Cochrane Library

Cochrane Database of Systematic Reviews

Probiotics for maintenance of remission in ulcerative colitis (Review)

Iheozor-Ejiofor Z, Kaur L, Gordon M, Baines PA, Sinopoulou V, Akobeng AK

Iheozor-Ejiofor Z, Kaur L, Gordon M, Baines PA, Sinopoulou V, Akobeng AK.
Probiotics for maintenance of remission in ulcerative colitis.
Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD007443.
DOI: 10.1002/14651858.CD007443.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Probiotics for maintenance of remission in ulcerative colitis

Zipporah Iheozor-Ejiofor[1], Lakhbir Kaur[1], Morris Gordon[1,2], Patricia Anne Baines[3], Vasiliki Sinopoulou[1], Anthony K Akobeng[4]

[1]School of Medicine, University of Central Lancashire, Preston, UK. [2]Families Division, Blackpool Victoria Hospital, Blackpool, UK. [3]Preston, UK. [4]Sidra Medicine, Doha, Qatar

Contact address: Anthony K Akobeng, Sidra Medicine, PO Box 26999, Doha, Qatar. aakobeng@sidra.org, akobeng@aol.com.

Editorial group: Cochrane IBD Group
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2020.

Citation: Iheozor-Ejiofor Z, Kaur L, Gordon M, Baines PA, Sinopoulou V, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2020, Issue 3. Art. No.: CD007443. DOI: 10.1002/14651858.CD007443.pub3.

ABSTRACT

Background

Ulcerative colitis is an inflammatory condition affecting the colon, with an annual incidence of approximately 10 to 20 per 100,000 people. The majority of people with ulcerative colitis can be put into remission, leaving a group who do not respond to first- or second-line therapies. There is a significant proportion of people who experience adverse effects with current therapies. Consequently, new alternatives for the treatment of ulcerative colitis are constantly being sought. Probiotics are live microbial feed supplements that may beneficially affect the host by improving intestinal microbial balance, enhancing gut barrier function and improving local immune response.

Objectives

The primary objective was to determine the efficacy of probiotics compared to placebo, no treatment, or any other intervention for the maintenance of remission in people with ulcerative colitis. The secondary objective was to assess the occurrence of adverse events associated with the use of probiotics.

Search methods

We searched CENTRAL, MEDLINE, Embase, and two other databases on 31 October 2019. We contacted authors of relevant studies and manufacturers of probiotics regarding ongoing or unpublished trials that may be relevant to the review, and we searched ClinicalTrials.gov. We also searched references of trials for any additional trials.

Selection criteria

Randomised controlled trials (RCTs) that compared probiotics against placebo or any other intervention, in both adults and children, for the maintenance of remission in ulcerative colitis were eligible for inclusion. Maintenance therapy had to be for a minimum of three months when remission has been established by any clinical, endoscopic,histological or radiological relapse as defined by study authors.

Data collection and analysis

Two review authors independently conducted data extraction and 'Risk of bias' assessment of included studies. We analysed data using Review Manager 5. We expressed dichotomous and continuous outcomes as risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs). We assessed the certainty of the evidence using the GRADE methodology.

Main results

In this review, we included 12 studies (1473 randomised participants) that met the inclusion criteria. Participants were mostly adults. The studies compared probiotics to placebo, probiotics to 5-aminosalicylic acid (5-ASA) and a combination of probiotics and 5-ASA to 5-ASA. The studies ranged in length from 12 to 52 weeks. The average age of participants was between 32 and 51, with a range between 18 and 88 years. Seven studies investigated a single bacterial strain, and five studies considered mixed preparations of multiple strains. The risk

of bias was high in all except three studies due to selective reporting, incomplete outcome data and lack of blinding. This resulted in low- to very low-certainty of evidence.

It is uncertain if there is any difference in occurrence of clinical relapse when probiotics are compared with placebo (RR 0.87, 95% CI 0.63 to 1.18; 4 studies, 361 participants; very low-certainty evidence (downgraded for risk of bias, imbalance in baseline characteristics and imprecision)). It is also uncertain whether probiotics lead to a difference in the number of people who maintain clinical remission compared with placebo (RR 1.16, 95% CI 0.98 to 1.37; 2 studies, 141 participants; very low-certainty evidence (downgraded for risk of bias, imbalance in baseline characteristics and imprecision)).

When probiotics are compared with 5-ASA, there may be little or no difference in clinical relapse (RR 1.01, 95% CI 0.84 to 1.22; 2 studies, 452 participants; low-certainty evidence) and maintenance of clinical remission (RR 1.06, 95% CI 0.90 to 1.25; 1 study, 125 participants; low-certainty evidence). It is uncertain if there is any difference in clinical relapse when probiotics, combined with 5-ASA are compared with 5-ASA alone (RR 1.11, 95% CI 0.66 to 1.87; 2 studies, 242 participants; very low-certainty evidence (downgraded due to risk of bias and imprecision)). There may be little or no difference in maintenance of remission when probiotics, combined with 5-ASA, are compared with 5-ASA alone (RR 1.05, 95% CI 0.89 to 1.24; 1 study, 122 participants; low-certainty evidence).

Where reported, most of the studies which compared probiotics with placebo recorded no serious adverse events or withdrawals due to adverse events. For the comparison of probiotics and 5-ASA, one trial reported 11/110 withdrawals due to adverse events with probiotics and 11/112 with 5-ASA (RR 1.02, 95% CI 0.46 to 2.25; 222 participants; very low-certainty evidence). Discontinuation of therapy was due to gastrointestinal symptoms. One study (24 participants) comparing probiotics combined with 5-ASA with 5-ASA alone, reported no withdrawals due to adverse events; and two studies reported two withdrawals in the probiotic arm, due to avascular necrosis of bilateral femoral head and pulmonary thromboembolism (RR 5.29, 95% CI 0.26 to 107.63; 127 participants; very low-certainty evidence).

Health-related quality of life and need for additional therapy were reported infrequently.

Authors' conclusions

The effectiveness of probiotics for the maintenance of remission in ulcerative colitis remains unclear. This is due to low- to very low-certainty evidence from poorly conducted studies, which contribute limited amounts of data from a small number of participants. Future trials comparing probiotics with 5-ASA rather than placebo will better reflect conventional care given to people with ulcerative colitis. Appropriately powered studies with a minimum length of 12 months are needed.

PLAIN LANGUAGE SUMMARY

Probiotics for maintenance of remission in ulcerative colitis

What is the aim of this review?

The aim of this Cochrane Review was to find out whether probiotics can maintain remission in people with ulcerative colitis. We collected and analysed data from 12 studies with a total of 1473 people to answer this question.

Key messages

The question on whether probiotics can maintain remission in people with ulcerative colitis remains unanswered. There were no serious adverse events when probiotics were compared with placebo. However, one study reported similar numbers of serious adverse events in people who had probiotics and those who received 5-aminosalicylic acid (5-ASA, an anti-inflammatory medicine used to treat ulcerative colitis and other conditions. . More information as to what these serious adverse events are, was not provided.

What was studied in the review?

Ulcerative colitis is a chronic disease of the large bowel, which causes inflammation (swelling). Some of the symptoms include tummy pain, diarrhoea and tiredness. Probiotics are living microscopic organisms that are thought to change the growth of bacteria in the bowel and reduce inflammation.

What are the main results of the review?

We searched for randomised controlled trials (RCTs; clinical studies where people are randomly put into one of two or more treatment groups) comparing probiotics with placebo (dummy treatment), probiotics with 5-ASA and a combination of probiotics and 5-ASA with 5-ASA. There were 12 RCTs involving 1473 participants. The trials looked at adult males and females. Only three studies clearly stated that participants were not allowed to take other medication outside of those being compared.

1) There was no clear difference in the number of people who had a clinical relapse when probiotics were compared with placebo.

2) There was also no clear difference in the number of people who had a clinical relapse when probiotics were compared with 5-ASA.

3) It is uncertain whether probiotics lead to a difference in the number of people who remain in clinical remission compared with placebo because the quality of evidence is very low.

4) There was no clear difference in the number of people who remained in clinical remission when probiotics were compared to 5-ASA.

5) When probiotics combined with 5-ASA was compared to 5-ASA alone, there was no clear difference in the number of people who remained in clinical remission.

6) It is uncertain whether probiotics combined with 5-ASA lead to a difference in the number of people who have a clinical relapse when compared with 5-ASA alone.

7) No serious adverse events were reported in the trials which compared probiotics with placebo. One study which compared probiotics with 5-ASA reported similar numbers of serious adverse events with both treatments. Discontinuation of therapy was due to gastrointestinal disorders, such as bloody stools, nausea, diarrhoea and abdominal pain.

8) There was not enough information from the studies on how probiotics affect people's quality of life and the need for additional therapy when compared to other treatments.

Conclusion

We are uncertain as to whether probiotics can maintain remission in people with ulcerative colitis. This is because the studies had very few participants and were not conducted using reliable methods. With the evidence presented in these studies, we are unable to make strong conclusions into the effectiveness of probiotics; better designed studies with more participants are needed.

How up-to-date is this review?

This review is up-to-date as of October 2019.

Summary of findings for the main comparison. Probiotics compared to placebo for maintenance of remission in ulcerative colitis

Probiotics compared to placebo for maintenance of remission in ulcerative colitis

Patient or population: people with ulcerative colitis in remission
Setting: hospitals
Intervention: probiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with probiotics				
Clinical relapse (12 to 52 weeks)	Study population		RR 0.87 (0.63 to 1.18)	361 (4 RCTs)	⊕⊖⊖⊖ **Very low**[a]	Clinical relapse was defined as a flare-up (NCT02361957), CAI ≤ 5 (Yasushi 2015) and persistence of a rectal bleeding score of ≤ 2 on Sutherland DAI score for 3 consecutive days and/or initiation of remission induction therapy for worsening of ulcerative colitis (Matsuoka 2018), respectively
	554 per 1000	493 per 1000 (399 to 609)				
Maintenance of clinical remission (52 weeks)	Study population		RR 1.16 (0.98 to 1.37)	141 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a]	Maintenance of remission is the number of participants who did not relapse. One additional study reported insufficient data for inclusion in the meta-analysis, therefore, we did not further analyse the results (reported P = 0.643).
	400 per 1000	532 per 1000 (308 to 924)				
Serious adverse events (48 to 52 weeks)	See comment	See comment	-	351 (4 RCTs)	-	Four studies reported that no serious adverse events occurred.
Withdrawal due to adverse events	See comment	See comment	-	113 (2 RCTs)	-	Two studies reported there were no withdrawals due to adverse events.
Need for additional therapy	Not reported in any of the studies					
Health-related quality of life (12 weeks)	Mean IBD-Q score with placebo was 3.5	MD 0.70 points lower (1.63 lower to 0.23 higher)	-	25 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	Scale: IBD-Q, range 1 -7, higher score = better quality of life

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CAI: colitis activity index **CI:** confidence interval; **DAI**: disease activity index; **IBD-Q**: inflammatory bowel disease questionnaire; **MD**: mean difference; **RCT**: randomised controlled trial; **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 three times: risk of reporting bias and other bias due to imbalance in baseline characteristics, imprecision due to small sample size.
[b]Downgraded two times: imprecision due to small sample size from a single study resulting in wide confidence interval.

Summary of findings 2. Probiotics compared to 5-aminosalicylic acid (5-ASA) (mesalazine) for maintenance of remission in ulcerative colitis

Probiotics compared to 5-ASA (mesalazine) for maintenance of remission in ulcerative colitis

Patient or population: people with ulcerative colitis in remission
Setting: hospitals
Intervention: probiotics
Comparison: 5-ASA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 5-ASA	Risk with probiotics				
Clinical relapse (52 weeks)	Study population 458 per 1000	458 per 1000 (380 to 554)	RR 1.01 (0.84 to 1.22)	452 (2 RCTs)	⊕⊕⊖⊖ **Low**[a]	Clinical relapse was based on the presence of all the following: CAI > 6 (or an increase in CAI of at least 3 points with CAI = 4 being exceeded at the same time); endoscopic index > 4; histological signs of acute inflammation (Kruis 2004) and appearance of ulcerative colitis symptoms or an increase in CAI to more than 4 points (Zocco 2006)
Maintenance of clinical remission (52 weeks)	Study population 800 per 1000	848 per 1000	RR 1.06 (0.90 to 1.25)	125 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	Maintenance of remission is the number of participants who did not relapse.

		(720 to 1000)				
Serious adverse events (52 weeks)	Study population		RR 1.19 (0.41 to 3.46)	327 (1 RCT)	⊕⊖⊖⊖ **Very low**[d]	Serious adverse events were not reported in detail
	36 per 1000	43 per 1000 (15 to 126)				
Withdrawal due to adverse events (52 weeks)	Study population		RR 1.02 (0.46 to 2.25)	222 (1 study)	⊕⊖⊖⊖ **Very low**[e]	Discontinuation of therapy was due to gastrointestinal disorders, such as bloody stools, nausea, diarrhoea, mucous secretion and abdominal pain
	98 per 1000	100 per 1000 (45 to 221)				
Need for additional therapy	Not reported in any of the studies					
Health-related quality of life (52 weeks)	Mean IBD-Q score with 5-ASA was 24.3 points	MD 0.80 points lower (2.01 lower to 0.41 higher)		222 (1 RCT)	⊕⊕⊖⊖ **Low**[c]	Scale: IBD-Q, range 1 -32, higher score = better quality of life

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

5-ASA: 5-aminosalicylic acid; **CAI**: colitis activity index **CI:** confidence interval; **IBD-Q**: inflammatory bowel disease questionnaire; **RCT**: randomised controlled trial; **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 two times: risk of attrition bias and other bias due to imbalance in baseline characteristics, imprecision due to sample size not meeting the optimal information size.
[b]Downgraded two times: risk of performance and detection bias from an open-label study and small number of events.
[c]Downgraded two times: risk of attrition bias and imprecision due to small sample size.
[d]Downgraded three times: risk of attrition bias, imprecision due to small number of events from a single study resulting in wide confidence interval which includes appreciable harm. Serious adverse events were not described in detail.[e]Downgraded three times: risk of attrition bias, imprecision due to small number of events from a single study resulting in wide confidence interval which includes appreciable harm.

Summary of findings 3. Probiotic + 5-aminosalicylic acid (5-ASA) (mesalazine) compared to 5-ASA (mesalazine) for maintenance of remission in ulcerative colitis

Probiotic + 5-ASA (mesalazine) compared to 5-ASA (mesalazine) for maintenance of remission in ulcerative colitis

Patient or population: people with ulcerative colitis in remission
Setting: hospitals
Intervention: probiotic + 5-ASA
Comparison: 5-ASA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 5-ASA	Risk with probiotic + 5-ASA				
Clinical relapse (12 to 52 weeks)	Study population 208 per 1000	229 per 1000 (144 to 371)	RR 1.11 (0.66 to 1.87)	242 (2 RCTs)	⊕⊖⊖⊖ **Very low**[a]	Clinical relapse was defined as CAI > 4 (Kruis 1997) and appearance of ulcerative colitis symptoms or an increase in CAI to more than 4 points (Zocco 2006).
Maintenance of clinical remission (24 to 52 weeks)	Study population 800 per 1000	840 per 1000 (712 to 992)	RR 1.05 (0.89 to 1.24)	122 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	Maintenance of clinical remission is the number of participants who did not relapse.
Serious adverse events	Not reported in any of the studies					
Withdrawal due to adverse events (12 to 52 weeks)	Study population See comment	See comment	RR 5.29 (0.26 to 107.63)	127 (2 RCTs)	⊕⊖⊖⊖ **Very low**[c]	Two discontinuations in the probiotic arm were due to avascular necrosis of bilateral femoral head and pulmonary thromboembolism. One study (n = 24) reported no events in either arm.
Need for additional therapy	Not reported in any of the studies					
Health-related quality of life	Not reported in any of the studies					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

5-ASA: 5-aminosalicylic acid; CAI: Colitis activity index **CI:** confidence interval; **RCT**: randomised controlled trial; **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 three times: risk of attrition bias, imprecision due to small number of events and confidence interval which includes appreciable harm.
[b]Downgraded two times: risk of performance and detection bias from an open-label study, imprecision due to small number of events.
[c]Downgraded three times: unclear risk of selection bias (lack of information on sequence generation), imprecision due to small number of events in a single study and confidence interval which include appreciable harm.

BACKGROUND

Description of the condition

Ulcerative colitis is a chronic relapsing disease, with the greatest reported incidence in mainland Europe and Scandinavia of 9.2 to 20.3 per 100,000 people (Loftus 2004), totalling approximately 2.2 million sufferers in Europe alone. The peak incidence of the disease occurs between 15 and 25 years of age, and there is another smaller prevalence at ages 55 to 65. The disease is characterised by abdominal pain, bloody diarrhoea and faecal urgency. The diagnosis of ulcerative colitis is based on medical history, signs and symptoms, and any endoscopic or histopathological findings.

The disease is caused by diffuse inflammation, which starts at the rectum, spreads proximally, and is limited to the colon. The aetiology behind the disease is unknown, but is likely to be multifactorial; consisting of a genetic predisposition, dysregulation of the mucosal and epithelial barrier and lastly dysbiosis, although whether dysbiosis causes or is a result of the disease remains unclear (Ungaro 2016). The genetic component was further evaluated by Cleynen 2016 and a strong association between HLA DRB1 and ulcerative colitis was found. The genetic predisposition creates a four-fold risk for first-degree relatives.

Description of the intervention

Probiotics are live micro-organisms, that when consumed, may provide multiple health benefits. They produce their benefits by altering the gut microbiome through either enhancing the activity, volume or both, of the normal flora. *Lactobacillus spp,* for example, is one of the more popular probiotics and is thought to secrete bacteriocin, blocking the adherence of translocation of harmful bacteria (Panigrahi 2014).

Lactobacillus rhamnosus GG (*L rhamnosus*) produced mixed responses in animal models of colitis (Dieleman 2003; Shibolet 2002), as did *Lactobacillus plantarum* (*L plantarum*) 299V (Dieleman 2003; Kennedy 2000; Schultz 2002). Studies investigating combinations of probiotic species incorporated within VSL#3 have demonstrated a partial reduction of colitis in animal models (Madsen 2001; Shibolet 2002). There has been increasing interest in the use of probiotics, as they are considered safe and easily accessible (Ong 2019). It is worth noting that there are a huge number of different preparations available, varying in the specific strains isolated, the use of mixed strains in a single preparation, the form of the preparation and finally the licensing arrangements surrounding the preparations (medicinal versus food products).

How the intervention might work

There is growing evidence looking at the effects of probiotics in the use of inducing remission in ulcerative colitis since a previous Cochrane review (Mallon 2007). Due to the part that dysbiosis plays in ulcerative colitis, there is potential benefit in trying to restore the endogenous flora. Several observations, both on humans and animal models, emphasised the importance of bacterial flora in inflammatory bowel disease pathogenesis, justifying the current interest in antibiotic and probiotic therapies aimed at the manipulation of enteric flora (Cui 2004). The therapeutic efficacy of probiotics has been demonstrated in various models of experimental colitis, including interleukin-10 deficient mice (Madsen 1999; Schultz 2002), and acetic acid-induced colitis in rats (Fabia 1993).

Why it is important to do this review

In the UK, National Institute for Health and Care Excellence (NICE) and USA guidelines state that first-line therapy for maintenance of remission in ulcerative colitis is 5-aminosalicylic acid (5-ASA) (NICE 2019). 5-ASA works by binding to PPAR-# and reducing cytokine production. Some of the adverse effects associated with 5-ASA include headache, rash, nausea (common), pancreatitis (uncommon), and agranulocytosis (rare). Due to these side effects, some people are unable to tolerate the drug. If 5-ASA fails to work then other therapies to maintain remission include immune suppressants, such as anti-tumour necrosis factor (TNF) monoclonals, vedolizumab and tofacitinib may be used . These drugs work by blocking leukocyte recruitment at the molecular and vascular level (Fiorino 2016), some of the side effects include headache, dizziness and arthralgia.

The relapsing and remitting nature of the disease means that people can be in and out of hospital, experimenting with different drug regimes. The treatment costs Europe between GBP 11 to 26 billion pounds annually, with per patient costs approximately GBP 8011 to 9306 (Cohen 2010). If an alternative, cheaper treatment can be found for ulcerative colitis, then it would greatly benefit not only a budget stricken National Health Service (NHS), but also improve patients' quality of life. Whilst some studies have suggested that probiotics may be useful for maintenance of remission in mild to moderate ulcerative colitis (Kruis 2004; Zocco 2006), others have failed to show any benefit (Kruis 1997; Rembacken 1999). In this review we investigate the available evidence on the use of probiotics for the maintenance of remission in ulcerative colitis.

OBJECTIVES

The primary objective was to determine the efficacy of probiotics compared to placebo, no treatment, or any other intervention for the maintenance of remission in people with ulcerative colitis. The secondary objective was to assess the occurrence of adverse events associated with the use of probiotics.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs), with a minimum duration of three months, for inclusion in the review.

Types of participants

People of any age with ulcerative colitis in remission, defined as clinical, endoscopic, histological or radiological relapse by study authors.

Types of interventions

Probiotics administered in any form (drink, powder, capsule), orally as a single species, or as a cocktail of multiple species compared to no treatment, placebo or any other intervention.

Types of outcome measures

Primary outcomes

- Relapse (clinical, endoscopic, histopathological or radiological), as defined by the authors of the primary studies.

Where studies reported on the number of participants who did not experience a relapse, i.e. those who remained in remission, this was noted under 'maintenance of clinical remission'.

Secondary outcomes

- Serious adverse events
- Withdrawal due to adverse events
- Need for additional therapy
- Health-related quality of life, as measured by a validated quality of life tool

Search methods for identification of studies

Electronic searches

We conducted a comprehensive and systematic search to identify RCTs from inception to 31 October 2019 using the following databases.

- Cochrane Inflammatory Bowel Disease (IBD) Specialized Trials Register
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE
- Embase
- CINAHL

We did not place any restrictions on publication dates (after 1966) or language. See Appendix 1 for the detailed search strategies.

Searching other resources

We inspected the reference lists of all identified studies for more trials. We also contacted leaders in the field and manufacturers of probiotics to identify potentially relevant studies. We also searched ClinicalTrials.gov (clinicaltrials.gov) for ongoing trials (Appendix 1).

Data collection and analysis

We conducted data collection and analysis according to methods stipulated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

We undertook study selection in Covidence. Using the above search strategy, two review authors (LK, ZIE) identified titles that appeared to be potentially relevant. These were independently screened and in circumstances of disagreement, a third review author (AA) was involved to reach consensus.

There is some evidence that data from abstract publications can be inconsistent with data from published articles (Pitkin 1999), therefore we considered abstract publications, but only if sufficient data were presented to judge inclusion criteria fully and reports of the primary and secondary outcomes were given. If these were not available, we contacted authors directly, and if data were not provided, we excluded such studies.

The review authors, after reading the full texts, independently assessed the eligibility of all trials identified using ad hoc eligibility, based on the inclusion criteria above. Disagreement among review authors was again discussed, and agreement was reached by consensus after involvement of a third review author. We contacted authors of multiple publications, which appeared to report on the same study, for clarification. A flow chart was included (Figure 1).

Figure 1. Study flow diagram.

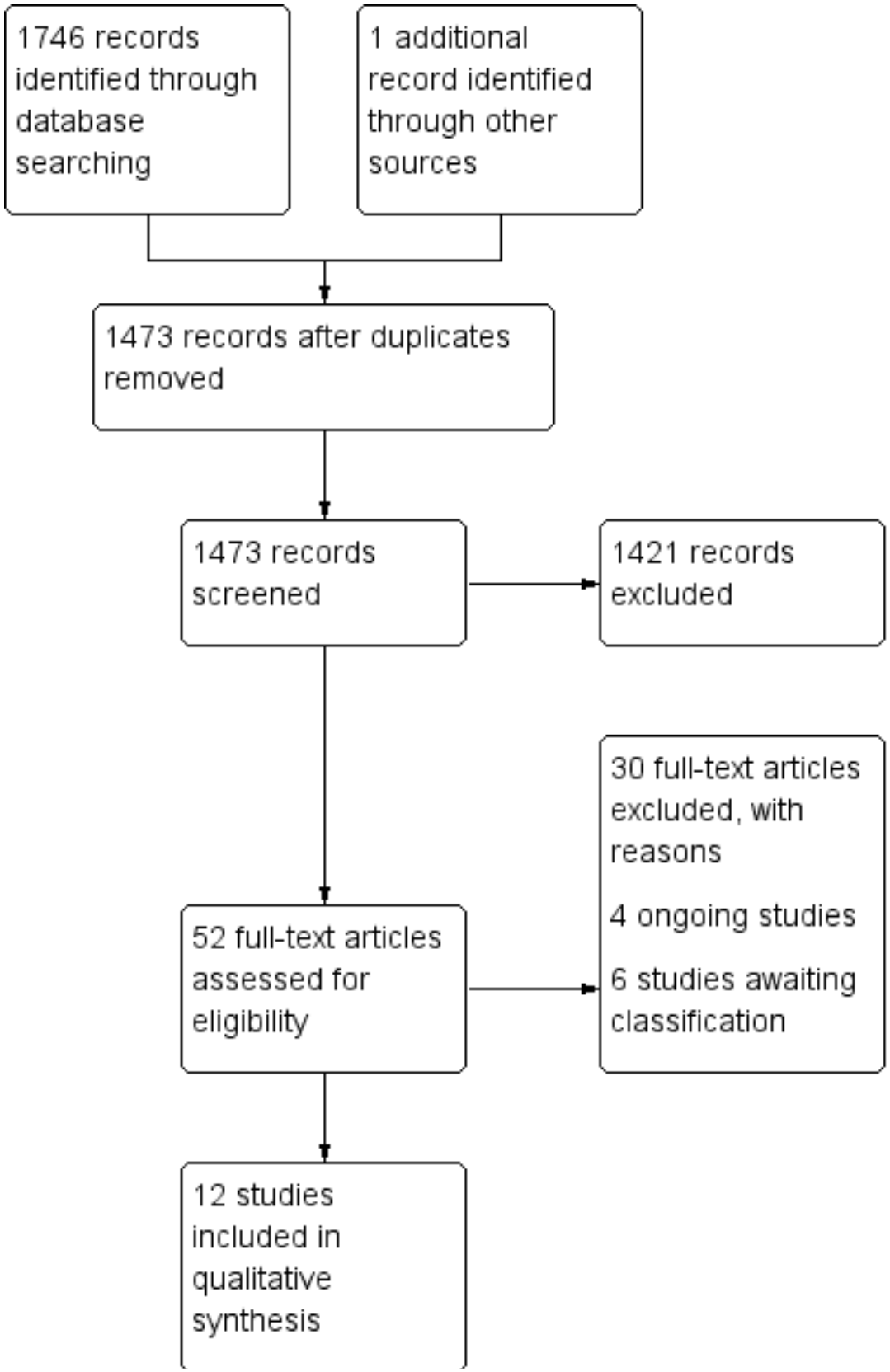
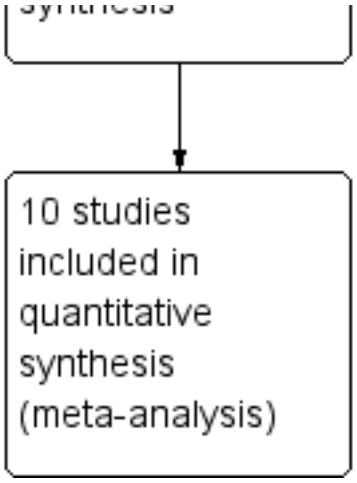


Figure 1. (Continued)



Data extraction and management

We developed a data extraction form and used it to extract information on relevant features and results of included studies. Two review authors (LK, ZIE) independently extracted and recorded data on a predefined checklist. Again, when disagreements occurred, a third review author (AA) was involved and consensus was reached. Extracted data included the following items.

- Characteristics of participants: age, sex, disease distribution, disease duration, disease activity index
- Total number of participants originally assigned to each intervention group
- Intervention: type and dose of probiotic(s)
- Control: no intervention, placebo or other interventions
- Concurrent medications
- Outcomes: time of assessment, length of follow-up, type of symptom score used or ulcerative colitis activity index, definition of remission and relapse, relapse rates, time to relapse, quality of life assessment, and adverse events

We resolved inconsistencies in data extraction, and transferred the information above into the Characteristics of included studies table.

Assessment of risk of bias in included studies

Two review authors (LK, ZIE) independently assessed risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011). We assessed the following domains.

- Selection bias
  - Sequence generation (i.e. was the allocation sequence adequately generated?)
  - Allocation sequence concealment (i.e. was allocation adequately concealed?)
- Performance bias (i.e. was knowledge of the allocated intervention adequately prevented during the study towards the participants?)
- Detection bias (i.e. were outcome assessors blinded adequately?)
- Attrition bias (were attritions and exclusions adequately reported?)
- Reporting bias: selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?)
- Other potential sources of bias (i.e. was the study apparently free of other problems that could put it at a high risk of bias?)

We considered subjective outcomes separately in our assessment of blinding and incompleteness of data. We judged studies to be at 'high', 'low' or 'unclear' risk of bias for each domain assessed. We judged the risk of bias across studies as follows.

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains are at low risk of bias.
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains are at unclear risk of bias.
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains are at high risk of bias.

Disagreements were resolved by consensus. We contacted study authors when insufficient information was provided to determine the risk of bias. Where we obtained information supporting our judgement on risk of bias through correspondence with study authors, we indicated this in the 'Risk of bias' table.

Measures of treatment effect

The measure of treatment effect for dichotomous outcomes was risk ratios (RRs). Where continuous outcomes reported with the same scale, we used mean differences (MDs).

Unit of analysis issues

The unit of analysis was the participant. Where studies assessed more than two interventions which are relevant to the review, we made multiple pair wise comparisons and analysed just the groups of interest. We did not include the same group of participants twice in the same meta-analysis. We were alert to the unit of analysis issues relating to outcome reporting at different follow-up times and only reported outcomes at final follow-up.

Dealing with missing data

We contacted study authors to request missing data. Where authors reported both intention-to-treat (ITT) and per protocol analysis, we preferred the former. However, where ITT analysis was not conducted or reported in the studies, we regarded withdrawals as failures. We undertook sensitivity analyses to exclude studies with missing data. We did not impute missing standard deviations (SDs). However, we noted any instances where data were extracted from graphs.

Assessment of heterogeneity

We assessed heterogeneity among trial results by inspection of graphical presentations and by calculating the Chi^2 test of heterogeneity; we regarded P = 0.10 as statistically significant. We used the I^2 statistic to quantity the effect of heterogeneity (Higgins 2003).

We based our interpretation of the I^2 statistic results on those suggested by Higgins 2011 (Section 9.5.2):

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

Assessment of reporting biases

We avoided different reporting biases by conducting an extensive literature search. It was not necessary to generate a funnel plot to investigate publication bias, as there were an insufficient number of studies contributing to the analysis.

Data synthesis

We pooled studies with the same population, intervention, comparator and outcomes; we did not pool studies which were clinically heterogenous. We used Review Manager 5 for data analysis (Review Manager 2014). For dichotomous variables, we calculated RRs and 95% confidence intervals (CIs) based on a random-effects model. For continuous variables, we calculated the MD and 95% CIs when continuous outcomes were measured using the same units. We used the fixed-effect model, as $I^2 = 0$. We had planned to use the random-effects model if I^2 had been > 0.

Subgroup analysis and investigation of heterogeneity

Had we included a sufficient number of studies, we would have carried out subgroup analyses based on:

- age (below 18 years and above 18 years); and
- species of probiotic.

Sensitivity analysis

We carried out the following sensitivity analyses, apart from the exclusion of studies at high risk of bias; this was not possible due to the paucity of data.

- Only including participants whose outcome is known (i.e. number of participants who completed the study used as denominator)
- Study quality (removing those at highest risk of bias)
- Random-effects versus fixed-effect models

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of evidence related to all outcomes listed in the Types of outcome measures (Schünemann 2011). The four levels of evidence certainty are 'high', 'moderate', 'low' or 'very low'. Certainty may be downgraded due to study limitations (risk of bias), imprecision, inconsistency, indirectness or publication bias. We derived the optimal information size for the primary outcomes from the included studies.

Two review authors (MG, ZIE) independently produced 'Summary of findings' tables using the GRADEpro GDT software for our main comparisons (GRADEpro GDT 2015). We presented the results for clinical relapse, maintenance of clinical remission, health-related quality of life, need for additional therapy, serious adverse events, and withdrawal due to serious adverse events.

RESULTS

Description of studies

Results of the search

The literature search returned 1473 unique records after duplicates were removed; we also identified an additional study from another source. After screening 1474 titles and abstracts, we found 52 studies that met our inclusion criteria. We obtained and screened the full-text copies of these 52 studies. We included 12 studies and excluded 30 studies with reasons. We contacted authors of eight studies for additional information (Bjarnason 2019; Copaci 2014; Shanahan 2006; Wildt 2011; Yasushi 2015; Zocco 2003; Zocco 2006; NCT02361957); we received responses from three authors (NCT02361957; Bjarnason 2019; Wildt 2011). We identified four ongoing studies and six studies are awaiting classification (Characteristics of ongoing studies; Characteristics of studies awaiting classification). The results of the search are presented in the PRISMA flow diagram Figure 1. Full details of the included and excluded studies are available in the Characteristics of included studies and Characteristics of excluded studies tables and are summarised below.

Included studies

Study design and setting

We included 12 studies (Bjarnason 2019; Copaci 2014; Kruis 1997; Kruis 2004; Matsuoka 2018; NCT02361957; Shanahan 2006; Vejdani 2017; Wildt 2011; Yasushi 2015; Zocco 2003; Zocco 2006). These studies were either single centre (Bjarnason 2019; Copaci 2014; NCT02361957; Shanahan 2006; Yasushi 2015; Zocco 2006), or multicentre (Kruis 1997; Kruis 2004; Matsuoka 2018; Vejdani 2017; Wildt 2011) parallel group RCTs. The studies were conducted in hospitals in Italy (Zocco 2003; Zocco 2006), Iran (Vejdani 2017), Ireland (Shanahan 2006), Japan (Yasushi 2015), the Netherlands (NCT02361957), Romania (Copaci 2014), the UK (Bjarnason 2019); multiple centres in Denmark (Wildt 2011) and Japan (Matsuoka 2018); multiple centres across Germany, the Czech Republic, Austria (Kruis 1997) and Germany, the Czech Republic, Austria, Estonia, Latvia, Lithuania, Slovak Republic, Sweden, Switzerland and the UK (Kruis 2004). In two studies (Copaci 2014; Shanahan 2006), where the setting was not explicitly stated, we have assumed this to be the authors' affiliation.

Participants

In five studies reporting mean age, the average age of participants was between 32 years in Zocco 2003 and 51 years in NCT02361957). In five studies reporting on age range, included participants were between 18 in Copaci 2014 and 88 years in Kruis 1997. Only one study (Yasushi 2015), which based on its inclusion criteria may have included paediatric patients (> 13 years). This study had an overall mean age of 43.9 +/- 14.8 years, therefore, it is unclear whether children were recruited. Ten out of 11 studies randomised 25 (NCT02361957) to 327 (Kruis 2004) participants. Copaci 2014 included 36 participants, some (number not stated) of which received interventions that are outside the scope of this review. The studies included male and female participants with ulcerative colitis who may or may not have been receiving medication at the time of recruitment, except for Vejdani 2017 who did not report on age and sex, making it unclear whether the study was conducted on adult and/or paediatric female and/or male patients. In 10 studies, participants had the following forms of ulcerative colitis: pancolitis, left-sided, total colitis, proctitis, proctosigmoiditis, total colitis, subtotal colitis, distal, left colon. However, three studies did not provide any information on the extent of disease (Vejdani 2017; Wildt 2011; Zocco 2003). The length of time participants had been in remission at the point of study entry was not stated in six studies (Bjarnason 2019; Copaci 2014; NCT02361957; Shanahan 2006; Vejdani 2017; Zocco 2003), and unclear in one study (Yasushi 2015). Three studies reported at recruitment, that participants had been in remission between one month in Kruis 1997 and Matsuoka 2018 and 12 years in Kruis 1997.

Intervention

All the included studies had two trial arms, except three studies (Shanahan 2006; Zocco 2003; Zocco 2006), which had three trial arms. Copaci 2014 had three trial arms, however, one arm was excluded for assessing an intervention (prebiotic) that is not relevant to the review. The studies investigated the following comparisons.

- Probiotics versus placebo (Bjarnason 2019; Matsuoka 2018; NCT02361957; Vejdani 2017; Wildt 2011; Yasushi 2015)
- Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine) (Kruis 2004)
- Probiotics plus 5-ASA versus 5-ASA (Copaci 2014)
- Probiotics plus 5-ASA versus 5-ASA plus placebo (Kruis 1997)
- Probiotics versus probiotics versus placebo (Shanahan 2006)
- Probiotics versus probiotics plus 5-ASA versus 5-ASA (Zocco 2003; Zocco 2006)

In seven studies (Copaci 2014; Kruis 1997; Kruis 2004; Shanahan 2006; Vejdani 2017; Zocco 2003; Zocco 2006), the probiotics contained single bacterial strains and probiotics in five studies contained multiple strains (Bjarnason 2019; Matsuoka 2018; NCT02361957; Wildt 2011; Yasushi 2015). These single bacterial strains include *Bifidobacterium longum* (*B longum*) W11 (Copaci 2014), *Echerichia coli* (*E coli*) Nissle 1917 (Kruis 1997; Kruis 2004), *Lactobacillus salivarius* (*L salivarius*) UCC118 (Shanahan 2006), *Bifidobacterium infantis* (*B infantis*) 35624 (Shanahan 2006), *Lactobacillus casei* (*L casei*) strain ATCC PTA-3945 (Vejdani 2017), and *Lactobacillus GG* 18 X 10^9 (Zocco 2003; Zocco 2006).

In studies with multiple strain probiotics, the following combinations were studied.

- *Lactobacillus rhamnosus (L rhamnosus) NCIMB 30174, Lactobacillus plantarum (L plantarum) NCIMB 30173, Lactobacillus acidophilus (L acidophilus) NCIMB 30175 and Enterococcus faecium (E faecium) NCIMB 30176* (Bjarnason 2019).
- *Bifidobacterium bifidum (B bifidum) W23, Bifidobacterium lactis (B lactis) W51, Bifidobacterium lactis (B lactis) W52, L acidophilus W22, L casei W56, Lactobacillus paracasei (L paracasei) W20, Lactobacillus plantarum (L plantarum) W62, L salivarius W24 and Lactococcus lactis (L lactis) W19* (NCT02361957).
- *Bifidobacterium breve* (*B breve) and L acidophilus* (Matsuoka 2018).
- *L acidophilus* strain La-5 + *Bifidobacterium animalis (B animalis) subsp. lactis* strain BB-12 (Wildt 2011).
- *Streptococcus faecalis* (*S faecalis)* T-110 (lactomin) + *Clostridium butyricum* TO-A + *Bacillus mesentericus* (Yasushi 2015).

Interventions were administered daily for four weeks in Bjarnason 2019 to 52 weeks (Kruis 2004; Shanahan 2006; Wildt 2011; Yasushi 2015; Zocco 2003; Zocco 2006). Concomittant treatments were not allowed in three studies (Kruis 2004; Wildt 2011; Zocco 2006), and in five studies it was not explicitly stated whether concomitant treatments were used or not. In four studies different concomitant treatments were used, such as 5-aminosalycilic preparation, low-dose azathioprine (1 mg/kg) and prednisolone < 4 mg/day (Bjarnason 2019), 2.4 g per day of mesalazine (NCT02361957), aminosalicylate (Shanahan 2006), unrestricted mesalazine and salazosulfapyridine plus topical antibiotics were not restricted (Yasushi 2015).

Outcomes

The studies reported data on all outcomes of interest except 'need for withdrawal of therapy'. We summarised outcome data in Table 1.

- Relapse was reported in all studies (Bjarnason 2019; Copaci 2014; Kruis 1997; Kruis 2004; Matsuoka 2018; NCT02361957; Shanahan 2006; Vejdani 2017; Wildt 2011; Yasushi 2015; Zocco 2003; Zocco 2006). Clinical relapse was reported in six studies (Bjarnason 2019; Kruis 1997; Kruis 2004; Matsuoka 2018; Yasushi 2015; Zocco 2006). In three studies, endoscopic and clinical relapse were not separated out (Vejdani 2017; Wildt 2011; Zocco 2003).
- Maintenance of remission (the number of participants who did not have a relapse) was reported in five studies (Copaci 2014; Matsuoka 2018; Wildt 2011; Yasushi 2015; Zocco 2006). Maintenance of clinical remission was reported in three studies (Bjarnason 2019; Yasushi 2015; Zocco 2006).
- Health related quality of life was reported in three studies (Bjarnason 2019; Kruis 2004; NCT02361957).
- Serious adverse events were reported in seven studies (Bjarnason 2019; Kruis 2004; Matsuoka 2018; Vejdani 2017; Wildt 2011; Yasushi 2015; Zocco 2006), although no full description was provided. Therefore, we were unable to ascertain the severity of the adverse events.
- Withdrawal due to adverse events was reported in five studies (Bjarnason 2019; Kruis 1997; Kruis 2004; Wildt 2011; Zocco 2003).

Funding and declaration of interest

The studies were government funded (Yasushi 2015), funded by manufacturing companies (Bjarnason 2019; Kruis 1997; Matsuoka 2018), part funded by industry and a charity (Wildt 2011), and part funded by government and industry (NCT02361957). The funding source was not reported in six studies (Copaci 2014; Kruis 2004; Shanahan 2006; Vejdani 2017; Zocco 2003; Zocco 2006).

Conflict of interest was not fully reported in any of the studies except Copaci 2014, in which the authors reported that they had none. Three studies reported that one author had no conflict of interest (Yasushi 2015), and two authors were funded by manufacturing companies (Bjarnason 2019; Matsuoka 2018). Two studies reported that authors were employed by a manufacturing company (NCT02361957; Wildt 2011). Conflicts of interest were not reported in five studies (Kruis 1997; Kruis 2004; Shanahan 2006; Zocco 2003; Zocco 2006).

Excluded studies

Thirty studies failed to meet the inclusion criteria and we excluded them for the following reasons.

- Wrong study design: review (Do 2010), commentary piece (Faubion 2000; Folwaczny 2000), not a RCT (Henker 2008; Venturi 1999).
- Wrong population: participants were not in remission at study entry (Fujimori 2009; IRCT20120415009475N5; Li 2013; Liu 2014; Miele 2009; NCT01772615; Rembacken 1999; Sanchez-Morales 2019; Zhang 2018a), a mixed population of active and inactive ulcerative colitis (Ishikawa 2011), mixed population of ulcerative colitis and Crohn's disease (Ballini 2019; Shadnoush 2013), participants had active ulcerative colitis (NCT00951548; Palumbo 2016; Solovyeva 2014; Tursi 2010), microscopic colitis (Rohatgi 2015).
- Wrong intervention (Bamba 2002).
- Short duration of follow-up (Ahmed 2013; Cui 2004).
- Insufficient information on study details and no response when authors were contacted (Ishikawa 2002; NCT00268164; NCT00374725; NCT00803829; Pelech 1998).

Risk of bias in included studies

The studies were either at high or unclear risk of bias. The risk of bias for the studies is summarised in Figure 2 and Figure 3. Further details are available in the Characteristics of included studies table.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

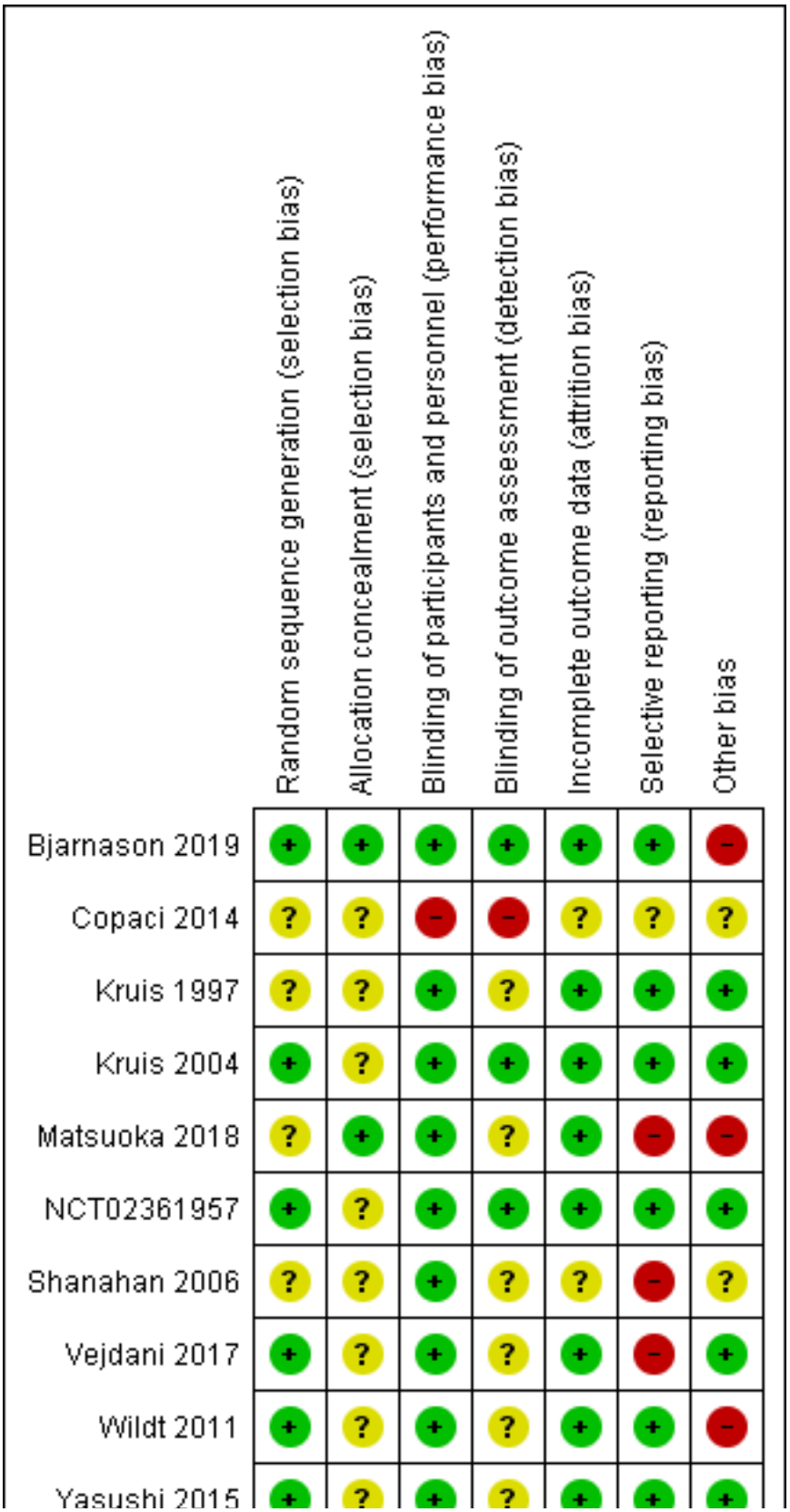


Figure 2. (Continued)

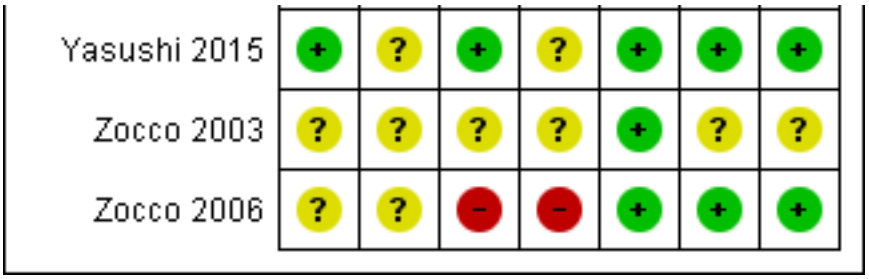
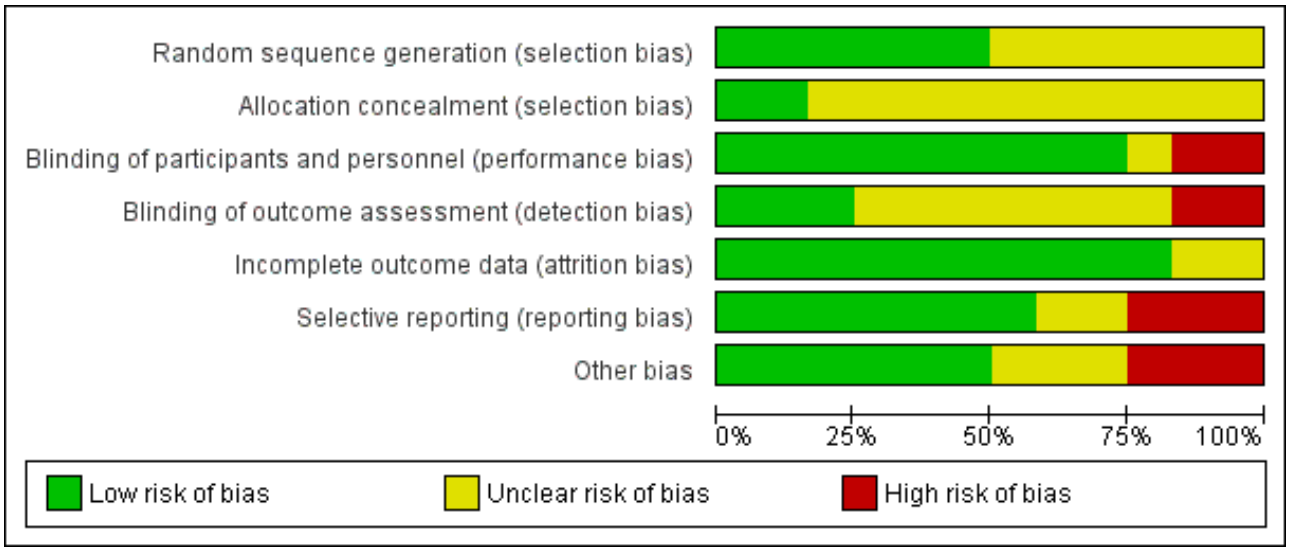


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

In all the included studies, allocation of participants to intervention or placebo was described as random. The method of randomisation was adequately described in six studies (Bjarnason 2019; Kruis 2004; NCT02361957; Vejdani 2017; Wildt 2011; Yasushi 2015), and not described in six studies (Copaci 2014; Kruis 1997; Matsuoka 2018; Shanahan 2006; Zocco 2003; Zocco 2006). We contacted the authors of these six studies to clarify the method of randomisation, but did not receive further information. We rated these studies as unclear risk of bias for sequence generation.

Allocation concealment

We rated allocation concealment as unclear for all except two studies (Bjarnason 2019; Matsuoka 2018). We contacted the authors to clarify allocation concealment, but did not receive a response. The interventions in Matsuoka 2018 were delivered in identical containers from the central pharmacy, therefore we rated this study as low risk of bias.

Blinding

Nine of the studies were described as double-blinded (Bjarnason 2019; Kruis 1997; Kruis 2004; Matsuoka 2018; NCT02361957; Shanahan 2006; Vejdani 2017; Wildt 2011; Yasushi 2015), and we rated them at low risk of performance bias. However, only three of these studies provided information (Bjarnason 2019; Kruis 2004; NCT02361957), which suggests that blinding was maintained until after outcome assessment. We rated all three studies at low risk of detection bias, and the remaining as unclear. Copaci 2014 and Zocco 2006 were open-label studies and we rated them at high risk of bias. There was insufficient information in Zocco 2003 to make a decision, therefore it we rated it at unclear risk of performance and detection bias.

Incomplete outcome data

Ten studies were at low risk of bias for reporting data for all participants (Bjarnason 2019; Zocco 2003; Zocco 2006), conducting full ITT analysis (NCT02361957; Vejdani 2017; Wildt 2011), a combination of low attrition rates and partial ITT analysis (Kruis 1997; Matsuoka 2018), and two studies had attrition rates of > 20% (Kruis 2004; Yasushi 2015), but balanced between both groups. Two studies were at unclear risk of bias (Copaci 2014; Shanahan 2006).

Selective reporting

Trial registrations were available for only three studies (Matsuoka 2018; NCT02361957; Wildt 2011).

Of the seven trials which we rated at low risk of reporting bias, two reported all outcomes which were prespecified in the trial

registration (NCT02361957; Wildt 2011), and five had no trial registration, but reported all expected outcomes (Bjarnason 2019; Kruis 1997; Kruis 2004; Yasushi 2015; Zocco 2006). We rated three studies at high risk of bias for reporting more outcomes than specified in the protocol (Matsuoka 2018), failing to report adverse events (Shanahan 2006), and results of biochemical tests (Vejdani 2017), Copaci 2014 and Zocco 2003 failed to provide sufficient information for a judgement to be made (unclear).

Other potential sources of bias

We rated six studies at low risk of bias for not having other apparent biases (Kruis 1997; Kruis 2004; NCT02361957; Vejdani 2017; Yasushi 2015; Zocco 2006). We rated three studies at high risk of bias due to an imbalance in baseline characteristics (Wildt 2011), a posthoc decision to discontinue the trial (Matsuoka 2018), and for being funded by the manufacturer of the probiotic product studied with no justification of the limits or level of involvement (Bjarnason 2019)

Effects of interventions

See: **Summary of findings for the main comparison** Probiotics compared to placebo for maintenance of remission in ulcerative colitis; **Summary of findings 2** Probiotics compared to 5-aminosalicylic acid (5-ASA) (mesalazine) for maintenance of remission in ulcerative colitis; **Summary of findings 3** Probiotic + 5-aminosalicylic acid (5-ASA) (mesalazine) compared to 5-ASA (mesalazine) for maintenance of remission in ulcerative colitis

Probiotics versus placebo

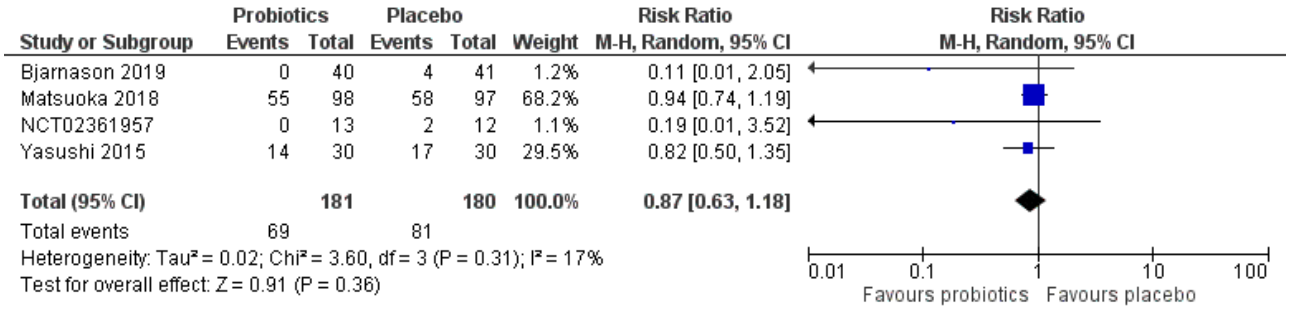
Seven studies compared probiotics with placebo (Bjarnason 2019; Matsuoka 2018; NCT02361957; Shanahan 2006; Vejdani 2017; Wildt 2011; Yasushi 2015). See Summary of findings for the main comparison.

Primary outcome

Clinical relapse

We found very low-certainty evidence that, on average, there was no clear difference in the incidence of clinical relapse between probiotics and placebo (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.63 to 1.18; 4 studies, 361 participants; very low-certainty evidence; Analysis 1.1, Figure 4). We downgraded the evidence three times for high risk of reporting and other bias due to imbalance in baseline characteristics, and imprecision due to small sample size.

Figure 4. Forest plot of comparison: 1 Probiotics versus placebo, outcome: 1.1 Clinical relapse.



Two other studies also reported on relapse (Vejdani 2017; Wildt 2011). In these studies, relapse data appear to have included a mix of endoscopic and clinical relapse. Vejdani 2017 defines relapse as: an increase in bowel frequency with blood for at least one week and a colonoscopy and biopsies to confirm relapse. Wildt 2011 defines relapse as: simple clinical colitis activity index (SCCAI) score > 4 and/or endoscopic changes grade 2 to 3. Due to concerns about clinical heterogeneity, we did not analyse the data. Number of relapses in the probiotics compared to the placebo group were 4/14 (28.6%) versus 7/15 (46.7%) in Vejdani 2017 and 15/20 (75%) versus 11/12 (91.7%) in Wildt 2011.

Maintenance of clinical remission

The number of participants who remained in clinical remission, i.e. did not have a relapse, was reported in three studies. It is uncertain whether probiotics lead to a difference in maintenance of remission when compared with placebo (RR 1.16, 95% CI 0.98 to 1.37; 2 studies, 141 participants; very low-certainty of evidence; Analysis 1.2). We downgraded the evidence three times for high risk of bias and imprecision due to wide CIs, which includes appreciable harm. One additional study with 205 participants (Matsuoka 2018), reported insufficient data for inclusion in the meta-analysis; we did not analyse the results further.

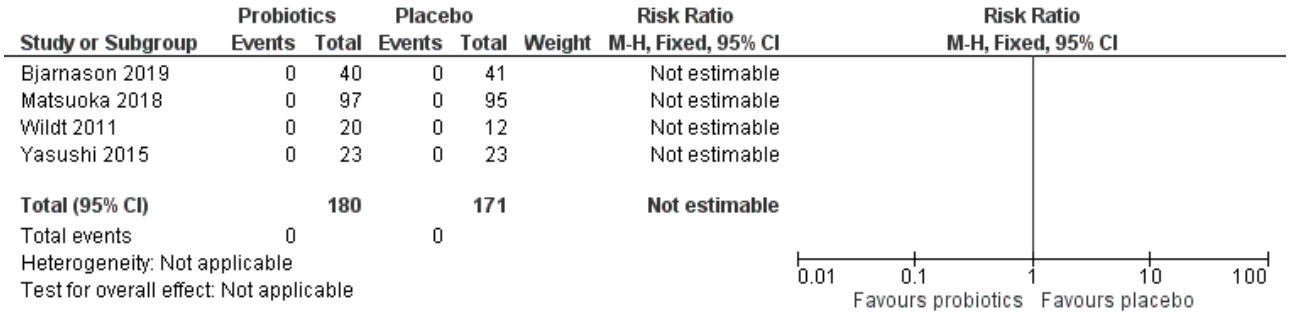
Wildt 2011 reported on the number of participants who remained in remission, however, the definition of the relapse suggests that the data potentially includes participants in endoscopic and clinical remission. The number of people on probiotics who remained in remission compared to those on placebo were 5/20 (25%) versus 1/12 (8.3%), respectively.

Secondary outcomes

Serious adverse events

In four studies with 351 participants which reported on serious adverse events, no events were recorded (Analysis 1.3, Figure 5).

Figure 5. Forest plot of comparison: 1 Probiotics versus placebo, outcome: 1.3 Serious adverse events.



Withdrawal due to adverse events

Two studies with 113 participants indicated that there were no withdrawals as a result of adverse events (Bjarnason 2019; Wildt 2011).

Need for additional therapy

This outcome was not reported.

Health-related quality of life

Health-related quality of life was reported in two studies and measured using the inflammatory bowel disease questionnaire (IBD-Q) scale in one of them (NCT02361957), and the UK IBD-Q in the other one (Bjarnason 2019). The IBD-Q scale ranges from 1 to 7, with a higher score representing better quality of life. We found low-certainty evidence that, on average, probiotics made no clear difference in health-related quality of life compared with placebo (mean difference (MD) -0.70, 95% CI -1.63 to 0.23; 1 study, 25 participants; low-certainty evidence; Analysis 1.5). We downgraded the evidence twice for imprecision due to inadequate sample size from a single study with wide CIs. The UK IBD-Q is similar, however, the authors that used it reported separately on the five overall parameters of the questionnaire (emotional symptoms, bowel function-1, social function, bowel function-2, systemic function). As there was no overall score reported, we could not include a quality of life value in our meta-analysis.

Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine)

Three trials compared probiotics with 5-ASA (Kruis 2004; Zocco 2003; Zocco 2006). See Summary of findings 2.

Primary outcome

Clinical relapse

We found low-certainty evidence that, on average, there was no clear difference in the incidence of relapse between probiotics and 5-ASA (RR 1.01, 95% CI 0.84 to 1.22; 2 studies, 452 participants; low-certainty evidence; Analysis 2.1). We downgraded the evidence twice for high risk of bias and imprecision due to the inadequate sample size.

In Zocco 2003, relapse was defined "by clinical and endoscopic features". Due to the heterogeneity, we decided not to analyse the data. The number of relapses in the probiotics versus placebo group were 2/12 (16.7%) versus 2/10 (20%), respectively.

Maintenance of clinical remission

We found low-certainty evidence that, on average, probiotics showed no clear difference in maintenance of clinical remission when compared with 5-ASA (RR 1.06, 95% CI 0.90 to 1.25; 1 study, 125 participants; low-certainty evidence; Analysis 2.2). We downgraded the evidence twice for high risk of bias and imprecision due to a small number of events.

Secondary outcomes

Serious adverse events

It is uncertain whether probiotics lead to a difference in serious adverse events when compared with 5-ASA (RR 1.19, 95% CI 0.41 to 3.46; 1 study, 327 participants; very low-certainty evidence; Analysis 2.3). We downgraded the evidence three times for high risk of bias and imprecision due to the small number of events and wide confidence interval, which includes appreciable harm.

Withdrawal due to adverse events

It is uncertain whether probiotics lead to a difference in serious adverse events when compared with 5-ASA (RR 1.02, 95% CI 0.46 to 2.25; 1 study, 222 participants; very low-certainty evidence; Analysis 2.4). We downgraded the evidence three times for high risk of bias and imprecision due to the small number of events in a single study and wide confidence interval, which includes appreciable harm.

Need for additional therapy

This outcome was not reported.

Health-related quality of life

One study reported quality of life scores at 12 months based on the IBDQ scale, ranging from 0 to 32, with a higher score representing a better quality of life (Kruis 2004). We found low-certainty evidence that there was no clear difference in health-related quality of life between probiotics and 5-ASA (MD -0.80, 95% CI -2.01 to 0.41; 1 study, 222 participants; low-certainty evidence Analysis 2.5). We downgraded the evidence twice for high risk of bias and imprecision due to small sample size.

Probiotic + 5-ASA (mesalazine) versus 5-ASA (mesalazine)

Four trials compared a probiotic plus 5-ASA with 5-ASA alone (Copaci 2014; Kruis 1997; Zocco 2003; Zocco 2006). See Summary of findings 3.

Primary outcome

Clinical relapse

It is uncertain whether probiotics combined with 5-ASA leads to a difference in the incidence of relapse when compared with 5-ASA alone (RR 1.11, 95% CI 0.66 to 1.87; 2 studies, 242 participants; very low-certainty evidence; Analysis 3.1). We downgraded the evidence three times for high risk of bias and imprecision due to the small number of events and confidence interval, which includes appreciable benefit or harm.

In Zocco 2003, relapse was defined "by clinical and endoscopic features". Due to the heterogeneity, we were unable to analyse the data. The number of relapses which occurred in the probiotics and 5-ASA group compared to 5-ASA alone was 4/14 (28.6%) versus 2/10 (20%).

Maintenance of clinical remission

The number of participants who remained in remission, i.e. did not have a relapse, was reported in two studies. We found low-certainty evidence that, on average, probiotics combined with and 5-ASA showed no clear difference in maintenance of remission compared with 5-ASA alone (RR 1.05, 95% CI 0.89 to 1.24; 1 study, 122 participants; Analysis 3.2). We downgraded the evidence twice for high risk of bias and imprecision due to the small number of events.

Secondary outcomes

Serious adverse events

This outcome was not reported.

Withdrawal due to adverse events

It is uncertain whether probiotics combined with 5-ASA leads to a difference in withdrawal due to adverse events compared with 5-ASA alone because the certainty of the evidence is very low. One study reported there were no withdrawals due to adverse events and one study reported two withdrawals in the probiotics combined with 5-ASA group (RR 5.29, 95% CI 0.26 to 107.63; 2 studies, 127 participants; very low-certainty evidence; Analysis 3.3). We downgraded the evidence three times for unclear risk of selection bias, small number of events and wide confidence interval, which includes appreciable harm.

Need for additional therapy

This outcome was not reported.

Health-related quality of life

This outcome was not reported.

Sensitivity analysis

We carried out sensitivity analyses using an available case analysis versus intention-to-treat (ITT) analysis as well as fixed-effect versus random-effects models. We did not find any differences between either set of analyses. See full data in Table 2.

DISCUSSION

Summary of main results

This review included 11 parallel group randomised controlled trials (RCTs) assessing the effectiveness of probiotics for the maintenance of remission in ulcerative colitis. All the studies, except two (Copaci 2014; Shanahan 2006), provided sufficient data for inclusion in a meta-analysis. The comparisons assessed by the studies were probiotics versus placebo, probiotics versus 5-aminosalicylic acid (5-ASA) and probiotic plus 5-ASA versus 5-ASA . We analysed and summarised data from nine studies (1031 participants): Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3. It is uncertain if there is any difference in occurrence of clinical relapse when probiotics are compared with placebo (very low-certainty evidence). When probiotics were compared with 5-ASA, there was no clear difference in relapse (low-certainty evidence). It is uncertain whether probiotics lead to a difference in maintenance of remission when compared with placebo because the certainty of the evidence is very low. There is no clear difference in maintenance of remission when probiotics are compared with 5-ASA, neither is there a difference when probiotics combined with 5-ASA is compared with 5-ASA alone (low-certainty evidence). It is uncertain whether probiotics combined with 5-ASA leads to a difference in the incidence of relapse when compared with 5-ASA alone because the certainty of the evidence is very low.

The studies comparing probiotics with placebo reported that no serious adverse events occurred. One study comparing probiotics and 5-ASA reported on similar numbers of serious adverse events in both groups. Further details were not provided on these serious adverse events.

No difference in efficacy was found between probiotics and placebo, which could reflect the clinical truth of no efficacy regarding these agents. However, no difference was found between probiotics and 5-ASA either. This is key, as 5-ASA are generally used as standard first-line interventional therapy, with their efficacy well demonstrated in previous systematic reviews (Wang 2016). As such, given the lack of efficacy of probiotics compared with placebo, it would be expected that they would be inferior to 5-ASA as standard therapy, which has not been demonstrated. We do not have enough evidence in this current synthesis to demonstrate the efficacy of probiotics, but feel these inconsistencies raise genuine questions for clinicians, researchers and users in the field.

Overall completeness and applicability of evidence

The capricious body of evidence synthesised in this review is highly heterogenous in terms of population and intervention, and as such, significantly limits its applicability to guide decision making. In considering application of the evidence, clinicians and patients require not just statistically significant results; the results need to reflect specific clinical contexts and problems for which they can apply these solutions. It is particularly striking that on updating this review after almost 10 years, the body of evidence has grown but is still far from complete and unable to be applied to practice.

The studies involved a wide range of people who had been in remission for various lengths (> 1 month to 12 years), but as recruiting studies ubiquitously made such judgements on clinical grounds, with the addition of activity scores, consideration of concepts, such as 'deep remission', which are key in practice, is completely absent from the discourse in these trials. The weaknesses of the primary studies have not allowed exploration of such wide ranging participant characteristics through subgroup analysis, which would be key for implementation of any findings from such a review.

There was minimal consideration of children in included studies, with all except Yasushi 2015 recruiting only adults. Based on its inclusion criteria, Yasushi 2015 attempted to recruit both adult and paediatric patients, but it is not clear if they actually achieved this, treating them as one population. As such, the applicability of this evidence to paediatric patients is a significant concern. Furthermore, almost half of the studies excluded participants who were receiving immunosuppressants at the point of recruitment, suggesting a preference for people with mild disease severity. This should be considered in applying the evidence in practice.

Study participants received probiotics which had either single or multiple strains for a maximum period of 12 to 52 weeks. Whilst it is common for reviews within Cochrane and the wider field to synthesis evidence that considers probiotics as a single interventional group, subgroup analysis is key for what are effectively a disparate family of interventional agents, and once again the limitations of the evidence in this review has not allowed this to be completed.

Relapse and maintenance of remission were reported in most of the studies. However, most of the secondary outcomes were not sufficiently reported. Serious adverse events were reported, however, this outcome was not described at all in any of the studies. Health-related quality of life and withdrawal due to adverse events were rarely reported. Need for withdrawal of therapy was not reported in any of the included studies. The effect of probiotics on these secondary outcomes remains unclear.

Certainty of the evidence

The certainty of evidence was either low or very low due to risk of bias and imprecision. Eight studies were at high risk of bias and three studies were at unclear risk of bias. Most of the studies failed to provide sufficient information on allocation concealment. Though the studies which used double-blinding had clearly included placebo or provided control which was identical to the study intervention to prevent performance bias, it was not explicitly stated whether outcome assessment was blinded or not. Indicating that a study was double-blinded without explicitly stating who (participants, caregiver, outcome assessor, etc.) the blinding was applied to is usually not helpful in 'Risk of bias' assessment. Five studies were published as abstracts and were at unclear risk of bias for most domains.

The studies had sample sizes of between 25 and 327 participants. We downgraded for imprecision as the trials either had small numbers of events or small sample sizes which were insufficient to meet the optimal information size, thus resulting in wide confidence intervals. Whilst power calculations were used, they were often based on estimates of effect, rather than previous trial data, and therefore this raises the question as to whether these studies were adequately powered. The definition of relapse reported in some of the studies suggests that people with endoscopic and clinical relapse or remission may have been lumped together. We carried out a narrative synthesis of such studies since they were dissimilar to the studies which clearly reported on clinical relapse only. This reduced the amount of data that were pooled for the outcome of clinical relapse/remission and increased imprecision.

Most of the analyses involved single studies. Where there was sufficient data for pooling, there was no heterogeneity (I^2 = 0%). Therefore, there was no reason to downgrade for inconsistency.

There was no indirectness, as the included studies all addressed the objectives of the review and fit within the scope. The number of studies included in the meta-analysis was insufficient to assess for publication bias.

The inconsistency within results has already been discussed, with no difference between probiotics and placebo nor probiotics and 5-ASA (a standard treatment with proven superiority over placebo). This point is highlighted in the context of the quality issues raised, given that all but one study comparing probiotics and placebo was at high risk of bias. It is therefore likely that this is the source of the inconsistency and is a key message for future researchers.

Potential biases in the review process

We are aware of the biases that could arise from missing data and made efforts to contact authors for additional information and clarifications. However, most of the authors we contacted failed to reply. To minimise bias, we included such studies in our narrative synthesis and carried out sensitivity analyses, where possible, to provide a conservative estimate of effect. We aim to include any data which become available from authors in future updates.

Other limitations in the review process are to do with risk of bias of individual studies. Three of the included studies are only available as abstracts. This meant that the studies had to be marked at unclear risk of bias for most of the domains. Given that we did not carry out sensitivity analyses to examine their impact on the results due to the insufficient number of studies included in each meta-analysis, the inclusion of these abstracts may further influence the validity of the data.

Finally, we are aware of the possible impact of industry funding on the validity of trial results. Funding from probiotic manufacturing companies or inclusion of company staff in the author team was noted in some of the studies and we considered the impact of this information on the 'Risk of bias' assessment of the studies and GRADE assessment of the evidence. Given that none of the studies showed a clear difference in favour of probiotics, we assumed that industry funding is unlikely to have compromised the results of this review.

Agreements and disagreements with other studies or reviews

There is currently no other known evidence-based guidance or systematic review around the use of probiotics for the maintenance of remission in ulcerative colitis, apart from the previous version of this review (Naidoo 2011). The European Crohn's and Colitis Organisation (ECCO) and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPHGAN) guideline briefly described the evidence on the efficacy of probiotics and made no recommendation regarding its use for the maintenance of remission (Turner 2018). The current National Institute for Health and Care Excellence (NICE) guideline does not cover probiotics either (NICE 2013). This review has found insufficient evidence on the effect of probiotics for maintenance of remission in ulcerative colitis, and therefore retains the same conclusion from Naidoo 2011.

AUTHORS' CONCLUSIONS

Implications for practice

The effectiveness of probiotics for the maintenance of remission in ulcerative colitis remains unclear. This is due to low- to very low-certainty evidence from poorly conducted studies, which contribute limited amounts of data from a small number of participants. It is uncertain whether probiotics lead to a difference in clinical relapse and the maintenance of remission when compared with placebo (very low-certainty evidence). Probiotics were compared with 5-aminosalicylic acid (5-ASA) (conventional therapy) and there was no clear difference in relapse or maintenance of remission (low-certainty evidence). There were no serious adverse events in all but one study, which reported similar numbers across the probiotics and 5-ASA groups, however, no further details were reported. Health-related quality of life and withdrawal due to adverse events were rarely reported.

Implications for research

This review highlights the need for further well-designed randomised controlled trials (RCTs) to investigate the efficacy and safety of probiotics for the maintenance of remission in ulcerative colitis. However, we believe it is key to define contextually what the attributes of such trials should be. The majority of the trials compared probiotics with placebo. Future trials comparing probiotics with 5-ASA would reflect conventional care given to people with ulcerative colitis. Additionally, the length of follow-up of most studies in this review is much less than in studies assessed by other published reviews on maintenance therapy. Maintenance studies investigating treatment effects for less than 12 months are simply too short to inform clinical practice, where the attrition rates from remission are such that a minimum of one year should be considered for study. We would also strongly suggest that study investigators work to ensure the homogenous nature of their baseline populations from a disease activity standpoint, as we believe it is difficult to consider patients in remission for one month on recruitment the same as those who are 12 years into their remission. The question of sample size is also a major concern, with a minimal use of power calculations using expected effect sizes which were estimated in wide ranging ways and have led to 11 studies with a little over 1000 participants. Given other studies exhibited in other reviews in the field, particularly the high placebo response rate seen (Jairath 2017), we believe it is likely that such calculations were too optimistic in projected effect sizes, and as such, may have been underpowered to appropriately investigate the agents under study. Considering the ongoing trials, none of these appears to be of the statistical power or length of follow up to address these issues.

ACKNOWLEDGEMENTS

Partial funding for Cochrane Inflammatory Bowel Disease (IBD) (1 April 2016 to 31 March 2018) has been provided by Crohn's and Colitis Canada (CCC).

Funding for Zipporah Iheozor-Ejiofor and partial funding for Morris Gordon was provided through the National Institute for Health Research (NIHR) Cochrane Programme Grant.

Yuhong Yuan, Information Specialist, Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) reran the search strategies in October 2019.

REFERENCES

References to studies included in this review

Bjarnason 2019 *{published data only}*

Bjarnason I, Sission G, Hayee B. A randomised, double-blind, placebo controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease. *Inflammopharmacology* 2019;**27**:465-73.

Copaci 2014 *{published data only}*

Copaci I, Chiriac G. Maintenance of remission of ulcerative colitis: prebiotics and dietary fiber. *United European Gastroenterology Journal* 2014;**1**:A375.

Kruis 1997 *{published data only}*

Kruis W, Schutz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 1997;**11**(5):853-8.

Kruis 2004 *{published data only}*

Kruis W, Fric P, Pokrotnieks J, Lukas M, Fixa B, Kascak M, et al. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004;**53**(11):1617-23.

Matsuoka 2018 *{published data only}*

Matsuoka K, Uemura Y, Kanai T. Efficacy of Bifidobacterium breve fermented milk in maintaining remission of ulcerative colitis. *Digestive Diseases and Sciences* 2018;**ns**:1-10. [org/10.1007/s10620-018-4946-2]

NCT02361957 *{unpublished data only}*

NCT02361957. The Effect of the Multispecies Probiotic Ecologic 825 Versus Placebo in Ulcerative Colitis Patients (CUPIDO). clinicaltrials.gov/ct2/show/NCT02361957 first posted 12 February 2015.

Shanahan 2006 *{published data only}*

Shanahan F, Guarner F, Von Wright A, Vilpponen-Salmela T, O'Donoghue, D, Kiely B, et al. A one year, randomised, double-blind, placebo controlled trial of a Lactobacillus or a Bidifobacterium probiotic for maintenance of steroid-induced remission of ulcerative colitis. *Gastroenterology* 2006;**130**(4 Suppl 2):A44.

Vejdani 2017 *{published data only}*

Vejdani R, Bahari A, Zadeh AM, Azmi M, Ebrahimi-Daryani N, Hashtroudi AA, et al. Effects of lactobacillus casei probiotic on mild to moderate ulcerative colitis: A placebo controlled study. *Indian Journal of Medical Sciences* January-March 2017;**69**(1):24-8.

Wildt 2011 *{published data only}*

Wildt S, Nordgaard I, Hansen U, Brockmann E, Rumessen JJ. A randomised double-blind placebo-controlled trial with Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp. lactis BB-12 for maintenance of remission in ulcerative colitis. *Journal of Crohn's and Colitis* 2011;**5**(2):115-21.

Yasushi 2015 *{published data only}*

Yasushi Y, Akihiro Y, Ryuichi F, Koji S, Aisaku O, Kentaro N, et al. Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. *World Journal of Gastroenterology* 2015;**21**(19):5985-94.

Zocco 2003 *{published data only}*

Zocco MA, dal Verme LZ, Armuzzi A, Nista EC, Papa A, Candelli M. Comparison of Lactobacillus GG and mesalazine in maintaining remission of ulcerative colitis and Crohn's disease. *Gastroenterology* 2003;**124**(4):A201.

Zocco 2006 *{published data only}*

Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 2006;**23**(11):1567-74.

References to studies excluded from this review

Ahmed 2013 *{published data only}*

Ahmed J, Reddy BS, Molbak L, Leser TD, Macfie J. Impact of probiotic on colonic microflora in patients with colitis: A prospective double blind randomised crossover study. *International Journal of Surgery* 2013;**11**(10):1131-6.

Ballini 2019 *{published data only}*

Ballini A, Santacroce L, Cantore S, Bottalico L, Dipalma G, Tope S, et al. Probiotics efficacy on oxidative stress values in inflammatory bowel disease: a randomized double-blinded placebo-controlled pilot study. *Endocrine, Metabolic & Immune Disorders - Drug Targets* 2019;**19**(3):1-8.

Bamba 2002 *{published data only}*

Bamba T, Kanauchi O, Andoh A, Fujiyama Y. A new prebiotic from germinated barley for nutraceutical treatment of ulcerative colitis. *Journal of Gastroenterology and Hepatology* 2002;**17**(8):818-24.

Cui 2004 *{published data only}*

Cui HH, Chen CL, Wang JD, Yang YJ, Cun Y, Wu JB, et al. Effects of probiotics on intestinal mucosa of patients with ulcerative colitis. *World Journal of Gastroenterology* 2004;**10**(10):1521-5.

Do 2010 *{published data only}*

Do VT, Baird BG, Kockler DR. Probiotics for maintaining remission of ulcerative colitis in adults. *Annals of Pharmacotherapy* 2010;**44**(3):565-71.

Faubion 2000 *{published data only}*

Faubion WA, Sandborn WJ. Probiotic therapy with E. Coli for ulcerative colitis: take the good with the bad. *Gastroenterology* 2000;**118**(3):630-1.

Folwaczny 2000 *{published data only}*

Folwaczny C. Probiotics for prevention of ulcerative colitis recurrence: alternative medicine added to standard treatment. *Zeitschrift de Gastroenterologie* 2000;**38**(6):547-50.

Fujimori 2009 *{published data only}*

Fujimori S, Gudis K, Mitsui K, Seo T, Yonezawa M, Tanaka S, et al. Randomized controlled trial on the efficacy of synbiotic versus probiotic or prebiotic treatment to improve the quality of life in patients with ulcerative colitis. *Nutrition* 2009;**25**(5):520-5.

Henker 2008 *{published data only}*

Henker J, Müller S, Laass MW, Schreiner A, Schulze J. Probiotic Escherichia coli Nissle 1917 (EcN) for successful remission maintenance of ulcerative colitis in children and adolescents: an open-label pilot study. *Zeitschrift fur Gastroenterologie* 2008;**46**(9):874-5.

IRCT20120415009475N5 *{published data only}*

IRCT20120415009475N5. Evaluation of the effects of Saccharomyces Boulardii on pain and quality of life in children with Inflammatory Bowel Disease (IBD) [Evaluation of the effects of lyophilized Saccharomyces Boulardii capsules on quality of life and clinical outcomes in children with inflammatory bowel disease (IBD)]. www.irct.ir/trial/32179 (registration date 10 October 2018). [IRCT: https://www.irct.ir/trial/32179]

Ishikawa 2002 *{published data only}*

Ishikawa H, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *Journal of the American College of Nutrition* 2002;**22**(1):56-63.

Ishikawa 2011 *{published data only}*

Ishikawa H, Matsumoto S, Ohashi Y, Imoaka A, Setoyama H, Umesaki Y, et al. Beneficial effects of probiotic bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: A randomized controlled study. *Digestion* 2011;**84**(2):128-33.

Li 2013 *{published data only}*

Li K, Zhang CF, Xia YH, Li Z J, Han Y. Efficacy of probiotics on ulcerative colitis and its mechanism. *Zhonghua Weichang Waike Zazhi* 2013;**16**(4):336-9.

Liu 2014 *{published data only}*

Liu P, Sun L, Zhang ZH, Zhang P, Zhang J. Clinical efficacy of Salofalk combined with beneficial bacteria in patients with ulcerative colitis. *World Chinese Journal of Digestology* 2014;**22**(22):3344-8.

Miele 2009 *{published data only}*

Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *American Journal of Gastroenterology* 2009;**104**(2):437-43.

NCT00268164 *{published data only}*

NCT00268164. Lactobacilus acidophilus and Bifidobaceterium animalis subsp. Lactis maintenance treatment in ulcerative colitis. clinicaltrials.gov/show/NCT00268164 First received 22 December 2005.

NCT00374725 *{published data only}*

NCT00374725. Treatment of Ulcerative Colitis With a Combination of Lactobacillus Rhamnosus and Lactobacillus Acidophilus. clinicaltrials.gov/show/NCT00374725 First posted 11 September 2006.

NCT00803829 *{published data only}*

NCT00803829. Sunbiotic treatment of ulcerative colitis patients. clinialtrials.gov/show/NCT00803829 First posted 8 December 2008.

NCT00951548 *{published data only}*

NCT00951548. Food Supplementation With VSL#3 as a Support to Standard Pharmaceutical Therapy in Ulcerative Colitis. clinicaltrials.gov/show/NCT00951548 First posted 4 August 2009.

NCT01772615 *{published data only}*

NCT01772615. Treatment of ulcerative colitis with ciprofloxacin and E. Coli Nissle. clinicaltrials/gov/show/NCT01772615 First posted 21 january 2013.

Palumbo 2016 *{published data only}*

Palumbo VD, Romeo M, Marino Gammazza A, Carini F, Damiani P, Damiano G, et al. The long-term effects of probiotics in the therapy of ulcerative colitis: A clinical study. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia* 2016;**160**(3):372-7.

Pelech 1998 *{published data only}*

Pelech T, Fric P, Fixa B, Komarkova O. Comparison of mutaflor and mesalazine in the maintenance treatment of inactive ulcerative colitis. *Prakticky Lekar* 1998;**78**(10):556-8.

Rembacken 1999 *{published data only}*

Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999;**354**(9179):635-9.

Rohatgi 2015 *{published data only}*

Rohatgi S, Ahuja V, Makharia GK, Rai T, Das P, Dattagupta S, et al. VSL#3 induces and maintains short-term clinical response in patients with active microscopic colitis: a two-phase randomised clinical trial. *BMJ Open Gastroenteroilogy* 2015;**2**(1):e000018.

Sanchez-Morales 2019 *{published data only}*

Sanchez-Morales A, Perez-Ayala MF, Cruz-Martinez M, Arenas-Osuna J, Ramirez-Mendoza P, Ceniceros RA, et al. [Efectividad de probioticos sobre sintomas, histologia, y tolerancia alimentaria en colitis ulcerativa]. *Revista Medica del Instituto Mexicano del Seguro Social* 2019;**57**(1):9-14.

Shadnoush 2013 *{published data only}*

Shadnoush M, Hosseini RS, Mehrabi Y, Delpisheh A, Alipoor E, Faghfoori Z, et al. Probiotic yogurt affects pro- and anti-inflammatory factors in patients with inflammatory bowel disease. *Iranian Journal of Pharamceutical Research* 2013;**12**(4):929-36.

Solovyeva 2014 *{published data only}*

Solovyeva O. Probiotics can extend remission of ulcerative colitis. *Journal of Crohn's and Colitis* 2014;**8**:221.

Tursi 2010 *{published data only}*

Tursi A, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL3 as adjunctive to a standard pharmaceutical treatment: A double-blind, randomized, placebo-controlled study. *American Journal of Gastroenterology* 2010;**105**(10):2218-27.

Venturi 1999 *{published data only}*

Venturi A, Gionchetti P, Rizzello F, Johansson R, Zucconi E, Brigidi P, et al. Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis. *Alimentary Pharmacology and Therapeutics* 1999;**13**(8):1103-8.

Zhang 2018a *{published data only}*

Zhang J. Effects of Bifidobacterium quadruplex live bacteria tablets on Mayo score and hs-CRP, IL-4, IL-8 in patients with mild to moderate ulcerative colitis. *World Chinese Journal of Digestology* 2018;**26**(6):373-7.

References to studies awaiting assessment

Fan 2019 *{published data only}*

Fan H, Du J, Liu X, Zheng WW, Zhuang ZH, Wang CD, et al. Effects of pentasa-combined probiotics on the microflora structure and prognosis of patients with inflammatory bowel disease. *Turkish Journal of Gastroenterology* 2019;**30**(8):680-5.

Fang 2018 *{published data only}*

Fang W, Cai Q. Effect of mesalazine combined with bifid on inflammatory response and rectal-anal dynamics in patients with ulcerative colitis. *World Chinese Journal of Digestology* 2018;**26**(10):594-600.

Huang 2018 *{published data only}*

Huang M, Chen Z, Lang C, Chen J, Yang B, Xue L, et al. Efficacy of mesalazine in combination with bifid triple viable capsules on ulcerative colitis and the resultant effect on the inflammatory factors. *Pakistan Journal of Pharmaceutical Sciences* 2018;**31**(6):2891-5.

Shi 2018 *{published data only}*

Shi XH, Tan FP, Jiang WH. Bacillus subtilis and Enterococcus faecium enteric-coated capsules combined with mesalazine for treatment of patients with ulcerative colitis: Efficacy and impact on serum levels of SOD, MDA, interleukins, and TNF-α. *World Chinese Journal of Digestology* 2018;**26**(12):748-54.

Yilmaz 2019 *{published data only}*

Yilmaz I, Dolar ME, Özpinar H. Effect of administering kefir on the changes in fecal microbiota and symptoms of inflammatory bowel disease: a randomized controlled trial. *Turkish Journal of Gastroenterology* 2019;**30**(3):242-53.

Zhang 2018b *{published data only}*

Zhang Y, Wu M, Chen Y. Effects of adjuvant therapy with bifidobacterium quadruplex on lipid peroxidation injury indices, inflammatory factors and immune function in patients with ulcerative colitis. *World Chinese Journal of Digestology* 2018;**26**(22):1348-54.

References to ongoing studies

NCT03415711 *{published data only}*

NCT03415711. PRObiotic VSL#3® for Maintenance of Clinical and Endoscopic REMission in Ulcerative Colitis (PROREM UC). clinicaltrials.gov/ct2/show/NCT03415711 First posted 30 January 2018.

NCT03565939 *{published data only}*

NCT03565939. Probiotic Treatment of Ulcerative Colitis With Trichuris Suis Ova (TSO) (PROCTO). clinicaltrials.gov/ct2/show/NCT03565939 First posted 21 June 2018.

NCT03798210 *{published data only}*

NCT03798210. Lactobacillus Reuteri ATCC PTA 4659 in Ulcerative Colitis (COLUS). clinicaltrials.gov/ct2/show/NCT03798210 First posted 9 January 2019.

NCT04006977 *{published data only}*

Liang J. Multistrain Probiotics Reduces UC Depression and Anxiety Scores. clinicaltrials.gov/ct2/show/NCT04006977 First posted 5 July 2019.

Additional references

Baron 1964

Baron JH, Connell AM, Lenard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *British medical journal* 1964;**1**:89-92.

Cleynen 2016

Cleynen I. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet* 2016;**387**(10014):156-67.

Cohen 2010

Cohen RD. Systematic review: the costs of ulcerative colitis in Western countries. *Alimentary Pharmaology and Therapeutics* 2010;**31**(7):693-707.

Dieleman 2003

Dieleman LA, Goerres MS, Arends A, Sprengers D, Torrice C, Hoentjen F, et al. Lactobacillus GG prevents recurrence of colitis in HLA-B27 transgenic rats after antibiotic treatment. *Gut* 2003;**52**(3):370-6.

Fabia 1993

Fabia R, Ar'Rajab A, Johansson ML, Willen R, Andersson R, Molin G, et al. The effect of exogenous administration of Lactobacillus reuteri R2LC and oat fiber on acetic-induced colitis in the rat. *Scandinavian Journal of Gastroenterology* 1993;**28**(2):155-62.

Fiorino 2016

Fiorino G. The clinical potential of etrolizumab in ulcerative colitis: hypes and hopes. *Therapeutic Advances in Gastroenerology* 2016;**9**(4):503-12.

GRADEpro GDT 2015 [Computer program]

McMaster University. GRADEpro GDT: GRADEpro Guideline Development Tool. McMaster University, 2015 (developed by Evidence Prime, Inc.).

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration.

Jairath 2017

Jairath V, Zou GY, Parker CP, MacDonald JK, AlAmeel T, Al Beshir M, et al. Placebo response and remission rates in randomised trials of induction and maintenance therapy for ulcerative colitis. *Cochrane Database of Systematic Reviews* 2017, Issue 9. [DOI: 10.1002/14651858.CD011572.pub2]

Kennedy 2000

Kennedy RJ, Hoper M, Deodhar K, Kirk SJ, Gardiner KR. Probiotic therapy fails to improve gut permeability in a hapten model of colitis. *Scandinavian Journal of Gastroenterology* 2000;**35**(12):1266-71.

Loftus 2004

Loftus EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004;**126**(6):1504-17.

Madsen 1999

Madsen KL, Doyle JS, Jewell LD, Tavernini MM, Fedorak RN. Lactobacillus species prevents colitis in interleukin 10 gene-deficient mice. *Gastroenterology* 1999;**116**(5):1107-14.

Madsen 2001

Madsen K, Cornish A, Soper P, McKaigney C, Jijon H, Yachimec C, et al. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. *Gastroenterology* 2001;**121**(3):580-91.

Mallon 2007

Mallon P, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2007, Issue 10. [DOI: 10.1002/14651858.CD005573.pub2]

NICE 2019

National Institute for Health and Care Excellence. Ulcerative Colitis Mangagement NG130. https://www.nice.org.uk/guidance/ng130 2019.

Ong 2019

Ong TG, Gordon M, Banks SS, Thomas MR, Akobeng AK. Probiotics to prevent infantile colic. *Cochrane Database of Systematic Reviews* 2019, Issue 3. [DOI: 10.1002/14651858.CD012473.pub2]

Panigrahi 2014

Panigrahi P. Probiotics and prebiotics in neonatal necrotizing enterocolitis: new opportunities for translational research. *Pathophysiology* 2014;**21**(1):35-46.

Pitkin 1999

Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. *JAMA* 1999;**281**:1110-1.

Review Manager 2014 [Computer program]

The Nordic Centre. Copenhagen: The Cochrane Collaboration, 13th June 2014.

Schultz 2002

Schultz M, Veltkamp C, Dieleman LA, Grenther WB, Wyrick PB, Tonkonogy SL, et al. Lactobacillus plantarum 299V in the treatment and prevention of spontaneous colitis in interleukin-10-deficient mice. *Inflammatory Bowel Diseases* 2002;**8**(2):71-80.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Shibolet 2002

Shibolet O, Karmeli F, Eliakim R, Swennen E, Brigidi P, Gionchetti P, et al. Variable response to probiotics in two models of experimental colitis in rats. *Inflammatory Bowel Diseases* 2002;**8**(6):399-406.

Truelove 1956

Truelove SC, Richards WC. Biopsy studies in ulcerative colitis. *British medical journal* 1956;**1**:1315-1318.

Turner 2018

Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of paediatric ulcerative colitis, Part 1: ambulatory care—an evidence-based guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2018;**67**(2):257-91. [DOI: 10.1097/mpg.0000000000002035]

Ungaro 2016

Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2016;**389**(10080):1756-70.

Wang 2016

Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: 10.1002/14651858.CD000544.pub4]

References to other published versions of this review

Fagbemi 2008

Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD007443]

Naidoo 2011

Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD007443.pub2]

CHARACTERISTICS OF STUDIES

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

Bjarnason 2019

Methods	RCT, double-blind, single centre **Setting**: King's College Hospital Gastroenterology Clinic, London **Study duration**: November 2010 to October 2014
Participants	81 patients with UC, 61 patients with CD (total IBD = 142) **Inclusion criteria**: patients attending routine clinical review with established UC and CD, age 18 to 70 years, diagnosed at least 6 months prior to the trial; patients were required to have stable inactive clinical disease, as defined by < 5 points on Harvey Bradshaw (which corresponded to a score of ≤ 4 on the Truelove-Witts criteria for UC, without a change in medication for 4 months. Patients on no treatment, maintenance treatment with a 5-aminosalycilic preparation or low-dose azathioprine (1 mg/kg) were eligible for inclusion in the trial. **Exclusion criteria**: patients on steroids (prednisolone > 4 mg/day) and biologics were excluded from the study; patients having undergone intestinal resection, patients with serious comorbidity including neurological, rheumatological, respiratory, nephrological, cardiovascular, psychiatric disease, patients with alcohol or drug addiction or dependency problems (within the last 5 years) and pregnant or lactating women; patients with previous intolerance or adverse reactions to probiotics or the use of these products within the preceeding 3 months were excluded. **Age (mean +/- SD)**: probiotic UC 47.3 +/- 14.4, placebo UC: 43.4 +/- 12.1; probiotic CD: 41.2 +/- 13.0, placebo CD: 39.0 +/- 13.0 **Sex**: not specified **Site of disease**: probiotics UC: proctosigmoid 16, left-sided 9, pancolonic 12; placebo UC: proctosigmoid 21, left-sided 10, pancolonic 9 probiotics CD: small bowel 14, colon 11, small and large bowel 9; placebo CD: small bowel 14, colon 7, small and large bowel 7 **Use of medication**: probiotics UC: 5-ASA 31, azathioprine 2, prednisolone 1, none 7 placebo UC: 5-ASA 33, azathioprine 2, prednisolone 0, none 6 probiotics CD: 5-ASA 15, azathioprine 4, prednisolone 1, none 13 placebo CD: 5-ASA 12, azathioprine 2, prednisolone 0, none 15 **Length of time remission at study entry:** not specified **Number randomised:** total probiotic: 73, total placebo: 70; probiotic UC: 40, placebo UC: 41; probiotic CD: 33, placebo CD: 29 **Number assessed:** all randomised completed the study **Postrandomisation exclusion**: 0

Bjarnason 2019 *(Continued)*

	No significant side effects were reported and the probiotic was well-tolerated by everyone
Interventions	Follow-up: 4 weeks IV: Symprove (Symprove Ltd. Farnham, Surrey UK), a dietary food supplement which contains 4 strains of bacteria (*Lactobacillus rhamnosus* NCIMB 30174, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus acidophilus* NCIMB 30175 and *Enterococcus faecium* NCIMB 30176), in a water-based suspension of barley extract with each 50 mL/dose containing about 10 billion live bacteria. **Control**: patients received placebo, which was an identical liquid in appearance and taste, containing water and flavouring and was provided in identical packaging supplied by the manufacturers identified by a trial batch and code number only. Patients were asked to keep the study medication refrigerated between 2 °C and 7 °C and to self-administer 1 mL/kg each morning on a fasting stomach. Foods and fluids were allowed 20 min later. Missed does could be taken later during the day provided that no food had been consumed during the preceding 3 hours.
Outcomes	**Primary efficacy outcome**: difference in overall change in the IBD QoL questionnaire results at week 4 **Secondary measures:** the differences in clinical disease activity scores between active and placebo treatment and changes in laboratory measures including FCAL (Ek-CAL, Buhlmann, Switzerland)
Notes	**Funding and conflict of interest**: supported by an unreserved research grant from Symprove Limited, the manufacturers of the probiotic Symprove to King's College Hospital. They also provided the probiotic used in the trial and a matching placebo free of charge. Prof Bjarnason has received financial support from Symprove Ltd for travel expenses to scientific meetings.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Study participants were randomised using a two-stage computerised randomisation protocol provided by the Department of Pharmacy at King's College Hospital"
Allocation concealment (selection bias)	Low risk	It is explained that preparations were identical liquids in appearance and taste, provided in identical packaging supplied by the manufacturers, identified by a trial batch and code number only, however no other information on allocation concealment are provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding of allocation to treatment was maintained until the completed study database was locked and passed over to an independent study statistician". Double-blinding. Preparations were identical liquids in appearance and taste, provided in identical packaging supplied by the manufacturers, identified by a trial batch and code number only
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinding of allocation to treatment was maintained until the completed study database was locked and passed over to an independent study statistician"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All reported
Selective reporting (reporting bias)	Low risk	All reported

Bjarnason 2019 *(Continued)*

Other bias	High risk	The study was funded by the manufacturers of the probiotics product studied in this article and the lead author has received financial support from the same company.

Copaci 2014

Methods	Open-label, parallel group, randomised clinical trial (abstract only) **Setting**: not stated, however authors' affiliation - Fundini clinical institute, Bucharest, Romania **Study period**: not stated
Participants	**Inclusion criteria**: people with UC in remission for over 3 months **Exclusion criteria**: not stated **Age (range)**: 18 to 65 years **Sex**: not stated **Site of disease**: ? (total colitis), ? (left-sided colitis) **Use of medication**: not stated **Length of time remission at study entry:** not stated **Number randomised (n = 36):** ? (probiotic + mesalamine)/? (mesalamine + prebiotic)*/? (mesalamine) **Number assessed:** ? (probiotic + mesalamine)/? (mesalamine + prebiotic)*/? (mesalamine) **Postrandomisation exclusion**: not stated
Interventions	• Mesalazine plus probiotic (*Bifidobacterium longum* W11) • Mesalazine plus prebiotic (*Plantago Ovata*)* • Mesalazine
Outcomes	**Duration of follow-up**: 24 weeks • Relapse • Continued remission. Remission - not defined • Safety (Gastrointestinal Symptom Rating Scale (GSRS): 1 to 7 - higher score = more troublesome symptom)
Notes	**Funding source**: not stated **Declaration of interest**: reported, none declared *Disregarded prebiotic data for not being within the scope of the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Open-label, parallel group, randomized clinical trial". Comment: not adequately described

Copaci 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label, parallel group, randomized clinical trial" Comment: there was no blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Open-label, parallel group, randomized clinical trial" Comment: no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not adequately reported
Selective reporting (reporting bias)	Unclear risk	Symptoms were monitored using a gastrointestinal symptom rating scale, however, the results were not fully reported
Other bias	Unclear risk	Not adequately described

Kruis 1997

Methods	Double-blind, multicentre RCT **Setting**: outpatient hospitals and private practices in Germany, the Czech Republic and Austria **Study period**: not stated
Participants	**Inclusion**: age > 17 years; presence of chronic UC currently in remission (defined by CAI score) **Exclusion**: active UC, infectious colitis, existing or intended pregnancy, any other medication for UC besides the study drugs, antibiotics or suphonamides, substantial cardiac, hepatic or renal disease, major operations on the bowels, and known intolerance to salicylates **Age* (range):** 19 to 88 years **Sex* (M/F):** 55/48 **Site of disease*:** 28 (proctitis); 40 (proctosigmoiditis); 19 (left-sided colitis); 18 (total/subtotal colitis) **Use of medication*:** 82 (salicylates); 25 (corticosteroids) **Length of time remission at study entry:** 14 (1 to 147 (probiotic)/12 (1 to 60) months (mesalazine) **Number randomised (n = 120):** 60? (probiotics)/60? (mesalazine) **Number assessed:** 50 (probiotics)/53 (mesalazine) **Postrandomisation exclusion:** 2 - not started taking study medication, 15 - had CAI of > 4 (8 versus 7)
Interventions	• Probiotics + mesalazine placebo: oral preparation containing *E coli* strain Nissle 1917. 200 mg/day (day 1 to 4, only 100 mg/day) of a preparation of viable *E coli* strain Nissle 1917 (Mutaflor, Ardeypharm GmbH, Herdecke, Germany) taken as a single dose during breakfast. Mutaflor 100 mg contains 25 X 10^9 viable *E coli* bacteria • Mesalazine + placebo: 500 mg mesalazine three times a day (Salofalk, Dr Falk Pharma GmbH, Freiburg, Germany) plus placebo indistinguishable from the *E coli* preparation
Outcomes	**Duration of follow-up**: 12 weeks (in one centre the total study period was 24 weeks)

Kruis 1997 *(Continued)*

- Relapse defined as CAI > 4
- Relapse-free time
- Adverse events
- Withdrawal due to adverse events

Notes	**Funding source**: supported by Ardeypharm GmbH, Herdecke, Germany **Declaration of interest**: not reported. *Baseline characteristics reported do not account for participants who were excluded postrandomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were reportedly randomised, however, the method of randomisation was not adequately described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind double-dummy. Both intervention arms included placebos.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind double-dummy, however, there was no specific information as to whether outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis (modified ITT) was partially applied as it failed to account for participants who were excluded postrandomisation. However, number and reasons for postrandomisation exclusion appear to have been equal across groups (16% versus 11%)
Selective reporting (reporting bias)	Low risk	Trial registration was not available, however, all expected outcomes were reported
Other bias	Low risk	No other apparent biases

Kruis 2004

Methods	Double-blind, multicentre RCT **Setting**: 60 hospitals and private settings in 10 European countries (Austria, Czech Republic, Estonia, Germany, Latvia, Lithuania, Slovak Republic, Sweden, Switzerland, UK) **Study period**: not stated
Participants	**Inclusion**: age 18 to 70; UC in remission (CAI ≤ 4, endoscopic index ≤ 4 and no sign of acute inflammation on histological examination); at least two acute attacks of UC prior to study; time since last relapse: < 12 months **Exclusion**: active UC; proctitis with up to 10 cm proximal spread; Crohn's disease, infectious colitis; severe accompanying illnesses or major colonic surgery; use of antibiotics, sulphonamides, steroids or

Kruis 2004 *(Continued)*

	other therapies for UC at entry into trial; administration of study intervention drug within the previous six months before trial entry; known intolerance to salicylates **Age:** 19 to 82 years **Sex (M/F):** 179/148 **Site of disease:** 61 (sub/total); 62 (left-sided); 190 (distal) **Use of medication:** 235 (oral salicylates - partly combined with steroids) **Length of time remission at study entry:** < 4 (probiotic)/< 3 months (mesalazine) **Number randomised (n = 327):** 162 (probiotic)/165 (mesalazine) **Number assessed:** 162 (probiotic)/165 (mesalazine) **Postrandomisation exclusion*:** 2 - deterioration of disease excluding relapse; 6 - newly emerged exclusion criterion during study; 22 - patient's request; 9 - adverse events; 12 - insufficient patient compliance; 9 - insufficient patient co-operation; 7 - dropped out; 3 - other; premature discontinuation - 39
Interventions	• Probiotic + placebo: oral preparation containing *E coli* strain Nissle 1917. Capsules contained 2.5 to 25 X 10^9 viable bacteria (Mutaflor 100 mg; Ardeypharm GmbH, Herdecke, Germany). Participants received one capsule of Mutaflor 100 mg once daily and one tablet of placebo 3 x daily for 4 days and 2 capsules of Mutaflor 100 mg once daily and one tablet of placebo 3 x daily from day 5 to the end of the study • Mesalazine + placebo: 5-aminosalicylic acid (Salofalk, Dr Falk Pharma GmbH, Freiburg, Germany). Participants received one capsule of placebo once daily and one tablet of Salofalk 500 mg 3 x daily for 4 days and two capsules of placebo once daily and one tablet of Salofalk 500 mg 3 x daily from day 5 to the end of the study No concomitant medication for UC was allowed throughout the study
Outcomes	**Duration of follow-up**: 12 months • Relapse defined as presence of all of the following: CAI > 6 (or an increase in CAI of at least 3 points with CAI = 4 being exceeded at the same time); endoscopic index > 4; histological signs of acute inflammation • Quality of life at 12 months • Serious adverse events • Adverse events requiring withdrawal of therapy
Notes	**Funding source**: not stated **Declaration of interest**: not reported *some participants may have had multiple reasons for being excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was carried out in a double blind manner in blocks of four patients using 1:1 allocation to the two treatment groups. Only complete blocks of random numbers were used for each centre. If patients were eligible for study entry, they were assigned to random numbers (= patient numbers) in ascending order within each centre according to the chronological order of their randomisation and were given the corresponding study medication." Comment: adequately described
Allocation concealment (selection bias)	Unclear risk	Confirmed via correspondence (quote): "Since Mutaflor and Mesalazine have a different dosage form (capsule vs. tablet), the double-dummy method was used to ensure double-blindness, i.e. a patient allocated to the test group was

Kruis 2004 *(Continued)*

		given Mutaflor verum and Mesalazine placebo, whereas a patient allocated to the control group was given Mesalazine verum and Mutaflor placebo)" Comment: unclear whether study interventions were provided in identical sequentially numbered containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind and double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Before unblinding the study, a steering committee assessed protocol violations in 105/327 (32.1%) patients." Comment: blinding appears to have been maintained until after outcomes were assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	High attrition, but balanced between the two groups.
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all measured outcomes were reported
Other bias	Low risk	Quote: "The two patient groups were matched with regard to demographic, clinical, and pretreatment characteristics" Comment: no other apparent biases

Matsuoka 2018

Methods	Double-blind, parallel group, Multicentre RCT **Setting**: Keio University School of Medicine; Tokyo Yamate Medical Center, Center for Infammatory Bowel Disease; Toho University Medical Center, Sakura Hospital; Kitasato University Hospital; Yokohama City University Medical Center, Infammatory Bowel Disease Center; Kannai-Suzuki Clinic; and Matsushima Clinic, Japan **Study period**: April 2012 to September 2013
Participants	**Inclusion**: diagnosed with UC, in remission, age 20 to 70, worsening symptoms within 2 years, defined as one or more of the following criteria: • persistent bloody stool > 1 week • initiation of 5-ASA treatment, dose escalation, change in medication type for worsening symptoms • initiation or dose escalation of cytapheresis or glucocorticoids • initiation or dose escalation of immuno modulators, immunosuppressants, anti-tumour necrosis factor **Exclusion**: • Diagnosed with proctitis-type UC • Visible bloody stools detected < 4 weeks before enrolment • Dose modification of 5-ASA, or change in medication for worsened UC < 4 weeks before enrolment • Local administration of 5-ASA • Administration of cytapheresis < 4 weeks before enrolment • Administration of immunomodulators (azathioprine, mercaptopurine) immunosuppressants (tacrolimus, cyclosporin) or anti-tumour necrosis factor (infliximab) < 12 weeks before enrolment

Matsuoka 2018 *(Continued)*

	• Unable to stop regular consumption of probiotic products other than the study beverage, or food products using lactic acid bacteria during the study period • Regular consumption of *B breve* strain Yakult used in the study < 10 days before enrolment **Age**: 20 to 70 years **Sex (M/F)**: 100/92 **Site of disease**: 100 (pancolitis); 92 (left-sided colitis) **Use of medication**: 190 (5-ASA) **Length of time remission at study entry (mean/range):** 362.7 (54 to 750) - probiotic/378.6 (41 to 846) days - placebo **Number randomised (n = 195)***: 98 (probiotics)/97 (placebo) **Number assessed**: 97 (probiotics)/95 (placebo) **Postrandomisation exclusion****: 67 - discontinuation of protocol specified treatment, 10 - prohibited concomitant treatment, 2 - adverse events, 13 - discontinuation of study beverage, 1 - other
Interventions	• Probiotic: one pack of *B breve* strain Yakult fermented milk (Mil–Mil) (10 billion bacteria) and *Lactobacillus acidophilus* (1 billion bacteria) per day • Placebo: one pack of energy beverage per day All participants received their allocated treatment for 48 Weeks
Outcomes	**Duration of follow-up**: 48 weeks • Incidence of relapse. Relapse defined as: persistence of a rectal bleeding score of greater or equal than 2 on Sutherland DAI score for 3 consecutive days and/or initiation of remission induction therapy for worsening of UC (as judged by investigator) • Maintence of remission. Remission defined as: Sutherland disease activity index (DAI) scale with rectal bleeding score of 0 and an endoscopic score of 0 or 1 • Serious adverse events
Notes	**Funding source**: "This work was supported by Yakult Honsha Co., Ltd." **Declaration of interest**: reported; Takanori Kanai received a financial donation from Yakult. Yasuo Suzuki, Toshifumi Hibi, Yukari Uemura, Kaoru Yokoyama, Naoki Yoshimura, Reiko Kunisaki, and Katsuyoshi Matsuoka have no conflicts of interest to declare *Statistical power calculated 300 in each intervention arm needed. However, study split into Period 1 and Period 2. Only period 1 conducted - this used 97 in intervention and 95 in control **Some participants discontinued for multiple reasons

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patient data were sent to the registration center via facsimile, where randomization was implemented by the central registration method. A statistician determined the algorithm of allocation. Patients were randomly allocated to the BFM group or placebo group at a ratio of 1:1 by dynamic allocation with the following randomization factors: age (≥ 40 years/12 weeks), study site (each study site), and compliance with 5-ASA" Comment: algorithm was determined by a statistician based on age, study site and compliance with 5-ASA as opposed to a computer

Matsuoka 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The study beverage and placebo beverage were packaged to be indistinguishable in appearance from each other and were delivered from the distribution center based on the allocation results at the time of enrolment. The distribution center, which was not informed of the groups to which patients were allocated, delivered the study beverage according to the provided numbers; this maintained blindness of the study." Comment: participants and personnel could not foresee assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "BFM and placebo consisted of 100 mL of an opaque white liquid that were identical" Comment: similar opaque liquid used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blinded, however, it is not clear if this includes blind outcome assessment. Though there was an independent data monitoring committee, the trial did not specifically report that they were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysed based on the "full study set". This full study set does not include all participants who were randomised, however, the difference (1 versus 1) across groups and reasons appear to be balanced
Selective reporting (reporting bias)	High risk	Trial registration available (UMIN000007593), however, there were more outcomes reported in the trial than prespecified
Other bias	High risk	Quote: "The interim analysis results showed that the Bayesian predictive power was 3.7%, which was markedly lower than the reference range for study continuation (20–25%). Based on this, the Independent Data Monitoring Committee recommended discontinuation of the study, so the study was discontinued" Comment: a posthoc decision was made to discontinue the study. This was not prespecified in the protocol.

NCT02361957

Methods	Double-blind, single centre RCT **Setting**: Hospital Gelderse Valei (Ede, The Netherlands) **Study period**: not stated
Participants	**Inclusion**: age 18 to 65; left-sided UC or pancolitis in clinical remission (serum concentrations of C-reactive protein of < 10 mg/L, which was checked with a point-of-care CRP test, and calprotectin of < 100 µg/g during their last medical check-up) **Exclusion**: history of GI surgery, diabetes mellitus, cancer; use of antibiotics during the last 3 months; current use of corticosteroids; alcohol consumption ≥ 21 servings a week for men and ≥ 14 for women; hypersensitivity to milk protein, gluten, or soy protein; currently pregnant or breastfeeding **Age (mean ± SD):** 51.5 ± 12.4 years **Sex (M/F):** 13/12 **Site of disease:** ? (left-sided), ? (pancolitis) **Use of medication**: not stated

NCT02361957 *(Continued)*

	Length of time remission at study entry: not stated **Number randomised (n = 25):** 13 (probiotic)/12 (placebo) **Number analysed:** 13 (probiotic)/12 (placebo); ITT principle applied **Postrandomisation exclusion:** 1 - prednisone prescribed for a flare-up; 1 - personal reasons
Interventions	**Duration of follow-up**: 12 weeks • Probiotic: patients used 2 sachets per day of 3 grams of the multi species probiotic food supplement Ecologic 825. The supplement contained nine bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W22, *Lactobacillus casei* W56, *Lactobacillus paracasei* W20, *Lactobacillus plantarum* W62, *Lactobacillus salivarius* W24 and *Lactococcus lactis* W19, in a concentration of 2.5 x 10^9 colony forming units per gram for 12 weeks with a total concentration of 1.5 x 10^{10} cfu/day • Placebo for 12 weeks Mesalazine with a maximum dose of 2.4 g/day was the only medication for UC that was permitted during the study
Outcomes	**Duration of follow-up**: • Relapse. Reported in the discussion section as a flare-up. However, no further description provided • Quality of life (IBD-Q: 1 to 7, higher score = better quality of life)
Notes	**Funding source:** funding was provided by the Dutch Ministry of Economy Affairs (IPCSFV2900) and Winclove Probiotics BV **Declaration of interest:** IBvdV is employee of Winclove Probiotics. Winclove develops, researches and markets probiotic food supplements

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization scheme was computer generated by Winclove using permuted blocks with block size equal to 4" Comment: adequate randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "It was impossible for research personnel involved with participants to adjust randomization or discern what product participants were receiving, ensuring true allocation concealment" Comment: method of allocation concealment was not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "It was impossible for research personnel involved with participants to adjust randomization or discern what product participants were receiving..." Comment: study was referred to as double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "It was impossible for research personnel involved with participants to adjust randomization or discern what product participants were receiving..." Comment: study was placebo-blinded and quality of life data were recorded by the participants
Incomplete outcome data (attrition bias)	Low risk	ITT analysis applied

NCT02361957 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial registration is available (NCT02361957) and all prespecified outcomes were reported
Other bias	Low risk	No other apparent biases

Shanahan 2006

Methods	Double-blind, single centre RCT (abstract only) **Setting**: not stated **Study period**: not stated
Participants	**Inclusion:** within one month of achieving clinical remission of UC following a documented relapse that required steroids to induce remission. Remission was defined as < 3 bowel movements/day (without frank/gross blood) out of 7, while off all steroids **Exclusion:** not stated **Age:** not stated, however, patients' demographic characteristics were similar across the three treatment groups **Sex:** not stated, however, patients' demographic characteristics were similar across the three treatment groups **Site of disease:** not stated, however, the extent of colitis which was similar across the groups was left-sided in about one-third, limited (proctitis) in one-third and pancolitis in one-third **Use of medication:** not stated, however, patients' demographic characteristics were similar across the three treatment groups **Length of time remission at study entry:** not stated **Number randomised (n = 157):** not stated (52/52/53?), however, there were similar numbers (52 to 53) per group **Number analysed:** not stated **Postrandomisation exclusion**: not stated
Interventions	• Probiotic: *Lactobacillus salivarius* subsp. Salivarius UCC118 • Probiotic: *Bifidobacterium infantis* 35624 • Placebo Each intervention was administered as a rehydrated blended yogurt powder (10^9 daily for one year). A stable dose of aminosalicylate was the only permitted concomitant medication for colitis
Outcomes	**Duration of follow-up**: 1 year • Relapse. Defined as < 3 bowel movements per day (without frank/gross blood) out of 7 • Time to relapse • Adverse events
Notes	**Funding source**: University College Cork **Declaration of interest**: not stated

Shanahan 2006 *(Continued)*

Emailed on 7 March 2018 - awaiting reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a prospective, balanced, randomised, parallel group, double blind, placebo-controlled trial..." Comment: not adequately described
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Selective reporting (reporting bias)	High risk	Not adequately described; adverse events mentioned but not gone into detail. Trial registration was available (NCT00510978)
Other bias	Unclear risk	Insufficient information to support judgement as study was published as an abstract.

Vejdani 2017

Methods	Multicentre, double-blind, randomised, placebo-controlled trial **Setting:** Multicentre, Iran, private practices **Study period:** not stated
Participants	**Inclusion criteria:** between 15 and 65 years of age, newly diagnosed or recently relapsed UC, based on clinical, endoscopic, and histological findings and had a mild to moderately active UC according to Truelove and Witts criteria and CAI ≥ 4 and ≤ 12. Additional external participants included in the maintenance of remission phase had to be in remission for less than 3 months. **Exclusion criteria:** substantial cardiac, renal or hepatic diseases, severe immunocompromised patients, existing or intended pregnancy or breastfeeding, regular treatment with NSAID drugs, intestinal major operation, steroid dependency, known intolerance to sulphate free preparations of mesalazine, UC exacerbated by infectious colitis, toxic megacolon, use of antibiotic within 14 days prior to first visit for more than 1 week, use of corticosteroid injection within the last 30 days, use of immunosuppressive treatment within the last 90 days and use of mesalazine enema or corton enema within the last 14 days **Age (mean ± SD):** not stated **Sex (M/F):** not stated **Site of disease:** not stated

Vejdani 2017 *(Continued)*

	Use of concurrent medication: conventional medical treatment for active UC **Treatment before study:** not stated **Length of time remission at study entry: less than three months** **Number randomised:** 14 (probiotic), 15 (placebo) **Number analysed:** 14 (probiotic), 15 (placebo) **Postrandomisation exclusion:** 2 - lost to follow-up, 1 - concurrent illness, 1 - poor compliance, 1 - taking antibiotics
Interventions	• Probiotic: *L Casei* strain ATCC PTA-3945, 5 x 10^5 live active cells. Oral, 1 capsule twice daily • Placebo: no detail Participants also received conventional medical treatment for active UC according to the severity and extension of their disease. Participants with mild proctitis, received mesalazine or sulfasalazine tablets after remission. In participants with moderate proctitis, mesalazine suppositories were stopped after remission. The rest of the drugs and their doses were kept unchanged.
Outcomes	**Duration of follow-up**: 4 months • Relapse (defined as an increase in bowel frequency with blood for at least 1 week. A colonoscopy was performed and biopsies were taken to confirm relapse) • Withdrawals • Serious adverse events
Notes	**Funding source**: not stated **Conflicts of interests**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisations were done using a random number table with odd numbers for probiotic and even numbers for placebo; randomisation was stratified according to the use of mesalazine or sulfasalazine and to the clinical severity of disease (mild or moderate)" Comment: use of random number table
Allocation concealment (selection bias)	Unclear risk	No mention in the text
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote 'Placebos were indistinguishable from the *L Casei* preparation'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was reportedly double-blinded however, there is no indication that outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate was over 26%, but balanced in both groups

Vejdani 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Trial registration not available, however, biochemical tests were recorded both at entry, remission and relapse, but not reported.
Other bias	Low risk	Quote: "There was not a significant difference between the two groups in factors such as age, sex, disease duration and extent, smoking, education taken and clinical activity index" Comment: baseline characteristics were balanced across groups and there were no other apparent risks of bias

Wildt 2011

Methods	Double-blinded, multicentre RCT **Setting***: "two participating centers in Denmark" **Study period**: June 2004 to March 2006
Participants	**Inclusion**: age ≥ 18 years; established diagnosis of UC left-sided disease (endoscopic changes distally to the splenic flexure) - including proctitis; time since relapse > 4 weeks during stable monotherapy with 5-ASA or no medication at all; ≥ 1 relapse within the last year. **Exclusion**: pregnancy (postive urine HCG) or breastfeeding; chronic liver or kidney disease; severe chronic disease of vascular or cardiopulmonary aetiology, malignancies; immunosuppressive disease or treatment; inflammatory bowel diseases besides UC, malabsorption syndromes, and former surgical procedures involving the gastrointestinal tract — with the exception of appendectomy. Treatment with azathioprine, 6-mercaptopurine, biological immunomodifiers, and treatment with steroids within 1 month of entry. **Sex (M/F)**: 10/22 **Age (median/range)**: 37.5 (23 to 68) years **Site of disease (location from anal valve - cm)**: 20 (5 to 70) - probiotic/22.5 (5 to 60) - placebo **Use of medication**: 24 (5-ASA orally, rectally and both); 1 (salazopyrine) **Length of time remission at study entry:** 4 (2 to 9) - probiotic/5 (2 to 11) months - placebo **Number randomised**: 20 (probiotics)/12 (placebo) **Number analysed**: 20 (probiotics)/12 (placebo) **Postrandomisation exclusion**: 1 - pregnancy, however, ITT principle was applied
Interventions	• Probiotics: oral preparation containing *L acidophilus* strain La-5 and *B animalis subsp. lactis* strain BB-12 • Placebo. Two capsules taken three times daily for 52 weeks. No other medications for UC were allowed during the study period

Outcomes	**Duration of follow-up**: 52 weeks
	
	• Number maintaining remission (1 year). Remission - presence of two out of three criteria:
	  * a simple clinical colitis activity index (SCCAI) score ≤ 4
	  * endoscopically grade 0-1 (Baron 1964) and/or
	  * histologically grade 0-1 (Truelove 1956)
	• Relapse (reported in the discussion section). Relapse was defined as SCCAI score > 4 and/or endoscopic changes grade 2 to 3

Wildt 2011 *(Continued)*

- Adverse events (flatulence, abdominal bloating and pain; changes in faecal consistency; musculoskeletal - arthralgia, sacroiliitis; various - tiredness, incontinence, stress, oral blisters, eye dryness; headache, dizziness; influenza, gastroenteritis, cystitis and pneumonia; serious adverse events)
- Serious adverse events
- Withdrawal due to serious adverse events

Notes	**Funding source**: "The study was supported by grants from Chr. Hansen A/S, Hoersholm, Denmark and by grants received from P. Carl Petersens Foundation and The Danish Crohn Colitis Organisation." **Declaration of interest**: "one of the authors (EB) is employed at the laboratory at Chr. Hansen A/S" *Presumably Gentofte and Hvidovre Hospital, University of Copenhagen Denmark judging by authors' affiliation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...randomised in blocks of 6 according to a table-generated randomisation list to receive either Probio-Tec AB-25 (two capsules three times daily, resulting in a total delivery of 1.5 X 10 11 CFU daily) or to receive placebo (two capsules three times daily) in a 2:1 ratio" Comment: adequate randomisation
Allocation concealment (selection bias)	Unclear risk	Correspondence with author: "At inclusion in the study an enclosed envelope was drawn from a batch of 6 envelopes - and the randomization revealed." Comment: no information as to whether envelopes were opaque and numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo medication […] was identical in appearance, size and taste" Comment: adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial was referred to as double-blinded placebo study, however, there were no details on blind outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was applied
Selective reporting (reporting bias)	Low risk	Study protocol available (NCT00268164) and all prespecified outcomes were reported
Other bias	High risk	Comment: imbalance in baseline characteristics - there were more participants receiving medication at inclusion in the intervention group compared to the control group (reported P = 0.018).

Yasushi 2015

Methods	Double-blind, placebo-controlled, single centre RCT **Setting**: Sakura Medical Center, Toho University, Japan

Yasushi 2015 *(Continued)*

	Study period: not stated
Participants	**Inclusion**: patients with UC in remission who were receiving treatment on an outpatient basis (UC was diagnosed in accordance with the diagnostic criteria proposed by the Survey Research Group of Intractable Inflammatory Intestinal Disorders/Specified Diseases, Japanese Ministry of Health, Labour and Welfare); 13 years or older in whom the CAI was maintained at 5 or less while receiving drugs such as mesalazine, salazosulfapyridine, or steroids, with no change in treatment regimens within 4 weeks before study entry. **Exclusion**: serious cardiac disease, serious renal disease, hypotension (systolic blood pressure, ≤ 80 mmHg), a history of shock during extracorporeal circulation, serious infections such as sepsis or pneumonia, or a serum haemoglobin concentration of less than 10 g/dL; newly began treatments such as leukocytapheresis, granulocyte adsorptive apheresis, or immunosuppressant therapy with drugs such as 6-mercaptopurine, azathioprine, and cyclosporine to improve symptoms, having milk allergy or a CAI of 6 or higher; pregnant women **Age (mean ± SD):** 43.9 ± 14.8 years* **Sex (M/F):** 28/18 **Site of disease:** 15 (left colon), 11 (proctosigmoiditis), 20 (total/subtotal) **Use of medication:** 24 (pentasa), 19 (salazopyrin), 1 (pentasa + salazopyrin), 2 (nothing) **Length of time remission at study entry:** unclear **Number randomised (n = 60):** 30 (probiotic)/30 (placebo) **Number analysed:** 23 (probiotic)/23 (probiotic) **Postrandomisation exclusions:** 14 (7 in each group) - prohibited use of drug and lack of consent
Interventions	• Probiotic: Bio-Three - 2 mg *Streptococcus faecalis* T-110 (lactomin) 10 mg *Clostridium butyricum* TO-A, 10 mg *Bacillus mesentericus* TO-A • Placebo prepared by substituting equivalent amounts of starch for the probiotic powder All participants received 3 tablets 3 x daily for 12 months. As concomitant medication, the use of mesalazine and salazosulfapyridine was unrestricted, but steroids could not be used as remission maintenance therapy. The use of drugs with similar effects as the study drug, potentially affecting the evaluation of effectiveness (i.e. other active live microbial preparations, laxatives, etc.) was prohibited from 1 week before study entry to the completion of the study. In principle, the use of oral antibiotics was also prohibited, but the use of topical antibiotics other than oral preparations was not particularly restricted. If a participant received a new treatment in addition to their basic therapy with drugs such as mesalazine or salazosulfapyridine, relapse was diagnosed, and the study treatment and faecal sample collection were discontinued.
Outcomes	**Duration of follow-up**: 12 months • Relapse at 3, 6, 9 and 12 months. Relapse was defined as CAI ≤ 5 • Remission maintenance at 12 months. Remission not absolutely defined • Serious adverse events
Notes	**Funding source**: This study was supported in part by a grant from the Japan Ministry of Health and Welfare. **Declaration of interest**: partially reported (YY - none, other authors - not reported) **Reported for the two intervention groups and pooled using an online calculator (www.statsto-do.com/CombineMeansSDs_Pgm.php)
Risk of bias	

Yasushi 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At the start of the study, 30 outpatients were randomly assigned to the Bio-Three group and 30 to the placebo group by means of a computer-generated scheme." Comment: adequately described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo tablets were identical to Bio-Three tablets and could not be distinguished from the active preparation on the basis of appearance.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition rate was over 20%, but balanced between the two groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all expected outcomes appear to have been reported
Other bias	Low risk	Quote: "After randomization, the baseline characteristics of sex, age, age at disease onset, disease duration, disease extent, and concomitant treatment did not differ between the groups" Comment: no other apparent biases

Zocco 2003

Methods	RCT (abstract only) **Setting**: not stated **Study period**: not stated
Participants	**Inclusion**: inactive UC and quiescent Crohn's disease* **Exclusion**: not stated **Age (mean)**: 32 years **Sex (M/F)**: 20/16 **Site of disease**: not stated **Use of medication**: not stated **Length of time remission at study entry:** not stated **Number randomised (n = 36)**: 12 (probiotic)/10 (mesalazine)/14 (probiotic + mesalazine) **Number assessed**: 12 (probiotic)/10 (mesalazine)/14 (probiotic + mesalazine)

Zocco 2003 *(Continued)*

	Postrandomisation exclusion: none
Interventions	• Probiotic alone: *Lactobacillus GG* 18 X 10^9 viable bacteria per day (Giflorex, Errekappa, Euroterapic, SpA, Milan, Italy) • Probiotic + mesalazine: *Lactobacillus GG* 18 X 10^9 viable bacteria and mesalazine 2.4 g per day • Mesalazine 2.4 g per day
Outcomes	**Duration of follow-up**: 12 months • Relapse (defined by clinical and endoscopic features. No further details) • Withdrawal due to adverse events
Notes	**Funding source**: not stated **Declaration of interest**: not reported Data from participants with CD were discarded due to the limited scope of the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were reportedly randomised, however, no further details were available
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appear to have been accounted for
Selective reporting (reporting bias)	Unclear risk	The study was published as an abstract. Insufficient information to make a judgement
Other bias	Unclear risk	The study was published as an abstract. Insufficient information to make a judgement

Zocco 2006

Methods	Open-label, single centre RCT **Setting:** Inflammatory Bowel Diseases Centre of the Catholic University, Rome, Italy **Study period**: June 2001 to December 2004
Participants	**Inclusion**: UC in clinical (CAI < 4), laboratory and endoscopic remission; time since last relapse: < 12 months

Zocco 2006 *(Continued)*

Exclusion: patients with active disease or complications, severe accompanying illness or major colonic surgery, gastrointestinal infections, serious concomitant diseases (renal or hepatic failure, severe hypertension), diabetes mellitus, immunosuppressive treatment being administered currently or in the month before enrolment, mesalazine intolerance, and pregnant or lactating woman

Age (mean ± SD): 33 ± 5.8 years*

Sex (M/F): 104/83

Site of disease: 35 (proctosigmoiditis), 25 (left colon), 12 (total/subtotal)

Use of medication: not stated

Length of time remission at study entry: ≤ 4 weeks in 12% (probiotic)/11% (probiotic + mesalazine)/10% (mesalazine); ≤ 3 months in 26% (probiotic)/25% (probiotic +mesalazine)/26% (mesalazine)

Number randomised (n = 187): 65 (probiotic)/62 (probiotic + mesalazine)/60 (mesalazine)

Number analysed: 65 (probiotic)/62 (probiotic + mesalazine)/60 (mesalazine)

Postrandomisation exclusion: none (premature discontinuation of the study for reasons other than relapse did not occur)

Interventions	• Probiotic: *Lactobacillus GG* treatment 18 x 10^9 viable bacteria/day divided into two oral administrations • Mesalazine 800 mg tablets (mesalazine Errekappa, Euroterapici SpA), three tablets (2400 mg) daily • Probiotic + mesalazine: *Lactobacillus GG* 118 x 10^9 viable bacteria/day plus mesalazine 2400 mg daily Participants were treated for 12 months. Treatment was interrupted in case of disease relapse, occurrence of side effects, poor compliance and inability to attend follow-up visit. Oral or rectal treatment with antibiotic or steroid medications, apart from the study drugs, was not allowed during the trial. Full clinical evaluation with symptoms assessment and physical examination was performed at baseline and every 3 months for all the 12-month study period.
Outcomes	**Duration of follow-up**: 12 months • Relapse (6 and 12 months). Relapse defined as the appearance of UC symptoms or an increase in CAI to more than 4 points. • Maintenance of remission at 6 and 12 months • Serious adverse events
Notes	**Funding source**: no external funding **Declaration of interests**: not reported *Reported for the three intervention groups and pooled using an online calculator (www.statsto-do.com/CombineMeansSDs_Pgm.php)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were reportedly randomised, however, no further details were provided
Allocation concealment (selection bias)	Unclear risk	Not stated

Zocco 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was an open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was an open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for
Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all participants were accounted for
Other bias	Low risk	Quote: "Demographic and prestudy clinical characteristics did not differ significantly among the three groups" Comment: no other apparent biases

5-ASA: 5-aminosalicylic acid; CAI: colitis activity Index; CD: crohn's disease; CFU: colony forming units; CRP; C-reactive protein; DAI: disease activity index; FCAL: fecal calprotectin; GI: gastrointestinal HCG: human chorionic gonadotropin; IBD: inflammatory bowel disease; IBD-Q: inflammatory bowel disease questionnaire; ITT: intention to treat IV: intervention; NSAID: non steroidal ant-inflammatory drugs; QoL; quality of life; RCT: randomised controlled trial; SCCAI: simple clinical colitis activity index; SD: standard deviation; UC: ulcerative colitis

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

Study	Reason for exclusion
Ahmed 2013	Insufficient duration of follow-up, i.e. less than 3 months; (quote): "if this could be altered with one months treatment with synbiotics"
Ballini 2019	Wrong patient population and not maintenance study
Bamba 2002	Wrong intervention, i.e. uses prebiotic; (quote): "A new prebiotic from germinated barley..."
Cui 2004	Insufficient duration of follow-up; (quote): "the patients were evaluated ....after 2 mo of treatment..."
Do 2010	Wrong study design, i.e. review article
Faubion 2000	Wrong study design, i.e. commentary piece
Folwaczny 2000	Wrong study design, i.e. not randomised
Fujimori 2009	Wrong patient population, i.e. patients were not in remission, so not maintenance trial
Henker 2008	Wrong study design, i.e. not randomised
IRCT20120415009475N5	Wrong study type
Ishikawa 2002	Insufficient information: emailed author for clarification, no reply
Ishikawa 2011	Wrong patient population: data from patients in remission presented together with those not in remission, unable to differentiate data

Study	Reason for exclusion
Li 2013	Wrong patient population: patients not in remission, so not maintenance trial
Liu 2014	Wrong patient population: translated from Chinese and confirmed not maintenance study
Miele 2009	Wrong patient population: patients not in remission, so not maintenance study
NCT00268164	Insufficinet information: university replied 26 February 2018 - no access to full paper
NCT00374725	Insufficient information: no reply from author - emailed 15 January 2018
NCT00803829	Insufficient information: author passed away - no access to full paper
NCT00951548	Insufficient information: emailed author for classification on 15 January 2018, replied and confirmed not maintenance trial
NCT01772615	Wrong patient population: author replied with full paper - patients not in remission so not maintenance study
Palumbo 2016	Wrong patient population: patients being induced, so not maintenance study
Pelech 1998	Insufficient information: emailed author for classification, no reply
Rembacken 1999	Includes both an induction and maintenance phase, however, participants were only randomised for induction. The maintenance phase was an observational study.
Rohatgi 2015	Wrong patient population: patient cohort have microscopic colitis so not ulcerative colitis study
Sanchez-Morales 2019	Induction study
Shadnoush 2013	Wrong patient population: study uses patients with inflammatory bowel disease - does not differentiate between ulcerative colitis and Crohn's
Solovyeva 2014	Wrong patient population: patients being induced, so not maintenance trial
Tursi 2010	Wrong patient population: patients being induced, so not maintenance trial
Venturi 1999	Wrong study design: this study was not a randomised controlled trial
Zhang 2018a	Induction study

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

Fan 2019

Methods	RCT, single centre **Setting**: The First Affiliated Hospital of Fujian Medical University **Study duration**: January 2015 to June 2016
Participants	40 with IBD randomised (19 control group, 21 observation group) UC total: 31, CD total: 9; UC control 15, CD IV 4; CD control 4, CD IV 5

Fan 2019 *(Continued)*

	Inclusion: confirmed IBD diagnosis with mild to moderate symptoms as per the current standards in China; no previous probiotic treatment; no allergy to drugs used in the present study; cognisance of the purpose of the present study and willingness to sign an informed consent **Exclusion**: severe heart, liver, kidney and other systemic diseases; pregnancy or lactation; unresponsive to medical treatment and with complications; immune system disorders **Sex** (M/F): 10/9 control group; 10/11 observation group **Age** (mean +/- SD): 39.97 +/- 8.68 control group; 42.56 +/- 7.58 observation group **Site of disease**: not specified **Use of medication**: not specified **Length of time remission at study entry:** not specified **Number randomised:** 40 **Number assessed:** not specified **Postrandomisation exclusion**: not specified **Follow-up**: 40 days
Interventions	**IV**: pentasa (mesalazine extended action tablet) as in the control regimen + probiotics (2 tablets Bifico once and three times/day + "a largely liquid-based high nutrition diet" **Control**: 1 to 2 pentasa tablets once and three times/day and a maintenance dose of 1 tablet once and three times/day
Outcomes	• Microflora composition • Biochemical indices • Inflammatory markers • Activity scores
Notes	Mixed: contacted author for UC data This work was supported by the Fujian Province Natural Science Fund Project The authors declare that there are no conflicts of interest

Fang 2018

Methods	RCT, multicentre **Setting**: Chunan County First People's Hospital and Taizhou Hospital **Study duration**: February 2016 to September 2017
Participants	84 patients with UC (42 control, 42 IV) Control: 18 mild, 24 moderate; IV: 19 mild, 23 moderate **Inclusion**: met the relevant diagnostic criteria for UC, confirmed by colonoscopy, barium enema, etc; course of disease ≥ 4 weeks; accompanied by persistent or recurrent diarrhoea, haemorrhagic stool with abdominal pain, acute aftermath etc; age ≥ 18 years; volunteer to participate in this study and sign informed consent **Exclusion**: those with allergies; combined with infectious colitis such as amoebiasis, bacterial disease, intestinal tuberculosis, chronic schistosomiasis; severe intestinal perforation, intestinal ob-

Fang 2018 *(Continued)*

	struction, toxic colonic dilatation etc; people with unconsciousness, serious insufficiency of important organs such as heart and kidney; people with radiation colitis, ischaemic colitis, Crohn's disease, mental illnesses, history of drug and alcohol abuse; pregnant, lactating women **Sex** (M/F): 26/16 control; 28/14 IV **Age:** 45.12 +/- 6.21 control; 45.13 +/- 6.2 IV **Site of disease**: control: whole colon 15, right half colon 19, left half colon 8; IV: whole colon 16, right half colon 17, left half colon 9 **Use of medication**: not specified **Length of time remission at study entry:** not specified **Number randomised:** 84 **Number assessed:** not specified **Postrandomisation exclusion**: not specified **Follow-up**: 2 months
Interventions	IV: mesalazine + gold bifid Control: mesalazine only
Outcomes	• Inflammation markers (IL-10, TNF-α, IL-18, sIL-2R) • Lesion activity scores (modified Mayo scores) • Clinical efficacy • Anorectal motility
Notes	Disease activity to be clarified. 95 versus 76% effective rate Main article in Chinese. Google translate was used for the translation. Funding and conflict of interest were not discussed in the article.

Huang 2018

Methods	RCT, single centre Study duration: May 2014 to February 2018 Setting: Bai'an Affiliation Sanxia Central Hospital of Chongqing
Participants	Abstract: 120 UC patients (control 60, IV 60) Main text: 360 UC patients (control 180, IV 180) ??? Inclusion: not specified Exclusion: not specified **Sex** (M/F): 81/99 control; 90/90 IV **Age** (mean +/- SD): 41.5 +/- 8.3 control; 42.2 +/- 9.4 IV **Site of disease**: not specified **Use of medication**: not specified

Huang 2018 *(Continued)*

	Length of time remission at study entry: not specified **Number randomised:** 120 or 360 **Number assessed: not stated** **Postrandomisation exclusion**: not stated **Follow-up**: 8 weeks
Interventions	Control: mesalazine only IV: mesalazine + bifid triple viable capsules enteric-coated tablet of mesalazine (Sunflower Group Jiamusi Luling Pharmaceutical Co, Ltd, 0.25 g/tablet, batch No.: 13001830), four tablets oral administration before meal, 3 times/day. Those in the research group would additionally take two bifid triple viable capsules (Jincheng Haisi Pharmaceutical Co, Ltd, 0.21 g/capsule, Batch No.: 13012365) prior to meal, 3 times/day
Outcomes	• Evaluation of clinical efficacy • DAI of UC • Score of clinical symptoms • Changes in inflammatory factors (TNF-α, IL-8 and IL-10) • Adverse reactions
Notes	Unclear whether active or inactive UC - emailed authors. Effectiveness rate = 90 versus 72% Funding and conflict of interest not discussed in the article.

Shi 2018

Methods	RCT, single centre **Setting**: Department of Gastroenterology, Anji County People's Hospital of Huzhou City **Study duration**: August 2014 to November 2016
Participants	86 UC patients (43 control, 43 IV) **Inclusion criteria**: all who met the diagnosis of ulcerative colitis in the "Consensus Opinions on the Diagnosis and Treatment of Inflammatory Bowel Diseases in China" formulated by the Collaborative Group of Inflammatory Bowel Diseases of the Chinese Medical Association Gastroenterology Branch Criterion, with typical clinical manifestations (diarrhoea, mucus, pus, blood, stool, etc.) and colonoscopy (continuous, diffuse distribution of ulcer surface); Patients agreed to the study and signed informed consent **Exclusion**: those who used contraindications to the study; those who had poor compliance during treatment; other reasons were not suitable for inclusion in the study **Sex** (M/F): IV: 14/27; control: 17/24 **Age** (mean +/- SD): IV: 47.1 +/- 4.9; control: 47.3 +/- 6.2 **Site of disease**: not specified **Use of medication**: not specified **Length of time remission at study entry:** not specified **Number randomised:** 86

Shi 2018 *(Continued)*

	Number assessed: not specified **Postrandomisation exclusion**: not specified **Follow-up**: treatment 2 months + 6 months
Interventions	IV: *Bacillus subtilis* and *Enterococcus faecium* + mesalazine Control: mesalazine only Mesalazine enteric-coated tablets (Sunflower Pharmacy, Chinese Medicine Standard: H19980148, (specification: 0.25 g/tablet), oral, 1 g/time, 6 h/time; the observation group was combined with the *Bacillus subtilis* double live enteric-coated capsules (trade name: Mei Changan, Beijing Hanmei Pharmaceutical Co, Ltd. based on the control group). Company, National Medicine Standard: S20030087, specification: 250 mg/capsule), 500 mg, orally, 3 times/day; two groups of patients were continuously taking medication for 2 months.
Outcomes	• Inflammation markers (IL-6, IL-8, IL-10, TNF-α, MDA, SOD, COX-2, NF-κB) • Clinical curative effect • Time to symptom relief • Rachmitewitz and Sutherland scores
Notes	Disease activity to be clarified. 93% versus 76% effective rate Article in Chinese. Google Translate was used for the translation. Funding and conflict of interest were not discussed in the article.

Yilmaz 2019

Methods	RCT, single centre, prospective, open-label **Study duration**: May 2015 to December 2016
Participants	45 IBD patients (25 IV, 20 control) UC = 15, CD = 10 **Inclusion/exclusion**: "Patients with IBD participated in the study. In the trial, CD Activity Index for CD and Truelove-Witts scoring systems for UC were used for disease assessment scores. If the score was <450, patients with CD were admitted to the study. If the score was higher, patients with UC were not admitted to the study. Volunteers also had to be >18 years old. Patients with alcohol consumption > 20 g/day, allergies or intolerance to milk, antibiotic treatment within the last 1 month, column or bowel operation history up to 3 months before the start of the study, and the presence of active infection within 1 month prior to the start of the study or during the study were excluded from the study. In addition, if a patient requested to leave on his/her own will, or if kefir was not consumed continuously for 2 weeks, the trial protocol was assessed and was not approved." **Sex** (M/F): IV: total 13/12, UC 9/6, CD: 4/6, control: total 10/10, UC: 4/6, CD: 6/4 **Age** (median): IV: 33, control: 43 **Site of disease**: IV: UC colon 15, CD colon 1, Ileum 6, colon + Ileum 3; control: UC colon 10, CD Ileum 10 **Use of medication**: not specified **Length of time remission at study entry:** not specified **Number randomised:** 45?

Yilmaz 2019 *(Continued)*

	Number assessed: 45 **Postrandomisation exclusion**: either 0 or 3. Authors mention 3 patients left the trial willingly, however participant and completers number are the same (n = 45) **Follow-up**: 4 weeks
Interventions	**IV**: 400 mL/day kefir x 2 day **Control**: ??? "The control group did not consume placebo because it was not possible to prepare a control product with a similar flavor, texture, and taste as those of kefir. Ayran and yogurt were similar to kefir, but they also have Lactobacillus and can affect the microbiota results."
Outcomes	• Symptoms diary questionnaire • Effects on *Lactobacillus* flora and their biochemical properties
Notes	Disease activity not clear. 96% versus 85% effective rate The authors declare no conflict of interest and that this study has received no financial support.

Zhang 2018b

Methods	RCT, single centre **Setting**: Department of Gastroenterology, Longyou County People's Hospital, Luzhou, Zhejiang Province **Study duration**: October 2016 to November 2017
Participants	110 UC patients (55 control (38 UC, 17 CD); 55 observation (36 UC, 19 CD)) **Inclusion**: in accordance with the diagnostic criteria of the "Consensus on the diagnosis and treatment of inflammatory bowel disease in China" formulated by the Chinese Medical Association; no significant abnormalities in liver and kidney function; no other severe chronic diseases; informed consent **Exclusion**: severe liver and kidney diseases; intestinal diseases such as intestinal tuberculosis, Crohn's disease, intestinal tumours; hormones, 5-aminosalicylic acid, and intestinal probiotics for nearly 4 weeks; patients taking other drugs; patients who are allergic to drugs such as mesalazine, Bifidobacterium quadruplex, etc.; pregnant and lactating women; patients with mental illness; patients who do not co-operate with treatment; younger than 18 years old **Sex** (M/F): IV 29/26; control 32/23 **Age** (mean +/- SD): IV: 44.6 +/- 5.8; control 45.3 +/- 5.5 **Site of disease**: not specified **Use of medication**: not specified **Length of time remission at study entry:** not specified **Number randomised: 110** **Number assessed:** not specified **Postrandomisation exclusion**: not specified **Follow-up**: 2 months

Zhang 2018b *(Continued)*

Interventions	**IV**: *Bifidobacterium* quadruplex bacteria tablets + mesalazine **Control**: mesalazine Both groups were given mesalazine enteric-coated tablets (trade name: Huidi, Manufacturer: Sunflower Pharmaceutical Group Jiamusi Luling Pharmaceutical Co, Ltd, National Medicine Standard H19980148, 0.25 g/tablet), oral, 1 g/3 times/day. The observation group was given a *Bifidobacterium* quadruple live bacteria tablets (brand name: Siliankang, manufacturer: Hangzhou Longda Xinke Biopharmaceutical Co, Ltd, National Medicine Standard) S20060010, 0.5 g/tablet), oral, 1.5 g/3 times/day
Outcomes	• Total effective rate • Lipid peroxidation injury indexes • Inflammatory factors • Peripheral T cell subsets • Adverse reactions
Notes	Article in Chinese. Google Translate was used for the translation. Funding and conflict of interest were not discussed in the article.

CD: crohn's disease; COX-2: cyclooxygenase-2; DAI: disease activity index; IBD: inflammatory bowel disease; IL: interleukin; IV: intervention; MDA: malondialdehyde; NF-κβ: nuclear factor kappa beta; RCT; randomised controlled trial; sIL-2R: soluble interleukin 2 receptor; SOD: superoxide dismutase; TNF- α: tumor necrosis factor alpha; UC: ulcerative colitis

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

NCT03415711

Trial name or title	PRObiotic VSL#3® for maintenance of clinical and endoscopic REMission in Ulcerative Colitis (PROREM UC)
Methods	RCT, double-blind, parallel assignment
Participants	39 UC participants
Interventions	• Group A: 13 participants will receive mesalamine 2.4 g/day in once daily administration plus VSL#3® 450 billion sachet, two sachets per day for 12 months (900 billion of bacteria per day) • Group B: 13 participants will receive mesalamine 2.4 g/day in once daily administration plus VSL#3® 450 billion sachet, two sachets twice a day (1800 billion of bacteria per day) for 12 months • Group C: 13 patients will receive mesalamine 2.4 g/day in once daily administration plus placebo for 12 months
Outcomes	• To characterise the efficacy of VSL#3® plus standard therapy (5-ASA) in maintaining clinical and endoscopic remission in patients with UC in remission (time frame: 12 months) • Proportion of subjects in clinical and endoscopic remission at 12 months, as defined by Total Mayo Score ≤ 2 with no individual subscore > 1 and rectal bleed subscore of 0
Starting date	April 2017
Contact information	Antonino Amato clinicaltrialcentre@policlinicogemelli.it
Notes	Sponsors and collaborators: VSL pharmaceuticals, Actial Farmaceutica S.r.l.

NCT03565939

Trial name or title	Probiotic Treatment of Ulcerative Colitis with Trichuris Suis Ova (PROCTO)
Methods	RCT, parallel assignment, double-blind, comparative, exploratory phase II proof of concept trial
Participants	120 UC participants
Interventions	**IV**: trichuris suis ova **Control**: placebo
Outcomes	**Primary outcome measures** • Response (full Mayo) (time frame: 24 weeks). The proportion of TSO participants, compared with placebo participants (i.e. a proportional difference), who obtain a reduction of 3 or more full Mayo score steps between the baseline visit and the end of trial visit (week 24). The full Mayo score (range 0-12) is the sum of 4 clinical scores (stool frequency, rectal bleeding, findings on endoscopy, physician's global assessment) each scored with a value 0 (normal), 1, 2, or 3 (worst). **Secondary outcome measures** • Remission (full Mayo) (time frame: 24 weeks). Proportion of TSO participants, compared with placebo participants (i.e.. a proportional difference), who obtain a full Mayo score ≤ 2 at the end of trial visit (week 24) (remission). • Reduction in use of steroid (time frame: 24 weeks). Mean value of total accumulated sum of milligram oral and rectal glucocorticosteroids taken by TSO participants during the trial compared with the corresponding mean value among placebo participants.
Starting date	May 2018
Contact information	Contact: Michelle V Prosberg, MD, michelle.vernstroem.prosberg@regionh.dk Contact: Andreas M Petersen, MD, Ph.D andreas.munk.petersen@regionh.dk
Notes	Sponsors and collaborators: ParaTech A/S

NCT03798210

Trial name or title	*Lactobacillus reuteri* ATCC PTA 4659 in ulcerative colitis (COLUS)
Methods	RCT, triple-blind, parallel assignment
Participants	40 UC patients
Interventions	*Lactobacillus reuteri* versus placebo
Outcomes	**Primary outcome measures** • Rectal bleeding with Mayo score ≥ 5 (time frame: 12 months). Rectal bleeding as sign of increased inflammatory activity as determined by the Mayor Clinic Score for evaluation of disease activity in ulcerative colitis **Secondary outcome measures** • Increased faecal calprotectin (time frame: 12 months)

NCT03798210 *(Continued)*

	• Gut inflammatory biomarker • Increased CRP (time frame: 12 months) • General inflammatory biomarker **Other outcome measures** • Serum zonulin (time frame: 12 months) • Gut permeability biomarker. Gut permeability (time frame: 12 months). Recovery of sugar molecules in urine as marker of increased permeability
Starting date	January 2017
Contact information	Contact: Per M Hellström, Prof +46 70 3727423 per.hellstrom@medsci.uu.se; Peter Benno, MD, PhD +46 70 5795554 peter.benno@endoskopienheten.se
Notes	Sponsors and collaborators: Uppsala University

NCT04006977

Trial name or title	Multistrain probiotics reduces UC depression and anxiety scores
Methods	RCT, double-blind, parallel assignment
Participants	60 UC patients
Interventions	**IV**: multistrain probiotic product (DSF) **Control**: placebo
Outcomes	**Primary outcome measures** • Reduction of anxiety and depression scores (time frame: 0 week, 8 weeks, 12 weeks, 16 weeks) • Reduction of anxiety and depression scores (with points as standard units) using HADS at 8 weeks and 16 weeks after randomised treatment **Secondary outcome measures** • Clinical response (time frame: 4 weeks, 8 weeks, 12 weeks, 16 weeks) measured by a ≥ 1.5(3) points reduction in Simple Clinical Colitis Activity Index score at week 8 and 16 • Clinical remission (time frame: 4 weeks, 8 weeks, 12 weeks, 16 weeks) measured by Simple Clinical Colitis Activity Index score ≤ 5(2) points at week 8 and 16 • Endoscopic remission/response (time frame: 0 week, 16 weeks) measured by a Mayo endoscopic subscore of < 1 point, or at least a 1-point reduction from baseline in the endoscopy subscore at week 16 • Changes in faecal-associated microbiota following probiotic therapy (time frame: 0 week, 16 weeks). Changes in faecal-associated microbiota using 16S ribosomal RNA sequencing and changes in the metabolomic profile of the faeces following probiotic therapy (at baseline and 16 weeks) will be assessed, stratified by both change in Simple Clinical Colitis Activity Index score following probiotic therapy and randomization • Identification of potential stressors (time frame: 0 weeks, 16 weeks). Participants will be asked to complete a modified practical and family problem list to identify 13 potential stressors Adverse events (time frame: 4 weeks, 8 weeks, 12 weeks, 16 weeks). Adverse events were assessed at weeks 8 and 16 by participant survey.
Starting date	October 2019

NCT04006977 *(Continued)*

Contact information	Prof Jie Liang liangjie@fmmu.edu.cn
Notes	Sponsors and collaborators: Xijing Hospital of Digestive Diseases, MENDES SA

5-ASA: 5-aminosalicylic acid; CRP; C-reactive protein; DSF: Disulfiram HADS: hospital anxiety and depression scale; TSO: trichuris suis ova; UC: ulcerative colitis

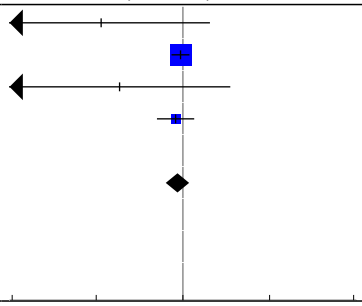
DATA AND ANALYSES

Comparison 1. Probiotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	4	361	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.18]
2 Maintenance of clinical remission	2	141	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.98, 1.37]
3 Serious adverse events	4	351	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Withdrawal due to adverse events	2	113	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Health-related quality of life	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.63, 0.23]

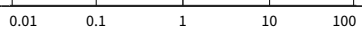
Analysis 1.1. Comparison 1 Probiotics versus placebo, Outcome 1 Clinical relapse.

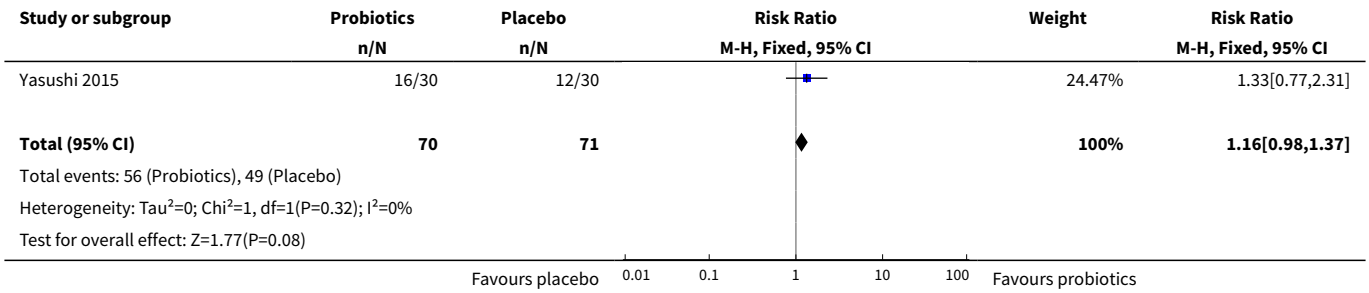
Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bjarnason 2019	0/40	4/41		1.15%	0.11[0.01,2.05]
Matsuoka 2018	55/98	58/97		68.21%	0.94[0.74,1.19]
NCT02361957	0/13	2/12		1.11%	0.19[0.01,3.52]
Yasushi 2015	14/30	17/30		29.52%	0.82[0.5,1.35]
Total (95% CI)	**181**	**180**		**100%**	**0.87[0.63,1.18]**
Total events: 69 (Probiotics), 81 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=3.6, df=3(P=0.31); I^2=16.66%					
Test for overall effect: Z=0.91(P=0.36)					



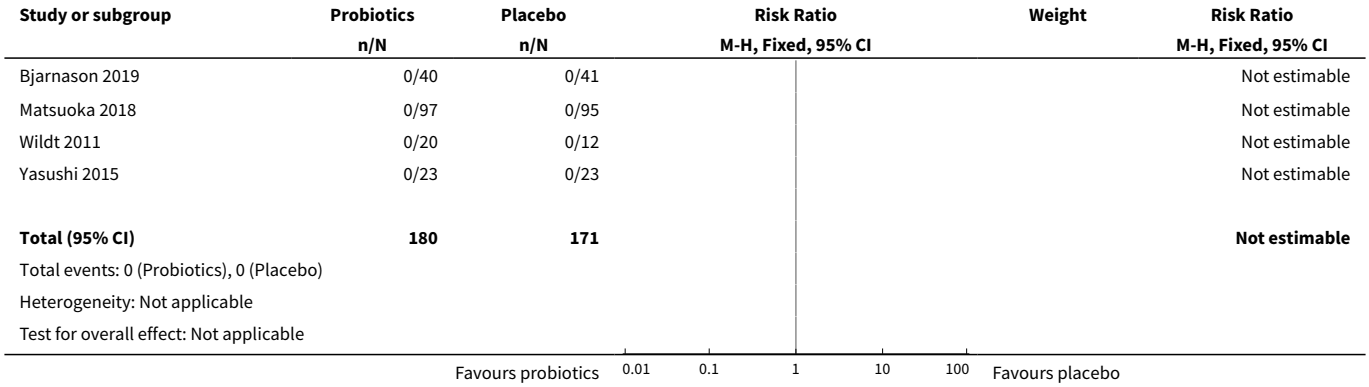
Analysis 1.2. Comparison 1 Probiotics versus placebo, Outcome 2 Maintenance of clinical remission.

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bjarnason 2019	40/40	37/41		75.53%	1.11[0.99,1.24]

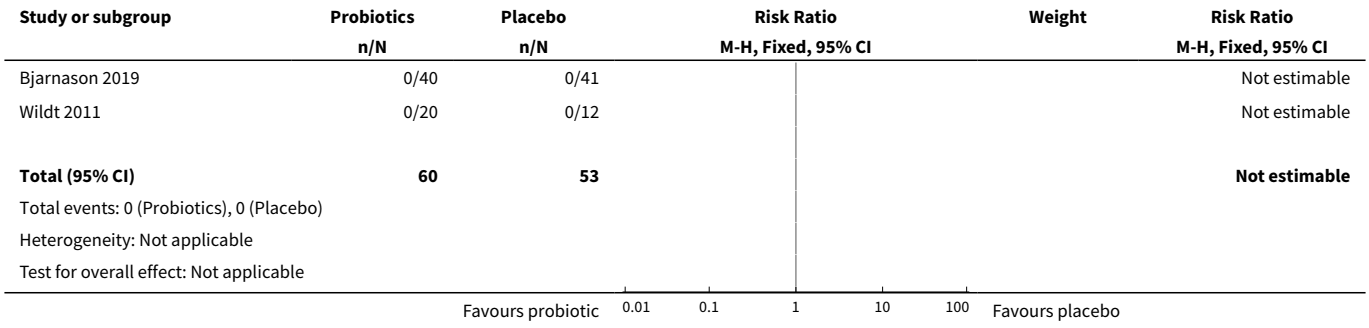




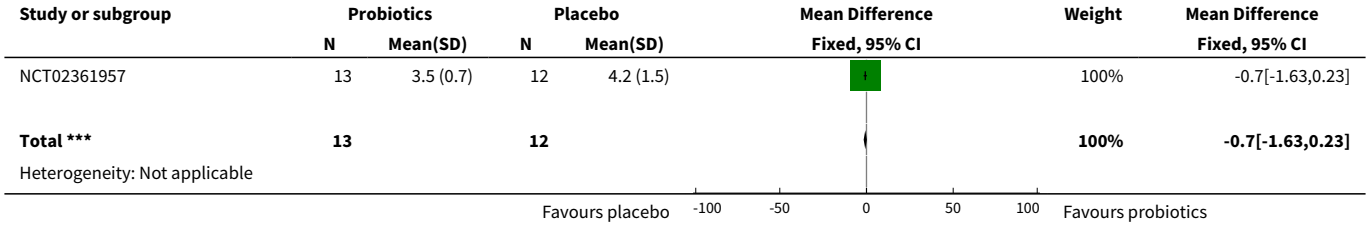
Analysis 1.3. Comparison 1 Probiotics versus placebo, Outcome 3 Serious adverse events.

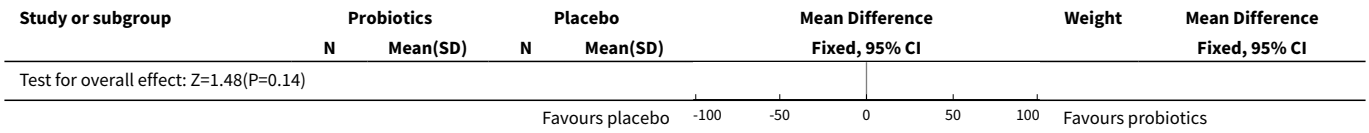


Analysis 1.4. Comparison 1 Probiotics versus placebo, Outcome 4 Withdrawal due to adverse events.



Analysis 1.5. Comparison 1 Probiotics versus placebo, Outcome 5 Health-related quality of life.

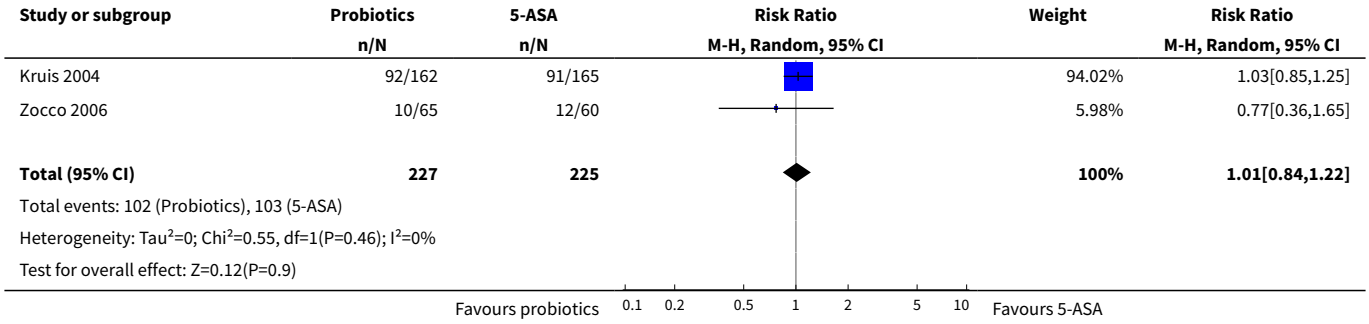




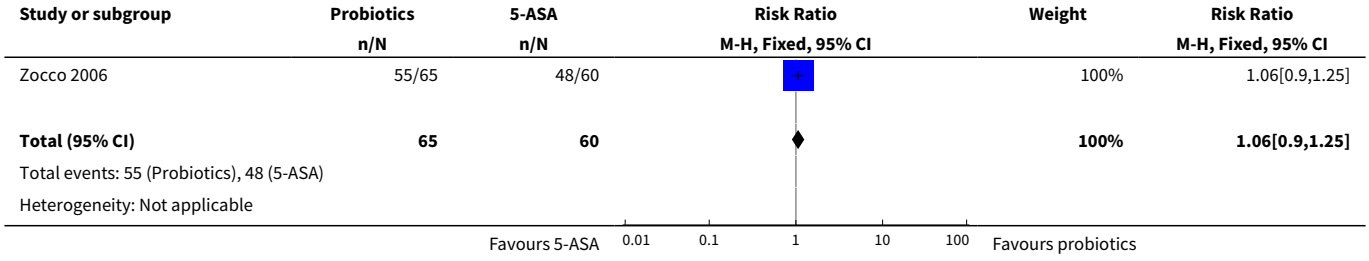
Comparison 2. Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine)

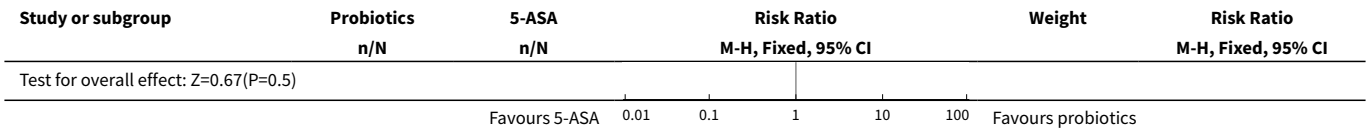
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical relapse	2	452	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.22]
2 Maintenance of clinical remission	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.25]
3 Serious adverse events	1	327	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.41, 3.46]
4 Withdrawal due to adverse events	1	222	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.46, 2.25]
5 Health-related quality of life	1	222	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.01, 0.41]

Analysis 2.1. Comparison 2 Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine), Outcome 1 Clinical relapse.

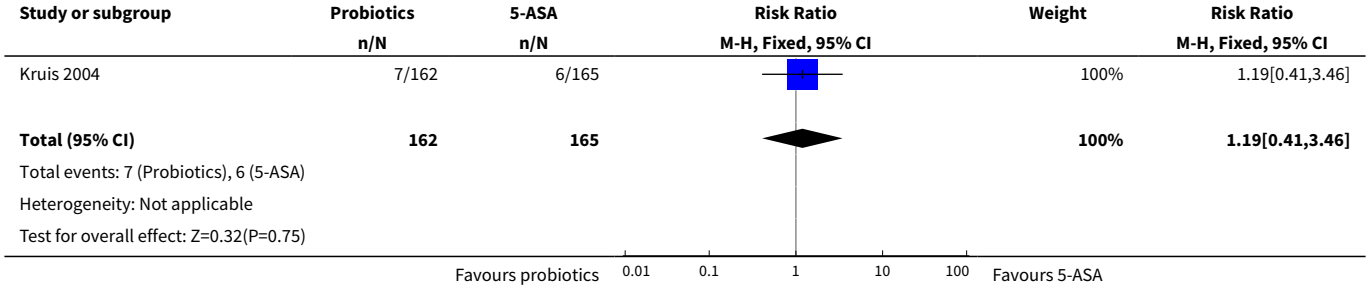


Analysis 2.2. Comparison 2 Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine), Outcome 2 Maintenance of clinical remission.

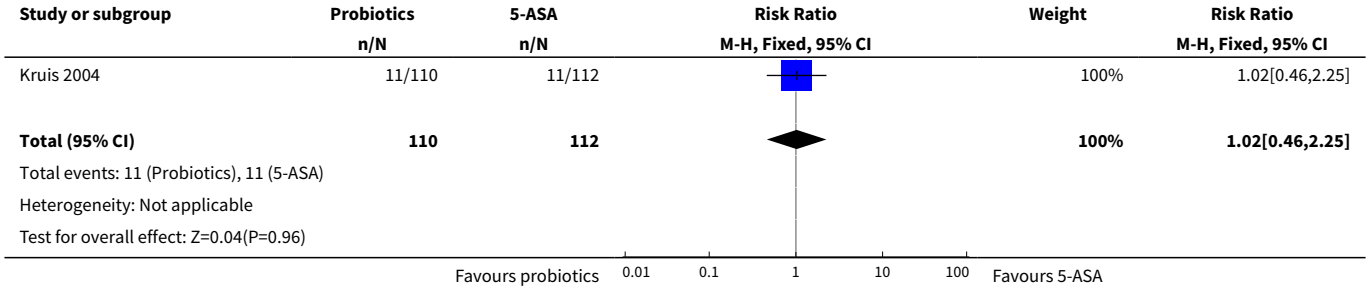




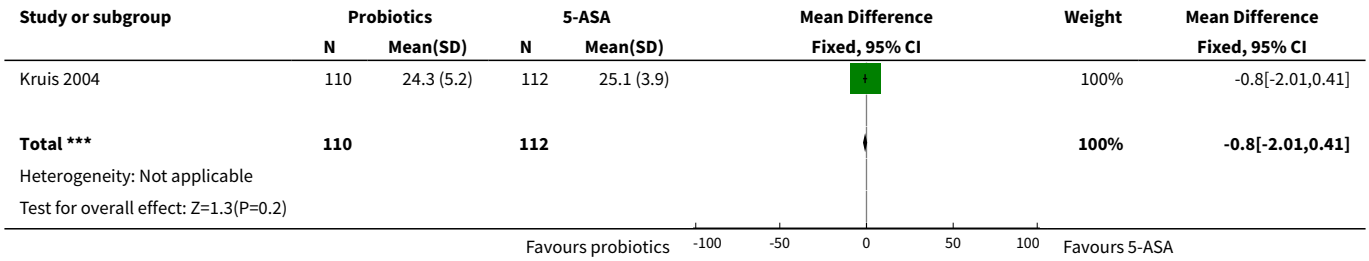
Analysis 2.3. Comparison 2 Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine), Outcome 3 Serious adverse events.



Analysis 2.4. Comparison 2 Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine), Outcome 4 Withdrawal due to adverse events.



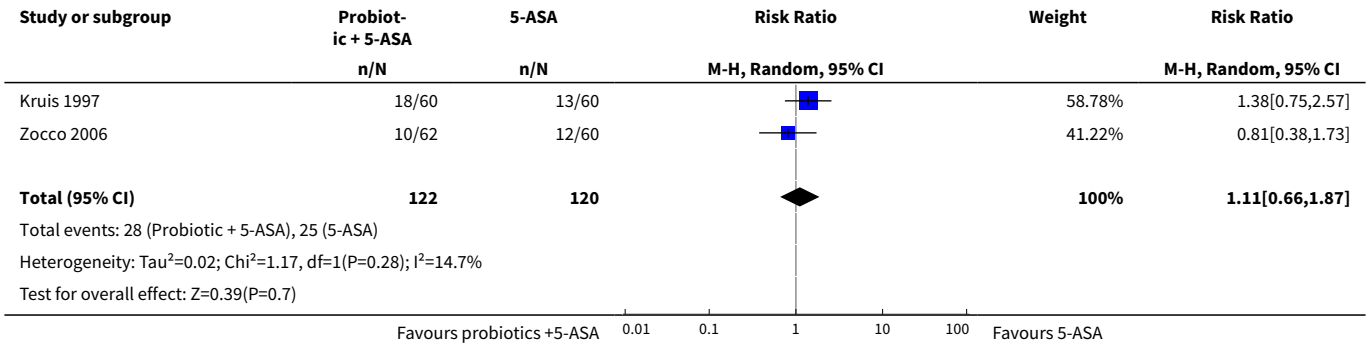
Analysis 2.5. Comparison 2 Probiotics versus 5-aminosalicylic acid (5-ASA) (mesalazine), Outcome 5 Health-related quality of life.



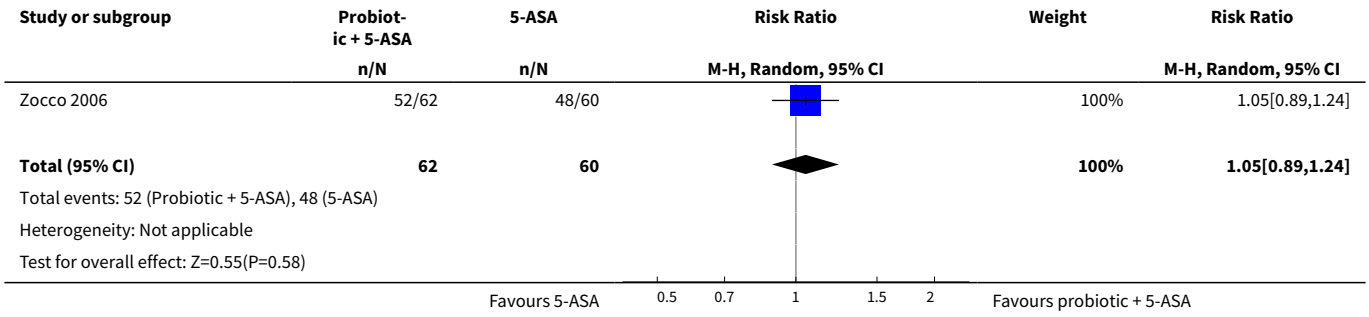
Comparison 3. Probiotic + 5-aminosalicylic acid (5-ASA) (mesalazine) versus 5-ASA (mesalazine)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	2	242	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.66, 1.87]
2 Maintenance of clinical remission	1	122	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]
3 Withdrawal due to serious adverse events	2	127	Risk Ratio (M-H, Fixed, 95% CI)	5.29 [0.26, 107.63]

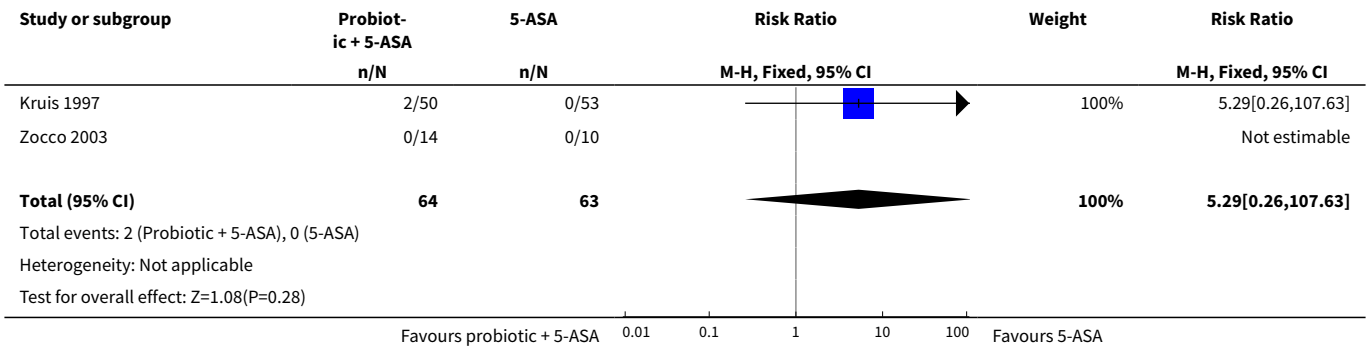
Analysis 3.1. Comparison 3 Probiotic + 5-aminosalicylic acid (5-ASA) (mesalazine) versus 5-ASA (mesalazine), Outcome 1 Clinical relapse.



Analysis 3.2. Comparison 3 Probiotic + 5-aminosalicylic acid (5-ASA) (mesalazine) versus 5-ASA (mesalazine), Outcome 2 Maintenance of clinical remission.



Analysis 3.3. Comparison 3 Probiotic + 5-aminosalicylic acid (5-ASA) (mesalazine) versus 5-ASA (mesalazine), Outcome 3 Withdrawal due to serious adverse events.



ADDITIONAL TABLES

Table 1. Outcome data table

Study ID	Number of relapses	Definition of relapse	Maintenance of remission	Quality of life	Serious adverse events	Withdrawal due to adverse events
Bjarnason 2019	0 versus 4	NR	NR	7.9 +/- 2.8 versus 8.0 +/- 2.5	None	None
NCT02361957	0/13 versus 1/12; 0/13 versus 2/12	Relapse was defined as a flare-up	NR	3.5 +/- 0.7 versus 4.2 +/- 1.5	NR	NR
Copaci 2014	30% versus 28%	NR	77% versus 90%	NR	NR	NR
Kruis 1997	8/50 versus 6/53; 18/60 versus 13/60	CAI > 4	NR	NR	NR	2/50 versus 1/53
Kruis 2004	40/110 versus 38/112; 92/162 versus 91/165	The presence of all of the following: CAI > 6 (or an increase in CAI of at least 3 points with CAI = 4 being exceeded at the same time); endoscopic index > 4; histological signs of acute inflammation	NR	24.3 +/- 5.2 versus 25.1 +/- 3.9	7/162 versus 6/165	11/110 versus11/112; 63/162 versus 64/165
Matsuoka 2018	22/97 versus 19/95 55/98 versus 58/97	The persistence of a rectal bleeding score of ≥ 2 on Sutherland DAI score for 3 consecutive days and/or initiation of remission induction therapy for worsening of UC	Reported P = 0.643	NR	0*	0/97 versus 2/95
Shanahan 2006	NR	Defined as < 3 bowel movements per day (without frank/gross blood) out of 7	NR	NR	NR	NR

Table 1. Outcome data table *(Continued)*

Vejdani 2017	2/14 versus 4/15; 4/14 versus 7/15	An increase in bowel frequency with blood for at least 1 week. A colonoscopy was performed and biopsies were taken to confirm relapse	NR	NR	0	NR
Wildt 2011	15/20 versus 11/12	SCCAI score > 4 and/or endoscopic changes grade 2–3	5/20 versus 1/12	NR	0/20 versus 0/12	0/20 versus 0/12
Yasushi 2015	7/23 versus 10/23; 14/30 versus 17/30	CAI ≤ 5	16/23 versus 13/23 16/30 versus 13/30	NR	0/23 versus 0/23	NR
Zocco 2003	2/12 versus 2/10 versus 4/14	Defined by clinical and endoscopic features	NR	NR	NR	0/12 versus 0/10 versus 0/14
Zocco 2006	10/65 (Probiotic) versus 12/60 (Mesalazine) versus 10/62 (Probiotic+Mesalazine)	The appearance of UC symptoms or an increase in CAI to more than 4 points	55/65 versus 48/60 versus 52/62	NR	0/65 versus 0/60 versus 0/62	NR

*Serious adverse events which occurred were reportedly not related to the intervention (avascular necrosis of bilateral femoral head and pulmonary thromboembolism)
CAI: colitis activity index; DAI: disease activity index; NR: not reported; SCCAI: simple clinical colitis activity index UC: ulcerative colitis

Table 2. Sensitivity analysis

Outcome	Fixed-effect	Random-effects
Probiotics versus placebo		
Clinical relapse	RR 0.85, 95% CI 0.68 to 1.05	RR 0.87, 95% CI 0.63 to 1.18
Maintenace of clinical remission	RR 1.16, 95% CI 0.98 to 1.37	RR 1.11, 95% CI 0.99 to 1.24
Probiotics versus 5-ASA		
Clinical relapse	RR 1.00, 95% CI 0.83 to 1.21	RR 1.01, 95% CI 0.84 to 1.22
Maintenace of clinical remission	RR 1.06, 95% CI 0.90 to 1.25	RR 1.06, 95% CI 0.90 to 1.25
Probiotics + 5-ASA versus 5-ASA		
Clinical relapse	RR 1.10, 95% CI 0.69 to 1.78	RR 1.11, 95% CI 0.66 to 1.87
Maintenance of clinical remission	RR 1.05, 95% CI 0.89 to 1.24	RR 1.05, 95% CI 0.89 to 1.24

5-ASA: 5-aminosalicylic acid; **CI**: confidence interval; **RR**: risk ratio

APPENDICES

Appendix 1. Search strategies

EMBASE

1. random$.tw.

2. factorial$.tw.

3. (crossover$ or cross over$ or cross-over$).tw.

4. placebo$.tw.

5. single blind.mp.

6. double blind.mp.

7. triple blind.mp.

8. (singl$ adj blind$).tw.

9. (double$ adj blind$).tw.

10. (tripl$ adj blind$).tw.

11. assign$.tw.

12. allocat$.tw.

13. crossover procedure/

14. double blind procedure/

15. single blind procedure/

16. triple blind procedure/

17. randomized controlled trial/

18. or/1-17

19. exp ulcerative colitis/

20. colitis.mp.

21. inflammatory bowel disease.mp.

22. IBD.mp.

23. UC.mp.

24. Or/19-23

25. exp Probiotics/

26. exp Synbiotics/

27. probiotic*.tw.

28. synbiotic*.tw.

29. exp Lactobacillus/

30. lactobacill*.tw.

31. bacill*.tw.

32. exp Bifidobacterium/

33. (bifidus or bifidobacter*).tw.

34. exp Streptococcus thermophilus/

35. streptococcus thermophilus.tw.

36. streptococc*.tw.

37. exp Lactococcus/

38. lactococc*.tw.

39. Bacillus subtilis/

40. bacillus subtilis.tw.

41. exp Enterococcus/

42. exp Enterococcus faecium/ or Enterococcus faecalis/

43. exp Saccharomyces/

44. saccharomyc*.tw.

45. leuconostoc.tw.

46. pediococc*.tw.

47. bulgarian bacillus.tw.

48. (beneficial adj3 bacter*).tw.

49. (Escherichia coli or "E. coli").tw.

50. Yeast.tw.

51. (fungus or fungi).tw.

52. (VSL# 3 or VSL 3).tw.

53. Or/25-52

54. 18 and 24 and 53

Medline

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1-13
15. exp ulcerative colitis/
16. colitis.mp.
17. inflammatory bowel disease.mp.
18. IBD.mp.

19.UC.mp.
20.Or/15-19
21.exp Probiotics/
22.exp Synbiotics/
23.probiotic*.tw.
24.synbiotic*.tw.
25.exp Lactobacillus/
26.lactobacill*.tw.
27.bacill*.tw.
28.exp Bifidobacterium/
29.(bifidus or bifidobacter*).tw.
30.exp Streptococcus thermophilus/
31.streptococcus thermophilus.tw.
32.streptococc*.tw.
33.exp Lactococcus/
34.lactococc*.tw.
35.Bacillus subtilis/
36.bacillus subtilis.tw.
37.exp Enterococcus/
38.exp Enterococcus faecium/ or Enterococcus faecalis/
39.exp Saccharomyces/
40.saccharomyc*.tw.
41.leuconostoc.tw.
42.pediococc*.tw.
43.bulgarian bacillus.tw.
44.(beneficial adj3 bacter*).tw.
45.(Escherichia coli or "E. coli").tw.
46.Yeast.tw.
47.(fungus or fungi).tw.
48.(VSL# 3 or VSL 3).tw.
49.Or/21-48
50.14 and 20 and 49

Cochrane CENTRAL

#1 MeSH descriptor: [Probiotics] explode all trees

#2 MeSH descriptor: [Synbiotics] explode all trees

#3 probiotic*

#4 synbiotic*

#5 MeSH descriptor: [Lactobacillus] explode all trees

#6 lactobacill*

#7 bacill*

#8 MeSH descriptor: [Bifidobacterium] explode all trees

#9 (bifidus or bifidobacter*)

#10 MeSH descriptor: [Streptococcus thermophilus] explode all trees

#11 streptococcus thermophilus

#12 streptococc*

#13 MeSH descriptor: [Lactococcus] explode all tree

#14 lactococc*

#15 MeSH descriptor: [Bacillus subtilis] explode all trees

#16 bacillus subtilis

#17 MeSH descriptor: [Enterococcus] explode all trees

#18 enterococcus faec*

#19 MeSH descriptor: [Saccharomyces] explode all trees

#20 saccharomyc*

#21 leuconostoc*

#22 pediococc*

#23 bulgarian bacillus

#24 (Escherichia coli or "E. coli").tw.

#25 Yeast.tw.

#26 (fungus or fungi).tw.

#27 Or/ #1- #26

#28 MeSH: [Ulcerative colitis] explode all trees

#29 UC

#30 Inflammatory bowel disease

#31 IBD

#32 #28 or #29 #30 and #31

#33 #27 and #32

The Cochrane IBD/FBD Review Specialised Trials Register

1. Probiotics and Inflammatory bowel disease

2. Probiotics and Ulcerative colitis

3. Synbiotics and Inflammatory bowel disease

4. Synbiotics and Ulcerative colitis

CINAHL

1. (TI probiotic* or AB probiotic*) OR (TI synbiotic* or AB synbiotic*) OR (TI probiotics* or AB probiotics*) OR (TI lactobacill* or AB lactobacill*) OR (TI bacill* or AB bacill*) OR (TI bifidobacter* or AB bifidobacter*) OR (TI bifidus* or AB bifidus*) OR (TI streptococc* or AB streptococc*) OR (TI lactococc* or AB lactococc*) OR (TI enterococcus* or AB enterococcus*) OR (TI saccharomyc* or AB saccharomyc*) OR (TI leuconostoc* or AB leuconostoc*) OR (TI pediococc* or AB pediococc*) OR (TI *coli or AB *coli) OR (TI yeast* or AB yeast*) OR (TI fung* or AB fung*) OR (TI VSL* or AB VSL*)

2. (TI Inflammatory bowel disease or AB Inflammatory bowel disease) OR (TI Ulcerative colitis or AB Ulcerative colitis) OR (TI UC or AB UC) OR (TI IBD or AB IBD)

3. 1 and 2

Clinical trials.gov

1. Probiotics and inflammatory bowel disease (37)

2. Probiotics and Ulcerative colitis (23)

3. Synbiotic and inflammatory bowel disease (3)

4. Synbiotic and Ulcerative colitis (1)

WHAT'S NEW

Date	Event	Description
29 November 2019	New citation required but conclusions have not changed	There remains insufficient evidence for the use of probiotics in maintaining remission in ulcerative colitis. Further research against placebo is unlikely to provide useful data, and instead comparisons to other therapies is proposed.
31 October 2019	New search has been performed	We updated the searches in December 2017 and reran them in October 2019; we added eight new studies to this update.

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 12, 2011

Date	Event	Description
8 May 2018	Amended	ZIE, LK and PB were added to the author team

CONTRIBUTIONS OF AUTHORS

Zipporah Iheozor-Ejiofor co-ordinated the review; extracted data and contacted authors; checked the quality of data extraction; analysed and interpreted data; undertook and checked quality assessment; performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing and editing the review; made an intellectual contribution to the review; and approved the final review prior to submission.

Lakhbir Kaur performed screening of titles and abstracts and full-text articles, extracted data and contacted authors; contributed to writing and editing the review; made an intellectual contribution to the review; and approved the final review prior to submission.

Morris Gordon performed screening of titles and abstracts and full-text articles, extracted data and contacted authors, analysed and interpreted data; contributed to writing and editing the review; made an intellectual contribution to the review; contributed to previous versions of the review; made final changes to the review, including the update search prior to publication and peer review changes; and approved the final review prior to submission.

Patricia Baines contributed to writing and editing the review; made an intellectual contribution to the review; approved the final review prior to submission

Vasiliki Sinopoulou made update changes to all sections of the review following peer review and repeated searches; and approved the final review.

Anthony Akobeng initiated and conceptualised the review; contributed to previous versions of the review; and approved the final review prior to submission.

DECLARATIONS OF INTEREST

Zipporah Iheozor-Ejiofor: my employment at the University of Central Lancashire is funded by the National Institute for Health Research (NIHR) UK and focuses on high priority Cochrane Reviews in Inflammatory Bowel Disease.

Lakhbir Kaur: none known

Morris Gordon: received travel grants from various companies to attend scientific meetings in the last three years, including Biogaia, Synergy, Tillots, Ferring and Allergan. None of these companies have had any involvement in the planning, completion, analysis or write up of this or any other reviews. This review has been completed as part of a UK funded National Institute for Health Research (NIHR) Cochrane Programme grant, with some time funded.

Patricia Baines: none known

Vasiliki Sinopoulou: none known

Anthony Akobeng: none known

SOURCES OF SUPPORT

Internal sources

- School of Medicine, University of Central Lancashire, UK.

External sources

- National Institute for Health Research, UK.

  This project was supported by the National institute for Health Research, via Cochrane Infrastructure and Cochrane Programme Grant funding (NIHR Cochrane Program Grant 16/114/13 - A programme of Cochrane systematic reviews to investigate optimal treatment strategies using emerging pharmacological interventions, dietary therapies and interventions to manage pain in inflammatory bowel disease) to the University of Central Lancashire (UCLAN). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made a posthoc decision not to collect data on biochemical markers of inflammation as an outcome. Biochemical markers as surrogate endpoints are unlikely to provide results which are helpful to clinicians or patients.

Since the previous review, we have updated the search strategy, 'Risk of bias' reporting and use of GRADE to current Cochrane standards.

INDEX TERMS

Medical Subject Headings (MeSH)

Colitis, Ulcerative [*therapy]; Probiotics [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction

MeSH check words

Humans