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Systematic Review: Effect of Fibre in Chronic Idiopathic Constipation.

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Suares and Ford

1 of 27

Title: Systematic Review: Effect of Fibre in Chronic Idiopathic Constipation.

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Abbreviations:

b.i.d	twice daily
CIC	chronic idiopathic constipation
GI	gastrointestinal
IBS	irritable bowel syndrome
MeSH	medical subject heading
RCT	randomised controlled trial
t.i.d	thrice daily

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Suares and Ford

2 of 27

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SUMMARY

Background: Patients with chronic idiopathic constipation (CIC) are often told to increase dietary fibre intake. Whether this is of any benefit remains unclear.

Aim: To conduct a systematic review of the efficacy of soluble and insoluble fibre supplementation in CIC.

Methods: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched to identify randomised controlled trials (RCTs) comparing fibre with placebo or no therapy in adult CIC patients. Studies had to report dichotomous data assessing response to therapy, or continuous data examining either effect of therapy on mean number of stools per week, or mean symptom scores. Adverse events data were extracted where reported.

Results: Six RCTs were eligible. Four used soluble fibre and two insoluble fibre. Formal meta-analysis was not undertaken due to concerns about methodological quality of identified studies. Compared with placebo, soluble fibre led to improvements in global symptoms (86.5% versus 47.4%), straining (55.6% versus 28.6%), pain on defaecation, and stool consistency, an increase in the mean number of stools per week (3.8 stools per week after therapy compared with 2.9 stools per week at baseline), and a reduction in the number of days between stools. Evidence for any benefit of insoluble fibre was conflicting. Adverse events data were limited, with no RCT reporting total numbers.

Conclusions: Soluble fibre may be of benefit in CIC, but data for insoluble fibre are conflicting. More data from high quality RCTs are required before the true efficacy of either fibre type in the treatment of CIC is known.

INTRODUCTION

Chronic idiopathic constipation (CIC) is a common condition affecting the gastrointestinal (GI) tract, with an estimated prevalence of between 4% and 20% in cross-sectional community surveys.¹⁻⁴ This functional disorder is defined as the infrequent and difficult passage of stools in the absence of any physiological abnormality.⁵ The condition is commoner in females, the elderly, and those with lower income,^{4, 6, 7} and is associated with reduced quality of life.⁸

Symptoms of CIC can be difficult to treat.⁹ Lack of dietary fibre is believed to contribute to constipation,¹⁰ and many physicians recommend an increase in fibre intake, along with other lifestyle modifications such as improved hydration, as an initial therapy. Insoluble fibres, such as wheat bran, are thought to exert their effect by **accelerating** intestinal transit time, thereby increasing stool frequency.¹¹ Psyllium, which is a soluble fibre derived from ground ispaghula husk, is ingested with water to increase stool bulk and increase stool frequency.¹²

There have been several randomised controlled trials (RCTs) studying the effects of both soluble and insoluble in individuals with CIC published previously, and current guidelines from national and international Gastroenterology organisations advocate the use of dietary fibre as a first line therapy for constipation.^{13, 14} Despite this, there has been no recent summary of all available published RCTs to determine what evidence there is, if any, to support the use of fibre in the treatment of CIC. We have therefore conducted a systematic review to examine this issue.

METHODS

Search Strategy and Study Selection

A search of the medical literature was conducted using MEDLINE (1950 to September 2010), EMBASE and EMBASE Classic (1947 to September 2010), and the Cochrane central register of controlled trials (Issue 3, July 2010) to identify RCTs examining the efficacy of soluble or insoluble fibre in adults (> 90% of participants over the age of 16 years) with CIC (box 1). The first period of cross-over RCTs were also eligible for inclusion. The presence of CIC could be defined according to clinical symptoms, a physician's diagnosis, or the Rome I, II, or III criteria,^{5, 15, 16} with organic causes excluded by negative investigations if trial investigators felt this necessary. Studies that recruited patients with organic constipation, drug-induced constipation, highly selected groups of patients (such as elderly patients or the institutionalised), or that enrolled a mixture of CIC patients and those suffering from either irritable bowel syndrome (IBS) or diverticular disease, were ineligible. The minimum duration of therapy considered was 1 week. Studies had to report dichotomous data assessing response to therapy, or continuous data examining the effect of therapy on either mean number of stools per week, or mean symptom scores.

Studies on CIC were identified using the terms: *constipation* or *gastrointestinal transit* (both as medical subject headings (MeSH) and free text terms), or *functional constipation*, *idiopathic constipation*, *chronic constipation*, or *slow transit* (as free text terms). These were combined using the set operator AND with studies identified via the following terms: *dietary fiber*, *cellulose*, *plant extracts*, *psyllium*, *cereals*, *plantago*, or *methylcellulose* (as MeSH and free text terms), or the

Suares and Ford

6 of 27

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3 following free text terms: *fiber, fibre, soluble fibre, insoluble fibre, bran, ispaghula,*
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6 *metamucil, fybogel, or ispaghula.*
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8 There were no language restrictions, and abstracts identified from the original
9 search were evaluated by two investigators for appropriateness and, for those deemed
10 eligible for inclusion, the full paper was obtained and evaluated. Foreign language
11 papers were translated. Abstract books of conference proceedings published between
12 2002 and 2010 were also hand searched for eligible studies. A recursive search of the
13 literature was performed using the bibliographies of identified studies. Studies were
14 assessed independently by two investigators using pre-defined eligibility criteria, with
15 disagreements resolved by discussion.
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29 **Data Extraction**

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31 Data were extracted independently by two investigators on to a Microsoft
32 Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as
33 dichotomous outcomes (response or no response to therapy), or mean symptom scores
34 or mean number of stools per week during treatment. The following clinical data were
35 also collected: setting (primary, secondary, or tertiary care), number of centres,
36 country of origin, dose and duration of therapy, concomitant medications allowed,
37 definition of CIC used, primary outcome measure used to define response to therapy,
38 method used to generate the randomisation schedule and conceal treatment allocation
39 (where reported), level of blinding, and proportion of female patients. Data were
40 extracted as intention-to-treat analyses, with all drop-outs assumed to be treatment
41 failures. If this was not clear from the original article then we performed an analysis
42 on all patients with reported evaluable data. Adverse events data were also extracted
43 where reported.
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Assessment of Risk of Bias

This was performed independently by two investigators, with disagreements resolved by discussion. By recording the methods used to generate the randomisation schedule and conceal treatment allocation, the level of blinding, the proportion of patients who completed follow-up, whether an intention-to-treat analysis was extractable, and whether there was evidence of selective reporting of outcomes, the risk of bias was assessed as described in the Cochrane handbook.¹⁷

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RESULTS

The search strategy identified 3146 citations, of which 14 appeared to be relevant to the systematic review, and were retrieved for further evaluation. Six of these studies were eligible for inclusion (Figure 1).¹⁸⁻²³ A formal meta-analysis was not performed due to concerns over the methodological quality and risk of bias of the studies identified. The characteristics of eligible and included trials are summarised in Table 1. Four of the eligible trials used soluble fibre. Of these, three used psyllium,^{19,20,23} and the fourth used a combination of inulin and maltodextrine.²² Two used insoluble fibre, wheat bran in one study,¹⁸ and rye bread in the other.²¹ The treatment period ranged from 2 to 8 weeks. No trial was at low risk of bias, and the majority were conducted in tertiary care, and recruited predominantly female patients. None of the trials allowed any active medications for the treatment of constipation to be co-administered to patients, though one study did allow a non-medicated cleansing enema as a rescue therapy for patients who did not have a bowel motion for 8 consecutive days.¹⁸

Efficacy of soluble fibre in chronic idiopathic constipation

The largest identified RCT was conducted by Fenn *et al.*²⁰ This single-blind trial recruited 201 patients, randomising 104 to psyllium and 97 to placebo during a 2-week treatment period. Overall, 90 (86.5%) patients allocated to psyllium reported an improvement in symptoms, compared with 46 (47.4%) patients receiving placebo ($P < 0.001$). The authors also reported a reduction in abdominal pain and discomfort with psyllium in those patients reporting these symptoms at baseline, with an improvement in 44 (80.0%) of 55 psyllium patients compared with 27 (64.3%) of 42 receiving placebo ($P = 0.035$). Finally, straining on defaecation was also reduced with psyllium, with 70

Suares and Ford

9 of 27

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psyllium and 63 placebo patients reporting this symptom at study entry, compared with 11 and 27 at trial completion ($P = 0.003$).

Ashraf *et al.* enrolled 22 patients with CIC,¹⁹ and randomised them in equal numbers to psyllium or placebo for 8 weeks. They reported a significant increase in mean stool frequency per week following treatment with psyllium (3.8 stools per week after 8 weeks of therapy, compared with 2.9 stools per week at baseline, $P < 0.05$), but no such change with placebo. Patients in the active treatment arm also reported improvements in individual parameters such as stool consistency, pain on defaecation, straining, and sense of complete evacuation compared with baseline, although only the former two differences were statistically significant ($P < 0.05$ for both).

In a Brazilian trial conducted by Nunes *et al.*,²³ 60 patients were recruited and randomised to either 10g of psyllium per day or placebo for 2 weeks in a double-blind fashion. The primary outcome measure used to define a response to therapy was normalisation of evacuation. This was achieved in 26 (86.7%) of 30 patients receiving psyllium compared with only 9 (30.0%) of 30 patients allocated to placebo ($P < 0.001$).

Finally, Lopez-Roman and colleagues used 20g of a soluble fibre mixture of inulin and maltodextrin, administered as a dairy preparation, in a placebo-controlled trial conducted in Spain.²² In total, 32 patients were randomised, with 15 allocated to fibre and 17 receiving placebo. There were significant reductions in the proportion of patients reporting straining during defaecation, sensation of incomplete evacuation, and sensation of obstruction with soluble fibre ($P < 0.001$ for all analyses). In addition, the number of days between bowel movements was also significantly reduced ($P < 0.001$).

Efficacy of insoluble fibre in chronic idiopathic constipation

The first trial reporting the efficacy of insoluble fibre in CIC was conducted in Italy by Badiali *et al.*¹⁸ The 24 patients recruited were allocated to receive 20g of bran per day or placebo. As this was a cross-over trial, only the first treatment period is described. Following the first 4-week period of the trial (prior to cross-over) no statistically significant difference in response, defined as having no further straining at stool, occurred with active treatment (5 (55.6%) of 9 patients who reported this at baseline) compared with placebo (2 (28.6%) of 7 patients).

The second RCT carried out by Hongisto and colleagues compared four diets: rye bread with *Lactobacillus* GG yoghurt, rye bread alone, *Lactobacillus* GG yoghurt alone, and low fibre bread.²¹ For the purposes of this systematic review, we only examined outcomes in patients randomised to rye bread alone and those given low fibre bread. The study took place over a 3-week period and recruited a total of 29 female patients in these two arms of the trial. Following the 3-week intervention period, the mean difference in number of stools per day was 0.4 for the patients randomised to rye bread compared with those assigned to low fibre bread ($P = 0.001$). Difficulty of defaecation was also significantly reduced with rye bread ($P < 0.001$), and stools were significantly softer ($P < 0.001$).

Adverse events with fibre

No single study reported total adverse events. One trial reported the number of patients in each trial arm who dropped out due to adverse events (one with psyllium and two with placebo).²⁰ Ashraf *et al.* recorded individual adverse events, with 18% of psyllium patients experiencing abdominal pain compared with 0% of placebo patients, but no differences in back pain, bloating, or cramping.¹⁹ Finally, there were higher

Suares and Ford

11 of 27

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3 combined symptom scores for gastrointestinal side effects such as abdominal pain,
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5 flatulence, borborygmi, and bloating with rye bread compared with low fibre toast (mean
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7 difference in scores = 1.6, $P < 0.001$).²¹
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DISCUSSION

This systematic review has summarised all the available published evidence examining the efficacy of fibre in patients with CIC. Despite recommendations from both national and international guidelines that increasing dietary fibre intake should be the first-line step in the management of the condition,^{13, 14} the evidence for any benefit of this approach appears limited. We identified only six RCTs, none of which were at low risk of bias, and the majority recruited only a small number of patients. Overall, soluble fibre may be more effective than placebo in patients with CIC. All four studies examining its efficacy,^{19, 20, 22, 23} three of which used psyllium,^{19, 20, 23} reported significant improvements in individual symptoms of CIC such as straining or pain on defaecation, stool consistency, sensation of incomplete evacuation, and sensation of obstruction. In addition, mean number of stools per week increased, and number of days between bowel movements was also significantly reduced. However, the two trials examining the effects of insoluble fibre compared with placebo or low fibre bread were conflicting, with one trial demonstrating a significant difference in mean number of stools per day with active therapy, as well as reduced difficulty in defaecation and increased stool softness,²¹ whilst the other cross-over RCT found no significant difference in response to therapy, defined as reporting no straining at stool, with active treatment versus placebo,¹⁸ **though as the trial contained only 24 patients this may have been due to a lack of power.** Adverse events were poorly reported. In one placebo-controlled trial of psyllium abdominal pain was reported more frequently among those assigned to active treatment,¹⁹ and in the study using fibre-rich rye bread, the combined symptom score for gastrointestinal side effects was higher in patients taking rye bread compared to those in the placebo arm.²¹

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3 We performed this systematic review using rigorous methodology. The
4 comprehensive literature search was conducted separately by two investigators. We
5 included and translated non-English language publications. Data extraction was
6 performed separately, again by two investigators, with discrepancies resolved by
7 consensus. We also used an intention-to-treat analysis, where we assumed all drop-
8 outs to be treatment failures, wherever possible. Limitations arise from the quality and
9 reporting of the trials included in the systematic review. None of the trials were at low
10 risk of bias, failing to report the method used to generate the randomisation schedule
11 or conceal allocation in all six cases, meaning that the benefit of fibre in CIC in these
12 RCTs may have been overestimated.²⁴ Duration of therapy was relatively short in
13 most instances, with only one study treating patients for more than 4 weeks.¹⁹ There
14 was also great variation in the definitions of improvement with therapy, or primary
15 outcome measurements, making comparisons between the trials difficult. Due to all of
16 the above, we elected not to perform a formal meta-analysis. In addition, only one
17 trial recruited patients from primary care,²⁰ which is where the majority of patients
18 with CIC will first consult a physician, and therefore the setting in which an increase
19 in dietary fibre intake is most likely to be used as a first therapeutic manoeuvre. The
20 fact that the majority of studies we identified, which were conducted in tertiary care,
21 will not be generalisable to this situation is therefore of concern. Finally, the patients
22 recruited were predominantly female, meaning that any potential benefit of fibre in
23 males with CIC is even less clear.

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There have been systematic reviews examining the efficacy of fibre in CIC
published previously. The earliest of these, which performed a meta-analysis,
concluded that fibre led to a modest improvement in stool frequency compared with
placebo or no treatment, which was of a similar magnitude to that achieved with

Suares and Ford

14 of 27

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3 laxatives.²⁵ However, the authors did not restrict their analysis to trials of patients
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5 with CIC, but also included RCTs conducted in mixed populations of IBS and CIC
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7 patients, patients with diverticular disease, and individuals in nursing homes and
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9 psychiatric units. A further meta-analysis that pooled data from placebo-controlled
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11 trials of fibre and laxatives together reported that any obvious benefit of the two over
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13 placebo could not be established.²⁶ Finally, a systematic review published in 2005
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15 examined the efficacy of various medical therapies, including soluble and insoluble
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17 fibre, in patients with CIC.²⁷ The authors included head-to-head trials of fibre versus
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19 laxatives as well as placebo-controlled trials. Some of the included RCTs included
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21 IBS patients, or were conducted in the elderly and institutionalised, post-hysterectomy
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23 patients, and pregnant women. No formal meta-analysis was undertaken, but the
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25 authors concluded that there was moderate evidence to support the use of psyllium in
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27 CIC, but that evidence for any benefit of insoluble fibre such as wheat bran was poor.
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29 The present systematic review provides an update to these previous studies, with half
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31 of the trials we identified being published in the intervening years,²¹⁻²³ as well as
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33 restricting the analysis only to RCTs of fibre versus placebo or no therapy, conducted
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35 among patients with true CIC.
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44 Current national and international guidelines recommend the use of fibre in
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46 both dietary and supplement form in the early management of constipation.^{13, 14}
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48 However, it is apparent from the trials identified by this systematic review that there
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50 is a relative paucity of high quality evidence to support such an approach. In a recent
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52 systematic review and meta-analysis of RCTs, which were generally of higher quality
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54 than those identified in the present study, both osmotic and stimulant laxatives, as
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56 well as newer agents such as prucalopride and linaclotide, were superior to placebo in
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58 the treatment of CIC.²⁸ **Two of the largest and most rigorously designed of the RCTs**
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3 included in this meta-analysis were conducted only very recently and confirmed
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5 efficacy of both bisacodyl and sodium picosulphate, two traditional, and perhaps
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7 neglected, therapies.^{29,30} This emphasises the need for trials of similar quality
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9 studying the efficacy of fibre in CIC. Another recently published meta-analysis has
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11 suggested that psyllium is of benefit in IBS,³¹ and a high quality RCT that studied the
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13 efficacy of both soluble and insoluble fibre in IBS demonstrated that both were better
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15 than placebo.³² Some investigators have reported a significant degree of overlap
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17 between IBS and CIC,³³ suggesting common pathophysiological mechanisms. This,
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19 together with the fact that previous studies have demonstrated that transit time in
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21 some constipated patients normalises with fibre,³⁴ means that fibre supplementation
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23 should not be excluded from the management of CIC, particularly as there are likely
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25 to be few risks arising from such an approach.
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32 In summary, this systematic review suggests that soluble fibre may be of some
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34 benefit in CIC. However, further large trials examining the efficacy of both soluble
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36 and insoluble fibre in CIC, that recruit patients from primary care, use validated
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38 outcome measures, adhere to the recommendations made by the Rome committee for
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40 the design of treatment trials in the functional GI disorders,³⁵ and that report adverse
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42 events fully are required before any firm recommendations for the role of either in the
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44 management of the condition can be made.
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50 STATEMENTS OF INTEREST

55 Authors' Declaration of Personal Interests:

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60 Nicole C Suares: none declared. Alexander C. Ford: none declared.

Suares and Ford

16 of 27

Declaration of Funding Interests:

None.

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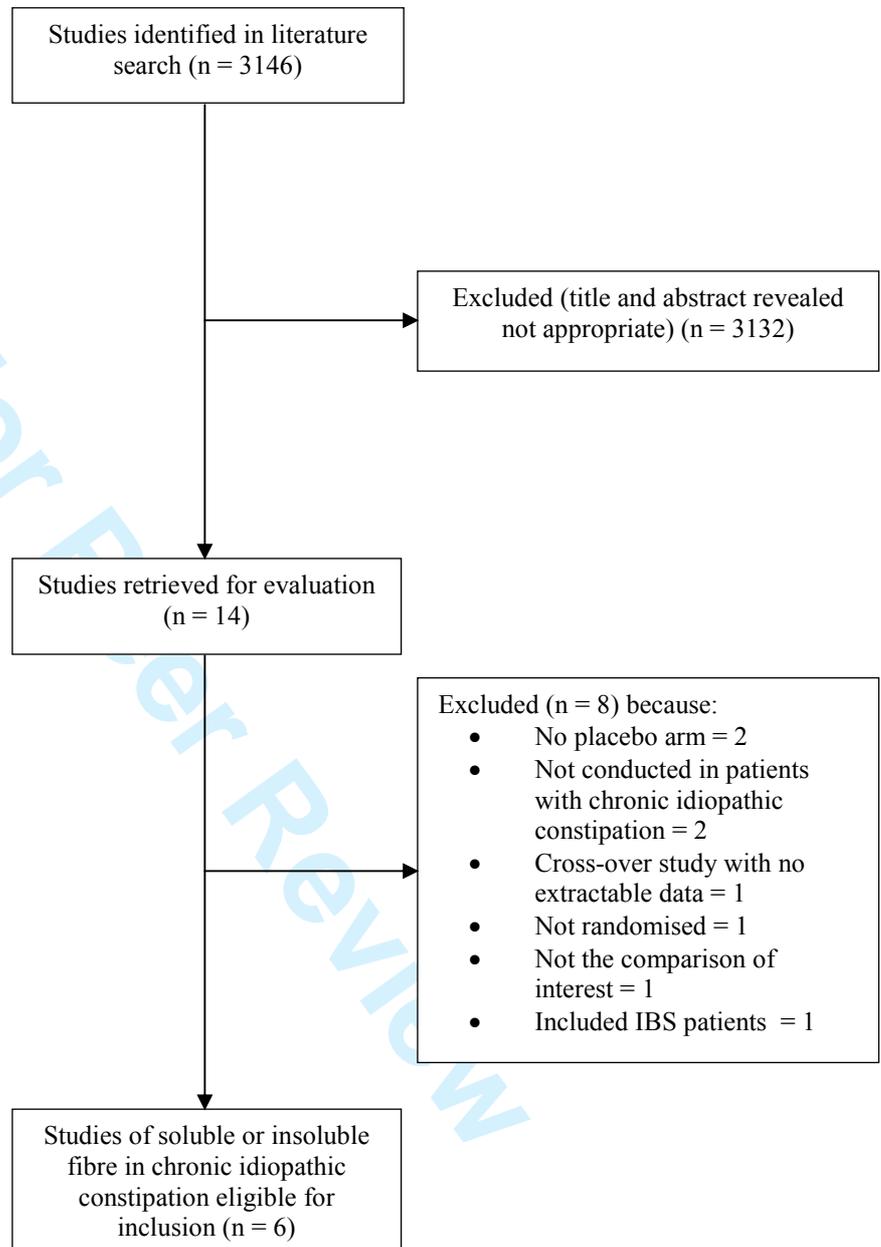
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Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.



Suares and Ford

24 of 27

Table 1 - Characteristics of randomised controlled trials of fibre versus placebo in the treatment of CIC

Study	Country, setting, and number of centres	Criteria used to define CIC*	Number of participants (% female)	Duration of therapy	Active intervention	Methodology
Fenn 1986 ²⁰	UK, primary care, 17 sites	Clinical diagnosis	201 (75.1)	2 weeks	Psyllium 3.6g t.i.d†	Randomisation and concealment unclear, single-blind
Ashraf 1995 ¹⁹	USA, tertiary care, 1 site	3 or less stools per week	22 (63.6)	8 weeks	Psyllium 5g b.i.d±	Randomisation and concealment unclear, double-blind
Nunes 2005 ²³	Brazil, tertiary care, number of sites not reported	Less than 3 stools per week	60 (65.0)	2 weeks	Psyllium 10g/day	Randomisation and concealment unclear, double-blind

Suares and Ford

25 of 27

Lopez Roman 2008 ²²	Spain, tertiary care, 3 sites	Rome II criteria	32 (87.5)	20 days	Inulin and maltodextrin 20g/day	Randomisation and concealment unclear, double-blind
Badiali 1995 ¹⁸	Italy, tertiary care, 1 site	Clinical diagnosis and negative investigations	24 (91.7)	4 weeks	Bran 6.6g t.i.d	Randomisation and concealment unclear, double-blind
Hongisto 2006 ²¹	Finland, tertiary care, 1 site	Clinical diagnosis	29 (100)	3 weeks	320g fibre-rich rye bread	Randomisation, concealment, and blinding unclear

*CIC; chronic idiopathic constipation

†t.i.d; thrice daily

±b.i.d; twice daily

Suares and Ford

26 of 27

Table 2 – Summary of results of individual randomised controlled trials of fibre versus placebo in the treatment of CIC

Study	Active intervention	Criteria used to define response to therapy	Number in fibre arm	Treatment effect in fibre arm	Number in placebo / no therapy arm	Treatment effect in placebo / no therapy arm
Fenn 1986 ²⁰	Psyllium	Proportion with an improvement in global symptoms	104	86.5%	97	47.4%
Ashraf 1995 ¹⁹	Psyllium	Increase in mean stool frequency per week	11	0.9	11	0.2
Nunes 2005 ²³	Psyllium	Proportion with normalisation of evacuation	30	86.7%	30	30.0%

Suarez and Ford

27 of 27

Lopez Roman 2008 22	Inulin and maltodextrin	Proportion with straining during defaecation	15	35.7%	17	78.6%
Badiali 1995 18	Bran	Proportion with no straining during defaecation	9*	55.6%	7*	28.6%
Hongisto 2006 ²¹	Fibre-rich rye bread	Mean number of stools per day	15	1.3	14	0.9

* 24 patients were randomised, but only 16 reported straining at baseline

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 and 16
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A

1	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
2	RESULTS			
3				
4	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 and 22
5				
6	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	23-24
7				
8	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	23-24
9				
10	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11
11				
12	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
13				
14	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, 23-24
15				
16	Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
17				
18	DISCUSSION			
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20	Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
21				
22	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
23				
24	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-15
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26	FUNDING			
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28	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15
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