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

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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 I^2 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.

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Strengths and limitations of this study

► This review will comprehensively assess the reliability of current evidence on non-pharmacological treatments in the management of irritable bowel syndrome.

► The review will evaluate between-study heterogeneity, small-study effect and excess significance bias through quantitative analysis, and it will classify the reliability level of each non-pharmacological treatment on the basis of the analysis.

► The review focuses on the evaluation of systematic reviews with meta-analyses, so it may miss some treatments that are assessed by systematic reviews with only narrative analysis.

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,[1] 7.0%–17.0% of the Asian population,[1] 12%–15% of the European population[1] and 7%–16% of the US population.[2] IBS is closely related to a decrease in quality of life and working days and increase in healthcare cost.[2 3] IBS causes reductions in all dimensions of quality of life.[4] At least two-thirds of patients with IBS miss 10 activities or social events every 3 months on average,[5] and at least two-thirds of the patients report at least moderate anxiety and depression due to IBS symptoms.[6] Patients with IBS take twice as many days off work than those without IBS[7]; 7% of patients with IBS have more than 2 weeks off work annually.[8] 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.[4]

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,[9–13] and multiple meta-analyses on the basis of the randomised controlled trials have therefore been performed.[14–16] 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[17]; dietary interventions also exhibit benefits in the improvement of global IBS symptoms[17]; and cognitive behavioural therapy significantly improves gastrointestinal symptom-specific anxiety and relieve symptom-induced disability.[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 behavioural therapy OR cognitive therapy OR hypnotherapy OR relaxation training OR biofeedback OR stress management OR meditation 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 "acupressure"[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 "Hynotism"[tiab] OR "hypnotherap*"[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 "Herbals 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 Gastroenterology[23 24]; they will include 5-hydroxytryptamine3 (5-HT$_3$) 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 Ycasd[29] 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 I^2 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 I^2 statistics (small heterogeneity, I^2 <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 criteria[27 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 ($I^2 < 50\%$); (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.

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