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Use acupuncture to treat functional constipation: a study protocol of an individual patient data meta-analysis

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ABSTRCT

Introduction: Functional constipation (FC) is a common gastrointestinal disease. Besides conventional western medicine, systematic reviews indicate that acupuncture may have effect on patients with FC. However, the conclusion is not convincing due to the quality, sample size, methodological heterogeneity of included studies. Therefore, it is necessary for us to conduct a meta-analysis of individual patient data (IPD) from high quality clinical trials to testify whether acupuncture is effective for FC patients.

Methods and analysis: Randomized controlled trials (RCTs) of acupuncture for adult patients with FC will be searched from several databases from inception to May, 2014. The corresponding authors of eligible studies will be contacted and invite to contribute the raw data. The primary outcome is the times of voluntary defecation per week after treatment. And the secondary outcomes include proportion of responders, the changes of stool quality, mean transit time, proportion of patients using laxatives and adverse events. We will check all data and perform re-analysis according to statistical methodology reported in previous publications. Then, we will harmonize the raw data and use the two-step method to conduct IPD meta-analysis. First, we will calculate the effect size of acupuncture of each trial by analysis of covariance, with the principal endpoint as the dependent variable and the baseline score as the covariates. Second, the effect size of acupuncture of each original study will be included into meta-analysis.

Dissemination: This review is based on the IPD meta-analysis of high quality RCTs about acupuncture treatment for patients with FC, which will answer whether acupuncture is effective for FC. The findings of this review will be disseminated through peer-review publications or conference presentations.

Trial registration number: PROSPERO 2014: CRD42014009901

Strengths and Limitations of this study

1. This article is a stud protocol of individual data meta-analysis to evaluate the effectiveness, efficacy and safety of acupuncture treatment for patients with functional constipation.

2. The results of this study will offer more valid and reliable evidence for clinicians to make decisions during clinical practice, and for academics and researchers to conduct further researches.

3. The most difficult part of this study is collecting all the raw data of eligible trials by systematically search. We will actively communicate with the authors and researchers of these trials to ensure as complete individual patient data as possible to collect and synthesize.

INTRODUCTION

Functional constipation (FC) is a common disease in clinical practice, which includes several symptoms such as decreased frequency of defecation, straining during defecation, hard stools, sensation of incomplete defecation, excessive time during defecation, and so on. The diagnosis of FC mainly depends on the individual's symptoms and several physiological examinations. The Rome Foundation published Rome III criteria in 2006, which gave the consensus criteria for FC [1].

It is reported that the incidence of FC are 12% to 19% in North American [2] and 11.6% in Asia [3], respectively. The prevalence of FC ranges from 0.7% to 29.6% in children [4], and 2%-35% in adults [5]. People with FC spend $7,522 every year on seeking health care, accounting for 6.5% of the total medical expenditure on lower gastrointestinal diseases [6]. With the high incidence and expensive expenditure of FC, the public quality of life is significantly undermined. Therefore, FC can be considered as a major public health problem [7].

Treatment for FC is various. Lifestyle and dietary modification, such as more physical activities and fiber-rich diet are widely accepted and recommended by experts as first-line therapy [8], although these may not be helpful all the time [9]. Conventional treatments for patients with FC are bulking agents, stool softeners, osmotic and stimulant laxatives, prokinetic agents (tegaserod, cisapride and mosapride) and so forth [10]. However, the side effects and the expensive expenditure are hard to be ignored. Therefore, more and more patients seek help from complementary and alternative medicine [11].

As an important part of traditional Chinese medicine (TCM), acupuncture has been used to treat gastroenterological disease for a long time, especially functional disorders, such as functional constipation, diarrhea and dyspepsia [12]. Many clinical trials, which were conducted to discuss the efficacy of acupuncture for patients with FC, indicated that acupuncture could relieve the patients' symptoms. However, the results of systematic reviews didn't make determinate conclusion. There are three systematic reviews of acupuncture therapy for patients with FC that we searched. First one was published in 2010 [13], which could not draw conclusion due to the serious methodological flaws in the included studies. Second and third ones were published in 2012 [14] and 2013 [15], respectively. Both of these two reviews made conclusion that acupuncture may have beneficial effect for FC, but the clinical, methodological and statistical heterogeneity of included studies made the results less convincing.

Since 2012, several new results of RCTs have been published, and two multicenter RCTs with large sample size have been underway [16, 17]. We think it is a good time to conduct a systematic review again. And this time a better method should be used to answer this uncertain question about acupuncture treatment for patients with FC. Therefore, we decided to do a meta-analysis based on the individual patient data (IPD) of high quality RCTs to find out whether acupuncture is effective and safe for population with FC, and what the effect size is.

METHODS AND ANALYSIS

Objectives

To establish the individual patient database by combing the raw data from high quality clinical trials of acupuncture treatment of FC, and to answer the question: Is acupuncture effective for patients with FC?

We will answer this question in the following aspects:

1. Compared with positive drugs, does acupuncture have the similar therapeutic effect?

2. Is real acupuncture superior to sham acupuncture for patients with functional constipation?

3. Is acupuncture superior to no treatment for patients with functional constipation?

4. Is acupuncture safe to patients with functional constipation?

Search strategy

We will conduct systematically search in the following databases: MEDLINE, EMBASE, Cochrane Library, Chinese BioMedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), China's Important Conference Papers Database, and China's Dissertation Database. The databases above are searched from inception to May, 2014.

The following search terms will be used individually or combined: "acupuncture", "acupuncture therapy", "auricular acupuncture", "moxibustion", "acupressure", "constipation", "functional constipation", "idiopathic constipation", "randomized controlled trial", etc. Terms in Chinese will be used in Chinese databases. The search strategies will be available in Additional file 1. We will include ongoing RCTs that evaluated the acupuncture treatment for FC through WHO

International Clinical Trial Registry Platform (ICTRP) portal and Clinical Trial Registry by US National Institutes of Health.

Criteria for study eligibility

Published, unpublished and ongoing studies will be included in individual patient database, if they meet the following criteria:

Type of studies

We will include randomized controlled trials (RCTs) only. Randomized and allocation concealment method should be clearly described in published papers. If not, we will contact the corresponding authors for further information about randomization process. Moreover, allocation concealment should be adequate to avoid the selection bias. In addition, considering the washout duration of acupuncture cannot be accurately evaluated, we will not include RCTs with crossover design. There will be no limitation on the sample size. But to guarantee the quality of study, the sample size less than 30 will not be considered. All studies which meet the inclusion criteria will be invited to share the raw data.

Type of participants

Adult patients who were diagnosed with FC according to the Rome Ⅱ/Ⅲ criteria will be included. Or patients who were diagnosed with FC (or chronic constipation, primary constipation, idiopathic constipation) with other criteria and excluded by examinations for pathological diseases, such as post-surgery, tumor or obstruction will be also included in this research.

Types of intervention/exposure

Patients received acupuncture treatment as the primary intervention, which means that patients in treatment group of each study were treated by acupuncture or acupuncture as the main intervention combined with other therapy, such as Chinese herbs, physical exercises. Any types of acupuncture will be included, such as manual acupuncture, electro-acupuncture, warming-needle moxibustion, auricular acupuncture, scalp acupuncture, pyonex, intradermal needling, acupoint injection with medicine, and so forth. One session of acupuncture treatment for FC is only an acute relief. So, at least 10 sessions of acupuncture treatment is able to meet the eligible criteria.

Types of controls

At least one control group of patients in study should receive one of the following interventions: positive drugs, placebo controls, or no treatment.

Positive drugs: positive drugs which are used to treat constipation include bulk-forming laxatives, emollients, lubricants, osmotic laxatives, stimulants, and chloride-channel [18, 19].

Placebo controls: placebo controls include sham acupuncture, placebo drugs, sham interventions and so forth. Sham acupuncture is used to keep patients from knowing whether he/she received real acupuncture or not, but make patients believe that he/she receive the acupuncture stimulation. Sham acupuncture includes superficially insertion with needles in the specific acupoints, non-specific acupoints, distal acupoints and non acupoints; placebo needles, such as Streitberger needles [20]; or other techniques which make patients feel like needling.

No treatment is defined as any kinds of methods as following: waiting list, which means that patients in control group will not receive any acupuncture treatment until completing the trial; general care or usual care, which means that patients in control group will only give advices and

education, such as diet and exercises recommendation.

Types of outcome measurements

1. Primary outcomes

The primary outcome of this review is the frequency of spontaneous defecation per week after treatment.

2. Secondary outcomes

The secondary outcomes are the following aspects: the changes of the stool quality, which were assessed by Bistol stool scale or other objective measurement; the mean transit time, which means that the time from the first perception of wanting to defecate to finish the defecation; the proportion of patients using laxatives, which means that we will counter the number of patients who used laxatives during trial to alleviate their symptoms. The proportion of adverse events will be also calculated according to the patients' reporting in each study.

Data collection

Study selection and data extraction

After electronically search in the databases, two reviewers will screen independently the titles and abstracts to exclude: 1) the duplicates; 2) the studies of which the participants were not met the criteria; 3) the studies which were not RCTs with parallel design. Then, our reviewers will screen the full copies of studies which are not clearly screened just by titles and abstracts (the full copies screening form is available in the Additional file 2). Any disagreement will be resolved by consensus, or a third reviewer will be consulted.

The next step will be our two reviewers work independently to extract data of studies. Training of how to extract the data and pretest will be held in advance to guarantee the quality of extraction. Reviewers will document the following information in Data Extraction Forms (Additional file 2): 1) the basic information of study (the date and reviewer of extraction, study details, such as first author, year of publication, country of publication and publication type); 2) the characteristics of study (design of the study, sample size, number of groups, methodology of randomization and allocation concealment, blinding, settings); 3) participants (age, gender, ethnicity, diagnosis, etc.); 4) interventions and controls (the type of interventions, the number and the frequency of sessions, the duration of treatment or follow-up, etc.); 5) outcomes (type of outcome, definition of outcome, time point of assessment, etc.) and 6) results (the statistic description of outcomes, such as mean, standard deviation, observed and total sample size, adverse events, etc.). Any disagreement on data extraction will require rechecking and discussion, or being judged by a third reviewer.

Methodological quality assessment

The assessment of methodological quality is of great importance to systematic review. After data extraction, two reviewers will evaluate the methodological quality of each original study independently, and document the detail in the Data collection form. Discrepancies will be resolved by consensus. According to the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook (Version 5.1.0)), the methodological quality will be assessed by the following criteria: 1) randomization allocation; 2) randomization concealment; 3) blinding: 4) data integrity; 5) selective reporting; 6) other bias, such as trial design, the baseline similarity of groups, early stopping of treatment and so on. For all the studies, the assessment should follow the six aspects in the above, and categorize as A, B or C grade of risk, which mean low, unclear

and high risk of bias, respectively. And grade will be used to evaluate the quality of all the studies as the Cochrane collaboration's recommendation.

Regarding the characteristics of acupuncture clinical trial, we will also assess the quality of acupuncture interventions according to STRICTA [21]. However, it is difficult to meet blinding for acupuncture treatment. Thus, we just ask for blinding assessment and statistical analysis. Any disagreements will be resolved by consensus.

Raw data collection and checking

Corresponding authors of eligible studies will be contacted and invited to contribute the raw data. If the authors of the older studies could not provide the original data, we will present the details in the final report. The raw data will be transported in any manner that recognized as convenient by authors (such as emails) in any type of electronics format, such as SPSS, STATA, R, Excel, etc.. After check the availability of the data files, all of them will be converted to a uniform format with its own name, which composed of first author's name and the year of publication.

Reviewers will check all data carefully to find out whether there are the irrationality, obvious errors and missing for all the variables. If yes, we will contact the authors for further information. After checking the data, we will calculate the data according to the statistical methodology of the published papers. If there is any inconsistent with the published results, we will require more information from investigators. For the studies which are still during the period of follow-up, we will ask the investigators to provide the latest data. Then, we will create a new data set for all the raw data, and harmonize the names and format of variables, which is convenient for further IPD meta-analysis.

For missing data, we will ask the investigator to recheck the missing part and find out whether it was happened during the data entry, if not, we will use multiple imputation by the propensity score methods.

Raw data management

All data will be stored in the computer with password in laboratory of Collage of Acupuncture and Moxibustion, Chengdu University of TCM, and only the authorized members of this IPD study will be allowed to access. Furthermore, there will be a Data Management Committee to supervise the reasonable and confidential use of the original data. Data governance is able to guarantee the safety of the relevant data from each study and guarantee the interests of multiple aspects. And confidential agreement will be asked to sign to make sure the anonymity of the individual patients' data.

Statistical methods

Heterogeneity

Heterogeneity test is an important step during conducting meta-analysis, which determines whether the data from studies are suitable and meaningful to synthesize or not. Only via heterogeneity test and reasonable explanation, the result of the meta-analysis will be validate and reliable. Although, there is still controversy about the investigation of heterogeneity in IPD meta-analysis, we will use conventional method that is I^2 value (tested by Higgins I-squared test) to detect the heterogeneity of eligible studies. According to the Handbook of Cochrane, I^2 value are divided into four categories, and the value > 50% will be considered as significant heterogeneity among included studies. The heterogeneity was significant in the previous

systematic reviews of acupuncture for patients with FC. And the sources of the heterogeneity that we speculate are the differences of patient's demographics, different style of acupuncture treatment (such as manual acupuncture, electro-acupuncture, or auricular acupuncture, etc.), the alliance of different interventions, outcomes and the time points, and so forth. But using IPD is a good way to deal with these problems. In our study, we will firstly calculate the effect size of acupuncture of each study, and then conduct heterogeneity test and meta-analysis. If there is still a significant heterogeneity, we will perform meta-regression analysis to find out the sources and take appropriate actions to deal with them then. Explicit explain and relevant sensitive analysis will be available in our final report.

Primary endpoint

The primary endpoint plays a vital role in final result. We will firstly identify primary endpoint (including outcome and time point) of each study. In this meta-analysis we use spontaneous defecation frequency per week evaluated at the end of treatment as primary endpoint. The frequency of spontaneous defecation is continuous variable. So, if outcomes are ordinal data, count data based on times of defecation, we will convert them to continuous variable. While, some studies use Cleveland Clinic Score (CCS) [22] or colonic transit time (CTT) [23] etc. after treatment as the primary endpoint. In this situation, we will create a standardized primary endpoint divided by pooled standard deviation.

Data analysis

1. Primary analysis

In this part we will analyze the effect size of acupuncture in two steps. First, each original study will be reanalyzed by analysis of covariance with the standardized principal endpoint as the

dependent variable, and the baseline characteristics as covariates (such as baseline scores, participate characteristics, etc.), to calculate the effect size of acupuncture of FC. Second, all the effect size from the original studies will be included into meta-analysis by *meta or metaphor package* in R project (www.r-project.org). During this process, we will choose an appropriate effects models, such as fixed effects model or random effects model according to the heterogeneity. When heterogeneity is not quite obviously, such as mild or moderate, we will perform both fixed and random effects model to calculate the effect size, and compare the differences. In this part of analysis, we will detect the effect size of acupuncture separately by comparing acupuncture with positive drugs, placebo controls and no acupuncture treatment.

2. Secondary analysis

We will reanalyze the effect size for the change of stool quality assessed by Bistol stool scale or other objective measurements, the mean transit time, the proportion of patients using laxatives, as well as the proportion of adverse events during the studies. Standardized mean differences will be used in the meta-analysis, if there are different measurement scales in the original studies. The continuous data were described as mean and standardized difference (SD), while the categorical data were described as counts or percentages. Missing values were handled by multiple imputation with the propensity score method.

Time point is a little difficult to determined, because of the different study design. According to the different observation course, for our data, 4 weeks will be the cut-off point (or other time). And before the cut-off point, the time points before 4 weeks will be regarded as the short-term of effects, while after will be regarded as the long-term of effects. We will harmonize the time variables, for example, the 1 month is equivalent to 4 weeks. Any time point that investigators designed for assessment being around our uniformed time point is considered as the time point

in this IPD study.

Sensitivity analysis

Sensitivity analysis will include the following aspects:

First, sensitivity analysis will be performed for publication bias. Although adequate inclusion and exclusion criteria that we design can decrease the publication bias, we will also perform the sensitivity analysis to detect it. And funnel plot will be used if there are more than 10 studied included in this IPD study. Furthermore, fail-safe number will be calculated to determine the degree of bias.

Second, because exclusion and drop-outs will be dealt with by the multiple imputation in the statistical analysis according to the available data, thus, sensitivity analysis will be conducted in this aspect.

Third, the omitted studies and subgroups will be analyzed by sensitivity analysis. According to the quality assessment, some studies with high risk of bias or the subgroup with small sample size will not be included in meta-analysis. So we will analyze all the data during conducting sensitivity analysis by synthesizing these studies or subgroups, and compare the results before and after.

Finally, as we mentioned above, we will perform both fixed and random effects model to detect the heterogeneity during meta-analysis. And for studies which contribute to the greater heterogeneity will be also conducted sensitivity analysis by omitting them.

Ethics and dissemination

Because each study has been approved by local institutional review board and ethical

committee before the trial was conducted, and all participants included in were required to sign the written informed consent, so this IPD meta-analysis study will not require further ethical approval.

This protocol of IPD meta-analysis of acupuncture for FC has been registered with PROSPERO (International Prospective Register of Systematic Reviews) at the NHS Centre for Reviews and Dissemination at the University of York (Registration number: CRD42014009901). The result of this review will provide valid and reliable evidence of acupuncture treatment for patients with FC. The findings of this review will also give implication for clinical practice and further researches, and will be disseminated by peer-review publication and conference presentations.

DICUSSION

Individual patient data meta-analysis with high quality trials will provide the most reliable evidence for clinical treatment decisions. Due to both clinical practice and research ability of all the collaboration in this study, we believe that the results of this study will be valid to make conclusion about acupuncture treatment to FC.

We design this IPD meta-analysis protocol referring to the previous relevant studies [24, 25]. But our study has limitations. Characteristics of acupuncture (such as number, frequency and duration of treatment sessions, prescription, stimulation of acupoints), or characteristics of patient (such as gender, age, disease duration and baseline situation) have influence on the therapeutic effects of acupuncture in clinical practice. And the changing of acupuncture effects with time course is also interesting for making treatment schedule. These aspects that we mentioned above will not in this protocol now, but we plan to analyze them in future. Moreover, the most difficult part of this study is acquiring the complete raw data from original trials. To

deal with this problem, we will take the following steps: first of all, we have established the strict inclusion criteria and conducted the systematically search to locate the eligible trials. Second, we will actively contact and communicate with authors and researchers to participant in this study and offer as complete data as possible. Third, we will draft relevant agreements and contracts to protect the mutual interests during conducting this study.

In a word, we sincerely hope that the findings of this review will guide future treatment of FC, and translate the contributions of clinical researches into patient benefit.

Abbreviations

RCTs: randomized controlled trials; TCM: traditional Chinese medicine; IPD: individual patient data; FC: functional constipation.

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Contributions

The study was conceived and overall design by QHZ and HZ. SR and WJH made contributions to the design of statistical analysis and monitor the quality of included RCTs. QHZ, HZ, SYZ, LYL, HBZ and JCL form the Data Management Committee and have responsibility for study research and data safety. LYL, JCL and SYZ are reviewers of data extraction, checking and collection. QHZ and HZ are responsible for overall data analysis. HZ, YL, ZSL and BZ, who form the Research Steering Committee, contribute suggestion to the design of this study and individual patient data to meta-analysis. YL is responsible for the whole quality of study. All authors read this manuscript and approved the publication of this protocol.

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Competing interests

The authors declare that they have no competing interests.

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Search strategy for **MEDLINE**

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. (randomized or randomised).ab.
4. placebo.ab.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp constipation/
10. functional constipation.ab,ti.
11. primary constipation.ab,ti.
12. chronic constipation.ab,ti.
13. idiopathic constipation.ab,ti.
14. slow transit constipation.ab,ti.
15. (obstipation or “fecal impaction” or astriction or costiveness or coprostasis).ab,ti.
16. 10 or 11 or 12 or 13 or 14 or 15
17. exp acupuncture therapy/
18. exp acupuncture/
19. (needling or needle or prod or pinprick or pricking).ab,ti.
20. exp acupuncture points/
21. (acupunctur* or acupoint or "acupoint application" or "point application" or "external application therapy" or "acupoint inject*" or "point inject*" or "inject* to point" or "inject* to acupoint").ab,ti.
22. exp electroacupuncture/
23. (electroacupunctur* or acusector* or "thermoelectric needle" or electro-acupunctur*).ab,ti.
24. exp auriculotherapy/
25. exp acupuncture, ear/
26. (otopoint* or "ear hole planted seeds" or "ear buried seeds" or auricular*).ab,ti.
27. exp moxibustion/
28. moxa*.ab,ti.
29. exp acupressure/
30. exp meridians/
31. (embedd* or "catgut implantation at acupoint*" or "acupoint catgut embedd*" or "catgut embedd* therap*").ab,ti.
32. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 8 and 16
34. 32 and 33

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

Use acupuncture to treat functional constipation: a study of an individual patient data meta-analysis

Study Eligibility Form

- for full copies screening

Ref ID:

First author:

Reviewers:

Included □

Excluded □ because:

1. Not adult FC subjects (FC should be diagnosed according to the Rome Ⅱ/Ⅲ criteria or other valid criteria without pathological diseases) □

2. Patients with FC not randomized to the treatment and control group □

3. Types of intervention not meet the included criteria □

4. No outcomes provided for FC patients □

5. Other reasons (specify)_____

Consultation required □

Included by consensus □ because:_____

Excluded by consensus □

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Data Extraction Form

Data:

Reviewers:

General information

Title	
First author	
Year of publication	
Country of publication	
Language	
Publication type	

Study methodology

Trial design	parallel group only □
Randomization method	
Allocation concealment method	
Blinding	
Setting	
Number of participants	
Number of groups	
Duration	
Follow-up duration	
Funding source	

Participants				
	Group 1	Group 2	Group 3	Group 4
Age (Mean ±SD)				

Gender (M/F)				
Ethnicity				
Diagnosis				
Concurrent condition				
Duration of condition				
Severity of condition				
Laboratory parameters				
Other				

Intervention and controls

Acupuncture therapy	
Stimulation type	
Number of sessions	
Frequency of sessions	
Duration of sessions	
Point prescription	
Combination with other acupuncture therapy	Yes □ (specify) No □
Information of acupuncturists	
Drug combination	
Others	
Controls (including the names, dose, duration of therapy, frequency duration etc.)	
Positive drugs	

Placebo controls	
No treatment	
Compliance	

Outcomes (including the names, methods, definitions, time points)	
Primary outcome (s)	
Secondary outcomes	

Results

Outcomes (including the names, mean, SD etc.)				
	Group 1	Group 2	Group 3	Group 4
Primary outcomes				
Secondary outcomes				
Observed events				
Total sample size				
Adverse events				
Total randomized				
Excludes*				
Withdrawals*				

Lost to follow-up*				
Request for further information				

*including reasons

Risk of bias assessment

1. Was randomized allocation sequence adequately generated?

Yes □ No □ Unclear □

2. Was allocation adequately concealed?

Yes □ No □ Unclear □

3. Who were blinded to the allocation during the study?

Patients	Yes □	No □	Unclear □
Investigators	Yes □	No □	Unclear □
Outcomes assessors	Yes □	No □	Unclear □
Data assessors	Yes □	No □	Unclear □

4. Was the data integrated in this reporting (including the description of the reasons of withdrawals and drop-outs)?

Yes □ No □ Unclear □

5. Were there any selective reporting?

Yes □ No □ Unclear □

6. Did the acupuncture intervention meet the criteria of STRICTA?

Yes □ No □ Unclear □

6. Other bias (specify)_____

Risk of bias	Interpretation	Relationship to individual criteria
A - Low risk of bias	Plausible bias unlikely to seriously alter the results	All of the criteria met
B – Moderate risk of bias	Plausible bias that raises some doubt about the results	One or more criteria parity met
C – High risk of bias	Plausible bias that seriously weakens confidence in the results	One or more criteria not met

Grade:_____

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Acupuncture to treat functional constipation: a study protocol for an individual patient data meta-analysis

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Primary Subject Heading:	Gastroenterology and hepatology
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Use acupuncture to treat functional constipation: a study protocol of an individual patient data meta-analysis

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ABSTRCT

Introduction: Functional constipation (FC) is a common gastrointestinal disease. Systematic reviews indicate that acupuncture may be effective for patients with FC. However, the conclusion is not convincing due to the quality, sample size, methodological heterogeneity of the included studies. Therefore, it is necessary for us to conduct a meta-analysis of individual patient data (IPD) from high quality clinical trials to testify whether acupuncture is effective for FC patients.

Methods and analysis: Randomized controlled trials (RCTs) of acupuncture for adult patients with FC will be searched from several databases from inception to May, 2014. The corresponding authors of eligible studies will be contacted and invited to contribute the raw data. The primary outcome is the change of the spontaneous defecation per week from baseline. And the secondary outcomes include proportion of responders, the changes of stool quality, mean transit time, proportion of patients using laxatives and adverse events. We will check all data and perform re-analysis according to statistical methodology reported in previous publications. Then, we will harmonize the raw data and use a two-step method to conduct the IPD meta-analysis. First, we will calculate the effect size of acupuncture of each trial by analysis of covariance, with the principal endpoint as the dependent variable and the baseline scores as the covariates. Second, the effect size of acupuncture of each original study will be included into meta-analysis.

Dissemination: Based on the IPD meta-analysis of high quality RCTs, this review will answer whether acupuncture is effective for FC. The findings of the review will be disseminated through peer-review publications and conference presentations.

Trial registration number: PROSPERO 2014: CRD42014009901

Strengths and Limitations of this study

1. This article is a study protocol of the individual data meta-analysis to evaluate the effectiveness, efficacy and safety of acupuncture treatment for patients with functional constipation.

2. The results of this study will offer more valid and reliable evidence for clinicians to make decisions during clinical practice, and for academics and researchers to conduct further researches.

3. The most difficult part of this study is collecting all the raw data of eligible trials by systematically search. We will actively communicate with the authors and researchers of these trials to ensure as complete individual patient data as possible to collect and synthesize.

INTRODUCTION

Functional constipation (FC) is a common disease in clinical practice, which includes several symptoms such as decreased frequency of defecation, straining during defecation, hard stools, sensation of incomplete defecation, excessive time during defecation, and so on. The diagnosis of FC mainly depends on the individual's symptoms and several physiological examinations. The Rome Foundation published the Rome III criteria in 2006, which gave the consensus criteria for FC [1].

It is reported that the incidence of FC are 12% to 19% in North American [2] and 11.6% in Asia [3], respectively. The prevalence of FC ranges from 0.7% to 29.6% in children [4], and 2%-35% in adults [5]. People with FC spend $7,522 every year on seeking health care, accounting for 6.5% of the total medical expenditure on lower gastrointestinal diseases [6]. With the high incidence and the expensive expenditure of FC, the public quality of life is significantly undermined.

Therefore, FC can be considered as a major public health problem [7].

Treatments for FC are various. Lifestyle and dietary modification, such as more physical activities and fiber-rich diet are widely accepted and recommended by experts as the first-line therapy [8], although these may not be helpful all the time [9]. Conventional treatments for patients with FC are bulking agents, stool softeners, osmotic and stimulant laxatives, prokinetic agents (tegaserod, cisapride and mosapride) and so forth [10]. However, the side effects and the expensive expenditure are hard to be ignored. Therefore, more and more patients seek help from the complementary and alternative medicine [11].

As an important part of traditional Chinese medicine (TCM), acupuncture has been used to treat gastroenterological diseases for a long time, especially functional disorders, such as functional constipation, diarrhea and dyspepsia [12]. Many clinical trials, which were conducted to discuss the efficacy of acupuncture for patients with FC, indicated that acupuncture could relieve the patients' symptoms. However, the results of systematic reviews didn't make determinate conclusion. There are three systematic reviews of acupuncture therapy for patients with FC that we searched. First one was published in 2010 [13], which could not draw a conclusion due to the serious methodological flaws in the included studies. Second and third ones were published in 2012 [14] and 2013 [15], respectively. Both of these two reviews made a conclusion that acupuncture may have beneficial effect for FC. But the clinical, methodological and statistical heterogeneity of the included studies made the results less convincing.

Since 2012, several new results of RCTs have been published, and two multicenter RCTs with large sample size have been underway [16, 17]. We think it is a good time to conduct a systematic review again. And this time a better method should be used to answer the uncertain question about acupuncture treatment for patients with FC. Therefore, we decided to do a

meta-analysis based on the individual patient data (IPD) of high quality RCTs to find out whether acupuncture is effective and safe for the population with FC, and what the effect size is.

METHODS AND ANALYSIS

Objectives

To establish the individual patient database by combing the raw data from high quality clinical trials of acupuncture treatment of FC, and to answer the question: is acupuncture effective for patients with FC?

We will answer this question in the following aspects:

1. Compared with the positive drugs, does acupuncture have the similar therapeutic effect?

2. Is the real acupuncture superior to the sham acupuncture for patients with functional constipation?

3. Is acupuncture superior to no treatment for patients with functional constipation?

4. Is acupuncture safe to patients with functional constipation?

Search strategy

We will conduct systematically search in the following databases: MEDLINE, EMBASE, Cochrane Library, Chinese BioMedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), China's Important Conference Papers Database, and China's Dissertation Database. The databases above are searched from inception to May, 2014.

The following search terms will be used individually or combinedly: "acupuncture",

"acupuncture therapy", "auricular acupuncture", "moxibustion", "acupressure", "constipation", "functional constipation", "idiopathic constipation", "randomized controlled trial", etc. Terms in Chinese will be used in Chinese databases. The search strategy will be available in Additional file 1. We will include ongoing RCTs that evaluated the acupuncture treatment for FC through WHO International Clinical Trial Registry Platform (ICTRP) portal and Clinical Trial Registry by US National Institutes of Health.

Criteria for study eligibility

Published, unpublished and ongoing studies will be included in individual patient database, if they meet the following criteria:

Type of studies

We will include randomized controlled trials (RCTs) only. Randomized and allocation concealment method should be clearly described in published papers. If not, we will contact the corresponding authors for further information about randomization process. Moreover, allocation concealment should be adequate to avoid the selection bias. In addition, considering the washout duration of acupuncture cannot be accurately evaluated, we will not include RCTs with crossover design. There will be no limitation on the sample size. But to guarantee the quality of study, the sample size less than 30 will not be considered. All studies which meet the inclusion criteria will be invited to share the raw data.

Type of participants

Adult patients who were diagnosed with FC according to the Rome Ⅱ/Ⅲ criteria will be included. Or patients who were diagnosed with FC (or chronic constipation, primary

constipation, idiopathic constipation) with other criteria and excluded by examinations for pathological diseases, such as post-surgery, tumor or obstruction will be also included in this research.

Types of intervention/exposure

Patients received acupuncture treatment as the primary intervention will be included, which means that patients in treatment group of each study were treated by acupuncture or acupuncture as the main intervention combined with other therapy, such as Chinese herbs, physical exercises. Any types of acupuncture will be included, such as manual acupuncture, electro-acupuncture, warming-needle moxibustion, auricular acupuncture, scalp acupuncture, pyonex, intradermal needling, acupoint injection with medicine, and so forth. One session of acupuncture treatment for FC is only an acute relief. So, at least 10 sessions of acupuncture treatment is able to meet the eligible criteria.

Types of controls

At least one control group of patients in the study should receive one of the following interventions: positive drugs, placebo controls, or no treatment.

Positive drugs: positive drugs which are used to treat constipation include bulk-forming laxatives, emollients, lubricants, osmotic laxatives, stimulants, and chloride-channel [18, 19].

Placebo controls: placebo controls include sham acupuncture, placebo drugs, sham interventions and so forth. Sham acupuncture is used to keep patients from knowing whether he/she receive real acupuncture or not, but to make patients believe that he/she receive the acupuncture stimulation. Sham acupuncture includes superficially insertion with needles in the specific acupoints; needles puncturing at non-specific acupoints, distal acupoints or non acupoints; placebo needles, such as Streitberger needles [20]; or other techniques which make

patients feel like needling.

No treatment is defined as any kinds of methods as following: waiting list, which means that patients in control group will not receive any acupuncture treatment until completing the trial; general care or usual care, which means that patients in control group will only give advices and/or healthy education, such as diet and/or exercises recommendation.

Types of outcome measurements

1. Primary outcomes

The primary outcome of this review is the change of the spontaneous defecation per week from the baseline.

2. Secondary outcomes

The secondary outcomes are the following aspects: proportion of responders, which is defined as the number of responders divided by the total number of participants in each group; the changes of the stool quality, which were assessed by Bistol stool scale or other objective measurements; mean transit time, which means that the time from the first perception of wanting to defecate to finish the defecation; proportion of patients using laxatives, which means that we will counter the number of patients who used laxatives during trial to alleviate their symptoms. The proportion of adverse events will be also calculated according to the patients' reporting in each study.

Data collection

Study selection and data extraction

After electronically search in the databases, two reviewers will screen independently the titles and abstracts to exclude: 1) the duplicates; 2) the studies of which the participants were not met the criteria of FC; 3) the studies which were not RCTs with parallel design; and 4) the studies which the participants in an experimental group were not receiving acupuncture treatment as the primary intervention. Then, our reviewers will screen the full copies of studies which cannot be clearly screened just by titles and abstracts (the full copies screening form is available in the Additional file 2). Any disagreement will be resolved by consensus, or a third reviewer will be consulted.

The next step will be our two reviewers working independently to extract data of the studies. Training of how to extract the data and pretest will be held in advance to guarantee the quality of extraction. Reviewers will document the following information in Data Extraction Form (Additional file 2): 1) the basic information of the study (the date and reviewer of extraction, study details, such as first author, year of publication, country of publication and publication type); 2) the characteristics of the study (design of the study, sample size, number of groups, methodology of randomization and allocation concealment, blinding, settings); 3) participants (age, gender, ethnicity, diagnosis, etc.); 4) interventions and controls (type of interventions, number and frequency of sessions, duration of treatment or follow-up, etc.); 5) outcomes (type of outcome, definition of outcome, time point of assessment, etc.) and 6) results (the statistic description of outcomes, such as mean, standard deviation, observed and total sample size, adverse events, etc.). Any disagreement on data extraction will require rechecking and discussion, or being judged by a third reviewer.

Methodological quality assessment

The assessment of methodological quality is of great importance to systematic review. After

data extraction, two reviewers will evaluate the methodological quality of each original study independently, and document the detail in the Risk of bias assessment form. Discrepancies will be resolved by consensus, or a third reviewer will be consulted. According to the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook (Version 5.1.0)), the methodological quality will be assessed by the following criteria: 1) randomization allocation; 2) randomization concealment; 3) blinding: 4) data integrity; 5) selective reporting; and 6) other bias, such as trial design, the baseline similarity of groups, early stopping of treatment and so on. For all the studies, the assessment should follow the six aspects in the above, and categorize as A, B or C grade of risk, which mean low, unclear and high risk of bias, respectively. And grade will be used to evaluate the quality of all the studies as the Cochrane collaboration's recommendation.

Regarding the characteristics of acupuncture clinical trial, we will also assess the quality of acupuncture interventions according to the STRICTA recommendation [21]. However, it is difficult to meet blinding for acupuncture treatment. Thus, we just ask for blinding assessment and statistical analysis. Any disagreements will be resolved by consensus, or a third reviewer will be consulted.

Raw data collection and checking

Corresponding authors of eligible studies will be contacted and invited to contribute the raw data. If the authors of the older studies could not provide the original data, we will present the details in the final report, and further analysis is necessary in the sensitivity analysis. The raw data will be transported in any manner that recognized as convenient by authors (such as emails) in any type of electronics format, such as SPSS, STATA, R, Excel, etc.. After checking the availability of the data files, all of them will be converted to a uniform format with its own name,

which composed of first author's name and the year of publication.

Reviewers will check all the data carefully to find out whether there are any irrationality, obvious errors or missing for all the variables. If yes, we will contact the authors for further information. After checking the data, we will calculate the data according to the statistical methodology of the published papers. If there is any inconsistent with the published results, we will require more information from investigators. For the studies which are still during the period of follow-up, we will ask the investigators to provide the latest data. Then, we will create a new data set for all the raw data, and harmonize the names and format of variables, which is convenient for further IPD meta-analysis.

For missing data, we will ask the investigator to recheck the missing part and find out whether it was happened during the data entry, if not, we will use multiple imputation by the propensity score methods.

Raw data management

All the data will be stored in the computer with password in laboratory of College of Acupuncture and Tuina, Chengdu University of TCM, and only the authorized members of this IPD study will be allowed to access to. Furthermore, there will be a Data Management Committee to supervise the reasonable and confidential use of the original data. Data governance is able to guarantee the safety of the relevant data from each study and guarantee the interests of multiple aspects. And confidential agreement will be asked to sign to make sure the anonymity of the individual patients' data.

Statistical methods

Heterogeneity

Heterogeneity test is an important step during conducting meta-analysis, which determines whether the data from studies are suitable and meaningful to synthesize or not. Only via heterogeneity test and reasonable explanation, the result of the meta-analysis will be validate and reliable. Although, there is still controversy about the investigation of heterogeneity in IPD meta-analysis, we will use conventional method that is I^2 value (tested by Higgins I-squared test) to detect the heterogeneity of eligible studies. According to the Handbook of Cochrane, I^2 values are divided into four categories, and the value > 50% will be considered as significant heterogeneity among the included studies. The heterogeneity was significant in the previous systematic reviews of acupuncture for patients with FC. And the sources of heterogeneity that we speculate are the differences of patients' demographics, different style of acupuncture treatment (such as manual acupuncture, electro-acupuncture, or auricular acupuncture, etc.), the alliance of different interventions, outcomes and the time points, and so forth. Using IPD is a good way to deal with these problems above. And there are more possibilities to obtain the quantitative results rather than the qualitative ones. In our study, we will firstly calculate the effect size of acupuncture of each study by the standardized principle, and then conduct heterogeneity test and meta-analysis. If there is still a significant heterogeneity, we will perform meta-regression analysis to find out the sources and take appropriate actions to deal with them then. Explicit explain and relevant sensitivity analysis will be available in our final report.

Primary endpoint

The primary endpoint plays a vital role in final result. We will firstly identify primary endpoint (including outcome and time point) of each study. In this meta-analysis we will use the change of spontaneous defecation frequency per week from baseline, which is a continuous variable. So, if outcomes are ordinal data, count data based on times of defecation, we will convert them to

continuous variable. While, some studies use Cleveland Clinic Score (CCS) [22] or colonic transit time (CTT) [23] etc. after treatment as the primary endpoint. In this situation, we will create a standardized primary endpoint divided by pooled standard deviation.

Data analysis

1. Primary analysis

In this part the effect size of acupuncture will be analyzed in two steps. First, each original study will be reanalyzed by analysis of covariance with the standardized principal endpoint as the dependent variable, and the baseline characteristics as covariates (such as baseline situation, participants' characteristics, etc.), to calculate the effect size of acupuncture of FC. Second, all the effect size from the original studies will be included into meta-analysis by *meta or metafor package* in R project (www.r-project.org). During this process, we will choose an appropriate effects models, such as the fixed effects model or random effects model according to the heterogeneity. When the heterogeneity is not quite obviously, such as mild or moderate, we will perform both fixed and random effects model to calculate the effect size, and compare the differences. In this part of analysis, we will detect the effect size of acupuncture separately by comparing acupuncture with positive drugs, placebo controls and no treatment.

2. Secondary analysis

We will reanalyze the effect size for the changes of stool quality assessed by Bistol stool scale or other objective measurements, the proportion of responders, the mean transit time, the proportion of patients using laxatives, as well as the proportion of adverse events during the studies. Standardized mean differences will be used in the meta-analysis, if there are different measurement scales in the original studies. The continuous data were described as mean and

standardized difference (SD), while the categorical data were described as counts or percentages. Missing values were handled by multiple imputation with the propensity score method.

Time point is a little difficult to determined, because of the different study design. According to the different observation course, for our data, 4 weeks will be the cut-off point (or other time). And before the cut-off point, the time points before 4 weeks will be regarded as the short-term effects, while after will be regarded as the long-term effects. We will harmonize the time variables, for example, the 1 month is equivalent to 4 weeks. Any time point that investigators designed for assessment being around our uniformed time point is considered as the time point in this IPD study.

Furthermore, considering some factors which may have influence on the clinical outcomes, in this study we will analyze the characteristics of patients with FC (such as the age, gender, ethnicity and course of disease) as well as the acupuncture treatment (such as the number, frequency and duration of treatment sessions, the number of acupoints, and the different types of acupuncture intervention) by using logistic regression method. We will find out whether these characteristics have influence on the effect of acupuncture for FC.

Sensitivity analysis

Sensitivity analysis will include the following aspects:

First, sensitivity analysis will be performed for publication bias. Although adequate inclusion and exclusion criteria that we design can decrease the publication bias, we will also perform the sensitivity analysis to detect it. And funnel plot will be used if there are more than 10 studied included in this IPD study. Furthermore, fail-safe number will be calculated to determine the degree of bias.

Second, because exclusion and drop-outs will be dealt with by the multiple imputation in the statistical analysis according to the available data, thus, sensitivity analysis will be conducted in this aspect.

Third, the omitted studies and subgroups will be analyzed by sensitivity analysis. According to the quality assessment, some studies with high risk of bias or the subgroup with small sample size will not be included in meta-analysis. So we will analyze all the data during conducting sensitivity analysis by synthesizing these studies or subgroups, and compare the results before and after.

Fourth, it is known that the most difficult part of carrying out the IPD meta-analysis is collecting all the raw data of the eligible studies. Although we will actively communicate with the authors and researchers to collect the raw data as complete as possible, there is still a possibility that the raw data is obtained incomplete. If so, we will firstly conduct the conventional meta-analysis on the published data of all the eligible studies according to our search strategy and of the studies which we can obtain the raw data separately. Then, we will compare the results of the two, in order to identify the possible selection bias.

Finally, as we mentioned above, we will perform both fixed and random effects model to detect the heterogeneity during meta-analysis. And studies which contribute to the greater heterogeneity will be also conducted sensitivity analysis by omitting them.

Ethics and dissemination

Because each study has been approved by local institutional review board and ethical committee before the trial was conducted, and all participants included in were required to sign the written informed consent, so this IPD meta-analysis study will not require further ethical

approval.

This protocol of IPD meta-analysis of acupuncture for FC has been registered with PROSPERO (International Prospective Register of Systematic Reviews) at the NHS Centre for Reviews and Dissemination at the University of York (Registration number: CRD42014009901). All procedures of this study will be performed in accordance with the guideline published by the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) Group [24] (the checklist is available in the PRISMA-P checklist). The result of this review will provide valid and reliable evidence of acupuncture treatment for patients with FC. The findings of this review will also give implication for clinical practice and further researches, and will be disseminated by peer-review publications and conference presentations.

DICUSSION

Individual patient data meta-analysis with high quality trials will provide the most reliable evidence for clinical treatment decisions. Due to both clinical practice and research ability of all the collaboration in this study, we believe that the results of this study will be valid to make a conclusion about acupuncture treatment to FC.

We design this IPD meta-analysis protocol referring to the previous relevant studies [25, 26]. But our study has limitations. Characteristics of acupuncture (such as number, frequency and duration of treatment sessions, prescription, stimulation of acupoints), or characteristics of patient (such as gender, age, disease duration and baseline situation) have influence on the therapeutic effects of acupuncture in clinical practice. And the changing of acupuncture effects with time course is also interesting for making treatment schedule. These aspects that we mentioned above will be partly in this protocol, but we plan to analyze all the relevant factors in

future, in order to offer more information for clinical practice and scientific research. Moreover, the most difficult part of this study is acquiring the complete raw data from original trials. To deal with this problem, we will take the following steps: first of all, we have established the strict inclusion criteria and conducted the systematically search to locate the eligible trials. Second, we will actively contact and communicate with authors and researchers to participant in this study and offer as complete data as possible. Third, we will draft relevant agreements and contracts to protect the mutual interests during conducting this study. If the raw data could not be fully obtained, we will report the details and the results of possible bias.

In a word, we sincerely hope that the findings of this review will guide the future treatments of FC, and translate the contributions of clinical researches into patient benefits.

Abbreviations

RCTs: randomized controlled trials; TCM: traditional Chinese medicine; IPD: individual patient data; FC: functional constipation.

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Contributions

The study was conceived and overall design by QHZ and HZ. SR and WJH made contributions to the design of statistical analysis and monitor the quality of included RCTs. QHZ, HZ, SYZ, LYL, HBZ and JCL form the Data Management Committee and have responsibility for study research and data safety. LYL, JCL and SYZ are reviewers of data extraction, checking and collection. QHZ and HZ are responsible for overall data analysis. HZ, YL, ZSL and BZ, who form the Research Steering Committee, contribute suggestion to the design of this study and individual patient data to meta-analysis. YL is responsible for the whole quality of study. This manuscript was written and revised by QHZ and HZ. All authors read this manuscript and approved the publication of this protocol.

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Competing interests

The authors declare that they have no competing interests.

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Search strategy for **MEDLINE**

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. (randomized or randomised).ab.
4. placebo.ab.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp constipation/
10. functional constipation.ab,ti.
11. primary constipation.ab,ti.
12. chronic constipation.ab,ti.
13. idiopathic constipation.ab,ti.
14. slow transit constipation.ab,ti.
15. (obstipation or “fecal impaction” or astriction or costiveness or coprostasis).ab,ti.
16. 10 or 11 or 12 or 13 or 14 or 15
17. exp acupuncture therapy/
18. exp acupuncture/
19. (needling or needle or prod or pinprick or pricking).ab,ti.
20. exp acupuncture points/
21. (acupunctur* or acupoint or "acupoint application" or "point application" or "external application therapy" or "acupoint inject*" or "point inject*" or "inject* to point" or "inject* to acupoint").ab,ti.
22. exp electroacupuncture/
23. (electroacupunctur* or acusector* or "thermoelectric needle" or electro-acupunctur*).ab,ti.
24. exp auriculotherapy/
25. exp acupuncture, ear/
26. (otopoint* or "ear hole planted seeds" or "ear buried seeds" or auricular*).ab,ti.
27. exp moxibustion/
28. moxa*.ab,ti.
29. exp acupressure/
30. exp meridians/
31. (embedd* or "catgut implantation at acupoint*" or "acupoint catgut embedd*" or "catgut embedd* therap*").ab,ti.
32. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 8 and 16
34. 32 and 33

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

Use acupuncture to treat functional constipation: a study of an individual patient data meta-analysis

Study Eligibility Form

- for full copies screening

Ref ID:

First author:

Reviewers:

Included □

Excluded □ because:

1. Not adult FC subjects (FC should be diagnosed according to the Rome Ⅱ/Ⅲ criteria or other valid criteria without pathological diseases) □

2. Patients with FC not randomized to the treatment and control group □

3. Types of intervention not meet the included criteria □

4. No outcomes provided for FC patients □

5. Other reasons (specify)_____

Consultation required □

Included by consensus □ because:_____

Excluded by consensus □

Use acupuncture to treat functional constipation: a study of an individual patient data meta-analysis

Data Extraction Form

Date:

Reviewers:

General information

Title	
First author	
Year of publication	
Country of publication	
Language	
Publication type	

Study methodology

Trial design	parallel group only □
Randomization method	
Allocation concealment method	
Blinding	
Setting	
Number of participants	
Number of groups	
Duration	
Follow-up duration	
Funding source	

Participants				
	Group 1	Group 2	Group 3	Group 4
Age (Mean ±SD)				

Gender (M/F)				
Ethnicity				
Diagnosis				
Concurrent condition				
Duration of condition				
Severity of condition				
Laboratory parameters				
Other				

Intervention and controls

Acupuncture therapy	
Stimulation type	
Number of sessions	
Frequency of sessions	
Duration of sessions	
Point prescription	
Combination with other acupuncture therapy	Yes □ (specify) _____ No □
Information of acupuncturists	
Drug combination	
Others	
Controls (including the names, dose, duration of therapy, frequency duration etc.)	
Positive drugs	

Placebo controls	
No treatment	
Compliance	

Outcomes (including the names, methods, definitions, time points)	
Primary outcome (s)	
Secondary outcomes	

Results

Outcomes (including the names, mean, SD etc.)				
	Group 1	Group 2	Group 3	Group 4
Primary outcomes				
Secondary outcomes				
Observed events				
Total sample size				
Adverse events				
Total randomized				
Excludes*				
Withdrawals*				

Lost to follow-up*				
Request for further information				

*including reasons

Risk of bias assessment

1. Was randomized allocation sequence adequately generated?

Yes □ No □ Unclear □

2. Was allocation adequately concealed?

Yes □ No □ Unclear □

3. Who were blinded to the allocation during the study?

Patients	Yes □	No □	Unclear □
Investigators	Yes □	No □	Unclear □
Outcomes assessors	Yes □	No □	Unclear □
Data assessors	Yes □	No □	Unclear □

4. Was the data integrated in this reporting (including the description of the reasons of withdrawals and drop-outs)?

Yes □ No □ Unclear □

5. Were there any selective reporting?

Yes □ No □ Unclear □

6. Did the acupuncture intervention meet the criteria of STRICTA?

Yes □ No □ Unclear □

6. Other bias (specify)_____

Risk of bias	Interpretation	Relationship to individual criteria
A - Low risk of bias	Plausible bias unlikely to seriously alter the results	All of the criteria met
B – Moderate risk of bias	Plausible bias that raises some doubt about the results	One or more criteria partly met
C – High risk of bias	Plausible bias that seriously weakens confidence in the results	One or more criteria not met

Grade:_____

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Section of this manuscript	Page No
Administrative information				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Title	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Notes under the Title, Author affiliations	1-2, 18-19
Contributions	3b	Describe contribution of protocol authors and identify the guarantor of the review	Contributions	19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Funding	19
Sponsor	5b	Provide name for the review funder and/ or sponsor	Funding	19
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	
Introduction				
Rationale	6	Describe the rational for the review in the context of what is already known	Introduction	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes(PICO)	Introduction, Objectives	4-6
Methods				

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Criteria for study eligibility	7-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Search strategy, Data collection (Raw data collection and checking)	6-7, 11-12
Search strategy	10	Present draft of search strategy to be used for at least on electronic database, including planned limits, such that it could be repeated	Search strategy, Additional file 1	6-7, Additional file 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Data collection (Raw data management)	12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Data collection (Study selection and data extraction)	9-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Data collection (Study selection and data extraction, Raw data collection and checking)	9-10, 11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Data collection (Study selection and data extraction), Additional file 2	9-10, Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Criteria for study eligibility (Types of outcomes measurements)	9
Risk of bias in individual studies	14	Describe anticipated methods of assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methodological quality assessment, Statistical methods (Heterogeneity, Sensitivity analysis)	10-11, 12-13, 15-16

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Criteria for study eligibility (Types of outcomes measurements), Statistical methods	9, 12-16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measure, methods of handing data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's T)	Statistical methods	12-16
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Statistical methods (Sensitivity analysis)	15-16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Statistical methods (Heterogeneity, Sensitivity analysis)	12-13, 15-16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Statistical methods	12-16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methodological quality assessment	10-11

BMJ Open

Acupuncture for functional constipation: protocol for an individual patient data meta-analysis

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Keywords:	COMPLEMENTARY MEDICINE, Functional bowel disorders < GASTROENTEROLOGY, Gastroenterology < INTERNAL MEDICINE

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

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ABSTRACT

Introduction: Functional constipation (FC) is a common gastrointestinal disease. Systematic reviews indicate that acupuncture may be effective for patients with FC. However, the conclusion is not convincing due to the quality, sample size, methodological heterogeneity of the included studies. Therefore, it is necessary for us to conduct a meta-analysis of individual patient data (IPD) from high quality clinical trials to testify whether acupuncture is effective for FC patients.

Methods and analysis: Randomized controlled trials (RCTs) of acupuncture for adult patients with FC will be searched from several databases from inception to May, 2014. The corresponding authors of eligible studies will be contacted and invited to contribute the raw data. The primary outcome is the change of the spontaneous defecation per week from baseline. And the secondary outcomes include proportion of responders, the changes of stool quality, mean transit time, proportion of patients using laxatives and adverse events. We will check all data and perform re-analysis according to statistical methodology reported in previous publications. Then, we will harmonize the raw data and use a two-step method to conduct the IPD meta-analysis. First, we will calculate the effect size of acupuncture of each trial by analysis of covariance, with the principal endpoint as the dependent variable and the baseline scores as the covariates. Second, the effect size of acupuncture of each original study will be combined in the meta-analysis.

Dissemination: Based on the IPD meta-analysis of high quality RCTs, this review will answer whether acupuncture is effective for FC. The findings of the review will be disseminated through peer-review publications and conference presentations.

Trial registration number: PROSPERO 2014: CRD42014009901

Strengths and Limitations of this study

1. This article is a study protocol of an individual data meta-analysis to evaluate the effectiveness, efficacy and safety of acupuncture treatment for patients with functional constipation.

2. The results of this study will offer more valid and reliable evidence for clinicians to make decisions during clinical practice.

3. The most difficult part of this study is collecting all the raw data of eligible trials by systematic search. We will actively communicate with the authors and researchers of these trials to ensure that the individual patient data can be collected and synthesized as complete as possible.

INTRODUCTION

Functional constipation (FC) is a common disease in clinical practice, which includes several symptoms such as decreased frequency of defecation, straining during defecation, hard stools, sensation of incomplete defecation, excessive time during defecation, and so on. The diagnosis of FC mainly depends on the individual's symptoms and several physiological examinations. The Rome Foundation published the Rome III criteria in 2006, which gave the consensus criteria for FC [1].

The incidences of FC are 12% to 19% in North American [2] and 14%in Asia [3], respectively. The prevalence of FC ranges from 0.7% to 81% worldwide [4, 5]. The annual cost for health care is $7,522 for constipation, accounting for 6.5% of the annual costs for lower gastrointestinal treatment [6]. Due to the high incidence and the expensive expenditure of FC, the public quality of life is significantly undermined. Therefore, FC can be considered as a major public health problem [7].

Treatments for FC are various. Lifestyle and dietary modification, such as more physical activities and fiber-rich diet are widely accepted and recommended by experts as the first-line therapy [8], although these may not be helpful all the time [9]. Conventional treatments for patients with FC are bulking agents, stool softeners, osmotic and stimulant laxatives, prokinetic agents (tegaserod, cisapride and mosapride) and so forth [10]. However, the side effects and the expensive expenditure are hard to be ignored. Therefore, more and more patients seek help from the complementary and alternative medicine [11].

As an important part of traditional Chinese medicine (TCM), acupuncture has been used to treat gastroenterological diseases for a long time, especially functional disorders, such as FC, diarrhea and dyspepsia [12]. Many clinical trials, which were conducted to discuss the efficacy of acupuncture for patients with FC, indicated that acupuncture could relieve the patients' symptoms. However, the results of systematic reviews didn't make determinate conclusion. There are three systematic reviews of acupuncture therapy for patients with FC that we have searched. The first one was published in 2010 [13], which could not draw a conclusion due to the serious methodological flaws of the included studies. The second and the third ones were published in 2012 [14] and 2013 [15], respectively. Both of these two reviews made a conclusion that acupuncture may have beneficial effect for FC. But according to the authors' conclusions, the clinical, methodological and statistical heterogeneity of the included studies made the results of these three systematic reviews above less convincing.

Since 2012, several new results of randomized controlled trials (RCTs) have been published, and two multicenter RCTs with large sample size have been ongoing [16, 17]. It is necessary to update the systematic review using a better method. Therefore, we will perform a meta-analysis based on the individual patient data (IPD) of high quality RCTs to find out whether acupuncture is effective and safe for the population with FC, and calculate the effect size.

METHODS AND ANALYSIS

Objectives

To establish the individual patient database by combining the raw data from high quality clinical trials of acupuncture treatment for FC, and to answer the question: is acupuncture effective for patients with FC?

We will answer this question in the following aspects:

1. Is acupuncture as effective as the positive drugs?

2. Is the real acupuncture superior to the sham acupuncture for patients with FC?

3. Is acupuncture superior to no treatment for patients with FC?

4. Is acupuncture safe for patients with FC?

Search strategy

We will conduct a systematic search in the following databases: MEDLINE, EMBASE, Cochrane Library, Chinese BioMedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), China's Important Conference Papers Database, and China's Dissertation Database from inception to May, 2014.

The following search terms will be used individually or combinedly: "acupuncture", "acupuncture therapy", "auricular acupuncture", "moxibustion", "acupressure", "constipation", "functional constipation", "idiopathic constipation", "randomized controlled trial", etc. Terms in Chinese will be used in Chinese databases. The search strategy is available in Additional file 1. We will include ongoing RCTs that evaluate the acupuncture treatment for FC through WHO

International Clinical Trial Registry Platform (ICTRP) portal and Clinical Trial Registry of the US National Institutes of Health.

Criteria for study eligibility

Published, unpublished and ongoing studies will be included in individual patient database, if they meet the following criteria:

Type of studies

We will include RCTs of acupuncture for FC only. Randomized and allocation concealment method should be clearly described. If not, we will contact the corresponding authors for further information about randomization process. Moreover, allocation concealment should be adequate to avoid the selection bias. In addition, considering the washout duration of acupuncture cannot be accurately evaluated, we will not include RCTs with crossover design. There will be no limitation on the sample size. But in order to guarantee the quality of included study, the sample size less than 30 will not be considered. All studies which meet the inclusion criteria will be invited to share the raw data.

Type of participants

Adult patients who are diagnosed with FC according to the Rome Ⅱ/Ⅲ criteria will be included. Or patients who are diagnosed with FC (or chronic constipation, primary constipation, idiopathic constipation) with other criteria and excluded by examinations for pathological diseases, such as post-surgery, tumor or obstruction will be also included in this research.

Types of intervention/exposure

Patients received acupuncture treatment as the primary intervention will be included, which means that patients in treatment group of each study were treated by acupuncture or acupuncture as the main intervention combined with other therapy, such as Chinese herbs, physical exercises. Any types of acupuncture will be included, such as manual acupuncture, electro-acupuncture, warming-needle moxibustion, auricular acupuncture, scalp acupuncture, pyonex, intradermal needling, acupoint injection with medicine, and so forth. According to the Rome Ⅱ/Ⅲ criteria, FC is not an acute disease. In order to alleviate the symptoms, several sessions of acupuncture treatment are necessary in clinical practice. One session of acupuncture treatment is only an acute relief. Through our previous study, the number of treatment sessions in RCTs range from 5 [18] to 28 [19]. And 10 to 20 sessions are most commonly used. So only the RCTs with a treatment protocol of at least 10 sessions will be included.

Types of controls

At least one control group of patients in the study should receive one of the following interventions: positive drugs, placebo controls, or no treatment.

Positive drugs: positive drugs which are used to treat constipation include bulk-forming laxatives, emollients, lubricants, osmotic laxatives, stimulants, and chloride-channel [20, 21].

Placebo controls: placebo controls include sham acupuncture, placebo drugs, sham interventions and so forth. Sham acupuncture is used to make patients believe they receive acupuncture stimulation, but without knowing if it is real or not. Sham acupuncture includes superficially insertion with needles in the specific acupoints; needles puncturing at non-specific acupoints, distal acupoints or non acupoints; placebo needles, such as Streitberger needles [22]; and other techniques which would make patients feel like needling.

No treatment is defined as any kind of methods as following: waiting list, which means that

patients in control group will not receive any acupuncture treatment until the trial is completed; general care or usual care, which means that patients in control group will only receive advices and/or healthy education, such as diet and/or exercises recommendation.

Types of outcome measurements

1. Primary outcomes

The primary outcome of this review is the change of the spontaneous defecation per week from the baseline.

2. Secondary outcomes

The secondary outcomes include the following aspects: proportion of responders, which is defined as the number of responders divided by the total number of participants in each group; the changes of the stool quality, which are assessed by Bistol stool scale or other objective measurements; mean transit time, which means that the time from the first perception of wanting to defecate to finish the defecation; proportion of patients using laxatives, which means that we will count the number of patients who used laxatives during trial to alleviate their symptoms. Besides, the proportion of adverse events will be also calculated according to the patients' reporting in each study.

Data collection

Study selection and data extraction

After electronic searches in the databases, two reviewers will independently screen the titles and abstracts to exclude: 1) the duplicates; 2) the studies of which the participants were not

met the criteria of FC; 3) the studies which were not RCTs with parallel design; and 4) the studies which the participants in an experimental group were not receiving acupuncture treatment as the primary intervention. Then, our reviewers will screen the full copies of studies which cannot be clearly screened just by titles and abstracts (the full copies screening form is available in the Additional file 2). Any disagreement will be resolved by consensus, or judged by a third reviewer.

The next step will be the two reviewers working independently to extract data of the studies. Training of data extraction and reviewer examination will be held in advance to guarantee the quality of extraction. Reviewers will document the following information in Data Extraction Form (Additional file 2): 1) the basic information of the study (the date and reviewer name of data extraction, study details, such as first author, year of publication, country of publication and publication type); 2) the characteristics of the study (design of the study, sample size, number of groups, methodology of randomization and allocation concealment, blinding, settings); 3) participants (age, gender, ethnicity, diagnosis, etc.); 4) interventions and controls (type of interventions, number and frequency of sessions, duration of treatment or follow-up, etc.); 5) outcomes (type of outcome, definition of outcome, time point of assessment, etc.) and 6) results (the statistic description of outcomes, such as mean, standard deviation, observed and total sample size, adverse events, etc.). Rechecking and discussion, or even the judgment from a third reviewer will be required, if there is any disagreement on data extraction.

Methodological quality assessment

The assessment of methodological quality is of great importance to systematic review. After data extraction, two reviewers will evaluate the methodological quality of each original study independently, and document the details in the Risk of bias assessment form. Discrepancies will

be resolved by consensus, or judged by a third reviewer. According to the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook (Version 5.1.0)), the methodological quality will be assessed by the following criteria: 1) randomization allocation; 2) randomization concealment; 3) blinding: 4) data integrity; 5) selective reporting; and 6) other bias, such as trial design, the baseline similarity of groups, early stopping of treatment and so on. For all the studies, the assessment should follow the above six aspects , and categorize as A, B or C grade of risk, which mean low, unclear and high risk of bias, respectively. And grade will be used to evaluate the quality of all the studies as the Cochrane collaboration's recommendation.

Regarding the characteristics of acupuncture clinical trial, we will also assess the quality of acupuncture interventions according to the STRICTA recommendation [23]. However, it is difficult to meet blinding for acupuncture treatment. Thus, we just ask for blinding assessment and statistical analysis. Any disagreements will be resolved by consensus, or a third reviewer will be consulted.

Raw data collection and checking

Corresponding authors of eligible studies will be contacted and invited to contribute the raw data. If the authors of the older studies could not provide the original data, we will present the details in the final report, and further analysis is necessary in the sensitivity analysis. The raw data will be transported in any manner that recognized as convenient by authors (such as emails) in any type of electronics format, such as SPSS, STATA, R, Excel, etc.. After checking the availability of the data files, all of them will be converted to a uniform format with its own name, which is composed of the first author's name and the year of publication.

Reviewers will check all the data carefully to find out whether there are any irrationality, obvious errors or missing of all the variables. If yes, we will contact the authors for further

information. After checking the data, we will calculate the data according to the statistical methodology of the published papers. If there is any inconsistent with the published results, we will require more information from investigators. For the studies which are still during the period of follow-up, we will ask the investigators to provide the latest data. Then, we will create a new data set for all the raw data, and harmonize the names and format of variables, which is convenient for further IPD meta-analysis.

For missing data, we will ask the investigator to recheck the missing part and find out whether it happened during the data entry, if not, we will use multiple imputation by the propensity score methods.

Raw data management

All the data will be stored in a computer with password protection at College of Acupuncture and Tuina, Chengdu University of TCM. Only the authorized members of this IPD study will be allowed to access to. Furthermore, there will be a Data Management Committee to supervise the reasonable and confidential use of the original data. Data governance is able to guarantee the safety of the relevant data from each study and the interests of multiple parties. And we will sign a confidential agreement with each raw data provider to make sure the anonymity of the individual patients' data.

Statistical methods

Heterogeneity

Heterogeneity test is an important step during conducting meta-analysis, which determines whether the data from studies are suitable and meaningful to synthesize or not. Only via

heterogeneity test and reasonable explanation, the result of the meta-analysis will be validate and reliable. Although, there is still controversy about the investigation of heterogeneity in IPD meta-analysis, we will use conventional method that is I^2 value (tested by Higgins I-squared test) to detect the heterogeneity of eligible studies. According to the Handbook of Cochrane, I^2 values are divided into four categories, and the value > 50% will be considered as significant heterogeneity among the included studies. As we mentioned before, the heterogeneity was significant in the previous systematic reviews of acupuncture for patients with FC. And the sources of heterogeneity that we speculate are the differences of patients' demographics, different style of acupuncture treatment (such as manual acupuncture, electro-acupuncture, or auricular acupuncture, etc.), the alliance of different interventions, outcomes and the time points, and so forth. Using IPD is a good way to deal with these problems above. And there are more possibilities to obtain the quantitative results rather than the qualitative ones. In our study, we will firstly calculate the effect size of acupuncture of each study by the standardized principle, and then conduct heterogeneity test and meta-analysis. If there is still a significant heterogeneity, we will perform meta-regression analysis to find out the sources and take appropriate actions to deal with them then. Explicit explain and relevant sensitivity analysis will be available in our final report.

Primary endpoint

The primary endpoint plays a vital role in final result. We will firstly identify primary endpoint (including outcome and time point) of each study. In this meta-analysis we will use the change of spontaneous defecation frequency per week from baseline, which is a continuous variable. So, if outcomes are ordinal data, count data based on times of defecation, we will convert them to continuous variable. While, some studies use Cleveland Clinic Score (CCS) [24] or colonic transit

time (CTT) [25] etc. after treatment as the primary endpoint. In this situation, we will create a standardized primary endpoint divided by pooled standard deviation.

Data analysis

1. Primary analysis

In this part the effect size of acupuncture will be analyzed in two steps. First, each original study will be reanalyzed by analysis of covariance with the standardized principal endpoint as the dependent variable, and the baseline characteristics as covariates (such as baseline situation, participants' characteristics, etc.), to calculate the effect size of acupuncture of FC. Second, all the effect size from the original studies will be included into meta-analysis by *meta or metafor package* in R project (www.r-project.org). During this process, we will choose an appropriate effects models, such as the fixed effects model or random effects model according to the heterogeneity. When the heterogeneity is not quite obviously, such as mild or moderate, we will perform both fixed and random effects model to calculate the effect size, and compare the differences. In this part of analysis, we will detect the effect size of acupuncture separately by comparing acupuncture with positive drugs, placebo controls and no treatment.

2. Secondary analysis

We will reanalyze the effect size for the changes of stool quality assessed by Bistol stool scale or other objective measurements, the proportion of responders, the mean transit time, the proportion of patients using laxatives, as well as the proportion of adverse events during the studies. Standardized mean differences will be used in the meta-analysis, if there are different measurement scales in the original studies. The continuous data will be described as mean and standardized difference (SD), while the categorical data will be described as counts or

percentages. Missing values will be handled by multiple imputation with the propensity score method.

Time point is a little difficult to determined, because of the different study design. According to the different observation courses, for our data, 4 weeks will be the cut-off point (or other time). And before the cut-off point, the time points before 4 weeks will be regarded as the short-term effects, while after will be regarded as the long-term effects. We will harmonize the time variables, for example, the 1 month is equivalent to 4 weeks. Any time point that investigators designed for assessment being around our uniformed time point is considered as the time point in this IPD study.

Furthermore, considering some factors which may have influence on the clinical outcomes, in this study we will analyze the characteristics of patients with FC (such as the age, gender, ethnicity and course of disease) as well as the acupuncture treatment (such as the number, frequency and duration of treatment sessions, the number of acupoints, and the different types of acupuncture intervention) by using logistic regression method. We will find out whether these characteristics have influence on the effect of acupuncture for FC.

Sen*sitivity analysis*

Sensitivity analysis will include the following aspects:

First, sensitivity analysis will be performed for publication bias. Although adequate inclusion and exclusion criteria that we designed can decrease the publication bias, we will also perform the sensitivity analysis to detect it. And funnel plot will be used if there are more than 10 studies included in this IPD study. Furthermore, the fail-safe number will be calculated to determine the degree of bias.

Second, because exclusion and drop-outs will be dealt with by the multiple imputation in the

statistical analysis according to the available data, thus, sensitivity analysis will be conducted in this aspect.

Third, the omitted studies and subgroups will be analyzed by sensitivity analysis. According to the quality assessment, some studies with high risk of bias or the subgroup with small sample size will not be included in meta-analysis. However, we will analyze all the data in sensitivity analysis by synthesizing these omitted studies or subgroups, and compare the results before and after data synthesis.

Fourth, it is known that the most difficult part of carrying out the IPD meta-analysis is collecting all the raw data of the eligible studies. Although we will actively communicate with the authors and researchers to collect the raw data as complete as possible, there is still a possibility that the raw data is obtained incomplete. If so, we will first conduct the conventional meta-analysis on the published data of all the eligible studies and of the studies with raw data available separately. Then, we will compare the analysis results of these two, in order to identify the possible selection bias.

Finally, as we mentioned above, we will perform both fixed and random effects model to detect the heterogeneity during conducting meta-analysis. Omitted studies which contribute to the greater heterogeneity will be also included in sensitivity analysis.

Ethics and dissemination

Because each eligible study has been approved by local institutional review board and ethical committee before the trial was conducted, and all participants included in were required to sign the written informed consent, this IPD meta-analysis study does not require further ethical approval.

This protocol of IPD meta-analysis of acupuncture for FC has been registered with PROSPERO (International Prospective Register of Systematic Reviews) at the NHS Centre for Reviews and Dissemination at the University of York (Registration number: CRD42014009901). All the items recommended by the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) [26] have been included in this protocol paper. The result of this review will provide valid and reliable evidence of acupuncture treatment for patients with FC. The findings of this review will also give implication for clinical practice and further research, and be disseminated by peer-review publications and conference presentations.

DISCUSSION

Individual patient data meta-analysis of high quality trials will provide the most reliable evidence for clinical treatment decisions. Based on the solid foundation of both clinical practice and academic research of our research team, we believe that the results of this study will be fruitful and valid to make a conclusion of acupuncture treatment for FC.

We design this IPD meta-analysis protocol referring to the previous relevant studies [27, 28]. However, our study has some limitations. Characteristics of both acupuncture and patients would possibly influence the therapeutic effects of acupuncture in clinical practice. And the changing of acupuncture effects with time course is also interesting for making treatment schedule. These factors that we mentioned above will be partly in this protocol, but we plan to analyze all the relevant factors in future, in order to offer more information for clinical practice and scientific research. Moreover, the most difficult part of this study is acquiring the complete raw data from original trials. To deal with this problem, we will take the following steps: first of all, we will follow the strict inclusion criteria and conduct the systematic search to locate the

eligible trials. Secondly, we will actively contact and communicate with authors and researchers of included RCTs, and invite them to participate in this study and offer data as complete as possible. Lastly, we will strictly follow relevant agreements and contracts signed with every data provider to protect the mutual interests during conducting this study. If the raw data could not be fully obtained, we will report the details and the results of possible bias.

In a word, we sincerely hope that the findings of this review will guide the future treatments for FC, and translate the contributions of clinical researches into patient benefits.

Abbreviations

RCTs: randomized controlled trials; TCM: traditional Chinese medicine; IPD: individual patient data; FC: functional constipation.

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Contributors

The study was conceived and overall design by QHZ and HZ. SR and WJH made contributions to the design of statistical analysis and monitor the quality of included RCTs. QHZ, HZ, SYZ, LYL, HBZ and JCL form the Data Management Committee and have responsibility for study research and data safety. LYL, JCL and SYZ are reviewers of data extraction, checking and collection. QHZ and HZ are responsible for overall data analysis. HZ, YL, ZSL and BZ, who form the Research Steering Committee, contribute suggestion to the design of this study and individual patient data to meta-analysis. YL is responsible for the whole quality of study. This manuscript was written and revised by QHZ and HZ. All authors read this manuscript and approved the publication of this protocol.

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Competing interests

The authors declare that they have no competing interests.

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Additional File 1. Search strategy for MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. (randomized or randomised).ab.
4. placebo.ab.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp constipation/
10. functional constipation.ab,ti.
11. primary constipation.ab,ti.
12. chronic constipation.ab,ti.
13. idiopathic constipation.ab,ti.
14. slow transit constipation.ab,ti.
15. (obstipation or “fecal impaction” or astriction or costiveness or coprostasis).ab,ti.
16. 10 or 11 or 12 or 13 or 14 or 15
17. exp acupuncture therapy/
18. exp acupuncture/
19. (needling or needle or prod or pinprick or pricking).ab,ti.
20. exp acupuncture points/
21. (acupunctur* or acupoint or "acupoint application" or "point application" or "external application therapy" or "acupoint inject*" or "point inject*" or "inject* to point" or "inject* to acupoint").ab,ti.
22. exp electroacupuncture/
23. (electroacupunctur* or acusector* or "thermoelectric needle" or electro-acupunctur*).ab,ti.
24. exp auriculotherapy/
25. exp acupuncture, ear/
26. (otopoint* or "ear hole planted seeds" or "ear buried seeds" or auricular*).ab,ti.
27. exp moxibustion/
28. moxa*.ab,ti.
29. exp acupressure/
30. exp meridians/
31. (embedd* or "catgut implantation at acupoint*" or "acupoint catgut embedd*" or "catgut embedd* therap*").ab,ti.
32. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 8 and 16
34. 32 and 33

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

Additional File 2.

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

Study Eligibility Form

- for full copies screening

Ref ID:

First author:

Reviewers:

Included □

Excluded □ because:

1. Not adult FC subjects (FC should be diagnosed according to the Rome Ⅱ/Ⅲ criteria or other valid criteria without pathological diseases) □

2. Patients with FC not randomized to the treatment and control group □

3. Types of intervention not meet the included criteria □

4. No outcomes provided for FC patients □

5. Other reasons (specify)_____

Consultation required □

Included by consensus □ because:_____

Excluded by consensus □

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

Data Extraction Form

Date:

Reviewers:

General information

Title	
First author	
Year of publication	
Country of publication	
Language	
Publication type	

Study methodology

Trial design	parallel group only □
Randomization method	
Allocation concealment method	
Blinding	
Setting	
Number of participants	
Number of groups	
Duration	
Follow-up duration	
Funding source	

Participants				
	Group 1	Group 2	Group 3	Group 4
Age (Mean ±SD)				
Gender (M/F)				
Ethnicity				
Diagnosis				
Concurrent condition				
Duration of condition				
Severity of condition				
Laboratory parameters				
Other				

Intervention and controls

Acupuncture therapy	
Stimulation type	
Number of sessions	
Frequency of sessions	
Duration of sessions	
Point prescription	
Combination with other acupuncture therapy	Yes □ (specify) _____ No □
Information of acupuncturists	
Drug combination	

Others	
Controls (including the names, dose, duration of therapy, frequency duration etc.)	
Positive drugs	
Placebo controls	
No treatment	
Compliance	

Outcomes (including the names, methods, definitions, time points)	
Primary outcome (s)	
Secondary outcomes	

Results

Outcomes (including the names, mean, SD etc.)				
	Group 1	Group 2	Group 3	Group 4
Primary outcomes				
Secondary outcomes				
Observed events				
Total sample size				
Adverse events				
Total randomized				
Excludes*				

Withdrawals*				
Lost to follow-up*				
Request for further information				

*including reasons

Risk of bias assessment

1. Was randomized allocation sequence adequately generated?

Yes □ No □ Unclear □

2. Was allocation adequately concealed?

Yes □ No □ Unclear □

3. Who were blinded to the allocation during the study?

Patients	Yes □	No □	Unclear □
Investigators	Yes □	No □	Unclear □
Outcomes assessors	Yes □	No □	Unclear □
Data assessors	Yes □	No □	Unclear □

4. Was the data integrated in this reporting (including the description of the reasons of withdrawals and drop-outs)?

Yes □ No □ Unclear □

5. Were there any selective reporting?

Yes □ No □ Unclear □

6. Did the acupuncture intervention meet the criteria of STRICTA?

Yes □ No □ Unclear □

6. Other bias (specify)_____

Risk of bias	Interpretation	Relationship to individual criteria
A - Low risk of bias	Plausible bias unlikely to seriously alter the results	All of the criteria met
B – Moderate risk of bias	Plausible bias that raises some doubt about the results	One or more criteria partly met
C – High risk of bias	Plausible bias that seriously	One or more criteria not met

	weakens confidence in the results	

Grade:_____

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Section of this manuscript	Page No
Administrative information				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Title	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Notes under the Title, Author affiliations	1-2, 18-19
Contributions	3b	Describe contribution of protocol authors and identify the guarantor of the review	Contributions	19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Funding	19
Sponsor	5b	Provide name for the review funder and/ or sponsor	Funding	19
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	
Introduction				
Rationale	6	Describe the rational for the review in the context of what is already known	Introduction	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes(PICO)	Introduction, Objectives	4-6
Methods				

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Criteria for study eligibility	7-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Search strategy, Data collection (Raw data collection and checking)	6-7, 11-12
Search strategy	10	Present draft of search strategy to be used for at least on electronic database, including planned limits, such that it could be repeated	Search strategy, Additional file 1	6-7, Additional file 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Data collection (Raw data management)	12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Data collection (Study selection and data extraction)	9-10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Data collection (Study selection and data extraction, Raw data collection and checking)	9-10, 11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Data collection (Study selection and data extraction), Additional file 2	9-10, Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Criteria for study eligibility (Types of outcomes measurements)	9
Risk of bias in individual studies	14	Describe anticipated methods of assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methodological quality assessment, Statistical methods (Heterogeneity, Sensitivity analysis)	10-11, 12-13, 15-16

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Criteria for study eligibility (Types of outcomes measurements), Statistical methods	9, 12-16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measure, methods of handing data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's T)	Statistical methods	12-16
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Statistical methods (Sensitivity analysis)	15-16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Statistical methods (Heterogeneity, Sensitivity analysis)	12-13, 15-16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Statistical methods	12-16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methodological quality assessment	10-11

BMJ Open

Acupuncture for functional constipation: protocol for an individual patient data meta-analysis

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Secondary Subject Heading:	Complementary medicine
Keywords:	COMPLEMENTARY MEDICINE, Functional bowel disorders < GASTROENTEROLOGY, Gastroenterology < INTERNAL MEDICINE

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

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ABSTRACT

Introduction: Functional constipation (FC) is a common gastrointestinal disease. Systematic reviews indicate that acupuncture may be effective for patients with FC. However, this conclusion is not convincing due to the quality, sample size, and methodological heterogeneity of the studies included by these systematic reviews. Therefore, it is necessary for us to conduct a meta-analysis of individual patient data (IPD) from high quality clinical trials to determine whether acupuncture is effective for FC patients.

Methods and analysis: Randomised controlled trials (RCTs) of acupuncture for adult patients with FC will be searched in several databases from inception to May 2014. The corresponding authors of eligible studies will be contacted and invited to contribute raw data. The primary outcome is the change in spontaneous defecation per week from baseline. The secondary outcomes include proportion of responders, changes in stool quality, mean transit time, proportion of patients using laxatives and adverse events. We will check all of the data and perform reanalysis according to statistical methodology reported in previous publications. Then, we will harmonise the raw data and use a two-step method to conduct the IPD meta-analysis. First, we will calculate the effect size of acupuncture of each trial by analysis of covariance, with the principal endpoint as the dependent variable and the baseline scores as the covariates. Second, the effect size of acupuncture in each original study will be combined in the meta-analysis.

Dissemination: Based on the IPD meta-analysis of high quality RCTs, this review will answer the question of whether acupuncture is effective for FC. The findings of the review will be disseminated through peer-review publications and conference presentations.

Trial registration number: PROSPERO 2014: CRD42014009901

Strengths and Limitations of this study

1. This article is a study protocol of an individual patient data meta-analysis to evaluate the effectiveness, efficacy and safety of acupuncture treatment for patients with functional constipation.

2. The results of this study will offer more valid and reliable evidence for clinicians to make decisions during clinical practice.

3. One difficult step of this study is collecting all the raw data of eligible trials by systematic search, which may be the limitation of this meta-analysis. We will actively communicate with the authors and researchers of these trials to ensure that the individual patient data can be collected and synthesised as completely as possible.

INTRODUCTION

Functional constipation (FC) is a common disease in clinical practice, and it includes several symptoms such as decreased frequency of defecation, straining during defecation, hard stools, sensation of incomplete defecation, and excessive time during defecation. The diagnosis of FC mainly depends on the individual's symptoms and several physiological examinations. The Rome Foundation published the Rome III criteria in 2006, which listed the consensus criteria for FC.[1]

Several systematic reviews have reported prevalence of constipation in different populations. It was reported that the prevalence of FC in North America ranged from 12% to 19%.[2] And the mean value of prevalence of constipation in general population of Europe and Oceania were 17.1% and 15.3%, respectively.[3] A meta-analysis found that a pooled prevalence of FC in the community was 14%.[4] The annual cost for health care was $7,522 for constipation, accounting for 6.5% of the annual costs for lower gastrointestinal treatment, reported by Nyrop KA et al.[5]

Due to the high incidence and the expensive expenditure of FC, patients' quality of life is significantly undermined. Therefore, FC can be considered as a major public health problem.[6]

Treatments for FC vary. Lifestyle and dietary modifications, such as increased physical activity and a fibre-rich diet are widely accepted and recommended by experts as first-line therapy,[7] although these methods may not be effective for every patient.[8] Conventional treatments for patients with FC include bulking agents, stool softeners, osmotic and stimulant laxatives, prokinetic agents (tegaserod, cisapride and mosapride) and so forth.[9] However, the side effects and the expensive expenditures of such treatments are difficult to ignore. Therefore, an increasing number of patients seek help from the complementary and alternative medicine.[10]

As an important part of traditional Chinese medicine (TCM), acupuncture has been used to treat gastroenterological diseases for a long time, especially functional disorders, such as FC, functional diarrhoea and functional dyspepsia.[11] Many clinical trials, which were conducted to investigate the efficacy of acupuncture for patients with FC, indicated that acupuncture could relieve the patients' symptoms. However, the results of systematic reviews did not reach a definitive conclusion. We found three systematic reviews of acupuncture therapy for patients with FC through systematic search. The first review was published in 2010,[12] which could not draw a conclusion due to the serious methodological flaws of the included studies. The second and third reviews were published in 2012[13] and 2013[14], respectively. Both of these reviews concluded that acupuncture may have beneficial effect for FC. However, according to the authors' conclusions, the clinical, methodological and statistical heterogeneity of the included studies made the results of these three systematic reviews less convincing.

Since 2012, several new results of randomised controlled trials (RCTs) have been published, and two multicentre RCTs with large sample sizes have been ongoing.[15 16] It is necessary to update the systematic review using a better method. Therefore, we will perform a meta-analysis

based on the individual patient data (IPD) of high quality RCTs to determine whether acupuncture is effective and safe for people with FC and to calculate the effect size.

METHODS AND ANALYSIS

Objectives

To establish the individual patient database by combining the raw data from high quality clinical trials of acupuncture treatment for FC, and to answer the question: is acupuncture effective for patients with FC?

We will answer this question in the following aspects:

1. Is acupuncture as effective as the positive drugs?
2. Is real acupuncture superior to sham acupuncture for patients with FC?
3. Is acupuncture superior to no treatment for patients with FC?
4. Is acupuncture safe for patients with FC?

Search strategy

We will conduct a systematic search of the following databases: MEDLINE, EMBASE, Cochrane Library, Chinese BioMedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), China's Important Conference Papers Database, and China's Dissertation Database from inception to May 2014.

The following search terms will be used individually or combined: "acupuncture", "acupuncture therapy", "auricular acupuncture", "moxibustion", "acupressure", "constipation",

"functional constipation", "idiopathic constipation", "randomized/randomised controlled trial", etc. Terms in Chinese will be used in Chinese databases. The search strategy is available in Additional file 1. We will include ongoing RCTs that evaluate acupuncture treatment for FC through WHO International Clinical Trial Registry Platform (ICTRP) portal and Clinical Trial Registry of the US National Institutes of Health.

Criteria for study eligibility

Published, unpublished and ongoing studies will be included in the individual patient database if they meet the following criteria.

Type of studies

We will include RCTs of acupuncture for FC only. Randomised and allocation concealment methods should be clearly described; if not, we will contact the corresponding authors for further information about the randomisation process. Moreover, allocation concealment should be adequate to avoid selection bias. Additionally, considering that the washout duration of acupuncture cannot be accurately evaluated, we will not include RCTs with crossover designs. To guarantee the quality of an included study, only sample sizes of more than 30 will be considered. The authors of the studies that meet the inclusion criteria will be invited to share the raw data.

Type of participants

Adult patients who are diagnosed with FC according to the Rome Ⅱ/Ⅲ criteria will be included. Patients who are diagnosed with FC (or chronic constipation, primary constipation, idiopathic

constipation) with other criteria and who are excluded by examinations for pathological diseases, such as post-surgery, tumour or obstruction, will also be included in this study.

Types of intervention/exposure

Patients who received acupuncture treatment as the primary intervention will be included, which means that patients in the treatment group of each study were treated by acupuncture or that acupuncture was the main intervention combined with other therapy, such as Chinese herbs or physical exercise. Any type of acupuncture will be included, such as manual acupuncture, electro-acupuncture, warming-needle moxibustion, auricular acupuncture, scalp acupuncture, pyonex, intradermal needling, acupoint injection with medicine, and so forth. According to the Rome Ⅱ/Ⅲ criteria, FC is not an acute disease. To alleviate the symptoms, several sessions of acupuncture treatment are necessary in clinical practice. One session of acupuncture treatment only provides acute relief. According to our previous study, the number of treatment sessions in RCTs ranged from 5[17] to 28[18], and 10 to 20 sessions are most commonly used. Therefore, only the RCTs with a treatment protocol of at least 10 sessions will be included.

Types of controls

At least one control group of patients in the study should receive one of the following interventions: positive drugs, placebo controls, or no treatment.

Positive drugs: positive drugs that are used to treat constipation include bulk-forming laxatives, emollients, lubricants, osmotic laxatives, stimulants, and chloride-channel activators.[19 20]

Placebo controls: placebo controls include sham acupuncture, placebo drugs, sham interventions and so forth. Sham acupuncture is used to make patients believe they receive acupuncture stimulation, without knowing whether it is real or not. Sham acupuncture includes

superficial insertion with needles at specific acupoints; needles puncturing at non-specific acupoints, distal acupoints or non acupoints; placebo needles, such as Streitberger needles;[21] and other techniques, which would make patients feel like needle penetration.

No treatment is defined as any of the following: waiting list, which means that patients in the control group do not receive any acupuncture treatment until the trial is completed; general care or usual care, which means that patients in the control group only receive advice and/or health education, such as diet and/or exercise recommendations.

Types of outcome measurements

1. Primary outcomes

The primary outcome of this review is the change in spontaneous defecation per week from baseline.

2. Secondary outcomes

The secondary outcomes include the following items: proportion of responders, which is the number of responders divided by the total number of participants in each group; changes in stool quality, which are assessed by the Bistol stool scale or other objective measurements; mean transit time, which is the time from the first perception of wanting to defecate to the finish of defecation; proportion of patients using laxatives, which is the number of patients who used laxatives during the trial to alleviate their symptoms. In addition, the proportion of adverse events will also be calculated according to patient reports in each study.

Data collection

Study selection and data extraction

After electronic searches in the databases, two reviewers will independently screen the titles and abstracts to exclude: 1) the duplicates; 2) the studies in which the participants did not meet the criteria of FC; 3) the studies that were not RCTs with parallel design; and 4) the studies in which the participants in the experimental group did not receive acupuncture treatment as the primary intervention. Then, our reviewers will screen the full copies of studies that cannot be clearly screened by titles and abstracts only (the full copies screening form is available in Additional file 2). Any disagreement will be resolved by consensus or judged by a third reviewer.

Next, two reviewers will independently extract the data from the studies. Training in data extraction and reviewer examination will be conducted in advance to guarantee the quality of extraction. Reviewers will document the following information on the Data Extraction Form (Additional file 2): 1) the basic information of the study (the date, reviewer name of data extraction, and study details, such as first author, year of publication, country of publication and publication type); 2) the study characteristics (design of the study, sample size, number of groups, methodology of randomisation and allocation concealment, blinding, settings); 3) participants (age, gender, ethnicity, diagnosis, etc.); 4) interventions and controls (type of interventions, number and frequency of sessions, duration of treatment or follow-up, etc.); 5) outcomes (type of outcome, definition of outcome, time point of assessment, etc.); and 6) results (the statistic description of outcomes, such as mean, standard deviation, observed and total sample size, adverse events, etc.). Rechecking and discussion, or even the judgment from a third reviewer will be required if there is any disagreement during the data extraction.

Methodological quality assessment

The assessment of methodological quality is of great importance to systematic reviews. After

data extraction, two reviewers will evaluate the methodological quality of each original study independently and will document the details in the Risk of bias assessment form. Discrepancies will be resolved by consensus or judged by a third reviewer. According to the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook (Version 5.1.0)), the methodological quality will be assessed by the following criteria: 1) randomisation allocation; 2) randomisation concealment; 3) blinding; 4) data integrity; 5) selective reporting; and 6) other bias, such as trial design, baseline similarity of groups, early cessation of treatment and so forth. For all of the studies, the assessment should follow the above six criteria and be categorised as A, B or C grade of risk (low, unclear and high risk of bias, respectively). The risk grade will be used to evaluate the quality of all the studies based on the Cochrane collaboration's recommendation.

Regarding the characteristics of acupuncture clinical trials, we will also assess the quality of acupuncture interventions according to the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) recommendation.[22] However, it is difficult to achieve blinding for acupuncture treatment. Therefore, we only ask for blinding assessment and statistical analysis. Any disagreements will be resolved by consensus; otherwise, a third reviewer will be consulted.

Raw data collection and checking

The corresponding authors of eligible studies will be contacted and invited to contribute the raw data. If the authors of the older studies cannot provide the original data, we will present the details in the final report, and further analysis will be necessary in the sensitivity analysis. The raw data will be provided in any manner that is convenient for authors (such as by email) in any type of electronic format, such as SPSS, STATA, R, Excel, etc. After checking the availability of the

data files, all of the data will be converted to a uniform format with its own name, which will be composed of the first author's name and the year of publication.

Reviewers will check all the data carefully to determine whether there are any of obvious errors, irrational or missing data; if any of these issues are found, we will contact the authors for further information. After checking the data, we will calculate the data according to the statistical methodology of the published papers. If there are any inconsistencies regarding the published results, we will require more information from the investigators. For the studies that are still being conducted, we will ask the investigators to provide the most recent data. Then, we will create a new dataset for all the raw data and harmonise the names and format of variables, which will be used for further IPD meta-analysis.

For missing data, we will ask the investigators to recheck the missing data and determine whether this omission happened during data entry. If not, we will use multiple imputation by the propensity score methods.

Raw data management

All the data will be stored in a computer with password protection at College of Acupuncture and Tuina, Chengdu University of TCM. Only authorised members of this IPD study will be allowed to access the computer. Furthermore, there will be a Data Management Committee to supervise the reasonable and confidential use of the original data. Data governance is intended to guarantee the safety of the relevant data from each study and the interests of multiple parties. We will sign a confidentiality agreement with each raw data provider to ensure the anonymity of the individual patients' data.

Statistical methods

Heterogeneity

Heterogeneity test is an important step in conducting a meta-analysis, as it determines whether the data from studies are suitable and meaningful to synthesise. The result of a meta-analysis will be valid and reliable if a heterogeneity test is conducted and a reasonable explanation is provided. However, there is still controversy regarding the investigation of heterogeneity in an IPD meta-analysis; thus, we will use a conventional method, I^2 value (tested by Higgins I-squared test), to detect the heterogeneity of eligible studies. According to the Handbook of Cochrane, I^2 values are divided into four categories, and a value > 50% will be considered as significant heterogeneity amongst the included studies. As previously mentioned, the heterogeneity was significant in the previous systematic reviews of acupuncture for patients with FC. The sources of heterogeneity that we speculate are differences in patients' demographics, different styles of acupuncture treatment (such as manual acupuncture, electro-acupuncture, or auricular acupuncture, etc.), the alliance of different interventions, different outcomes and time points. Using IPD is an effective way to address these heterogeneity issues. Therefore, there are more possibilities to obtain quantitative results rather than qualitative results. In this study, we will first calculate the effect size of acupuncture of each study by the standardised principle and then conduct a heterogeneity test and meta-analysis. If significant heterogeneity remains, we will perform a meta-regression analysis to determine the sources and will take appropriate action to address them. An explicit explanation and relevant sensitivity analysis will be available in our final report.

Primary endpoint

The primary endpoint plays a vital role in final result. We will first identify the primary endpoint (including outcome and time point) of each study. In this meta-analysis, we will use the change

in spontaneous defecation frequency per week from baseline, which is a continuous variable. If outcomes are ordinal data or count data based on times of defecation, we will convert them to continuous variables. Some studies use Cleveland Clinic Score (CCS)[23] or colonic transit time (CTT)[24] after treatment as the primary endpoint. In this situation, we will create a standardised primary endpoint divided by pooled standard deviation.

Data analysis

1. Primary analysis

The effect size of acupuncture will be analysed in two steps. First, each original study will be reanalysed by analysis of covariance with the standardised principal endpoint as the dependent variable and the baseline characteristics as covariates (such as baseline situation, participants' characteristics, etc.) to calculate the effect size of acupuncture for FC. Second, all the effect sizes from the original studies will be included into the meta-analysis by *meta or metafor package* in R project (www.r-project.org). During this process, we will choose an appropriate effects model, such as the fixed effects model or random effects model according to the heterogeneity. If the heterogeneity is not obvious, e.g., mild or moderate, we will perform both fixed and random effects models to calculate the effect size and compare the differences. In this step of the analysis, we will detect the effect size of acupuncture separately by comparing acupuncture with positive drugs, placebo controls and no treatment.

2. Secondary analysis

We will reanalyse the effect size for the changes in stool quality assessed by the Bistol stool scale or other objective measurements, the proportion of responders, the mean transit time, the proportion of patients using laxatives, and the proportion of adverse events during the

studies. Standardised mean differences will be used in the meta-analysis if there are different measurement scales in the original studies. The continuous data will be described as mean and standardised difference (SD), and the categorical data will be described as counts or percentages. Missing values will be addressed by multiple imputation with the propensity score method.

Time points are difficult to determine, because of the different study designs. According to the different observation courses, for our data, 4 weeks will be the cut-off point. Before the cut-off point, the time points before 4 weeks will be regarded as the short-term effects, and the points there after will be regarded as the long-term effects. We will harmonise the time variables (e.g., 1 month is equivalent to 4 weeks). Any time point that investigators designed for assessment close to our uniformed time point will be considered as the time point in this IPD study.

Furthermore, considering some factors that may influence clinical outcomes, we will analyse the characteristics of patients with FC (such as the age, gender, ethnicity and course of disease) as well as the characteristics of acupuncture treatment (such as the number, frequency and duration of treatment sessions, the number of acupoints, and the different types of acupuncture interventions) using a logistic regression method. We will determine whether these characteristics influence the effect of acupuncture for FC.

Sen*sitivity analysis*

Sensitivity analysis will include the following aspects:

First, sensitivity analysis will be performed for publication bias. Although the inclusion and exclusion criteria that we designed can decrease publication bias, we will also perform the sensitivity analysis to detect it. A funnel plot will be used if more than 10 studies are included in this IPD study. Furthermore, the fail-safe number will be calculated to determine the degree of

bias.

Second, because exclusion and drop-outs will be processed by multiple imputation in the statistical analysis according to the available data, a sensitivity analysis will be conducted.

Third, the omitted studies and subgroups will be analysed by sensitivity analysis. According to the quality assessment, some studies with a high risk of bias or a subgroup with a small sample size will not be included in the meta-analysis. However, we will analyse all the data in sensitivity analysis by synthesising these omitted studies or subgroups and will compare the results before and after data synthesis.

Fourth, it is known that one difficult step of conducting the IPD meta-analysis is collecting all the raw data from the eligible studies. Although we will actively communicate with the authors and researchers to collect the raw data as completely as possible, there is still a possibility that the raw data will be incomplete. If so, we will first conduct the conventional meta-analysis on the published data of all the eligible studies and of the studies with raw data available separately. Then, we will compare the analysis results of these two, in order to identify the possible selection bias.

Finally, as we mentioned above, we will perform both fixed and random effects models to detect heterogeneity during the meta-analysis. Omitted studies that contribute to greater heterogeneity will also be included in the sensitivity analysis.

Ethics and dissemination

Because each eligible study was approved by local institutional review boards and ethical committees before the trial was conducted, and all of the participants included were required to sign the written informed consent, this IPD meta-analysis study does not require further ethical

approval.

This protocol of IPD meta-analysis of acupuncture for FC has been registered with International Prospective Register of Systematic Reviews (PROSPERO) at the NHS Centre for Reviews and Dissemination at the University of York (Registration number: CRD42014009901). All the items recommended by the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[25] have been included in this protocol paper. The result of this review will provide valid and reliable evidence of acupuncture treatment for patients with FC. The findings of this review will also provide implications for clinical practice and further research, and will be disseminated by peer-review publications and conference presentations.

DISCUSSION

Individual patient data meta-analysis of high quality trials will provide the most reliable evidence for clinical treatment decisions. Based on the solid foundation of both clinical practice and academic research of our research team, we believe that the results of this study will be fruitful and valid to determine definitive conclusions regarding acupuncture treatment for FC.

We designed this IPD meta-analysis protocol based on previous relevant studies.[26 27] However, our study has some limitations. Characteristics of both acupuncture and patients can possibly influence the therapeutic effects of acupuncture in clinical practice. The changes in acupuncture effects over time play a role in creating a treatment schedule. The factors discussed above will be included in this protocol, but we plan to analyse all of the relevant factors in the future, to offer more information for clinical practice and scientific research. Moreover, one difficult step of this study is acquiring the complete raw data from original trials. To address this problem, we will take the following steps: first, we will follow the strict inclusion criteria and conduct the

systematic search to locate the eligible trials. Second, we will actively contact and communicate with the authors and researchers of included RCTs and invite them to participate in this study and to offer data as completely as possible. Finally, we will strictly follow relevant agreements and contracts signed with every data provider to protect mutual interests during this study. If the raw data cannot be fully obtained, we will report the details and the results of possible bias.

We sincerely hope that the findings of this review will guide future treatments for FC and translate the contributions of clinical research into patient benefits.

Abbreviations

RCTs: randomised controlled trials; TCM: traditional Chinese medicine; IPD: individual patient data; FC: functional constipation.

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Contributors

The study was conceived and designed by QHZ and HZ. SR and WJH contributed to the design of statistical analysis and will monitor the quality of the included RCTs. QHZ, HZ, SYZ, LYL, HBZ and JCL form the Data Management Committee and have responsibility for study research and data safety. LYL, JCL and SYZ are reviewers of data extraction, checking and collection. QHZ and HZ are responsible for overall data analysis. HZ, YL, ZSL and BZ, who form the Research Steering Committee, contribute suggestions to the design of this study and individual patient data to meta-analysis. YL is responsible for the overall quality of the study. This manuscript was written and revised by QHZ and HZ. All authors read this manuscript and approved the publication of this protocol.

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Competing interests

The authors declare that they have no competing interests.

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Search strategy for **MEDLINE**

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. (randomized or randomised).ab.
4. placebo.ab.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp constipation/
10. functional constipation.ab,ti.
11. primary constipation.ab,ti.
12. chronic constipation.ab,ti.
13. idiopathic constipation.ab,ti.
14. slow transit constipation.ab,ti.
15. (obstipation or “fecal impaction” or astriction or costiveness or coprostasis).ab,ti.
16. 10 or 11 or 12 or 13 or 14 or 15
17. exp acupuncture therapy/
18. exp acupuncture/
19. (needling or needle or prod or pinprick or pricking).ab,ti.
20. exp acupuncture points/
21. (acupunctur* or acupoint or "acupoint application" or "point application" or "external application therapy" or "acupoint inject*" or "point inject*" or "inject* to point" or "inject* to acupoint").ab,ti.
22. exp electroacupuncture/
23. (electroacupunctur* or acusector* or "thermoelectric needle" or electro-acupunctur*).ab,ti.
24. exp auriculotherapy/
25. exp acupuncture, ear/
26. (otopoint* or "ear hole planted seeds" or "ear buried seeds" or auricular*).ab,ti.
27. exp moxibustion/
28. moxa*.ab,ti.
29. exp acupressure/
30. exp meridians/
31. (embedd* or "catgut implantation at acupoint*" or "acupoint catgut embedd*" or "catgut embedd* therap*").ab,ti.
32. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 8 and 16
34. 32 and 33

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

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

Study Eligibility Form

- for full copies screening

Ref ID:

First author:

Reviewers:

Included □

Excluded □ because:

1. Not adult FC subjects (FC should be diagnosed according to the Rome Ⅱ/Ⅲ criteria or other valid criteria without pathological diseases) □

2. Patients with FC not randomized to the treatment and control group □

3. Types of intervention not meet the included criteria □

4. No outcomes provided for FC patients □

5. Other reasons (specify)_____

Consultation required □

Included by consensus □ because:_____

Excluded by consensus □

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

Data Extraction Form

Date:

Reviewers:

General information

Title	
First author	
Year of publication	
Country of publication	
Language	
Publication type	

Study methodology

Trial design	parallel group only □
Randomization method	
Allocation concealment method	
Blinding	
Setting	
Number of participants	
Number of groups	
Duration	
Follow-up duration	
Funding source	

Participants				
	Group 1	Group 2	Group 3	Group 4
Age (Mean ±SD)				

Gender (M/F)				
Ethnicity				
Diagnosis				
Concurrent condition				
Duration of condition				
Severity of condition				
Laboratory parameters				
Other				

Intervention and controls

Acupuncture therapy	
Stimulation type	
Number of sessions	
Frequency of sessions	
Duration of sessions	
Point prescription	
Combination with other acupuncture therapy	Yes □ (specify) No □
Information of acupuncturists	
Drug combination	
Others	
Controls (including the names, dose, duration of therapy, frequency duration etc.)	
Positive drugs	

Placebo controls	
No treatment	
Compliance	

Outcomes (including the names, methods, definitions, time points)	
Primary outcome (s)	
Secondary outcomes	

Results

Outcomes (including the names, mean, SD etc.)				
	Group 1	Group 2	Group 3	Group 4
Primary outcomes				
Secondary outcomes				
Observed events				
Total sample size				
Adverse events				
Total randomized				
Excludes*				
Withdrawals*				

Lost to follow-up*				
Request for further information				

*including reasons

Risk of bias assessment

1. Was randomized allocation sequence adequately generated?

Yes □ No □ Unclear □

2. Was allocation adequately concealed?

Yes □ No □ Unclear □

3. Who were blinded to the allocation during the study?

Patients	Yes □	No □	Unclear □
Investigators	Yes □	No □	Unclear □
Outcomes assessors	Yes □	No □	Unclear □
Data assessors	Yes □	No □	Unclear □

4. Was the data integrated in this reporting (including the description of the reasons of withdrawals and drop-outs)?

Yes □ No □ Unclear □

5. Were there any selective reporting?

Yes □ No □ Unclear □

6. Did the acupuncture intervention meet the criteria of STRICTA?

Yes □ No □ Unclear □

6. Other bias (specify)_____

Risk of bias	Interpretation	Relationship to individual criteria
A - Low risk of bias	Plausible bias unlikely to seriously alter the results	All of the criteria met
B – Moderate risk of bias	Plausible bias that raises some doubt about the results	One or more criteria partly met
C – High risk of bias	Plausible bias that seriously weakens confidence in the results	One or more criteria not met

Grade:_____

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Section of this manuscript	Page No
Administrative information				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Title	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Notes under the Title, Author affiliations	1-2, 18-19
Contributions	3b	Describe contribution of protocol authors and identify the guarantor of the review	Contributors	19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Funding	19
Sponsor	5b	Provide name for the review funder and/ or sponsor	Funding	19
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	
Introduction				
Rationale	6	Describe the rational for the review in the context of what is already known	Introduction	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes(PICO)	Introduction, Objectives	4-6
Methods				

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Criteria for study eligibility	7-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Search strategy, Data collection (Raw data collection and checking)	6-7, 11-12
Search strategy	10	Present draft of search strategy to be used for at least on electronic database, including planned limits, such that it could be repeated	Search strategy, Additional file 1	6-7, Additional file 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Data collection (Raw data management)	12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Data collection (Study selection and data extraction)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Data collection (Study selection and data extraction, Raw data collection and checking)	10, 11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Data collection (Study selection and data extraction), Additional file 2	10, Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Criteria for study eligibility (Types of outcomes measurements)	9
Risk of bias in individual studies	14	Describe anticipated methods of assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methodological quality assessment, Statistical methods (Heterogeneity, Sensitivity analysis)	10-11, 13, 15-16

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Criteria for study eligibility (Types of outcomes measurements), Statistical methods	9, 12-16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measure, methods of handing data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's T)	Statistical methods	12-16
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Statistical methods (Sensitivity analysis)	15-16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Statistical methods (Heterogeneity, Sensitivity analysis)	13, 15-16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Statistical methods	12-16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methodological quality assessment	10-11

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Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

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Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

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ABSTRACT

Introduction: Functional constipation (FC) is a common gastrointestinal disease. Systematic reviews indicate that acupuncture may be effective for patients with FC. However, this conclusion is not convincing due to the quality, sample size, and methodological heterogeneity of the studies included by these systematic reviews. Therefore, it is necessary for us to conduct a meta-analysis of individual patient data (IPD) from high quality clinical trials to determine whether acupuncture is effective for FC patients.

Methods and analysis: Randomised controlled trials (RCTs) of acupuncture for adult patients with FC will be searched in several databases from inception to April 2015. The corresponding authors of eligible studies will be contacted and invited to contribute raw data. The primary outcome is the change in spontaneous defecation per week from baseline. The secondary outcomes include proportion of responders, changes in stool quality, mean transit time, proportion of patients using laxatives and adverse events. We will check all of the data and perform reanalysis according to statistical methodology reported in previous publications. Then, we will harmonise the raw data and use a two-step method to conduct the IPD meta-analysis. First, we will calculate the effect size of acupuncture of each trial by analysis of covariance, with the principal endpoint as the dependent variable and the baseline scores as the covariates. Second, the effect size of acupuncture in each original study will be combined in the meta-analysis.

Dissemination: Based on the IPD meta-analysis of high quality RCTs, this review will answer the question of whether acupuncture is effective for FC. The findings of the review will be disseminated through peer-review publications and conference presentations.

Trial registration number: PROSPERO 2014: CRD42014009901

Strengths and Limitations of this study

- To our best knowledge, this will be the first individual patient data meta-analysis to evaluate the effectiveness, efficacy and safety of acupuncture treatment for adult patients with functional constipation. Standardised statistical analysis, adjusted baseline characteristics and subgroups analysis may increase statistical power and reduce heterogeneity.
- Rigorous design of eligible study criteria, methodology of quality assessment, data collection and analysis will guarantee the quality of this study.
- One difficult step of this study is collecting all the raw data of eligible trials by systematic search, which may be the limitation of this meta-analysis. We will actively communicate with the authors and researchers of these trials to ensure that the individual patient data can be collected and synthesised as completely as possible. If not all the raw data can be included, retrieval bias will be analysed in sensitivity analysis.

INTRODUCTION

Functional constipation (FC) is a common disease in clinical practice, and it includes several symptoms such as decreased frequency of defecation, straining during defecation, hard stools, sensation of incomplete defecation, and excessive time during defecation. The diagnosis of FC mainly depends on the individual's symptoms and several physiological examinations. The Rome Foundation published the Rome III criteria in 2006, which listed the consensus criteria for FC.[1]

Several systematic reviews have reported prevalence of constipation in different populations. It was reported that the prevalence of FC in North America ranged from 12% to 19%.[2] And the

mean value of prevalence of constipation in general population of Europe and Oceania were 17.1% and 15.3%, respectively.[3] A meta-analysis found that a pooled prevalence of FC in the community was 14%.[4] The annual cost for health care was $7,522 for constipation, accounting for 6.5% of the annual costs for lower gastrointestinal treatment in the USA, reported by Nyrop KA et al.[5] Due to the high incidence and the expensive expenditure of FC, patients' quality of life is significantly undermined. Therefore, FC can be considered as a major public health problem.[6]

Treatments for FC vary. Lifestyle and dietary modifications, such as increased physical activity and a fibre-rich diet are widely accepted and recommended by experts as first-line therapy,[7] although these methods may not be effective for every patient.[8] Conventional treatments for patients with FC include bulking agents, stool softeners, osmotic and stimulant laxatives, prokinetic agents (tegaserod, cisapride and mosapride) and so forth.[9] However, the side effects and the expensive expenditures of such treatments are difficult to ignore.

Nowadays, an increasing number of patients with gastrointestinal diseases seek help from the complementary and alternative medicine.[10] Acupuncture, as an important part of traditional Chinese medicine (TCM), has been used to treat gastroenterological diseases for a long time, especially functional disorders, such as FC, functional diarrhoea and functional dyspepsia.[11] Many clinical trials, which were conducted to investigate the efficacy of acupuncture for patients with FC, indicated that acupuncture could relieve the patients' symptoms. However, the results of systematic reviews did not reach a definitive conclusion. We found three systematic reviews of acupuncture therapy for patients with FC through systematic search. The first review was published in 2010,[12] which could not draw a conclusion due to the serious methodological flaws of the included studies. The second and third reviews were published in 2012[13] and 2013[14], respectively. Both of these reviews concluded that acupuncture may have beneficial effect for FC. However, according to the authors' conclusions, the clinical,

methodological and statistical heterogeneity of the included studies made the results of these three systematic reviews less convincing.

Since 2012, several new results of randomised controlled trials (RCTs) have been published. It is necessary to update the systematic review using a better method. Therefore, we will perform a meta-analysis based on the individual patient data (IPD) of high quality RCTs to determine whether acupuncture is effective and safe for people with FC and to calculate the effect size.

METHODS AND ANALYSIS

Objectives

To establish the individual patient database by combining the raw data from high quality clinical trials of acupuncture treatment for FC, and to answer the question: is acupuncture effective for patients with FC?

We will answer this question in the following aspects:

1. Is acupuncture as effective as the positive drugs?
2. Is real acupuncture superior to sham acupuncture for patients with FC?
3. Is acupuncture superior to no treatment for patients with FC?
4. Is acupuncture safe for patients with FC?

Search strategy

We will conduct a systematic search of the following databases: MEDLINE, EMBASE, Cochrane Library, Chinese BioMedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), China's

Important Conference Papers Database, and China's Dissertation Database from inception to April 2015.

The following search terms will be used individually or combined: "acupuncture", "acupuncture therapy", "auricular acupuncture", "moxibustion", "acupressure", "constipation", "functional constipation", "idiopathic constipation", "randomized/randomised controlled trial", etc. Terms in Chinese will be used in Chinese databases. The search strategy is available in Additional file 1. We will also conduct a literature search through WHO International Clinical Trial Registry Platform (ICTRP) portal and Clinical Trial Registry of the US National Institutes of Health for ongoing registered clinical trials and unpublished articles. Data of ongoing studies will be included after the relevant articles published in peer-review journals.

Criteria for study eligibility

Studies will be included in the individual patient database if they meet the following criteria.

Type of studies

We will include RCTs of acupuncture for FC only. Randomised and allocation concealment methods should be clearly described; if not, we will contact the corresponding authors for further information about the randomisation process. Moreover, allocation concealment should be adequate to avoid selection bias. Additionally, considering that the washout duration of acupuncture cannot be accurately evaluated, we will not include RCTs with crossover designs. To guarantee the quality of an included study, only sample sizes of more than 30 will be considered. The authors of the studies that meet the inclusion criteria will be invited to share the raw data.

Type of participants

Adult patients who are diagnosed with FC according to the Rome Ⅱ/Ⅲ criteria will be included. Patients who are diagnosed with FC (or chronic constipation, primary constipation, idiopathic constipation) with other criteria and who are excluded by examinations for pathological diseases, such as post-surgery, tumour or obstruction, will also be included in this study.

Types of intervention/exposure

Patients who received acupuncture treatment as the primary intervention will be included, which means that patients in the treatment group of each study were treated by acupuncture or that acupuncture was the main intervention combined with other therapy, such as Chinese herbs or physical exercise. Any type of acupuncture will be included, such as manual acupuncture, electro-acupuncture, warming-needle moxibustion, auricular acupuncture, scalp acupuncture, pyonex, intradermal needling, acupoint injection with medicine, and so forth. According to the Rome Ⅱ/Ⅲ criteria, FC is not an acute disease. To alleviate the symptoms, several sessions of acupuncture treatment are necessary in clinical practice. One session of acupuncture treatment only provides acute relief. According to our previous study, the number of treatment sessions in RCTs ranged from 5[15] to 28[16], and 10 to 20 sessions are most commonly used. Therefore, only the RCTs with a treatment protocol of at least 10 sessions will be included.

Types of controls

At least one control group of patients in the study should receive one of the following interventions: positive drugs, placebo controls, or no treatment.

Positive drugs: positive drugs that are used to treat constipation include bulk-forming laxatives, emollients, lubricants, osmotic laxatives, stimulants, and chloride-channel activators.[17]

[18]

Placebo controls: placebo controls include sham acupuncture, placebo drugs, sham interventions and so forth. Sham acupuncture is used to make patients believe they receive acupuncture stimulation, without knowing whether it is real or not. Sham acupuncture includes superficial insertion with needles at specific acupoints; needles puncturing at non-specific acupoints, distal acupoints or non acupoints; placebo needles, such as Streitberger needles;[19] and other techniques, which would make patients feel like needle penetration.

No treatment is defined as any of the following: waiting list, which means that patients in the control group do not receive any acupuncture treatment until the trial is completed; general care or usual care, which means that patients in the control group only receive advice and/or health education, such as diet and/or exercise recommendations.

Types of outcome measurements

1. Primary outcomes

The primary outcome of this review is the change in spontaneous defecation per week from baseline.

2. Secondary outcomes

The secondary outcomes include the following items: proportion of responders, which is the number of responders divided by the total number of participants in each group; changes in stool quality, which are assessed by the Bristol stool scale or other objective measurements; mean transit time, which is the time from the first perception of wanting to defecate to the finish of defecation; proportion of patients using laxatives, which is the number of patients who

used laxatives during the trial to alleviate their symptoms. In addition, the proportion of adverse events will also be calculated according to patient reports in each study.

Data collection

Study selection and data extraction

After electronic searches in the databases, two reviewers will independently screen the titles and abstracts to exclude: 1) the duplicates; 2) the studies in which the participants did not meet the criteria of FC; 3) the studies that were not RCTs with parallel design; and 4) the studies in which the participants in the experimental group did not receive acupuncture treatment as the primary intervention. Then, our reviewers will screen the full copies of studies that cannot be clearly screened by titles and abstracts only (the full copies screening form is available in Additional file 2). Any disagreement will be resolved by consensus or judged by a third reviewer.

Next, two reviewers will independently extract the data from the studies. Training in data extraction and reviewer examination will be conducted in advance to guarantee the quality of extraction. Reviewers will document the following information on the Data Extraction Form (Additional file 2): 1) the basic information of the study (the date, reviewer name of data extraction, and study details, such as first author, year of publication, country of publication and publication type); 2) the study characteristics (design of the study, sample size, number of groups, methodology of randomisation and allocation concealment, blinding, settings); 3) participants (age, gender, ethnicity, diagnosis, etc.); 4) interventions and controls (type of interventions, number and frequency of sessions, duration of treatment or follow-up, etc.); 5) outcomes (type of outcome, definition of outcome, time point of assessment, etc.); and 6) results (the statistic description of outcomes, such as mean, standard deviation, observed and

total sample size, adverse events, etc.). Rechecking and discussion, or even the judgment from a third reviewer will be required if there is any disagreement during the data extraction.

Methodological quality assessment

The assessment of methodological quality is of great importance to systematic reviews. After data extraction, two reviewers will evaluate the methodological quality of each original study independently and will document the details in the Risk of bias assessment form. Discrepancies will be resolved by consensus or judged by a third reviewer. According to the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook (Version 5.1.0)), the methodological quality will be assessed by the following criteria: 1) randomisation allocation; 2) randomisation concealment; 3) blinding; 4) data integrity; 5) selective reporting; and 6) other bias, such as trial design, baseline similarity of groups, early cessation of treatment and so forth. For all of the studies, the assessment should follow the above six criteria and be categorised as A, B or C grade of risk (low, unclear and high risk of bias, respectively). The risk grade will be used to evaluate the quality of all the studies based on the Cochrane collaboration's recommendation.

Regarding the characteristics of acupuncture clinical trials, we will also assess the quality of acupuncture interventions according to the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) recommendation.[20] However, it is difficult to achieve blinding for acupuncture treatment. Therefore, we only ask for blinding assessment and statistical analysis. Any disagreements will be resolved by consensus; otherwise, a third reviewer will be consulted.

Raw data collection and checking

The corresponding authors of eligible studies will be contacted and invited to contribute the raw

data. If the authors of the older studies cannot provide the original data, we will present the details in the final report, and further analysis will be necessary in the sensitivity analysis. The raw data will be provided in any manner that is convenient for authors (such as by email) in any type of electronic format, such as SPSS, STATA, R, Excel, etc. After checking the availability of the data files, all of the data will be converted to a uniform format with its own name, which will be composed of the first author's name and the year of publication.

Reviewers will check all the data carefully to determine whether there are any of obvious errors, irrational or missing data; if any of these issues are found, we will contact the authors for further information. After checking the data, we will calculate the data according to the statistical methodology of the published papers. If there are any inconsistencies regarding the published results, we will require more information from the investigators. For the studies that are still being conducted, we will ask the investigators to provide the most recent data. Then, we will create a new dataset for all the raw data and harmonise the names and format of variables, which will be used for further IPD meta-analysis.

For missing data, we will ask the investigators to recheck the missing data and determine whether this omission happened during data entry. If not, we will use multiple imputation by the propensity score methods.

Raw data management

All the data will be stored in a computer with password protection at College of Acupuncture and Tuina, Chengdu University of TCM. Only authorised members of this IPD study will be allowed to access the computer. Furthermore, there will be a Data Management Committee to supervise the reasonable and confidential use of the original data. Data governance is intended to guarantee the safety of the relevant data from each study and the interests of multiple

parties. We will sign a confidentiality agreement with each raw data provider to ensure the anonymity of the individual patients' data.

Statistical methods

Heterogeneity

Heterogeneity test is an important step in conducting a meta-analysis, as it determines whether the data from studies are suitable and meaningful to synthesise. The result of a meta-analysis will be valid and reliable if a heterogeneity test is conducted and a reasonable explanation is provided. However, there is still controversy regarding the investigation of heterogeneity in an IPD meta-analysis; thus, we will use a conventional method, I^2 value (tested by Higgins I-squared test), to detect the heterogeneity of eligible studies. According to the Handbook of Cochrane, I^2 values are divided into four categories, and a value > 50% will be considered as significant heterogeneity amongst the included studies. As previously mentioned, the heterogeneity was significant in the previous systematic reviews of acupuncture for patients with FC. The sources of heterogeneity that we speculate are differences in patients' demographics, different styles of acupuncture treatment (such as manual acupuncture, electro-acupuncture, or auricular acupuncture, etc.), the alliance of different interventions, different outcomes and time points. Using IPD is an effective way to address these heterogeneity issues. Therefore, there are more possibilities to obtain quantitative results rather than qualitative results. In this study, we will first calculate the effect size of acupuncture of each study by the standardised principle and then conduct a heterogeneity test and meta-analysis. If significant heterogeneity remains, we will perform a meta-regression analysis to determine the sources and will take appropriate action to address them. An explicit explanation and relevant sensitivity analysis will be available

in our final report.

Primary endpoint

The primary endpoint plays a vital role in final result. We will first identify the primary endpoint (including outcome and time point) of each study. In this meta-analysis, we will use the change in spontaneous defecation frequency per week from baseline, which is a continuous variable. If outcomes are ordinal data or count data based on times of defecation, we will convert them to continuous variables. Some studies use Cleveland Clinic Score (CCS)[21] or colonic transit time (CTT)[22] after treatment as the primary endpoint. In this situation, we will create a standardised primary endpoint divided by pooled standard deviation.

Data analysis

1. Primary analysis

The effect size of acupuncture will be analysed in two steps. First, each original study will be reanalysed by analysis of covariance with the standardised principal endpoint as the dependent variable and the baseline characteristics as covariates (such as baseline situation, participants' characteristics, etc.) to calculate the effect size of acupuncture for FC. Second, all the effect sizes from the original studies will be included into the meta-analysis by *meta or metafor package* in R project (www.r-project.org). During this process, we will choose an appropriate effects model, such as the fixed effects model or random effects model according to the heterogeneity. If the heterogeneity is not obvious, e.g., mild or moderate, we will perform both fixed and random effects models to calculate the effect size and compare the differences. In this step of the analysis, we will detect the effect size of acupuncture separately by comparing acupuncture with positive drugs, placebo controls and no treatment.

2. Secondary analysis

We will reanalyse the effect size for the changes in stool quality assessed by the Bristol stool scale or other objective measurements, the proportion of responders, the mean transit time, the proportion of patients using laxatives, and the proportion of adverse events during the studies. Standardised mean differences will be used in the meta-analysis if there are different measurement scales in the original studies. The continuous data will be described as mean and standardised difference (SD), and the categorical data will be described as counts or percentages. Missing values will be addressed by multiple imputation with the propensity score method.

Time points are difficult to determine, because of the different study designs. According to the different observation courses, for our data, 4 weeks will be the cut-off point. Before the cut-off point, the time points before 4 weeks will be regarded as the short-term effects, and the points there after will be regarded as the long-term effects. We will harmonise the time variables (e.g., 1 month is equivalent to 4 weeks). Any time point that investigators designed for assessment close to our uniformed time point will be considered as the time point in this IPD study.

Furthermore, considering some factors that may influence clinical outcomes, we will analyse the characteristics of patients with FC (such as the age, gender, ethnicity and course of disease) as well as the characteristics of acupuncture treatment (such as the number, frequency and duration of treatment sessions, the number of acupoints, and the different types of acupuncture interventions) using a logistic regression method. We will determine whether these characteristics influence the effect of acupuncture for FC.

Sen*sitivity analysis*

Sensitivity analysis will include the following aspects:

First, sensitivity analysis will be performed for publication bias. Although the inclusion and exclusion criteria that we designed can decrease publication bias, we will also perform the sensitivity analysis to detect it. A funnel plot will be used if more than 10 studies are included in this IPD study. Furthermore, the fail-safe number will be calculated to determine the degree of bias.

Second, because exclusion and drop-outs will be processed by multiple imputation in the statistical analysis according to the available data, a sensitivity analysis will be conducted.

Third, the omitted studies and subgroups will be analysed by sensitivity analysis. According to the quality assessment, some studies with a high risk of bias or a subgroup with a small sample size will not be included in the meta-analysis. However, we will analyse all the data in sensitivity analysis by synthesising these omitted studies or subgroups and will compare the results before and after data synthesis.

Fourth, it is known that one difficult step of conducting the IPD meta-analysis is collecting all the raw data from the eligible studies. Although we will actively communicate with the authors and researchers to collect the raw data as completely as possible, there is still a possibility that the raw data will be incomplete. If so, we will first conduct the conventional meta-analysis on the published data of all the eligible studies and of the studies with raw data available separately. Then, we will compare the analysis results of these two, in order to identify the possible selection bias.

Finally, as we mentioned above, we will perform both fixed and random effects models to detect heterogeneity during the meta-analysis. Omitted studies that contribute to greater heterogeneity will also be included in the sensitivity analysis.

Ethics and dissemination

Because each eligible study was approved by local institutional review boards and ethical committees before the trial was conducted, and all of the participants included were required to sign the written informed consent, this IPD meta-analysis study does not require further ethical approval.

This protocol of IPD meta-analysis of acupuncture for FC has been registered with International Prospective Register of Systematic Reviews (PROSPERO) at the NHS Centre for Reviews and Dissemination at the University of York (Registration number: CRD42014009901). All the items recommended by the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[23] have been included in this protocol paper. The result of this review will provide valid and reliable evidence of acupuncture treatment for patients with FC. The findings of this review will also provide implications for clinical practice and further research, and will be disseminated by peer-review publications and conference presentations.

DISCUSSION

Individual patient data meta-analysis of high quality trials will provide the most reliable evidence for clinical treatment decisions. Based on the solid foundation of both clinical practice and academic research of our research team, we believe that the results of this study will be fruitful and valid to determine definitive conclusions regarding acupuncture treatment for FC.

We designed this IPD meta-analysis protocol based on previous relevant studies.[24 25] However, our study has some limitations. Characteristics of both acupuncture and patients can possibly influence the therapeutic effects of acupuncture in clinical practice. The changes in acupuncture effects over time play a role in creating a treatment schedule. The factors discussed above will

be included in this protocol, but we plan to analyse all of the relevant factors in the future, to offer more information for clinical practice and scientific research. Moreover, one difficult step of this study is acquiring the complete raw data from original trials. To address this problem, we will take the following steps: first, we will follow the strict inclusion criteria and conduct the systematic search to locate the eligible trials. Second, we will actively contact and communicate with the authors and researchers of included RCTs and invite them to participate in this study and to offer data as completely as possible. Finally, we will strictly follow relevant agreements and contracts signed with every data provider to protect mutual interests during this study. If the raw data cannot be fully obtained, we will report the details and the results of possible bias.

We sincerely hope that the findings of this review will guide future treatments for FC and translate the contributions of clinical research into patient benefits.

Abbreviations

RCTs: randomised controlled trials; TCM: traditional Chinese medicine; IPD: individual patient data; FC: functional constipation.

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Contributors

The study was conceived and designed by QHZ and HZ. WJH contributed to the design of statistical analysis and will monitor the quality of the included RCTs. QHZ, HZ, SYZ, LYL, HBZ and JCL form the Data Management Committee and have responsibility for study research and data safety. LYL, JCL and SYZ are reviewers of data extraction, checking and collection. QHZ and HZ are responsible for overall data analysis. HZ, YL, ZSL and BZ, who form the Research Steering Committee, contribute suggestions to the design of this study and individual patient data to meta-analysis. YL is responsible for the overall quality of the study. This manuscript was written and revised by QHZ and HZ. All authors read this manuscript and approved the publication of this protocol.

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Competing interests

The authors declare that they have no competing interests.

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Search strategy for **MEDLINE**

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. (randomized or randomised).ab.
4. placebo.ab.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp constipation/
10. functional constipation.ab,ti.
11. primary constipation.ab,ti.
12. chronic constipation.ab,ti.
13. idiopathic constipation.ab,ti.
14. slow transit constipation.ab,ti.
15. (obstipation or “fecal impaction” or astriction or costiveness or coprostasis).ab,ti.
16. 10 or 11 or 12 or 13 or 14 or 15
17. exp acupuncture therapy/
18. exp acupuncture/
19. (needling or needle or prod or pinprick or pricking).ab,ti.
20. exp acupuncture points/
21. (acupunctur* or acupoint or "acupoint application" or "point application" or "external application therapy" or "acupoint inject*" or "point inject*" or "inject* to point" or "inject* to acupoint").ab,ti.
22. exp electroacupuncture/
23. (electroacupunctur* or acusector* or "thermoelectric needle" or electro-acupunctur*).ab,ti.
24. exp auriculotherapy/
25. exp acupuncture, ear/
26. (otopoint* or "ear hole planted seeds" or "ear buried seeds" or auricular*).ab,ti.
27. exp moxibustion/
28. moxa*.ab,ti.
29. exp acupressure/
30. exp meridians/
31. (embedd* or "catgut implantation at acupoint*" or "acupoint catgut embedd*" or "catgut embedd* therap*").ab,ti.
32. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 8 and 16
34. 32 and 33

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

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

Study Eligibility Form

- for full copies screening

Ref ID:

First author:

Reviewers:

Included □

Excluded □ because:

1. Not adult FC subjects (FC should be diagnosed according to the Rome Ⅱ/Ⅲ criteria or other valid criteria without pathological diseases) □

2. Patients with FC not randomized to the treatment and control group □

3. Types of intervention not meet the included criteria □

4. No outcomes provided for FC patients □

5. Other reasons (specify)_____

Consultation required □

Included by consensus □ because:_____

Excluded by consensus □

Acupuncture for functional constipation: protocol of an individual patient data meta-analysis

Data Extraction Form

Date:

Reviewers:

General information

Title	
First author	
Year of publication	
Country of publication	
Language	
Publication type	

Study methodology

Trial design	parallel group only □
Randomization method	
Allocation concealment method	
Blinding	
Setting	
Number of participants	
Number of groups	
Duration	
Follow-up duration	
Funding source	

Participants				
	Group 1	Group 2	Group 3	Group 4
Age (Mean ±SD)				

Gender (M/F)				
Ethnicity				
Diagnosis				
Concurrent condition				
Duration of condition				
Severity of condition				
Laboratory parameters				
Other				

Intervention and controls

Acupuncture therapy	
Stimulation type	
Number of sessions	
Frequency of sessions	
Duration of sessions	
Point prescription	
Combination with other acupuncture therapy	Yes □ (specify) No □
Information of acupuncturists	
Drug combination	
Others	
Controls (including the names, dose, duration of therapy, frequency duration etc.)	
Positive drugs	

Placebo controls	
No treatment	
Compliance	

Outcomes (including the names, methods, definitions, time points)	
Primary outcome (s)	
Secondary outcomes	

Results

Outcomes (including the names, mean, SD etc.)				
	Group 1	Group 2	Group 3	Group 4
Primary outcomes				
Secondary outcomes				
Observed events				
Total sample size				
Adverse events				
Total randomized				
Excludes*				
Withdrawals*				

Lost to follow-up*				
Request for further information				

*including reasons

Risk of bias assessment

1. Was randomized allocation sequence adequately generated?

Yes □ No □ Unclear □

2. Was allocation adequately concealed?

Yes □ No □ Unclear □

3. Who were blinded to the allocation during the study?

Patients	Yes □	No □	Unclear □
Investigators	Yes □	No □	Unclear □
Outcomes assessors	Yes □	No □	Unclear □
Data assessors	Yes □	No □	Unclear □

4. Was the data integrated in this reporting (including the description of the reasons of withdrawals and drop-outs)?

Yes □ No □ Unclear □

5. Were there any selective reporting?

Yes □ No □ Unclear □

6. Did the acupuncture intervention meet the criteria of STRICTA?

Yes □ No □ Unclear □

6. Other bias (specify)_____

Risk of bias	Interpretation	Relationship to individual criteria
A - Low risk of bias	Plausible bias unlikely to seriously alter the results	All of the criteria met
B – Moderate risk of bias	Plausible bias that raises some doubt about the results	One or more criteria partly met
C – High risk of bias	Plausible bias that seriously weakens confidence in the results	One or more criteria not met

Grade:_____

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Section of this manuscript	Page No
Administrative information				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Title	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Notes under the Title, Author affiliations	1-2, 19
Contributions	3b	Describe contribution of protocol authors and identify the guarantor of the review	Contributors	19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Funding	20
Sponsor	5b	Provide name for the review funder and/ or sponsor	Funding	20
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	
Introduction				
Rationale	6	Describe the rational for the review in the context of what is already known	Introduction	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes(PICO)	Introduction, Objectives	4-6
Methods				

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Criteria for study eligibility	7-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Search strategy, Data collection (Raw data collection and checking)	6-7, 11-12
Search strategy	10	Present draft of search strategy to be used for at least on electronic database, including planned limits, such that it could be repeated	Search strategy, Additional file 1	6-7, Additional file 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Data collection (Raw data management)	12-13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Data collection (Study selection and data extraction)	10-11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Data collection (Study selection and data extraction, Raw data collection and checking)	10-11, 11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Data collection (Study selection and data extraction), Additional file 2	10-11, Additional file 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Criteria for study eligibility (Types of outcomes measurements)	9-10
Risk of bias in individual studies	14	Describe anticipated methods of assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methodological quality assessment, Statistical methods (Heterogeneity, Sensitivity analysis)	11, 13-14, 15-16

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Criteria for study eligibility (Types of outcomes measurements), Statistical methods	9-10, 13-16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measure, methods of handing data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's T)	Statistical methods	13-16
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Statistical methods (Sensitivity analysis)	15-16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Statistical methods (Heterogeneity, Sensitivity analysis)	13-14, 15-16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Statistical methods	13-16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methodological quality assessment	11