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Prebiotics in irritable bowel syndrome and other functional bowel disorders in adults: a systematic review and meta-analysis of randomized controlled trials

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Short running head

Prebiotics in functional bowel disorders

Abbreviations:

FBD Functional bowel disorder

GOS	Galacto-oligosaccharide
IBS	Irritable bowel syndrome
ITF	Inulin type fructan
SMD	Standard mean difference
WMD	Weighted mean difference

1 **ABSTRACT**

2 **Background**

3 Irritable bowel syndrome (IBS) and other functional bowel disorders (FBD) are
4 prevalent disorders with altered microbiota. Prebiotics positively augment gut
5 microbiota and may offer therapeutic potential.

6 **Objective**

7 To investigate the effect of prebiotics compared to placebo on global response,
8 gastrointestinal symptoms, quality of life (QoL) and gut microbiota, via systematic
9 review and meta-analysis of randomized controlled trials (RCTs) in adults with IBS
10 and other FBD.

11 **Design**

12 Studies were identified using electronic databases, back-searching reference lists
13 and hand-searching abstracts. RCTs that compared prebiotics to placebo in adults
14 with IBS or other FBD were included. Two reviewers independently performed
15 screening, data extraction, and bias assessment. Outcome data were synthesized
16 using odd ratios (OR), weighted mean differences (WMD) or standardized mean
17 differences (SMD) using a random-effects model. Sub-analyses were performed for
18 type of FBD and dose, type and duration of prebiotic.

19 **Results**

20 Searches identified 2332 records, and 11 RCTs were eligible (729 patients).
21 Response to intervention was 52/97 (54%) for prebiotic and 59/94 (63%) for placebo,
22 with no difference between groups (OR 0.62; 95%CI 0.07, 5.69; p=0.67). Similarly,
23 no differences were found for severity of abdominal pain, bloating and flatulence, and
24 quality of life score between prebiotics and placebo. However, flatulence severity was
25 improved by prebiotics at doses ≤ 6 g/d (SMD -0.35, 95%CI -0.71, 0.00, p=0.05) and

26 by non-inulin type fructan prebiotics (SMD -0.34, 95%CI -0.66, -0.01, p=0.04), while
27 inulin-type fructans worsened flatulence (SMD 0.85, 95%CI 0.23, 1.47, p=0.007).
28 Prebiotics increased absolute abundance of bifidobacteria (WMD 1.16 log₁₀ copies
29 16S rRNA gene; 95%CI 0.06, 2.26; p=0.04). No studies were at low risk of bias
30 across all bias categories.

31 **Conclusions**

32 Prebiotics do not improve gastrointestinal symptoms or quality of life in patients with
33 IBS or other FBD, but they do increase bifidobacteria. Variations in prebiotic type and
34 dose impacted symptom improvement or exacerbation.

35 **Keywords:** Prebiotics, IBS, FBD, inulin type fructans, galactooligosaccharides

36 INTRODUCTION

37 Functional bowel disorders (FBD) are a 'spectrum of chronic gastrointestinal disorders
38 characterized by predominant symptoms or signs of abdominal pain, bloating,
39 distension, and/or bowel habit abnormalities' [1]. Irritable bowel syndrome (IBS) is
40 characterized by abdominal pain associated with changes in defecation. Systematic
41 reviews report a global prevalence of 11.2% for IBS [2], however recent surveys using
42 updated definitions report a prevalence of 5.7% for IBS, 9.3% for functional diarrhea,
43 0.9% for functional bloating [3]. Not only are FBD and IBS prevalent disorders, they
44 can impact quality of life, are a common cause of consultation with healthcare systems
45 and treatment satisfaction is variable [4, 5].

46 IBS and other FBD share some aspects of etiology, some of which relate to the gut
47 microbiota. Case-control studies report altered gut microbiota in the majority of people
48 with IBS [6-8], a key feature of which is lower bifidobacteria [9], a microbial signature
49 associated with a greater number of days of abdominal pain in both healthy adults and
50 IBS [10, 11]. Further, gastrointestinal infection leads to a higher likelihood of developing
51 both IBS or functional diarrhea, implicating the gut microbiota in these FBDs [12]. Low
52 grade inflammation is present in some people with IBS, which may be mediated via gut
53 microbiota signaling to the gastrointestinal immune system [13, 14]. Furthermore,
54 altered pain signaling/visceral hypersensitivity has been reported in both IBS and
55 functional bloating, which may be influenced by the effect of serotonin on
56 enterochromaffin cells [1, 15].

57 Prebiotics are 'substrates that are selectively utilized by host microorganisms
58 conferring a health benefit to the host' [16]. Prebiotics are typically dietary
59 carbohydrates, with inulin-type fructans (ITF) (fructose polymers) and
60 galactooligosaccharides (GOS) (galactose polymers) being the most extensively

61 studied, however, other novel classes of prebiotic are under investigation [17].
62 Extensive studies have demonstrated the capacity of prebiotics to specifically enhance
63 the growth of bifidobacteria in healthy adults [18]. Additionally, prebiotics have been
64 shown to increase fecal short chain fatty acids (SCFA) and reduce gut-associated
65 inflammatory markers [14, 19], thus providing a mechanistic rationale for their role in
66 managing symptoms in IBS and other FBD.

67 A systematic review published in 2014 [20] only identified one randomized controlled
68 trial (RCT) of prebiotics in IBS [21] and its update identified only three RCTs [22]
69 However, these systematic reviews were specific to IBS rather than more broadly to
70 FBDs that may share a common etiology, presentation and overlapping symptoms [23]
71 and the latest did not meta-analyze the three trials [22]. Therefore, the aim of this study
72 was to investigate the effect of prebiotics compared to placebo on response,
73 gastrointestinal symptoms, stool form and frequency, quality of life and gut microbiota,
74 via a systematic review and meta-analysis of RCTs in adults with IBS or other FBD.

75 **METHODS**

76 This review was undertaken in line with recommendations of the Cochrane Handbook
77 for Systematic Reviews of Interventions [24] and reported in line with the guidelines of
78 Preferred Reporting Items for Systematic reviews and Meta-Analyses [25].
79 Identification, screening, eligibility and inclusion of eligible papers were agreed
80 between the researchers in advance and published prior to the literature search being
81 conducted (PROSPERO CRD42017074072).

82 **Eligibility criteria**

83 The inclusion criteria were any RCTs reporting the effect of the administration of a
84 prebiotic compared to a placebo on patients with IBS or other FBD. Details of the full
85 inclusion and exclusion criteria are described in **Table 1**.

86 Studies of patients with functional constipation only were not included because the
87 presenting symptoms and etiology do not completely overlap with other FBD (e.g.
88 abdominal pain not a dominant feature as in IBS). In addition, as most prebiotics are
89 fermentable, non-viscous and non-bulking, there is limited mechanistic rationale for
90 prebiotics in functional constipation, and because higher bifidobacteria have been
91 reported in functional constipation compared with other FBD, and therefore inclusion
92 may have confounded the microbiota findings [26].

93 **Search strategy**

94 Studies were identified through systematic search of electronic databases, hand-
95 searching of conference abstracts, clinical trial databases, and back-searching of
96 reference lists of all eligible studies.

97 The following six electronic databases were searched: MEDLINE (US National Library
98 of Medicine, USA; Ovid interface) from 1946 to November 2018; EMBASE (Elsevier
99 B.V., The Netherlands; Ovid interface) from 1974 to November 2018; CINAHL
100 (CINAHL Information Systems, USA, EBSCO host interface) from 1946 to 2018;
101 CENTRAL (The Cochrane Library, Chichester, Wiley InterScience) for all years; and
102 Web of Science (ISI Thomson Scientific, UK; Web of Knowledge portal) from 1900 to
103 November 2018. The final search date was 8 November 2018. Combinations of the
104 terms 'prebiotics,' 'irritable bowel syndrome' and 'functional bowel disorder' were
105 searched for as MeSH headings and key or free text words. A list of the search strategy
106 is presented in Supplemental Table 1.

107 Hand searching of abstracts from 2007 to 2018 from annual conferences of the
108 following organizations was undertaken: Digestive Disease Week (*Gastroenterology*);
109 British Society of Gastroenterology (*Gut*), United European Gastroenterology Week
110 (*United European Gastroenterology J*); Gastroenterological Society of Australia (*J*

111 *Gastroenterol Hepatol*); European Society of Neurogastroenterology and Motility
112 (*Neurogastroent Motil*); British Dietetic Association (*J Human Nutrition Dietetics*);
113 Academy of Nutrition and Dietetics (*J Amer Dietetic Assoc / J Academy Nutrition*
114 *Dietetics*); and the Dietitians Association of Australia (*Nutrition & Dietetics*).

115 The clinical trials databases of the World Health Organization (ISCTRN registry) and
116 the US National Institute of Health (Clinicaltrials.gov) were also searched to identify
117 completed but unpublished trials.

118 **Screening**

119 References were imported into a bibliographic database and duplicates were removed
120 automatically (EndNote X7; Thomson Reuters). Titles and abstracts were screened
121 against the eligibility criteria (Table 1) and two researchers then independently
122 screened all potentially eligible full text articles against the eligibility criteria (BW, MR).
123 The percentage agreement in study eligibility and a kappa statistic were calculated to
124 check concordance between reviewers [24]. Disagreements about study eligibility were
125 resolved through discussion with a third researcher (KW).

126 **Data extraction**

127 Data were extracted from each eligible study relating to the patient or group, the
128 intervention, the comparator, outcomes measured and the study design, as detailed in
129 Table 1. A standardized data extraction sheet was developed, and two reviewers
130 extracted the data from eligible papers (BW, MR). Discrepancies were reviewed and
131 resolved. Where papers contained insufficient or missing data, the corresponding
132 author was contacted for further information.

133 The Cochrane risk of bias tool was used to assess each study individually. The two
134 reviewers independently assessed risk of bias using seven domains: adequacy of
135 randomization, allocation concealment, blinding methods, complete outcome data,

136 selective reporting and other sources of bias [24]. Percentage agreement and kappa
137 statistic were calculated to check concordance between reviewers, and differences
138 resolved by a third reviewer (KW) [24].

139 **Data synthesis**

140 Meta-analysis was performed where two or more studies reported data for the same
141 outcome. Data for meta-analyses were entered into proprietary software (RevMan
142 version 5.3; The Nordic Cochrane Centre, Cochrane Collaboration). For dichotomous
143 outcomes (e.g. response), frequencies were entered to obtain an odds ratio (OR). For
144 continuous outcomes that were reported in the same units and measured using the
145 same tool, a weighted mean difference (WMD) was calculated, whereas for continuous
146 outcomes that were measured or reported differently, a standardized mean difference
147 (SMD) was calculated [27], using a random-effects model. For cross-over studies, the
148 intervention and control periods were entered separately. Where a single study used
149 several doses of a prebiotic, each dose was treated as a separate study for the meta-
150 analysis, whereby the different prebiotic doses were compared to the control
151 independently, with the sample size in the control group divided by the number of
152 different doses to reduce effect-size error as recommended [24]. Forest plots with 95%
153 CIs were generated for all outcomes.

154 Heterogeneity between results was assessed using the I^2 statistic and the chi-square
155 test, a P-value <0.10 was used to define significant heterogeneity [24]. I^2 statistic
156 values of 25%, 50% and 75% were defined as low, moderate and high heterogeneity,
157 respectively [24]. Where heterogeneity was high and outlier studies were observed,
158 sensitivity analysis was performed and data analysis with and without the outlier study
159 was reported, as recommended [24]. Publication bias assessment was planned using
160 funnel plot analysis if the number of available studies was >10 .

161 Predefined subgroup analyses were planned to investigate differences by: (i) FBD
162 subtypes (IBS, functional diarrhea etc.); (ii) prebiotic type (ITF, non-ITF); (iii) prebiotic
163 dose; and (iv) prebiotic duration.

164 **RESULTS**

165 **Study identification**

166 A total of 2332 non-duplicated papers were identified by the search strategy. The titles
167 and abstracts were reviewed and 35 were deemed potentially eligible (**Figure 1**). The
168 two reviewers agreed on the eligibility (inclusion/exclusion) of 31/35 (89%) of the
169 studies, with a kappa statistic of 0.74 representing substantial agreement [28]. Eleven
170 studies fulfilled the inclusion criteria (**Table 2**).

171 **Study Characteristics**

172 The 11 eligible RCTs compared a prebiotic intervention to a placebo and involved 729
173 adult patients with either IBS (8 studies) or other FBD (3 studies). These consisted of
174 seven studies of ITF, two studies of β -galactooligosaccharides, and one study each of
175 partially-hydrolyzed guar gum and pectin powder. Ten studies were published in
176 English and one in Chinese, which was then translated to English [29]. Ten studies
177 were full articles and one was in abstract form only [30]. Corresponding authors of eight
178 studies were contacted to obtain supplementary information. Of these, six replied [21,
179 30-34], and three provided data for inclusion in the analyses [30, 31, 34]. One study
180 did not report the data on the outcomes of interest despite measuring these [33] and
181 one study did not report any outcome data in a format that could be meta-analyzed
182 [35]. Authors were contacted but no further data were supplied.

183 **Clinical outcomes**

184 The results of the meta-analyses are summarized in **Table 3**.

185 *Response to treatment*

186 Three studies measured dichotomous overall symptom response to treatment
187 including 191 patients [32, 36, 37]. Overall, 52/97 (54%) patients responded to the
188 prebiotic and 59/94 (63%) responded to placebo, with no significant difference between
189 the groups (OR 0.62; 95% CI 0.07, 5.69; $p=0.67$; $I^2=91%$, $p<0.00001$). Subgroup
190 analysis was possible for FBD type, in which two studies of IBS alone showed no
191 difference in the odds of response (OR 0.22; 95% CI 0.02, 2.74; $p=0.24$; $I^2=89%$
192 $p=0.002$) [32, 36], and for dose, in which two studies of prebiotics >6 g/d showed no
193 difference in odds of response (OR 0.22; 95% CI 0.02, 2.74; $p=0.24$; $I^2=89%$ $p=0.002$)
194 [32, 36], and duration, in which two studies ≥ 4 -weeks showed no difference in odds of
195 response (OR 1.88; 95% CI 0.27, 13.18; $p=0.53$; $I^2=85%$, $p=0.01$) [36, 37], compared
196 with placebo.

197 *Integrative symptom scores, abdominal pain, bloating and flatulence*

198 A range of integrative symptom scores (subjective global assessment, IBS severity
199 scoring system (IBS-SSS), visual analogue scales and Likert scales) were measured
200 in eight studies and sufficient data were reported in seven studies including 538
201 patients [21, 29, 31, 32, 34, 36, 38]. Prebiotics did not result in a significant difference
202 in integrative symptom scores compared to placebo (**Figure 2**). Heterogeneity was
203 high and an outlier was identified [34] and analysis with (SMD -0.39; 95% CI -1.43,
204 0.64; $p=0.46$; $I^2=97%$, $p<0.00001$) and without (SMD 0.12; 95% CI -0.22, 0.45; $p=0.49$;
205 $I^2=61%$, $p=0.02$) the outlier was performed, which reduced but did not remove
206 heterogeneity (Supplemental Figure 1). Two studies used the IBS-SSS to measure
207 symptoms, including 185 patients [31, 38], however prebiotics did not result in a
208 significantly different IBS-SSS score compared with placebo (WMD -5.4; 95% CI -35.7,
209 24.9; $p=0.73$; $I^2=0%$, $p=0.59$). The study that did not report data for overall symptoms
210 did present graphs showing no difference in the overall symptoms scores between the

211 placebo group and prebiotic group after 4-weeks supplementation with 6 g/d of an ITF
212 [33].

213 Severity of individual gastrointestinal symptoms were reported as follows: abdominal
214 pain in ten studies with sufficient data reported in nine studies (628 patients) [21, 29-
215 32, 34, 36-38], bloating in nine studies with sufficient data reported in eight studies (551
216 patients) [21, 29, 30, 32, 34, 36-38], and flatulence in seven studies with sufficient data
217 reported in six studies (374 patients) [21, 32, 34, 36, 38]. Heterogeneity was high, and
218 an outlier was identified for abdominal pain, bloating and flatulence [34], analysis with
219 (Figure 2) and without this outlier was performed (Supplemental Figure 1). There were
220 no significant differences in the severity of any of these symptoms between prebiotic
221 and placebo, either with or without the outlier. The study that did not report data for
222 symptom outcomes did present graphs that showed no difference in the severity of
223 abdominal pain, bloating or flatulence between the placebo group and prebiotic group
224 after 4-weeks supplementation with 8 g/d of an ITF [35].

225 Subgroup analyses of the effect on type of FBD, or of prebiotic type, dose and duration
226 were performed. Due to the outlier contributing disproportionate heterogeneity to
227 symptom outcomes, symptom analysis is presented here without the outlier and data
228 including the outlier is presented as Online Supporting Material. There was no effect
229 on integrative symptom scores, although severity of abdominal pain significantly
230 improved in the study of FBD but not in the seven studies of IBS. Improvement in both
231 abdominal pain and bloating severity with non-ITF prebiotics failed to reach statistical
232 significance (**Figure 3**). Severity of flatulence significantly worsened with ITF prebiotics
233 (Figure 3) (SMD 0.85; 95% CI 0.23, 1.47; $p=0.007$; $I^2=57%$, $p=0.13$) and significantly
234 improved with both non-ITF (Figure 3) (SMD -0.34; 95% CI -0.66, -0.01; $p=0.04$; $I^2=0%$,
235 $p=0.78$) and ≤ 6 g/d (**Figure 4**) (SMD -0.35; 95% CI -0.71, -0.00; $p=0.050$; $I^2=0%$,

236 p=0.51) . Data for subgroup analyses without the outlier are presented in Figures 3 and
237 4 and Supplemental figures 2 and 3. Data for subgroup analyses with the outlier
238 included are presented in Supplemental figures 4-7.

239 *Stool output*

240 Stool frequency was measured in five studies [21, 30, 34, 36, 38] and stool consistency
241 was measured in two studies [21, 34]. Data were not meta-analyzed as three of the
242 five studies included all IBS-subtypes and one study did not categorize by predominant
243 bowel habit making it not possible to define what a beneficial outcome would be as
244 patients from either end of the stool output spectrum (IBS-diarrhea, IBS-constipation)
245 were included. Of these studies, when comparing the effect of prebiotics, neither stool
246 frequency nor consistency were different between prebiotic and placebo.

247 One study was conducted only in people with IBS-C however data were not compared
248 between the placebo and prebiotic for stool frequency [30].

249 Two studies reported data for incomplete fecal evacuation (90 patients) [30, 37].
250 Prebiotics did not reduce severity of incomplete evacuation in patients with IBS or FBD
251 (SMD 0.03; 95% CI -0.38, 0.45; p=0.88; I²=0%, p=0.33).

252 *Quality of life*

253 Quality of life (QoL) was measured in four studies (322 patients) using either the
254 validated IBS-QoL questionnaire or the IBS-36 questionnaire [21, 29, 34, 38].
255 Prebiotics did not affect QoL scores in IBS or FBD, and no outliers were identified (SMD
256 0.06; 95% CI -0.14, 0.25; p=0.57 I²=0%, p=0.41). Neither doses of ≤6 g/d (SMD -0.02;
257 95% CI -0.21, 0.25; p=0.85 I²=0%, p=0.56) or doses of >6 g/d (SMD 0.00; 95% CI -
258 0.77, 0.76; p=0.1, I²=59%, p=0.12) impacted QoL compared with placebo. Subgroup
259 analysis on type of FBD and type or duration of prebiotic could not be performed due
260 to insufficient studies in these subgroups.

261 Three studies used the validated IBS-QoL questionnaire (239 patients) [21, 29, 38].
262 There was no significant effect of prebiotics on IBS-QoL (SMD 0.00; 95% CI -0.31,
263 0.31; $p=0.99$ $I^2=22%$, $p=0.28$).

264 *Anxiety and depression*

265 The Hospital Anxiety and Depression Scale (HADS) was measured in two studies (162
266 patients) [31, 34]. Prebiotics did not impact HADS scores in IBS or FBD (WMD -0.12;
267 95% CI -0.83, 0.58; $p=0.73$; $I^2=0%$, $p=0.82$). Anxiety was measured in three studies
268 (171 patients) [21, 31, 37]. Prebiotics did not impact anxiety in IBS or FBD (SMD -0.23;
269 95% CI -0.54, 0.08; $p=0.14$; $I^2=0%$, $p=0.76$). Subgroup analyses were possible for two
270 studies in IBS specifically showing that prebiotics did not impact anxiety (SMD -0.12;
271 95% CI -0.59, 0.25; $p=0.52$; $I^2=0%$, $p=1.00$), two studies on prebiotic type showing that
272 ITF did not impact anxiety (SMD -0.27; 95% CI -0.62, 0.09; $p=0.14$; $I^2=2%$, $p=0.31$),
273 and on two studies for dose showing that ≤ 6 g/d did not impact anxiety (SMD -0.24;
274 95% CI -0.57, 0.08; $p=0.14$; $I^2=0%$, $p=0.56$). There were insufficient studies to meta-
275 analyze the impact of prebiotic duration.

276 Depression was measured in two studies in IBS only (121 patients) using the HADS
277 [21, 31]. Prebiotics did not impact depression (SMD -0.23; 95% CI -1.49, 1.02; $p=0.71$;
278 $I^2=0%$, $p=0.65$).

279 **Microbiota outcomes**

280 Fecal microbiota was measured in four studies, [21, 29, 31, 35], with three studies
281 reporting data for absolute abundance (measured using real-time polymerase chain
282 reaction) [29, 31, 35] and one reporting only relative abundance (measured using
283 fluorescence *in situ* hybridization) and authors were unable to provide further data [21].
284 Therefore, meta-analysis was conducted for absolute abundance only (**Figure 5**).

285 *Bifidobacteria*

286 Four studies measured bifidobacteria, three of which reported absolute abundance
287 (200 patients) [29, 31, 35]. Prebiotics significantly increased bifidobacteria in IBS or
288 FBDs (WMD 1.16 log₁₀ copies of 16S rRNA gene; 95% CI 0.06, 2.26; p=0.04; I²=92%,
289 p<0.00001) (Figure 5). The study that did not provide absolute abundance reported
290 significantly greater relative abundance of bifidobacteria for both 3.5 g/d and 7 g/d of
291 β-galactooligosaccharide compared to placebo.

292 Subgroup analyses were possible for two studies of prebiotic type, showing that ITF
293 increased bifidobacteria abundance (WMD 0.59 log₁₀ copies of 16S rRNA gene; 95%
294 CI 0.14, 1.03; p= 0.009; I²=22% p=0.26), and two studies of prebiotic dose, showing
295 that doses >6 g/d increased bifidobacteria abundance (WMD 1.55 log₁₀ copies of 16S
296 rRNA gene; 95% CI 0.31, 2.78; p= 0.01; I²=88% p=0.004), compared with placebo. It
297 was not possible for study duration to be meta-analyzed for subgroups as all relevant
298 studies were 4-weeks or longer.

299 *Lactobacilli*

300 Two studies measured absolute abundance of lactobacilli (164 patients) [29, 31].
301 Prebiotics did not impact absolute abundance of lactobacilli in IBS or FBD (WMD 0.22
302 log₁₀ copies of 16S rRNA gene; 95% CI -0.31, 0.75; p=0.41; I²=66%, p=0.09). Two
303 different prebiotics were used, ITF prebiotic (5 g/d) increased lactobacilli compared to
304 the control [31] whereas 24 g/d of pectin did not [29] (Figure 5).

305 **Safety outcomes**

306 There were inadequate data to analyze the number of adverse events and some
307 patients reported multiple adverse events. Four studies (355 patients) [21, 36-38]
308 described the number of patients reporting adverse events, with no significant

309 difference between the prebiotic and placebo groups (OR 0.77; 95% CI 0.47, 1.26;
310 $p=0.30$; $I^2=0\%$; $p=0.69$).

311 Subgroup analyses were performed where possible and demonstrated no effect in
312 studies of IBS only (OR 0.85; 95% CI 0.47, 1.55; $p=0.59$; $I^2=0\%$; $p=0.60$) or for ITF (OR
313 0.71; 95% CI 0.39, 1.28; $p=0.25$; $I^2=0\%$; $p=0.68$), non-ITF (OR 0.93; 95% CI 0.38, 2.28;
314 $p=0.87$; $I^2=0\%$; $p=0.41$), or for doses ≤ 6 g/d (OR 0.81; 95% CI 0.42, 1.55; $p=0.53$;
315 $I^2=0\%$; $p=0.52$), or doses of >6 g/d (OR 0.71; 95% CI 0.33, 1.54; $p=0.39$; $I^2=0\%$;
316 $p=0.34$). Subgroup analyses were not possible for prebiotic duration.

317 **Risk of bias**

318 The risk of bias for individual studies are presented in **Figure 6**. No studies were at low
319 risk of bias for all categories and no categories were at low risk of bias across all studies
320 Data for abdominal pain was presented in 10 studies and therefore a funnel plot was
321 constructed to detect publication bias (Supplemental figure 8). One study was visually
322 identified to contribute to asymmetry [34] of the data. The asymmetry may be explained
323 by true heterogeneity in effect size for this study or by sampling variation given it was
324 the only study that recruited patients via a database [24].

325 **DISCUSSION**

326 This systematic review and meta-analysis identified 11 RCTs investigating the effect
327 of prebiotics in IBS or other FBD on gastrointestinal symptoms, stool output, quality of
328 life and gut microbiota. Based on the current body of evidence, overall, prebiotics do
329 not benefit symptom management or improve quality of life in IBS or other FBD,
330 however they do increase fecal bifidobacteria.

331 Meta-analysis showed prebiotics did not significantly impact integrative symptom
332 scores, severity of abdominal pain, bloating or flatulence. However, there was

333 considerable heterogeneity in these symptom findings that was explained in part by
334 the presence of an outlier study and to some degree by variations in prebiotic dose and
335 type. For example, prebiotics at a dose of ≤ 6 g/d improved flatulence, but higher doses
336 did not impact this or any other symptoms. Furthermore, ITF significantly worsened
337 flatulence, whereas non-ITF (including GOS and guar gum) significantly improved
338 flatulence. This highlights the importance of considering prebiotic dose and type in both
339 clinical nutrition practice and research, as well as in the conduct of meta-analyses.
340 Previous systematic reviews of prebiotics have synthesized data from RCTs in
341 metabolic syndrome blood biomarkers [39] and chronic kidney disease [40] and
342 reported significant heterogeneity when meta-analyzing outcomes. Few have
343 performed subgroup analyses based upon prebiotic type and dose, which may be in
344 part responsible for the heterogeneity, but also neutralizes any observed benefit or
345 harm of specific prebiotic doses or types. For these reasons, meta-analyses of prebiotic
346 interventions should perform subgroup analysis on prebiotic type and dose [41].

347 The analysis of the data without the outlier should be interpreted with caution and
348 should be considered alongside the analyses of all studies together as presented in
349 Figure 2 and Supplemental figures 4-7. The outlier study [34] reported significant
350 benefit over placebo for all symptoms however the effect sizes were much greater than
351 for similar studies including one that used a similar dose of the same prebiotic [21].
352 Therefore, symptom analysis was too heterogeneous to be able to detect meaningful
353 differences when all data were combined. The reason for the results seen in this outlier
354 is unclear except that the participants were selected from a database and this may
355 have introduced recruitment bias.

356 Subgroup analysis of duration of prebiotics did not provide insight into the length of
357 time a prebiotic should be trialed, although this is likely owing to the limited data

358 available. A recent proof of concept study in healthy adults supplemented with 2.8 g/d
359 of GOS for three weeks reported an adaptation period where initial consumption led to
360 increased flatulence, which had subsided by three weeks, indicating that patients
361 should take a prebiotic for a minimum of three weeks to ascertain if it will be of benefit
362 to them [42].

363 The gut-brain axis is a mechanism hypothesized to be involved in the etiology of IBS
364 and other FBD. Patients with IBS score lower on QOL scales than healthy controls and
365 IBS is associated with anxiety related co-morbidities [4, 5]. The meta-analysis did not
366 support a role for prebiotics in improving QOL, anxiety or depression in patients with
367 IBS or other FBD, neither did subgroup analysis find any effect for dose, type or
368 duration of prebiotics. However, only four studies included quality of life and/or
369 psychological outcome measures and each of the four used a different type of prebiotic
370 making the results too heterogenous to draw firm conclusions.

371 The majority of the RCTs that have investigated the effect of prebiotics on IBS and
372 other FBD used ITF, with subgroup analysis showing a worsening of flatulence. This is
373 in line with current understanding of one of the mechanisms underpinning a diet
374 commonly used for treating IBS that is low in ITF and other fermentable oligo-, di-,
375 mono- saccharides and polyols (low FODMAP diet). The low FODMAP diet aims to
376 reduce small bowel water content and colonic gas production through specific
377 carbohydrate restriction [43]. Clinical trials have shown that the low FODMAP diet is
378 effective in managing symptoms in 50-80% of patients with IBS, although the effect on
379 the gastrointestinal microbiota may be of concern as it has been shown to specifically
380 reduce fecal bifidobacteria [44, 45]. Further, the low FODMAP diet has been
381 demonstrated to alleviate common symptoms of FBDs and IBS such as loose stool,
382 urgency, abdominal bloating, abdominal pain and flatulence [44-47].

383 Due to the effectiveness of restricting fermentable carbohydrates on the low FODMAP
384 diet, it seems contradictory that supplementation with prebiotic fermentable
385 carbohydrates would also decrease symptoms in IBS and may relate to differences in
386 chemical structure and microbial metabolism. The GOS in foods such as beans, pulses
387 and legumes are α -GOS (i.e. raffinose, stachyose and verbascose) and produce gas
388 on fermentation and are therefore restricted on the low FODMAP diet along with ITF
389 [48]. However, non-ITF prebiotic supplements that were shown to significantly reduce
390 flatulence (with the effect on abdominal pain and bloating approaching significance) in
391 the current meta-analysis included β -GOS, which in contrast to α -GOS, are specifically
392 metabolized by bifidobacteria that produce less gas [17, 49]. Further, frequency of mild
393 distension, borborygmi and flatulence increased with ITF dose in healthy adults, and
394 short-chain ITF are fermented more rapidly than longer chain ITF indicating that both
395 the dose and structure of prebiotics are important [50]. ITF stimulate similar volumes
396 of colonic gas in both healthy individuals and patients with IBS, however the induction
397 of abdominal pain and discomfort only occurs in the latter [51]. This suggests that IBS
398 is more complex than merely the volume of colonic gas production and is likely related
399 to colonic hypersensitivity.

400 Although not included in this review, the use of prebiotics in functional constipation has
401 been investigated in two systematic reviews [20, 52], identifying three trials [53-55]. In
402 elderly subjects, prebiotics increased bifidobacteria and led to increased passage of
403 stool and softer stool form compared to placebo [53, 54], however in women with
404 constipation a mixture of ITF and PHGG (doses undefined) showed no benefit over
405 placebo for any symptoms [55].

406 Gastrointestinal microbiota is implicated in IBS, with acute gastroenteritis and water-
407 borne infections increasing the odds of developing IBS up to eight years later [56, 57].

408 In the current study it was found that prebiotic supplementation significantly increased
409 fecal bifidobacteria abundance compared to placebo in patients with IBS and other
410 FBD. A recent meta-analysis confirmed that established prebiotic fibers (ITF, GOS)
411 and novel prebiotic fibers (e.g. arabinoxylan-oligosaccharide, manno-oligosaccharide,
412 resistant starch, xylo-oligosaccharide) increase bifidobacteria in healthy people,
413 whereas non-prebiotic fibers did not [18]. This meta-analysis confirms these findings in
414 people with IBS with both β -GOS and pectin powder, demonstrating an increase in
415 relative and absolute abundance of bifidobacteria respectively [21, 29]. One
416 mechanism of action of prebiotics in IBS may therefore be the modulation of the altered
417 microbiota. Although proving the prebiotic effect is a mechanism, and not merely an
418 epiphenomenon, in any potential clinical effect in IBS is challenging given the lack of
419 validated animal models of IBS that would enable microbiome manipulation.

420 This is the largest systematic review and only meta-analysis to investigate the effect of
421 prebiotic supplementation in IBS and other FBD on response, gastrointestinal
422 symptoms, quality of life and gut microbiota. Broad inclusion criteria were used to
423 identify all placebo-controlled trials to shed light on this under-researched, yet clinically-
424 relevant question. As a consequence, the broad inclusion criteria enabled the inclusion
425 of one study that was designed to investigate if high-dose ITF prebiotics (19 g/d) could
426 induce symptoms compared to a placebo in patients that had previously responded to
427 a low FODMAP diet [32]. It is likely that this introduced significant bias in favor of the
428 placebo. Nonetheless, when this study was excluded from the meta-analysis the
429 overall findings for response (OR 1.88, 95% CI 0.27, 13.18, P=0.53) and integrative
430 symptom score (SMD -0.02, 95% CI -0.22, 0.17, P=0.83) remained non-significant.

431 This meta-analysis used a robust design in line with PRISMA guidelines and the
432 protocol was defined and published prior to the literature searches taking place, thus

433 limiting the potential for reviewer bias. However, the findings are limited by the small
434 number of RCTs conducted. A further limitation is the varied methodology used by
435 authors in defining IBS and other FBD. The data were largely heterogeneous but
436 overall suggested that the net effect of prebiotics on clinical outcomes is neutral. Non-
437 ITF prebiotics show some promise in individual symptom improvement however these
438 results came from pooling data from different types of prebiotics and so the strength of
439 this conclusion is weak.

440 **Conclusion**

441 In conclusion the current review suggests that overall prebiotics do not affect response,
442 gastrointestinal symptoms or quality of life in patients with FBD or IBS, but they do
443 increase bifidobacteria. Further, subgroup analysis revealed that neither type, dose nor
444 duration influenced overall symptoms. Differences were seen between type and dose
445 on individual symptoms, including that non-ITF prebiotics improved flatulence whereas
446 ITF worsened flatulence, whilst prebiotics at a dose of ≤ 6 g/d reduced flatulence
447 whereas higher doses had no effect. This review did not find sufficient evidence to
448 establish an optimal duration of treatment.

449 Overall the quality of evidence is poor across studies investigating the effect of
450 prebiotics on symptoms, QoL and microbiota in IBS and FBD, and this review highlights
451 the need for more clinical trials of robust design and may direct future researchers
452 towards lower dose, novel prebiotics rather than conducting further trials of ITF type
453 prebiotics in patients with IBS or FBD. Further studies investigating the role of non-ITF
454 and of novel prebiotics in symptom management and modulation of gut microbiota in
455 IBS and other FBD should be performed in order to clarify the compounds most likely
456 to impact symptoms.

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Table 1: Table of inclusion and exclusion criteria following the PICOS¹ approach

PICOS ¹	Inclusion and exclusion criteria	Data extraction
Participants	<p>Adult populations ≥ 18 and ≤ 64 with IBS (any subtype) or FBD as defined by the authors were included. Studies with a median age between these values were eligible.</p> <p>Participants with drug-induced constipation or diarrhea, inflammatory bowel disease, acute gastrointestinal disorders (e.g. traveler's diarrhea) or functional constipation alone were excluded, unless data specifically for participants with IBS or other FBD alone could be extracted.</p>	Age, sex, IBS subtype, type of FBD, method for diagnosis, setting, location, number of patients of each IBS-subtype randomized to intervention and comparator groups, inclusion and exclusion criteria.
Intervention	<p>Prebiotics defined as ITF, GOS, or any other compound defined by the author as a prebiotic if justification for the compound fulfilling criteria as a prebiotic were explicitly stated. Prebiotics to be administered at a dose of >1 g/d for a minimum of one week and could be presented as powders, capsules, tablets, softgel, or fortified food forms. Trials that included other interventions (e.g. drug use) were included if the effect of the prebiotic alone could be isolated. Multiple intervention arms were eligible.</p> <p>Trials of symbiotic were excluded, unless there was an arm of prebiotic alone.</p>	Prebiotic type, dose, frequency, formulation, extraction method, degree of polymerization, degree of purity and duration of intervention, compliance.
Comparators	<p>Only trials that used a placebo control were eligible. The effect of the prebiotic alone had to be able to be isolated.</p> <p>Trials where the comparator did not allow the effect of the prebiotic alone to be isolated were excluded (e.g. prebiotic <i>versus</i> probiotic).</p>	Type and dose of comparator, compliance.

Outcomes	Trials reporting clinical subjective and objective outcome data including IBS or other FBD response, symptoms, quality of life, stool form and frequency and gut microbiota were included.	Outcomes measured, method of assessment. Acceptability and compliance measures, and adverse events.
Study design	Only randomized controlled trials with ≥ 2 study groups, where it was possible to extract data on just the prebiotic vs placebo interventions were included. Both parallel and crossover trial design were eligible.	Type of study design, intention to treat analysis, number of excluded patients, adequacy of randomization and blinding methods of participants and investigators.

¹PICOS: Participants, Intervention, Comparator, Outcome, Study type; IBS: Irritable Bowel Syndrome; FBD: Functional Bowel Disorder.

Table 2: Characteristics of eligible studies

Study	Country	Trial Design	Blinding	Outcomes		Prebiotic	Form	Dose	Duration
				Included in Meta-analysis	Sample size (% FBD or IBS female) (subtypes)				
Azpiroz 2017a [35]	Spain	Parallel	Double	Symptoms, microbiota	40 (NR) FBD unclassified	Inulin	Powder	8 g/d	4 weeks
Azpiroz 2017b [31]	France and Spain	Parallel	Double	Symptoms, microbiota	79 (39) IBS (all subtypes)	Short-chain fructo-oligosaccharide	Powder	5 g/d	4 weeks
Hunter 2009 [33]	UK	Cross-over	Double	Symptoms	21 (81) IBS (all subtypes)	Oligofructose	Powder	6 g/d	4 weeks
Isakov 2013 [30]	Russia	Parallel	Unclear	Symptoms	40 (NR) IBS-C	Inulin	Yogurt	3 g/d	2 weeks
Niv 2016 [38]	Israel	Parallel	Double	Symptoms, QoL	108 (66) IBS (all subtypes)	Partially hydrolyzed guar gum	Powder sachet	6 g/d (3 g/d for first week)	12 weeks
Olesen and Gudmand-Hoyer 2000 [36]	Denmark	Parallel	Double	Symptoms	98 (82) IBS (all subtypes)	Fructo-oligosaccharide	Powder	20 g/d (10 g/d for first two weeks)	12 weeks
Paineau 2008 [37]	France	Parallel	Double	Symptoms, QoL	105 (NR) FBD mixed	Short-chain fructo-oligosaccharide	Powder	5 g/d	6 weeks
Shepherd 2008 [32]	Australia	Cross-over	Double	Symptoms	24 (92) IBS (all subtypes) LFD responsive + fructose malabsorption	Oligofructose	Orange flavored drink	19 g/d (7 g for 3-days, 14 g for 3-days 19 g for 8-days)	2 weeks

Silk 2009 [21]	UK	Parallel	Double	Symptoms, QoL, microbiota	44 (64)	IBS (all subtypes)	β - galactooligosacchar ide	Flavored powder	3.5 g/d or 7 g/d	4 weeks
Vulevic 2018 [34]	UK	Cross-over	Double	Symptoms, QoL	83 (57)	FBD (moderate to severe)	β - galactooligosacchar ide	Powder	2.75 g/d	2 weeks
Xu 2015 [29]	China	Parallel	Double	Symptoms, QoL, microbiota	87 (55)	IBS-D	Pectin powder	Powder	24 g/d	6 weeks

All trials except Vulevic (2018) [34] were conducted in primary care setting and all included a placebo control group or treatment period if cross-over design was used.

NR: not reported; LFD: low FODMAP diet; QoL: Quality of life, IBS: irritable bowel syndrome, FBD: functional bowel disorder

Table 3: Results of the meta-analysis comparing prebiotics to placebo for symptoms, quality of life, microbiota and adverse events in patients with IBS or FBD

Outcome	No of studies in meta-analysis (reference nos.)	Patients (n)	Results	Heterogeneity			
			Meta-analysis overall estimate (95% CI)	P	Chi-square test	P	I ² (%)
Response to treatment	3 [32, 36, 37]	191	OR 0.62 (0.07, 5.69)	0.67	21.47	<0.00001	91
IBS-SSS	2 [31, 38]	185	WMD -5.40 (-35.70, 24.90)	0.73	0.3	0.59	0
Incomplete evacuation	2 [30, 37]	90	SMD 0.03 (-0.38, 0.45)	0.88	0.94	0.33	0
Quality of life	4 [21, 29, 34, 38]	322	SMD 0.06 (-0.14, 0.25)	0.57	1.4	0.41	0
Anxiety	3 [21, 31, 37]	171	SMD -0.23 (-0.54, 0.08)	0.14	1.19	0.76	0
Depression	2 [21, 31]	121	WMD -0.23 (-1.49, 1.02)	0.71	0.86	0.65	0
Bifidobacteria	3 [29, 31, 35]	200	WMD 1.16 (0.06, 2.26)	0.04	24.3	<0.00001	92
Lactobacilli	2 [29, 31]	164	WMD 0.22 (-0.31, 0.75)	0.41	2.94	0.09	66
Adverse events	4 [21, 36-38]	355	OR 0.77 (0.47, 1.26)	0.30	2.25	0.69	0

FIGURE LEGENDS

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

Figure 2: Forest plot of integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.

Figure 3: Forest plot of subgroup analysis of prebiotic type (inulin type fructan *versus* non-inulin type fructan) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.

Figure 4: Forest plot of subgroup analysis of different prebiotic dose (≤ 6 g/d vs >6 g/d) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.

Figure 5: Forest plot of absolute abundance of fecal bifidobacteria and lactobacilli in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as weighted mean differences (95% CI) using a random effects model.

Figure 6: Risk of bias in A: individual studies and B: overall for each category of randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD.

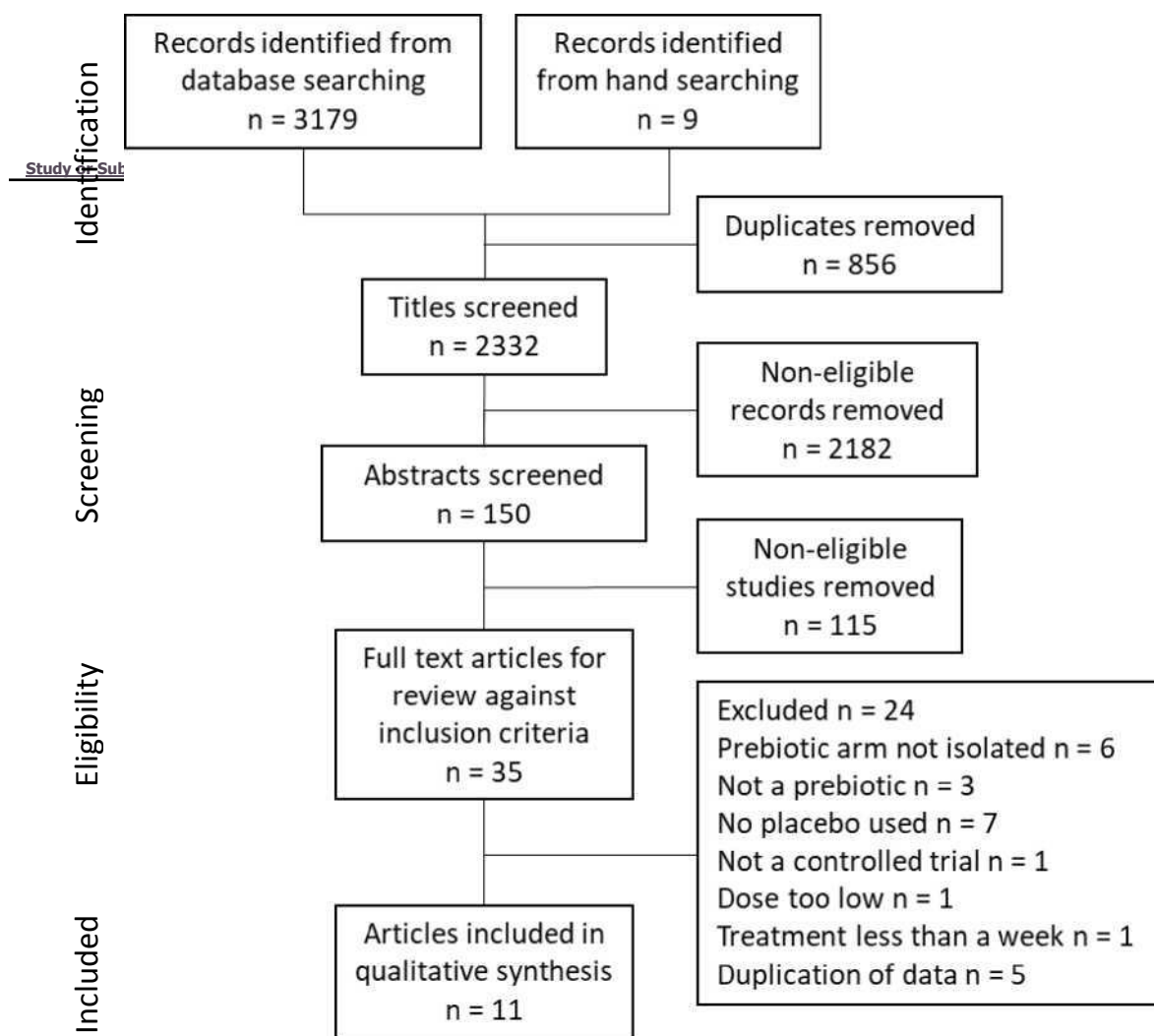


Figure 1

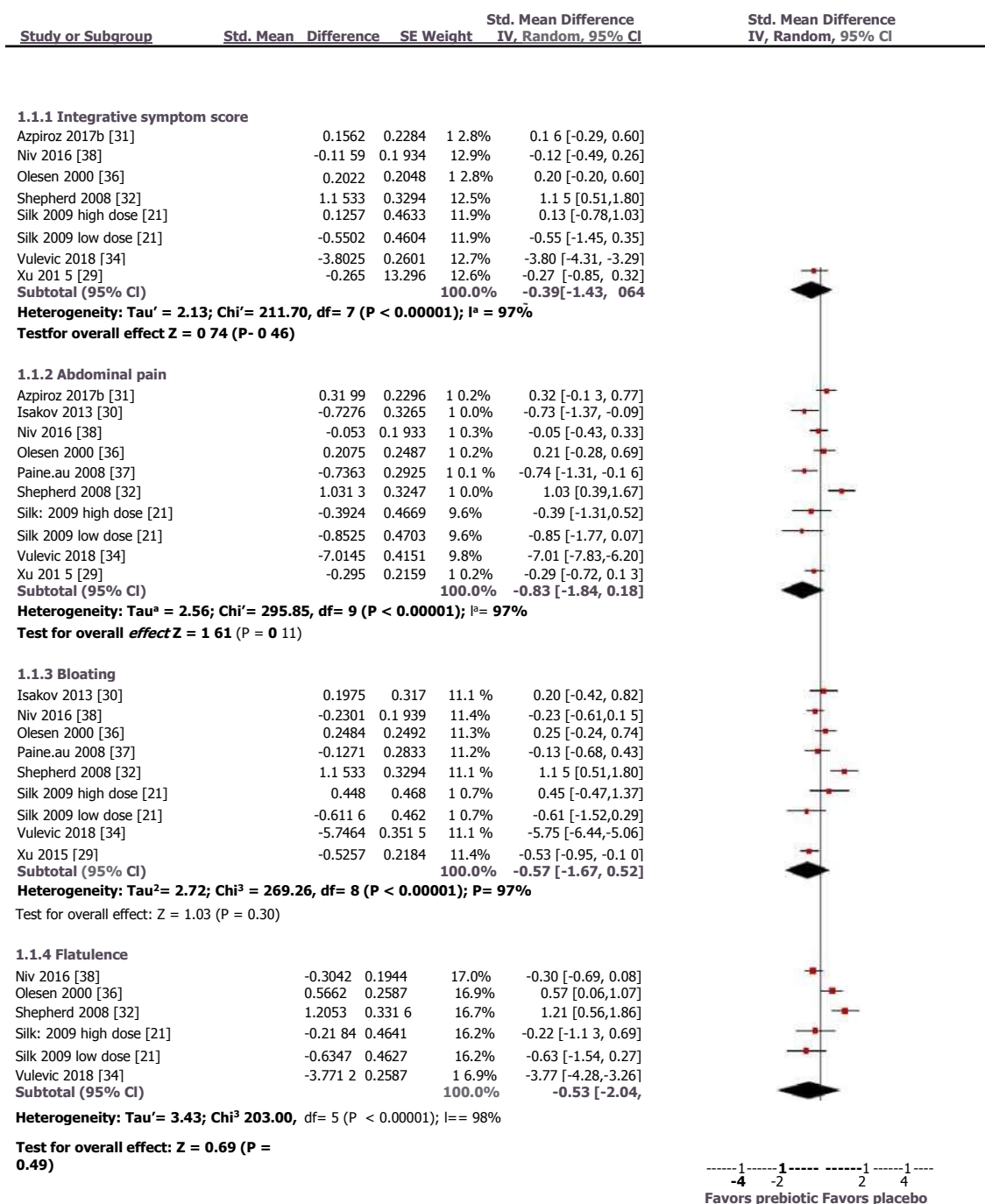


Figure 2

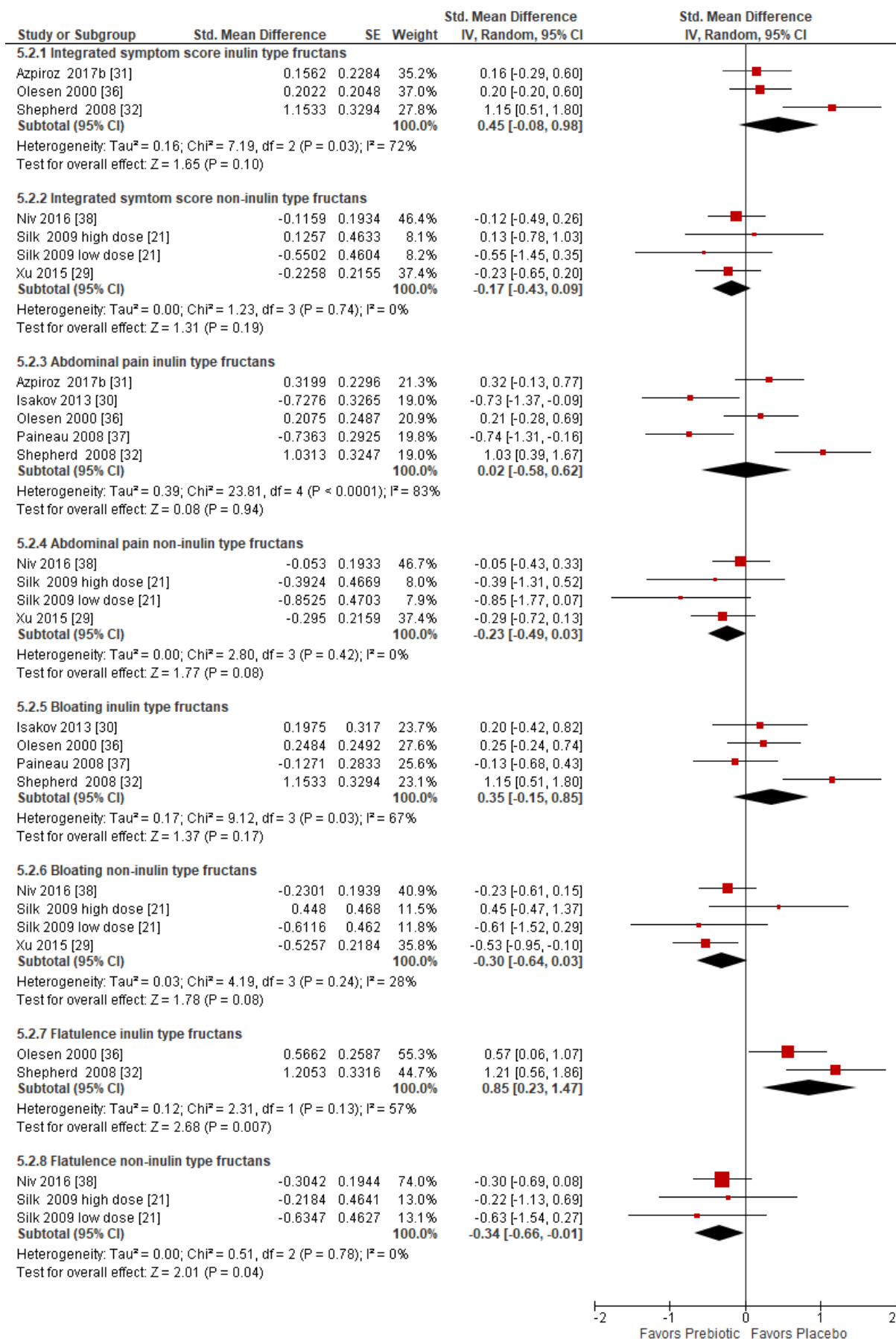


Figure 3

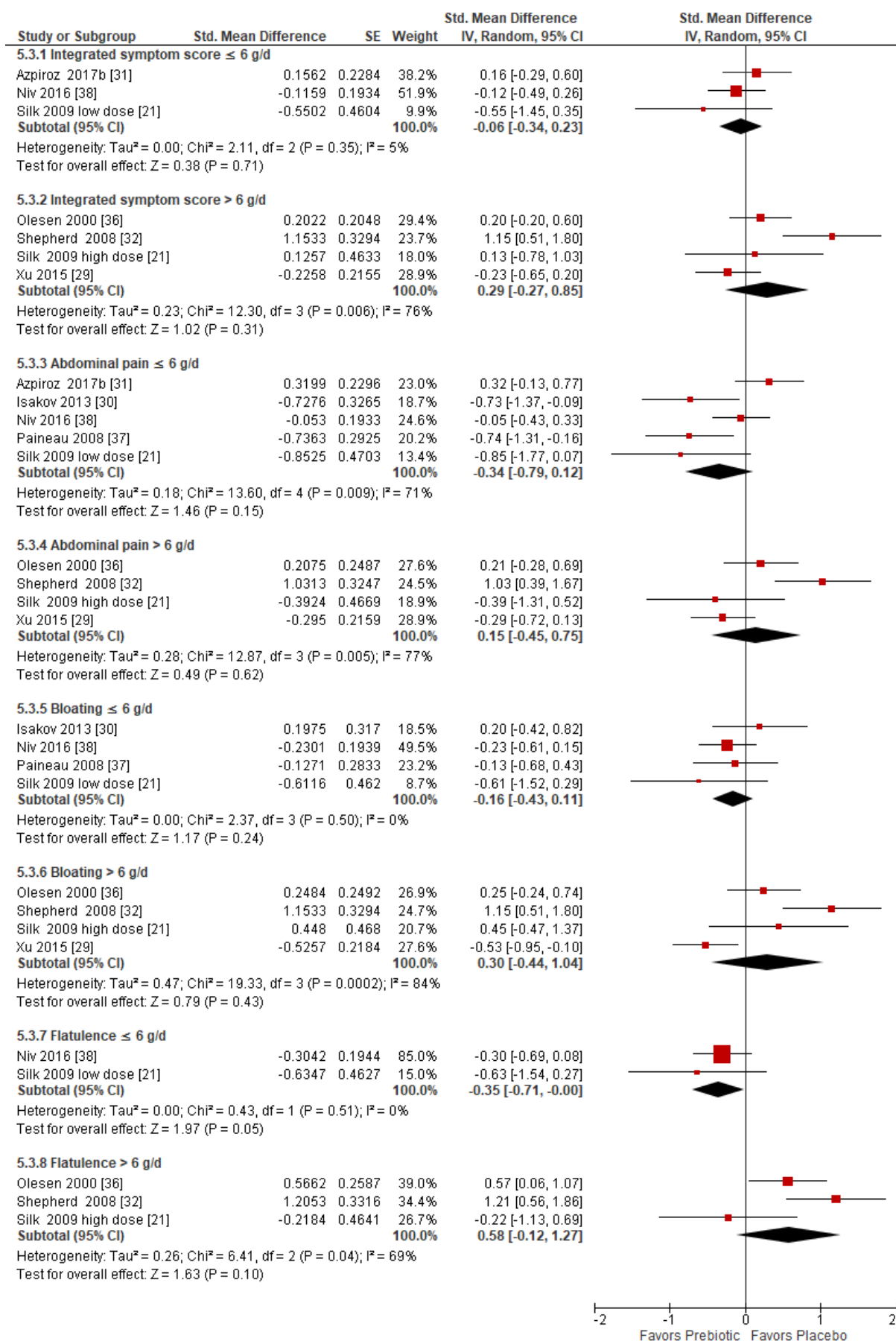


Figure 4

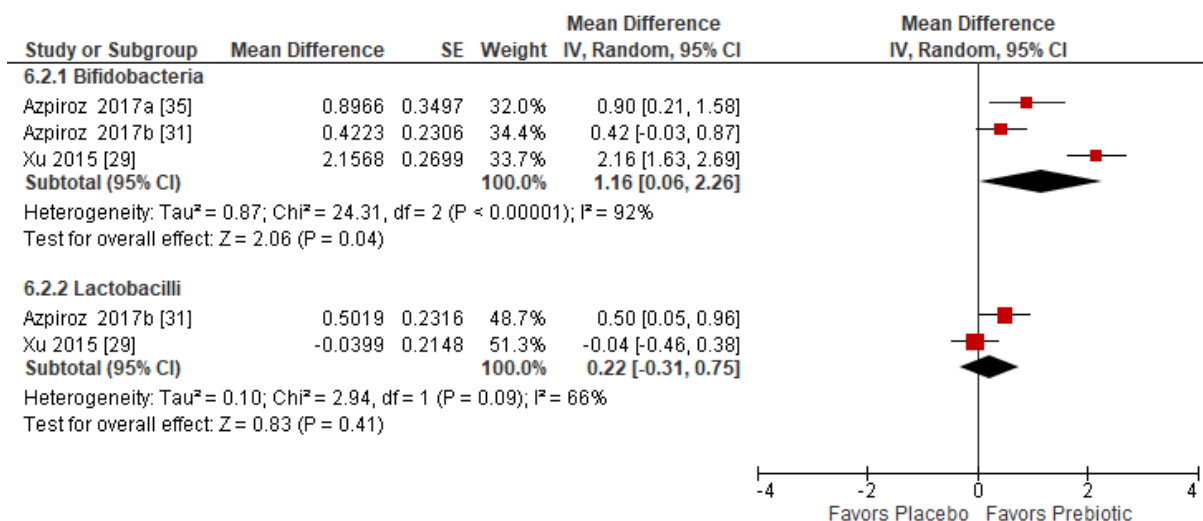
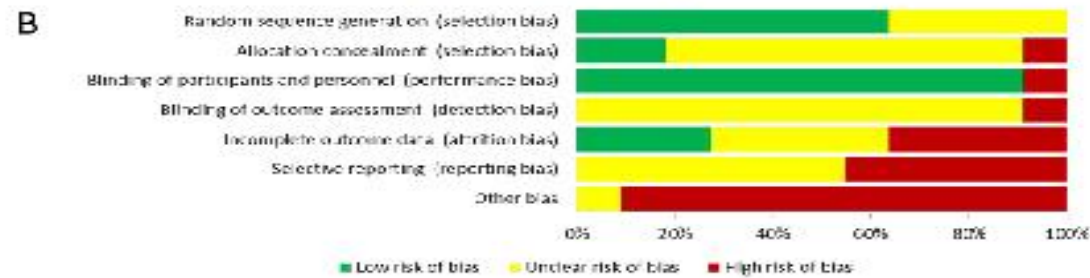
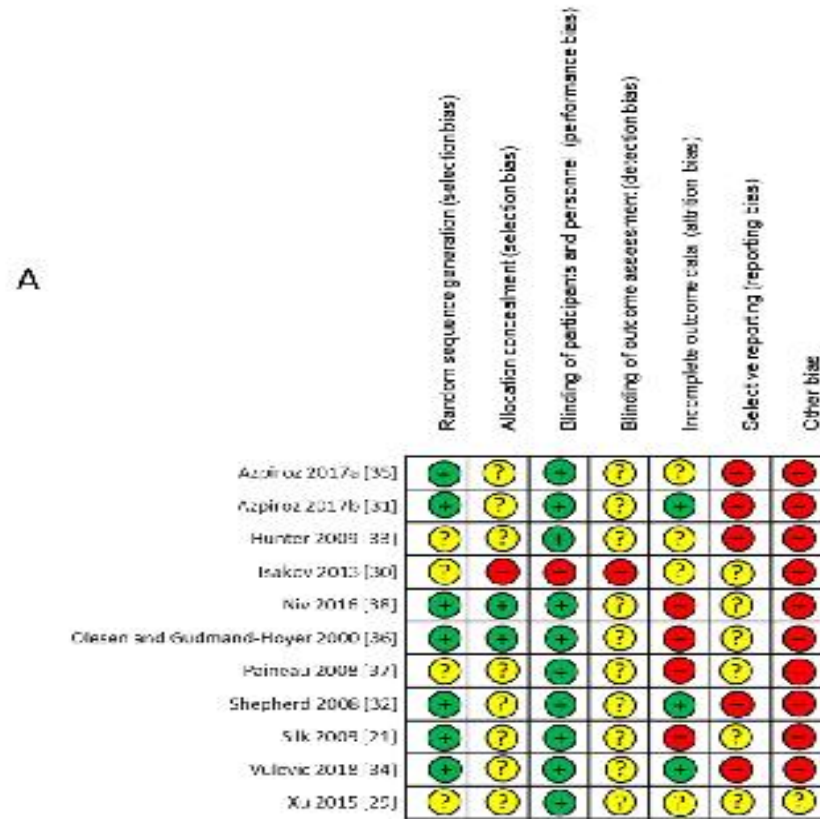
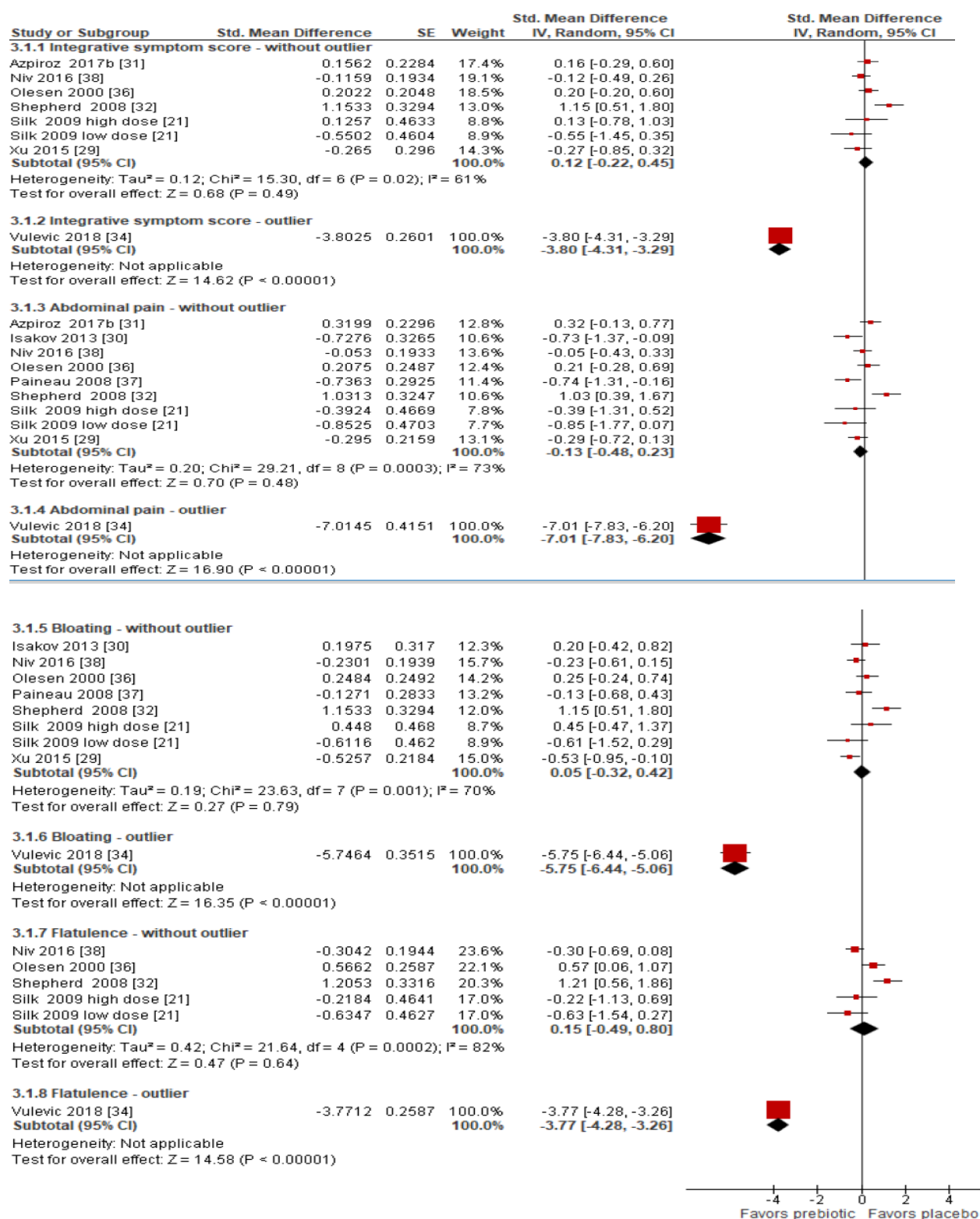


Figure 5

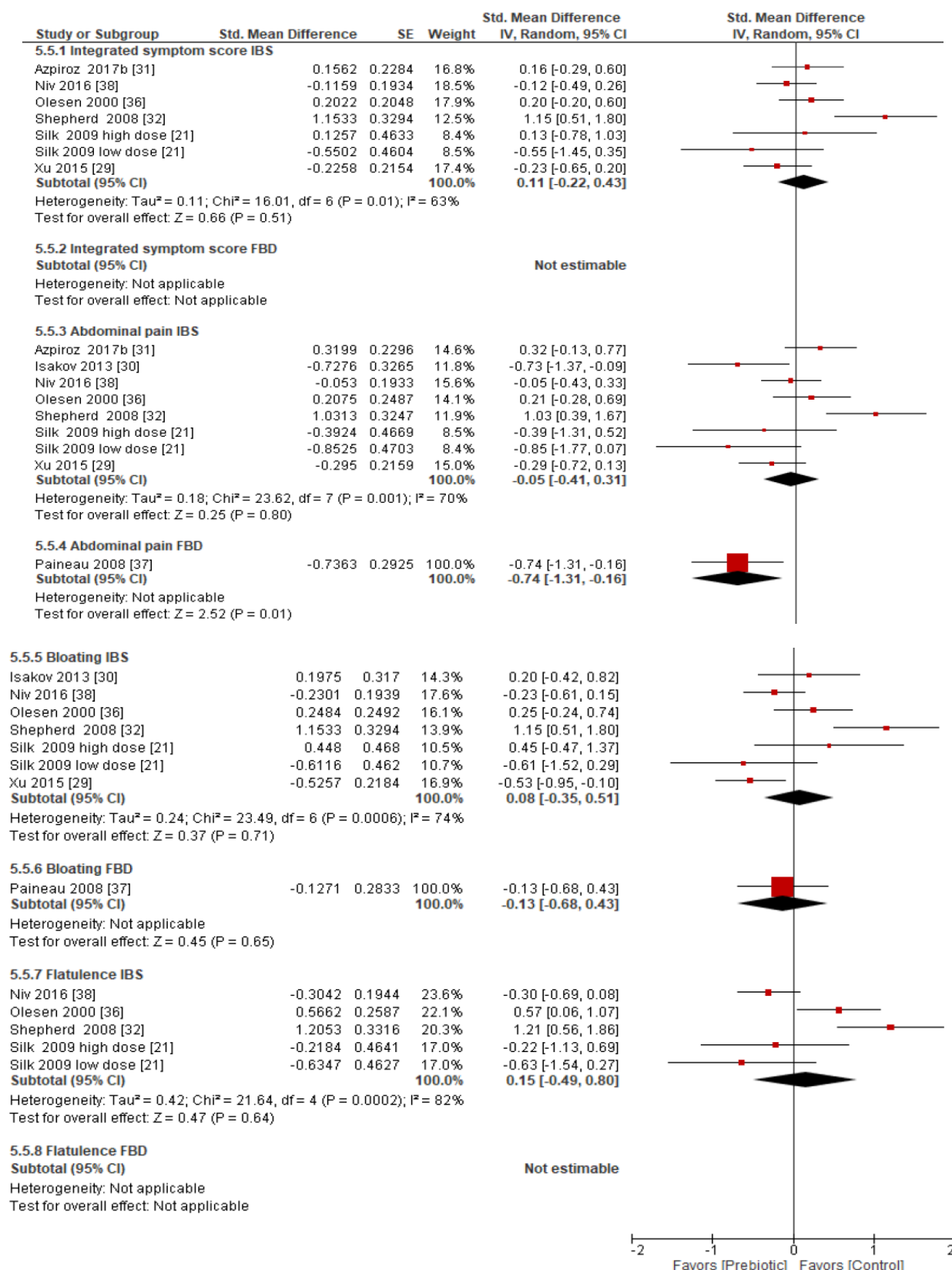


Supplemental table 1**Detailed Search Strategy Embase 1947 to 2018 November 8**

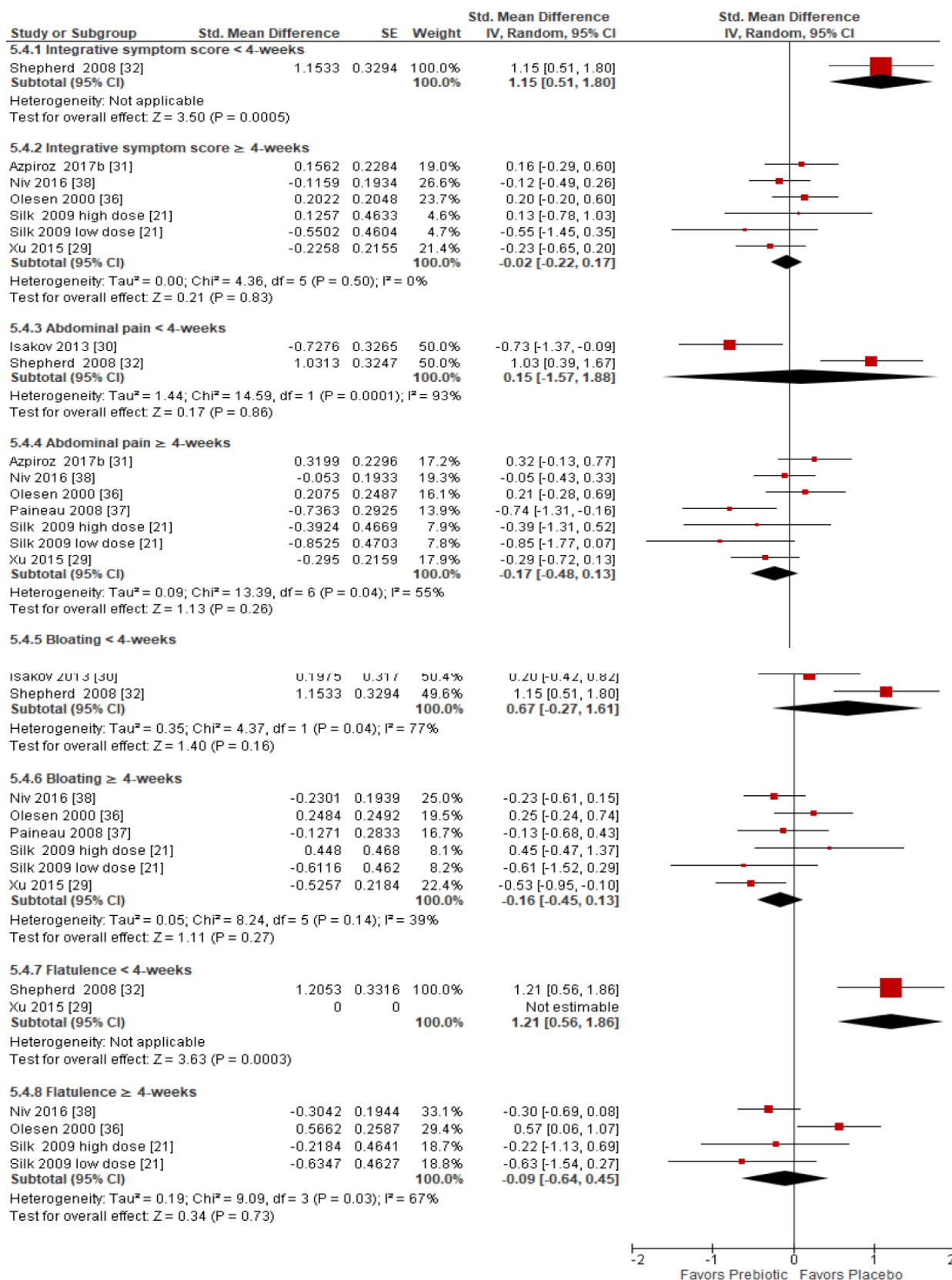
<p>Prebiotic agent/ OR prebiotic*.mp. OR exp inulin/ OR inulin.mp. OR inulin type fruct*.mp. OR chicory.mp. OR exp chicory/ OR exp fructan/ OR fructan*.mp. OR fructo-oligosaccharide*.mp. OR fructooligosaccharide*.mp. OR oligofructose.mp. OR exp oligomer/ or oligomers.mp. OR large size polymer*.mp. OR exp oligosaccharide/ or oligosaccharide*.mp. OR galactooligosaccharide*.mp. OR galactooligosaccharide*.mp. OR trans-galactooligosaccharide*.mp. OR soya-oligosaccharide*.mp. OR partially hydrolysed guar gum.mp. OR sc-FOS.mp. OR fermentable.mp.</p>
AND
<p>irritable bowel syndrome.mp. OR functional bowel disorder.mp. OR functional bloating.mp. OR functional diarr*.mp. OR IBS.mp. OR IBS?C.mp. OR IBS-C.mp. OR IBS?D.mp. OR IBS-D.mp. OR IBS?U.mp. OR IBS?M.mp. OR IBS-U.mp. OR IBS-M.mp.</p>
<p>Limit to human studies, limit to "not review"</p>



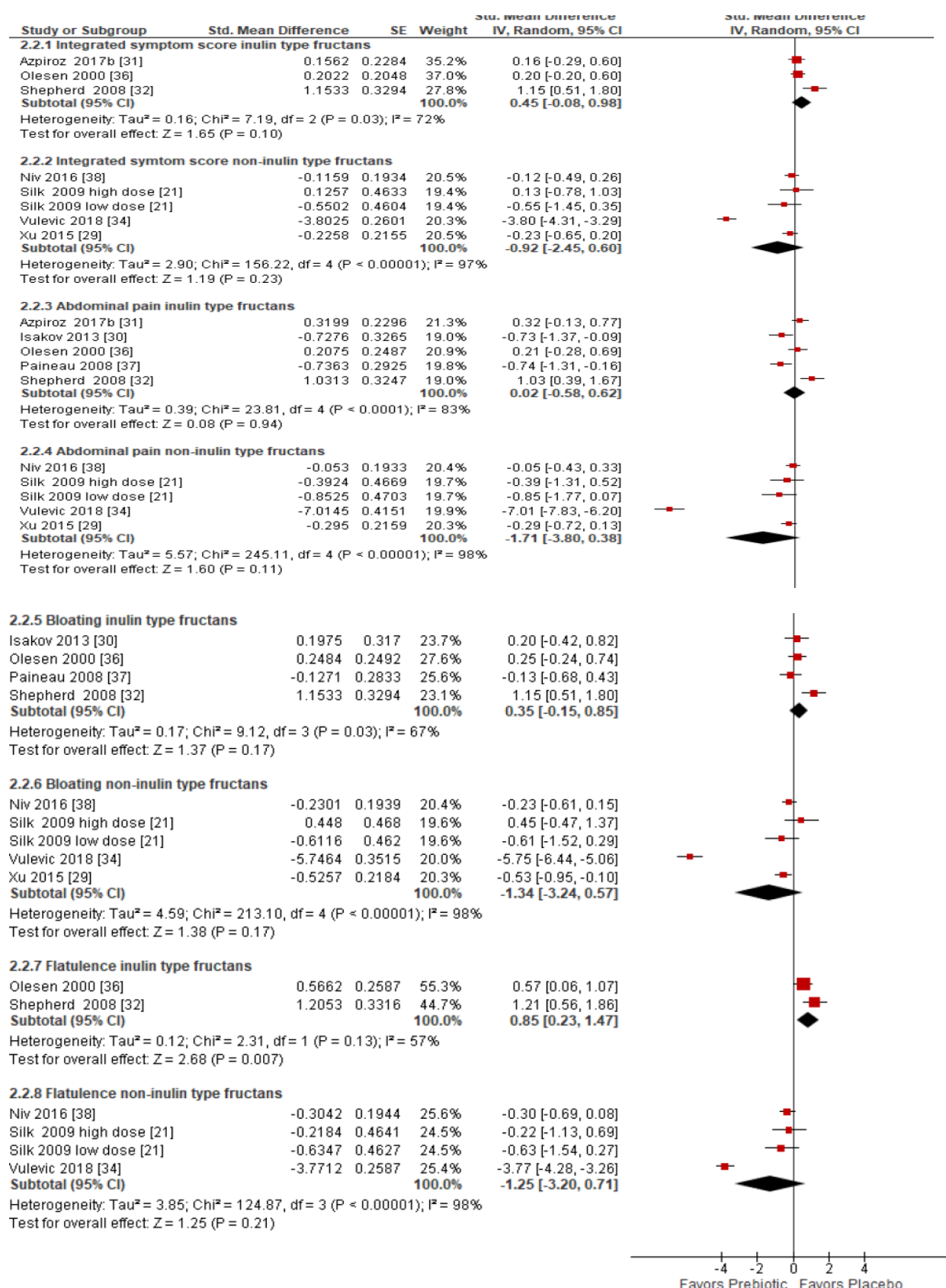
Supplemental figure 1 Forest plot of integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with irritable bowel syndrome (IBS) or other functional bowel disorder (FBD) with outlier study separated. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.



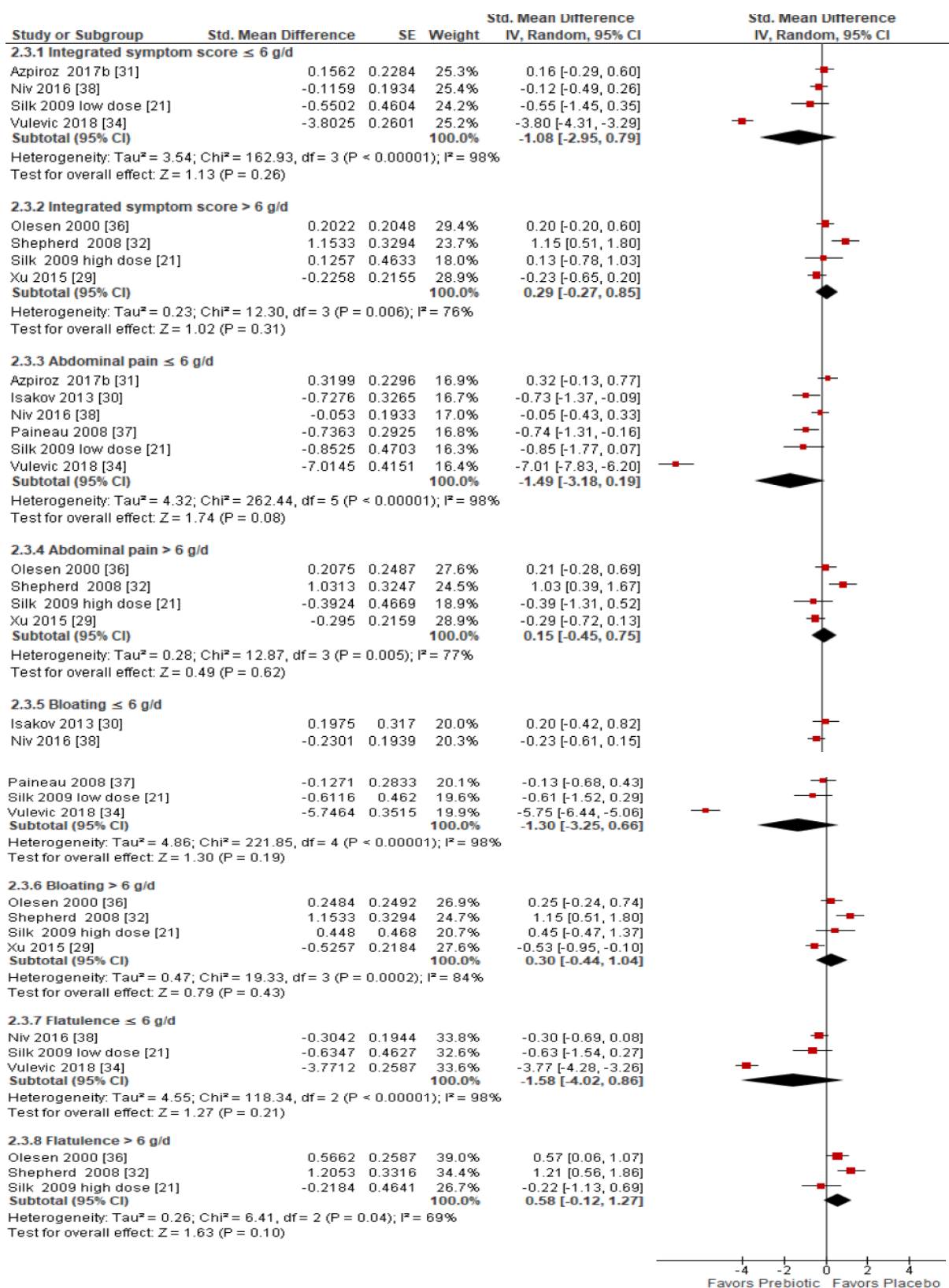
Supplemental figure 2 Forest plot of subgroup analysis of bowel disorder type IBS vs other FBD on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.



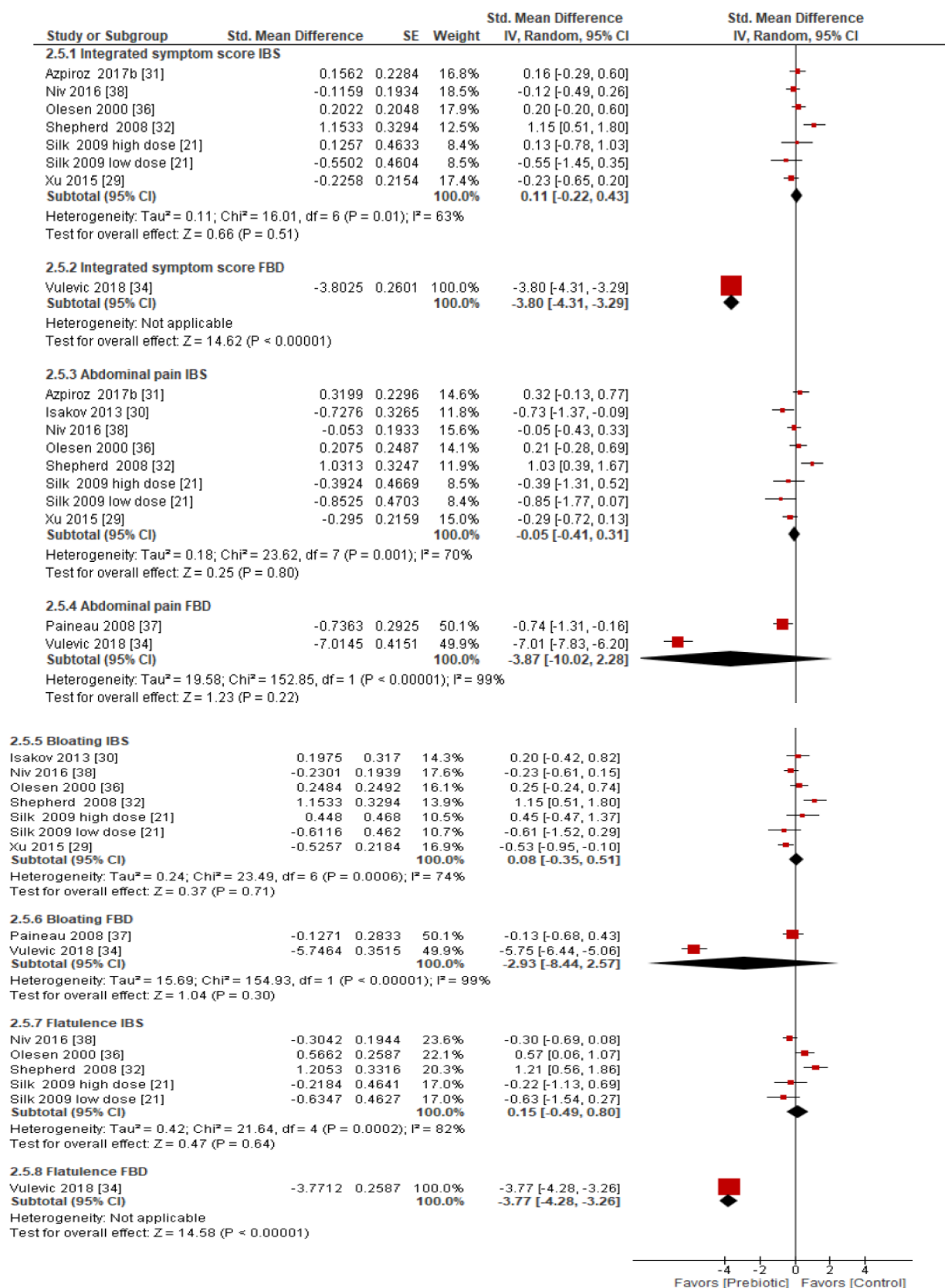
Supplemental figure 3 Forest plot of subgroup analysis of prebiotic duration (<4 weeks vs ≥4 weeks) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model.



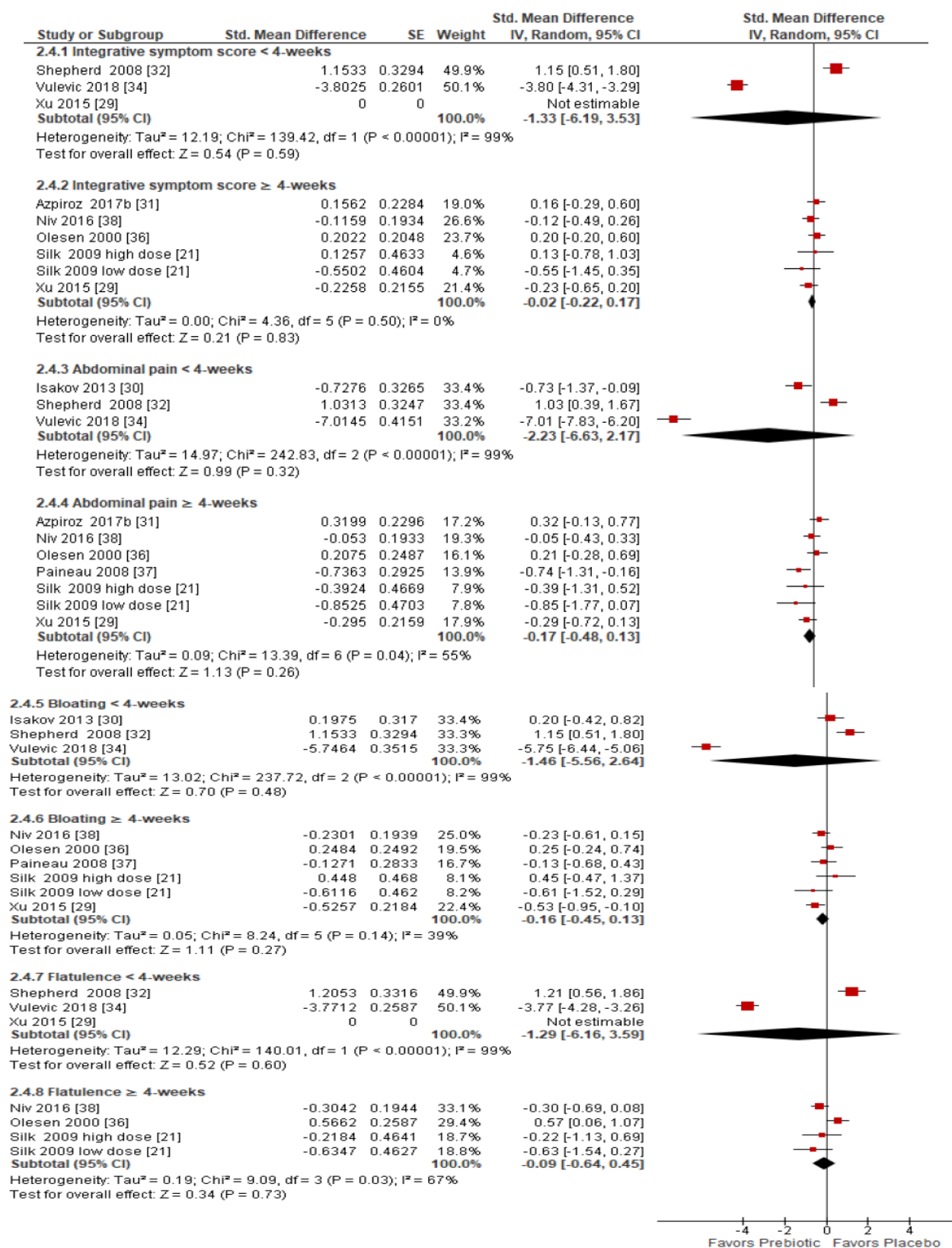
Supplemental figure 4 Forest plot of subgroup analysis of prebiotic type (inulin type fructan *versus* non-inulin type fructan) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



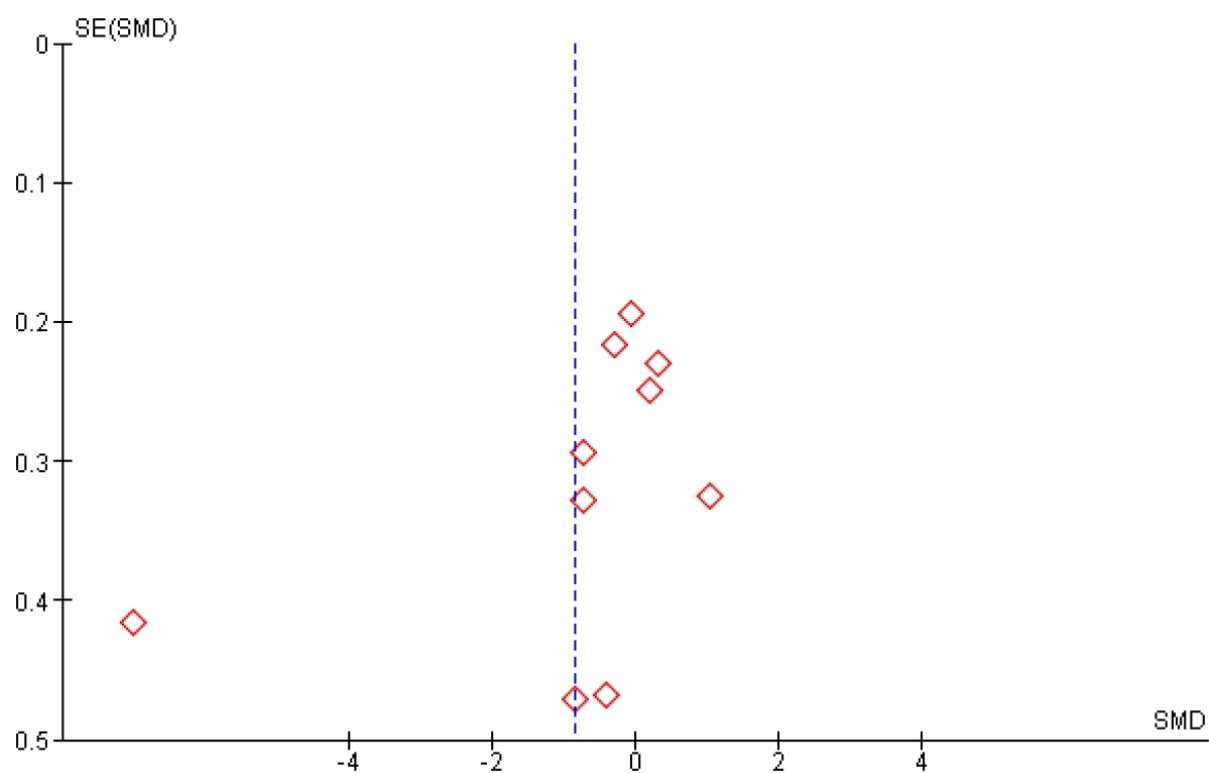
Supplemental figure 5 Forest plot of subgroup analysis of different prebiotic dose (≤ 6 g/d vs > 6 g/d) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. One outlier study was removed, and values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



Supplemental figure 6 Forest plot of subgroup analysis of bowel disorder type IBS vs other FBD on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



Supplemental figure 7 Forest plot of subgroup analysis of prebiotic duration (<4 weeks vs ≥4 weeks) on integrative symptom score, severity of abdominal pain, bloating, and flatulence in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD. Values were calculated as standardized mean differences (95% CI) for clinical outcomes using a random effects model. The outlier study is included in the forest plot.



Supplemental figure 8 Funnel plot of abdominal pain outcome in randomized controlled trials comparing prebiotic to placebo in adults with IBS or other FBD.