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Probiotics for patients with hepatic encephalopathy (Review)

McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC

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Probiotics for patients with hepatic encephalopathy.
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[Intervention Review]

Probiotics for patients with hepatic encephalopathy

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ABSTRACT

Background

Hepatic encephalopathy is a disorder of brain function as a result of liver failure and/or portosystemic shunt. Both hepatic encephalopathy (clinically overt) and minimal hepatic encephalopathy (not clinically overt) significantly impair patient's quality of life and daily functioning and represent a significant burden on health care resources. Probiotics are live microorganisms, which when administered in adequate amounts may confer a health benefit on the host.

Objectives

To quantify the beneficial and harmful effects of any probiotic in any dosage, compared with placebo or no intervention, or with any other treatment for patients with any grade of acute or chronic hepatic encephalopathy as assessed from randomised trials.

Search methods

We searched the *The Cochrane Hepato-Biliary Group Controlled Trials Register*, *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE*, *Science Citation Index Expanded*, conference proceedings, reference lists of included trials and the WHO international clinical trials registry until April 2011 registry platform to identify new and ongoing trials.

Selection criteria

We included randomised trials that compared probiotics in any dosage with placebo or no intervention, or with any other treatment in patients with hepatic encephalopathy.

Data collection and analysis

Three authors independently assessed the risk of bias of the included trials and extracted data on relevant outcomes, with differences resolved by consensus. We conducted random-effects model meta-analysis due to obvious heterogeneity of patients and interventions. A P value of 0.05 or less was defined as significant. Dichotomous outcomes are expressed as risk ratio (RR) and continuous outcomes as mean difference (MD) with 95% confidence intervals (CI).

Main results

We included seven trials of which 550 participants were randomised. Four of the seven trials compared a probiotic with placebo or no treatment in 245 participants, another trial compared a probiotic with lactulose in 40 participants , and the remaining two trials compared a probiotic with both placebo and lactulose in 265 participants. Each trial used different types of probiotics. Duration of administration of the experimental intervention varied from 10 days to 180 days. Two trials were industry funded, and five were unclear about origin of funding. All trials had high risk of bias.

When probiotics were compared with no treatment, there was no significant difference in all-cause mortality (2 trials, 105 participants; 1/57 (2%) versus 1/48 (2%): RR 0.72; 95% CI 0.08 to 6.60), lack of recovery (4 trials, 206 participants; 54/107 (50%) versus 68/99 (69%): RR 0.72; 95% CI 0.49 to 1.05), adverse events (3 trials, 145 participants; 2/77 (3%) versus 6/68 (9%): RR 0.34; 95% CI 0.08 to 1.42), quality of life (1 trial, 20 participants contributed to the physical quality of life measurement, 20 participants contributed to the mental quality of life: MD Physical 0.00; 95% CI -5.47 to 5.47; MD Mental 4.00; 95% CI -1.82 to 9.82), or change of/or withdrawal from treatment (3 trials, 175 participants; 11/92 (12%) versus 7/83 (8%): RR 1.28; 95% CI 0.52 to 3.19). No trial reported sepsis or duration of hospital stay as an outcome. Plasma ammonia concentration was significantly lower for participants treated with probiotic at one month (3 trials, 226 participants: MD -2.99 µmol/L; 95% CI -5.70 to -0.29) but not at two months (3 trials, 181 participants: MD -1.82 µmol/L; 95% CI -14.04 to 10.41). Plasma ammonia decreased the most in the participants treated with probiotic at three months (1 trial, 73 participants: MD -6.79 µmol/L; 95% CI -10.39 to -3.19).

When probiotics were compared with lactulose no trial reported all-cause mortality, quality of life, duration of hospital stay, or septicaemia. There were no significant differences in lack of recovery (3 trials, 173 participants; 47/87 (54%) versus 44/86 (51%): RR 1.05; 95% CI 0.75 to 1.47), adverse events (2 trials, 111 participants; 3/56 (5%) versus 6/55 (11%): RR 0.57; 95% CI 0.06 to 5.74), change of/or withdrawal from treatment at one month (3 trials, 190 participants; 8/95 (8%) versus 7/95 (7%): RR 1.10; 95% CI 0.40 to 3.03), plasma ammonia concentration (2 trials, 93 participants: MD -6.61 µmol/L; 95% CI -30.05 to 16.84), or change in plasma ammonia concentration (1 trial, 77 participants: MD 1.16 µmol/L; 95% CI -1.96 to 4.28).

Authors' conclusions

The trials we located suffered from a high risk of systematic errors ('bias') and high risk of random errors ('play of chance'). While probiotics appear to reduce plasma ammonia concentration when compared with placebo or no intervention, we are unable to conclude that probiotics are efficacious in altering clinically relevant outcomes. Demonstration of unequivocal efficacy is needed before probiotics can be endorsed as effective therapy for hepatic encephalopathy. Further randomised clinical trials are needed.

PLAIN LANGUAGE SUMMARY

Probiotics for patients with hepatic encephalopathy

Hepatic encephalopathy is a disorder of the brain function as a result of liver failure and/or portosystemic shunt. It results in confusion, drowsiness, coma, and in some patients, in death. While the cause of hepatic encephalopathy is not fully understood, it is thought to develop as a result of the failure to clear various toxic substances, such as ammonia, from the blood, either because of poor function of the liver cells or because the blood from the intestine is shunted around the liver and is not seen by the liver cells. Protein metabolising bacterial species in the intestine of hepatic encephalopathy patients contribute to ammonia production. Probiotics are live microorganisms who may reduce the prevalence of these harmful ammonia-producing bacteria. This review identified seven trials of which 550 participants were randomised. Each trial used different types of probiotics. Duration of administration of the experimental intervention varied from 10 days to 180 days. The authors of the review assessed a range of outcomes including death, recovery, adverse events, and quality of life. There was no benefit of probiotics shown for any of the primary outcomes including mortality. The authors of the review found a significant difference in plasma ammonia concentration after one month, and a significant change in plasma ammonia concentration at three months treatment compared with no treatment. However, this finding is of questionable importance. Therefore, the use of probiotics for patients with hepatic encephalopathy cannot be currently recommended. Furtehr randomised clinical trials are required.

Summary of findings for the main comparison. Probiotic versus placebo/ no intervention for patients with hepatic encephalopathy

Probiotic versus placebo/ no intervention for patients with hepatic encephalopathy

Patient or population: patients with patients with hepatic encephalopathy.
Settings: inpatients.
Intervention: probiotic versus placebo/ no intervention.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Probiotic versus placebo/ no intervention				
All cause mortality Follow-up: 2 to 3 months	**Study population**		**RR 0.72** (0.08 to 6.60)	105 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	21 per 1000	**21 per 1000** (2 to 189)				
	Low					
	0 per 1000	**0 per 1000** (0 to 0)				
	High					
	25 per 1000	**25 per 1000** (3 to 227)				
No recovery (incomplete resolution of clinical symptoms) Follow-up: 1 to 3 months	**Study population**		**RR 0.72** (0.49 to 1.05)	206 (4 studies)	⊕⊕⊖⊖ **low**[1,3]	
	687 per 1000	**488 per 1000** (323 to 742)				
	Low					
	500 per 1000	**355 per 1000** (235 to 540)				
	High					

	900 per 1000	**639 per 1000** (423 to 972)				
Number of adverse events Follow-up: 1 to 3 months	**Study population**		**RR 0.34** (0.08 to 1.42)	145 (3 studies)	⊕⊕⊖⊖ **low**[1,3]	
	88 per 1000	**26 per 1000** (4 to 141)				
	Low					
	0 per 1000	**0 per 1000** (0 to 0)				
	High					
	250 per 1000	**72 per 1000** (13 to 400)				
Quality of life SF-36 physical/ mental Follow-up: median 2 months	See comment	See comment	Not estimable	40 (1 study)	⊕⊕⊖⊖ **low**[1,3]	The results of a single study cannot be pooled.
Change of/or withdrawal from treatment Follow-up: 1 to 3 months	**Study population**		**RR 1.28** (0.52 to 3.19)	175 (3 studies)	⊕⊕⊖⊖ **low**[1,3]	
	84 per 1000	**121 per 1000** (47 to 308)				
	Low					
	0 per 1000	**0 per 1000** (0 to 0)				
	High					
	110 per 1000	**157 per 1000** (62 to 402)				
Plasma ammonia concentration (µmol/L) Follow-up: 1 to 2 months		The mean plasma ammonia concentration (µmol/l) in the intervention groups was **2.99 lower** (5.7 to 0.29 lower)		226 (3 studies)	⊕⊖⊖⊖ **very low**[1,2,4]	

Change in plasma ammonia concentration (μmol/L)	See comment	See comment	Not estimable	73 (1)	See comment	The results of a single study cannot be pooled.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Studies judged as high risk of bias.
[2] Inconsistent interventions.
[3] Wide confidence intervals.
[4] Surrogate marker for clinically important outcomes.

Summary of findings 2. Probiotic versus lactulose for hepatic encephalopathy

Probiotic versus lactulose for hepatic encephalopathy

Patient or population: patients with hepatic encephalopathy.
Settings: inpatients.
Intervention: probiotic versus lactulose.

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Probiotic versus lactulose**				
No recovery (incomplete resolution of clinical symptoms) Follow-up: median 1 months	**Study population**		**RR 1.05** (0.75 to 1.47)	173 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	
	512 per 1000	**532 per 1000** (373 to 747)				
	Low					
	450 per 1000	**468 per 1000**				

		(329 to 657)			
	High				
	600 per 1000	**624 per 1000** (438 to 876)			
Number of adverse events Follow-up: mean 1 months	**Study population**		**RR 0.57** (0.06 to 5.74)	111 (2 studies)	⊕⊕⊝⊝ **low**[1,3]
	109 per 1000	**56 per 1000** (5 to 559)			
	Low				
	100 per 1000	**51 per 1000** (5 to 512)			
	High				
	250 per 1000	**128 per 1000** (13 to 1000)			
Change of/or withdrawal from treatment Follow-up: median 1 months	**Study population**		**RR 1.10** (0.40 to 3.03)	190 (3 studies)	⊕⊕⊝⊝ **low**[1,3]
	74 per 1000	**71 per 1000** (25 to 203)			
	Low				
	90 per 1000	**86 per 1000** (31 to 248)			
	High				
	110 per 1000	**106 per 1000** (37 to 302)			
Plasma ammonia concentration (µmol/L) Follow-up: median 1 months		The mean plasma ammonia concentration (µmol/l) in the intervention groups was **6.61 lower** (30.05 lower to 16.84 higher)		93 (2 studies)	⊕⊝⊝⊝ **very low**[1,2,3,4]

Change in plasma ammonia concentration (μmol/L) Follow-up: mean 3 months		The mean change in plasma ammonia concentration (μmol/l) in the intervention groups was **1.16 higher** (1.96 lower to 4.28 higher)	77 (1 study)	⊕⊖⊖⊖ **very low**[1,3,4]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Studies judged as high risk of bias.
[2] Inconsistent interventions.
[3] Wide confidence intervals.
[4] Surrogate marker for clinically important outcomes.

BACKGROUND

Description of the condition

Hepatic encephalopathy (also known as portosystemic encephalopathy) is a reversible neuropsychiatric disorder seen in the context of either acute or chronic liver failure or portosystemic shunting, or both (Ferenci 2002). Hepatic encephalopathy is characterised by complex cognitive dysfunction, which is independent of sleep dysfunction or problems with overall intelligence (Blei 2001). Minimal hepatic encephalopathy (MHE) is a milder form of the same condition, which does not have obvious clinical signs (Stewart 2007; Bajaj 2011). The onset of hepatic encephalopathy indicates a poor prognostic outcome. It may also reduce quality of life and level of daily functioning (Groeneweg 1998; Arguedas 2003). The pathophysiology of hepatic encephalopathy is still uncertain, but the prevailing assumption is that different toxins, such as false neurotransmitters, natural benzodiazepines, short chain fatty acids, and mercaptans enhance the negative effects of ammonia on the level of consciousness (Butterworth 1987; Blei 2001; Vaquero 2003). Current therapeutic options include intensive supportive care, identification and correction of the precipitating causes, tailored dietary restrictions, non-absorbable disaccharides, L-ornithine L-aspartate, and/or oral antibiotics (Riordan 1997; Blei 2001; Als-Nielsen 2003; Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2004c; Jiang 2009).

Description of the intervention

Probiotics are live microorganisms, which when administered in adequate amounts may confer a health benefit on the host (Schrezenmeir 2001). However, the dose needed to confer a health benefit is unknown for many conditions. Probiotics commonly come from two groups of bacteria, *Lactobacillus* or *Bifidobacterium*. Within each group, there are different species (for example, *Lactobacillus acidophilus* and *Bifidobacterium bifidus*), and within each species, different strains (or varieties). A few common probiotics, such as *Saccharomyces boulardii*, are yeasts, which are different from bacteria. Therapeutic effects may be strain specific, and so caution must be exerted in generalising results from one species to another. While probiotics are generally considered safe, adverse events have been attributed to their use (Besselink 2008).

How the intervention might work

There is some evidence for an alteration in the composition of the gastrointestinal bacterial flora of patients with liver disease (Rolfe 2000). Amongst other potential reasons, one rationale behind the use of probiotics for hepatic encephalopathy is to reduce the prevalence of harmful ammonia-producing bacteria in the gastrointestinal system.

Why it is important to do this review

Hepatic encephalopathy significantly impairs patient's quality of life and daily functioning (Groeneweg 1998; Arguedas 2003). Caring for and treating patients with hepatic encephalopathy is a significant burden on the health care system. In 2003 hepatic encephalopathy cost the US health-care system an estimated $932 million (Poordad 2007). Previous Cochrane Hepato-Biliary Group systematic reviews have only shown moderate, and in some cases, no benefit for current therapies for hepatic encephalopathy, which include non-absorbable disaccharides and oral antibiotics (Als-Nielsen 2003; Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2004c).

OBJECTIVES

To determine the beneficial and harmful effects associated with the use of probiotics in any dosage, compared with placebo or no intervention or with any other treatment for patients with any grade of acute or chronic hepatic encephalopathy. This review does not consider the primary prophylaxis of hepatic encephalopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials that compared probiotics with placebo or no intervention, or with any other treatment for patients with hepatic encephalopathy. We did not apply any restrictions on language of publication, publication date, or publication status. We excluded quasi-randomised trials.

Types of participants

Inclusion criteria

We included all patients with any grade of acute or chronic hepatic encephalopathy in connection with acute and chronic liver disease as well as acute hepatic failure, no matter the aetiology of liver disease or factors precipitating the hepatic encephalopathy.

Exclusion criteria

We excluded trials with patients in whom a diagnosis of hepatic encephalopathy was not confirmed, ie, where altered mental status or cognitive function was not confirmed by a standardised neuropsychological assessment. Where co-interventions such as medication was being administered, they had to be administered equally across the relevant intervention groups of the trial, so that fair comparisons could be made.

Types of interventions

Any probiotic at any dose for any duration. Additional co-interventions were allowed if received by all trial intervention groups and were deemed sufficiently similar across trial groups. Where synbiotics were used (a combination of a prebiotic and a probiotic), the control group must have received a similar prebiotic to be included in the review; such that across trial groups, the difference in intervention(s) was probiotic alone. For example, probiotic and lactulose versus antibiotic plus lactulose. Here the comparison would have been probiotics versus antibiotic. If a trial compared probiotics and prebiotics versus prebiotics, the trial would have been considered a probiotic versus placebo trial, as the difference between the two groups would have been probiotic alone. A prebiotic is a substance that stimulates the growth of probiotics.

Types of outcome measures

All outcomes were assessed at time points reported by authors, but, where possible, also summarised at one, two, three, six months, and one year.

Primary outcomes

1. All-cause mortality: number of participants dead.

2. Number of participants who did not recover from hepatic encephalopathy (defined as incomplete resolution of clinical symptoms).
3. Adverse events: number and type of adverse events defined as patients with any untoward medical occurrence. We summarised adverse events that lead to treatment discontinuation and those that did not lead to treatment discontinuation separately. Serious adverse events were defined according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that led to death, was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event, which may have jeopardised the patient or required intervention to prevent it. All other adverse events were considered non-serious.
4. Quality of life: as measured by the SF-36 scale or other similar validated scales (Brazier 1992; Ware 1994).

Secondary outcomes

1. Change of or withdrawal from treatment: number of participants who changed/withdrew from their allocated treatment regimen.
2. Sepsis: the number of participants with one or more episodes of sepsis (confirmed by a positive blood culture).
3. Change in plasma ammonia concentration.
4. Duration of stay in hospital: measured in days.

Search methods for identification of studies

Electronic searches

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register,* the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE* (Ovid SP), *EMBASE* (Ovid SP), and *Science Citation Index Expanded* (Web of Science) (Royle 2003). The search strategies with the time span of the searches are given in Appendix 1. The search filter for randomised trials in MEDLINE (via Ovid SP) was created by Lefebvre 2011, and the search filter for randomised trials in EMBASE (via Ovid SP) was created by Sharon 2006.

We also searched the World Health Organisation (WHO) international clinical trials registry platform for ongoing and unpublished trials (October 2010) (http://apps.who.int/trialsearch/AdvSearch.aspx) using an advanced search for the condition 'hepatic encephalopathy' and intervention 'probiotic'.

Searching other resources

We hand-searched the proceedings of three relevant conferences:
1. The American Association for the Study of Liver Disease (AASLD) from 2005 to 2009.
2. The European Association for the Study of the Liver (EASL) from 2005 to 2010.
3. Digestive Diseases Week (DDW) from 2005 to 2010, using the following keywords: 'hepatic encephalopathy', 'probiotic', 'bifidobacterium', 'lactobacillus', and 'liver disease'.

We identified further trials through reference lists of relevant articles and by contacting content experts and authors of included trials. We applied no date or language restrictions. We translated non-English language articles using Google translate (http://translate.google.com.au/).

Data collection and analysis

Selection of studies

Three authors, working independently of one another, conducted trial selection and data extraction. None of them was blinded to journal or author names. Authors resolved disagreements by consensus.

Data extraction and management

We extracted the following information using a standardised data extraction form:
• General information: author(s), title, source, contact address, year of trial, country of trial, language of publication, year of publication.
• Trial characteristics: design (randomised clinical trial), randomisation method, manner of recruitment, sampling method, duration of intervention period, length of follow up, reason for and number of dropouts and withdrawals, adverse events.
• Patients: baseline characteristics of participants in treatment groups such as sex, age, prevalence of co-morbidities (eg, diabetes), inclusion and exclusion trial criteria.
• Trial setting: eg, in-patient/out-patient department, emergency department.
• Detailed description of both the intervention and the comparison intervention, type, dose, and duration of probiotic(s).
• Outcomes: specific outcome reported, assessment instrument used, scoring range where appropriate.
• Any co-interventions.

We entered data into Review Manager 5 software (RevMan 2011) and checked the data for accuracy.

Assessment of risk of bias in included studies

Methodological quality was defined as the confidence that the design and the report of the randomised clinical trial would restrict bias in the comparison of the intervention (Moher 1998). According to empirical evidence (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008), the methodological quality of the trials, hence risk of bias, was based on the following domains:

Sequence generation

- Low risk of bias: the methods used was either adequate eg, computer-generated random numbers, table of random numbers or unlikely to introduce bias.
- Uncertain risk of bias: there was insufficient information to assess whether the method used was likely to introduce confounding.
- High risk of bias: the method used was not best practise for randomisation.

Allocation concealment

- Low risk of bias: the method used (eg, central allocation) was unlikely to induce bias on the final observed effect.
- Uncertain risk of bias: there was insufficient information to assess whether the method used was likely to induce bias on the estimate of effect.
- High risk of bias: the method used (eg, open random allocation schedule) was likely to induce bias on the final observed effect.

Blinding of participants

- Low risk of bias: blinding was performed adequately, or the outcome was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether the type of blinding used was likely to induce bias on the effect.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding.

Blinding of personnel

- Low risk of bias: blinding was performed adequately, or the outcome was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether the type of blinding used was likely to induce bias on the effect.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: blinding was performed adequately, or the outcome measurement was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether the type of blinding used was likely to induce bias on the estimate of effect.
- High risk of bias: no blinding or incomplete blinding, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: the underlying reasons for missing data were unlikely to make treatment effects depart from plausible values, or appropriate methods have been employed to handle missing data.
- Uncertain risk of bias: there was insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data was likely to induce bias on the estimate of effect.
- High risk of bias: the crude estimate of effects (eg, complete case estimate) were clearly biased due to the underlying reasons for missing data, and the methods used to handle missing data were unsatisfactory.

Selective outcome reporting

- Low risk of bias: the trial protocol was available or the study author provided further information about pre-specified outcomes and all of the trial's pre-specified outcomes that were of interest in the review were reported or similar.
- Uncertain risk of bias: there was insufficient information to assess whether the magnitude and direction of the observed effect were related to selective outcome reporting.
- High risk of bias: not all of the trial's pre-specified primary outcomes were reported or similar.

Other bias

- Low risk of bias: the trial was independently funded, eg, by a government organisation or university.
- Uncertain risk of bias: the trial did not declare its funding source.
- High risk of bias: the trial was industry funded, eg, by a pharmaceutical company or an author was an employee of a pharmaceutical company.

Trials judged as having 'low risk of bias' in all of the specified individual domains were considered 'trials with low risk of bias'. Trials judged as having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified individual domains were considered 'trials with high risk of bias'. Authors of the original reports were contacted to provide further details when any of the above information was unclear.

Measures of treatment effect

We conducted data analysis according to the guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2011).

Dichotomous data: we presented results as summary risk ratio (RR) with 95% confidence intervals (CI).
Continuous data: we presented results as mean difference (MD) if outcomes were measured in the same way amongst trials.

Dealing with missing data

Data for all participants were analysed in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports, participants were not analysed in the group to which they were randomised and there was sufficient information in the trial report, we attempted to restore them to the correct group, ie, intention-to-treat analysis was conducted where it was possible to do so. Where data were missing, we sought clarification from the authors of the trial. If intention-to-treat analysis was not possible, we conducted available case analysis or per protocol analysis.

Assessment of heterogeneity

We assessed heterogeneity amongst trials, when appropriate, using the I^2 and Cochran Q statistics. Where substantial heterogeneity was detected (I^2 more than 50% or P less than 0.10), we explored it by pre-specified subgroup analysis and sensitivity analysis.

Assessment of reporting biases

Where reporting bias was suspected (see selective reporting bias above), we made an attempt to contact trial authors to provide missing outcome data. When missing data were thought to potentially introduce serious bias, the impact of including such trials in the overall assessment of results was explored by a sensitivity analysis. Funnel plot asymmetry was used to assess the existence of bias where there were at least ten trials.

Data synthesis

We conducted statistical analysis with random-effects model meta-analyses using the Review Manager 5 software (RevMan 2011). Random-effects models were used for all analyses where trials examined the same intervention, and the trials populations and methods were judged sufficiently similar. We originally planned to conduct also fixed-effect model meta-analysis, but abstained due

to obvious heterogeneity of patients and intervention. A P value of 0.05 or less was defined as significant.

Subgroup analysis and investigation of heterogeneity

Priori subgroup analyses were:
- Type of probiotic (by genus): *Lactobacillus*, *Bifidobacteria*, mixed, or unclear.
- Grade of hepatic encephalopathy: minimal compared to overt.
- Duration of therapy.
- MELD (model for end-stage liver disease) score.
- Co-interventions used.
- Trials with low risk of bias compared to trials with high risk of bias.

We assessed differences among subgroups by test of interaction (Altman 1996).

Sensitivity analysis

We carried out sensitivity analysis when significant heterogeneity was detected (I^2 more than 50% or P less than 0.10) to determine the source, that is trials were sequentially removed from the analysis to determine which trial or trials were contributing to the heterogeneity.

RESULTS

Description of studies

Results of the search

The process of identifying randomised clinical trials for inclusion in the review is outlined in Figure 1.

Figure 1. Study flow diagram.

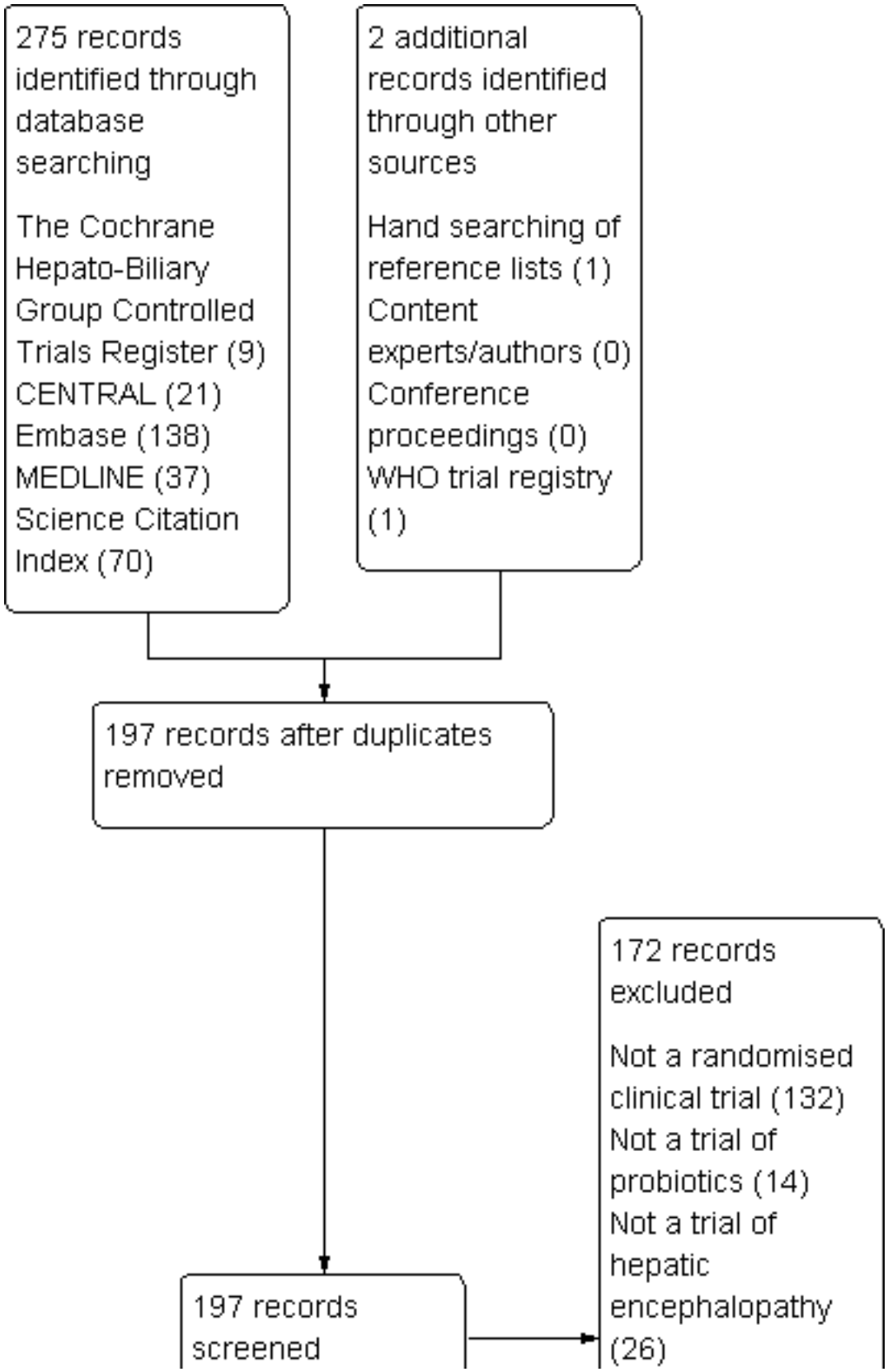


Figure 1. (Continued)

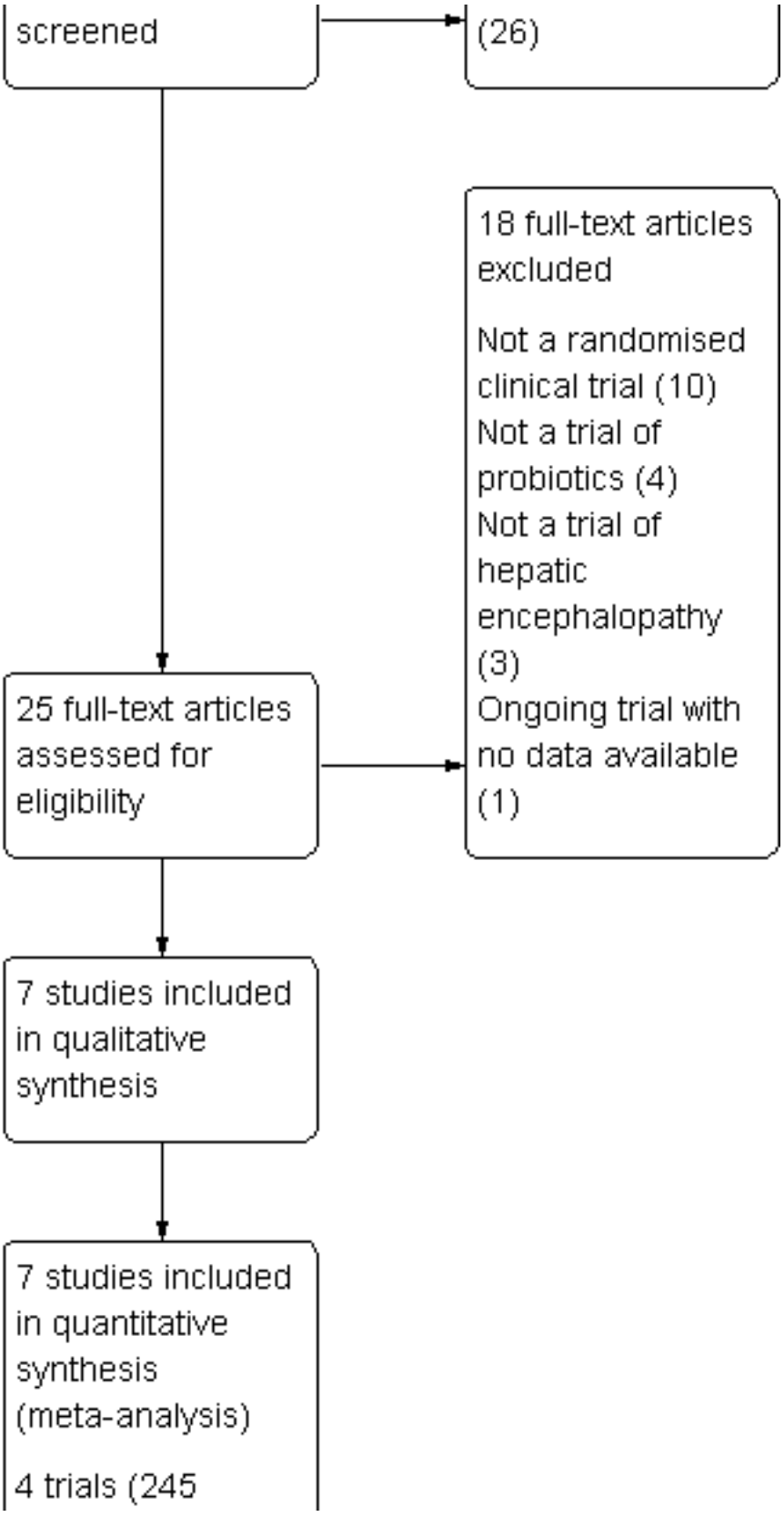
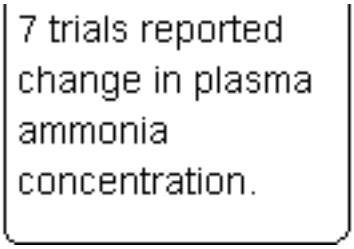


Figure 1. (Continued)

4 trials (245 participants) compared probiotic to placebo/no intervention. 1 trial (40 participants) compared probiotic to lactulose. 2 trial (265 participants) compared probiotic to placebo and lactulose.	2 trials reported all cause mortality. 5 trials reported recovery. 5 trials reported adverse events. 1 trial reported quality of life. 4 trials reported change of/or withdrawal from treatment. 1 trial reported sepsis. 7 trials reported

Figure 1. (Continued)



The electronic searches of The Cochrane Hepato-Biliary Group Controlled Trials Register (n = 9), the Cochrane Central Register of Controlled Trials (n = 21), MEDLINE (n = 37), EMBASE (n = 138), and Science Citation Index Expanded (n = 70) identified a total of 275 publications. Two additional trials were identified from reference lists and trial registry searching. Hand searching of conference proceedings, contacting content experts and authors produced no extra trials. After excluding duplicates, 197 unique records remained. Of these 172 were excluded after reviewing titles and abstracts and of the remaining 25 publications, which were assessed after reviewing their full texts, a further 18 trials were excluded. Therefore, a total of seven trials reported in nine publications were included in the review.

One of these seven trials (Mittal 2009) was available as an abstract, whilst the remaining six trials were published in four different journals. One ongoing trial (Sharma 2010) was identified; therefore, the results were not available for use in the review. However, information about the trial is provided in the characteristics of ongoing studies table (Characteristics of ongoing studies).

Included studies

Of the seven included trials, four trials compared a probiotic with placebo or no treatment in 245 participants (Liu 2004; Bajaj 2008; Malaguarnera 2010; Pereg 2011). One trial compared a probiotic with lactulose in 40 participants (Loguercio 1987). Two trials compared a probiotic both with placebo and with lactulose in 265 participants (Mittal 2009; Sharma 2008). Each trial used different probiotics see Table 1.

Five trials enrolled participants with minimal hepatic encephalopathy (Liu 2004; Bajaj 2008; Sharma 2008; Mittal 2009; Pereg 2011) and two trials enrolled participants with overt hepatic encephalopathy (grade I or II according to the West-Haven criteria) (Loguercio 1987; Malaguarnera 2010).

Excluded studies

A total of 190 records were excluded.

Risk of bias in included studies

Reporting of trial methodology was incomplete for the majority of the domains as summarised in Figure 2 and Figure 3. Therefore, we classified all trials as having a high risk of bias.

Figure 2. Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

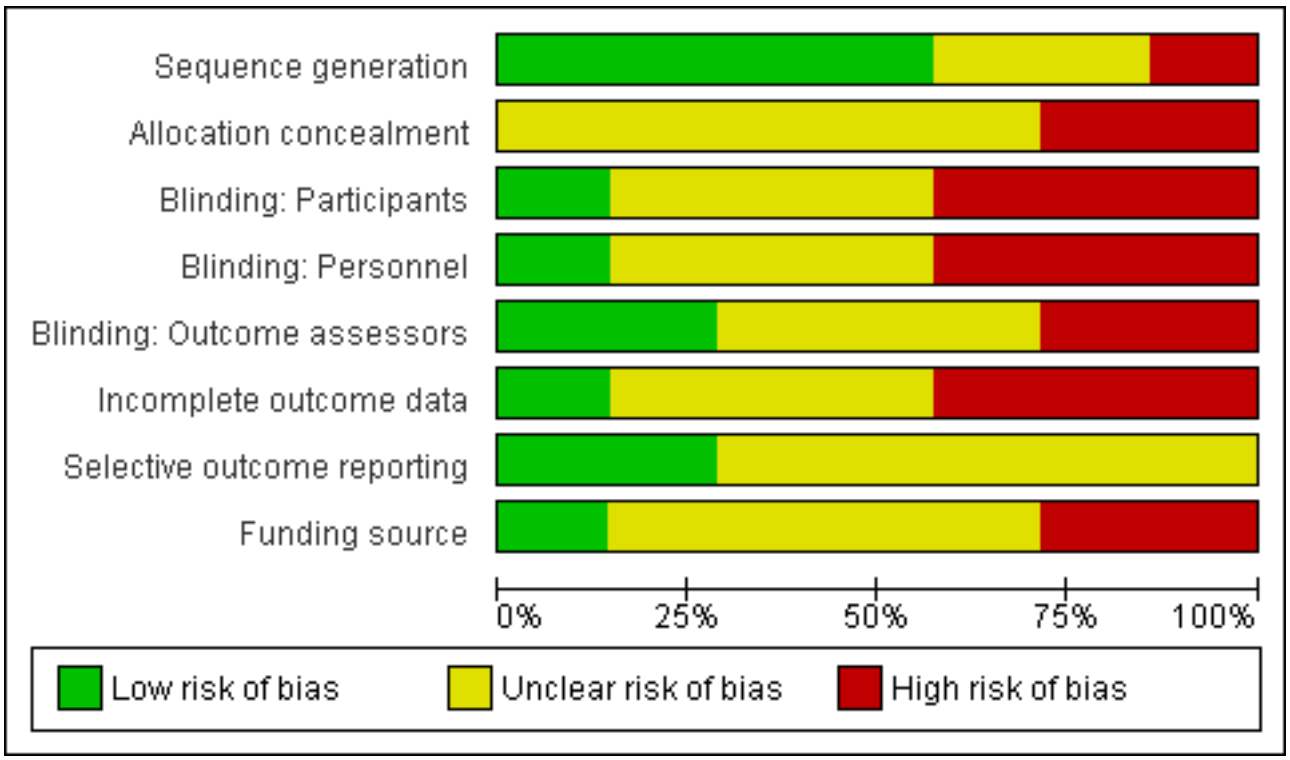
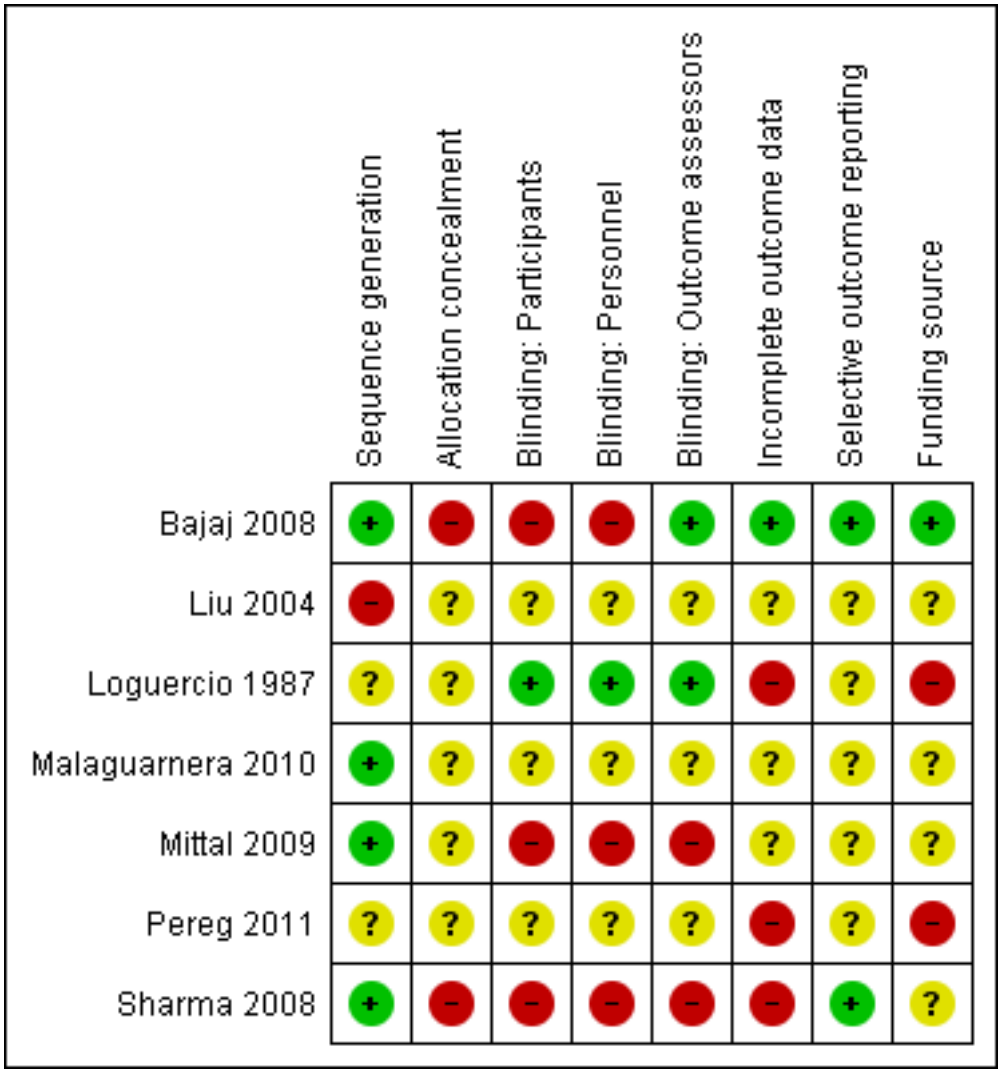


Figure 3. Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



Allocation

Sequence generation was adequately performed in four trials (Bajaj 2008; Sharma 2008; Mittal 2009; Malaguarnera 2010), inadequately performed in one trial (Liu 2004), and unclear in two trials (Loguercio 1987; Pereg 2011).

No trial reported adequate allocation concealment. Two trials reported inadequate allocation concealment (Bajaj 2008; Sharma 2008), and five trials were unclear about their method of allocation concealment (Loguercio 1987; Liu 2004; Mittal 2009; Malaguarnera 2010; Pereg 2011).

Blinding

One trial adequately reported blinding of participants, outcome assessors, and personnel (Loguercio 1987). One trial adequately reported blinding of outcome assessors, but no blinding of participants and personnel (Bajaj 2008). Two trials did not blind participants, personnel, or outcome assessors (Sharma 2008; Mittal 2009). The remaining trials were unclear concerning the conduct of blinding (Liu 2004; Malaguarnera 2010; Pereg 2011).

Incomplete outcome data

Incomplete outcome data were adequately addressed in one trial (Bajaj 2008), inadequately in three (Loguercio 1987; Sharma 2008; Pereg 2011), while the remainder were unclear (Liu 2004; Mittal 2009; Malaguarnera 2010).

Selective reporting

Two trials were free of selective outcome reporting (Bajaj 2008; Sharma 2008), while the remainder were unclear (Loguercio 1987; Liu 2004; Mittal 2009; Malaguarnera 2010; Pereg 2011).

Other potential sources of bias

Three trials declared their funding source (Loguercio 1987; Bajaj 2008; Pereg 2011). One of these trials was independently funded (Bajaj 2008), and two were industry funded (Loguercio 1987; Pereg 2011). The remainder did not disclose their funding source (Liu 2004; Sharma 2008; Mittal 2009; Malaguarnera 2010).

Effects of interventions

See: **Summary of findings for the main comparison** Probiotic versus placebo/ no intervention for patients with hepatic encephalopathy; **Summary of findings 2** Probiotic versus lactulose for hepatic encephalopathy

Probiotic versus no treatment

Primary outcomes

There were no significant differences in all-cause mortality (Analysis 1.1; 2 trials, 105 participants, RR 0.72, 95% CI 0.08 to 6.60) or in lack of recovery (Analysis 1.2; 4 trials, 206 participants: RR 0.72; 95% CI 0.49 to 1.05). At one, two, and three months there was no significant differences in number of adverse events (Analysis 1.3; 3 trials, 145 participants: RR 0.34; 95% CI 0.08 to 1.42). There was no evidence of a difference in quality of life (either physical or mental) at two months (Analysis 1.4; 1 trial, 20 participants contributed to the physical quality of life measurement, 20 participants contributed to the mental quality of life: MD Physical 0.00; 95% CI -5.47 to 5.47, MD Mental 4.00; 95% CI -1.82 to 9.82).

Secondary outcomes

There were no significant differences in change of/or withdrawal from treatment at one, two, and three months (Analysis 1.5; 3 trials, 175 participants: RR 1.28; 95% CI 0.52 to 3.19). No trial reported sepsis as an outcome. Plasma ammonia concentration was significantly lower for participants treated with probiotic than with no intervention at one month (Analysis 1.6 (Analysis 1.6.1)); 3 trials, 226 participants: MD -2.99 µmol/L; 95% CI -5.70 to -0.29) but not at two months when compared with no intervention (Analysis 1.6 (Analysis 1.6.2)); 3 trials, 181 participants: MD -1.82 µmol/L; 95% CI -14.04 to 10.41). Plasma ammonia decreased the most at three months in the participants treated with probiotic compared with no intervention (Analysis 1.7; 1 trial, 73 participants: MD -6.79 µmol/L; 95% CI -10.39 to -3.19). Duration of hospital stay was not reported in any trial.

Subgroup analysis

Subgroup analyses were performed for the outcomes 'no recovery' (Analysis 1.2) and plasma ammonia concentration (Analysis 1.6) using the prespecified subgroups (Subgroup analysis and investigation of heterogeneity). Subgroup analyses could not be performed by MELD score, as this was not reported in the trials. Nor could it be performed by risk of bias, as all trials were judged as suffering from high risk of bias.

No recovery

A significant difference was detected for the subgroup analysis on duration of therapy (Analysis 1.10), test for subgroup differences: $Chi^2 = 9.21$, df = 2 (P = 0.01).

No significant differences were detected for the following subgroup analyses: type of probiotic used (Analysis 1.8), test for subgroup differences: $Chi^2 = 1.17$, df = 1 (P = 0.28); grade of hepatic encephalopathy (Analysis 1.9), test for subgroup differences: $Chi^2 = 1.93$, df = 1 (P = 0.16); and co-interventions used (Analysis 1.11), test for subgroup differences: $Chi^2 = 1.94$, df = 2 (P = 0.38).

Plasma ammonia

No significant differences were detected for the following subgroup analyses: type of probiotic used (Analysis 1.12), test for subgroup differences: $Chi^2 = 1.83$, df = 1 (P = 0.18); grade of hepatic encephalopathy (Analysis 1.13), test for subgroup differences: $Chi^2 = 2.05$, df = 1 (P = 0.15); duration of therapy (Analysis 1.14), test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.87); and co-interventions used (Analysis 1.15), test for subgroup differences: $Chi^2 = 5.60$, df = 2 (P = 0.06).

Heterogeneity

Heterogeneity was demonstrated for the outcome 'no recovery' Analysis 1.2 ($Chi^2 = 6.93$, df = 3; P=0.07, $I^2 = 57\%$) and seemed largely attributable to duration of therapy (Analysis 1.10). Heterogeneity was demonstrated for the outcome plasma ammonia concentration at two months Analysis 1.6 ($Chi^2 = 6.16$, df = 2; P = 0.05, $I^2 = 68\%$) and did not seem attributable to type of probiotic used (Analysis 1.12), grade of hepatic encephalopathy (Analysis 1.13), grade of hepatic encephalopathy (Analysis 1.13), or co-interventions used (Analysis 1.15).

Probiotic versus lactulose

Primary outcomes

The three trials that compared probiotic with lactulose did not report all-cause mortality (Mittal 2009 provided information about mortality in the probiotic arm but not the lactulose arm), and we were unable to obtain these data from the authors. There was no significant difference in lack of recovery (Analysis 2.1; 3 trials, 173 participants: RR 1.05; 95% CI 0.75 to 1.47). There was no significant difference in the number of adverse events (Analysis 2.2; 2 trials, 111 participants: RR 0.57; 95% CI 0.06 to 5.74). Quality of life was not reported in either trial.

Secondary outcomes

There was no significant difference in change of/or withdrawal from treatment at one month (Analysis 2.3; 3 trials, 190 participants: RR 1.10; 95% CI 0.40 to 3.03). There were no reports of septicaemia attributable to probiotic in any trial. At one month there was no significant difference in plasma ammonia concentration (Analysis 2.4; 2 trials, 93 participants: MD -6.61 µmol/L; 95% CI -30.05 to 16.84) or change in plasma ammonia concentration (Analysis 2.5; 1 trial, 77 participants: MD 1.16 µmol/L; 95% CI -1.96 to 4.28). Duration of hospital stay was not reported in any trial.

Subgroup analysis

Subgroup analyses were performed for the outcome plasma ammonia concentration (Analysis 2.4) using the prespecified subgroups (Subgroup analysis and investigation of heterogeneity). Subgroup analyses could not be performed by MELD score, risk of bias, co-interventions used or, duration of therapy as there was no differences in these subgroups amongst the trials. Significant differences were detected for the following subgroup analyses: type of probiotic used (Analysis 2.6), test for subgroup differences: $Chi^2 = 6.15$, df = 1 (P = 0.01) and grade of hepatic encephalopathy (Analysis 2.7), test for subgroup differences: $Chi^2 = 6.15$, df = 1 (P = 0.01).

Heterogeneity

Heterogeneity was demonstrated for the outcome plasma ammonia concentration Analysis 2.4 ($Chi^2 = 6.15$, df = 1; P = 0.01, $I^2 = 84\%$). Heterogeneity seemed largely attributable to the type of probiotic used (Analysis 2.6) and grade of hepatic encephalopathy (Analysis 2.7).

DISCUSSION

Summary of main results

We included seven trials in this review. Each trial used different probiotics (Table 1), and the duration of administration ranged from 10 days to 180 days. The risk of bias of all the included trials was high. No analysis demonstrated an advantage of probiotics compared with no treatment on all-cause mortality, number of adverse events, quality of life, or change of/or withdrawal from treatment (while sepsis and duration of hospital stay were unreported). When probiotics were compared with lactulose, no analysis demonstrated a significant difference for any outcome (while quality of life, septicaemia, and duration of hospital stay were unreported). The use of probiotics compared with no treatment suggested a statistically significant difference in plasma ammonia concentration after one month (Analysis 1.6) and after three months (Analysis 1.7).

Overall completeness and applicability of evidence

There were a small number of trials identified. Moreover, the number of included patients were few. In the review, trial populations and interventions varied widely across the included trials. Outcomes were inconsistently reported as were interventions, controls and associated treatments, for example, dietary protein intake. Therefore, due to the lack of evidence of a clinically important benefit with probiotics, their use currently cannot be recommended.

Quality of the evidence

There is insufficient evidence to draw meaningful conclusions about the benefits and harms of probiotics in hepatic encephalopathy. Overall, the methodological quality of trials was far from optimal.

Potential biases in the review process

This systematic review with meta-analysis was undertaken with broad inclusion criteria to assess the totality of available evidence. Our literature search was comprehensive and did not exclude trials based on language of publication or publication status. An attempt was made to contact authors wherever trial data and methodology was unclear. All data extraction and analysis were undertaken by several authors working independently to minimise bias. Despite these strengths, there were some limitations; for example, we were not blinded to authorship during data extraction and risk of bias assessment. While we did make an attempt to contact study authors, it was not always certain if our messages were received and we did not attempt to make any further contact if our initial emails were not responded to. In addition, due to the small sample sizes of the included trials, trial sequential analysis may have been a more appropriate analytic technique (Thorlund 2009).

Agreements and disagreements with other studies or reviews

A review published in 2011 discusses the effect of prebiotics, probiotics, and synbiotics in minimal hepatic encephalopathy (Shukla 2011a). As our review did not look at the combination of probiotics, prebiotics, and synbiotics, it is not possible to make direct comparisons between the reviews. Of note, Shukla 2011a were only able to locate two trials of probiotics compared to our five trials including patients with minimal hepatic encephalopathy, which suggests we utilised a more sensitive search strategy.

AUTHORS' CONCLUSIONS

Implications for practice

We did not find convincing evidence that probiotics had a significant beneficial or harmful effect on patients with hepatic encephalopathy. The methodological quality of trials to date are far from optimal. Probiotics cannot be recommended based on the findings of this review.

Implications for research

Hepatic encephalopathy has a poor clinical outcome and is a significant burden on the health care system. Current treatment options are of limited efficacy. Probiotics represent a cheap alternative option; however, their benefits and harms are still uncertain and many fundamental questions concerning their use remain. First, we need to assess the benefits and harms of probiotics in randomised trials with low risk of systematic errors ('bias') and low risk of random errors ('play of chance'). Moreover, it is unknown whether all probiotics are of equal effectiveness or what dose or duration of probiotic therapy is necessary for treatment. It is also unknown whether colonisation though multiple dosing is necessary for benefit or if a single dose of probiotic would suffice (McGee 2010). Future research should take these considerations into account and consider alternative study designs; for example, factorial trials would allow multiple comparisons to be made in the one trial. Future trials should also adhere to the recently published ISHEN consensus statement, which makes recommendations for trials in patients with hepatic encephalopathy (Bajaj 2011). The human microbiome project (Turnbaugh 2007) is one important initiative that will likely contribute to a better understanding of the complex relationship between humans and microbes.

The high response rate in the control arms of this review reflect the natural history of hepatic encephalopathy, with its spontaneously fluctuating nature and possibility for spontaneous remission. Future trials should account for this when assessing the efficacy of interventions. It is also important that those conducting trials also account for the time of day in which assessments are made. Consideration should also be given to the type of placebo used; for example, inactivated probiotic. All trials should at a minimum assess important outcomes such as mortality, quality of life, and adverse events. Trials should also be reported following the CONSORT Statement http://www.consort-statement.org/.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bajaj 2008

Methods	Design: a prospective randomised trial with open allocation. A 2:1 randomisation to the treatment arm was performed. Trial duration: 60 days. Treatment duration: 60 days.
Participants	Setting: outpatient single tertiary centre trial. Country: United States of America. Age range (years): 44 to 60. Total numbers randomised (group A/group B): 25 (17/8). Sex (M/F): not stated. Language: English. Stage/severity of hepatic encephalopathy: Child-Pugh score A/B/C: 22/3/0. Cause of hepatic encephalopathy: nonalcoholic etiology of cirrhosis. Inclusions: nonalcoholic participants with cirrhosis with minimal hepatic encephalopathy. Defined by no alcohol intake within 3 months of the trial and a nonalcoholic etiology of cirrhosis. Exclusions: 1. Alcohol use within 3 months. 2. Alcoholic etiology of cirrhosis. 3. Current psychoactive medication use. 4. On current therapy for prevention or treatment of overt hepatic encephalopathy. 5. Lack of English fluency. 6. History of overt hepatic encephalopathy. 7. Antibiotic use within 6 weeks of the trial. 8. Diabetes mellitus.
Interventions	Treatment group (A) probiotic yogurt: 1. Streptococcus thermophilus (log 9 CFU/g on Day 0) for 60 days. 2. Lactobacillus bulgaricus (log 8.7 CFU/g on Day 0) for 60 days. 3. Lactobacillus acidophilus and Lactobacillus casei (log 5.9 CFU/g on Day 0) for 60 days. 4. Bifidobacteria (log 5.2 CFU/g on Day 0) for 60 days. Participants received 12 ounces of yogurt a day. The specific probiotic used in this yogurt was Yo-Fast 88 manufactured by Chr-Hansen Inc in Denmark. Yogurt is manufactured by CC Jersey Crème, Spring Valley, Wisconsin. Control group (B): no treatment.
Outcomes	1. Minimal hepatic encephalopathy reversal. 2. Overt hepatic encephalopathy development. 3. Adherence. 4. Child-Pugh score. 5. Meld score. 6. SF-36 score. 7. Venous ammonia. 8. IL-6 and TNF-alpha levels.
Notes	Contacted Prof. JS. Bajaj on the 14th of October 2010. Additional information provided by the author.
Risk of bias	

Bajaj 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Adequate sequence generation. A 2:1 randomisation was performed using a random numbers table.
Allocation concealment	High risk	The treatment allocation was not concealed from the principal investigator.
Blinding Participants	High risk	Participants knew whether they were in the treatment group or in the control group.
Blinding Personnel	High risk	The investigator knew whether a patient was included in the treatment group or in the control group.
Blinding Outcome assessors	Low risk	The outcome scorer was blinded.
Incomplete outcome data All outcomes	Low risk	3 out of 17 patients in the treatment group dropped out; 1 died from sepsis unrelated to the trial on day 67 but did not come to his first visit, and 2 did not like the taste and dropped out on days 13 and 17, respectively. 2 out of 8 patients in the control group dropped out; they developed OHE on days 22 and 35. Primary analysis used an intention-to-treat analysis.
Selective outcome reporting	Low risk	All outcomes mentioned in the methods (minimal hepatic encephalopathy reversal, overt hepatic encephalopathy development and adherence) were described in the results at baseline, after 30 days and after 60 days. Personal communication with the author revealed no other outcomes were assessed.
Funding source	Low risk	The General Clinical Research Center at the Medical College of Wisconsin sponsored by the NIH supported this study.

Liu 2004

Methods	Design: a parallel group randomised trial. Study duration: unknown. Treatment duration: 30 days.
Participants	Setting: outpatient. Country: China. Age range (years): 43 to 69. Total numbers randomised (group A/group B/group C): 55 (20/20/15). Group C was not relevant to our analysis. Sex (M/F): 53/2. Language: English. Stage/severity of hepatic encephalopathy: Child-Pugh score A/B+C: 8/47. Cause of hepatic encephalopathy: patients with cirrhosis and hepatic encephalopathy without known precipitants of hepatic encephalopathy, like renal impairment, alcohol related hepatic encephalopathy, complicating hepatocellular carcinoma, etc. Inclusions: 1. Cirrhotic patients with minimal hepatic encephalopathy, without over hepatic encephalopathy. 2. Patients who had been abstinent from alcohol for at least two months, as corroborated by family members and/or caregivers. Exclusions:

Liu 2004 *(Continued)*

	1. Histological features of alcoholic hepatitis. 2. A history within the previous six weeks of factors including infection, treatment with antibiotics, lactulose or immunomodulatory drugs, and gastrointestinal haemorrhage. 3. Other causes of reversible hepatic functional decompensation, such as drug-related hepatotoxicity and choledocholithiasis. 4. Other known precipitants of hepatic encephalopathy, including renal impairment, electrolyte imbalance, and complicating hepatocellular carcinoma.
Interventions	Treatment group (A) Oral supplementation with a synbiotic preparation containing Pediacoccus pentoseceus, Leuconostoc mesenteroides, Lactobacillus paracasei and Lactobacillus plantarum (each probiotic at 10^{10} CFU's/day, total dose of probiotics in a day: 4 x 10^{10} CFU's) plus 10 g of bioactive fermentable fibre (2.5 g beta glucan, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch) for 30 days. Treatment group (B) 10 g of bioactive fermentable fibre (2.5 g beta glucan, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch) for 30 days. Control group (C) Placebo (non fermentable fibre) for 30 days.
Outcomes	1. Faecal pH. 2. Venous ammonia levels. 3. Serum endotoxin levels. 4. Minimal hepatic encephalopathy status. 5. Child-Pugh score. 6. Adverse events. 7. Overt hepatic encephalopathy development.
Notes	Contacted Dr. Q. Liu on the 15th of October 2010, no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	High risk	One sachet was randomly drawn from a pool for each patient, which is equivalent to drawing lots. We feel that this does not represent best practice for randomisation and so according to our predefined criteria have judged this category as high risk of bias.
Allocation concealment	Unclear risk	Not stated.
Blinding Participants	Unclear risk	Not stated for participants.
Blinding Personnel	Unclear risk	Which sachets (A, B, or C) contained the synbiotic, fermentable fibre or non fermentable fibre preparations was unknown to the investigators until after the completion of the study and results had been analysed.
Blinding Outcome assessors	Unclear risk	Not stated for outcome assessors.
Incomplete outcome data All outcomes	Unclear risk	Unclear from the study.
Selective outcome reporting	Unclear risk	Unclear from the study.
Funding source	Unclear risk	Not stated.

Loguercio 1987

Methods	Design: a parallel group randomised trial. Study duration: 23 days. Treatment duration: 10 days.
Participants	Setting: outpatient. Country: Italy. Age range (years): 25 to 68. Total numbers randomised (group A/group B): 40 (20/20). Sex (M/F): 26/14. Language: English. Stage/severity of hepatic encephalopathy: grade I or II. Cause of hepatic encephalopathy: alcohol, hepatitis, cirrhosis. Inclusions: cirrhotic patients with non-advanced hepatic encephalopathy (grade I or II). Exclusions: 1. HE degree > 2. 2. Alcohol use at the moment of the study. 3. Mental disorders and/or benzodiazepine use. 4. Non compliance.
Interventions	Treatment group (A) Enterococcus Lactic Acid bacteria strain SF68 (two capsules, each containing 75 x 10^6 CFU's, three times daily, for 10 days) Bioflorin is a trade name of Giuliani and is distributed by Gipharmex SpA, Italy. Control group (B) 30 ml lactulose four times daily, for 10 days.
Outcomes	1. Mental state. 2. Bowel function. 3. Presence/absence abdominal pain. 4. Blood ammonia level. 5. Presence/absence meteorism. 6. Reitan's test (number connection test). 7. Adverse events.
Notes	Additional information on risk of bias criteria provided by the author. Contacted Prof. C. Loguercio on the 15th of October 2010.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Patients were randomly assigned to a treatment group. No further information about randomisation.
Allocation concealment	Unclear risk	Information not provided.
Blinding Participants	Low risk	Participants were blinded.
Blinding Personnel	Low risk	Personnel was blinded.
Blinding Outcome assessors	Low risk	The outcome scorer was blinded.

Loguercio 1987 *(Continued)*

Incomplete outcome data All outcomes	High risk	All patients completed the treatment period. Five patients given lactulose and four given Enterococcus SF68 did not arrive for post-treatment follow-up. On day 15, two patients given lactulose were withdrawn from the study because of marked hyperammonaemia and a worsening of hepatic encephalopathy.
Selective outcome reporting	Unclear risk	Unclear from study.
Funding source	High risk	Gipharmex (Milan, Italy) supported this study.

Malaguarnera 2010

Methods	Design: a double-blind parallel group randomised trial. Study duration: 2004 to 2007. Treatment duration: 60 days.
Participants	Setting: inpatient. Country: Italy. Age range (years): not stated. Total numbers randomised (group A/group B): 125 (63/62). Sex (M/F): 62/63. Language: English. Stage/severity of hepatic encephalopathy: Child-Pugh score A/B/C: 46/59/20. Cause of hepatic encephalopathy: chronic hepatitis and cryptogenic cirrhosis with spontaneous hepatic encephalopathy. Inclusions: 1. Chronic hepatitis with spontaneous manifest hepatic encephalopathy (mental state grade I or II. according to the West-Haven criteria) and a Number Collection Test-A performance time > 30 seconds. 2. Hyperammonemia (venous ammonia concentration > 50 mmol/l). 3. Co-operative, hospitalised, adult patients with liver cirrhosis diagnosed by clinical, histological and ultrasonographic findings (reduced dimensions of the liver as well as splenomegaly) and oesophageal varices (stages II or III) observed by endoscopy. Exclusions: 1. Major complications of portal hypertension, such as gastrointestinal blood loss, hepatorenal syndrome or bacterial peritonitis. 2. Acute superimposed liver injury. 3. Other neurological disease and metabolic disorders such as alcoholism, diabetes mellitus, unbalanced heart failure and/or respiratory failure or end-stage renal disease. 4. Severe hepatic encephalopathy (mental state grade III-IV). 5. Administration of anti-hepatic encephalopathy medications such as neomycin, branched-chain amino acids. 6. Any additional precipitating factors such as high protein intake (additional high-protein meals), constipation or intake of psychostimulants, sedatives, antidepressants, benzodiazepines or benzodiazepines antagonists (flumazenil). 7. Fever, sepsis, or shock were also excluded to avoid variations caused by body temperature.
Interventions	Treatment group (A) Bifidobacterium (subtype not stated) + (FOS) fructo-oligosaccharides for 60 days (dose not stated). Control group (B) Lactulose for 60 days (dose not stated). Note: FOS and lactulose were considered comparable because they are both complex carbohydrates, which are indigestible to humans but digestible to bacteria. We were unable to locate any efficacy data comparing FOS to lactulose in hepatic encephalopathy patients.

Malaguarnera 2010 *(Continued)*

Outcomes	1. Trail making test. 2. Cognitive functions. 3. Grade of hepatic encephalopathy. 4. Child-Pugh score.
Notes	Contacted Dr. M. Malaguarnera on the 15th of October 2010, no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Randomisation was based on a computer-generated list.
Allocation concealment	Unclear risk	Stated it was a double-blind trial, but not for whom.
Blinding Participants	Unclear risk	Stated it was a double-blind trial, but not for whom.
Blinding Personnel	Unclear risk	Stated it was a double-blind trial, but not for whom.
Blinding Outcome assessors	Unclear risk	Not stated for outcome assessors.
Incomplete outcome data All outcomes	Unclear risk	Unclear from study.
Selective outcome reporting	Unclear risk	Unclear from the study.
Funding source	Unclear risk	Not stated.

Mittal 2009

Methods	Design: a parallel randomised trial. Study duration: October 2007 to October 2009. Treatment duration: three months.
Participants	Setting: outpatient. Country: India. Age range (years): 32 to 54. Total numbers randomised (group A/group B/group C/group D): 160 (40/40/40/40). We did not use group B and D in our analysis as these were not useful to compare to probiotics. Sex (M/F): 123/37. Language: English. Stage/severity of hepatic encephalopathy: not stated. Cause of hepatic encephalopathy: cirrhosis due to alcoholic liver disease, hepatitis B, hepatitis C or other causes. Inclusions: patients with cirrhosis who have minimal hepatic encephalopathy, diagnosed by two or more abnormal (+2SD from the mean) psychometric tests. Exclusions: 1. Overt HE based on detailed neurological examination or history of overt HE in past 6 weeks. 2. Recent history (< 6 wk) of gastrointestinal bleed. 3. Active ongoing infection. 4. Renal impairment with serum creatinine > 1.5mg%.

Mittal 2009 *(Continued)*

	5. Electrolyte impairment (S. Sodium < 130 or > 150 meq/dL, S. Potassium < 3.0 or > 5.5 meq/dL). 6. Recent alcohol use (< 6wk) as reported by the patient, recent use of antibiotic, lactulose or LOLA (< 6wk), use of psychotropic drugs in last 6 weeks. 7. TIPS, shunt surgery. 8. Hepatocellular carcinoma. 9. Severe co-morbidity as congestive heart failure, pulmonary disease, neurological & psychiatric problems impairing quality of life, or poor vision precluding neuropsychiatric assessment.
Interventions	Control group (A) No treatment. Treatment group (B) 30ml to 60 ml lactulose twice daily for three months. Treatment group (C) VSL#3 (containing Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus) 110 billion CFU's twice daily for three months. Treatment group (D) 6 g (LOLA) L-ornithine L-aspartate three times daily for three months.
Outcomes	1. Minimal hepatic encephalopathy recovery. 2. Minimal hepatic encephalopathy improvement. 3. Arterial ammonia level. 4. Development of overt hepatic encephalopathy. 5. Sickness impact profile score (quality of life).
Notes	Additional information on risk of bias criteria provided by the author. Contacted Prof. BC. Sharma on the 14th of October 2010. Unpublished data provided by the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Patients were randomised to one of the treatment groups using computer-generated random tables.
Allocation concealment	Unclear risk	Not stated.
Blinding Participants	High risk	Different way of administering for every treatment and therefore patients knew which treatment they received.
Blinding Personnel	High risk	Compliance was assessed primarily using pill and bottle count and therefore blinding was not possible.
Blinding Outcome assessors	High risk	Compliance was assessed primarily using pill and bottle count and therefore blinding was not possible.
Incomplete outcome data All outcomes	Unclear risk	11 patients were lost to follow up, 3 from group A, 1 from group B, 3 from group C, and 4 from group D. During treatment, 7 patients had to be admitted to the hospital for causes other than overt hepatic encephalopathy. Of these 7 patients, 2 patients died, one each in group A and D. Primary analysis used an intention-to-treat analysis, probably with imputation.

Mittal 2009 *(Continued)*

Selective outcome reporting	Unclear risk	Unclear from the trial.
Funding source	Unclear risk	Not stated.

Pereg 2011

Methods	Design: a parallel randomised trial. Study duration: unclear. Treatment duration: six months.
Participants	Setting: outpatient. Country: Israel. Age range (years): 53 to 74. Total numbers randomised (group A/group B): 40 (20/20). Sex (M/F): unclear. Language: English. Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy. Cause of hepatic encephalopathy: cirrhosis due to alcoholic liver disease, hepatitis B, hepatitis C or other causes. Inclusions: patients with liver cirrhosis and at least one major complication of cirrhosis in the past, clinical evidence of portal hypertension, or decreased hepatic synthetic function. Exclusions: 1. Any sign of decompensation from any precipitant including gastrointestinal bleeding, infections, acute renal failure, electrolyte impairment, or hepatocellular carcinoma. 2. Those chronically treated with antibiotics or lactulose. 3. Patients with alcoholic cirrhosis, for whom alcohol abstinence for at least 2 months prior to enrolment could not be confirmed.
Interventions	Control group (A) Wheat-based non-fermentable fiber placebo. Treatment group (B) Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium bifidum, and Streptococcus thermophiles (Bio-plus, Supherb, Israel), each at a daily dose of $2x10^{10}$ colony forming units.
Outcomes	1. Plasma ammonia. 2. Adverse events.
Notes	Th study was registered in ClinicalTrials.gov (ID: NCT00312910).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Sequence generation	Unclear risk	Not stated.
Allocation concealment	Unclear risk	Not stated.
Blinding Participants	Unclear risk	Only stated in the title that the trial was double-blinded - no specific details provided of who or how blinding was conducted.

Pereg 2011 *(Continued)*

Blinding Personnel	Unclear risk	Only stated in the title that the trial was double-blinded - no specific details provided of who or how blinding was conducted.
Blinding Outcome assessors	Unclear risk	Only stated in the title that the trial was double-blinded - no specific details provided of who or how blinding was conducted.
Incomplete outcome data All outcomes	High risk	Four patients 'dropped out', no further details are provided.
Selective outcome reporting	Unclear risk	Unclear from the trial.
Funding source	High risk	Supported by Supherb Ltd, Israel.

Sharma 2008

Methods	Design: open-label randomised trial. Treatment duration: 1 month. Time period: February 2005 to August 2006.
Participants	Setting: India. Age range (years): 30 to 54. Total numbers randomised (group A/group B/group C): 105 (35/35/35). Sex (M/F): 79/26. Language: English. Stage/severity of hepatic encephalopathy: Child-Pugh score A/B/C: 36/39/30. Cause of hepatic encephalopathy: cirrhosis due to alcohol consumption, chronic hepatitis and cryptogenic cirrhosis. Inclusions: cirrhotic patients with minimal hepatic encephalopathy without overt encephalopathy. Exclusions: 1. The presence of overt hepatic encephalopathy or history of hepatic encephalopathy. 2. History of taking lactulose or any antibiotics. 3. Alcohol intake. 4. Gastrointestinal haemorrhage or spontaneous bacterial peritonitis during the past six weeks. 5. Earlier transjugular intrahepatic portosystemic shunt or shunt surgery. 6. Significant comorbid illness such as heart failure, respiratory failure, or renal failure. 7. Any neurologic diseases such as Alzheimer's disease, Parkinson's disease, and non hepatic metabolic encephalopathies. 8. Colour blindness and mature cataract, diabetic retinopathy and patients on psychoactive drugs, such as antidepressants or sedatives.
Interventions	Control group (A) 30ml to 60 ml lactulose/day for one month. Treatment group (B) One capsule (containing Streptococcus faecalis, Clostridium butyricum, Bacillus mesentricus, Lactic acid bacillus) three times daily for one month, dose not stated. Treatment group (C) 30ml to 60 ml lactulose plus probiotics daily for one month.
Outcomes	1. Venous ammonia level. 2. Child-Pugh score. 3. Minimal hepatic encephalopathy recovery.

Sharma 2008 *(Continued)*

Notes	Additional information provided by the author. Contacted Prof. BC. Sharma on the 14th of October 2010.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Patients were randomised according to a computer-generated randomisation chart.
Allocation concealment	High risk	Trial personnel were able to view the allocation sequence.
Blinding Participants	High risk	The trial was not blinded.
Blinding Personnel	High risk	The trial was not blinded.
Blinding Outcome assessors	High risk	The trial was not blinded.
Incomplete outcome data All outcomes	High risk	Thirteen patients in the control group and five patients in the lactulose plus probiotic group were lost to follow-up. Reasons are unclear.
Selective outcome reporting	Low risk	All outcomes reported in the methods (Psychometric tests outcomes, P300 auditory event-related potential, venous ammonia level and Child's-Pugh classification) were measured and discussed on baseline and after one month. Personal communication with the author revealed no other outcomes were assessed.
Funding source	Unclear risk	Not stated.

M = male.
F = female.
S = serum.
SD = standard deviation.
Wk = week.

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

Study	Reason for exclusion
Adams 2006	No hepatic encephalopathy patients involved.
Al 2009	Not a randomised trial.
Albillos 2002	No hepatic encephalopathy patients involved.
Almeida 2006	Not a randomised trial.
Arya 2010	Not a randomised trial.
Bajaj 2008a	Not a randomised trial.
Bajaj 2008b	Not a randomised trial.

Study	Reason for exclusion
Ballongue 1997	No probiotic used.
Barclay 2011	Not a randomised trial.
Barreto-Zuniga 2001	No hepatic encephalopathy patients involved.
Bass 2007	Not a randomised trial.
Baumgart 2007	Not a randomised trial.
Behm 2006	Not a randomised trial.
Bengmark 2004	Not a randomised trial.
Bengmark 2006	Not a randomised trial.
Bengmark 2009	No hepatic encephalopathy patients involved.
Bereswill 2010	No probiotic used.
Bircher 1971	No probiotics used.
Bismuth 2011	Not a randomised trial.
Boca 2004	Not a randomised trial.
Bongaerts 2005	Not a randomised trial.
Burrowes 2005	No hepatic encephalopathy patients involved.
Buscher 2004	No hepatic encephalopathy patients involved.
Cabre 2005	Not a randomised trial.
Cachin 1969	No probiotics used.
Cada 2010	Not a randomised trial.
Calamita 2007	Not a randomised trial.
Cash 2010	Not a randomised trial.
Chadalavada 2010	Not a randomised trial.
Chen 2007	No probiotic used.
Colle 1989	Hepatic encephalopathy not confirmed.
Colman 1976	No probiotics used.
Conn 1970	Not a randomised trial.
Conn 1978	No probiotics used.
Crum 2005	Not a randomised trial.

Study	Reason for exclusion
Dasarathy 2003	No probiotic used.
Dbouk 2006	Not a randomised trial.
Demeter 2006	Not a randomised trial.
Dhiman 2004	Not a randomised trial.
Dhiman 2007	Not a randomised trial.
Dhiman 2009	Not a randomised trial.
Dhiman 2010	Not a randomised trial.
Diamant 2011	Not a randomised trial.
Diehl 2005	Not a randomised trial.
Diehl 2010	Not a randomised trial.
Doron 2005	Not a randomised trial.
Edmison 2007	Not a randomised trial.
Eguchi 2011	Not probiotic.
Elkington 1970	No probiotics used.
Esposito 2009	No humans involved.
Fan 2009	No hepatic encephalopathy patients involved.
Ferenci 2001	Not a randomised trial.
Ferenci 2007	Not a randomised trial.
Feret 2010	Not probiotic.
Ferreira 2010	Not a randomised trial.
Finney 2007	No probiotics used.
Foster 2010	Not a randomised trial.
Fujita 2008	No hepatic encephalopathy patients involved.
Fuster 2007	Not a randomised trial.
Garcia-Tsao 2003	Not a randomised trial.
Gratz 2010	Not a randomised trial.
Greco 2007	Groups non-comparable.
Gronbaek 2008	Not a randomised trial.

Study	Reason for exclusion
Guarner 2009	Not a randomised trial.
Guerrero 2008	Not a randomised trial.
Haemmerli 1969	Not a randomised trial.
Harding 2008	No hepatic encephalopathy patients.
Higashikawa 2010	No hepatic encephalopathy patients involved.
Hong 2009	No hepatic encephalopathy patients.
Hotten 2003	No hepatic encephalopathy patients involved.
Hulkova 2009	Not a randomised trial.
Iannitti 2010	Not a randomised trial.
Imler 1971	Not a randomised trial.
Jeejeebhoy 2004	Not a randomised trial.
Jia 2005	No hepatic encephalopathy patients involved.
Jiang 2008	No probiotics used.
Jonkers 2007	Not a randomised trial.
Kachaamy 2011	Not a randomised trial.
Kadayifci 2007	Not a randomised trial.
Karczewski 2010	No hepatic encephalopathy patients involved.
Keeffe 2007	Not a randomised trial.
Khan 2010	Not a randomised trial.
Kim 2008	No hepatic encephalopathy patients involved.
Kirpich 2008	No hepatic encephalopathy patients involved.
Koo 2010	Not a randomised trial.
Kramer 2004	Not a randomised trial.
Kremer 1974	Not a randomised trial.
Krueger 2004	Not a randomised trial.
Kumashiro 2008	Not a randomised trial.
Lata 2006	No hepatic encephalopathy patients involved.
Lata 2007	No hepatic encephalopathy patients involved.

Study	Reason for exclusion
Lata 2009	No hepatic encephalopathy patients involved.
Lawrence 2003	Not a randomised trial.
Li 2002	Not a randomised trial.
Lighthouse 2004	No hepatic encephalopathy patients involved.
Lirussi 2007	Not a randomised trial.
Liu 2010	Not a randomised trial.
Loguercio 2002	No hepatic encephalopathy patients involved.
Loguercio 2005	No hepatic encephalopathy patients involved.
Madsen 2008	No hepatic encephalopathy patients.
Malaguarnera 2007	Not a probiotic alone.
Marotta 2003	No hepatic encephalopathy patients involved.
Marteau 2001	Not a randomised trial.
Marteau 2002	Not a randomised trial.
Marteu 2001	Not a randomised trial.
McAvoy 2006	Not a randomised trial.
McClave 2009	Not a randomised trial.
Medina 2004	Not a randomised trial.
Meier 2005	Not a randomised trial.
Mencin 2009	Not a randomised trial.
Mennigen 2009	Not a randomised trial.
Michelfelder 2010	Not a randomised trial
Montgomery 2011	Not a randomised trial.
Montineri 2008	Not a randomised trial.
Montrose 2005	Not a randomised trial.
Moreno-Luna 2011	Not a randomised trial.
Morgan 2007	Not a randomised trial.
Mullen 2007	Not a randomised trial.
Muting 1972	No probiotics used.

Study	Reason for exclusion
Nair 2008	Abstract unavailable.
Narayan 2010	Not hepatic encephalopathy.
Nazir 2010	Prophylaxis not treatment.
Nolan 2010	Not a randomised trial.
Nomura 2007	No hepatic encephalopathy patients involved.
Norman 2008	Not a randomised trial.
O'Brien 2008	Not a randomised trial.
Oben 2008	Not a randomised trial.
Ojetti 2009	Not a randomised trial.
Okada 2010	Not a randomised trial.
Ooi 2010	No hepatic encephalopathy patients involved.
Oshea 2010	Not a randomised trial.
Pande 2009	No hepatic encephalopathy patients involved.
Park 2007	Not a randomised trial.
Phongsamran 2010	Not a randomised trial.
Pimentel-Nunes 2010	Not a randomised trial.
Portincasa 2005	Not a randomised trial.
Pradere 2010	Not a randomised trial.
Quercioli 2009	Not a randomised trial.
Quigley 2006	Not a randomised trial.
Rafiq 2009	Not a randomised trial.
Ratziu 2005	Not a randomised trial.
Rayes 2002	No hepatic encephalopathy patients involved.
Read 1966	Not a randomised trial.
Riddle 2008	No probiotics involved.
Rifatbegovic 2010	No hepatic encephalopathy patients involved.
Riggio 1990	No probiotic used.
Riggio 2009	Not a randomised trial.

Study	Reason for exclusion
Riordan 2003	No hepatic encephalopathy patients involved.
Riordan 2007	No hepatic encephalopathy patients involved.
Riordan 2010	No probiotic used.
Roberts 2006	Not a randomised trial.
Romero-Gomez 2010	Not a randomised trial.
Sanyal 2008	No probiotics used.
Scevola 1989	No probiotics used.
Schiano 2010	Not a randomised trial.
Seva-Pereira 2003	No hepatic encephalopathy patients involved.
Shawcross 2005	Not a randomised trial.
Sheth 2008	Not a randomised trial.
Shin 2010	Not a randomised trial.
Shukla 2009	Not a randomised trial
Shukla 2011	Not a randomised trial.
Simons 2006	Not hepatic encephalopathy.
Solga 2003	Not a randomised trial
Sotelo 2010	Not a randomised trial.
Stadlbauer 2008	No hepatic encephalopathy patients involved.
Stewart 2003	Not a randomised trial.
Stewart 2007	Not a randomised trial.
Story 2010	Not a randomised trial.
Strauss 2006	Not a randomised trial.
Sun 2007	Not a randomised trial.
Sundaram 2009	Not a randomised trial.
Szabo 2010	Not a randomised trial.
Szilagyi 2004	Not a randomised trial.
Tandon 2009	Not a randomised trial.
Tarao 1995	No probiotics used.

Study	Reason for exclusion
Thoma 2003	Not a randomised trial.
Tolman 2007	Not a randomised trial.
Toris 2011	Not a randomised trial.
Valenti 2009	Not a randomised trial.
Van Erpecum 2006	Not a randomised trial.
Vanovski 1975	Not a randomised trial.
Vince 1974	No probiotics used.
Vinnitskaia 2008	Not a randomised trial.
Vleggaar 2008	No hepatic encephalopathy patients involved.
Wierzbicka 2008	Not a randomised trial.
Wilbur 2009	Not a randomised trial.
Wright 2007	Not a randomised trial.
Wu 2008	Not a randomised trial.
Xu 2009	No hepatic encephalopathy patients involved.
Yakabe 2009	No hepatic encephalopathy patients involved.
Yoshikawa 2006	Not a randomised trial.
Younossi 2008	Not a randomised trial.
Zafirova 2010	Not a randomised trial
Zhang 2006	Not a randomised trial.
Zhao 2004	No hepatic encephalopathy patients involved.

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

Sharma 2010

Trial name or title	Secondary Prophylaxis of Hepatic Encephalopathy in Cirrhosis: an Open Label, Randomized Controlled Trial of Lactulose, Probiotics, and No-therapy.
Methods	Phase IV study. The investigators will assess the effects of lactulose and probiotics for the prevention of recurrence of HE (secondary prophylaxis) in patients after the recovery of an episode of overt hepatic encephalopathy.

Sharma 2010 *(Continued)*	
	One treatment group receives lactulose and the other treatment group receives probiotics for six months.
Participants	Patients with cirrhosis and previous history of recovery from hepatic encephalopathy, between 18 and 75 years old.
Interventions	Treatment group (A): lactulose (30ml to 60 ml of lactulose in 2 or 3 divided doses so that patient passed 2 to 3 semi soft stools per day). Treatment group (B): probiotics: VSL#3 (110 billion CFU's three times a day).
Outcomes	Primary outcome: episode of overt hepatic encephalopathy. Secondary outcome: side effects to therapy.
Starting date	September 2008.
Contact information	G B Pant Hospital, New Delhi, Delhi, India, 110002. Contact: Barjesh C Sharma, MD, DM. tel. 9718599203; drbcsharma@hotmail.com Principal Investigator: Barjesh C Sharma, MD,DM.
Notes	Data obtained from trial registry ClinicalTrials.gov, ID: NCT01178372.

Abbreviations: tel.-telephone.

DATA AND ANALYSES

Comparison 1. Probiotic versus placebo/ no intervention

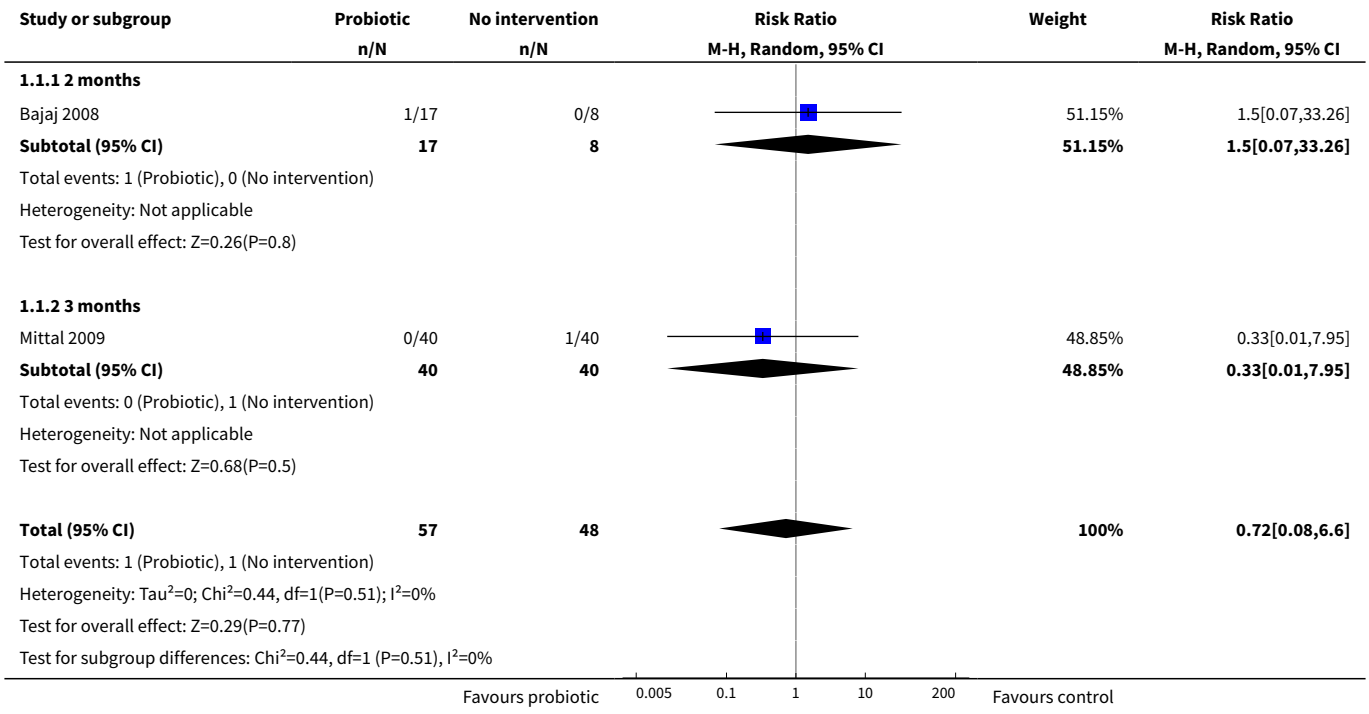
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	2	105	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.08, 6.60]
1.1 2 months	1	25	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.07, 33.26]
1.2 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.95]
2 No recovery (incomplete resolution of clinical symptoms)	4	206	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.05]
2.1 1 month	2	101	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.64, 1.48]
2.2 2 months	1	25	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.66]
2.3 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.93]
3 Number of adverse events	3	145	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.08, 1.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 1 month	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 2 months	1	25	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.87]
3.3 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.10, 2.58]
4 Quality of life SF-36 physical/ mental	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Physical 2 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Mental 2 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Change of/or withdrawal from treatment	3	175	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.52, 3.19]
5.1 1 month	1	70	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.37, 4.27]
5.2 2 months	1	25	Risk Ratio (M-H, Random, 95% CI)	3.5 [0.20, 60.70]
5.3 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.21, 4.66]
6 Plasma ammonia concentration (µmol/L)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 1 month	3	226	Mean Difference (IV, Random, 95% CI)	-2.99 [-5.70, -0.29]
6.2 2 months	3	181	Mean Difference (IV, Random, 95% CI)	-1.82 [-14.04, 10.41]
7 Change in plasma ammonia concentration (µmol/L)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 3 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 No recovery (subgroup type of probiotic used)	4	206	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.05]
8.1 Lactobacillus	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.54, 1.86]
8.2 Mixed	3	166	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.40, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 No recovery (subgroup grade of hepatic encephalopathy)	4	206	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.05]
9.1 Minimal	2	105	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.23, 1.15]
9.2 Overt	2	101	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.64, 1.48]
10 No recovery (subgroup duration of therapy)	4	206	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.51, 1.25]
10.1 1 month and less	2	101	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.64, 1.48]
10.2 Between 1 and 2 months	1	25	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.66]
10.3 More than 2 months	1	80	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.86, 1.16]
11 No recovery (subgroup co-interventions used)	4	206	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.05]
11.1 No treatment	2	105	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.23, 1.15]
11.2 Bioactive fermentable fibre	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.54, 1.86]
11.3 Lactulose	1	61	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.55, 1.69]
12 Plasma ammonia concentration (subgroup type of probiotic used)	4	279	Mean Difference (IV, Random, 95% CI)	-4.47 [-10.62, 1.69]
12.1 Bifidobacterium	1	125	Mean Difference (IV, Random, 95% CI)	-9.35 [-16.09, -2.61]
12.2 Mixed	3	154	Mean Difference (IV, Random, 95% CI)	-0.72 [-11.23, 9.79]
13 Plasma ammonia concentration (subgroup grade of hepatic encephalopathy)	5	315	Mean Difference (IV, Random, 95% CI)	-4.71 [-9.97, 0.56]
13.1 Minimal	4	190	Mean Difference (IV, Random, 95% CI)	-1.80 [-9.65, 6.06]
13.2 Overt	1	125	Mean Difference (IV, Random, 95% CI)	-9.35 [-16.09, -2.61]
14 Plasma ammonia concentration (subgroup duration of therapy)	5	282	Mean Difference (IV, Random, 95% CI)	-3.10 [-8.15, 1.96]

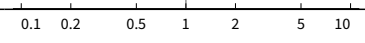
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 1 month and less	2	101	Mean Difference (IV, Random, 95% CI)	-2.82 [-5.63, -0.02]
14.2 Between 1 and 2 months	3	181	Mean Difference (IV, Random, 95% CI)	-1.82 [-14.04, 10.41]
15 Plasma ammonia concentration (subgroup co-interventions used)	4	246	Mean Difference (IV, Random, 95% CI)	-2.86 [-8.79, 3.07]
15.1 No treatment	1	20	Mean Difference (IV, Random, 95% CI)	10.0 [-3.83, 23.83]
15.2 Bioactive fermentable fibre	1	40	Mean Difference (IV, Random, 95% CI)	-2.90 [-5.51, -0.29]
15.3 Lactulose	2	186	Mean Difference (IV, Random, 95% CI)	-7.88 [-14.29, -1.47]

Analysis 1.1. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 1 All cause mortality.



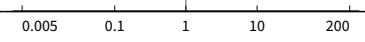
Analysis 1.2. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 2 No recovery (incomplete resolution of clinical symptoms).

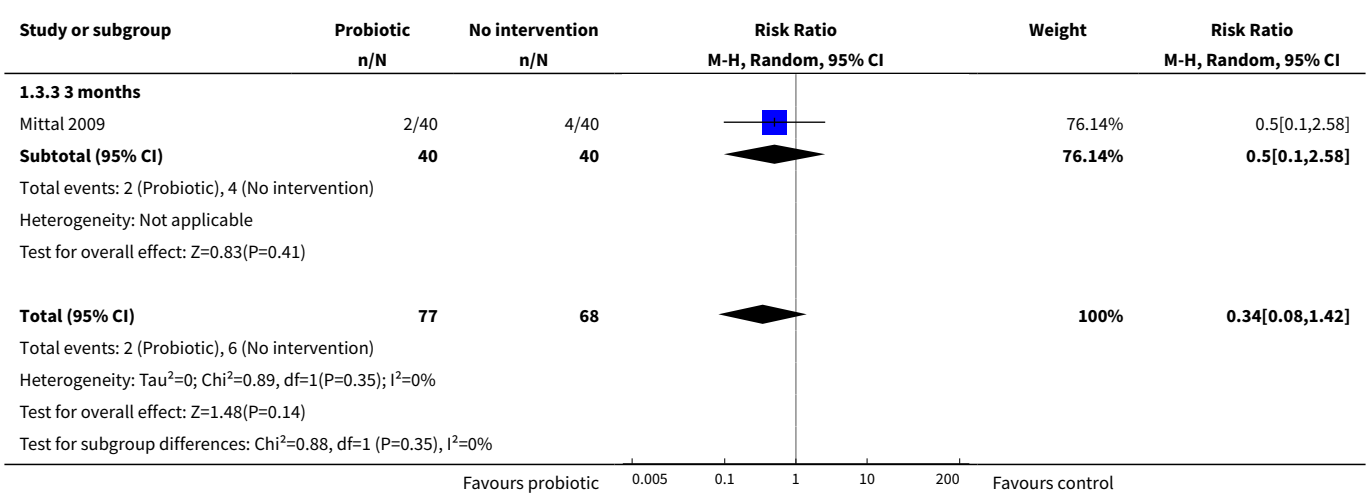
Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 1 month					
Liu 2004	10/20	10/20		20.92%	1[0.54,1.86]
Sharma 2008	13/30	14/31		23.07%	0.96[0.55,1.69]
Subtotal (95% CI)	**50**	**51**		**43.99%**	**0.98[0.64,1.48]**
Total events: 23 (Probiotic), 24 (No intervention)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=0.11(P=0.92)					
1.2.2 2 months					
Bajaj 2008	5/17	8/8		17.77%	0.32[0.16,0.66]
Subtotal (95% CI)	**17**	**8**		**17.77%**	**0.32[0.16,0.66]**
Total events: 5 (Probiotic), 8 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.1(P=0)					
1.2.3 3 months					
Mittal 2009	26/40	36/40		38.24%	0.72[0.56,0.93]
Subtotal (95% CI)	**40**	**40**		**38.24%**	**0.72[0.56,0.93]**
Total events: 26 (Probiotic), 36 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.55(P=0.01)					
Total (95% CI)	**107**	**99**		**100%**	**0.72[0.49,1.05]**
Total events: 54 (Probiotic), 68 (No intervention)					
Heterogeneity: Tau^2=0.08; Chi^2=6.93, df=3(P=0.07); I^2=56.72%					
Test for overall effect: Z=1.7(P=0.09)					
Test for subgroup differences: Chi^2=6.88, df=1 (P=0.03), I^2=70.92%					



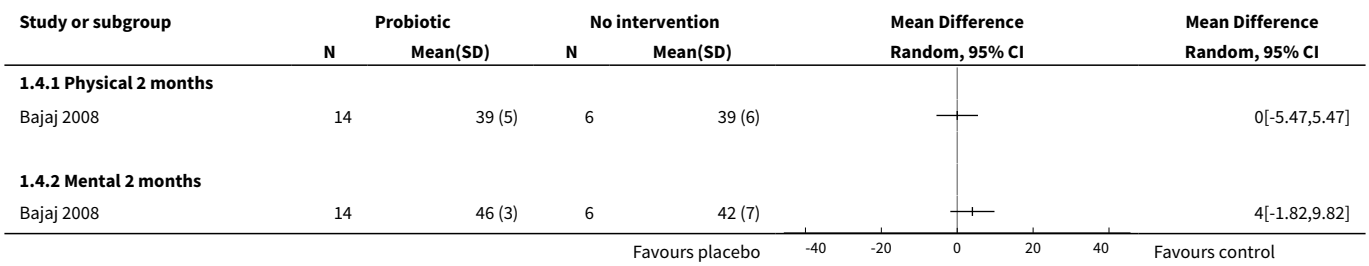
Analysis 1.3. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 3 Number of adverse events.

Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 1 month					
Liu 2004	0/20	0/20			Not estimable
Subtotal (95% CI)	**20**	**20**			**Not estimable**
Total events: 0 (Probiotic), 0 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.2 2 months					
Bajaj 2008	0/17	2/8		23.86%	0.1[0.01,1.87]
Subtotal (95% CI)	**17**	**8**		**23.86%**	**0.1[0.01,1.87]**
Total events: 0 (Probiotic), 2 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.54(P=0.12)					

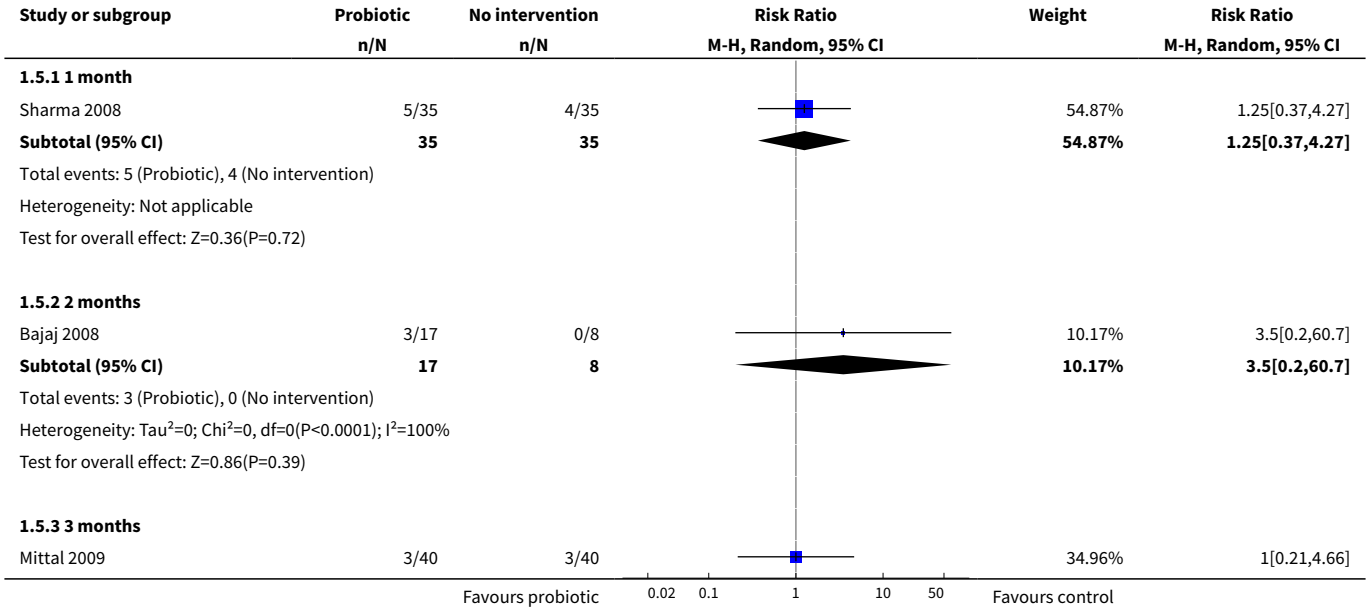


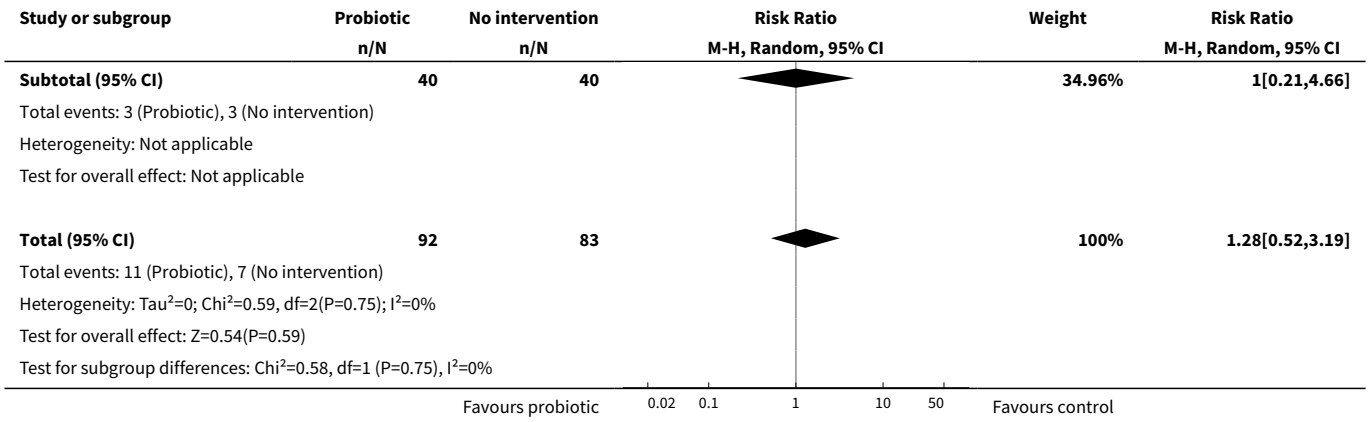


Analysis 1.4. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 4 Quality of life SF-36 physical/ mental.

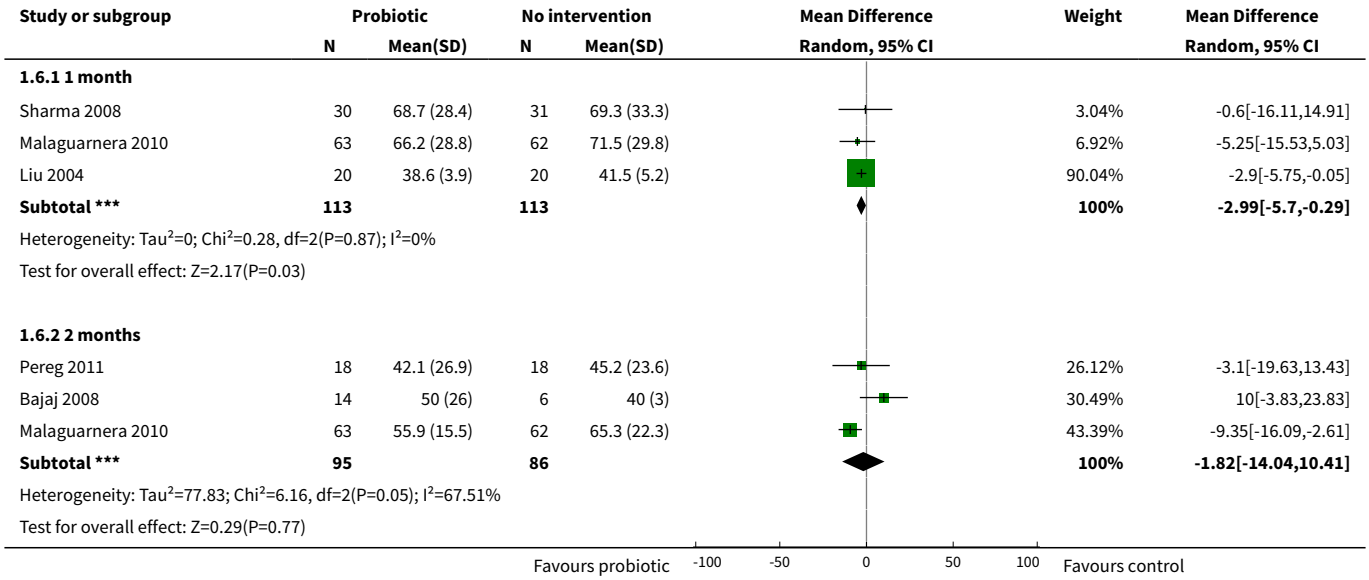


Analysis 1.5. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 5 Change of/or withdrawal from treatment.

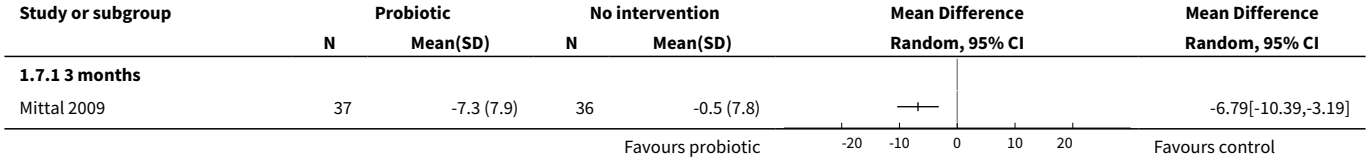




Analysis 1.6. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 6 Plasma ammonia concentration (µmol/L).

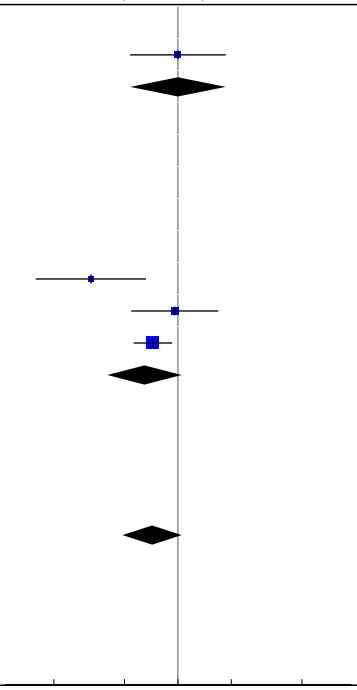


Analysis 1.7. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 7 Change in plasma ammonia concentration (µmol/L).



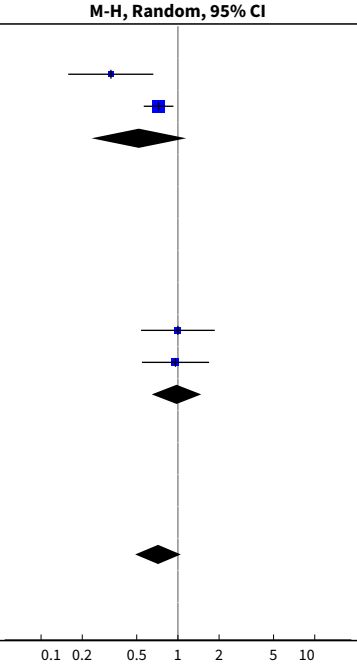
Analysis 1.8. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 8 No recovery (subgroup type of probiotic used).

Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Lactobacillus					
Liu 2004	10/20	10/20		20.92%	1[0.54,1.86]
Subtotal (95% CI)	**20**	**20**		**20.92%**	**1[0.54,1.86]**
Total events: 10 (Probiotic), 10 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.8.2 Mixed					
Bajaj 2008	5/17	8/8		17.77%	0.32[0.16,0.66]
Sharma 2008	13/30	14/31		23.07%	0.96[0.55,1.69]
Mittal 2009	26/40	36/40		38.24%	0.72[0.56,0.93]
Subtotal (95% CI)	**87**	**79**		**79.08%**	**0.65[0.4,1.05]**
Total events: 44 (Probiotic), 58 (No intervention)					
Heterogeneity: Tau^2=0.12; Chi^2=5.75, df=2(P=0.06); I^2=65.21%					
Test for overall effect: Z=1.76(P=0.08)					
Total (95% CI)	**107**	**99**		**100%**	**0.72[0.49,1.05]**
Total events: 54 (Probiotic), 68 (No intervention)					
Heterogeneity: Tau^2=0.08; Chi^2=6.93, df=3(P=0.07); I^2=56.72%					
Test for overall effect: Z=1.7(P=0.09)					
Test for subgroup differences: Chi^2=1.17, df=1 (P=0.28), I^2=14.74%					

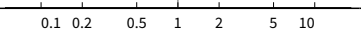


Analysis 1.9. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 9 No recovery (subgroup grade of hepatic encephalopathy).

Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Minimal					
Bajaj 2008	5/17	8/8		17.77%	0.32[0.16,0.66]
Mittal 2009	26/40	36/40		38.24%	0.72[0.56,0.93]
Subtotal (95% CI)	**57**	**48**		**56.01%**	**0.52[0.23,1.15]**
Total events: 31 (Probiotic), 44 (No intervention)					
Heterogeneity: Tau^2=0.26; Chi^2=4.53, df=1(P=0.03); I^2=77.93%					
Test for overall effect: Z=1.63(P=0.1)					
1.9.2 Overt					
Liu 2004	10/20	10/20		20.92%	1[0.54,1.86]
Sharma 2008	13/30	14/31		23.07%	0.96[0.55,1.69]
Subtotal (95% CI)	**50**	**51**		**43.99%**	**0.98[0.64,1.48]**
Total events: 23 (Probiotic), 24 (No intervention)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=0.11(P=0.92)					
Total (95% CI)	**107**	**99**		**100%**	**0.72[0.49,1.05]**
Total events: 54 (Probiotic), 68 (No intervention)					
Heterogeneity: Tau^2=0.08; Chi^2=6.93, df=3(P=0.07); I^2=56.72%					



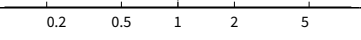
Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.7(P=0.09)					
Test for subgroup differences: Chi²=1.93, df=1 (P=0.16), I²=48.16%					



Favours probiotic — Favours control

Analysis 1.10. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 10 No recovery (subgroup duration of therapy).

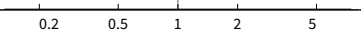
Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 1 month and less					
Liu 2004	10/20	10/20		21.73%	1[0.54,1.86]
Sharma 2008	13/30	14/31		23.41%	0.96[0.55,1.69]
Subtotal (95% CI)	**50**	**51**		**45.14%**	**0.98[0.64,1.48]**
Total events: 23 (Probiotic), 24 (No intervention)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%					
Test for overall effect: Z=0.11(P=0.92)					
1.10.2 Between 1 and 2 months					
Bajaj 2008	5/17	8/8		19.13%	0.32[0.16,0.66]
Subtotal (95% CI)	**17**	**8**		**19.13%**	**0.32[0.16,0.66]**
Total events: 5 (Probiotic), 8 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.1(P=0)					
1.10.3 More than 2 months					
Mittal 2009	36/40	36/40		35.73%	1[0.86,1.16]
Subtotal (95% CI)	**40**	**40**		**35.73%**	**1[0.86,1.16]**
Total events: 36 (Probiotic), 36 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**107**	**99**		**100%**	**0.8[0.51,1.25]**
Total events: 64 (Probiotic), 68 (No intervention)					
Heterogeneity: Tau²=0.14; Chi²=10.57, df=3(P=0.01); I²=71.6%					
Test for overall effect: Z=0.99(P=0.32)					
Test for subgroup differences: Chi²=9.21, df=1 (P=0.01), I²=78.29%					



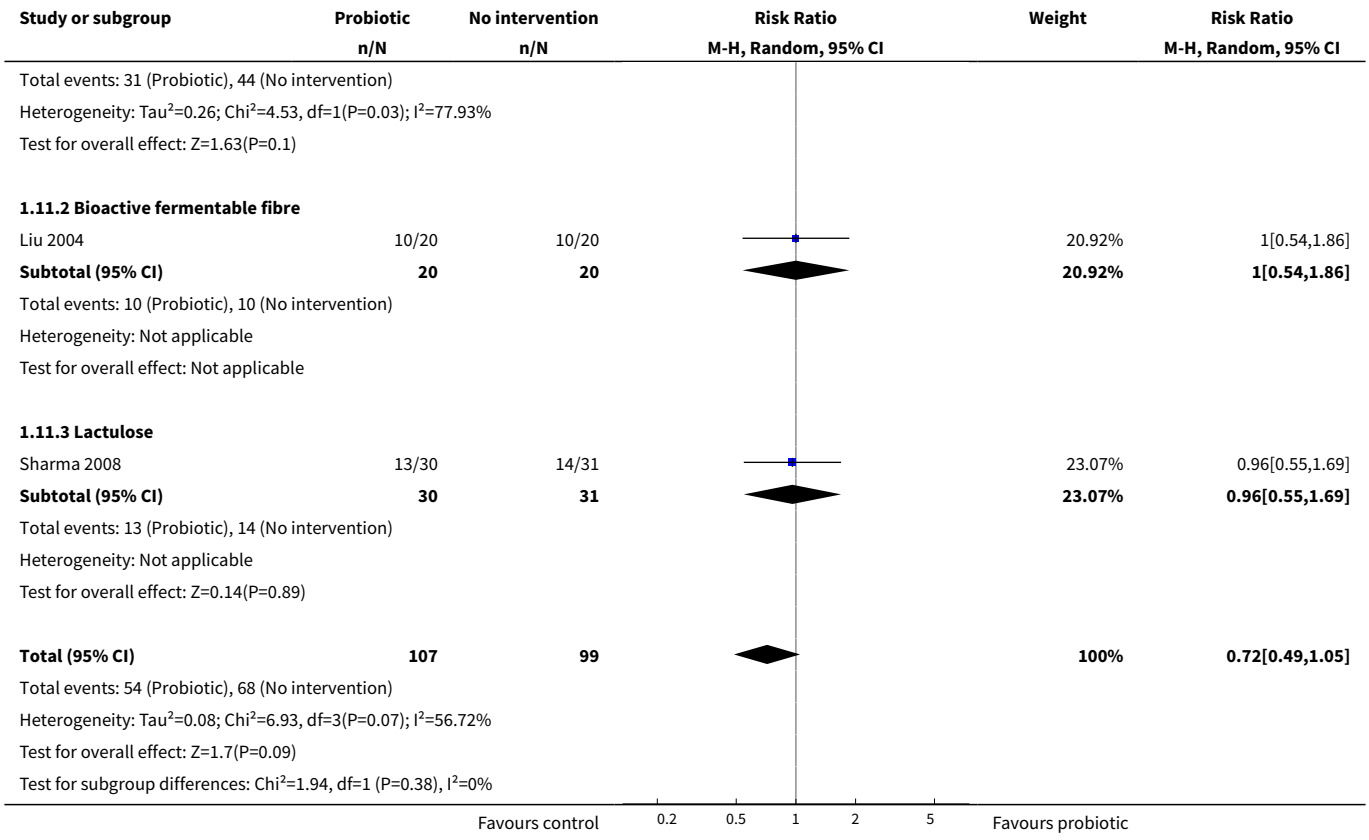
Favours probiotic — Favours control

Analysis 1.11. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 11 No recovery (subgroup co-interventions used).

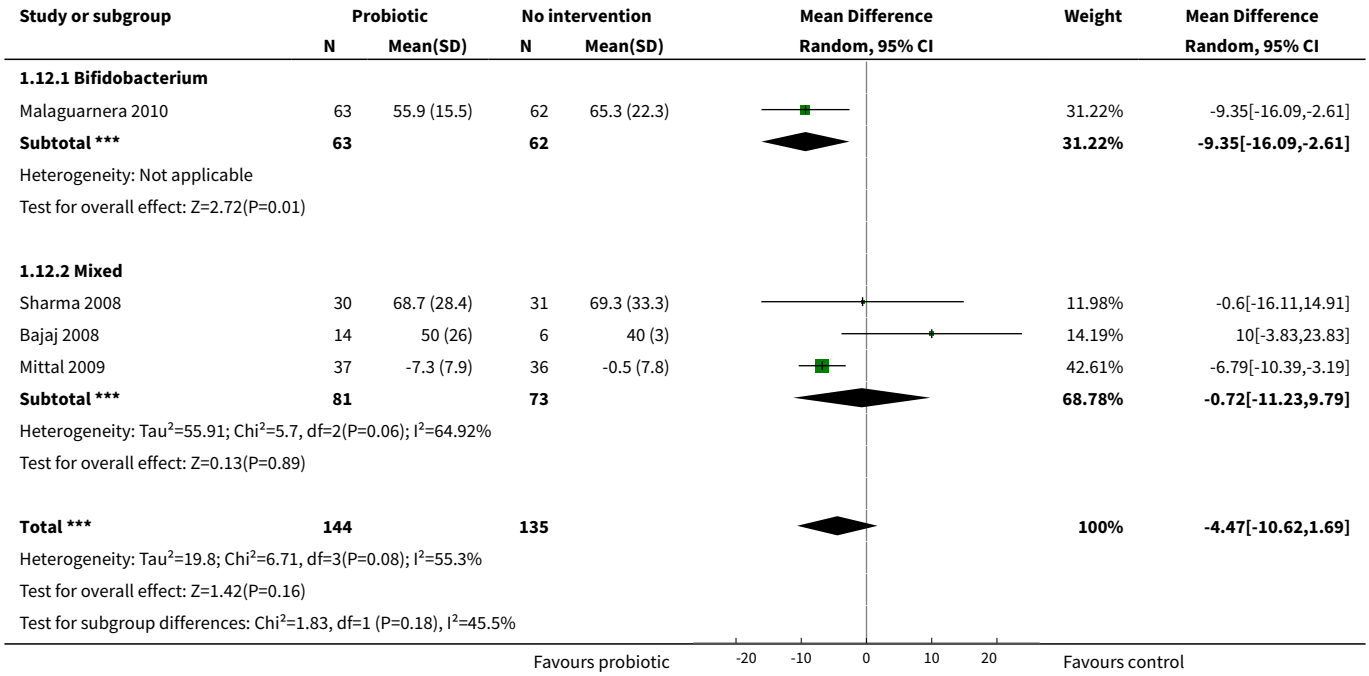
Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 No treatment					
Bajaj 2008	5/17	8/8		17.77%	0.32[0.16,0.66]
Mittal 2009	26/40	36/40		38.24%	0.72[0.56,0.93]
Subtotal (95% CI)	**57**	**48**		**56.01%**	**0.52[0.23,1.15]**



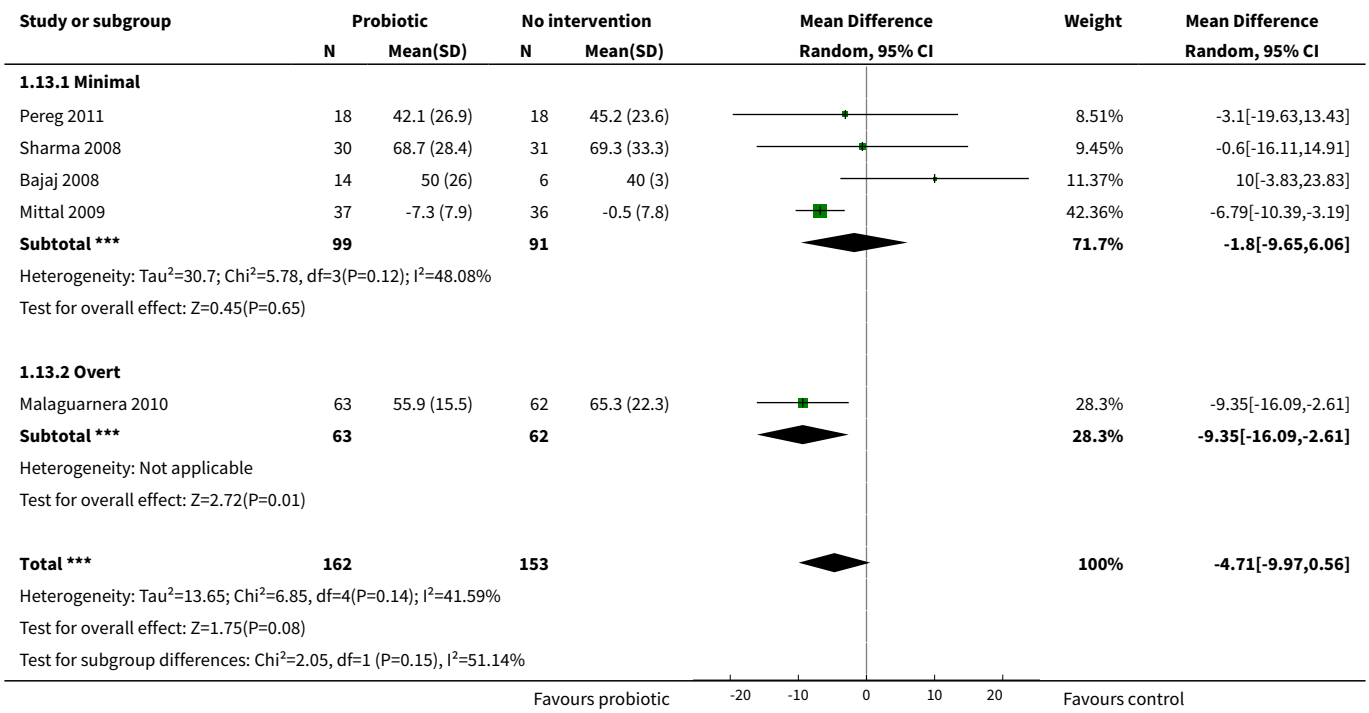
Favours control — Favours probiotic



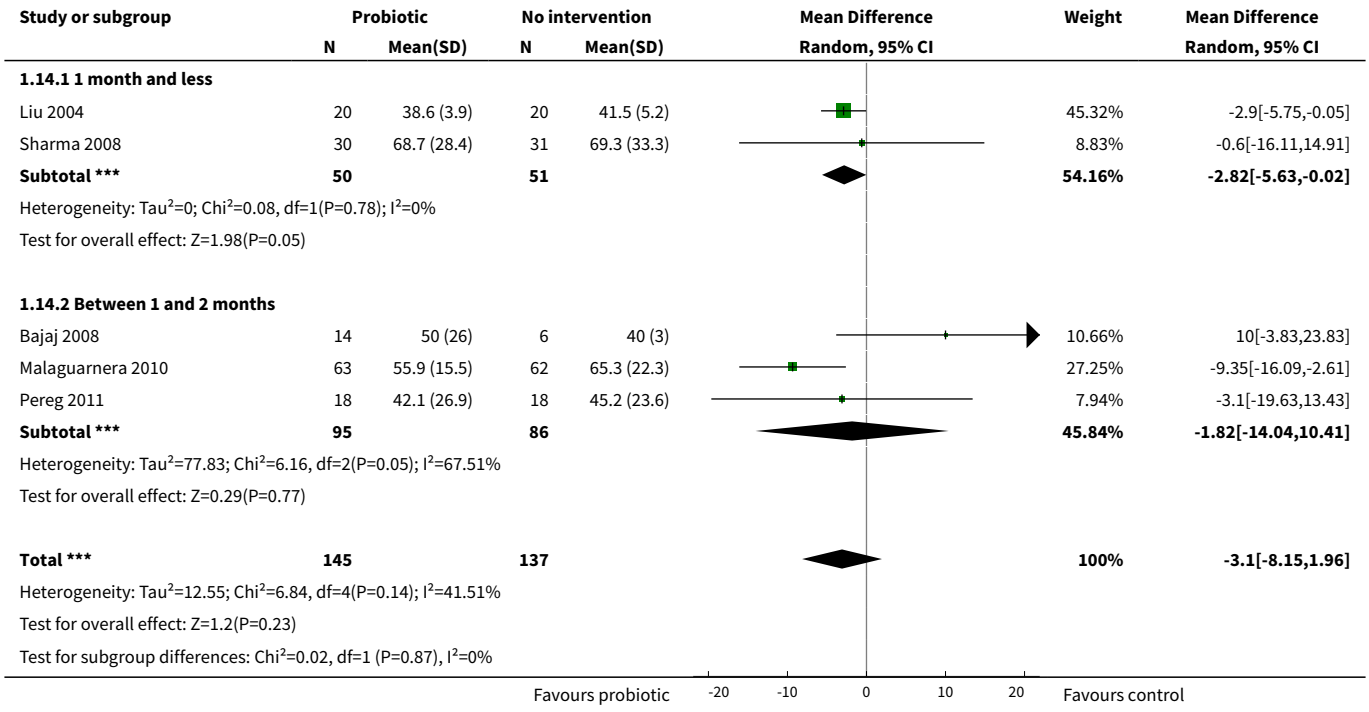
Analysis 1.12. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 12 Plasma ammonia concentration (subgroup type of probiotic used).



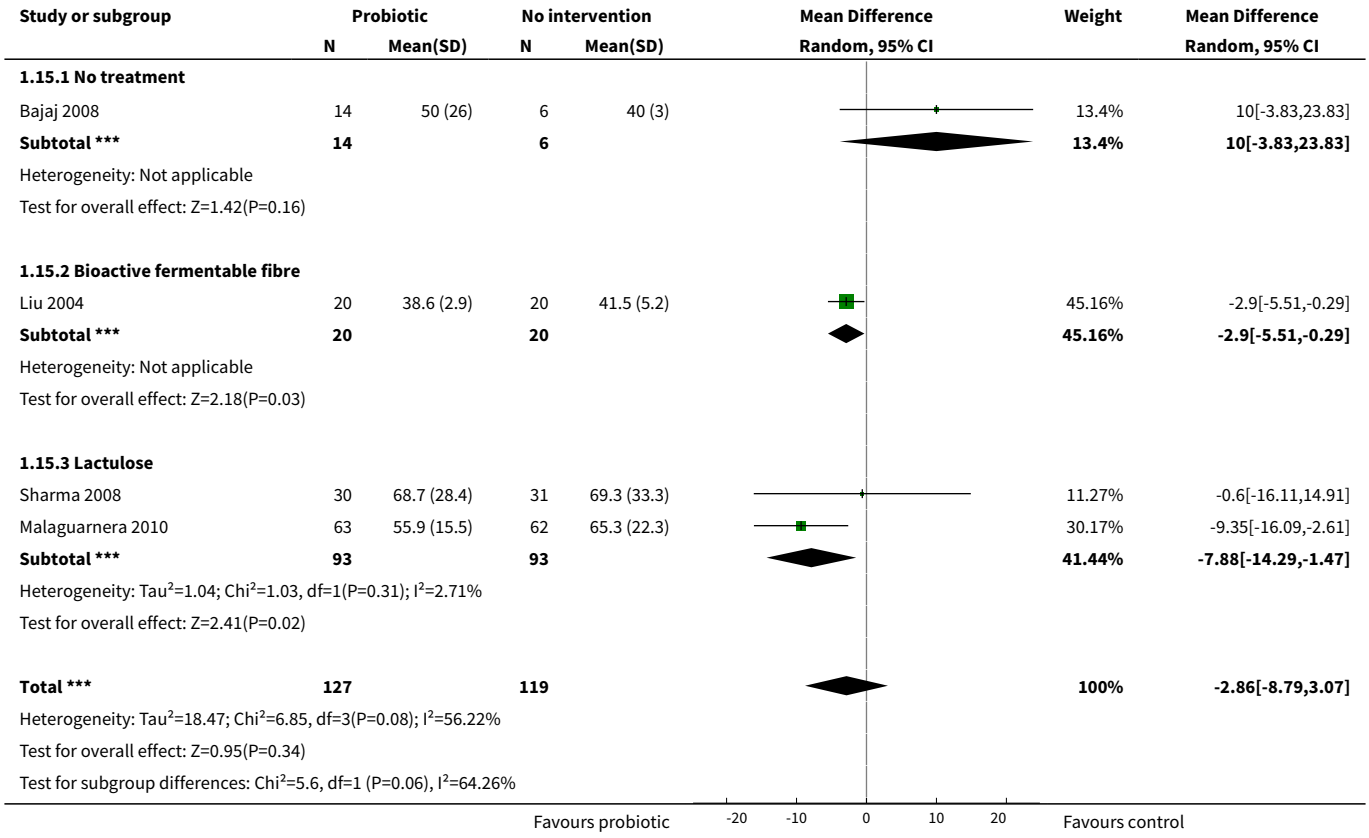
Analysis 1.13. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 13 Plasma ammonia concentration (subgroup grade of hepatic encephalopathy).



Analysis 1.14. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 14 Plasma ammonia concentration (subgroup duration of therapy).



Analysis 1.15. Comparison 1 Probiotic versus placebo/ no intervention, Outcome 15 Plasma ammonia concentration (subgroup co-interventions used).



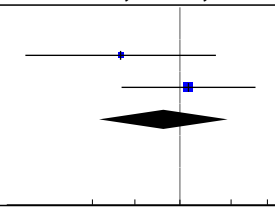
Comparison 2. Probiotic versus lactulose

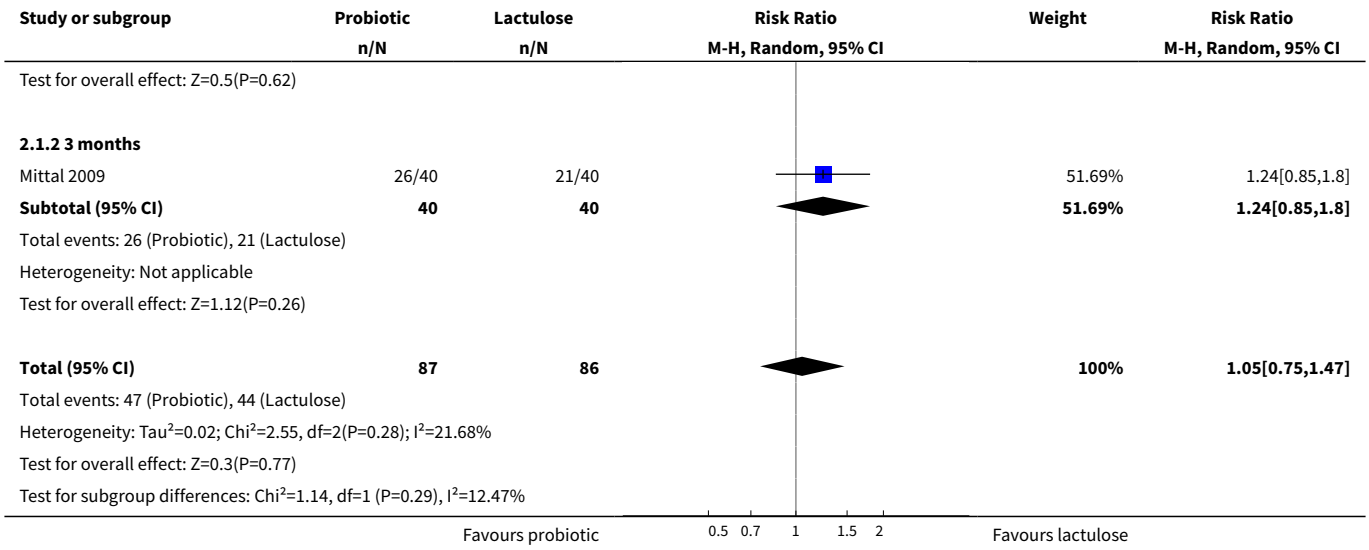
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No recovery (incomplete resolution of clinical symptoms)	3	173	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.75, 1.47]
1.1 1 month	2	93	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.53, 1.46]
1.2 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.85, 1.80]
2 Number of adverse events	2	111	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.06, 5.74]
2.1 1 month	1	31	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.19, 21.18]
3 Change of/or withdrawal from treatment	3	190	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.40, 3.03]
3.1 1 month	2	110	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.27, 2.64]
3.2 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 27.63]
4 Plasma ammonia concentration (µmol/L)	2	93	Mean Difference (IV, Random, 95% CI)	-6.61 [-30.05, 16.84]
4.1 1 month	2	93	Mean Difference (IV, Random, 95% CI)	-6.61 [-30.05, 16.84]
5 Change in plasma ammonia concentration (µmol/L)	1	77	Mean Difference (IV, Random, 95% CI)	1.16 [-1.96, 4.28]
6 Plasma ammonia concentration (subgroup type of probiotic used)	2	93	Mean Difference (IV, Random, 95% CI)	-6.61 [-30.05, 16.84]
6.1 Enterococcus SF68	1	31	Mean Difference (IV, Random, 95% CI)	-17.61 [-26.98, -8.24]
6.2 Mixed	1	62	Mean Difference (IV, Random, 95% CI)	6.40 [-10.10, 22.90]
7 Plasma ammonia concentration (subgroup grade of hepatic encephalopathy)	2	93	Mean Difference (IV, Random, 95% CI)	-6.61 [-30.05, 16.84]
7.1 Minimal	1	62	Mean Difference (IV, Random, 95% CI)	6.40 [-10.10, 22.90]
7.2 Overt	1	31	Mean Difference (IV, Random, 95% CI)	-17.61 [-26.98, -8.24]

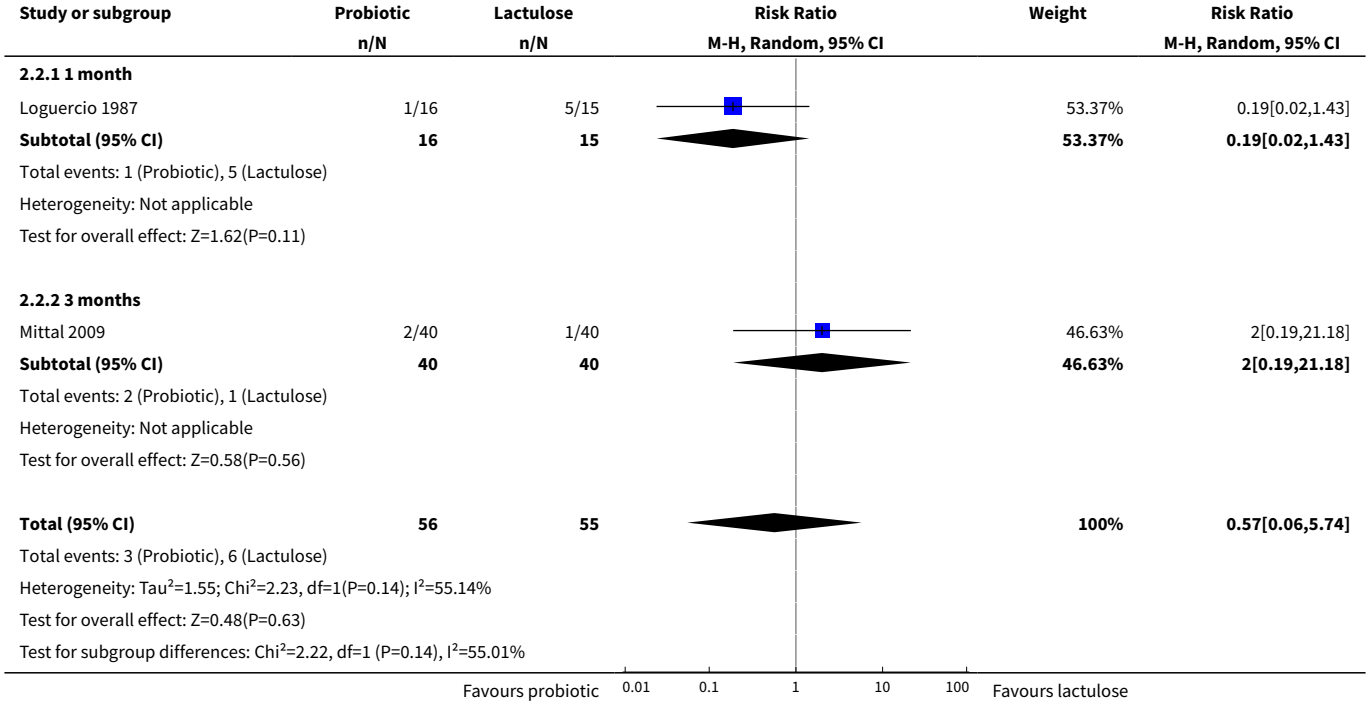
Analysis 2.1. Comparison 2 Probiotic versus lactulose, Outcome 1 No recovery (incomplete resolution of clinical symptoms).

Study or subgroup	Probiotic n/N	Lactulose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 1 month					
Loguercio 1987	6/16	9/15		17.26%	0.63[0.29,1.33]
Sharma 2008	15/31	14/31		31.05%	1.07[0.63,1.82]
Subtotal (95% CI)	**47**	**46**		**48.31%**	**0.88[0.53,1.46]**
Total events: 21 (Probiotic), 23 (Lactulose)					
Heterogeneity: Tau^2=0.03; Chi^2=1.31, df=1(P=0.25); I^2=23.53%					

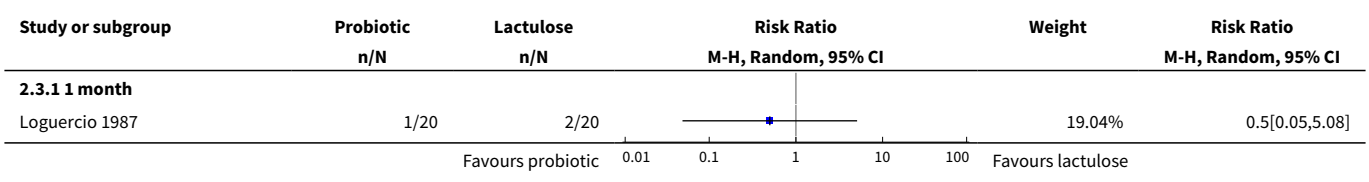


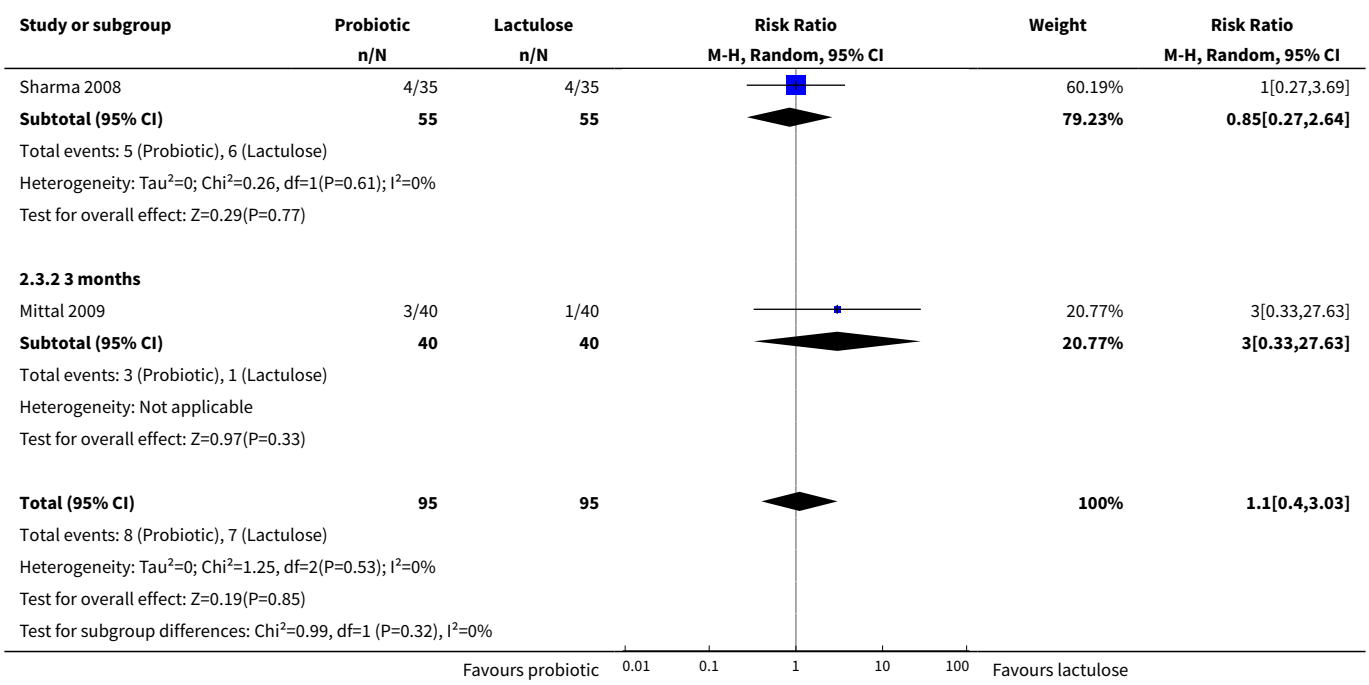


Analysis 2.2. Comparison 2 Probiotic versus lactulose, Outcome 2 Number of adverse events.

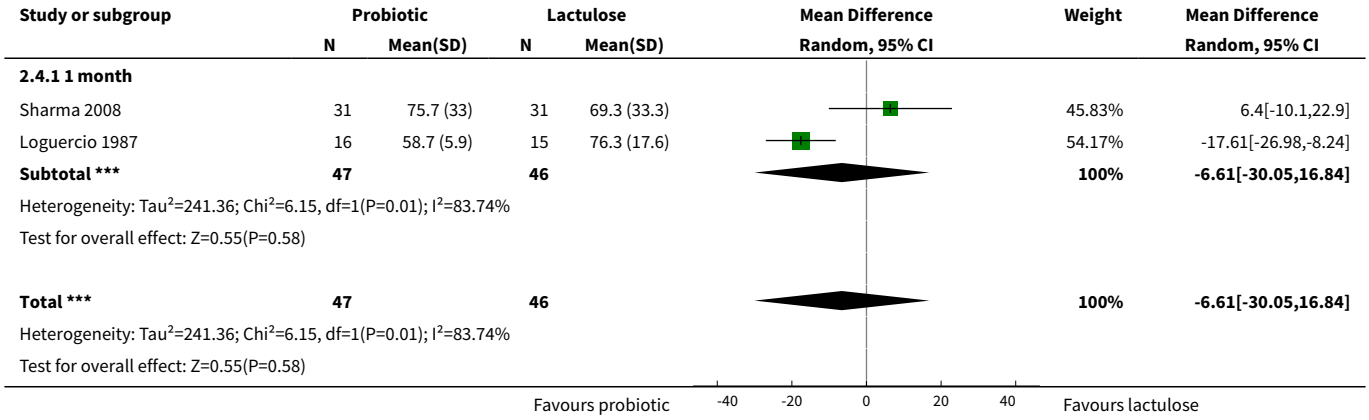


Analysis 2.3. Comparison 2 Probiotic versus lactulose, Outcome 3 Change of/or withdrawal from treatment.

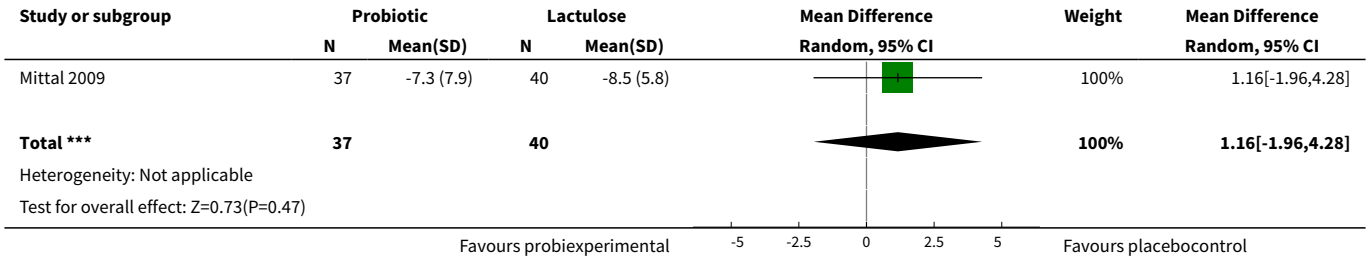




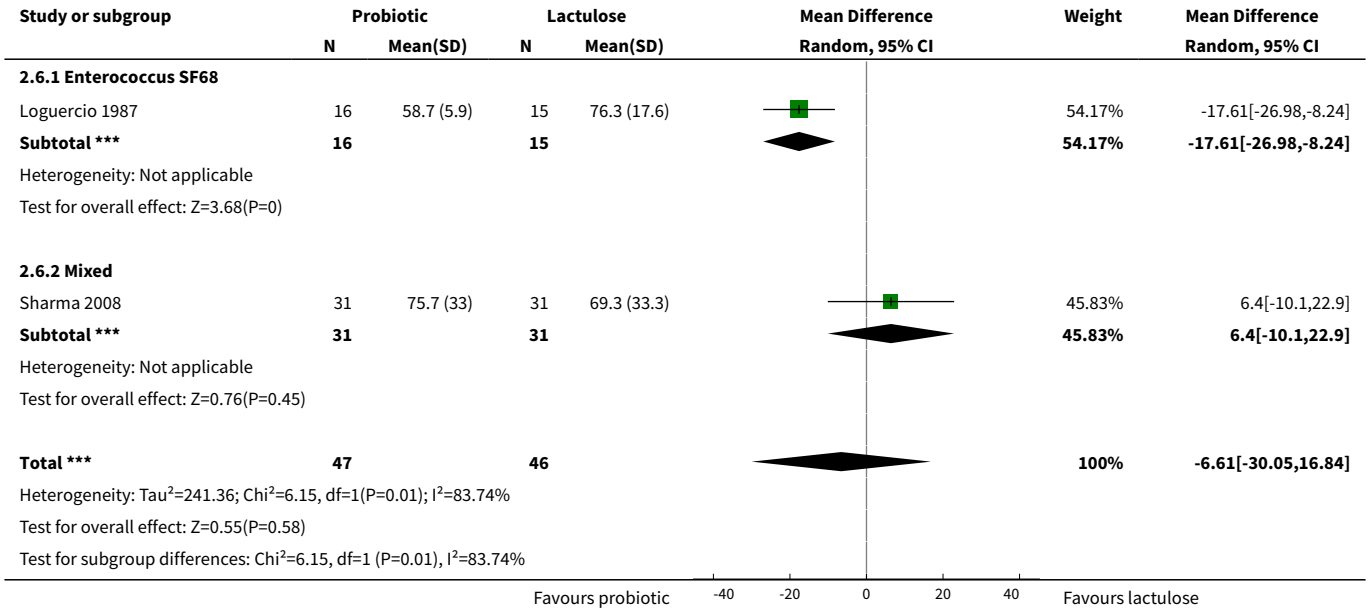
Analysis 2.4. Comparison 2 Probiotic versus lactulose, Outcome 4 Plasma ammonia concentration (µmol/L).



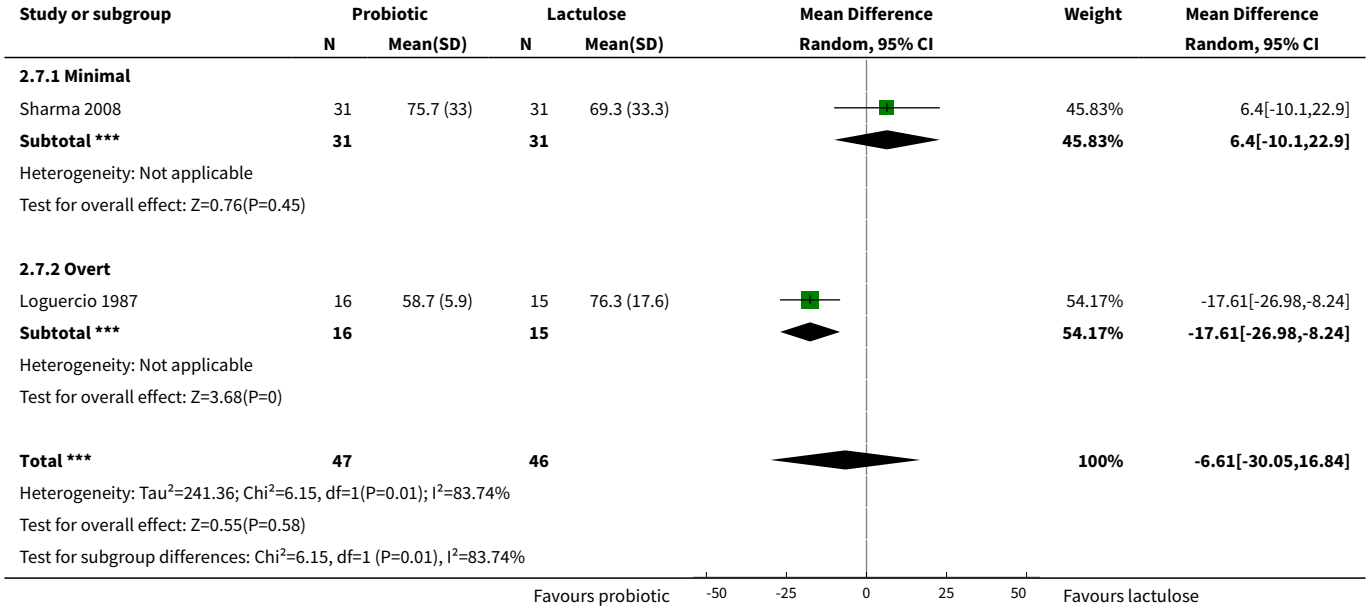
Analysis 2.5. Comparison 2 Probiotic versus lactulose, Outcome 5 Change in plasma ammonia concentration (µmol/L).



Analysis 2.6. Comparison 2 Probiotic versus lactulose, Outcome 6 Plasma ammonia concentration (subgroup type of probiotic used).



Analysis 2.7. Comparison 2 Probiotic versus lactulose, Outcome 7 Plasma ammonia concentration (subgroup grade of hepatic encephalopathy).



ADDITIONAL TABLES

Table 1. Types of probiotics used across studies

Study	Probiotics used
Bajaj 2008	*Streptococcus thermophilus, Lactobacillus bulgaricus, Lactobacillus acidophilus, Lactobacillus casei,* and *Bifidobacteria*.
Liu 2004	*Pediacoccus pentoseceus, Leuconostoc mesenteroides, Lactobacillus paracasei,* and *Lactobacillus plantarum*.
Loguercio 1987	*Enterococcus Lactic Acid bacteria* strain SF68.
Malaguarnera 2010	*Bifidobacterium* (subtype not available).
Mittal 2009	VSL#3 (containing *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus*).
Pereg 2011	Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium bifidum, and Streptococcus thermophiles (Bio-plus, Supherb, Israel).
Sharma 2008	*Streptococcus faecalis, Clostridium butyricum, Bacillus mesentricus,* and *Lactic acid bacillus.*

APPENDICES

Appendix 1. Search strategies

Database	Span of search	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	April 2011.	(probiot* OR lactobacil* OR bifidobacter*) AND ('hepatic encephalopath*' OR (liver AND (diseas* OR cirrhosis*)))
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 1, 2011.	#1 LIVER CIRRHOSIS explode all trees (MeSH) #2 (liver cirrhosis):ti,ab,kw #3 HEPATIC ENCEPHALOPATHY explode all trees (MeSH) #4 (hepatic encephalopathy):ti,ab,kw #5 (liver next cirrhosis) #6 (hepatic next encephalopathy) #7 (#1 or #2 or #3 or #4 or #5 or #6) #8 probiotics explode all trees (MeSH) #9 (probiotics):ti,ab,kw #10 lactobacillus explode all trees (MeSH) #11 (lactobacillus):ti,kw,ab #12 bifidobacterium explode all trees (MeSH) #13 (bifidobacterium):ti,kw,ab #14 (#8 or #9 or #10 or #11 or #12 or #13) #15 (#7 and #14)
MEDLINE (Ovid SP)	1950 to April 2011.	#1 randomised controlled trial.pt. #2 controlled clinical trial.pt. #3 randomized.ab. #4 placebo.ab. #5 drug therapy.fs.

(Continued)

		#6 randomly.ab. #7 trial.ab. #8 groups.ab. #9 or/1-8 #10 animals.sh. #11 9 not 10 #12 exp hepatic encephalopathy/ #13 hepatic encephalopathy.tw #14 exp liver cirrhosis/ #15 liver cirrhosis.tw #16 12 or 13 or 14 or 15 #17 exp probiotics/ #18 probiotic.tw #19 exp lactobacillus/ #20 lactobacillus.tw #21 exp bifidobacterium/ #22 bifidobacterium.tw #23 17 or 18 or 19 or 20 or 21 or 22 #24 11 and 16 and 23
EMBASE (OvidSP)	1980 to April 2011.	#1 random:.tw. #2 clinical trial:.mp. #3 exp health care quality/ #4 1 or 2 or 3 #5 exp hepatic encephalopathy/ #6 hepatic encephalopathy.tw #7 exp liver cirrhosis/ #8 liver cirrhosis.tw #9 5 or 6 or 7 or 8 #10 exp probiotics/ #11 probiotic.tw #12 exp lactobacillus/ #13 lactobacillus.tw #14 exp bifidobacterium/ #15 bifidobacterium.tw #16 10 or 11 or 12 or 13 or 14 or 15 #17 4 and 9 and 16
Science Citation Index Expanded (http://apps.isi-knowledge.com)	1900 to April 2011.	#1 Topic=(probiotic OR probiot* OR lactobacil* OR bifidobacter*) #2 Topic=(hepatic encephalopath* OR liver diseas*) #3 #1 AND #2 #4 Topic=(random* OR blind* OR placebo*) #5 #3 AND #4

CONTRIBUTIONS OF AUTHORS

RMG: Conceived the review, designed the protocol, and participated in all stages of the review.
AB: Was responsible for conducting the literature search, trial selection, data extraction, and manuscript preparation.
KW: Drafted the protocol and was responsible for trial selection, data extraction, and reviewed the manuscript.
SMR: Drafted the protocol, contributed to the search, provided content area advice, and reviewed the manuscript.
ACW: Drafted the protocol, provided methodological advice, contributed to study design, and reviewed the manuscript.

DECLARATIONS OF INTEREST

RMG: is a recipient of a postgraduate research scholarship from the National Health and Medical Research Council (NHMRC), Australia. This scholarship had no influence on the conduct of this review.
AB: None to declare.
KW: None to declare.
SMR: is an author of a trial included in the review. SMR had no influence on its inclusion, or data extraction and analysis.

ACW: None to declare.

SOURCES OF SUPPORT

Internal sources

- No financial support was received for the conduct of this review, Australia.

External sources

- No financial support was received for the conduct of this review, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The secondary outcome 'improvement: number of participants showing improvement or change in status as defined by each trial' was dropped from the review as it was not reported in any of the included trials and was felt to be unnecessary because the outcome 'recovery' conveyed similar information. While we initially planned to assess change in plasma ammonia concentration, this could not be achieved in all cases due to the presentation of results in articles. Therefore, we created a new outcome 'plasma ammonia concentration'. The time of day that outcomes were assessed was not reported in any trial and, therefore, not recorded in the review. Although it was not a component of our protocol, we acknowledge the importance of searching trial registers to locate ongoing and unpublished trials. Therefore, we searched the WHO international clinical trials registry platform. Details of this search are available under Electronic searches. We did not conduct fixed-effect meta-analyses as we anticipated heterogeneity, and hence favoured the more conservative random-effects model meta-analysis which allowed for within and amongst trial variability.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Gastrointestinal Agents [*therapeutic use]; Hepatic Encephalopathy [mortality] [*therapy]; Lactulose [*therapeutic use]; Probiotics [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans