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Systematic review with meta-analysis: Effects of probiotic supplementation on symptoms in functional dyspepsia

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ABSTRACT

The pathophysiology of functional dyspepsia (FD) remains poorly understood, but alterations of the small intestinal microbiome have been observed. The place of probiotics in treatment is uncertain. We performed a systematic review and meta-analysis of the currently available randomized, controlled trials (RCTs) to evaluate the potential beneficial effects and risks of probiotics in FD. Pubmed, EMBASE, Scopus, Web of Science and the Cochrane Controlled Trials Register were searched (up to May 2019) for RCTs evaluating the effects of probiotic supplementation compared to placebo in adults with FD. Two reviewers independently assessed eligibility, trial quality and extracted information from identified articles. To compare the effects of probiotics with placebo, risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using random effects models. Six trials, including 422 participants were included but only three RCTs could be included in the meta-analysis. *Lactobacillus* strains showed potential positive effects in terms of improving upper gastrointestinal (GI) symptoms in patients with FD. Probiotic supplementation tended to improve global dyspepsia score (n = 3 RCTs, risk ratio [RR]: 1.35, 95% CI 0.99 to 1.84; P = 0.061) and bacterial composition in the GI tract. Probiotics were well tolerated without any serious adverse events. While the available data suggest that supplementation with probiotics may improve GI symptoms in patients with FD, the evidence is insufficient to draw clear conclusions regarding efficacy. Thus, high-quality RCTs are needed to establish the beneficial effects of probiotic supplementation on FD outcomes.

1. Introduction

Functional dyspepsia (FD) is a chronic disorder characterised by recurrent or persistent upper abdominal symptoms that occur mainly during or after meals (Talley & Ford, 2015). The prevalence of FD ranges from ~11–30%, depending on the geographic region and the definition adopted (El-Serag & Talley, 2004; Zagari et al., 2010). Primary FD symptoms include postprandial fullness, early satiety, and epigastric burning and/or pain based on the Rome III. However Rome III criteria is currently updated as Rome IV criteria(Drossman, 2016) (Carbone, Holvoet, Vanuytsel, & Tack, 2017). but these patients often report other symptoms including heartburn, nausea or bloating (Walker, Potter, & Talley, 2019).

In addition, One of the important diagnosis criteria of FD, is the absence of organic lesions by routine clinical evaluation(Nishizawa, Masaoka, & Suzuki, 2016).

The pathophysiology of FD is poorly understood, but altered gastrointestinal motility, heightened visceral sensitivity and psychosocial

Abbreviations: FD, functional dyspepsia; RCTs, randomized, controlled; RRs, risk ratios; CI, confidence interval; GI, gastrointestinal; IBS, irritated bowel syndrome

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factors have all been implicated (Tack, Bisschops, & Sarnelli, 2004). The treatment of FD is challenging, and no effective cure has been established(Talley, 2016). In the majority of cases, symptoms disappear and return frequently in the long-term, and this adversely affects the quality of life of patients(Aro et al., 2011). Eradication of *H. pylori* results in a small subset with FD experiencing symptom resolution 12 months after treatment, but *H. pylori* is not associated with specific FD symptoms (Ronkainen et al., 2019) leading to the speculation the reason anti-*H. pylori* therapy is efficacious might be through impacting the intestinal microbiome rather than only *H. pylori,* although this is controversial (Talley, 2016; Talley & Ford, 2015). Other research has identified subtle duodenal inflammation in FD (characterized by excess eosinophils) (Talley et al., 2007; Zhong et al., 2017). Diet is one of the main factors in triggering or exacerbating symptoms in FD(Feinle-Bisset & Azpiroz, 2013; Filipović et al., 2011; Pilichiewicz, Horowitz, Holtmann, Talley, & Feinle–Bisset, 2009). Several foods and dietary components, including coffee, alcohol, citrus fruits, high-fat meals, carbohydrates, carbonated and soft drinks, and some vegetables, have been reported to induce symptoms(Mullan et al., 1994; Saito, Locke III, Weaver, Zinsmeister, & Talley, 2005). Further, diet does alter gut microbiota composition(Turnbaugh et al., 2009). The non-absorbable antibiotic rifaximin in one small randomized trial from Hong Kong improved global dyspepsia symptoms (Tan et al., 2017). There is also evidence that probiotics may be beneficial for FD (Vandenplas & Benninga, 2009) but no systematic review has been conducted.

Probiotics are live microbial supplements, which are intended to have a range of health benefits on the host when consumed in adequate amounts (AFRC, 1989). Probiotics have been shown to have beneficial effects in several GI disorders, including diarrhea (Hempel et al., 2012), constipation (Chmielewska & Szajewska, 2010) and IBS(Brenner, Moeller, Chey, & Schoenfeld, 2009; Moayyedi et al., 2010). Recent studies have indicated that probiotic supplementation may significantly decrease GI symptoms, including nausea, postprandial fullness and upper GI pain(Gomi et al., 2018; Ianiro et al., 2013). Moreover, studies on the effects of probiotics in dyspeptic patients who are *H. pylori*-positive show that several probiotic bacteria, including *Lactobacillus* strains, may have beneficial effects on dyspeptic symptoms by suppressing *H. pylori* and decreasing related inflammation (Cruchet, Obregon, Salazar, Diaz, & Gotteland, 2003; Deguchi et al., 2012; Zhang, Qian, Qin, He, & Zhou, 2015). Another possible mechanism underlying the effects of probiotics in alleviating FD symptoms may be through normalization of the disturbed microbiota(Sánchez et al., 2017). We have therefore performed a comprehensive literature review, which has revealed six primary studies that have specifically examined the effects of probiotic supplementation on FD. Thus, the aim of this systematic review was to assess the up-to-date-evidence on probiotic interventions for reducing symptoms of FD.

2. Methods

2.1. Literature search

We systematically searched MEDLINE, EMBASE, Cochrane Central Library, Web of Science and Scopus electronic databases from inception up to May 2019 to identify randomized, controlled clinical trials (RCTs) that evaluated the effects of probiotic supplementation on FD symptoms. The following search terms were used in combination; 'functional dyspepsia' OR 'dyspepsia' OR 'non-ulcer dyspepsia' OR 'functional GI disorder' OR 'epigastric pain' OR 'upper GI symptoms' AND 'probiotics' OR 'prebiotics' OR 'synbiotics OR 'saccharomyces' OR 'Lactobacillus' OR 'bifidobacterium'. The full search strategy is presented in ***Appendix S1. The electronic searches were supplemented by manual screening of the references of included papers as well as those of related reviews. There was no language restriction in the search of databases.

2.2. Study selection

Studies were eligible for inclusion if they were randomized, controlled trials using parallel or cross-over designs and studies that compared the effects of any probiotic, prebiotic or synbiotic intervention (regardless of dose, type and duration of intervention) with placebo in adult patients with FD aged 18 years or older, and which evaluated FD symptoms and their frequency and duration as the primary outcome. symptoms should defined according to the ROME IV(Drossman, 2016) criteria's. Secondary outcomes were adverse events or side effects of probiotics. In case of cross-over studies we only consider first phrase before cross-over, to avoid carry-over effect. We exclude review articles, case reports, case control, cross-sectional and conference proceedings studies.

2.3. Data extraction and quality assessment

Two reviewers (JH and AA) independently screened all articles following the guidelines outlined by the Cochrane collaboration (Higgins & Green, 2008). Inclusion of articles into the systematic review were determined by the two reviewers, and disagreements were resolved with a third reviewer (MS). The following data were extracted from included articles: first author's name, year of publication, country of origin, type and dosage of probiotic intervention, duration of supplementation, participant characteristics, including sex, age and sample size in intervention and placebo group, as well as main primary and secondary outcomes of the studies. Methodologic quality assessment of the included articles was evaluated using the Cochrane risk of bias assessment tools(Higgins et al., 2011).

2.4. Statistical analysis

Meta-analysis was performed using Stata software version 11 (Stata Corporation, College Station, Texas). The effect size was measured as the risk ratio (RR) with corresponding 95% confidence intervals (CIs) obtained by Mantel-Hansel method. Data were combined using the random-effects model. Heterogeneity of the studies was assessed graphically with forest plots and statistically by chi-square-based Q statistic and I^2 value. Heterogeneity was considered significant at a P-value of < 0.10 in Q-test or $I^2 > 40\%$. Meta-analysis was performed only when two or more studies reported the same outcome.

3. Results

Fig. 1 presents the PRISMA flow diagram for the selection process of included studies. An initial search yielded 1695 articles; after removing duplicates, 1337 titles and abstracts were screened independently by two researchers (AA and MM). By evaluating the titles and abstracts, an additional 1313 studies were excluded as irrelevant (animal studies, unrelated topics or irrelevant design). Of the 24 remaining articles subjected to full-text evaluation, 18 were excluded (reasons indicated in Fig. 1), and a total of 6 articles were included in the final review.

The characteristics of the included studies (Emara, Mohamed, & Abdel-Aziz, 2014; Ianiro et al., 2013; Igarashi et al., 2017; Ohtsu et al., 2017; Rosania et al., 2012; Takagi et al., 2016) are presented in Table 1. The studies involved a total of 422 participants and were all published after 2011. All participants were middle-aged adults (aged 31–50 years), and studies were performed in a variety of geographical regions (3 in Asia, 2 in Europe and one in Africa). Four studies used a single strain, i.e. one study used *Lactobacillus reuteri*(Emara et al., 2014) and 3 studies used *Lactobacillus gasseri* OLL2716 (LG21) (Igarashi et al., 2017; Ohtsu et al., 2017; Takagi et al., 2016), while two further studies used combinations of probiotic strains (Ianiro et al., 2013; Rosania et al., 2012). The duration of the probiotic supplementation ranged from 1 −12 weeks. Thus, there was substantial variability in the designs of these studies.

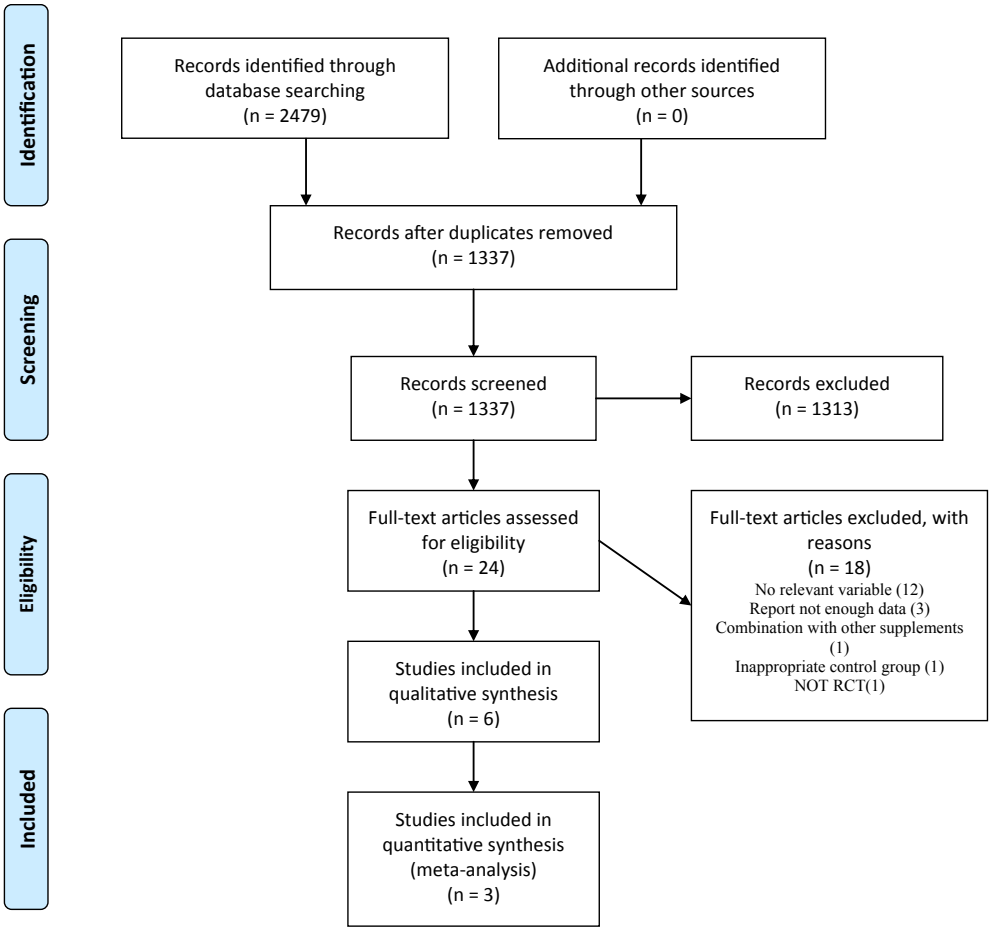

Fig. 1. PRISMA flow diagram of study selection.

3.1. Effect of probiotics on symptoms in functional dyspepsia

Lactobacillus strains showed potential positive effects in terms of improving upper GI symptoms in patients with FD. *Lactobacillus reuteri* significantly decreased the severity of nausea, abdominal pain, acid regurgitation, abdominal distension, increased flatus after 8 weeks of supplementation (Emara et al., 2014). In addition, *Lactobacillus reuteri* in combination with other probiotics (*Lactobacillus rhamnosus and Saccharomyces boulardi*) reduced postprandial distention and fullness (Ianiro et al., 2013). *Lactobacillus gasseri*-fortified yogurt treatment for a 12-week periods significantly improved epigastric pain/discomfort, postprandial distress and nausea compared with placebo (Ohtsu et al., 2017). *Lactobacillus gasseri* improved postprandial fullness, early satiety, epigastric burning, epigastric bloating, heartburn, reflux feeling of gastric acid, measured using a 7-point Likert scale, after 12 weeks intake compared with theplacebo group(Ohtsu et al., 2017). A further study found an effect of *Lactobacillus gasseri* on postprandial fullness in the treatment group compared with the placebo group, however, there were no statistically significant effect on the other symptoms (Takagi et al., 2016).

3.2. Effects of probiotic supplementation on H. pylori

Two studies suggested a moderate effect of probiotic supplementation on *H. pylori* eradication (Emara et al., 2014; Rosania et al., 2012). In one study (Emara et al., 2014), *Lactobacillus reuteri* increased *H. pylori* eradication rate by 8.6% (from 74.3% in the treatment group vs. 65.7% in the control group). Moreover, multi-strain probioic supplementation resulted in a 32.5% eradication rate of *H. pylori* vs. 0% in the control group(Rosania et al., 2012), Which can be interprete as the separate effect of probiotic supplementation on H. pylori-associated FD-like symptoms

3.3. Effects of probiotic supplementation on other GI microbiota

Lactobacillus gasseri supplementation reduced the count of pathogen bacteria in stool, notably *Escherichia/Shigella* and *Staphylococcus aureus* (Giordani et al., 2019; Itoh, Fujimoto, Kawai, Toba, & Saito, 1995), and reduced the dominance of *Bacteroidetes* over *Proteobacteria*, with the bacteroides ratio reducing from 7.0 $\pm$ 7.6 to 2.2 $\pm$ 4.0 after *Lactobacillus gasseri* supplementation; the bacteroides ratio in healthy subjects was 1.2 $\pm$ 1.0. *Lactobacillus gasseri* also increased Acidobacteria (Igarashi et al., 2017).

3.4. Effects of probiotic supplementation on inflammation

The severity of gastric inflammation in response to probiotics was evaluated in one study based on the number of poly- and mono-nuclear inflammatory cells using a routine pathological grading system(Emara et al., 2014). The *Lactobacillus reuteri* treated group showed a greater reduction in the inflammatory cell score than the placebo-treated group ($p < 0.001$). No studies have evaluated duodenal inflammation post probiotic intervention.

3.5. Adverse events

Generally, probiotics were well tolerated in these studies by the majority of subjects without any serious adverse events. One study reported minor side effects including diarrhea (one of 35 participants-treated with *Lactobacillus reuteri* versus 10 of 35 in control group), taste

Table 1
Main characteristics of included studies.

Study	Country	Subjects characteristics	FD diagnosis criteria	Sample size (n)		Probiotic species	Probiotics dosage (CFU[¥])	Duration (w)	Age (mean ± SD)		Gender (percentage of women)	method was used to measure outcome	Main outcomes (intervention vs control after supplementation)
				Intervention Group	Control Group				Intervention Group	Control Group			
Emara et al., 2014	Egypt	H pylori infected FD patients	Abdominal ultrasound examination	35	35	1	2×10^8	4	33.20 ± 13.97	36.80 ± 11-.08	65.75	Gastrointestinal Symptom Rating Scale (GSRS)	↓Diarrhea ↓H. pylori infection
Igarashi et al., 2017	Japan	FD patients	Rome III criteria	24	21	2	1×10^9	12	44 (36–50)[§]	42 (35–50)	42.22	Frequency scale for symptoms of gastroesophageal reflux disease (FSSG) questionnaire	↓ pathogen bacteria rate of gastric fluid
Ianiro et al., 2013	Italy	FD patients	Rome III criteria	4	4	1,3,4	L. reuterii $= 1 \times 10^{11}$ L.rhamnosus $= 3.5 \times 10^{11}$ S.boulardi $= 2 \times 10^{11}$	1	–	–	–	visual analogue scale (VAS)	↓Postprandial gastric distention ↓Postprandial fullness ↓Belching
Ohtsu et al., 2017	Japan	H. pylori -Uninfected FD Individuals	Rome III criteria	54	52	2	1×10^9	12	42.4 ± 9.1	43.1 ± 8.9	74.5	Individual Symptom Scores questionnaire	↓Postprandial fullness ↔Early satiety ↔Epigastric pain ↔epigastric burning
Rosania et al., 2012	Italy	FD patients	Rome III criteria	40	40	5,6,7,8,9,10,11,12	Each = 1.8×10^{11}	1.4	52.4 ± 21.7	48.7 ± 25.3	57.5	–	↓H. pylori infection
Takagi et al., 2016	Japan	Helicobacter pylori-Associated FD	–	61	63	2	1×10^9	12	51.0 ± 69.4	48.0 ± 75.9	64.5	Functional dyspepsia Japanese guidelines and using a visual analogue scale (VAS)	↓Postprandial fullness ↓Pain ↓Bloating ↔Heartburn ↔Nausea

*Probiotic Species: 1- Lactobacillus reuteri, 2-Lactobacillus gasseri OLL2716 (LG21) 3- Lactobacillus rhamnosus GG 4-Saccharomyces boulardi, 5-Streptococcus thermophilus, 6-Lactobacillus acidophilus, 7-Bifidobacterium longum, 8- Lactobacillus plantarum, 9-Bifidobacteriuym breve, 10-Lactobacillus paracasei, 11-Bifidobacterium infantis, 12-Lactobaccilus delbrueckii.
*↓ This symbol is a sign of decreasing variables in the intervention group, ↑ This symbol is a sign of increasing variables in the intervention group, ↔ This sign indicates that there is no difference between the two groups. NR: not reported.
[¥] CFU; colony-forming units, FD; functional dyspepsia, M; male, F; Female.
[§] Median (IQR).

disorder (two of 35 cases versus 8 of 35 in control group) and abdominal distention (5 of 35 versus 4 of 35 in control group). None of the participants ceased reatment because of them. Moreover, the majority of these side effects were lower in the probiotic group than in the placebo group(Emara et al., 2014).

3.6. Risk of bias assessment

The result of the risk of bias assessments for the included studies is summarized in ***Appendix S2. The included articles were found to have low (n = 4, (Emara et al., 2014; Ohtsu et al., 2017; Rosania et al., 2012; Takagi et al., 2016) or high (n = 2) risk of random sequence generation. Two studies had high risk(Ianiro et al., 2013; Igarashi et al., 2017), three studies low risk(Emara et al., 2014; Ianiro et al., 2013; Ohtsu et al., 2017; Rosania et al., 2012), and one was judged to have unclear risk(Takagi et al., 2016) of bias for randomisation concealment. There was high risk of performance bias in one study(Igarashi et al., 2017), and no study was found to have a high risk of attrition bias. According to the meta-analysis model, there was moderate heterogeneity between studies (P = 0.228; I^2 = 32.8%) (Fig. 2).

3.7. Meta-analysis

Because of low quality only three studies of six, wer included in meta-analysis model. Pooling results from three trials (Emara et al., 2014; Ohtsu et al., 2017; Takagi et al., 2016), which included a control arm, and included 300 participants (150 cases and 150 controls), there was a consistent trend for improvement in GI symptoms, including postprandial fullness, epigastric pain and nausea, in response to probiotics (n = 3 RCTs, RR: 1.35, 95% CI 0.99 to 1.84; P = 0.061, Fig. 2).

4. Discussion

To our knowledge, this is the first systematic review to assess the role of probiotics in the management of FD symptoms. Taken together, the results indicate that probiotic supplementation may have beneficial effects on GI symptoms in FD but the findings are not definitive possibly reflecting a type II error. However, only a few studies have been performed, and there was significant heterogeneity among the included studies, particularly in terms of population characteristics, study design, types of probiotics used, outcome measures and follow up duration. Thus, the findings must be interpreted with caution, and much more research is warranted, particularly carefully controlled, long-term studies to firmly establish the beneficial role for probiotics in the management and treatment of FD symptoms.

Almost all the probiotics used in the included studies showed positive effects on improvement of GI symptoms in adult FD patients. The results of the present review are consistent with prior studies that have shown probiotics supplementation to be effective at improving lower digestive tract pain and discomfort (Derwa, Gracie, Hamlin, & Ford, 2017; Didari, Mozaffari, Nikfar, & Abdollahi, 2015; Hempel et al., 2012; Jin et al., 2018; Korterink et al., 2014; Moayyedi et al., 2010). In contrast, a previous systematic review of studies in children with IBS indicated that species, such as *Lactobacillus ruteri*, were not effective in reducing the severity or frequency of abdominal pain, although *Lactobacillus rhamnosus* GG was effective in reducing the severity or frequency of abdominal pain (Ianiro et al., 2013). Interestingly, our systematic review also indicates that the effects on FD symptoms may also be strain-specific, and not all probiotics strains ameliorated all symptoms. In particular, *Lactobacillus gasseri* and *Lactobacillus reuteri* species may have larger effects on GI symptoms than other lactobacilli strains but this remains to be established. Clearly, more well-designed RCTs using standardized outcome measures are needed to identify which strains, therapy duration and doses, may be most effective.

It is widely acknowledged that acute GI infections caused by bacteria, viruses or parasites are major risk factors for FD-related disorders (Barbara et al., 2016). Studies have shown that the composition of bacterial flora in the GI tract of people with FD may be significantly

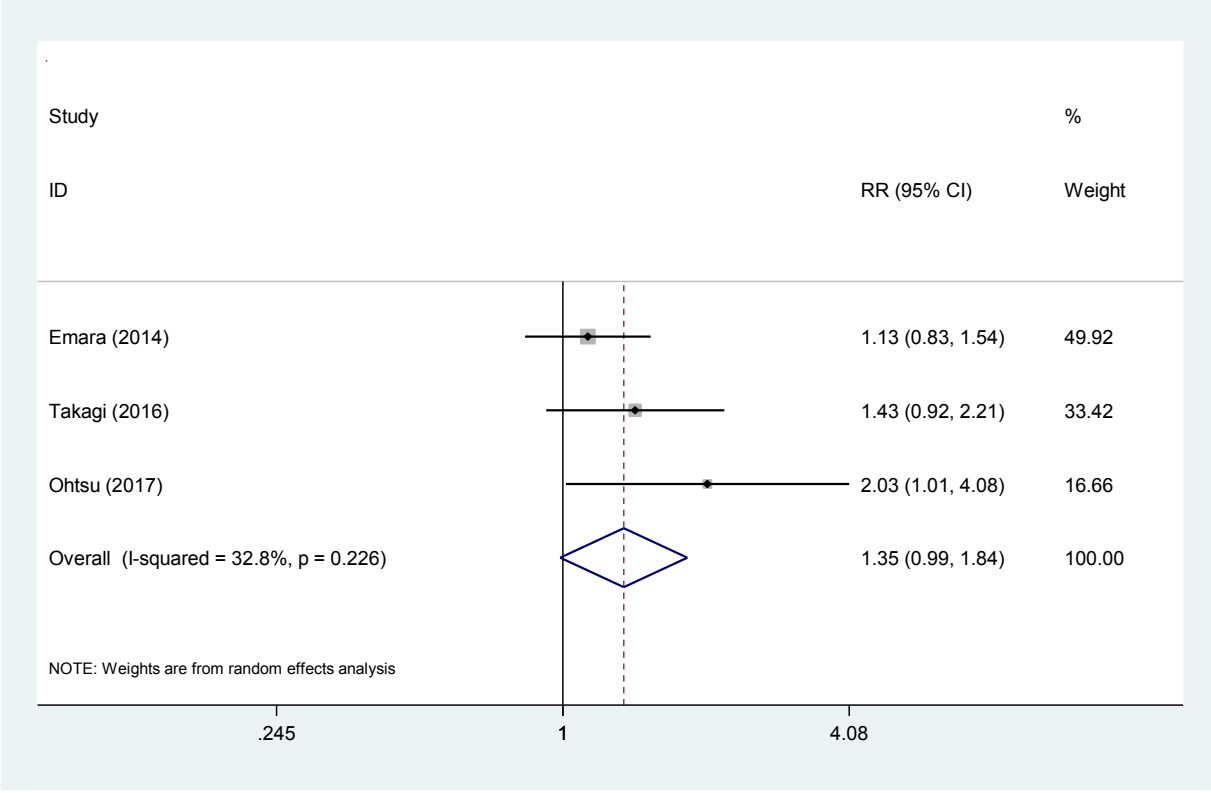

Fig. 2. Pooling results from three trials, which compared elimination rate for major FD symptoms between experimental and control.

different from that of healthy people(Igarashi et al., 2017; Walker et al., 2019). Thus, one of the putative mechanisms for any benefit of probiotics on FD is their effect on the alteration of GI bacterial compositions (Unno et al., 2015). Eradication of *H. pylori* infection is one potentially important change in bacterial composition due to supplementation of probiotics. The results of the current systematic review indicate that supplementation of probiotics can be effective in reducing *H. pylori* infection in a proportion of patients. These results are consistent with previous studies that demonstrated that probiotics could be helpful in reducing *H. pylori* infection (Tong, Ran, Shen, Zhang, & Xiao, 2007; Zhang et al., 2015; Zhu et al., 2014). Several mechanisms could explain the *H. pylori* effects of probiotics. First, probiotic supplementation may amplify GI innate defence such as by reinforcing the mucosal barrier function as demonstrated in *in vitro* and clinical studies(Salminen, Isolauri, & Salminen, 1996). Second, probiotic supplementation could lead to stimulation of the expression of gastric mucins which may subsequently prevent *H. pylori* adherence to epithelial tissues (Mack, Michail, Wei, McDougall, & Hollingsworth, 1999). Third, probiotic supplementation could modulate the immune response of the host to *H. pylori*(Blum, Lesbros-Pantoflickova, & Corthésy-Theulaz, 2007). However, the observed eradication rate with a probiotic alone is at best low; perhaps, combination therapy should be considered in future clinical trials, and the reasons for a lack of greater effect requires investigation.

Another change that occurs in the stool? composition of GI bacterial flora following probiotic use is a change in the ratio of *Bacteroidetes* to *Proteobacteria* and the presence of *Acidobacteria* (Igarashi et al., 2017). In FD patients, the ratio of *Bacteroidetes* to *Proteobacteria* is in favour of *Bacteroidetes* (Qiu et al., 2017), and *Acidobacteria* are absent (Naito, Fukui, Kashiwagi, & Takagi, 2018). Supplementation of probiotics facilitated the restoration of *Acidobacteria* in the GI bacterial flora and also changed the ratio of *Bacteroidetes* to *Proteobacteria* by reducing *Bacteroidetes* amount(Igarashi et al., 2017). Whether these changes are important in driving symptom improvement or are only secondary phenomena is unknown. Another possible mechanism by which probiotics may improve GI symptoms in FD may relate to their effects on bile acids. Previous research has shown that gut microbiota promote deconjugation of bile acids and increase their excretion into the feces. In addition, gut microbiota also inhibit bile acid synthesis in the liver (Sayin et al., 2013). Thus, amelioration of upper GI symptoms by probiotics may, in part, be due to their effects on reducing the secretion of bile acids in the proximal GI tract(Jones, Tomaro-Duchesneau, & Prakash, 2014).

This systematic review has several strengths. We followed rigorous systematic review methods as recommended by the Cochrane collaboration to decrease possible bias (e.g., two independent reviewers to search, screen and conduct quality assessment of studies and as well as extract relevant data). We also did not impose any language restrictions or time periods. However, some limitations are worth highlighting. In particular, there was significant variation in the quality of the included studies. There was also potential risk of bias, such as unclear blinding of outcomes, in almost all studies. Another limitation was the small sample size in the majority of included trials. Finally, the Kyoto consensus suggested *H. pylori* positive dyspepsia responding to eradication therapy should be considered in a separate category from all other FD and while this was not possible in the current study, the arbitrary division remains contentious(Sugano et al., 2015).

In conclusion, the results of this systematic review involving a small number of studies suggest that supplementation with probiotics could potentially improve GI dyspeptic symptoms in patients with FD. However, the available evidence is marred by significant heterogeneity across the available studies. Further high-quality RCTs are needed to clarify the effects of probiotic supplementation on FD outcomes. Moreover, since we could not completely dissect out the direct or indirect effect of probiotics on dyspeptic symptoms and *H. pylori* eradication, this issue also requires future investigation.

Guarantor of the article: Shahram Agah.

Author contributions

SHA: study concept and design; AA, JH: acquisition of data; MS, FF, MMO: analysis and interpretation of data; PA: drafting of the manuscript; SHA, CFB, ROA, NJT, JH, MMA: review of data and critical revision of the manuscript for important intellectual content; MMO, JH, MS, AA, CFB, NJT, SHA: Approval of the final manuscript.

Disclosures

All authors has nothing to disclose.

Ethics statements

This systematic review is accordance with the World Medical Association Declaration of Helsinki.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2020.103902.

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