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Systematic review and meta-analysis of randomized controlled trials: *Lactobacillus rhamnosus* GG for abdominal pain-related functional gastrointestinal disorders in childhood

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7 **Systematic review and meta-analysis of randomized controlled trials:**
8 ***Lactobacillus rhamnosus* GG for abdominal pain-related functional**
9 **gastrointestinal disorders in childhood**
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ABSTRACT

Background: A lack of reliable treatments for abdominal pain-related functional gastrointestinal disorders (FGD) prompts interest in new therapies.

Aim: To systematically evaluate the effect of *Lactobacillus rhamnosus* GG (LGG) for treating abdominal pain-related FGD in children.

Methods: MEDLINE, EMBASE, CINAHL, the Cochrane Library, **trial registries, and proceedings of major meetings** were searched for randomized controlled trials (RCTs) evaluating LGG supplementation in children with abdominal pain-related FGD based on the Rome II or Rome III criteria. **Risk of bias was assessed for generation of the allocation sequence, allocation concealment, blinding, and follow-up.**

Results: Compared with placebo, LGG supplementation was associated with a significantly higher rate of treatment responders (defined as no pain or a decrease in pain intensity) in the overall population with abdominal pain-related FGD (3 RCTs, n=290; **relative risk, RR 1.31, 95% CI 1.08 to 1.59, number needed to treat, NNT 7, 95% CI 4 to 22**) and in the irritable bowel syndrome (IBS) subgroup (3 RCTs, n=167; **RR 1.70, 95% CI 1.27 to 2.27, NNT 4, 95% CI 3 to 8**). However, no difference was found in the rate of treatment responders between children with functional abdominal pain or functional dyspepsia who received placebo or LGG. The intensity of pain was significantly reduced in the overall study population and in the IBS subgroup. The frequency of pain was significantly reduced in the IBS subgroup only.

Conclusion: The use of LGG moderately increases treatment success in children with abdominal pain-related FGD, particularly among children with IBS.

INTRODUCTION

According to the Rome III criteria,^{1,2} abdominal pain-related functional gastrointestinal disorders (FGD) in children may be categorized as functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine, and functional abdominal pain (FAP). Because of their obscure pathophysiology, management of abdominal pain-related FGD remains difficult, prompting interest in new and safe treatment options.

Recently, probiotics, defined as *'live microorganisms which when administered in adequate amounts confer a health benefit on the host'*³, have been proposed as treatment for FGD. While the exact mechanisms by which probiotics may exert their actions in patients with FGD are not fully understood, several mechanisms have been suggested. These include changes in colonic fermentation by displacement of gas-producing, bile salt-deconjugating bacteria strains, down-regulation of the local proinflammatory response, control of intestinal motor functions, and reducing visceral hypersensitivity by inducing the expression of u-opioid and cannabinoid receptors in human intestinal epithelial cells.⁴

Previously, 4 meta-analyses^{5 6 7 8} and 1 systematic review⁹ evaluated the effects of probiotics for the treatment of IBS, primarily in the adult population, and reached slightly different conclusions. For adults, despite the equivocal results, the American College of Gastroenterology recently concluded that *'in single organism studies, lactobacilli do not appear effective; bifidobacteria and certain combinations of probiotics demonstrate some efficacy.'*¹⁰ Regarding the pediatric population, a Cochrane systematic review¹¹ (search date: December 2006) concluded that there is no evidence that lactobacillus supplementation is effective in the management of children with recurrent abdominal pain. New studies^{12,13} have been published since this meta-analysis, prompting interest in re-evaluating the role of probiotics in the management of abdominal pain-related FGD in children. With this systematic review, we aimed to update and synthesize the available **randomized controlled**

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3 clinical trial evidence of the likely effects of *Lactobacillus rhamnosus* GG (LGG)
4 compared with placebo or no intervention in children affected by abdominal pain-
5 related FGD. In contrast to previous meta-analyses, whether performed in adults or
6 in children, we focused on a single probiotic microorganism. This is because the
7 beneficial effects of probiotics seem to be strain specific, thus, pooling data on
8 different strains may result in misleading conclusions. The choice of the probiotic
9 LGG was determined by the fact that it is available and commonly used in many
10 countries, and it has demonstrated efficacy in the treatment of some gastrointestinal
11 conditions in children.^{14 15}

22 METHODS

24 Criteria for considering studies for this review

25 All relevant RCTs that compared the effects of LGG supplementation with the effects
26 of placebo or no supplementation for treating abdominal pain-related FGD in
27 children were considered for this review.

34 Search methods for identification of studies

35 The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane
36 Library, Issues 4, 2010), MEDLINE (1966-2010), and EMBASE (1980-2010) were
37 systematically searched up to December 2010. In addition, we searched 2 trial
38 registries (ClinicalTrials.gov, www.clinicaltrials.gov, and EU Clinical Trials
39 Register, www.clinicaltrialsregister.eu) and proceedings from major scientific
40 gastrointestinal meetings such as ESPGHAN, NASPGHAN, UEGW, and DDW
41 published in the last 3 years. The reference lists of identified studies and key review
42 articles, including previously published reviews, were also searched. In all cases, the
43 searches were for studies that assessed the effects of probiotic supplementation on
44 abdominal pain-related FGD in children up to 18 years of age. No language
45 restrictions were imposed. The search strategy included the use of a validated filter
46 for identifying RCTs, which was combined with a topic-specific strategy using the
47 following PubMed MeSH terms: ("probiotics"[MeSH Terms] OR "probiotics"[All
48 Fields] OR "probiotic"[All Fields]) OR ("lactobacillus"[MeSH Terms] OR

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3 "lactobacillus"[All Fields]) OR (LGG [All Fields]) OR ("lactobacillus
4 rhamnosus"[MeSH Terms] OR ("lactobacillus rhamnosus"[All Fields]) AND
5 (recurrent[All Fields] AND ("abdominal pain"[MeSH Terms] OR ("abdominal"[All
6 Fields] AND "pain"[All Fields]) OR "abdominal pain"[All Fields])) OR (functional[All
7 Fields] AND ("abdominal pain"[MeSH Terms] OR ("abdominal"[All Fields] AND
8 "pain"[All Fields]) OR "abdominal pain"[All Fields])) OR ("irritable bowel
9 syndrome"[MeSH Terms] OR ("irritable"[All Fields] AND "bowel"[All Fields] AND
10 "syndrome"[All Fields]) OR "irritable bowel syndrome"[All Fields]) OR
11 (functional[All Fields] AND ("dyspepsia"[MeSH Terms] OR "dyspepsia"[All Fields])
12 OR (("abdomen"[MeSH Terms] OR "abdomen"[All Fields] OR "abdominal"[All
13 Fields]) AND pain-related[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All
14 Fields] OR "disorders"[All Fields])) OR "Rome criteria"[All Fields]) AND
15 ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) OR
16 ("adolescent"[MeSH Terms] OR "adolescent"[All Fields]). Two of the reviewers (PD,
17 AH) searched the databases independently and screened bibliographies of retrieved
18 studies and recent review articles. The primary outcome measure was the rate of
19 responders to the treatment (defined as no pain or a clinically meaningful decrease in
20 pain intensity). The secondary outcome measures were the frequency and
21 intensity/severity of abdominal pain reported by patients and adverse events.
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41 **Selection of studies**

42 We excluded studies if the title and abstract were not relevant; however, we obtained
43 papers for all potentially relevant studies if the abstract contained insufficient
44 information to warrant exclusion. All areas of disagreement were discussed by the
45 researchers in order to achieve a consensus.
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52 **Data extraction and management**

53 Data from each study were extracted by all of the reviewers using standardized data
54 extraction forms. The data sought included baseline characteristics of the participants
55 (age, diagnostic criteria), the LGG dose and duration of the intervention, follow-up
56 duration, the nature of the placebo, and all outcome measures with their definitions,
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3 as reported by the authors. After extraction, all data were compared in order to
4 minimize the possibility of errors.
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8 **Assessment of risk of bias in included studies**

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10 The reviewers independently, but without being blinded to the authors or journal,
11 assessed the risk of bias in the studies that met the inclusion criteria. We used the
12 Cochrane Collaboration's tool for assessing risk of bias, which includes the following
13 criteria: adequacy of sequence generation, allocation concealment, and blinding of
14 participants, personnel and outcome assessors; and incomplete outcome data are
15 addressed. In all cases, an answer of 'yes' indicates a low risk of bias, and an answer
16 of 'no' indicates a high risk of bias.¹⁶
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26 **Measures of treatment effect**

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28 The dichotomous outcomes, the results for individual studies, and pooled statistics
29 are reported as the risk ratio (RR) between the experimental and control groups with
30 95% confidence intervals (CI). The standardized mean difference (SMD) between the
31 treatment and control groups was selected to represent the difference in continuous
32 outcomes (with 95% CI). For all outcomes, subgroup analyses based on the diagnosis
33 (i.e., IBS, FAP, FD) were performed.
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41 **Dealing with missing data**

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43 We assessed pooled data using available case analysis, i.e., an analysis in which data
44 are analyzed for every participant for whom the outcome was obtained, rather than
45 intention-to-treat analysis with imputation.¹⁷
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50 **Assessment of heterogeneity**

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52 Heterogeneity was quantified by χ^2 and I^2 , which can be interpreted as the percentage
53 of the total variation between studies that is attributable to heterogeneity rather than
54 to chance. A value of 0% indicates no observed heterogeneity, and larger values show
55 increasing heterogeneity. If heterogeneity was not revealed, we present results of
56 only the fixed effects model. If there was substantial heterogeneity (over 50%), all
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3 analyses were based on the random effects model if it was still considered
4 appropriate to pool the data.
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8 9 **Data synthesis (Statistical methods)**

10 The data were analyzed using Review Manager (RevMan) [Computer program.
11 Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration,
12 2008]. The number needed to treat (NNT), with a 95% CI, was calculated using
13 StatsDirect statistical software (version 2,7,8 [2010-03-15]). **The weights given to each
14 study were based on the inverse of the variance.**
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20 21 **RESULTS**

22 23 **Included studies**

24 The literature search initially yielded 45 articles, of which 3 RCTs met the inclusion
25 criteria (**Figure 1**).^{12,18,19} All were published in English. These trials randomized a total
26 of 290 patients. **Table 1** summarizes the characteristics of the included studies. All 3
27 studies enrolled patients with IBS,^{12,18,19} 2 RCTs enrolled patients with FAP,^{12,19} and 1
28 RCT also enrolled children with FD.¹⁹ In all of the studies, the diagnoses were made
29 according to the Rome II criteria. The sample size ranged from 64 to 141 participants.
30 In all of the studies, LGG was compared with placebo. The daily dose of LGG ranged
31 from 10⁹ CFU twice daily¹⁸ to 3 x 10⁹ CFU twice daily,^{12,19} and supplementation lasted
32 for 4 weeks¹⁹, 6 weeks,¹⁸ or 8 weeks¹². Two RCTs were undertaken in the 2 European
33 countries Poland (one RCT)¹⁹ and Italy (one RCT),¹² and one RCT was conducted in
34 the United States.¹⁸
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49 **Risk of bias in included trials**

50 **Table 2** shows the results of the methodological quality assessment. All of the studies
51 had good methodological quality. The main limitation of the study by Bausserman *et*
52 *al.* was incomplete outcome data (more than 20% lost to follow-up).¹⁸
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58 **Heterogeneity**

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3 No heterogeneity for the primary outcome was found ($I^2=0\%$). For the secondary
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5 outcomes, significant heterogeneity ($I^2 \geq 50\%$) was found for the overall study
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7 population for the frequency of pain ($\chi^2=9.15$, $p=0.002$, $I^2=89\%$) and the intensity of
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9 pain ($\chi^2=2.21$, $p=0.14$, $I^2=55\%$). In all cases, the observed statistical heterogeneity
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11 was not judged to be clinically relevant (i.e., studies consistently reported results in
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13 the same direction with clinically insignificant differences between the studies).
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15 However, there were too few studies to adequately determine heterogeneity.²⁰
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18 Effects of intervention

19 Primary outcome

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21 All 3 RCTs reported responders to the treatment or treatment success defined as no
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23 pain or a decrease in pain intensity (Figure 2). One RCT¹⁹ reported both treatment
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25 success (defined as no pain) and improvement of symptoms (defined as a change in
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27 the Faces Pain Scale by at least 2 faces scores). For this review, data related to those 2
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29 outcomes were combined into a single outcome.
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33 For the overall study population with abdominal pain-related FGD, compared with
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35 placebo, LGG supplementation was associated with a significantly higher rate of
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37 responders to the treatment (defined as no pain or a decrease in pain intensity)(3
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39 RCTs, $n=290$, RR 1.31, 95% CI 1.08 to 1.59, NNT 7, 95% CI 4 to 22). For a subgroup of
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41 children with IBS, those in the LGG group were more likely to respond to the
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43 treatment than those in the placebo group (3 RCTs, $n=167$, RR 1.70, 95% CI 1.27 to
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45 2.27, NNT 4, 95% CI 3 to 8). For the FAP group (2 RCTs, $n=103$, RR 1.08, 95% CI 0.77
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47 to 1.50), as well as for the FD group (1 RCT, $n=20$, RR 0.83, 95% CI 0.37 to 1.85), we
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49 found no evidence that LGG supplementation influenced the treatment response in
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51 these children.
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54 Secondary outcomes

55 Frequency of pain

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57 Only for a subgroup of children with IBS, the frequency of pain was reduced in those
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59 in the LGG group compared with those in the placebo group (2 RCTs, $n=117$; SMD -
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3 1.04, 95% CI -1.43 to -0.65). For the overall study population, as well as for the
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5 subgroups of children with FAP or FD, there were no differences in the frequency of
6
7 pain between the groups that received placebo or LGG (**Figure 3**).
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10 *Intensity/severity of pain*

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12 Compared with placebo, the use of LGG was associated with a significant decrease in
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14 the perception of pain intensity in the overall study population with abdominal pain-
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16 related FGD (2 RCTs, n=240; SMD -0.44, 95% CI -0.82 to -0.05). Similarly, there was a
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18 reduction in pain intensity in the subgroup of children with IBS who received LGG
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20 compared with placebo (2 RCTs, n=117; SMD -0.60, 95% CI -0.97 to -0.23), but not in
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22 children with FAP and FD (**Figure 4**).
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26 *Adverse effects*

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28 The LGG was well tolerated and no adverse effects were reported.
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32 **DISCUSSION**

33 **Summary of main results**

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35 This meta-analysis provides a summary of current knowledge regarding the effects
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37 of a single probiotic microorganism, LGG, in children affected by abdominal pain-
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39 related FGD. With the limited evidence available, we found that the use of LGG
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41 increased the proportion of responders to the treatment (defined as no pain or a
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43 decrease in pain intensity) in children with abdominal pain-related FGD, particularly
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45 among children with IBS. Additionally, LGG reduced the frequency and intensity of
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47 pain, again particularly among children with IBS. Of note, although positive and
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49 statistically significant, the effects were clinically modest.
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53 **Overall completeness and applicability of evidence**

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55 Our search included 3 major databases, with no language restrictions. The searching,
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57 extraction of the data, and assessment of the validity of the studies were performed
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59 independently by 2 reviewers to decrease the likelihood of reviewer error or bias.
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Still, we cannot fully exclude the possibility of publication bias, which is an

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3 important threat to the validity of systematic reviews and is difficult to combat
4 except through the registration of all RCTs. We did not perform a statistical test for
5 the detection of publication bias, as we are aware that these tests have very low
6 power in the meta-analysis of only a few trials.²¹ One strength of our review, which
7 distinguishes it from other reviews, is that it focuses on only one probiotic
8 microorganism. This is because probiotic supplementation is not a homogeneous
9 intervention. Pooling data from different genera, species, strains, and doses of
10 probiotics may result in misleading conclusions.
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20 **Quality of evidence**

21 Any systematic review is only as good as the constituent studies. In general, the
22 included RCTs were of sound methodology with adequate randomization, allocation
23 concealment, blinding, and follow-up. One potential limitation of the review is that it
24 included a small number of trials with a small sample size, particularly when
25 subgroups of patients with specific diagnoses were evaluated. However, to increase
26 power is one of the reasons why a meta-analysis is performed within a systematic
27 review.
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37 In all of the included trials, the probiotic intervention lasted not less than 4 weeks,
38 which is in line with the Rome Foundation document providing guidance for the
39 design of treatment trials in patients with FGD.²² However, there is a lack of data on
40 the long-term effects of LGG treatment for abdominal pain-related FGD. Only one
41 study¹² analyzed children for 8 weeks after cessation of the therapy.
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49 According to the published recommendations,²² the primary outcome measure for
50 treatment studies in patients with FGD should be defined as 'adequate relief' or
51 'satisfactory relief'. However, studies assessing this outcome measure in the pediatric
52 population are lacking. To our knowledge, no outcome measures for FGD are
53 sufficiently validated to be recommended unequivocally for use as the primary
54 outcome measure.²² The studies included in our review used different scales and
55 different definitions in assessing treatment success and treatment response. While in
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3 2 trials, validated tools (Faces Pain Scale and Visual Analog Scale) were used, the
4 definition of treatment success was subjective.^{12,19} In the remaining study,¹⁸ the
5 investigators used a psychometric scale that was not validated for the pediatric
6 population.
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12 *All 3 RCTs were placebo controlled, which is considered an essential requirement for*
13 *interventional studies of FGD. However, there were differences in the choice of*
14 *placebo. Two of the 3 RCTs used inulin and maltodextrin as their placebos.^{18 19} As*
15 *these are potential prebiotics, it could have affected the outcome. However, this was*
16 *not observed in our analysis. Still, the choice of the placebo should be taken into*
17 *account when designing future studies.*
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27 **Agreement and disagreement with other studies or reviews**

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29 Compared with the previously published Cochrane review,¹¹ which concluded that
30 there is no evidence that lactobacillus supplementation is effective in the
31 management of children with recurrent abdominal pain, our review focuses on a
32 single probiotic microorganism and also includes recent data. Thus, our results more
33 precisely define the effects of LGG. In adults, *as discussed in the Introduction*, some
34 meta-analyses^{6 7 8} have shown that some probiotics are clinically more effective than
35 placebo in the treatment of irritable bowel syndrome. However, there are no data on
36 LGG given as a single probiotic.
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46 **Implications for practice**

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48 The results of our systematic review provide preliminary evidence that LGG may be
49 useful for treating children with abdominal pain-related FGD, particularly in a
50 subgroup of children with IBS. While it is too soon to recommend its routine use in
51 clinical practice, given the lack of effective therapy for abdominal pain-related FGD
52 and the generally good safety profile of LGG in an otherwise healthy population, this
53 therapeutic option could be discussed with patients and/or caregivers.
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Implications for research

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3 LGG seems to be a good candidate for a large multicenter trial in children with
4 abdominal pain-related FGD, properly categorized into IBS, FAP, and FD. Due to the
5 relapsing nature of the disease and that effects of probiotics may endure only for as
6 long as the organism is administered, the treatment duration and follow-up period
7 after cessation of treatment should allow for the adequate assessment of short- and
8 long-term effects of LGG. There is also a strong need for a standardized, properly
9 validated outcome assessments scale. Due to the fact that the exact mechanism of
10 action of LGG is not known, experimental studies are desirable.
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20 **CONTRIBUTORS**

21 AH and HS initially conceptualized this study. AH and PD were responsible for data
22 collection. All authors were responsible for data analysis, interpretation, and
23 preparation of the report. All authors contributed to the writing of this manuscript
24 and agreed upon the final version.
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FIGURE LEGENDS

Figure 1. Identification process for eligible trials

Figure 2. Primary outcome: Effect of *Lactobacillus* GG on responder rates

Figure 3. Secondary outcome: Effect of *Lactobacillus* GG on frequency of pain

Figure 4. Secondary outcome: Effect of *Lactobacillus* GG on intensity/severity of pain

For Peer Review

Table 1. Characteristics of included studies

Study	Participants	Diagnostic criteria	LGG (dose)	Comparison	Primary outcome	Secondary outcomes
Bausserman et al. 2005 ¹⁸	Children & adolescents (mean age: 12 y, range: 6-17 y)	Rome II criteria for IBS	10 ¹⁰ CFU, twice daily, for 6 wk	Placebo (inulin)	Change in the abdominal pain severity score.	Number of responders vs. nonresponders in each group and changes in the symptoms on the Gastrointestinal Symptom Rating Scale (15-item GSRS) by syndrome. Responders were classified as patients with a decrease in abdominal pain severity (1 point or more on the 4-point Likert scale)
Francavilla et al. 2010 ¹²	Children (mean age: 6.4 y, range: 5-14 y)	Rome II criteria for IBS or FAP	3 x 10 ⁹ CFU, twice daily, for 8 wk	Placebo (inert powder)	Change in abdominal pain (frequency/severity) according to the VAS score from baseline to the end of the treatment period.	(1) A decrease of at least 50% in the number of episodes and intensity of pain (treatment success); (2) A decrease in the perception of children's pain according to their parents; (3) Modification of intestinal permeability.
Gawronska et al. 2007 ¹⁹	Children (mean age: 11.6 y, range: 6-16 y)	Rome II criteria for IBS, FAP, FD	3 x 10 ⁹ CFU, twice daily, for 4 wk	Placebo (maltodextrin)	Treatment success defined as no pain (a relaxed face, score of 0, on the Faces Pain Scale) at the end of the intervention.	Improvements defined as a change in: 1) the Faces Pain Scale by at least 2 faces scores; 2) self-reported severity of pain during the preceding week measured on the Faces Pain Scale; 3) self-reported frequency of pain during the preceding week; 4) use of medication for abdominal

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							pain; and 5) school absenteeism due to abdominal pain.
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CFU, colony forming units; IBS, irritable bowel syndrome; FAP, functional abdominal pain; FD, functional dyspepsia

For Peer Review

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For Peer Review

Table 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study

Study ID	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete data addressed?
Bausserman et al. 2005 ¹⁸	Yes	Yes	Yes	No 50/64 (78%)
Gawronska et al. 2007 ¹⁹	Yes	Yes	Yes	Yes 104/104 (100%)
Francavilla et al. 2010 ¹²	Yes	Yes	Yes	Yes 136/141 (96%)

In all cases, an answer of 'yes' indicates a low risk of bias, and an answer of 'no' indicates a high risk of bias.

Figure 1. Identification process for eligible trials

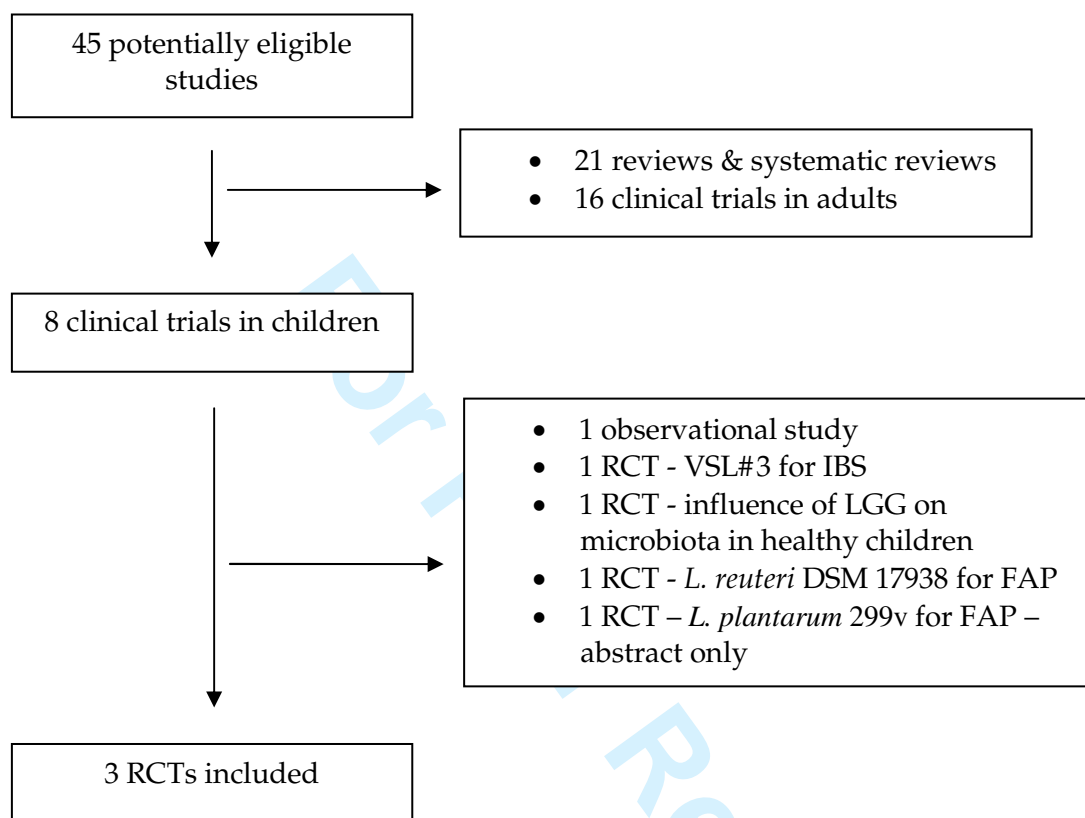


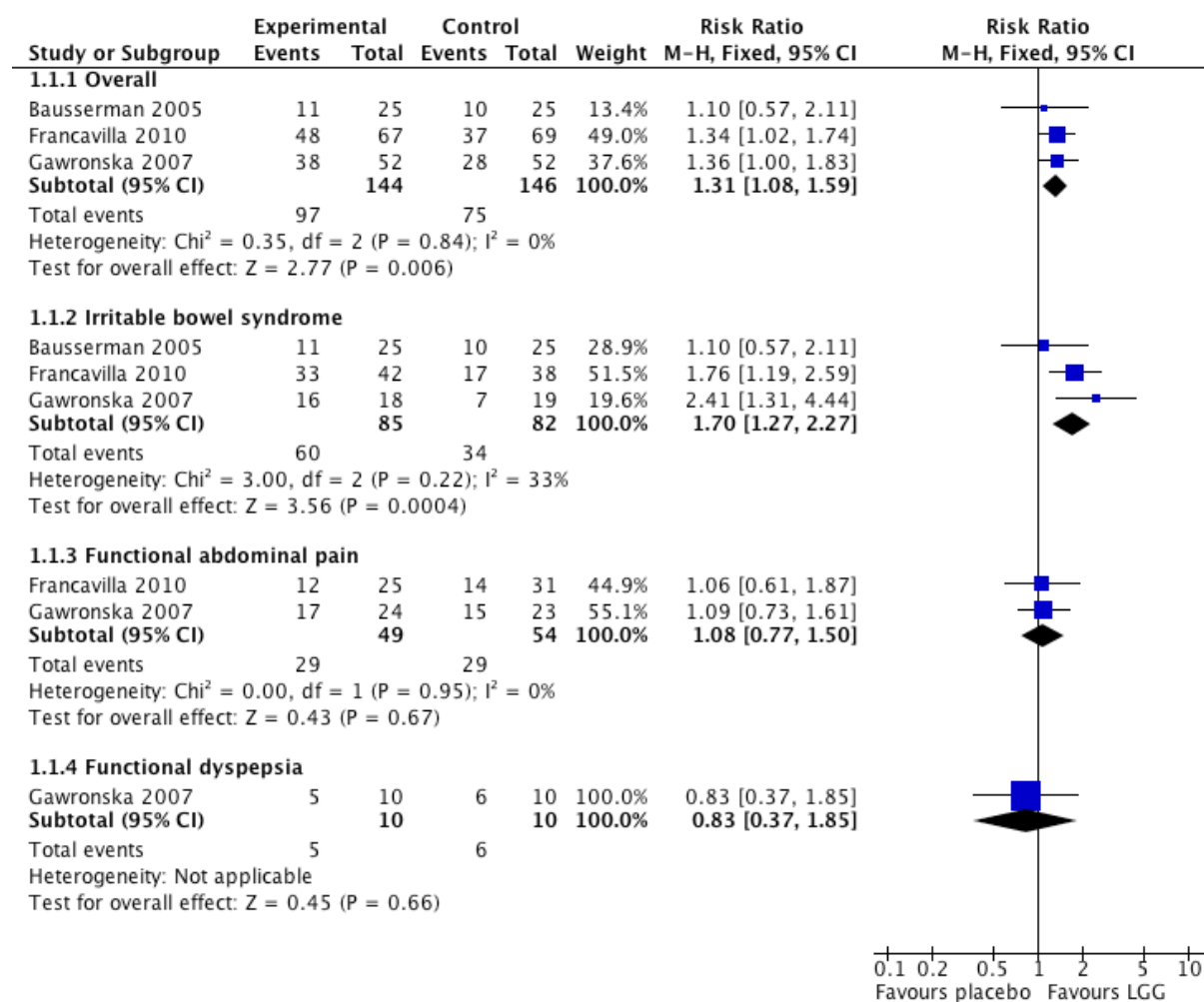
Figure 2. Primary outcome: Effect of *Lactobacillus* GG on responder rates

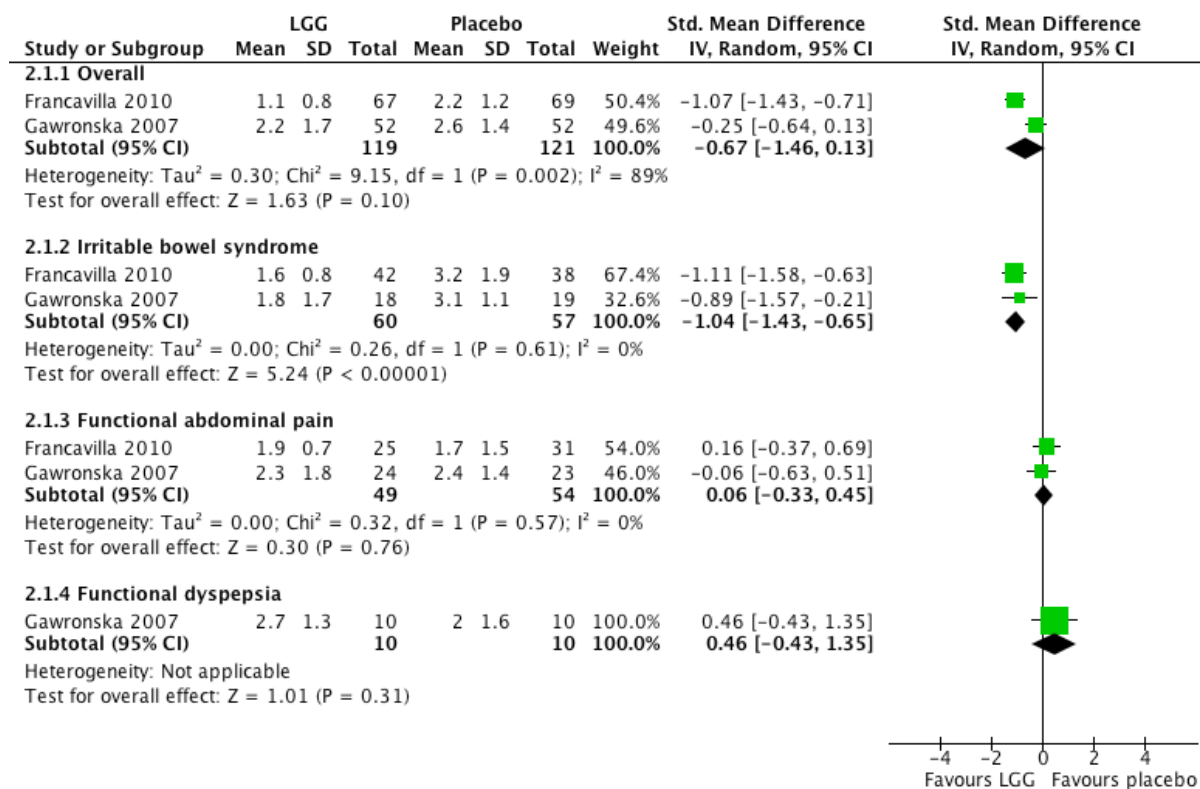
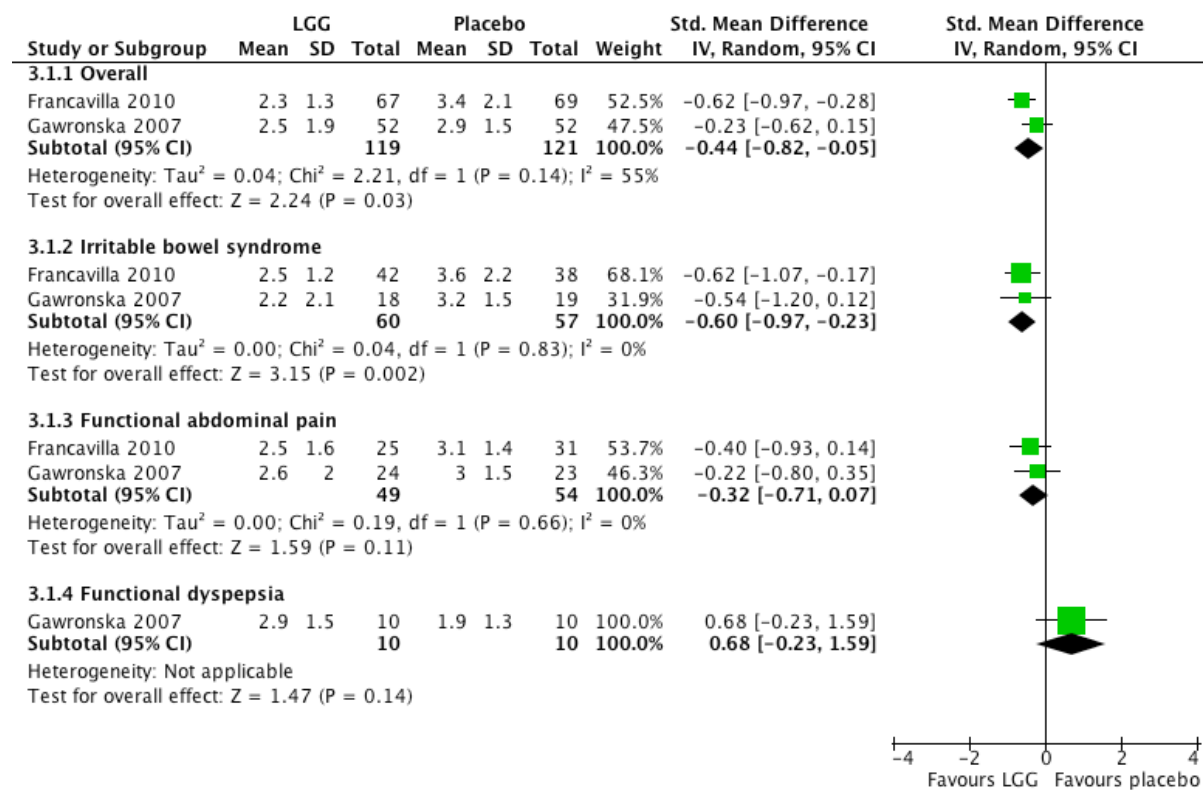
Figure 3. Secondary outcome: Effect of *Lactobacillus* GG on frequency of pain

Figure 4. Secondary outcome: Effect of *Lactobacillus* GG on intensity/severity of pain



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3,4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4,5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7 Tab. 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7 Tab. 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8 Fig.3 Fig.4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8 Fig.3 Fig.4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11



PRISMA 2009 Checklist

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