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The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review

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ABSTRACT

Introduction Probiotics may benefit irritable bowel syndrome (IBS) symptoms, but randomised controlled trials (RCTs) have been conflicting; therefore a systematic review was conducted.
Methods MEDLINE (1966 to May 2008), EMBASE (1988 to May 2008) and the Cochrane Controlled Trials Register (2008) electronic databases were searched, as were abstracts from DDW (Digestive Diseases Week) and UEGW (United European Gastroenterology Week), and authors were contacted for extra information. Only parallel group RCTs with at least 1 week of treatment comparing probiotics with placebo or no treatment in adults with IBS according to any acceptable definition were included. Studies had to provide improvement in abdominal pain or global IBS symptoms as an outcome. Eligibility assessment and data extraction were performed by two independent researchers. Data were synthesised using relative risk (RR) of symptoms not improving for dichotomous data and standardised mean difference (SMD) for continuous data using random effects models.
Results 19 RCTs (18 papers) in 1650 patients with IBS were identified. Trial quality was generally good, with nine reporting adequate methods of randomisation and six a method of concealment of allocation. There were 10 RCTs involving 918 patients providing outcomes as a dichotomous variable. Probiotics were statistically significantly better than placebo (RR of IBS not improving $= 0.71$; 95% CI 0.57 to 0.88) with a number needed to treat (NNT) $= 4$ (95% CI 3 to 12.5). There was significant heterogeneity ($\chi^2 = 28.3$, p $= 0.001$, $I^2 = 68\%$) and possible funnel plot asymmetry. Fifteen trials assessing 1351 patients reported on improvement in IBS score as a continuous outcome (SMD $= -0.34$; 95% CI -0.60 to -0.07). There was statistically significant heterogeneity ($\chi^2 = 67.04$, p<0.001, $I^2 = 79\%$), but this was explained by one outlying trial.
Conclusion Probiotics appear to be efficacious in IBS, but the magnitude of benefit and the most effective species and strain are uncertain.

Patients with irritable bowel syndrome (IBS) have a complex of symptoms[1] which can be difficult to treat. Antispasmodics and bulking agents have modest efficacy,[2] and even newer agents such as $5HT_4$ agonists[3] and $5HT_3$ antagonists[4] only have a 10% therapeutic gain over placebo. These newer drugs are now unavailable ($5HT_4$) or have restrictions for general use ($5HT_3$) because of concerns about possible cardiovascular risks[5] and ischaemic colitis,[6] respectively. Therapeutic options for IBS are therefore limited, which can be frustrating for patients and clinicians.

Attention has therefore focused on intestinal microflora, as these are important for intestinal function, and changes in gut microbiota are found in patients with IBS.[7 8] Whether these changes are a cause or a consequence of IBS remains uncertain.[9] The possibility that alterations in intestinal commensal bacteria have a causal role in some patients with IBS is supported by observations that IBS symptoms are more common following infectious gastroenteritis,[10] and that this association may persist for several years.[11] These findings could be due to bias or confounding, however, and altering intestinal flora in patients with IBS in a randomised controlled trial (RCT) would provide more compelling evidence for the role of gut microbiota in this disorder. Researchers have attempted this using probiotics in IBS but the results have been inconclusive. Studies have reported an improvement in global symptoms with probiotics,[12] whilst others have failed to demonstrate any benefit.[13] Other trials have not found a clear effect of probiotics on primary endpoints, but have found benefits for secondary endpoints such as bloating.[14] However, the resolution of specific symptoms has not been consistent even in studies performed by the same group of investigators.[15] Some of this variation may be attributable to the type of probiotic used, as well as methodological differences between trials. We have therefore conducted a systematic review of the literature to evaluate the impact of probiotics on IBS and to explore potential reasons for heterogeneity in study findings.

METHODS
Search strategy and study selection
A search of the medical literature was conducted using MEDLINE (1950 to June 2008), EMBASE (1980 to June 2008) and the Cochrane Controlled Trials Register (2007). RCTs comparing the effect of probiotics with placebo or no treatment in adult patients with IBS (over the age of 16 years) were eligible for inclusion. Trials that permitted other concomitant therapies were eligible, as long as these were administered to both the intervention and control arms. The first period of crossover RCTs were also eligible for inclusion. Minimum duration of treatment and follow-up was 7 days. The diagnosis of IBS could be based on either a doctor's opinion or symptom-based diagnostic criteria, supplemented by the results of investigations to exclude organic disease, where studies deemed this necessary. The primary outcome of this systematic review was change in global IBS symptoms reported as a dichotomous or continuous variable. Abdominal pain data were included in the

review if data for global symptoms were not available. Where studies did not report extractable data, but were otherwise eligible for inclusion in the systematic review, we attempted to contact the original investigators in order to obtain further information.

Studies on IBS were identified with the terms irritable bowel syndrome and functional diseases, colon (both as medical subject heading (MeSH) and free text terms), and IBS, spastic colon, irritable colon, and functional adj5 bowel (as free text terms). These were combined using the set operator AND, with studies identified with the terms: Saccharomyces, Lactobacillus, Bifidobacterium, Escherichia coli or probiotics (MeSH and free text terms).

There were no language restrictions, and abstracts of the papers identified by the initial search were evaluated by the lead reviewer for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated where necessary. Abstract books of conference proceedings between 2001 and 2007 were hand-searched to identify potentially eligible studies published only in abstract form. 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 predesigned eligibility forms, according to the prospectively defined eligibility criteria. Any disagreement between investigators was resolved by consensus between the two researchers, adjudicated with the support of a third investigator.

Outcome assessment

The primary outcome assessed was the effect of probiotics compared with placebo on global IBS symptoms (or abdominal pain if global symptoms were not reported) at the end of treatment. Dichotomous data included either symptom cure or improvement, and if multiple strata were given to define improvement then the cut-off point with the greatest improvement was utilised (eg, if the scale was 1, no improvement; 2, a little improvement; 3, a moderate amount of improvement; 4, symptoms very much improved; the latter descriptor was used). Patient-reported outcomes were included where possible in the review, but investigator-reported outcomes were included if these were the only data available. Continuous data were defined as ean total IBS symptom scores or abdominal pain scores from questionnaire data. Secondary outcomes included effect of treatment on bloating, urgency and flatus, and adverse events as a result of treatment.

Data extraction

All data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, Washington, USA). All data extraction was then checked by a third reviewer. In addition, the following clinical data were extracted for each trial: setting (primary, secondary or tertiary care-based); number of centres; country of origin; dose and duration of treatment; total number of adverse events reported; criteria used to define IBS; primary outcome measure used to define symptom improvement or cure following treatment; duration of treatment; duration of follow-up; proportion of female patients; and proportion of patients according to predominant stool pattern. Data were extracted as intention-to-treat analyses, where all drop-outs are assumed to be treatment failures, wherever trial reporting allowed this.

Study quality

Assessment of study quality was performed independently by two reviewers according to the Jadad scale,[16] which records whether a study is described as randomised and double-blind, the method of generation of the allocation schedule and method of double-blinding, and whether there is a description of drop-outs during the trial.

Data synthesis and statistical analysis

Data were pooled using a random effects model.[17] The impacts of probiotics on dichotomous outcomes were expressed as a relative risk (RR) of global IBS symptoms or abdominal pain persisting with intervention compared with control with 95% CIs. The number needed to treat (NNT) and 95% CIs were calculated from the reciprocal of the risk difference from the meta-analysis. The effect of probiotics on total IBS symptom scores and abdominal pain scores after completion of treatment was examined using a standardised mean difference (SMD) with a 95% CI.

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. This quantity is termed I^2, and its value ranges from 0 to 100%, with 0% representing no observed heterogeneity, and larger values indicating increasing heterogeneity. A value below 25% is arbitrarily chosen to represent low levels of heterogeneity.[18] Where the degree of statistical heterogeneity was greater than this among trial results in this meta-analysis, possible explanations were investigated using sensitivity analyses according to trial setting, criteria used to define IBS, whether the methods of randomisation or concealment of allocation were reported, level of blinding, and study quality according to the Jadad scale. These are exploratory only, and may explain some of the observed variability, but the results should be interpreted with caution.

Review Manager version 4.2.8 (RevMan for Windows 2003, the Nordic Cochrane Center, Copenhagen, Denmark) and StatsDirect version 2.4.4 (StatsDirect, Sale, Cheshire, UK) were used to generate Forest plots of pooled RRs and risk differences 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, using the Egger test.[19]

RESULTS

A total of 185 citations were identified, of which 18 papers[12–15 20–33] were eligible (figure 1) evaluating 1650 participants. Extra information was obtained from the authors of five papers.[14 15 22 25 31] The quality of the studies was generally good, with 11 (58%)[12–15 20–33] scoring at least 4 out of 5 on the Jadad scale (table 1). Nine trials[14 15 22 24 25 27 31–33] reported an adequate method of randomisation, and six studies[14 15 25 27 31 33] described appropriate methods of concealment of allocation (table 1). The majority of trials recruited patients with Rome II IBS,[12–15 22 23 25–27 29–31] but two[20 28] used an author-defined definition of IBS, two used Rome I,[21 24] and one each employed the Manning[32] and Rome III[33] criteria (table 1).

Efficacy of probiotics on overall IBS symptoms

Ten studies[14 21 22 24–26 30–33] with 918 participants reported IBS symptoms as a dichotomous outcome. Probiotics had a statistically significant effect in reducing IBS symptoms (RR of
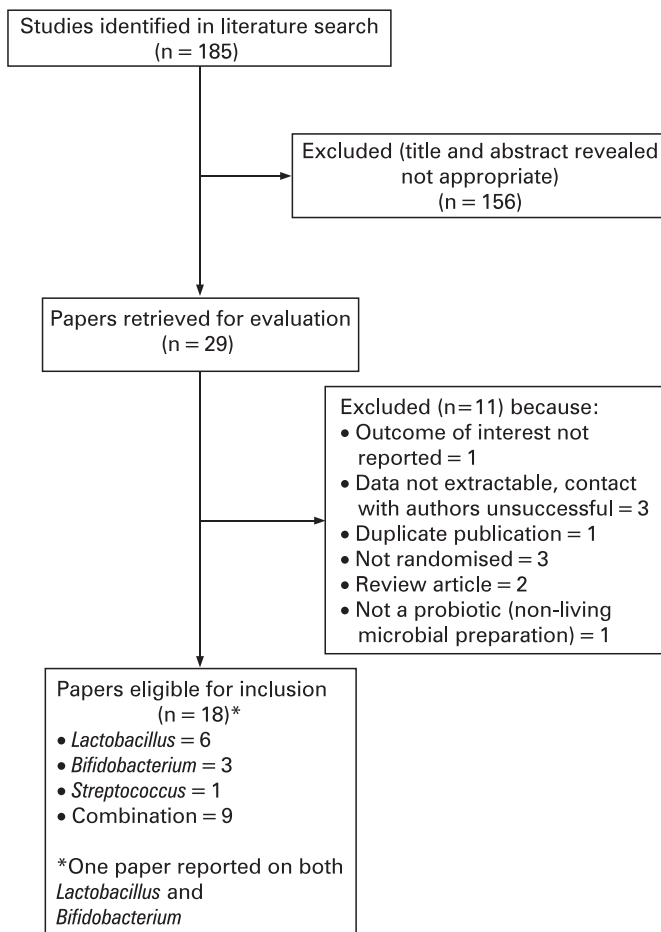
Figure 1 Flow diagram of trials evaluated in the systematic review.

symptoms persisting in probiotic group = 0.71; 95% CI 0.57 to 0.88) (figure 2) with an NNT of 4 (95% CI 3 to 12.5). There was significant heterogeneity among studies (χ^2 = 28.3, degrees of freedom (d.f.) = 9, p = 0.001, I^2 = 68%). There was no difference between the different types of probiotics used, with *Lactobacillus* (three trials, 140 patients),[20 21 33] *Bifidobacterium* (two trials, 422 patients),[30 31] *Streptococcus* (one trial, 54 patients)[32] and combinations of probiotics (four trials, 302 patients)[14 24–26] all showing a trend towards benefit (figure 2). There was, however, some asymmetry in the funnel plot (figure 3) (Egger test = −2.97; 95% CI −5.54 to −0.41, p = 0.028), suggesting publication bias or other small study effects. Trials with a Jadad score ≥4[14 21 26 31–33] had significantly less of a treatment effect (RR = 0.86; 95% CI 0.72 to 1.03) than those with a Jadad score <4[20 24 25 30] (RR = 0.52; 95% CI 0.35 to 0.77) (Cochrane Q = 5.2, p = 0.02).

Fifteen trials described in 14 papers[12–15 21–29 31] with 1351 participants reported IBS symptoms as a continuous variable. Probiotics had a statistically significant effect in improving IBS symptoms compared with placebo (SMD = −0.34; 95% CI −0.60 to −0.07) (figure 4). There was statistically significant heterogeneity (χ^2 = 67.04, d.f. = 14, p<0.001, I^2 = 79%), but this was explained by one outlying trial.[25] When this trial was excluded, the statistically significant effect of probiotics in improving IBS symptoms remained (SMD = −0.18; 95% CI −0.29 to −0.06) but heterogeneity was no longer apparent (χ^2 = 12.1, d.f. = 13, p = 0.52, I^2 = 0%). There was no significant funnel plot asymmetry (Egger test = −1.75; 95% CI −5.15 to 1.64, p = 0.29). There was a trend for higher quality studies to

report less of a treatment effect than lower quality studies, but this was driven by one outlier.[25] When this study was removed, the treatment effect was similar in trials with a Jadad score ≥4[12–15 21 22 26 27 31] (SMD = −0.19; 95% CI −0.31 to −0.03) and those with a Jadad score <4[23–25 28 29] (SMD = −0.13; 95% CI −0.45 to 0.17). Four trials[13 20–22] evaluated *Lactobacillus* in 200 patients and found no effect on IBS symptoms, nine trials[12–15 24–29] evaluated combinations of probiotics in 772 patients with a significant effect in improving IBS symptoms, whilst two trials[22 31] evaluated *Bifidobacterium* in 379 patients with a trend towards improving IBS symptoms that did not reach statistical significance (figure 4).

Efficacy of probiotics on individual IBS symptoms
Individual IBS symptoms were almost exclusively given as a continuous outcome. Ten trials (from nine papers)[14 15 21 22 24–26 28 31] with 834 participants reported on abdominal pain. There was a statistically significant effect in favour of probiotics improving pain scores (SMD = −0.51; 95% CI −0.91 to −0.09, p = 0.016) with significant heterogeneity among studies (χ^2 = 61,08, d.f. = 9, p<0.0001, I^2 = 85%). This was due to one outlying study,[25] and when this was removed the statistically significant effect on improving IBS symptoms remained (SMD = −0.22; 95% CI −0.37 to −0.06, p = 0.002) but heterogeneity was no longer apparent (χ^2 = 7.29, d.f. = 8, p = 0.51, I^2 = 0%).

Eight trials (from seven papers)[14 15 22 24 25 28 31] with 682 patients reported on bloating. There was a trend towards probiotics improving bloating (SMD = −0.54; 95% CI −1.10 to 0.02, p = 0.058), but this did not reach statistical significance. There was significant heterogeneity among studies (χ^2 = 66.12, d.f. = 7, p<0.001, I^2 = 89%), but again this was due to one outlying study,[25] and when it was excluded this disappeared (χ^2 = 3.35, d.f. = 7, p = 0.76, I^2 = 0%).

Six trials[14 15 21 27 28 31] evaluating 566 patients reported on flatulence. Probiotics statistically significantly improved flatulence (SMD = −0.22; 95% CI −0.42 to −0.01, p = 0.04) with no significant heterogeneity among studies (χ^2 = 5.74, d.f. = 7, p = 0.33, I^2 = 13%).

Three trials[14 15 31] evaluating 394 patients reported on urgency. There was no statistically significant change in the scoring of urgency as a symptom compared with placebo (SMD = −0.08; 95% CI −0.3 to 0.14, p = 0.49).

Adverse events associated with probiotics in IBS patients
Six trials[14 15 20 21 32 33] reported that there were no adverse events in either the control or active treatment arm. Three trials[12 13 27] reported on overall adverse events in 407 patients. There was no significant difference in adverse events between probiotics and placebo (RR of adverse event on probiotic = 0.93; 95% CI 0.64 to 1.36). All other studies did not report on adverse events or did not provide extractable data.

DISCUSSION
The intestine has between 1012 and 1014 organisms per millilitre, which is ∼100-fold greater than the number of eukaryotic cells in the human body.[34] We provide a stable environment for our commensal bacteria and these organisms in turn are important for the host metabolism as well as intestinal and immune function.[34] It is biologically plausible that gut microflora have an aetiological role in IBS and that modulating this environment may improve symptoms. This systematic

Irritable bowel syndrome

Table 1 Characteristics of included studies

Trial	Design	Participants	Interventions	Methodology	Outcomes	Jadad score
Niedzielin (2001)[20]	Polish RCT, single-centre study.	Author-defined IBS. 40 secondary care patients. 80% female. IBS subtypes not stated.	*Lactobacillus plantarum* 299V 5×10^7 cfu/ml 200 ml twice daily vs placebo for 4 weeks.	Method of randomisation and concealment not stated. Double blind. No other IBS medications permitted.	Any improvement in IBS symptoms	3
Nobaek (2000)[21]	Swedish RCT, single-centre study.	Rome I IBS. 60 patients recruited from the population. 69% female. IBS subtypes not stated.	*Lactobacillus plantarum* DSM 9843 5×10^7 once daily vs placebo for 4 weeks.	Method of randomisation and concealment not stated. Double blind. Unclear whether other IBS medications permitted.	>1.5 improvement in VAS scale for abdominal pain.	4
Niv (2005)[13]	Israeli RCT, two centres.	Rome II IBS. 54 secondary care patients. C 18.5%, D 37%, A 44.4%.	*Lactobacillus reuteri* ATCC 55 730 1×10^8 four times daily for 2 weeks then twice daily vs placebo for 6 months.	Method of randomisation and concealment not stated. Double blind. Other IBS medications permitted.	Continuous scale for global IBS symptoms.	4
O'Mahony (2005)[22]	Irish RCT, single-centre study.	Rome II IBS. 80 patients recruited by advertising and from secondary care. 64% female. C 26%, D 28%, A 45%.	*Lactobacillus salivarius* 1×10^{10} UCC4331 vs *Bifidobacterium infantis* 35624 1×10^{10} vs placebo for 8 weeks.	Adequate method of randomisation, no concealment, double blind. No other IBS treatment allowed.	Continuous scale for global IBS symptoms measured on a Likert scale and VAS (Likert used for meta-analysis).	5
Simren (2006)[23]	Swedish RCT, single-centre study.	Rome II IBS. 76 patients recruited by advertising. 63% female.	*Lactobacillus plantarum* 299V 5×10^7 once daily vs placebo for 6 weeks.	Method of randomisation and concealment not stated. Double blind. Unclear whether other IBS medications permitted.	Continuous scale for global IBS symptoms. Validated questionnaire.	3
Kajander (2005)[24]	Finnish RCT, single-centre study.	Rome I and II IBS. 103 patients recruited by advertising. 76% female. C 21%, D 50%, A 29%.	*Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC705, *Propionibacterium freudenreichii* ssp. *shermanii* JS, *Bifidobacterium breve* Bb99 vs placebo for 6 months.	Adequate method of randomisation, method of concealment not stated. Double blind. Other IBS treatment allowed.	Continuous scale for global IBS symptoms.	3
Tsuchiya (2004)[25]	Italian RCT, single-centre study.	Rome II IBS. 68 patients recruited by advertising. 71% female. IBS subtypes not stated.	A symbiotic preparation of *Lactobacillus acidophilus* 1.5×10^6, *L helveticus* 1.3×10^9, *Bifidobacterium* 4.95×10^9 in a vitamin and phytoextract-enriched medium (SCM III) vs placebo for 12 weeks.	Adequate method of randomisation and concealment. Double blind. Unclear whether other IBS medications permitted.	Patient rates the treatment effective or very effective.	3
Guyonnet (2007)[12]	French RCT, 35 centres.	Rome II IBS. 267 patients recruited from primary care. 75% female. C 100%.	*Bifidobacterium animalis* DN-173 010 1.25×10^{10}, S thermophilus and *L. bulgaricus* 1.2×10^9 twice daily vs placebo for 6 weeks.	Method of randomisation and concealment not stated. Double blind. Other IBS medications permitted (not fibre or fermented dairy products).	Continuous scale for global IBS symptoms.	4
Drouault-Holowacz (2008)[26]	French RCT.	Rome II IBS. 116 patients recruited from primary care. 76% female. C 29%, D 29%, A 41%.	Lactibiane (*Bifidobacterium longum* 101 (29%), *Lactobacillus acidophilus* 102 (29%), *Lactococcus lactis* 103 (29%), *Streptococcus thermophilus* 104 (13%) 1×10^{10} in total) once daily vs placebo for 4 weeks.	Method of randomisation and concealment not stated. Double blind. IBS medications not permitted apart from laxatives.	Continuous scale for global IBS symptoms. Do you have satisfactory relief of overall IBS symptom during last week for dichotomous.	4
Kajander (2008)[27]	Finnish RCT, single-centre study.	Rome II IBS. 86 primary care patients. 93% female. C 30%, D 45%, A 25%.	*Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC705, *Propionibacterium freudenreichii* ssp. *shermanii* JS DSM 7067, *Bifidobacterium animalis* ssp. *lactis* Bb12 DSM 15954 vs placebo for 20 weeks.	Adequate method of randomisation and concealment. Double blind. Other IBS medications permitted.	Continuous scale for global IBS symptoms.	5
Kim (2003)[14]	US RCT single-centre study.	Rome II IBS. 25 secondary care patients. 72% female. D 100%.	VSL #3 vs placebo for 8 weeks.	Adequate method of randomisation and concealment. Double blind. No other IBS medications permitted apart from antidepressants.	Continuous scale for global IBS symptoms.	5
Kim (2005)[15]	US RCT single-centre study.	Rome II IBS. 48 patients recruited by advertising or secondary care patients. 94% female. C 33%, D 42%, A 25%. In addition, all had to have bloating score >24 on a 100 mm VAS.	VSL #3 vs placebo for 4—8 weeks.	Adequate method of randomisation and concealment. Double blind. No other IBS medications permitted apart from antidepressants.	Satisfactory relief of IBS symptoms for 50% of weeks.	5
Kim (2006)[28]	Korean RCT, single-centre study.	Author definition of IBS. 40 secondary care patients. 26% female. D 71.6%, A 29.4%.	Medilac DS (*Bacillus subtilis* 1×10^8, *Streptococcus faecium* 9×10^8) vs placebo for 4 weeks.	Method of randomisation and concealment not stated. Blinding not stated. Unclear whether other IBS medications permitted.	Continuous scale for global IBS symptoms.	2

Table 1 Continued

Trial	Design	Participants	Interventions	Methodology	Outcomes	Jadad score
Simren (2007)[29]	Swedish RCT, unclear number of centres.	Rome II IBS. 118 patients. Recruitment unclear. 68% female.	Yoghurt (*Lactobacillus paracasei* ssp. *paracasei*, *Lactobacillus acidophilus* and *Bifidobacterium lactis* (active) all 5×10^7 daily vs placebo for 8 weeks.	Method of randomisation and concealment not stated. Double blind. Unclear whether other IBS medications permitted.	Continuous scale for global IBS symptoms.	3
Long (2006)[30]	Chinese RCT, single-centre study.	Rome II IBS. 60 secondary care patients. 42% female.	*Bifidobacterium* 2×10^8 three times daily+acupuncture vs acupuncture alone for 2 weeks.	Pseudorandomised (alternate consecutive patients), not concealed, not blinded. Unclear whether other IBS medications permitted.	IBS symptoms resolved.	0
Whorwell (2006)[31]	UK RCT, 20 centres.	Rome II IBS. 362 primary care patients. 100% women. C 20.7%, D 55.5%, A 23.8%.	*Bifidobacterium infantis* 35624 1×10^6 vs 1×10^8 vs 1×10^{10} vs placebo for 4 weeks (post hoc analysis suggested higher dose of probiotic was clumped).	Adequate method of randomisation and concealment. Double blind. Loperamide for diarrhoea and bisocodyl for constipation permitted.	Adequate relief of IBS symptoms.	5
Gade (1989)[32]	Danish RCT, 13 centres.	Manning IBS. 54 primary care patients. 78% women. IBS subtypes not stated.	Paraghurt (*Streptococcus faecium*) vs placebo for 4 weeks.	Adequate method of randomisation. Method of concealment unclear. Double blind. Other IBS medications not permitted.	IBS symptoms "significantly improved".	4
Sinn (2008)[33]	Korean RCT, single-centre.	Rome III IBS. 40 secondary care patients. 65% women. C 27.5%, D 10%, A 62.5%.	*Lactobacillus acidophilus*-SDC 2012, 2013 2×10^9 cfu/ml vs placebo for 4 weeks.	Adequate method of randomisation and concealment. Double blind. All other IBS medications discontinued if possible.	Any improvement in abdominal pain measured on a 10-point Likert scale.	5

A, C and D, represent the alternating pattern, constipation-predominant and diarrhoea-predominant subtypes of irritable bowel syndrome (IBS), respectively.
cfu, colony-forming units, RCT, randomised controlled trial; VAS, visual analogue scale.

Review: probiotics for IBS
Comparison: 01 probiotics vs placebo
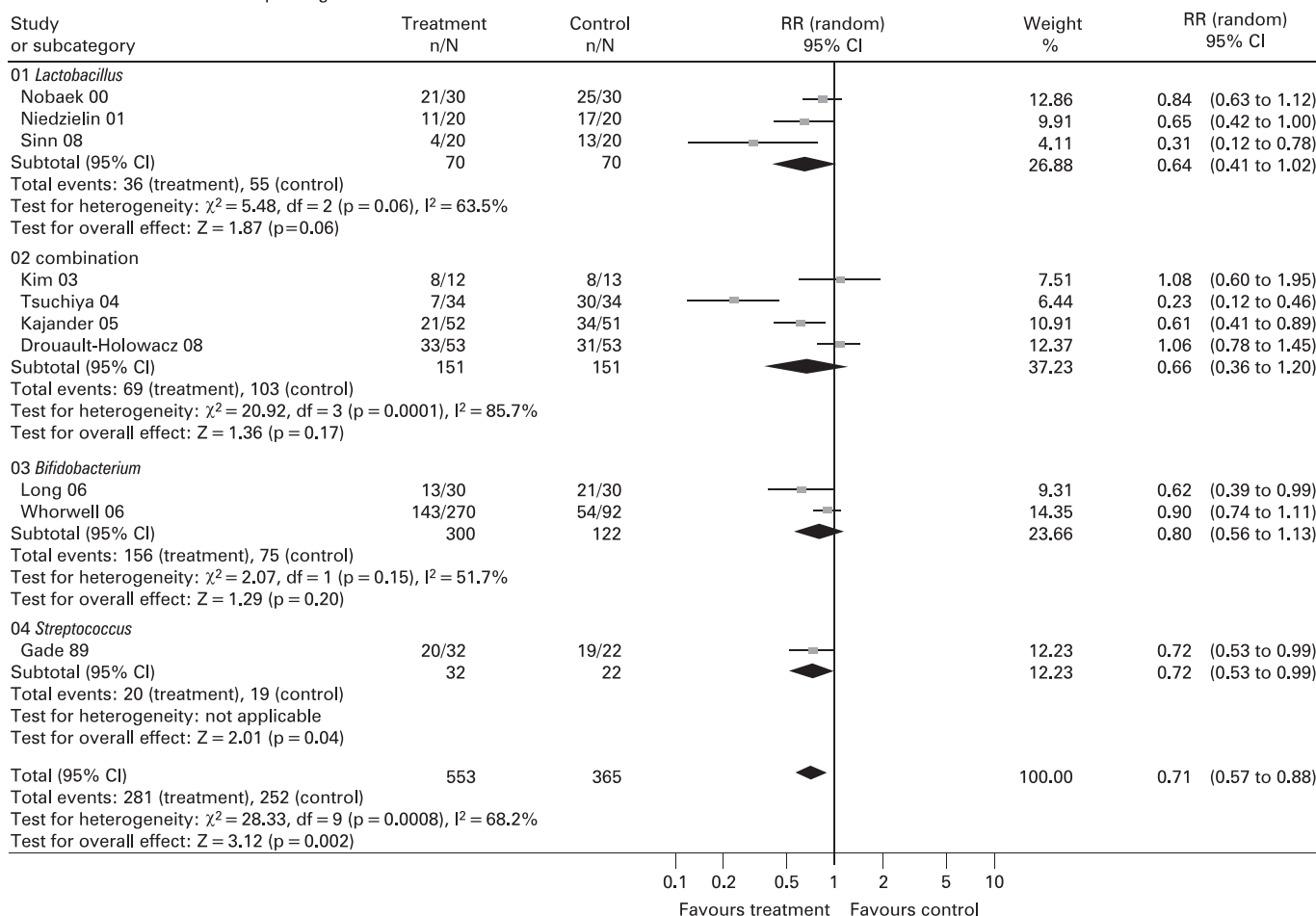Outcome: 01 risk of IBS not improving

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Lactobacillus					
Nobaek 00	21/30	25/30		12.86	0.84 (0.63 to 1.12)
Niedzielin 01	11/20	17/20		9.91	0.65 (0.42 to 1.00)
Sinn 08	4/20	13/20		4.11	0.31 (0.12 to 0.78)
Subtotal (95% CI)	70	70		26.88	0.64 (0.41 to 1.02)
Total events: 36 (treatment), 55 (control)					
Test for heterogeneity: $\chi^2 = 5.48$, df = 2 (p = 0.06), $I^2 = 63.5\%$					
Test for overall effect: Z = 1.87 (p=0.06)					
02 combination					
Kim 03	8/12	8/13		7.51	1.08 (0.60 to 1.95)
Tsuchiya 04	7/34	30/34		6.44	0.23 (0.12 to 0.46)
Kajander 05	21/52	34/51		10.91	0.61 (0.41 to 0.89)
Drouault-Holowacz 08	33/53	31/53		12.37	1.06 (0.78 to 1.45)
Subtotal (95% CI)	151	151		37.23	0.66 (0.36 to 1.20)
Total events: 69 (treatment), 103 (control)					
Test for heterogeneity: $\chi^2 = 20.92$, df = 3 (p = 0.0001), $I^2 = 85.7\%$					
Test for overall effect: Z = 1.36 (p = 0.17)					
03 Bifidobacterium					
Long 06	13/30	21/30		9.31	0.62 (0.39 to 0.99)
Whorwell 06	143/270	54/92		14.35	0.90 (0.74 to 1.11)
Subtotal (95% CI)	300	122		23.66	0.80 (0.56 to 1.13)
Total events: 156 (treatment), 75 (control)					
Test for heterogeneity: $\chi^2 = 2.07$, df = 1 (p = 0.15), $I^2 = 51.7\%$					
Test for overall effect: Z = 1.29 (p = 0.20)					
04 Streptococcus					
Gade 89	20/32	19/22		12.23	0.72 (0.53 to 0.99)
Subtotal (95% CI)	32	22		12.23	0.72 (0.53 to 0.99)
Total events: 20 (treatment), 19 (control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (p = 0.04)					
Total (95% CI)	553	365		100.00	0.71 (0.57 to 0.88)
Total events: 281 (treatment), 252 (control)					
Test for heterogeneity: $\chi^2 = 28.33$, df = 9 (p = 0.0008), $I^2 = 68.2\%$					
Test for overall effect: Z = 3.12 (p = 0.002)					

0.1   0.2   0.5   1   2   5   10
Favours treatment   Favours control

Figure 2   Forest plot of trials comparing probiotics with placebo reporting a dichotomous outcome. IBS, irritable bowel syndrome.
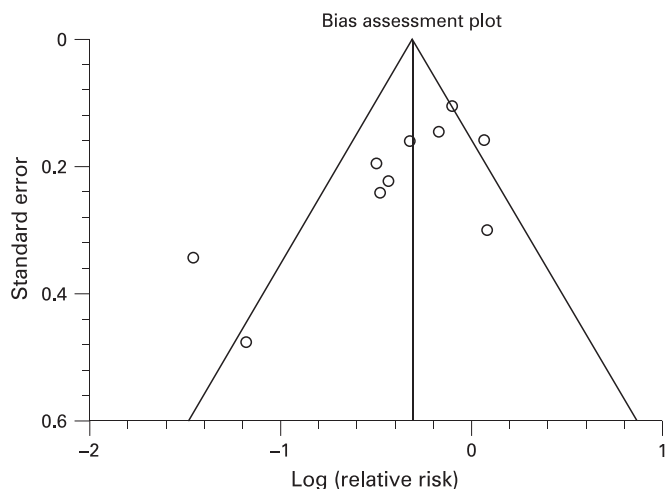
Figure 3 Funnel plot of studies reporting a dichotomous outcome.

review indicates that probiotics have a therapeutic benefit in improving IBS symptoms. The dichotomous data would suggest probiotics are very effective, with an NNT of 4. This is probably an overestimate, however, as there is heterogeneity in these data and possible evidence of funnel plot asymmetry, suggesting there may be publication bias, with an over-representation of small positive studies in the published literature. Furthermore, the higher quality studies reported a more modest treatment effect compared with lower quality trials. In addition, IBS is a condition that is well recognised to have a high placebo response rate to treatment in RCTs, and this may also have contributed to the small number of patients needed to treat to prevent one patient's

symptoms persisting. While the NNT is likely to be >4, studies reporting continuous data still suggest that probiotics are likely to have some impact in reducing IBS symptoms. This is coherent with the effect of probiotics in other gastrointestinal disorders. Probiotics have been shown to reduce the risk of antibiotic-induced gastrointestinal symptoms,[35][36] traveller's diarrhoea,[37] and a systematic review and meta-analysis has demonstrated their efficacy in shortening the duration of illness in infectious diarrhoea compared with placebo or no treatment.[38]

The prevailing paradigms of IBS highlight the role of dysmotility and hypersensitivity.[39] *Lactobacillus paracasei* NCC2461 was reported to attenuate postinfectious intestinal dysmotility in a mouse model.[40] A number of animal models have also shown that probiotics improve visceral hypersensitivity.[41–43] *Lactobacillus acidophilus* NCFM administration induces the expression of cannabinoid and opioid receptors on intestinal cells,[44] and this may explain the effect of probiotics on visceral hypersensitivity. Subtle intestinal inflammation and subsequent neuromodulation have been hypothesised as the underlying pathology driving the pathophysiology of IBS.[45] Probiotics can have potent anti-inflammatory properties,[46] and *Bifidobacterium infantis* 35624 normalised circulating interleukin 12 (IL10) and IL12 levels in IBS patients in an RCT included in this review.[22]

This systematic review has several strengths. A large number of RCTs were identified, and in general the study quality was reasonable. We were also rigorous in obtaining information from the trials. The presentation of the data was not ideal in five papers[14][15][22][25][31] so we obtained additional information from the authors for these. Probiotics have been evaluated in North American, European and Asian patients with IBS in both primary and secondary care. However, there are also a number of
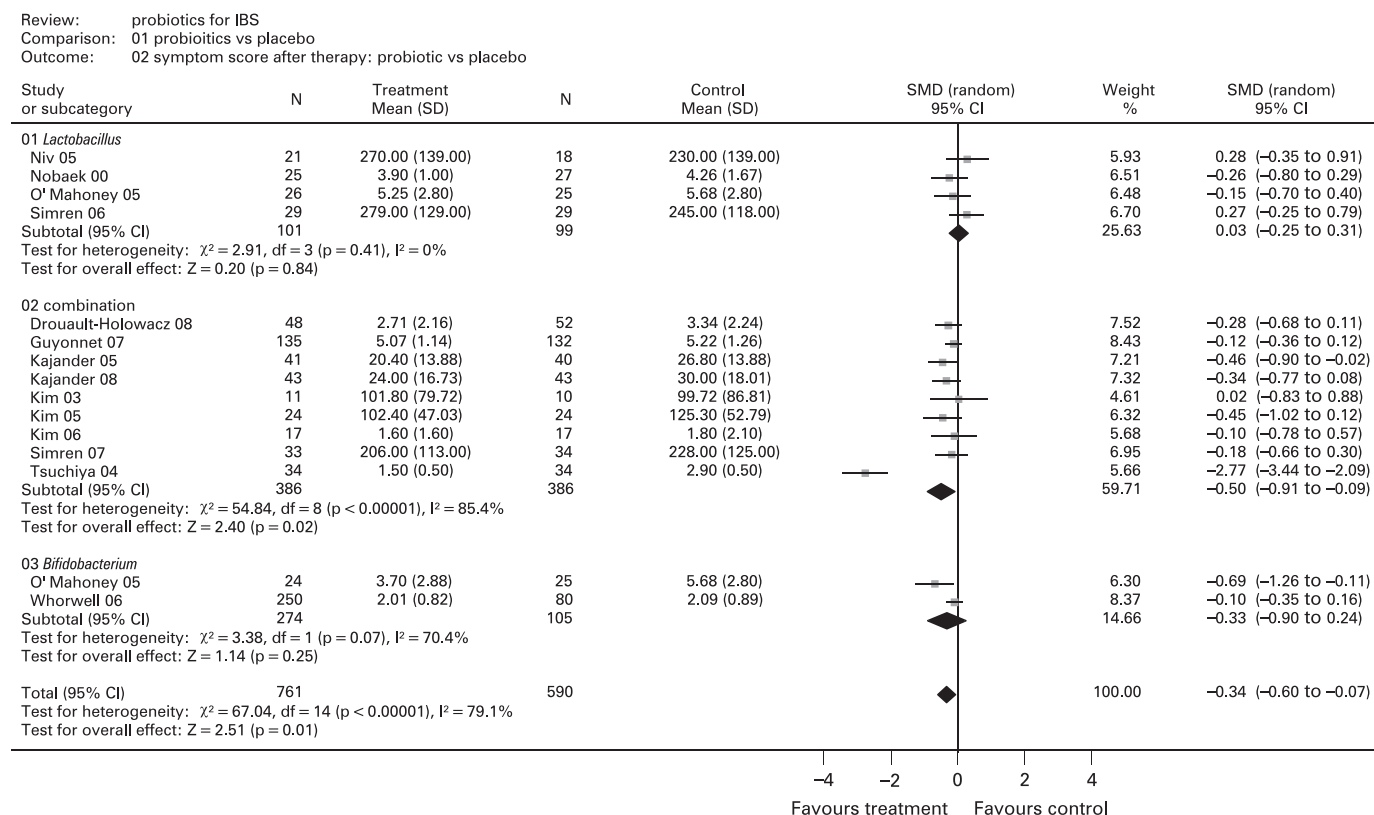
Review: probiotics for IBS
Comparison: 01 probioitics vs placebo
Outcome: 02 symptom score after therapy: probiotic vs placebo

Study or subcategory	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
01 *Lactobacillus*							
Niv 05	21	270.00 (139.00)	18	230.00 (139.00)		5.93	0.28 (−0.35 to 0.91)
Nobaek 00	25	3.90 (1.00)	27	4.26 (1.67)		6.51	−0.26 (−0.80 to 0.29)
O' Mahoney 05	26	5.25 (2.80)	25	5.68 (2.80)		6.48	−0.15 (−0.70 to 0.40)
Simren 06	29	279.00 (129.00)	29	245.00 (118.00)		6.70	0.27 (−0.25 to 0.79)
Subtotal (95% CI)	101		99			25.63	0.03 (−0.25 to 0.31)
Test for heterogeneity: $\chi^2 = 2.91$, df = 3 (p = 0.41), $I^2 = 0\%$							
Test for overall effect: Z = 0.20 (p = 0.84)							
02 combination							
Drouault-Holowacz 08	48	2.71 (2.16)	52	3.34 (2.24)		7.52	−0.28 (−0.68 to 0.11)
Guyonnet 07	135	5.07 (1.14)	132	5.22 (1.26)		8.43	−0.12 (−0.36 to 0.12)
Kajander 05	41	20.40 (13.88)	40	26.80 (13.88)		7.21	−0.46 (−0.90 to −0.02)
Kajander 08	43	24.00 (16.73)	43	30.00 (18.01)		7.32	−0.34 (−0.77 to 0.08)
Kim 03	11	101.80 (79.72)	10	99.72 (86.81)		4.61	0.02 (−0.83 to 0.88)
Kim 05	24	102.40 (47.03)	24	125.30 (52.79)		6.32	−0.45 (−1.02 to 0.12)
Kim 06	17	1.60 (1.60)	17	1.80 (2.10)		5.68	−0.10 (−0.78 to 0.57)
Simren 07	33	206.00 (113.00)	34	228.00 (125.00)		6.95	−0.18 (−0.66 to 0.30)
Tsuchiya 04	34	1.50 (0.50)	34	2.90 (0.50)		5.66	−2.77 (−3.44 to −2.09)
Subtotal (95% CI)	386		386			59.71	−0.50 (−0.91 to −0.09)
Test for heterogeneity: $\chi^2 = 54.84$, df = 8 (p < 0.00001), $I^2 = 85.4\%$							
Test for overall effect: Z = 2.40 (p = 0.02)							
03 *Bifidobacterium*							
O' Mahoney 05	24	3.70 (2.88)	25	5.68 (2.80)		6.30	−0.69 (−1.26 to −0.11)
Whorwell 06	250	2.01 (0.82)	80	2.09 (0.89)		8.37	−0.10 (−0.35 to 0.16)
Subtotal (95% CI)	274		105			14.66	−0.33 (−0.90 to 0.24)
Test for heterogeneity: $\chi^2 = 3.38$, df = 1 (p = 0.07), $I^2 = 70.4\%$							
Test for overall effect: Z = 1.14 (p = 0.25)							
Total (95% CI)	761		590			100.00	−0.34 (−0.60 to −0.07)
Test for heterogeneity: $\chi^2 = 67.04$, df = 14 (p < 0.00001), $I^2 = 79.1\%$							
Test for overall effect: Z = 2.51 (p = 0.01)							

−4 −2 0 2 4
Favours treatment   Favours control

Figure 4 Forest plot of trials comparing probiotics with placebo reporting a continuous outcome. IBS, irritable bowel syndrome; SMD, standardised mean difference.

limitations of this review. The size of the therapeutic effect in the studies reporting dichotomous outcomes is uncertain due to possible publication bias. The heterogeneity in the continuous data is due to one strongly positive study,[25] though it is not clear why this trial, an Italian study evaluating 68 Rome II patients with IBS using a prebiotic and probiotic cocktail, gave different results. There was ambiguity in the paper as to whether this was an RCT, but we determined that there were adequate methods of randomisation and concealment of allocation by contacting the senior author (Dr Marotta, personal communication). The main limitation of this review is that there were a variety of species, strains and doses of probiotics used, and therefore it was difficult to come to any conclusion about the optimum probiotic strategy to use in IBS.[47] Individual probiotics may differ greatly in their effects on host immune function, and the reason for their potential therapeutic efficacy remains unclear. Therefore, combining the effects of probiotics in a meta-analysis may not be an appropriate method of estimating their effect on IBS symptoms. These underlying differences between probiotics may explain some of the heterogeneity we observed when data from individual RCTs were pooled. On the other hand, evaluating all RCTs of probiotics in a systematic review allows the identification of patterns that would not be apparent if trials were considered individually. The dichotomous data suggest that all probiotics have a trend for being efficacious in IBS. The continuous data suggest that Lactobacilli have no impact on symptoms, whilst probiotic combinations improve symptoms in patients with IBS. There was a trend for Bifidobacteria to improve IBS symptoms, but this effect did not reach statistical significance. The review was conservative as we decided a priori to include all doses of probiotics. One trial[31] of *B infantis* 35624 was a dose-ranging study in which the authors found that the preparation methods had resulted in organisms being clumped together in the higher dose and inactivated in a post hoc evaluation. We still included this dose in the analysis and, had we excluded these patients, the Bifidobacteria data would have reached statistical significance. Almost all probiotic combinations contained both Bifidobacteria and Lactobacilli, and the latter did not have an effect in the continuous data meta-analysis. It is therefore possible that Bifidobacteria constitute the active treatment in probiotic combinations. Alternatively it is possible that different species of probiotics are synergistic in promoting a therapeutic effect on IBS.

Future studies need to establish which species, strain and dose of probiotics are most efficacious in IBS. Factorial designed RCTs that compare individual bacterial species with combinations are also required to establish whether probiotics can have a synergistic effect. While we need more information, this systematic review suggests that probiotic treatment is a promising strategy to treat patients with IBS.

Competing interests Declared (the declaration can be viewed on the Gut website at http://www.gut.bmj.com/supplemental).

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Editor's quiz: GI snapshot

An inflammatory condition causing abdominal pain and weight loss

Emad El-Omar, *Editor*

CLINICAL PRESENTATION

A 46-year-old female presented with a history of dysphagia, nausea and postprandial epigastric and right upper quadrant pain. Upper gastrointestinal endoscopy and biopsies were normal. Manometry revealed non-specific oesophageal dysmotility, while ultrasound imaging revealed gallstones. Consequently an extended Heller's myotomy and cholecystectomy was undertaken.

Despite surgical intervention she intermittently experienced dysphagia and recurrent episodes of abdominal pain refractory to analgesics, leading to malnutrition and weight loss necessitating hospital admission for nasogastric feeding, which unfortunately aggravated the symptoms. Small bowel studies, abdominal CT and porphyria screen were negative. Colonoscopy and biopsies were normal, as was magnetic resonance angiography (MRA) of the mesenteric vessels.

The patient subsequently developed postprandial vomiting, resulting in a dramatic decrease in appetite and significant weight loss. A gut transit study revealed delayed transit. The patient was referred for a full-thickness small bowel biopsy (figure 1) and insertion of a surgical feeding jejunostomy.

Figure 1 Small bowel biopsy.

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QUESTION

What is the diagnosis and what is the treatment?