Non-pharmacological treatments for irritable bowel syndrome: study protocol of an umbrella review of systematic review and meta-analyses

Song Jin, Yi-Fan Li, Di Qin, Dan-Qing Luo, Hong Guo, Xiu-Hua Gao, Ling Yue, Hui Zheng

ABSTRACT

Introduction Non-pharmacological treatments are used in the management of irritable bowel syndrome, and their effectiveness has been evaluated in multiple meta-analyses. The robustness of the results in the meta-analyses was not evaluated. We aimed to assess whether there is evidence of diverse biases in the meta-analyses and to identify the treatments without evidence of risk of bias.

Methods and analysis We will search MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science and CINAHL Plus for meta-analyses that evaluate the effectiveness of non-pharmacological treatments. The time of publication will be limited from inception to December 2018. The credibility of the meta-analyses will be evaluated by assessing between-study heterogeneity, small-study effect and excess significance bias. The between-study heterogeneity will be assessed using the Cochrane’s Q test, and the extent of the heterogeneity will be classified using the I² statistics. The existence of a small-study effect in a meta-analysis will be evaluated using the funnel plot method and confirmed by Egger’s test. Excess significance bias will be evaluated by comparing the expected number of clinical studies with positive findings with the observed number.

Ethics and dissemination No formal ethical approval is required since we will use publicly available data. We will disseminate the findings of the umbrella review through publication in a peer-reviewed journal and conference presentations.

PROSPERO registration number CRD42018111516.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disease characterised by altered bowel habits and abdominal pain. It affects 11.2% of the general population, 7.0%–17.0% of the Asian population, 12%–15% of the European population and 7%–16% of the US population. IBS is closely related to a decrease in quality of life and working days and increase in healthcare cost. IBS causes reductions in all dimensions of quality of life. At least two-thirds of patients with IBS miss 10 activities or social events every 3 months on average, and at least two-thirds of the patients report at least moderate anxiety and depression due to IBS symptoms. Patients with IBS take twice as many days off work than those without IBS; 7% of patients with IBS have more than 2 weeks off work annually. It is reported that 15%–43% of patients with IBS pay for remedies, and the annual cost for each patient is estimated at $742–$7547 in the USA and £90–£316 in the UK.

Pharmacological treatments are developed and recommended for the treatment of IBS. Due to the chronicity of IBS symptoms and intolerability to pharmacological treatments, patients often select non-pharmacological treatments as an alternative option or as an add-on treatment. Plenty of randomised controlled trials have been conducted to examine the effect of several non-pharmacological treatments on IBS, and multiple meta-analyses on the basis of the randomised controlled trials have therefore been performed. Many of the meta-analyses showed that non-pharmacological treatments have some benefits for patients with IBS. Probiotics seem to improve
global IBS symptoms and abdominal pain\textsuperscript{17}; dietary interventions also exhibit benefits in the improvement of global IBS symptoms\textsuperscript{17}; and cognitive behavioural therapy significantly improves gastrointestinal symptom-specific anxiety and relieve symptom-induced disability.\textsuperscript{15} Although the meta-analyses show the effectiveness of non-pharmacological treatments, they also mention that the reliability of the evidence might be influenced by between-study heterogeneity and other risks of bias.

It is known that the reliability of evidence from meta-analyses could be affected by between-study heterogeneity, small-study effect or excess of significant bias. These biases are acknowledged to cause overestimation of effect size (ES) and false-positive findings, which lessen the credibility of the evidence. Based on the aforementioned facts, we will conduct an umbrella review to evaluate between-study heterogeneity, publication bias (assessing whether the result of a meta-analysis is biased by a small-study effect) and excess of significance in meta-analyses assessing the efficacy of non-pharmacological treatments in the management of IBS, and we will try to screen out the non-pharmacological treatments with the most convincing evidence.

**METHODS AND ANALYSIS**

**Patient and public involvement**

The development of the research question and outcome measures was informed by patients’ priorities, experience and preference as reported in the published clinical studies in this domain, although patients were not involved in the design of this study. The findings of this review will provide patients with knowledge on the credibility of current non-pharmacological treatments for treating IBS.

**Search methods for identification of studies**

We will search MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science and CINAHL Plus from inception to December 2018. We will use the following keywords in searching the electronic databases: (systematic review OR meta-analysis) AND (irritable bowel syndrome) AND (conservative or nonpharmacological OR diet OR lifestyle modification OR acupuncture OR psychological treatments OR treatment OR cognitive therapy OR hypnotherapy OR relaxation training OR biofeedback OR stress management OR medication OR mindfulness OR moxibustion OR herbs). The keywords will be used in combination to develop search strategy for each electronic database (table 1).

**Criteria for considering studies for this review**

We will include systematic reviews or meta-analyses that are published in English and in full-text format. Systematic reviews or meta-analyses that are published as letter to the editor, abstract or conference poster will be excluded unless sufficient data could be acquired from the authors.

| Table 1: Search strategy (through PubMed) |
|---|
| Search Query |
| 1 | Search “Irritable bowel syndrome”[Mesh] OR “IBS”[tiab] OR “diarrhea-predominated IBS”[tiab] OR “constipation-dominated IBS”[tiab] OR “mixed IBS”[tiab] OR “irritable bowel syndrome without constipation”[tiab] OR “diarrhoea IBS”[tiab] OR “constipation IBS”[tiab] |
| 2 | Search systematic[sb] OR “Systematic Review”[tiab] OR “Umbrella Review”[tiab] OR “Meta-Analysis”[Mesh] OR “Meta-Analysis as Topic”[Mesh] OR “meta-analysis”[tiab] OR “meta analysis”[tiab] |
| 3 | Search 1 AND 2 |
| 4 | Search “Acupuncture Therapy”[Mesh] OR “Acupuncture”[Mesh] OR “Acupressure”[Mesh] OR “acupuncture”[tiab] OR “acupuncture”[tiab] OR “electroacupuncture”[tiab] |
| 5 | Search “Diet”[Mesh] OR “Diet, Western”[Mesh] OR “Diet, Gluten-Free”[Mesh] OR “Diet, Carbohydrate-Restricted”[Mesh] OR “Diet, Mediterranean”[Mesh] OR “Diet, Protein-Restricted”[Mesh] OR “Diet, Fat-Restricted”[Mesh] OR “Diet Records”[Mesh] OR “Diet Therapy”[Mesh] OR “Healthy Diet”[Mesh] OR “FODMAP”[tiab] |
| 6 | Search “Cognitive Therapy”[Mesh] OR “Cognitive Therapy”[tiab] OR “behav” therapy[tiab] OR “Relaxation Therapy”[Mesh] OR “relaxation training”[tiab] OR “relaxation techniqu”[tiab] OR “Hypnosis”[Mesh] OR “Hypnosis”[tiab] OR “Hypnotism”[tiab] OR “hynotherap”[tiab] OR “psychology”[tiab] OR “Biofeedback, Psychology”[Mesh] OR “biofeedback”[tiab] |
| 7 | Search “Meditation”[Mesh] OR “Mindfulness”[Mesh] OR “Moxibustion”[Mesh] OR “stress management”[tiab] OR “meditation”[tiab] OR “mindfulness”[tiab] OR “moxibustion”[tiab] |
| 8 | Search “Plants, Medicinal”[Mesh] OR “Herbs as Topic”[Mesh] OR “Herbal Medicine”[Mesh] OR “herb”[tiab] OR “tong”[tiab] |
| 9 | Search 4 OR 5 OR 6 OR 7 OR 8 |
| 10 | Search 3 AND 9 |
| 11 | Search 10 AND “English”[lang] |
Types of studies
We will search for systematic reviews or meta-analyses examining the effectiveness of conservative non-pharmacological treatments in treating IBS. Systematic reviews with only narrative summary will be excluded, since we will not be able to perform analyses based on narrative information.

Types of participants
We will include systematic reviews or meta-analyses focusing on IBS or its subtypes (diarrhoea-predominated IBS, constipation-dominated IBS or mixed IBS), and the diagnostic criteria of IBS and its subtypes should be one of the Rome criteria versions (Rome II, III or IV).18–20

Types of interventions
We will include non-pharmacological treatments used as monotherapy or as add-on to pharmacological treatments. The non-pharmacological treatments to be included will be diet, lifestyle modification, acupuncture, behaviour cognitive therapy, psychological therapy, hypnotherapy, relaxation, biofeedback, stress management, meditation, mindfulness, moxibustion and herbal remedies. The pharmacological treatments are defined as treatments recommended in the National Institute for Health and Care Excellence guideline,21 the American College of Gastroenterology,22 and the British Society of Gastroenterology23 24; they will include 5-hydroxytryptamine3 (5-HT3) receptor antagonists, opioid receptor ligands, antidepressants and antibiotics.25

Types of outcomes
We will include meta-analyses that evaluate any of the following outcomes: global IBS symptoms, abdominal pain, defaecation urgency, stool frequency, stool consistency (Bristol score), responder rate (a responder is defined according to the improvement in global IBS symptoms or abdominal pain) or adverse event rate. The extent of global IBS symptoms, abdominal pain or defaecation urgency could be evaluated using a visual analogue scale or other Likert scales.26

Selection of studies
Two reviewers (DQ and D-QL) will independently screen the titles and abstracts of the retrieved articles. We will also acquire the full text of an article for screening when we could not determine its eligibility on the basis of titles or abstracts. Discrepancy in the eligibility of an article will be solved by discussion and arbitrated by a third reviewer (HZ). We will exclude meta-analyses with the number of included trials less than 10.27 28 When multiple meta-analyses focusing on the same clinical questions are found, we will select the most updated one. Meta-analyses with missing 95% CI will be excluded. We set no restriction on the IBS subtypes to ensure the generalisability of the result of this review.

Data extraction
Two reviewers (HG and X-HG) will independently extract data from eligible meta-analyses through standardised extraction form, and they will subsequently enter the information into Epi Info (V.7.2) for data analysis. Data items to be extracted will include study characteristics (name of the first author, publication year and total sample size), disease conditions (diagnosis of IBS and its subtypes), intervention and control (name of the intervention and its sample size) and outcomes (name of outcome, ES and its related 95% CI). We will extract data for every subtype of IBS separately. When the data are only provided in the form of plots, we will use Ycasd29 to determine the ES and its 95% CI. We will use the primary outcome defined in each original meta-analysis. When the primary outcome is not defined in a meta-analysis, we will preferentially select global IBS symptoms or abdominal pain as the primary outcome.

Data analysis
General characteristics of the eligible trials will be summarised and described, including the total sample size of a meta-analysis, interventions, and their ES and related 95% CIs. We will recalculate the summary ES and 95% CI for eligible meta-analyses using both fixed-effect and random-effect models (package meta in R V.3.5.0; http://www.r-project.org), and we will examine the consistency between the result of our calculation and the result of the published meta-analysis. We will estimate the 95% prediction interval (95% PI) of each meta-analysis and examine whether the 95% PIs exclude the null value.28 The 95% PI provides information for estimating the ES and its 95% CI of an intervention being tested in future trials. We will calculate the 95% PIs and account for between-study heterogeneity, and the between-study heterogeneity of each meta-analysis will be evaluated using the Cochrane’s Q test and I2 statistics. The existence of between-study heterogeneity will be determined using the Cochrane’s Q test, and the extent of the heterogeneity will be quantified using the I2 statistics (small heterogeneity, I2 <25%; moderate heterogeneity, 25%–49%; large heterogeneity, 50%–74%; very large heterogeneity >75%).

It has been widely accepted that small-sample size trials tend to demonstrate larger ES than large-sample size trials,30 and the tendency of small studies showing positive findings makes them easier to get published (publication bias). To evaluate the small-study effect and publication bias, we will first examine whether there is evidence of small-study effect in the included meta-analyses through funnel plot.31 The funnel plot is a scatter plot of ES against SE or inverse variance for measuring precision in estimating the ES; the ES in small studies scatters wider at the bottom of the funnel plot, while larger studies scatter narrower at the top. The funnel plot is a symmetrical diagonal plot when there is no evidence of small-study effect; it is asymmetrical with more scatter of small studies at one side of the bottom of the plot when a small-study effect exists. Contour funnel plot will be drawn to determine
the number of significant findings in small studies, and the significance level will be set at 0.1, 0.05 and 0.01, respectively. Second, we will use linear regression model to test the significance of the small-study effect in each meta-analysis, and we will use the model to analyse the existence of publication bias.32

We will test excess significance bias in the included meta-analyses by comparing the observed number of trials with statistical significance (positive findings) with their expected number. The number of the expected significance will be the sum of the study power of all trials in a meta-analyses.33 Supposed that type II error is 0 (no false-negative error) in each trial, the number of expected significance will be equal to their observed number.33 When the observed number significantly exceeds the expected number, we will claim the evidence of excess significance bias in a meta-analysis. The difference between these two numbers will be examined using generic z test, and p<0.10 will be considered statistically significant.34 In estimating the power of each component trial in a meta-analysis, we need the true ES of an intervention. Since the true ES is impossible to acquire, we will use the ES of the largest trial (the trial showing the smallest SE) instead. The power of each component trial will be estimated through an algorithm using a non-central t distribution (performed using the z test function in G*Power V.3.1.9.2).

We will categorise the evidence of the effectiveness of a non-pharmacological treatment into strongest validity, highly suggestive, suggestive or weak evidence according to the following criteria27 28: (1) p<0.05 in a fixed-effects model or p<0.001 in a random-effects model; (2) at least 1000 participants; (3) low or moderate between-study heterogeneity (I²<50%); (4) 95% PI that excludes the null value; and (5) no evidence of small-study effects and excess significance bias. The strongest validity evidence should meet all the five criteria; the highly suggestive evidence should meet criteria 1–4; the suggestive evidence should meet 1 and 2; and weak evidence will meet only 1.

DISCUSSION
To the best of our knowledge, this umbrella review will be the first to generally evaluate currently available non-pharmacological treatments through quantitative methods. The result of this review will provide patients, physicians and clinical research investigators with information on the credibility of current evidence and research direction for future studies.

ETHICS AND DISSEMINATION
We will use publicly available data from systematic reviews and meta-analyses; hence, no formal ethical approval is required. We will disseminate the findings of the review through publication in a peer-reviewed journal and conference presentations.

REFERENCES

1. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012;10:712–21.
2. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. N Engl J Med Overseas Ed 2017;376:2566–78.
3. Sullivan S, Malhotra A. Irritable Bowel Syndrome. Ann Intern Med 2017;166:ITC81–96.
4. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. Aliment Pharmacol Ther 2014;40:1023–34.
5. Hulliz D. The burden of illness of irritable bowel syndrome: current challenges and hope for the future. J Manag Care Pharm 2004;10:298–309.
6. Smith GD, Steinke DT, Kinneir M, et al. A comparison of irritable bowel syndrome patients managed in primary and secondary care: the Epidose IBS study. Br J Gen Pract 2004;54:503–7.
7. Hungin AP, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643–50.
8. Silk DB. Impact of irritable bowel syndrome on personal relationships and working practices. Eur J Gastroenterol Hepatol 2001;13:1327–32.
9. Forbes A, Jackson S, Walter C, et al. Acupuncture for irritable bowel syndrome: a blinded placebo-controlled trial. World J Gastroenterol 2005;11:4040–4.
10. Yoon JS, Sohn W, Lee OY, et al. Effect of multispecies probiotics on irritable bowel syndrome: A randomized, double-blind, placebo-controlled trial. J Gastroenterol Hepatol 2014;29:52–9.
11. Vazquez-Roque MI, Camilleri M, Smyrk T, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. Gastroenterology 2013;144:933–43.
12. Tang QL, Lin GY, Zhang MQ. Cognitive-behavioral therapy for the management of irritable bowel syndrome. World J Gastroenterol 2013;19:8605.
13. Staudacher HM, Lomer MCE, Farquharson FM, et al. A Diet Low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and a probiotic restores bifidobacterium species; a randomized controlled trial. Gastroenterology 2017;153:936–47.
14. Hannlon I, Hewitt C, Bell K, et al. Systematic review with meta-analysis: online psychological interventions for mental and physical health outcomes in gastrointestinal disorders including irritable bowel syndrome and inflammatory bowel disease. Aliment Pharmacol Ther 2018;48:244–59.
15. Laird KT, Tanner-Smith EE, Russell AC, et al. Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: A systematic review and meta-analysis. Clin Psychol Rev 2017;51:142–52.
16. Rao SS, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther* 2015;41:1256–70.

17. Ford AC, Harris LA, Lacy BE, et al. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment Pharmacol Ther* 2018;48:1044–60.

18. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. *Gastroenterology* 2016;1262–79 (Published Online First: 19 Feb 2016).

19. Williams RE, Black CL, Kim HY, et al. Stability of irritable bowel syndrome using a Rome II-based classification. *Aliment Pharmacol Ther* 2006;23:197–205.

20. Ford AC, Bercik P, Morgan DG, et al. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gastroenterology* 2013;145:1262–70.

21. Hookway C, Buckner S, Crosland P, et al. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. *BMJ* 2015;350:h701.

22. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 2014;109:S2–S26.

23. Jones J, Boorman J, Cann P, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000;47(Suppl 2):i1–i9.

24. Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut* 2007;56:1770–98.

25. Yue L, Chen M, Tang TC, et al. Comparative effectiveness of pharmacological treatments for patients with diarrhea-predominant irritable bowel syndrome: Protocol of a systematic review and network meta-analysis. *Medicine* 2018;97:e11682.

26. Spiegel B, Bolus R, Harris LA, et al. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. *Aliment Pharmacol Ther* 2009;30:1159–70.

27. Dragioti E, Karathanos V, Gerdle B, et al. Does psychotherapy work? An umbrella review of meta-analyses of randomized controlled trials. *Acta Psychiatr Scand* 2017;136:236–46.

28. Belbasis L, Bellou V, Evangelou E, et al. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol* 2015;14:263–73.

29. Gross A, Schirm S, Scholz M. Ycasd - a tool for capturing and scaling data from graphical representations. *BMC Bioinformatics* 2014;15:219.

30. Nüesch E, Trelle S, Reichenbach S, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;341:c3515.

31. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54:1046–55.

32. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.

33. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials* 2007;4:245–53.

34. Ioannidis JPA. Clarifications on the application and interpretation of the test for excess significance and its extensions. *J Math Psychol* 2013;57:184–7.