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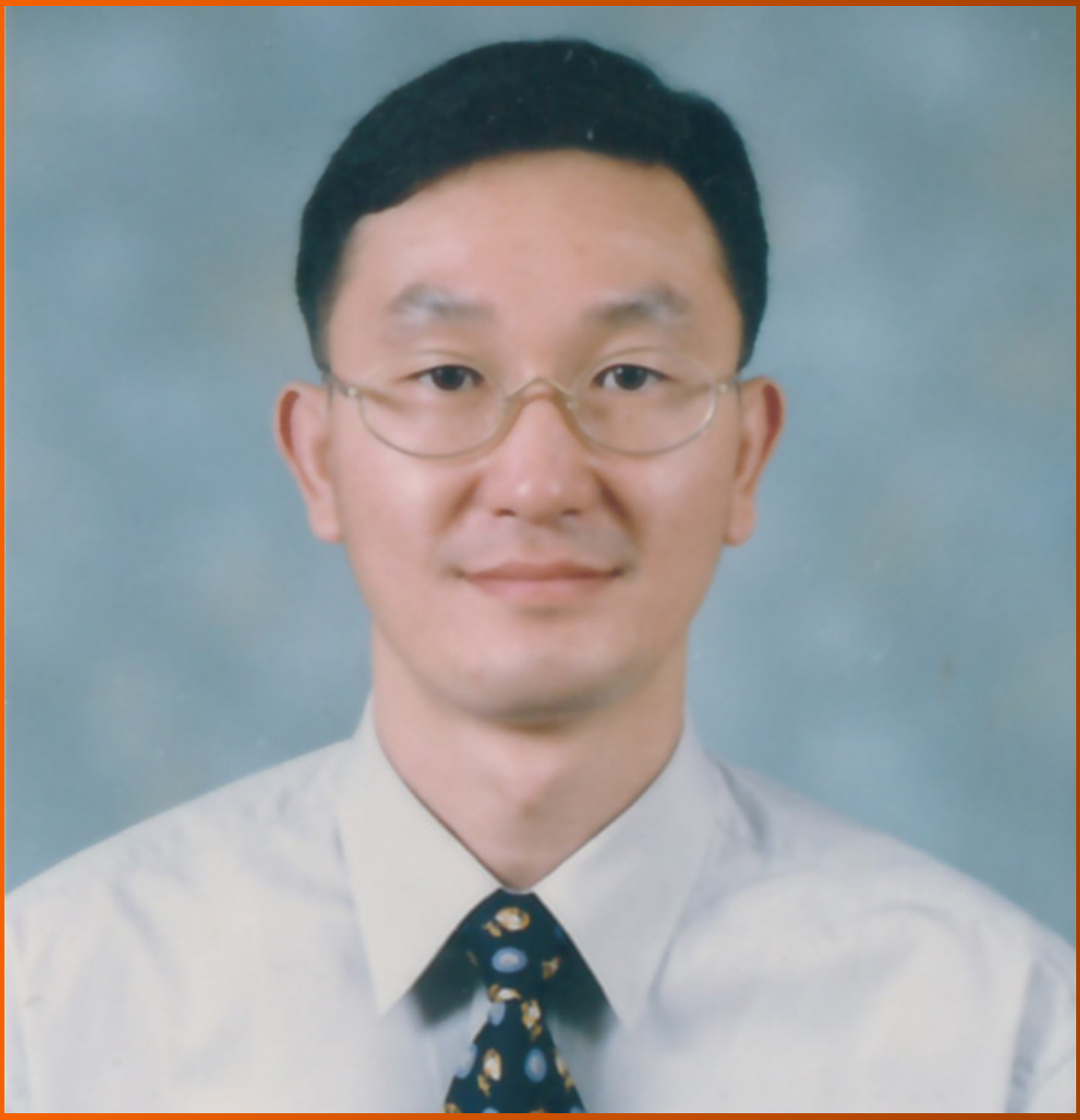

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ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Dr. Ki Mun Kang is a Distinguished Professor at the Gyeongsang National University College of Medicine (Jinju, South Korea). Having received his Bachelor's degree from the College of Medicine of Chosun University in 1990, Dr. Kang undertook his postgraduate training, first at the Catholic College of Medicine, receiving his Master's degree in 1996, and then at Catholic University, receiving his PhD in 2004. He became Assistant Professor in Radiation Oncology at Gyeongsang National University in 2001 and has held the position since. His ongoing research interests include various aspects of immuno-radiobiology for GI and prostate cancers. Currently, he serves as President of the Department of Radiation Oncology, College of Medicine, Gyeongsang National University with Clinical Radiation Oncology and President of the Department of Radiation Oncology, Gyeongsang National University Changwon Hospital. (L-Editor: Filipodia)

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META-ANALYSIS

Efficacy and safety of non-pharmacological interventions for irritable bowel syndrome in adults

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Author contributions: Hu L and Lu LM conceived and designed the study; Dai YK and Wu YB performed the experiment and analyzed the data; Dai YK wrote the paper; Li RL, Chen WJ, Tang CZ, Lu LM and Hu L supervised the study; All authors approved the final manuscript as submitted.

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Abstract

BACKGROUND

Although nonpharmacological interventions (NPI) for irritable bowel syndrome (IBS) have been applied clinically, their relative efficacy and safety are poorly understood.

AIM

To compare and rank different NPI in the treatment of IBS.

METHODS

Five electronic databases were searched from their inception to January 12, 2020. Data of included publications were analyzed using network meta-analysis (NMA). Quality of endpoints were assessed by tools of the Cochrane Handbook and the GRADEpro software. Pooled relative risk or standardized mean difference with their corresponding 95% confidence intervals were used for statistical analysis. Surface under the cumulative ranking curve (SUCRA) probability value was conducted to rank the examined interventions. Sensitivity analysis was performed to verify the robustness of results and test the source of heterogeneity.

RESULTS

Forty randomized controlled trials with 4196 participants were included in this NMA. Compared with routine pharmacotherapies and placebo, acupuncture and cognitive behavioral therapy (CBT) had better efficacy in relieving IBS symptoms. Based on the SUCRA values, acupuncture ranked first in improving overall clinical efficacy and avoiding adverse effects. CBT ranked first in lowering the scores of IBS symptom severity scale, self-rating anxiety scale and self-rating depression scale.

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CONCLUSION

This study confirmed the efficacy and safety of NPI for improving IBS symptoms, which to some extent recommended several interventions for clinical practice.

Key Words: Nonpharmacological interventions; Irritable bowel syndrome; Network meta-analysis; Randomized controlled trials; Adults; Clinical practice

Core Tip: This is the first study to compare nonpharmacological interventions including biofeedback, cognitive behavioral therapy, probiotics, dietary, acupuncture, and moxibustion using network meta-analysis.

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INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common chronic functional gastrointestinal disorders, which is characterized by abdominal pain, irregular defecation or changes in stool property[1,2]. Currently, about 15% of the general population around the world are suffering from this condition[3]. Because of its symptoms IBS affects patients' work and daily lives and could lead to an increase in healthcare cost[4,5]. According to the latest Rome criteria (Rome IV)[6], IBS is classified into diarrhea predominant, constipation predominant, mixed and unclassified.

However, the pathogenesis of IBS remains unclear. Some factors such as unhealthy lifestyles and diets, psychological factors, visceral allergies, gastrointestinal motility dysfunction and intestinal microbiota alteration have been taken into consideration[7]. Therefore, routine pharmacotherapies (RPs) such as antipsychotics, antispasmodics, promotility agents, laxatives and antidiarrheics are recommended for the management of IBS. Although these interventions can relieve symptoms like abdominal pain, their effects are inadequate and may produce some unwelcome reactions including ischemic colitis and cardiovascular events[8]. Due to the chronicity and recurrence of IBS, many patients are intolerability to pharmacological interventions for a long time and then put their eyes on nonpharmacological interventions (NPI).

As an add-on treatment or alternative option, NPI for IBS include dietary and physical interventions, biofeedback therapy (BFT), cognitive behavioral therapy (CBT), probiotics, acupuncture and moxibustion therapy. Although previous meta-analyses of these therapies showed good efficacy in improving global IBS symptoms[9-14], these studies have concentrated on individual aspects of NPI and are not comprehensive. Therefore, the reliability of the evidence might fluctuate by various assessment outcomes, thereby leading to between-study heterogeneity and mitigating their efficacies in guiding clinical practice.

Network meta-analysis (NMA) is a powerful statistical technique that combines direct and indirect evidence to analyze multiple treatments from different studies and estimate the relative effects of all included treatments in the network simultaneously[15]. Moreover, NMA has the advantage of assisting medical decision-making through providing useful and evidence-based data[16]. Based on these, we used NMA to evaluate the comparative effects and rankings of all known NPIs on IBS.

MATERIALS AND METHODS

This study was conducted according to the Cochrane criteria, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[17] and relevant meta-analysis guidance[18].

Data sources and search strategy

Five electronic databases including OVID EMBASE, MEDLINE, Cochrane Library, PubMed and the Chinese database of CNKI were searched from their inception to January 12, 2020 without language limitation for randomized controlled trials (RCTs). Search strategies were performed with a combination of the following terms: Irritable bowel syndrome, randomized controlled trial, nonpharmacological interventions, biofeedback, cognitive behavioral therapy, probiotics, dietary, acupuncture and moxibustion. Detailed information for each database is displayed in Supporting Information S1. Some unpublished articles were searched in ClinicalTrials.gov and relevant data were obtained through contacting the investigators or authors. In case of duplicates, the most updated one was selected.

Inclusion and exclusion criteria

Relevant titles and abstracts were blindly evaluated and details of selected studies were independently analyzed by two researchers (Dai YK, Wu YB). Based on the PICOS (participants, interventions, comparisons, outcomes and study design) criteria, the following items were included in this NMA: IBS participants whose ages are 18 years or over should meet one of the Rome criteria versions (Rome II, III or IV)[19-21]; NPI should include at least one of the following treatments: Diet, biofeedback, CBT, probiotics, acupuncture or moxibustion; Outcomes should be at least one of these items such as overall clinical efficacy, IBS-SSS (symptom severity scale), SAS (self-rating anxiety scale) and SDS (self-rating depression scale). Moreover, treatment courses should be 4 wk or over. Studies with a Jadad score above 1 was selected for further analysis.

However, publications would be excluded once the following items appeared: Meeting abstracts; incomplete or imprecise data; ambiguous treatment courses; unavailable full texts; cross-sectional studies or reviews.

Data abstraction and quality evaluation

Two investigators (Dai YK, Wu YB) independently performed data extraction and methodological quality assessment. The following data should be extracted from each included trial: Study ID (first author and publication year), general characteristics of patients (gender, age and sample size), diagnostic criteria, details of interventions, treatment courses, primary and secondary outcomes and adverse events. Some absent information was obtained by contacting corresponding authors. The risk of bias of each study was assessed using the Cochrane Collaboration Recommendations assessment tool[22]. Six domains with the evaluation of risk bias were as follows: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data and selective reporting. Each domain of the included publications was judged as low, unclear or high risk. As for the evaluation of evidence quality, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used with the online guideline development tool (https://gdt.gradepro.org/app/). Quality of evidence in this NMA was assessed as high, moderate, low and very low quality[23].

Statistical analysis

Compared with results of standard and pairwise analyses, NMA results can afford more precise estimates and rank interventions to inform clinical decisions[24,25]. Therefore, in order to compare the efficacy and safety of each NPI across RCTs, a NMA was conducted using Stata version 13.0 software. For each treatment, we produced a pooled relative risk for dichotomous outcomes or standardized mean difference (SMD) for continuous variable data with their corresponding 95% confidence intervals (CI) to summarize the effect of each comparison tested using a random-effect model as a conservative estimate. Evidence of direct and indirect multiple-intervention comparisons were examined through producing a network plot where node sizes corresponded to the number of study participants while connection sizes referred to the number of studies for each intervention. According to the Bayesian framework and the Markov chain Monte Carlo method, we evaluated and processed research data *a priori* using WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom). Three Markov chains and noninformative uniform and normal priori distributions were used to fit the model[26,27]. Then, 10 thinning intervals each Markov chain and 50000 iterations were equipped so as to obtain their posterior distributions. Of all the simulation iterations, the first 20000 were applied to annealing for the elimination of impacts of the initial value while the last 30000 were used for sampling. Heterogeneity analysis was quantified using the inconsistency index

statistic (I^2)[28]. The I^2 value above 50% was regarded as heterogeneity throughout the study. Accordingly, we conducted sensitivity analysis to verify the robustness of results and test the source of heterogeneity in each RCT. Surface under the cumulative ranking curve (SUCRA) probability value was used to rank the examined interventions[29].

RESULTS

Study selection

All of the 1592 articles were identified from five data libraries based on the well-established retrieval. Ultimately, 40 RCTs[30-69] including 4196 participants were selected in the NMA according to the inclusion and exclusion criteria. The study selection process is shown in Figure 1. The baseline characteristics of the included studies are summarized in Table 1.

Risk of bias evaluation

The quality of each included RCT was evaluated using the Cochrane Risk of Bias Assessment Tool[70] including these factors:

(1) Selection bias: Thirty trials grouped patients according to detailed randomized algorithms while the remaining ten only described "randomization." Therefore, the thirty trials were assessed as "low risk" while the other ten were viewed as "unclear risk." As for the allocation concealment, four trials were evaluated as "low risk" within detailed information while the remaining 36 trials were viewed as "unclear risk" because of insufficient information.

(2) Performance bias and detection bias: Twelve trials provided information on blinding and were blinded to the outcome assessors. Therefore, both performance bias and detection bias were assessed as "low risk." However, the remaining 28 trials failed to provide adequate information on blinding. Therefore, both of the two biases were viewed as "unclear risk."

(3) Attrition bias: Twenty-three trials were evaluated as "unclear risk" for their incomplete data while the remaining seventeen trials were estimated as "low risk" because they reported withdrawal or dropout.

(4) Reporting bias: Because the complete implementation scheme could be acquired, the bias of all the trials was assessed as "low risk."

(5) Other bias: Considering the lack of information in this item, all included RCTs were estimated as "unclear risk." The detailed quality evaluation of the included studies is shown in Figure 2.

Network evidence

There were ten regimens in this study as follows: RPs, placebo, probiotics, probiotics + RPs, BFT, BFT + probiotics, CBT, acupuncture, moxibustion and acupuncture + moxibustion. The network graphs of these regimens with different outcomes are displayed in Figure 3.

Primary outcome

Overall clinical efficacy: There were 30 RCTs reporting overall clinical efficacy. As displayed in Table 2, RPs, probiotics, probiotics + RPs, acupuncture, BFT and acupuncture + moxibustion had better overall clinical efficacy than placebo; Probiotics + RPs, acupuncture and BFT had better overall clinical efficacy than RPs and probiotics. The differences among the above mentioned treatments were statistically significant. As shown in Figure 4, the SUCRA plot indicated that acupuncture ranked first, followed by BFT and probiotics + RPs. Meanwhile, heterogeneity analysis (Figure 5A) showed good homogeneity (I^2 = 0.0%, P = 0.997), and sensitivity analysis (Figure 5B) indicated strong stability in the ranking of all treatments for overall clinical efficacy. Furthermore, the symmetry funnel plot of this endpoint was observed in Figure 6.

Secondary outcomes

IBS-SSS: The improvement of IBS-SSS was reported in seven RCTs with five interventions (RPs, placebo, probiotics, CBT and acupuncture). Compared with

Table 1 Characteristics of the studies included in the network analysis

Ref.	Country	Classification of IBS, criterion	Sample size		Age in yr	Course of disease in yr	Treatment cycle in wk	Intervention		Endpoints	Follow-up	Side effects
			EG, M/F	CG, M/F				EG	CG			
Yang *et al*[30], 2019	China	IBS-D (Rome III)	43/30	44/29	E: 43.93 ± 13.58 C: 45.00 ± 16.67	E: 3.74 ± 5.02 C: 4.12 ± 4.94	4	AP	Placebo	a, f, h	N/A	N/A
He *et al*[31], 2019	China	IBS-D (Rome IV)	13/12	14/11	E: 47.88 ± 15.16 C: 48.56 ± 17.4	N/A	4	AP	Probiotics	a, f, j	N/A	N/A
Li[32], 2019	China	IBS-D (Rome IV)	15/14	15/13	E: 45.30 ± 11.52 C: 48.33 ± 12.13 mo	E: 10.98 ± 5.12 C: 10.79 ± 5.04 mo	4	AP + MB	RPs	a, d, h, i	N/A	N/A
Wang *et al*[33], 2019	China	IBS (Rome IV)	25/31	23/32	E: 46.00 ± 2.50 C: 46.80 ± 2.70	E: 3.20 ± 1.40 C: 3.12 ± 1.38	4	AP + MB	RPs	a, h, j	N/A	N/A
Zhang *et al*[34], 2019	China	IBS (Rome III)	23/21	25/19	E: 47.23 ± 2.18 C: 47.66 ± 2.12	E: 5.22 ± 0.11 C: 5.26 ± 0.16	8	Probiotics	placebo	a, j	N/A	N/A
Peng *et al*[35], 2019	China	IBS-D (Rome IV)	14/16	16/14	E: 46.85 ± 14.45 C: 45.43 ± 13.58	E: 3.65 ± 1.15 C: 3.84 ± 1.32	4	BFT	Probiotics	a, d, f	N/A	N/A
Kou *et al*[36], 2018	China	IBS-D (Rome III)	16/29	18/27	E: 38.24 ± 6.58 C: 38.37 ± 6.60	N/A	4	Probiotics + RPs	RPs	a, b, e	N/A	E: 1 C: 2
Sun[37], 2018	China	IBS-D (Rome III)	63/42	53/42	E: 43.00 ± 12.45 C: 44.91 ± 13.01	N/A	4	Probiotics	placebo	b, d, f, k,	N/A	E: 6 C: 2
Qin *et al*[38], 2018	China	IBS (Rome III)	45/47	45/48	E: 42.8 ± 8.7 C: 44.2 ± 8.8	E: 4.5 ± 1.1 C: 4.5 ± 1.2	4	Probiotics + RPs	RPs	a, g, n	N/A	E: 0 C: 0
Zhang *et al*[39], 2018	China	IBS (Rome II)	15/28	17/26	E: 42.16 ± 7.24 C: 43.68 ± 9.09	N/A	4	CBT	RPs	d, o	N/A	N/A
Chen *et al*[40], 2017	China	IBS-D (Rome III)	31/13	30/14	E: 46.52 ± 3.75 C: 46.13 ± 3.82	N/A	4	Probiotics + RPs	RPs	a, g, j	N/A	N/A
Wang *et al*[41], 2017	China	IBS-D (Rome III)	17/21	16/22	E: 46.5 ± 2.3 C: 46.3 ± 2.2	E: 3.3 ± 0.8 C: 3.2 ± 0.7	4	Probiotics + RPs	RPs	a, b	N/A	E: 3 C: 1
Hod *et al*[42], 2017	United States	IBS-D (Rome III)	54	53	E: 29.0 C: 30.0	N/A	4	Probiotics	Placebo	a, b, e	N/A	E: 0 C: 0
Joo *et al*[43], 2017	Korea	IBS (Rome III)	9/17	5/19	E: 32.5 C: 33.0	N/A	4	Probiotics	Placebo	a, b, p	N/A	E: 0 C: 0
Liu *et al*[44], 2017	China	IBS-C (Rome III)	17/23	17/23	43.86 ± 10.29	2.93 ± 1.06	8	Probiotics + RPs	RPs	a, b, e, g	N/A	E: 0 C: 0
Huang[45], 2017	China	IBS-C (Rome III)	16/23	15/25	E: 44.23 ± 11.92 C: 41.54 ± 12.24	E: 4.11 ± 1.94 C: 3.54 ± 2.19	4	BFT	RPs	a, e, u	N/A	N/A

Cheng *et al*[46], 2017	China	IBS-D (Rome III)	19/22	18/21	E: 36.27 ± 2.78 C: 41.69 ± 12.63	N/A	8	CBT	RPs	d, f, o	N/A	N/A
Kang *et al*[47], 2016	China	IBS-D (Rome III)	17/23	16/24	E: 44.5 ± 6.4 C: 42.5 ± 7.2	N/A	4	Probiotic + RPs	RPs	a, i, j	N/A	N/A
Robin *et al*[48], 2016	France	IBS (Rome III)	31/161	31/156	E: 45.3 ± 15.7 C: 45.4 ± 14.1	N/A	12	Probiotics	Placebo	a, b, e, m	N/A	E: 10 C: 0
Zhang *et al*[49], 2016	China	IBS (Rome III)	12/18	14/16	E: 40.7 ± 11.4 C: 36.3 ± 14.1	E: 3.58 ± 2.04 C: 3.88 ± 2.36	4	Probiotics	RPs	a	N/A	E: 0 C: 2
Han *et al*[50], 2016	Korea	IBS (Rome III)	13/10	11/12	E: 45.7 ± 9.55 C: 42.5 ± 10.07	N/A	4	Probiotics	Placebo	a, k, l, p	N/A	N/A
Jia *et al*[51], 2016	China	IBS (Rome III)	16/14	22/10	E: 40.08 ± 13.23 C: 41.31 ± 11.82	N/A	8	CBT	RPs	f, o	N/A	N/A
Choi *et al*[52], 2015	South Korea	IBS (Rome III)	a: 20/34 b: 35/25 C: 35/23 d: 25/31	26/31	E: a: 44.8 ± 13.4 b: 48.9 ± 14.2 C: 46.2 ± 13.8 d: 45.9 ± 12.8 C: 48.5 ± 13.2	N/A	6	Probiotics + RPs	Placebo	a, b, m	N/A	E: 4/8/8/8 C: 6
Jia *et al*[53], 2015	China	IBS (Rome III)	N/A	N/A	E: 44.74 ± 11.98 C: 40.85 ± 13.87	N/A	8	CBT	RPs	d, o	N/A	N/A
Shi *et al*[54], 2015	China	IBS-D (Rome III)	28/32	25/35	E: 40.2 ± 10.8 C: 38.5 ± 9.1	E: 8.6 ± 3.8 C: 7.3 ± 2.1	4	AP	RPs	a	N/A	N/A
Li[55], 2015	China	IBS-D (Rome III)	N/A	N/A	E: 46 C: 46	E: 4.2 C: 4.2	4	AP	RPs + Probiotics	a, e, g	N/A	N/A
Ye *et al*[56], 2015	China	IBS (Rome III)	N/A	N/A	43.59 ± 12.17	2.42 ± 1.27	4	BFT + Probiotics	Probiotics	o, r, v	N/A	N/A
Zheng[57], 2014	China	IBS-D (Rome III)	49/40 49/36 40/42	52/34	E: 38.75 ± 18.32 42.66 ± 16.75 42.51 ± 16.78 C: 42.29 ± 18.30	E: 72.91 ± 76.70 78.83 ± 99.19 77.51 ± 84.56 C: 87.67 ± 90.28 d	4	AP	RPs	b, k, l, o, q, s	N/A	E: 3 C: 0
Zhu *et al*[58], 2014	China	IBS-D (Rome III)	9/6	7/6	E: 47.470 ± 0.896 C: 40.920 ± 10.136	E: 3.0 C: 3.5	4	MB	Placebo	d, t, u	N/A	N/A
Kong[59], 2014	China	IBS-D (Rome III)	14/16	9/21	E: 40 ± 9 C: 38 ± 11	E: 5.87 ± 6.52 C: 6.21 ± 6.33	4	AP+MB	RPs	a, d, e	N/A	N/A
He *et al*[60], 2014	China	IBS-D (Rome III)	N/A	N/A	37.3 ± 10.4	3.7 ± 2.1	4	BFT + RPs	RPs	a, g, i, n, v	N/A	N/A
Cheryl *et al*[61], 2014	South Africa	IBS (Rome III)	2/52	0/27	E: 48.15 ± 13.48 C: 47.27 ± 12.15	E: 9.58 ± 10.32 C: 10.05 ± 9.36	6	Probiotics	Placebo	b, d	N/A	E: 1 C: 0
Lesley	Britain	IBS (Rome III)	15/73	15/76	E: 44.66 ± 11.98	N/A	4	Probiotics	Placebo	a, d, e, f, m	N/A	N/A

et al[62], 2013					C: 43.71 ± 12.76						
Ge[63], 2013	China	IBS (Rome III)	34/26	32/28	E: 38.9 ± 11.2 C: 39.1 ± 10.3	E: 6.5 C: 6.4	4	AP	RPs	a, c	E: 6/52 C: 12/43	N/A
Pei *et al*[64], 2012	China	IBS-D (Rome III)	13/17	10/20	E: 39.10 ± 11.80 C: 37.93 ± 11.45	E: 4.33 ± 3.93 C: 5.23 ± 7.35	4	AP	RPs	a	N/A	N/A
Kruis *et al*[65], 2012	Germany	IBS (Rome II)	12/48	16/44	E: 46.3 ± 12.1 C: 45.1 ± 12.7	E: 12.3 ± 11.5 C: 11.7 ± 12.0	12	Probiotics	Placebo	a, b	N/A	E: 0 C: 1
Sun *et al*[66], 2011	China	IBS-D (Rome III)	13/18	20/12	E: 38.81 ± 11.80 C: 38.59 ± 11.45	E: 4.23 ± 3.96 C: 5.63 ± 7.35	4	AP	RPs	a, b, d, e	NA	E: 0 C: 0
Zeng *et al*[67], 2011	China	IBS-D (Rome III)	39/30	41/28	E: 38.5 ± 8.4 C: 37.9 ± 9.6	E: 3.7 ± 1.8 C: 3.5 ± 2.1	8	Probiotics + RPs	RPs	a, b, r	N/A	E: 14 C: 12
Zhao *et al*[68], 2011	China	IBS (Rome III)	N/A	N/A	38.6 ± 11.2	UN	4	BFT	RPs	o, r, v	N/A	N/A
Wang *et al*[69], 2008	China	IBS-D (Rome II)	N/A	N/A	E: 42.8 ± 12.4 C: 43.7 ± 11.7	E: 3.41 ± 1.02 C: 3.23 ± 1.31	4	AP	RPs	a	N/A	N/A

AP: Acupuncture; BFT: Biofeedback therapy; C: Control group; CBT: Cognitive behavior therapy; E: Experiment group; F: Female; IBS: Irritable bowel syndrome; IBS-C: Constipation-predominant irritable bowel syndrome; IBS-D: Diarrhea-predominant irritable bowel syndrome; M: Male; MB: Moxibustion; N/A: Not applicable; RPs: Routine pharmacotherapies (including antispasmodic, laxative, antidiarrheic, antidepressant, glutathione); TCM: Traditional Chinese medicine. a: Overall clinical efficacy; b: Adverse effect rate; c: Recurrent rate; d: IBS-QOL (Quality of life); e: Clinical symptoms scores (abdominal pain/discomfort, flatulence, diarrhea, stool frequency, stool consistency); f: IBS-SSS (IBS symptom severity scale); g: The expression of immunohistochemistry (5-HT, TNF-α, IL-8, IL-10,); h: TCM symptom scores; i: HAMA & HAMD (The Hamilton Anxiety & Depression Rating Scale); j: Change in intestinal flora (*Escherichia coli*, *Lactobacillus*, *Bifidobacterium*, *Enterococcus faecalis*); k: Bristol Stool Form Scale; l: Frequency of clinical symptoms (abdominal pain, diarrhea, constipation); m: SGA (subject's global assessment); n: BSS (Bowel Symptoms Scale); o: SAS and SDS (self-rating anxiety scale and self-rating depression scale); p: VAS-IBS (Visual Analogue Scale); q: SF-36 (The Medical Outcomes Study 36-item Short-form Healthy Survey); r: Total and specific scores of GSRS (Gastrointestinal Symptom Rating Scale); s: The weekly average number of days with normal defecations; t: fMRI Examination; u: The Birmingham IBS Symptom Scale; v: Rectal distention threshold comparison; w: Visceral Pain threshold.

placebo (Table 3), CBT (SMD = 2.39, 95%CI: 1.71, 3.07), RPs (SMD = 2.15, 95%CI: 1.39, 2.90) and probiotics (SMD = 0.30, 95%CI: 0.07, 0.52) had significantly statistical differences. CBT (SMD = 2.09, 95%CI: 1.46, 2.73) and RPs (SMD = 1.85, 95%CI: 1.13, 2.57) were superior to probiotics. CBT (SMD = 0.24, 95%CI: -0.09, 0.57) was better than RPs. According to the SUCRA plot (Figure 7), CBT was the optimal intervention, RPs was the second and acupuncture was the third.

SAS and SDS: In this NMA, seven RCTs with five treatments (RPs, probiotics, BFT, CBT and acupuncture) reported improvement of SAS and SDS. As show in Table 4, CBT (SMD = 3.44, 95%CI: 1.49, 5.39), acupuncture (SMD = 3.39, 95%CI: 1.19, 5.58) and RPs (SMD = 3.13, 95%CI: 1.28, 4.97) had better significant improvement of SAS than probiotics. CBT (SMD = 0.31, 95%CI: -0.31, 0.94) was superior to RPs. As for the improvement of SDS, Table 4 showed that CBT (SMD = 2.97, 95%CI: 1.70, 4.23), BFT (SMD = 2.81, 95%CI: 1.86, 3.77), acupuncture (SMD = 2.36, 95%CI: 1.01, 3.72) and RPs (SMD = 2.27, 95%CI: 1.06, 3.49) were better than probiotics. CBT (SMD = 0.15, 95%CI: -0.68, 0.99) was superior to BFT. Acupuncture (SMD = 0.09, 95%CI: -0.51, 0.69) was better than RPs. Meanwhile, the SUCRA plot suggested that CBT was the most

Table 2 Risk ratios with 95% confidence interval of overall clinical efficacy

RPs					
0.99 (0.85, 1.17)[a]	Probiotics				
0.81 (0.75, 0.88)[a]	0.82 (0.69, 0.97)[a]	RPs + probiotics			
0.77 (0.70, 0.86)[a]	0.78 (0.66, 0.91)[a]	0.95 (0.84, 1.07)	Acupuncture		
0.78 (0.64, 0.94)[a]	0.78 (0.64, 0.95)[a]	0.96 (0.78, 1.17)	1.01 (0.82, 1.23)	BFT	
0.88 (0.77, 1.01)[a]	0.88 (0.72, 1.09)	1.08 (0.92, 1.27)	1.14 (0.96, 1.35)	1.13 (0.89, 1.43)	Acupuncture + moxibustion

[a]*P* < 0.05. The highlighted results indicate statistical significance. BFT: Biofeedback therapy; RPs: Routine pharmacotherapies.

Table 3 Standardized mean difference with 95% confidence interval of irritable bowel syndrome symptom severity scale

CBT				
0.24 (-0.09, 0.57)[a]	RPs			
1.29 (0.43, 2.16)[a]	1.05 (0.13, 1.97)	Acupuncture		
2.09 (1.46, 2.73)[a]	1.85 (1.13, 2.57)[a]	0.80 (0.22, 1.38)	Probiotics	
2.39 (1.71, 3.07)[a]	2.15 (1.39, 2.90)[a]	1.10 (0.48, 1.72)	0.30 (0.07, 0.52)[a]	Placebo

[a]*P* < 0.05. CBT: Cognitive behavioral therapy; RPs: Routine pharmacotherapies.

Table 4 Standardized mean difference with 95% confidence interval of self-rating anxiety scale and self-rating depression scale

SMD (95%CI)				
SAS				
CBT				
0.05 (-1.29, 1.39)	Acupuncture			
0.31 (-0.31, 0.94)[a]	0.26 (-0.92, 1.45)	RPs		
2.28 (0.83, 3.74)	2.24 (0.47, 4.01)	1.97 (0.66, 3.29)	BFT	
3.44 (1.49, 5.39)[a]	3.39 (1.19, 5.58)[a]	3.13 (1.28, 4.97)[a]	1.15 (-0.15, 2.45)	Probiotics
SDS				
CBT				
0.15 (-0.68, 0.99)[a]	BFT			
0.61 (-0.10, 1.31)	0.45 (-0.51, 1.42)	Acupuncture		
0.69 (0.33, 1.06)	0.54 (-0.21, 1.29)	0.09 (-0.51, 0.69)[a]	RPs	
2.97 (1.70, 4.23)[a]	2.81 (1.86, 3.77)[a]	2.36 (1.01, 3.72)[a]	2.27 (1.06, 3.49)[a]	Probiotics

[a]*P* < 0.05. BFT: Biofeedback therapy; CBT: Cognitive behavioral therapy; CI: Confidence interval; RPs: Routine pharmacotherapies; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; SMD: Standardized mean difference.

favorable treatment in the improvement of SAS and SDS (Figure 8).

Adverse effects

A total of sixteen RCTs with six interventions (RPs, placebo, probiotics, probiotics + RPs, acupuncture and moxibustion) reported adverse effects. There were no significant statistical differences among these treatments (Table 5). According to the SUCRA plot (Figure 9), acupuncture was the most favorable intervention, probiotics was the second and moxibustion was the third.

Table 5 Risk ratios with 95% confidence interval of adverse effects

RPs					
0.99 (0.35, 2.81)	Placebo				
0.85 (0.45, 1.59)	0.86 (0.37, 1.97)	BFT			
0.39 (0.02, 9.12)	0.39 (0.01, 10.93)	0.46 (0.02, 11.47)	Moxibustion		
0.50 (0.13, 1.89)	0.51 (0.22, 1.15)	0.59 (0.18, 1.90)	1.29 (0.04, 39.33)	Probiotics	
0.40 (0.09, 1.88)	0.41 (0.06, 2.62)	0.47 (0.09, 2.51)	1.03 (0.07, 16.13)	0.80 (0.10, 6.13)	Acupuncture

BFT: Biofeedback therapy; RPs: Routine pharmacotherapies.

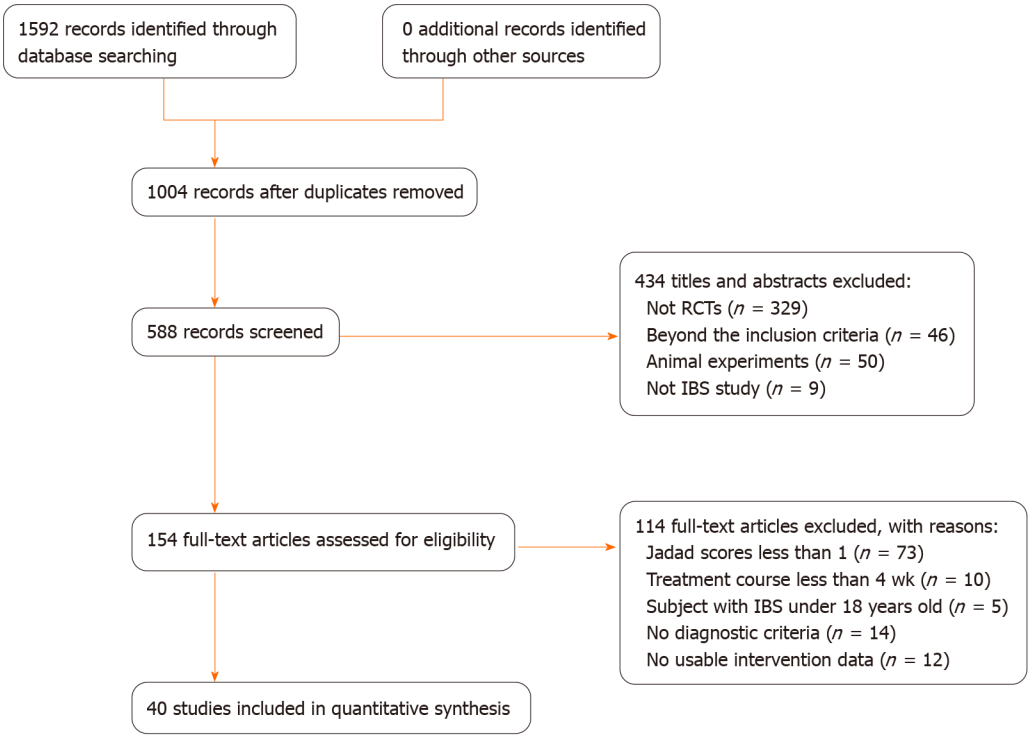

Figure 1 Flow diagram. IBS: Irritable bowel syndrome; RCTs: Randomized controlled trials.

Quality estimates based on the GRADE system

For the primary endpoint, the quality of estimates was "low" (Figure 10). Considering the details of GRADE criteria, the result was possibly derived from quality ratings of direct and indirect comparisons within RCTs, thereby leading to imprecision and unclear risk of bias.

DISCUSSION

NMA is used to analyze trials with multiple interventions and provides rankings for them[71]. Although RPs for IBS can benefit patients, inevitable adverse effects have to be admitted. Accordingly, NPI for IBS have been developed. In this study, to compare the different NPIs, a NMA of multiple NPI comparisons was conducted. Results showed the comprehensive analysis of data for retrievable IBS interventions at present. Based on the SUCRA values, acupuncture was most likely to improve overall clinical efficacy and least likely to result in adverse effects. CBT was most likely to lower the scores of IBS-SSS and SAS and SDS. In summary, when NPIs are used as an alternative therapy in treating IBS, acupuncture and CBT had better efficacy in relieving IBS symptoms.

With the exception of the potential factors mentioned earlier, genetic findings in IBS pathogenesis should also be taken into consideration. Gazouli *et al*[72] confirmed that

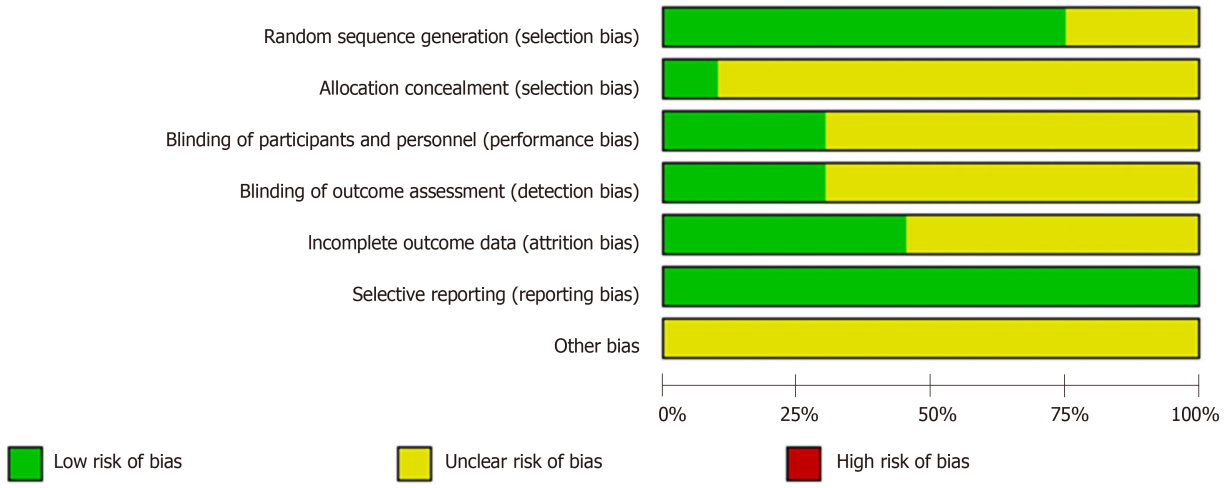

Figure 2 Risk of bias graph.

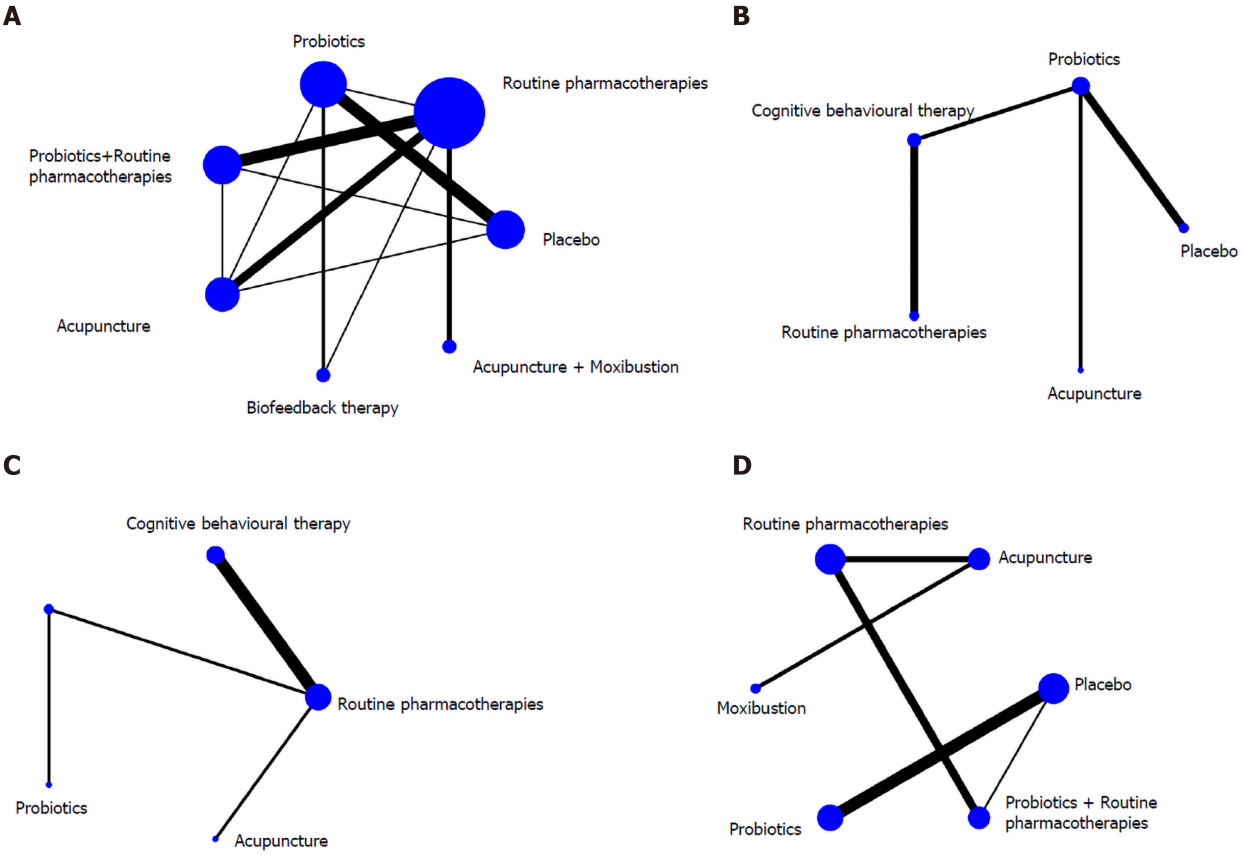

Figure 3 Network evidence of four endpoints. A: Overall clinical efficacy; B: Irritable bowel syndrome symptom severity scale; C: Self-rating anxiety scale and self-rating depression scale; D: Adverse effects.

single nucleotide polymorphisms in genes of serotonergic signaling pathway are associated with at least a subgroup of IBS. For instance, patients who carry an S allele or S/S genotype have differences in the central processing of visceral pain, which could result in a high susceptibility to negative emotional memory and contribute to enhanced visceral pain perception[73,74]. As is well-known, visceral hypersensitivity has been deemed as an important neurological evidence underlying the pathogenesis of abdominal pain in IBS, and visceral pain is associated with a dysregulation of the brain-gut axis[75,76]. Some clinical investigations have confirmed the efficacy of acupuncture in the regulation of the abnormal brain activities and improving visceral

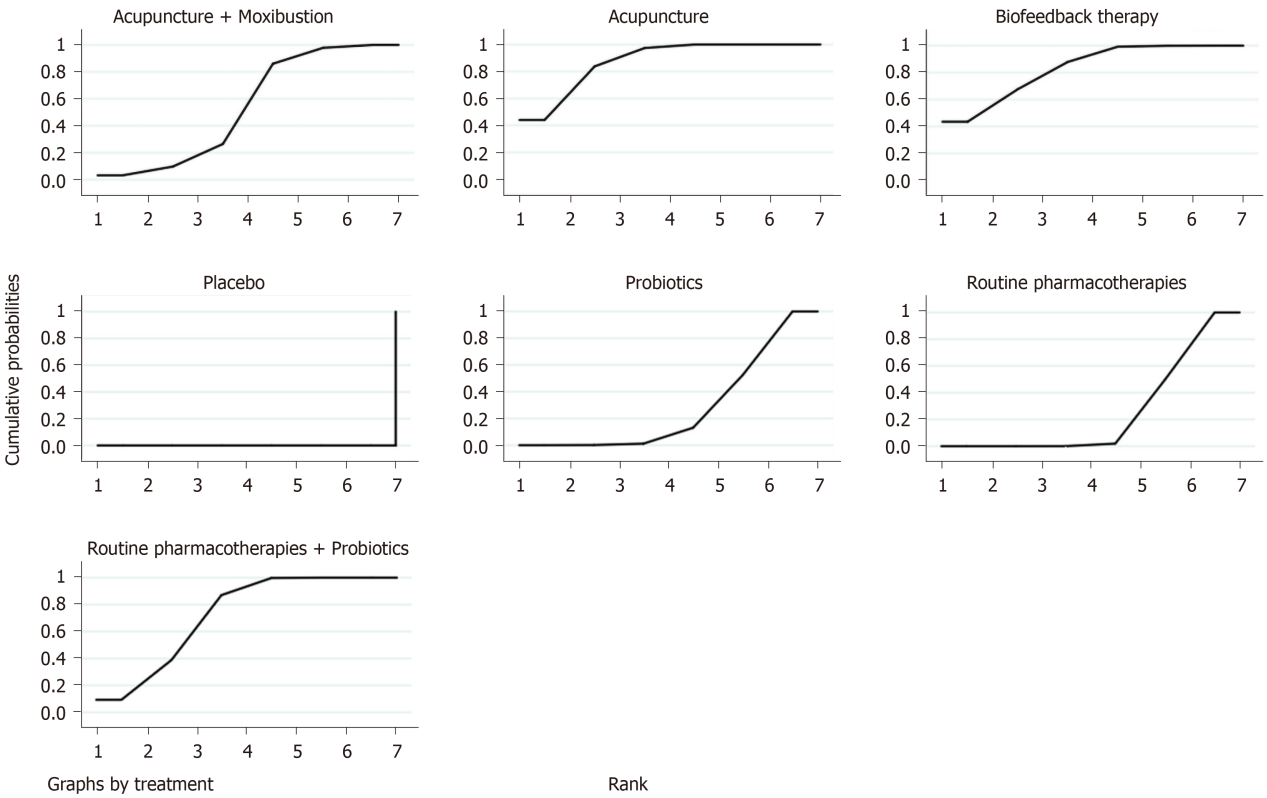

Figure 4 Surface under the cumulative ranking curve plot of overall clinical efficacy.

hypersensitivity in IBS sufferers[77,78]. Moreover, numerous animal studies have also suggested that acupuncture could significantly reduce the peripheral blood flow of rats with 5-hydroxytryptamine positive reactant content and improve visceral hypersensitivity[79-81].

As a typical psychosomatic disease, IBS sufferers have more or less cognitive biases and negative coping styles[82,83]. A few studies have shown that CBT could improve these negative emotions and mental tension by means of relaxation training, respiratory training and hypnotherapy, which made them identify uncontrollable stressors[84-86]. Not only that, CBT could also correct their negative coping styles to relieve psychosomatic damage caused by IBS symptoms, thereby improving the overall well-being and quality of life of these patients[87]. Based on this evidence, our findings may supplement the recommendations of existing guidelines and identify specific NPI with better effects.

Consistency is viewed as a one-way comparative relationship between direct and indirect evidence in an NMA[88]. It would be lack of transitivity if there was an inconsistency in a statistical analysis. In this paper, although heterogeneity analysis indicated good homogeneity and sensitivity analysis suggested strong stability in overall clinical efficacy, clinical heterogeneity such as the improvement of IBS-SSS, SAS and SDS, which were evaluated by an excessive personal opinion from professional practitioners or participants should be noticed. Meanwhile, comprehensive evaluation of outcome measurements on different IBS types should also be seriously considered.

There were several limitations in this study. First, although RCTs are insusceptible to many biases, some certain defects in them including design, conduct, analysis and reporting may lead to bias. In this NMA, the methodological quality of all RCTs was moderate and quality estimates based on the GRADE system showed "Low," which may originate from some overlooked details on randomization and blinding, especially for CBT, BFT, acupuncture and moxibustion that were hard to blind. Second, strict inclusion and exclusion criteria were used in this study, but the number of each NPI in all included trials had relatively large differences (acupuncture /moxibustion: 13 trials, CBT: 4 trials, BFT: 5 trials and probiotics: 18 trials), which was likely to influence the strength of the evidence. Third, although all included RCTs were assessed based on the Cochrane Risk of Bias Assessment Tool, any assessment of bias is subjective. We have to admit that no quantitative index could assess only

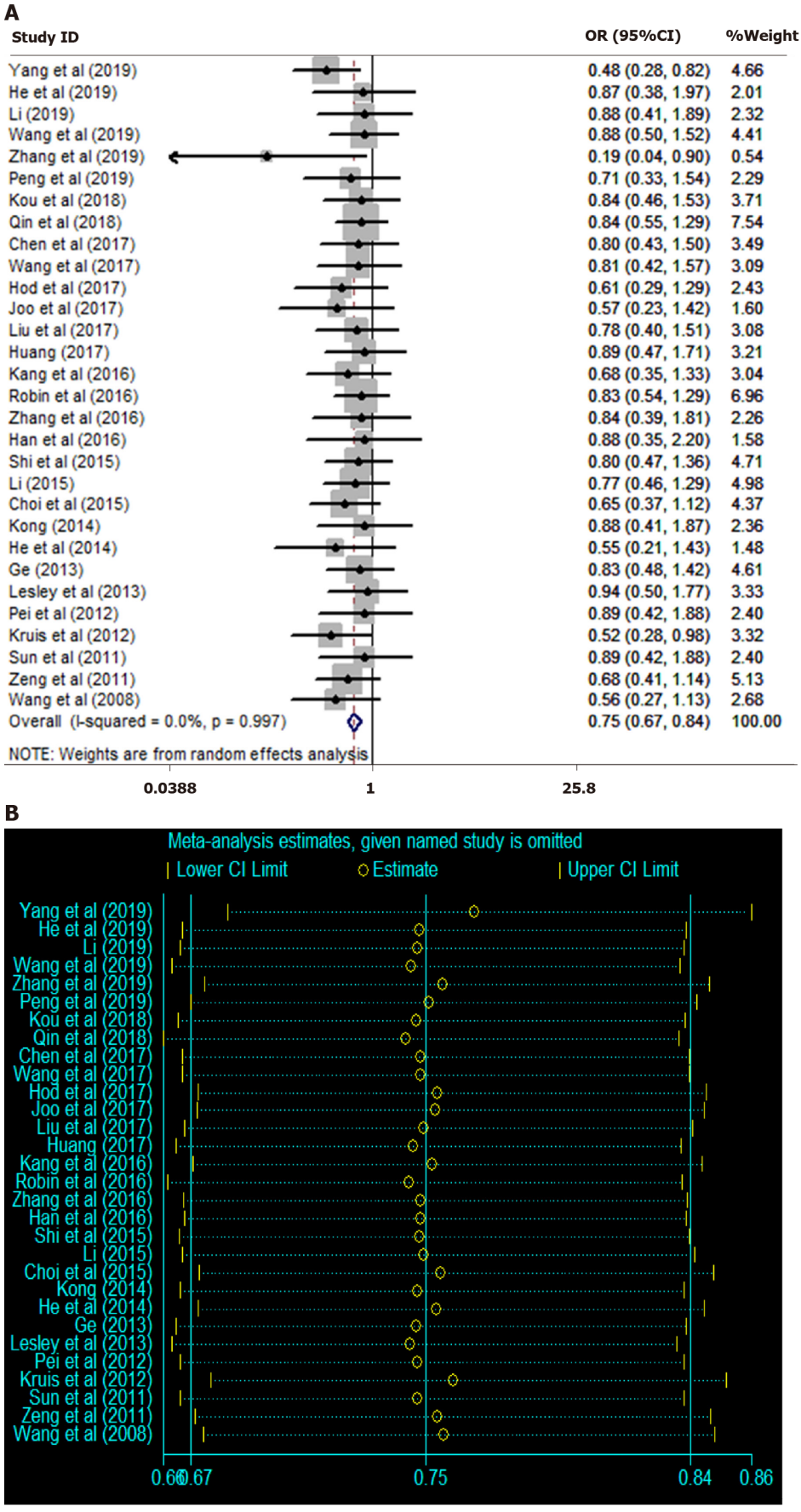

Figure 5 Heterogeneity and sensitivity analysis. A: Heterogeneity analysis; B: Sensitivity analysis. CI: Confidence interval; OR: Odds ratio.

artificial risk of bias so far. Finally, 32 (80%) of the included RCTs were conducted in China, which may reduce the universality of our results.

CONCLUSION

In conclusion, evidence from this NMA showed that acupuncture could be beneficial for patients with IBS because of improved overall clinical efficacy and less adverse effects. CBT had preferable effects in lowering the scores of IBS-SSS, SAS and SDS. However, more RCTs should be performed to confirm the impact of NPIs on other IBS symptoms, and additional high-quality clinical research should be conducted to offer more powerful evidence in the future.

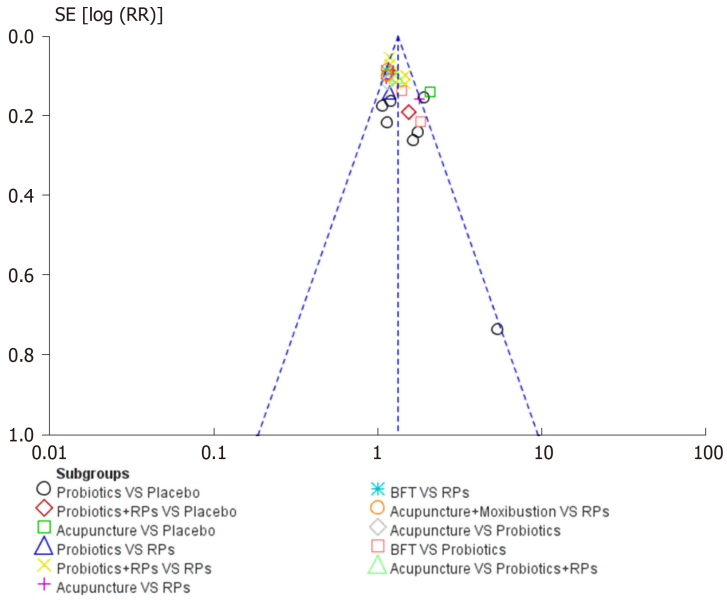

Figure 6 Funnel plot of overall clinical efficacy. BFT: Biofeedback therapy; RPs: Routine pharmacotherapies.

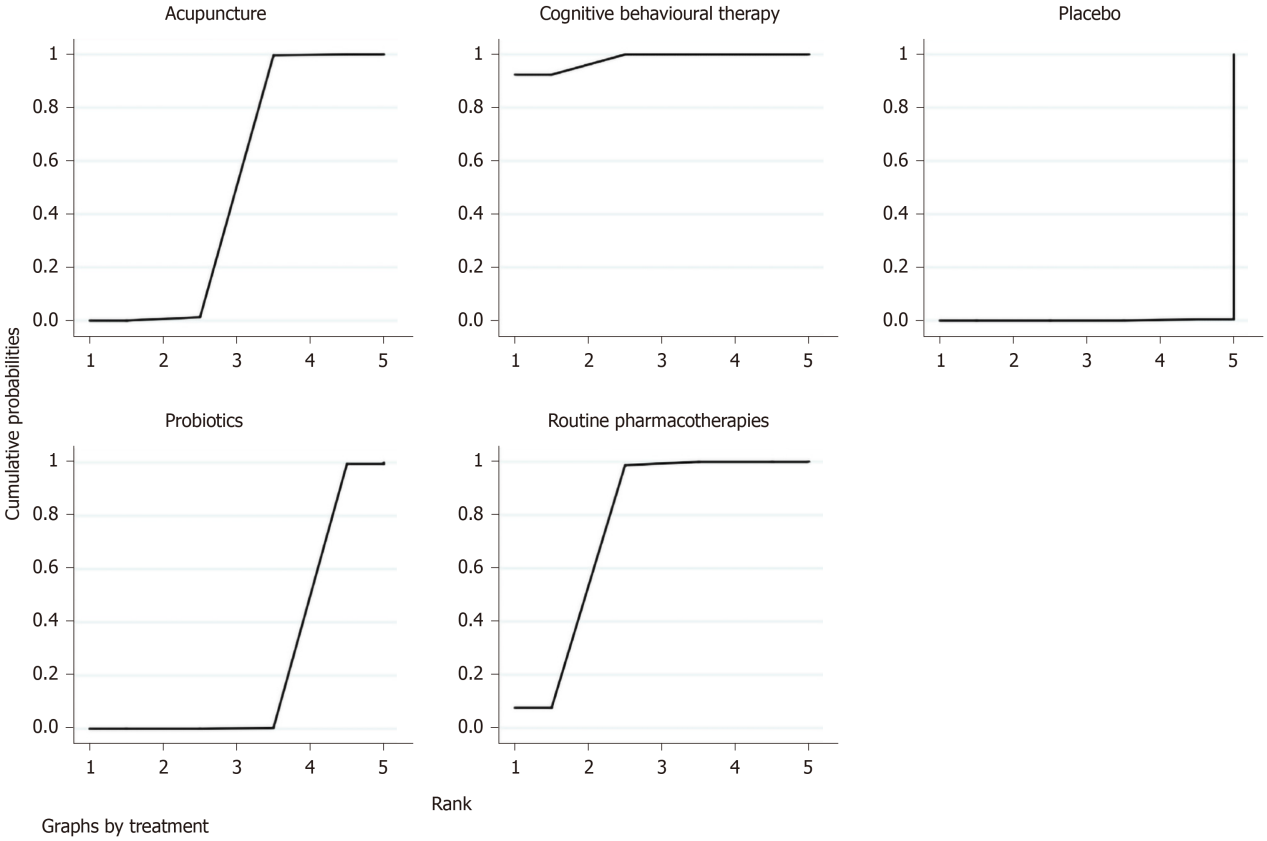

Figure 7 Surface under the cumulative ranking curve plot of irritable bowel syndrome symptom severity scale.

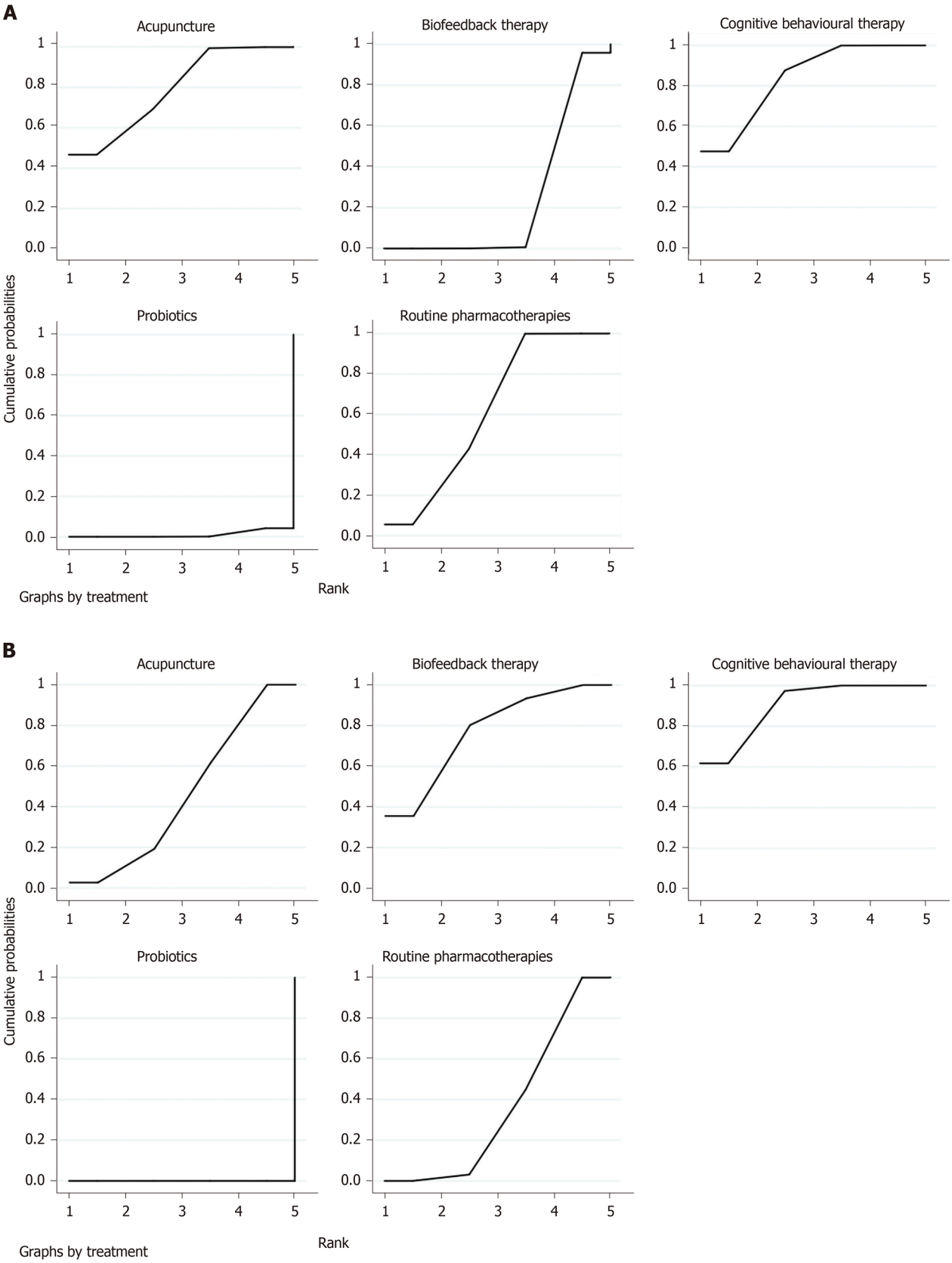

Figure 8 Surface under the cumulative ranking curve plot of self-rating anxiety scale and self-rating depression scale. A: Self-rating anxiety scale; B: Self-rating depression scale.

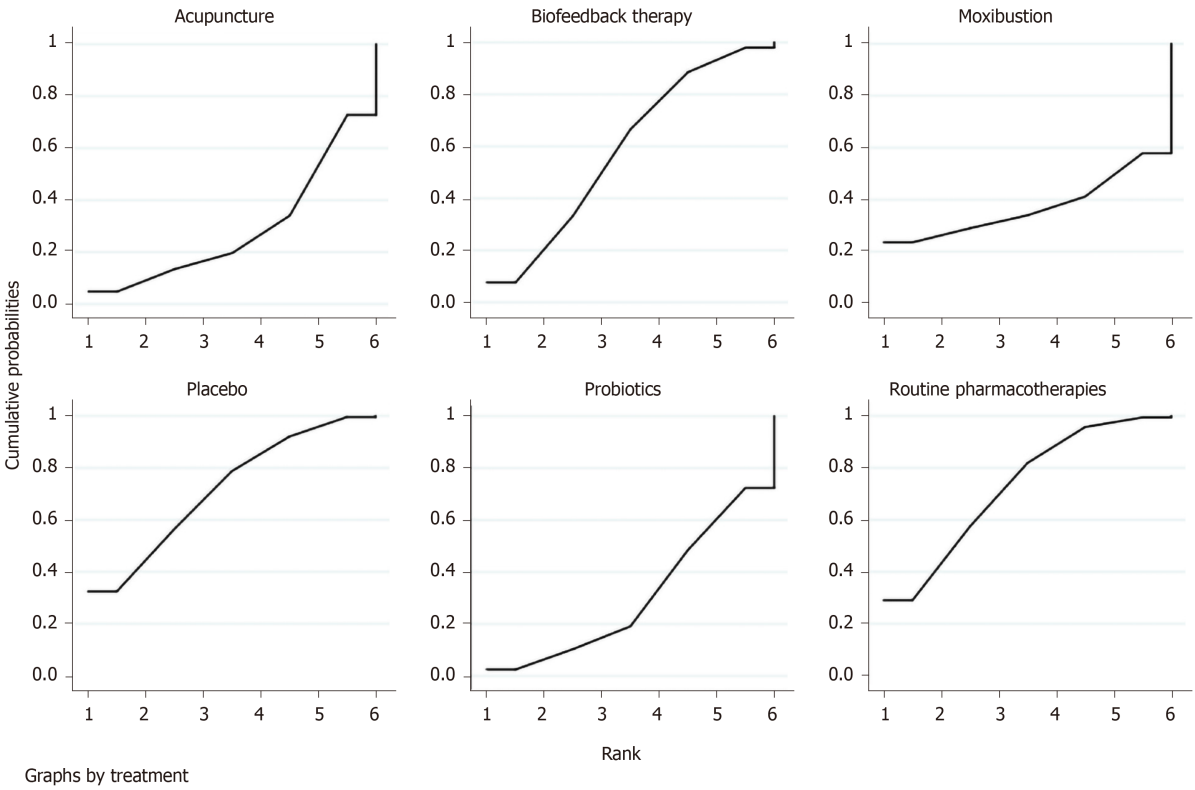

Figure 9 Surface under the cumulative ranking curve plot of adverse effects.

Non-pharmacological Interventions for Irritable Bowel Syndrome (IBS)

Patient or population: patients with Irritable Bowel Syndrome (IBS)
Settings:
Intervention: Non-pharmacological Interventions

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Non-pharmacological Interventions	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Response Rate	Study population		RR 1.33 (1.27 to 1.39)	3143 (30 studies)	⊕⊕⊖⊖ low[1,2,3]	
	588 per 1000	782 per 1000 (747 to 817)				
	Moderate					
	694 per 1000	923 per 1000 (881 to 965)				
Response Rate - Probiotics VS Placebo	Study population		RR 1.44 (1.23 to 1.68)	842 (7)		
	336 per 1000	484 per 1000 (413 to 564)				
	Moderate					
	458 per 1000	660 per 1000 (563 to 769)				
Response Rate - Probiotics+RPs VS Placebo	Study population		RR 1.55 (1.07 to 2.25)	285 (1)	See comment	
	351 per 1000	544 per 1000 (375 to 789)				
	Moderate					
	351 per 1000	544 per 1000 (376 to 790)				
Response Rate - Acupuncture VS Placebo	Study population		RR 2.1 (1.59 to 2.77)	146 (1)	See comment	
	425 per 1000	892 per 1000 (675 to 1000)				
	Moderate					
	425 per 1000	892 per 1000 (676 to 1000)				
Response Rate - Probiotics VS RPs	Study population		RR 1.19 (0.9 to 1.58)	60 (1)	See comment	
	700 per 1000	833 per 1000 (630 to 1000)				
	Moderate					
	700 per 1000	833 per 1000 (630 to 1000)				
Response Rate - Probiotics+RPs VS RPs	Study population		RR 1.28 (1.2 to 1.37)	737 (7)		
	737 per 1000	944 per 1000 (885 to 1000)				
	Moderate					
	750 per 1000	960 per 1000 (900 to 1000)				
Response Rate - Acupuncture VS RPs	Study population		RR 1.27 (1.16 to 1.4)	436 (5)		
	711 per 1000	903 per 1000 (825 to 995)				
	Moderate					
	733 per 1000	931 per 1000 (850 to 1000)				
Response Rate - BFT VS RPs	Study population		RR 1.12 (0.94 to 1.32)	79 (1)	See comment	
	825 per 1000	924 per 1000 (775 to 1000)				
	Moderate					
	825 per 1000	924 per 1000 (775 to 1000)				
Response Rate - Acupuncture+Moxibustion VS RPs	Study population		RR 1.14 (1.02 to 1.27)	226 (3)		
	802 per 1000	914 per 1000 (818 to 1000)				
	Moderate					
	821 per 1000	936 per 1000 (837 to 1000)				
Response Rate - Acupuncture VS Probiotics	Study population		RR 1.15 (0.92 to 1.44)	50 (1)	See comment	
	800 per 1000	920 per 1000 (736 to 1000)				
	Moderate					
	800 per 1000	920 per 1000 (736 to 1000)				
Response Rate - BFT VS Probiotics	Study population		RR 1.55 (1.23 to 1.95)	102 (2)		
	608 per 1000	942 per 1000 (748 to 1000)				
	Moderate					
	595 per 1000	922 per 1000 (732 to 1000)				
Response Rate - Acupuncture VS Probiotics+RPs	Study population		RR 1.3 (1.06 to 1.6)	180 (1)	See comment	
	689 per 1000	896 per 1000 (730 to 1000)				
	Moderate					
	689 per 1000	896 per 1000 (730 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Blinding with less literature.
[2] Indirect comparison
[3] Different interventions

Figure 10 Grading of Recommendations Assessment, Development and Evaluation quality grading assessment.

ARTICLE HIGHLIGHTS

Research background

Although nonpharmacological interventions (NPI) for irritable bowel syndrome (IBS) have been applied clinically, their relative efficacy and safety are poor understood.

Research motivation

The key significance of this network analysis is to compare and rank different NPIs in the treatment of IBS in clinical practice.

Research objectives

The aim of this study was to determine the rates of overall clinical efficacy and adverse effects, the scores of IBS symptom severity scale (IBS-SSS), self-rating anxiety scale (SAS) and self-rating depression scale (SDS).

Research methods

Five electronic databases were searched from their inception to January 12, 2020. Data of included publications were analyzed using network meta-analysis (NMA). Quality of endpoints were assessed by tools of the Cochrane Handbook and the GRADEpro software. Pooled relative risk or standardized mean difference with their corresponding 95% confidence intervals were used for statistical analysis. Surface under the cumulative ranking curve (SUCRA) probability value was conducted to rank the examined interventions. Sensitivity analysis was performed to verify the robustness of results and test the source of heterogeneity.

Research results

Forty randomized controlled trials with 4196 participants were included in this NMA. Compared with routine pharmacotherapies and placebo, acupuncture and cognitive behavioral therapy (CBT) had better efficacy in relieving IBS symptoms. Based on the SUCRA values, acupuncture ranked first in improving overall clinical efficacy and avoiding adverse effects. CBT ranked first in lowering the scores of IBS-SSS, SAS and SDS.

Research conclusions

This study confirmed the efficacy and safety of NPIs for improving IBS symptoms, which to some extent recommended several interventions for clinical practice.

Research perspectives

Future large RCTs should be performed to confirm the impact of NPIs on other IBS symptoms, and additional high-quality clinical researches should be conducted to offer more powerful evidence in the future.

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