interventions, and participants, there still was residual heterogeneity across the trials that was not explained by these characteristics. Future research is needed to identify the contexts and clients for whom psychotherapy for IBS may be most or least effective.

A second limitation is that no trials included in the meta-analysis were rated as having a low risk of bias in every domain assessed in the risk of bias tool. This was in part due to the consistently high risk of bias related to lack of blinding of participants and personnel, a risk that is pervasive in psychological trials. However, even after excluding this specific risk of bias domain, only nine trials included in the meta-analysis were rated as low risk of bias in all remaining domains. Future studies should follow the CONSORT guidelines for reporting randomized controlled trials (Schulz et al., 2010), use ITT designs, use active control conditions to control for nonspecific treatment effects, and assess treatment credibility and expectancy.

A third limitation derives from the inconsistent reporting of participants' demographic information (e.g., race, SES, duration of symptoms) in the included trials, which precluded our ability to systematically explore variability in efficacy across different populations. With better reporting of demographic characteristics, including consistent reporting of results by demographic subgroups, future meta-analyses will be able to investigate whether there are individual characteristics that increase the efficacy of certain psychotherapy types or of psychotherapy in general.

A final limitation is that the majority of studies used interventions that combined several different treatment modalities, making it difficult to sort studies into discrete categories. Furthermore, studies did not always provide sufficient details regarding the components of their intervention and the method in which it was delivered. To investigate the components of psychotherapies that are most effective at alleviating symptoms and improving daily functioning in IBS, clearer reporting of treatment protocols is needed in the primary research literature.

Due to the limited number of trials, it was impossible in the current analysis to investigate whether certain CBTs are more effective than others. For example, only two trials of mindfulness-based therapy (a third-wave CBT) for IBS were identified (Gaylord et al., 2011; Zernicke et al., 2013). A third trial incorporated mindfulness skills into a more traditional CBT protocol (Ljótsson et al., 2010). A meta-analysis of acceptance-based therapies for treatment of chronic pain (i.e., mindfulness-based stress reduction and acceptance and commitment therapy) found that these interventions had a significant effect on reducing pain (SMD = 0.25) (Veehof et al., 2011). The magnitude of this effect was similar to the effect of CBT for reducing chronic pain (SMD = 0.21 compared to non-active control groups) (Williams et al., 2012). Because so few mindfulness-based therapies for IBS were identified in the current meta-analysis, we were unable to compare the efficacy of these therapies compared to other forms of CBT. Further research is needed in this area.

Mental health and daily functioning were assessed less frequently than gastrointestinal symptoms in our sample of eligible RCTs of psychotherapy for IBS. In particular, we located only 18 trials assessing daily functioning, compared to the 41 RCTs that assessed gastrointestinal symptoms (Laird et al., 2016). We believe that daily functioning is an important outcome for investigation, as some adults with IBS experience profound impairment to daily activities. Assessment of functioning allows for the differentiation between individuals who experience frequent gastrointestinal symptoms but little or no functional limitations versus those with significant work, social, and activity limitations. Future trials should consistently assess daily functioning using a measure with good psychometric properties, such as the complete SF-36 or the 4-item Role Physical scale that assesses role limitations due to physical health (the most commonly reported measure of daily functioning in our eligible sample of trials) (Ware & Sherbourne, 1992).

Future work should continue to consider the mechanisms by which psychotherapy for IBS improves physical symptoms, mental health, and daily functioning, as this will provide insight into the processes that should be targeted through treatment. Careful dismantling studies and longitudinal assessment of hypothesized mediators will facilitate the development of more effective and efficient treatments for improving gastrointestinal symptoms, mental health, and daily functioning in IBS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cpr.2016.11.001.

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