Received: 27 April 2024 | Accepted: 27 June 2024

DOI: 10.1002/ueg2.12636

ORIGINAL ARTICLE

ueg journal WILEY

Efficacy and safety of probiotics in IBD: An overview of systematic reviews and updated meta-analysis of randomized controlled trials

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Abstract

Background and objective: Probiotics show promise in inflammatory bowel disease (IBD), yet knowledge gaps persist. We performed an overview of systematic reviews and an updated metanalysis of randomized controlled trials (RCT) assessing the effect of probiotics on Crohn's disease (CD) and ulcerative colitis (UC).

Methods: MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials were searched up to September 2023. Primary outcomes were clinical remission and recurrence; secondary outcomes included endoscopic response and remission, and adverse events. We calculated odds ratios (OR) using a random-effects model in R. The quality of systematic reviews was assessed using the AMSTAR-2; the trials' risk of bias was evaluated using the Cochrane Collaboration tool. Evidence certainty was rated using the GRADE framework.

Results: Out of 2613 results, 67 studies (22 systematic reviews and 45 RCTs) met the eligibility criteria. In the updated meta-analysis, the OR for clinical remission in

UC and CD was 2.00 (95% CI 1.28–3.11) and 1.61 (95% CI 0.21–12.50), respectively. The subgroup analysis suggested that combining 5-ASA and probiotics may be beneficial for inducing remission in mild-to-moderate UC (OR 2.35, 95% CI 1.29–4.28). Probiotics decreased the odds of recurrence in relapsing pouchitis (OR 0.03, 95% CI 0.00–0.25) and trended toward reducing clinical recurrence in inactive UC (OR 0.65, 95% CI 0.42–1.01). No protective effect against recurrence was identified for CD. Multi-strain formulations appear superior in achieving remission and preventing recurrence in UC. The use of probiotics was not associated with better endoscopic outcomes. Adverse events were similar to control. However, the overall certainty of evidence was low.

Conclusion: Probiotics, particularly multi-strain formulations, appear efficacious for the induction of clinical remission and the prevention of relapse in UC patients as well as for relapsing pouchitis. Notwithstanding, no significant effect was identified for CD. The favorable safety profile of probiotics was also highlighted.

KEYWORDS

clinical outcomes, clinical remission, Crohn's disease, endoscopic response, inflammatory bowel disease, microbiome modulation, probiotic, RCT, recurrence, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD) arises from the combination of host genetics, microbial and environmental factors.[1] Even though there is a substantial consensus regarding the microbial underpinnings of IBD, significant knowledge gaps persist, particularly concerning the strategies to modulate microbiome.[2,3] Over the last decades, several pharmacological treatments have been developed for IBD, covering a wide variety of molecular targets. However, besides enabling sustained remission in less than half of the patients, the difference in effect between the new active drugs and placebo has remained relatively stable over time.[4] This suggests the existence of a therapeutic ceiling[4] and underscores a knowledge gap. Another important point to consider is that advanced therapies may entail adverse effects, particularly for specific patient cohorts.[5]

Probiotics are viable microorganisms that confer advantageous health effects upon the host.[5] Several pre-clinical and clinical studies have shown the promising role of probiotics for IBD, particularly for UC and pouchitis.[6,7] The mechanisms underlying these outcomes are variable but most likely attributable to the production of butyrate, immunoglobulin A (IgA) and short-chain fatty acid (SCFA, known to be trophic factors), upregulation of defensins and mucin-2 expression, and downregulation of pro-inflammatory cytokines.[6,8] Notwithstanding, some studies and pooled analyses have suggested that probiotics may be insufficient to reach clinical remission and prevent recurrence.[9,10] Besides differences among patient populations, the probiotic effect is likely strain-specific, dose-dependent, and influenced by engraftment ability, which in turn may depend on host factors and the stability and resilience of the pre-existing microbiota.[1] Additionally, the effects of single-strain and multi-strain probiotics may differ due to higher coverage or synergy.[5,11] Considering this variability, the selection of probiotics should be guided by the best available evidence. Currently, the use of probiotics for Crohn's disease (CD) is not supported by European guidelines.[12]

Key summary

Summarize the established knowledge on this subject

- Despite the growing evidence on the microbial underpinnings of IBD, significant knowledge gaps persist on the modulation of inflammatory bowel disease (IBD) patients' microbiome, particularly using probiotics.
- We performed the largest meta-analysis evaluating the use of probiotics in the context of IBD.

What are the significant and/or new findings of this study?

- Probiotics had a significant effect in inducing clinical remission in UC. A subgroup analysis suggested that combining 5-ASA and probiotics may be beneficial for inducing remission in UC. Likewise, probiotics decreased the odds of clinical recurrence in UC and in relapsing pouchitis.
- Probiotics lacked significant effect in CD.
- Our results highlight the favorable safety profile of probiotics.
- The overall certainty of evidence (GRADE assessment) was low.

Conversely, experts agree that probiotics (mostly *Escherichia coli* Nissle 1917 and a multi-strain probiotic that includes lactic acid bacteria, *Streptococcus*, and *Bifidobacterium*) may be useful in ulcerative colitis (UC) and relapsing pouchitis.[13,14]

To provide an up-to-date evidence review on this topic, we performed an overview of reviews and updated meta-analysis including all randomized controlled trials that assessed probiotics' effect on clinical and endoscopic outcomes of patients with active or quiescent CD or UC.

MATERIALS AND METHODS

This study adheres to the Cochrane collaboration guidelines,[15] the Preferred Reporting Items for Overviews of Reviews (PRIOR), and the Preferred Reporting Items for Systematic Reviews and Metanalysis (PRISMA) statements.[16]

Search strategy

MEDLINE (via PubMed), Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from database inception up until 30 September 2023. The search strategy combined the following terms: ((probiotics[MeSH Terms])) AND ((inflammatory bowel disease[MeSH Terms]) OR (Crohn's disease [Title/Abstract]) OR (ulcerative colitis[Title/Abstract])) (Table S1). Considering that we intended to perform an overview of systematic reviews and an updated metanalysis, our search was divided into two steps, as previously done elsewhere.[17] First, we aimed to identify all systematic reviews regarding the effect of probiotics on IBD. Subsequently, we utilized the same search results to identify all randomized controlled trials (RCTs) that assessed probiotics on IBD. No language restrictions were imposed. To ensure that all pertinent articles were included, backward citation searching was performed for selected studies.

Eligibility criteria

For the overview of systematic reviews, inclusion criteria were: (i) being a systematic review (with or without meta-analysis), and (ii) evaluating the clinical remission and/or recurrence in IBD patients receiving probiotics, independently of disease severity or activity. For the updated meta-analysis, the inclusion criteria were: (i) RCTs evaluating the effectiveness of probiotics in active or quiescent CD (including the post-operative setting) or UC (including pouchitis), regardless of disease severity or activity; (ii) RCTs with control groups receiving either 5-aminosalicylates (5-ASA) and/or placebo; (iii) reporting outcomes related to the achievement of clinical remission or the recurrence of disease activity (in quiescent IBD). The exclusion criteria were: (i) non-systematic reviews, animal studies, guidelines, editorials, letters, meeting abstracts, and case reports; (ii) studies with less than 4 weeks of follow-up (only for RCTs).

Study selection and data collection

Two reviewers evaluated the titles and abstracts of the search results to determine their relevance. Any papers deemed potentially relevant were thoroughly assessed. The eligibility criteria were applied independently, and any disagreements were resolved through consensus. The information abstracted into an ad hoc designed data form was: (i) authors' name, year of publication, country, study design, population, disease type, type of probiotic used, RCTs included, investigated outcomes - for systematic reviews; (ii) authors' name, year of publication, country, study design, population and disease characteristics, number of patients, probiotic (type and daily dose), comparator (placebo and/or 5-ASA), follow-up duration, outcomes (remission, recurrence, side effects, number of cases in each group).

Quality assessment

The risk of bias for each RCT was evaluated using the Cochrane Collaboration tool,[18] which assesses sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Each parameter is categorized as "uncertain risk", "low risk", or "high risk". To estimate publication bias, funnel plots were evaluated for asymmetry and the Egger's test was performed.

The methodological quality of the systematic reviews was assessed using the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews[19]). The systematic reviews with at least one critical weakness were rated as "low confidence", while those without critical flaws but with more than one non-critical weakness were classified as "moderate" and those with up to one non-critical weakness were classified as "high confidence".

The overall certainty in evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[20] The scores were independently used by two investigators and any disagreements were reconciled by discussion and consensus.

Data synthesis and statistical analysis

The primary endpoints were clinical remission (induction trials) and recurrence (maintenance trials, following medical or surgical induction of remission), while the secondary outcomes were endoscopic remission and recurrence, and side effects. Outcomes were defined as per each study's definition, as we were not able to process individual patient data and reclassify endpoints. For each previous systematic review, we re-calculated the odds ratio (OR) for achieving clinical remission and preventing clinical recurrence, including only the studies from that review that specifically evaluated the effect of probiotics on IBD patients. In addition, we incorporated all RCTs and performed an updated meta-analysis of probiotics' efficacy and safety in IBD (primary and secondary endpoints). The OR for each endpoint and the corresponding 95% confidence interval (CI) were calculated using a random-effects model (DerSimonian-Laird method). Heterogeneity was evaluated using the Cochran Q test and the I^2 statistic; values of <30%, 30%–60%, 61%–75%, and >75% suggested low, moderate, substantial, and considerable heterogeneity, respectively. A sensitivity analysis, excluding one RCT at a time, was performed to assess the influence of each study on the pooled results. Subgroup analyses for the disease setting (UC, CD, post-operative CD, chronic pouchitis), type of probiotic (specific formulation), and type of comparison in UC trials (i) probiotics vs. 5-ASA, (ii) probiotics vs. placebo; iii] probiotics + 5-ASA vs. 5-ASA) were performed to address heterogeneity. Considering the lower statistical power, the results of the subgroup analysis were interpreted cautiously when the number of studies per category was less than three. The analyses were performed using R (v.4.1.1) *meta* package.

RESULTS

Bibliographic search and study selection

The study selection process is described in Figure 1. The search yielded 2613 results, 775 were duplicated. By screening the title and abstract, 1838 records were excluded. One hundred and nine papers were considered for full-text analysis, from which 43 were excluded mostly because they evaluated outcomes not of interest (e.g., focused on metabolic pathways, cytokine profiles or gut microbiome analysis, without providing data on clinical endpoints), or for being non-randomized trials. Therefore, 67 studies (22 systematic reviews and 45 RCT) matched the eligibility criteria for this overview of systematic reviews and updated meta-analysis.

Characteristics of the included studies

The characteristics of the 22 systematic reviews are summarized in Table 1; two[7,23] did not provide metanalytical data. Most evaluated the effect of probiotics in both UC and CD (*n* = 13[7,9,22–24,28,29,31,32,34,35,37,38]), seven[10,26,27,30,33,36,39] only in UC, one[21] in pouchitis, and other in post-operative CD.[25] Likewise, the number of RCTs included varied (from 2[21] to 33[22]) as well as the type of probiotic. The majority (*n* = 18) analyzed several different probiotics, while three regarded only *De Simone* formulation.[21,27,36]

The details of the 45 RCTs included in the updated meta-analysis are provided in Table 2. The studies varied regarding the disease (32[40–45,47–50,52–56,58–66,69,72–75,82,83,85] included UC patients, 13[42,44,46,51,57,67,68,70,71,76,79,80,84] individuals with CD, and three[77,78,81] patients with pouchitis), the number of participants (between 11[76] and 360[45]) and follow-up duration (from 4[44] to 104[71] weeks). Twenty-two RCTs evaluated the induction of remission in patients with active IBD, mostly in mild-to-moderate UC (*n* = 19), three[77,78,81] evaluated only UC patients submitted to ileal pouch-anal anastomosis, and four[51,68,70,79] focused solely on CD patients after ileocecal resection. The type of probiotic was also variable, for example, *De Simone* formulation was used in nine[51,62,64–66,73,77,78,81] trials, preparations containing only *Lactobacillus* in nine,[48,60,68,70,71,76,79,86,87] and *Escherichia coli* Nissle 1917 in seven.[40,55,63,74,82–84] Twenty RCTs evaluated clinical remission, 22 analyzed clinical recurrence, five evaluated endoscopic remission, and four evaluated endoscopic recurrence (Table 2 and Table S3).

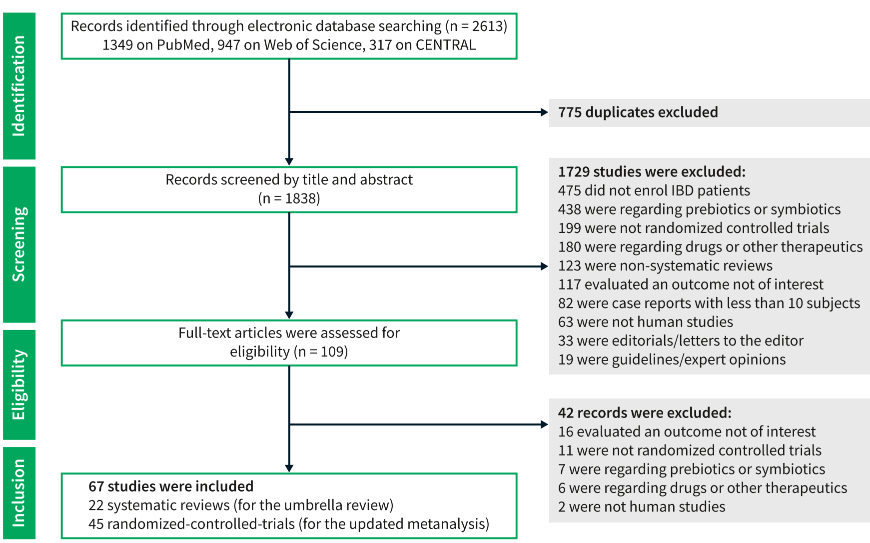

FIGURE 1 Flow diagram of the study selection and data collection process.

TABLE 1 Characteristics of the systematic reviews included in the umbrella review.

Authors	Country	Inclusion criteria	Studies included (n)	RCT on probiotics (n)	Population	Probiotic	Pooled clinical remission (probiotics vs. control)[a]	Pooled clinical recurrence (probiotics vs. control)[a]	AMSTAR-2 rating	AMSTAR-2 rating commentaries
Alphonsus et al.[21]	Canada	RCTs on medical therapies for pouchitis	20	2	UC	*De Simone* formulation	NA	OR = 0.07 (95% CI 0.00–0.20), I^2 = 77% (*n* = 2)	High	No data on individual studies' funding
Vakadaris et al.[22]	Greece	RCTs on probiotics for IBD	33	33	CD (*n* = 11), UC (*n* = 25)	Several	OR = 1.87 (95% CI 1.07–3.25), I^2 = 55% (*n* = 9)	OR = 0.66 (95% CI 0.44–0.99), I^2 = 38% (*n* = 17)	Critically low	No data on individual studies' funding; no information if the methods were established before/published protocol; only one database used on electronic search; no assessment of the likely impact of publication bias; the title only refers probiotics but studies on symbiotics and prebiotics were also included
Lorentz and Müller[23] (systematic review)	Germany	RCTs on probiotics for IBD	22	20	CD (*n* = 7), UC (*n* = 16)	Several	OR = 1.71 (95% CI 0.92–3.12), I^2 = 54% (*n* = 8)	OR = 0.81 (95% CI 0.44–1.50), I^2 = 17% (*n* = 7)	Critically low	No explanation for including only RCT; no data on studies' funding; no information if the methods were established before/published protocol; only one database used on electronic search; not clear if studies' selection and data extraction was done independently by at least two authors
Zhang et al.[24]	China	RCTs on probiotics, prebiotics or symbiotic in IBD	32	25	UC (*n* = 23) and CD (*n* = 8)	Several	OR = 2.28 (95% CI 1.33–3.90), I^2 = 64% (*n* = 14)	OR = 0.59 (95% CI 0.40–0.88), I^2 = 52% (*n* = 15)	Moderate	No explanation for including only RCT; no data on individual studies' funding; no reference list searching

TABLE 1 (Continued)

Authors	Country	Inclusion criteria	Studies included (n)	RCT on probiotics (n)	Population	Probiotic	Pooled clinical remission (probiotics vs. control)[a]	Pooled clinical recurrence (probiotics vs. control)[a]	AMSTAR-2 rating	AMSTAR-2 rating commentaries
Chen et al.[9]	China	RCTs on probiotics for IBD	10	10	CD (n = 4) and UC (n = 6)	Several	OR = 1.76 (95% CI 1.01–3.09), I^2 = 0% (n = 4)	OR = 0.79 (95% CI 0.54–1.15), I^2 = 0% (n = 5)	Low	No explanation for including only RCT, heterogeneity is not evaluated nor discussed, no report on the funding for the studies included in the review; no information if the methods were established before/published protocol; did not account for the impact of bias on pooled results
Zhuang et al.[25]	China, Israel	RCTs on probiotics for post-surgical CD	7	4	CD	Several	NA	OR = 1.50 (95% CI 0.64–3.50), I^2 = 0% (n = 3)	Moderate	No explanation for including only RCT; references' list of the included studies was not analyzed; no data on individual studies' funding
Kaur et al.[26]	UK, Qatar	RCTs on probiotics for active UC	14	14	UC (n = 14), 2 on pediatric population	Several	OR = 2.02 (95% CI 1.27–3.22), I^2 = 30% (n = 11)	NA	High	-
Dang et al.[27]	China	RCTs on FMT and *De Simone* formulation on UC	7	3	UC (n = 3)	*De Simone* formulation	OR = 2.42 (95% CI 1.32–4.42), I^2 = 26% (n = 3)	NA	Moderate	No explanation for including only RCT; no data on i studies' funding; no information if the methods were established before/published protocol
Darb Emamie et al.[7] (systematic review)	Iran	RCTs on probiotics, prebiotics or symbiotic in IBD	21	14	UC (n = 13), CD (n = 4)	Several	OR = 2.61 (95% CI 1.39–4.90), I^2 = 26% (n = 4)**	OR = 0.58 (95% CI 0.34–0.98), I^2 = 26% (n = 11)**	Low	No explanation for including only RCT; no data on individual studies' funding; no information if the methods were established before/published protocol; no justification for excluding studies

(Continues)

TABLE 1 (Continued)

Authors	Country	Inclusion criteria	Studies included (n)	RCT on probiotics (n)	Population	Probiotic	Pooled clinical remission (probiotics vs. control)[a]	Pooled clinical recurrence (probiotics vs. control)[a]	AMSTAR-2 rating	AMSTAR-2 rating commentaries
Pabón-Carrasco et al.[28]	Spain	RCTs on probiotics or symbiotics for IBD	19	14	CD (*n* = 3), UC (*n* = 12)	Several	OR = 1.33 (95% CI 0.62–2.84), I^2 = 72% (*n* = 7)	OR = 0.77 (95% CI 0.52–1.14), I^2 = 0% (*n* = 5)	High	No data on individual studies' funding
Iheozor-Ejiofor et al.[10]	UK, Quatar	RCTs on probiotics for inactive UC	12	10	UC	Several	NA	OR = 0.94 (95% CI 0.71–1.24), I^2 = 0% (*n* = 9)	High	–
Dore et al.[29]	Italy	RCTs on probiotics for IBD	9	9	CD (*n* = 2), UC (*n* = 7)	Several	OR = 2.37 (95% CI 1.44–3.90), I^2 = 15% (*n* = 4)	OR = 1.01 (95% CI 0.62–1.66), I^2 = 0% (*n* = 3)	Moderate	No explanation for including only RCT; no data on individual studies' funding
Astó et al.[30]	Spain	RCTs on probiotics, prebiotics or symbiotic in IBD	18	15	UC	Several	OR = 1.79 (95% CI 0.90–3.56), I^2 = 58% (*n* = 8)	OR = 0.80 (95% CI 0.52–1.22), I^2 = 44% (*n* = 7)	Moderate	No information if the methods were established before/published protocol; No explanation for including only RCT; no reference list searching; no data on individual studies' funding.
Derwa et al.[31]	UK	RCTs on probiotics for IBD	22	22	UC (*n* = 14), CD (*n* = 8)	Several	OR = 1.43 (95% CI 0.76–2.71), I^2 = 63% (*n* = 10)	OR = 0.75 (95% CI 0.40–1.40), I^2 = 51% (*n* = 8)	High	No data on individual studies' funding
Ganji-Arjenaki and Rafieian-Kopaei[32]	Iran	RCTs on probiotics, prebiotics or symbiotic in IBD	27	23	CD (*n* = 9) and UC (*n* = 18), 3 on pediatric population	Several	OR = 2.40 (95% CI 1.22–4.68), I^2 = 60% (*n* = 11)	OR = 0.95 (95% CI 0.73–1.24), I^2 = 0% (*n* = 10)	Low	No information on duplicates, no explanation for including only RCT, no reference list searching, not clear if study selection was performed in duplicate, no report on the funding for the studies included in the review; no information if the methods were established before/protocol

TABLE 1 (Continued)

Authors	Country	Inclusion criteria	Studies included (n)	RCT on probiotics (n)	Population	Probiotic	Pooled clinical remission (probiotics vs. control)[a]	Pooled clinical recurrence (probiotics vs. control)[a]	AMSTAR-2 rating	AMSTAR-2 rating commentaries
Losurdo et al.[33]	Italy	RCTs on probiotics for UC	6	5	UC	Escherichia coli Nissle 1917	OR = 0.75 (95% CI 0.18–3.15), I^2 = 75% (n = 3)	OR = 1.16 (95% CI 0.79–1.71), I^2 = 0% (n = 2)	Moderate	No explanation for including only RCT; no data on studies' funding; no reference list searching
Saez-Lara et al.[34]	Spain	RCTs on probiotics, prebiotics or symbiotic in IBD	60	18	UC (n = 13), CD (n = 5)	Several	OR = 1.98 (95% CI 1.16–3.37), I^2 = 0% (n = 5)	OR = 0.60 (95% CI 0.24–1.51), I^2 = 68% (n = 8)	Critically low	No explanation for including only RCT; no data on individual studies' funding; no information if the methods were established before/protocol; no justification for excluding studies; no information if studies' selection and data extraction was done independently by at least two authors
Fujiya et al.[35]	Japan	RCTs on probiotics for IBD	20	20	UC (n = 16), CD (n = 4)	Several	OR = 2.60 (95% CI 1.69–3.99), I^2 = 0% (n = 6)	OR = 0.58 (95% CI 0.31–1.07), I^2 = 72% (n = 13)	Moderate	No information if the methods were established before/published protocol; No explanation for including only RCT; no reference list searching; no data on individual studies' funding.
Mardini and Grigorian[36]	USA	RCTs on probiotics for active UC	5	4	UC	*De Simone* formulation	OR = 2.42 (95% CI 1.55–3.79), I^2 = 0% (n = 4)	NA	Low	No information if the methods were established before/published protocol; no explanation for including only RCT; no reference list searching; no justification for excluding individual studies; no data on individual studies' funding.

(Continues)

TABLE 1 (Continued)

Authors	Country	Inclusion criteria	Studies included (n)	RCT on probiotics (n)	Population	Probiotic	Pooled clinical remission (probiotics vs. control)[a]	Pooled clinical recurrence (probiotics vs. control)[a]	AMSTAR-2 rating	AMSTAR-2 rating commentaries
Shen et al.[37]	China, USA	RCTs on probiotics for IBD	23	23	UC (n = 16), CD (n = 7)	Several	OR = 2.40 (95% CI 1.59–3.62), I^2 = 0% (n = 8)	OR = 0.56 (95% CI 0.31–1.02), I^2 = 70% (n = 14)	Moderate	No data on individual studies' funding; no information if the methods were established before/published protocol;
Jonkers et al.[38]	The Netherlands	RCTs on probiotics for IBD	18	18	UC (n = 11), CD (n = 4)	Several	OR = 1.92 (95% CI 1.14–3.25), I^2 = 39% (n = 7)	OR = 0.78 (95% CI 0.42–1.44), I^2 = 57% (n = 9)	Critically low	No data on studies' funding; no information if the methods were established before/published protocol; only one database for electronic search; no information if studies' selection and data extraction were done independently by at least two authors; no assessment of the likely impact of publication bias
Naidoo et al.[39]	UK	RCTs on probiotics for inactive UC	4	4	UC	Several	NA	OR = 1.05 (95% CI 0.74–1.49), I^2 = 0% (n = 4)	High	–

Note: A Measurement Tool to Assess Systematic Reviews version 2 (AMSTAR-2).

Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel disease; *n*, number; NA, not applicable; OR, odds ratio; RCT, randomized controlled trial; UC, ulcerative colitis; UK, United Kingdom; USA, United States of America.

[a]The OR were calculated using all RCTs included in each systematic review that provided data on clinical remission and/or recurrence.

Mild and severe side effects were discriminated in 27 and 26 trials, respectively (Table S3). From the 32 studies that enrolled patients with UC, 10 graded clinical activity using the Ulcerative Colitis Disease Activity Index (UCDAI),[45,47,49,54,60,62–65,73] eight used the Clinical Activity Index (CAI),[48,52,55,66,69,72,74,83] three used the Mayo score,[40,50,58] two used the Truelove and Witts criteria,[43,44] and two[41,59] used the Simple Clinical Colitis Activity Index (SCCAI); seven did not use a specific scoring system. The endoscopic activity in UC studies was evaluated mostly using the UCDAI[47,62,65,73] or the Mayo[40,49,50,58] endoscopic subscores. The symptoms and the degree of inflammation in pouch studies were ascertained using the Pouchitis Disease Activity Index (PDAI).[77,78,81] Concerning CD, nine trials used the Crohn's Disease Activity Index (CDAI),[42,51,57,67,68,76,79,80,84] three used the Rutgeerts score,[51,68,70] and one used the Harvey-Bradshaw Index (HBI).[44] The outcomes were presented as proportions in 41 studies (Table S3). Forty-four trials had been included in previous meta-analyses a varying number of times (Table S2).

Methodological quality and risk of bias

The results of the methodological appraisal of the systematic reviews (AMSTAR-2 rating) are presented in Table 1. Six studies were classified as "high" quality and eight as "moderate"; four were identified as "critically low". Indeed, some studies presented significant flaws, as

TABLE 2 Characteristics of the randomized controlled trials included in the updated metanalysis.

Authors	Trial design	Disease characteristics	Patients	Follow-up	Probiotic	Comparison	Outcomes
Park et al.[40]	RCT, multicenter	Active UC, mild to moderate (UCDAI); adults	*N* = 118, 58 received probiotics	8 weeks	*Escherichia coli* Nissle 1917 (one capsule/day [2.5 × 10^9 CFU] up to day 4, two capsules/day from day 5)	Probiotics versus placebo (~50% in both groups received 5-ASA)	HRQL (IBDQ), clinical remission (Mayo subscore ≤2), endoscopic remission (endoscopic Mayo score = 0)
Amiriani et al.[41]	RCT, single center	Active UC, mild to moderate (SCCAI); adults	*N* = 60, 30 received probiotics	8 weeks	Lactocare® (4 strains of *Lactobacillus*, 2 strain of *Bifidobacterium*, *Streptococcus thermophiles* - 2.0 × 10^9 CFU)	Probiotics versus placebo	Clinical activity (reduction in SCCAI)
Fan et al.[42]	RCT, single center	Active IBD (31 UC, 9 CD), mild to moderate symptoms; adults	*N* = 40, 21 received probiotics	5 weeks	*Enterococcus faecalis*, *Bifidobacterium longum* and *Lactobacillus acidophilus* (BTV), 2 tablets 3 times a day	Probiotics + 5-ASA versus 5-ASA	Microflora composition, biochemical indices, inflammatory markers, recurrence rate (UCAI and CDAI, no cutoffs defined), adverse events
Sánchez-Morales et al.[43]	RCT, single center	Active UC, mild to moderate (TW criteria); adults	*N* = 34, 17 received probiotics	12 weeks	*Lactobacillus plantarum*, *L. acidophilus*, *L. rhamnosus*, *L. bifidus*, *L. casei* and *Bifidobacterium infantis*, 4.0 × 10^7 UFC per day	Probiotics + 5-ASA versus 5-ASA	Clinical improvement (decrease ≥1 point in TW), clinical remission, histological improvement (decrease ≥1 point in Gupta index)
Bjarnason et al.[44]	RCT, single center	UC in remission (TW criteria) or CD in remission (HBI); adults	*N* = 142 (81 with UC, 61 with CD), 73 received probiotics	4 weeks	*L. rhamnosus*, *L.plantarum*, *L. acidophilus* and *E. faecium* (10 billion bacteria/day)	Probiotics versus placebo	HRQL (IBDQ), clinical activity (TW and HBI), fecal calprotectin, adverse events
Huang et al.[45]	RCT, single center	Active UC, mild to moderate (UCDAI); adults	*N* = 360, 180 received probiotics	8 weeks	*E. faecalis*, *Bifidobacterium longum* and *L. acidophilus* (BTV), 4 tablets 3 times a day	Probiotics + 5-ASA versus 5-ASA	Clinical activity (UCDAI), inflammatory factors (TNF-*α*, IL-8 and IL-10), adverse events
Su et al.[46]	RCT, single center	Active CD; adults	*N* = 83, 43 received probiotics	Not reported	*E. faecalis*, *Bifidobacterium longum* and *L. acidophilus* (BTV), 4 tablets 2 times a day	Probiotics + 5-ASA + steroids versus 5-ASA	Remission rate (symptoms resolution and endoscopic healing), gut microbiota changes
Matsuoka et al.[47]	RCT, multicenter	UC in remission; adults	*N* = 195, 98 received probiotics	48 weeks	*Bifidobacterium breve* + *L. acidophilus* (a pack per day, 1 billion bacteria)	Probiotics versus placebo	Relapse (rectal bleeding score ≥2 on UCDAI, and/or initiation of remission induction therapy), maintenance of remission (rectal bleeding score of 0 and an endoscopic score of 0 or 1), adverse events
Vejdani et al.[48]	RCT, multicenter	Active UC, mild to moderate (TW criteria and UCDAI); adults	*N* = 34, 17 received probiotics	8 weeks	*L. casei* strain ATCC PTA-3945, 5 × 10^5 live active cells, 1 capsule twice daily	Probiotics versus placebo	Clinical remission (CAI <4), withdrawals, adverse events

(Continues)

TABLE 2 (Continued)

Authors	Trial design	Disease characteristics	Patients	Follow-up	Probiotic	Comparison	Outcomes
Tamaki et al.[49]	RCT, multicenter	Active UC, mild to moderate (UCDAI); adults	*N* = 56, 28 received probiotics	8 weeks	*Bifidobacterium longum* (2–3 × 10^{11} freeze-dried viable bacteria)	Probiotics versus placebo	Clinical remission (UCDAI scores of 0–2), endoscopic remission (Mayo subscore = 0 or 1), adverse events
Palumbo et al.[50]	RCT, single center	Active UC, moderate-to-severe (UCDAI); adults	*N* = 60, 30 received probiotics	24 weeks	*Lactobacillus salivarius*, *L. acidophilus* and *Bifidobacterium bifidus* (BGN4 - 2 capsules per day)	Probiotics + 5-ASA versus 5-ASA	Clinical activity (modified Mayo score), endoscopic activity (Mayo score)
Fedorak et al.[51]	RCT, multicenter	CD after ileo-cecal resection; adults	*N* = 119, 58 received probiotics	12 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*" - 900 billion viable bacteria)	Probiotics versus placebo	Endoscopic recurrence (Rutgeerts score (i3 and i4), clinical activity (CDAI), IBQD, cytokine analysis
Yoshimatsu et al.[52]	RCT, single center	UC in remission; adolescents and adults	*N* = 46, 23 received probiotics (50% under 5-ASA also)	12 weeks	*Streptococcus faecalis* + *Clostridium butyricum* + *Bacillus mesentericus*, 9 tablets a day (18 mg + 90 mg+90 mg)	Probiotics versus placebo	Clinical remission, relapse (need for additional medication), adverse events
Yasushi et al.[53]	RCT, single center	UC in remission; adults	*N* = 60, 30 received probiotics	52 weeks	Bio-three - 2 mg *Streptococcus faecalis*, 10 mg *Clostridium butyricum*, 10 mg *Bacillus mesentericus* (3 tablets 3 × daily)	Probiotics + 5-ASA versus 5-ASA	Clinical remission (not defined), relapse (CAI>5), adverse events
Liu et al.[54]	RCT, single center	Active UC, mild to moderate (UCDAI); adults	*N* = 84, 42 received probiotics	8 weeks	3 strains of *Bifidobacterium*	Probiotics + 5-ASA versus 5-ASA	Clinical remission (UCDAI), adverse events
Petersen et al.[55]	RCT, single center	Active UC, mild to moderate (CAI score of at least 6); adults	*N* = 50 (50% under 5-ASA), 25 received probiotics	8 weeks	*E. coli* Nissle 1917 (100 mg in the first 4 days, 200 mg afterward)	Probiotics versus placebo	Clinical remission (CAI<4)
Copaci et al.[56] (abstract)	RCT, single center	UC in remission; adults	*N* = 36, 10 received probiotics	24 weeks	*Bifidobacterium longum* W11	Probiotics + 5-ASA versus 5-ASA	Clinical remission and relapse (no definition)
Bourreille et al.[57]	RCT, single center	CD in remission (CDAI <150); adults	*N* = 159, 80 received probiotics	52 weeks	*Saccharomyces boulardii* (1 g/day)	Probiotics versus placebo	Recurrence rate (CDAI >220, CDAI between 150 and 220 with an increase of at least 70 points over the baseline, or by the need for CD-related surgery or medical therapy)
Li et al.[58]	RCT, single center	Active UC, mild, moderate or severe (Mayo score); adults	*N* = 82, 41 received probiotics	8 weeks	*E. faecalis*, *Bifidobacterium longum* and *L. acidophilus* (BTV), 2 capsules 3 times daily	Probiotics + 5-ASA versus 5-ASA	Clinical activity (Mayo score), endoscopic activity (Mayo score)
Wildt et al.[59]	RCT, single center	UC in remission; adults	*N* = 32, 20 received probiotics	52 weeks	*L.acidophilus*, *Bifidobacterium animalis* (Probio-Tec AB-25), 6 capsules per day (1.5 × 10^{11} CFU)	Probiotics versus placebo	Maintenance of remission (SCCAI ≤4, endoscopic Baron grade 0–1, and/or histological grade 0–1 [TW]), adverse events

TABLE 2 (Continued)

Authors	Trial design	Disease characteristics	Patients	Follow-up	Probiotic	Comparison	Outcomes
Oliva et al.[60]	RCT, single center	Active UC, mild to moderate (UCDAI); pediatric patients	*N* = 40, 20 received probiotics	8 weeks	*Lactobacillus reuteri* ATCC 55730 (10^{10} CFU, rectal infusion)	Probiotics versus placebo	Remission (UCDAI score <2 points), rectal histology and cytokine mucosal expression, adverse events
D'Incà et al.[61]	RCT, single center	Active UC, mild (2–3 stools daily, blood in less than 50%, hyperemia with indistinct vascular pattern, chronic inflammatory infiltrate in lamina propria); adults	*N* = 26, 19 received probiotics	8 weeks	*L. casei* DG, enema or oral (1.6×10^9 CFU)	Probiotics + 5-ASA versus 5-ASA	Clinical activity, histological activity, microbiome composition, TLR expression
Tursi et al.[62]	RCT, multicenter	Active UC, mild to moderate (UCDAI score 3–8); adults	*N* = 131, 71 received probiotics	8 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*" - 2 sachets twice a day, 3.6×10^{12} bacteria per day)	Probiotics + 5-ASA versus 5-ASA	Clinical improvement (decrease in UCDAI of 50% of more), clinical remission (UCDAI score<2), improvement in endoscopic scores, serious adverse events
Matthes et al.[63]	RCT, multicenter	Active UC, mild to moderate (UCDAI 4–9); adults	*N* = 112, 70 received probiotics	8 weeks	*E. coli* Nissle 1917 (10^8/mL, enemas of 40 mL, 20 mL or 10 mL)	Probiotics versus placebo	Clinical remission (UCDAI≤2), endoscopic healing (UCDAI = 0), no significant inflammation on histology
Ng et al.[64]	RCT, single center	Active UC, mild to moderate (UCDAI score 3–8); adults	*N* = 28, 14 received probiotics	8 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*" - 900 billion viable bacteria), twice daily	Probiotics versus placebo	Clinical remission (UCDAI≤2), histological inflammation
Sood et al.[65]	RCT, multicenter	Active UC, mild to moderate (UCDAI 3–9); adults	*N* = 147, 77 received probiotics	12 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*", 2 sachets twice a day, 3.6×10^{12} bacteria)	Probiotics versus placebo	Clinical remission (UCDAI≤2), endoscopic remission (UCDAI = 0) adverse events
Miele et al.[66]	RCT, single center	Active UC, newly diagnosed; pediatric patients	*N* = 29, 14 received probiotics	52 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*", 2 sachets twice a day, 3.6×10^{12} bacteria)	Probiotics + steroid induction treatment + 5-ASA versus placebo + steroid induction treatment + 5-ASA	Clinical remission (sustained drop in CAI to <2 after steroid therapy), relapse (occurrence or worsening of symptoms + CAI>3), adverse events
Garcia Vilela et al.[67]	RCT, single center	CD in remission (CDAI <150); adults	*N* = 34, 15 received probiotics	12 weeks	*Saccharomyces boulardii* (250 mg, 3 times a day)	Probiotics versus placebo	Clinical remission (CDAI <150)

(Continues)

TABLE 2 (Continued)

Authors	Trial design	Disease characteristics	Patients	Follow-up	Probiotic	Comparison	Outcomes
Van Gossum et al.[68]	RCT, multicenter	CD after ileo-cecal resection; adults	*N* = 70, 34 received probiotics	12 weeks	*Lactobacillus johnsonii* (a packet - 10^{10} CUF/day)	Probiotics versus placebo	Endoscopic recurrence (Rutgeerts score i3-i4), clinical relapse (CDAI >150, increase of CDAI >70 points from baseline)
Zocco et al.[69]	RCT, single center	UC in remission (CAI <4, endoscopic and histological remission [Baron and Truelove-Richard's scores])	*N* = 187, 127 received probiotics (62 in co-therapy with 5-ASA)	52 weeks	*L. johnsonii* (1.8 × 10^{10} viable bacteria/day)	Probiotics versus probiotics + 5-ASA versus 5-ASA	Clinical recurrence (CAI), variations of clinical, endoscopic, and histological scores
Marteau et al.[70]	RCT, multicenter	CD after ileo-cecal resection; adults	*N* = 98, 48 received probiotics	24 weeks	*L. johnsonii* (two packets per day - 20^{10} CFU/day)	Probiotics versus placebo	Clinical remission, endoscopic recurrence (Rutgeerts score i3 and i4)
Bousvaros et al.[71]	RCT, single center	CD in remission (PCDAI score ≤10); children	*N* = 75, 39 received probiotics	104 weeks	*L. rhamnosus*, 1 capsule per day (containing at least 10^{10} bacteria)	Probiotics versus placebo	Relapse (PCDAI >30 points on a single visit; PCDAI >15 points on two consecutive visit; need for corticosteroid, other rescue therapy, surgery, or hospitalization)
Kato et al.[72]	RCT, multicenter	Active UC, mild to moderate (TW criteria)	*N* = 20, 10 received probiotics	12 weeks	*Bifidobacterium breve* + *Bifidobacterium bifidum* + *L. acidophilus* (BFM, 100 mL - 10 billion per day)	Probiotics + 5-ASA versus 5-ASA	Clinical remission (no rectal bleeding, no mucosal erythema, granularity, or friability), decrease CAI ≥3 points, endoscopic and histologic scores, adverse events
Tursi et al.[73]	RCT, multicenter	Active UC, mild to moderate (UCDAI score 3–8)	*N* = 90, 30 received probiotics	8 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*", 2 sachets twice a day, 3.6 × 10^{12} bacteria)	Probiotics + 5-ASA versus 5-ASA	Clinical remission (normal bowel movements and absence of rectal bleeding), improvement in clinical and endoscopic scores (UCDAI)
Kruis et al.[74]	RCT, multicenter	UC in remission (CAI ≤4, endoscopic index ≤4, no acute inflammation on histology)	*N* = 327, 162 received probiotics	52 weeks	*E. coli* Nissle 1917 (2.5–25 × 10^9 per capsule, one tablet per day in the first 4 days, two per day from the fifth day onwards)	Probiotics versus 5-ASA	Recurrence (CAI >6, increase in CAI ≥3 points, endoscopic index >4 or acute inflammation on histology), quality of life, adverse events
Cui et al.[75]	RCT, single center	UC in remission (clinical and endoscopic)	*N* = 30, 15 received probiotics	8 weeks	*E. faecalis*, *Bifidobacterium longum* and *L. acidophilus* (BTV), 2 tablets 3 times a day (1260 mg)	Probiotics versus placebo	Recurrence rate (no definition given), gut microbiota changes

TABLE 2 (Continued)

Authors	Trial design	Disease characteristics	Patients	Follow-up	Probiotic	Comparison	Outcomes
Schultz et al.[76]	RCT, single center	Active CD, moderate activity (CDAI 150–300)	*N* = 11, 5 received probiotics	24 weeks	*L. rhamnosus* (2×10^9 CFU), after 2 weeks of oral antibiotic treatment	Probiotics versus placebo	Remission rate, relapse (increase in CDAI of >100 points)
Mimura et al.[77]	RCT, single center	UC patients submitted to ileal pouch-anal anastomosis, with refractory or recurrent ATB-responsive pouchitis; adults	*N* = 36, 20 received probiotics	52 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*" - 2 sachets twice a day, 3.6×10^{12} bacteria per day)	Probiotics versus placebo	Remission (clinical PDAI score ⩽2 + endoscopic PDAI score ⩽1); relapse (increased clinical PDAI score ⩾2 and increased endoscopic PDAI score ⩾3), histologic activity, HRQL (IBDQ)
Gionchetti et al.[78]	RCT, single center	UC patients submitted to ileal pouch-anal anastomosis, immediately after ileostomy closure; adults	*N* = 40, 20 received probiotics	52 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*" - 1 sachet, 1.8×10^{12} bacteria per day)	Probiotics versus placebo	Clinical, endoscopic, and histologic activity (PDAI score ⩾7 defined as active pouchitis; PDAI score <7 as remission), HRQL (IBDQ)
Prantera et al.[79]	RCT, single center	CD after ileo-cecal resection; adults	*N* = 45, 23 received probiotics	52 weeks	*L. rhamnosus* (6 billion CFU)	Probiotics versus placebo	Clinical remission (CDAI <150), endoscopic recurrence (Rutgeerts score 2–4)
Guslandi et al.[80]	RCT, single center	CD in remission (CDAI <150)	*N* = 32, 16 received probiotics	24 weeks	*Saccharomyces boulardii* (1 g/day)	Probiotics + 5-ASA versus 5-ASA	Recurrence rate (CDAI >150)
Gionchetti et al.[81]	RCT, single center	UC patients submitted to ileal pouch-anal anastomosis, with ATB-responsive relapsing pouchitis; adults	*N* = 40, 20 received probiotics	36 weeks	4 strains of *Lactobacilli* + 3 strains of *Bifidobacteria* + *Streptococcus thermophilus* ("*De Simone formulation*" - 1 sachet, 1.8×10^{12} bacteria per day)	Probiotics versus placebo	Clinical, endoscopic, and histologic activity (PDAI score ⩾7 defined as active pouchitis; PDAI score <7 as remission), HRQL (IBDQ)
Rembacken et al.[82]	RCT, single center	Active UC (>4 liquid stools for 7 days, erythema on sigmoidoscopy and histologic activity)	*N* = 116, 57 received probiotics	12 weeks	*E. coli* Nissle 1917 (2 capsules a day, 2.5×10^{10})	Probiotics versus 5-ASA (+ steroids and gentamicin in both groups)	Remission rate, recurrence rate (clinical and endoscopic activity)
Kruis et al.[83]	RCT, multicenter	UC in remission (CAI ≤4)	*N* = 103, 50 received probiotics	12 weeks	*E. coli* Nissle 1917 (2 capsules a day, 2.5×10^{10})	Probiotics versus 5-ASA	Relapse (CAI >4), relapse-free time, adverse events
Malchow et al.[84]	RCT, single center	Colonic CD in remission	*N* = 28, 16 received probiotics	52 weeks	*E. coli* Nissle 1917 (one capsule/day - 2.5×10^9 CFU)	Probiotics versus placebo	Clinical remission (CDAI <150), clinical relapse

Abbreviations: 5-ASA, Aminosalicylic acids; CAI, clinical activity index; CD, Crohn's disease; CDAI, clinical disease activity index; CFU, colony-forming unit; *E, Enterococcus; E. coli, Escherichia coli*; HBI, Harvey-Bradshaw index; HRQL, health-related quality of life; IBD, inflammatory bowel disease; IBDQ, inflammatory bowel disease questionnaire; L, *Lactobacillus*; PCDAI, pediatric Crohn's Disease activity index; PDAI, Pouchitis disease activity index; RCT, randomized controlled trial; SCCAI, simple clinical colitis activity index; TLR, toll-Like receptor; TW, Truelove and Witts severity Index; TNF, tumor necrosis factor; UC, ulcerative colitis; vs, versus.

only one electronic database had been searched,[22,23,38] no information on whether studies' selection and data extraction had been performed independently by two authors,[23,34,38] and there was no assessment of the likely impact of publication bias.[9,22,38] Concerning RCT risk of bias (Figure S1) in 14 trials, it was not described how random sequences were generated. Regarding allocation concealment, 16 trials were classified as low risk. The risk associated with the blinding and/or outcome assessment was judged to be high in 10 studies. Five articles were judged to be high-risk due to incomplete outcome assessment, mostly because of the high attrition rates.[74] Lastly, four articles were classified as high-risk in terms of selective reporting, as, for example, it did not provide the remission and relapse rates.[48]

Clinical remission and recurrence

Twenty RCTs provided data on the induction of clinical remission (Table S3). The effect of probiotics was positive in patients with UC (OR 2.00, 95% CI 1.28–3.11, I^2 = 57%) but not in those with CD (OR 1.61, 95% CI 0.21–12.50, I^2 = 65% - Figure 2). A subgroup analysis was performed to explore the effect of different comparisons (probiotics + 5-ASA vs. 5-ASA alone; or probiotics vs. placebo) on the odds of achieving clinical remission in UC (Figure S2). This analysis suggested the superiority of combining probiotics with 5-ASA to induce clinical remission in UC (OR 2.35, 95% CI 1.29–4.28, I^2 = 56%). However, the number of studies was small (*n* = 8), the heterogeneity was significant and not eliminated by excluding individual studies. Concerning the type of probiotic, the subgroup analysis of the UC trials revealed that the odds of attaining clinical remission were significant for the *De Simone* formulation (Figure S3).

The prevention of clinical recurrence in inactive disease was reported in 23 trials. The effect of probiotics as maintenance therapy was not significant for CD with or without prior ileocecal resection (OR 1.49, 95% CI 0.64–3.50, I^2 = 0%; and OR 0.71, 95% CI 0.28–1.75, I^2 = 44%, respectively). On the other hand, probiotics significantly decreased the odds of relapsing pouchitis (OR 0.03, 95% CI 0.00–0.25, I^2 = 64%) (Figure 2), while there was a trend towards the reduction of clinical recurrence in inactive UC (OR 0.65 [95% CI 0.42–1.01, I^2 = 52%). In the analysis per type of comparison in UC trials, the effect of probiotics was significant when compared to placebo (OR 0.29, 95% CI 0.09–0.96, I^2 = 66%), but not to 5-ASA (Figure S4). Additionally, the available data do not favor probiotics as an add-on to 5-ASA for maintenance of clinical remission (OR 0.44, 95% CI 0.12–1.57, I^2 = 52%; Figure S4). In the analysis per probiotic type, the odds for recurrence of clinical activity in UC were only significant for the trials that administered a mixture of *Enterococcus*, *Bifidobacterium*, and *Lactobacillus* (OR 0.05, 95% CI 0.01–0.27) or the *De Simone* formulation (OR 0.04, 95% CI 0.01–0.20 - Figure S5). The funnel plots and the Egger's test (Figure S6) suggested a low risk of publication bias except for clinical recurrence. Indeed, most studies evaluating the later outcome had a small sample size, with inherently broader confidence intervals. Notwithstanding, no outliers were detected in the sensitivity analysis. The certainty in evidence (GRADE) was considered low for the induction of clinical remission in UC but very low for the remaining clinical outcomes.

From the prior systematic reviews, 19 included studies for estimating pooled clinical remission or recurrence rates (Table 1). Although the effect size varied across reviews, in most cases (*n* = 14[7,9,22–24,26,27,29,32,34–38]) the pooled analysis favored probiotics over control in achieving clinical remission, with only five[23,28,30,31,33] reviews showing no significant differences. Conversely, the pattern for maintenance was different, as most previous meta-analyses (*n* = 13[9,10,23,28–35,38,39]) failed to demonstrate a significant effect in the prevention of clinical recurrence.

Endoscopic remission and recurrence

Four studies provided data on the induction of endoscopic remission (one[46] in CD and three[40,49,65] in UC). The pooled analysis for UC suggested that probiotics may have a role in inducing endoscopic remission (OR 2.38, 95% CI 1.41–4.01, I^2 = 0%) (Figure 3). On the other hand, the odds of preventing endoscopic recurrence after ileocecal resection in CD was not significant in the pooled analysis of four trials (OR 0.83, 95% CI 0.45–1.54, I^2 = 13%, Figure 3). The risk of publication bias for these outcomes was deemed low (Figure S6) and the confidence in the evidence was considered low for induction of endoscopic remission in UC, and very low for the other endpoints. Notably, no studies have evaluated the effect of probiotics in maintaining endoscopic remission in UC.

Side effects

Information on side effects was conveyed in 27 trials (Table S3), with low susceptibility to publication bias (Figure S6). In the pooled analysis, the odds for side effects were not higher in patients receiving probiotics versus those in the control group: OR 0.79 (95% CI 0.49–1.29) for mild and OR 0.48 (95% CI 0.13–1.81) for severe adverse events (Figure 4); the confidence in evidence was moderate.

DISCUSSION

Microbiota-based treatments[88] are promising strategies to complement the IBD drug armamentarium. However, the effectiveness of these interventions, particularly probiotics, in inducing and sustaining remission in patients with IBD remains a subject of debate.[89] European guidelines suggest that using enemas containing *Lactobacillus reuteri* and the eight-strain oral preparation may be a viable option for patients with active mild-to-moderate UC,[90] particularly in patients who do not tolerate 5-ASA.[85] On the other hand, the use of probiotics to induce or maintain remission in CD is discouraged, while no formal recommendations are made for pouch-related disorders.[90]

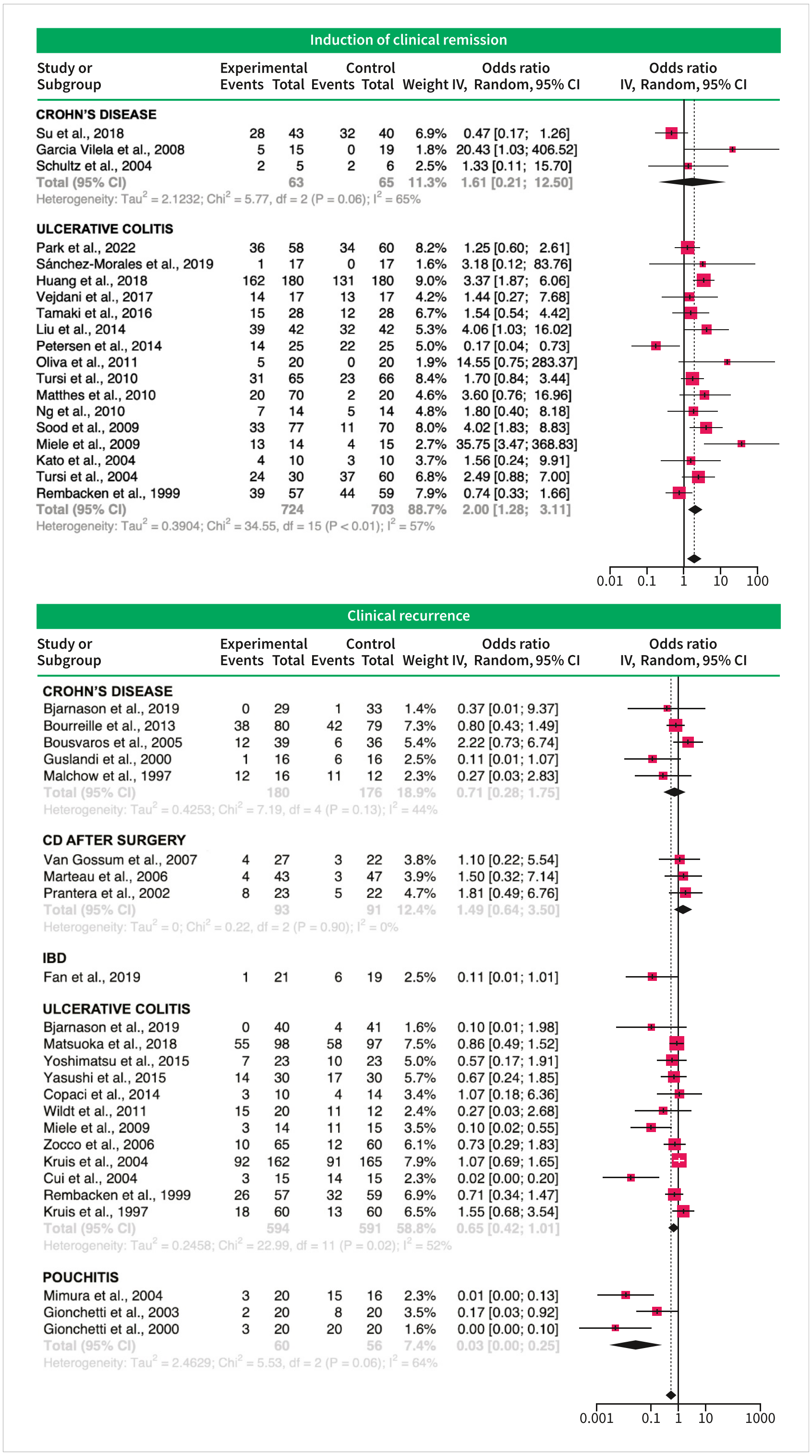

FIGURE 2 Effect of probiotics on the induction of clinical remission and clinical recurrence, presented as odds ratio - results from the updated metanalysis. As shown in the lower chart, subgroup analyses were performed for the different disease settings.

However, these statements are mostly based on small-sized trials and meta-analyses, highlighting the need for higher-quality evidence.

In this context, we aimed to provide a more complete insight into the effect and safety of probiotics for CD (including after ileocecal resection), UC, and pouchitis. For such, an overview of 22 systematic reviews and an updated meta-analysis of 45 RCTs were performed. A positive effect in the induction of clinical remission was found for UC (OR 2.00, 95% CI 1.28–3.11) but not for CD. In terms of preventing recurrence, probiotics demonstrated a protective effect against relapsing pouchitis (OR 0.03, 95% CI 0.00–0.25) and exhibited a

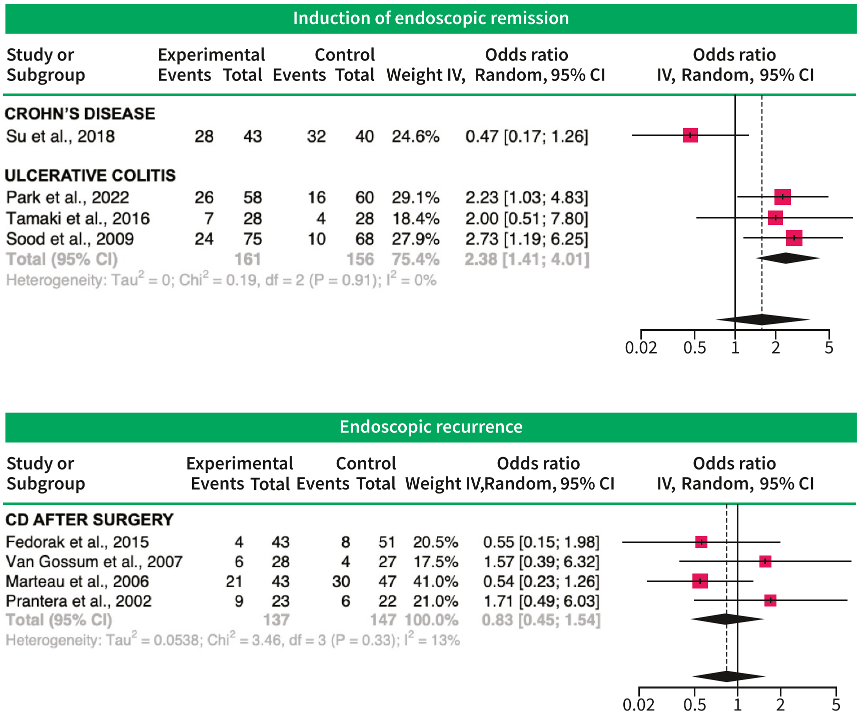

FIGURE 3 Odds ratio for the induction of endoscopic remission and endoscopic recurrence in patients with ulcerative colitis and Crohn's disease - results from the updated metanalysis.

tendency to maintain remission in UC (OR 0.65, 95% CI 0.42–1.01). However, they were found to be ineffective for CD with or without prior ileocecal resection. It should be noted, however, that in the subgroup analysis considering the type of probiotic, only studies using multi-strain formulations outperformed the comparator in achieving remission and preventing recurrence in UC patients. The results of the subgroup analysis of UC trials suggested that combining 5-ASA (the mainstay of therapy in mild to moderate UC) and probiotics may be beneficial for inducing remission, while no effect of the add-on approach was seen for the prevention of clinical recurrence. Our data corroborated the favorable safety profile of probiotics, as the likelihood of experiencing mild and severe adverse events was comparable to that of the placebo group. Based on the GRADE framework, the certainty in evidence was considered moderate for side effects. On the other hand, it was classified as low for the induction of clinical remission and endoscopic remission in UC, as there were trial limitations (risk of bias) and inconsistency between the studies (high heterogeneity). For the remaining outcomes, the certainty was classified as very low, particularly for the prevention of clinical recurrence as publication bias could not be discarded.

The discrepancy in the effect of probiotics for UC and CD may be attributable to disease location (being the colon the greatest reservoir of gut microbiota, it is expected that its modulation influences more colonic inflammation[91]), the depth and phenotype of the disease (widely variable in CD, making it difficult to find a one-size-fits-all probiotic approach), and different immunological assets. Indeed, while UC patients possess increased activation markers on circulating CD4+ or CD8+T cells, individuals with CD display a marked reduction of CD27+ memory B cells, and a significant increase of naïve CD23+ B cells.[92] Gut microbiome modulation therapies, as probiotics, have been hypothesized to restore bacterial species that induce regulatory T cells,[93] essential for immunological homeostasis, and decrease the activation of CD4+ T-helper 1 and 17 cells.[94] Also, pattern recognition-mediated innate immune pathways (through Toll-like receptors [TLR] 2 and 4) appear to be significantly elevated in UC but not in CD.[93]

The superiority of multi-strain probiotics has been suggested before. Studies conducted in mouse models have demonstrated that such formulations suppress NF-κB and TNF-α expression via the TLR4-NF-κB signaling pathway while increasing the expression of regulatory cytokines.[95]

As far as we know, this is the largest meta-analysis evaluating the impact of probiotics on IBD and intends to shed some light on this topic, easing the use of probiotics in everyday clinical practice. The thorough search strategy and the large number of studies included are key advantages of this review. However, this study also has some limitations. First, the type, dose, and duration of probiotic therapy and follow-up duration varied among studies, introducing variability that is not manageable with statistical tools. Second, the impact of individual disease characteristics, such as disease extension and duration, was not addressed. Third, we were unable to assess the effect of probiotics in specific populations, such as pediatric or elderly patients. Forth, none of the trials had data on probiotic engraftment.

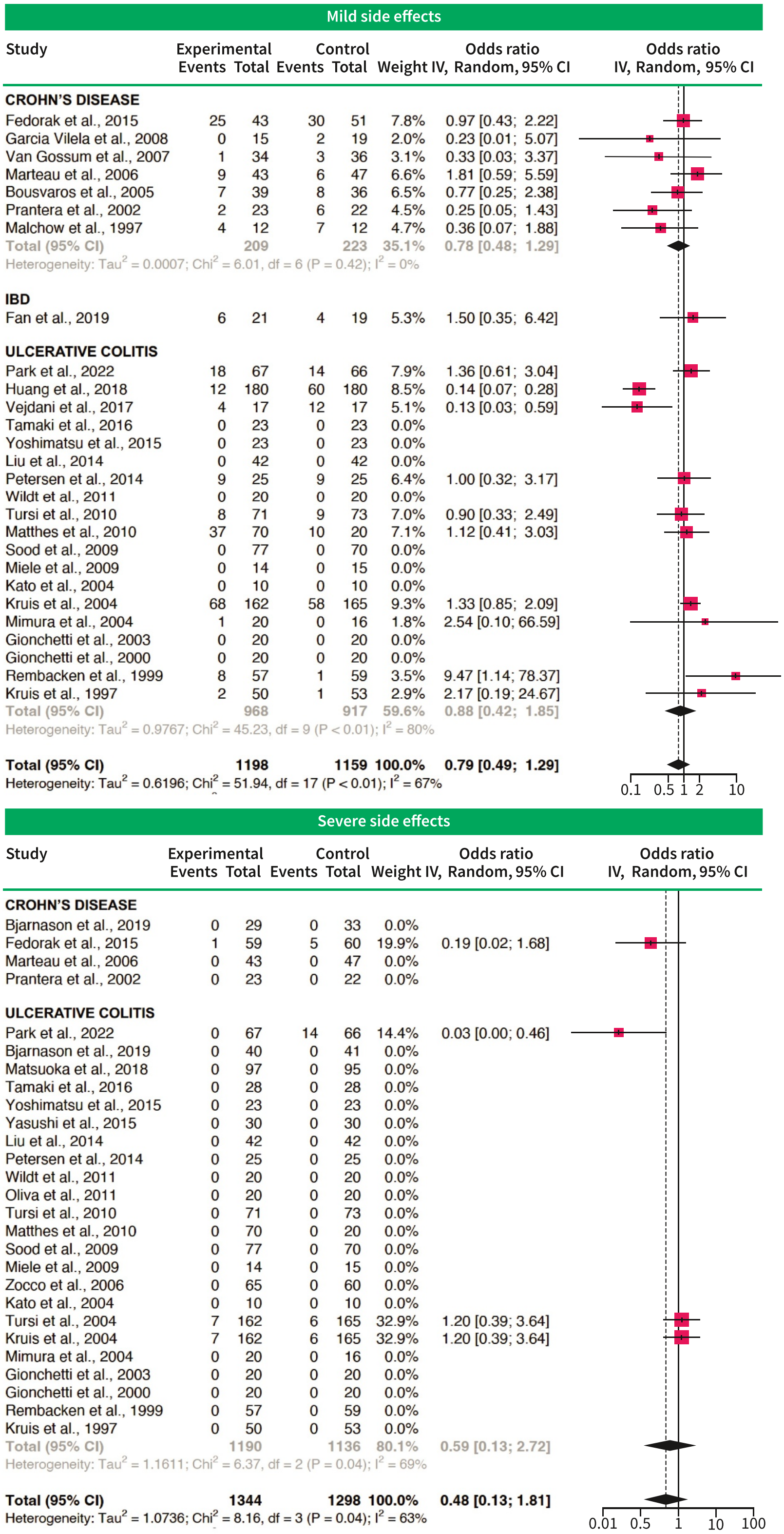

FIGURE 4 Mild and severe side effects (odds ratio) associated with probiotic intake in patients with ulcerative colitis and Crohn's disease.

Lastly, our comprehensive analysis raised questions for future research: (i) is there a benefit of combining probiotics with advanced therapy in UC, particularly during flares? (ii) can probiotics be routinely used by patients after ileoanal resection to decrease the risk of pouchitis? (iii) are probiotics effective for colonic CD? (iv) can patient microbiome characteristics be used to select the type of probiotic? A solid conceptual foundation supports the use of probiotics in UC; nonetheless, there is a scarcity of studies elucidating factors such as dosage, treatment duration, strains (or combinations), and the optimal timing of intervention throughout the disease course. Besides this, while the use of probiotics alone yields unsatisfactory results in CD patients, it is conceivable that emerging technologies focused on genetically enhanced bacteria may present a viable option.

AUTHOR CONTRIBUTIONS

Maria Manuela Estevinho, **Yuhong Yuan**, **Mário Sousa-Pimenta**, and **Cláudia Camila Dias** were involved in study selection, data collection, analysis, and interpretation. **Maria Manuela Estevinho** coordinated the drafting of the manuscript. **Iago Rodríguez-Lago**, **Manuel Barreiro-de Acosta**, and **Vipul Jairath** contributed to data analysis, manuscript drafting, and critical revision. **Fernando Magro** coordinated the study design, data analysis, and revision. All authors were involved in drafting the manuscript and approved its final version.

ACKNOWLEDGMENTS

This study did not receive funding.

CONFLICT OF INTEREST STATEMENT

IRL has received financial support for traveling and educational activities or has served as an advisory board member for MSD, Pfizer, Abbvie, Takeda, Janssen, Tillotts Pharma, Kern, Celltrion, Roche, Ferring, Dr. Falk Pharma, Galapagos, Otsuka Pharmaceutical and Adacyte. MBA has received financial support for traveling and educational activities or has served as an advisory board member for Pfizer, MSD, Takeda, AbbVie, Kern, Janssen, Fresenius Kabi, Biogen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Gebro Pharma, Otsuka Pharmaceuticals, and Tillotts Pharma. FM served as a speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratórios Vitória, Pfizer, Ferring, Hospira, and Biogen. VJ has received consulting/advisory board fees from AbbVie, Alimentiv Inc. [formerly Robarts Clinical Trials], Arena pharmaceuticals, Asieris, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genetech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Reistone Biopharma, Roche, Sandoz, Takeda and Topivert; and speaker's fees from, Abbvie, Ferring, Janssen Pfizer Shire and Takeda. Alimentiv, Inc. is an academic gastrointestinal contract research organization (CRO), operating under the Alimentiv Health Trust. Alimentiv, Inc. provides centralized imaging management solutions in clinical trials, including endoscopy, histopathology and magnetic resonance imaging; VJ is a consultant and has neither equity positions nor shares in the corporation. The remaining authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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How to cite this article: Estevinho MM, Yuan Y, Rodríguez-Lago I, Sousa-Pimenta M, Dias CC, Barreiro-de Acosta M, et al. Efficacy and safety of probiotics in IBD: an overview of systematic reviews and updated meta-analysis of randomized controlled trials. United European Gastroenterol J. 2024;12(7):960–81. https://doi.org/10.1002/ueg2.12636