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Effect of Brain-gut Behavioral Treatments on Abdominal Pain in Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis.

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PII: S0016-5085(24)04932-1
DOI: <https://doi.org/10.1053/j.gastro.2024.05.010>
Reference: YGAST 66261

To appear in: *Gastroenterology*
Accepted Date: 9 May 2024

Please cite this article as: Goodoory VC, Khasawneh M, Thakur ER, Everitt HA, Gudleski GD, Lackner JM, Moss-Morris R, Simren M, Vasant DH, Moayyedi P, Black CJ, Ford AC, Effect of Brain-gut Behavioral Treatments on Abdominal Pain in Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis., *Gastroenterology* (2024), doi: <https://doi.org/10.1053/j.gastro.2024.05.010>.

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TITLE PAGE

Title: Effect of Brain-gut Behavioral Treatments on Abdominal Pain in Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis.

Short title: Brain-gut Behavioral Treatments for Abdominal Pain in IBS: Network Meta-analysis.

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Grant support: None

Abbreviations:

AGA	American Gastroenterology Association
BGBT	brain-gut behavioral treatment
CBT	cognitive behavioral therapy
CI	confidence interval
DGBI	disorder of gut-brain interaction
FDA	Food and Drug Administration
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhea
IBS-M	IBS with mixed stool pattern
RCT	randomized controlled trial
RR	relative risk
SNRI	serotonin norepinephrine reuptake inhibitor
TCA	tricyclic antidepressant

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Disclosures: VCG: none. MK: none. ERT: speakers fees and advisory board honorariums for Mahana Therapeutics and Salix Pharmaceuticals. HAE is a beneficiary of a license agreement signed between King's College London and Mahana Therapeutics and received honorariums for consultancy to Mahana Therapeutics. GDG: none. JML: none. RMM reports fees from training in CBT for irritable bowel syndrome intervention for Central and Northwest London NHS Foundation Trust and University of East Anglia. She is a beneficiary of a license agreement signed between King's College London and Mahana Therapeutics and received honorariums for consultancy to Mahana Therapeutics. MS: none. DHV: none. PM: none. CJB: none. ACF: none.

Specific author contributions: Study concept and design: VCG, MK, ERT, PM, CJB and ACF conceived and drafted the study. VCG, MK, PM, CJB, and ACF analyzed, and interpreted the data. ACF, JML, and ERT drafted the manuscript. All authors have approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Guarantor: ACF is guarantor.

Writing assistance: None.

Data statement: Study data will be made available to other investigators on reasonable request.

Word count: 6360

ABSTRACT

Background and Aims: Some brain-gut behavioral treatments (BGBTs) are beneficial for global symptoms in irritable bowel syndrome (IBS). US management guidelines suggest their use in patients with persistent abdominal pain but their specific effect on this symptom has not been assessed systematically.

Methods: We searched the literature through 16th December 2023 for randomized controlled trials (RCTs) assessing efficacy of BGBTs for adults with IBS, compared with each other, or a control intervention. Trials provided an assessment of abdominal pain resolution or improvement at treatment completion. We extracted data as intention-to-treat analyses, assuming dropouts to be treatment failures and reporting pooled relative risks (RRs) of abdominal pain not improving with 95% confidence intervals (CIs), ranking therapies according to P-score.

Results: We identified 42 eligible RCTs, containing 5220 participants. After treatment completion, the BGBTs with the largest numbers of trials, and patients recruited, demonstrating efficacy for abdominal pain, specifically, included self-guided/minimal contact cognitive behavioral therapy (CBT) (RR = 0.71; 95% CI 0.54-0.95, P-score 0.58), face-to-face multicomponent behavioral therapy (RR = 0.72; 95% CI 0.54-0.97, P score 0.56), and face-to-face gut-directed hypnotherapy (RR = 0.77; 95% CI 0.61-0.96, P-score 0.49). Among trials recruiting only patients with refractory global IBS symptoms, group CBT was more efficacious than routine care for abdominal pain, but no other significant differences were detected. No trials were low risk of bias across all domains and there was evidence of funnel plot asymmetry.

Conclusions: Several BGBTs, including self-guided/minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy may be efficacious for abdominal pain in IBS, although none were superior to another.

Key words: abdominal pain; hypnosis; cognitive behavior therapy; evidence-based practice

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI),¹ and one of the most common conditions seen by gastroenterologists.² It affects between 5% and 10% of people globally,³ and is characterized by abdominal pain in association with a change in stool frequency or form.⁴ The pathophysiology is multifactorial and incompletely understood,⁵ meaning it can be difficult to manage clinically, but the role of the gut-brain axis in its etiology is increasingly recognized as important. IBS impacts quality of life and ability to work and socialize.^{6, 7} Direct costs to the health service are substantial, estimated at more than \$10 billion in the US.⁸

Although most novel drug therapies for IBS target predominant stool pattern,^{9, 10} recent evidence suggests there are subgroups of patients with IBS beyond those based on stool pattern alone.¹¹⁻¹³ In these alternative classification systems, one-in-five patients report abdominal pain as their predominant gastrointestinal symptom.⁴ Current US management guidelines for IBS also recognize abdominal pain may be a persistent feature for some patients.^{14, 15} Suggested treatments for abdominal pain in the American Gastroenterology Association (AGA) Clinical Decision Support Tool for IBS include antispasmodics or peppermint oil and, if persistent, gut-brain neuromodulators, such as tricyclic antidepressants (TCAs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or brain-gut behavioral treatments (BGBTs), including cognitive behavioral therapy (CBT) or gut-directed hypnotherapy.¹⁶ BGBTs have been defined as clinician-administered, short-term, non-pharmacologic interventions that prioritize the remediation of gastrointestinal symptoms over improvement of psychological comorbidity, although the latter is also possible.¹⁷

Although antispasmodic drugs appeared efficacious for abdominal pain in a meta-analysis,¹⁸ results of individual randomized controlled trials (RCTs) were inconsistent. In another meta-analysis peppermint oil was beneficial for abdominal pain,¹⁹ but efficacy was modest and more rigorously designed RCTs did not show any benefit. TCAs demonstrated a benefit for abdominal pain in a meta-analysis,¹⁸ but based on four trials containing less than 200 patients. A definitive trial of

amitriptyline, published subsequently, has confirmed the drug to be superior to placebo for abdominal pain.²⁰ To our knowledge, there has been only one 12-week RCT of an SNRI assessing abdominal pain in IBS in 34 patients.²¹ In this trial, venlafaxine led to significantly reduced abdominal pain frequency, compared with placebo. Given the overlap between predominant abdominal pain and psychological symptoms,^{11, 12} and the role of the gut-brain axis in IBS, BGBTs seem a rational treatment choice because they not only have effects within the CNS, but also peripheral effects on pain perception and visceral hypersensitivity.²²⁻²⁵ A prior network meta-analysis demonstrated several BGBTs were superior to a control in IBS,²⁶ but this was based on global symptom improvement in 38 of the 41 eligible trials. Less is known about the extent to which BGBTs impact abdominal pain, specifically, in IBS.

Given BGBTs are suggested by the AGA Clinical Decision Support Tool for IBS for patients with persistent abdominal pain,¹⁶ assessment of their efficacy in this regard is warranted to support current, and inform future, management guidelines for IBS. We, therefore, undertook a network meta-analysis to assess efficacy of BGBTs for abdominal pain in IBS, rather than global symptoms, to estimate relative efficacy of the active interventions studied, as well as the control interventions, in all patients recruited to individual trials, as well as in those with refractory global symptoms. Network meta-analysis allows indirect, as well as direct, comparisons to be made across different RCTs, increases the number of participants' data available for analysis, and produces a credible ranking system of the likely efficacy of different psychological therapies, and control interventions, even when there are no trials making direct comparisons.

METHODS

Search Strategy and Study Selection

We searched MEDLINE (1st January 1947 to 16th December 2023), EMBASE, EMBASE Classic (1st January 1947 to 16th December 2023), PsychINFO (1st January 1806 to 16th December 2023), and the Cochrane central register of controlled trials to identify potential studies. We searched conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2023 to identify studies published only in abstract form. Finally, we used the bibliographies of all articles to perform a recursive search.

Eligible RCTs examined the effect of BGBTs (Supplementary Table 1) on abdominal pain, specifically, in adults (≥ 16 years) with IBS. We included the first period of cross-over trials prior to cross-over to the second treatment (Table 1). The diagnosis of IBS could be based on either a physician's opinion or accepted symptom-based diagnostic criteria. Trials compared BGBTs with each other, or with a control. Eligible control interventions included any of waiting list "attention" control, where patients were left on a waiting list to receive the active intervention after the trial had ended, education and/or support, dietary and/or lifestyle advice, or routine care. Minimum duration of therapy and follow-up was ≥ 4 weeks. Trials had to report abdominal pain resolution or improvement as a dichotomous endpoint, preferably patient-reported, but if this was not recorded then as documented by the investigator, or mean abdominal pain scores, after completion of therapy. Where studies included patients with IBS among patients with other DGBI or did not report dichotomous or continuous data but were otherwise eligible, we contacted original investigators to obtain further information. We published the study protocol on the PROSPERO international prospective register of systematic reviews (registration number CRD42023466440). Ethical approval was not required.

We conducted a literature search, with the search strategy provided in the Supplementary Materials. We applied no language restrictions, with foreign language articles translated, if required. Two investigators (VCG or MK and ACF) evaluated all abstracts identified for eligibility, independently from each other. We obtained all potentially relevant papers, evaluating them in more detail, using pre-designed forms, to assess eligibility independently, according to the pre-defined criteria, with any disagreements between investigators resolved by discussion.

Outcome Assessment

The primary outcome assessed was efficacy of all BGBTs and control interventions in IBS, in terms of effect on abdominal pain after completion of treatment. Secondary outcomes included adverse events during therapy (total numbers, as well as adverse events leading to study withdrawal, and individual adverse events), if reported.

Data Extraction

We extracted all data independently. This was done by two investigators (VCG or MK and ACF) onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as a dichotomous outcome (abdominal pain unimproved). Otherwise, if mean abdominal pain scores at baseline and after completion of treatment were available, along with a SD, we imputed dichotomous responder and non-responder data, according to the methodology described by Furukawa *et al.*²⁷ A 30% improvement in abdominal pain score is determined from the formula: number of participants in each treatment arm at final follow-up x normal SD. The latter corresponds to (70% of the baseline mean abdominal pain score – follow-up mean abdominal pain score) / follow-up SD.

We also extracted the following data for each trial, where available: country, setting (primary, secondary, or tertiary care-based), whether concomitant IBS medications were allowed, type of

BGBT used, including duration of therapy and number of sessions, method of delivery, IBS criteria used, primary outcome measure utilized to define abdominal pain improvement or resolution following therapy and the instrument used to assess this, proportion of female patients, proportion of patients according to predominant stool pattern (IBS with constipation (IBS-C), diarrhea (IBS-D), or mixed stool pattern (IBS-M)), and whether trials recruited only patients whose global IBS symptoms were refractory to standard medical therapy. The BGBT used was assessed by a practicing gastrointestinal psychologist (ERT), based on the approach that it was felt to align with most closely. Hence, for some BGBTs, the therapy reported in the original study was reclassified for the purposes of this meta-analysis. We recorded the control interventions used, as we pooled these separately in the analysis to assess their relative efficacy. We extracted data as intention-to-treat analyses at the first point of follow-up after completion of treatment, with all dropouts assumed to be treatment failures (*i.e.*, abdominal pain unimproved at follow-up), wherever trial reporting allowed.

Quality Assessment and Risk of Bias

We performed risk of bias assessment at the study level. This was done by two investigators (VCG or MK and ACF) independently. We used the Cochrane risk of bias tool.²⁸ We resolved disagreements by discussion. We recorded the methods used to generate the randomization schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We used the frequentist model to perform a network meta-analysis, with “netmeta” (version 0.9-0, <https://cran.r-project.org/web/packages/netmeta/index.html>) in R (version 4.0.1). We reported the network meta-analysis according to the PRISMA extension statement for network meta-

analyses.²⁹ Network meta-analysis results can give more precise estimates, compared with results from standard, pairwise analyses,^{30,31} and allow ranking of treatments to inform decisions.³²

We produced a network plot with node and connection size corresponding to the number of study subjects and number of studies, respectively to examine the symmetry and geometry of the evidence, using Stata version 14 (Stata Corp., College Station, TX, USA). We produced comparison-adjusted funnel plots to explore publication bias or other small study effects, for all available comparisons, where sufficient numbers of studies existed,³³ using R (version 4.0.1). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates absence of publication bias, or small study effects.³⁴ We summarized efficacy of each active and control intervention tested with a pooled relative risk (RR) and 95% confidence interval (CI), using a random effects model as a conservative estimate. We used an RR of abdominal pain remaining unimproved at the first point of follow-up post-treatment; if the RR is less than 1 and the 95% CI does not cross 1 there is a significant benefit of one intervention over another.

Many meta-analyses use the I^2 statistic to measure heterogeneity.³⁵ Although this statistic is easy to interpret and does not vary with the number of studies, its value does increase with the number of patients included in the meta-analysis.³⁶ We, therefore, assessed global statistical heterogeneity across all comparisons using the τ^2 measure. Measures of τ^2 of 0.04, 0.16, and 0.36 are considered to represent low, moderate, and high heterogeneity, respectively.³⁷ We assessed inconsistency in the network analysis by comparing direct and indirect evidence, where available, by splitting the network estimates into the contribution of direct and indirect evidence, and looking for any statistically significant differences.

We ranked both active treatments and control interventions according to their respective P-score, which is a value between 0 and 1. P-scores are based on the point estimates and standard errors of the network estimates, and measure mean extent of certainty that one intervention is better

than another, averaged over all competing interventions.³⁸ The higher the score the greater the probability of the intervention being ranked as best.³⁸ However, magnitude, as well as rank, of the P-score should be considered. As the mean value of the P-score is always 0.5, individual treatments clustering around this value are likely to be of similar efficacy. Nevertheless, when interpreting the results, it is also important to take the RR and corresponding 95% CI for each comparison into account, rather than relying on rankings alone.³⁹ Due to the sparseness of information derived from direct comparisons for some active interventions, we performed a sensitivity analysis where only trials that had direct connections of active interventions to the four control interventions were included. Given the multitude of therapies studied and the fact that, in the US, BGBTs are suggested in patients with persistent abdominal pain,¹⁶ we conducted subgroup analyses, where trials were grouped according to the type of BGBT studied, rather than how it was delivered, and also where only trials recruiting patients with refractory global IBS symptoms were included.

For our primary outcome of the effect of BGBTs on abdominal pain after completion of treatment, we used the Confidence in Network Meta-Analysis (CINeMA) framework to evaluate confidence in the direct and indirect treatment estimates from the network,^{40, 41} which is endorsed by the Cochrane Collaboration. This includes the Risk of Bias from Missing Evidence in Network Meta-Analysis tool for evaluating reporting bias.⁴²

RESULTS

Our search strategy generated 3134 citations, 123 articles of which we retrieved for further assessment as they appeared relevant (Supplementary Figure 1). Of these, 83 were excluded, leaving 40 eligible articles.^{s1-s40} These contained 42 separate RCTs, comprising 5220 participants, 3726 of whom received a BGBT and 1494 a control intervention, as described in Supplementary Table 2. All were fully published. The agreement between investigators for trial eligibility was excellent (Kappa statistic = 0.89). We obtained abdominal pain data from authors of 12 RCTs.^{s1-s3, s9, s10, s12, s15, s16, s18, s30, s39, s40} Four trials that reported using digital CBT were re-classified as it was felt the BGBT utilized aligned more closely with digital acceptance and commitment therapy.^{s1, s23, s24, s39} Adverse events were reported in insufficient detail in most trials, meaning data could not be pooled. Detailed characteristics of individual RCTs, including comparisons made, are provided in Supplementary Table 3 and risk of bias items in Supplementary Table 4. Only eight trials required a minimum abdominal pain threshold as part of their entry criteria.^{s7, s12, s20, s26-s28, s30, s37} None of the trials were low risk of bias across all domains, although blinding as to whether a BGBT was received or not would be extremely difficult for both patients and therapists. Eight RCTs were judged as low risk of bias across all other domains.^{s6, s10, s16, s23, s28, s39, s40} Efficacy by type of BGBT is provided in the Supplementary Materials.

Efficacy in Terms of Effect on Abdominal Pain at First Point of Follow-up Post-treatment

Thirteen RCTs provided dichotomous data for likelihood of abdominal pain being unimproved at completion of therapy,^{s2, s5, s9, s12, s14-17, s20, s22, s24, s31, s37} and for the other 29 trials we imputed data. The network plot is provided in Figure 1. When data were pooled, there was minimal heterogeneity ($\tau^2 = 0.0332$). Funnel plot examination according to control intervention used suggested evidence of publication bias for trials comparing BGBTs with either routine care or waiting list control (Supplementary Figures 2 and 3), but there were too few studies comparing

efficacy with education/support or dietary/lifestyle advice to assess this. The netsplit analysis revealed significant differences between the direct and indirect treatment effect estimates only for face-to-face CBT versus routine care and versus waiting list control (Supplementary Table 5). Of all the BGBTs studied, digital gut-directed hypnotherapy was ranked first (RR of abdominal pain remaining unimproved = 0.19; 95% CI 0.09 to 0.43, P-score 0.99) (Figure 2a), but based on only one trial containing 188 patients assigned to active therapy.^{s37} Digital relaxation therapy or training performed similarly (RR = 0.22; 95% CI 0.11 to 0.44, P-score 0.97), based on only two trials containing 230 patients assigned to active therapy.^{s37, s38} Face-to-face stress management, mindfulness meditation training, and group CBT were also more efficacious than waiting list control (RR = 0.52; 95% CI 0.29 to 0.95, P-score 0.79, RR = 0.55; 95% CI 0.31 to 0.99, P-score = 0.75, and RR = 0.61; 95% CI 0.40 to 0.92, P-score 0.72) but only in two trials containing 31 patients,^{s19, s33} one RCT containing 36 patients,^{s13} and three trials containing 80 patients receiving active therapy,^{s17, s21, s32} respectively. 95% CIs around the estimates for all these therapies were wide. The BGBTs with the largest numbers of trials and/or patients recruited, with evidence for efficacy for abdominal pain, included self-guided or minimal contact CBT (RR = 0.71; 95% CI 0.54 to 0.95, P-score 0.58), face-to-face multicomponent behavioral therapy (RR = 0.72; 95% CI 0.54 to 0.97, P score 0.56), and face-to-face gut-directed hypnotherapy (RR = 0.77; 95% CI 0.61 to 0.96, P-score 0.49). Among control interventions, dietary and/or lifestyle advice was ranked last (P-score 0.12), followed by waiting list control (P-score 0.14).

On indirect comparison, digital gut-directed hypnotherapy was superior to all other BGBTs, except digital relaxation therapy or training, and digital relaxation therapy or training was superior to all other BGBTs, except face-to-face stress management or emotional awareness training (Supplementary Table 6). No other BGBT was superior to any of the other active therapies. Only digital gut-directed hypnotherapy and digital relaxation therapy or training were superior to all four of the control interventions including waiting list control, education and/or support, dietary and/or

lifestyle advice, and routine care. Face-to-face stress management, group CBT, and face-to-face multicomponent behavioral therapy were all superior to both routine care and waiting list control. Using the CINeMA framework to evaluate confidence in the results of this endpoint and classifying the eight RCTs judged as low risk of bias across all domains other than blinding as being at low risk of bias,^{s6, s10, s16, s23, s28, s39, s40} most direct comparisons across the network were rated as either very low or low confidence (Supplementary Table 7). Some indirect comparisons, including those related to digital gut-directed hypnotherapy, digital relaxation therapy, digital stress management, group relaxation therapy, and dietary and/or lifestyle advice, were moderate confidence.

When we performed an analysis where only trials that had direct connections of active interventions to the four control interventions were included, excluding four RCTs,^{s1, s24, s37, s38} the pooled estimates of efficacy were unchanged. In this analysis face-to-face stress management, mindfulness meditation training, and emotional awareness training were ranked first (RR = 0.52; 95% CI 0.29 to 0.95, P-score 0.85), second (RR = 0.55; 95% CI 0.31 to 0.99, P-score = 0.80), and third (RR = 0.56; 95% CI 0.27 to 1.13, P-score 0.77) but only in two trials containing 31 patients,^{s19, s33} one RCT containing 36 patients,^{s13} and one trial containing 36 patients receiving active therapy,^{s29} respectively (Figure 2b). Again, 95% CIs around the estimates for all these therapies were wide, and the BGBTs with the largest numbers of trials and/or patients recruited, with evidence for efficacy for abdominal pain, included self-guided or minimal contact CBT (RR = 0.71; 95% CI 0.54 to 0.95, P-score 0.61), face-to-face multicomponent behavioral therapy (RR = 0.72; 95% CI 0.54 to 0.97, P score 0.59), and face-to-face gut-directed hypnotherapy (RR = 0.77; 95% CI 0.61 to 0.96, P-score 0.51). On indirect comparison, no BGBT was superior to any of the other active therapies (Supplementary Table 8).

When we restricted the analysis to the 15 RCTs that stated that they only recruited patients with global IBS symptoms refractory to treatment,^{s2, s3, s5, s10, s12, s15, s17-s19, s26, s30, s32, s35, s36} there was low heterogeneity between studies ($\tau^2 = 0.0560$). Contingency management ranked first (RR = 0.52;

95% CI 0.19 to 1.42, P-score 0.79) based on one RCT assigning 23 patients to active therapy,^{s19} and group CBT second (RR = 0.58; 95% CI 0.30 to 1.15, P-score 0.77) (Supplementary Figure 4), based on two RCTs containing 68 patients receiving active therapy.^{s17, s32} On indirect comparison, group CBT was superior to routine care (RR = 0.59; 95% CI 0.36 to 0.98) (Supplementary Table 9), but none of the other BGBTs were significantly more efficacious than each other or than any of the control interventions for the specific symptom of abdominal pain after indirect comparison.

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DISCUSSION

BGBTs are suggested for persistent abdominal pain in IBS by the AGA Clinical Decision Support Tool.¹⁶ However, to our knowledge, there has been no evidence synthesis to assess whether they are beneficial for this symptom. Our systematic review and network meta-analysis of 42 RCTs demonstrated several BGBTs were more efficacious than a control intervention of waiting list control for abdominal pain. These included digital gut-directed hypnotherapy, digital relaxation therapy or training, face-to-face stress management, mindfulness meditation training, group CBT, self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy. However, the first four of these treatments were assessed in only one or two trials and, in some cases, contained small numbers of patients. After indirect comparison, digital gut-directed hypnotherapy and digital relaxation therapy or training were significantly more efficacious than almost all other active therapies, but this was only in one and two RCTs, respectively, and these estimates were based solely on indirect comparisons in the network. The BGBTs with the largest numbers of trials, and some of the largest numbers of patients recruited, with evidence for efficacy included self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy. Of these three, only face-to-face multicomponent behavioral therapy was more efficacious than more than one control intervention, including both routine care and waiting list control. Most comparisons across this network were rated as either low or very low confidence. In patients with global IBS symptoms that were refractory to treatment, only group CBT appeared more efficacious than a control intervention of routine care. In terms of BGBT studied, digital acceptance and commitment therapy, CBT, and gut-directed hypnotherapy were superior to waiting list control and, in patients with refractory symptoms, CBT was superior to routine care. Regrettably, detailed adverse events were reported by few studies,^{s15, s18} precluding any meaningful analysis, but underscoring the importance of this issue in the design of future trials.⁴³

We were able to make indirect comparisons between over 5000 participants in the included RCTs. Because the individual trials took place across a wide variety of settings and countries, and many recruited patients with IBS with any stool pattern, results are likely to be generalizable to many patients with IBS. We used an intention-to-treat analysis, with all trial dropouts assumed to be symptomatic. We imputed dichotomous data for 29 trials, without which they would have been ineligible for inclusion, and contacted authors of 12 studies to obtain supplementary data and further maximize number of eligible trials. When imputing data, we used a 30% or more improvement in abdominal pain after treatment, approximating the Food and Drug Administration (FDA)-recommended endpoint for drug trials in IBS.⁴⁴ As four trials provided data for this endpoint as a dichotomous outcome,^{s2, s15, s16, s37} this means for 33 of 42 included trials we used this outcome measure. Heterogeneity was minimal or low in all analyses. We conducted subgroup analysis of trials according to BGBT studied, and those that only recruited patients with global IBS symptoms refractory to treatment, to approximate an assessment of whether current suggestions to use BGBTs for persistent abdominal pain are evidence-based.¹⁶

There were differences between individual trials, in terms of the population studied, study setting, the interventions themselves (e.g., the protocols used by different individual studies assessing the same intervention) and the way they were applied, the duration of follow-up and, in nine trials, the endpoint used to define symptom improvement.^{s5, s9, s12, s14, s17, s20, s22, s24, s31} Due to the high variability in treatment interventions and small sample sizes in many of the RCTs, there is limited generalizability of the data to all BGBTs. Moreover, several of the interventions were only studied in one or two trials, recruiting small numbers of patients, and most included IBS of all subtypes. This makes it difficult to draw definitive conclusions and determine which of the therapies are most efficacious, and in which patients. The netsplit analysis revealed evidence of inconsistency between the direct and indirect treatment evidence for face-to-face CBT versus routine care and versus waiting list control. There was evidence of funnel plot asymmetry in our main analysis, suggesting

publication bias or other small study effects. The efficacy of BGBTs may, therefore, have been overestimated. “Unpacking” validated questionnaires to impute only abdominal pain data may limit interpretation of the results, as the psychometric properties of some of these as measures of abdominal pain varies. On this note, the binary outcome of a 30% or more improvement in abdominal pain may be viewed as an over-simplification of treatment response and, in trials that are often small and only powered for the primary endpoint, means that these trials will be underpowered for this endpoint. This together with our use of an intention-to-treat analysis could have underestimated efficacy. However, the fact that only one trial used the Rome IV criteria,^{s37} which mandate the presence of abdominal pain for the diagnosis of IBS, means that some individuals in the included RCTs may have had relatively mild pain severity at baseline. This could have affected the proportions of individuals meeting the 30% or more threshold for improvement we stipulated. Although we identified 42 trials, the number of patients receiving each individual therapy was lower than the numbers assigned to most licensed drugs whose effects on abdominal pain have been studied in other network meta-analyses.^{9, 10} As most RCTs were conducted in Western populations, with two trials conducted in Japan,^{s5, s32} two in Iran,^{s29, s38} and one in Israel,^{s6} our findings are not necessarily generalizable to other populations. In addition, no RCTs were judged as being at low risk of bias across all domains, because blinding the patient or therapist to treatment assignment would be almost impossible in trials of BGBTs. Only two RCTs were described as being double-blind,^{s30, s37} although neither trial stated how this was done. Eight RCTs were judged as being low risk of bias across all other domains.^{s6, s10, s16, s23, s28, s39, s40} Lack of blinding is less of an issue where trials do not use subjective endpoints, but this is not the case in trials in IBS. Efforts to mitigate potential bias due to lack of blinding by assessing pre-treatment expectancy of efficacy and credibility, as recommended by others,⁴⁵ was done by 10 of the included trials.^{s1, s8, s13-s15, s17, s21, s24, s27} Finally, although we conducted a subgroup analysis including only trials that stated they recruited patients with refractory

symptoms, how this was defined may differ between individual RCTs, which may limit generalizability, and this is only a proxy measure for persistent abdominal pain.

The current study reveals evidence for a benefit of some BGBTs for abdominal pain, specifically, which is a cardinal symptom of IBS. The mechanism likely involves targeting cognitive and affective drivers of IBS through stress-sensitive pathways that regulate the gut-brain axis and modulate visceral pain.⁴⁶ However, there was little evidence for benefit for abdominal pain in patients whose global IBS symptoms are judged as being refractory to medical treatment. This suggests restricting their use to patients with persistent abdominal pain may be inappropriate. Beyond gastrointestinal symptom presentation, BGBTs are most appropriate for patients who have accepted their diagnosis, understand the gut-brain connection and the role of stress, have deficits in coping and/or present with maladaptive behaviors associated with gastrointestinal symptoms, and have the time, interest, and motivation to invest in behavior change. Other factors, including severe psychopathology, disordered eating, trauma, or lack of insight or motivation, may make patients inappropriate for BGBTs depending on severity and the therapist's skill level or expertise.¹⁷ We also found that digitally delivered treatments may be beneficial for abdominal pain in IBS. Other than digital gut-directed hypnotherapy and digital relaxation therapy, for which estimates were based solely on indirect comparisons, no single BGBT was significantly more efficacious than any other active therapy, although it is uncertain whether this is due to insufficient numbers of trials, comparable outcomes, or other factors.^{47, 48} Indeed, it is important to understand patient characteristics, including pain, when considering appropriate digital therapeutic options. It has been suggested that patients with severe pain, or multiple somatic, extra-intestinal symptoms, may benefit most from gut-directed hypnotherapy, as opposed to patients with skills deficits and maladaptive behaviors who may benefit from CBT.⁴⁸

Very few trials used currently accepted endpoints to assess the effect of BGBTs on abdominal pain. Future RCTs could consider assessing this in patients with IBS with persistent

abdominal pain according to accepted FDA-recommended endpoints. Given there was little evidence of a benefit in patients with refractory global IBS symptoms, this should also be examined in future studies. The trials we identified in this network meta-analysis utilized a variety of delivery methods for the therapies of interest and some, such as digital, telehealth, or home-based methods appeared promising. These delivery methods may be particularly welcome, as digital therapeutics improve access and reduce costs,⁴⁸ and many patients with IBS experience interference in their social activities and may, therefore, find it difficult to attend appointments in-person.⁷ However, these latter findings need to be replicated by others, and none of the included trials compared digitally delivered BGBTs with therapist-delivered ones directly. The comparable efficacy of most BGBTs across different approaches and delivery systems underscores the importance of conducting more detailed research that identifies specific subgroups of patients for whom these treatments are more effective.⁴⁹ Additionally, factors beyond efficacy including rapidity of response, cost effectiveness, accessibility, durability, time scale, safety profile, and breadth and scope of treatment gains, including improvement in quality of life and abdominal pain, may inform treatment selection to deliver optimal responses. All of this will assist in informing future management guidelines for IBS.

In summary, we found several BGBTs to be efficacious for abdominal pain, specifically, in IBS including self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, face-to-face gut-directed hypnotherapy, digital gut-directed hypnotherapy, digital relaxation therapy or training, face-to-face stress management, mindfulness meditation training, and group CBT. Self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy had the largest numbers of trials and patients. However, certainty in the evidence was mostly low to very low. Future RCTs should examine the impact of administering BGBTs in a way that allows better understanding of their benefit in specific groups of patients, particularly those in whom persistent abdominal pain is the main issue.^{12, 13} Exploration of whether adapting protocols for some of the BGBTs studied could serve as a more targeted approach for

patients in whom abdominal pain is the predominant symptom would also be worthwhile.

Investigators should also consider relevant adverse events, such as worsening of symptoms or deterioration of mood, which may affect efficacy, as well as which control condition to select, given the minimal differences between active treatment and either education and/or support or routine care in most of our analyses.

ACKNOWLEDGEMENTS

We are grateful to Brjann Ljotsson and Jenny Lovdahl for providing extra information and data from their studies.

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Table 1. Eligibility Criteria.

Randomized controlled trials
Adults (participants aged ≥ 16 years)
Diagnosis of IBS based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.
Compared BGBTs with each other or with a control intervention, including waiting list control, education and/or support, dietary and/or lifestyle advice, or routine care.
Minimum duration of therapy 4 weeks.
Minimum duration of follow-up 4 weeks
Dichotomous assessment of response to therapy in terms of effect on abdominal pain, or continuous data in the form of effect on abdominal pain scores, following therapy.†

*Manning criteria, Kruis score, Rome I, II, III, or IV criteria.

†Preferably patient-reported, but if this was not available then as assessed by a physician.

FIGURE LEGENDS

Figure 1. Network Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment.

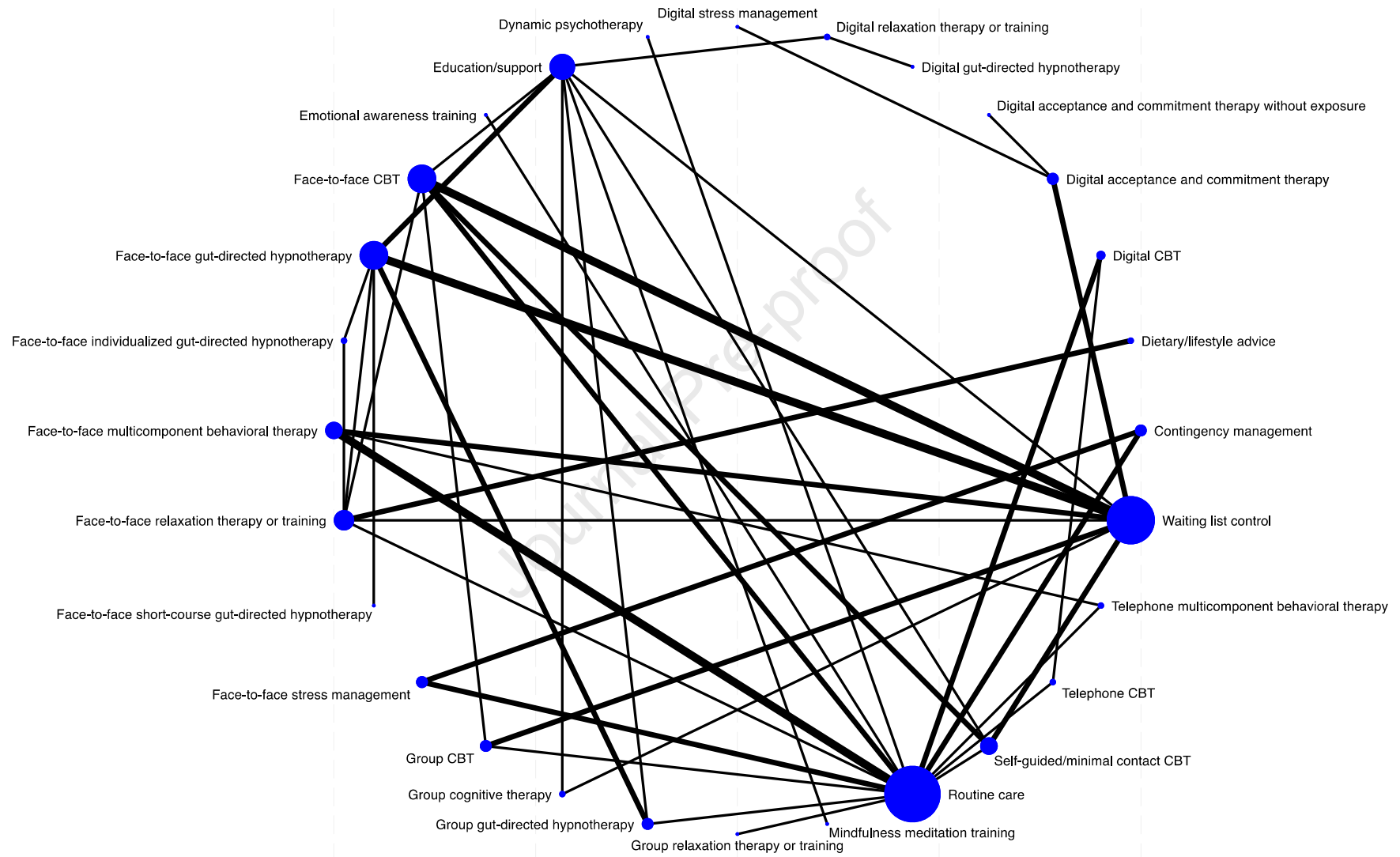
Note: Circle (node) size is proportional to the number of study participants assigned to receive each intervention. The line width (connection size) corresponds to the number of studies comparing the individual treatments.

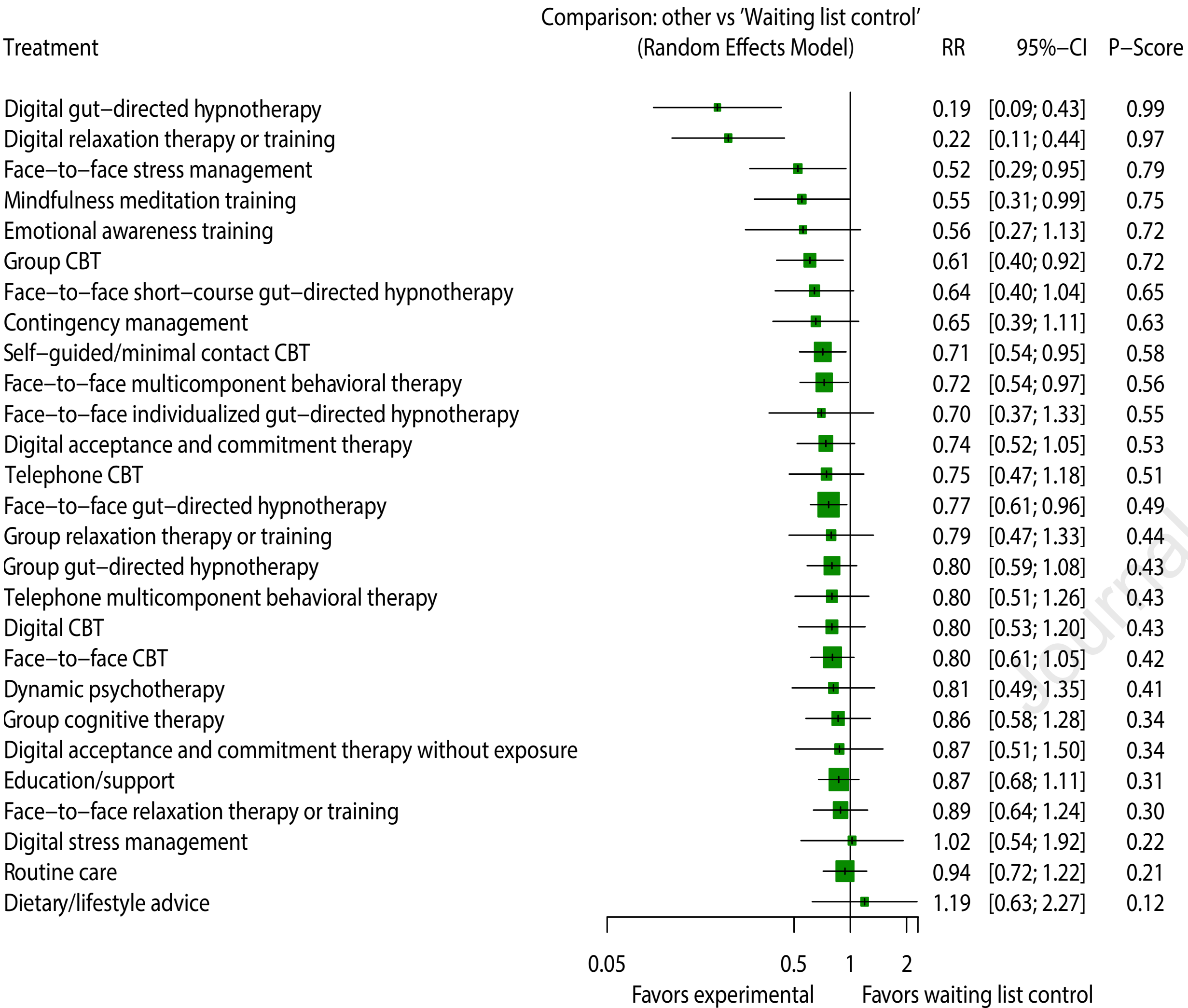
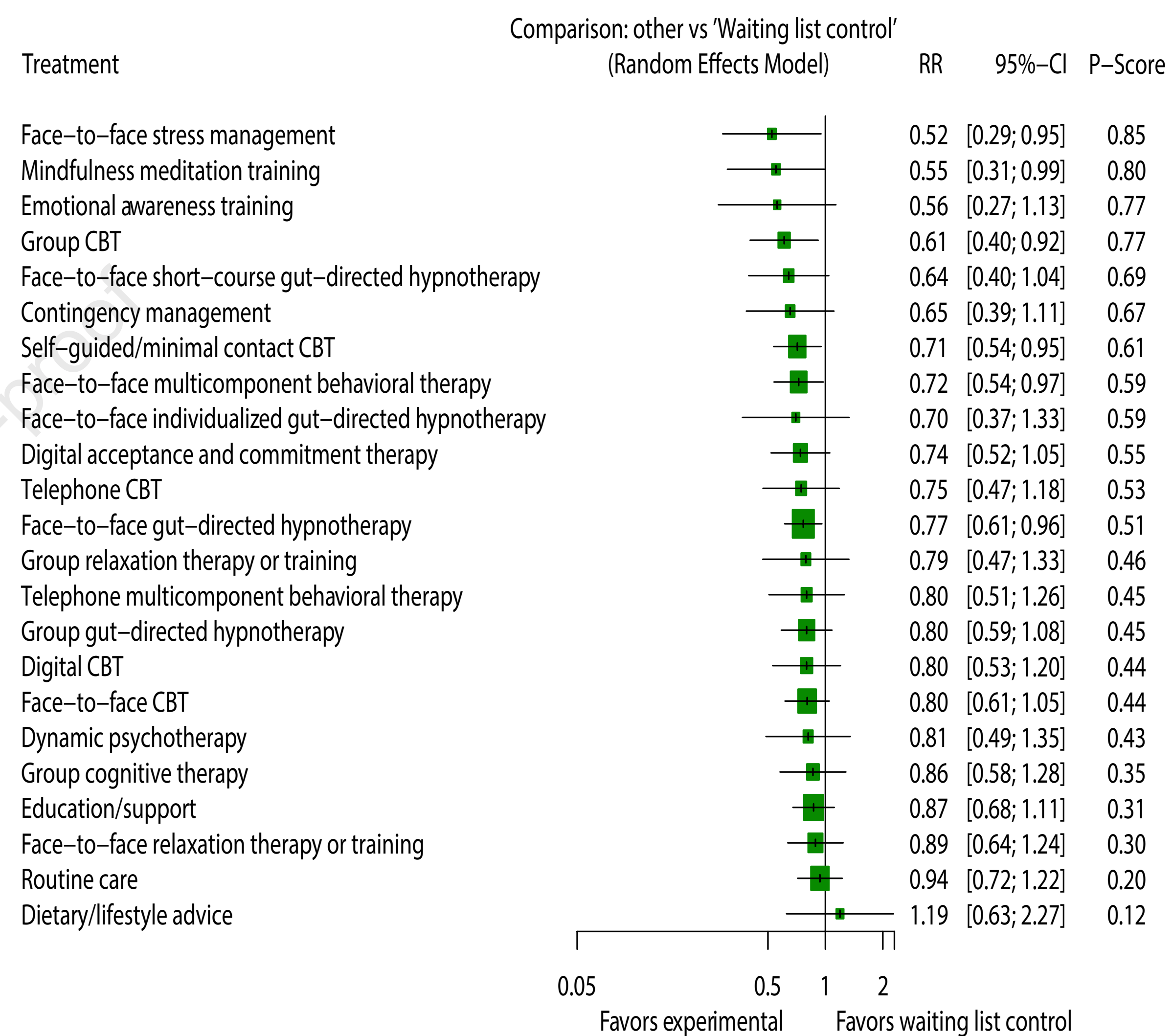
Figure 2a. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Figure 2b. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment Including Only Trials with A Direct Connection to the Four Control Interventions.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.



A**B**

SUPPLEMENTARY METHODS

Search Strategy

Studies on IBS were identified with the terms: *irritable bowel syndrome* and *functional diseases, colon* (both as medical subject heading (MeSH) and free text terms), and *IBS, spastic colon, irritable colon, or functional adj5 bowel* (as free text terms). These were combined using the set operator AND with studies identified with the terms: *cognitive therapy, psychotherapy, behaviour therapy, relaxation therapy, or hypnosis* (both as MeSH terms and free text terms), and the following free text terms: *cognitive behavioral therapy, cognitive behavioural therapy, cognitive behaviour therapy, relaxation technique, stress management, contingency management, mindfulness meditation, dynamic psychotherapy, behavioral therapy, behavioural therapy, behavior therapy, hypnotherapy, mesmerism, or imagery*.

SUPPLEMENTARY RESULTS

Efficacy by Type of Brain-gut Behavioral Treatment in Terms of Effect on Abdominal Pain at First Point of Follow-up Post-treatment

Three trials compared different delivery methods of the same type of brain-gut behavioral treatment without any comparison with a control intervention and were, therefore, excluded from this analysis,^{s1-s3} leaving 39 eligible RCTs.^{s4-s40} There was low heterogeneity between studies ($\tau^2 = 0.0439$). Of all the brain-gut behavioral treatments studied, emotional awareness training ranked first (RR = 0.56; 95% CI 0.27 to 1.17 P-score 0.80) (Supplementary Figure 5), but based on only one trial containing 36 patients assigned to active therapy.^{s29} Digital acceptance and commitment therapy was ranked second (RR = 0.65;

95% CI 0.46 to 0.92, P-score 0.75), based on three trials containing 171 patients assigned to active therapy.^{s23, s24, s39} CBT and gut-directed hypnotherapy were also efficacious for abdominal pain (RR = 0.75; 95% CI 0.59 to 0.94, P-score 0.61 and RR = 0.77; 95% CI 0.61 to 0.97, P-score 0.55), in 12 trials containing 955 patients,^{s7, s11, s14-s18, s21, s25, s32, s34, s40} and 8 trials containing 686 patients receiving active therapy,^{s10, s22, s26, s30, s35-s37} respectively. None of the other therapies were more efficacious than any of the control interventions. After indirect comparison, CBT was superior to both routine care and waiting list control, but there were no other significant between-group differences (Supplementary Table 10).

When we restricted the analysis to the 13 RCTs that stated that they only recruited patients with global IBS symptoms refractory to treatment,^{s5, s10, s12, s15, s17-s19, s26, s30, s32, s35, s36} there was low heterogeneity between studies ($\tau^2 = 0.0324$). Contingency management was ranked first (RR = 0.54; 95% CI 0.24 to 1.21, P-score 0.85) (Supplementary Figure 6), based on one RCT assigning 23 patients to active therapy.^{s19} However, none of the different types of brain-gut behavioral treatment studied were more efficacious for abdominal pain. After indirect comparison, CBT was superior to dietary/lifestyle advice (RR = 0.75; 95% CI 0.57 to 0.98) (Supplementary Table 11) and contingency management was superior to dietary/lifestyle advice (RR = 0.18; 95% CI 0.03 to 0.96), but there were no other significant differences detected.

Supplementary Table 1. Description of the Brain-gut Behavioral Treatments Considered in This Systematic Review and Network Meta-analysis.

Brain-gut Behavioral Treatment	Description of the intervention
Multicomponent behavioral therapy	A multicomponent therapy approach; this can vary, but involves components such as psychoeducation, relaxation, dietary counselling, thermal biofeedback, and cognitive behavioral strategies.
Cognitive behavioral therapy (CBT)	A skills-based therapy approach that focuses on modifying behaviors and cognitions; this can vary, but often involves psychoeducation, relaxation, cognitive restructuring, problem-solving skills, and exposure techniques.
Dynamic psychotherapy	A therapy approach that helps patients stay with their symptoms and tune in to the mental and physical aspects of their experience; it involves altering problematic aspects of the patient's life and relationships (uses statements rather than questions, non-verbal cues, negotiating style, and an understanding hypothesis to help guide treatment).
Stress management	A therapy approach using coping skills to reduce the psychological and physiological effects of stress and tension.
Relaxation therapy or training	A therapy approach using purposeful relaxation strategies that reduce physiological arousal (e.g., diaphragmatic breathing or progressive muscle relaxation).
Acceptance and commitment therapy	An action-oriented therapy approach that stems from CBT; it involves acceptance and mindfulness strategies alongside commitment and behavior strategies to increase psychological flexibility and enhance engagement in valued activities, with systematic exposure to IBS-related situations and symptoms.
Acceptance and commitment therapy without exposure	As for acceptance and commitment therapy but without systematic exposure to IBS-related situations and symptoms.

Mindfulness meditation training	A therapy approach using mindfulness strategies (e.g., body scan, meditation, mindful yoga) that cultivates a non-judgmental awareness of one's physical and emotional states to enhance emotional processing and coping.
Contingency management	A therapy approach that focuses on decreasing social reinforcement of symptoms and inadequate behaviors and simultaneously focusing attention on conditions of well-being. It also involves other behavioral techniques such as self-observation and shaping, stimulus control, restructuring in time, and social skills training.
Gut-directed hypnotherapy	A therapy approach using a series of sessions that address gut-brain dysregulation. It involves deep relaxation, concentration, focused attention, and visualization of peaceful imagery, so a patient is in a mental state in which they have an enhanced capacity to respond to suggestions automatically and effortlessly.
Individualized gut-directed hypnotherapy	As for gut-directed hypnotherapy but with the addition of an approach to address psychological symptoms reported by the patient.
Emotional awareness training	A therapy approach educating patients to increase conscious awareness of eight primary emotions (anger, fear, joy, sadness, disgust, acceptance, surprise, and anticipation). This approach includes the use of schematic faces, role-playing, semantic examples, and discussion.
Cognitive therapy	A therapy approach that involves modifying cognitions; this can include psychoeducation and identifying and modifying unhealthy thought patterns (including cognitive distortions) and maladaptive core beliefs; problem solving is also incorporated.

Supplementary Table 2. Total Number of Trials of Each Intervention, and Total Number of Included Patients Assigned to Each Brain-gut Behavioral Treatment and Control Intervention.

Active or control intervention	Intervention	Number of RCTs	Total Number of Patients	References
Active intervention	Face-to-face gut-directed hypnotherapy	8	551	s2, s3, s10, s22, s26, s30, s36
	Face-to-face CBT	6	248	s7, s14-s16, s21, s25
	Face-to-face multicomponent behavioral therapy	5	204	s8, s9, s20, s31
	Face-to-face relaxation therapy or training	5	94	s4-s6, s16, s30
	Digital acceptance and commitment therapy	4	324	s1, s23, s24, s39
	Self-guided/minimal contact CBT	4	218	s11, s14, s15, s40
	Group gut-directed hypnotherapy	3	255	s3, s22, s35
	Group CBT	3	80	s17, s21, s32
	Digital relaxation therapy or training	2	230	s37, s38
	Digital CBT	2	223	s18, s34
	Contingency management	2	33	s19, s33
	Face-to-face stress management	2	31	s19, s33
	Face-to-face short-course gut-directed hypnotherapy	1	210	s2
	Digital gut-directed hypnotherapy	1	188	s37
	Telephone CBT	1	186	s18

	Digital acceptance and commitment therapy without exposure	1	156	s1
	Group cognitive therapy	1	120	s27
	Digital stress management	1	97	s24
	Dynamic psychotherapy	1	85	s12
	Telephone multicomponent behavioral therapy	1	64	s20
	Group relaxation therapy or training	1	40	s28
	Emotional awareness training	1	36	s29
	Mindfulness meditation training	1	36	s13
	Face-to-face individualized gut-directed hypnotherapy	1	17	s30
Control intervention	Routine care	15	769	s9, s12, s16, s18-s20, s25, s28, s29, s31-s35, s40
	Waiting list control	14	327	s4, s7, s8, s10, s11, s14, s17, s21, s23, s26, s27, s36, s39
	Education/support	6	369	s10, s13, s15, s22, s27, s38
	Dietary/lifestyle advice	2	29	s5, s6

Supplementary Table 3. Characteristics of Randomized Controlled Trials of Brain-gut Behavioral Treatments for Irritable Bowel Syndrome.

Study	Country and setting	Abdominal pain threshold required for trial entry and concomitant IBS medications allowed	Brain-gut behavioral treatment used and number of patients	Control intervention used and number of patients	Criteria used to define symptom improvement following therapy	Number (%) female, diagnostic criteria used for IBS, and number (%) with each subtype	Number (%) of patients with global IBS symptoms refractory to treatment
Corney 1991 <small>s25</small>	England, tertiary care	Not reported, not reported	22 patients assigned to between 6 and 15 1-hour face-to-face CBT sessions delivered over 4 months	20 patients assigned to routine care	≥30% improvement in abdominal pain on a VAS (imputed)	31 (73.8%), clinical diagnosis, subtype not stated	Not stated

*Blanchard 1992a ^{s8}	USA, tertiary care	Not reported, not reported	10 patients assigned to face-to-face multicomponent behavioral therapy consisting of two 1-hour sessions per week for 4 weeks of a combination of relaxation therapy, thermal biofeedback, education and training in stress coping strategies then one session per week for a further 4 weeks	10 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	17 (85.0%), clinical diagnosis, subtype not stated	Not stated
*Blanchard 1992b ^{s8}	USA, tertiary care	Not reported, not reported	38 patients assigned to face-to-face multicomponent behavioral therapy consisting of two 1-hour sessions per week for 4 weeks of a combination of relaxation therapy, thermal biofeedback, education and training in stress coping strategies then one session per week for a further 4 weeks	39 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	41 (66.1%), clinical diagnosis, 15 (24.2%) IBS- C, 18 (29.0%) IBS-D, 29 (46.8%) IBS-M†	Not stated

Blanchard 1993 ^{s4}	USA, tertiary care	Not reported, not reported	14 patients assigned to two face-to-face relaxation training sessions per week for 2 weeks then one session per week for a further 6 weeks, with regular home practice emphasized (at least 25 minutes per day)	9 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	18 (78.3%), clinical diagnosis, 5 (21.7%) IBS-C, 6 (26.1%) IBS-D, 12 (52.2%) IBS-M	Not stated
Greene 1994 ^{s7}	USA, tertiary care	Weekly, not reported	10 patients assigned to two 1-hour face-to-face CBT sessions per week for 2 weeks then one session per week for a further 6 weeks	10 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	15 (75.0%), clinical diagnosis, subtype not stated	Not stated
Fernandez 1998 ^{s19}	Spain, secondary care	Not reported, not reported	44 patients assigned to one 1-hour session per week of either face-to-face stress management (21 patients) or contingency management (23 patients) for 12 weeks	23 patients assigned to routine care	≥30% improvement in abdominal pain on a Likert scale (imputed)	46 (70.1%), Manning criteria, subtype not stated	67 (100%) refractory

Vollmer 1998 ^{s21}	USA, tertiary care	Not reported, not reported	24 patients assigned to one 1-hour face-to-face CBT session per week (12 patients), or one 90-minute group CBT session per week (12 patients), for 10 weeks	10 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	27 (79.4%), Rome I, 5 (14.7%) IBS-C, 13 (38.2%) IBS-D, 16 (47.1%) IBS-M	Not stated
Palsson 2002 ^{s26}	USA, tertiary care	Weekly, not reported	15 patients assigned to 7 45-minute face-to-face gut-directed hypnotherapy sessions delivered over 12 weeks	15 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	15 (62.5%), Rome I, subtype not stated†	30 (100%) refractory
Boyce 2003 ^{s16}	Australia, tertiary care	Not reported, current IBS medications prohibited	71 patients assigned to one 1-hour face-to-face CBT session per week (35 patients), or one 30-minute face-to-face relaxation therapy session per week, for 8 weeks (36 patients)	34 patients assigned to routine care	≥30% improvement in abdominal pain on the BSSS	85 (81.0%), Rome I, subtype not stated	0 (0%) refractory

Creed 2003 ^{s12}	England, tertiary care	Severe, defined as >59 on a VAS, not reported	85 patients assigned to one 2-hour dynamic psychotherapy session and seven further 45-minute sessions over 3 months	86 patients assigned to routine care	Improvement in abdominal pain on a VAS by at least 1 SD (data from the authors)	135 (78.9%), Rome I, 39 (22.8%) IBS-C, 53 (31.0%) IBS- D	171 (100%) refractory
Tkachuk 2003 ^{s17}	Canada, tertiary care	Not reported, current IBS medications continued	14 patients assigned to two 90-minute group CBT sessions per week for 1 week then one session per week for 8 weeks	14 patients assigned to waiting list	Patient-reported considerable relief of IBS-related abdominal pain or discomfort	27 (96.4%), Rome I, subtype not stated	28 (100%) refractory
Heitkemper 2004 ^{s9}	USA, tertiary care	Not reported, current IBS medications prohibited	48 patients assigned to one 1-hour weekly face-to-face multicomponent behavioral therapy session per week for 8 weeks	47 patients assigned to routine care	≥50% improvement in abdominal pain on a Likert scale (data from the authors)	95 (100%), Rome I, 13 (15.5%) IBS-C, 7 (8.3%) IBS-D, 47 (56.0%) IBS-M†	Not stated

Fernandez 2006 ^{s33}	Spain, secondary care	Not reported, not reported	20 patients assigned to one 40-minute session per week of either face-to-face stress management (10 patients) or contingency management (10 patients) for 6 weeks	10 patients assigned to routine care	≥30% improvement in abdominal pain on a Likert scale (imputed)	Not reported, clinician's diagnosis of IBS, subtype not stated	Not stated
Roberts 2006 ^{s36}	England, primary care	Not reported, current IBS medications continued	40 patients assigned to one 30-minute face-to-face gut-directed hypnotherapy session per week for 5 weeks	41 patients assigned to waiting list	≥30% improvement in abdominal pain on the Birmingham IBS questionnaire (imputed)	69 (85.2%), clinician's diagnosis of IBS, subtype not stated	81 (100%) refractory
Blanchard 2007 ^{s27}	USA, tertiary care	Moderate to severe, in a daily diary, not reported	120 patients assigned to one 90-minute group cognitive therapy session for 10 weeks	44 patients assigned to waiting list and 46 to education and/or support	≥30% improvement in abdominal pain on a Likert scale (imputed)	173 (82.4%), Rome II, 48 (22.9%) IBS-C, 81 (38.6%) IBS- D, 80 (38.1%) IBS-M	Not stated

Sanders 2007 ^{s11}	USA, tertiary care	Not reported, not reported	17 patients assigned to self-guided CBT mailed as five modules over at least 10 weeks	11 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	22 (78.6%), Rome II, 13 (46.4%) IBS-C, 5 (17.8%) IBS-D, 10 (35.7%) IBS- M	Not stated
Lackner 2008 ^{s14}	USA, primary, secondary, and tertiary care	Not reported, current IBS medications continued	48 patients assigned to one 1-hour face- to-face CBT session per week (23 patients), or one 1-hour minimal contact CBT session on four occasions (25 patients), over 10 weeks	27 patients assigned to waiting list	Patient-reported adequate relief of IBS-related abdominal pain or discomfort	65 (86.7%), Rome II, 19 (25.3%) IBS-C, 40 (53.3%) IBS- D, 16 (21.3%) IBS-M	Not stated

Jarrett 2009 s20	USA, not reported	At least 25% of days, in a daily diary, current IBS medications prohibited	126 patients assigned to one 1-hour face-to-face multicomponent behavioral therapy session per week for 9 weeks (62 patients), or one 1-hour session per week delivered face-to-face for 2 weeks, then six sessions delivered via the telephone with the final session delivered face-to-face (64 patients)	62 patients assigned to routine care	≥50% improvement in abdominal pain on a Likert scale	152 (86.4%), Rome II, 39 (22.2%) IBS-C, 93 (52.8%) IBS-D, 35 (19.9%) IBS-M†	Not stated
Lahmann 2010 s28	Germany, tertiary care	≥10 on a NRS, current IBS medications prohibited	40 patients assigned to 10 1-hour relaxation therapy sessions delivered over 5 weeks	40 patients assigned to routine care	≥30% improvement in abdominal pain on a NRS (imputed)	53 (66.3%), Rome II, 13 (16.3%) IBS-C, 21 (26.3%) IBS-D, 46 (57.5%) IBS-M	Not stated
Ljotsson 2010 s23	Sweden, not reported	Not reported, not reported	43 patients assigned to digital acceptance and commitment therapy, consisting of five steps, and delivered via the internet over 10 weeks	43 patients assigned to waiting list	≥30% improvement in abdominal pain on a Likert scale (imputed)	72 (84.7%), Rome III, subtype not stated†	Not stated

Moss-Morris 2010 ^{s40}	New Zealand, primary care	Not reported, not reported	31 patients assigned to a self-guided CBT program divided into seven chapters and completed over 7 to 8 weeks, with one face-to-face 1-hour session at baseline, one 1-hour telephone session midway, and one 1-hour telephone session towards treatment end	33 patients assigned to routine care	≥30% improvement in abdominal pain on the IBS-SSS (imputed)	46 (71.9%), Rome I or Rome II, subtype not stated	Not stated
Shinozaki 2010 ^{s5}	Japan, tertiary care	Not reported, current IBS medications continued	11 patients assigned to one 30 to 40-minute face-to-face relaxation training session per week for 8 weeks	10 patients assigned to dietary and/or lifestyle advice	Patient-reported adequate relief of IBS-related abdominal pain or discomfort	11 (52.4%), Rome II, 4 (19.0%) IBS-C, 7 (33.3%) IBS-D, 10 (47.6%) IBS-M	21 (100%) refractory

Gaylord 2011 ^{s13}	USA, not reported	Not reported, current IBS medications continued	36 patients assigned to one 2-hour mindfulness meditation training session per week for 8 weeks plus one half-day retreat	39 patients assigned to education and/or support	≥30% improvement in abdominal pain on the IBS-SSS (imputed)	75 (100%), Rome II, subtype not stated	Not stated
Ljotsson 2011a ^{s24}	Sweden, not reported	Not reported, not reported	195 patients assigned to digital acceptance and commitment therapy (98 patients), or digital stress management‡ (97 patients), both delivered via the internet over 10 weeks	No control intervention	Patient-reported adequate relief of IBS-related abdominal pain or discomfort	154 (79.0%), Rome III, subtype not stated	Not stated
Ljotsson 2011b ^{s39}	Sweden, not reported	Not reported, current psychotropic medications prohibited	30 patients assigned to digital acceptance and commitment therapy, consisting of five steps, and delivered via the internet over 10 weeks	31 patients assigned to waiting list	≥30% improvement in abdominal pain on the GSRS-IBS (imputed)	45 (73.8%), Rome III, 13 (21.3%) IBS-C, 18 (29.5%) IBS-D, 30 (49.2%) IBS-M	Not stated

Oerlemans 2011 ^{s34}	Netherlands, primary care	Not reported, not reported	38 patients assigned to digital CBT, dealing with five topics with psychologist feedback and delivered via a personal digital assistant over 4 weeks	38 patients assigned to routine care	≥30% improvement in abdominal pain on a Likert scale (imputed)	64 (84.2%), Rome III, subtype not stated	Not stated
*Lindfors 2012a ^{s10}	Sweden, tertiary care	Not reported, current IBS medications continued	45 patients assigned to one 1-hour face- to-face gut-directed hypnotherapy session per week for 12 weeks	45 patients assigned to education and/or support	≥30% improvement in abdominal pain on a Likert scale (imputed)	71 (78.9%), Rome II, 14 (15.6%) IBS-C, 30 (33.3%) IBS- D, 46 (51.1%) IBS-M	90 (100%) refractory
*Lindfors 2012b ^{s10}	Sweden, secondary care	Not reported, current IBS medications continued	25 patients assigned to one 1-hour face- to-face gut-directed hypnotherapy session per week for 12 weeks	23 patients assigned to waiting list	≥30% improvement in abdominal pain on the GSRS-IBS (imputed)	39 (81.3%), Rome II, 11 (22.9%) IBS-C, 16 (33.3%) IBS- D, 21 (43.8%) IBS-M	48 (100%) refractory

Moser 2013 ^{s35}	Austria, primary and tertiary care	Not reported, current IBS medications continued	51 patients assigned to 10 45-minute group gut-directed hypnotherapy sessions over 12 weeks	49 patients assigned to routine care	≥30% improvement in abdominal pain on a VAS (imputed)	71(78.9%), Rome III, 22 (24.4%) IBS-C, 46 (51.1%) IBS-D, 22 (24.4%) IBS- M†	100 (100%) refractory
Farnam 2014 ^{s29}	Iran, tertiary care	Not reported, not reported	36 patients assigned to two 30-minute emotional awareness training sessions delivered over 5 weeks	34 patients assigned to routine care	≥30% improvement in abdominal pain on a VAS (imputed)	34 (48.6%), Rome III, subtype not stated	Not stated
Ljotsson 2014 ^{s1}	Sweden, not reported	Not reported, not reported	309 patients assigned to digital acceptance and commitment therapy, consisting of five steps, and delivered via the internet over 10 weeks (153 patients) or digital acceptance and commitment therapy without exposure‡, consisting of four steps, and delivered via the internet over 10 weeks (156 patients)	No control intervention	≥30% improvement in abdominal pain on the GSRS-IBS (imputed)	246 (79.5%), Rome III, 82 (26.5%) IBS-C, 125 (40.5%) IBS- D, 40 (12.9%) IBS-M	Not stated

Boltin 2015 s6	Israel, tertiary care	Not reported, current IBS medications continued	16 patients assigned to one 3-hour face-to-face relaxation training session per week for 8 weeks	19 patients assigned to dietary and/or lifestyle advice	≥30% improvement in abdominal pain on the IBS-SSS (imputed)	26 (76.5%), Rome III, 10 (29.4%) IBS-C, 16 (47.1%) IBS-D, 8 (23.5%) IBS-M†	Not stated
Phillips-Moore 2015 s30	Australia, not reported	Moderate for ≥4 days, during a 2-week screening period, current IBS medications continued	51 patients assigned to five face-to-face gut-directed hypnotherapy sessions (17 patients), five face-to-face individualized gut-directed hypnotherapy sessions (17 patients), or five face-to-face relaxation therapy sessions (17 patients) delivered over 9 weeks	No control intervention	≥30% improvement in abdominal pain on the BSSS (imputed)	44 (86.3%), Rome II, 23 (44.9%) IBS-C, 26 (51.0%) IBS-D, 2 (4.1%) IBS-M	51 (100%) refractory

Jarrett 2016 s31	USA, not reported	Not reported, current IBS medications prohibited	46 patients assigned to eight 1-hour face-to-face multicomponent behavioral therapy sessions over 12 weeks	46 patients assigned to routine care	≥50% improvement in abdominal pain on a Likert scale	75 (88.2%), Rome III, 11 (12.9%) IBS-C, 27 (31.8%) IBS-D, 38 (44.7%) IBS-M†	Not stated
Lackner 2018 s15	USA, secondary and tertiary care	Not reported, current IBS medications continued	291 patients assigned to one 1-hour face-to-face CBT session per week (146 patients), or one minimal contact CBT session on four occasions (145 patients), over 10 weeks	145 patients assigned to education and/or support	≥30% improvement in abdominal pain on a VAS (data from the authors)	350 (80.3%), Rome III, 130 (29.8%) IBS-C, 188 (43.1%) IBS-D, 98 (22.5%) IBS-M	426 (97.7%) refractory

Everitt 2019 ^{s18}	England, primary and secondary care	Not reported, current IBS medications continued	371 patients assigned to eight therapist- supported digital CBT sessions delivered via the internet with three 30- minute telephone therapy calls (185 patients), or six 1-hour therapist- delivered telephone CBT sessions (186 patients) over 9 weeks	187 patients assigned to routine care	≥30% improvement in abdominal pain on the IBS-SSS (imputed)	423 (75.8%), Rome III, 76 (13.6%) IBS-C, 178 (31.9%) IBS- D, 287 (51.5%) IBS-M	558 (100%) refractory
Flik 2019 ^{s22}	Netherlands, secondary and tertiary care	Not reported, current IBS medications continued	288 patients assigned to one 45-minute face-to-face gut-directed hypnotherapy session every 2 weeks for 12 weeks (142 patients), or one 60-minute group gut-directed hypnotherapy session every 2 weeks for 12 weeks (146 patients)	54 patients assigned to education and/or support	Patient-reported adequate relief of IBS-related abdominal pain or discomfort	269 (78.4%), Rome III, 50 (14.8%) IBS-C, 83 (24.6%) IBS- D, 196 (58.1%) IBS-M†	Not stated

Hasan 2021 ^{s2}	England, secondary and tertiary care	Not reported, current IBS medications continued	489 patients assigned to one 1-hour face-to-face gut-directed hypnotherapy session per week for 12 weeks (246 patients), or one 1-hour face-to-face gut-directed hypnotherapy sessions delivered over 6 weeks (243 patients)	No control intervention	≥30% improvement in abdominal pain on the IBS-SSS	378 (84.4%), Rome III, 132 (29.5%) IBS-C, 160 (35.7%) IBS- D, 156 (34.8%) IBS-M†	489 (100%) refractory
Kikuchi 2022 ^{s32}	Japan, tertiary care	Not reported, current IBS medications continued	54 patients assigned to one 90-minute group CBT session per week for 10 weeks plus one booster session	60 patients assigned to routine care	≥30% improvement in abdominal pain on the IBS-SSS (imputed)	72 (63.2%), Rome III or IV, 5 (4.4%) IBS-C, 67 (58.8%) IBS-D, 19 (16.7%) IBS- M	114 (100%) refractory
Lovdahl 2022 ^{s3}	Sweden, tertiary care	Not reported, current IBS medications continued	119 patients assigned to eight face-to- face gut-directed hypnotherapy sessions over 12 weeks (61 patients) or to eight group gut-directed hypnotherapy sessions over 12 weeks (58 patients)	No control intervention	≥30% improvement in abdominal pain on the IBS-SSS (imputed)	87 (73.1%), Rome III, 29 (24.4%) IBS-C, 45 (37.8%) IBS- D, 45 (37.8%) IBS-M	119 (100%) refractory

Berry 2023 s37	USA, not reported	Average worst daily pain severity of ≥ 3 on an 11-point NRS, current IBS medications continued	378 patients assigned to seven digital relaxation therapy sessions (190) or seven digital gut-directed hypnotherapy sessions (188 patients) for 12 weeks	No control intervention	$\geq 30\%$ improvement in average daily abdominal pain intensity	289 (79.8%), Rome IV, 122 (33.7%) IBS-C, 122 (33.7%) IBS-D, 117 (32.3%) IBS-M†	Not stated
Zargar 2023 s38	Iran, tertiary care	Not reported, not reported	40 patients assigned to digital relaxation therapy for 4 weeks	40 patients assigned to education and/or support	$\geq 30\%$ improvement in abdominal pain on the GSRS (imputed)	34 (56.7%), Rome III, subtype not stated‡	Not stated

*Two separate studies reported in one paper.

†Proportions based on per protocol population.

‡Classed as a control intervention by the authors but contained a protocol and some elements of active treatments for IBS. Therefore, classed as an active intervention for the purposes of this network meta-analysis, as single studies which were not pooled with arms from other trials.

BSSS; Bowel Symptom Severity Scale, GSRS; Gastrointestinal Symptom Rating Scale, GSRS-IBS; Gastrointestinal Symptom Rating Scale-IBS, IBS-SSS; Irritable Bowel Syndrome Severity Scoring System, NRS; numeric rating scale, VAS; visual analog scale.

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Supplementary Table 4. Risk of Bias of Randomized Controlled Trials of Brain-Gut Behavioral Treatments for Irritable Bowel Syndrome.

Study	Method of Generation of Randomization Schedule	Method of Concealment of Treatment Allocation	Blinding	Evidence of Incomplete Outcomes Data	Evidence of Selective Reporting of Outcomes
Corney 1991 ^{s25}	Unclear	Unclear	High	Low	Low
*Blanchard 1992a ^{s8}	Unclear	Unclear	High	Low	Low
*Blanchard 1992b ^{s8}	Unclear	Unclear	High	Low	Low
Blanchard 1993 ^{s4}	Unclear	Unclear	High	Low	Low
Greene 1994 ^{s7}	Unclear	Unclear	High	Low	Low
Fernandez 1998 ^{s19}	Unclear	Unclear	High	High	Low
Vollmer 1998 ^{s21}	Unclear	Unclear	High	Low	Low
Palsson 2002 ^{s26}	Unclear	Unclear	High	Low	Low
Boyce 2003 ^{s16}	Low	Low	High	Low	Low
Creed 2003 ^{s12}	Low	Low	High	High	Low
Tkachuk 2003 ^{s17}	Unclear	Unclear	High	Low	Low
Heitkemper 2004 ^{s9}	Unclear	Unclear	High	High	Low
Fernandez 2006 ^{s33}	Unclear	Unclear	High	Low	Low

Roberts 2006 ^{s36}	Low	Low	High	High	Low
Blanchard 2007 ^{s27}	Low	Unclear	High	High	Low
Sanders 2007 ^{s11}	Low	Unclear	High	Low	Low
Lackner 2008 ^{s14}	Low	Unclear	High	Low	Low
Jarrett 2009 ^{s20}	Unclear	Unclear	High	High	Low
Lahmann 2010 ^{s28}	Low	Low	High	Low	Low
Ljotsson 2010 ^{s23}	Low	Low	High	Low	Low
Moss-Morris 2010 ^{s40}	Low	Low	High	Low	Low
Shinozaki 2010 ^{s5}	Unclear	Unclear	High	Low	Low
Gaylord 2011 ^{s13}	Low	Unclear	High	Low	Low
Ljotsson 2011a ^{s24}	Low	Low	High	Low	Low
Ljotsson 2011b ^{s39}	Low	Low	High	High	Low
Oerlemans 2011 ^{s34}	Low	Unclear	High	High	Low
*Lindfors 2012a ^{s10}	Low	Low	High	Low	Low
*Lindfors 2012b ^{s10}	Low	Low	High	Low	Low
Moser 2013 ^{s35}	Low	Low	High	High	Low
Farnam 2014 ^{s29}	Unclear	Unclear	High	High	Low
Ljotsson 2014 ^{s1}	Low	Low	High	High	Low

Boltin 2015 ^{s6}	Low	Low	High	Low	Low
Phillips-Moore 2015 ^{s30}	Low	Low	Low	High	Low
Jarrett 2016 ^{s31}	Low	Unclear	High	High	Low
Lackner 2018 ^{s15}	Low	Low	High	High	Low
Everitt 2019 ^{s18}	Low	Low	High	High	Low
Flik 2019 ^{s22}	Low	Low	High	Low	Low
Hasan 2021 ^{s2}	Low	Unclear	High	High	Low
Kikuchi 2022 ^{s32}	Low	Low	High	High	Low
Lovdahl 2022 ^{s3}	Low	Low	High	High	Low
Berry 2023 ^{s37}	Unclear	Unclear	Low	High	Low
Zargar 2023 ^{s38}	Unclear	Unclear	High	High	Low

Supplementary Table 5. *Netsplit* Analysis of Inconsistency for Failure to Achieve an Improvement in Abdominal Pain Post-treatment.

Comparison	k	Prop.	NMA	Direct	Indirect	RoR	z	p-value
Contingency management: Face-to-face stress management	2	0.96	1.25	1.20	3.44	0.35	-0.65	0.5165
Contingency management: Routine care	2	1.00	0.70	0.69	7.11	0.10	-0.59	0.5582
Digital CBT: Telephone CBT	1	0.91	1.07	1.07	1.03	1.04	0.06	0.9493
Education/support: Face-to-face CBT	1	0.51	1.08	1.01	1.16	0.86	-0.50	0.6159
Education/support: Face-to-face gut-directed hypnotherapy	2	0.64	1.13	1.25	0.96	1.30	1.08	0.2817
Education/support: Group cognitive therapy	1	0.76	1.01	0.98	1.09	0.90	-0.21	0.8310
Education/support: Group gut-directed hypnotherapy	1	0.58	1.09	1.13	1.03	1.09	0.30	0.7676
Education/support: Self-guided/minimal contact CBT	1	0.57	1.22	1.06	1.47	0.72	-1.05	0.2917
Education/support: Waiting list control	1	0.27	0.87	0.83	0.88	0.94	-0.21	0.8310
Face-to-face CBT: Face-to-face relaxation therapy or training	1	0.62	0.90	0.99	0.78	1.28	0.72	0.4692
Face-to-face CBT: Group CBT	1	0.18	1.32	1.00	1.40	0.71	-0.59	0.5526
Face-to-face CBT: Routine care	2	0.54	0.86	1.14	0.61	1.88	2.25	0.0245
Face-to-face CBT: Self-guided/minimal contact CBT	2	0.67	1.13	1.10	1.18	0.94	-0.20	0.8384
Face-to-face CBT: Waiting list control	3	0.31	0.80	0.51	0.98	0.52	-2.19	0.0283

Face-to-face gut-directed hypnotherapy: Face-to-face individualized gut-directed hypnotherapy	1	0.87	1.09	1.22	0.53	2.29	0.88	0.3773
Face-to-face gut-directed hypnotherapy: Face-to-face relaxation therapy or training	1	0.29	0.86	1.10	0.78	1.41	0.88	0.3773
Face-to-face gut-directed hypnotherapy: Group gut-directed hypnotherapy	2	0.77	0.96	0.89	1.24	0.72	-1.04	0.2964
Face-to-face gut-directed hypnotherapy: Waiting list control	3	0.61	0.77	0.83	0.67	1.24	0.93	0.3526
Face-to-face individualized gut-directed hypnotherapy: Face-to-face relaxation therapy or training	1	0.83	0.79	0.90	0.42	2.12	0.88	0.3773
Face-to-face multicomponent behavioral therapy: Routine care	3	0.80	0.77	0.73	0.96	0.76	-0.90	0.3664
Face-to-face multicomponent behavioral therapy: Telephone multicomponent behavioral therapy	1	0.74	0.91	0.76	1.51	0.50	-1.45	0.1483
Face-to-face multicomponent behavioral therapy: Waiting list control	2	0.48	0.72	0.83	0.63	1.32	0.90	0.3664
Face-to-face relaxation therapy or training: Routine care	1	0.56	0.95	1.23	0.68	1.82	1.73	0.0839
Face-to-face relaxation therapy or training: Waiting list control	1	0.23	0.89	0.96	0.87	1.11	0.27	0.7904
Face-to-face stress management: Routine care	2	1.00	0.56	0.55	296.22	0.00	-1.20	0.2307
Group CBT: Routine care	1	0.66	0.65	0.65	0.64	1.01	0.03	0.9737
Group CBT: Waiting list control	2	0.42	0.61	0.59	0.62	0.94	-0.14	0.8848
Group cognitive therapy: Waiting list control	1	0.82	0.86	0.84	0.94	0.89	-0.21	0.8310
Group gut-directed hypnotherapy: Routine care	1	0.40	0.85	0.74	0.94	0.79	-0.71	0.4804

Routine care: Self-guided/minimal contact CBT	1	0.27	1.31	1.88	1.15	1.64	1.36	0.1752
Routine care: Telephone CBT	1	0.92	1.25	1.25	1.31	0.96	-0.06	0.9493
Routine care: Telephone multicomponent behavioral therapy	1	0.88	1.17	1.30	0.54	2.43	1.45	0.1483
Self-guided/minimal contact CBT: Waiting list control	2	0.42	0.71	0.70	0.72	0.97	-0.11	0.9136

Legend

Comparison: Treatment comparison

K: Number of studies providing direct evidence

Prop: Direct evidence proportion

NMA: Estimated treatment effect (RR) in network meta-analysis

Direct: Estimated treatment effect (RR) derived from direct evidence

Indirect: Estimated treatment effect (RR) derived from indirect evidence

RoR: Ratio of Ratios (direct versus indirect)

z: z-value of test for disagreement (direct versus indirect)

p-value: p-value of test for disagreement (direct versus indirect)

Supplementary Table 6. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Pain Post-treatment.

DGH T	0.87 (0.60 ; 1.27)																								
0.87 (0.60 ; 1.27)	DRT T																	0.26 (0.13 ; 0.49)							
0.37 (0.14 ; 0.97)	0.42 (0.17 ; 1.03)	FFS M					0.83 (0.45 ; 1.52)															0.55 (0.32 ; 0.93)			
0.35 (0.14 ; 0.88)	0.40 (0.18 ; 0.93)	0.95 (0.42 ; 2.14)	MM T															0.64 (0.37 ; 1.08)							
0.35 (0.12 ; 0.98)	0.40 (0.15 ; 1.05)	0.94 (0.40 ; 2.18)	0.99 (0.40 ; 2.42)	EAT																		0.60 (0.31 ; 1.15)			
0.32 (0.13 ; 0.76)	0.37 (0.17 ; 0.80)	0.86 (0.45 ; 1.65)	0.91 (0.45 ; 1.81)	0.92 (0.43 ; 1.96)	GCB T										1.00 (0.36 ; 2.75)							0.65 (0.41 ; 1.04)	0.59 (0.31 ; 1.11)		
0.30 (0.12 ; 0.74)	0.35 (0.15 ; 0.78)	0.82 (0.39 ; 1.71)	0.86 (0.42 ; 1.76)	0.87 (0.38 ; 2.01)	0.95 (0.51 ; 1.75)	FFS- CGH T						0.84 (0.55 ; 1.29)													
0.30 (0.12 ; 0.75)	0.34 (0.15 ; 0.79)	0.80 (0.44 ; 1.45)	0.84 (0.39 ; 1.80)	0.85 (0.38 ; 1.90)	0.93 (0.51 ; 1.68)	0.98 (0.49 ; 1.96)	CM															0.69 (0.44 ; 1.09)			
0.27 (0.12 ; 0.61)	0.31 (0.15 ; 0.64)	0.74 (0.40 ; 1.36)	0.77 (0.42 ; 1.42)	0.78 (0.38 ; 1.62)	0.85 (0.54 ; 1.35)	0.90 (0.53 ; 1.54)	0.92 (0.53 ; 1.60)	S- G/M- CCB T							0.91 (0.63 ; 1.31)						0.95 (0.63 ; 1.41)	0.53 (0.29 ; 0.98)	0.70 (0.45 ; 1.09)		
0.27 (0.12 ; 0.61)	0.31 (0.15 ; 0.64)	0.72 (0.41 ; 1.29)	0.76 (0.40 ; 1.43)	0.77 (0.38 ; 1.55)	0.84 (0.54 ; 1.29)	0.89 (0.51 ; 1.53)	0.90 (0.54 ; 1.51)	0.98 (0.68 ; 1.41)	FFM BT					0.76 (0.48 ; 1.22)								0.73 (0.56 ; 0.95)	0.83 (0.54 ; 1.28)		
0.28 (0.10 ; 0.75)	0.32 (0.13 ; 0.80)	0.75 (0.32 ; 1.75)	0.79 (0.34 ; 1.82)	0.80 (0.31 ; 2.03)	0.87 (0.41 ; 1.82)	0.92 (0.43 ; 1.96)	0.93 (0.42 ; 2.08)	1.02 (0.52 ; 2.01)	1.04 (0.52 ; 2.05)	FFI GHT			0.82 (0.42 ; 1.60)								0.90 (0.45 ; 1.81)				
0.26 (0.11 ; 0.62)	0.30 (0.14 ; 0.65)	0.71 (0.36 ; 1.41)	0.74 (0.34 ; 1.47)	0.75 (0.34 ; 1.67)	0.82 (0.48 ; 1.41)	0.87 (0.48 ; 1.58)	0.88 (0.47 ; 1.67)	0.96 (0.61 ; 1.52)	0.98 (0.62 ; 1.55)	0.95 (0.45 ; 1.97)	DAC T							0.85 (0.57 ; 1.27)			0.72 (0.43 ; 1.22)		0.74 (0.52 ; 1.05)		
0.26 (0.11 ; 0.63)	0.30 (0.13 ; 0.67)	0.70 (0.37 ; 1.34)	0.74 (0.36 ; 1.51)	0.75 (0.35 ; 1.59)	0.81 (0.48 ; 1.39)	0.86 (0.45 ; 1.64)	0.88 (0.49 ; 1.58)	0.95 (0.59 ; 1.56)	0.97 (0.62 ; 1.51)	0.94 (0.44 ; 2.00)	0.99 (0.56 ; 1.77)	TCB T			0.93 (0.63 ; 1.39)							0.80 (0.54 ; 1.18)			

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the strategy labels, and indirect comparisons are below.

CM; contingency management, DACT; digital acceptance and commitment therapy, DACTWE; digital acceptance and commitment therapy without exposure, DCBT; digital cognitive behavioral therapy, DGHT; digital gut-directed hypnotherapy, D/LA; dietary and/or lifestyle advice, DP; dynamic psychotherapy, DRTT; digital relaxation therapy or training, DSM; digital stress management, EAT; emotional awareness training, E/S; education and/or support, FFCBT; face-to-face cognitive behavioral therapy, FFGHT; face-to-face gut-directed hypnotherapy, FFIGHT; face-to-face individualized gut-directed hypnotherapy, FFMBT; face-to-face multicomponent behavioral therapy, FFRTT; face-to-face relaxation therapy or training, FFS-CGHT; face-to-face short-course gut-directed hypnotherapy, FFSM; face-to-face stress management, GCBT; group cognitive behavioral therapy, GCT; group cognitive therapy, GGHT; group gut-directed hypnotherapy, GRTT; group relaxation therapy or training, MMT; mindfulness meditation training, RC; routine care, S-G/M-CCBT; self-guided/minimal-contact cognitive behavioral therapy, TCBT; telephone cognitive behavioral therapy, TMBT; telephone multicomponent behavioral therapy, WLC; waiting list control.

Supplementary Table 7. Confidence in Network Meta-Analysis Framework Evaluating the Confidence in the Indirect and Direct Treatment Estimates from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Pain Post-treatment.

Comparison	No. of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Contingency management: Face-to-face stress management	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Routine care	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Face-to-face relaxation therapy or training	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Digital CBT: Routine care	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Telephone CBT	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Digital acceptance and commitment therapy without exposure	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy: Digital stress management	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Digital acceptance and commitment therapy: Waiting list control	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital gut-directed hypnotherapy: Digital relaxation therapy or training	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital relaxation therapy or training: Education/support	1	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Dynamic psychotherapy: Routine care	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Face-to-face CBT	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Face-to-face gut-directed hypnotherapy	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Group cognitive therapy	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Group gut-directed hypnotherapy	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Mindfulness meditation training	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Education/support: Self-guided/minimal contact CBT	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Waiting list control	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Routine care	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Face-to-face relaxation therapy or training	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Face-to-face CBT: Group CBT	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Routine care	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very Low	Within-study bias; Imprecision; Incoherence
Face-to-face CBT: Self-guided/minimal contact CBT	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Waiting list control	3	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very Low	Within-study bias; Imprecision; Heterogeneity; Incoherence
Face-to-face gut-directed hypnotherapy: Face-to-face individualized gut-directed hypnotherapy	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face gut-directed hypnotherapy: Face-to-face relaxation therapy or training	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Face-to-face short-course gut-directed hypnotherapy	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Group gut-directed hypnotherapy	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Waiting list control	3	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Face-to-face individualized gut-directed hypnotherapy: Face-to-face relaxation therapy or training	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Routine care	3	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Face-to-face multicomponent behavioral therapy: Telephone multicomponent behavioral therapy	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face multicomponent behavioral therapy: Waiting list control	2	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Face-to-face relaxation therapy or training: Routine care	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Face-to-face relaxation therapy or training: Waiting list control	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Routine care	2	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Group CBT: Routine care	1	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Group CBT: Waiting list control	2	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Group cognitive therapy: Waiting list control	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group gut-directed hypnotherapy: Routine care	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group relaxation therapy or training: Routine care	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Routine care: Self-guided/minimal contact CBT	1	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias; Imprecision; Heterogeneity

Routine care: Telephone CBT	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Routine care: Telephone multicomponent behavioral therapy	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Self-guided/minimal contact CBT: Waiting list control	2	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
INDIRECT EVIDENCE									
Contingency management: Dietary/lifestyle advice	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Digital CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Digital acceptance and commitment therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Digital acceptance and commitment therapy without exposure	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Digital gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias

Contingency management: Digital relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Contingency management: Digital stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Education/support	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Face- to-face CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Face- to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Face- to-face individualized gut- directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Face- to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Contingency management: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Contingency management: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Contingency management: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Digital CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Digital acceptance and commitment therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Digital acceptance and commitment therapy without exposure	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Digital gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Dietary/lifestyle advice: Digital relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Dietary/lifestyle advice: Digital stress management	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Dietary/lifestyle advice: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Education/support	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Dietary/lifestyle advice: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Face-to- face CBT	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Dietary/lifestyle advice: Face-to- face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Face-to- face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Face-to- face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Face-to- face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Face-to- face stress management	N/A	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias; Imprecision; Heterogeneity
Dietary/lifestyle advice: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Dietary/lifestyle advice: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Group relaxation therapy or training	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Dietary/lifestyle advice: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Routine care	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Dietary/lifestyle advice: Self-guided/minimal contact CBT	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Dietary/lifestyle advice: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dietary/lifestyle advice: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Digital CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Digital CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital CBT: Digital gut directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital CBT: Digital relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital CBT: Digital stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Education/support	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Face-to-face CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Face-to-face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital CBT: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital CBT: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital CBT: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Digital gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital acceptance and commitment therapy: Digital relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital acceptance and commitment therapy: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Education/support	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Face-to-face CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy: Face-to-face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Digital gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital acceptance and commitment therapy without exposure: Digital relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital acceptance and commitment therapy without exposure: Digital stress management	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Digital acceptance and commitment therapy without exposure: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Education/support	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy without exposure: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Face-to-face CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Face-to-face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy without exposure: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy without exposure: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital acceptance and commitment therapy without exposure: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital acceptance and commitment therapy without exposure: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital gut-directed hypnotherapy: Digital stress management	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Education/support	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Digital gut-directed hypnotherapy: Face-to-face CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias

Digital gut-directed hypnotherapy: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Face-to-face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Digital gut-directed hypnotherapy: Group CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias

Digital gut-directed hypnotherapy: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Routine care	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital gut-directed hypnotherapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias

Digital gut-directed hypnotherapy: Waiting list control	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Digital stress management	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital relaxation therapy or training: Face-to-face CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Face-to-face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias

Digital relaxation therapy or training: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias; Imprecision; Heterogeneity
Digital relaxation therapy or training: Group CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias

Digital relaxation therapy or training: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Routine care	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Telephone CBT	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital relaxation therapy or training: Waiting list control	N/A	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Digital stress management: Dynamic psychotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Education/support	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital stress management: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Face-to-face CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Face-to-face individualized gut- directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Face-to-face short-course gut- directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Digital stress management: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Group relaxation therapy or training	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Digital stress management: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Self- guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Digital stress management: Waiting list control	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Dynamic psychotherapy: Education/support	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Dynamic psychotherapy: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Face- to-face CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Face- to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Face- to-face individualized gut- directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Face- to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Face- to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Face- to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Face- to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Dynamic psychotherapy: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Group relaxation therapy or training	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Dynamic psychotherapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Dynamic psychotherapy: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Emotional awareness training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Face-to-face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Education/support: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Education/support: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Face-to-face CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Emotional awareness training: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Face-to-face individualized gut- directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Face-to-face short-course gut- directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Emotional awareness training: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Group relaxation therapy or training	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Emotional awareness training: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Emotional awareness training: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Face-to-face gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Face-to-face individualized gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face CBT: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Group relaxation therapy or training	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Face-to-face CBT: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face CBT: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face gut-directed hypnotherapy: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face gut-directed hypnotherapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face gut-directed hypnotherapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Face-to-face multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face individualized gut-directed hypnotherapy: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face individualized gut-directed hypnotherapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face individualized gut-directed hypnotherapy: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Face-to-face relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face multicomponent behavioral therapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face multicomponent behavioral therapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Face-to-face short-course gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face relaxation therapy or training: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Group relaxation therapy or training	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Face-to-face relaxation therapy or training: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face relaxation therapy or training: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face short-course gut-directed hypnotherapy: Face-to-face stress management	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face short-course gut-directed hypnotherapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face short-course gut-directed hypnotherapy: Waiting list control	N/A	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias; Imprecision; Heterogeneity
Face-to-face stress management: Group CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Face-to-face stress management: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Face-to-face stress management: Waiting list control	N/A	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Group CBT: Group cognitive therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group CBT: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group CBT: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group CBT: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group CBT: Self- guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Group CBT: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group CBT: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group cognitive therapy: Group gut-directed hypnotherapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group cognitive therapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group cognitive therapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group cognitive therapy: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group cognitive therapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group cognitive therapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group cognitive therapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group gut-directed hypnotherapy: Group relaxation therapy or training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Group gut-directed hypnotherapy: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group gut-directed hypnotherapy: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group gut-directed hypnotherapy: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group gut-directed hypnotherapy: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group gut-directed hypnotherapy: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group relaxation therapy or training: Mindfulness meditation training	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group relaxation therapy or training: Self-guided/minimal contact CBT	N/A	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Group relaxation therapy or training: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Group relaxation therapy or training: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Group relaxation therapy or training: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Mindfulness meditation training: Routine care	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Mindfulness meditation training: Self-guided/minimal contact CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Mindfulness meditation training: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Mindfulness meditation training: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Mindfulness meditation training: Waiting list control	N/A	Major concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias; Heterogeneity
Routine care: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Self-guided/minimal contact CBT: Telephone CBT	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

Self-guided/minimal contact CBT: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Telephone CBT: Telephone multicomponent behavioral therapy	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Telephone CBT: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision
Telephone multicomponent behavioral therapy: Waiting list control	N/A	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias; Imprecision

N/A; not applicable.

This table shows the confidence rating of evidence for all direct and indirect comparisons across the network.

Within-study bias: This relates to the risk of bias assessment made for each included study. The studies' contributions are combined with the risk of bias judgments to evaluate within-study bias for each estimate from a network meta-analysis.

Reporting bias: This relates to the assessment of the risk of bias from missing data or incomplete reporting.

Indirectness: Each study included in the network is evaluated according to its relevance to the research question, classified into low, moderate, or high indirectness.

Imprecision: The evaluation of imprecision requires that the relative treatment effect representing a clinically important difference is defined. We set this at 0.05 which creates a range of equivalence between 0.95 and 1.05. The treatment effect of the 95% CI of each comparison is compared with the range of equivalence. A rating of “major concerns” is given if the 95% CI extends beyond the range of equivalence on the opposite side of the null effect line as the point estimate, i.e., compatible with clinically important treatment effects in both directions, and a rating of “some concerns” is given if the 95% CI extends into, but not beyond, the range of equivalence on the opposite side of the null effect line as the point estimate.

Heterogeneity: Network meta-analysis assumes a single heterogeneity variance across all comparisons, expressed as τ^2 , and this can, in turn, be expressed as a prediction interval. The prediction interval shows where the true effect of a new study similar to the existing studies is expected to lie. The 95% CI of each comparison is compared to the prediction interval, with reference to the range of equivalence. If both lead to the same conclusions, then there are “no concerns” regarding heterogeneity. A rating of “major concerns” is given if the prediction interval extends beyond the range of equivalence on the opposite side of the null effect line as the point estimate, i.e., compatible with clinically important treatment effects in both directions, and a rating of “some concerns” is given if the prediction interval extends into, but not beyond, the range of equivalence on the opposite side of the null effect line as the point estimate.

Incoherence: This evaluates the agreement between direct and indirect evidence for certain comparisons in the network (also referred to as inconsistency). Where the 95% CI of the direct and indirect treatment estimate for a comparison would lead to the same conclusion with reference to the range of equivalence, a rating of “no concerns” is given.

Overall confidence rating and process of downgrading confidence: The quality of evidence was downgraded by one level if there were “major concerns” in one area, or “some concerns” in two areas. Consequently, the overall confidence rating for each comparison was based on the additive effect of ratings across all assessment domains.

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Supplementary Table 8. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Pain Post-treatment: Including Only Trials with A Direct Connection to the Four Control Interventions.

FFSM					0.83 (0.45; 1.52)															0.55 (0.32; 0.93)		
0.95 (0.42; 2.14)	MMT																			0.64 (0.37; 1.08)		
0.94 (0.40; 2.18)	0.99 (0.40; 2.42)	EAT																			0.60 (0.31; 1.15)	
0.86 (0.45; 1.65)	0.91 (0.45; 1.81)	0.92 (0.43; 1.96)	GCBT											1.00 (0.36; 2.75)							0.65 (0.41; 1.04)	0.59 (0.31; 1.11)
0.82 (0.39; 1.71)	0.86 (0.42; 1.76)	0.87 (0.38; 2.01)	0.95 (0.51; 1.75)	FFS- CGHT						0.84 (0.55; 1.29)												
0.80 (0.44; 1.45)	0.84 (0.39; 1.80)	0.85 (0.38; 1.90)	0.93 (0.51; 1.68)	0.98 (0.49; 1.96)	CM																0.69 (0.44; 1.09)	
0.74 (0.40; 1.36)	0.77 (0.42; 1.42)	0.78 (0.38; 1.62)	0.85 (0.54; 1.35)	0.90 (0.53; 1.54)	0.92 (0.53; 1.60)	S-G/M- CCBT								0.91 (0.63; 1.31)			0.95 (0.63; 1.41)			0.53 (0.29; 0.98)	0.70 (0.45; 1.09)	
0.72 (0.41; 1.29)	0.76 (0.40; 1.43)	0.77 (0.38; 1.55)	0.84 (0.54; 1.29)	0.89 (0.51; 1.53)	0.90 (0.54; 1.51)	0.98 (0.68; 1.41)	FFMB T						0.76 (0.48; 1.22)								0.73 (0.56; 0.95)	0.83 (0.54; 1.28)
0.75 (0.32; 1.75)	0.79 (0.34; 1.82)	0.80 (0.31; 2.03)	0.87 (0.41; 1.82)	0.92 (0.43; 1.96)	0.93 (0.42; 2.08)	1.02 (0.52; 2.01)	1.04 (0.52; 2.05)	FFIGH T			0.82 (0.42; 1.60)										0.90 (0.45; 1.81)	
0.71 (0.36; 1.41)	0.74 (0.38; 1.47)	0.75 (0.34; 1.64)	0.82 (0.48; 1.41)	0.87 (0.48; 1.41)	0.88 (0.47; 1.58)	0.96 (0.61; 1.67)	0.98 (0.62; 1.55)	0.95 (0.45; 1.97)	DACT													0.74 (0.52; 1.05)
0.70 (0.37; 1.34)	0.74 (0.36; 1.51)	0.75 (0.35; 1.59)	0.81 (0.48; 1.39)	0.86 (0.45; 1.64)	0.88 (0.49; 1.58)	0.95 (0.59; 1.56)	0.97 (0.62; 1.51)	0.94 (0.44; 2.00)	0.99 (0.56; 1.77)	TCBT				0.93 (0.63; 1.39)								0.80 (0.54; 1.18)
0.68 (0.37; 1.26)	0.72 (0.40; 1.28)	0.73 (0.35; 1.50)	0.79 (0.51; 1.23)	0.84 (0.51; 1.29)	0.85 (0.50; 1.47)	0.93 (0.68; 1.28)	0.95 (0.67; 1.33)	0.91 (0.49; 1.71)	0.97 (0.64; 1.47)	0.97 (0.60; 1.57)	FFGH T		0.89 (0.66; 1.20)				0.80 (0.60; 1.07)	1.10 (0.58; 2.09)			0.83 (0.63; 1.11)	

0.66 (0.33; 1.32)	0.70 (0.33; 1.48)	0.71 (0.32; 1.56)	0.77 (0.43; 1.38)	0.81 (0.41; 1.61)	0.83 (0.44; 1.56)	0.90 (0.52; 1.56)	0.92 (0.55; 1.52)	0.89 (0.40; 1.96)	0.94 (0.50; 1.76)	0.94 (0.53; 1.69)	0.97 (0.57; 1.66)	GRTT																			0.84 (0.54; 1.32)						
0.66 (0.34; 1.26)	0.69 (0.34; 1.41)	0.70 (0.33; 1.50)	0.76 (0.45; 1.31)	0.81 (0.42; 1.53)	0.82 (0.45; 1.49)	0.89 (0.55; 1.46)	0.91 (0.61; 1.36)	0.88 (0.41; 1.88)	0.93 (0.52; 1.65)	0.94 (0.55; 1.60)	0.96 (0.60; 1.55)	0.99 (0.55; 1.79)	TMBT																				0.77 (0.51; 1.16)				
0.66 (0.35; 1.22)	0.69 (0.38; 1.26)	0.70 (0.34; 1.46)	0.76 (0.48; 1.22)	0.81 (0.49; 1.33)	0.82 (0.47; 1.43)	0.89 (0.62; 1.29)	0.91 (0.63; 1.32)	0.88 (0.45; 1.71)	0.93 (0.58; 1.48)	0.94 (0.57; 1.54)	0.96 (0.74; 1.25)	0.99 (0.57; 1.72)	1.00 (0.61; 1.64)	GGHT											0.89 (0.61; 1.29)								0.74 (0.44; 1.24)				
0.66 (0.36; 1.21)	0.69 (0.35; 1.37)	0.70 (0.34; 1.45)	0.76 (0.47; 1.24)	0.81 (0.44; 1.48)	0.82 (0.47; 1.42)	0.89 (0.57; 1.39)	0.91 (0.62; 1.34)	0.88 (0.42; 1.82)	0.93 (0.54; 1.59)	0.94 (0.64; 1.37)	0.96 (0.63; 1.48)	0.99 (0.58; 1.70)	1.00 (0.61; 1.64)	1.00 (0.64; 1.57)	DCBT																			0.85 (0.63; 1.16)			
0.65 (0.36; 1.18)	0.69 (0.38; 1.25)	0.70 (0.34; 1.42)	0.76 (0.49; 1.16)	0.80 (0.48; 1.35)	0.81 (0.48; 1.39)	0.89 (0.66; 1.20)	0.90 (0.65; 1.26)	0.87 (0.45; 1.68)	0.92 (0.59; 1.44)	0.93 (0.59; 1.48)	0.95 (0.71; 1.28)	0.98 (0.58; 1.66)	0.99 (0.62; 1.58)	0.99 (0.70; 1.40)	0.99 (0.66; 1.50)	FFCBT									0.99 (0.67; 1.48)	0.99 (0.66; 1.50)							1.14 (0.79; 1.66)	0.51 (0.32; 0.83)			
0.65 (0.33; 1.28)	0.68 (0.32; 1.43)	0.69 (0.31; 1.51)	0.75 (0.42; 1.33)	0.79 (0.40; 1.56)	0.81 (0.43; 1.51)	0.88 (0.51; 1.50)	0.89 (0.55; 1.46)	0.86 (0.39; 1.90)	0.91 (0.49; 1.69)	0.92 (0.52; 1.63)	0.94 (0.56; 1.59)	0.97 (0.52; 1.81)	0.98 (0.55; 1.75)	0.98 (0.57; 1.69)	0.98 (0.58; 1.67)	0.99 (0.59; 1.65)	DP																	0.87 (0.56; 1.34)			
0.61 (0.30; 1.23)	0.64 (0.33; 1.25)	0.65 (0.29; 1.45)	0.71 (0.40; 1.23)	0.75 (0.41; 1.37)	0.76 (0.40; 1.45)	0.83 (0.52; 1.32)	0.84 (0.52; 1.36)	0.81 (0.39; 1.71)	0.86 (0.51; 1.46)	0.87 (0.48; 1.57)	0.89 (0.58; 1.36)	0.92 (0.48; 1.74)	0.93 (0.51; 1.67)	0.93 (0.58; 1.48)	0.93 (0.53; 1.61)	0.93 (0.59; 1.47)	0.94 (0.50; 1.77)	GCT	1.02 (0.64; 1.62)															0.84 (0.54; 1.31)			
0.60 (0.33; 1.11)	0.64 (0.37; 1.08)	0.64 (0.31; 1.33)	0.70 (0.45; 1.10)	0.74 (0.46; 1.21)	0.75 (0.44; 1.30)	0.82 (0.61; 1.11)	0.84 (0.59; 1.18)	0.81 (0.42; 1.55)	0.85 (0.53; 1.32)	0.86 (0.53; 1.39)	0.88 (0.70; 1.11)	0.91 (0.53; 1.56)	0.92 (0.57; 1.49)	0.92 (0.69; 1.23)	0.93 (0.70; 1.42)	0.94 (0.55; 1.23)	0.99 (0.66; 1.49)	E/S																	0.83 (0.51; 1.34)		
0.59 (0.32; 1.11)	0.62 (0.33; 1.18)	0.63 (0.30; 1.32)	0.69 (0.42; 1.11)	0.72 (0.42; 1.26)	0.74 (0.42; 1.30)	0.80 (0.55; 1.18)	0.82 (0.56; 1.20)	0.79 (0.42; 1.49)	0.83 (0.51; 1.36)	0.84 (0.51; 1.39)	0.86 (0.61; 1.22)	0.89 (0.51; 1.56)	0.90 (0.54; 1.49)	0.90 (0.61; 1.34)	0.90 (0.57; 1.42)	0.90 (0.65; 1.25)	0.92 (0.53; 1.58)	0.97 (0.59; 1.60)	0.98 (0.68; 1.41)	FFRTT	1.23 (0.79; 1.93)	0.96 (0.48; 1.95)	0.74 (0.43; 1.29)														
0.56 (0.33; 0.95)	0.59 (0.32; 1.08)	0.60 (0.31; 1.15)	0.65 (0.44; 0.95)	0.69 (0.41; 1.16)	0.70 (0.44; 1.10)	0.76 (0.55; 1.04)	0.77 (0.61; 0.98)	0.75 (0.39; 1.45)	0.79 (0.51; 1.23)	0.80 (0.55; 1.16)	0.82 (0.61; 1.10)	0.84 (0.54; 1.32)	0.85 (0.58; 1.25)	0.85 (0.61; 1.18)	0.85 (0.63; 1.16)	0.86 (0.65; 1.13)	0.87 (0.56; 1.34)	0.92 (0.58; 1.45)	0.93 (0.68; 1.26)	0.95 (0.68; 1.33)	RC																
0.52 (0.29; 0.95)	0.55 (0.31; 0.99)	0.56 (0.27; 1.13)	0.61 (0.40; 0.92)	0.64 (0.40; 1.04)	0.65 (0.39; 1.11)	0.71 (0.54; 0.95)	0.72 (0.54; 0.97)	0.70 (0.37; 1.33)	0.74 (0.52; 1.05)	0.75 (0.47; 1.18)	0.77 (0.61; 0.96)	0.79 (0.47; 1.33)	0.80 (0.51; 1.26)	0.80 (0.59; 1.08)	0.80 (0.53; 1.20)	0.80 (0.61; 1.05)	0.81 (0.49; 1.35)	0.86 (0.58; 1.28)	0.87 (0.68; 1.11)	0.89 (0.64; 1.24)	0.94 (0.72; 1.22)	WLC															
0.44 (0.19; 1.01)	0.46 (0.20; 1.08)	0.47 (0.19; 1.18)	0.51 (0.25; 1.06)	0.54 (0.25; 1.18)	0.55 (0.25; 1.21)	0.60 (0.30; 1.17)	0.61 (0.31; 1.19)	0.59 (0.25; 1.36)	0.62 (0.30; 1.29)	0.63 (0.30; 1.32)	0.64 (0.33; 1.23)	0.66 (0.30; 1.45)	0.67 (0.32; 1.41)	0.67 (0.34; 1.32)	0.67 (0.33; 1.37)	0.67 (0.35; 1.28)	0.68 (0.31; 1.48)	0.72 (0.34; 1.52)	0.73 (0.38; 1.41)	0.74 (0.43; 1.29)	0.79 (0.41; 1.50)	0.84 (0.44; 1.60)	DLA														

CM; contingency management, DACT; digital acceptance and commitment therapy, DCBT; digital cognitive behavioral therapy, D/LA; dietary and/or lifestyle advice, DP; dynamic psychotherapy, EAT; emotional awareness training, E/S; education and/or support, FFCBT; face-to-face cognitive behavioral therapy, FFGHT; face-to-face gut-directed hypnotherapy, FFIGHT; face-to-face individualized gut-directed hypnotherapy,

FFMBT; face-to-face multicomponent behavioral therapy, FFRTT; face-to-face relaxation therapy or training, FFS-CGHT; face-to-face short-course gut-directed hypnotherapy, FFSM; face-to-face stress management, GCBT; group cognitive behavioral therapy, GCT; group cognitive therapy, GGHT; group gut-directed hypnotherapy, GRTT; group relaxation therapy or training, MMT; mindfulness meditation training, RC; routine care, S-G/M-CCBT; self-guided/minimal-contact cognitive behavioral therapy, TCBT; telephone cognitive behavioral therapy, TMBT; telephone multicomponent behavioral therapy, WLC; waiting list control.

Supplementary Table 9. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Pain Post-treatment: Trials Recruiting Only Patients with Global IBS Symptoms Refractory to Treatment.

CM		0.91 (0.39; 2.13)												0.53 (0.25; 1.10)		
0.90 (0.37; 2.18)	GCBT													0.65 (0.38; 1.13)	0.45 (0.19; 1.10)	
0.91 (0.39; 2.13)	1.02 (0.42; 2.46)	FFSM												0.58 (0.28; 1.19)		
0.79 (0.26; 2.42)	0.89 (0.37; 2.10)	0.87 (0.29; 2.63)	FFS- CGHT			0.84 (0.50; 1.41)										
0.81 (0.24; 2.78)	0.91 (0.33; 2.48)	0.89 (0.26; 3.03)	1.03 (0.42; 2.52)	FFIGHT	0.90 (0.42; 1.92)	0.82 (0.39; 1.71)										
0.73 (0.22; 2.46)	0.82 (0.31; 2.19)	0.80 (0.24; 2.68)	0.92 (0.38; 2.22)	0.90 (0.42; 1.92)	FFRTT	0.91 (0.45; 1.84)										0.26 (0.06; 1.05)
0.67 (0.25; 1.78)	0.74 (0.37; 1.48)	0.73 (0.28; 1.94)	0.84 (0.50; 1.41)	0.82 (0.39; 1.71)	0.91 (0.45; 1.84)	FFGHT		0.87 (0.49; 1.53)					0.81 (0.47; 1.37)		0.82 (0.58; 1.15)	
0.66 (0.27; 1.60)	0.74 (0.37; 1.49)	0.73 (0.30; 1.73)	0.83 (0.32; 2.20)	0.81 (0.27; 2.45)	0.90 (0.31; 2.66)	0.99 (0.44; 2.26)	TCBT		0.93 (0.57; 1.53)					0.80 (0.49; 1.30)		
0.64 (0.26; 1.59)	0.72 (0.37; 1.38)	0.70 (0.29; 1.72)	0.81 (0.39; 1.68)	0.79 (0.32; 1.93)	0.87 (0.36; 2.10)	0.96 (0.57; 1.61)	0.97 (0.47; 2.00)	GGHT						0.74 (0.41; 1.34)		
0.62 (0.26; 1.49)	0.69 (0.34; 1.39)	0.68 (0.28; 1.61)	0.78 (0.29; 2.05)	0.76 (0.25; 2.28)	0.84 (0.29; 2.48)	0.93 (0.41; 2.10)	0.93 (0.57; 1.53)	0.96 (0.47; 1.99)	DCBT					0.86 (0.53; 1.40)		
0.61 (0.25; 1.50)	0.68 (0.33; 1.41)	0.67 (0.27; 1.63)	0.77 (0.29; 2.07)	0.75 (0.25; 2.29)	0.83 (0.28; 2.50)	0.92 (0.39; 2.13)	0.92 (0.45; 1.89)	0.95 (0.45; 2.02)	0.99 (0.48; 2.02)	DP				0.87 (0.51; 1.46)		
0.57 (0.17; 1.93)	0.63 (0.23; 1.72)	0.62 (0.18; 2.10)	0.71 (0.29; 1.75)	0.70 (0.25; 1.96)	0.77 (0.28; 2.13)	0.85 (0.41; 1.76)	0.86 (0.29; 2.57)	0.89 (0.36; 2.16)	0.92 (0.31; 2.75)	0.93 (0.31; 2.83)	S-G/M- CCBT	0.95 (0.58; 1.57)	0.95 (0.58; 1.56)			
0.54 (0.16; 1.84)	0.60 (0.22; 1.64)	0.59 (0.18; 2.00)	0.68 (0.28; 1.66)	0.66 (0.24; 1.86)	0.74 (0.27; 2.03)	0.81 (0.39; 1.68)	0.82 (0.27; 2.44)	0.84 (0.35; 2.06)	0.88 (0.29; 2.62)	0.89 (0.29; 2.69)	0.95 (0.58; 1.57)	FFCBT	0.99 (0.61; 1.63)			

0.54 (0.18; 1.64)	0.60 (0.25; 1.43)	0.59 (0.19; 1.79)	0.68 (0.32; 1.42)	0.66 (0.27; 1.63)	0.73 (0.30; 1.77)	0.81 (0.47; 1.37)	0.81 (0.30; 2.16)	0.84 (0.40; 1.76)	0.87 (0.33; 2.31)	0.88 (0.32; 2.38)	0.95 (0.58; 1.56)	0.99 (0.61; 1.63)	E/S			
0.53 (0.25; 1.10)	0.59 (0.36; 0.98)	0.58 (0.28; 1.19)	0.67 (0.29; 1.54)	0.65 (0.24; 1.74)	0.72 (0.28; 1.90)	0.79 (0.41; 1.54)	0.80 (0.49; 1.30)	0.83 (0.48; 1.41)	0.86 (0.53; 1.40)	0.87 (0.51; 1.46)	0.93 (0.35; 2.49)	0.98 (0.37; 2.61)	0.99 (0.42; 2.30)	RC		
0.52 (0.19; 1.42)	0.58 (0.30; 1.15)	0.57 (0.21; 1.54)	0.66 (0.36; 1.22)	0.64 (0.29; 1.44)	0.71 (0.33; 1.56)	0.79 (0.56; 1.09)	0.79 (0.34; 1.83)	0.82 (0.46; 1.46)	0.85 (0.37; 1.96)	0.86 (0.36; 2.02)	0.92 (0.41; 2.05)	0.97 (0.44; 2.15)	0.98 (0.52; 1.83)	0.99 (0.50; 1.95)	WLC	
0.19 (0.03; 1.21)	0.21 (0.04; 1.17)	0.21 (0.03; 1.32)	0.24 (0.05; 1.25)	0.23 (0.05; 1.15)	0.26 (0.06; 1.05)	0.29 (0.06; 1.37)	0.29 (0.05; 1.68)	0.30 (0.06; 1.54)	0.31 (0.05; 1.80)	0.31 (0.05; 1.84)	0.34 (0.06; 1.89)	0.35 (0.06; 1.98)	0.35 (0.07; 1.85)	0.36 (0.07; 1.96)	0.36 (0.07; 1.80)	D/LA

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the strategy labels, and indirect comparisons are below.

CM; contingency management, DCBT; digital cognitive behavioral therapy, D/LA; dietary and/or lifestyle advice, DP; dynamic psychotherapy, E/S; education and/or support, FFCBT; face-to-face cognitive behavioral therapy, FFGHT; face-to-face gut-directed hypnotherapy, FFIGHT; face-to-face individualized gut-directed hypnotherapy, FFS-CGHT; face-to-face short-course gut-directed hypnotherapy, FFSM; face-to-face stress management, GCBT; group cognitive behavioral therapy, FFRTT; face-to-face relaxation therapy or training, GGHT; group gut-directed hypnotherapy, RC; routine care, S-G/M-CCBT; self-guided/minimal-contact cognitive behavioral therapy, TCBT; telephone cognitive behavioral therapy, WLC; waiting list control.

Supplementary Table 10. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Pain Post-treatment by Type of Brain-gut Behavioral Treatment.

EAT											0.60 (0.30; 1.19)			
0.87 (0.39; 1.91)	ACT		0.72 (0.41; 1.27)											0.74 (0.50; 1.08)
0.90 (0.35; 2.30)	1.04 (0.51; 2.12)	MMT											0.64 (0.36; 1.12)	
0.82 (0.36; 1.85)	0.95 (0.61; 1.47)	0.91 (0.43; 1.94)	SM	0.83 (0.45; 1.55)							0.55 (0.32; 0.95)			
0.80 (0.35; 1.84)	0.92 (0.52; 1.65)	0.89 (0.40; 1.95)	0.97 (0.56; 1.71)	CM							0.69 (0.43; 1.12)			
0.76 (0.37; 1.54)	0.87 (0.59; 1.30)	0.84 (0.45; 1.57)	0.92 (0.58; 1.46)	0.94 (0.57; 1.56)	CBT		0.99 (0.63; 1.58)				0.83 (0.67; 1.03)		0.97 (0.63; 1.50)	0.62 (0.44; 0.86)
0.75 (0.36; 1.56)	0.87 (0.56; 1.34)	0.83 (0.43; 1.63)	0.91 (0.56; 1.49)	0.94 (0.55; 1.59)	0.99 (0.74; 1.33)	MBT					0.77 (0.58; 1.01)			0.83 (0.52; 1.31)
0.74 (0.35; 1.53)	0.85 (0.55; 1.30)	0.82 (0.43; 1.55)	0.90 (0.55; 1.46)	0.92 (0.54; 1.56)	0.97 (0.75; 1.26)	0.98 (0.70; 1.37)	RTT	1.10 (0.77; 1.56)			1.02 (0.72; 1.44)	0.73 (0.41; 1.31)	0.26 (0.13; 0.50)	0.96 (0.46; 2.00)
0.73 (0.35; 1.52)	0.84 (0.56; 1.26)	0.81 (0.44; 1.50)	0.89 (0.55; 1.43)	0.91 (0.54; 1.55)	0.96 (0.74; 1.25)	0.97 (0.70; 1.35)	0.99 (0.77; 1.28)	GHT			0.74 (0.42; 1.29)		0.83 (0.60; 1.14)	0.82 (0.60; 1.13)
0.69 (0.30; 1.59)	0.79 (0.43; 1.48)	0.76 (0.34; 1.69)	0.84 (0.44; 1.60)	0.86 (0.44; 1.68)	0.91 (0.54; 1.52)	0.92 (0.54; 1.57)	0.94 (0.54; 1.61)	0.94 (0.55; 1.62)	DP		0.87 (0.54; 1.40)			
0.62 (0.27; 1.43)	0.71 (0.41; 1.24)	0.69 (0.33; 1.41)	0.75 (0.41; 1.40)	0.77 (0.40; 1.50)	0.82 (0.51; 1.31)	0.82 (0.49; 1.38)	0.84 (0.52; 1.37)	0.85 (0.53; 1.35)	0.90 (0.46; 1.77)	CT			1.02 (0.61; 1.69)	0.84 (0.52; 1.37)
0.60 (0.30; 1.19)	0.69 (0.46; 1.02)	0.66 (0.35; 1.25)	0.73 (0.47; 1.12)	0.75 (0.47; 1.19)	0.79 (0.65; 0.96)	0.79 (0.62; 1.02)	0.81 (0.63; 1.05)	0.82 (0.63; 1.06)	0.87 (0.54; 1.40)	0.96 (0.60; 1.56)	RC			
0.54 (0.21; 1.37)	0.62 (0.30; 1.28)	0.60 (0.25; 1.41)	0.66 (0.31; 1.40)	0.67 (0.31; 1.47)	0.71 (0.38; 1.34)	0.72 (0.37; 1.40)	0.73 (0.41; 1.31)	0.74 (0.39; 1.39)	0.78 (0.35; 1.73)	0.87 (0.41; 1.86)	0.90 (0.48; 1.70)	D/LA		
0.57 (0.27; 1.21)	0.66 (0.43; 1.02)	0.64 (0.36; 1.12)	0.70 (0.42; 1.15)	0.72 (0.41; 1.24)	0.76 (0.58; 1.00)	0.76 (0.53; 1.09)	0.78 (0.58; 1.05)	0.79 (0.61; 1.00)	0.83 (0.48; 1.46)	0.93 (0.59; 1.44)	0.96 (0.72; 1.29)	1.06 (0.56; 2.04)	E/S	0.83 (0.49; 1.40)
0.56 (0.27; 1.17)	0.65 (0.46; 0.92)	0.63 (0.33; 1.17)	0.69 (0.44; 1.08)	0.71 (0.42; 1.18)	0.75 (0.59; 0.94)	0.75 (0.56; 1.01)	0.77 (0.58; 1.01)	0.77 (0.61; 0.97)	0.82 (0.48; 1.40)	0.91 (0.59; 1.41)	0.95 (0.74; 1.21)	1.05 (0.55; 1.99)	0.99 (0.75; 1.29)	WLC

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the strategy labels, and indirect comparisons are below.

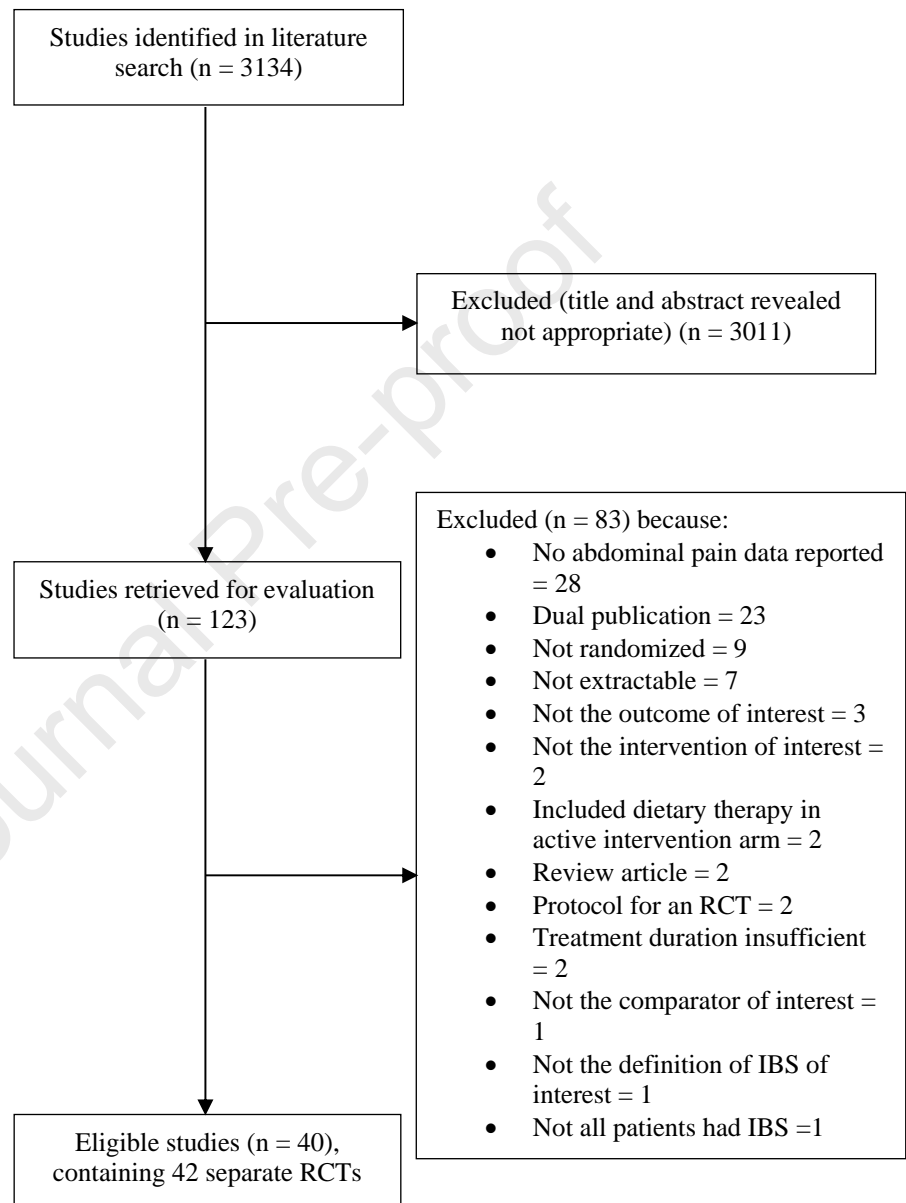
ACT; acceptance and commitment therapy, CBT; cognitive behavioral therapy, CM; contingency management, CT; cognitive therapy, D/LA; dietary and/or lifestyle advice, DP; dynamic psychotherapy, EAT; emotional awareness training, E/S; education and/or support, GHT; gut-directed hypnotherapy, MBT; multicomponent behavioral therapy, MMT; mindfulness meditation training, RC; routine care, RTT; relaxation therapy or training, SM; stress management, WLC; waiting list control.

Supplementary Table 11. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Pain Post-treatment by Type of Brain-gut Behavioral Treatment: Trials Recruiting Only Patients with Global IBS Symptoms Refractory to Treatment.

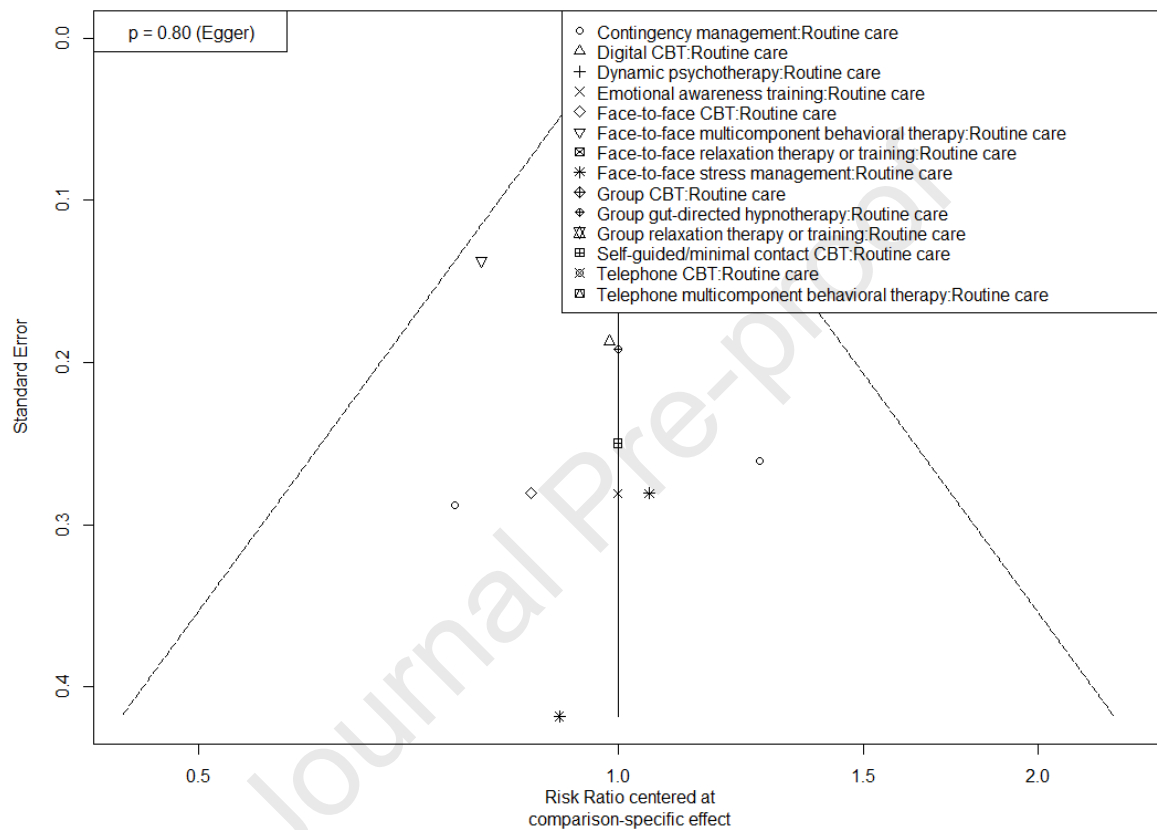
CM	0.91 (0.41; 2.02)							0.53 (0.27; 1.03)	
0.91 (0.41; 2.02)	SM							0.58 (0.30; 1.11)	
0.71 (0.35; 1.46)	0.78 (0.38; 1.58)	CBT			0.97 (0.66; 1.42)		0.45 (0.20; 1.05)	0.75 (0.56; 1.01)	
0.69 (0.32; 1.49)	0.76 (0.36; 1.62)	0.98 (0.67; 1.42)	GHT	1.00 (0.55; 1.82)	0.81 (0.52; 1.25)		0.83 (0.63; 1.11)	0.74 (0.44; 1.23)	
0.69 (0.26; 1.84)	0.76 (0.29; 2.00)	0.98 (0.48; 1.98)	1.00 (0.55; 1.82)	RTT					0.26 (0.07; 1.02)
0.63 (0.29; 1.36)	0.69 (0.32; 1.48)	0.89 (0.64; 1.23)	0.91 (0.63; 1.30)	0.91 (0.45; 1.83)	E/S				
0.61 (0.28; 1.35)	0.67 (0.31; 1.46)	0.86 (0.52; 1.42)	0.88 (0.50; 1.56)	0.88 (0.38; 2.02)	0.97 (0.54; 1.73)	DP		0.87 (0.57; 1.33)	
0.54 (0.24; 1.21)	0.60 (0.27; 1.31)	0.77 (0.50; 1.18)	0.78 (0.60; 1.03)	0.78 (0.41; 1.52)	0.87 (0.56; 1.33)	0.89 (0.48; 1.65)	WLC		
0.53 (0.27; 1.03)	0.58 (0.30; 1.11)	0.75 (0.57; 0.98)	0.76 (0.52; 1.12)	0.76 (0.37; 1.56)	0.84 (0.57; 1.24)	0.87 (0.57; 1.33)	0.97 (0.62; 1.52)	RC	
0.18 (0.03; 0.96)	0.20 (0.04; 1.05)	0.25 (0.05; 1.18)	0.26 (0.06; 1.15)	0.26 (0.07; 1.02)	0.29 (0.06; 1.33)	0.29 (0.06; 1.46)	0.33 (0.07; 1.51)	0.34 (0.07; 1.58)	D/LA

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the strategy labels, and indirect comparisons are below.

CBT; cognitive behavioral therapy, CM; contingency management, D/LA; dietary and/or lifestyle advice, DP; dynamic psychotherapy, E/S; education and/or support, GHT; gut-directed hypnotherapy, RC; routine care, RTT; relaxation therapy or training, SM; stress management, WLC; waiting list control.

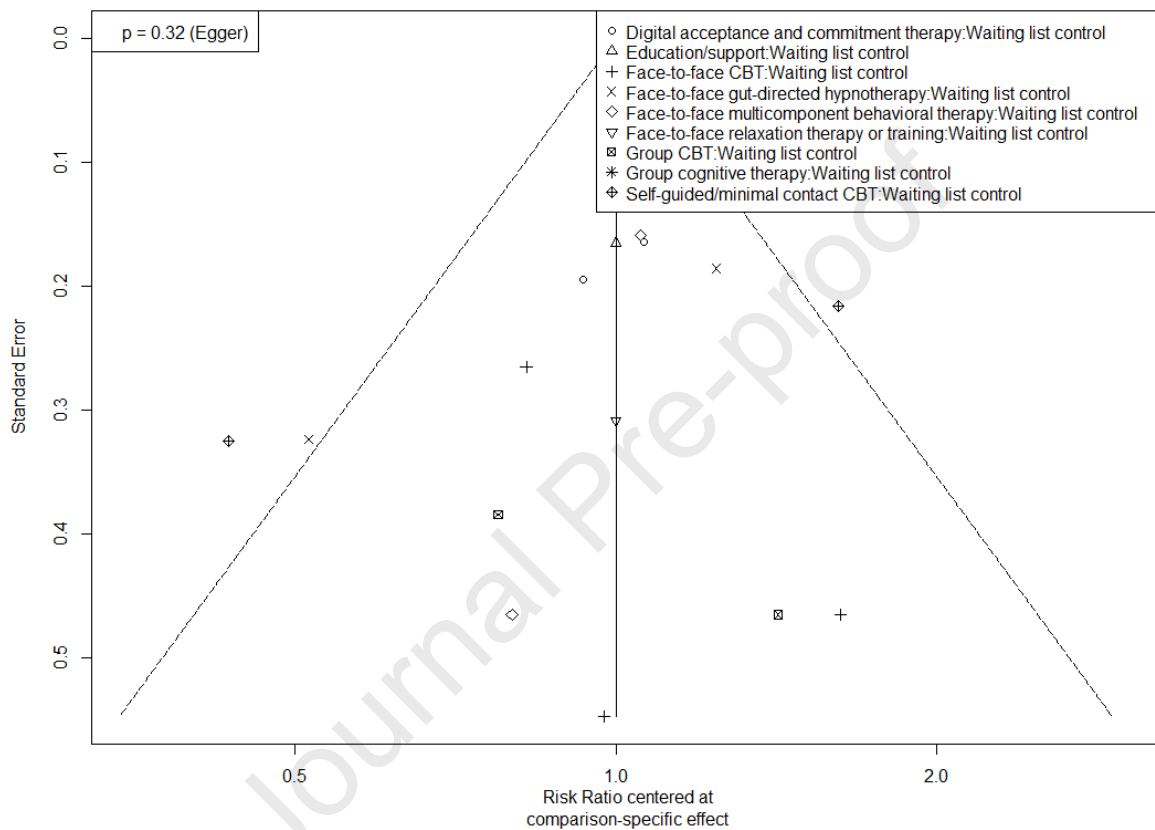
SUPPLEMENTARY FIGURES**Supplementary Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.**

Supplementary Figure 2. Funnel Plot for Failure to Achieve an Improvement in Abdominal Pain at First Point of Follow-up Post-treatment: Trials Comparing with Routine Care.



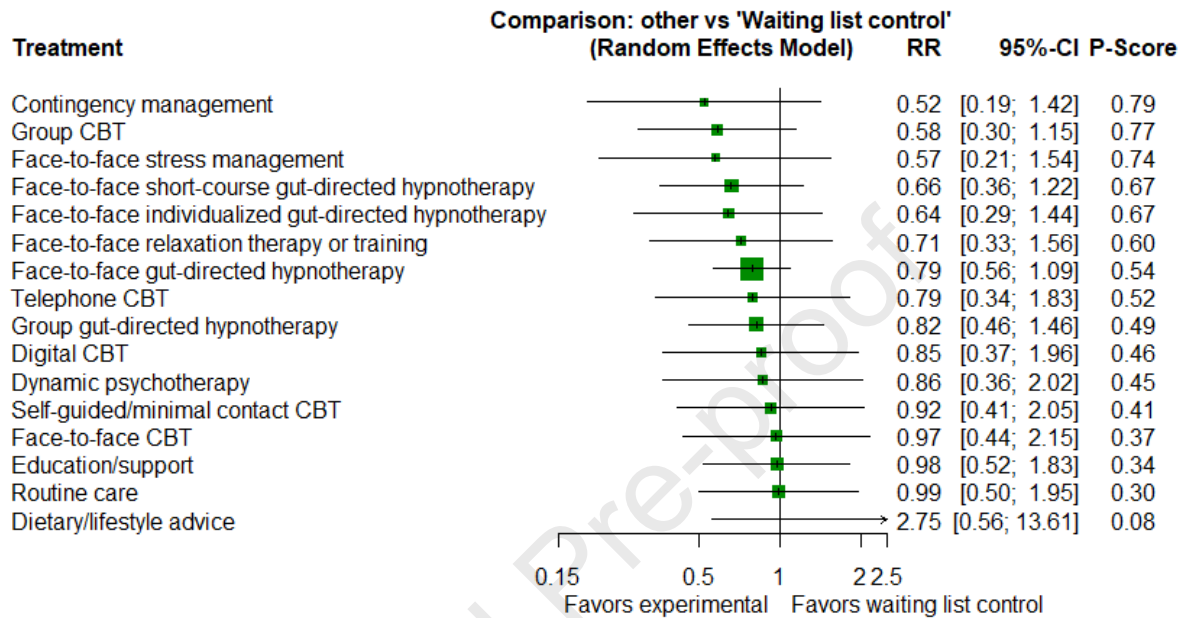
Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

Supplementary Figure 3. Funnel Plot for Failure to Achieve an Improvement in Abdominal Pain at First Point of Follow-up Post-treatment: Trials Comparing with Waiting List Control.



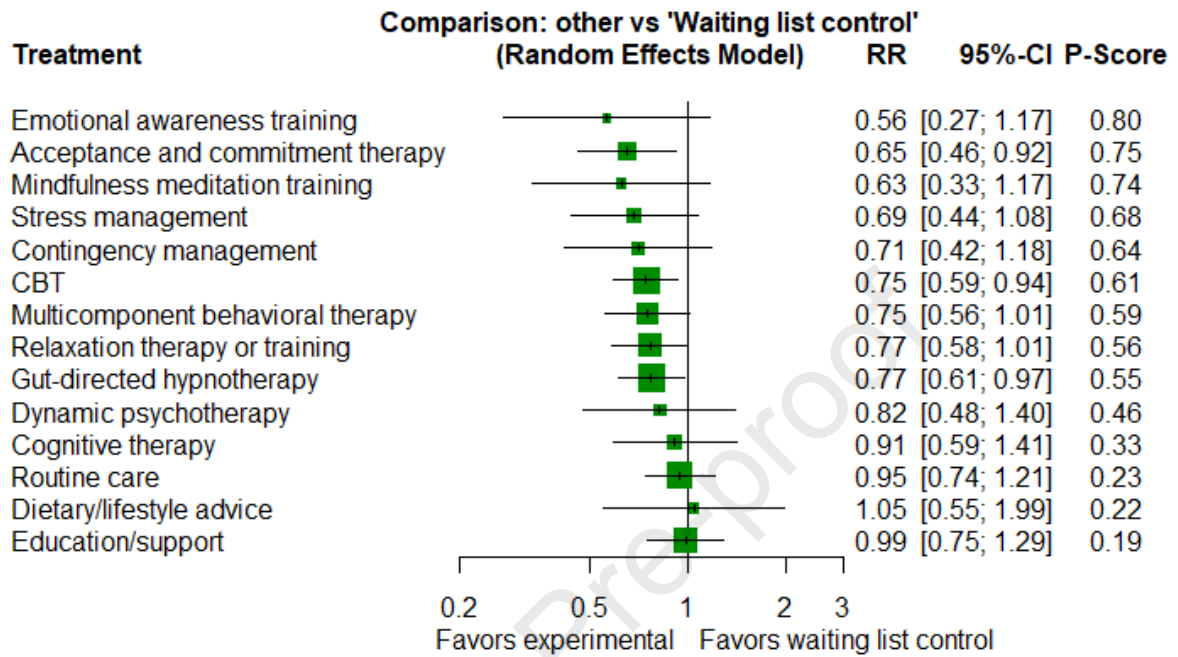
Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

Supplementary Figure 4. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment: Trials Recruiting Only Patients with Global IBS Symptoms Refractory to Treatment.



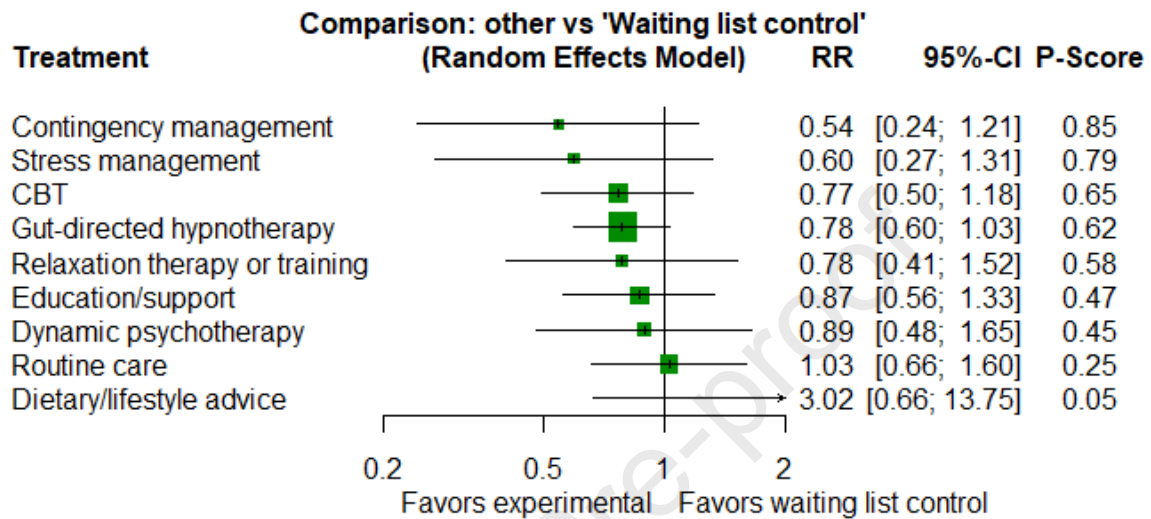
Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Supplementary Figure 5. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment by Type of Brain-gut Behavioral Treatment.



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Supplementary Figure 6. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment by Type of Brain-gut Behavioral Treatment: Trials Recruiting Only Patients with Global IBS Symptoms Refractory to Treatment.



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

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WHAT YOU NEED TO KNOW

Background and context

US management guidelines suggest the use of brain-gut behavioral treatments for persistent abdominal pain in irritable bowel syndrome (IBS) but their efficacy in this regard is uncertain.

New findings

In network meta-analysis, brain-gut behavioral treatments demonstrating efficacy for abdominal pain, specifically, included self-guided or minimal contact cognitive behavioral therapy, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy.

Limitations

There was evidence of possible publication bias and few trials were powered to report effect on abdominal pain in IBS as a primary or secondary endpoint.

Clinical research relevance

Several brain-gut behavioral treatments, including self-guided or minimal contact cognitive behavioral therapy, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy, may be efficacious for abdominal pain in IBS. However, none were superior to another.

Basic research relevance

NA

LAY SUMMARY

We studied efficacy of behavioral treatments for abdominal pain in IBS. Self-guided/minimal contact cognitive behavioral therapy, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy were better than a control intervention.

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