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Prebiotics for induction and maintenance of remission in ulcerative colitis (Review)

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[Intervention Review]

Prebiotics for induction and maintenance of remission in ulcerative colitis

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ABSTRACT

Background

People affected by ulcerative colitis (UC) are interested in dietary therapies as treatments that can improve their health and quality of life. Prebiotics are a category of food ingredients theorised to have health benefits for the gastrointestinal system through their effect on the growth and activity of intestinal bacteria and probiotics.

Objectives

To assess the efficacy and safety of prebiotics for the induction and maintenance of remission in people with active UC.

Search methods

We searched CENTRAL, MEDLINE, Embase, ClinicalTrials.gov, and WHO ICTRP on 24 June 2023.

Selection criteria

We included randomised controlled trials (RCTs) on people with UC. We considered any type of standalone or combination prebiotic intervention, except those prebiotics combined with probiotics (known as synbiotics), compared to any control intervention. We considered interventions of any dose and duration.

Data collection and analysis

We followed standard Cochrane methodology.

Main results

We included 9 RCTs involving a total of 445 participants. Study duration ranged from 14 days to 2 to 3 months for induction and 1 to 6 months for maintenance of remission. All studies were on adults. Five studies were on people with mild to moderate active disease, three in remission or mild activity, and one did not mention.

We judged only one study as at low risk of bias in all areas.

Two studies compared prebiotics with placebo for induction of remission. We cannot draw any conclusions about clinical remission (70% versus 67%; risk ratio (RR) 1.05, 95% confidence interval (CI) 0.57 to 1.94); clinical improvement (mean Rachmilewitz score on day 14 of 4.1 versus 4.5; mean difference (MD) −0.40, 95% CI −2.67 to 1.87); faecal calprotectin levels (mean faecal calprotectin on day 14 of 1211 µg/mL versus 3740 µg/mL; MD −2529.00, 95% CI −6925.38 to 1867.38); interleukin-8 (IL-8) levels (mean IL-8 on day 7 of 2.9 pg/mL versus 5.0 pg/mL; MD −2.10, 95% CI −4.93 to 0.73); prostaglandin E2 (PGE-2) levels (mean PGE-2 on day 7 of 7.1 ng/mL versus 11.5 ng/mL; MD −4.40,

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95% CI −20.25 to 11.45); or withdrawals due to adverse events (21% versus 8%; RR 2.73, 95% CI 0.51 to 14.55). All evidence was of very low certainty. No other outcomes were reported.

Two studies compared inulin and oligofructose 15 g with inulin and oligofructose 7.5 g for induction of remission. We cannot draw any conclusions about clinical remission (53% versus 12.5%; RR 4.27, 95% CI 1.07 to 16.96); clinical improvement (67% versus 25%; RR 2.67, 95% CI 1.06 to 6.70); total adverse events (53.5% versus 31%; RR 1.71, 95% CI 0.72 to 4.06); or withdrawals due to adverse events (13% versus 25%; RR 0.53, 95% CI 0.11 to 2.50). All evidence was of very low certainty. No other outcomes were reported.

One study compared prebiotics and anti-inflammatory therapy with anti-inflammatory therapy alone for induction of remission. We cannot draw any conclusions about clinical improvement (mean Lichtiger score at 4 weeks of 6.2 versus 10.3; MD −4.10, 95% CI −8.14 to −0.06) or serum C-reactive protein (CRP) levels (mean CRP levels at 4 weeks 0.55 ng/mL versus 0.50 ng/mL; MD 0.05, 95% CI −0.37 to 0.47). All evidence was of very low certainty. No other outcomes were reported.

Three studies compared prebiotics with placebo for maintenance of remission. There may be no difference between groups in rate of clinical relapse (44% versus 33%; RR 1.36, 95% CI 0.79 to 2.31), and prebiotics may lead to more total adverse events than placebo (77% versus 46%; RR 1.68, 95% CI 1.18 to 2.40). The evidence was of low certainty. We cannot draw any conclusions about clinical improvement (mean partial Mayo score at day 60 of 0.428 versus 1.625; MD −1.20, 95% CI −2.17 to −0.22); faecal calprotectin levels (mean faecal calprotectin level at day 60 of 214 µg/mL versus 304 µg/mL; MD −89.79, 95% CI −221.30 to 41.72); quality of life (mean Inflammatory Bowel Disease Questionnaire (IBDQ) score at day 60 of 193.5 versus 188.0; MD 5.50, 95% CI −8.94 to 19.94); or withdrawals due to adverse events (28.5% versus 11%; RR 2.57, 95% CI 1.15 to 5.73). The evidence for these outcomes was of very low certainty. No other outcomes were reported.

One study compared prebiotics with synbiotics for maintenance of remission. We cannot draw any conclusions about quality of life (mean IBDQ score at 4 weeks 182.4 versus 176.1; MD 6.30, 95% CI −6.61 to 19.21) or withdrawals due to adverse events (23% versus 20%; RR 1.13, 95% CI 0.48 to 2.62). All evidence was of very low certainty. No other outcomes were reported.

One study compared prebiotics with probiotics for maintenance of remission. We cannot draw any conclusions about quality of life (mean IBDQ score at 4 weeks 182.4 versus 168.6; MD 13.60, 95% CI 1.22 to 25.98) or withdrawals due to adverse events (22.5% versus 22.5%; RR 1.00, 95% CI 0.44 to 2.26). All evidence was of very low certainty. No other outcomes were reported.

Authors' conclusions

There may be no difference in occurrence of clinical relapse when adjuvant treatment with prebiotics is compared with adjuvant treatment with placebo for maintenance of remission in UC. Adjuvant treatment with prebiotics may result in more total adverse events when compared to adjuvant treatment with placebo for maintenance of remission. We could draw no conclusions for any of the other outcomes in this comparison due to the very low certainty of the evidence. The evidence for all other comparisons and outcomes was also of very low certainty, precluding any conclusions.

It is difficult to make any clear recommendations for future research based on the findings of this review given the clinical and methodological heterogeneity among studies. It is recommended that a consensus is reached on these issues prior to any further research.

PLAIN LANGUAGE SUMMARY

Prebiotics for treatment of ulcerative colitis

Key messages

We found that prebiotics may not differ from placebo in preventing relapses of ulcerative colitis. For adults in remission, prebiotics may result in more side effects than placebo.

The evidence was of poor quality for remission, improvement in disease activity, inflammation, and quality of life, therefore we could not reach any conclusions for these outcomes.

There needs to be more high-quality research on this topic before any firm conclusions can be reached.

What is ulcerative colitis?

Ulcerative colitis is one of the two main forms of inflammatory bowel disease. It is a lifelong condition that causes inflammation and ulcers in the large bowel. Symptoms include bloody stools, diarrhoea, stomach pain, fever, weight loss, and feeling tired. We don't know exactly what causes ulcerative colitis. It is probably a mix of genes, immune system problems, bacteria in the gut, and something in the environment. There is no known cure, but the symptoms are usually managed with medicine and sometimes surgery.

Most people with ulcerative colitis have times when they have symptoms (active disease) and times when their symptoms are under control (remission). When symptoms come back after being in remission, it is called relapse. When medicines are used to get ulcerative colitis

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under control, it is called induction of remission. When medicines are used to keep ulcerative colitis under control, it is called maintenance of remission.

What did we want to find out?

We wanted to find out if prebiotics work and are safe for the treatment of ulcerative colitis. Prebiotics are foods that affect the balance of good and bad bacteria in your gut.

We wanted to find out if prebiotics can get active ulcerative colitis into remission, prevent relapses, and improve disease activity, inflammation, and quality of life. We also wanted to find out how many people have side effects from prebiotics, and how many people stop taking prebiotics because of side effects.

What did we do?

We searched for randomised controlled trials (studies where people are assigned to one of two or more treatment groups using a random method) comparing prebiotics with any other treatment, standard treatment, dummy treatment (placebo), or different dosages of prebiotics.

What did we find?

We found 9 studies involving a total of 445 people with ulcerative colitis. The studies lasted from 14 days to 6 months. Five studies included people with active disease; three included people in remission; and one study did not report this information. In most studies, people continued taking their usual ulcerative colitis medicines.

Two studies compared prebiotics with dummy treatment for induction of remission. There was no information on rate of side effects. We do not know if prebiotics affect any of the other outcomes we looked at because the quality of the evidence was very low.

Two studies compared different doses of prebiotics for induction of remission. We do not know if prebiotics affect any of the outcomes we looked at because the quality of the evidence was very low.

One study compared prebiotics plus anti-inflammatory therapy with anti-inflammatory therapy alone for induction of remission. There was no information on remission, quality of life, side effects, or rate of withdrawals due to side effects. We do not know if prebiotics affect any of the other outcomes we looked at because the quality of the evidence was very low.

Three studies compared prebiotics with dummy treatment for maintenance of remission. There may be no difference in rate of relapse between prebiotics and dummy treatment. Prebiotics may lead to more side effects than dummy treatment. We do not know if prebiotics affect any of the other outcomes we looked at because the quality of the evidence was very low.

One study compared prebiotics with prebiotics plus probiotics for maintenance of remission. There was no information on relapse, disease activity, inflammation, or rate of side effects. We do not know if prebiotics affect any of the other outcomes we looked at because the quality of the evidence was very low.

One study compared prebiotics with probiotics for maintenance of remission. There was no information on relapse, disease activity, inflammation, or rate of side effects. We do not know if prebiotics affect any of the other outcomes we looked at because the quality of the evidence was very low.

What are the limitations of the evidence?

The evidence is mostly of very low and low quality. This is because of problems with the way the studies were performed and how results were reported. Additionally, there very small numbers of people included for most of the outcomes we examined.

How up-to-date is this review?

This review is current to June 2023.

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SUMMARY OF FINDINGS

Summary of findings 1. Prebiotics compared to placebo for induction of remission

Prebiotics compared to placebo for induction of remission

Patient or population: people with mild-to-moderate disease (Rachmilewitz index) or active disease (SCCAI score of 4 to 10)
Setting: outpatient and inpatient departments in Spain and Denmark
Intervention: prebiotics (inulin plus oligofructose or ispaghula husk)
Comparison: placebo

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Comments
				Risk with placebo for induction of remission	Risk difference with prebiotics	
Clinical remission (14 days)	19 (1 study)	⊕⊖⊖⊖ Very low[a]	RR 1.05 (0.57 to 1.94)	Study population 667 per 1000	 700 per 1000 (380 to 1000)	
Clinical improvement (Rachmilewitz index) (14 days)	15 (1 study)	⊕⊖⊖⊖ Very low[a]	-	The mean score in the control group was 4.5.	MD 0.40 lower (2.67 lower to 1.87 higher)	Gravesen 2016 reported SCCAI by individual participant number but not by treatment arm, therefore these results could not be included in the analysis.
Quality of life (IBDQ) (2 or 3 months)	8 (1 study)	⊕⊖⊖⊖ Very low[a]	-	-	-	Gravesen 2016 reported IBDQ by individual participant number but not by treatment arm, therefore these results could not be included in the analysis.
Total adverse events	-	-	-	-	-	No data
Withdrawals due to adverse events (14 days to 2 or 3 months)	31 (2 studies)	⊕⊖⊖⊖ Very low[b]	RR 2.73 (0.51 to 14.55)	Study population 77 per 1000	 210 per 1000 (39 to 1000)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MD:** mean difference; **RR:** risk ratio; **SCCAI:** Simple Clinical Colitis Activity Index

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GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to very serious imprecision (very low event numbers) and once due to risk of selection and selective reporting bias.
[b]Downgraded twice due to very serious imprecision (very low event numbers) and once due to risk of selection, performance, attrition, and selective reporting bias.

Summary of findings 2. Inulin and oligofructose 15 g compared to inulin and oligofructose 7.5 g daily for induction of remission

Inulin and oligofructose 15 g compared to inulin and oligofructose 7.5 g for induction of remission

Patient or population: people with mild to moderately active ulcerative colitis
Setting: presumed outpatient study in Canada and an unreported country
Intervention: inulin plus oligofructose 15 g daily
Comparison: inulin plus oligofructose 7.5 g daily

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Comments
				Risk with **inulin and oligofructose** 7.5 g daily	Risk difference with **inulin and oligofructose** 15 g daily	
Clinical remission (9 weeks)	31 (1 study)	⊕⊖⊖⊖ Very low[a]	RR 4.27 (1.07 to 16.96)	Study population 125 per 1000	 534 per 1000 (134 to 1000)	Morse 2010 reported that 7/24 participants achieved remission, but did not report results separately for the 2 treatment arms. Consequently, these data could not be included in the meta-analysis.
Clinical improvement (Mayo score) (9 weeks)	31 (1 study)	⊕⊖⊖⊖ Very low[a]	RR 2.67 (1.06 to 6.70)	Study population 250 per 1000	 668 per 1000 (265 to 1000)	Morse 2010 reported that UCDAI score improved by 2.9 in participants treated withinulin and oligofructose15 g vs 0.75 for participants treated with inulin and oligofructose 7.5 g. However, these data could not be used in meta-analysis due to lack of variance.
Quality of life	-	-	-	-	-	No data
Total adverse events	31 (1 study)	⊕⊖⊖⊖ Very low[a]	RR 1.71 (0.72 to 4.06)	Study population		

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(9 weeks)				313 per 1000	535 per 1000 (225 to 1000)	
Withdrawals due to adverse events (9 weeks)	31 (1 study)	⊕⊖⊖⊖ Very low[a]	RR 0.53 (0.11 to 2.50)	Study population 250 per 1000	132 per 1000 (28 to 625)	Morse 2010 reported 6/24 withdrawals due to adverse events, but did not report results separately for the 2 treatment arms. Consequently, these data could not be included in the meta-analysis.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **UCDAI:** Ulcerative Colitis Disease Activity Index

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to very serious imprecision (very low event numbers) and once due to risk of selection, performance, and detection bias.

Summary of findings 3. Prebiotics and anti-inflammatory therapy compared to anti-inflammatory therapy for induction of remission

Prebiotics and anti-inflammatory therapy compared to anti-inflammatory therapy for induction of remission

Patient or population: people with mild-to-moderate ulcerative colitis based on Truelove and Witts criteria
Setting: 8 hospitals in Japan
Intervention: germinated barley foodstuffs 20 to 30 g daily and baseline anti-inflammatory therapy
Comparison: baseline anti-inflammatory therapy

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Comments
				Risk with anti-inflammatory therapy for induction of remission	Risk difference with prebiotics and anti-inflammatory therapy	
Clinical remission	-	-	-	-	-	No data
Clinical improvement (Lichtiger index)	18 (1 study)	⊕⊖⊖⊖ Very low[a]	-	The mean score in the control group was 10.3.	MD 4.10 lower (8.14 lower to 0.06 lower)	The results included in this meta-analysis were presented

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(4 weeks)						as a chart, therefore the numerical data are approximate.
Quality of life	-	-	-	-	-	No data
Total adverse events	-	-	-	-	-	No data
Withdrawals due to adverse events	-	-	-	-	-	No data

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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Summary of findings 4. Prebiotics compared to placebo for maintenance of remission

Prebiotics compared to placebo for maintenance of remission

Patient or population: people with histologically confirmed diagnosis of ulcerative colitis in remission
Setting: outpatient or presumed outpatient departments in Italy, Sweden, or Canada
Intervention: prebiotics (sodium butyrate capsules, ispaghula capsules, or inulin plus oligofructose)
Comparison: placebo

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Comments
				Risk with placebo for maintenance of remission	Risk difference with prebiotics	
Clinical relapse (6 months)	89 (1 study)	⊕⊕⊖⊖ Low[a]	RR 1.36 (0.79 to 2.31)	Study population		
				326 per 1000	443 per 1000 (256 to 753)	

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Clinical improvement (partial Mayo score) (60 days)	30 (1 study)	⊕⊖⊖⊖ Very low[b]	-	The mean score in the control group was 1.625.	MD 1.20 lower (2.17 lower to 0.22 lower)	Hallert 1991 was a cross-over study that did not provide pre-cross-over data.
Quality of life (IBDQ) (60 days)	30 (1 study)	⊕⊖⊖⊖ Very low[b]	-	The mean score in the control group was 188.	MD 5.50 higher (8.94 lower to 19.94 higher)	
Total adverse events (6 months)	89 (1 study)	⊕⊕⊖⊖ Low[a]	RR 1.68 (1.18 to 2.40)	Study population 457 per 1000	767 per 1000 (539 to 1000)	
Withdrawals due to adverse events (60 days to 6 months)	125 (2 studies)	⊕⊖⊖⊖ Very low[b]	RR 2.57 (1.15 to 5.73)	Study population 111 per 1000	285 per 1000 (128 to 636)	Hallert 1991 was a cross-over study that did not provide pre-cross-over data.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to very serious imprecision (very low event numbers).
[b]Downgraded twice due to very serious imprecision (very low event numbers) and once due to risk of selective reporting bias.

Summary of findings 5. Prebiotics compared to probiotics for maintenance of remission

Prebiotics compared to probiotics for maintenance of remission

Patient or population: people in remission or with mildly activeulcerative colitis
Setting: 2 outpatient centres in Japan
Intervention: prebiotics (oral psyllium 4 g twice daily)
Comparison: probiotics (*Bifidobacterium longum* capsule once daily)

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Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Comments
				Risk with probiotics for maintenance of remission	Risk difference with prebiotics	
Clinical relapse (4 weeks)	-	-	-	-	-	No data
Clinical improvement	-	-	-	-	-	No data
Quality of life (IBDQ) (4 weeks)	62 (1 study)	⊕⊖⊖⊖ Very low[a]	-	The mean score in the control group was 168.8.	MD 13.6 higher (1.22 higher to 25.98 higher)	
Total adverse events	-	-	-	-	-	Fujimori 2009 reported that there were no adverse events related to blood variables (which were only measured in a subset of participants), but overall adverse events were not reported.
Withdrawals due to adverse events (4 weeks)	80 (1 study)	⊕⊖⊖⊖ Very low[a]	RR 1.00 (0.44 to 2.26)	Study population		
				225 per 1000	225 per 1000 (99 to 509)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to very serious imprecision (very low event numbers) and once due to risk of selection, performance, detection, and selective reporting bias.

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Summary of findings 6. Prebiotics compared to synbiotics for maintenance of remission

Prebiotics compared to synbiotics for maintenance of remission

Patient or population: people in remission or with mildly activeulcerative colitis
Setting: 2 outpatient centres in Japan
Intervention: prebiotics (oral psyllium 4 g twice daily)
Comparison: synbiotics (oral psyllium 4 g twice daily plus*Bifidobacterium longum* capsule once daily)

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Comments
				Risk with synbiotics for maintenance of remission	Risk difference with prebiotics	
Clinical relapse (4 weeks)	-	-	-	-	-	No data
Clinical improvement	-	-	-	-	-	No data
Quality of life (IBDQ) (4 weeks)	63 (1 study)	⊕⊖⊖⊖ Very low[a]	-	The mean score in the control group was 176.1.	MD 6.3 higher (6.61 lower to 19.21 higher)	
Total adverse events	-	-	-	-	-	Fujimori 2009 reported that there were no adverse events related to blood variables (which were only measured in a subset of participants), but did not report overall adverse events.
Withdrawals due to adverse events (4 weeks)	80 (1 study)	⊕⊖⊖⊖ Very low[a]	RR 1.13 (0.48 to 2.62)	Study population		
				200 per 1000	226 (96 to 524)	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IBDQ:** Inflammatory Bowel Disease Questionnaire; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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BACKGROUND

Description of the condition

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD), a chronic condition that can alternate between remission and periods of active disease. It is characterised by inflammation of the intestinal mucosa, starting at the rectum and extending proximally; it is limited to the colon (Feuerstein 2014). Symptoms can include bloody diarrhoea, abdominal pain, urgency, and tenesmus; quality of life can be impacted to a significant degree. It can be diagnosed in children and adults alike, and diagnosis is based on individual medical history, clinical assessment of signs and symptoms, and endoscopic or histopathological findings. (Yangyang 2017).

The global incidence of UC is on the rise, especially in newly industrialised regions, such as Africa, Asia, and South America, where certain areas have reported increases of up to 15% since 1990 (Ng 2017). Even though incidence is stabilising in Western countries, such as Denmark, prevalence remains above 0.3%, representing a high burden for the individual, carers, and healthcare systems (Vadstrup 2020).

The aetiology of UC is purported to be complex and multifactorial, caused by the interaction of a multitude of environmental, genomic, immunological, and microbial factors. These interactions can lead to dysregulations that manifest as UC (De Souza 2017). More specifically, genetic predisposition, epithelial barrier defects, and a dysregulated immune response are thought to play a role in the development of UC (Kaur 2020).

Ulcerative colitis can be classified as mild, moderate, severe, or fulminant (very severe), which may guide treatment choices (Pabla 2020).

Description of the intervention

Prebiotics are a category of food ingredients considered to have health benefits for the gastrointestinal system (de Vrese 2008). Prebiotics were first defined in 1995 (Gibson 1995); their definition has evolved many times throughout the years (Carlson 2015). The word 'prebiotic' comes from the Greek words 'pre', meaning 'prior to', and 'bios', meaning 'life', relating to their significance as an energy source for the gut microbiome. Prebiotics cannot be hydrolysed or absorbed by humans; instead, they are fermented by micro-organisms that inhabit the gut, producing short-chain fatty acids (SCFA), which have multiple effects on the gut and other areas of the body (Markowiak 2017). Prebiotics are mostly subsets of carbohydrates, mainly oligo-saccharides (Roberfroid 2007).

The main prebiotic subcategories are soluble fibres, which are largely indigestible by the human gut where they can be hydrolysed and fermented by the microbiome; these include fructans, which are made up by chains of fructose, and include inulin and fructo-oligosaccharide; galacto-oligosaccharides, which are made of chains of galactose and glucose; glucose-derived oligosaccharides, such as polydextrose, and pectin and its derivatives, which are made of glucose polymers; and resistant starch, which is indigestible starch. Some theories link certain types of prebiotics with the growth of particular bacterial strains; however, the debate is still ongoing (Davani-Davari 2019).

Prebiotics are found in a variety of foods and supplements. Natural prebiotics are more commonly found in fruits, vegetables, legumes, and cereals. They can also be chemically synthesised, and used in a variety of food products, such as sports drinks, isotonic beverages, and cereal bars (Carlson 2015).

Short-chain fatty acids (e.g. butyrate) have a number of beneficial effects on intestinal function, including modulation of mucosal inflammation, epithelial barrier function, and intestinal motility (Barbara 2021; Canani 2011). They are usually formed in the large intestine as byproducts of prebiotic fermentation by the intestinal microflora, and are one of the main mediators of prebiotics' purported beneficial effects (Barbara 2021; Canani 2011). Short-chain fatty acid formulations that reach the colon would be anticipated to have similar effects to prebiotics (Canani 2011).

How the intervention might work

The proposed method of action for prebiotics is through their effect on the growth and activity of intestinal bacteria and probiotics (Bindels 2015).

There are vast numbers of microbes in the gastrointestinal system that live in symbiosis with their host, meaning that both the micro-organisms and the host benefit from co-existing. They can have immunomodulatory effects, prevent infection, and produce nutrients, such as SCFA, through prebiotic fermentation (Shokryazdan 2017). As such, prebiotics are a source of energy for these micro-organisms, and their mechanism of action is mediated via their effect on these micro-organisms (Sanders 2019).

Intestinal microbiota play a major role in maintaining homeostasis, as key regulators of the proposed gut-brain axis (Cryan 2019). There is growing evidence that microbiota dysbiosis contributes to the development and clinical course of a number of conditions, including inflammatory bowel diseases such as UC (Barbara 2021). The mucus barrier of the intestine is in constant bidirectional communication with the intestinal microbiome, and disruptions in the homeostasis that this communication maintains can cause inflammation (Fang 2021). Microbiome diversity has been found to be reduced in UC (LeBlanc 2021). Prebiotics can potentially benefit people affected by UC by playing a modulator role (Wilson 2019).

Anticipated comparators to prebiotics can be probiotics and synbiotics. Microbes that are introduced into the body through the diet are known as probiotics. They can be found in raw or fermented fruits and vegetables, fermented dairy, and commercial products known as functional foods, or taken as pharmaceutical preparations (Davani-Davari 2019). Preparations that contain both probiotics and prebiotics are known as synbiotics (Swanson 2020). Probiotics and synbiotics can have favourable effects on the intestinal microbiota by promoting and maintaining a healthy balance of the microbial gut ecosystem (Markowiak 2017).

Why it is important to do this review

People affected by UC, especially those with active UC, are in constant search for treatments that can improve their health and quality of life, and dietary therapies are an area of great interest (Jamieson 2007). Prebiotics have been the focus of a number of recent randomised controlled trials and systematic reviews for other gastrointestinal conditions, in which the prebiotics were mainly in the form of prepared prebiotic preparations, not as whole foods (Asha 2020; Ford 2018; McFarland 2019). However, the effects of prebiotics on UC remain unclear.

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Previous Cochrane reviews have reported low-certainty evidence for the efficacy of prebiotics on conditions such as infant eczema and neonate hyperbilirubinaemia (Armanian 2019; Osborn 2013). There is also evidence to suggest that UC, IBD, and other related diseases may benefit from probiotics and dietary interventions (Iheozor-Ejiofor 2020; Kaur 2020; Limketkai 2019; Limketkai 2020; Sharif 2020).

The mention of prebiotics in current UC evidence-based and clinical practice guidelines is scarce. The latest British Society of Gastroenterology IBD guidelines provide a literature overview of prebiotics, probiotics, and synbiotics, without reaching a conclusion about prebiotics specifically (Lamb 2019). In their latest iteration, the European Society for Clinical Nutrition and Metabolism practical IBD guidelines do not include prebiotics as a point of consideration. However, they briefly discuss that "prebiotic fibres may be useful in maintenance of remission in some patients with UC", but not as part of a formal recommendation (Bischoff 2020).

Prebiotics are very unlikely to replace other therapies as the sole agent to induce remission in UC, as they are essentially a dietary intervention. Instead, they are more likely to be used with other therapies, such as probiotics and standard pharmacological therapy. This might have resulted in them being overlooked as a Cochrane review topic for UC. We have thus determined that it is important to systematically review the evidence for their effectiveness and safety on induction and maintenance of remission in UC (Ford 2018; Ooi 2019).

OBJECTIVES

To assess the efficacy and safety of prebiotics for the induction and maintenance of remission in people with active ulcerative colitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished, and ongoing randomised controlled trials (RCT) on prebiotic interventions for people with ulcerative colitis (UC). We considered cross-over and cluster-RCTs. We considered studies published as full text or abstract; we also considered unpublished data. We excluded quasi-randomised trials (using no or non-appropriate randomisation).

Types of participants

We included people of all ages and genders with UC. We considered all studies that were described by their authors to be on UC, with or without mention of diagnostic criteria.

We considered studies with only a subset of eligible participants for inclusion. If the subset had been planned for a subgroup analysis, we explored its impact through the methods described in Subgroup analysis and investigation of heterogeneity. If a subgroup analysis had not been planned, the review authoring team liaised to discuss the effect this may have on the planned outcomes and whether further subgroup analysis was necessary.

Types of interventions

We considered any type of standalone or combination prebiotic intervention, except those prebiotics combined with probiotics (known as synbiotics), as these include live bacteria as well as prebiotics. We considered short-chain fatty acid (SCFA) formulations delivered to the colon for inclusion.

Control interventions could be placebo, any other type of intervention (including probiotics or synbiotics), or no intervention. We considered interventions of any dose and duration.

We listed all intervention and comparator groups in Characteristics of included studies.

Types of outcome measures

We considered both dichotomous and continuous outcomes. If both dichotomous and continuous outcome data were available for the same outcomes, we analysed and reported them separately.

Primary outcomes

- Clinical remission for induction studies, at end of study, as defined by the authors, and measured on recognised scales
- Clinical relapse for maintenance studies, at end of study, as defined by the authors, and measured on recognised scales

Secondary outcomes

- Disease improvement, at end of study, as defined by the authors, and measured on recognised scales:
  - clinical improvement;
  - endoscopic improvement;
  - histological improvement;
  - biochemical markers of inflammation;
  - quality of life.
- Escalation of therapy, at end of study, as defined by the authors:
  - addition of therapy (including increasing dosage of existing therapy);
  - surgery.
- Adverse events:
  - number of total adverse events, at end of study, as defined by the authors;
  - withdrawals due to adverse events, at end of study. We considered all participants who did not complete the study protocol due to adverse events according to the authors, or for unclear reasons, as withdrawals due to adverse events.

Search methods for identification of studies

Electronic searches

Our Information Specialist searched the following sources on 13 December 2021 and 24 June 2023.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library (Issue 6 of 12; 2023; Appendix 1)
- MEDLINE Ovid SP (1946 to 22 June 2023; Appendix 2)
- Embase Ovid SP (1974 to 2023 Week 25; Appendix 3)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) (24 June 2023; Appendix 4)

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- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/) (24 June 2023; Appendix 5)

We translated the MEDLINE search strategy into the syntax of other resources, adapting it to the other databases. We used Cochrane's sensitivity-maximising version of the MEDLINE RCT search filter for this search strategy (Lefebvre 2021). There were no limitations on language, date, document type, or publication status (Aali 2021).

Searching other resources

As complementary search methods, we carefully handsearched the reference lists of relevant systematic reviews for potentially eligible studies. In addition, we scrutinised the references of included studies. We sought unpublished trials by contacting experts in the field.

We obtained translations of papers when necessary.

Data collection and analysis

We carried out data collection and analysis according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

Selection of studies

Two review authors (VS and AS) independently screened the titles and abstracts identified during the literature search using Covidence (Covidence), discarding studies that clearly did not meet the inclusion criteria. We obtained the full report of studies that appeared to be relevant, or for which there was insufficient information to make a final decision. Two review authors (VS and AS) independently assessed the full reports for inclusion in the review. We resolved any disagreements by discussion, or by consulting a third review author (MG) if resolution was not possible. We entered studies rejected at this or subsequent stages in the Characteristics of excluded studies tables, and recorded the main reasons for exclusion. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (PRISMA 2020).

Where studies had multiple publications, we identified and excluded duplicates and collated reports of the same study so that each study, rather than each report, was the unit of interest for the review; in such cases, we assigned a single identifier with multiple references.

Data extraction and management

Two review authors (VG and AS) independently carried out data extraction using data extraction forms that were initially piloted on two studies. Any disagreements were resolved by consulting a third review author (MG). We extracted the following data from the included studies.

- Trial setting: country and number of trial centres
- Methods: study design, total study duration and date
- Participant characteristics: age, gender, diagnostic criteria, disease activity (mild, moderate, or severe), concomitant therapies, and total number
- Eligibility criteria: inclusion and exclusion criteria
- Intervention and comparator
- Participant outcomes: outcome definition, unit of measurement, and time of collection
- Results: number of participants allocated to each group, missing participants, sample size, outcome results
- Funding source and conflicts of interest
- Author contact information

When multiple trial arms were reported in a single trial, we included only the comparisons within the scope of this review. One review author manually entered data into RevMan (RevMan 2024), and another review author double-checked the data entry. In the case of unclear or incomplete information or data, we contacted the study authors for clarification.

After data extraction, the two review authors compared the extracted data to discuss and resolve discrepancies before the information was transferred into the Characteristics of included studies table.

No studies required translation.

Assessment of risk of bias in included studies

Following data extraction, two review authors independently assessed risk of bias in the included studies using the original Cochrane risk of bias (RoB 1) tool and criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the following domains.

- 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

We judged the studies to be at low, high, or unclear risk of bias for each domain assessed, based on the original risk of bias guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

In the case of cluster-RCTs, we planned to assess risk of bias for the following domains: recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials, as outlined in Section 23.1.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, no cluster-RCTs met our inclusion criteria.

Measures of treatment effect

For dichotomous outcomes, we expressed treatment effect as risk ratios (RR) with corresponding 95% confidence intervals (CIs). For continuous outcomes, we expressed the treatment effect as mean difference (MD) with 95% CI if studies used the same scales and methods. However, if studies assessed the same continuous outcome using different methods, we estimated the treatment effect using the standardised mean difference (SMD) with 95% CIs. We presented SMDs as standard deviation (SD) units and interpreted them as follows: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect, as outlined in Section 12.6.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

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Unit of analysis issues

The participant was the unit of analysis. For studies comparing more than two intervention groups, we made multiple pairwise comparisons between all possible pairs of intervention groups. To avoid double-counting, we divided shared intervention groups evenly among the comparisons. For dichotomous outcomes, we divided both the number of events and the total number of participants. For continuous outcomes, we divided the total number of participants, and left the means and SDs unchanged.

In the case of cross-over studies, we only used data if separately reported before the crossing over occurred; we only used data from the first phase for our analysis. In the case of cluster-RCTs, we planned to use study data only if the authors used appropriate statistical methods to take the clustering effect into account.

Dealing with missing data

We contacted study authors in the event of missing data, or if data were not reported in sufficient detail. If studies reported standard errors, interquartile ranges, or CIs, we converted them to estimate missing SDs, using relevant statistical tools and calculators (Higgins 2021b). We judged studies that failed to report measures of variance as being at high risk of selective reporting bias.

Assessment of heterogeneity

We scrutinised studies to ensure that they were clinically homogeneous in terms of participants, intervention, comparator, and outcome. We used a Chi^2 test to test for statistical heterogeneity. A P value of less than 0.1 indicated the presence of heterogeneity. We quantified and represented inconsistency using the I^2 statistic, based on the following thresholds (Higgins 2021a):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%; may represent substantial heterogeneity;
- 75% to 100%: may represent considerable heterogeneity.

Assessment of reporting biases

We minimised most reporting biases by using an inclusive search strategy. We planned to investigate publication bias using a funnel plot if there were 10 or more studies for a given outcome; however, this did not occur. We planned to determine the magnitude of publication bias by visually inspecting the asymmetry of the funnel plot. In addition, we planned to test funnel plot asymmetry by undertaking a linear regression of the intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (Egger 1997).

Data synthesis

To summarise the study characteristics, we undertook a narrative synthesis of all included studies. This included key summary data of characteristics of participants in the included studies. We performed meta-analyses for all outcomes for which data had been reported appropriately for use in meta-analysis. We synthesised data using the random-effects model in RevMan (RevMan 2024). We combined effect estimates of studies that reported data in a similar way in the meta-analysis. We pooled RRs for dichotomous outcomes, and MDs or SMDs for continuous outcomes, with 95% CIs.

When meta-analysis of effect estimates was not possible, we summarised effect estimates (e.g. range and distribution of observed effects), combined P values (e.g. evidence that there is an effect in at least one study), or vote count, based on the direction of effect (e.g. is there any evidence of an effect?) (Higgins 2021a).

Subgroup analysis and investigation of heterogeneity

In the case of heterogeneity, we planned to investigate possible causes, addressing them by using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). If substantial heterogeneity remained that could not be explained or addressed, we would not perform meta-analysis.

We planned to perform subgroup analyses of potential effect modifiers, for all outcomes, if there were 10 studies or more (Deeks 2021). In the case of sufficient data, we would perform subgroup analyses by age, sex or gender (if enough separate data were provided by the primary studies, we would report and analyse these factors separately), disease activity, long-term (≥ 4 weeks) or short-term (< 4 weeks) study duration, and prebiotic/SCFA type/preparation. These were chosen by the review author team as the most likely subgroup characteristics that could have differences in efficacy.

Sensitivity analysis

If data availability allowed, we planned to perform sensitivity analyses for the primary outcomes of clinical remission/relapse, to assess whether the findings of the review were robust to the decisions made during the review process. The pre-planned sensitivity analyses were:

- inclusion of studies at low risk of bias across all risk of bias domains;
- inclusion of studies with no risk of bias domains rated as high risk;
- when data analyses included studies with reported and estimated SDs, we would exclude studies with estimated SDs to assess whether this affected the findings of the review;
- to explore heterogeneity, we would investigate whether the choice of model (fixed-effect versus random-effects) impacted the results;
- exclusion of cluster-RCTs to assess their impact on the results.

Summary of findings and assessment of the certainty of the evidence

Two review authors independently assessed the certainty of the evidence, with any disagreements resolved by consulting and reaching consensus with a third review author (Schünemann 2021). We presented the primary outcome, as well as the outcomes of clinical improvement, quality of life, total adverse events, and withdrawals due to adverse events, in summary of findings tables. We exported each comparison and all outcomes to GRADEpro GDT software (GRADEpro GDT), rating the certainty of the evidence for each outcome as high, moderate, low, or very low based on the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias). These ratings have been defined as follows.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

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- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We justified all decisions to downgrade the certainty of the evidence using footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

Our search identified 830 records. After removal of duplicates, we screened 828 records based on title and abstract, excluding 792 records. We assessed the full texts of 36 records, of which 7 studies (10 records) were excluded. Five studies are ongoing, and three studies are awaiting classification.

We included 9 RCTs (18 records) with a total of 445 randomised participants in the review.

The results of the search are presented in a study flow diagram (Figure 1).

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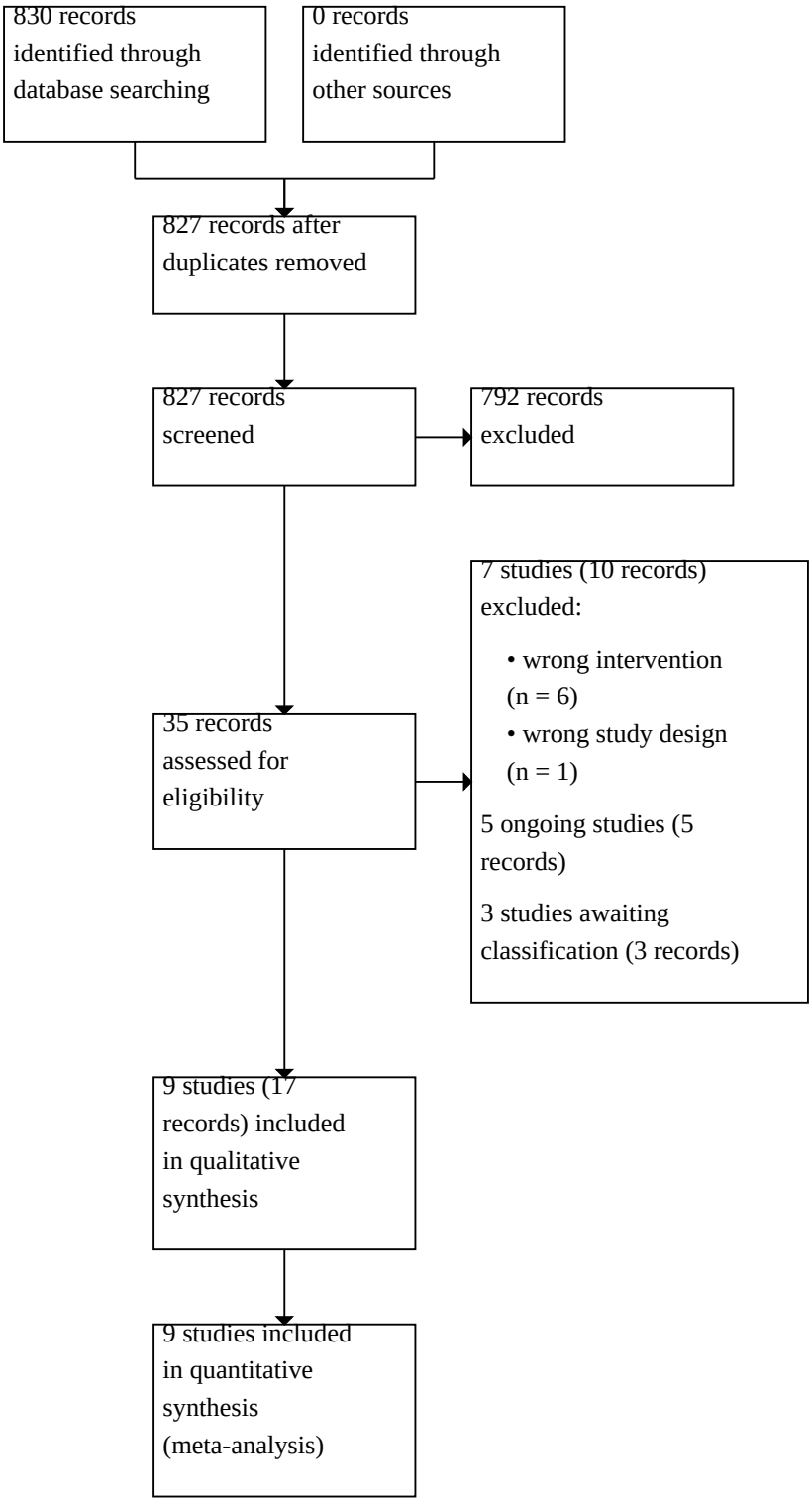
Figure 1. Study flow diagram.



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Included studies

A summary of key characteristics and interventions across the included studies is shown in Table 1. Outcome data are provided in Table 2 and Table 3 . We contacted the authors of eight studies for further information (Casellas 2007; Facchin 2020; Fujimori 2009; Gravesen 2016; Kanauchi 2002; Morse 2010; Valcheva 2019; Valcheva 2022); we received responses from four (Facchin 2020; Gravesen 2016; Kanauchi 2002; Valcheva 2022). We were unable to contact the authors of Hallert 1991.

Study design

Four studies were small, single-centre RCTs conducted in Spain (Casellas 2007), Italy (Facchin 2020), Denmark (Gravesen 2016), or Canada (Valcheva 2022). Two studies were multicentre RCTs conducted in Japan (Fujimori 2009; Kanauchi 2002).

One study was a small, multicentre cross-over RCT conducted in Sweden (Hallert 1991).

For two RCTs, it was not clear if they were single-centre or multicentre. One of these was conducted in Canada (Valcheva 2019); the other study did not report where it was conducted (Morse 2010).

Interventions

- Casellas 2007: 14 days of oral oligofructose-enriched inulin 12 g daily compared to oral placebo (maltodextrin) 12 g daily. All participants also received oral mesalazine and a low-fibre diet.
- Facchin 2020: 60 days of oral sodium-butyrate 3 capsules daily (1800 mg) compared to oral placebo (starch) 3 capsules daily. All participants also continued on their baseline therapy. The study included people with ulcerative colitis and Crohn's disease; we included only data from the ulcerative colitis cohort in the analysis.
- Fujimori 2009: four weeks of oral synbiotics (*Bifidobacterium longum* 2 x 10^9 colony-forming units (CFU) daily plus 4 g psyllium dissolved in 100 mL water twice daily) compared to oral probiotics (*Bifidobacterium longum* 2 x 10^9 CFU daily) compared to oral prebiotics (4 g psyllium dissolved in 100 mL water twice daily) (three study arms).
- Gravesen 2016: two or three months of oral ispaghula husk 30 mL daily compared to oral placebo (breadcrumb powder) 30 mL daily. All participants also received stable doses of oral aminosalicylates (5-ASAs).
- Hallert 1991: two months of oral lactose-free ispaghula husk 4 g twice daily compared to oral placebo (crushed crispbread) twice daily. All participants also continued on their baseline therapy. This was a cross-over study with two trial periods of two months each. The protocol allowed participants who were feeling worse during either trial period to be switched to the next period or to leave the trial.
- Kanauchi 2002: four weeks of 20 to 30 g daily germinated barley foodstuffs plus baseline anti-inflammatory therapy compared to baseline anti-inflammatory therapy only.
- Morse 2010: nine weeks of oral inulin plus oligofructose 15 g daily compared to oral inulin plus oligofructose 7.5 g daily.
- Valcheva 2019: nine weeks of oral oligofructose-enriched inulin 15 g daily compared to oral oligofructose-enriched inulin 7.5 g daily.
- Valcheva 2022: six months of oral β-fructans 7.5 to 15 g daily compared to oral placebo (maltodextrin) 7.5 to 15 g daily. All participants also continued on their baseline therapy. This study was prematurely terminated due to lack of efficacy, and further recruitment was halted.

Concurrent therapies

Three studies allowed concurrent use of 5-ASAs (Casellas 2007; Gravesen 2016; Valcheva 2019). A further two studies allowed continued use of 5-ASAs or prednisone, or both (Fujimori 2009; Kanauchi 2002). In Morse 2010, participants were stable on 5-ASAs or azathioprine at baseline. It is not clear whether they continued these throughout the study.

Hallert 1991 allowed participants to continue regular medication, mostly 5-ASAs.

Facchin 2020 allowed concurrent use of 5-ASAs, biologics, steroids, probiotics, immunosuppressants or proton pump inhibitors. Valcheva 2022 allowed concurrent use of any combination of 5-ASAs, azathioprine, and biologics.

Disease activity

Three studies reported baseline disease activity as in remission or mildly active (Fujimori 2009; Hallert 1991; Valcheva 2022). Valcheva 2022 defined remission as a total Mayo score ≤ 2 and endoscopic score 0 or 1. Fujimori 2009 and Hallert 1991 did not provide a definition of remission.

Five studies reported baseline disease activity as mild to moderate based on Rachmilewitz index (Casellas 2007), Simple Clinical Colitis Activity Index (SCCAI) score (Gravesen 2016), Truelove and Witts score (Kanauchi 2002), Ulcerative Colitis Disease Activity Index (UCDAI) (Morse 2010), or total Mayo score (Valcheva 2019).

Baseline disease activity was not reported in Facchin 2020.

Disease duration

Casellas 2007 reported a median disease duration of 7.4 years in the prebiotic arm and 6 years in the placebo arm. Fujimori 2009 reported mean disease duration of 7.5 years in the prebiotic arm, 7.8 years in the probiotic arm, and 8.3 years in the synbiotic (probiotic plus prebiotic) arm. Hallert 1991 (cross-over trial) reported a mean disease duration of 11 years for all participants. Kanauchi 2002 reported a mean disease duration of 8.5 years in the prebiotic arm and 9.6 years in the control arm.

Five studies did not report disease duration (Facchin 2020; Gravesen 2016; Morse 2010; Valcheva 2019; Valcheva 2022).

Location of disease

In the studies that reported disease location, 132 participants had pancolitis; 103 had left-sided colitis; 44 had proctitis; 1 had proctosigmoiditis; and location was unknown for 12 participants (Casellas 2007; Facchin 2020; Fujimori 2009; Hallert 1991; Gravesen 2016; Valcheva 2019; Valcheva 2022).

Two studies did not report location of disease (Kanauchi 2002; Morse 2010).

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Age

Morse 2010 did not report participant age at baseline. Mean or median participant age was reported in all other studies and ranged from 35 to 51 years.

Conflicts of interest

Casellas 2007, Facchin 2020, and Valcheva 2019 reported that they received funding or material support from manufacturers of the interventions being studied.

Gravesen 2016 and Valcheva 2022 reported funding sources unrelated to the interventions being studied, and the authors declared that they had no conflicts of interest.

Funding sources or conflicts of interest were not reported in Fujimori 2009, Hallert 1991, Kanauchi 2002, or Morse 2010.

Excluded studies

We excluded seven studies for the following reasons:

- wrong study design (Ryan 2021);
- wrong study intervention (Copaci 2000; Fernandez-Barrarez 1999; Hafer 2007; Langhorst 2012; Nyman 2020; Seidner 2005).

Risk of bias in included studies

A risk of bias summary is displayed in Figure 2. We contacted study authors or sponsors for clarification of any unclear judgements.

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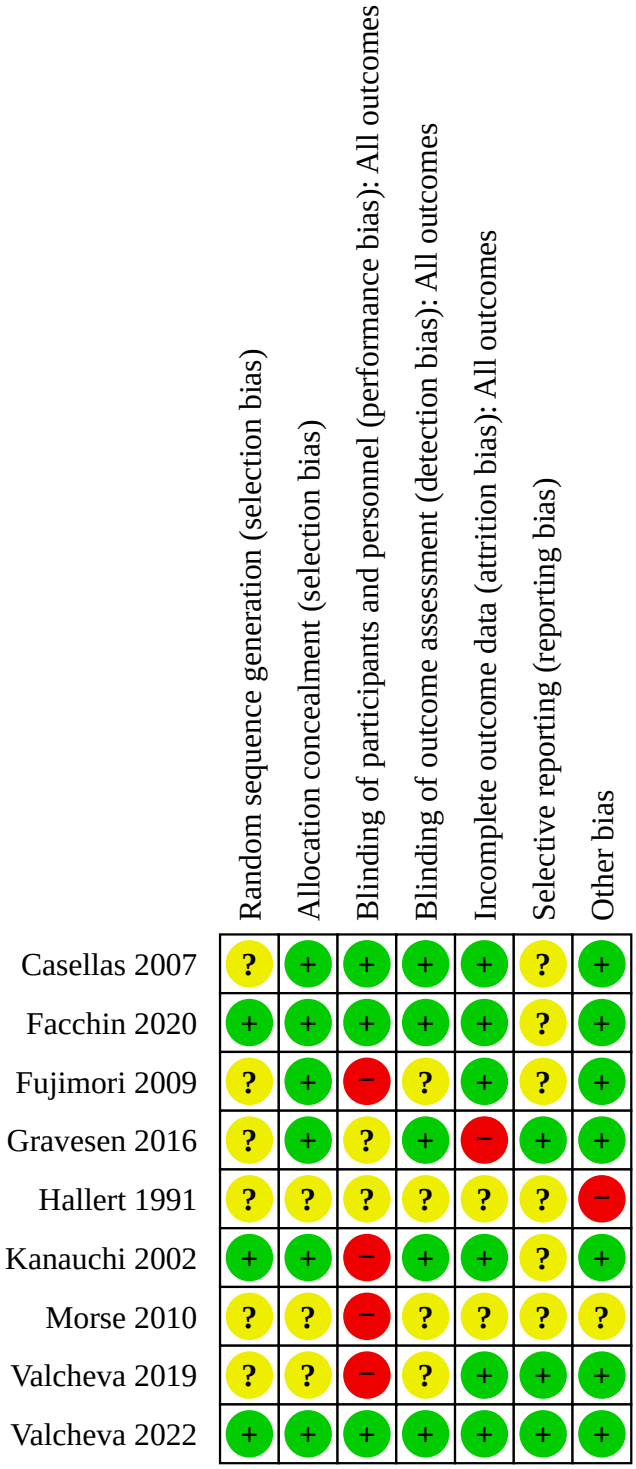
Figure 2. Risk of bias summary.



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Allocation

Randomisation

Three studies provided enough information about randomisation to be judged at low risk of bias (Facchin 2020; Kanauchi 2002; Valcheva 2022). We assessed the remaining six studies as at unclear risk (Casellas 2007; Fujimori 2009; Gravesen 2016; Hallert 1991; Morse 2010; Valcheva 2019).

Allocation

Six studies provided enough information on allocation concealment to be judged at low risk of bias (Casellas 2007; Facchin 2020; Fujimori 2009; Gravesen 2016; Kanauchi 2002; Valcheva 2019). We assessed the other three studies as at unclear risk (Hallert 1991; Morse 2010; Valcheva 2019).

Blinding

Performance bias

We assessed three studies as at low risk of performance bias (Casellas 2007; Facchin 2020; Valcheva 2022). We assessed two studies as at unclear risk of performance bias (Gravesen 2016; Hallert 1991). Four studies were open-label and were therefore judged to be at high risk of performance bias (Fujimori 2009; Kanauchi 2002; Morse 2010; Valcheva 2019).

Detection bias

Five studies provided enough information to be judged at low risk of detection bias (Casellas 2007; Facchin 2020; Gravesen 2016; Kanauchi 2002; Valcheva 2022). We assessed four studies as at unclear risk of detection bias (Fujimori 2009; Hallert 1991; Morse 2010; Valcheva 2019).

Incomplete outcome data

We judged six studies to be at low risk of attrition bias (Casellas 2007; Facchin 2020; Fujimori 2009; Kanauchi 2002; Valcheva 2019; Valcheva 2022). We judged two studies as at unclear risk of attrition bias (Hallert 1991; Morse 2010). We assessed one study as at high risk of attrition bias (Gravesen 2016).

Selective reporting

We judged three studies as at low risk of reporting bias (Gravesen 2016; Valcheva 2019; Valcheva 2022). We judged the remaining six studies as at unclear risk of reporting bias (Casellas 2007; Facchin 2020; Fujimori 2009; Hallert 1991; Kanauchi 2002; Morse 2010).

Other potential sources of bias

We judged seven studies as at low risk of other bias (Casellas 2007; Facchin 2020; Fujimori 2009; Gravesen 2016; Kanauchi 2002; Valcheva 2019; Valcheva 2022). We judged one study as at unclear risk of other bias (Morse 2010). One cross-over study allowed participants who were feeling worse during either test period to switch to the next test period, and was therefore judged to have a high risk of other bias (Hallert 1991).

Effects of interventions

See: **Summary of findings 1** Prebiotics compared to placebo for induction of remission; **Summary of findings 2** Inulin and oligofructose 15 g compared to inulin and oligofructose 7.5 g daily for induction of remission; **Summary of findings 3** Prebiotics and anti-inflammatory therapy compared to anti-inflammatory therapy for induction of remission; **Summary of findings 4** Prebiotics compared to placebo for maintenance of remission; **Summary of findings 5** Prebiotics compared to probiotics for maintenance of remission; **Summary of findings 6** Prebiotics compared to synbiotics for maintenance of remission

Prebiotics versus placebo for induction of remission

Two studies compared prebiotics with placebo for induction of remission in ulcerative colitis (Casellas 2007; Gravesen 2016).

Primary outcomes

Clinical remission

One study compared the rate of clinical remission in participants taking prebiotics to participants taking placebo (Casellas 2007). The rate of clinical remission was 7/10 for participants taking prebiotics compared to 6/9 for participants taking placebo (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.57 to 1.94; Analysis 1.1; Summary of findings 1). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Secondary outcomes

Disease improvement

Disease improvement: clinical activity scale

One study compared clinical activity measured by Rachmilewitz index in participants taking prebiotics to participants taking placebo (Casellas 2007). There was a mean difference of −0.40 (95% CI −2.67 to 1.87, Analysis 1.2; Summary of findings 1). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Gravesen 2016 reported SCCAI by individual participant number but not by treatment arm, therefore the results could not be included in the meta-analysis.

Disease improvement: biochemical markers of inflammation

One study compared faecal calprotectin score in participants taking prebiotics to participants taking placebo (Casellas 2007). There was a mean difference of −2529.00 (95% CI −6925.38 to 1867.38, Analysis 1.3; Summary of findings 1). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

One study compared interleukin-8 (IL-8) concentration in rectal dialysis samples in participants taking prebiotics to participants taking placebo (Casellas 2007). There was a mean difference of −2.10 (95% CI −4.93 to 0.73, Analysis 1.4; Summary of findings 1). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

One study compared prostaglandin E2 (PGE-2) concentration in rectal dialysis samples in participants taking prebiotics to participants taking placebo (Casellas 2007). There was a mean difference of −4.40 (95% CI −20.25 to 11.45, Analysis 1.5; Summary of findings 1). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Disease improvement: quality of life score

Gravesen 2016 reported Inflammatory Bowel Disease Questionnaire (IBDQ) by individual participant number but not by

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treatment arm, therefore the results could not be included in the meta-analysis.

Escalation of therapy

Neither study reported escalation of therapy.

Adverse events

Number of adverse events

Neither study reported the overall rate of adverse events in participants taking prebiotics versus participants taking placebo.

Withdrawals due to adverse events

Both studies compared the rate of withdrawals due to adverse events in participants taking prebiotics to participants taking placebo (Casellas 2007; Gravesen 2016). The rate of withdrawals due to adverse events was 5/18 for participants taking prebiotics compared to 1/13 for participants taking placebo (RR 2.73, 95% CI 0.51 to 14.55, Analysis 1.6; Summary of findings 1). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Inulin and oligofructose 15 g versus inulin and oligofructose 7.5 g for induction of remission

Two studies compared inulin and oligofructose 15 g with inulin and oligofructose 7.5 g for induction of remission in ulcerative colitis (Morse 2010; Valcheva 2019).

Primary outcomes

Clinical remission

One study compared the rate of clinical remission in participants taking inulin and oligofructose 15 g to participants taking inulin and oligofructose 7.5 g (Valcheva 2019). The rate of clinical remission was 8/15 for participants taking inulin and oligofructose 15 g compared to 2/16 for participants taking inulin and oligofructose 7.5 g (RR 4.27, 95% CI 1.07 to 16.96, Analysis 2.1; Summary of findings 2). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Morse 2010 reported remission rates for all study participants but did not report results separately for the two treatment arms, therefore this information could not be included in the meta-analysis.

Secondary outcomes

Disease improvement

Disease improvement: clinical activity scale

One study compared the rate of clinical response measured by Mayo score in participants taking inulin and oligofructose 15 g to participants taking inulin and oligofructose 7.5 g (Valcheva 2019). The rate of clinical response was 10/15 for participants taking inulin and oligofructose 15 g compared to 4/16 for participants taking inulin and oligofructose 7.5 g (RR 2.67, 95% CI 1.06 to 6.70, Analysis 2.2; Summary of findings 2). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Morse 2010 reported the rate of disease improvement for all study participants (8/24), but did not report results separately for the two treatment arms or the definition of disease improvement. Consequently, these results could not be included in the meta-analysis. Morse 2010 also reported average decrease in UCDAI score by treatment arm (2.9 for inulin and oligofructose 15 g versus 0.75 for inulin and oligofructose 7.5 g). However, the study did not include participant numbers or a measure of variability, therefore these data could not be included in the meta-analysis.

Disease improvement: biochemical markers of inflammation

Neither study reported disease improvement by biochemical markers of inflammation.

Disease improvement: quality of life score

Neither study reported disease improvement by quality of life score.

Escalation of therapy

Neither study reported escalation of therapy.

Adverse events

Number of adverse events

One study compared the rate of adverse events in participants taking inulin and oligofructose 15 g to participants taking inulin and oligofructose 7.5 g (Valcheva 2019). The rate of adverse events was 8/15 for participants taking inulin and oligofructose 15 g compared to 5/16 for participants taking inulin and oligofructose 7.5 g (RR 1.71, 95% CI 0.72 to 4.06, Analysis 2.3; Summary of findings 2). No serious adverse events were reported. We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Withdrawals due to adverse events

One study compared the rate of withdrawals due to adverse events in participants taking inulin and oligofructose 15 g to participants taking inulin and oligofructose 7.5 g (Valcheva 2019). The rate of withdrawals due to adverse events was 2/15 for participants taking inulin and oligofructose 15 g compared to 4/16 for participants taking inulin and oligofructose 7.5 g (RR 0.53, 95% CI 0.11 to 2.50, Analysis 2.4; Summary of findings 2). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Morse 2010 reported the rate of withdrawals due to adverse events for all study participants (6/24) but did not report results separately for the two treatment arms, therefore this information could not be included in the analysis.

Prebiotics and anti-inflammatory therapy versus anti-inflammatory therapy for induction of remission

One study compared prebiotics and anti-inflammatory therapy with anti-inflammatory therapy alone for induction of remission in ulcerative colitis (Kanauchi 2002).

Primary outcomes

Clinical remission

Kanauchi 2002 did not report the rate of clinical remission in participants treated with prebiotics and anti-inflammatory therapy or anti-inflammatory therapy.

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Secondary outcomes

Disease improvement

Disease improvement: clinical activity scale

One study compared clinical activity measured by Lichtiger index in participants taking prebiotics and anti-inflammatory therapy to participants taking anti-inflammatory therapy (Kanauchi 2002). There was a mean difference of −4.10 (95% CI −8.14 to −0.06, Analysis 3.1; Summary of findings 3). The results were presented as a chart, and the numerical data are therefore approximate. We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Disease improvement: biochemical markers of inflammation

One study compared serum C-reactive protein (CRP) concentration in participants taking prebiotics and anti-inflammatory therapy to participants taking anti-inflammatory therapy (Kanauchi 2002). There was a mean difference of 0.05 (95% CI −0.37 to 0.47, Analysis 3.2; Summary of findings 3). The results were presented as a chart, and the numerical data are therefore approximate. We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Disease improvement: quality of life score

Kanauchi 2002 did not report disease improvement by quality of life score.

Escalation of therapy

Kanauchi 2002 did not report escalation of therapy.

Adverse events

Number of adverse events

Kanauchi 2002 did not report the number of adverse events.

Withdrawals due to adverse events

Kanauchi 2002 did not report the rate of withdrawals due to adverse events in the intervention group.

Prebiotics versus placebo for maintenance of remission

Three studies compared prebiotics with placebo for maintenance of remission (Facchin 2020; Hallert 1991; Valcheva 2022). Facchin 2020 was a study on the effect of a preparation of an SCFA, butyrate, delivered to the colon.

Primary outcomes

Clinical relapse

One study compared the rate of clinical relapse in participants taking prebiotics to participants taking placebo (Valcheva 2022). The rate of clinical relapse was 19/43 for participants prebiotics compared to 10/46 for participants taking placebo (RR 1.36, 95% CI 0.79 to 2.31, Analysis 4.1; Summary of findings 4). There may be no difference in rate of clinical relapse between prebiotics and placebo. The evidence was of low certainty due to very serious imprecision.

Facchin 2020 and Hallert 1991 did not report rate of clinical relapse.

Secondary outcomes

Disease improvement

Disease improvement: clinical activity scale

One study compared partial Mayo score in participants taking a butyrate preparation to participants taking placebo (Facchin 2020). There was a mean difference of −1.20 (95% CI −2.17 to −0.22, Analysis 4.2; Summary of findings 4). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Disease improvement: biochemical markers of inflammation

One study compared faecal calprotectin score in participants taking a butyrate preparation to participants taking placebo (Facchin 2020). There was a mean difference of −89.79 (95% CI −221.30 to 41.72, Analysis 4.3; Summary of findings 4). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Disease improvement: quality of life score

One study compared total IBDQ score in participants taking a butyrate preparation to participants taking placebo (Facchin 2020). There was a mean difference of 5.50 (95% CI −8.94 to 19.94, Analysis 4.4; Summary of findings 4). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Hallert 1991 reported disease improvement parameters for the whole trial but did not report separate data for the first trial period (pre-cross-over). Consequently, the data could not be included in the meta-analysis.

Valcheva 2022 did not report any disease improvement parameters.

Escalation of therapy

No study reported escalation of therapy.

Adverse events

Number of adverse events

One study compared the number of adverse events in participants taking prebiotics to participants taking placebo (Valcheva 2022). The number of adverse events was 33/43 for participants taking prebiotics compared to 21/46 for participants taking placebo (RR 1.68, 95% CI 1.18 to 2.40, Analysis 4.5; Summary of findings 4). No serious adverse events were reported. Prebiotics may lead to more adverse events than placebo. The evidence was of low certainty due to very serious imprecision.

Facchin 2020 and Hallert 1991 did not report the overall rate of adverse events in participants taking prebiotics versus participants taking placebo.

Withdrawals due to adverse events

Two studies compared the rate of withdrawals due to adverse events in participants taking prebiotics/butyrate preparation to participants taking placebo (Facchin 2020; Valcheva 2022). The rate of withdrawals due to adverse events was 8/62 for participants taking prebiotics compared to 7/63 for participants taking placebo (RR 2.57, 95% CI 1.15 to 5.73, Analysis 4.6; Summary of findings 4). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

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The subgroup analysis between prebiotics and SCFAs did not suggest any differences from the main analysis (Analysis 4.6).

Hallert 1991 reported withdrawals due to adverse events for the whole trial (11/36) but did not report treatment arm for all withdrawals or provide pre-cross-over data. Consequently, these data could not be included in the analysis.

Prebiotics versus synbiotics for maintenance of remission

One study compared prebiotics with synbiotics for maintenance of remission (Fujimori 2009).

Primary outcomes

Clinical relapse

Fujimori 2009 did not report the rate of clinical relapse in participants taking prebiotics or synbiotics.

Secondary outcomes

Disease improvement

Disease improvement: clinical activity scale

Fujimori 2009 did not report disease improvement by clinical activity scale.

Disease improvement: biochemical markers of inflammation

Fujimori 2009 did not report disease improvement by biochemical markers of inflammation.

Disease improvement: quality of life score

Fujimori 2009 compared total IBDQ score in participants taking prebiotics to participants taking synbiotics. There was a mean difference of 6.30 (95% CI −6.61 to 19.21, Analysis 5.1; Summary of findings 5). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Fujimori 2009 compared scores for different components of the IBDQ in participants taking prebiotics to participants taking synbiotics, as follows.

- For the bowel component, the mean difference was 1.30 (95% CI −2.65 to 5.25, Analysis 5.2). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.
- For the systemic component, the mean difference was 1.00 (95% CI −1.49 to 3.49, Analysis 5.3). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.
- For the emotional component, the mean difference was 2.60 (95% CI −3.16 to 8.36, Analysis 5.4). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.
- For the social component, the mean difference was 1.30 (95% CI −1.42 to 4.02, Analysis 5.5). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Fujimori 2009 also reported disease improvement in terms of serum CRP concentration. However, this was only reported for a subgroup of participants and therefore could not be included in the analysis.

Escalation of therapy

Fujimori 2009 did not report escalation of therapy.

Adverse events

Number of adverse events

Fujimori 2009 did not report the number of adverse events in participants taking prebiotics versus those taking synbiotics. The study states that there were no adverse events related to blood variables (measured in only a subset of participants), but overall adverse events were not reported.

Withdrawals due to adverse events

Fujimori 2009 compared the rate of withdrawals due to adverse events in participants taking prebiotics to participants taking synbiotics. The rate of withdrawals due to adverse events was 9/40 for participants taking prebiotics compared to 8/40 for participants taking synbiotics (RR 1.13, 95% CI 0.48 to 2.62, Analysis 5.6; Summary of findings 5). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Prebiotics versus probiotics for maintenance of remission

One study compared prebiotics with probiotics for maintenance of remission (Fujimori 2009).

Primary outcomes

Clinical relapse

Fujimori 2009 did not report the rate of clinical relapse in participants taking prebiotics or probiotics.

Secondary outcomes

Disease improvement

Disease improvement: clinical activity scale

Fujimori 2009 did not report disease improvement by clinical activity scale.

Disease improvement: biochemical markers of inflammation

Fujimori 2009 did not report disease improvement by biochemical markers of inflammation.

Disease improvement: quality of life scores

Fujimori 2009 compared IBDQ score in participants taking prebiotics to participants taking probiotics. There was a mean difference of 13.60 (95% CI 1.22 to 25.98, Analysis 6.1; Summary of findings 6). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Fujimori 2009 compared scores for different components of the IBDQ in participants taking prebiotics to participants taking probiotics, as follows.

- For the bowel component, the mean difference was 5.70 (95% CI 1.48 to 9.92, Analysis 6.2). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.
- For the systemic component, the mean difference was 1.10 (95% CI −1.18 to 3.38, Analysis 6.3). We could draw no conclusions

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as the evidence was of very low certainty due to very serious imprecision and risk of bias.

- For the emotional component, the mean difference was 4.30 (95% CI −1.40 to 10.00, Analysis 6.4). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.
- For the social component, the mean difference was 2.50 (95% CI 0.34 to 4.66, Analysis 6.5). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

Fujimori 2009 also reported disease improvement in terms of serum CRP concentration. However, this was only reported for a subgroup of participants and therefore could not be included in the analysis.

Escalation of therapy

Fujimori 2009 did not report escalation of therapy.

Adverse events

Number of adverse events

Fujimori 2009 did not report the number of adverse events in participants taking prebiotics versus those taking probiotics. The study states that there were no adverse events related to blood variables (measured in only a subset of participants), but overall adverse events were not reported.

Withdrawals due to adverse events

Fujimori 2009 compared the rate of withdrawals due to adverse events in participants taking prebiotics to participants taking probiotics. The rate of withdrawals due to adverse events was 9/40 for participants taking prebiotics compared to 9/40 for participants taking probiotics (RR 1.00, 95% CI 0.44 to 2.26, Analysis 6.6; Summary of findings 6). We could draw no conclusions as the evidence was of very low certainty due to very serious imprecision and risk of bias.

DISCUSSION

Summary of main results

We included 9 RCTs with a total of 445 participants in the review. Study duration ranged from 14 days to 2 to 3 months for induction and 1 to 6 months for maintenance of remission. Trials of one-month duration for maintenance of remission may have minimal clinical significance for an incurable lifelong condition.

All studies were on adults. Five studies were on people with mild to moderate active disease, three on people in remission or with mild activity, and one study did not provide this information.

Two studies compared prebiotics with placebo for induction of remission. We cannot draw any conclusions about clinical remission, clinical improvement, faecal calprotectin levels, IL-8 levels, PGE-2 levels, or withdrawals due to adverse events. All evidence was of very low certainty. No other outcomes were reported.

Two studies compared inulin and oligofructose 15 g with inulin and oligofructose 7.5 g for induction of remission. We cannot draw any conclusions about clinical remission, clinical improvement, total adverse events, or withdrawals due to adverse events. All evidence was of very low certainty. No other outcomes were reported.

One study compared prebiotics and anti-inflammatory therapy with anti-inflammatory therapy alone for induction of remission. We cannot draw any conclusions about clinical improvement or serum CRP levels. All evidence was of very low certainty. No other outcomes were reported.

Three studies compared prebiotics with placebo for maintenance of remission. There may be no difference between prebiotics and placebo in rate of clinical relapse, and prebiotics may lead to more total adverse events than placebo. The evidence was of low certainty. We cannot draw any conclusions about clinical improvement, faecal calprotectin levels, quality of life, or withdrawals due to adverse events. The evidence for these outcomes was of very low certainty. No other outcomes were reported.

One study compared prebiotics with synbiotics for maintenance of remission. We cannot draw any conclusions about quality of life or withdrawals due to adverse events. All evidence was of very low certainty. No other outcomes were reported.

One study compared prebiotics with probiotics for maintenance of remission. We cannot draw any conclusions about quality of life or withdrawals due to adverse events. All evidence was of very low certainty. No other outcomes were reported.

Overall completeness and applicability of evidence

The evidence is incomplete in a number of ways. The lack of clear consensus on the role of prebiotics is evident in the variety of contexts of primary studies. This includes the use of prebiotics combined with probiotics or in isolation, in addition to all range of therapies or head-to-head with other dietary measures.

Given the lack of homogeneity across all clinical and methodological facets of this evidence base, applicability is limited.

Of note was the range of prebiotics, which further compounds the complexity and limits the utility of the evidence to practice.

Finally, the sample size of trials has resulted in issues with precision in most of the GRADE assessments in this review. This is a pervasive issue within the field (Iheozor-Ejiofor 2021), with a need for adequate sample size calculations using published resources (Gordon 2021).

Quality of the evidence

We thoroughly reviewed the included studies for quality and risk of bias. We judged only one study as at low risk of bias in all areas.

The GRADE assessments were predominately very low certainty, with only an occasional low-certainty judgement. The impact of risk of bias was pervasive, but imprecision was also a key factor impacting the certainty of the evidence produced. This was exacerbated by the methodological and clinical heterogeneity issues mentioned above that did not appear purposeful or related to planned study of specific populations or treatments. As such, this has reduced the overall certainty of evidence further.

Reporting of adverse events was also very sparse and was reflected in the GRADE assessments.

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Potential biases in the review process

Lack of information to judge risk of bias was common, as discussed above. The review team considered it prudent to reach out to primary authors to request clarification or additional information; however, many did not respond, and as such, judgements were based on information from the published studies.

We aim to include data that may become available in future updates, but this could represent a source of bias in the review, with three ongoing studies identified in the review process. Conversely, the use of such unpublished data can also be seen as a source of bias.

We are aware of the possibility of industry funding affecting the validity of the results. Funding from manufacturing companies or any conflicts of interests from both primary studies and the review team have been reported.

Agreements and disagreements with other studies or reviews

Major international guidelines do not discuss the role of prebiotics in inflammatory bowel disease (Feuerstein 2020; Raine 2022). The 2019 UK guidelines discuss prebiotics but make no recommendation for their use (Lamb 2019).

AUTHORS' CONCLUSIONS

Implications for practice

There may be no difference in the occurrence of clinical relapse when adjuvant treatment with prebiotics is compared with adjuvant treatment with placebo for maintenance of remission in ulcerative colitis. Adjuvant treatment with prebiotics may result in more total adverse events when compared to adjuvant treatment with placebo in maintenance of remission. We could draw no conclusions for any other outcomes for this comparison due to the very low certainty of the evidence. The evidence for all other comparisons and outcomes was also of very low certainty, and no conclusions can be drawn.

Implications for research

It is difficult to make any clear recommendations for future research based on the findings of this review.

The evidence has demonstrated major issues with clinical and methodological heterogeneity that reflect a lack of consensus among the core researching community regarding the role of prebiotics, the combinations of therapy, the specific prebiotics to use, or the doses of these prebiotics.

It is recommended that a consensus is reached on these issues prior to any further research. This will ensure future studies are focused on these areas of interest and will enhance certainty in these areas.

Within all such studies, reporting in a manner that is consistent with clarity for risk of bias judgements is vital.

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Editorial contributions

Cochrane Gut supported the authors in the development of this systematic review. The following people conducted the editorial process for this article.

- **Sign-off Editor** (final editorial decision): Grigorios Leontiadis, McMaster University, Canada; **Managing Editor** (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Marwah Anas El-Wegoud, Cochrane Central Editorial Service; **Information Scientist**: Farhad Shokraneh, Systematic Review Consultants LTD, UK; **Editorial Assistant** (conducted editorial policy checks and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service; **Copy Editor** (copy editing and production): Lisa Winer, Cochrane Central Production Service.
- **Peer reviewers** (provided comments and recommended an editorial decision): David R Mack MD, FRCPC (**clinical review**); Jordan Axelrad, MD, MPH, NYU Grossman School of Medicine (**clinical review**); Dr Kevan Jacobson, MBBCh, FRCPC, FCP, AGAF Professor of Pediatrics, Head, Division of Gastroenterology, Hepatology and Nutrition Senior Clinician Scientist, British Columbia's Children's Hospital and British Columbia Children's Hospital Research Institute University of British Columbia (**clinical review**); Alysia De Nino, MPH (**consumer review**); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (**methods review**); Steve McDonald, Cochrane Australia (**search review**). One additional peer reviewer provided clinical peer review but chose not to be publicly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Casellas 2007

Study characteristics	
Methods	**Study design and number of study arms** Randomised, double-blind, controlled study. 2 arms **Single-centre or multicentre?** Single centre **Countries** Spain **Study chronology** 12 months **Setting** Outpatient/inpatient **Trial registration number** NR
Participants	**Inclusion criteria** Age 18 to 75, diagnosed with UC by colonoscopy and histology, presented with mild to moderate disease according to Rachmilewitz index, score > 6 and < 19

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Casellas 2007 *(Continued)*

Exclusion criteria

Pregnancy or breastfeeding, severe concomitant disease involving the liver, heart, lungs or kidneys, known allergy or hypersensitivity to mesalazine, inulin, or oligofructose, and treatment with azathioprine, cyclosporin, or antibiotics during the previous 4 weeks

Induction or maintenance

Induction

Baseline clinical disease activity

Mild to moderate. Rachmilewitz index (median and range): IG 8.9 ± 0.52; CG 8.3 ± 0.37

Baseline endoscopic disease activity per IG/CG

NR

Baseline disease characteristics, per IG/CG

Location of disease

IG: Total = 3. Left sided = 2. Proctitis = 5. CG: Total = 3. Left sided = 3. Proctitis = 3 (n)

Duration or length of disease since diagnosis

IG: 89 (17 to 164). CG: 72 (36 to 84) Median and range (months)

Concomitant medicines

IG mesalazine (n = 1); CG no medications at baseline. On study entry, all participants were prescribed oral mesalazine (1 g, 3 times daily) and a low-fibre diet.

Diet information

NR

IF induction study: length of active disease per IG/CG

NR

IF maintenance study: how was remission achieved? Duration of remission per IG/CG

NA

Age at beginning of study per IG/CG

IG 37 (30 to 40); CG 36 (29 to 44) Median and range (years)

Sex (m/f) per IG/CG (numbers of participants)

IG 2/8; CG 4/5

Smoking per IG/CG

IG 1/3/6; CG 0/5/4 Y/N/former (n)

Number randomised per IG/CG

IG 10; CG 9 (n)

Number reaching end of study per IG/CG (numbers of participants)

IG 7; CG 8 (n)

(IG: 1 participant returned all the sachets of study product the day after signing the consent form and did not provide the initial faecal sample; 1 participant reported worsening of their disease condition af-

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Casellas 2007 *(Continued)*

	ter taking the trial product and voluntarily stopped the intake during the first week; 1 participant abandoned the trial after the visit on day 7 by indication of the physician for increase of 4 points in the Rachmilewitz score (from 10 to 14) CG: 1 participant reported worsening of their disease condition after taking the trial product and voluntarily stopped the intake during the first week)
Interventions	**IG regimen, dosage** Oral Beneo Synergy 1, 4 g, 3 times daily. Beneo Synergy 1 (Orafti, Tienen, Belgium) consists of a selected combination of long-inulin chains together with the shorter oligofructose chains (oligofructose-enriched inulin), both obtained from the chicory root. **CG regimen, dosage** Oral maltodextrin, 4 g, 3 times daily **Duration of study** 14 days **Measurement time points during study** Day 0, 7, 14 **Any follow-up measurements after study end? If yes, what time points?** NR
Outcomes	**Primary trial outcomes as defined by study authors** Anti-inflammatory effect as determined by reduction of calprotectin and human DNA in faeces **Secondary trial outcomes as defined by study authors** None defined. Other reported endpoints were change in: Rachmilewitz index (physician-scored); concentration of IL-8 and PGE-2 in rectal dialysis fluid; dyspepsia-related health scores (patient-rated).
Notes	**Funding source** This work was supported in part by grants from Generalitat de Catalunya (RE: 2001SGR00389), an Instituto de Salud Carlos III (Ciberehd, Spain) and Orafti (Tienen, Belgium). **Conflicts of interest** Authors declared no conflicts.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors state that allocation 'randomly assigned' but do not state how. Authors contacted for clarification.
Allocation concealment (selection bias)	Low risk	Interventions were supplied in coded packets and clinicians, participants and lab staff were unaware of assigned product
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors state that interventions were supplied in coded packets and clinicians, participants and lab staff were unaware of assigned product

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Casellas 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Authors state that clinicians, participants and lab staff were unaware of assigned product
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients abandoned the trial before the first visit at day 7. One patient in the test group returned all the sachets of study product the day after signing the consent form and did not provide the initial faecal sample. He had proctitis with a clinical score of 7. Two patients (one test and one placebo) referred worsening of their disease condition after taking the trial product and voluntarily stopped the intake during the first week. The patient in the test group had proctitis, initial clinical score of 10, and faecal calprotectin of 3816 lg/g at day 0. The patient in the placebo group had history of pancolitis, initial score of 9 and faecal calprotectin of 5092 lg/g at day 0. Another patient in the test group abandoned the trial after the visit on day 7 by indication of the physician for increase of 4 points in the Rachmilewitz score (from 10 to 14; left-sided colitis; faecal calprotectin went up from 1436 to 2529 lg/g). Thus, data for analysis at day 0 include nine test and nine placebo patients, at day 7, eight test and eight placebo patients, and at day 14, seven test and eight placebo patients.
Selective reporting (reporting bias)	Unclear risk	All outcome measures stated in the methodolgy were reported except for IBD related quality of life questionarres, for which the authors state "Scores of IBD-related quality of life increased in both groups, suggesting an improvement of quality of life, but changes did not reach statistical significance (data not shown)." Some data was defined as significant but this was compared to baseline not compared to CG. On study entry, patients were prescribed oral mesalazine (1 g, three times daily), and low fibre diet, so cannot ascribe effects to IG. No safety data reported. Protocol mentioned but no details or trial registration presented. Authors contacted for clarification.
Other bias	Low risk	Baseline data balanced. No other concerns

Facchin 2020

Study characteristics	
Methods	**Study design and number of study arms** Randomised, double-blind, placebo-controlled; 2 arms **Single-centre or multicentre?** Single **Countries** Italy **Study chronology** May 2017 to May 2018 **Setting**

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Facchin 2020 *(Continued)*

NR

Trial registration number

The study was approved by the Regional Ethical Committee for Clinical Trials (n. 4049/AO/17).

Participants	**Inclusion criteria** Consecutive patients, aged > 18 years, with histologically confirmed diagnosis of CD or UC in the last 6 months and undergoing follow-up colonoscopy **Exclusion criteria** Prior proctocolectomy; presence of IBD extraintestinal manifestation; treatment with antibiotics in the last 60 days; extensive surgical resection; presence of stoma **Induction or maintenance** NR, but mixed active and inactive disease on baseline endoscopic Mayo score **Baseline clinical disease activity per IG/CG** NR **Baseline endoscopic disease activity per IG/CG** Endoscopic Mayo score at baseline in UC cohort who completed study(n) (data NR for participants randomised) 0: IG 7; CG 7 1: IG 4; CG 4 2: IG 3; CG 2 3: IG 0; CG 3 **Baseline disease characteristics, per IG/CG** *Location of disease* Baseline location for UC cohort who completed study (n) (data NR for participants randomised) E1 (proctitis): IG 1; CG 1 E2 (left-sided): IG 6; CG 7 E3 (pancolitis): IG 7; CG 8 *Duration or length of disease since diagnosis (months)* NR **Concomitant medicines** NR for UC cohort separately, but participants continued their current therapy For combined UC and CD cohorts who completed study: biologics: IG: 8 CG: 12; 5-ASA IG: 20 CG: 25; probiotics (ECN) IG: 2 CG: 2; steroids IG: 1 CG: 6; immunosuppressant IG: 3 CG: 3; PPI IG: 1 CG: 6 (n) Data NR for participants randomised. **Diet information** Participants were asked to continue their current therapy and diet. **IF induction study: length of active disease per IG/CG**

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Facchin 2020 *(Continued)*

	NR **IF maintenance study: how was remission achieved? Duration of remission per IG/CG** NR **Age at beginning of study per IG/CG** NR for UC cohort separately Baseline age for combined UC and CD cohort who completed study: median age (range) in years IG: 51(19 to 69); CG: 50 (25 to 73) Data NR for participants randomised. **Sex (m/f) per IG/CG (numbers of participants)** NR for UC cohort separately Baseline sex for combined UC and CD cohort who completed study: male, n, % CG: 21, 75% IG: 15, 71.4% Data NR for participants randomised. **Smoking per IG/CG** 2 smokers in UC cohort; treatment arm NR Baseline smoking status for combined UC and CD cohort who completed study: IG: 2 CG: 3 (n) Data NR for participants randomised. **Number randomised per IG/CG** UC cohort only (from data provided by authors upon request) IG: 19 CG: 17 **Number reaching end of study per IG/CG** UC cohort: IG: 14; CG: 16 (CD cohort: IG: 7; CG: 12) For combined UC and CD cohort: IG: 21 (1 did not receive allocated intervention due to hospitalisation; 2 lost to follow-up; 3 discontinued due to non-compliance (n = 1), taking antibiotics (n = 1), taking probiotics (n = 1); 1 excluded due to no PCR reaction on microbiota analysis) CG: 28 (1 lost to follow-up)
Interventions	**IG regimen, dosage** Oral formulation of sodium-butyrate (Butyrose Lsc Microcaps-EP2352386B1, BLM, Sila Srl), 3 capsules/d (1800 mg/d) during the main meals The study specifically uses a colonic release formulation of butyrate contained in a lipophilic microcapsule that provides extensive capacity for intestinal diffusion and allows absorption even in the distal portion of the colon. **CG regimen, dosage** 3 starch capsules per day with similar colour, flavour, and size

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Facchin 2020 *(Continued)*

	Duration of study 60 days **Measurement time points during study** Day 0, 60 **Any follow-up measurements after study end? If yes, what time points?** NR
Outcomes	**Primary trial outcomes as defined by study authors** Modulation of the gut microbial composition after butyrate treatment **Secondary trial outcomes as defined by study authors** The potential effect of butyrate on clinical activity, faecal calprotectin levels, and quality of life
Notes	**Funding source** This work was partially supported by the Department of Surgery, Oncology, and Gastroenterology, University of Padua (SID2016 MicroIBD). Drug and placebo were provided by SILA srl, Noale Venice, Italy. This study and post hoc analysis were supported by an unrestricted grant from Sila srl, Noale, VE. SF and CM were supported, respectively, by SID2016 MicroIBD and BIRD2018 Grants from University of Padua. MC was supported by a grant from the Italian Group of Inflammatory Bowel Disease. **Conflicts of interest** None declared (but study was partially funded by an unrestricted grant from the manufacturer of the intervention).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study coordinator generated the allocation sequence and enrolled the partcipants. After stratification by clinical assessment, colonoscopy, and fecal calprotectin (FC) levels, patients were randomized. Randomization was performed using a randomly generated computer sequence (www.randomizer.org). The assignment of patients was hidden and carried out by a non-nurse involved in the study.
Allocation concealment (selection bias)	Low risk	A nurse not involved in the study assigned particpants to interventions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double blind. Placebo had similar similar colour, flavor, and size to intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All the analysis as well as the clinical and microbiota assessment has been blindly performed to the condition of the patients and to the therapy/placebo assumed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low and reasons were provided. Flow chart presented in supplementary material shows some mismatch between IG and CG. 1 withdrawal in CG (lost to follow up) vs 7 withdrawals in IG (1 did not receive intervention, 1 lost to follow up, 3 discontinued - 1 for non-

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Facchin 2020 *(Continued)*

		compliance, 1 for antibiotics, 1 for taking probiotics - and 1 did not have PCR reaction). Authors provided withdrawal data for CD and UC cohort separately on request.
Selective reporting (reporting bias)	Unclear risk	Ethics approval mentioned; protocol provided by authors on request. Effect on systemic and intestinal inflammatory indices as assessed by CRP and FCP listed as one of the primary objectives of the trial but CRP results not reported. TEAEs and SAEs listed in protocol as evaluation criteria but not reported.
Other bias	Low risk	Baseline characteristics were balanced for CD and UC cohort combined but many baseline characteristcs NR for UC cohort alone.

Fujimori 2009

Study characteristics	
Methods	**Study design and number of study arms** Randomised, open-label, 3 arms **Single-centre or multicentre?** 2 centres: Main Hospital and Chiba Hokusou Hospital of Nippon Medical School **Countries** Japan **Study chronology** 3 months **Setting** Hospital/outpatient **Trial registration number** NR
Participants	**Inclusion criteria** Patients in remission or with mildly active UC without a history of operation for UC. UC diagnosed by established clinical, endoscopic, radiologic, and histologic criteria **Exclusion criteria** Patients with induction therapy for UC **Induction or maintenance** Maintenance **Baseline clinical disease activity per IG/CG** In remission or mildly active **Baseline endoscopic disease activity per IG/CG**

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Fujimori 2009 *(Continued)*

	NR **Baseline disease characteristics, per IG/CG** *Location of disease* CG 1 (probiotics): total colitis 16; left sided colitis 6; proctitis 3; unknown 6 (n) CG 2 (prebiotics): total colitis 12; left sided colitis 10; proctitis 5; unknown 4 (n) IG (synbiotics): total colitis 15; left sided colitis 8; proctitis 7; unknown 2 (n) *Duration or length of disease since diagnosis* Years, mean ± SD: CG 1: 7.8 ± 6.5; CG 2: 7.5 ± 5.6; IG: 8.3 ± 5.4 **Concomitant medicines** All participants were on stable doses of aminosalicylates and/or prednisolone for at least 4 weeks before enrolment and continued their individual regimens throughout the trial. The doses of aminosalicylates and prednisolone for UC treatment remained the same throughout the trial in all groups. **Diet information** NR **IF induction study: length of active disease per IG/CG** NA **IF maintenance study: how was remission achieved? Duration of remission per IG/CG** NR **Age at beginning of study per IG/CG** Mean (SD) CG 1: 36 ± 16; CG 2: 37 ± 13; IG: 35 ± 10 **Sex(m/f) per IG/CG** M/F CG 1: 11/20; CG 2: 14/17; IG: 14/18 (n) **Smoking per IG/CG** NR **Number randomised per IG/CG** CG 1: 40; CG 2: 40; IG: 40 (n) **Number reaching end of study per IG/CG** CG 1: 31; CG 2: 31; IG: 32 (n)
Interventions	**IG regimen, dosage** Oral probiotics (*Bifidobacterium longum* 2 x 10^9 colony-forming units/capsule) once a day PLUS oral prebiotics (4.0 g of psyllium dissolved in 100 mL of water) twice daily **CG regimen, dosage** CG 1: oral probiotics (*Bifidobacterium longum* 2 x 10^9 colony-forming units/capsule) once a day CG 2: oral prebiotics (4.0 g of psyllium dissolved in 100 mL of water) twice daily **Duration of study**

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Fujimori 2009 *(Continued)*

	4 weeks **Measurement time points during study** Baseline, week 2, week 4 **Any follow-up measurements after study end? If yes, what time points?** NR
Outcomes	**Primary trial outcomes as defined by study authors** Change in IBDQ was the only outcome measured. **Secondary trial outcomes as defined by study authors** None defined.
Notes	**Funding source** NR **Conflicts of interest** NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated. Authors contacted
Allocation concealment (selection bias)	Low risk	Allocation was conducted by Crohn and Colitis Japan, an independent organization of patients with IBD
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported. Requested confirmation from author.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow of all exclusions given with plausible reasons and no mismatch in dropouts between groups
Selective reporting (reporting bias)	Unclear risk	All outcome measures stated in the methodolgy were reported, but no safety data was reported. No protocol or trial registration reported. Authors contacted
Other bias	Low risk	Baseline characteristics all balanced. No other concerns

Gravesen 2016

Study characteristics

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Gravesen 2016 *(Continued)*

Methods	**Study design and number of study arms** Randomised double-blind, placebo-controlled trial. 2 arms **Single-centre or multicentre?** Single **Countries** Denmark **Study chronology** NR **Setting** Outpatient **Trial registration number** NR
Participants	**Inclusion criteria** Patients with active UC with an SCCAI score of 4 to 10. All participants were on stable-dose, oral treatment with 5-ASA for a minimum of 1 month before inclusion and throughout the studies. Stable dose of rectal 5-ASA was allowed. **Exclusion criteria** Use of steroids, patients with impaired renal or liver function, use of gluco-corticosteroids within 1 month prior to study entry or during study period, ileostomy, pregnancy, coeliac disease, and not being able to communicate in Danish **Induction or maintenance** Induction **Baseline clinical disease activity per IG/CG** IBDQ IG: 135 to 199 (158 to 199); CG: 133 to 196 (range)* SCCAI IG: 4 to 8 (4 to 8); CG: 4 to 10 (range)* *Data are estimated as intention-to-treat; data shown in brackets are per-protocol **Baseline endoscopic disease activity per IG/CG** NR **Baseline disease characteristics, per IG/CG** *Location of disease* Proctitis IG: 3 (2) CG: 1; proctosigmoiditis: IG: 1 (0) CG: 1; left sided colitis: IG: 2 (1) CG: 1; extensive colitis/pancolitis: IG: 2 (1) CG: 1 (n)* *Data are estimated as intention-to-treat; data shown in brackets are per-protocol *Duration or length of disease since diagnosis* NR **Concomitant medicines**

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Gravesen 2016 *(Continued)*

	Mesalazine: IG: 8 CG: 4 Data are estimated as intention-to-treat **Diet information** Unrestricted diet **IF induction study: length of active disease per IG/CG** NR **IF maintenance study: how was remission achieved? Duration of remission per IG/CG** NA **Age at beginning of study per IG/CG** IG: 23 to 54 (23 to 33); CG: 35 to 33 (range)* *Data are estimated as intention-to-treat; data shown in brackets are per-protocol **Sex (m/f) per IG/CG** IG: 4 (3)/4 (1) CG: 2/2 (n)* *Data are estimated as intention-to-treat; data shown in brackets are per-protocol **Smoking per IG/CG** NR **Number randomised per IG/CG** IG: 8; CG: 4 (n) **Number reaching end of study per IG/CG** IG: 4; CG: 4 (n)
Interventions	**IG regimen, dosage** 30 mL ispaghula husk powder per day mixed with food or a cold beverage for 2 or 3 months **CG regimen, dosage** 30 mL breadcrumb powder (placebo) per day mixed with food or a cold beverage for 2 or 3 months **Duration of study** 2 to 3 months **Measurement time points during study** 0, 2 months or 3 months **Any follow-up measurements after study end? If yes, what time points?** NA
Outcomes	**Primary trial outcomes as defined by study authors** Change in SCCAI and IBDQ **Secondary trial outcomes as defined by study authors**

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Gravesen 2016 *(Continued)*

	Change in total urinary 5-ASA excretion in participants with UC in relapse
Notes	**Funding source** Scholarship from Vibeke Binder and Poul Riis's Foundation. No funding from other sources **Conflicts of interest** None declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The author provided us with the study protocol which stated that the randomization process took via sealed envelopes containing notes with the text placebo or fiber. The protocol or published study do not report how distribution of the envelopes was randomised.
Allocation concealment (selection bias)	Low risk	Allocation concelament was done by using sealed envelopes with tinfoil to ensure blindness
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Manuscript states trial was double-blind. Patients received a box of Isphagula Husk or blended breadcrumbs and were directed to take an amount of 30 ml powder per day mixed with food or a cold beverage for 2 or 3 months. It is not clear if they tasted or smelled similar. The author responded "The blinding was not accurate (taste smell etc, but they were very similar. An experienced patient could probably break the code, but no one told us (they were asked at control visit)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The author confirmed that the outcome assessors were blind to the interventions.
Incomplete outcome data (attrition bias) All outcomes	High risk	4 patients were excluded (out of a total of only 12). All were in the IG leading to significant attrition imbalance. 1 was due to change in dose and 1 due to lack of efficacy. so could have significantly affected results. Other 2 never started treatment. Results were reported by patient number, but which patient number was in which treatment group was not reported The author could not provide further data.
Selective reporting (reporting bias)	Low risk	The author provided us with the study protocol. The prespecified outcomes were reported. Adverse events were not noted in the protocol but were collected. The author responded that "No side effects noted, that could be ascribed to the treatment."
Other bias	Low risk	Baseline characteristics balanced. No other concerns

Hallert 1991

Study characteristics

Methods	**Study design and number of study arms**

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Hallert 1991 *(Continued)*

	Randomised, double-blind, placebo-controlled cross-over study. 2 arms **Single-centre or multicentre?** Multicentre **Countries** Sweden **Study chronology** 6 months **Setting** Outpatient **Trial registration number** NR
Participants	**Inclusion criteria** Adults with histologically proven UC in remission reporting at least 3 of the following in the last week on questioning: abdominal pain, diarrhoea, loose stools when pain present, urgency when pain present, bloating, incomplete evacuation, mucus discharge, and constipation **Exclusion criteria** Acute colitis, difficulties in swallowing, mental instability, or unwillingness to participate or when requiring change in ongoing medication **Induction or maintenance** Maintenance **Baseline clinical disease activity per IG/CG** In remission clinically and sigmoidoscopically **Baseline endoscopic disease activity per IG/CG** In remission clinically and sigmoidoscopically **Baseline disease characteristics, per IG/CG** *Location of disease* Total colitis = 14; distal colitis = 14; proctitis = 8 (n) *Duration or length of disease since diagnosis* 11 years (1 to 28) Mean (range) **Concomitant medicines** 25 participants were receiving medication regularly, mostly sulfasalazine (70%). **Diet information** NR **IF induction study: length of active disease per IG/CG** NA

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Hallert 1991 *(Continued)*

	IF maintenance study: how was remission achieved? Duration of remission per IG/CG NR **Age at beginning of study per IG/CG** 43 years (20 to 75) Mean (range) **Sex (m/f) per IG/CG** 14/22 (n) **Smoking per IG/CG** NR **Number randomised per IG/CG** 36 (n) (cross-over study, so all participants received both interventions) **Number reaching end of study per IG/CG** 29 (n) (7 dropouts before the first assessment: 4 due to colitis relapse (3 while taking placebo and 1 while taking ispaghula); 1 due to increased abdominal pain (placebo); 2 due to non-compliance (treatment arm NR))
Interventions	**IG regimen, dosage** Lactose-free ispaghula husk (Vi-Siblin S granules, Parke-Davis) 4 g twice daily **CG regimen, dosage** Placebo (crushed crispbread) twice daily **Note**: this was a cross-over study, so all participants received both interventions. The test protocol allowed participants who were feeling worse during either test period to be switched to the next period or to leave the trial. **Duration of study** 4 months (2 months for each treatment period) **Measurement time points during study** Month 0, 2, 4 **Any follow-up measurements after study end? If yes, what time points?** NR
Outcomes	**Primary trial outcomes as defined by study authors** None defined. Change in symptoms based on an 8-item VAS were the only variables reported. **Secondary trial outcomes as defined by study authors** None defined.
Notes	**Funding source** NR **Conflicts of interest**

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Hallert 1991 *(Continued)*

	NR Note that this was a cross-over trial. The test protocol allowed participants who were feeling worse during either test period to be switched to the next period or to leave the trial. The authors report that some participants took ispaghula at a higher dose than specified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors state that the study was randomised but do not state the method used. Authors contacted.
Allocation concealment (selection bias)	Unclear risk	Not reported. Authors contacted.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors state the study was double-blind but do not state how the interventions were presented. Authors contacted.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors state the study was double-blind but do not state how the interventions were presented.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 7 withdrawals after randomisation and before the first assessment: 4 due to colitis relapse (3 while taking placebo and 1 while taking ispaghula); 1 due to increased abdominal pain (placebo); 2 due to non-compliance (treatment arm not reported, therefore unlcear risk) Authors contacted.
Selective reporting (reporting bias)	Unclear risk	Symptom scores reported. Authors state that intervention was well tolerated and safe but do not present any AE or safety data. Authors contacted.
Other bias	High risk	This was a crossover trial in which the test protocol allowed patients who were feeling worse during either test period to be switched to the next period

Kanauchi 2002

Study characteristics

Methods	**Study design and number of study arms** Randomised, open-label, 2 arms **Single-centre or multicentre?** Multicentre 8 hospitals: Sapporo Kosei General Hospital, Keio University School of Medicine, Shiga University of Medical Science, Fujita Health University School of Medicine, Niigata University School of Medicine, Hyogo College of Medicine, Kawasaki Medical School, and Kurume University School of Medicine **Countries** Japan **Study chronology**

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Kanauchi 2002 *(Continued)*

NR

Setting

Hospital

Trial registration number

NR

Participants	**Inclusion criteria** Mild-to-moderate UC based on the criteria of Truelove and Witts. No change of activity for at least 4 weeks, confirmed by a centre controller **Exclusion criteria** NR **Induction or maintenance** Induction **Baseline clinical disease activity per IG/CG** Truelove and Witts score (mild 1: moderate 2) (mean ± SD converted from mean ± SEM using the formula SD = SE x √N) • IG: 1.6 ± 1.66; CG: 1.7 ± 1.32 • IG: N = 11; CG: N = 7 Data as stated in the paper (mean ± SEM) are: IG: 1.6 ± 0.5; CG: 1.7 ± 0.5. Approx clinical activity index scored by the Lichtiger method at week 0 (mean +/− SD). Numbers are read from chart and are approximately: • IG: ~8.9 ± 3.9 • CG: ~7.8 ± 3.9 **Baseline endoscopic disease activity per IG/CG** NR Colonoscopic examinations were performed before and after the treatment period, and the macroscopic appearance of the mucosa was evaluated by an endoscopist who was unaware of the mode of treatment. 5 variables - erythema, oedema, friability, granularity, and erosion - were scored. No scores were reported. **Baseline disease characteristics, per IG/CG** *Location of disease* NR *Duration or length of disease since diagnosis* Years (mean ± SD converted from mean ± SEM using the formula SD = SE x √N): CG: 9.6 ± 15.3; IG: 8.5 ± 12.6 Data as stated in the paper (mean ± SEM) are: CG: 9.6 ± 5.8; IG: 8.5 ± 3.8. **Concomitant medicines** Prednisolone (Predonine) mean dose (mg/day) ± SEM: CG: 10 ± 2.5; IG: 6.5 ± 2.2 Sulfasalazine mean dose (mg/day) ± SEM: CG: 1500 ± 0; IG: 1625 ± 250

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Kanauchi 2002 *(Continued)*

	5-ASA mean dose (mg/day) ± SEM: CG: 2100 ± 335; IG: 1821 ± 400 Cannot convert mean ± SEM to mean ± SD because there is no information on how many participants had each of the concomitant medicines. **Diet information** No dietary alterations were made once participants entered the study. **IF induction study: length of active disease per IG/CG** NR **IF maintenance study: how was remission achieved? Duration of remission per IG/CG** NA **Age at beginning of study per IG/CG** Mean ± SD converted from mean ± SEM using the formula SD = SE x √N: CG: 39.4 ± 34.1; IG: 34.7 ± 47.4 Data as stated in the paper (mean ± SEM) are: CG: 39.4 ± 12.9; IG: 34.7 ± 14.3. **Sex (m/f) per IG/CG** NR **Smoking per IG/CG** NR **Number randomised per IG/CG** IG: 11; CG: 7 (n) **Number reaching end of study per IG/CG (numbers of participants)** NR
Interventions	**IG regimen, dosage** Germinated barley foodstuffs 20 to 30 g daily PLUS baseline anti-inflammatory therapy, for 4 weeks **CG regimen, dosage** Baseline anti-inflammatory therapy for 4 weeks **Duration of study** 4 weeks **Measurement time points during study** −4 weeks, 0 weeks, 4 weeks **Any follow-up measurements after study end? If yes, what time points?** NR
Outcomes	• Clinical activity index score • Endoscopic index score • Laboratory parameters • Faecal microflora analysis

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Kanauchi 2002 *(Continued)*

Notes	**Funding source** NR **Conflicts of interest** NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used a random allocation protocol. The allocation sequence was computer-generated.
Allocation concealment (selection bias)	Low risk	The randomization was governed by a centrally held code to ensure an equal and random allocation at all hospitals.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Activity index was scored after 4 weeks by two physicians who were unaware of the patients' treatment assignments or the results of any laboratory studies. Colonoscopic examinations were performed before and after the treatment period, and the macroscopic appearance of the mucosa was evaluated by an endoscopist who was unaware of the mode of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition data not reported not reported in the paper. The author was contacted and confirmed there were no withdrawals.
Selective reporting (reporting bias)	Unclear risk	No trial registration or protocol reported, and the author confirmed they have no access to the study data and documentation anymore. The endoscopy outcome results have not been reported because according to the author many study participants refused to be examined and statistical analysis was not possible.
Other bias	Low risk	No Baseline imbalance. No other concerns

Morse 2010

Study characteristics

Methods	**Study design and number of study arms** Randomised, open-label study. 2 arms **Single-centre or multicentre?** NR **Countries** NR **Study chronology**

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Morse 2010 *(Continued)*

NR

Setting

NR

Trial registration number

NR

Participants	**Inclusion criteria** Mild to moderately active UC, stable on oral 5-ASA or azathioprine **Exclusion criteria** NR **Induction or maintenance** Induction **Baseline clinical disease activity per IG/CG** Mild to moderately active **Baseline endoscopic disease activity per IG/CG** NR **Baseline disease characteristics, per IG/CG** *Location of disease* NR *Duration or length of disease since diagnosis (months)* NR **Concomitant medicines** NR **Diet information** NR **IF induction study: length of active disease per IG/CG** NR **IF maintenance study: how was remission achieved? Duration of remission per IG/CG** NA **Age at beginning of study per IG/CG** NR **Sex (m/f) per IG/CG** NR **Smoking per IG/CG** NR

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Morse 2010 *(Continued)*

	Number randomised per IG/CG n = 24 in total; number in IG/CG not reported **Number reaching end of study per IG/CG** n = 18 in total; number in IG/CG not reported
Interventions	**IG regimen, dosage** 15 g daily inulin plus oligofructose **CG regimen, dosage** 7.5 g daily inulin plus oligofructose **Duration of study** 9 weeks **Measurement time points during study** Week 0, 9 **Any follow-up measurements after study end? If yes, what time points?** NR
Outcomes	**Primary trial outcomes as defined by study authors** Not defined **Secondary trial outcomes as defined by study authors** Not defined
Notes	**Funding source** NR **Conflicts of interest** NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors state random allocation, but method not reported. Authors contacted
Allocation concealment (selection bias)	Unclear risk	Not reported. Authors contacted
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported. Authors contacted

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Morse 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/24 patients withdrew. Reasons not reported. Authors do not report which group withdrawals were in or how many assigned to each group. Authors contacted
Selective reporting (reporting bias)	Unclear risk	Adverse event data collected but not reported and no protocol details available. Authors contacted
Other bias	Unclear risk	No baseline characteristic data given. Authors contacted

Valcheva 2019

Study characteristics	
Methods	**Study design and number of study arms** Randomised, open-label **Single-centre or multicentre?** NR **Countries** Canada **Study chronology** NR **Setting** NR **Trial registration number** NCT02093767
Participants	**Inclusion criteria** • Males and females 18 to 65 years of age • Diagnosis of UC established by previous endoscopies, with histology and clinical course consistent with diagnosis • Colitis must extend for more than 15 cm above the anal verge, and involve at least the rectosigmoid • Mild to moderately active UC defined by a minimum score of 3 and a maximum score of 8 on the 12-point Mayo scale. Mayo scores are assigned by (1) stool frequency, (2) rectal bleeding, (3) endoscopic findings, and (4) physician's overall assessment of disease severity. • At least 1 previous episode of UC, prior to the current episode • Duration of current symptomatic episode less than 4 weeks • Ability to give valid informed consent • For females of childbearing potential, a negative pregnancy test **Exclusion criteria** • Crohn's disease or pouchitis • Current infectious enteritis • Use of oral steroids within the last 4 weeks of the screening visit • Use of antibiotics within the last 2 weeks of the screening visit • Change in dose of oral 5-ASA products within the last 2 weeks of the screening visit

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Valcheva 2019 *(Continued)*

- Topical 5-ASA or steroids within 7 days prior to the baseline endoscopy
- Use of immunosuppressive or biological agent within 3 months of screening
- Use of NSAIDs 1 week before screening
- Use of antidiarrhoeal drugs within the last 1 week of the screening visit
- Use of probiotic preparations either prescribed or over-the-counter within 2 weeks of screening
- Use of natural health products within 2 weeks of screening (except multivitamins and minerals)
- Significant hepatic, renal, endocrine, respiratory, neurological or cardiovascular disease as determined by the investigator
- Imminent need for colectomy
- Presence of severe UC (defined as Mayo score ≥ 9)
- Pregnancy or lactation
- Inability to give a valid informed consent or to properly comply with study procedures for any reason

Induction or maintenance

Induction

Baseline clinical disease activity per IG/CG

Total Mayo score (mean ± SD converted from mean ± SE using the formula SD = SE x √N, with N being the number the mean was calculated from rather than ITT (IG: n = 13; CG: n = 12))

IG: 5.5 ± 1.8; CG: 6.1 ± 1.4

Baseline endoscopic disease activity per IG/CG

Endoscopic score (mean ± SD converted from mean ± SE using the formula SD = SE x √N, with N being the number the mean was calculated from rather than ITT (IG: n = 13; CG: n = 12))

IG: 1.7 ± 0.72; CG: 2 ± 0.69

Baseline disease characteristics, per IG/CG

Location of disease

Left sided colitis IG: 11; CG: 9 (n)

Pancolitis IG: 2; CG: 3 (n)

Duration or length of disease since diagnosis

NR

Concomitant medicines

5-ASA IG: 9; CG: 11 (n)

Diet information

NR

IF induction study: length of active disease per IG/CG

Duration of current symptomatic episode less than 4 weeks

IF maintenance study: how was remission achieved? Duration of remission per IG/CG

NA

Age at beginning of study per IG/CG

Mean (range) in years IG: 39 (20 to 65); CG: 36 (18 to 58)

Sex (m/f) per IG/CG

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Valcheva 2019 *(Continued)*

	M/F IG: 5/8; CG: 6/6 (n) **Smoking per IG/CG** NR **Number randomised per IG/CG** IG: 15; CG: 16 (n) **Number reaching end of study per IG/CG** IG: 13; CG: 12 (n)
Interventions	**IG regimen, dosage** 15 g of oligofructose-enriched inulin (OraftiSynergy1) daily **CG regimen, dosage** 7.5 g of oligofructose-enriched inulin (OraftiSynergy1) daily **Duration of study** 9 weeks **Measurement time points during study** Baseline, week 9 **Any follow-up measurements after study end? If yes, what time points?** NR
Outcomes	**Primary trial outcomes as defined by study authors** Clinical response, defined as a decrease in the Mayo score of ≥ 3 compared to baseline in participants that remained with active disease (Mayo score ≥ 3) or an induction of clinical remission after 9 weeks of treatment (Mayo score < 2) **Secondary trial outcomes as defined by study authors** Number of participants who enter remission. Clinical and endoscopic remission is defined as a score of 0 in the rectal bleeding and stool frequency parts of the Mayo together with a score of 0 or 1 in the sigmoidoscopic portion of the Mayo. The total Mayo score must not be greater than 2.
Notes	**Funding source** The study was sponsored by an operating grant from the Canadian Institutes of Health Research (CIHR MOP-81396), Grants in Aid from the Crohn's and Colitis Foundation of Canada (CCFC G599000767), and an industry grant from Beneo-Orafti. Dr R Valcheva was the recipient of a fellowship from the Canadian Association of Gastroenterology-CIHR-Abbott. **Conflicts of interest** L Dieleman received research grants from CIHR, Broad Foundation, Agriculture Funding Consortium, and consultancy fees from Abbvie, Shire, Takeda, Johnson & Johnson for biologics unrelated to the submitted study. M Gänzle received research grants from NSERC, ALMA, Al Bio, Ernst Böcker GmbH & Co, KG, Mindel, as well as honorarium as visiting professor at Hibei University of Technology, China. No conflicts declared for the remaining authors.

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Valcheva 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised but method of randomisation is not stated. Authors contacted
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported. Authors contacted
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	IG: 2/15 withdrew due to worsening of symptoms (n=1) or incompliance (n=1) CG: 4/16 withdrew due to worsening of symptoms (n=1) or incompliance (n=3)
Selective reporting (reporting bias)	Low risk	Predefined endpoints reported. Safety data presented. Trial registration given.
Other bias	Low risk	Baseline data balanced. No other concerns

Valcheva 2022

Study characteristics	
Methods	**Study design and number of study arms** Double-blind, randomised, parallel-group, placebo-controlled trial. 2 arms **Single-centre or multicentre?** Single **Countries** Canada **Study chronology** 4 July 2016 to December 2020 **Setting** NR **Trial registration number** NCT02865707
Participants	**Inclusion criteria** • Age 18 to 75

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Valcheva 2022 *(Continued)*

- Patients with UC with confirmed diagnosis by histology and endoscopy
- Currently in clinical remission defined as total Mayo score of ≤ 2 and endoscopic score of 0 or 1) who have experienced at least 1 flare in the past 18 months
- On stable doses of oral 5-ASA for 2 weeks and/or stable doses of azathioprine and/or anti-tumour necrosis factor biologics for 2 months
- Colonic involvement of > 15 cm from the anal verge
- Ability to give valid informed consent
- For females of childbearing potential, a negative pregnancy test and an agreement to use appropriate birth control over the study period

Exclusion criteria

- Crohn's disease, indeterminate colitis, or infectious colitis
- Active UC (total Mayo score of ≥ 3)
- Taking prednisone (or steroid equivalent) within 1 month of enrolment
- Used topical 5-ASA or steroids within 2 weeks of enrolment
- Using immunosuppressive treatments of 6-mercaptopurine or methotrexate
- Used antibiotics within 2 months
- Used antidiarrhoeal agents within the previous 3 days
- Pregnancy or lactation
- Significant chronic disorders such as severe cardiac disease, significant renal failure, severe pulmonary disease (need for oxygen)
- Active gastrointestinal infection
- Severe psychiatric disorder
- Not able to consent to the study

Induction or maintenance

Maintenance

Baseline clinical disease activity per IG/CG

Partial Mayo score (mean ± SD converted from mean ± SE using the formula SD = SE x √N, with N being the number the mean was calculated from rather than ITT (IG: n = 35; CG: n = 41))

IG: 0.0 ± 0.0; CG: 0.0 ± 1.28

Baseline endoscopic disease activity per IG/CG

Endoscopic score (mean ± SD converted from mean ± SE using the formula SD = SE x √N, with N being the number the mean was calculated from rather than ITT (IG: n = 35; CG: n = 41))

IG: 0.5 ± 2.96; CG: 0.5 ± 3.2

Baseline disease characteristics, per IG/CG

Location of disease

Left sided colitis: IG: 11; CG: 13 (n)

Pancolitis: IG: 23; CG: 23 (n)

Proctitis: IG: 1; CG: 5 (n)

Duration or length of disease since diagnosis

NR

Concomitant medicines

5-ASA: IG: 14; CG: 17 (n)

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Valcheva 2022 *(Continued)*

Immunosuppressants (azathioprine (Imuran)): IG: 1; CG: 1 (n)

Biologics: IG: 4; CG: 6 (n)

Combined 5-ASA/Imuran: IG: 1; CG: 5 (n)

Combined 5-ASA/biologics: IG: 5; CG: 4 (n)

Combined 5-ASA/Imuran/biologics: IG: 2; CG: 1 (n)

Combined Imuran/biologics: IG: 1; CG: 2 (n)

Diet information

Participants were required to maintain a stable dietary pattern, monitored by web-based Diet History Questionnaire II (DHQII) completed at baseline and 6-months/relapse.

IF induction study: length of active disease per IG/CG

NA

IF maintenance study: how was remission achieved? Duration of remission per IG/CG

NR

Age at beginning of study per IG/CG

IG: 44.1 ± 13.7; CG: 45.2 ± 13.8 years (mean ± SD)

Sex (m/f) per IG/CG

IG: 16/19; CG: 17/24 (n)

Smoking per IG/CG

NR

Number randomised per IG/CG

IG: 43; CG: 46 (n)

Note that the trial was prematurely terminated due to lack of efficacy, and further recruitment was halted.

Number reaching end of study per IG/CG

IG: 29; CG: 36 (n)

Interventions	**IG regimen, dosage** Weeks 0 to 2: 7.5 g daily β-fructans (Prebiotin/Synergy1, oligofructose and inulin in ratio 1:1) dissolved in 200 mL warm water (or other beverage) with a meal for first 2 weeks Week 3 to end (or flare): 15 g daily β-fructans (Prebiotin/Synergy1, oligofructose and inulin in ratio 1:1) dissolved in 200 mL warm water (or other beverage) with meals **CG regimen, dosage** Weeks 0 to 2: 7.5 g daily placebo (Agenamalt 22.222 maltodextrin DE19) dissolved in 200 mL warm water (or other beverage) with a meal for first 2 weeks Week 3 to end (or flare): 15 g daily placebo (Agenamalt 22.222 maltodextrin DE19) dissolved in 200 mL warm water (or other beverage) with meals **Duration of study** 6 months

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Valcheva 2022 *(Continued)*

	Measurement time points during study Month 0, 1, 2, 3, 4, 5, 6 **Any follow-up measurements after study end? If yes, what time points?** Month 12
Outcomes	**Primary trial outcomes as defined by study authors** Patient clinical relapse rate over 6 months of active supplemental intervention, based on partial Mayo score ≥ 3 **Secondary trial outcomes as defined by study authors** • Change in FCP at month 6 or at relapse, versus baseline FCP • Change in partial Mayo clinical score at month 6 or at relapse, versus baseline Mayo • Change in endoscopic score at month 6 or at relapse, versus baseline endoscopic score • Time to relapse **Secondary outcome measures listed on ClinicalTrials.gov but not in preprint** • Patient compliance, assessed by package counting at 3 and 6 months or at relapse • Patient tolerability, defined as the number of participants that experience adverse events related to treatment, assessed by structured questionnaire at 3 and 6 months or at relapse
Notes	**Funding source** CEGIIR provided material support. LD was supported by CIHR and Weston Family Foundation grants and also sponsored by Jackson GI; along with Weston Family Foundation funding awarded to EW, HA, LD, and RV. The funders had no role in study design, collection, or interpretation of data. **Conflicts of interest** The authors have no competing interests to declare. Note that the trial was prematurely terminated due to lack of efficacy, and further recruitment was halted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized in 1:1 fashion to one of the treatment arms using random block sizes of 2 and 4, stratified based on sex (males versus females). The randomization sequence was generated by University of Alberta Epidemiology Coordinating and Research (EPICORE) Centre and embedded into REDCap (Research Electronic Data Capture) electronic case report form (eCRF) system. **Note that the trial was prematurely terminated due to lack of efficacy and further recruitment was halted**
Allocation concealment (selection bias)	Low risk	Allocation concealment was attained as per the central computer allocation stated above.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The author was contacted and confirmed that the packaging of the interventions was identical

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Valcheva 2022 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The author was contacted and confirmed that assessors were blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	IG: 8/43 were excluded from analysis (not assessed for any variable after baseline n=6; allergic reaction n=1; lost eligibility n=1). A further 5/43 withdrew due to flatulence and bloating but were included in analysis. CG: 5/46 were excluded from analysis (not assessed for any variable after baseline n=4; lost eligibility n=1). A further 1/46 withdrew due to severe constipation but was included in analysis.
Selective reporting (reporting bias)	Low risk	All predefined clinical endpoints and safety data reported. Patient compliance not reported (but withdrawals are reported) Trial registration reported.
Other bias	Low risk	Baseline balance with full details reported. No other concerns

5-ASA: 5-aminosalicylic acid
CD: Crohn's disease
CG: control group
ECN: *Escherichia coli* strain Nissle 1917
FCP: faecal calprotectin
IBD: inflammatory bowel disease
IBDQ: Inflammatory Bowel Disease Questionnaire
IG: intervention group
IL-8: interleukin-8
ITT: intention-to-treat
NA: not applicable
NR: not reported
NSAIDs: non-steroidal anti-inflammatory drugs
PCR: polymerase chain reaction
PGE-2: prostaglandin E_2
PPI: protein pump inhibitors
SCCAI: Simple Clinical Colitis Activity Index
SD: standard deviation
SE: standard error
SEM: standard error of mean
UC: ulcerative colitis
VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Copaci 2000	Wrong intervention
Fernandez-Barrarez 1999	Wrong intervention
Hafer 2007	Wrong intervention
Langhorst 2012	Wrong intervention
Nyman 2020	Wrong intervention

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Study	Reason for exclusion
Ryan 2021	Wrong study type
Seidner 2005	Wrong intervention

Characteristics of studies awaiting classification *[ordered by study ID]*

Davies 1978

Methods	**Study design and number of study arms** Controlled trial, 2 arms. Randomisation not mentioned. **Single-centre or multicentre?** NR **Countries** UK **Study chronology** NR **Setting** NR **Trial registration number** NR
Participants	**Inclusion criteria** In remission with colitis **Exclusion criteria** NR **Induction or maintenance** Maintenance **Baseline clinical disease activity (mild, moderate, severe or CDAI mean (SD) per IG/CG)** NR other than "in remission" **Baseline endoscopic disease activity per IG/CG** NR **Baseline disease characteristics, per IG/CG (mean (SD), median (range), or percentages/numbers of participants)** *Fistulating disease* NR *Location of disease* NR

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Davies 1978 *(Continued)*

Duration or length of disease since diagnosis (months)

Mean 8.5 years (both groups combined)

Concomitant medicines

It is implied, but not specifically stated, that all participants were on sulfasalazine at the start of the trial (dose NR).

Diet information

NR

IF induction study: length of active disease per IG/CG

NA

IF maintenance study: how was remission achieved? Duration of remission per IG/CG

How remission was achieved NR, but it is implied (though not specifically stated) that all participants were on sulfasalazine at the start of the trial. Sulfasalazine was discontinued in IG after 2 weeks if diet was tolerated.

Mean duration of remission 1.4 years (both groups combined)

In IG: 11 had been in remission > 1 year, 4 had been in remission > 3 years

Age at beginning of study per IG/CG (mean (SD) or median (range))

Mean 40 years (both groups combined)

Sex (m/f) per IG/CG (numbers of participants)

NR

Smoking per IG/CG (mean (SD), median (range), or percentages/numbers of participants)

NR

Number randomised per IG/CG (numbers of participants)

IG: 24; CG: 15

Number reaching end of study per IG/CG (numbers of participants)

IG: 20; CG: 15

Interventions	**IG regimen, dosage** Increased fibre intake by taking whole-wheat bread, vegetables, and supplement of 25 g of bran (given as Kellogg's All Bran or Allinson's Bran Plus). If tolerated, participants discontinued sulfasalazine after 2 weeks. **CG regimen, dosage** Continued on sulfasalazine without a change in diet **Duration of study** 6 months **Measurement time points during study** Baseline, 1 month, 3 months, 6 months (and if participant experienced a recurrence in symptoms lasting more than 48 hours)

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Davies 1978 *(Continued)*

	Any follow-up measurements after study end? If yes, what time points? NR
Outcomes	**Primary trial outcomes as defined by study authors** Not defined, but number of relapses is the only measure reported **Secondary trial outcomes as defined by study authors** Not defined
Notes	**Funding source** Kellogg Company of Great Britain Limited and Allinson's supplied All Bran and Bran Plus, respectively. **Conflicts of interest** NR Note that it is not clear if this is a randomised trial, and this is not mentioned in the text. We are unable to contact the authors through any means.

Ikegami 2023

Methods	RCT
Participants	40 people with mild-to-moderate active UC
Interventions	1-kestose (N = 20) or placebo (maltose, N = 20) orally for 8 weeks in addition to the standard treatment
Outcomes	The Lichtiger clinical activity index and Ulcerative Colitis Endoscopic Index of Severity were determined. Faecal samples were analysed to evaluate the gut microbiome and metabolites.
Notes	This study was identified during the update search for this review, and will be included in a future review update.

Voisin 2023

Methods	RCT
Participants	Unclear number of UC patients in remission
Interventions	B-fructan supplementation (15 g/day) in people with UC in remission
Outcomes	"We validated pathways of interest in IBD patient colonic biopsies cultured ex vivo with beta-fructans (targeted proteomics and mesoscale discovery). We examined structural changes (microscopy; e.g., tumorigenic architecture) in these biopsies. Further, cell invasion, migration and proliferation were examined using scratch wound assays and chick chorioallantoic membrane assays"
Notes	This study was identified during the search update, and will be included in a future review update. This might be an abstract for a wider RCT.

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CG: control group
CD: Crohn's disease
IBD: inflammatory bowel disease
IG: intervention group
NR: not reported
RCT: randomised control trial
SD: standard deviation
UC: ulcerative Colitis

Characteristics of ongoing studies *[ordered by study ID]*

NCT04520594

Study name	OptiMized REsistaNt Starch in Inflammatory Bowel Disease: The MEND Trial
Methods	**Study design and number of study arms** A single-centre, randomised, placebo-controlled, double-blind, parallel, pilot clinical trial **Single-centre or multicentre?** Single centre **Countries** Canada **Trial registration number** NCT04520594
Participants	**Inclusion criteria** • Age 5 to 17 years • Capable of giving informed consent, or have an acceptable representative capable of giving consent on the participant's behalf if appropriate • Enrolled in the main parent study • Existing Crohn's disease or ulcerative colitis diagnosis • In clinical remission or with mild disease (wPCDAI of 0 to 39.5 for CD; PUCAI of 0 to 30 for UC) with no changes in standard-of-care treatment for the previous month and without anticipated changes for the next month • Ability and willingness to comply with study procedures (e.g. stool collections) for the entire length of the study • Willing to provide consent/assent for the collection of stool samples **Exclusion criteria** • Allergy to resistant starch or excipients • Co-existing diagnosis with diabetes mellitus • Treatment with another investigational drug or intervention throughout the study • Current drug or alcohol dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements • Inability or unwillingness of an individual or legal guardian to give written informed consent • Concomitant chronic disease requiring medications • Requirement for antibiotic therapy > 2 weeks duration • Participant's microbiota does not respond to any of the resistant starch from the assembled panel as measured through the RapidAIM evaluation following the initial stool sample collection • Patients with previous intestinal surgery **Induction or maintenance**

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NCT04520594 *(Continued)*

	Maintenance
Interventions	**IG regimen, dosage** Once-daily oral consumption of 7.5 g/m^2 of an individually optimised resistant starch **CG regimen, dosage** Once-daily oral consumption of a food-grade cornstarch that is readily digestible (placebo) **Duration of study** Approximately 6 months **Measurement time points during study** Varies by outcome measure (see below) - inc 0, 3, 6 months **Any follow-up measurements after study end? If yes, what time points?** Some outcome measures at approximately 9 months and 12 months
Outcomes	**Primary outcome measures** • Increased potential of butyrate production following the use of individualised resistant starch, as assessed by meta-omics analysis. [Time Frame: 6 ± 1 months] • Sustained potential for butyrate production following 6 months use of individualised resistant starch postrandomisation as assessed by meta-omics analysis. [Time Frame: 12 ± 2 months] • Change in microbiome composition of cases towards the microbiome of controls as assessed by meta-omics analysis. [Time Frame: 6 ± 1 months and 12 ± 2 months] **Secondary outcome measures** • Changes in patient-reported disability outcomes as measured by the IBD-DI. [Time Frame: Enrolment, 3 ± 1 months, 6 ± 1 months, 9 ± 1 months, and 12 ± 2 months] The IBD-DI consists of 28 questions, and a higher overall score is indicative of greater disability. • Changes in patient, parent/caregiver reported quality of life outcomes as measured by the IMPACT III Questionnaires. [Time Frame: Enrolment, 3 ± 1 months, 6 ± 1 months, 9 ± 1 months, and 12 ± 2 months] The IMPACT III questionnaire (a health-related quality of life questionnaire) consists of 35 questions and ranges in score from 0 to 231. A higher score represents a higher quality of life. The IMPACT III-P questionnaire is to be completed by the caregiver/guardian, with a higher score also representing a higher quality of life. • Changes in intestinal mucosal inflammation by measuring faecal calprotectin through stool samples. [Time Frame: Enrolment, 3 ± 1 months, 6 ± 1 months, 9 ± 1 months, and 12 ± 2 months] Change in clinical disease activity as measured by the wPCDAI for Crohn's disease. [Time Frame: Enrolment, 3 ± 1 months, 6 ± 1 months, 9 ± 1 months, and 12 ± 2 months] wPCDAI ranges from 0 to 125 points (< 12.5 = remission, 12.5 to 40.0 = mild, > 40.0 = moderate, > 57.5 = severe). • Change in clinical disease activity as measured by the PUCAI for ulcerative colitis. [Time Frame: Enrollment, 3 ± 1 months, 6 ± 1 months, 9 ± 1 months, and 12 ± 2 months] The PUCAI ranges from 0 to 85 points (< 10 = remission, 10 to 34 = mild, 35 to 64 = moderate, > 65 = severe). • Change in clinical disease activity as measured by the partial Mayo score for ulcerative colitis. [Time Frame: Enrolment, 3 ± 1 months, 6 ± 1 months, 9 ± 1 months, and 12 ± 2 months] The partial Mayo score ranges from 0 to 9 points (0 to 1 = remission, 2 to 4 = mild, 5 to 6 = moderate, 7 to 9 = severe). • Change in clinical disease activity as measured by the PGA for both Crohn's disease and ulcerative colitis. [Time Frame: Enrolment, 3 ± 1 months, 6 ± 1 months, 9 ± 1 months, and 12 ± 2 months] The PGA ranges from 0 to 3 points (0 = normal, 1 = mild, 2 = moderate, 3 = severe).
Starting date	3 March 2021
Contact information	David Mack, MD, FRCPC (613) 737-7600 ext 2516; dmack@cheo.on.ca

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NCT04520594 *(Continued)*	
	Ruth Singleton (613) 737-7600 ext 4123; rsingleton@cheo.on.ca
Notes	

NCT04522271	
Study name	Resistant starch in pediatric inflammatory bowel disease (Crohn's disease or ulcerative colitis)
Methods	**Study design and number of study arms** A single-centre, randomised, placebo-controlled, double-blinded, parallel, pilot clinical trial **Single-centre or multicentre?** Single centre **Countries** Canada **Trial registration number** NCT04522271
Participants	**Inclusion criteria** • Age 5 to 17 years • Capable of giving informed consent, or have an acceptable representative capable of giving consent on the participant's behalf if appropriate • Enrolled in the main parent study • New ulcerative colitis diagnosis (mild/moderate) or Crohn's disease diagnosis (moderate/severe) with colonic disease with or without terminal ileum disease, already started on oral corticosteroid or aminosalicylates for induction therapy at a time following diagnostic colonoscopy • Clinically responsive to induction medical therapy at enrolment (Crohn's disease participants with a weighted paediatric CDAI decrease of ≥ 17.5 points or ulcerative colitis participants with a PUCAI decrease of ≥ 15 points) • Ability and willingness to comply with study procedures (e.g. stool collections) for the entire length of the study • Willing to provide consent/assent for the collection of stool samples **Exclusion criteria** • Allergy to resistant starch or excipients • Co-existing diagnosis with diabetes mellitus • Treatment with another investigational drug or intervention throughout the study • Current drug or alcohol dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements • Inability or unwillingness of an individual or legal guardian to give written informed consent • Requirement for antibiotic therapy as part of standard Crohn's disease therapy (i.e. those patients with penetrating disease as manifested by intra-abdominal abscess or perianal abscess) • Requirement of oral antibiotics for other conditions (e.g. acne) • Participant's microbiota does not produce butyrate in response to any of the assembled panel of resistant starch as measured through the Rapid Assay of an Individual's Microbiome (RapidAIM) evaluation following enrolment • Requirement of therapy other than oral corticosteroid/aminosalicylates for induction therapy • Patients diagnosed with Inflammatory Bowel Disease - Unclassified

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NCT04522271 *(Continued)*

- Refusal to undergo follow-up colonoscopy as part of current clinical practice guidelines for Crohn's disease standard of care

Induction or maintenance

Maintenance

Interventions

IG regimen, dosage

Once-daily oral consumption of 7.5 g/m^2 of an individually optimised resistant starch

CG regimen, dosage

Once-daily oral consumption of a food-grade cornstarch that is readily digestible (placebo)

Duration of study

Approximately 5 months

Measurement time points during study

Varies by outcome measure (see below) - inc 0, 1, 2, 3, 4, 5 months

Any follow-up measurements after study end? If yes, what time points?

Varies by outcome measure (see below) - inc 8, 10, 12 months

Outcomes

Primary outcome measures

- Increased potential for butyrate production and its level at the mucosal luminal interface following ingestion of an individualised resistant starch as assessed by meta-omics analysis. [Time Frame: 5 ± 1 months]
- Sustained increased potential of butyrate production 6 months following cessation of the use of individualised resistant starch as assessed by meta-omics analysis of stools. [Time Frame: 12 ± 2 months]
- The percentage of eligible IBD patients who will enter a resistant starch-based ingestion trial. [Time Frame: Enrolment] Threshold of interest will be 50%.
- Compliance of resistant starch intake by patient report. [Time Frame: 5 ± 1 months]
- Compliance of resistant starch intake by product reconciliation. [Time Frame: 5 ± 1 months]

Secondary outcome measures

- Change in microbiome composition of cases towards the microbiome of controls as assessed by meta-omics analysis. [Time Frame: 5 ± 1 months and 12 ± 2 months]
- Changes in mitochondrial function due to ingestion of resistant starch as assessed by host proteomics of biopsy sampling. [Time Frame: Enrolment, and 5 ± 1 months]
- Change in clinical disease activity as measured by the wPCDAI for Crohn's disease, the PUCAI and partial Mayo score for ulcerative colitis, and the PGA for both Crohn's disease and ulcerative colitis. [Time Frame: Enrollment, 5 ± 1 months, and 12 ± 2 months]
- The wPCDAI ranges from 0 to 125 points (< 12.5 = remission, 12.5 to 40.0 = mild, > 40.0 = moderate, > 57.5 = severe). The PUCAI ranges from 0 to 85 points (< 10 = remission, 10 to 34 = mild, 35 to 64 = moderate, > 65 = severe). Partial Mayo score ranges from 0 to 9 points (0 to 1 = remission, 2 to 4 = mild, 5 to 6 = moderate, 7 to 9 = severe). The PGA ranges from 0 to 3 points (0 = normal, 1 = mild, 2 = moderate, 3 = severe).
- Changes in patient-reported disability outcomes as measured by the IBD-DI. [Time Frame: Enrolment, 5 ± 1 months, and 12 ± 2 months] The IBD-DI consists of 28 questions, and a higher overall score is indicative of greater disability.
- Changes in patient-, parent/caregiver-reported quality of life outcomes as measured by the IMPACT III Questionnaires. [Time Frame: Enrolment, 5 ± 1 months, and 12 ± 2 months] The IMPACT III questionnaire (a health-related quality of life questionnaire) consists of 35 questions and ranges in score from 0 to 231. A higher score represents a higher quality of life. The IMPACT III-P Ques-

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NCT04522271 *(Continued)*

	tionnaire is to be completed by the caregiver/guardian, with a higher score also representing a higher quality of life. • Changes in intestinal mucosal inflammation by measuring faecal calprotectin through stool samples. [Time Frame: Enrolment, 1, 2, 3, 4, 5, 6, 8, 10, and 12 months] Change in endoscopic disease activity measured during colonoscopies using the SES-CD for Crohn's disease and the Mayo Endoscopic Sub Score and UCEIS for ulcerative colitis. [Time Frame: Enrolment, and 5 ± 1 months] • The SES-CD measures disease inflammation (0 to 2 = inactive, 3 to 6 = mild, 7 to 15 = moderate, > 16 = severe). Mayo Endoscopic Sub Scores range from 0 to 3, with 0 representing a normal mucosa or inactive disease and 3 representing severe activity (spontaneous bleeding and large ulcerations). The UCEIS ranges from 0 to 8 (0 to 1 = remission, 2 to 4 = mild, 5 to 6 = moderate, and 7 to 8 = severe). • Change in histological scoring of acute and chronic inflammation collected through biopsies during colonoscopies and assessed using Naini and Cortina score for Crohn's disease and the Robarts Histopathological Index for ulcerative colitis. [Time Frame: Enrolment, and 5 ± 1 months] The Naini and Cortina score ranges from 0 to 10 for ileitis and 0 to 17 for colitis. For ileitis, the histopathological support for having IBD is either low (< 2), moderate (3 to 4), or high (≥ 5). For colitis, the likelihood of having IBD is either low (≤ 3), moderate (4 to 8), or high (≥ 9). The Robarts Histopathological Index score ranges from 0 to 33, with a higher score representing more severe inflammation.
Starting date	25 August 2020
Contact information	David Mack, MD, FRCPC (613) 737-7600 ext 2516; DMack@cheo.on.ca Ruth Singleton (613) 737-7600 ext 4123; RSingleton@cheo.on.ca
Notes	

NCT05579483

Study name	PREDUCTOME
Methods	RCT
Participants	60
Interventions	Prebiotics vs placebo
Outcomes	**Primary outcome** Response between arms at T = 8 weeks **Secondary outcomes** • Disease activity over time (T = 0, 4, 8, 12, and 60 weeks) • Mucosal inflammation • Gastrointestinal complaints • Stool consistency • Stool frequency • Faecal microbiota composition • Faecal short-chain fatty acids concentrations • Health-related quality of life • Number of participants with increased or decreased medication use • Incidence of adverse events **Other outcome measures**

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NCT05579483 *(Continued)*

- Habitual dietary intake
- Participant demographics and characteristics

Starting date	December 2023
Contact information	erwin.zoetendal@wur.nl zhuang.liu@wur.nl
Notes	

NCT05615779

Study name	Personalized B-fructan diet in inflammatory bowel disease patients
Methods	RCT
Participants	600
Interventions	Pectin vs B-fructan
Outcomes	**Primary outcome** • Diet tolerability **Secondary outcome** • Inflammatory response to diet • Microbiota changes in response to diet
Starting date	1 June 2023
Contact information	heather.armstrong@umanitoba.ca wine@umanitoba.ca
Notes	

Sadeghi 2020

Study name	Effects of soy milk consumption on gut microbiota, inflammatory markers, and disease severity in patients with ulcerative colitis: a study protocol for a randomized clinical trial
Methods	**Study design and number of study arms** A single-centre, randomised, controlled, parallel-group trial **Single-centre or multicentre?** 2 centres **Countries** Iran **Trial registration number**

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Sadeghi 2020 *(Continued)*

	Registered in the Iranian Registry of Clinical Trials (www.irct.ir) with ID IRCT20181205041859N1
Participants	**Inclusion criteria** • Mild-to-moderate UC • Age 20 to 60 years • In remission on stable medication • BMI 18.5 to 30 kg/m^2 **Exclusion criteria** • Changed type or dosage of medicines over the last 3 months • Hospitalised in the last 3 months • Diagnosis of diabetes, coeliac disease or other gastrointestinal diseases including cancers and infectious diseases • Pregnant or lactacting • Taken antibiotics, pre- or probiotic products, multivitamin, and mineral supplements during the last 3 months • Current smokers **Induction or maintenance** Maintenance
Interventions	**IG regimen, dosage** 250 mL/d preservative-free soy milk plus routine treatments taken for their condition at baseline **CG regimen, dosage** Routine treatments taken for their condition at baseline **Duration of study** 4 weeks **Measurement time points during study** Baseline, weeks 2, 3, 4 **Any follow-up measurements after study end? If yes, what time points?** Varies by outcome measure (see below) - inc 8, 10, 12 months
Outcomes	**Primary outcome measures** • Serum concentrations of inflammatory biomarkers • Faecal concentrations of calprotectin and lactoferrin • Quantity of selected bacteria in faecal samples (qRT-PCR) • IBD severity (partial Mayo score) • Disability (IBD-DI) **Secondary outcome measures** • Complete blood counts • Erythrocyte sedimentation rate • Quality of life (IBDQ-9) • Mental health (Iranian-validated version of HADS) • Anthropometric measures (weight, height, BMI) • Blood pressure

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Sadeghi 2020 *(Continued)*

Starting date	January 2019
Contact information	Omid Sadeghi; omidsadeghi69@yahoo.com Ahmad Esmaillzadeh; a-esmaillzadeh@sina.tums.ac.ir
Notes	Funded by Tehran University of Medical Sciences

BMI: body mass index
CD: Crohn's disease
CDAI: Crohn's Disease Activity Index
CG: control group
HADS: Hospital Anxiety and Depression Scale
IBD: inflammatory bowel disease
IBD-DI: Inflammatory Bowel Disease Disability Index
IBDQ-9: Inflammatory Bowel Disease Questionnaire 9
IG: intervention group
PGA: Physician Global Assessment
PUCAI: Pediatric Ulcerative Colitis Activity Index
qRT-PCR: quantitative real-time reverse-transcription polymerase chain reaction
RCT: randomised control trial
SES-CD: Simple Endoscopic Score for Crohn's Disease
UC: ulcerative colitis
UCEIS: Ulcerative Colitis Endoscopic Index of Severity
wPCDAI: Weighted Pediatric Crohn's Disease Activity Index

DATA AND ANALYSES

Comparison 1. Prebiotics versus placebo for induction of remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Clinical remission	1	19	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.57, 1.94]
1.2 Disease improvement: clinical activity scale (Rachmilewitz index)	1	15	Mean Difference (IV, Random, 95% CI)	-0.40 [-2.67, 1.87]
1.3 Disease improvement: biochemical markers of inflammation (faecal calprotectin)	1	15	Mean Difference (IV, Random, 95% CI)	-2529.00 [-6925.38, 1867.38]
1.4 Disease improvement: biochemical markers of inflammation (IL-8 in rectal dialysis fluid)	1	15	Mean Difference (IV, Random, 95% CI)	-2.10 [-4.93, 0.73]
1.5 Disease improvement: biochemical markers of inflammation (PGE-2 in rectal dialysis fluid)	1	15	Mean Difference (IV, Random, 95% CI)	-4.40 [-20.25, 11.45]
1.6 Withdrawals due to adverse events	2	31	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.51, 14.55]

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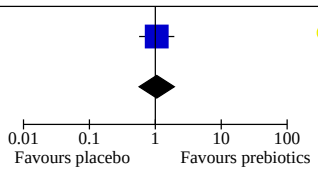
Analysis 1.1. Comparison 1: Prebiotics versus placebo for induction of remission, Outcome 1: Clinical remission

Study or Subgroup	Prebiotics Events	Prebiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Casellas 2007	7	10	6	9	100.0%	1.05 [0.57 , 1.94]
Total (95% CI)		**10**		**9**	**100.0%**	**1.05 [0.57 , 1.94]**
Total events:	7		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.88)
Test for subgroup differences: Not applicable

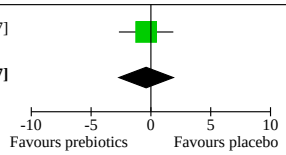


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Prebiotics versus placebo for induction of remission, Outcome 2: Disease improvement: clinical activity scale (Rachmilewitz index)

Study or Subgroup	Prebiotics Mean	Prebiotics SD	Prebiotics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Casellas 2007	4.1	1.06	7	4.5	3.08	8	100.0%	-0.40 [-2.67 , 1.87]
Total (95% CI)			**7**			**8**	**100.0%**	**-0.40 [-2.67 , 1.87]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable

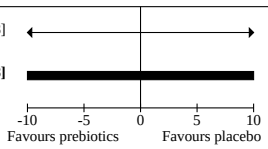


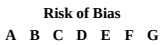
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Prebiotics versus placebo for induction of remission, Outcome 3: Disease improvement: biochemical markers of inflammation (faecal calprotectin)

Study or Subgroup	Prebiotics Mean	Prebiotics SD	Prebiotics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Casellas 2007	1211	1188	7	3740	6216	8	100.0%	-2529.00 [-6925.38 , 1867.38]
Total (95% CI)			**7**			**8**	**100.0%**	**-2529.00 [-6925.38 , 1867.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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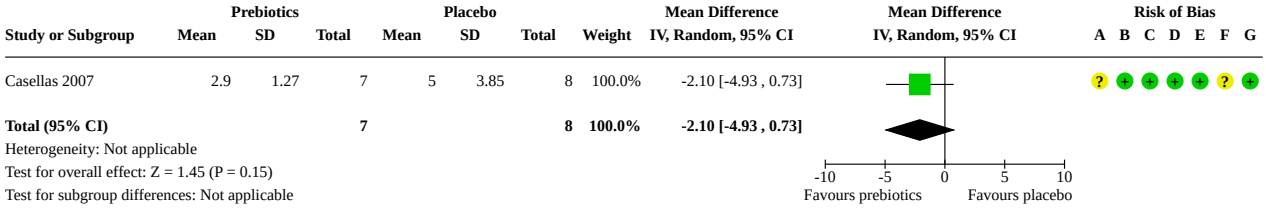
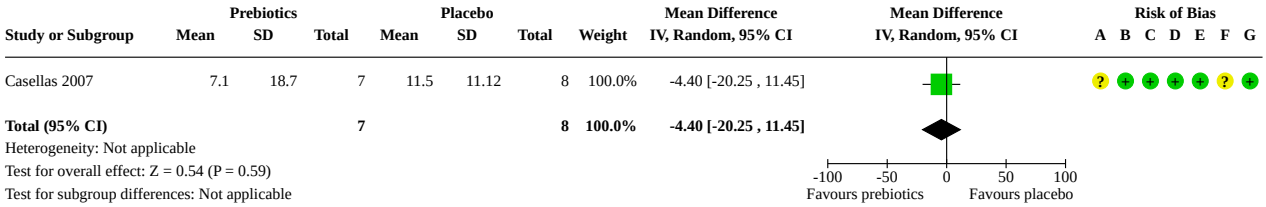
Analysis 1.4. Comparison 1: Prebiotics versus placebo for induction of remission, Outcome 4: Disease improvement: biochemical markers of inflammation (IL-8 in rectal dialysis fluid)



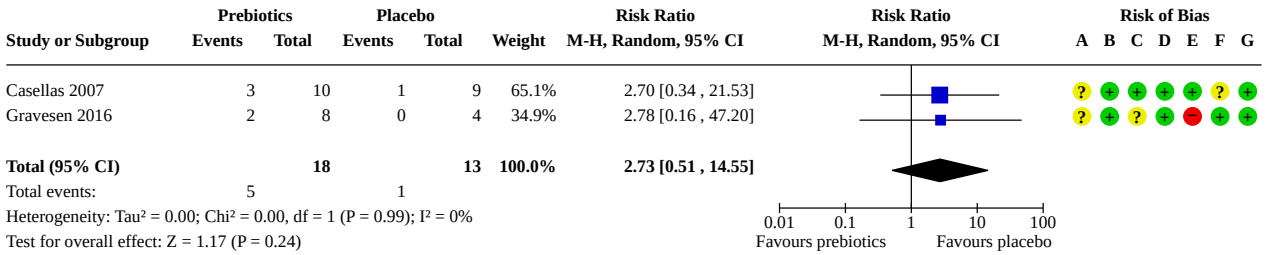
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Prebiotics versus placebo for induction of remission, Outcome 5: Disease improvement: biochemical markers of inflammation (PGE-2 in rectal dialysis fluid)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Prebiotics versus placebo for induction of remission, Outcome 6: Withdrawals due to adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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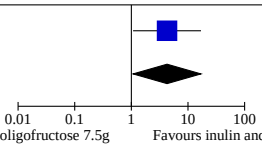
Comparison 2. Inulin and oligofructose 15 g versus inulin and oligofructose 7.5 g daily for induction of remission

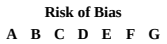
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Clinical remission	1	31	Risk Ratio (M-H, Random, 95% CI)	4.27 [1.07, 16.96]
2.2 Disease improvement: clinical activity scale (Mayo score)	1	31	Risk Ratio (IV, Random, 95% CI)	2.67 [1.06, 6.70]
2.3 Number of adverse events	1	31	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.72, 4.06]
2.4 Withdrawals due to adverse events	1	31	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.11, 2.50]

Analysis 2.1. Comparison 2: Inulin and oligofructose 15 g versus inulin and oligofructose 7.5 g daily for induction of remission, Outcome 1: Clinical remission

Study or Subgroup	Inulin and oligofructose 15g Events	Total	Inulin and oligofructose 7.5g Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Valcheva 2019	8	15	2	16	100.0%	4.27 [1.07 , 16.96]
Total (95% CI)		**15**		**16**	**100.0%**	**4.27 [1.07 , 16.96]**
Total events:	8		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)
Test for subgroup differences: Not applicable



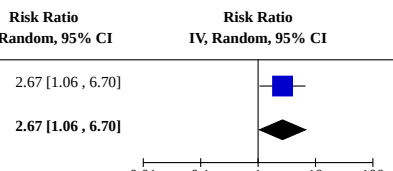


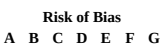
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Inulin and oligofructose 15 g versus inulin and oligofructose 7.5 g daily for induction of remission, Outcome 2: Disease improvement: clinical activity scale (Mayo score)

Study or Subgroup	Inulin and oligofructose 15g Events	Total	Inulin and oligofructose 7.5g Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Valcheva 2019	10	15	4	16	100.0%	2.67 [1.06 , 6.70]
Total (95% CI)		**15**		**16**	**100.0%**	**2.67 [1.06 , 6.70]**
Total events:	10		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.09 (P = 0.04)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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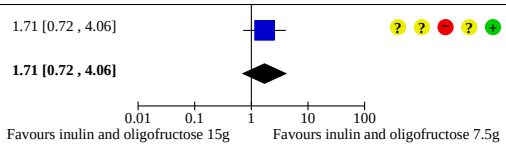
Analysis 2.3. Comparison 2: Inulin and oligofructose 15 g versus inulin and oligofructose 7.5 g daily for induction of remission, Outcome 3: Number of adverse events

Study or Subgroup	Inulin and oligofructose 15g Events	Total	Inulin and oligofructose 7.5g Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Valcheva 2019	8	15	5	16	100.0%	1.71 [0.72 , 4.06]
Total (95% CI)		**15**		**16**	**100.0%**	**1.71 [0.72 , 4.06]**
Total events:	8		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable

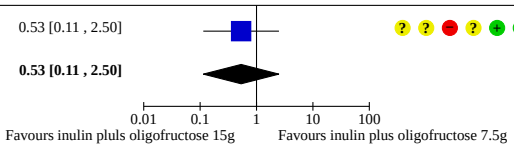


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Inulin and oligofructose 15 g versus inulin and oligofructose 7.5 g daily for induction of remission, Outcome 4: Withdrawals due to adverse events

Study or Subgroup	Inulin plus oligofructose 15g Events	Total	Inulin plus oligofructose 7.5g Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Valcheva 2019	2	15	4	16	100.0%	0.53 [0.11 , 2.50]
Total (95% CI)		**15**		**16**	**100.0%**	**0.53 [0.11 , 2.50]**
Total events:	2		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Prebiotics and anti-inflammatory therapy versus anti-inflammatory therapy for induction of remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Disease improvement: clinical activity scale (Lichtiger index)	1	18	Mean Difference (IV, Random, 95% CI)	-4.10 [-8.14, -0.06]
3.2 Disease improvement: biochemical markers of inflammation (serum CRP)	1	18	Mean Difference (IV, Random, 95% CI)	0.05 [-0.37, 0.47]

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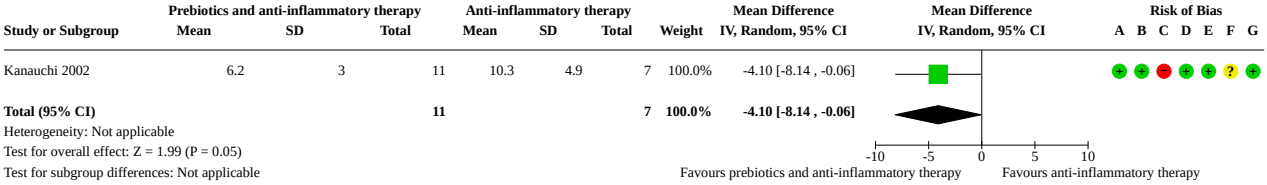
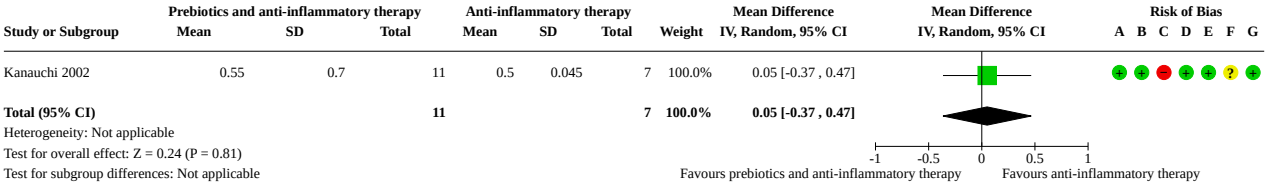
Analysis 3.1. Comparison 3: Prebiotics and anti-inflammatory therapy versus anti-inflammatory therapy for induction of remission, Outcome 1: Disease improvement: clinical activity scale (Lichtiger index)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Prebiotics and anti-inflammatory therapy versus anti-inflammatory therapy for induction of remission, Outcome 2: Disease improvement: biochemical markers of inflammation (serum CRP)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 4. Prebiotics versus placebo for maintenance of remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Clinical relapse	1	89	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.79, 2.31]
4.2 Disease improvement: clinical activity scale (partial Mayo score)	1	30	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.17, -0.22]
4.3 Disease improvement: biochemical markers of inflammation (faecal calprotectin)	1	30	Mean Difference (IV, Random, 95% CI)	-89.79 [-221.30, 41.72]
4.4 Disease improvement: quality of life score (IBDQ)	1	30	Mean Difference (IV, Random, 95% CI)	5.50 [-8.94, 19.94]
4.5 Number of adverse events	1	89	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.18, 2.40]
4.6 Withdrawals due to adverse events	2	125	Risk Ratio (M-H, Random, 95% CI)	2.57 [1.15, 5.73]

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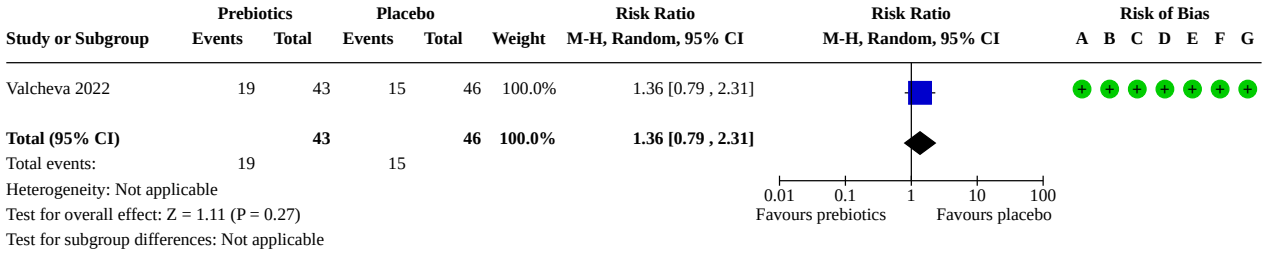
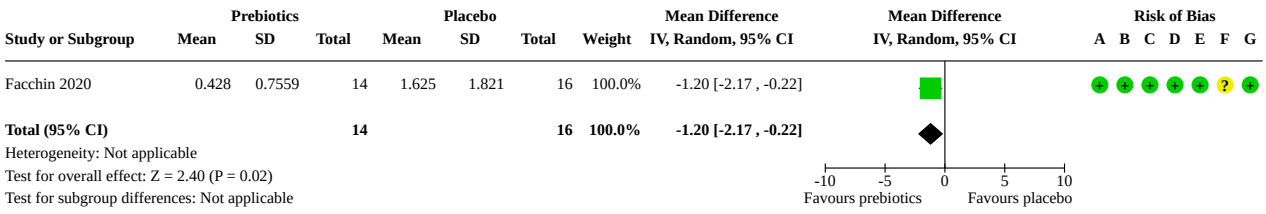
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6.1 Prebiotics	1	89	Risk Ratio (M-H, Random, 95% CI)	2.32 [0.97, 5.55]
4.6.2 Short-chain fatty acids	1	36	Risk Ratio (M-H, Random, 95% CI)	4.47 [0.58, 34.57]

Analysis 4.1. Comparison 4: Prebiotics versus placebo for maintenance of remission, Outcome 1: Clinical relapse



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Prebiotics versus placebo for maintenance of remission, Outcome 2: Disease improvement: clinical activity scale (partial Mayo score)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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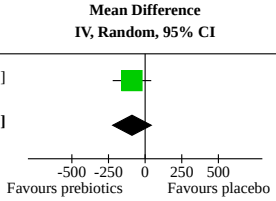
Analysis 4.3. Comparison 4: Prebiotics versus placebo for maintenance of remission, Outcome 3: Disease improvement: biochemical markers of inflammation (faecal calprotectin)

Study or Subgroup	Prebiotics Mean	Prebiotics SD	Prebiotics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Facchin 2020	214.21	171.5	14	304	196	16	100.0%	-89.79 [-221.30 , 41.72]	+ + + + + ? +
Total (95% CI)			**14**			**16**	**100.0%**	**-89.79 [-221.30 , 41.72]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable

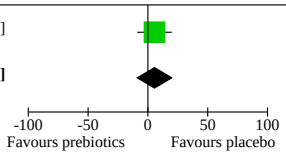


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.4. Comparison 4: Prebiotics versus placebo for maintenance of remission, Outcome 4: Disease improvement: quality of life score (IBDQ)

Study or Subgroup	Prebiotics Mean	Prebiotics SD	Prebiotics Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Facchin 2020	193.5	17.25	14	188	23	16	100.0%	5.50 [-8.94 , 19.94]	+ + + + + ? +
Total (95% CI)			**14**			**16**	**100.0%**	**5.50 [-8.94 , 19.94]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)
Test for subgroup differences: Not applicable

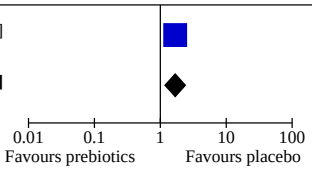


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.5. Comparison 4: Prebiotics versus placebo for maintenance of remission, Outcome 5: Number of adverse events

Study or Subgroup	Prebiotics Events	Prebiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Valcheva 2022	33	43	21	46	100.0%	1.68 [1.18 , 2.40]	+ + + + + + +
Total (95% CI)		**43**		**46**	**100.0%**	**1.68 [1.18 , 2.40]**	
Total events:	33		21				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.86 (P = 0.004)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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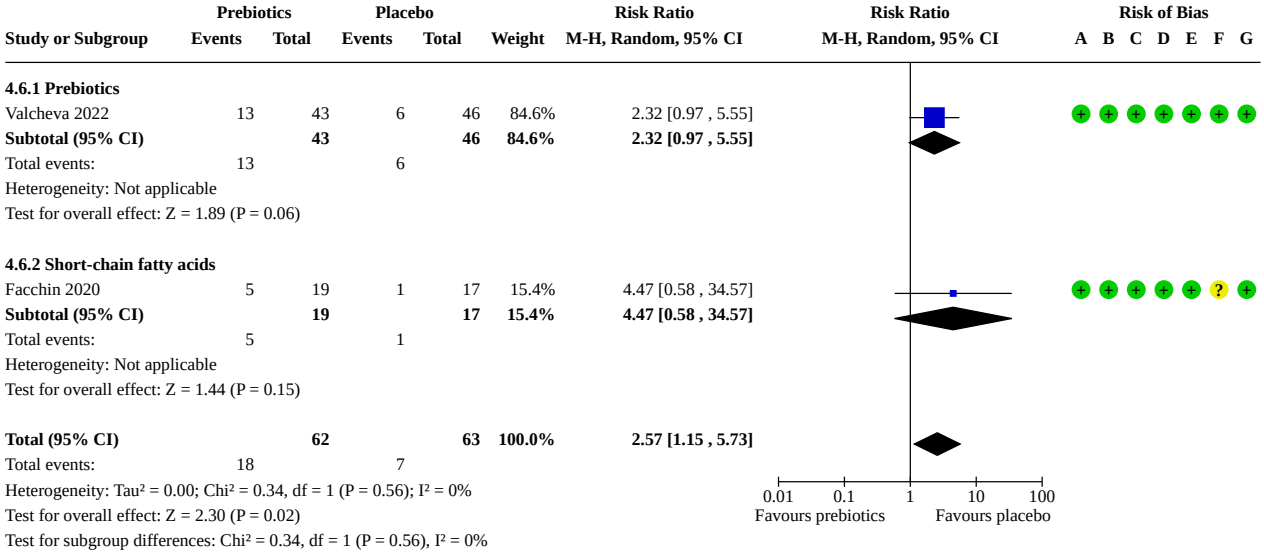
Analysis 4.6. Comparison 4: Prebiotics versus placebo for maintenance of remission, Outcome 6: Withdrawals due to adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 5. Prebiotics versus synbiotics for maintenance of remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Disease improvement: quality of life score (IBDQ)	1	63	Mean Difference (IV, Random, 95% CI)	6.30 [-6.61, 19.21]
5.2 Disease improvement: quality of life score (bowel component of IBDQ)	1	63	Mean Difference (IV, Random, 95% CI)	1.30 [-2.65, 5.25]
5.3 Disease improvement: quality of life score (systemic component of IBDQ)	1	63	Mean Difference (IV, Random, 95% CI)	1.00 [-1.49, 3.49]
5.4 Disease improvement: quality of life score (emotional component of IBDQ)	1	63	Mean Difference (IV, Random, 95% CI)	2.60 [-3.16, 8.36]
5.5 Disease improvement: quality of life score (social component of IBDQ)	1	63	Mean Difference (IV, Random, 95% CI)	1.30 [-1.42, 4.02]
5.6 Withdrawals due to adverse events	1	80	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.48, 2.62]

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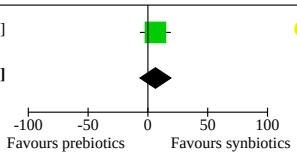
Analysis 5.1. Comparison 5: Prebiotics versus synbiotics for maintenance of remission, Outcome 1: Disease improvement: quality of life score (IBDQ)

Study or Subgroup	Prebiotics Mean	Prebiotics SD	Prebiotics Total	Synbiotics Mean	Synbiotics SD	Synbiotics Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	182.4	24.1	31	176.1	28.1	32	100.0%	6.30 [-6.61 , 19.21]	? + − ? + ? +
Total (95% CI)			**31**			**32**	**100.0%**	**6.30 [-6.61 , 19.21]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

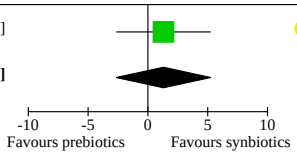


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.2. Comparison 5: Prebiotics versus synbiotics for maintenance of remission, Outcome 2: Disease improvement: quality of life score (bowel component of IBDQ)

Study or Subgroup	Prebiotics Mean	Prebiotics SD	Prebiotics Total	Synbiotics Mean	Synbiotics SD	Synbiotics Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	59.3	7.7	31	58	8.3	32	100.0%	1.30 [-2.65 , 5.25]	? + − ? + ? +
Total (95% CI)			**31**			**32**	**100.0%**	**1.30 [-2.65 , 5.25]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable

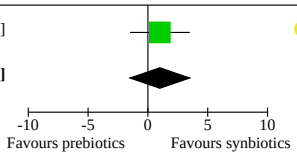


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.3. Comparison 5: Prebiotics versus synbiotics for maintenance of remission, Outcome 3: Disease improvement: quality of life score (systemic component of IBDQ)

Study or Subgroup	Prebiotics Mean	Prebiotics SD	Prebiotics Total	Synbiotics Mean	Synbiotics SD	Synbiotics Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	25.6	5.1	31	24.6	5	32	100.0%	1.00 [-1.49 , 3.49]	? + − ? + ? +
Total (95% CI)			**31**			**32**	**100.0%**	**1.00 [-1.49 , 3.49]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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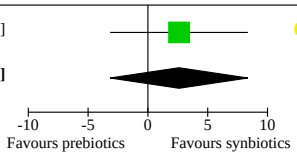
Analysis 5.4. Comparison 5: Prebiotics versus synbiotics for maintenance of remission, Outcome 4: Disease improvement: quality of life score (emotional component of IBDQ)

Study or Subgroup	Prebiotics Mean	SD	Total	Synbiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	66	11	31	63.4	12.3	32	100.0%	2.60 [-3.16 , 8.36]	? + − ? + ? +
Total (95% CI)			**31**			**32**	**100.0%**	**2.60 [-3.16 , 8.36]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

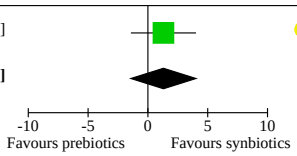


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.5. Comparison 5: Prebiotics versus synbiotics for maintenance of remission, Outcome 5: Disease improvement: quality of life score (social component of IBDQ)

Study or Subgroup	Prebiotics Mean	SD	Total	Synbiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	31.5	3.7	31	30.2	6.9	32	100.0%	1.30 [-1.42 , 4.02]	? + − ? + ? +
Total (95% CI)			**31**			**32**	**100.0%**	**1.30 [-1.42 , 4.02]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable

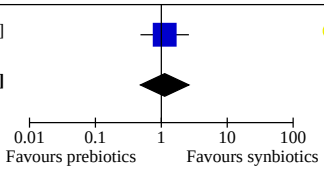


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.6. Comparison 5: Prebiotics versus synbiotics for maintenance of remission, Outcome 6: Withdrawals due to adverse events

Study or Subgroup	Prebiotics Events	Total	Synbiotics Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	9	40	8	40	100.0%	1.13 [0.48 , 2.62]	? + − ? + ? +
Total (95% CI)		**40**		**40**	**100.0%**	**1.13 [0.48 , 2.62]**	
Total events:	9		8				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.78)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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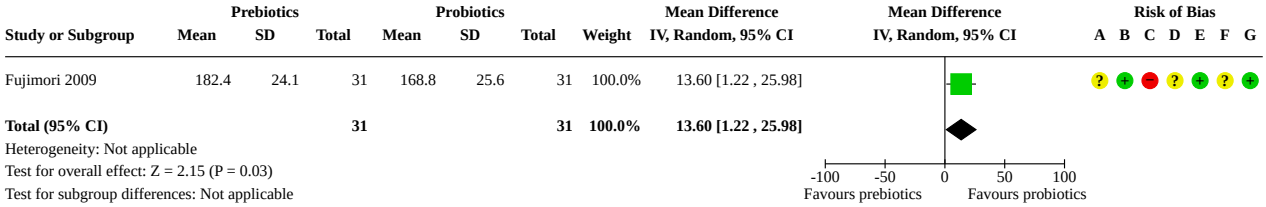
Comparison 6. Prebiotics versus probiotics for maintenance of remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Disease improvement: quality of life score (IBDQ)	1	62	Mean Difference (IV, Random, 95% CI)	13.60 [1.22, 25.98]
6.2 Disease improvement: quality of life score (bowel component of IBDQ)	1	62	Mean Difference (IV, Random, 95% CI)	5.70 [1.48, 9.92]
6.3 Disease improvement: quality of life score (systemic component of IBDQ)	1	62	Mean Difference (IV, Random, 95% CI)	1.10 [-1.18, 3.38]
6.4 Disease improvement: quality of life score (emotional component of IBDQ)	1	62	Mean Difference (IV, Random, 95% CI)	4.30 [-1.40, 10.00]
6.5 Disease improvement: quality of life score (social component of IBDQ)	1	62	Mean Difference (IV, Random, 95% CI)	2.50 [0.34, 4.66]
6.6 Withdrawals due to adverse events	1	80	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.44, 2.26]

Analysis 6.1. Comparison 6: Prebiotics versus probiotics for maintenance of remission, Outcome 1: Disease improvement: quality of life score (IBDQ)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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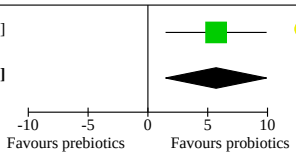
Analysis 6.2. Comparison 6: Prebiotics versus probiotics for maintenance of remission, Outcome 2: Disease improvement: quality of life score (bowel component of IBDQ)

Study or Subgroup	Prebiotics Mean	SD	Total	Probiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	59.3	7.7	31	53.6	9.2	31	100.0%	5.70 [1.48 , 9.92]	? + − ? + ? +
Total (95% CI)			**31**			**31**	**100.0%**	**5.70 [1.48 , 9.92]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.65 (P = 0.008)
Test for subgroup differences: Not applicable

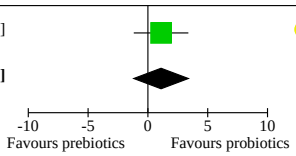


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.3. Comparison 6: Prebiotics versus probiotics for maintenance of remission, Outcome 3: Disease improvement: quality of life score (systemic component of IBDQ)

Study or Subgroup	Prebiotics Mean	SD	Total	Probiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	25.6	5.1	31	24.5	4	31	100.0%	1.10 [-1.18 , 3.38]	? + − ? + ? +
Total (95% CI)			**31**			**31**	**100.0%**	**1.10 [-1.18 , 3.38]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.34)
Test for subgroup differences: Not applicable

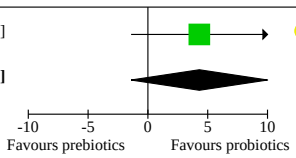


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.4. Comparison 6: Prebiotics versus probiotics for maintenance of remission, Outcome 4: Disease improvement: quality of life score (emotional component of IBDQ)

Study or Subgroup	Prebiotics Mean	SD	Total	Probiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Fujimori 2009	66	11	31	61.7	11.9	31	100.0%	4.30 [-1.40 , 10.00]	? + − ? + ? +
Total (95% CI)			**31**			**31**	**100.0%**	**4.30 [-1.40 , 10.00]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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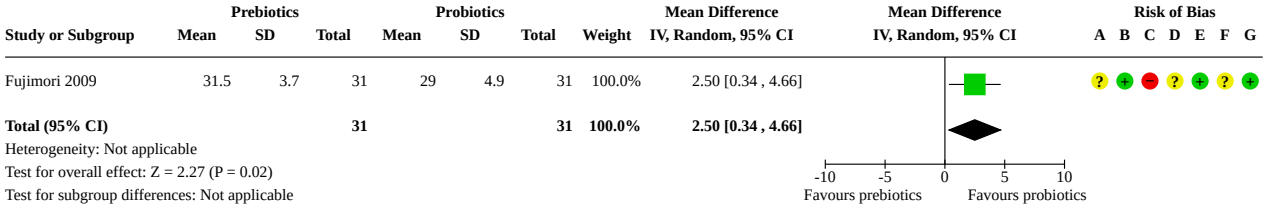
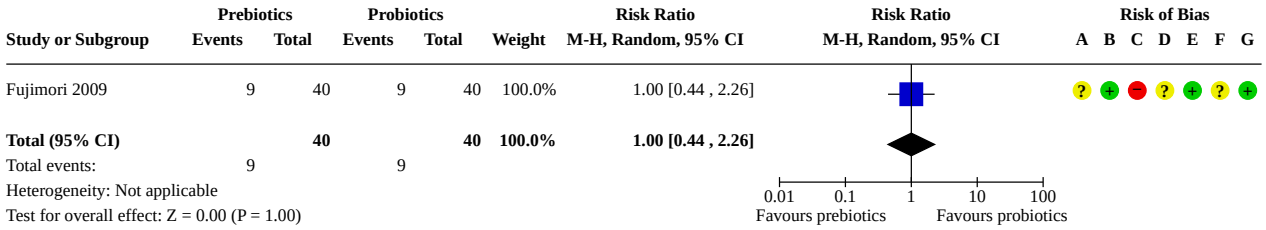
Analysis 6.5. Comparison 6: Prebiotics versus probiotics for maintenance of remission, Outcome 5: Disease improvement: quality of life score (social component of IBDQ)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.6. Comparison 6: Prebiotics versus probiotics for maintenance of remission, Outcome 6: Withdrawals due to adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Details of included studies

Study ID	Intervention	Control	Concomitant medication	Definition of induction/maintenance
Casellas 2007	Oral Beneo Synergy 1, 4 g, 3 times daily. Beneo Synergy 1 (Orafti, Tienen, Belgium) consists of a selected combination of long-inulin chains together with the shorter oligofructose chains (oligofructose-enriched inulin), both obtained from the chicory root.	Oral maltodextrin, 4 g, 3 times daily	Oral mesalazine 1 g, 3 times daily, and low-fibre diet	Remission defined as Rachmilewitz score < 6

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Table 1. Details of included studies *(Continued)*

Fujimori 2009	Oral probiotics (*Bifidobacterium longum* 2 x 10^9 colony-forming units/capsule) once a day PLUS oral prebiotics (4.0 g of psyllium dissolved in 100 mL of water) twice daily	CG1: Oral probiotics (*Bifidobacterium longum* 2 x 10^9 colony-forming units/capsule) once a day CG2: Oral prebiotics (4.0 g of psyllium dissolved in 100 mL of water) twice daily	Stable doses of aminosalicylates or prednisolone, or both. Participants continued their individual regimens throughout the trial with no dose change.	Not defined
Kanauchi 2002	Germinated barley foodstuffs 20 to 30 g daily PLUS baseline anti-inflammatory therapy, for 4 weeks	Baseline anti-inflammatory therapy for 4 weeks	Prednisolone mean dose (mg/day) ± SEM: CG: 10 ± 2.5; IG: 6.5 ± 2.2 Sulfasalazine mean dose (mg/day) ± SEM: CG: 1500 ± 0; IG: 1625 ± 250 5-ASA mean dose (mg/day) ± SEM: CG: 2100 ± 335; IG: 1821 ± 400 Cannot convert mean ± SEM to mean ± SD because there is no information on how many participants had each of the concomitant medicines.	Not defined
Morse 2010	15 g daily inulin plus oligofructose	7.5 g daily inulin plus oligofructose	Not specifically reported, but authors describe it as "adjunctive therapy", so it is presumed that participants continued on 5-ASA or azathioprine.	Not defined
Gravesen 2016	30 mL ispaghula husk powder per day mixed with food or a cold beverage for 2 or 3 months	30 mL breadcrumb powder (placebo) per day mixed with food or a cold beverage for 2 or 3 months	Mesalazine: IG: 8 CG: 4 Data are estimated as intention-to-treat	Not defined
Valcheva 2019	15 g oligofructose-enriched inulin (OraftiSynergy1) daily	7.5 g oligofructose-enriched inulin (OraftiSynergy1) daily	5-ASA IG: 9; CG: 11	Clinical remission defined as Mayo score < 2.
Facchin 2020	3 sodium-butyrate capsules daily (Butyrose Lsc Microcaps-EP2352386B1, BLM, Sila Srl) with meals Total daily dose 1800 mg	3 starch capsules daily	NR for UC cohort separately, but participants continued their current therapy For combined UC and CD cohorts who completed study: Biologics: IG: 8; CG: 12 5-ASA: IG: 20; CG: 25 Probiotics (*Escherichiacoli* strain Nissle): IG: 2; CG: 2 Steroids: IG: 1; CG: 6 Immunosuppressant: IG: 3; CG: 3 Proton pump inhibitors: IG: 1; CG: 6	Not defined

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Table 1. Details of included studies *(Continued)*

			Data NR for participants randomised.	
Valcheva 2022	Weeks 0 to 2: 7.5 g daily β-fructans (Prebiotin/Synergy1, oligofructose and inulin in ratio 1:1) dissolved in 200 mL warm water (or other beverage) with a meal for first 2 weeks Week 3 to end (or flare): 15 g daily β-fructans (Prebiotin/Synergy1, oligofructose and inulin in ratio 1:1) dissolved in 200 mL warm water (or other beverage) with meals	Weeks 0 to 2: 7.5 g daily placebo (Agenamalt 22.222 maltodextrin DE19) dissolved in 200 mL warm water (or other beverage) with a meal for first 2 weeks Week 3 to end (or flare): 15 g daily placebo (Agenamalt 22.222 maltodextrin DE19) dissolved in 200 mL warm water (or other beverage) with meals Maltodextrin (placebo)	5-ASA: IG 14; CG 17 Immunosuppressants (azathioprine (Imuran)): IG 1; CG 1 Biologics: IG 4; CG 6 Combined 5-ASA/Imuran: IG 1; CG 5 Combined 5-ASA/biologics: IG 5; CG 4 Combined 5-ASA/Imuran/biologics: IG 2; CG 1 Combined Imuran/biologics: IG 1; CG 2	Clinical remission defined as total Mayo score ≤ 2. Clinical relapse defined as partial Mayo score ≥ 3.
Hallert 1991	Lactose-free ispaghula husk (Vi-Siblin S granules, Parke-Davis) 4 g twice daily	Placebo (crushed crispbread) twice daily	25/36 participanats were receiving medication regularly, mostly sulfasalazine (70%).	Not defined

5-ASA: 5-aminosalicylic acid
CD: Crohn's disease
CG: control group
IG: intervention group
NR: not reported
SD: standard deviation
SEM: standard error of the mean
UC: ulcerative colitis

Table 2. Induction outcomes

Study ID	Clinical remission	Disease improvement	Escalation of therapy	Withdrawals due to adverse events	Numbers of participants with adverse events
Casellas 2007	IG: 7/10 (denominator includes 1 who withdrew after randomisation but before taking any intervention; 1 who withdrew in the 1st week due to worsening of their disease condition; 1 who was withdrawn by physi-	Clinical activity using Rachmilewitz index at day 0/7/14 (mean ± SD **converted from mean ± SE using the formula SD = SE x √N**): IG: 8.9 ± 1.56/7.8 ± 3.68/4.1 ± 1.06 CG: 8.3 ± 1.11/6.4 ± 1.78/4.5 ± 3.08 Faecal calprotectin at day 0/7/14 (mean ± SD **converted from mean ± SE using the formula SD = SE x √N**): IG: 4377 +/− 1977; 1033 +/− 1112; 1211 +/− 1188	NR	IG: 3/10 (numerator and denominator include 1 who withdrew after randomisation but before taking any intervention; 1 who withdrew in the 1st week due to worsening of disease condition; 1 who was withdrawn by physician on day 7	NR The paper says "No significant side-effects were reported" with no further information provided.

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Table 2. Induction outcomes *(Continued)*

	cian on day 7 due to worsening of Rachmilewitz score) CG: 6/9 (denominator includes 1 who withdrew in the 1st week due to worsening of their disease condition)	CG: 5834 +/− 4689; 4084 +/− 3946; 3740 +/− 6216 IL-8 in rectal dialysis fluid at day 0/7 (mean +/− SD **converted from mean ± SE using the formula SD = SE x √N**): IG: 3.8 +/− 1.38; 2.9 +/− 1.27 CG: 5.1 +/− 0.82; 5.0 +/− 3.85 PGE-2 in rectal dialysis fluid at day 0/7 (mean +/− SD **converted from mean ± SE using the formula SD = SE x √N**): IG: 12.6 +/− 23.9; 7.1 +/− 18.7 CG: 12.6 +/− 14.7; 11.5 +/− 11.12 Dyspepsia-related health scores only reported as a chart - not possible to extract accurate mean or SD. Number analysed at day 0/7/14: IG: 9/8/7; CG: 9/8/8		due to worsening of Rachmilewitz score) CG: 1/9 (numerator and denominator include 1 who withdrew in the 1st week due to worsening of their disease condition)	
Kanauchi 2002	NR	Approx clinical activity index scored by the Lichtiger method at week −4, 0 (baseline) and 4 (mean +/− SD): IG: ~7.8 +/− 4.1; 8.9 +/− 3.9; 6.2 +/− 3.0 CG: ~8.0 +/− 2.0; 7.8 +/− 3.9; 10.3 +/− 4.9 Numbers are read from a chart and are approximate. CRP at week 0 and 4 (mean +/− SD): IG: ~1.05 +/− 1.70; 0.55 +/− 0.70 CG: ~0.55 +/− 0.8; 0.5 +/− 0.45 Numbers are read from a chart and are approximate.	NR	NR	IG: 0/11 CG: NR But withdrawal or exclusion data not reported.
Morse 2010	Remission not defined by authors, but only UCDAI, adverse events, and faecal microflora were assessed, therefore remission must be based on UCDAI. 7/24 (IG and CG combined - data NR for separate groups; denominator includes 6 who	'Response' (must be based on UCDAI) 8/24 in total (denominator includes 6 who withdrew for unspecified reasons) IG: average decrease in UCDAI of 2.9 points (number in IG not reported; SE not reported) CG: average decrease in UCDAI of 0.75 points (number in CG not reported; SE not reported)	NR	6/24 in total (numerator and denominator include 6 who withdrew for reasons not reported)	NR

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Table 2. Induction outcomes *(Continued)*

	withdrew for unspecified reasons)				
Gravesen 2016	NR	**IBDQ baseline/2 months:** patient 5: 192/165 patient 10: 199/189 patient 11: 158/175 patient 12: 161/199 patient 3: 133/166 patient 4: 142/122 patient 7: 161/189 patient 9: 196/198 **SCCAI baseline/2 months:** patient 5: 8/8 patient 10: 5/5 patient 11: 4/3 patient 12: 5/2 patient 3: 6/5 patient 4: 10/11 patient 7: 7/2 patient 9: 4/4 **Total urinary 5-ASA excretion baseline/2 months/3 months:** patient 5: 0.5/0/0.8 patient 10: 26.7/18/21 patient 11: 27.1/27.3/17.2 patient 12: 7.7/7.9/16.5 patient 3: 2.7/3.7/0.6 patient 4: 14.9/11.5/11.5 patient 7: 23.9/36.6/44.7 patient 9: 26/33/33.2 No information provided on which patient was in which treatment group. No data reported for 4 participants who withdrew - all in IG.	NR	IG: 2/8 (numerator and denominator include 1 participant who was excluded from the final analysis due to change in medication dose, 2 participants who did not start treatment, and 1 participant who discontinued due to lack of effect) CG: 0/4	NR
Valcheva 2019	IG: 8/15 (denominator includes 1 who withdrew due to worsening of symptoms and 1 who withdrew due to non-compliance) CG: 2/16 (denominator includes 1 who withdrew due to worsening of symptoms and 3 who withdrew due to non-compliance)	**Clinical response** (decrease in Mayo score of ≥ 3 compared to baseline in participants that remained with active disease (a Mayo score of ≥ 3) or an induction of clinical remission after 9 weeks of treatment (Mayo score < 2)) IG: 10/15 (denominator includes 1 who withdrew due to worsening of symptoms and 1 who withdrew due to non-compliance) CG: 4/16 (denominator includes 1 who withdrew due to worsening of symptoms and 3 who withdrew due to non-compliance)	NR	IG: 2/15 (numerator and denominator include 1 who withdrew due to non-compliance) CG: 4/16 (numerator and denominator include 3 who withdrew due to non-compliance)	IG: 8/15 (numerator and denominator include 1 who withdrew due to worsening of symptoms and 1 who withdrew due to non-compliance) CG: 5/16 (numerator and denominator include 1 who withdrew due to worsening of symptoms and 3 who withdrew due to non-compliance)

CG: control group
CRP: C-reactive protein
IBDQ: Inflammatory Bowel Disease Questionnaire
IG: intervention group

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IL-8: interleukin 8
NR: not reported
PGE-2: prostaglandin E_2
SCCAI: Simple Clinical Colitis Activity Index
SD: standard deviation
SE: standard error
UCDAI: Ulcerative Colitis Disease Activity Index

Table 3. Maintenance outcomes

Study ID	Clinical relapses	Disease improvement	Escalation of therapy	Withdrawals due to adverse events	Numbers of participants with adverse events
Fujimori 2009	NR	NR Change in IBDQ (mean +/− SD) Total score 2 weeks/4 weeks: CG1 probiotics: 166.7 ± 25.5/168.8 ± 25.6 CG2 prebiotics: 183.1 ± 19.4 (P < 0.01)/182.4 ± 24.1 IG synbiotics: 174.8 ± 30/176.1 ± 28.1 IBDQ bowel score (mean +/− SD): 2 weeks/4 weeks: CG1: 54.1 ± 9.4/53.6 ± 9.2 CG2: 59.4 ± 6.6 (P < 0.05)/59.3 ± 7.7 IG: 57.9 ± 8/58.0 ± 8.3 IBDQ systemic score (mean +/− SD): 4 weeks CG1 probiotics: 24.5 ± 4.0 CG2 prebiotics: 25.6 ± 5.1 IG synbiotics: 24.6 ± 5.0 IBDQ emotional score (mean +/− SD): 4 weeks CG1 probiotics: 61.7 ± 11.9 CG2 prebiotics: 66.0 ± 11.0 IG synbiotics: 63.4 ± 12.3 IBDQ social score (mean +/− SD): 4 weeks CG1 probiotics: 29.0 ± 4.9 CG2 prebiotics: 31.5 ± 3.7 IG synbiotics: 30.2 ± 6.9	NR	CG1: 9/40 (numerator and denominator includes 9 withdrawals or exclusions for the following reasons: did not complete questionnaires 2; incomplete ingestion of biotics 2; changed therapy 1; did not ingest biotics 1; did not answer questionnaire 3) CG2: 9/40 (numerator and denominator includes 9 withdrawals or exclusions for the following reasons: did not complete questionnaires 1; incomplete ingestion of biotics 2; changed therapy 1; did not answer questionnaire 5) IG: 8/40 (numerator and denominator includes 8 withdrawals or exclusions for the following reasons: did not complete questionnaires 2; incomplete ingestion of biotics 1; did not ingest biotics 1; did not answer questionnaire 4)	NR Paper states there were no AEs related to blood variables (only measured in a subset of participants), but overall AEs not reported.

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Table 3. Maintenance outcomes *(Continued)*

		CRP before/after - **reported for subgroup only** (CG1: n = 10; CG2: n = 10; IG: n = 12); reason for not including all group participants is not reported: CG1: 0.12 ± 0.11/0.1 ± 0.07 CG2: 0.26 ± 0.25/0.17 ± 0.12 IG: 0.59 ± 1.1/0.14 ± 0.14 (P < 0.01)			
Facchin 2020	NR	**Per-protocol results only; not possible to calculate ITT results** Mean partial Mayo score (SD provided by author on request) T0/T1 IG: 0.857 (1.027)/0.428 (0.7559); CG: 1.5 (1.932)/1.625 (1.821) Mean (SD **converted from IQR using formula SD = IQR/1.35**) Faecal calprotectin T0/T1 IG: 187.93 (123.0)/214.21 (171.5); CG: 684.57 (904.1)/304 (196.1) Median IBDQ at T0/T1 (range provided by author on request; **converted to SD using formula SD = range/4**): IG: 170 (22.75)/193.5 (17.25) (14 participants) CG: 188 (30.75)/188 (23) (16 participants) Reduction of 30% of FC index for UC > 150 µg/mL: IG 57.1%; CG 55.5%	NR	NR for UC cohort separately in publication Total withdrawals for CD and UC cohorts combined: IG: 7/28 (1 did not receive allocated intervention due to hospitalisation; 2 lost to follow-up; 3 discontinued due to non-compliance (n = 1), taking antibiotics (n = 1), taking probiotics (n = 1); 1 excluded due to no PCR reaction on microbiota analysis) CG: 1/29 (lost to follow-up) Based on information provided upon request from authors on UC cohort separately: IG: 5/19 CG: 1/17	NR
Valcheva 2022	**During 6-month intervention period** IG: 19/43 (numerator and denominator include 8 participants who were excluded after randomi-	NR	NR	IG: 13/43 (numerator and denominator include 8 participants who were excluded after randomisation (not assessed for any variable after baseline n = 6; allergic reaction n = 1; lost eligibility n = 1)) CG: 6/46 (numerator and denominator include 5 participants who were exclud-	IG: 33/43 (numerator and denominator include 8 participants who were excluded after randomisation (not assessed for any variable after baseline n = 6; allergic reac-

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Table 3. Maintenance outcomes *(Continued)*

	sation (not assessed for any variable after baseline n = 6; allergic reaction n = 1; lost eligibility n = 1)) CG: 15/46 (numerator and denominator include 5 participants who were excluded after randomisation (not assessed for any variable after baseline n = 4; lost eligibility n = 1))			ed after randomisation (not assessed for any variable after baseline n = 4; lost eligibility n = 1))	tion n = 1; lost eligibility n = 1)) CG: 21/46 (numerator and denominator include 5 participants who were excluded after randomisation (not assessed for any variable after baseline n = 4; lost eligibility n = 1))
Hallert 1991	NR	No endpoints defined. 20/36 reported generally fewer symptoms while taking ispaghula. 7/36 felt better with placebo (P < 0.001). Denominator includes 7 withdrawals during 1st treatment period. IG was associated with lower score on all of the 8 scales (mean 0.92, 95% CI 0.52 to 1.30) (P < 0.001) (mean score for each of 8 questionnaire items available as a chart). During ispaghula treatment, scores decreased a mean of 1.90 (95% CI 0.86 to 2.99) (P < 0.001), compared with 0.99 (95% CI 0.42 to 1.52) (P < 0.001) for placebo. Addressing the possibility of a carry-over effect, analysis of outcome disclosed no difference in scores between participants starting with ispaghula and those starting with placebo.	NR	11/36 (numerator and denominator include 7 withdrawals during the 1st treatment period (4 due to colitis relapse (3 while taking placebo and 1 while taking ispaghula); 1 due to increased abdominal pain (placebo); 2 due to non-compliance (treatment arm NR)) and 4 withdrawals during 2nd treatment period (4 due to "feeling worse" (all placebo))) Unable to calculate for separate treatment arms, as treatment arm NR for withdrawals due to non-compliance	NR

AEs: adverse events
CG: control group
CI: confidence interval

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CRP: C-reactive protein
FC: faecal calprotectin
IBDQ: Inflammatory Bowel Disease Questionnaire
IG: intervention group
IQR: interquartile range
ITT: intention-to-treat
NR: not reported
SD: standard deviation
UC: ulcerative colitis

APPENDICES

Appendix 1. CENTRAL search strategy

Date Run: 24/06/2023 10:35:33

#1 ([mh "Colitis, Ulcerative"] or [mh ^"Inflammatory Bowel Diseases"] or (Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis):ti,ab) AND ([mh ^Oligosaccharides] or [mh Prebiotics] or [mh "Dietary Fiber"] or [mh "Resistant Starch"] or [mh "Gum Arabic"] or [mh Inulin] or [mh Lactoferrin] or [mh Lactulose] or (Dietary Fiber* or Dietary Fibre* or Fructooligosaccharide* or Oligofructose or Oligofructan or FOS or FOSS or Galactooligosaccharide* or Gum Arabic or Gum Acacia or Acacia Gum or Hi-Maize or Inulin* or Lactoferrin* or Lactotransferrin* or Lactulose* or Oligosaccharide* or PreBiotic* or Pre-Biotic* or Polydextrose or Resistant Starch or Roughage* or Wheat Bran* or Idolax or "Raftilose P95" or "RP G28" or "HAM RS2" or Duphalac or Normase or Amivalex):ti,ab) in Trials 197

Appendix 2. MEDLINE search strategy

Database: Ovid MEDLINE(R) ALL <1946 to June 22, 2023>

1 Colitis, Ulcerative/ or Inflammatory Bowel Diseases/ or (Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis).ti,ab. (77781)

2 Oligosaccharides/ or Prebiotics/ or exp Dietary Fiber/ or Resistant Starch/ or Gum Arabic/ or Inulin/ or Lactoferrin/ or Lactulose/ or (Dietary Fiber? or Dietary Fibre? or Fructooligosaccharide* or Oligofructose or Oligofructan or FOS or FOSS or Galactooligosaccharide* or Gum Arabic or Gum Acacia or Acacia Gum or Hi-Maize or Inulin* or Lactoferrin* or Lactotransferrin* or Lactulose* or Oligosaccharide* or Prebiotic* or Pre-biotic* or Polydextrose or Resistant Starch or Roughage? or Wheat Bran? or Idolax or "Raftilose P95" or "RP G28" or "HAM RS2" or Duphalac or Normase or Amivalex).ti,ab. (145683)

3 ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or (Randomi?ed or Placebo or Randomly or Trial or Groups).ab. or Drug Therapy.fs.) not (exp Animals/ not Humans.sh.) (4983746)

4 1 and 2 and 3 (339)

Appendix 3. Embase search strategy

Database: Embase <1974 to 2023 Week 25>

1 Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention $1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (6347934)

2 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (9489)

3 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or (randomi?ed controlled or control group$1).ti,ab.) (351194)

4 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (21693)

5 (Systematic review not (trial or study)).ti. (264254)

6 (nonrandom$ not random$).ti,ab. (19010)

7 ("Random field$" or (random cluster adj3 sampl$)).ti,ab. (4531)

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8 (review.ab. and review.pt.) not trial.ti. (1126831)

9 "we searched".ab. and (review.ti. or review.pt.) (50155)

10 ("update review" or (databases adj4 searched)).ab. (63325)

11 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1231071)

12 Animal experiment/ not (human experiment/ or human/) (2586096)

13 or/2-12 (4356360)

14 1 not 13 (5601522)

15 exp Ulcerative Colitis/ or Inflammatory Bowel Disease/ or (Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis).ti,ab. (141339)

16 Oligosaccharide/ or Prebiotic Agent/ or exp Dietary Fiber/ or Resistant Starch/ or Gum Arabic/ or Inulin/ or Lactoferrin/ or Lactulose/ or (Dietary Fiber? or Dietary Fibre? or Fructooligosaccharide* or Oligofructose or Oligofructan or FOS or FOSS or Galactooligosaccharide* or Gum Arabic or Gum Acacia or Acacia Gum or Hi-Maize or Inulin* or Lactoferrin* or Lactotransferrin* or Lactulose* or Oligosaccharide* or Prebiotic* or Pre-biotic* or Polydextrose or Resistant Starch or Roughage? or Wheat Bran? or Idolax or "Raftilose P95" or "RP G28" or "HAM RS2" or Duphalac or Normase or Amivalex).ti,ab. (177226)

17 14 and 15 and 16 (518)

Appendix 4. ClinicalTrials.gov search strategy

Advanced Search (Classic)

Condition or disease*: Ulcerative Colitis

Study type: Interventional Studies (Clinical Trials)

Intervention/treatment*: Oligosaccharides OR Prebiotics OR Dietary Fiber OR Resistant Starch

* These lines contain the terms that retrieve at least one unique record.

23 Studies found

Appendix 5. WHO ICTRP search strategy

Advanced Search

Ulcerative Colitis OR Idiopathic Proctocolitis OR Colitis Gravis *in the Condition*

Oligosaccharides OR Prebiotics OR Dietary Fiber OR Resistant Starch *in the Intervention*

Recruitment status is ALL

5 records for 5 trials

HISTORY

Protocol first published: Issue 3, 2022

CONTRIBUTIONS OF AUTHORS

VS: developed, contributed to writing and editing, made an intellectual contribution to, advised on, approved the final version of the review prior to submission

MG: conceived the review question, secured funding, developed, contributed to writing and editing, made an intellectual contribution to, advised on, approved the final version of the review prior to submission; is a guarantor of the review

VG: contributed to writing and editing, made an intellectual contribution to, advised on, approved the final version of the review prior to submission

AS: contributed to writing, made an intellectual contribution to, approved the final version of the review prior to submission

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AA: made an intellectual contribution to, advised on, approved the final version of the review prior to submission

DECLARATIONS OF INTEREST

VS: none

MG: Morris Gordon is a Cochrane editor. He was not involved in the editorial process for this review.

VG: Vicki Gregory's post at Crohn's & Colitis UK is funded by a grant from the Leona M and Harry B Helmsley Charitable Trust.

AS: none

AA: Anthony Akobeng is a Cochrane editor. He was not involved in the editorial process for this review.

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Internal sources

- National Institute for Health Research, UK

  NIHR funded project (Project:NIHR132748) - a programme of high priority Cochrane systematic Reviews to investigate the management of Inflammatory Bowel Disease during and after the COVID-19 pandemic: Optimal biologic and immunomodulator therapies, diet therapies, telehealth and education interventions

External sources

- None, Other

  None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have changed the scope of this review to also include maintenance outcomes. The primary outcome for maintenance studies is clinical relapse.

We have separated our secondary outcomes into subcategories where appropriate. None of the studies reported escalation of therapy or surgery, so we have not included this outcome in the summary of findings tables.

Lack of data precluded our pre-planned subgroup and sensitivity analyses.

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