



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

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# Non-pharmacological therapies for patients with functional constipation: a 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 summarize 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-HT<sub>4</sub> 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

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3 recent reviews that pharmacological therapies are effective for relieve constipation symptoms, but  
4 more adverse events happened in patients receiving those treatments[10 11]. Traditional herbal  
5 medicine was reported to be helpful with less adverse events for relieving constipation symptoms,  
6 however, systematic reviews could not reach this conclusion, instead, the reviews concluded that  
7 more trials with rigorous design are needed to confirm the effectiveness of traditional herbal  
8 medicine for FC[12 13].  
9

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

### 28 **Criteria for considering studies for this review**

#### 29 **Types of studies**

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

42  
43 We aim to include participants who were diagnosed as functional constipation according to  
44 ROME II or III criteria in this systematic review. Participants were also included although ROME  
45 II or III criteria was not mentioned, if they were diagnosed as constipation and excluded for  
46 specific pathological cause, such as underlying structural or metabolic diseases. We will focus on  
47 constipation in the adult population, so trials included participants with age under 18 will be  
48 excluded.  
49

#### 50 **Types of interventions**

51  
52 We plan to include trials, in which no pharmacological treatments were used in experimental  
53 group, including herbs, traditional medicine, etc. So we will first exclude trials using any  
54 pharmacological interventions, after we search the databases. After excluding articles reporting  
55 pharmaceutical treatments, we will include trials that non-pharmacological treatments were used  
56 at least once a week for a minimum total of 4 weeks. We will not limit the procedure of the  
57 non-pharmacological interventions, e.g., manipulation methods of acupuncture or massage will  
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3 not be necessary for judgment of inclusion. To assess the effectiveness of non-pharmacological  
4 treatments, we plan to compare them with positive control. According to the guideline and recent  
5 systematic reviews[10 20 21], laxatives, selective 5-HT4 agonists, patient's education are reported  
6 to be effective for managing constipation, so we set these interventions as positive controls. To  
7 assess the efficacy of non-pharmacological treatments, we plan to compare these treatments with  
8 placebo control, which includes placebo drugs, sham interventions, etc. To measure the effect size  
9 of non-pharmacological treatments, we consider comparing these treatments with waiting list  
10 control.  
11

### 12 13 **Types of outcome assessments**

14 The primary outcome of this review will be improvement of bowel movement per week after  
15 finishing all treatment sessions. Since the non-pharmacological treatment sessions are different  
16 across studies, so it is impossible to make an exact time point for primary outcome measure.  
17 Therefore, we agree that after finish of treatment is relatively suitable timing for primary outcome  
18 assessment. The secondary outcomes are proportion of responders, mean transit time, proportion  
19 of patients using laxatives, quality of life (QOL) and proportion of adverse events. The parameter  
20 proportion of responders is that we count up the number of responders (participants responded to  
21 the treatment and was reported as responders in the included trials) in each study, and calculate the  
22 proportion of them. The transit time is defined as the time from the first perception of wanting to  
23 defecate to finish of the defecation, and we will calculate the mean transit time. The participants  
24 who used laxatives (types of the laxatives will not be limited in this review) during the trial will be  
25 counted up, and we will calculate the proportion of patients using laxatives. The outcome QOL  
26 will be measured by scales that normally used by constipation studies, such as The Short Form 36  
27 Health Surveys (SF-36), etc. We will sum up the number of patients reporting adverse events in  
28 each study, and calculate the proportion of adverse events.  
29

### 30 **Search methods for identification of studies**

#### 31 **Electronic searches**

32 We electronically searched the following database OVID MEDLINE, EMBASE, Cochrane  
33 library, CINAHL, AMED and ISI web of knowledge from 2003 to 2013, without any language  
34 restrictions. The search strategy will be developed after a discussion among reviewers, according  
35 to the guidance of the Cochrane handbook[22]. To ensure a broad search, we included the medical  
36 subject headings such as randomized controlled trial, constipation, etc. Titles, abstracts and subject  
37 headings were also searched for the above Mesh words and several other words related to  
38 randomized controlled trials, functional constipation, etc. The search strategy for OVID  
39 MEDLINE was shown in table 1.  
40

#### 41 **Other sources**

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

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

### 48 **Data collection and analysis**

#### 49 **Selection of studies**

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

#### 21 Data extraction and management

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

#### 41 Assessment of risk of bias in included studies

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

#### 48 Measures of treatment effect

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

#### 56 Unit of analysis issues

57 In this review, we include data from parallel design trials. And if there are multiple  
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3 observations at different time points, we will defined the data assessed within 4 weeks as  
4 short-term outcomes, and those assessed over 4 weeks as long-term outcomes. As most of the  
5 treatment length of non-pharmacological therapies will usually last at least 4 weeks, so we will  
6 focus on the long-term outcomes in the analysis.  
7

#### 8 Dealing with missing data

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10 If there are missing data in the included studies, we will try to contact the investigators of the  
11 studies to get enough information. If we fail to contact the investigators and get the missing data,  
12 we will firstly exclude the studies with missing data and synthesize the evidence, and secondly use  
13 the worst-case strategy (missing values in experimental group will be categorized as poor  
14 outcomes, on the contrary, missing values in control group will be considered as good outcomes) .  
15 Lastly, we will perform a sensitivity analysis to find out whether the results of using the above two  
16 methods are consistent.  
17

#### 18 Assessment of heterogeneity

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20 Before the meta-analysis, we will perform a heterogeneity examination, using the Higgins  $I^2$   
21 test. We will calculate the  $I^2$  statistics to find out if there are inconsistencies in the included trials.  
22 We set a cut-off point of 50% for the  $I^2$  statistics. An  $I^2 > 50\%$  will be considered as existence of  
23 significant heterogeneity among studies. In that case, we will perform a meta-regression analysis  
24 to find out the source of the heterogeneity. Moreover, we will run subgroup analysis according to  
25 the source of the heterogeneity. Additionally, we will combine the outcome using a random effect  
26 model when the significant heterogeneity exist, but explain the results with caution.  
27

#### 28 Assessment of reporting biases

29  
30 We will use funnel plots to assess reporting biases as well as small study effects. If 10 or  
31 more studies are included in a meta-analysis, we will use Egger's method to test funnel plot  
32 asymmetry.  
33

#### 34 Data synthesis

35  
36 Data synthesis will be performed using Stata 12.0 (Stata Corp, College station, TX) and R  
37 project 3.02 (www.r-project.org). For dichotomous data, we will combine RR of each study and  
38 calculate 95%CI using fixed effect model, if no heterogeneity is detected. And if significant  
39 heterogeneity is found, we will combine the data using random effect model and explain the  
40 results with caution. Moreover, we will provide a p value for a comparison of  
41 non-pharmacological therapies with positive drug control, sham intervention control or waiting list  
42 control. For continuous data, we will combine the WMD of each study and compute the 95%CI, if  
43 the same outcome measurement is used; if not, we will combine SMD instead. Additionally, we  
44 will also choose fixed or random effect model according to the result of heterogeneity test, and  
45 provide p values.  
46

#### 47 Subgroup analysis

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49 We will perform a subgroup analysis according to different non-pharmacological treatments,  
50 which is considered to be the most significant source of heterogeneity among studies. Also, we  
51 will run subgroup analysis according to the source of the heterogeneity using meta-regression  
52 method.  
53

#### 54 Sensitivity analysis

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

#### 9 10 11 **Ethics and dissemination**

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

#### 17 18 **DISCUSSION**

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

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

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

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

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3 Science Foundation, grant number [81102656].  
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6 **Competing interests** None.  
7

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## Identification

- Search electronic databases
- Search other sources

## Screening

- Screen titles and abstracts
- Screen full copies for eligibility

## Data extraction and synthesis

- Extract information from included studies
- Assess risk of bias
- Test heterogeneity
- Synthesize data
- Subgroup analysis
- Sensitivity analysis

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**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.

# BMJ Open

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

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

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40 *protocol*

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42 Word Count: 2830



## 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 summarize 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 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 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-HT<sub>4</sub> 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

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

#### 5 6 **Types of participants**

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

#### 12 13 **Types of interventions**

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

#### 26 27 28 29 **Types of outcome assessments**

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

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

#### 51 52 **Search methods for identification of studies**

##### 53 **Electronic searches**

54 We will electronically search the following database OVID MEDLINE, EMBASE, Cochrane  
55 library, CINAHL, AMED and ISI web of knowledge from inception to 2014, without any  
56 language restrictions. The search strategy will be developed after a discussion among reviewers,  
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3 according to the guidance of the Cochrane handbook[22]. To ensure a broad search, we will  
4 include the medical subject headings (Mesh) such as randomized controlled trial, constipation, etc.  
5 Titles, abstracts and subject headings will also be searched for the above Mesh words and several  
6 other words related to randomized controlled trials, functional constipation, etc. The search  
7 strategy for OVID MEDLINE is shown in table 1.  
8

#### 9 Other sources

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

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

##### 19 Selection of studies

20 Before a selection of studies, a procedure for screening will be developed by discussion  
21 among all the reviewers. After electronic searches, the outputs will be cited in a database created  
22 by endnote software (version X6). Studies obtained from other sources will also be cited in the  
23 same database. Two reviewers (HZ and JL) will independently screen the titles and abstracts in  
24 this database through the following steps: first, find out the duplicates (studies published in  
25 different languages, or studies published as a journal article as well as a conference abstract, or at  
26 least two articles reported the same trial in different aspects); second, exclude studies in which  
27 participants receiving pharmacological treatment in an experimental group or participants were  
28 diagnosed as constipation due to structural or metabolic diseases; third, exclude studies which  
29 were not designed as randomized controlled trials with parallel design; fourth, exclude studies in  
30 which participants under the age of 18 were recruited. Full copies will be achieved, if the  
31 reviewers (HZ and JL) could not clearly screen studies based on titles and abstracts. And another  
32 two reviewers (MC and QC) will screen the full copies of these studies. If disagreements occur  
33 between reviewers during screening, they will be resolved through discussion and consensus. If  
34 the disagreement persists, a third author (DQH or JQF) will be consulted.  
35  
36

##### 37 Data extraction and management

38 Before data extraction, all the reviewers will discuss and develop a standardized data  
39 extraction form. We will extract information from at least 3 studies using this form to check its  
40 applicability. Two independent reviewers (HZ and JL) will extract the following information from  
41 the studies: organizational aspects (including reference ID, reviewer's name, the first author of the  
42 article, year of publication, publication source, etc.), trial characteristics (design of the study,  
43 number of participants, number of groups, method of randomization, method of allocation  
44 concealment, blinding, primary aims of the study, etc.), participants (age, ethnicity, gender,  
45 diagnosis, concurrent conditions, laboratory parameters, etc.), interventions and controls (name of  
46 the intervention, length of treatment, type and name of a control, information for care providers,  
47 additional treatment, etc.), outcome measurements (type of outcome, definition of the outcome,  
48 time point of an assessment, length of follow-up, etc.), results (name of the outcome, mean,  
49 standard deviation, observed events after intervention, total sample size, etc.), other research  
50 information. When there is discrepancy between the two reviewers, consensus will be achieved by  
51 discussion among all the reviewers. The extraction data will be entered into R project 3.02  
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(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  $I^2$  statistics to find out if there are inconsistencies among the included trials. We will set a cut-off point of 50% for the  $I^2$  statistics. 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.



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3 The strength of this review lies in that the results will give an overview of current evidence  
4 on non-pharmacological treatments for adult patients with functional constipation. The limitations  
5 of this review may be that, first, we focus on the adult population only, because there is a recent  
6 systematic review studying the effectiveness of non-pharmacological therapies for pediatric  
7 constipation[14], however, this may restrict the generalization of the results; second, we define the  
8 primary outcome of this protocol as the mean spontaneous bowel movements per week at the first  
9 week after finishing all treatment sessions, which may introduce bias to the results since treatment  
10 session may be different across studies. But after discussion, we agree that defining a specific time  
11 point (e.g., 4 weeks after randomization) may bring a higher risk of bias, since different studies  
12 used different assessment time points.  
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15 This systematic review will give a summary of the current evidence on the effectiveness and  
16 safety of non-pharmacological therapies for patients with FC. And this review will benefit FC  
17 patients and care providers for that they will have more treatment options.  
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9 **Authors' contributions** MC, HZ and JQF contributed to the conception and design of the study  
10 protocol. The search strategy was developed and run by HZ and JL, who will also screen the title  
11 and abstract of the studies after running the search strategy. MC and QC will screen full copies of  
12 remaining studies after title and abstract selection. HZ and JL will extract information of included  
13 studies and enter into electronic database; QC will check the accuracy and completeness of the  
14 data entry. DQH and JQF will give analysis suggestions for during data synthesis. All the authors  
15 drafted and revised this study protocol and approved for publication.  
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20 **Competing interests** None.  
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### 23 **Figure legend**

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26 Figure 1 The flowchart of performing the systematic review  
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**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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**Non-pharmacological therapies treatments for adult patients  
with functional constipation: a 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 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 ~~therapiestreatments~~, 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-obeseobesity[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 influenceing 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,

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

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

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## 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 ~~were~~ 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 ~~aim to will~~ include participants who were diagnosed as functional constipation according  
to ROME II ~~o~~ for III criteria in this systematic review. Participants ~~were also will be~~ included  
~~although if~~ ROME II or III criteria was not mentioned in literatures, ~~if they but 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 pharmaceuticals.

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

### Types of outcome assessments

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

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

### Search methods for identification of studies

#### Electronic searches

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

#### Other sources

51  
52 Potentially eligible studies will also be obtained through the following methods:

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

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3 contact the authors for the data;

- 4 > Hand searching a list of medical journals in the university library, such as Chinese Medical  
5 Journal, etc.  
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### 7 **Data collection and analysis**

#### 8 **Selection of studies**

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

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

51 Two reviewers (MC and HZ) will ~~independently~~ assess the risk of bias ~~independently~~, using  
52 the Cochrane collaboration's tool for assessing risk of bias of the included trials[22], which is  
53 composed of six domains of a trial, such as sequence generation, allocation concealment, blinding,  
54 incomplete data, etc. After assessing all the domains, the reviewers will summarize the  
55 assessments, and categorize the included trials into 3 levels of bias: low, unclear and high risk of  
56 bias.  
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### 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 this meta-analysis, we will perform a heterogeneity examination, using the Higgins  $I^2$  test. We will calculate the  $I^2$  statistics to find out if there are inconsistencies in among the included trials. We will set a cut-off point of 50% for the  $I^2$  statistics. 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, 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~~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 ~~therapiestreatments~~, we also use non-pharmacological interventions commonly applied in clinical ~~pratieeppractice~~ 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



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

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

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

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

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36 Science Foundation, grant number [81102656].

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39 **Competing interests** None.

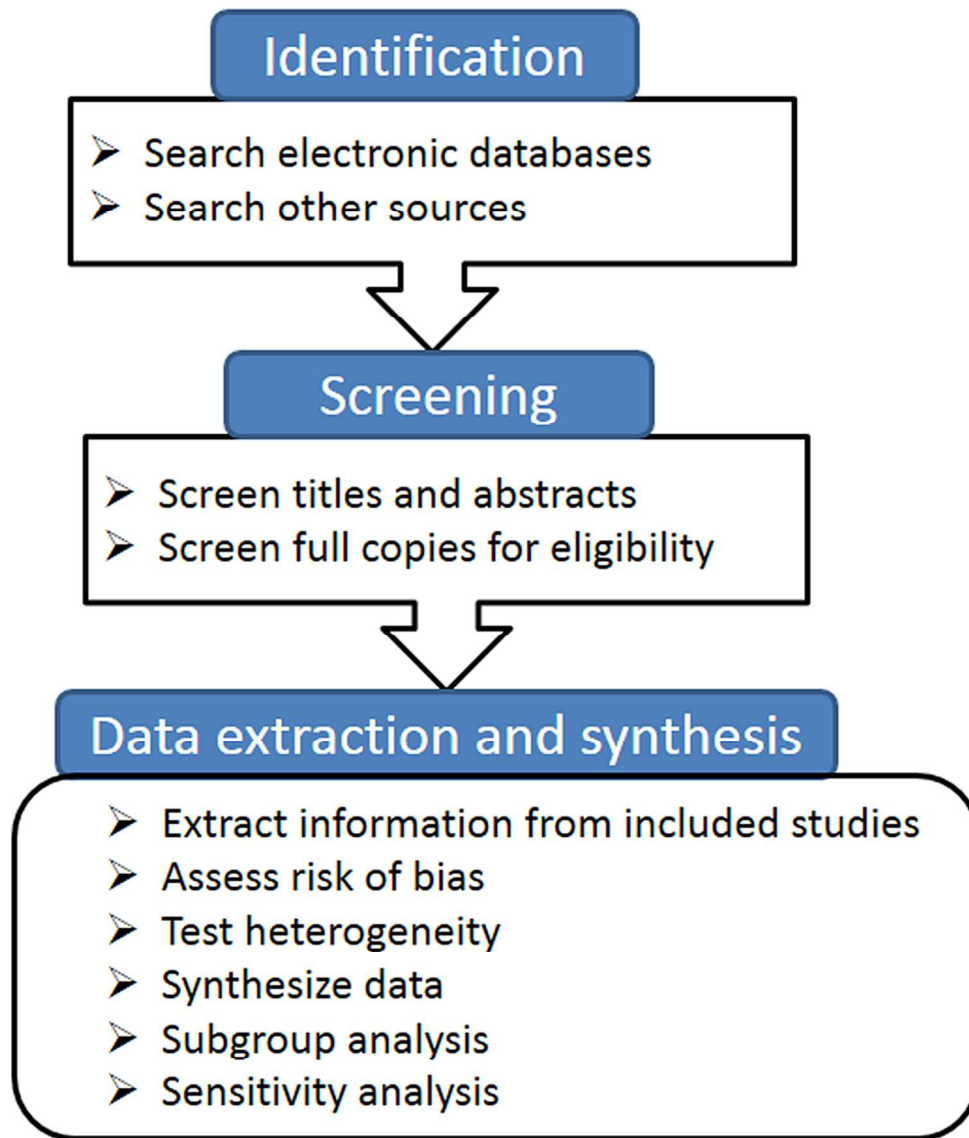
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42 [Figure 1 The flowchart of performing the systematic review](#)

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The flowchart of performing the systematic review  
90x104mm (300 x 300 DPI)