

# **Systematic review with meta-analysis: effect of fibre supplementation on chronic idiopathic constipation in adults**

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## **ABSTRACT**

**Background** Chronic idiopathic constipation is a common symptom-based gastrointestinal disorder responsible for a substantial economic health service burden. Current guidelines recommend the use of fibre as first-line treatment.

**Aim** To investigate the effect of fibre (including prebiotic) supplementation on global symptom response, stool output, gut microbiota composition and adverse events in adults with chronic idiopathic constipation.

**Methods** Medline, Embase, Web of Science, Scopus, and the Cochrane central register of controlled trials were searched through to February 2016. Conference proceedings from 2003-2015 were hand searched. There were no language restrictions. Forest plots with 95% CIs were generated using a random effects model.

**Results** The search strategy generated 1072 citations, of which 7 individual randomised controlled trials were eligible. Overall, 113 of 147 (77%) patients assigned to fibre responded to therapy, compared with 61 of 140 (44%) allocated to placebo (RR of success to respond 1.71, 95% CI 1.20 to 2.42,  $P=0.003$ ). Fibre significantly increased stool frequency (SMD=0.39; 95% CI 0.03 to 0.76;  $P=0.03$ ) and softened stool consistency (SMD=0.35; 95% CI 0.04 to 0.65;  $P=0.02$ ) compared with placebo. Flatulence was significantly higher with fibre compared to placebo (SMD 0.56, 0.12 to 1.00,  $P=0.01$ ). Overall quality of evidence was low.

**Conclusions** This meta-analysis demonstrates that fibre is moderately effective but also causes moderate gastrointestinal side effects. However, these findings need to be treated with caution due to high risk of bias. Accordingly, further large, methodologically rigorous trials are required, before any definitive recommendation regarding its risk-benefit profile can be made.

## INTRODUCTION

Chronic idiopathic constipation (CIC) is a heterogeneous symptom-based disorder with an estimated global prevalence of 14%<sup>1</sup> characterized by infrequent defecation, difficult stool passage, or a combination of the two in the absence of an organic cause.<sup>2</sup> Females have been shown to be two to three times more likely to have CIC than men.<sup>3</sup> CIC is associated with impaired quality of life,<sup>4</sup> increased risk of colorectal cancer<sup>5</sup> and is responsible for a substantial economic health service burden.<sup>6</sup> The pathophysiology of CIC is multifactorial and incompletely understood. Beyond simple lifestyle advice (e.g. increasing fluid intake and levels of exercise), laxatives are a widely used treatment<sup>7</sup> but are associated with suboptimal outcomes due to variable efficacy, adverse events, cost, taste and inconvenience.<sup>8</sup>

First line management as recommended in British, American, European and other global guidelines, as well as expert commentaries, is fibre supplementation.<sup>9-13</sup> Fibre intake may accelerate whole gut transit time, by increasing luminal bulk resulting in increased peristalsis.<sup>14</sup> Fibre can also influence bulking directly via water retention which also normalises stool form.<sup>15-16</sup> Further, fermentation of fibre can increase stool bulk by increasing microbial biomass and fermentation by-products, such as short chain fatty acids.<sup>17</sup> Gut transit time may also be indirectly accelerated through lowering of luminal pH and possibly through secondary effects on the gut microbiota.<sup>18</sup> Nevertheless, up to 50% of patients do not respond or become dissatisfied with fibre as a treatment stratagem.<sup>19</sup> The term fibre refers to carbohydrate polymers with three or more monomers that are not hydrolysed by endogenous enzymes in the human small intestine.<sup>20</sup> This definition also includes prebiotics, which are soluble fibres that are selectively fermented and result in

specific changes in the composition and/or activity of the gut microbiota, and are postulated to confer health benefit(s) upon the host.<sup>21</sup>

The efficacy of fibre in the management of CIC in adults has been documented in a previous systematic review.<sup>22</sup> However, to date there has been no definitive quantitative summary of available evidence and outcomes (particularly on the effect of prebiotics on gut microbiota composition). Thus, we aimed to address this knowledge gap by objectively assessing the effect of fibre supplementation on measures of: (I) response to therapy, (II) stool output, (III) gut microbiota composition, and (IV) adverse events in adults with CIC.

## **METHODS**

A systematic review and meta-analysis was performed following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions,<sup>23</sup> and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>24</sup>

### **Search strategy and study selection**

A literature search for randomised controlled trials (RCTs) evaluating fibre supplementation used in the treatment of CIC in adults was conducted. A database search was performed in February 2016 using MEDLINE, EMBASE, WEB OF SCIENCE, SCOPUS and The Cochrane Central Register of Controlled Trials. No date limitations were applied and searches were not restricted by language. Studies on CIC were identified with the terms: constipation OR gastrointestinal transit [both as medical subject headings (MeSH) and free text terms]. These were combined using the set operator AND with studies identified with the terms: fibre OR psyllium (both as MeSH terms and free text terms). Results were then further combined with the operator AND with highly sensitive search filter for identifying RCTs. The detailed search strategy for MEDLINE is presented in **Table S1**. Reference lists of eligible studies, as well as reference lists of previous systematic reviews on fibre and constipation, were manually scanned for additional studies not identified by the electronic searches. An attempt to identify completed but unpublished trials was performed by searching the ClinicalTrials.gov and www.isrctn.com databases. Finally, abstracts of the following conference proceedings were hand-searched to identify potentially relevant studies: Digestive Diseases Week (2003–2015), British Society of Gastroenterology Annual Meeting (2003-2015), and United European

Gastroenterology Week (2009–2015). Titles and abstracts identified from the search strategy were evaluated by two independent investigators (SC and ED) using pre-defined eligibility criteria. The full text of any title or abstract deemed potentially eligible by either investigator was retrieved and foreign language papers were translated when required. Subsequently, the two reviewers independently assessed the eligibility of each full-text article and disagreements were resolved by consensus with a third researcher (SMS).

### **Eligibility criteria**

The eligibility criteria were developed using the Population, Intervention, Comparator, Outcomes, Study design (PICOS) approach.<sup>25</sup> *Population* - adults ( $\geq 18$  years old) with CIC diagnosed using clinical diagnosis, self-report or Rome criteria. Only studies in which patients were recruited from community or outpatient settings were included. *Intervention* - studies using supplementary fibre as defined by the Commission of European Communities (2008).<sup>20</sup> *Comparator* - studies comparing fibre (including prebiotic) supplements with placebo/control. Trials were also included if they reported interventions with supplementary fibre in combination with other ingredients (active comparators) as long as the effect of fibre could be isolated. *Outcomes* - studies reporting either dichotomous or continuous data on overall response to therapy, stool output, gut microbiota concentrations and adverse events. *Study Design* - RCTs with parallel group design, or the first period of crossover RCTs (to reduce the risk of carryover effect) were considered eligible for inclusion.

## **Data extraction**

Two investigators (SC and ED) independently extracted data on patient characteristics, interventions, comparators, measure outcomes, and study design using standardised data extraction forms. Authors of included studies were contacted for missing data and their responses were included in the analyses. Whenever allowed by trial reporting, data were extracted as intention-to-treat analyses, with all drop-outs assumed to be treatment failures for dichotomous outcomes (i.e. no response to therapy). If this was not clear from the original article, an analysis on all patients with reported evaluable data was undertaken.

## **Assessment of risk of bias**

The two investigators independently assessed risk of bias according to the Cochrane Collaboration handbook,<sup>23</sup> with disagreements resolved by discussion. Studies were assessed for the methods used to generate randomisation, conceal allocation, blinding, incomplete outcome data, selective reporting, and other sources of bias. Furthermore, the overall quality of evidence (confidence in effect estimates) for each outcome was rated by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>26</sup> Quality of evidence was rated from high to very low.<sup>27</sup>

## **Data synthesis and statistical analysis**

Data were pooled using a random effects model, to give a more conservative estimate of the effect of fibre supplementation on CIC, allowing for heterogeneity between studies.<sup>28</sup> The estimates of treatment effects were expressed as relative risk (RR) and 95% confidence interval (CI) for dichotomous outcomes (response to



therapy) and standardized mean difference (SMD) with 95% CI for continuous outcomes (stool frequency, stool consistency, gut microbiota concentrations, adverse events). SMD was used as a summary statistic for all continuous outcomes because the studies measured the same outcome using varied scales or because no details of the scale and scoring system were reported, which prevented the data being converted to the same unit, thus prevented calculation of the mean difference. SMD values of 0.2, 0.5 and 0.8 were defined as small, moderate and large effect size respectively.<sup>29</sup> The number needed to treat (NNT) and 95% CIs were calculated for response to therapy using the formula:  $NNT = 1 / (1 - RR) \times \text{assumed control group risk}$ .<sup>23</sup> Furthermore, the precision of the estimate of effect for the primary outcome was tested by calculating the optimal information size using  $\alpha$  (0.05) and  $\beta$  (0.20) values, and a relative risk reduction of response to therapy of 30%.<sup>30</sup> Heterogeneity between studies was assessed using the  $I^2$  statistic with a cut-off of 25%,<sup>31</sup> and/or the chi-square test, with a P-value <0.10 to define significant heterogeneity.  $I^2$  statistic values of 25%, 50% and 75% were defined as low, moderate and high heterogeneity respectively.<sup>32</sup> Subgroup analyses were carried out to explore possible causes of heterogeneity and subgroup-treatment interactions using the chi-square significance test.<sup>33</sup> An interaction p-value of <0.10 was considered as a cut-off.<sup>34</sup> Forest plots with 95% CIs were generated for all outcomes using Review Manager v. 5.3 (Copenhagen, Denmark) and Stata v.12.0 (StataCorp, Stata Statistical Software, College Station, Texas, USA). Funnel plots were generated, where sufficient number of studies were identified, to assess for evidence of asymmetry and therefore possible publication bias or other small study effects;<sup>35</sup> these were evaluated by both observing the funnel plots and using Egger's test analysis.<sup>36</sup> A two-tailed p-value

$\leq 0.05$  was adopted as the statistical criterion. The kappa statistic for inter-observer agreement between the two reviewers was also calculated.<sup>37</sup>

## RESULTS

### Study selection

The search strategy generated 1072 citations, of which 1064 studies were identified from the primary electronic databases and 8 studies identified through manual search. Of these, 377 were duplicates leaving 695 records to be screened, of which 52 were potentially relevant and retrieved for full-text review (**Figure 1**). Of these, 45 were excluded with 7 RCTs ultimately eligible.<sup>38-44</sup> Agreement between investigators for trial eligibility was substantial (kappa statistic=0.80).

### Study characteristics

The seven RCTs comparing fibre supplementation with placebo/control involved a total of 430 adults with CIC.<sup>38-44</sup> Six studies were published in English and one in Spanish.<sup>42</sup> Authors of six of the trials were contacted to obtain supplementary information about the methodology used.<sup>39-44</sup> Of these, four provided responses that were included in the analyses.<sup>39-41, 44</sup> **Table 1** shows the definition of chronic idiopathic constipation used in the included studies, and **Table 2** details the characteristics of the included studies. There was considerable variability in the type (e.g. psyllium, inulin) and dose (10 to 22.5g/d) of fibre studied. Treatment periods varied from two to eight weeks and the proportion of women in the trials ranged between 64% and 100%.

### Efficacy and safety of fibre in the treatment of CIC

#### Response to therapy

Dichotomous data on response to therapy, measured by symptomatic improvement, were reported by four RCTs<sup>38, 41-42, 44</sup> including 287 patients. Overall, 113 of 147

(77%) patients assigned to fibre responded to therapy, compared with 61 of 140 (44%) allocated to placebo (RR of success to respond=1.71; 95% CI 1.20 to 2.42;  $P=0.003$ ), with borderline heterogeneity between studies ( $I^2=24%$ ,  $\chi^2 P=0.27$ ). Overall, the NNT with fibre to result in response in one patient was 3 (95% CI 2.6 to 3.4). Given the borderline heterogeneity, subgroup analyses were conducted (**Table 3**). The NNT were relatively stable in all these analyses. However, there was no heterogeneity between trials when only the two trials that used “proportion with no straining during defecation” to define response to therapy ( $I^2=0%$ ,  $\chi^2 P=0.77$ ), the two trials that used non-prebiotics ( $I^2=0%$ ,  $\chi^2 P=0.69$ ), and when the three studies that used high dose ( $I^2=0%$ ,  $\chi^2 P=0.61$ ) were included in the analysis. Sub-group analyses demonstrated no statistically significant differences in efficacy according to definition of response to therapy, type of fibre used, fibre solubility in water, and prebiotics *versus* non-prebiotics (interaction  $P > 0.10$ ). In contrast, the subgroup analysis evaluating low ( $\leq 15\text{g/d}$ ) *versus* high dose ( $> 15\text{g/d}$ ) suggested an increased effect with high dose (interaction  $P=0.09$ ), partly explaining the heterogeneity observed across all studies. The optimal information size was calculated on the basis of a relative risk reduction of response to therapy of 30%. Optimal information size (617 individuals) was greater than the total sample size (287 participants), while the number of events across trials was relatively low (174 events) (**Table 4**).

### Stool frequency

Continuous data on stool frequency were reported by six studies including 406 patients.<sup>38-43</sup> Overall, fibre supplementation significantly increased stool frequency compared with placebo (SMD=0.39; 95% CI 0.03 to 0.76;  $P=0.03$ ), indicating a moderate effect size, albeit with statistically significant heterogeneity between studies

( $I^2=56\%$ ,  $\chi^2 P=0.04$ ) (**Figure S1**). Results of subgroup analyses (**Figure 2**) showed no differences in efficacy according to type of fibre used (interaction  $P=0.81$ ), and prebiotics *versus* non-prebiotics (interaction  $P=0.91$ ), although psyllium and non-prebiotics increased stool frequency ( $P=0.0005$ ). In addition, there was no heterogeneity between trials when only the two trials that used psyllium, and the two trials that used non-prebiotics were included in the analysis ( $I^2=0\%$ ,  $\chi^2 P=0.87$ ). Subgroup analyses suggested a possible increased effect with high dose (interaction  $P=0.17$ ). High dose ( $>15\text{g/d}$ ) fibre supplementation significantly increased stool frequency compared with placebo (SMD=0.77; 95% CI 0.03 to 1.51;  $P=0.04$ ), indicating a large effect size. However, statistically significant heterogeneity between studies existed ( $I^2=71\%$ ,  $\chi^2 P=0.06$ ). Results of subgroup analysis according to sample size revealed a borderline statistically significant increase in stool frequency when studies that recruited less than 50 participants ( $P=0.003$ ) were included in the analysis (interaction  $P=0.10$ ).

### Stool consistency

Stool consistency was reported as a continuous end point in five studies including 346 patients.<sup>38-40, 42-43</sup> Overall, fibre supplementation significantly softened stool consistency compared with placebo (SMD=0.35; 95% CI 0.04 to 0.65;  $P=0.02$ ), indicating a moderate effect size, however heterogeneity between studies existed ( $I^2=34\%$ ,  $\chi^2 P=0.19$ ) (**Figure S2**). Heterogeneity between trials was lower when only the two trials that used psyllium and when only the two trials that used non-prebiotics were included in the analysis ( $I^2=8\%$ ,  $\chi^2 P=0.30$ ). Sub-group analyses showed no difference in efficacy according to type of fibre used (interaction  $P=0.18$ ) (**Figure 3**). However, psyllium ( $P=0.009$ ) and a mixture of inulin with resistant maltodextrin

( $P=0.008$ ) softened stool consistency. Results of the subgroup analysis comparing prebiotics *versus* non-prebiotics, showed borderline statistically significant improvement in stool consistency when studies that used non-prebiotics ( $P=0.009$ ) or a mixture of a prebiotic/non-prebiotic ( $P=0.008$ ) were included in the analysis (interaction  $P=0.10$ ). The subgroup hypothesis evaluating single fibres *versus* mixtures of (multiple) fibre suggested an increased effect with mixtures of fibre ( $P=0.008$ ) (interaction  $P=0.09$ ). Furthermore, there were subgroup differences by dose of fibre used (interaction  $P=0.06$ ) showing an increased effect on stool consistency with high dose ( $>15\text{g/d}$ ) ( $P=0.006$ ), partly explaining the heterogeneity observed across all studies.

#### Gut microbiota concentrations

The effect of fibre supplementation on fecal bifidobacteria and clostridia concentrations was reported in three studies. Bacterial counts were assessed via molecular techniques [two studies used the quantitative polymerase chain reaction<sup>40, 41</sup> and one study used fluorescence *in situ* hybridization<sup>43</sup>]. Bifidobacteria counts were reported in three studies, including 151 patients.<sup>40-41, 43</sup> Overall, fibre supplementation did not significantly increase bifidobacteria numbers compared with placebo (SMD=0.43; 95% CI -0.20 to 1.07;  $P=0.18$ ), and statistically significant heterogeneity between studies existed ( $I^2=72\%$ ,  $\chi^2 P=0.03$ ) (**Figure S3**). Sub-group analyses were performed to explore possible causes of the significant heterogeneity observed (**Figure 4**). The subgroup analysis comparing prebiotics *versus* non-prebiotics showed a statistically significant increase in bifidobacteria counts with prebiotics (SMD=0.75; 95% CI 0.33 to 1.18;  $P=0.0005$ ) [inulin ( $P=0.02$ ) and galacto-oligosaccharides (GOS) ( $P=0.01$ )] (interaction  $P=0.008$ ). In addition, there was no

heterogeneity between trials when only the two trials that used prebiotics were included in the analysis ( $I^2=0\%$ ,  $\chi^2 P=0.78$ ) (**Figure S3**). Two studies, including 101 patients, reported data on clostridia counts.<sup>41, 43</sup> Clostridia levels were significantly reduced with fibre supplementation compared to placebo (SMD=-0.66; 95% CI -1.29 to -0.02;  $P=0.04$ ), indicating a moderate effect size, although heterogeneity between studies existed ( $I^2=56\%$ ,  $\chi^2 P=0.13$ ).

#### Adverse events

None of the studies reported total number of adverse events or patient withdrawal because of fibre side effects. Nevertheless, three studies reported continuous data regarding individual gastrointestinal adverse events (flatulence and bloating). Three studies, including 115 patients, provided data on flatulence.<sup>40, 43-44</sup> Overall, flatulence was significantly higher with fibre supplementation compared to placebo (SMD=0.56; 95% CI 0.12 to 1.00;  $P=0.01$ ), indicating a moderate effect size, with low heterogeneity between studies detected ( $I^2=23\%$ ,  $\chi^2 P=0.27$ ) (**Figure S4**). Bloating was reported in three studies, including 115 patients.<sup>40, 43-44</sup> Fibre supplementation increased bloating compared with placebo (SMD=0.36; 95% CI -0.01 to 0.74;  $P=0.06$ ) with borderline statistical significance. No heterogeneity between studies existed ( $I^2=0\%$ ,  $\chi^2 P=0.94$ ) (**Figure S5**).

#### Publication bias

The studies identified herein were too few in number to assess for evidence of asymmetry, and in turn for evidence of publication bias or other small study effects.<sup>36</sup>

## **Risk of bias**

None of the studies was at low risk of bias, both at the study (**Figure S6**) and outcome level (**data available on request**), and none of the trials followed an intention-to-treat analysis. Attrition bias (incomplete outcome data) and reporting bias (selective reporting) were prevalent, whereas performance bias (blinding of participants and personnel) and other bias were low amongst trials, both at the study (**Figure S6**) and outcome level (**data available on request**). GRADE criteria were applied to interpret results and assess overall quality of evidence (confidence in effect estimates) for each outcome (**Table 4**). The quality of evidence in terms of response to therapy, stool frequency, and adverse events was graded as low, whereas the confidence in the effect estimates for stool consistency and gut microbiota concentrations was graded as very low.



## DISCUSSION

This meta-analysis demonstrates that fibre supplementation is more effective than placebo for the treatment of CIC in adults. However, there is only low quality evidence that fibre is moderately effective. Furthermore, individual gastrointestinal side effects (e.g. flatulence) were higher in patients receiving fibre, although no patient withdrew because of fibre side effects. Only four trials<sup>38, 41-42, 44</sup> adhered to the ROME committee's recommendations<sup>45</sup> by reporting global dichotomous data on response to therapy. The NNT with fibre to result in response to therapy was between 2 and 3, with subgroup analyses suggesting that high dose (>15g) was the most effective, with a NNT of 2. However, the definitions of response to therapy were inconsistent, and placebo rate of 44% was very high (e.g. in comparison to a placebo response of 27%, shown in a meta-analysis of laxatives in CIC).<sup>46</sup> In addition, the optimal information size (617 individuals) was not met (287 participants), thus lowering confidence in estimates of effect for imprecision.<sup>30</sup> Hence the effect size and NNT obtained from this meta-analysis need to be treated with caution.

Prebiotics (inulin and GOS) seem to have no benefit over placebo in increasing stool frequency. The most robust evidence for an individual fibre seems to be for psyllium (a non-prebiotic). High fibre dose (>15g) was found to increase stool frequency with a large effect size. The most recent meta-analysis on the efficacy of laxatives in CIC demonstrated similar efficacy to the data for high fibre dose;<sup>46</sup> both osmotic laxatives, including polyethylene glycol (~17g once or twice daily), and stimulant laxatives [e.g. bisacodyl (10 mg)] significantly increased stool frequency with a large effect size.<sup>46</sup> However, the fact that small sample-sized studies (<50 participants) showed higher

increases in stool frequency suggests the possibility of small study bias, given that smaller studies tend to show larger estimated effects than larger studies.<sup>47</sup>

Fibre supplementation moderately softened stool consistency, also with a dose-dependent effect. Psyllium showed greater effect on stool consistency compared to prebiotics (GOS and inulin). Psyllium (ispaghula husk), obtained from the seeds of *plantago ovata*, is a soluble viscous fibre with a high water-holding capacity that normalizes stool form.<sup>48</sup> Stool water content has been highly associated with stool consistency, and a relatively small increase in stool water content has been shown to result in a relatively large stool softening effect.<sup>15,49</sup> GOS and inulin are highly fermentable and are almost completely fermented in the colon, and despite high initial water-holding capacity, their fermentation results in a loss of water holding capacity and thus they have little effect on stool consistency.<sup>16</sup> In contrast, psyllium is only partially fermented in the gut and the stool softening effect is a direct consequence of its ability to form a gel and hold many times its own weight in water.<sup>16</sup>

In terms of side effects, flatulence and bloating were moderately increased after fibre consumption with a trend towards a dose-dependent effect. This might partly explain why patients (especially those with pre-existing symptoms of bloating) often poorly tolerate fibre supplementation.<sup>18</sup> However, some degree of spontaneous unblinding was arguably present in these trials because of the effect of fibre on bowel symptoms, and it is likely to have affected subjective symptom assessments.<sup>50</sup>

Preliminary data have proposed a role for abnormal gut microbiota composition, so-called dysbiosis, in the pathogenesis of CIC.<sup>51</sup> Patients with CIC have been found to have lower concentrations of 'beneficial' bacteria (e.g. bifidobacteria) and higher concentrations of 'pathogenic' bacteria (e.g. clostridia).<sup>51</sup> Pooled results with prebiotics (GOS and inulin) showed a statistically significant increase in bifidobacteria counts with a large effect size. Both GOS and inulin can be metabolized by bifidobacteria,<sup>52</sup> though GOS is more bifidogenic,<sup>53</sup> compatible with a higher effect size. In addition, fibre supplementation significantly lowered clostridia counts compared to placebo, with a moderate effect size. However, whether these beneficial quantitative changes in gut microbiota composition can lead to changes in gastrointestinal transit, which may benefit symptoms of constipation, is still unknown. Consequently, findings in relation to the microbiota-dependent or microbiota-independent effect of fibre on gastrointestinal transit require confirmation in future studies.

### **Strengths and limitations**

This systematic review and meta-analysis strictly adhered to recommended methodology, including a comprehensive search strategy, which included searching the 'grey' literature to minimize publication bias. Only RCTs were selected, and foreign language articles were translated to further minimize bias. Both the eligibility assessment and data extraction were performed independently and in duplicate. Authors of individual studies were also contacted in order to obtain supplementary information, where required. We used an intention-to-treat analysis and data were pooled with a random effects model to provide a more conservative estimate of the efficacy of fibre in CIC. We also conducted subgroup analyses to assess

heterogeneity in results. Finally, we used the GRADE approach, an internationally recognized method of rating evidence, to assess quality of evidence in addition to reporting risk of bias. Limitations of the present study derive from the quality and reporting of the included trials. None of the studies identified was at low risk of bias, both at the study and outcome level, sufficient in itself to negatively affect the interpretation of results.<sup>54</sup> Furthermore, none of the trials followed an intention-to-treat analysis potentially resulting in an over-estimation of efficacy of fibre supplementation.<sup>55</sup> Application of GRADE criteria indicated results were of low quality, mainly due to study limitations, inconsistency and imprecision. Controversy remains over whether a meta-analysis should be performed due to concerns over the methodological quality of the studies identified, due to the considerable variability in the type of fibre studied, and due to the different habitual fibre intake level among the participants. The detection of heterogeneity in some of our analyses might reflect this variability. Different types of fibre have different physiological properties,<sup>50</sup> and therefore, the therapeutic benefit may be fibre-specific. Unfortunately, the small number of studies available with each type of fibre in the subgroup analyses did not enable us to perform robust type-specific comparisons, and thus results should be interpreted with caution. Insoluble fibre has been also shown to alter colonic function through a stool bulking effect<sup>17</sup> and through mechanical stimulation/irritation of the gut mucosa,<sup>56-57</sup> but only one trial used insoluble fibre.<sup>44</sup>

### **Comparison with other studies**

To the best of our knowledge, this is the first meta-analysis to assess available data on the efficacy of fibre supplementation in adults with CIC. Another recent meta-analysis<sup>58</sup> mainly focused on pediatric patients, with only one trial including adult

patients.<sup>44</sup> This study also included patients with organic constipation rather than being conducted exclusively in patients with CIC. A systematic review performed exclusively in adult patients with CIC was published in 2011,<sup>22</sup> and comprised six trials.<sup>38-39, 42, 44, 59-60</sup> Of these, we excluded two studies<sup>59-60</sup> (in which the effect of fibre supplementation could not be isolated), and identified three additional studies,<sup>40-41, 43</sup> two of which<sup>40-41</sup> were published in the intervening four years, underlining the continuing interest in the manipulation of the gut microbiota through prebiotic supplementation as a potential therapy for CIC. Our meta-analysis demonstrated that prebiotic supplementation can beneficially alter gut microbiota concentrations. Within the most recent American College of Gastroenterology guidelines on the management of CIC in adults,<sup>11</sup> a meta-analysis examining the effect of fibre on response to therapy identified only three trials,<sup>38, 42, 59</sup> with pooled results suggesting a beneficial effect of fibre compared to placebo, with a NNT of 2, similar to that found in the current study. Finally, a systematic review without meta-analysis by Rao and colleagues was published in 2015,<sup>61</sup> though the database search for this review was limited to a 10 year time period (2004-2014). Furthermore, studies with cross-over design and short washout periods (1–2 weeks) were considered eligible, thus increasing the carryover effect risk. Moreover, not all studies included were RCTs, and studies that used natural fibre (e.g. prunes), instead of a fibre supplement, were not excluded. Prunes also contain sorbitol, a polyol with osmotic laxative effect,<sup>62</sup> which might have skewed results.

### **Implications for fibre supplementation recommendations**

Fibre supplements are food products and therefore are relatively safe, inexpensive and are widely available.<sup>63</sup> Moreover, their use has been also associated with a

diminution in colorectal cancer risk compared to non-fibre laxative use.<sup>64</sup> Therefore, they are a reasonable first-line therapy for CIC albeit with the caveat that up to 50% of patients will be dissatisfied with their effect.<sup>19</sup> It remains unclear which type of fibre is the most efficacious, although the most robust evidence seems to be for psyllium (a soluble, non-prebiotic fibre). It also remains unclear whether one type of fibre will provide relief to all patients, or whether there may be particular subtypes of this heterogeneous condition that might respond preferentially.<sup>65</sup> The aforementioned dissatisfaction with fibre is likely to be a consequence of increased gastrointestinal adverse events, such as flatulence and bloating,<sup>8</sup> and warrants discussion with the patient prior to institution.

## **Conclusion**

Current guidelines recommend the use of fibre supplementation as first-line treatment for CIC. However, overall there is only low quality evidence to support such a recommendation. Meta-analysis demonstrated that fibre supplementation is moderately effective with a dose-dependent effect but also causes moderate gastrointestinal side effects, again in a dose-dependent manner. Nevertheless, none of the studies included was at low risk of bias, sufficient in itself to negatively affect the interpretation of results. Hence, the paucity of high quality data highlights the need for further large, methodologically rigorous RCTs of fibre supplementation in CIC, adhering to the ROME Foundation criteria, before any recommendation regarding its risk-benefit profile can be definitively promoted.

## **AUTHORSHIP**

**Guarantor of the article:** SMS

**Author contributions:** SC, SMS and KW conceived and designed the review. SC, SMS and KW developed the review protocol. SC and ED performed eligibility screening, carried out the data extraction and methodological quality assessment. SMS provided advice and arbitration on the selection process, data extraction, and methodological quality assessment. SC and KCF analyzed the data. SC, ADF, SMS and KW interpreted the data. SC wrote the original draft, and the other authors revised the draft critically for important intellectual content and approved the final version of the paper, including the authorship list.

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## TABLES

**Table 1.** Definition of chronic idiopathic constipation used in randomised controlled trials of fibre supplementation in adults.

Study	Diagnostic criteria for CIC	Details of diagnostic criteria
<b>Fenn, 1986</b> <sup>38</sup>	Clinical diagnosis	Patients suffering from functional constipation
<b>Ashraf, 1995</b> <sup>39</sup>	Clinical diagnosis	Patients with chronic idiopathic constipation confirmed by prospectively administered stool diaries
<b>Marteau, 2011</b> <sup>40</sup>	Rome III criteria	Patients suffering from functional constipation according to the Rome definition (<3 stools/week and/or straining in defecation)
<b>Waitzberg, 2012</b> <sup>41</sup>	Self-reported	Females with at least 3 months of primary constipation defined as less than 3 bowel movements per week
<b>Lopez Roman, 2008</b> <sup>42</sup>	Rome II criteria	Patients meeting the Rome II criteria for chronic idiopathic constipation
<b>Surakka, 2009</b> <sup>43</sup>	Self-reported	Patients with difficulties in intestinal function (including fewer than 5 BM per week or continuous difficulties in defecation or both)
<b>Badiali, 1995</b> <sup>44</sup>	Clinical diagnosis	Patients with prolonged large bowel transit seeking medical advice for chronic primary constipation

CIC=chronic idiopathic constipation; BM=bowel movements.

**Table 2.** Characteristics of included randomised controlled trials of fibre supplementation in chronic idiopathic constipation in adults.

Study	Country	Setting	Study design	Criteria used to define response to therapy	No. of patients (% female)	Age Mean (range) (years)	Fibre used	Water solubility	Prebiotics	Daily Dose (g)	Form	Duration of therapy
<b>Fenn, 1986</b> <sup>38</sup>	UK	Primary care	Single blind, parallel group	Proportion with an improvement in global symptoms	201 (75%)	49 (17-70)	Psyllium	Soluble	Non prebiotic	19.2	Powder	2 weeks
<b>Ashraf, 1995</b> <sup>39</sup>	USA	Tertiary care	Double blind, parallel group	NR	22 (64%)	51 (40-75)	Psyllium	Soluble	Non prebiotic	10.2	Powder	8 weeks
<b>Marteau, 2011</b> <sup>40</sup>	France	Primary care	Double blind, parallel group	NR	50 (88%)	57 (50-70)	Inulin	Soluble	Prebiotic	15	Powder	4 weeks
<b>Waitzberg, 2012</b> <sup>41</sup>	Brazil	Primary care	Double blind, parallel group	Proportion with constipation relief	60 (100%)	38 (18-65)	Inulin & PHGG	Soluble	Prebiotic & non prebiotic	15	Powder	3 weeks
<b>Lopez Roman, 2008</b> <sup>42</sup>	Spain	Tertiary care	Double blind, parallel group	Proportion with no straining during defecation	32 (88%)	47 (17-77)	Inulin & RM	Soluble	Prebiotic & non prebiotic	22.5	Milk	20 days
<b>Surakka, 2009</b> <sup>43</sup>	Finland	Tertiary care	Double blind, cross-over	NR	41 (76%)	68 (60-80)	GOS	Soluble	Prebiotic	10	Yoghurt	3 weeks
<b>Badiali, 1995</b> <sup>44</sup>	Italy	Tertiary care	Double blind, cross-over	Proportion with no straining during defecation	24 (92%)	41 (18-65)	Wheat bran	Insoluble	Non prebiotic	19.8	Powder	4 weeks

GOS=galacto-oligosaccharides; NR=not reported (study did not report any dichotomous data on response to therapy); PHGG=partially hydrolyzed guar gum; RM=resistant maltodextrin.



**Table 3.** Sub-group analyses of efficacy of fibre in resulting in response to therapy in adults with chronic idiopathic constipation.

	Number of studies	Number of patients	RR of success to respond to therapy (95% CI)	Sig.	Interaction P value	$\chi^2$ P value	I <sup>2</sup>	Number needed to treat (95% CI)
<b>All studies</b>	4 <sup>38,41-42,44</sup>	287	1.71 (1.2 to 2.42)	0.003*		0.27	24%	3 (2.6 to 3.4)
<b>Definition of response to therapy</b>					0.23			
Proportion with no straining during defecation	2 <sup>42,44</sup>	44	2.70 (1.19 to 6.11)	0.02*		0.77	0%	2 (1.7 to 2.3)
Other definition	2 <sup>38,41</sup>	243	1.46 (0.82 to 2.58)	0.20		0.10	64%	N/A
<b>Type of fibre</b>					0.90			
Psyllium	1 <sup>38</sup>	197	1.80 (1.45 to 2.25)	<0.00001*		N/A	N/A	3 (2.9 to 3.1)
Wheat bran	1 <sup>44</sup>	16	2.33 (0.66 to 8.22)	0.19		N/A	N/A	N/A
Mixture of inulin with PHGG or RM	2 <sup>41-42</sup>	74	1.59 (0.53 to 4.75)	0.41		0.08*	67%	N/A
<b>Fibre solubility</b>					0.61			
Soluble fibre	3 <sup>38,41-42</sup>	271	1.65 (1.03 to 2.62)	0.04*		0.16	46%	3 (2.5 to 3.5)
Insoluble fibre	1 <sup>44</sup>	16	2.33 (0.66 to 8.22)	0.19		N/A	N/A	N/A
<b>Prebiotics vs. non-prebiotics</b>					0.81			
Mixture of a prebiotic/non-prebiotic	2 <sup>41-42</sup>	74	1.59 (0.53 to 4.75)	0.41		0.08*	67%	N/A
Non-prebiotics	2 <sup>38,44</sup>	213	1.82 (1.46 to 2.26)	<0.00001*		0.69	0%	2 (1.9 to 2.1)
<b>Dose of treatment</b>					0.09*			
Low dose ( $\leq$ 15g)	1 <sup>41</sup>	46	0.98 (0.49 to 1.96)	0.96		N/A	N/A	N/A
High dose ( $>$ 15g)	3 <sup>38,42,44</sup>	241	1.85 (1.50 to 2.29)	<0.00001*		0.61	0%	2 (1.8 to 2.2)

\*=statistically significant; CI=confidence interval; Interaction P value=P value of tests for interactions; N/A=not applicable (too few studies to assess heterogeneity and/or relative risk not statistically significant to calculate number needed to treat); PHGG=partially hydrolyzed guar gum; RM=resistant maltodextrin; RR=relative risk; Sig.=significance.

**Table 4.** GRADE system approach for quality of evidence assessment of each outcome.

Outcome	No. of studies	No. of patients	Study limitations	Quality assessment				Quality of evidence
				Inconsistency	Indirectness	Imprecision	Publication bias	
<b>Response to therapy</b>	4 <sup>38,41-42,44</sup>	287	Serious limitations*	⊕	⊕	OIS greater than number of patients; relatively low number of events	Not evaluable	⊕⊕⊕⊕, <b>Low</b>
<b>Stool frequency</b>	6 <sup>38-43</sup>	406	Serious limitations*	Significant heterogeneity between studies; variability in results	⊕	Modest number of patients studied with wide 95% CIs	⊕	⊕⊕⊕⊕⊕, <b>Low</b>
<b>Stool consistency</b>	5 <sup>38-40,42-43</sup>	346	Serious limitations*	Moderate heterogeneity between studies	⊕	Very modest number of patients studied with wide 95% CIs	Not evaluable	⊕⊕⊕⊕, <b>Very low</b>
<b>Gut microbiota concentrations</b>	3 <sup>40-41,43</sup>	151	Serious limitations*	Significant heterogeneity between studies; variability in results	⊕	Only a small number of patients studied with wide 95% CIs	Not evaluable	⊕⊕⊕⊕, <b>Very low</b>
<b>Adverse events</b>	3 <sup>40,43-44</sup>	115	Serious limitations*	⊕	⊕	Only a small number of patients studied with wide 95% CIs	Not evaluable	⊕⊕⊕⊕, <b>Low</b>

\*=all trials were at high risk of bias and all failed to adhere to an intention-to-treat analysis, there was also high attrition (incomplete outcome data) and reporting bias (selective reporting) amongst trials; ⊕ The criterion was fulfilled; ⊖ The criterion was not fulfilled; CI=confidence interval; OIS=optimal information size.

## FIGURES

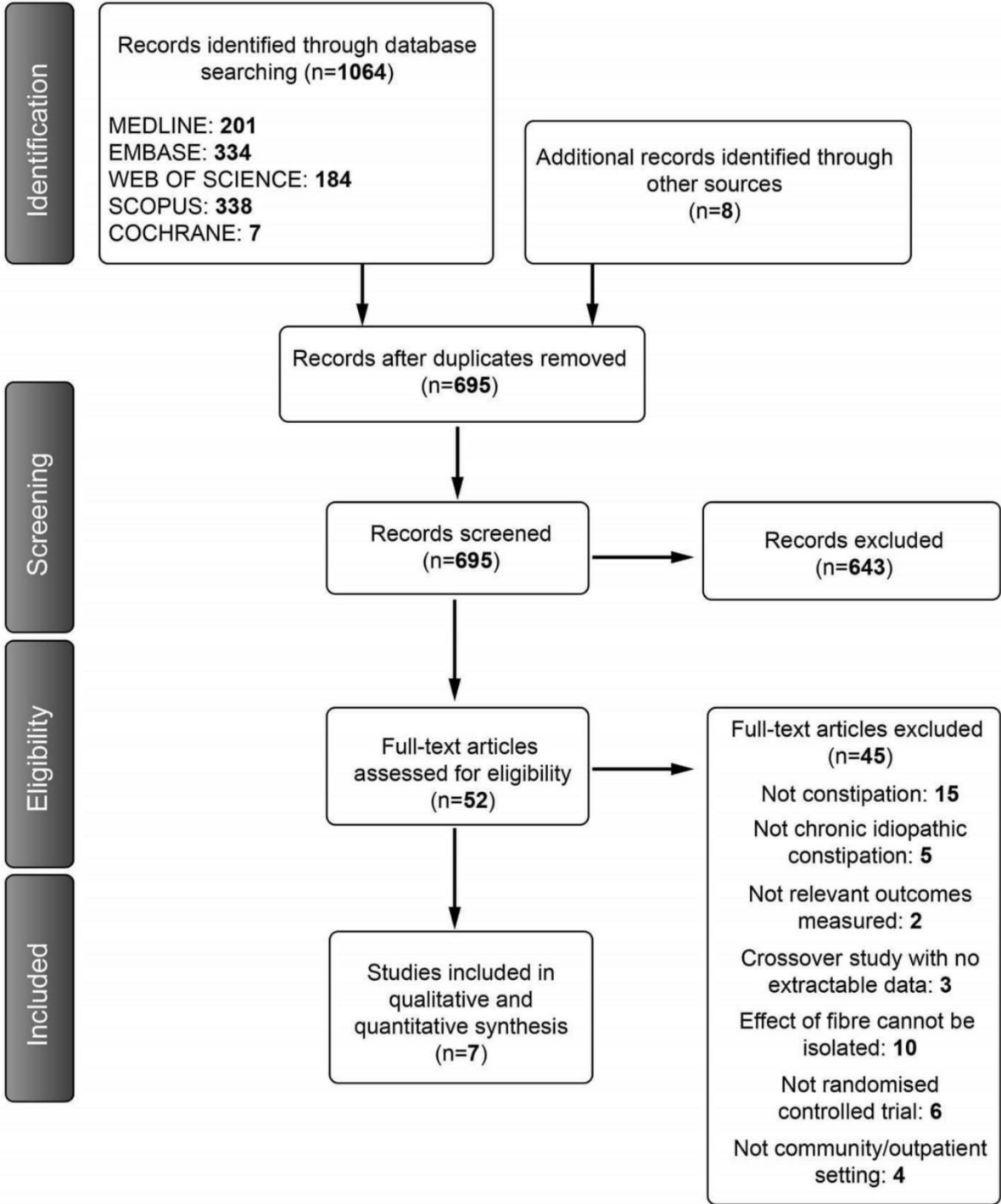
**Figure 1** PRISMA flow diagram of studies in systematic review.

**Figure 2** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for stool frequency among subgroups with the use of a random-effects model. GOS=galacto-oligosaccharides; PHGG=partially hydrolyzed guar gum; RM=resistant maltodextrin.

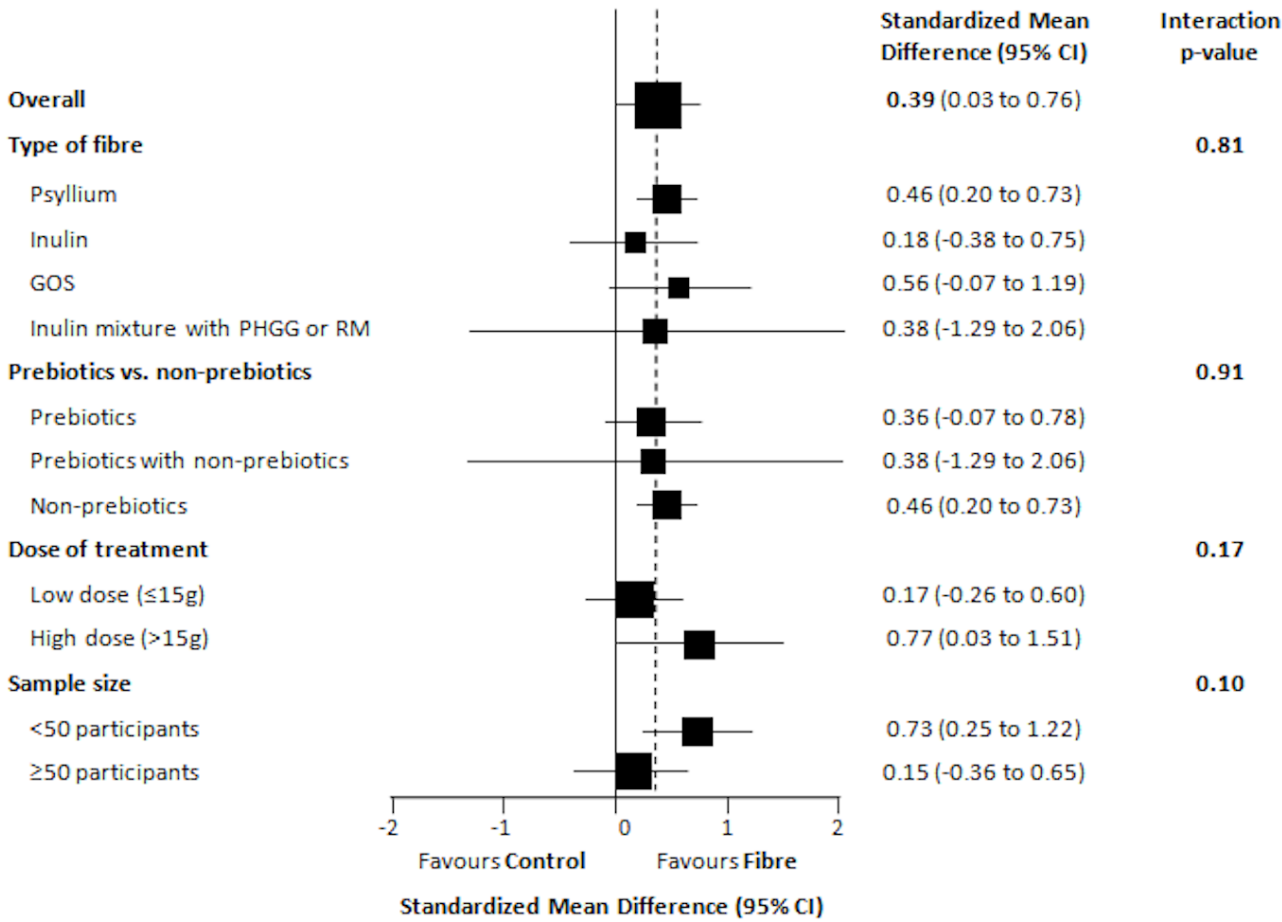
**Figure 3** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for stool consistency among subgroups with the use of a random-effects model. GOS=galacto-oligosaccharides; RM=resistant maltodextrin.

**Figure 4** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for fecal bifidobacteria concentrations among subgroups with the use of a random-effects model. GOS=galacto-oligosaccharides; PHGG=partially hydrolyzed guar gum.

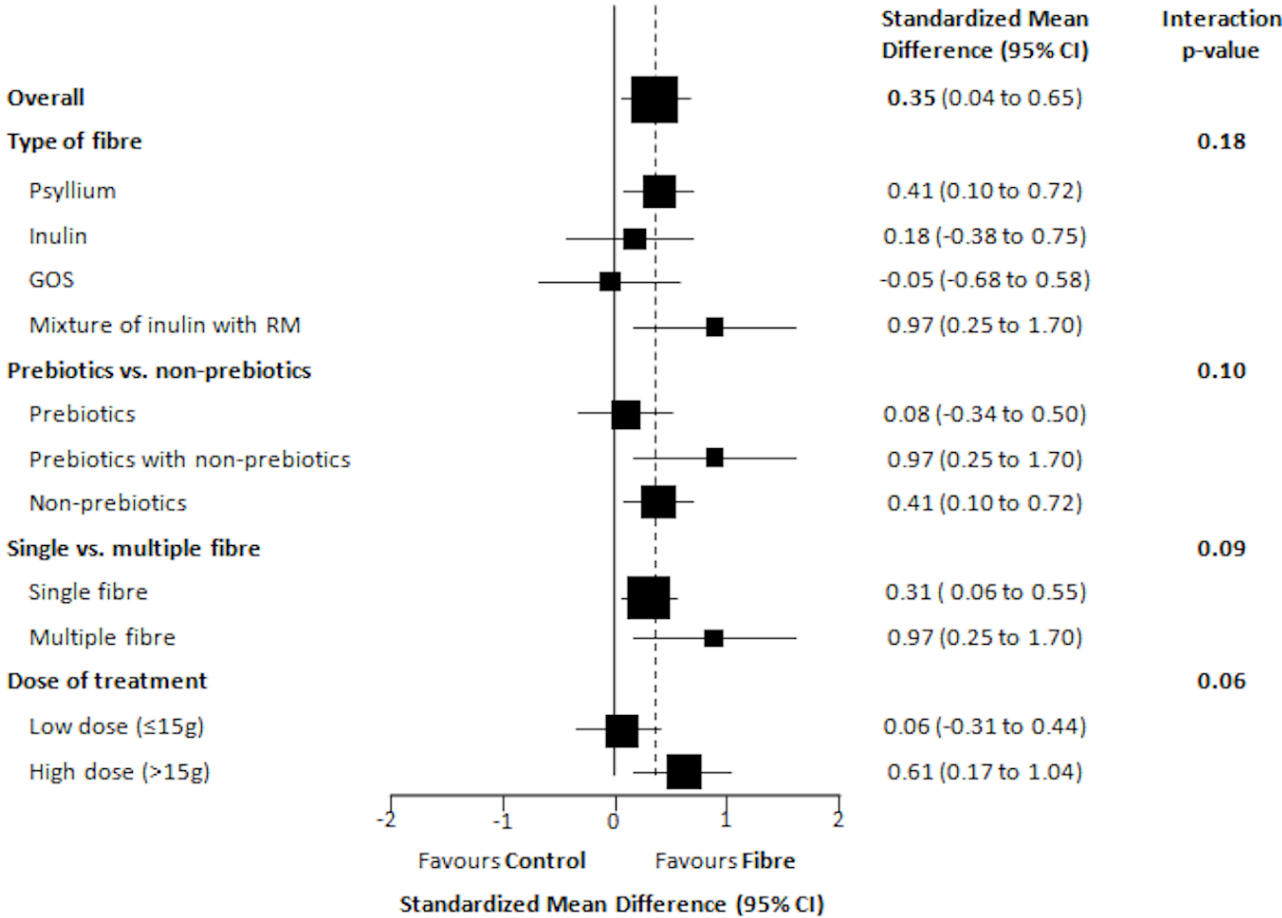
**Figure 1**



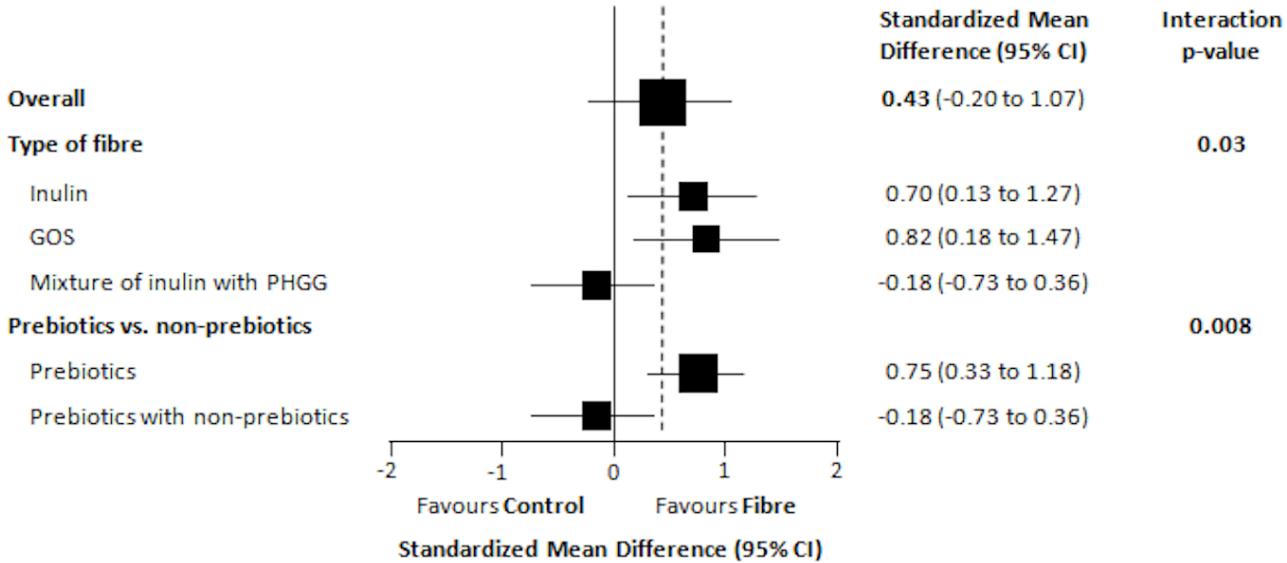
**Figure 2**



**Figure 3**



**Figure 4**



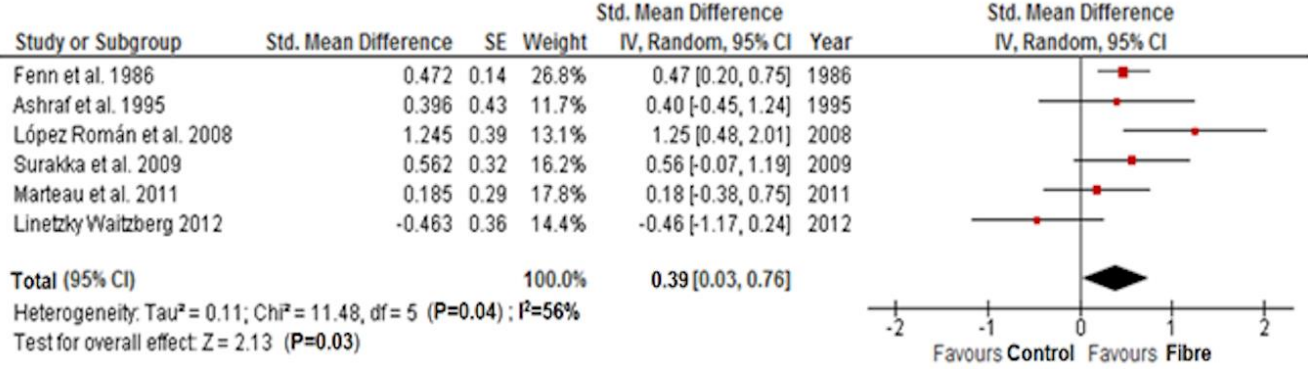
**SUPPORTING INFORMATION**

**Table S1** Detailed Search Strategy – Medline.

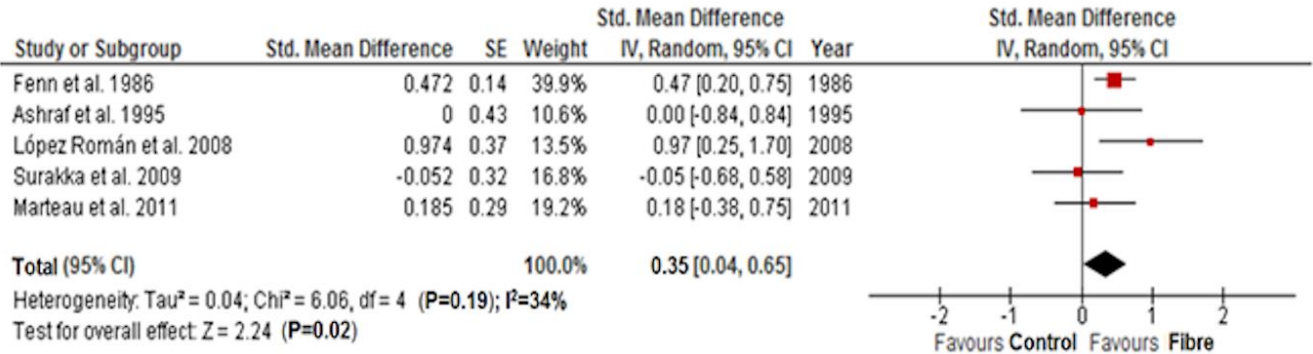
Constipation/ OR constipation.mp. OR defecation disorders.mp. OR evacuation disorders.mp. OR gastrointestinal transit/ OR gastrointestinal transit.mp. OR slow transit.mp.
AND
Adult/
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AND
Randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti.



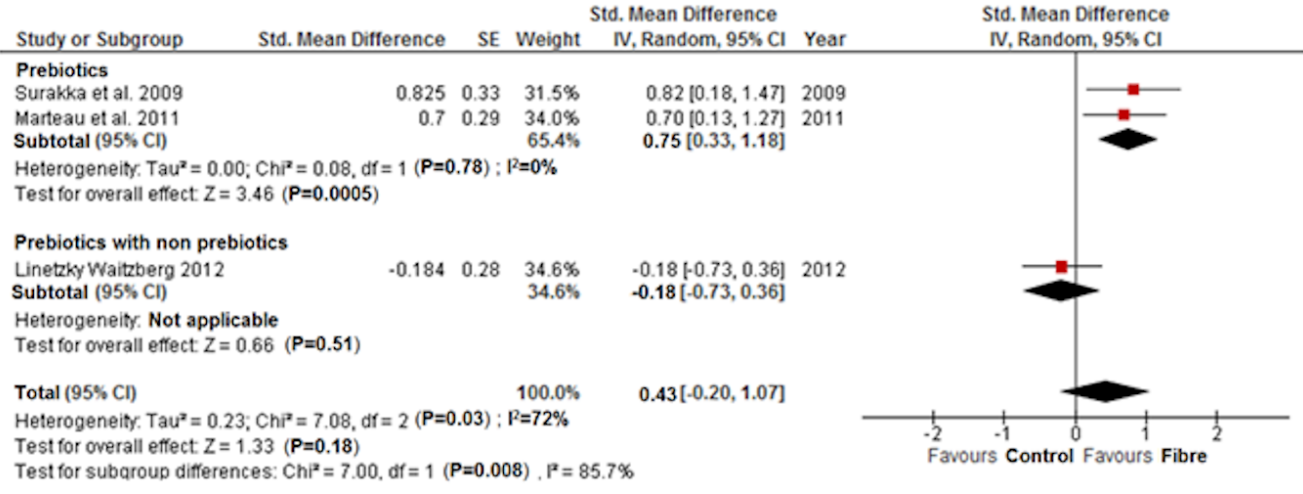
**Figure S1** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for stool frequency with the use of a random-effects model. IV=inverse variance.



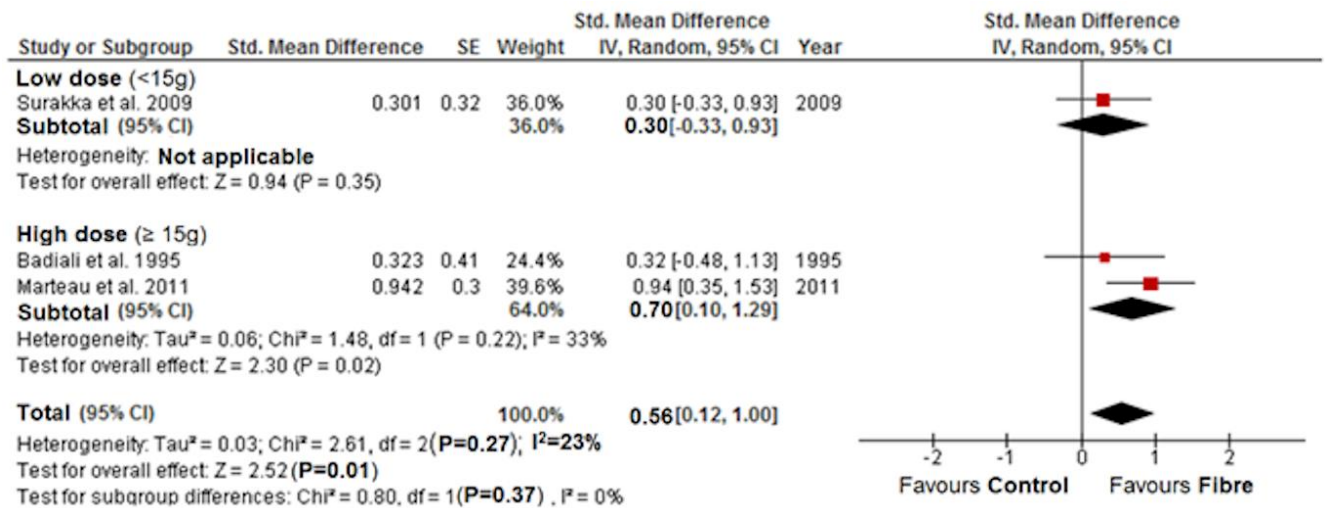
**Figure S2** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for stool consistency with the use of a random-effects model. IV=inverse variance.



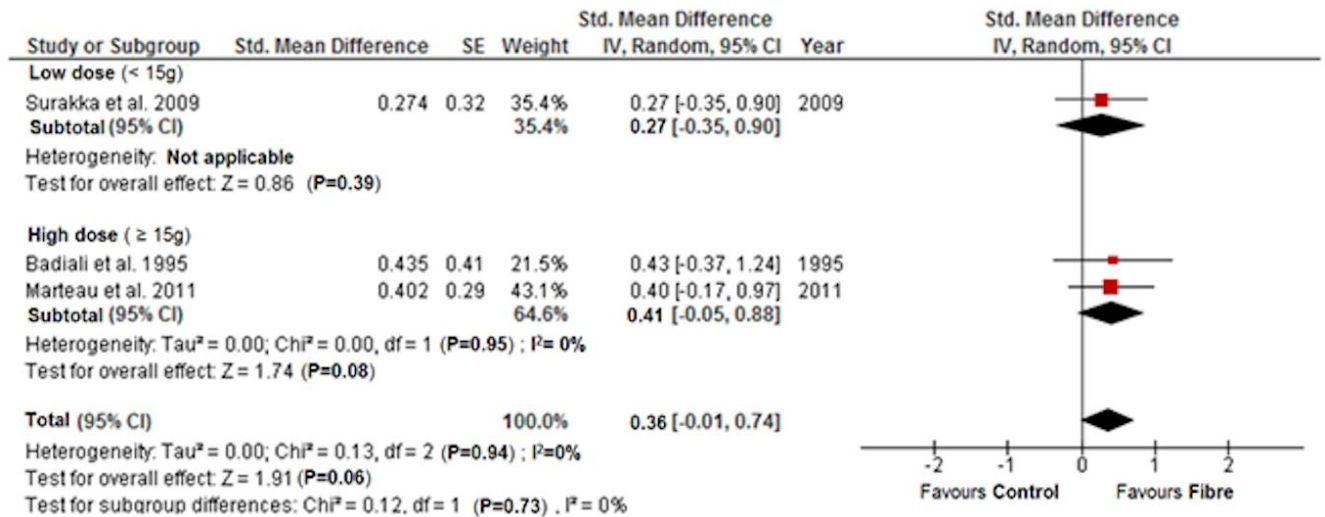
**Figure S3** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for fecal bifidobacteria concentrations (prebiotics *versus* non-prebiotics) with the use of a random-effects model. IV=inverse variance.



**Figure S4** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for flatulence (low dose *versus* high dose) with the use of a random-effects model. IV=inverse variance.



**Figure S5** Forest plot of randomised controlled trials in adults with chronic idiopathic constipation comparing fibre with placebo/control. Standardized mean differences (95% CIs) for bloating (low dose *versus* high dose) with the use of a random-effects model. IV=inverse variance.



**Figure S6** Overall risk of bias summary and risk of bias graph for all studies and outcomes together (study level).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fenn 1986 (38)	?	?	-	-	-	+	+
Ashraf 1995 (39)	+	?	+	+	+	-	+
Marteau 2011 (40)	+	+	+	+	+	-	-
Waitzberg 2012 (41)	+	?	+	+	-	-	+
Lopez Roman 2008 (42)	?	+	+	?	?	-	+
Surakka 2009 (43)	?	+	+	?	-	-	+
Badiali 1995 (44)	?	+	+	?	-	+	+

■ Low risk of bias   
 ■ Unclear risk of bias   
 ■ High risk of bias

