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Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease

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Summary

Background: Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBD). Evidence implicates disturbances of the gastrointestinal microbiota in their pathogenesis.

Aim: To perform a systematic review and meta-analysis to examine the efficacy of probiotics in IBD.

Methods: MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched (until November 2016). Eligible randomised controlled trials (RCTs) recruited adults with UC or CD, and compared probiotics with 5-aminosalicylates (5-ASAs) or placebo. Dichotomous symptom data were pooled to obtain a relative risk (RR) of failure to achieve remission in active IBD, or RR of relapse of disease activity in quiescent IBD, with 95% confidence intervals (CIs).

Results: The search identified 12 253 citations. Twenty-two RCTs were eligible. There was no benefit of probiotics over placebo in inducing remission in active UC (RR of failure to achieve remission=0.86; 95% CI=0.68-1.08). However, when only trials of VSL#3 were considered there appeared to be a benefit (RR=0.74; 95% CI=0.63-0.87). Probiotics appeared equivalent to 5-ASAs in preventing UC relapse (RR=1.02; 95% CI=0.85-1.23). There was no benefit of probiotics in inducing remission of active CD, in preventing relapse of quiescent CD, or in preventing relapse of CD after surgically induced remission.

Conclusions: VSL#3 may be effective in inducing remission in active UC. Probiotics may be as effective as 5-ASAs in preventing relapse of quiescent UC. The efficacy of probiotics in CD remains uncertain, and more evidence from RCTs is required before their utility is known.

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As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as the inflammatory bowel diseases (IBD), are chronic inflammatory disorders of the gastrointestinal (GI) tract, with a combined prevalence of 450 per 100 000 in Western populations.[1] Their precise aetiology is unknown, but is thought to relate to a complex interplay of genetic and environmental factors, including enteric immune dysregulation and alterations in the intestinal microbiome.[2,3] The relationship between host genetic factors and the microbiome may be particularly important.

Individuals with IBD-related genes are more likely to display associated microbiome alterations, despite not displaying phenotypic IBD characteristics.[4] Moreover, antibiotic use is associated with greater odds of an incident diagnosis of Crohn's disease (CD), perhaps as a consequence of reduced intestinal microbial diversity, leading to disordered enteric immune function.[5] Typical microbiome changes in IBD include an increase in the relative abundance of pro-inflammatory species, a reduction in anti-inflammatory bacterial species such as *Faecalibacterium prausnitzii*, and a reduction in overall alpha bacterial diversity, when compared with healthy controls without IBD.[6] Furthermore, differences in the microbiome have been observed between those with active and quiescent disease.[7] Reduced abundance of *F. prausnitzii* has been observed in the mucosa-associated microbiome of some patients with CD following surgical resection for active disease, with these changes associated with higher rates of endoscopic recurrence at 6 months.[8] These findings highlight that manipulation of the microbiome may be an attractive target for therapeutic interventions in IBD.[9]

The natural history of IBD is that of quiescent disease interspersed with flare-ups of disease activity. Current management strategies focus on reducing the inflammatory burden in patients with active disease, and attempting to maintain remission in those with inactive disease. To date these are centred upon drug therapy, including 5-aminosalicylates, glucocorticosteroids, immunomodulator therapy, and biological agents.[10,11] However, some of these treatments are costly, or are associated with serious adverse events.[12-14] As a consequence, alternative therapies, aimed at treating disease activity via manipulation of the enteric flora may be of interest.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Some probiotics have been shown to have anti-inflammatory effects and promote maintenance of the gut intestinal barrier in vitro, and in murine models of IBD.[15] This may give credence to their use as a treatment option in IBD. Results in clinical trials have been mixed, with some studies showing an improvement in maintenance of remission or induction of remission with probiotics[16-19] while other trials have failed to show any benefit.[20-25] This could be due to the species or strain of probiotic used, or methodological differences between studies.

Previous meta-analyses have examined the benefit of probiotics in specific subgroups of patients with IBD,[26-36] but none have synthesised all current available evidence for their role in IBD, and some have important limitations which have been reported previously.[37] Most notably, several prior meta-analyses have combined data from trials of probiotics and synbiotics,[28,29,33,36] or pooled data from studies in paediatric and adult populations.[28-30,33,35] Furthermore, only two meta-analyses have assessed the effect of probiotics on relapse of disease activity in post-operative CD,[36,38] but neither provided data on the efficacy of preventing endoscopic recurrence at differing severities of Rutgeerts' endoscopic score, nor did they extract data using intention-to-treat analysis.

We therefore conducted an up to date systematic review and meta-analysis to assess the overall efficacy of probiotics in adult patients with IBD and, where possible, the effect of individual probiotic preparations in inducing remission in active UC and CD, maintaining remission in quiescent UC and CD, and preventing relapse in post-operative CD.

2 | METHODS

2.1 | Search strategy and study selection

We conducted a search of the medical literature using MEDLINE (1946 to November 2016), EMBASE and EMBASE Classic (1947 to November 2016), and the Cochrane central register of controlled trials. We also searched conference proceedings from United European Gastroenterology Week and Digestive Diseases Week up to November 2016. Randomised controlled trials (RCTs) examining the efficacy of probiotics in adult patients (>90% of participants >16 years) with active or quiescent IBD were eligible for inclusion. The first period of cross-over RCTs were also eligible for inclusion. The control arms were required to receive 5-aminosalicylates (5-ASAs) or placebo. The diagnosis of IBD had to be confirmed via endoscopy, histology or radiology. Studies had to report either an assessment of failure of remission in active IBD, or relapse of disease activity in quiescent IBD. The eligibility criteria, which were defined a priori, are summarised in Table 1. The study protocol was published on the PROSPERO international prospective register of systematic reviews (registration number CRD42016053431).

Studies in IBD were identified with the terms *Crohn disease*, *inflammatory bowel disease*, *colitis*, *ileitis*, or *ulcerative colitis* (both as medical subject headings (MeSH) and free text terms), and *Crohn$ disease* or *regional enteritis* (as free text terms). These were combined using the set operator AND with studies identified with the terms: *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *Escherichia coli*, or

TABLE 1 Eligibility criteria

- Randomised controlled trials.
- Adults (>90% of patients aged >16 years) with inflammatory bowel disease.
- Compared probiotics with 5-ASAs or placebo.
- Assessment of failure of remission in active UC or CD, relapse of disease activity in quiescent UC or CD, or relapse of disease activity in CD in remission following a surgical resection, at last time point of assessment in the trial.

probiotics (both as MeSH and free text terms). There were no language restrictions, and titles and abstracts of the papers identified by the initial search were evaluated by two reviewers, independently, for appropriateness to the study question. All potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated where necessary. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature. Articles were independently assessed by two reviewers using pre-designed eligibility forms, according to the prospectively defined eligibility criteria. Any disagreement between investigators was resolved by consensus.

2.2 | Outcome assessment

The primary dichotomous outcomes assessed were the efficacy of probiotics, compared with 5-ASAs or placebo in terms of failure to achieve remission in active IBD, and relapse of disease activity in quiescent IBD. Secondary outcomes included assessing incidence of adverse events occurring as a result of therapy.

2.3 | Data extraction

All data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (remission or failure of remission in active IBD, and relapse or no relapse of disease activity in quiescent IBD). In addition, the following clinical data were extracted for each trial, where available: gender of trial participants, country of origin, setting (primary, secondary or tertiary care-based), dosage and schedule of probiotics, dosage and schedule of control therapy, duration of therapy, number of individuals incurring any adverse event, and primary outcome measure used to define remission or relapse following therapy. Data were extracted as intention-to-treat analyses, with all drop-outs assumed to be treatment failures (ie failed to achieve remission in active IBD trials, and disease activity relapsed in quiescent IBD trials), wherever trial reporting allowed this.

2.4 | Assessment of risk of bias

This was conducted by two investigators in accordance with guidance published in the Cochrane handbook.[39] Any disagreement was resolved by discussion. Risk of bias was assessed by recording the methods used to generate the randomisation schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

2.5 | Data synthesis and statistical analysis

The degree of agreement between the two investigators, in terms of judging study eligibility, was measured using a Kappa statistic. Dichotomous outcome data were pooled using a random effects model,[40] to give a more conservative estimate of the effect of probiotics in IBD, allowing for any heterogeneity between studies. The impact of probiotics, compared with 5-ASA or placebo was expressed as a relative risk (RR) of failure to achieve remission with 95% confidence intervals (CIs) in trials of therapy for active UC or CD, or RR of relapse of disease activity in trials of therapy for quiescent UC, CD, or post-operative CD. Adverse events data were also summarised with RRs and 95% CIs. The number needed to treat (NNT) and the number needed to harm (NNH), with 95% CIs, were calculated using the formula NNT or NNH=1/(control event rate$\times$(1$-$RR)). All these analyses were defined a priori.

The results of individual studies can be diverse, and this inconsistency within a single meta-analysis can be quantified with a statistical test of heterogeneity, to assess whether the variation across trials is due to true heterogeneity, or chance. Heterogeneity between studies was assessed using both the I^2 statistic with a cut off of $\geq$50%, and the chi-squared test with a $P<.10$, used to define a significant degree of heterogeneity.[41] Review Manager version 5.1.4 (RevMan for Windows 2008; the Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect version 2.7.7 (StatsDirect Ltd, Sale, Cheshire, England) were used to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. The latter were assessed for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test,[42] if there were sufficient ($\geq$10) eligible studies included in the meta-analysis, in line with recent recommendations.[43]

3 | RESULTS

The search strategy generated a total of 12 253 citations, of which 76 published articles appeared to be relevant, and were retrieved for further assessment (Figure S1). Of these, 54 were excluded for various reasons leaving 22 eligible articles.[16-25, 44-55] Agreement between reviewers for assessment of trial eligibility was excellent (Kappa statistic=0.94). There were eight trials studying the efficacy of probiotics in inducing remission in active UC,[16,18,25,44-48] six studying their efficacy in preventing relapse of quiescent UC,[17,19,23,49-51] two studying the efficacy of probiotics in inducing remission in active CD,[52,53] two studying their efficacy in preventing relapse of quiescent CD,[24,55] and four studying their efficacy in preventing relapse of CD in remission following a surgical resection.[20-22,54] None of the RCTs were cross-over trials. Only two trials were at low risk of bias (Table S1).[22,25] The concomitant medications permitted and excluded in each of these studies is described in Table S2.

3.1 | Efficacy of probiotics in inducing remission in active UC

One of the eight eligible trials compared probiotics with 5-ASAs for induction of remission of active UC,[44] and the other seven trials were placebo-controlled.[16,18,25,45-48] Two trials were at low risk of bias.[25] Detailed study characteristics are provided in Table 2. The

TABLE 2 Characteristics of randomised controlled trials of probiotics vs 5-ASA or placebo in inducing remission in active UC

Study, country, and setting	Criteria used to define remission	Sample size (% female) and disease distribution	Probiotic used and duration of therapy	Control used and duration of therapy	Methodology
Rembacken[44], UK, secondary care	≤3 stools per day, no erythema, granularity or friability of rectal mucosa, and histologically inactive disease	116 (47.4), 29% proctitis, 31% left-sided, 38% extensive	Two capsules containing *Escherichia coli* Nissle 1917 (2.5×10^{10} viable organisms/capsule) b.d. for 12 weeks. All patients also received gentamicin 80 mg t.d.s. for 1 week at study entry	Mesalazine 800 mg t.d.s. for 12 weeks. All patients also received gentamicin 80 mg t.d.s. for 1 week at study entry	Method of randomisation not stated. Method of concealment of allocation stated. Double-blind. All patients also received usual medical therapy
Kato[16], Japan, tertiary care	Absence of rectal bleeding, no erythema, granularity or friability of rectal mucosa, and normal or near-normal sigmoidoscopy	20 (50.0), proctitis 25%, 35% left-sided, 40% extensive	100 mL of fermented milk drink containing *Bifidobacterium breve*, *Bifidobacterium bifidum*, *Lactobacillus acidophilus* (10 billion per bottle) o.d. for 12 weeks	Identical appearing placebo o.d for 12 weeks	Method of randomisation and concealment of allocation stated. Investigator-blinded. All patients also received usual medical therapy
Sood[18], India, tertiary care	UC disease activity index ≤2	147 (40.1), 45% proctitis, 32% left-sided, 23% extensive		Identical appearing placebo b.d. for 12 weeks	Method of randomisation and concealment of allocation stated. Double-blind. All patients also received usual medical therapy
Matthes[45], Germany, secondary and tertiary care	UC disease activity index ≤2	90 (43.3), 100% left-sided	One 40 ml, 20 ml, or 10 ml enema containing *Escherichia coli* Nissle 1917 (10^8 viable organisms/mL) o.d for at least 2 weeks	Identical appearing placebo b.d. for 12 weeks	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. All patients also received usual medical therapy
Ng[46]	UC disease activity index ≤2	28 (60.7), 54% left-sided, 46% extensive	Two sachets containing *VSL#3* (900 billion bacteria/sachet) b.d. for 8 weeks	Identical appearing placebo b.d. for 8 weeks	Method of randomisation and concealment of allocation not stated. Double-blind. All patients also received usual medical therapy
Tursi[47], Italy, secondary and tertiary care	UC disease activity index ≤2	144 (35.4), 51% proctitis, 31% left-sided, 17% extensive	Two sachets containing *VSL#3* (900 billion bacteria/sachet) b.d. for 8 weeks	Identical appearing placebo b.d. for 8 weeks	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. All patients also received usual medical therapy

(Continues)

TABLE 2 (Continued)

Study, country, and setting	Criteria used to define remission	Sample size (% female) and disease distribution	Probiotic used and duration of therapy	Control used and duration of therapy	Methodology
Petersen[25], Denmark, tertiary care	Rachmilewitz clinical activity index ≤4	50 (60.0), 14% proctitis, 64% left-sided, 22% extensive	100 mg of *Escherichia coli* Nissle 1917 (2.5-25×10^9 viable organisms/capsule) o.d. for 4 days, then b.d for 45 days	Identical appearing placebo for 7 weeks	Method of randomisation and concealment of allocation stated. Double-blind. All patients also received usual medical therapy
Tamaki[48], Japan, secondary and tertiary care	UC disease activity index ≤2	56 (51.8), 30% proctitis, 64% left-sided, 5% extensive	One sachet containing *Bifidobacterium longum 356* (2-3×10^{11} viable organisms/sachet) t.d.s. for 8 weeks	Identical appearing placebo t.d.s. for 8 weeks	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. All patients also received usual medical therapy

single trial that compared probiotics with 5-ASAs for inducing remission in active UC contained 116 patients.[44] Overall, 18 (31.6%) of 57 patients randomised to probiotics failed to achieve remission, compared with 15 (25.4%) of 59 receiving 5-ASAs (RR of failure to achieve remission=1.24; 95% CI=0.70-2.22; Figure 1). Adverse events occurred in nine (15.8%) patients assigned to probiotics compared with 7 (11.9%) of those allocated to 5-ASAs (*P*=.54).

The seven placebo-controlled RCTs contained a total of 535 patients with active UC.[16,18,25,45-48] In total, 166 (56.3%) of 295 patients assigned to probiotics failed to achieve remission, compared with 159 (66.3%) of 240 allocated to placebo (RR of failure to achieve remission=0.86; 95% CI=0.68-1.08; Figure 1), with heterogeneity between studies (I^2=53%, *P*=.05). There were too few studies to assess for evidence of publication bias. Adverse events data were provided by six trials.[16,18,25,45,47,48] Adverse events occurred in 69 (24.6%) of 281 patients receiving probiotics, compared with 28 (12.4%) of 226 randomised to placebo, although this difference was not statistically significant (RR=1.21; 95% CI=0.64-2.27).

Three of the trials, containing 319 patients, used VSL#3 (Ferring Pharmaceuticals Ltd., West Drayton, UK), a combination of probiotics.[18,46,47] When only these three studies were considered in the analysis, 91 (56.2%) of 162 patients randomised to VSL#3 failed to achieve remission, compared with 118 (75.2%) of 157 who received

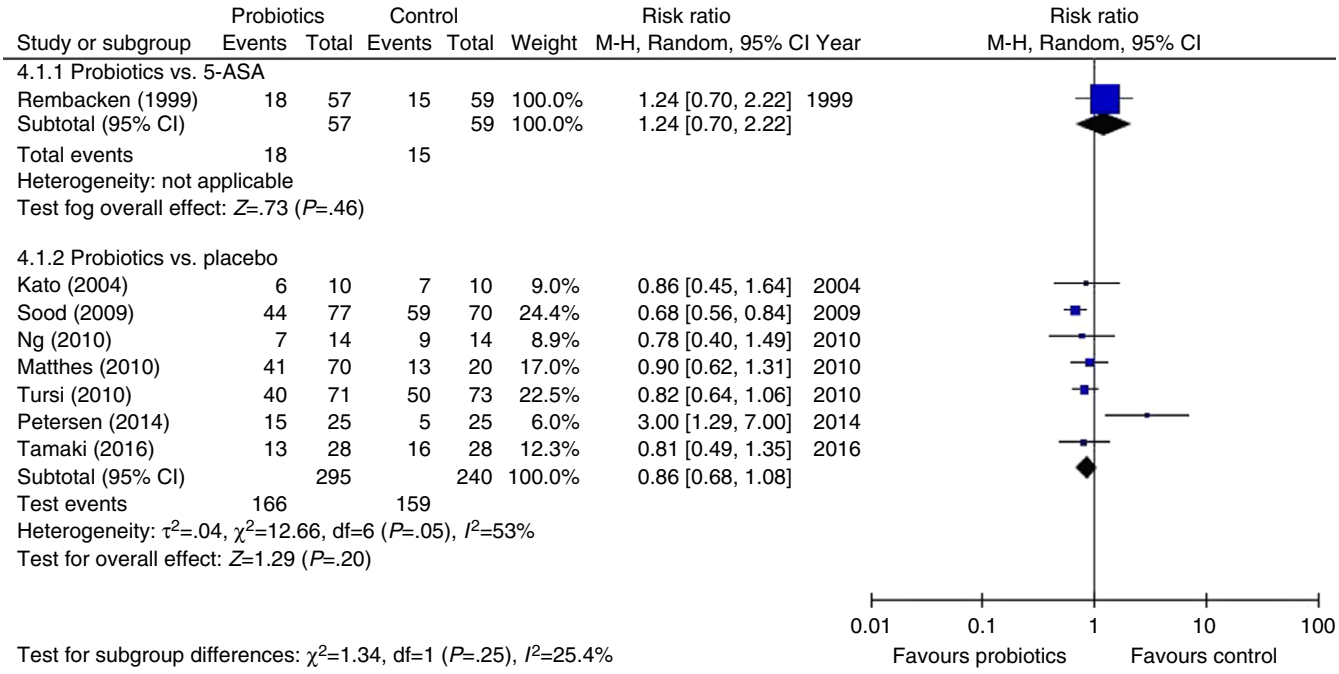

FIGURE 1 Forest plot of randomised controlled trials reporting the efficacy of probiotics vs 5-aminosalicylates or placebo in inducing remission in active UC

placebo (RR of failure to achieve remission=0.74; 95% CI=0.63-0.87), with no heterogeneity between studies (I^2=0%, P=.52) (Figure S2). The number needed to treat with VSL#3 to prevent one patient with active UC failing to achieve remission was 5 (95% CI=4-10). Two RCTs used *E. coli* Nissle 1917, containing 140 patients. Overall, 56 (58.9%) of 95 patients assigned to active therapy failed to achieve remission, compared with 18 (40.0%) of 45 allocated to placebo (RR=1.56; 95% CI=0.44-5.53).

3.2 | Efficacy of probiotics in preventing relapse in quiescent UC

Three of the six RCTs compared probiotics with 5-ASA,[17,49,51] and three compared probiotics with placebo.[19,23,50] No trials were at low risk of bias. Detailed study characteristics are provided in Table 3. The three RCTs that compared probiotics with 5-ASAs for preventing relapse of quiescent UC contained 555 patients.[17,49,51] Overall, 110 (39.7%) of 277 patients assigned to probiotics experienced a relapse of disease activity, compared with 109 (39.2%) of 278 allocated to 5-ASAs. The RR of relapse of disease activity in patients with quiescent UC with probiotics vs 5-ASAs was 1.02 (95% CI=0.85-1.23; Figure 2), with no heterogeneity detected between studies (I^2=0%, P=.62). There were too few studies to assess for evidence of publication bias. Adverse events data were reported by all three RCTs.[17,49,51] There were 73 (25.6%) patients randomised to probiotics who reported at least one adverse event, compared with 66 (23.2%) patients receiving 5-ASAs (RR=1.09; 95% CI=0.71-1.67).

When data from the three RCTs that compared probiotics with placebo,[19,23,50] containing 122 patients with quiescent UC, were pooled there were 32 (49.2%) of 65 patients randomised to probiotics who experienced a relapse of disease activity, compared with 42 (73.7%) of 57 receiving placebo (RR of relapse of disease activity=0.62; 95% CI=0.33-1.16; Figure 2), with heterogeneity between studies (I^2=76%, P=.02). Again, there were too few studies to assess for evidence of publication bias. Only one of these RCTs reported adverse events data,[19] with none in either treatment arm.

3.3 | Efficacy of probiotics in inducing remission in active CD

There were only two trials,[52,53] containing 37 patients, reporting the efficacy of probiotics vs placebo in terms of inducing remission of active CD. Neither trial was at low risk of bias. Detailed study characteristics are provided in Table S3. In total, 6 (31.6%) of 19 patients randomised to probiotics failed to achieve remission, compared with 6 (33.3%) of 18 receiving placebo (RR of failure to achieve remission=0.99; 95% CI=0.57-1.72; Figure S3). There was no heterogeneity between these two studies, although power to detect this would be low, and too few studies to assess for publication bias. Only one of these RCTs reported adverse events data,[52] with none in either treatment arm.

3.4 | Efficacy of probiotics in preventing relapse in quiescent CD

There were only two trials,[24,55] containing 195 patients, reporting the efficacy of probiotics vs placebo in terms of preventing relapse of quiescent CD. Neither trial was at low risk of bias. Detailed study characteristics are provided in Table S4. Overall, 52 (52.0%) of 100 patients allocated to probiotics experienced a relapse of disease activity, compared with 50 (52.6%) of 95 receiving placebo (RR of relapse of disease activity=1.03; 95% CI=0.70-1.51; Figure S3). There was no heterogeneity between these two studies, although again power to detect this would be low, and too few studies to assess for publication bias. Only one of these RCTs reported adverse events data,[24] with 49 (58.3%) of 84 patients assigned to probiotics experiencing one or more adverse events, compared with 45 (55.6%) of 81 with placebo (P=.72).

3.5 | Efficacy of probiotics in preventing relapse in CD in remission following a surgical resection

There were four placebo-controlled trials,[20-22,54] containing 333 patients, reporting the efficacy of probiotics vs placebo in terms of preventing either clinical or endoscopic relapse of CD in remission following a surgical resection. One trial was at low risk of bias.[22] Detailed study characteristics are provided in Table 4. In terms of clinical relapse, three trials reported these data.[20-22] In total, 28 (26.7%) of 105 patients allocated to probiotics experienced a clinical relapse of disease activity, compared with 28 (25.9%) of 108 receiving placebo (RR of clinical relapse of disease activity=1.06; 95% CI=0.59-1.92; Figure 3). There was no heterogeneity between these three studies (I^2=37%, P=.20), and again too few studies to assess for publication bias.

All four RCTs reported efficacy of probiotics in terms of prevention of endoscopic relapse of disease activity.[20-22,54] All trials used a Rutgeerts score to define endoscopic relapse,[56] and reported data according to scores from 1 to 4. There was no effect of probiotics in preventing endoscopic relapse defined according to Rutgeerts score of ≥1, ≥2, or ≥3 (Figure 3). There was heterogeneity between studies when a Rutgeerts score of ≥1 was used to define endoscopic relapse (I^2=53%, P=.10), but no heterogeneity in the other two analyses.

Three trials reported adverse events data.[20,22,54] Overall, 39 (30.2%) of 129 patients allocated to probiotics experienced at least one adverse event, compared with 52 (38.8%) of 134 assigned to placebo (RR=0.81; 95% CI=0.61-1.08).

4 | DISCUSSION

This systematic review and meta-analysis has demonstrated that the probiotic VSL#3 may have beneficial effects in terms of inducing remission in active UC, with a NNT of 5. Our analysis also suggests that probiotics may be as effective as 5-ASAs in preventing relapse

TABLE 3 Characteristics of randomised controlled trials of probiotics vs 5-ASA or placebo in preventing relapse in quiescent UC

Study, country, and setting	Criteria used to define relapse	Sample size (% female) and disease distribution	Probiotic used and duration of therapy	Control used and duration of therapy	Methodology
Kruis[49], Austria, Czech Republic and Germany, secondary and tertiary care	Rachmilewitz clinical activity index >4	103 (46.6), 66% proctitis, 18% left-sided, 17% extensive	200 mg of *Escherichia coli* Nissle 1917 (25×10^9 viable organisms/100 mg) o.d. for 12 weeks	Mesalazine 500 mg t.d.s. for 12 weeks	Method of randomisation and concealment of allocation not stated. Double-blind. No concomitant medications allowed
Cui[50], China, tertiary care	Clinical, endoscopic, or histologic relapse	30 (not reported), disease distribution not reported	Bifid triple capsule (1.26 g containing *Enterococci*, *Bifidobacteria* & *Lactobacilli*) o.d for 8 weeks	Identical appearing placebo o.d for 8 weeks	Method of randomisation and concealment of allocation not stated. Blinding not reported. All patients also received usual medical therapy
Kruis[51], 10 European countries, secondary and tertiary care	Rachmilewitz clinical activity index >6, or >4 with an increase of ≥3, endoscopic index >4, and histological inflammation	327 (45.3), 58% proctitis, 19% left-sided, 19% extensive	200 mg of *Escherichia coli* Nissle 1917 ($2.5\text{-}25\times10^9$ viable organisms/100 mg) o.d. for 12 months	Mesalazine 500 mg t.d.s. for 12 months	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. No concomitant medications allowed
Zocco[17], Italy, tertiary care	Symptoms and/or signs of UC needing additional medical therapy, or Rachmilewitz clinical activity index >4. Endoscopy with biopsies performed to confirm relapse	125 (44.0), disease distribution not reported	*Lactobacillus rhamnosus* GG (18×10^9 viable organisms/day) for 12 months	Mesalazine 800 mg t.d.s. for 12 months	Method of randomisation and concealment of allocation not stated. Unblinded. No immunosuppressants or rectal therapies allowed
Wildt[23], Denmark, tertiary care	Simple clinical colitis activity index >4 and/or endoscopic index ≥2	32 (68.8), disease distribution not reported	Two Probio-Tec AB-25 capsules (Chr. Hansen A/S, Hoersholm, Denmark) (1.25×10^{10} colony forming units/ capsule of *Lactobacillus acidophilus* LA-5 and *Bifidobacterium animalis* BB-12) t.d.s. for 52 weeks	Identical appearing placebo t.d.s. for 52 weeks	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. No concomitant medications allowed
Yoshimatsu[19], Japan, tertiary care	Escalation of therapy	60 (39.1), 24% proctitis, 33% left-sided, 43% extensive	Three Bio-three tablets (Toa Pharmaceutical Co., Ltd., Toyama, Japan) (2 mg *Streptococcus faecalis* T-110, 10 mg *Clostridium butyricum* TO-A, 10 mg *Bacillus mesentericus* TO-A) t.d.s. for 12 months	Identical appearing placebo t.d.s. for 12 months	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. All patients also received usual medical therapy

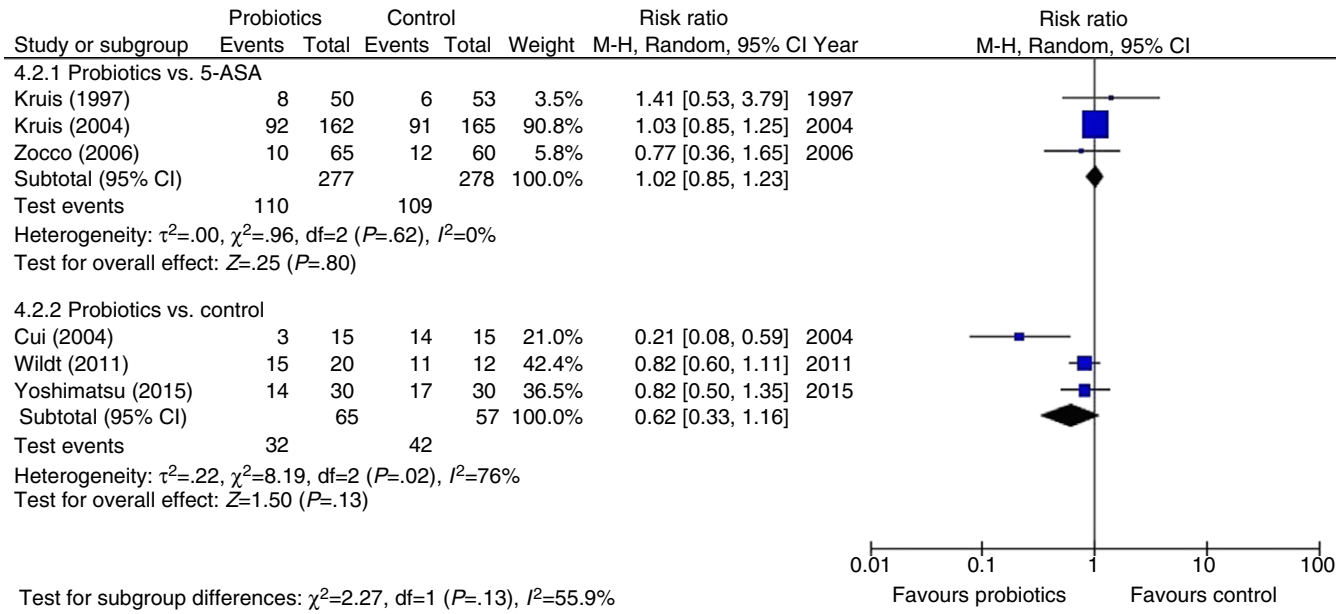

FIGURE 2 Forest plot of randomised controlled trials reporting the efficacy of probiotics vs 5-aminosalicylates or placebo in preventing relapse in quiescent UC

of quiescent UC. There was no benefit associated with the use of probiotics when compared with placebo in inducing remission in active CD, preventing relapse of quiescent UC or CD, or preventing clinical or endoscopic relapse of post-operative CD. There was no difference in adverse event reporting when probiotics were compared with placebo or 5-ASAs.

TABLE 4 Characteristics of randomised controlled trials of probiotics vs placebo in preventing relapse in CD in remission following a surgical resection

Study, country, and setting	Criteria used to define relapse	Sample size (% female)	Probiotic used and duration of therapy	Control used and duration of therapy	Methodology
Prantera[20], Italy, tertiary care	Clinical: Escalation of medical therapy, need for surgery, or Crohn's disease activity index >150 Endoscopic: Rutgeerts score	45 (35.6)	One 2.46 g bag containing *Lactobacillus rhamnosus* GG (6 billion colony forming units/bag) b.d for 52 weeks	Identical appearing placebo b.d. for 52 weeks	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. Anti-diarrhoeals allowed
Marteau[22], France, secondary and tertiary care	Clinical: Crohn's disease activity index ≥200 Endoscopic: Rutgeerts score	98 (52.0)	One packet of *Lactobacillus johnsonii* LA1 (2×10^9 colony forming units/packet) b.d. for 6 months	Identical appearing placebo b.d. for 6 months	Method of randomisation and concealment of allocation stated. Double-blind. No concomitant medications allowed
Van Gossum[21], Belgium, secondary and tertiary care	Clinical: Crohn's disease activity index >150 with an increase of ≥70 over baseline Endoscopic: Rutgeerts score	70 (47.1)	One 2 g sachet of *Lactobacillus johnsonii* LA1 (10^{10} colony forming units/sachet) o.d for 12 weeks	Identical appearing placebo o.d for 12 weeks	Method of randomisation and concealment of allocation stated. Double-blind. No concomitant medications allowed
Fedorak[54], Canada, tertiary care	Endoscopic: Rutgeerts score	120 (48.3)	One packet containing *VSL#3* (900 billion bacteria/sachet) b.d. for 3 months	Identical appearing placebo b.d. for 3 months	Method of randomisation stated. Method of concealment of allocation not stated. Double-blind. No concomitant medications allowed

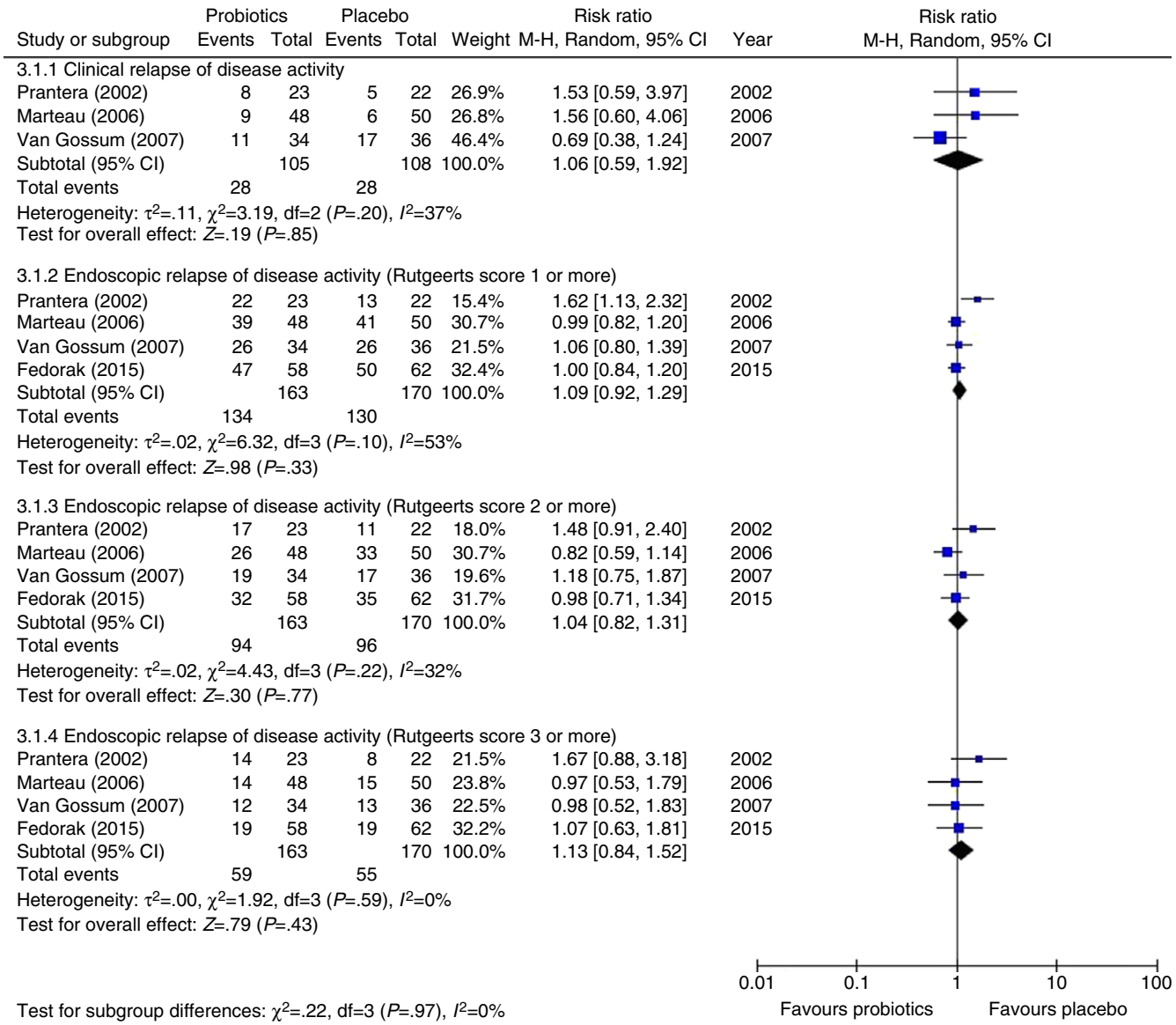

FIGURE 3 Forest plot of randomised controlled trials reporting the efficacy of probiotics vs placebo in preventing clinical or endoscopic relapse in CD in remission following a surgical resection

We conducted a comprehensive and contemporaneous search and also searched the "grey" literature to maximise the likelihood that all eligible trials examining the effects of probiotics in IBD were included. This means we have identified RCTs missed by previous meta-analyses, as well as including data from studies published after these meta-analyses were conducted.[19,24,48,54,55] Eligibility assessment and data extraction was performed by two independent investigators, with any disagreement resolved by discussion or by consultation with a third researcher. We used an intention-to-treat analysis, with all drop-outs assumed to be treatment failures, and data were pooled using a random effects model, in order to provide a more conservative estimate of the effects of the intervention, and to adjust for heterogeneity that was observed in some of our analyses. Finally, where sufficient trials were available, we performed subgroup analyses to examine the treatment effect according to the specific probiotic used.

The limitations of this systematic review and meta-analysis arise from the size and quality of the studies available for synthesis and the outcomes that were recorded. The US Food and Drug Administration now advocates the use of patient reported outcome measure as endpoints in clinical trials in IBD.[57] However, given the majority of studies were conducted prior to this guidance, data on such endpoints was not available for extraction. Furthermore, gold-standard endpoints such as mucosal healing in trials of the efficacy of probiotics in the induction of remission of active IBD were not available. Only two trials were at a low risk of bias according to the criteria we used.[22,25] There was evidence of heterogeneity between studies when data were pooled from placebo-controlled RCTs investigating the effect of probiotics on remission rates in active UC, although this disappeared when only trials of VSL#3 were included. Heterogeneity was also observed in the meta-analysis of placebo-controlled RCTs investigating the effect of probiotics in preventing relapse of

quiescent UC. The cause of this heterogeneity is unclear, but pooling data from studies utilising a variety of species, strains, doses and durations of probiotics in these analyses may have contributed. A further limitation is that the length of follow-up, and methods used to assess disease activity, whilst independently validated and appropriate in their own right, were not uniform throughout the included studies This may have introduced other biases that have not been accounted for, including the possibility that the severity of disease activity in patients included in studies investigating the effect of probiotics in the induction of remission of active IBD may have differed between the included studies, and that the concomitant medications permitted in each of these studies was not uniform. Aside from this, the inclusion of trials of combination probiotics means that the effect of the individual bacterial strains contained within these preparations cannot be assessed. However, some combinations of probiotics are of proven benefit in other GI disorders, where their use is associated with an improvement in abdominal pain scores and a reduction in the persistence of bowel symptoms.[58] The paucity of data on probiotics for the induction of remission in active CD, and to a lesser extent, for the maintenance of remission in quiescent CD, means that drawing conclusions on their efficacy is unreliable. Finally, although our findings suggest that the combination probiotic VSL#3 may be beneficial in the treatment of active UC, the bacterial composition of this product has recently been altered in the United Kingdom and Holland which may limit the applicability of these findings in IBD populations in these countries.[59]

A Cochrane review investigating the effects of probiotics on the maintenance of remission of quiescent UC was conducted in 2012.[26] The authors suggested that there was insufficient evidence to support their routine use. Three further systematic reviews with meta-analysis have examined the effect of probiotics on disease activity in UC and CD with similar results to those presented here.[27-29] However, the most recent of these only searched for RCTs until 2013,[28,29] but since this time a further five RCTs,[19,24,25,48,54] including an additional 455 patients have been published and are included in our analyses. These previous systematic reviews also pooled data from RCTs that did not meet our inclusion criteria, including studies that examined the effect of probiotics in children with IBD, and the effect of synbiotics in IBD.[28,29]

Studies investigating the effect of manipulation of the microbiome on disease activity in IBD are in their infancy, yet an understanding of the role of treatments targeting IBD-related dysbiosis is of interest. It is proposed that probiotics may confer beneficial effects on outcomes in IBD via manipulation of the microbiome. However, only four of the 22 studies included in this analysis made any attempt to assess the impact of these preparations on the microbiome post-treatment.[16,19,23,50] Of these studies, only two reported an improvement in clinical or endoscopic outcomes in association with beneficial alterations in the microbiome, a reduction in pro-inflammatory cytokine expression and an increase in faecal short chain fatty acids.[16,50] From the available data, it is not possible to conclude that probiotic use is associated with an overall benefit in disease outcomes in IBD. However, whether this is a consequence of a failure to modulate the GI flora, an inability to overcome the effects of other confounding medications such as proton pump inhibitors or antibiotics,[60,61] or the absence of associated beneficial metabolomic effects remains uncertain.

Despite this, probiotics appeared to be well tolerated, and could be useful adjuncts to conventional medical therapy, independent of their effects on inflammatory disease activity. Numerous trials of probiotics have been conducted in patients with irritable bowel syndrome, where beneficial effects on abdominal pain and quality of life have been observed with some species and strains.[58,62,63] Given that the prevalence of functional GI symptoms in clinically quiescent IBD is as high as 35%,[64] and one-in-four patients with quiescent IBD still report these symptoms when disease activity assessment is performed using objective measures of intestinal inflammation, such as faecal calprotectin,[65] trials of probiotics in this difficult-to-treat cohort of patients may be of value.

In summary, this meta-analysis has demonstrated that VSL#3 may be effective in inducing remission in active UC. Probiotics appeared to be safe in IBD, and may also have a role as an alternative to 5-ASA preparations when used as maintenance treatment in UC. There is little evidence for the use of probiotics in the treatment of CD, either for inducing remission or preventing relapse. However, the number of studies that have examined this issue is small and further high quality RCTs are required to determine their efficacy in this situation. The role of probiotics in subgroups of IBD patients, particularly those with persistent GI symptoms in the absence of inflammation, is uncertain as trials of probiotics for this novel indication are lacking.

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AUTHORSHIP

Guarantor of the article: Professor AC Ford.

Author contributions: YD, DJG, PJH and ACF conceived the study. YD, DJG and ACF collected all data. YD, DJG, PJH and ACF analysed and interpreted the data. YD, DJG, PJH and ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the article.

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SUPPORTING INFORMATION

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