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Non-pharmacological therapies for patients with functional constipation: a systematic review protocol

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Keywords: Non-pharmacological therapies, constipation, systematic review, protocol

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Abstract

Introduction: The aim of this review is to assess the effectiveness, efficacy and safety of non-pharmacological therapies for patients with functional constipation.
Methods and analysis: We will electronically search OVID MEDLINE, EMBASE, Cochrane library, CINAHL, AMED and ISI web of knowledge without any language restrictions. We will also try to obtain literatures from other sources, such as hand search library journals or conference abstracts. After searching and screening of the studies, we will run a meta-analysis of the included randomized controlled trials. We will summarize the results as risk ratio for dichotomous data, standardized or weighted mean difference for continuous data.
Dissemination: This systematic review will summarized current evidence for using non-pharmacological therapies to treat functional constipation, and will be disseminated through peer-review publication or conference presentation.
Protocol registration: PROSPERO CRD42014006686

Keywords: Non-pharmacological therapies, constipation, systematic review, protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first systematic review protocol to assess the effectiveness, efficacy and safety of non-pharmacological therapies for patients with functional constipation.
- The results of this systematic review will help clinicians making decisions on clinical practice, and help functional constipation patients seeking more treatment options.
- Difficult to locate all the non-pharmacological treatments for functional constipation may be the limitation of this systematic review, we will use several steps advised by specialists in informatics to ensure a broad search of studies.

INTRODUCTION

Functional constipation (FC), is a common clinical condition without a specific physiological cause. The prevalence of constipation ranged from 0.7% to 81% around the world[1 2], whereas the prevalence of FC varied from 2.4% to 27.2%[3-5]. A mean prevalence for FC is reported to be 14% in a recent systematic review[4]. FC is a chronic and refractory condition; a study showed that 89% of the constipated patients still reported constipation during a mean follow-up period of 14.7 months[5]. Constipation symptoms significantly reduce the patients' quality of life, both mentally and physically[2 6]. Additionally, it is reported that constipation is related to higher possibility of patients becoming obese[7]. Direct cost of chronic FC for each patient ranged from $1912 to $7522 per year[8]. Considering that FC brings significant impact on quality of life, influencing physical and emotional well-being, it should be considered as a major public health problem.

Lots of therapies were used to manage constipation symptoms for FC patients, such as laxatives, selective 5-HT4 agonists, etc. Recent systematic reviews reported that Laxatives, prucalopride, lubiprostone and linaclotide are effective for managing FC compared to placebo, however, more events of diarrhea were reported[9]. Similar findings were discovered in several

recent reviews that pharmacological therapies are effective for relieve constipation symptoms, but more adverse events happened in patients receiving those treatments[10 11]. Traditional herbal medicine was reported to be helpful with less adverse events for relieving constipation symptoms, however, systematic reviews could not reach this conclusion, instead, the reviews concluded that more trials with rigorous design are needed to confirm the effectiveness of traditional herbal medicine for FC[12 13].

Non-pharmacological therapies are popular among patients with FC; however, most of them were lack of evidence support. A systematic review focusing on non-pharmacological treatments for children with constipation concluded that, there is a lack of well-designed randomized controlled trials of high quality to verify whether these treatments were effective[14]. Although several non-pharmacological therapies were claimed to be beneficial for FC patients[15-19], but most of them were concluded by systematic reviews that, firm conclusion could not be drawn due to lack of evidence support. Therefore, we raised the following questions: 1. Are non-pharmacological therapies effective and efficacious for patients with FC? 2. If so, are non-pharmacological therapies safe for patients with FC? To answer these questions, we will conduct a systematic review of non-pharmacological therapies for patients with functional constipation, hoping to find the answers. In this article, we present a protocol of the systematic review.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Types of studies

Before running the review, we have done a pre-search to get a general understanding of recent studies on this topic. We found that there were a few randomized controlled trials, so we agreed that including randomized controlled trials only is reliable and feasible for this review, to ensure the reliability of the evidence. Furthermore, randomized controlled trials with crossover design were not common in studying non-pharmacological treatments, because the washout periods of these interventions could not be accurately evaluated, which may bring bias to outcome assessments. Therefore, we will include randomized controlled trial with parallel design. And we will include trials using open label, single blind or double blind design.

Types of participants

We aim to include participants who were diagnosed as functional constipation according to ROME II of III criteria in this systematic review. Participants were also included although ROME II or III criteria was not mentioned, if they were diagnosed as constipation and were excluded for specific pathological cause, such as underlying structural or metabolic diseases. We will focus on constipation in the adult population, so trials included participants with age under 18 will be excluded.

Types of interventions

We plan to include trials, in which no pharmacological treatments were used in experimental group, including herbs, traditional medicine, etc. So we will first exclude trials using any pharmacological interventions, after we search the databases. After excluding articles reporting pharmaceutical treatments, we will include trials that non-pharmacological treatments were used at least once a week for a minimum total of 4 weeks. We will not limit the procedure of the non-pharmacological interventions, e.g., manipulation methods of acupuncture or massage will

not be necessary for judgment of inclusion. To assess the effectiveness of non-pharmacological treatments, we plan to compare them with positive control. According to the guideline and recent systematic reviews[10 20 21], laxatives, selective 5-HT4 agonists, patient's education are reported to be effective for managing constipation, so we set these interventions as positive controls. To assess the efficacy of non-pharmacological treatments, we plan to compare these treatments with placebo control, which includes placebo drugs, sham interventions, etc. To measure the effect size of non-pharmacological treatments, we consider comparing these treatments with waiting list control.

Types of outcome assessments

The primary outcome of this review will be improvement of bowel movement per week after finishing all treatment sessions. Since the non-pharmacological treatment sessions are different across studies, so it is impossible to make an exact time point for primary outcome measure. Therefore, we agree that after finish of treatment is relatively suitable timing for primary outcome assessment. The secondary outcomes are proportion of responders, mean transit time, proportion of patients using laxatives, quality of life (QOL) and proportion of adverse events. The parameter proportion of responders is that we count up the number of responders (participants responded to the treatment and was reported as responders in the included trials) in each study, and calculate the proportion of them. The transit time is defined as the time from the first perception of wanting to defecate to finish of the defecation, and we will calculate the mean transit time. The participants who used laxatives (types of the laxatives will not be limited in this review) during the trial will be counted up, and we will calculate the proportion of patients using laxatives. The outcome QOL will be measured by scales that normally used by constipation studies, such as The Short Form 36 Health Surveys (SF-36), etc. We will sum up the number of patients reporting adverse events in each study, and calculate the proportion of adverse events.

Search methods for identification of studies

Electronic searches

We electronically searched the following database OVID MEDLINE, EMBASE, Cochrane library, CINAHL, AMED and ISI web of knowledge from 2003 to 2013, without any language restrictions. The search strategy will be developed after a discussion among reviewers, according to the guidance of the Cochrane handbook[22]. To ensure a broad search, we included the medical subject headings such as randomized controlled trial, constipation, etc. Titles, abstracts and subject headings were also searched for the above Mesh words and several other words related to randomized controlled trials, functional constipation, etc. The search strategy for OVID MEDLINE was shown in table 1.

Other sources

Potentially eligible studies will also be obtained through the following methods:

- Review the reference list of the previously published reviews for possible candidates;
- If applicable, we will review the conference abstract to find out the unpublished trials, and contact the authors for the data;
- Hand searching a list of medical journals in the university library, such as Chinese Medical Journal, etc.

Data collection and analysis

Selection of studies

Before selection of the studies, a procedure for screening will be developed by discussion

among all the reviewers. After electronic searches, the outputs will be cited in a database created by endnote software (version X6). Studies obtained from other sources will also be cited in the same database. Two reviewers (HZ and JL) will independently screen the titles and abstracts in this database through the following steps: first, find out the duplicates (studies published in different languages, or studies published as a journal article as well as a conference abstract, or at least two articles reported the same trial in different aspects); second, exclude studies in which participants receiving pharmacological treatment in an experimental group or participants were diagnosed as constipation due to structural or metabolic diseases; third, exclude studies which were not designed as randomized controlled trials with parallel design; fourth, exclude studies in which participants under the age of 18 were recruited. Full copies will be achieved, if the reviewers (HZ and JL) could not clearly exclude studies based on titles and abstracts. And another two reviewers (MC and QC) will screen the full copies of these studies. If disagreements occur between reviewers during screening, they will be resolved through discussion and consensus. If the disagreement persists, a third author (DQH or JQF) will be consulted.

Data extraction and management

Before data extraction, all the reviewers will discuss and develop a standardized data extraction form, and we will extract information from at least 3 studies using this form to check its applicability. Two independent reviewers (HZ and JL) would extract the following information from the studies: organizational aspects (including reference ID, reviewer's name, the first author of the article, publication year, source/journal, etc.), trial characteristics (design of the study, number of participants, number of groups, method of randomization, method of allocation concealment, blinding, primary aims of the study, etc.), participants (age, ethnicity, gender, diagnosis, concurrent conditions, laboratory parameters, etc.), interventions and controls (name of the intervention, length of treatment, type and name of control, information for care providers, additional treatment, etc.), outcome measurement (type of outcome, definition of the outcome, time point of assessment, length of follow-up, etc.), results (name of the outcome, mean, standard deviation, observed events after intervention, total sample size, etc.) , other research information. When there is discrepancy between the two reviewers, consensus will achieved by discussion among all the reviewers. The extraction data will be entered into Stata 12.0 (Stata Corp, College station, TX), and QC will check the data to ensure there are no data entry errors.

Assessment of risk of bias in included studies

Two reviewers (MC and HZ) will assess the risk of bias independently, using the Cochrane collaboration's tool for assessing risk of bias of the included trials[22], which is composed of six domains of a trial, such as sequence generation, allocation concealment, blinding, incomplete data, etc. After assessing all the domains, the reviewers will summarize the assessments, and categorize the included trials into 3 levels of bias: low, unclear and high risk of bias.

Measures of treatment effect

We will calculate the risk ratio (RR) for the dichotomous data during synthesis, and provide the p values for the RR during comparison of experimental group with control. For continuous data, we will calculate the weighted mean differences (WMD) if all the studies using the same measurement tool and the same unit, if not, we will calculate the standardized mean difference (SMD). 95% confidence intervals (CI) will be calculated for RR, WMD or SMD.

Unit of analysis issues

In this review, we include data from parallel design trials. And if there are multiple

observations at different time points, we will defined the data assessed within 4 weeks as short-term outcomes, and those assessed over 4 weeks as long-term outcomes. As most of the treatment length of non-pharmacological therapies will usually last at least 4 weeks, so we will focus on the long-term outcomes in the analysis.

Dealing with missing data

If there are missing data in the included studies, we will try to contact the investigators of the studies to get enough information. If we fail to contact the investigators and get the missing data, we will firstly exclude the studies with missing data and synthesize the evidence, and secondly use the worst-case strategy (missing values in experimental group will be categorized as poor outcomes, on the contrary, missing values in control group will be considered as good outcomes) . Lastly, we will perform a sensitivity analysis to find out whether the results of using the above two methods are consistent.

Assessment of heterogeneity

Before the meta-analysis, we will perform a heterogeneity examination, using the Higgins I^2 test. We will calculate the I^2statistics to find out if there are inconsistencies in the included trials. We set a cut-off point of 50% for the I^2statistics. An I^2>50% will be considered as existence of significant heterogeneity among studies. In that case, we will perform a meta-regression analysis to find out the source of the heterogeneity. Moreover, we will run subgroup analysis according to the source of the heterogeneity. Additionally, we will combine the outcome using a random effect model when the significant heterogeneity exist, but explain the results with caution.

Assessment of reporting biases

We will use funnel plots to assess reporting biases as well as small study effects. If 10 or more studies are included in a meta-analysis, we will use Egger's method to test funnel plot asymmetry.

Data synthesis

Data synthesis will be performed using Stata 12.0 (Stata Corp, College station, TX) and R project 3.02 (www.r-project.org). For dichotomous data, we will combine RR of each study and calculate 95%CI using fixed effect model, if no heterogeneity is detected. And if significant heterogeneity is found, we will combine the data using random effect model and explain the results with caution. Moreover, we will provide a p value for a comparison of non-pharmacological therapies with positive drug control, sham intervention control or waiting list control. For continuous data, we will combine the WMD of each study and compute the 95%CI, if the same outcome measurement is used; if not, we will combine SMD instead. Additionally, we will also choose fixed or random effect model according to the result of heterogeneity test, and provide p values.

Subgroup analysis

We will perform a subgroup analysis according to different non-pharmacological treatments, which is considered to be the most significant source of heterogeneity among studies. Also, we will run subgroup analysis according to the source of the heterogeneity using meta-regression mothod.

Sensitivity analysis

First, we will conduct a sensitivity analysis to assess the impact of missing data on the results of this review. In the analysis, we will compare the results of excluding studies with missing values to the results of using the worst-case strategy to combine the studies. Second, we will

assess the impact of including studies with high risk of bias on the results of this review. So we will compare the results of excluding studies with high risk of bias with those not, to find that if the results are consistent. Third, to clarify whether different models affect the results of data synthesis, we combine the outcomes using both fixed and random effect models, and check if the results remain the same. Fourth, to assess the impact of sample size on the results of this review, we will compare the results of excluding small sample size trials (< 100 participants) to those not.

Ethics and dissemination

This systematic review does not need ethical approval because data we used will not be linked to individual data and privacy. The results of this review will provide a general view and evidence of non-pharmacological treatments for management of functional constipation. The findings of this review will also give implication for clinical practice and further research, and will be disseminated by a peer-review publication and conference presentations.

DISCUSSION

In this article, we present a protocol of a systematic review of using non-pharmacological therapies to treat functional constipation, which is becoming a major public health problem. The most difficult part of this review is to define non-pharmacological interventions and to run a broad search for them. After a consultation with the specialists of informatics, we decided to locate the studies we want to include through 3 steps: first, we use keywords related to non-pharmacological therapies, we also use non-pharmacological interventions commonly applied in clinical pratice as search keywords, such as dietary fiber, probiotics, acupuncture, moxibustion, etc. Second, after running search strategy, we will screen the titles and abstracts to exclude studies using any pharmacological interventions. Third, we will screen the full copies of the potential studies to ensure we locate the correct studies.

The second difficult part of this review is to define the condition functional constipation in the studies. We consulted several specialists in the field of gastroenterology, who suggested that it will better to include studies using ROME II or III as diagnostic criteria in this review. So we took the advice, moreover, we use the several keywords in addition to functional constipation, such as constipation, idiopathic constipation, etc., to ensure that we run a broad search of studies on this topic.

This systematic review will give a summary of the current evidence on the effectiveness and safety of non-pharmacological therapies for patients with FC. And this review will benefit FC patients and care providers for that they will have more treatment options.

Authors' contributions MC, HZ and JQF contributed to the conception and design of the study protocol. The search strategy was developed and run by HZ and JL, who will also screen the title and abstract of the studies after running the search strategy. MC and QC will screen full copies of remaining studies after title and abstract selection. HZ and JL will extract information of included studies and enter into electronic database; QC will check the accuracy and completeness of the data entry. DQH and JQF will give analysis suggestions for during data synthesis. All the authors drafted and revised this study protocol and approved for publication.

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Competing interests None.

REFERENCE

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best practice & research. Clinical gastroenterology 2011;**25**(1):3-18 doi: 10.1016/j.bpg.2010.12.010[published Online First: Epub Date]|.
2. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC gastroenterology 2008;**8**:5 doi: 10.1186/1471-230x-8-5[published Online First: Epub Date]|.
3. Iraji N, Keshteli AH, Sadeghpour S, Daneshpajouhnejad P, Fazel M, Adibi P. Constipation in Iran: SEPAHAN Systematic Review No. 5. International journal of preventive medicine 2012;**3**(Suppl 1):S34-41
4. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. The American journal of gastroenterology 2011;**106**(9):1582-91; quiz 81, 92 doi: 10.1038/ajg.2011.164[published Online First: Epub Date]|.
5. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. The American journal of gastroenterology 2004;**99**(4):750-9 doi: 10.1111/j.1572-0241.2004.04114.x[published Online First: Epub Date]|.
6. Belsey JD, Geraint M, Dixon TA. Systematic review and meta analysis: polyethylene glycol in adults with non-organic constipation. International journal of clinical practice 2010;**64**(7):944-55 doi: 10.1111/j.1742-1241.2010.02397.x[published Online First: Epub Date]|.
7. Pashankar DS, Loening-Baucke V. Increased prevalence of obesity in children with functional constipation evaluated in an academic medical center. Pediatrics 2005;**116**(3):e377-e80
8. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. Journal of managed care pharmacy : JMCP 2013;**19**(9):755-674
9. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;**60**(2):209-18 doi: 10.1136/gut.2010.227132[published Online First: Epub Date]|.
10. Shin A, Camilleri M, Kolar G, Erwin P, West CP, Hassan Murad M. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag or naronapride) in chronic constipation. Alimentary pharmacology & therapeutics 2013 doi: 10.1111/apt.12571[published Online First: Epub Date]|.
11. Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. The American journal of gastroenterology 2013;**108**(10):1566-74; quiz 75 doi: 10.1038/ajg.2013.169[published Online First: Epub Date]|.
12. Lin LW, Fu YT, Dunning T, et al. Efficacy of traditional Chinese medicine for the management of constipation: a systematic review. Journal of alternative and complementary medicine (New York, N.Y.) 2009;**15**(12):1335-46 doi: 10.1089/acm.2008.0373[published Online First: Epub Date]|.

13. Cheng CW, Bian ZX, Wu TX. Systematic review of Chinese herbal medicine for functional constipation. World journal of gastroenterology : WJG 2009;**15**(39):4886-95
14. Tabbers MM, Boluyt N, Berger MY, Benninga MA. Nonpharmacologic treatments for childhood constipation: systematic review. Pediatrics 2011;**128**(4):753-61 doi: 10.1542/peds.2011-0179[published Online First: Epub Date]|.
15. Zhang T, Chon TY, Liu B, et al. Efficacy of acupuncture for chronic constipation: a systematic review. The American journal of Chinese medicine 2013;**41**(4):717-42 doi: 10.1142/s0192415x13500493[published Online First: Epub Date]|.
16. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Alimentary pharmacology & therapeutics 2011;**33**(8):895-901 doi: 10.1111/j.1365-2036.2011.04602.x[published Online First: Epub Date]|.
17. Jarrett ME, Mowatt G, Glazener CM, et al. Systematic review of sacral nerve stimulation for faecal incontinence and constipation. The British journal of surgery 2004;**91**(12):1559-69 doi: 10.1002/bjs.4796[published Online First: Epub Date]|.
18. Lee MS, Choi TY, Park JE, Ernst E. Effects of moxibustion for constipation treatment: a systematic review of randomized controlled trials. Chinese medicine 2010;**5**:28 doi: 10.1186/1749-8546-5-28[published Online First: Epub Date]|.
19. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. World journal of gastroenterology : WJG 2010;**16**(1):69-75
20. Bharucha AE, Pemberton JH, Locke GR, 3rd. American Gastroenterological Association technical review on constipation. Gastroenterology 2013;**144**(1):218-38 doi: 10.1053/j.gastro.2012.10.028[published Online First: Epub Date]|.
21. Lindberg G, Hamid SS, Malfertheiner P, et al. World Gastroenterology Organisation global guideline: Constipation--a global perspective. Journal of clinical gastroenterology 2011;**45**(6):483-7 doi: 10.1097/MCG.0b013e31820fb914[published Online First: Epub Date]|.
22. JPT CHH, Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. The Cochrane Collaboration 2011

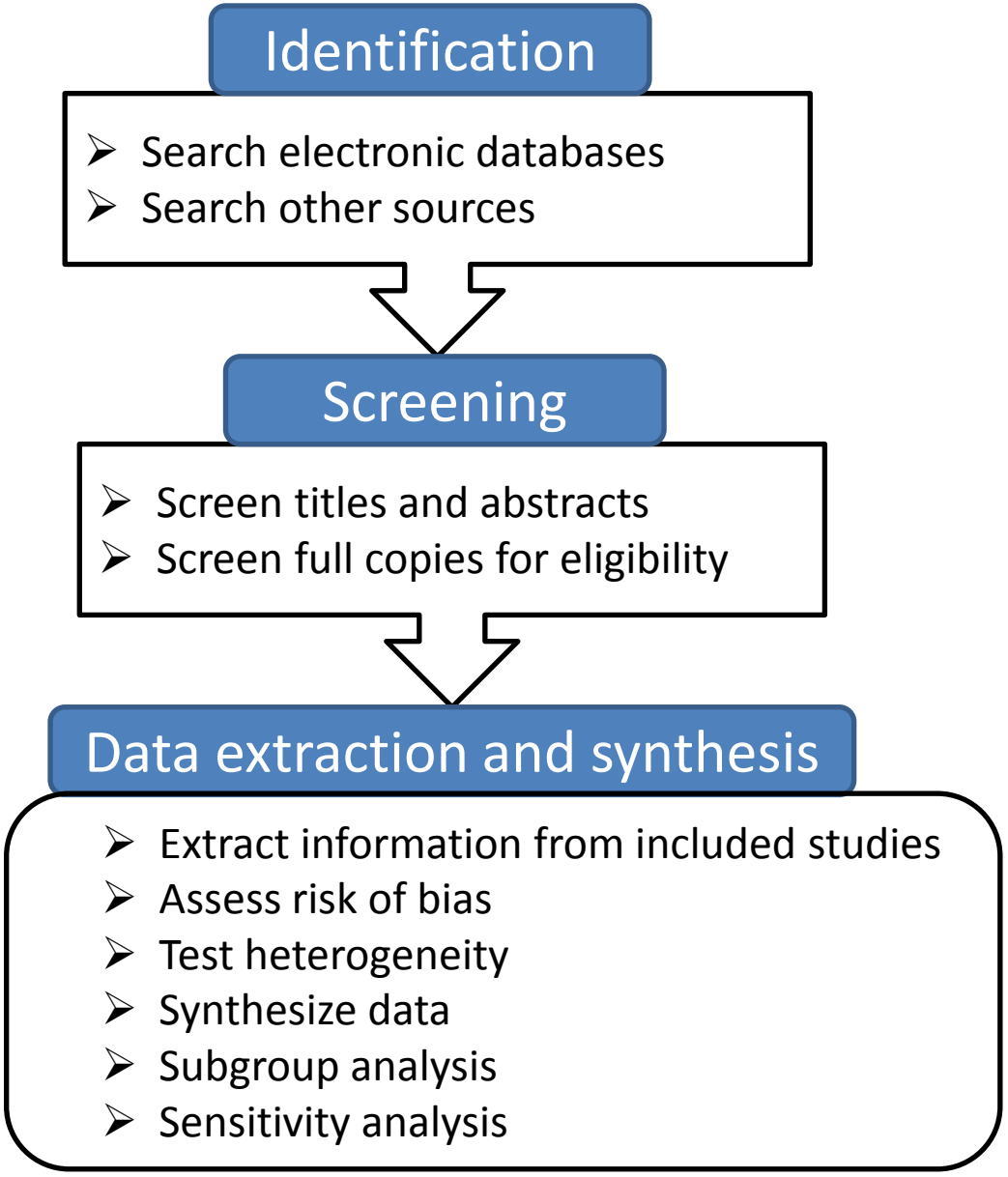

Table 1 Search strategy used in OVID MEDLINE database

No.	Search terms
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	randomised.ab.
5	placebo.ab.
6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp constipation/
11	functional constipation. ti, ab. {Including Related Terms}
12	idiopathic constipation. ti, ab. {Including Related Terms}
13	slow transit constipation. ti, ab. {Including Related Terms}
14	10 or 11 or 12 or 13
15	nonpharmacological. ti, ab. {Including Related Terms}
16	non pharmacological. ti, ab. {Including Related Terms}
17	nonpharmacologic. ti, ab. {Including Related Terms}
18	non pharmacologic. ti, ab. {Including Related Terms}
19	dietary fiber. sh, ti, ab. {Including Related Terms}
20	probiotics. sh, ti, ab. {Including Related Terms}
21	behavioral medicine. sh, ti, ab. {Including Related Terms}
22	cognitive therapy. sh, ti, ab. {Including Related Terms}
23	biofeedback. sh, ti, ab. {Including Related Terms}
24	fluid therapy. sh, ti, ab. {Including Related Terms}
25	acupuncture. sh, ti, ab. {Including Related Terms}
26	massage. sh, ti, ab. {Including Related Terms}
27	ear acupuncture. sh, ti, ab. {Including Related Terms}
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	9 and 14 and 28

This search strategy was modified to be suitable for other electronic databases.

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Primary Subject Heading:	Complementary medicine
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Protocol registration: PROSPERO 2014: CRD42014006686

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first systematic review protocol to assess the effectiveness, efficacy and safety of non-pharmacological therapies for adult patients with functional constipation.
- The results of this systematic review will help clinicians making decisions in clinical practice, and help functional constipation patients seeking more treatment options.
- Difficult to locate all the non-pharmacological treatments for functional constipation may be the limitation of this systematic review, we will use several steps advised by specialists in informatics to ensure a broad search for studies.

INTRODUCTION

Functional constipation (FC) is a common clinical condition without any specific physiological causes. The prevalence of constipation ranged from 0.7% to 81% around the world[1 2], whereas the prevalence of FC varied from 2.4% to 27.2%[3-5]. A mean prevalence for FC is reported to be 14% in a recent systematic review[4]. FC is a chronic and refractory condition; a study showed that 89% of the constipated patients still reported constipation during a mean follow-up period of 14.7 months[5]. Constipation symptoms significantly reduce the patients' quality of life, both mentally and physically[2 6]. Additionally, it is reported that constipation is related to higher possibility of obesity[7]. Direct cost of chronic FC for each patient ranged from $1912 to $7522 per year[8]. Considering that FC brings significant impact on quality of life and influences physical and emotional well-being, it should be considered as a major public health problem.

Lots of therapies were used to manage constipation symptoms for FC patients, such as laxatives, selective 5-HT4 agonists, etc. Recent systematic reviews reported that Laxatives, prucalopride, lubiprostone and linaclotide are effective for managing FC compared to placebo, however, more events of diarrhea were reported[9]. Similar findings were discovered in several recent reviews that pharmacological therapies are effective for relieving constipation symptoms, but more adverse events happened in patients receiving those treatments[10 11]. Traditional herbal medicine was reported to be helpful with less adverse events in the treatment of FC, however, recent reviews concluded that more trials with rigorous design are needed to confirm the effectiveness of traditional herbal medicine for FC[12 13].

Non-pharmacological therapies are popular among patients with FC; however, most of them were lack of evidence support. A systematic review reporting non-pharmacological treatments for pediatric constipation concluded that, there is a lack of well-designed randomized controlled trials to verify whether these treatments are effective[14]. Although several non-pharmacological therapies were claimed to be beneficial for FC patients[15-19], most of them were lack of evidence support. Therefore, we raised the following questions: 1. Are non-pharmacological therapies effective and efficacious for patients with FC? 2. If so, are non-pharmacological therapies safe for patients with FC? To answer these questions, we will conduct a systematic review of non-pharmacological therapies for patients with functional constipation, hoping to find the answers. In this article, we present a protocol of the systematic review.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Types of studies

Before starting this review, we have done a pre-search to get a general understanding of recent studies on this topic. We found a few randomized controlled trials. To ensure the reliability of the evidence, we agreed that it is reliable and feasible to include randomized controlled trials only for this review. Furthermore, we found that crossover design was not common in trials studying non-pharmacological treatments, because the washout periods of these interventions could not be accurately evaluated, which may bring bias to outcome assessments. Therefore, we

will only include randomized controlled trial with parallel design. And we will include trials using open label, single blind or double blind design.

Types of participants

We will include participants who were diagnosed as functional constipation according to ROME II or III criteria in this systematic review. Participants will be included if ROME II or III criteria was not mentioned in literatures, but were excluded for specific pathological causes, such as underlying structural or metabolic diseases. We will focus on constipation in the adult population, so trials included participants with age under 18 will be excluded.

Types of interventions

We plan to include trials testing non-pharmacological treatments. So after we search the databases, we will first exclude trials using any pharmacological interventions, including pharmaceutics, herbs, traditional medicine, etc. Second, we will include trials that non-pharmacological treatments were used at least once a week for a minimum total of 4 weeks. We will not limit the procedure of the non-pharmacological interventions, e.g., manipulation methods of acupuncture or massage will not be a necessary judgment for inclusion. To assess the effectiveness of non-pharmacological treatments, we plan to compare them with positive control. According to the guideline and recent systematic reviews[10 20 21], laxatives, selective 5-HT4 agonists, patient's education are reported to be effective for managing constipation, so we will set these interventions as positive controls. To assess the efficacy of non-pharmacological treatments, we plan to compare these treatments with placebo control, which includes placebo drugs, sham interventions, etc.

Types of outcome assessments

The primary outcome of this review will be the mean spontaneous bowel movements per week, at the first week after finishing all treatment sessions. Since the non-pharmacological treatment sessions are different across studies, so it is impossible to define an exact time point for the primary outcome. Therefore, we agree that after finish of treatment is a relatively suitable time point for primary outcome assessment. The secondary outcomes will be proportion of responders, mean transit time, proportion of patients using laxatives, quality of life (QOL) and proportion of adverse events. The proportion of responders is defined by that we count up the number of responders (participants responded to the treatment and was reported as responders in the included trials) in each study, and calculate the proportion of them. The transit time is defined as the time from the first perception of wanting to defecate to finish of the defecation, and we will calculate the mean transit time. The participants who used laxatives (types of the laxatives will not be limited in this review) during the trial will be counted up, and we will calculate the proportion of patients using laxatives. The outcome QOL will be measured by scales that normally used by constipation studies, such as The Short Form 36 Health Surveys (SF-36), etc. We will sum up the number of patients reporting adverse events in each study, and calculate the proportion of adverse events.

The workflow of this systematic review is shown in figure 1.

Search methods for identification of studies

Electronic searches

We will electronically search the following database OVID MEDLINE, EMBASE, Cochrane library, CINAHL, AMED and ISI web of knowledge from inception to 2014, without any language restrictions. The search strategy will be developed after a discussion among reviewers,

according to the guidance of the Cochrane handbook[22]. To ensure a broad search, we will include the medical subject headings (Mesh) such as randomized controlled trial, constipation, etc. Titles, abstracts and subject headings will also be searched for the above Mesh words and several other words related to randomized controlled trials, functional constipation, etc. The search strategy for OVID MEDLINE is shown in table 1.

Other sources

Potentially eligible studies will also be obtained through the following methods:

- Review the reference list of the previously published reviews for possible candidates;
- If applicable, we will review the conference abstract to find out the unpublished trials, and contact the authors for the data;
- Hand search a list of medical journals in the university library, such as Chinese Medical Journal, etc.

Data collection and analysis

Selection of studies

Before a selection of studies, a procedure for screening will be developed by discussion among all the reviewers. After electronic searches, the outputs will be cited in a database created by endnote software (version X6). Studies obtained from other sources will also be cited in the same database. Two reviewers (HZ and JL) will independently screen the titles and abstracts in this database through the following steps: first, find out the duplicates (studies published in different languages, or studies published as a journal article as well as a conference abstract, or at least two articles reported the same trial in different aspects); second, exclude studies in which participants receiving pharmacological treatment in an experimental group or participants were diagnosed as constipation due to structural or metabolic diseases; third, exclude studies which were not designed as randomized controlled trials with parallel design; fourth, exclude studies in which participants under the age of 18 were recruited. Full copies will be achieved, if the reviewers (HZ and JL) could not clearly screen studies based on titles and abstracts. And another two reviewers (MC and QC) will screen the full copies of these studies. If disagreements occur between reviewers during screening, they will be resolved through discussion and consensus. If the disagreement persists, a third author (DQH or JQF) will be consulted.

Data extraction and management

Before data extraction, all the reviewers will discuss and develop a standardized data extraction form. We will extract information from at least 3 studies using this form to check its applicability. Two independent reviewers (HZ and JL) will extract the following information from the studies: organizational aspects (including reference ID, reviewer's name, the first author of the article, year of publication, publication source, etc.), trial characteristics (design of the study, number of participants, number of groups, method of randomization, method of allocation concealment, blinding, primary aims of the study, etc.), participants (age, ethnicity, gender, diagnosis, concurrent conditions, laboratory parameters, etc.), interventions and controls (name of the intervention, length of treatment, type and name of a control, information for care providers, additional treatment, etc.), outcome measurements (type of outcome, definition of the outcome, time point of an assessment, length of follow-up, etc.), results (name of the outcome, mean, standard deviation, observed events after intervention, total sample size, etc.) , other research information. When there is discrepancy between the two reviewers, consensus will achieved by discussion among all the reviewers. The extraction data will be entered into R project 3.02

(www.r-project.org), and QC will check the data to ensure there are no data entry errors.

Assessment of risk of bias in included studies

Two reviewers (MC and HZ) will independently assess the risk of bias, using the Cochrane collaboration's tool for assessing risk of bias of the included trials[22], which is composed of six domains of a trial, such as sequence generation, allocation concealment, blinding, incomplete data, etc. After assessing all the domains, the reviewers will summarize the assessments, and categorize the included trials into 3 levels of bias: low, unclear and high risk of bias.

Measures of treatment effect

We will calculate the risk ratio (RR) for the dichotomous data during synthesis, and provide p values for comparison of experimental group with control. For continuous data, we will calculate the weighted mean differences (WMD) if all the studies using the same measurement tool and the same unit, if not, we will calculate the standardized mean difference (SMD). We will calculate 95% confidence intervals (95%CI) for RR, WMD or SMD.

Unit of analysis issues

In this review, we include data from parallel design trials. And if there are multiple observations at different time points, we will defined the data assessed within 4 weeks as short-term outcomes, and those assessed over 4 weeks as long-term outcomes. As most of the treatment length of non-pharmacological therapies will usually last at least 4 weeks, so we will focus on the long-term outcomes in the analysis.

Dealing with missing data

If there are missing data in the included studies, we will try to contact the investigators of the included studies to get original data for analysis. If we could not access the missing data, we will exclude the studies with missing data and synthesize the rest of the included studies.

Assessment of heterogeneity

Before this meta-analysis, we will perform a heterogeneity examination, using the Higgins I^2 test. We will calculate the I^2statistics to find out if there are inconsistencies among the included trials. We will set a cut-off point of 50% for the I^2statistics. An I^2>50% will be considered as an existence of significant heterogeneity among studies. In that case, we will perform a meta-regression analysis to find out the source of the heterogeneity. Moreover, we will run subgroup analysis according to the source of the heterogeneity. Additionally, we will combine the outcome using a random effect model when the significant heterogeneity exist, and explain the results with caution.

Assessment of reporting biases

We will use funnel plots to assess reporting biases as well as small study effects. If 10 or more studies are included in a meta-analysis, we will use Egger's method to test funnel plot asymmetry.

Data synthesis

Data synthesis will be performed using R project 3.02 (www.r-project.org). For dichotomous data, we will combine RR of each study and calculate 95%CI using fixed effect model, if no heterogeneity is detected. And if significant heterogeneity is found, we will combine the data using random effect model and explain the results with caution. Moreover, we will provide a p value for a comparison of non-pharmacological therapies with positive drug control, sham intervention control or waiting list control. For continuous data, we will combine the WMD of each study and compute the 95%CI, if the same outcome measurement is used; if not, we will

combine SMD instead. Additionally, we will also choose fixed or random effect model according to the result of heterogeneity test, and provide p values.

Subgroup analysis

Non-pharmacological treatments will include a lot different therapies, so we will first calculate the overall effect size of all the treatments. Second, we will perform a subgroup analysis according to different non-pharmacological treatments, which is considered to be the most significant source of heterogeneity among studies. Also, we will run subgroup analysis according to the source of the heterogeneity using meta-regression method.

Sensitivity analysis

First, we will assess the impact of including studies with high risk of bias on the results of this review. So we will compare the results of excluding studies with high risk of bias with those not, to find that if the results are consistent. Second, to clarify whether different models affect the results of data synthesis, we combine the outcomes using both fixed and random effect models, and check if the results remain the same. Third, to assess the impact of sample size on the results of this review, we will compare the results of excluding small sample size trials (< 100 participants) to those not.

Ethics and dissemination

This systematic review does not need ethical approval because data we used will not be linked to individual data and privacy. The results of this review will provide a general view and evidence of non-pharmacological treatments for the management of functional constipation. The findings of this review will also give implication for clinical practice and further research, and will be disseminated by a peer-review publication and conference presentations.

DISCUSSION

In this article, we present a protocol of a systematic review of using non-pharmacological treatments to treat functional constipation, which is becoming a major public health problem. The most difficult part of this review is to define non-pharmacological interventions and to run a broad search for them. After a consultation with the specialists of informatics, we decided to locate the studies we want to include through 3 steps: first, we use keywords related to non-pharmacological treatments, we also use non-pharmacological interventions commonly applied in clinical practice as search keywords, such as dietary fiber, probiotics, acupuncture, moxibustion, etc. Second, after running search strategy, we will screen the titles and abstracts to exclude studies using any pharmacological interventions. Third, we will screen the full copies of the potential studies to ensure we locate the correct studies.

The second difficult part of this review is to define the condition functional constipation in the studies. We consulted several specialists in the field of gastroenterology, who suggested that it will better to include studies using ROME II or III as diagnostic criteria in this review. So we took the advice, moreover, we use the several keywords in addition to functional constipation, such as constipation, idiopathic constipation, etc., to ensure that we run a broad search of studies on this topic.

How to deal with missing data is also a major concern in this protocol. According to the Cochrane handbook[22], there are 4 options for dealing with missing data. After discussion, we agree that analyzing only the available data will be the best choice, because imputing the missing data may cause bias to the results.

The strength of this review lies in that the results will give an overview of current evidence on non-pharmacological treatments for adult patients with functional constipation. The limitations of this review may be that, first, we focus on the adult population only, because there is a recent systematic review studying the effectiveness of non-pharmacological therapies for pediatric constipation[14], however, this may restrict the generalization of the results; second, we define the primary outcome of this protocol as the mean spontaneous bowel movements per week at the first week after finishing all treatment sessions, which may introduce bias to the results since treatment session may be different across studies. But after discussion, we agree that defining a specific time point (e.g., 4 weeks after randomization) may bring a higher risk of bias, since different studies used different assessment time points.

This systematic review will give a summary of the current evidence on the effectiveness and safety of non-pharmacological therapies for patients with FC. And this review will benefit FC patients and care providers for that they will have more treatment options.

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Authors' contributions MC, HZ and JQF contributed to the conception and design of the study protocol. The search strategy was developed and run by HZ and JL, who will also screen the title and abstract of the studies after running the search strategy. MC and QC will screen full copies of remaining studies after title and abstract selection. HZ and JL will extract information of included studies and enter into electronic database; QC will check the accuracy and completeness of the data entry. DQH and JQF will give analysis suggestions for during data synthesis. All the authors drafted and revised this study protocol and approved for publication.

Competing interests None.

Figure legend

Figure 1 The flowchart of performing the systematic review

REFERENCE

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best practice & research. Clinical gastroenterology 2011;**25**(1):3-18 doi: 10.1016/j.bpg.2010.12.010[published Online First: Epub Date]|.
2. Peppas G, Alexiou VG, Mourtzoukou E, et al. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC gastroenterology 2008;**8**:5 doi: 10.1186/1471-230x-8-5[published Online First: Epub Date]|.
3. Iraji N, Keshteli AH, Sadeghpour S, et al. Constipation in Iran: SEPAHAN Systematic Review No. 5. International journal of preventive medicine 2012;**3**(Suppl 1):S34-41
4. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. The American journal of gastroenterology 2011;**106**(9):1582-91; quiz 81, 92 doi: 10.1038/ajg.2011.164[published Online First: Epub Date]|.
5. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. The American journal of gastroenterology 2004;**99**(4):750-9 doi: 10.1111/j.1572-0241.2004.04114.x[published Online First: Epub Date]|.
6. Belsey JD, Geraint M, Dixon TA. Systematic review and meta analysis: polyethylene glycol in adults with non-organic constipation. International journal of clinical practice 2010;**64**(7):944-55 doi: 10.1111/j.1742-1241.2010.02397.x[published Online First: Epub Date]|.
7. Pashankar DS, Loening-Baucke V. Increased prevalence of obesity in children with functional constipation evaluated in an academic medical center. Pediatrics 2005;**116**(3):e377-e80
8. Nellesen D, Yee K, Chawla A, et al. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. Journal of managed care pharmacy : JMCP 2013;**19**(9):755-674
9. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;**60**(2):209-18 doi: 10.1136/gut.2010.227132[published Online First: Epub Date]|.
10. Shin A, Camilleri M, Kolar G, et al. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag or naronapride) in chronic constipation. Alimentary pharmacology & therapeutics 2013 doi: 10.1111/apt.12571[published Online First: Epub Date]|.
11. Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. The American journal of gastroenterology 2013;**108**(10):1566-74; quiz 75 doi: 10.1038/ajg.2013.169[published Online First: Epub Date]|.
12. Lin LW, Fu YT, Dunning T, et al. Efficacy of traditional Chinese medicine for the management of constipation: a systematic review. Journal of alternative and complementary medicine (New York, N.Y.) 2009;**15**(12):1335-46 doi: 10.1089/acm.2008.0373[published Online First: Epub Date]|.
13. Cheng CW, Bian ZX, Wu TX. Systematic review of Chinese herbal medicine for functional constipation. World journal of gastroenterology : WJG 2009;**15**(39):4886-95
14. Tabbers MM, Boluyt N, Berger MY, et al. Nonpharmacologic treatments for childhood constipation: systematic review. Pediatrics 2011;**128**(4):753-61 doi: 10.1542/peds.2011-0179[published

Online First: Epub Date]|.

15. Zhang T, Chon TY, Liu B, et al. Efficacy of acupuncture for chronic constipation: a systematic review. The American journal of Chinese medicine 2013;**41**(4):717-42 doi: 10.1142/s0192415x13500493[published Online First: Epub Date]|.
16. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Alimentary pharmacology & therapeutics 2011;**33**(8):895-901 doi: 10.1111/j.1365-2036.2011.04602.x[published Online First: Epub Date]|.
17. Jarrett ME, Mowatt G, Glazener CM, et al. Systematic review of sacral nerve stimulation for faecal incontinence and constipation. The British journal of surgery 2004;**91**(12):1559-69 doi: 10.1002/bjs.4796[published Online First: Epub Date]|.
18. Lee MS, Choi TY, Park JE, et al. Effects of moxibustion for constipation treatment: a systematic review of randomized controlled trials. Chinese medicine 2010;**5**:28 doi: 10.1186/1749-8546-5-28[published Online First: Epub Date]|.
19. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. World journal of gastroenterology : WJG 2010;**16**(1):69-75
20. Bharucha AE, Pemberton JH, Locke GR, 3rd. American Gastroenterological Association technical review on constipation. Gastroenterology 2013;**144**(1):218-38 doi: 10.1053/j.gastro.2012.10.028[published Online First: Epub Date]|.
21. Lindberg G, Hamid SS, Malfertheiner P, et al. World Gastroenterology Organisation global guideline: Constipation--a global perspective. Journal of clinical gastroenterology 2011;**45**(6):483-7 doi: 10.1097/MCG.0b013e31820fb914[published Online First: Epub Date]|.
22. JPT CHH, Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. The Cochrane Collaboration 2011

Table 1 Search strategy used in OVID MEDLINE database

No.	Search terms
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	randomised.ab.
5	placebo.ab.
6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp constipation/
11	functional constipation. ti, ab. {Including Related Terms}
12	idiopathic constipation. ti, ab. {Including Related Terms}
13	slow transit constipation. ti, ab. {Including Related Terms}
14	10 or 11 or 12 or 13
15	nonpharmacological. ti, ab. {Including Related Terms}
16	non pharmacological. ti, ab. {Including Related Terms}
17	nonpharmacologic. ti, ab. {Including Related Terms}
18	non pharmacologic. ti, ab. {Including Related Terms}
19	dietary fiber. sh, ti, ab. {Including Related Terms}
20	probiotics. sh, ti, ab. {Including Related Terms}
21	behavioral medicine. sh, ti, ab. {Including Related Terms}
22	cognitive therapy. sh, ti, ab. {Including Related Terms}
23	biofeedback. sh, ti, ab. {Including Related Terms}
24	fluid therapy. sh, ti, ab. {Including Related Terms}
25	acupuncture. sh, ti, ab. {Including Related Terms}
26	massage. sh, ti, ab. {Including Related Terms}
27	ear acupuncture. sh, ti, ab. {Including Related Terms}
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	9 and 14 and 28

This search strategy was modified to be suitable for other electronic databases.

Non-pharmacological ~~therapies~~ treatments for adult patients with functional constipation: a systematic review protocol

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Running Title: Non-pharmacological ~~therapies~~ treatments for constipation: a protocol

Keywords: Non-pharmacological ~~therapies~~treatments, constipation, systematic review, protocol

Word Count: 2830~~768~~

Abstract

Introduction: The aim of this review is to assess the effectiveness, efficacy and safety of non-pharmacological therapies for patients with functional constipation.
Methods and analysis: We will electronically search OVID MEDLINE, EMBASE, Cochrane library, CINAHL, AMED and ISI web of knowledge without any language restrictions. We will also try to obtain literatures from other sources, such as a hand search of ~~–~~library journals or conference abstracts. After searching and screening of the studies, we will run a meta-analysis of the included randomized controlled trials. We will summarize the results as risk ratio for dichotomous data, standardized or weighted mean difference for continuous data.
Dissemination: This systematic review will summarized current evidence for using non-pharmacological therapies to treat functional constipation, and will be disseminated through peer-review publication or conference presentation.
Protocol registration: PROSPERO 2014: CRD42014006686

Keywords: Non-pharmacological ~~therapies~~treatments, constipation, systematic review, protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first systematic review protocol to assess the effectiveness, efficacy and safety of non-pharmacological therapies for adult patients with functional constipation.
- The results of this systematic review will help clinicians making decisions in~~on~~ clinical practice, and help functional constipation patients seeking more treatment options.
- Difficult to locate all the non-pharmacological treatments for functional constipation may be the limitation of this systematic review, we will use several steps advised by specialists in informatics to ensure a broad search ~~of~~ for studies.

INTRODUCTION

Functional constipation (FC)~~,~~ is a common clinical condition without any specific physiological causes. The prevalence of constipation ranged from 0.7% to 81% around the world[1 2], whereas the prevalence of FC varied from 2.4% to 27.2%[3-5]. A mean prevalence for FC is reported to be 14% in a recent systematic review[4]. FC is a chronic and refractory condition; a study showed that 89% of the constipated patients still reported constipation during a mean follow-up period of 14.7 months[5]. Constipation symptoms significantly reduce the patients' quality of life, both mentally and physically[2 6]. Additionally, it is reported that constipation is related to higher possibility of ~~patients becoming obese~~obesity[7]. Direct cost of chronic FC for each patient ranged from $1912 to $7522 per year[8]. Considering that FC brings significant impact on quality of life~~,~~ and ~~influencing~~ influences physical and emotional well-being, it should be considered as a major public health problem.

Lots of therapies were used to manage constipation symptoms for FC patients, such as laxatives, selective 5-HT4 agonists, etc. Recent systematic reviews reported that Laxatives, prucalopride, lubiprostone and linaclotide are effective for managing FC compared to placebo,

however, more events of diarrhea were reported[9]. Similar findings were discovered in several recent reviews that pharmacological therapies are effective for relieving constipation symptoms, but more adverse events happened in patients receiving those treatments[10 11]. Traditional herbal medicine was reported to be helpful with less adverse events for relieving constipation symptoms in the treatment of FC, however, systematic reviews could not reach this conclusion, instead, recentthe reviews concluded that more trials with rigorous design are needed to confirm the effectiveness of traditional herbal medicine for FC[12 13].

Non-pharmacological therapies are popular among patients with FC; however, most of them were lack of evidence support. A systematic review focusing onreporting non-pharmacological treatments for children with constipationpediatric constipation concluded that, there is a lack of well-designed randomized controlled trials of high quality to verify whether these treatments wereare effective[14]. Although several non-pharmacological therapies were claimed to be beneficial for FC patients[15-19], but most of them were lack of evidence supportconcluded by systematic reviews that, firm conclusion could not be drawn due to lack of evidence support. Therefore, we raised the following questions: 1. Are non-pharmacological therapies effective and efficacious for patients with FC? 2. If so, are non-pharmacological therapies safe for patients with FC? To answer these questions, we will conduct a systematic review of non-pharmacological therapies for patients with functional constipation, hoping to find the answers. In this article, we present a protocol of the systematic review.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Types of studies

Before running starting ththeis review, we have done a pre-search to get a general understanding of recent studies on this topic. We found that there were a few randomized controlled trials, . so To ensure the reliability of the evidence, we agreed that including randomized controlled trials only it is reliable and feasible to include randomized controlled trials only for this review, to ensure the reliability of the evidence. Furthermore, we found that randomized controlled trials with crossover design werewas not common in trials studying non-pharmacological treatments, because the washout periods of these interventions could not be accurately evaluated, which may bring bias to outcome assessments. Therefore, we will only include randomized controlled trial with parallel design. And we will include trials using open label, single blind or double blind design.

Types of participants

We aim towill include participants who were diagnosed as functional constipation according to ROME II ofor III criteria in this systematic review. Participants were alsowill be included although if ROME II or III criteria was not mentioned in literatures, if theybut were diagnosed as constipation and were excluded for specific pathological causes, such as underlying structural or metabolic diseases. We will focus on constipation in the adult population, so trials included participants with age under 18 will be excluded.

Types of interventions

We plan to include trials, in which testing non--pharmacological treatments, were used in experimental group, including herbs, traditional medicine, etc. So after we search the databases, we will first exclude trials using any pharmacological interventions, including pharmaceutics,

herbs, traditional medicine, etc ~~after we search the databases~~. ~~After excluding articles reporting pharmaceutical treatments,~~ Second, we will include trials that non-pharmacological treatments were used at least once a week for a minimum total of 4 weeks. We will not limit the procedure of the non-pharmacological interventions, e.g., manipulation methods of acupuncture or massage will not be a necessary ~~for~~ judgment ~~of~~ for inclusion. To assess the effectiveness of non-pharmacological treatments, we plan to compare them with positive control. According to the guideline and recent systematic reviews[10 20 21], laxatives, selective 5-HT4 agonists, patient's education are reported to be effective for managing constipation, so we will set these interventions as positive controls. To assess the efficacy of non-pharmacological treatments, we plan to compare these treatments with placebo control, which includes placebo drugs, sham interventions, etc. ~~To measure the effect size of non-pharmacological treatments, we consider comparing these treatments with waiting list control.~~

Types of outcome assessments

The primary outcome of this review will be the mean spontaneous bowel movements per week, ~~improvement of bowel movement per week~~ at the first week after finishing all treatment sessions. Since the non-pharmacological treatment sessions are different across studies, so it is impossible to ~~make~~ define an exact time point for the primary outcome ~~measure~~. Therefore, we agree that after finish of treatment is a relatively suitable time point ~~ing~~ for primary outcome assessment. The secondary outcomes will be~~are~~ proportion of responders, mean transit time, proportion of patients using laxatives, quality of life (QOL) and proportion of adverse events. The ~~parameter~~ proportion of responders is defined by that we count up the number of responders (participants responded to the treatment and was reported as responders in the included trials) in each study, and calculate the proportion of them. The transit time is defined as the time from the first perception of wanting to defecate to finish of the defecation, and we will calculate the mean transit time. The participants who used laxatives (types of the laxatives will not be limited in this review) during the trial will be counted up, and we will calculate the proportion of patients using laxatives. The outcome QOL will be measured by scales that normally used by constipation studies, such as The Short Form 36 Health Surveys (SF-36), etc. We will sum up the number of patients reporting adverse events in each study, and calculate the proportion of adverse events.

The workflow of this systematic review is shown in figure 1.

Search methods for identification of studies

Electronic searches

We will electronically search ~~searched~~ the following database OVID MEDLINE, EMBASE, Cochrane library, CINAHL, AMED and ISI web of knowledge from inception to 2014 ~~from 2003 to 2013~~, without any language restrictions. The search strategy will be developed after a discussion among reviewers, according to the guidance of the Cochrane handbook[22]. To ensure a broad search, we ~~included~~ will include the medical subject headings (Mesh) such as randomized controlled trial, constipation, etc. Titles, abstracts and subject headings ~~were~~ will also be searched for the above Mesh words and several other words related to randomized controlled trials, functional constipation, etc. The search strategy for OVID MEDLINE ~~was~~ is shown in table 1.

Other sources

Potentially eligible studies will also be obtained through the following methods:

- Review the reference list of the previously published reviews for possible candidates;
- If applicable, we will review the conference abstract to find out the unpublished trials, and

contact the authors for the data;

- Hand search~~ing~~ a list of medical journals in the university library, such as Chinese Medical Journal, etc.

Data collection and analysis

Selection of studies

Before a selection of ~~the~~ studies, a procedure for screening will be developed by discussion among all the reviewers. After electronic searches, the outputs will be cited in a database created by endnote software (version X6). Studies obtained from other sources will also be cited in the same database. Two reviewers (HZ and JL) will independently screen the titles and abstracts in this database through the following steps: first, find out the duplicates (studies published in different languages, or studies published as a journal article as well as a conference abstract, or at least two articles reported the same trial in different aspects); second, exclude studies in which participants receiving pharmacological treatment in an experimental group or participants were diagnosed as constipation due to structural or metabolic diseases; third, exclude studies which were not designed as randomized controlled trials with parallel design; fourth, exclude studies in which participants under the age of 18 were recruited. Full copies will be achieved, if the reviewers (HZ and JL) could not clearly ~~exclude~~ screen studies based on titles and abstracts. And another two reviewers (MC and QC) will screen the full copies of these studies. If disagreements occur between reviewers during screening, they will be resolved through discussion and consensus. If the disagreement persists, a third author (DQH or JQF) will be consulted.

Data extraction and management

Before data extraction, all the reviewers will discuss and develop a standardized data extraction form~~, and~~. ~~w~~We will extract information from at least 3 studies using this form to check its applicability. Two independent reviewers (HZ and JL) ~~would~~ will extract the following information from the studies: organizational aspects (including reference ID, reviewer's name, the first author of the article, year of publication ~~year~~, publication source~~/journal~~, etc.), trial characteristics (design of the study, number of participants, number of groups, method of randomization, method of allocation concealment, blinding, primary aims of the study, etc.), participants (age, ethnicity, gender, diagnosis, concurrent conditions, laboratory parameters, etc.), interventions and controls (name of the intervention, length of treatment, type and name of a control, information for care providers, additional treatment, etc.), outcome measurements (type of outcome, definition of the outcome, time point of an assessment, length of follow-up, etc.), results (name of the outcome, mean, standard deviation, observed events after intervention, total sample size, etc.) , other research information. When there is discrepancy between the two reviewers, consensus will achieved by discussion among all the reviewers. The extraction data will be entered into R project 3.02 (www.r-project.org)~~Stata 12.0 (Stata Corp, College station, TX)~~, and QC will check the data to ensure there are no data entry errors.

Assessment of risk of bias in included studies

Two reviewers (MC and HZ) will independently assess the risk of bias ~~independently~~, using the Cochrane collaboration's tool for assessing risk of bias of the included trials[22], which is composed of six domains of a trial, such as sequence generation, allocation concealment, blinding, incomplete data, etc. After assessing all the domains, the reviewers will summarize the assessments, and categorize the included trials into 3 levels of bias: low, unclear and high risk of bias.

Measures of treatment effect

We will calculate the risk ratio (RR) for the dichotomous data during synthesis, and provide ~~the~~ p values for ~~the RR during~~ comparison of experimental group with control. For continuous data, we will calculate the weighted mean differences (WMD) if all the studies using the same measurement tool and the same unit, if not, we will calculate the standardized mean difference (SMD). We will calculate 95% confidence intervals (95%CI) ~~will be calculated~~ for RR, WMD or SMD.

Unit of analysis issues

In this review, we include data from parallel design trials. And if there are multiple observations at different time points, we will defined the data assessed within 4 weeks as short-term outcomes, and those assessed over 4 weeks as long-term outcomes. As most of the treatment length of non-pharmacological therapies will usually last at least 4 weeks, so we will focus on the long-term outcomes in the analysis.

Dealing with missing data

If there are missing data in the included studies, we will try to contact the investigators of the included studies to get ~~enough information~~original data for analysis. If we ~~fail to~~could not ~~contact the investigators and get~~access the missing data, we will ~~firstly~~ exclude the studies with missing data and synthesize the ~~evidence~~rest of the included studies~~,~~ . ~~and secondly use the worst-case strategy (missing values in experimental group will be categorized as poor outcomes, on the contrary, missing values in control group will be considered as good outcomes) . Lastly, we will perform a sensitivity analysis to find out whether the results of using the above two methods are consistent.~~

Assessment of heterogeneity

Before th~~is~~e meta-analysis, we will perform a heterogeneity examination, using the Higgins I^2 test. We will calculate the I^2statistics to find out if there are inconsistencies ~~in~~ among the included trials. We will set a cut-off point of 50% for the I^2statistics. An I^2>50% will be considered as an existence of significant heterogeneity among studies. In that case, we will perform a meta-regression analysis to find out the source of the heterogeneity. Moreover, we will run subgroup analysis according to the source of the heterogeneity. Additionally, we will combine the outcome using a random effect model when the significant heterogeneity exist, and~~but~~ explain the results with caution.

Assessment of reporting biases

We will use funnel plots to assess reporting biases as well as small study effects. If 10 or more studies are included in a meta-analysis, we will use Egger's method to test funnel plot asymmetry.

Data synthesis

Data synthesis will be performed using ~~Stata 12.0 (Stata Corp, College station, TX) and~~ R project 3.02 (www.r-project.org). For dichotomous data, we will combine RR of each study and calculate 95%CI using fixed effect model, if no heterogeneity is detected. And if significant heterogeneity is found, we will combine the data using random effect model and explain the results with caution. Moreover, we will provide a p value for a comparison of non-pharmacological therapies with positive drug control, sham intervention control or waiting list control. For continuous data, we will combine the WMD of each study and compute the 95%CI, if the same outcome measurement is used; if not, we will combine SMD instead. Additionally, we

will also choose fixed or random effect model according to the result of heterogeneity test, and provide p values.

Subgroup analysis

Non-pharmacological treatments will include a lot different therapies, so we will first calculate the overall effect size of all the treatments. Second, ~~W~~we will perform a subgroup analysis according to different non-pharmacological treatments, which is considered to be the most significant source of heterogeneity among studies. Also, we will run subgroup analysis according to the source of the heterogeneity using meta-regression ~~mothod~~method.

Sensitivity analysis

First~~, we will conduct a sensitivity analysis to assess the impact of missing data on the results of this review. In the analysis, we will compare the results of excluding studies with missing values to the results of using the worst-case strategy to combine the studies. Second~~, we will assess the impact of including studies with high risk of bias on the results of this review. So we will compare the results of excluding studies with high risk of bias with those not, to find that if the results are consistent. ~~Third~~Second, to clarify whether different models affect the results of data synthesis, we combine the outcomes using both fixed and random effect models, and check if the results remain the same. ~~Fourth~~Third, to assess the impact of sample size on the results of this review, we will compare the results of excluding small sample size trials (< 100 participants) to those not.

Ethics and dissemination

This systematic review does not need ethical approval because data we used will not be linked to individual data and privacy. The results of this review will provide a general view and evidence of non-pharmacological treatments for the management of functional constipation. The findings of this review will also give implication for clinical practice and further research, and will be disseminated by a peer-review publication and conference presentations.

DISCUSSION

In this article, we present a protocol of a systematic review of using non-pharmacological ~~therapies~~ treatments to treat functional constipation, which is becoming a major public health problem. The most difficult part of this review is to define non-pharmacological interventions and to run a broad search for them. After a consultation with the specialists of informatics, we decided to locate the studies we want to include through 3 steps: first, we use keywords related to non-pharmacological ~~therapies~~treatments, we also use non-pharmacological interventions commonly applied in clinical ~~pratice~~practice as search keywords, such as dietary fiber, probiotics, acupuncture, moxibustion, etc. Second, after running search strategy, we will screen the titles and abstracts to exclude studies using any pharmacological interventions. Third, we will screen the full copies of the potential studies to ensure we locate the correct studies.

The second difficult part of this review is to define the condition functional constipation in the studies. We consulted several specialists in the field of gastroenterology, who suggested that it will better to include studies using ROME II or III as diagnostic criteria in this review. So we took the advice, moreover, we use the several keywords in addition to functional constipation, such as constipation, idiopathic constipation, etc., to ensure that we run a broad search of studies on this topic.

How to deal with missing data is also a major concern in this protocol. According to the

Cochrane handbook[22], there are 4 options for dealing with missing data. After discussion, we agree that analyzing only the available data will be the best choice, because imputing the missing data may cause bias to the results.

The strength of this review lies in that the results will give an overview of current evidence on non-pharmacological treatments for adult patients with functional constipation. The limitations of this review may be that, first, we focus on the adult population only, because there is a recent systematic review studying the effectiveness of non-pharmacological therapies for pediatric constipation[14], however, this may restrict the generalization of the results; second, we define the primary outcome of this protocol as the mean spontaneous bowel movements per week at the first week after finishing all treatment sessions, which may introduce bias to the results since treatment session may be different across studies. But after discussion, we agree that defining a specific time point (e.g., 4 weeks after randomization) may bring a higher risk of bias, since different studies used different assessment time points.

This systematic review will give a summary of the current evidence on the effectiveness and safety of non-pharmacological therapies for patients with FC. And this review will benefit FC patients and care providers for that they will have more treatment options.

Authors' contributions MC, HZ and JQF contributed to the conception and design of the study protocol. The search strategy was developed and run by HZ and JL, who will also screen the title and abstract of the studies after running the search strategy. MC and QC will screen full copies of remaining studies after title and abstract selection. HZ and JL will extract information of included studies and enter into electronic database; QC will check the accuracy and completeness of the data entry. DQH and JQF will give analysis suggestions for during data synthesis. All the authors drafted and revised this study protocol and approved for publication.

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Competing interests None.

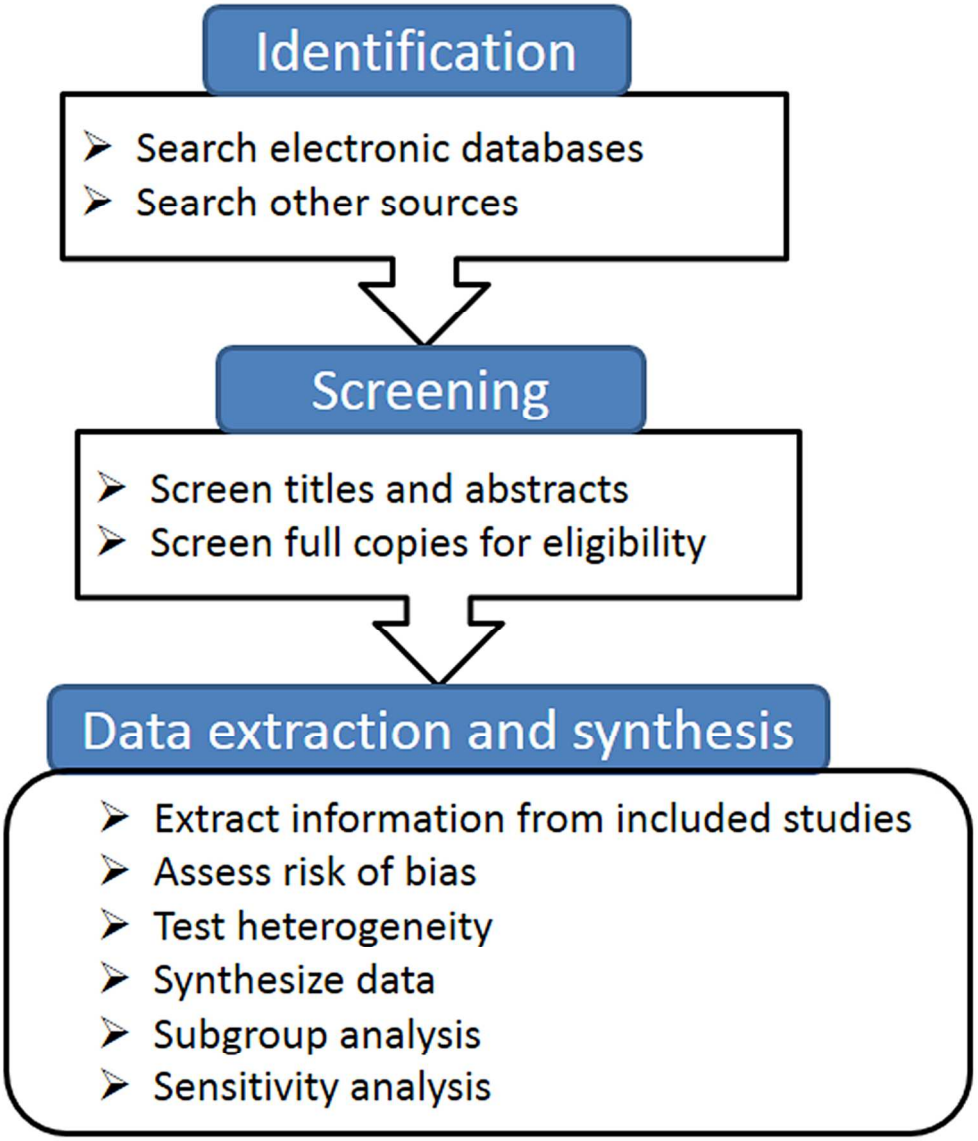
Figure 1 The flowchart of performing the systematic review

REFERENCE

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best practice & research. Clinical gastroenterology 2011;**25**(1):3-18 doi: 10.1016/j.bpg.2010.12.010[published Online First: Epub Date]|.
2. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC gastroenterology 2008;**8**:5 doi: 10.1186/1471-230x-8-5[published Online First: Epub Date]|.
3. Iraji N, Keshteli AH, Sadeghpour S, Daneshpajouhnejad P, Fazel M, Adibi P. Constipation in Iran: SEPAHAN Systematic Review No. 5. International journal of preventive medicine 2012;**3**(Suppl 1):S34-41

4. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. The American journal of gastroenterology 2011;**106**(9):1582-91; quiz 81, 92 doi: 10.1038/ajg.2011.164[published Online First: Epub Date]|.
5. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. The American journal of gastroenterology 2004;**99**(4):750-9 doi: 10.1111/j.1572-0241.2004.04114.x[published Online First: Epub Date]|.
6. Belsey JD, Geraint M, Dixon TA. Systematic review and meta analysis: polyethylene glycol in adults with non-organic constipation. International journal of clinical practice 2010;**64**(7):944-55 doi: 10.1111/j.1742-1241.2010.02397.x[published Online First: Epub Date]|.
7. Pashankar DS, Loening-Baucke V. Increased prevalence of obesity in children with functional constipation evaluated in an academic medical center. Pediatrics 2005;**116**(3):e377-e80
8. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. Journal of managed care pharmacy : JMCP 2013;**19**(9):755-674
9. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;**60**(2):209-18 doi: 10.1136/gut.2010.227132[published Online First: Epub Date]|.
10. Shin A, Camilleri M, Kolar G, Erwin P, West CP, Hassan Murad M. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag or naronapride) in chronic constipation. Alimentary pharmacology & therapeutics 2013 doi: 10.1111/apt.12571[published Online First: Epub Date]|.
11. Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. The American journal of gastroenterology 2013;**108**(10):1566-74; quiz 75 doi: 10.1038/ajg.2013.169[published Online First: Epub Date]|.
12. Lin LW, Fu YT, Dunning T, et al. Efficacy of traditional Chinese medicine for the management of constipation: a systematic review. Journal of alternative and complementary medicine (New York, N.Y.) 2009;**15**(12):1335-46 doi: 10.1089/acm.2008.0373[published Online First: Epub Date]|.
13. Cheng CW, Bian ZX, Wu TX. Systematic review of Chinese herbal medicine for functional constipation. World journal of gastroenterology : WJG 2009;**15**(39):4886-95
14. Tabbers MM, Boluyt N, Berger MY, Benninga MA. Nonpharmacologic treatments for childhood constipation: systematic review. Pediatrics 2011;**128**(4):753-61 doi: 10.1542/peds.2011-0179[published Online First: Epub Date]|.
15. Zhang T, Chon TY, Liu B, et al. Efficacy of acupuncture for chronic constipation: a systematic review. The American journal of Chinese medicine 2013;**41**(4):717-42 doi: 10.1142/s0192415x13500493[published Online First: Epub Date]|.
16. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Alimentary pharmacology & therapeutics 2011;**33**(8):895-901 doi: 10.1111/j.1365-2036.2011.04602.x[published Online First: Epub Date]|.
17. Jarrett ME, Mowatt G, Glazener CM, et al. Systematic review of sacral nerve stimulation for faecal incontinence and constipation. The British journal of surgery 2004;**91**(12):1559-69 doi: 10.1002/bjs.4796[published Online First: Epub Date]|.

18. Lee MS, Choi TY, Park JE, Ernst E. Effects of moxibustion for constipation treatment: a systematic review of randomized controlled trials. Chinese medicine 2010;**5**:28 doi: 10.1186/1749-8546-5-28[published Online First: Epub Date]|.
19. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. World journal of gastroenterology : WJG 2010;**16**(1):69-75
20. Bharucha AE, Pemberton JH, Locke GR, 3rd. American Gastroenterological Association technical review on constipation. Gastroenterology 2013;**144**(1):218-38 doi: 10.1053/j.gastro.2012.10.028[published Online First: Epub Date]|.
21. Lindberg G, Hamid SS, Malfertheiner P, et al. World Gastroenterology Organisation global guideline: Constipation--a global perspective. Journal of clinical gastroenterology 2011;**45**(6):483-7 doi: 10.1097/MCG.0b013e31820fb914[published Online First: Epub Date]|.
22. JPT CHH, Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. The Cochrane Collaboration 2011



The flowchart of performing the systematic review
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