


# BMJ Open Efficacy and safety of inulin supplementation for functional constipation: a systematic review protocol

Xinyuan Liu ,<sup>1,2</sup> Qing Yang,<sup>3</sup> Zhongning He,<sup>2,4</sup> Shukun Yao<sup>5</sup>

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<sup>1</sup>Department of Gastroenterology of Traditional Chinese Medicine, Department of Gastroenterology, China-Japan Friendship Hospital, Beijing, China

<sup>2</sup>Graduate School, Beijing University of Chinese Medicine, Beijing, China

<sup>3</sup>Graduate School, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

<sup>4</sup>Medical Oncology, China Academy of Chinese Medical Sciences Guanganmen Hospital, Xicheng District, Beijing, China

<sup>5</sup>Institute of Integrated Chinese and Western Medicine, Department of Gastroenterology, China-Japan Friendship Hospital, Beijing, China

## Correspondence to

Professor Shukun Yao; yaoshukundr@163.com

## ABSTRACT

**Introduction** Functional constipation (FC) is a common digestive system disease, with an uptrend in morbidity and mortality, resulting in huge social and economic losses. Although the guidelines recommend lifestyle intervention as a first-line treatment, lifestyle intervention is not widely used in clinic. Inulin can be used as the basic material of functional food. Clinical studies have shown that inulin supplementation is associated with increased frequency of bowel movements, but has certain side effects. Therefore, the efficacy and safety of inulin in the treatment of FC need to be further evaluated.

**Methods and analysis** We will search Medline, Web of Science, Embase, China National Knowledge Infrastructure Database, Wanfang Database and China Biomedical Literature Database. We will also search the China Clinical Trial Registry, the Cochrane Central Register of Controlled Trials and related conference summaries. This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. RevMan V.5.3.5 will be used for analysis.

**Ethics and dissemination** This systematic review will evaluate the efficacy and safety of inulin supplementation for the treatment of FC. All included data will be obtained from published articles, there is no need for the ethical approval, and it will be published in a peer-reviewed journal. Due to lack of a new systematic review in this field, this study will combine relevant randomised controlled trials to better explore the evidence of inulin supplementation in the treatment of FC and guide clinical practice and clinical research.

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## INTRODUCTION

Functional constipation (FC) is a common functional gastrointestinal disease, and it is also one of the most common gastrointestinal diseases in outpatients of digestive department. Worldwide, the incidence of constipation is about 15%.<sup>1 2</sup> The prevalence rate of constipation in China from 2010 to 2016 was 6%–13%.<sup>3 4</sup> FC generally is not a life-threatening disease, but it can seriously affect patients' quality of life (QOL) and lead to high medical costs.<sup>5–7</sup> The mechanisms of

## Strengths and limitations of this study

- We will search for randomised controlled trials of inulin supplementation in the treatment of functional constipation (FC) and complete a systematic review to comprehensively evaluate the efficacy and safety of inulin supplementation in the treatment of FC.
- In fact, inulin is a representative of the seventh nutrient, dietary fibre. By completing this systematic review, it may be possible to better understand the role of dietary fibre supplementation in FC treatment.
- However, as the supplemental inulin used in various studies may not be the same type or brand, the research conclusions may be biased to a certain extent.
- In addition, studies published in languages other than English or Chinese may be omitted due to language limitations.

FC include prolonged colonic transit time and pelvic floor muscle dysfunction.<sup>7</sup> Gender, age, diet, education level and neurological diseases are the main factors affecting FC. It should be emphasised that the occurrence of constipation is closely related to the insufficiency of dietary fibre (fruits and vegetables). The latest FC diagnosis is based on Roma IV criteria,<sup>8 9</sup> including difficulty in defecation, dry stool, incomplete defecation, anorectal obstruction, prolonged defecation cycle and manual defecation. Two or more of the above projects need to be included, each with a frequency of at least 25%. Spontaneous bowel movement less than three times a week and constipation should last for more than 6 months. At the same time, irritable bowel syndrome (IBS) should be excluded. The treatment of constipation should attach importance to comprehensive treatment.<sup>1 2</sup> Routine treatment of FC for adults includes lifestyle intervention, pelvic floor intervention (rectal emptying disturbance) and drug therapy. At present, drug therapy is not satisfactory in continuously improving the

symptoms and QOL of patients with FC, and side effects such as electrolyte disorders, diarrhoea and nausea are often reported. Therefore, it is necessary to find a safe and effective treatment. It has been reported that among 6318 adult constipation patients in China, only 25.1% of them chose laxatives, while 81.7% preferred lifestyle and eating habits intervention as treatment options.<sup>10</sup> Based on the recognised health benefits of eating dietary fibre, such as reducing blood lipids and blood sugar, the recommended dietary fibre intake for adult men and women in different parts of the world, including Germany and the USA, ranges from 25 g/d to 38 g/d.<sup>8</sup> However, studies have shown that the daily fibre intake of the general population is lower than the recommended level.<sup>11</sup>

Inulin fructan is a natural food ingredient widely found in a variety of vegetables, such as leek, onion, wheat, garlic, chicory and artichoke. Inulin is a mixture of polymers and oligomers, which is composed of fructose units connected by  $\beta$  (2-1) glycosidic bonds.<sup>12 13</sup> Because of this  $\beta$  configuration, inulin is resistant to the hydrolysis of human digestive enzymes and cannot be digested, so it can completely reach the large intestine and be selectively fermented by colonic bacteria.<sup>14</sup> Inulin fructan is a kind of dietary fibre with established probiotic effect, which can have a beneficial effect on the composition or activity of gastrointestinal microflora.<sup>15 16</sup> In recent years, there are more and more studies on inulin, such as the intervention effect of inulin on type 2 diabetes, obesity, hyperlipidaemia and other diseases.<sup>17-20</sup> Some preliminary evidence suggests that inulin can improve constipation, increase the proportion of bifidobacteria in the intestines, reduce the proportion of choleroophiles, improve insulin resistance and regulate intestinal PH (Potential of Hydrogen, PH).<sup>21 22</sup> However, some research results show that inulin can improve constipation and cause side effects such as abdominal distension and increased exhaust.<sup>23</sup> Therefore, a systematic review of the role of inulin in FC is necessary. In this review, we aim to systematically evaluate the efficacy and safety of inulin in the treatment of FC.

## METHOD AND ANALYSIS

### Inclusion criteria for study selection

#### Types of studies

All prospective randomised controlled trials (RCTs) of inulin for FC will be included. Animal studies, case reports, quasi-RCTs, trials without detailed data will be excluded.

#### Types of participants

FC refers to chronic constipation with the exception of IBS and the absence of organic causes, structural abnormalities or metabolic disorders and so on. Patients with FC in different age ranges can be included in the study, regardless of nationality, gender, race, occupation or education. Constipation caused by hypothyroidism, type 2 diabetes, congenital diseases such as Hirschsprung's disease will be

excluded. Patients with mental illnesses such as anxiety and depression, malignant tumours, severe heart, brain and kidney disease, and those who had undergone intestinal surgery would also be excluded.

#### Types of interventions

We will include a number of randomised controlled studies using chicory inulin-type fructans as the sole treatment or as an adjuvant treatment with other treatments, regardless of the degree of polymerisation chain length (eg, oligofructose, inulin, mixed of oligofructose and inulin). The control group will include placebo, no intervention, acupuncture, massage, traditional Chinese medicine, diet therapy, exercise therapy, western medicine or any other intervention.

#### Types of outcome measures

##### Primary outcomes

The primary outcome is complete spontaneous bowel movements (CSBM) number. Safety indicators include liver and kidney function, blood routine and adverse events during treatment, such as abdominal cramps, abdominal pain, nausea, vomiting, dizziness, diarrhoea, rash, oral ulcers, constipation, insomnia, bradycardia, skin diseases and flatulence.

##### Secondary outcomes

The secondary outcomes of this review will include:

1. Patient Assessment of Constipation Symptom.
2. Patient Assessment of Constipation Quality of Life.
3. Self-rating anxiety scale and self-rating depression scale.
4. Through time measurement (opaque markers), rectal function evaluation (colonoscopy, anorectal manometry, defecography, cinematographic defecography) or electromyography.
5. The number and type of adverse effects.

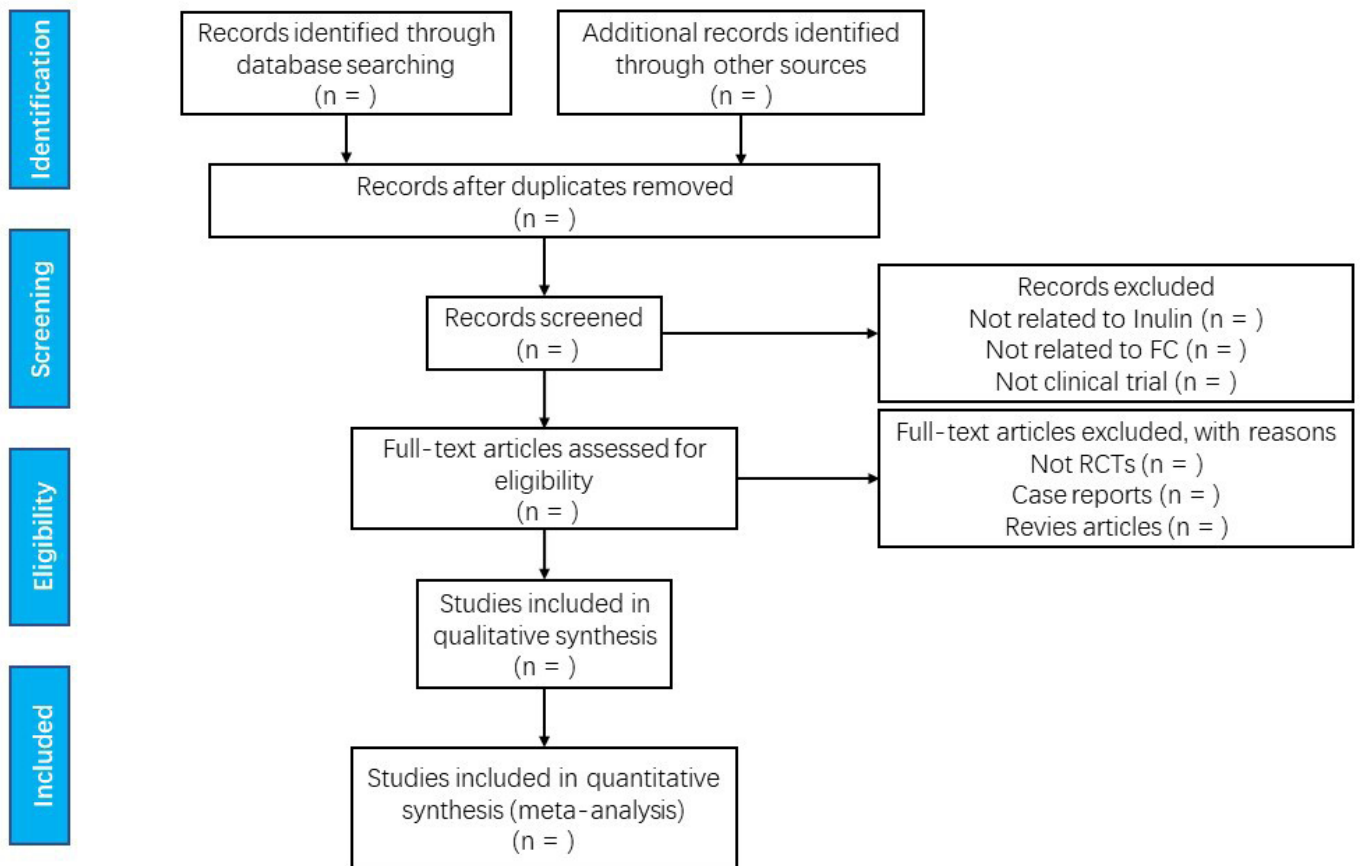
#### Search methods for identification of studies

##### Electronic searches

The electronic search will begin on 1 July 2020. We will search the following electronic databases: Medline, Embase, Web of Science (Science and Social Science Citation Index), the Cochrane Central Register of Controlled Trials, China Biological Medicine Disc, China National Knowledge Infrastructure Database (CNKI), Wanfang Database and China Science Journal Database (VIP).

##### Search strategy

A search strategy was developed with a medical librarian; the three-part strategy includes terms to identify studies relating to (1) inulin and its products, (2) FC and (3) RCT. In the online supplemental appendix, we show the search strategy in the Medline database, Embase, CNKI and other databases (online supplemental appendix), search strategies for other database are set accordingly.



**Figure 1** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of the selection process. FC, functional constipation; RCTs, randomised controlled trials.

### Searching other resources

In order to obtain as much research data as possible, we will conduct relevant searches on the website of nih clinical registry clinicaltrials.gov, the WHO International Clinical Trials Registration Platform and the Chinese Clinical Registration website.

### Data collection and analysis

#### Selection of studies

We will search the above database for related literatures, import them into the database created by Endnote V.X9, and filter for duplicates. The two reviews will independently filter the titles, abstracts and keywords of all retrieved records. If necessary, the full text will be reviewed in accordance with the inclusion criteria for further assessment of inclusion. If there are any differences, we will discuss and resolve them with the third author. The screening flow chart of this study is shown in [figure 1](#) (process and results of studies selection).

#### Data extraction and management

We will make a standard data collection form before data extraction. The two reviewers will independently extract data from the selected study and fill out the data collection form. Differences and uncertainties will be resolved through consensus between the two reviewers or by

requiring the third author to make a final decision. We will extract the following data:

1. General information: first author, title, journal, type of publication, year of publication.
2. Methods: design, sample size, randomisation, distribution concealment method, blind method, inclusion criteria and exclusion criteria were studied.
3. Subjects: age, gender, FC severity, FC diagnostic criteria, baseline CSBM.
4. Intervention: control type, course of treatment and times of treatment.
5. Results: primary and secondary outcomes, treatment costs, adverse effects and follow-up.

#### Assessment of bias in the included studies

The risk of bias (RoB) of included trials will be assessed by two independent reviewers (XL and QY) using the RoB tool in the Cochrane Handbook 5.1.0. The indicators of RoB include random sequence generation, allocation concealment, blinding of patients and caregivers, blinding of outcome assessment, data completeness, selective outcome reporting and other biases. Each indicator will be judged as high risk, low risk or unclear of risk for the result of evaluation. Different opinions on the evaluation indicators will be resolved through discussion with the third researcher.

### Measures of treatment effect

The dichotomous outcomes will be conducted using the risk ratio with 95% CIs. The continuous outcomes will be analysed as the weighted mean difference or the standard mean difference.

### Unit of analysis issues

In crossover trials, only the data from the first phase will be used. If the experiment has multiple experimental groups or control groups, we will combine the related control groups and experimental groups before analysing.

### Management with missing data

The research will be carried out based on existing data as much as possible. If necessary, we will try to contact the corresponding author via email to obtain missing data and detailed reports. We will consider excluding the corresponding research if the corresponding author cannot be contacted.

### Assessment of heterogeneity

Heterogeneity will be estimated by standard  $\chi^2$  test and  $I^2$  statistic. Heterogeneity will be considered as high when  $I^2 > 50\%$ . Conversely, heterogeneity will be considered as high. To clarify the potential sources of heterogeneity, sensitivity analysis or subgroup analysis will be performed.

### Assessment of reporting bias

We will detect reporting biases by using funnel plots if more than 10 studies are included.

### Data synthesis

The Review Manager V.5.3.5 software (RevMan V.5.3.5) will be used for data analysis and synthesis. Continuous variables will be expressed in MD (Mean Difference, MD) / SMD (Standard Mean Difference, SMD) with 95% CIs, and categorical variables will be expressed in RR (Risk Ratio, RR) with 95% CIs. When  $I^2 < 50\%$ , we will use the fixed effects model to analyse the results. Otherwise, the random effect model will be selected.

### Subgroup analysis

When the data included in the study are possible and appropriate, we will conduct a subgroup analysis to explore whether there are differences in the research conclusions in different subgroups. We may conduct a subgroup analysis based on gender, inulin type and severity of constipation.

### Sensitivity analysis

We will conduct sensitivity analysis based on the method quality, sample size and statistical model of the Cochrane Handbook, and evaluate the robustness of the research conclusions for clinical decision making. According to research characteristics or types such as methodological quality, the influence on the total effect can be explored by excluding some low-quality research or non-blinded research.

### Patient and public involvement

No patient involved.

### DISCUSSION

At present, the commonly used drugs for the treatment of FC are volumetric laxatives, irritant laxatives, permeable laxatives, lubricating laxatives, microecological agents and others.<sup>167</sup> However, its systemic and local side effects have been reported, such as diarrhoea, abdominal distension, black edge of colon, electrolyte disturbance and so on. Moreover, the long-term use of these drugs will cause drug resistance and can not always effectively improve constipation symptoms. Therefore, it is important to find safer and more effective drugs to manage constipation.

Inulin is a soluble dietary fibre that cannot be digested and absorbed by human gastrointestinal tract. In the intestine, inulin can be used as a medium for probiotics to improve the structure of intestinal flora, increase gastrointestinal peristalsis and exhaust, and thus improve stool characteristics and frequency. Inulin was approved by the FDA (Food and Drug Administration, FDA) as a safe substance in 2003, and it has a slightly sweet taste and can be taken with good compliance.<sup>18 24 25</sup> A number of clinical studies have shown that inulin is effective in the treatment of FC with high safety.<sup>23 26 27</sup> We hope that this systematic review can provide more reliable evidence for the treatment of FC.

This review still remains some limitations. We only include articles in English or Chinese and may miss relevant research.

### Ethics and dissemination

This systematic review aims to evaluate the efficacy and safety of supplemental inulin for FC. The data of this study will be obtained from published studies, so ethical approval is not required. This research will be published in a peer-reviewed journal. Due to lack of a new systematic review in this field, this study will combine relevant RCTs to better explore the evidence of inulin supplementation in the treatment of FC and guide clinical practice and clinical research.

**Contributors** XL and SY put forward the concept of research, formulated the retrieval strategy. XL and QY drafted the manuscript. SY contributed to the revision of the manuscript and provided suggestions for the research. XL and QY will assess the risk of deviations and complete the data synthesis. In the event of disagreement, SY will act as arbitrator. XL and ZH will conduct statistical analysis. All the authors read and approved the final manuscript. Special thanks to Dr LJF for his assistance and suggestions during the design process. Thanks very much to ZYM for the overall polishing and modification of the article. She made the content of the article more smooth and standardised. XL, SY contributed to conceptualisation; XL, ZH, QY contributed to data planners; XL, ZH contributed to formal analysis; XL, SY contributed to project management; XL, QY are producer; XL, QY contributed to text manuscript; SY contributed to author revision.

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**Author note** If it is necessary to revise this protocol, we will provide the explanation, reason and date of each revision.

#### ORCID iD

Xinyuan Liu <http://orcid.org/0000-0002-3914-9035>

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