

Article

Probiotics for management of functional abdominal pain disorders in children

Gordon, Morris, Farrell, Michael, Thomas, Adrian G, Akobeng, Anthony K and Wallace, Chris

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Probiotics for management of functional abdominal pain disorders in children (Protocol)

Gordon M, Farrell M, Thomas AG, Akobeng AK, Wallace C

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	6
REFERENCES	7
APPENDICES	7
DECLARATIONS OF INTEREST	11

[Intervention Protocol]

Probiotics for management of functional abdominal pain disorders in children

Morris Gordon¹, Michael Farrell², Adrian G Thomas³, Anthony K Akobeng⁴, Chris Wallace⁵

¹School of Medicine, University of Central Lancashire, Preston, UK. ²Medical Education, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, UK. ³Royal Manchester Children's Hospital, Manchester, UK. ⁴Sidra Medical & Research Center, Doha, Qatar. ⁵Pennine Acute Hospitals NHS Trust, Manchester, UK

Contact address: Morris Gordon, School of Medicine, University of Central Lancashire, Preston, UK. morris@betterprescribing.com, mgordon@uclan.ac.uk.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The primary objectives are to evaluate the efficacy and safety of probiotics for the management of IBS, abdominal migraine and functional abdominal pain in children.

BACKGROUND

Description of the condition

'Functional abdominal pain' is pain occurring in the abdomen that is not associated with any visible or detectable pathology. This represents a number of conditions and can be continuous or sporadic (recurrent). Although the exact cause is not identified, nervous signalling from the brain or chemicals from the gut may cause the bowel to be more sensitive to factors that normally do not cause pain (examples include gaseous distention or bowel stretching). Because of this change in bowel function associated with this type of pain, this is often referred to as functional abdominal pain.

The prevalence of childhood Irritable bowel syndrome (IBS) in the United States has been shown to be approximately 2.9% (Saps 2012), compared to a prevalence of 9.3% for childhood abdominal migraine and 0.3% for childhood functional abdominal pain (Van

Tilburg 2014). Functional abdominal pain disorders are extremely common in paediatric patients seen by gastroenterologists. In fact, almost 25% of children assessed for bowel problems are diagnosed with functional abdominal pain (Williams 1996).

The diagnosis of functional abdominal pain in children has evolved with time, most noticeably through the work of the ROME III process that led to the recognition of a group of 'abdominal pain-related functional gastrointestinal disorders' (Rasquin 2006). More recently, the Rome IV process has updated this to 'functional abdominal pain disorders' (Hyams 2016). Rome III notes that the term functional abdominal pain was used generically and interchangeably to refer to the whole group of abdominal pain-related problems and this clarification particularly has impact for research purposes.

The current categorization of functional abdominal pain includes: IBS, abdominal migraine and functional abdominal pain. Functional dyspepsia is not included in this category as this condi-

tion includes a different set of symptoms, treatments, and a much more discrete presentation than the other three conditions (Hyams 2016).

The diagnosis of IBS must include all of the following:

1. Abdominal pain at least four days per month associated with one or more of the following:
 - a. Related to defecation;
 - b. A change in frequency of stool; and
 - c. A change in form (appearance) of stool.
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS).
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

These criteria should be fulfilled for the last three months with symptom onset at least six months before diagnosis of IBS.

The diagnosis of abdominal migraine must include all of the following:

1. Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting one hour or more (should be the most severe and distressing symptom);
2. Episodes are separated by periods of usual health lasting weeks to months;
3. The pain is incapacitating and interferes with normal activities;
4. Stereotypical pattern and symptoms in the individual patient;
5. The pain is associated with 2 or more of the following:
 - a. Anorexia;
 - b. Nausea;
 - c. Vomiting;
 - d. Headache;
 - e. Photophobia;
 - f. Pallor; and
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

These criteria should be fulfilled two or more times in the past 12 months.

The diagnosis of functional abdominal pain must include all of the following:

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g. eating, menses);
2. Insufficient criteria for IBS, functional dyspepsia, or abdominal migraine;
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition.

These criteria should be met at least once per week for at least two months prior to diagnosis.

Description of the intervention

Probiotics are microorganisms that, when ingested, are thought to have beneficial effects on a person's health. Research is ongoing into the use of probiotics for the treatment of various gastroin-

testinal illnesses including inflammatory pathological disorders, functional disorders, and chronic non-pathological disorders. In infants, it has been proposed that supplying probiotic bacteria can redress the balance of intestinal bacteria and provide a healthier intestinal microbiota landscape with resulting impact on transit through the gut (Savino 2013). In the context of constipation, these mechanisms have been proposed to enhance colonic peristalsis and shorten whole gut transit time (Waller 2011).

How the intervention might work

The use of microorganisms might change the composition bacterial colonies in the bowel and reduce inflammation, as well as promoting normal gut physiology and thereby reducing functional symptoms. Some probiotics may influence colonic motility by softening the stool, changing secretion and absorption of water and electrolytes, modifying smooth muscle cell contractions, increasing the production of lactate and short-chain fatty acids, and lowering intraluminal pH (Waller 2011). Additionally, as essentially a food supplement, probiotics are generally perceived as having a good safety profile, particularly when compared with other treatments.

Why it is important to do this review

As interest in probiotics for the treatment of gastrointestinal disorders is relatively new, until recently there has been a general paucity of research on the use of these agents. In the context of functional abdominal pain, a previous Cochrane review found only three studies examining probiotics (Huertas-Ceballos 2009). It must be noted that as Huertas-Ceballos 2009 considered several dietary interventions, the search strategy was not focused on probiotics. Additionally, more contemporaneous studies have now been published (Francavilla 2010; Romano 2010). With this recent increase in published studies, a new and focused synthesis of the evidence using the Cochrane Collaboration approach is needed.

OBJECTIVES

The primary objectives are to evaluate the efficacy and safety of probiotics for the management of IBS, abdominal migraine and functional abdominal pain in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) will be considered for inclusion.

Types of participants

Participants will include children between 4 and 18 years of age with a diagnosis of functional abdominal pain disorder. Participants could include children with IBS, abdominal migraine and functional abdominal pain as defined by Rome IV criteria (Hyams 2016). This is in line with the Rome IV criteria which do not cover infants or toddlers. A separate set of diagnostic criteria address this group (Hyams 2016). Participants who meet earlier Rome criteria will also be included. Studies including children with Hirschsprung's disease, previous bowel surgery or complex congenital disorders will not be included.

Types of interventions

Studies that assess probiotic preparations in any form (powder, liquid, capsule) through any route (either oral or rectal) as a single species or as a cocktail of multiple species or treatments (for example, symbiotic) compared to placebo, no treatment or any other interventional preparation will be considered for inclusion. Studies with probiotics as adjunct therapy will also be considered for inclusion.

Types of outcome measures

Primary outcomes

The primary outcomes measures considered will be:

- a. Global improvement or treatment success as defined by primary studies;
- b. Severity of pain or change in severity of pain; and
- c. Frequency of pain or change in frequency of pain.

Secondary outcomes

Secondary outcomes will include:

- a. Serious adverse events;
- b. Withdrawal due to adverse events;
- c. Adverse events;
- d. School performance or change in school performance or attendance;
- e. Social and psychological functioning or change in social and psychological functioning; and
- f. Quality of life or change in quality life measured using any validated measurement tool.

Search methods for identification of studies

Electronic searches

Electronic Resources

We will identify relevant trials by searching the following electronic sources:

1. PubMed (from inception to present);
2. MEDLINE (from inception to present);
3. EMBASE (from inception to present);
4. CENTRAL; and
5. The Cochrane IBD Group Specialized Trials Register.

The search strategies are shown in [Appendix 1](#). We will not restrict the searches by date or language. Studies published in a non-English language will be professionally translated in full.

Searching other resources

Reference Searching

We will search the references of all included studies and relevant systematic reviews to identify studies missed by the search strategies.

Personal contacts

We will contact leaders in the field to try and identify other relevant studies.

Manufacturers

Manufacturers of probiotic agents will be contacted to try and identify other studies.

Trial Registries

We will also search [clinicaltrials.gov](#) and the WHO Trials portal (ICTRP) to identify ongoing studies.

Grey Literature

We will search Google, Google Scholar and the OpenGrey Repository using the main search terms. We will hand-search conference proceedings from Digestive Disease Week, United European Gastroenterology Week and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition annual scientific meeting from the past two years to identify other potentially relevant studies that may not be published in full. Concerns have been raised regarding the accuracy of data reported in abstract publications (Pitkin 1999). Therefore, where references to relevant unpublished or ongoing studies are identified, we will make attempts to collect sufficient extra information to allow inclusion in this systematic review. Studies from the grey literature will only be included if sufficient data are reported to judge eligibility for inclusion. If data are incomplete, we will contact the study authors in order to verify the eligibility of the study and we will only include the study if suitable data to assess quality and outcomes are supplied.

Data collection and analysis

Selection of studies

Two authors (CW and MG) will independently screen titles, abstracts, and full reports for eligibility against the inclusion criteria. Specifically, they will:

- Collate the search results using reference management software and remove any duplicate records;
- Examine titles and abstracts to remove results that are not relevant;
- Retrieve full texts of potentially relevant reports;
- Link together multiple reports that are found for the same study;
- Examine full text reports for studies that meet the inclusion criteria;
- Correspond with primary study investigators, to clarify study eligibility when needed; and
- At all stages, the authors will record reasons for inclusion and exclusion of studies, resolving any disagreements through reaching consensus. When consensus cannot be reached, we will consult with a third author (AA).

Data extraction and management

We will develop data extraction forms a priori to extract information on relevant features and results of included studies. Two authors (CW and MG) will independently extract and record data on a predefined checklist. Extracted data will include the following items:

- Characteristics of patients (age, gender, disease distribution, disease duration, activity index);
- Inclusion and exclusion criteria of studies;
- Total number of patients originally assigned to each intervention group;
- Intervention: type and amount of probiotics;
- Control: no intervention, placebo or other interventions;
- Concurrent medications; and
- Outcomes: time of assessment, length of follow-up, type of symptom score used, and adverse events.

Assessment of risk of bias in included studies

Two review authors (CW and MG) will independently assess the risk of bias of included studies using the Cochrane risk of bias tool (Higgins 2011a). We will assess the following items: sequence generation; allocation concealment; blinding of participants, parents and health professionals; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other potential threats to validity. We will judge each domain as being at 'low', 'high', or 'unclear' risk of bias. We will compare the judgments and discuss and resolve any inconsistencies in the assessments. A third review author (AA) will resolve any disagreements.

Sequence generation for randomisation

We will only consider RCTs for inclusion in the review. We will assess randomisation as being at low risk of bias where the procedure for random sequence generation was explicitly described. Examples include computer-generated random numbers, a random numbers table, or coin-tossing. Where no description is given, we will contact the authors for further information.

Allocation concealment

We will assess concealment of treatment allocation as being at low risk of bias if the procedure was explicitly described and adequate efforts were made to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment. Examples include centralised randomisation, numbered or coded containers, or sealed envelopes. Procedures considered to have a high risk of bias include alternation or reference to case record numbers or dates of birth. Where no description was given of the method of allocation concealment, we will contact the study authors and, where we don't receive a response, we will assign a judgment of unclear risk of bias.

Blinding of participants, parents and health professionals

In this context, the intervention is administered by parents as well as directly by children, so in effect, we will consider them both the targets of the blinding procedures. We will primarily assess the risk of bias associated with the blinding of participants based on the likelihood that such blinding is sufficient to ensure they had no knowledge of which intervention they received. We will note the blinding of health professionals if reported.

Blinding of outcome assessment

For each included study, we will describe the methods used, if any, to blind the outcome assessors from knowledge of which intervention a participant received. We will judge studies to be at low risk of bias if outcome assessors blinded, or where we consider that the lack of blinding could not have affected the results. If blinding was not done or was not possible because of the nature of the intervention, we will judge the study to be at high risk of bias because it is possible that the lack of blinding influenced the results. If no description is given, we will contact the study authors for more information, and if we do not receive a response, we will assign a judgment of unclear risk of bias.

Incomplete outcome data

Incomplete outcome data essentially includes attrition, exclusions, and missing data. We will assign a judgment of low risk of bias in the following instances:

1. If participants included in the analysis are exactly those who were randomised into the trial; missing outcome data are balanced in terms of numbers across intervention groups, with similar reasons for missing data across groups; or if there are no missing outcome data;

2. If for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not sufficient to have a clinically relevant impact on the intervention effect estimate;

3. If for continuous outcome data, the plausible effect size (mean difference) among missing outcomes is not sufficient to have a clinically relevant impact on observed effect size; or

4. If missing data have been imputed using appropriate methods.

We will assign a judgment of high risk of bias in the following instances:

1. When reasons for missing outcome data are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups;

2. When for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is sufficient to induce clinically relevant bias in the intervention effect estimate;

3. When for continuous outcome data, the plausible effect size (mean difference) among missing outcomes is sufficient to induce clinically relevant bias in the observed effect size;

4. When an 'as-treated' analysis is carried out in cases where there is a substantial departure of the intervention received from that assigned at randomisation; or

5. When there is a potentially inappropriate application of simple imputation.

We will assign a judgment of unclear risk of bias in the following instances:

1. When there is insufficient reporting of attrition or exclusions, or both, to permit a judgment of low or high risk of bias;

2. When the study reported incomplete outcome data; or

3. When the trial did not clearly report the numbers randomised to intervention and control groups.

Selective outcome reporting

We will assess the reporting of outcomes as being at low risk of bias if all outcomes pre-specified in the study protocol are reported in the study manuscript or secondary publications. If no protocol exists we will assign a rating of low risk of bias if the authors report on the outcomes described in the methods section of the study manuscript. We will evaluate all study publications (primary and secondary) to ensure that there is no evidence of selective outcome reporting. If no description is given, we will contact the authors for more information, and if we do not receive a response, we will assign a judgment of unclear risk of bias. If there is evidence of se-

lective reporting (deviation from protocol, key planned outcomes not reported), we will assign a judgment of high risk of bias.

Other potential threats to validity

We will consider other potential sources of bias including early trial termination (e.g. if a study was stopped early due to a data-dependent process) and baseline imbalance between treatment groups. We will assess the study as being at low risk of bias if it appears to be free from such threats to validity. When the risk of bias is unclear from the published information, we will attempt to contact the study authors for clarification. If this is not forthcoming, we will assess these studies as being at unclear risk of bias.

GRADE and 'Summary of findings' tables

We will assess the overall quality of evidence supporting the primary outcomes (i.e. global improvement or treatment success, severity of pain and frequency of pain) and selected secondary outcomes (adverse events, serious adverse events and withdrawal due to adverse events) using the GRADE approach (Guyatt 2008; Schünemann 2011). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect, or association, reflects the item being assessed. RCTs start as high-quality evidence, but may be downgraded due to risk of bias (methodological quality), indirectness of evidence, unexplained heterogeneity, imprecision (sparse data), and publication bias. Two review authors (CW and MG) will independently assess the overall quality of the evidence for each outcome after considering each of these factors and grade them as follows:

1. high quality: further research is very unlikely to change confidence in the estimate of effect;

2. moderate quality: further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate;

3. low quality: further research is very likely to have an important impact on confidence in the estimate of effect, and is likely to change the estimate; or

4. very low quality: any estimate of effect is very uncertain.

Measures of treatment effect

Dichotomous outcomes

For dichotomous outcomes, we will calculate the risk ratio (RR) and corresponding 95% confidence interval (95%CI).

Continuous outcomes

For continuous outcomes, we will calculate the mean difference (MD) and corresponding 95% CI.

Unit of analysis issues

Where cross-over trials are included, we will extract data from the first phase of the study (i.e. before the cross-over occurred). We will conduct separate analyses for comparisons between probiotics versus placebo, and probiotics versus active comparator (e.g. lactulose). To deal with repeated observations on participants, we will determine appropriate fixed intervals for follow-up for each outcome. To deal with events that may re-occur (e.g. adverse events), we will report on the proportion of participants who experience at least one event. If we encounter multiple treatment groups (e.g. different probiotic dose groups or different probiotic species), we will divide the placebo group across the treatment groups or we will combine probiotic groups to create a single pair-wise comparison as appropriate.

Dealing with missing data

Where data are missing, we will contact the corresponding authors of included studies to supply any unreported data. For all outcomes in all studies, we will carry out analyses as far as possible on an intention-to-treat (ITT) basis; that is, we will attempt to include all participants randomised to each group in the analyses, and we will analyse all participants in the group to which they were allocated regardless of whether or not they received the allocated intervention. For missing continuous data, we will estimate standard deviations from other available data, such as standard errors, or we will impute them using the methods suggested in [Higgins 2011b](#). We will conduct analyses for continuous outcomes based on participants completing the trial, in line with available case analysis; this will assume that data are missing at random. If there is a discrepancy between the number randomised and the number analysed in each treatment group, we will calculate and report the percentage lost to follow-up in each group. When it is not possible to obtain missing data, we will record this in the data collection form, report it in the 'Risk of bias' table, and discuss the extent to which the missing data could alter the results and hence the conclusions of the review. We will conduct sensitivity analyses to explore the impact of including studies with high levels of missing data on the overall estimate of treatment effect.

Assessment of heterogeneity

Heterogeneity among trial results will be assessed by visual inspection of forest plots and by calculating the Chi^2 test (a P value of 0.10 is regarded as statistically significant heterogeneity). We will also use the I^2 statistic to quantify the effect of heterogeneity ([Higgins 2003](#)). We will conduct sensitivity analyses as appropriate to investigate heterogeneity. For example, if a pooled analysis shows statistically significant heterogeneity and a visual inspection of the forest plot identifies studies that may have contributed to this heterogeneity, the analysis will be repeated excluding these studies to see if this explains the heterogeneity.

Assessment of reporting biases

If an appropriate number of studies are pooled for meta-analysis (≥ 10 studies), we plan to investigate the possibility of publication bias through the construction of funnel plots (trial effects versus trial size).

Data synthesis

Data from individual trials will be combined for meta-analysis when the interventions, patient groups and outcomes are deemed to be sufficiently similar (determined by consensus). We will calculate the pooled RR and corresponding 95% CI for dichotomous outcomes. We will calculate the pooled MD and corresponding 95% CI for continuous outcomes that were measured using the same units. We will calculate the pooled standardised mean difference (SMD) and 95% CI when different scales are used to measure the same underlying construct evaluate the same underlying construct. Meta-analysis will be carried out using a random-effects model. The Cochrane Collaboration review manager (RevMan) software will be used for data analysis. Data will be analysed according to ITT principle. Patients with final missing outcomes will be assumed to be treatment failures. Analyses will be grouped by length of follow-up. Data will not be pooled for meta-analysis if a high degree of heterogeneity is detected (i.e. $I^2 > 75\%$).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be carried out to further study the effects of a number of variables on the outcomes including:

- a. Specific probiotic preparation or species;
- b. Probiotic dose;
- c. Length of therapy, follow-up;
- d. Specifically what, if any agents, were initially allowed in the protocol to clear any impaction (such as enemas);
- e. Whether the probiotic was sole therapy or adjunct therapy; and
- f. Type of functional pain disorder (i.e. IBS, abdominal migraine or functional abdominal pain, in line with Rome IV criteria ([Hyams 2016](#))).

Sensitivity analysis

Sensitivity analyses will be conducted based on the following:

- a. Dropouts and exclusions, by conducting worst-case versus best-case scenario analyses;
- b. Random-effects versus fixed-effect models;
- c. Studies published in full versus abstract; and
- d. Removing studies judged to be at high risk of bias.

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REFERENCES

Additional references

Francavilla 2010

Francavilla R, Miniello V, Magistà AM, De Canio A, Bucci N, Gagliardi F, et al. A randomized controlled trial of *Lactobacillus GG* in children with functional abdominal pain. *Pediatrics* 2010;**126**(6):1445–52.

Higgins 2011a

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

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Huertas-Ceballos 2009

Huertas-Ceballos AA, Logan S, Bennett C, Macarthur C. Dietary interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD003019.pub3]

Hyams 2016

Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood Functional Gastrointestinal Disorders: Child/Adolescent. *Gastroenterology* 2016;**150**(6):1456–68.

Pitkin 1999

Pitkin RM, Branagan MA, Burmeister LF. Accuracy of Data in Abstracts of Published Research Articles. *JAMA* 1999; **281**(12):1110–1.

Rasquin 2006

Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staino A, et al. Childhood Functional Gastrointestinal Disorders: Child/Adolescent. *Gastroenterology* 2006;**130**(5): 1527–37.

Romano 2010

Romano C, Ferrau V, Cavataio F, Iacono G, Spina M, Lionetti E, et al. *Lactobacillus reuteri* in children with functional abdominal pain (FAP). *Journal of Paediatrics and Child Health* 2010;**50**(10):E68-71.

Saps 2012

Saps M, Adams P, Bonilla S, Chogle A, Nichols-Vinueza D. Parental report of abdominal pain and abdominal pain-related functional gastrointestinal disorders from a community survey. *Journal of Pediatric Gastroenterology and Nutrition* 2012;**55**(6):707–10.

Savino 2013

Savino F, Ceratto S, Opramolla A, Locatelli E, Tarasco V, Amaretti A, et al. Coliforms and infant colic: fish analysis of fecal samples of breast fed and formula fed infants. *Journal of Pediatric Gastroenterology and Nutrition* 2013;**56**:472.

Van Tilburg 2014

Van Tilburg MAL, Walker L, Palsson O, Kim SK, Spiegel BM, Spiller RC, et al. Prevalence of child/adolescent functional gastrointestinal disorders in a national U.S. community sample. *Gastroenterology* 2014;**146**(5 Suppl 1): S143–4.

Waller 2011

Waller PA, Gopal PK, Leyer GJ, Ouwehand AC, Reifer C, Stewart ME, et al. Dose-response effect of Bifidobacterium lactis HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. *Scandinavian Journal of Gastroenterology* 2011;**46**(9):1057–64.

Williams 1996

Williams K, Chambers M, Logan S, Robinson D. Association of common health symptoms with bullying in primary school children. *BMJ* 1996;**313**(7048):17–9.

* Indicates the major publication for the study

APPENDICES

Appendix I. Sample search strategy

EMBASE

1. random\$.mp.
2. factorial\$.mp.
3. (crossover\$ or cross over\$ or cross-over\$).mp.
4. placebo\$.mp.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).mp.
9. (double\$ adj blind\$).mp.
10. (tripl\$ adj blind\$).mp.
11. assign\$.mp.
12. allocat\$.mp.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. exp Probiotics/
20. exp Synbiotics/
21. probiotic*.tw.
22. synbiotic*.tw.
23. exp Lactobacillus/
24. lactobacill*.tw.
25. bacill*.tw.
26. exp Bifidobacterium/
27. (bifidus or bifidobacter*).tw.
28. exp Streptococcus thermophilus/
29. streptococcus thermophilus.tw.
30. streptococc*.tw.
31. exp Lactococcus/
32. lactococc*.tw.
33. Bacillus subtilis/
34. bacillus subtilis.tw.
35. exp Enterococcus/
36. exp Enterococcus faecium/ or Enterococcus faecalis/
37. exp Saccharomyces/
38. saccharomyc*.tw.
39. leuconostoc.tw.
40. pediococc*.tw.
41. bulgarian bacillus.tw.
42. (beneficial adj3 bacter*).tw.
43. (Escherichia coli or "E. coli").tw.
44. Yeast.tw.
45. (fungus or fungi).tw.
46. (VSL# 3 or VSL 3).tw.
47. or/19-46

48. (abdominal pain or FAPS).tw.
49. Functional abdominal.tw.
50. Bowel pain.tw.
51. Bowel discomfort.tw.
52. Stomach pain.tw.
53. Stomach discomfort.tw.
54. (chronic functional abdominal pain or CFAP).tw.
55. exp irritable bowel syndrome/
56. (irritable bowel or IBS).tw.
57. functional dyspepsia.tw.
58. abdominal migraine.tw.
59. or/48-58
60. 18 and 47 and 59

MEDLINE

1. random\$.mp.
2. factorial\$.mp.
3. (crossover\$ or cross over\$ or cross-over\$).mp.
4. placebo\$.mp.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).mp.
9. (double\$ adj blind\$).mp.
10. (tripl\$ adj blind\$).mp.
11. assign\$.mp.
12. allocat\$.mp.
13. randomized controlled trial/
14. or/1-13
15. exp Probiotics/
16. exp Synbiotics/
17. probiotic*.tw.
18. synbiotic*.tw.
19. exp Lactobacillus/
20. lactobacill*.tw.
21. bacill*.tw.
22. exp Bifidobacterium/
23. (bifidus or bifidobacter*).tw.
24. exp Streptococcus thermophilus/
25. streptococcus thermophilus.tw.
26. streptococc*.tw.
27. exp Lactococcus/
28. lactococc*.tw.
29. Bacillus subtilis/
30. bacillus subtilis.tw.
31. exp Enterococcus/
32. exp Enterococcus faecium/ or Enterococcus faecalis/
33. exp Saccharomyces/
34. saccharomyc*.tw.
35. leuconostoc.tw.
36. pediococc*.tw.
37. bulgarian bacillus.tw.
38. (beneficial adj3 bacter*).tw.
39. (Escherichia coli or "E. coli").tw.

- 40. Yeast.tw.
- 41. (fungus or fungi).tw.
- 42. (VSL# 3 or VSL 3).tw.
- 43. or/15-42
- 44. (abdominal pain or FAPS).tw.
- 45. Functional abdominal.tw.
- 46. Bowel pain.tw.
- 47. Bowel discomfort.tw.
- 48. Stomach pain.tw.
- 49. Stomach discomfort.tw.
- 50. (chronic functional abdominal pain or CFAP).tw.
- 51. exp irritable bowel syndrome/
- 52. (irritable bowel or IBS).tw.
- 53. functional dyspepsia.tw.
- 54. abdominal migraine.tw.
- 55. or/44-54
- 56. 14 and 43 and 55

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- #1 MeSH descriptor: [Probiotics] explode all trees
- #2 MeSH descriptor: [Synbiotics] explode all trees
- #3 probiotic*
- #4 synbiotic*
- #5 MeSH descriptor: [Lactobacillus] explode all trees
- #6 lactobacill*
- #7 bacill*
- #8 MeSH descriptor: [Bifidobacterium] explode all trees
- #9 (bifidus or bifidobacter*)
- #10 MeSH descriptor: [Streptococcaceae thermophilus] explode all trees
- #11 streptococcus thermophilus
- #12 streptococc*
- #13 MeSH descriptor: [Lactococcus] explode all trees
- #14 lactococc*
- #15 MeSH descriptor: [Bacillus subtilis] explode all trees
- #16 bacillus subtilis
- #17 MeSH descriptor: [Enterococcus] explode all trees
- #18 enterococcus faec*
- #19 MeSH descriptor: [Saccharomyces] explode all trees
- #20 saccharomyc*
- #21 leuconostoc*
- #22 pediococc*
- #23 bulgarian bacillus
- #24 (Escherichia coli or "E. coli").tw.
- #25 Yeast.tw.
- #26 (fungus or fungi).tw.
- #27 (#1 or #2 or #3 or #4 of #5 or #6 or #7 or #8 or #9 or #10 or #11 of #12 or #13 or #14 or #15 or #16 or #17 of #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)
- #28 functional abdominal pain or "FAPS"
- #29 chronic functional abdominal pain or "CFAP"
- #30 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees
- #31 irritable bowel or "IBS"
- #32 functional dyspepsia
- #33 abdominal migraine
- #34 #28 or #29 or #30 or #31 or #32 or #33

#35 #27 and #34

CINAHL

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

2. (TI abdominal pain* or AB abdominal pain*) OR (TI functional abdominal* or AB functional abdominal *) OR (TI bowel pain* or AB bowel pain*) OR (TI bowel discomfort* or AB bowel discomfort*) OR (TI stomach pain* or AB stomach pain*) OR (TI stomach discomfort* or AB stomach discomfort*) OR (TI FAPS or AB FAPS) OR (TI CFAP or AB CFAP) OR (TI chronic functional abdominal pain or AB chronic functional abdominal pain) OR (TI irritable bowel* or AB irritable bowel*) OR (TI IBS or AB IBS*) OR (TI functional dyspepsia or AB functional dyspepsia) OR (TI abdominal migraine* or AB abdominal migraine*)

3. 1 AND 2

PsycInfo

ti(probiotic* OR synbiotic* OR lactobacill* OR bacill* OR bifidobacter* OR bifidus* OR streptococc* OR lactococc* OR enterococcus* OR saccharomyc* OR leuconostoc* OR pediococc* OR *coli OR yeast* OR fung* OR VSL*) AND ti(abdominal pain OR functional abdominal OR bowel pain OR bowel discomfort OR stomach pain OR stomach discomfort OR FAPS OR CFAP OR chronic functional abdominal pain OR irritable bowel* OR IBS OR functional dyspepsia OR abdominal migraine)

clinical trials.gov

conditions: abdominal pain OR functional abdominal OR bowel pain OR bowel discomfort OR stomach pain OR stomach discomfort OR FAPS OR CFAP OR chronic functional abdominal pain OR irritable bowel* OR IBS OR functional dyspepsia OR abdominal migraine

interventions: probiotic OR synbiotic OR lactobacill OR bacill OR bifidobacter OR bifidus OR streptococc OR lactococc OR enterococcus OR saccharomyc OR leuconostoc OR pediococc OR coli OR yeast OR fung OR VSL

DECLARATIONS OF INTEREST

Morris Gordon has received travel fees to attend international scientific and training meeting such as DDW, Advances in IBD, ESPGHAN, BSPGHAN and Cochrane focused international events from companies including: Abbott, Nutricia, Biogaia, Ferring, Allergan, Tillots. None of these companies have had any involvement in any works completed by Morris Gordon and he has never received any payments for any other activities from these companies.

Michael Farrell: None known

Adrian G Thomas: None known

Anthony K Akobeng: None known

Chris Wallace: A previous review looking at probiotics as treatment for chronic constipation was accepted for a poster presentation at the ESPGHAN Annual Meeting, and funding was received through the Young Investigators Award for travel and accommodation to attend. No input given into current or past reviews. No other interests to declare relevant to current or past reviews/research.