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Recurrent abdominal pain in children: summary evidence from three systematic reviews of treatment effectiveness

Rebecca A **Abbott**[1], Alice E **Martin**[1,2], Tamsin V **Newlove-Delgado**[3], Alison**Bethel**[1], Rebecca S **Whear**[1], Jo**Thompson Coon**[1], Stuart**Logan**[1]

1 NIHR CLAHRC South West Peninsula (PenCLAHRC), University of Exeter Medical School, Exeter EX1 2LU, UK

2 Bristol Royal Hospital for Children, Bristol, Marlborough Street, Bristol BS1 3NU, UK

3 University of Exeter Medical School, St Luke's Campus, Exeter, EX1 2LU, UK

ABSTRACT

Objectives

Between 4% and 25% of school-aged children complain of recurrent abdominal pain (RAP) severe enough to interfere with their daily activities.

Methods

We carried out a systematic review of randomised controlled trials (RCTs) in eleven databases and two trials registries from inception to June 2016. An update search was run in November 2017. All screening was performed by two independent reviewers. Included studies were appraised using the Cochrane risk of bias tool and the evidence assessed using GRADE. We included any dietary, pharmacological or psychosocial intervention for recurrent abdominal pain (RAP), defined by Apley or an abdominal pain-related functional gastrointestinal disorder, as defined by the Rome III criteria, in children and adolescents.

Results

We included 55 RCTs, involving 3572 children with RAP (21 dietary, 15 pharmacological, 19 psychosocial, and 1 multi-arm). We found probiotic diets, cognitive behavioural therapy (CBT) and hypnotherapy were reported to reduce pain in the short-term and there is some evidence of medium term effectiveness. There was insufficient evidence of effectiveness for all other dietary interventions and psychosocial therapies. There was no robust evidence of effectiveness for pharmacological interventions.

Conclusions

Overall the evidence base for treatment decisions is poor. These data suggest that probiotics, CBT and hypnotherapy could be considered as part of holistic management of children with RAP. The evidence regarding relative effectiveness of different strains of probiotics is currently

insufficient to guide clinical practice. The lack of evidence of effectiveness for any drug suggests that there is little justification for their use outside of well-conducted clinical trials. There is an urgent need for high quality RCTs to provide evidence to guide management of this common condition.

Key Words: recurrent abdominal pain, RAP, functional abdominal pain, FAP, chronic pain, children, systematic review

What is known?

- Between 4% and 25% of school-aged children experience recurrent abdominal pain (RAP) sufficient to interfere with activities of daily living; often causing significant anxiety for parents and carers.
- The lack of guidelines or consensus on management of patients with RAP means that treatment is inconsistent.

What is new?

- There is some evidence to suggest that probiotics, cognitive behavioural therapy and hypnotherapy may be effective in the treatment of RAP.
- The lack of evidence of effectiveness for any drug suggests that they should be used with caution outside of well-conducted clinical trials.

INTRODUCTION

Recurrent abdominal pain (RAP) is a common problem in paediatric practice, with prevalence estimates ranging from 2% to 41% [1]. Between 4% and 25% of school-aged children intermittently suffer from RAP, sufficient to interfere with their activities of daily living [2, 3]. RAP is associated with school absences, hospital admissions and on occasions, unnecessary surgical intervention [4-6]. The abdominal pain is commonly associated with other symptoms, including headaches, recurrent limb pains, pallor, and vomiting[7-9] and can continue into adulthood [6, 10]. RAP can cause significant anxiety in parents and carers, who may become overwhelmed by fear of serious disease or feel helpless because they are unable to relieve their child's symptoms [11].

RAP in children represents a group of functional gastrointestinal disorders that have an unclear aetiology. The latest consensus from the Rome Foundation suggest these disorders are related to motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota and altered central nervous system processing. They suggest RAP is "the product of ... interactions of psychosocial factors and altered gut physiology via the brain–gut axis"(12). For the purpose of this review, RAP has been used as an umbrella term to describe what are now referred to as *functional abdominal pain disorders* under the new Rome IV classification: functional dyspepsia, irritable bowel syndrome, abdominal migraine and functional abdominal pain (with the caveat that most of the studies were carried out prior to this, commonly using the Rome III classification) [12, 13].

There is no consensus or guidelines on which treatments to offer patients, hence treatment of RAP remains inconsistent. We have systematically reviewed the effectiveness of dietary, pharmacological and psychological interventions for children of school age presenting with

RAP, published as three companion Cochrane reviews [14-16]. Summarising these review, this paper brings together the current evidence to underpin treatment decisions in young people with RAP.

METHODS

A full protocol for each review was published in the Cochrane Library [17-19] . The systematic review was conducted following the general principles published by Cochrane [20] and has been reported in accordance with the PRISMA statement [21].

Inclusion/exclusion criteria

Children aged five to 18 years old with RAP or an abdominal pain-related functional gastrointestinal disorder, as defined by the Rome III criteria [13], were included. Any dietary, pharmacological or psychosocial intervention compared to placebo, waiting list, no treatment, active control (psychosocial interventions only) or standard care were included. Included studies were restricted to randomised controlled trials (RCTs) and randomised cross-over studies. The primary outcome was pain: intensity, frequency, duration or the proportion of participants with significant improvement in pain (as defined by the trial authors). Studies were grouped according to duration of follow-up: short term follow-up (zero to three months), medium-term follow-up (three to six months post-intervention) and long-term follow-up (six months or longer). Secondary outcomes were school performance, social or psychological functioning, quality of daily life and adverse events. Findings related to secondary outcomes are not reported here, but are reported in the published Cochrane reviews [14-16].

Search Strategy

The search strategy was developed by an information specialist (AB) in consultation with topic and methods experts (AM, TND, SL, RA, JTC, RW), an example of which for MEDLINE is shown in Appendix File 1. Eleven databases were searched from inception to June 2016: AMED, ASSIA, British Education Index, CENTRAL, CINAHL, Embase, ERIC, Lilacs, MEDLINE, OpenGrey and PsycINFO. No date or language restrictions were used. We also searched ClinicalTrials.gov and the WHO International Clinical Trials Registry for recently completed and ongoing studies. Forward and backward citation chasing of included articles was conducted. Two reviewers (RA, TND, AM, BW, JTC, AB) independently screened titles, abstracts and full texts using the eligibility criteria. Discrepancies were discussed and resolved by a third reviewer where necessary. An update search was undertaken in MEDLINE (21st November 2017).

Data collection

We extracted data on study characteristics (number of participating children, type of intervention and comparison, intervention characteristics, number of withdrawals, study design), participant characteristics (gender, age, diagnosis e.g. RAP or syndrome defined by the Rome III criteria) and outcome measures (measurement of pain and any secondary outcome measured). Data was extracted by one reviewer and checked by a second.

Risk of bias

Risk of bias within studies was assessed using the Cochrane risk of bias tool [(22)]. We also assessed whether the data collection tools were valid, whether there was sufficient power in terms of appropriate sample size, whether baseline parameters were similar, and whether data analyses were appropriate. Two review authors (RA, AM, TND, AB, JTC, or RW) independently assessed each study. We resolved any disagreements by discussion until consensus was reached. Risk of bias across studies was assessed using the approach outlined by

the 'Grading of Recommendations Assessment Development and Evaluation' (GRADE) working group [23] . The GRADE assessment assigned a measure of the quality of evidence; high, moderate, low or very low.

Data analysis and synthesis

We used Review Manager 5 for statistical analysis (Review Manager 2014). We analysed dichotomous data using odds ratios (ORs). We calculated numbers needed to treat for an additional beneficial outcome (NNTB) using the risk in the control arm as an estimate of baseline population risk. For continuous data we analysed mean differences and standard deviations, if these were available or could be calculated, and there was no clear evidence of skewness in the distribution[24]. When different scales were used to measure the same clinical outcome, we combined standardised mean differences across the studies. We conducted meta-analyses where possible for studies within the same intervention type, assessing equivocal outcomes at similar time points. We used a random-effects model because we anticipated significant statistical and clinical heterogeneity. We provided a narrative description of the results when, due to the heterogeneity of the intervention or the variety of methods used to measure pain, meta-analysis was not appropriate.

Role of the funding source

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RESULTS

The electronic searches and hand searching retrieved a total of 14,700 results. Excluding duplicates, 9649 titles and abstracts were screened and after full-text screening a total of 52 studies, reported across 68 articles, were included. Reasons for exclusion at the full text stage can be seen in Figure 1. The update search identified three further RCTs.

Characteristics of included studies

Twenty-one studies assessed a dietary intervention, 15 assessed pharmacological intervention and 19 investigated some form of psychosocial intervention. One study had both a dietary and pharmacological arm. The studies were conducted in 15 countries, recruiting children from secondary/tertiary paediatric gastroenterology or pain clinics (n=37), primary care (n=1), the community (n=1), or from a combination of these (n=10), or not described (n=3). A summary of the populations and interventions is shown in Table 1.

Study quality

The majority of dietary studies were rated as low risk of bias for most of the domains. The pharmacological studies which reported effective treatments were either small, single studies or had key methodological weaknesses with a substantial risk of bias. None of these 'positive' results have been reproduced in subsequent studies. We judged the evidence of effectiveness to be of low quality. For the psychosocial studies, most (16 out of the 18) were considered to be at high risk of bias for blinding of outcome assessment as the majority of outcomes were self-reported, and children were aware of their treatment group. The other domains were mainly considered low risk or were unclear. Detailed reports on the risk of bias for each study are available in the three reviews[14-16].

Dietary Intervention

Effects of probiotics: 15 studies [25-39] *, 1123 children*

The trials ranged in duration from 4-12 weeks, and used a range of probiotic preparations. The precise dose, frequency and strains used are shown in Supplementary File 1 (Supplemental Digital Content 1, http://links.lww.com/MPG/B284), but in summary: five trials used *Lactobacillus rhamnosus GG*; five used *Lactobacillus reuteri DSM 17938*; two used *Bacillus coagulans* with fructo-oligosaccharides; one used a patented mixture called VSL#3 containing 8 different strains (*Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaris, Streptococcus thermophiles*); one used a combination of three Bifidobacterium species (*Bifidobacterium longum BB536, Bifidobacterium infantis M-63* and *Bifidobacterium breve M-16V*; and one used *Lactobacillus plantarum LP299V*). Probiotics were assessed as one intervention type and not assessed according to strain in line with our protocol. The majority of studies measured short-term outcomes at zero to three months' post-intervention only. We found that probiotic intervention improved pain in the meta-analysis of nine probiotic trials at this time point (OR 1.61, 95% CI 1.15 to 2.27; P = 0.006), (see Figure 2) with an estimated NNTB of eight, meaning that eight children would need to receive probiotics for one to experience improvement in pain in this timescale[26-31, 35, 38, 39]. Longer term data for this outcome was limited. The pooled analysis from two studies at three to six months' post-intervention for improvement in pain was 1.94 (95% CI 1.10 to 3.43; P = 0.023), with a NNTB of seven [28, 35]. For all children, we also found a reduction in pain frequency (SMD -0.48, 95% CI -0.87 to -0.09; P = 0.02) [25, 27-29, 33, 36, 39] and pain intensity (SMD -0.62, 95% CI -1.04 to -0.21; P = 0.003) [25, 27-29, 32, 33, 36, 38, 39], in those treated with probiotics compared to placebo at zero to three months'

post-intervention (see Supplementary File 2, Supplemental Digital Content 2, http://links.lww.com/MPG/B285). Post-hoc sub-group analyses of outcomes according to probiotic strain are shown in Figures 3, 4 and 5.

Effects of fibre-based interventions: 4 studies [40-43] , 299 children

Four trials used fibre-based interventions: a fibre biscuit containing 5 g of corn fibre [38], a preparation of glucomannan [39], a preparation of partially hydrolysed guar gum [40] and psyllium fibre [41]. Two studies were included in the meta-analysis for the outcome of improvement of pain, with a pooled OR of 1.83 (95% CI 0.92 to 3.65; P = 0.09)(40, 41). Two different studies were pooled for the outcome of change in pain intensity: the SMD of effect across the studies was -1.24 (95% CI -3.41 to 0.94; P = 0.27); both studies included only children with irritable bowel syndrome[42, 43]. No long term data were reported.

Effects of a FODMAP diet (1 study, 34 children) and fructose restricted diet (1 study, 103 children)

Only one small, short duration study each examined the effects of a low fermentable, oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) diet [44] and a fructose-restricted diet [45] on pain in children with RAP. Both studies reported reductions in pain frequency and Wirth et al [45] also reported a reduction in pain intensity.

Pharmacological Interventions

Meta-analyses were not possible due to the heterogeneity of the interventions and variation in outcome measures.

Effects of antispasmodics: 4 studies [25, 46-48] , 377 children

Two studies investigating peppermint oil found discordant results: significant reductions in pain intensity, duration and frequency compared to placebo in one study [25] and no significant

changes in the above compared to placebo in another [46] . The studies had key methodological weaknesses. Therefore these studies provide insufficient evidence to support the use of peppermint oil in the treatment of RAP. Narang [47] reported significant differences in pain episodes over 4 weeks (MD 11.3 (95%CI 2.1 to 20.1)) but not in the number of pain free days over the same period (MD 1.8, -1.2 to 4.8) in children given drotaverine compared to placebo. Pourmoghaddas [48] found no difference in self-reported or physician rated pain in children treated with mebeverine compared to placebo.

Effects of tricyclic antidepressants: 2 studies [49, 50], 213 children

Both studies reported no significant differences in self-reported pain in children receiving amitriptyline compared to placebo.

Effects of antibiotics: 2 studies [51, 52], 112 children

The studies assessing the effect of rifaximin [51] or co-trimoxazole [52] found no difference in reported pain outcomes in children receiving either drug compared to placebo.

Effects of other pharmacological interventions: 8 single studies, 412 children

Single studies assessed the effectiveness of eight different pharmacological agents compared to usual care or placebo: the anti-muscarinic drug trimebutine [53], the 5-HTA agonist tegaserod [54], the antihistamine cyproheptadine [55], the serotonin agonist pizotifen [56], the selective serotonin reuptake inhibitor citalopram[57], the hormone melatonin (58), the dopamine receptor agonist domperidone [59], and the H2 receptor agonist famotidine [60]. Four studies reported significant reductions in pain[53-56], two reported mixed findings [59, 60], and two no effect on pain outcomes [57, 58]. Small sample sizes, poor reporting, and a lack of recognised pain outcome measures meant there was insufficient evidence of effectiveness for these single studies of pharmacological intervention.

Psychosocial Interventions

Effects of cognitive-behavioural therapy: 11 studies [14, 61-71] , 687 children

CBT improved pain immediately post intervention, in the meta-analysis of four trials (OR 5.67, 95% CI 1.18 to 27.32, P = 0.03, see Figure 6) with an estimated NNTB of 4. This means that four children would need to receive CBT for one to experience improvement in pain at this time point [61, 63, 66, 67]. Three of the four studies provided medium term 3-6 month follow-up data on pain improvement [63, 66, 67]. The pooled OR for medium-term pain improvement was 3.08 (95% CI 0.93 to 10.16; P = 0.06) with a NNTB of 5. Two of the four studies provided long-term (12 months or more) follow-up data on pain improvement [63, 67]. The pooled OR for long-term pain improvement was 1.29 (95% CI 0.50 to 3.33; P = 0.60).

Data from seven studies was available to estimate the effects of CBT intervention compared to control groups on pain intensity post-intervention [61, 63, 65, 67-70]. The pooled SMD of pain intensity across the studies was -0.33 (95% CI -0.74 to 0.08; P = 0.12). Three additional studies reported post-intervention pain intensity outcome data [62, 64, 66] which could not be pooled with the studies above due to insufficient data, such as missing standard deviations (SDs). Two studies reported significant benefits of decreased pain intensity with CBT compared to control [62, 66], and one found no difference (64). Three studies provided long-term follow-up data [63, 65, 67]for these the pooled SMD of pain intensity was -0.04 (95% CI -0.39 to 0.31, P value = 0.82).

Effects of hypnotherapy (4 studies [72-75], 152 children)

Data from all four studies [72-75] were entered into a meta-analysis to estimate the effect of hypnotherapy compared to control groups on pain improvement immediately post-intervention. The pooled OR for pain improvement was 6.78 (95% CI 2.41 to 19.07; P < 0.0003) with an estimated NNTB of three (see Figure 7). Long-term data from Vlieger et al [76] in their five-year

follow-up, which included 45 of the original 49 children, found 68% of the intervention group were symptom free compared to 20% in the control arm (P = 0.005).

The same studies provided data on pain intensity and pain frequency post-intervention. The pooled SMDs of pain intensity and pain frequency across the four studies post-intervention were -1.01 (95% CI -1.41 to -0.61; P < 0.00001) and -1.28 (95% CI -1.84 to -0.72; P < 0.00001) respectively. Long term data from Vlieger et al [76] reported that pain both intensity and frequency remained significantly lower at five years (P < 0.001 for both) in the group that had received three months of hypnotherapy.

Effects of yoga (3 studies [77-79], 127 children) and written self-disclosure (1 study (80), 63 children)

The pooled SMD of pain intensity immediately post-intervention across three yoga studies was -0.31 (95% CI -0.67 to 0.05; P = 0.09). One study [78] provided long-term data (12 months), and found no significant effect for the yoga intervention compared to usual care (P = 0.09). The single study on written self-disclosure, found no evidence of effect on pain immediately post-intervention, but did report a significant effect at 6 months follow-up[80].

Quality of the evidence

As evaluated using the GRADE approach [22], we found the overall certainty of evidence across the reviews ranged from very low to moderate, due to the high or unclear risk of bias across the studies. There was significant heterogeneity (greater than 70%), wide confidence intervals and low number of participants in many of the studies. Future research in this area is therefore likely to impact on our confidence in the estimate of the majority of effects observed in this review.

DISCUSSION

RAP is common, causes considerable distress to families and consumes substantial health service resources but we found relatively little high quality evidence to guide treatment decisions. Many of the trials had a significant risk of bias, few assessed outcome in the medium or long term, and for many interventions, particularly drugs, we found no high quality studies.

These data provide some moderate quality evidence suggesting that probiotics may be effective in the management of children with RAP. Probiotics were reported to result in reduced pain intensity and frequency in the short-term, but there was limited evidence to suggest that this was sustained up to 3-6 months after treatment. The evidence regarding relative effectiveness of different strains of probiotics is currently insufficient to guide clinical practice. The review also found low quality evidence to suggest that CBT and hypnotherapy may be effective in treating RAP, with both reported to be effective in reducing pain in the short term. Sustained effects of CBT and hypnotherapy were also reported but the evidence is limited. We found insufficient evidence to support the use of fibre based diets, FODMAP diets or fructose-restricted diets, yoga therapy or written self-disclosure. We found no evidence that pharmacological approaches were effective in treating RAP.

The findings are in keeping with other systematic reviews of dietary, pharmacological and psychosocial interventions for children with RAP and pain more widely. Horvath et al [81], and more recently Rutten et al[82], reported that *Lactobacillus rhamnosus* GG and VSL#3 were associated with significantly more treatment responders than placebo in their systematic review of non-pharmacological treatments; the same authors found inconclusive data regarding the effects of fibre based supplements. Rutten et al [82] also concluded there was some evidence for CBT and hypnotherapy, but a lack of evidence for yoga. In a review of face-to-face

interventions for children with pain (dichotomised as headache and non-headache pain), Eccleston et al [83] produced pooled estimates of effect comparable with those reported here for CBT and hypnotherapy. A Cochrane review evaluating the effectiveness of antidepressants in pain-related functional abdominal disorders in children reported no evidence of effectiveness[84]. We found few trials conducted in specific subgroups of RAP as defined by the Rome III criteria[13], most including children within the broad diagnosis of RAP, which encompasses children with a variety of RAP classifications such as IBS, functional abdominal pain, or functional dyspepsia. Therefore we were unable to conclude of the effectiveness of interventions on particular subgroups of RAP [12].

Strengths and Limitations

We used robust methods, published in protocol form before the review was started [17-19]. We contacted authors of included studies for additional data when the presented data were insufficient or missing to maximise our ability to pool data. We did not include studies that had a mix of ages or reported only mean age of participants greater than 20 where it was not possible to separate the data for those less than 18 years of age. We did not contact these authors asking whether they collected data for children less than 18 years of age which raises the possibility that we may have missed important data.

Implications for practice

Overall there is some evidence to suggest that probiotics, CBT and hypnotherapy may be effective in improving pain in the short term, supporting the advice given in the 'Practical Management' review of functional abdominal pain, published in this journal in July 2016 [85]. It is unclear from existing evidence whether there are differences in the relative effectiveness of different strains of probiotics. Indeed, the small number of studies investigating each particular

strain means we need to exert considerable caution in making recommendations. Clinicians may want to consider and discuss these treatments as part of a holistic management strategy for children with RAP and their families. However, we are unable to recommend the optimum strain and dosage of probiotics or the format of CBT or hypnotherapy.

There is extremely weak evidence for the efficacy of any pharmacological agents in children with RAP and limited evidence of any effect for fibre-based diets, FODMAP diets, and yoga therapy. While clinicians may choose to prescribe a “therapeutic trial” of drugs to children whose symptoms are severe and who have not responded to simple management they need to be aware that RAP is a fluctuating condition and any 'response' may reflect the natural history of the condition or a placebo effect, rather than drug efficacy.

Implications for research

The evidence for the effectiveness of probiotics and cognitive behavioural therapy is based largely on shorter-term outcomes. Further trials are required to assess whether improvements in pain are maintained over the longer term. Future research on probiotics should address the question of the optimal strain and dosage schedule, as well as consider the effectiveness of probiotics in different settings. For CBT interventions, the mode (face-to face versus remote delivered) and dose of delivery warrants further exploration. The pathogenesis of RAP in children remains unclear [(86)] and there is a need for further studies to elucidate this aetiology. It may be that the complaint of abdominal pain is a unifying manifestation for a wide variety of causal pathways and triggers relating to psychological and physical processes rather than a single entity. It has been suggested that there are distinct clinical sub-types of RAP and that these should guide treatment choice [(12)] but this is not currently based on high quality evidence. Further large trials, stratified by postulated sub-types are therefore needed not only to guide the

management of children with RAP, but also to validate the usefulness of suggested classifications[13] .

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Legends

Figure 1. PRISMA flow chart of study identification and selection

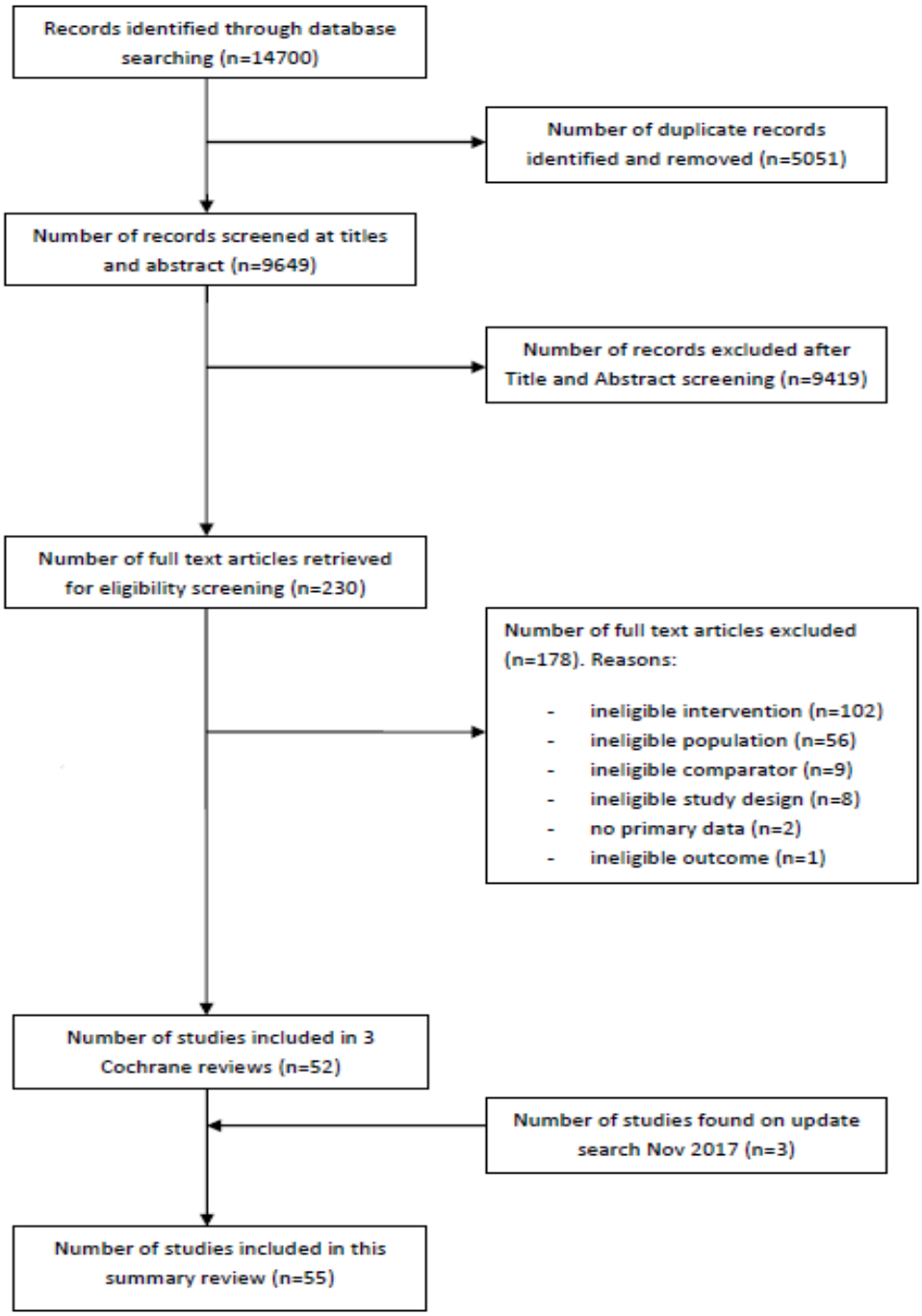

Figure 2. Forest plot showing odds ratio for improvement in pain post-intervention for probiotics compared to placebo

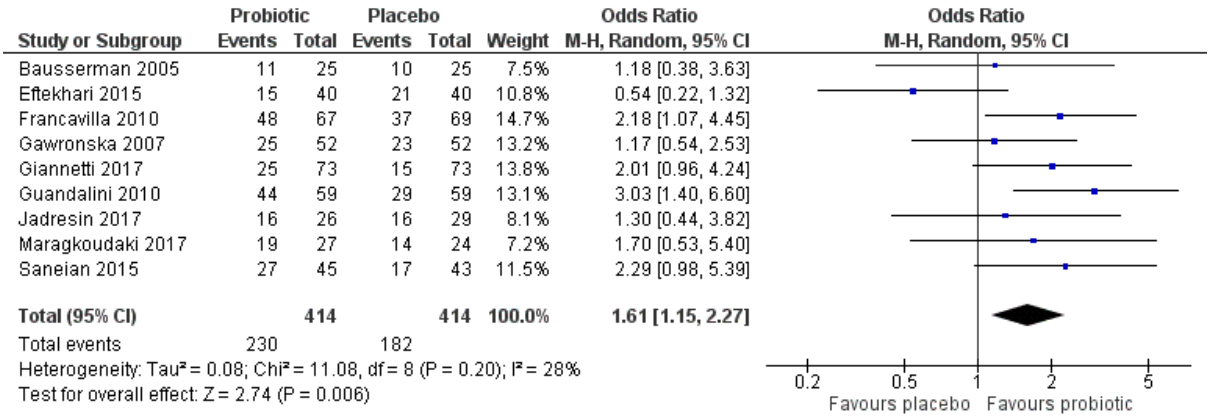

Figure 3. Forest plot of pain improvement post-intervention for probiotics compared to placebo, by strain of probiotics

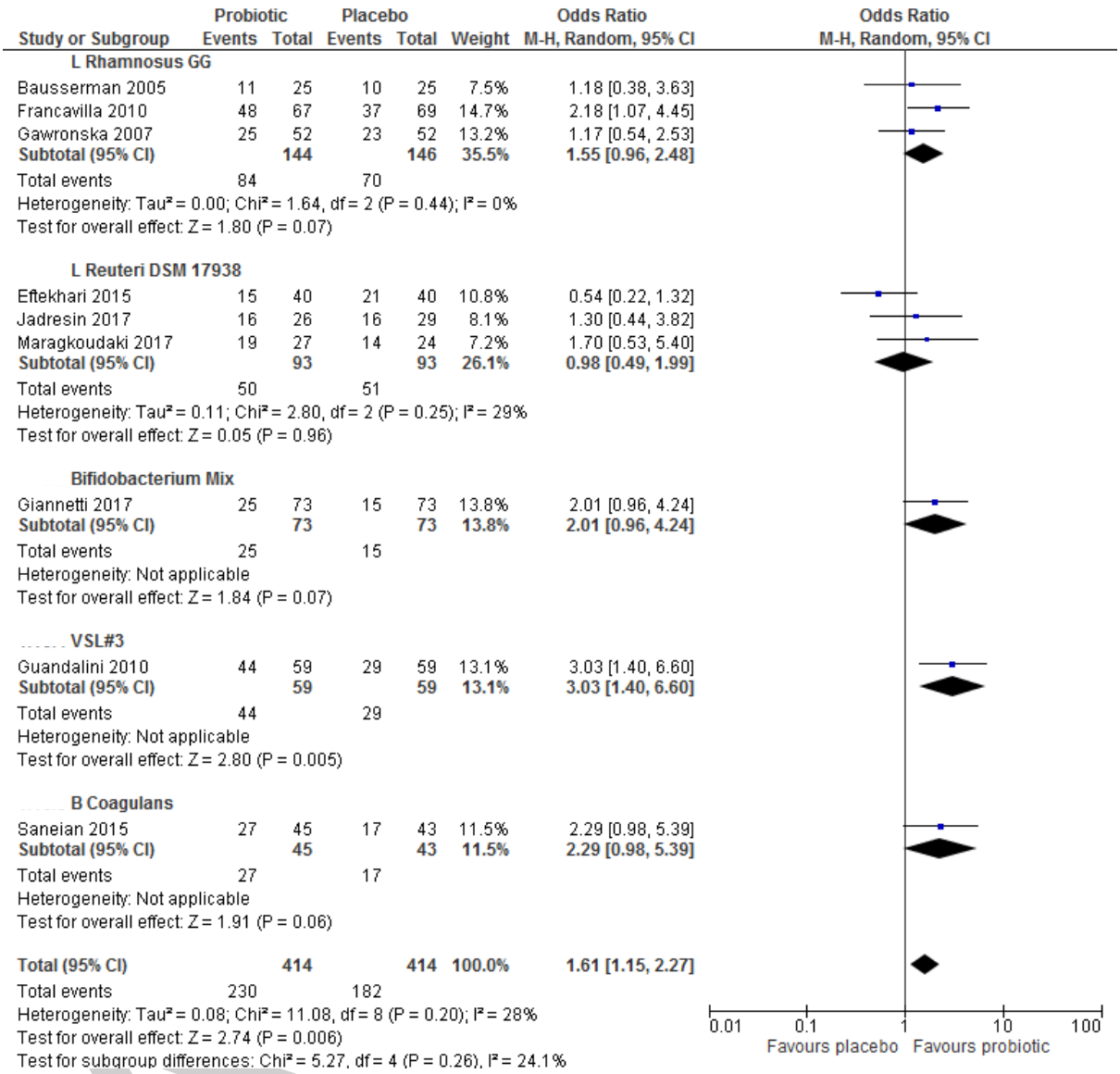

Figure 4. Forest plot of change in pain intensity post-intervention for probiotics compared to placebo, by strain of probiotics

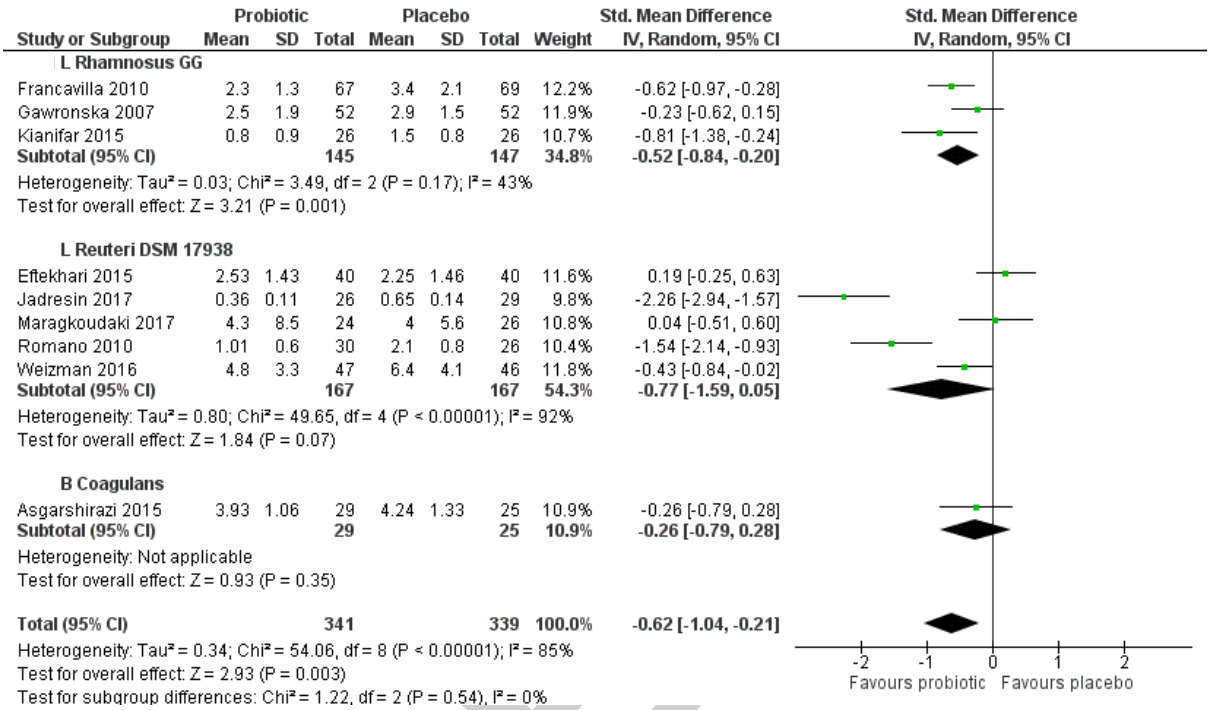

Figure 5. Forest plot of change in pain frequency post-intervention for probiotics compared to placebo, by strain of probiotics

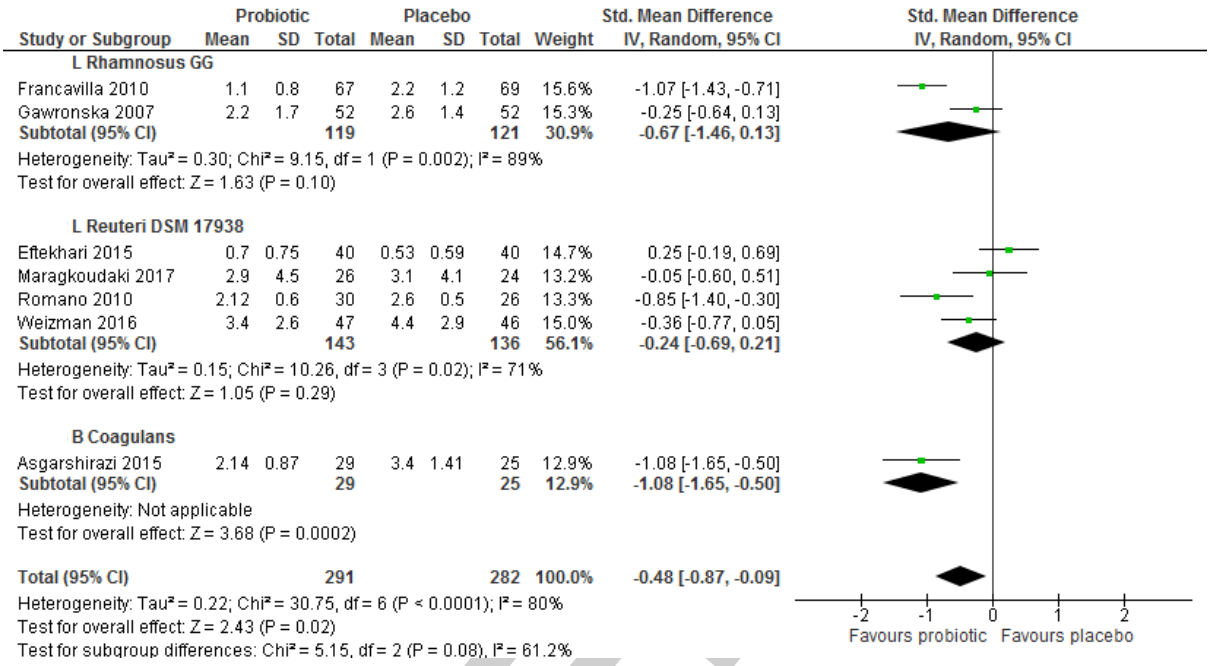

Figure 6. Forest plot showing the odd ratio of pain improvement post-intervention for those receiving cognitive behavioural therapy (CBT) compared to control (shown according to 'control' group type).

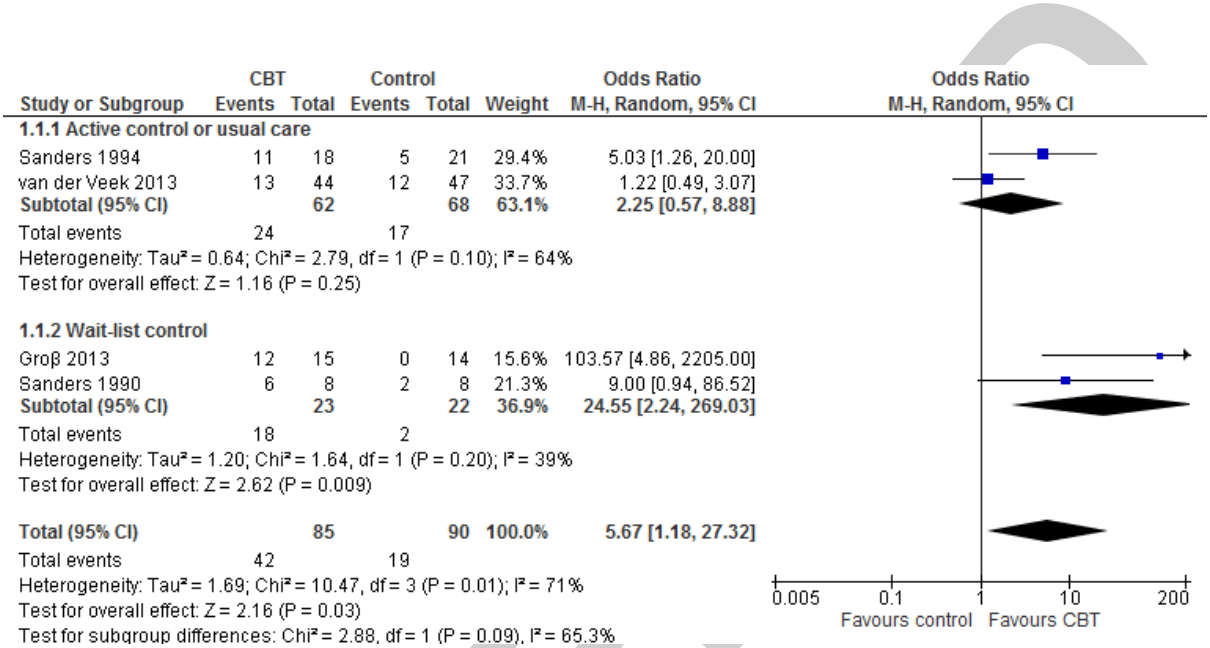

Figure 7. Forest plot showing the odd ratio of pain improvement post-intervention for those receiving hypnotherapy compared to control (shown according to 'control' group type).

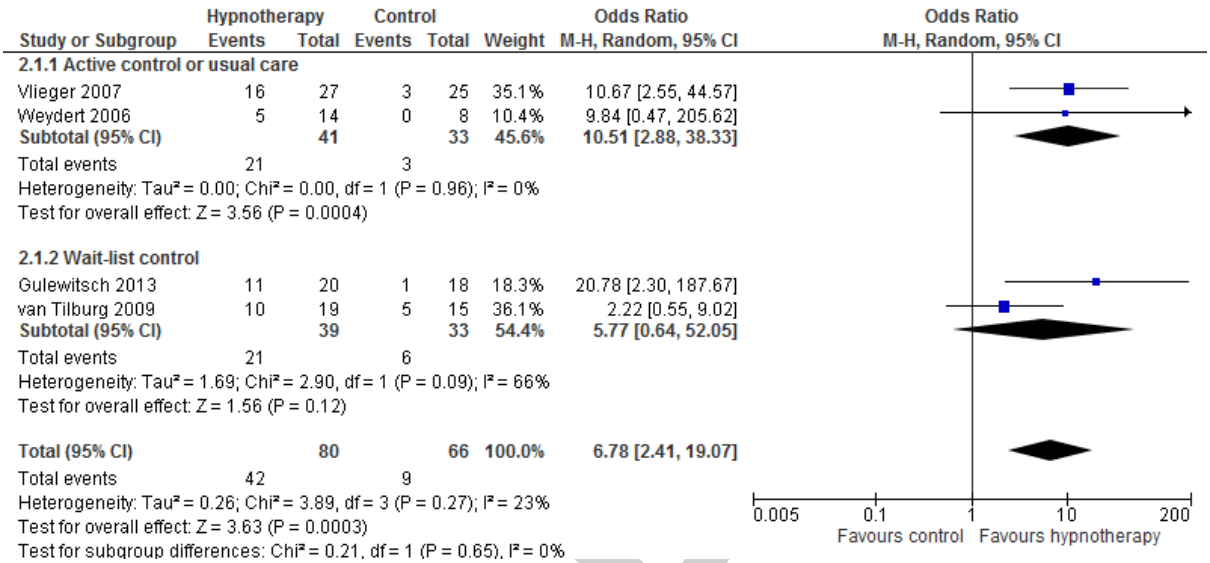

Table 1. Characteristics of studies

	No. of Children	Clinical presentation (No. of trials)	Type of Intervention (No. of trials)
Dietary (n=21) *	1519	RAP/ FGID (n=15 IBS (n=5) RAP and IBS (n=1)	Probiotics (n=15) Fibre-based (n=4) FODMOP (n=1) Fructose-restricted (n=1)
Pharmacological (n=15) *	1024	RAP/ FGID (n=10 IBS (n=4) RAP and IBS (n=2	Antispasmodics (n=4) Tricyclic antidepressants (n=2) Antibiotics (n=2) Antimuscarinics (n=1) Selective serotonin re-uptake inhibitors (n=1) 5-HT4 receptor agonist (n=1) Antihistamines (n=1) H2 receptor antagonists (n=1) Serotonin antagonist (n=1) Dopamine receptor antagonist (n=1) Hormone (n=1)
Psychosocial (n=19)	1029	RAP/ FGID (n=14 IBS (n=3) RAP and IBS (n=2	Cognitive-Behavioural Therapy (n=11) Hypnotherapy (n=4) Yoga (n=3) Written Disclosure (n=1)

FGID Functional Gastrointestinal Disorder
RAP Recurrent Abdominal Pain
IBS Irritable Bowel Syndrome
* 1 study three arms: dietary, pharmacological and control