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ORIGINAL RESEARCH

Probiotics improve the efficacy of standard triple therapy in the eradication of *Helicobacter pylori*: a meta-analysis

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Introduction: *Helicobacter pylori* colonization is present in half of the world's population and can lead to numerous gastrointestinal diseases if left untreated, including peptic ulcer disease and gastric cancer. Although concurrent triple therapy remains the recommended treatment regimen for *H. pylori* eradication, its success rate and efficacy have been declining. Recent studies have shown that the addition of probiotics can significantly increase eradication rates by up to 50%. This meta-analysis examines the impact of probiotic supplementation on the efficacy of standard triple therapy in eradicating *H. pylori*.

Methods: A comprehensive literature search was conducted using PubMed, Cochrane Central Registry of Controlled Trials, and Google Scholar (time of inception to 2016) to identify all published randomized control trials (RCTs) assessing the use of probiotics in addition to triple therapy for the treatment of *H. pylori*. Searches were conducted using the keywords "probiotics", "triple therapy", and "*Helicobacter pylori*". RCTs comparing the use of probiotics and standard triple therapy with standard triple therapy alone for any duration in patients of any age diagnosed with *H. pylori* infection were included. *H. pylori* eradication rates (detected using urea breath test or stool antigen) were analyzed as-per-protocol (APP) and intention-to-treat (ITT).

Results: A total of 30 RCTs involving 4,302 patients APP and 4,515 patients ITT were analyzed. The addition of probiotics significantly increased eradication rates by 12.2% (relative risk [RR] =1.122; 95% confidence interval [CI], 1.091–1.153; $P<0.001$) APP and 14.1% (RR =1.141; 95% CI, 1.106–1.175; $P<0.001$) ITT. Probiotics were beneficial among children and adults, as well as Asians and non-Asians. No significant difference was observed in efficacy between the various types of probiotics. The risk of diarrhea, nausea, vomiting, and epigastric pain was also reduced.

Conclusion: The addition of probiotics is associated with improved *H. pylori* eradication rates in both children and adults, as well as Asians and non-Asians. *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and mixtures of probiotics appear beneficial in *H. pylori* eradication. Furthermore, the reduction in antibiotic-associated side effects such as nausea, vomiting, diarrhea, and epigastric pain improves medication tolerance and patient compliance. Given the consequences associated with chronic *H. pylori* infection, the addition of probiotics to the concurrent triple therapy regimen should be considered in all patients with *H. pylori* infection. However, further studies are required to identify the optimal probiotic species and dose.

Keywords: probiotics, *Helicobacter pylori*, triple therapy, meta-analysis

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Introduction

Helicobacter pylori, previously referred to as *Campylobacter pylori*, is a Gram-negative, spiral bacterium that is present on the gastric epithelium mucus layer.[1] *H. pylori* colonization almost always leads to acute gastritis, with neutrophilic and mononuclear

infiltrates in the gastric mucosa.[2] If left untreated, it can cause chronic gastritis, which is associated with various gastrointestinal diseases.[2] Various extragastric manifestations of *H. pylori* have also been reported, including idiopathic thrombocytopenia purpura, vitamin B12 deficiency, and metabolic syndrome.[3] Studies have reported *H. pylori* colonization to be as high as 90% among patients with gastric ulcers or cancer.[4,5] Furthermore, virtually, all patients with mucosa-associated lymphoid tissue lymphomas (MALTomas) are colonized with *H. pylori*.[6,7] It is estimated that over half of the current world population has *H. pylori* in their gastric flora.[1] Early *H. pylori* eradication has been associated with a sixfold reduction in the recurrence of ulcers as well as a two- to threefold reduction in the risk of gastric carcinoma.[8]

Current treatment guidelines recommend concomitant triple therapy for the eradication of *H. pylori*, utilizing clarithromycin, either amoxicillin or metronidazole, as well as a proton pump inhibitor for 7–14 days.[9–11] Despite initial successes, there has been a constant decline in *H. pylori* eradication rates with standard triple therapy in both adult and pediatric populations, from 75 to 55% between 2009 and 2014.[12] Although several mechanisms have been proposed, most of the studies agree that the main reasons for the declining efficacy are the increasing resistance to clarithromycin and poor medication compliance as a result of antibiotic-induced nausea, vomiting, and diarrhea.[13–15] While eradication rates of 88% are seen with clarithromycin-sensitive *H. pylori* strains, eradication rates are only 14% among strains resistant to clarithromycin.[16] As with all antibiotics, *H. pylori* medications often cause diarrhea, nausea, and vomiting, which lead to poor tolerance and ultimately decreased patient compliance, the single most important factor in *H. pylori* eradication.[14,17] Graham et al[18] reported *H. pylori* eradication rates of 96% in high medication-compliant patients (taking ≥60% of the prescribed antibiotics), while only 69% eradication rates were observed among low medication-compliant patients (taking <60% of prescribed antibiotics). With the decline in *H. pylori* eradication rates, novel therapeutic alternatives are being studied and evaluated. Eradication rates are highest during the early phase of treatment when antibiotic sensitivity and patient compliance are greatest. Early treatment failure results in elevated risk of secondary antibiotic resistance due to the need for additional, less effective antibiotics used over longer periods of time with the possibility of additional medication side effects, thereby perpetuating the increase in antibiotic resistance and decreased medication compliance cycle.[19] Since medication compliance has been considered the most important factor in *H. pylori* eradication, a major goal of therapy is aimed at improving the compliance. Recently, the use of probiotic supplementation has been proposed for both preventing and treating various gastrointestinal conditions, including antibiotic-induced side effects such as diarrhea, which may in turn increase medication tolerability and patient compliance.

Probiotics are defined by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) as living microorganisms that could potentially benefit health.[20] Although a variety of different probiotic species have been studied, the *Lactobacillus* genus, *Bifidobacterium* genus, and *Saccharomyces* genus remain the most commonly studied.[20] Probiotics act in numerous pathways, and both immune-mediated and nonimmune-mediated mechanisms have been documented.[14]

Gong et al[21] reported lower odds of *H. pylori* eradication with triple therapy alone, compared to triple therapy with probiotic supplementation (odds ratio [OR] 0.58; 95% confidence interval [CI], 0.50–0.68; $P<0.05$). Significant reductions in side effects, including nausea, vomiting, bloating, epigastric pain, diarrhea, constipation, taste distortion, and skin rash, were also observed.[21] Numerous randomized control trials (RCTs) not included in the Gong et al study have recently been published. Furthermore, no subgroup analysis has been conducted to determine whether probiotics are beneficial in all populations, such as adults and children, as well as Asians and non-Asians.

Given the grave long-term consequences associated with chronic *H. pylori* infection, this meta-analysis provides an updated analysis on the efficacy of probiotic supplementation to triple therapy on *H. pylori* eradication rates in both children and adults, as well as the Asian and non-Asian populations.

Methods

Study selection

A comprehensive literature search of PubMed, Cochrane Central Registry of Controlled Trials, and Google Scholar from the time of inception (1966) to the present day (2016) was conducted to identify all published RCTs evaluating the effect of probiotic supplementation on the efficacy of standard triple therapy in the treatment of *H. pylori*. Using the yielded search results, additional references and studies were searched. The last search was performed on February 22, 2016. Combinations of the keywords "probiotics", "triple therapy", "*Campylobacter pylori*", "*Helicobacter pylori*", and "*H. pylori*" were used. Studies comparing the use of probiotics and

standard triple therapy with standard triple therapy alone for any duration in patients of any age diagnosed with *H. pylori* infection were included. If there were duplicate publications of the same study, only the most updated and comprehensive data set for the study was included.

Data extraction

Each article retrieved from the database searches as described earlier was reviewed and assessed for eligibility and study inclusion. Data related to the patients, comparison groups (probiotic and standard triple therapy group vs standard triple therapy alone group), clinical outcomes, and study methodology were extracted (Figure 1). The incidence rates of *H. pylori* eradication (detected via urea breath test or stool antigen) and adverse events (including nausea, vomiting, diarrhea, and epigastric pain) were assessed.

Statistical analysis

Relative risk (RR) along with a 95% CI for the incidence of *H. pylori* eradication and medication side effects was calculated for each included study. If any study reported a zero incidence in either the intervention (standard triple therapy and probiotic) or the control (standard triple therapy alone) group, a "0.5" continuity correction factor was applied to allow for calculation of RR and variance. Depending on the heterogeneity of the included study, either a fixed-effects model or a random-effects model was used. Both Cochrane's Q statistic and I^2 statistic were used to assess heterogeneity, and a $P<0.05$ or $I^2>50$ was utilized for determining the presence of significant heterogeneity. Data were analyzed using a random-effects model when heterogeneity was deemed significant, while a fixed-effects model was used in the absence of heterogeneity. Sensitivity analysis to determine the influence of each individual included study on the overall effect size (RR estimates) was assessed by removing each study one-by-one and calculating the overall effect sizes. Publication bias for the pooled *H. pylori* eradication rates was evaluated, both visually using a funnel plot and quantitatively using Egger's and Begg's tests. Subgroup analysis was performed to determine any differences based on probiotic genus (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and mixed), patient age (children vs adults), ethnicity (Asians vs non-Asians), as well as the control group utilized (placebo vs no treatment). All meta-analyses of pooled study data were conducted using Comprehensive Meta-Analysis Software Version 3 (Biostat, Englewood, NJ, USA), and statistical significance was accepted at a level of $P<0.05$ (two tail).

Results

A total of 30 RCTs meeting the inclusion criteria were identified (Table 1). There were 4,302 patients when analyzed

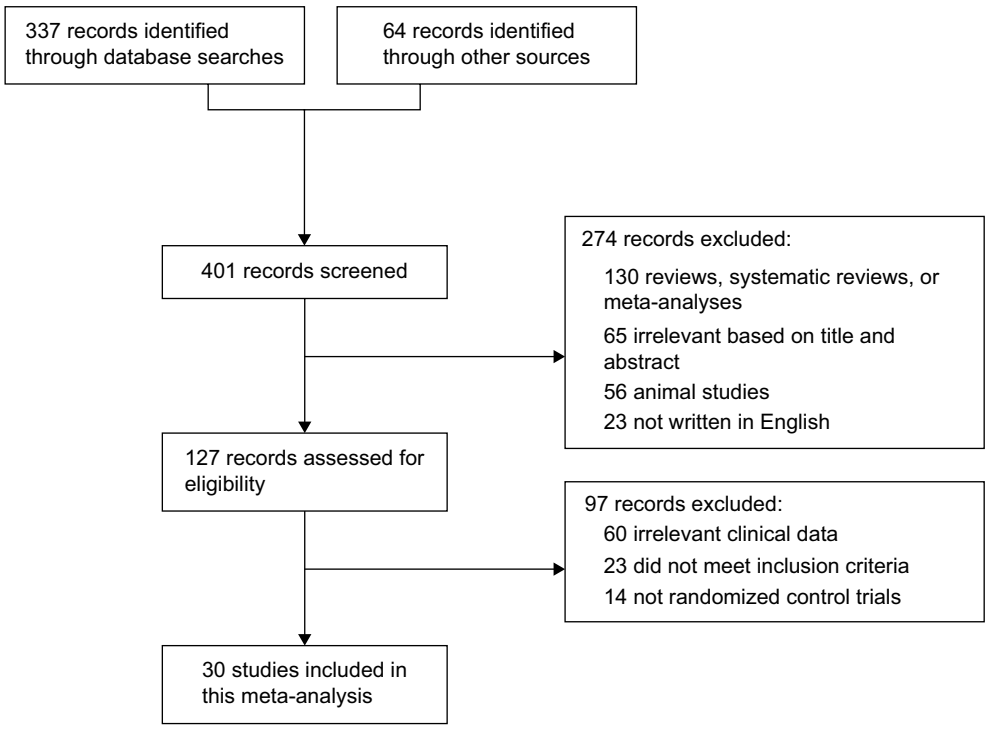

Figure 1 CONSORT diagram detailing the study selection process.
Abbreviation: CONSORT, consolidated standards of reporting trials.

Table 1 Characteristics of all published randomized control trials evaluating the use of probiotic supplementation on standard triple therapy in *Helicobacter pylori* eradication (1966–2016)

Study	Antibiotic regimen and duration	Probiotic	Method of diagnosing *H. pylori*	Method of detecting *H. pylori* eradication	Age	Country
Akcam et al[35]	Lansoprazole, clarithromycin, amoxicillin (14 days)	*L. acidophilus*, *L. casei*, *Bifidobacterium*	Histology	UBT	Children	Turkey
Bin et al[36]	Omeprazole, clarithromycin, amoxicillin (or metronidazole) (14 days)	*S. boulardii*	Serology, histology	UBT	Children	China
Hauser et al[37]	Omeprazole or pantoprazole, clarithromycin, amoxicillin (or metronidazole) (14 days)	*L. rhamnosus* GG, *Bifidobacterium*	Histology, UBT, stool antigen	Rapid urease test, UBT, or stool antigen	Adults	Croatia
Ma et al[38]	Omeprazole, clarithromycin, metronidazole (7 days)	*L. acidophilus*	Histology	UBT, histology, union of ulcer	Adults	China
Emara et al[39]	Omeprazole, clarithromycin, amoxicillin (14 days)	*L. reuteri*	Stool antigen, histology	Stool antigen, histology	Adults	Egypt
Francavilla et al[40]	PPI, clarithromycin, amoxicillin (7 days)	*L. reuteri*	UBT, serology of gastrin-17, histology	UBT	Adults	Italy
Srinarong et al[41]	Lansoprazole, clarithromycin, amoxicillin, bismuth (7 or 14 days)	*B. lactis*, *L. acidophilus*, *L. paracasei*	Histology	UBT	Adults	Thailand
Wang et al[31]	PPI, clarithromycin, amoxicillin (or metronidazole) (14 days)	*L. acidophilus*, *B. bifidum*	UBT	UBT	Children	China
Navarro-Rodriguez et al[19]	Lansoprazole, furazolidone, tetracycline (7 days)	*L. acidophilus*, *L. rhamnosus*, *B. bifidum*, *S. faecium*	UBT and histology	UBT or histology	Adults	Brazil
Du et al[42]	Omeprazole, clarithromycin, amoxicillin (7 days)	*L. acidophilus*	UBT and histology	UBT	Adults	China
Mirzaee and Rezahosseini[43]	Pantoprazole, clarithromycin, amoxicillin (7 days)	Probiotic yogurt	UBT	UBT	Adults	Iran
Bekar et al[44]	Lansoprazole, clarithromycin, amoxicillin (14 days)	Kefir	UBT	UBT	Adults	Turkey
Deguchi et al[45]	Rabeprazole, clarithromycin, amoxicillin (7 days)	Yogurt – *L. gasseri*	Histology, culture	UBT and stool antigen	Adults	Japan
Medeiros et al[46]	Esomeprazole, clarithromycin, amoxicillin (8 days)	*L. acidophilus*	Histology	UBT	Adults	Portugal
Song et al[47]	Omeprazole, clarithromycin amoxicillin (7 days)	*S. boulardii*	Histology	UBT	Adults	Korea
Yasar et al[48]	Pantoprazole, clarithromycin, amoxicillin (7 days)	*Bifidobacterium*	Histology	UBT	Adults	Turkey
Hurduc et al[49]	Omeprazole or esomeprazole, clarithromycin, amoxicillin (7–10 days)	*S. boulardii*	Histology	Histology	Children	Romania
Szajewska et al[50]	Omeprazole, clarithromycin, amoxicillin (7 days)	*L. rhamnosus* GG	UBT, histology, rapid urease test	UBT	Children	Poland

(*Continued*)

Table 1 (*Continued*)

Study	Antibiotic regimen and duration	Probiotic	Method of diagnosing *H. pylori*	Method of detecting *H. pylori* eradication	Age	Country
Kim et al[51]	PPI, clarithromycin, amoxicillin (7 days)	*L. acidophilus*, *L. casei*, *B. longum*, *S. thermophiles*	UBT, histology, rapid urease test	UBT	Adults	Korea
Scaccianoce et al[52]	Lansoprazole, clarithromycin, amoxicillin (7 days)	*L. reuteri*, *L. plantarum*, *L. casei*, *B. infantis*, *B. longum*, *L. salivarius*, *L. acidophilus*, *S. termophilus*, *L. sporogenes*	Histology	UBT	Adults	Italy
Cindoruk et al[53]	Lansoprazole, clarithromycin, amoxicillin (14 days)	*S. boulardii*	Histology	UBT	Adults	Turkey
Goldman et al[54]	Omeprazole, clarithromycin, amoxicillin (7 days)	*L. casei*, *B. animalis*	Histology, UBT	UBT	Children	Argentina
Ziemniak[55]	PPI, clarithromycin, amoxicillin (10 days)	*L. acidophilus*, *L. rhamnosus*	Histology and UBT	UBT	Adults	Poland
Myllyluoma et al[56]	Lansoprazole, clarithromycin, amoxicillin (7 days)	*L. rhamnosus* GG, *L. rhamnosus*, *P. freudenreichii*, *B. breve*	Rapid whole blood test, UBT, serology	UBT	Adults	Finland
Sykora et al[57]	Omeprazole, clarithromycin amoxicillin (7 days)	*L. casei*	Histology, rapid urease test, culture, stool antigen	UBT, stool antigen	Children	Czech Republic
Nista et al[58]	Rabeprazole, clarithromycin, amoxicillin (7 days)	*B. clausii*	UBT	UBT	Adults	Italy
Cremonini et al[15]	Rabeprazole, tinidazole, amoxicillin (7 days)	*L. rhamnosus* GG, *S. boulardii*, *L. acidophilus*	UBT	UBT	Adults	Italy
Sheu et al[59]	Lansoprazole, clarithromycin, amoxicillin (7 days)	*Lactobacillus*, *Bifidobacterium*	Histology and rapid urease test	UBT	Adults	Taiwan
Armuzzi et al[60]	Pantoprazole, tinidazole clarithromycin (7 days)	*L. rhamnosus* GG	UBT, IgG antibodies	UBT	Adults	Italy
Canducci et al[61]	Rabeprazole, clarithromycin, amoxicillin (7 days)	*L. acidophilus*	UBT, histology	UBT	Adults	Italy

Abbreviations: *B*, *Bifidobacterium*; *L*, *Lactobacillus*; *P, Propionibacterium*; PPI, proton-pump inhibitor; *S*, *Saccharomyces*; UBT, urea breath test.

as-per-protocol (APP) and 4,515 patients when analyzed intention-to-treat (ITT).

Effects of probiotics on triple therapy efficacy in H. pylori eradication rates (APP treated)

All studies reported on *H. pylori* eradication rates in both the probiotic-supplemented and triple therapy alone groups. The addition of probiotics to the triple therapy regimen significantly increased eradication rates compared to triple therapy alone (1,786/2,140 [83.5%] vs 1,602/2,162 [74.1%]). No significant heterogeneity between trials (P=0.321, I^2<8.993) was found, and a fixed-effects model was therefore utilized. There was a 12.2% increase in eradication rates with probiotic supplementation (RR =1.122; 95% CI, 1.091–1.153; P<0.001) (Figure 2).

Subgroup analysis by patient age revealed that probiotic supplementation improved the efficacy of triple therapy in both children (RR =1.176; 95% CI, 1.050–1.317; P=0.005) and adults (RR =1.118; 95% CI, 1.087–1.150; P<0.001) with no significant between group heterogeneity (P=0.491).

Subgroup analysis by the type of probiotic identified benefit for *Lactobacillus* (RR =1.142; 95% CI, 1.084–1.203; P<0.001), *Saccharomyces* (RR =1.088; 95% CI, 1.022–1.158; P=0.008), and mixture of probiotics (RR =1.135; 95% CI, 1.088–1.185; P<0.001). A trend toward an increase in eradication rates with *Bifidobacterium* (RR =1.094; 95% CI, 0.992–1.207; P=0.073) was also observed. There was no significant between group heterogeneity (P=0.589).

Subgroup analysis by ethnicity identified that probiotic supplementation improved the efficacy of triple therapy in both Asians (RR =1.108; 95% CI, 1.066–1.152; P<0.001) and non-Asians (RR =1.136; 95% CI, 1.092–1.181; P<0.001), with no statistically significant between group differences (P=0.826).

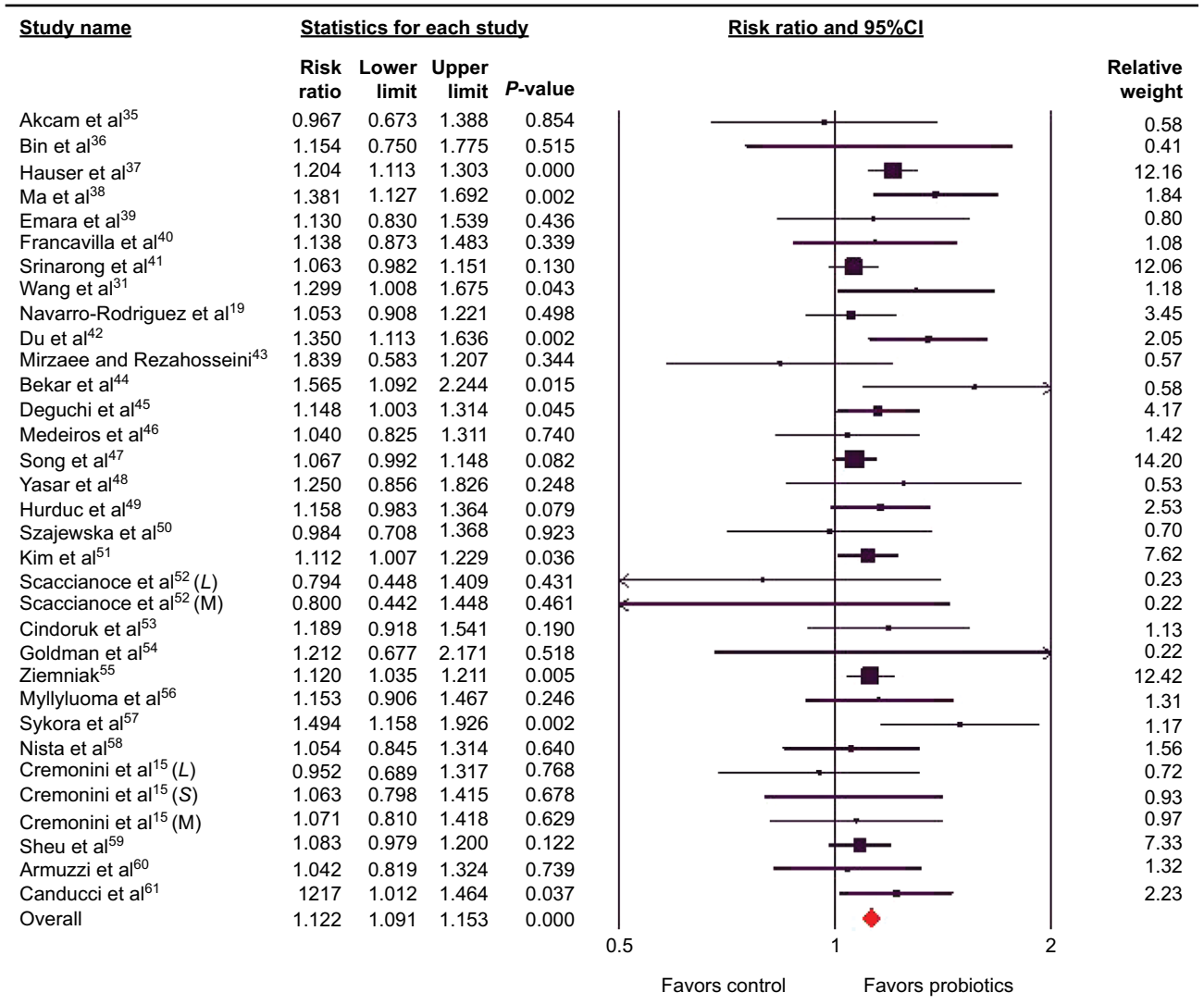

Figure 2 Forest plot evaluating the relative risk of *Helicobacter pylori* eradication associated with probiotic supplementation (as-per-protocol treated).
Abbreviation: CI, confidence interval; *L*, *Lactobacillus*; *S*, *Saccharomyces*; M, mixture of probiotics.

Subgroup analysis based on the type of control group utilized revealed a significant improvement in triple therapy efficacy in both the no treatment group (RR =1.152; 95% CI, 1.106–1.200; $P<0.001$) and placebo group (RR =1.122; 95% CI, 1.075–1.170; $P<0.001$), with no significant difference between the two groups ($P=0.365$).

Effects of probiotics on triple therapy efficacy in *H. pylori* eradication rates (ITT)

The addition of probiotics to the triple therapy regimen significantly increased eradication rates compared to triple therapy alone (1,744/2,222 [78.5%] vs 1,564/2,293 [68.2%]). Heterogeneity between trials was deemed not significant ($P=0.459$, $I^2<0.445$), and therefore a fixed-effects model was employed. There was a 14.1% increase in eradication rates with the addition of probiotics (RR =1.141; 95% CI, 1.106–1.176; $P<0.001$) (Figure 3).

Subgroup analysis based on patient age showed that probiotic supplementation improved the efficacy of triple therapy in both children (RR =1.193; 95% CI, 1.106–1.176; $P<0.001$) and adults (RR =1.138; 95% CI, 1.102–1.174; $P<0.001$), with no significant between group heterogeneity ($P=0.557$).

Subgroup analysis based on the type of probiotic identified benefit for *Lactobacillus* (RR =1.153; 95% CI, 1.092–1.217; $P<0.001$), *Bifidobacterium* (RR =1.168; 95% CI, 1.031–1.324; $P=0.015$), *Saccharomyces* (RR =1.127; 95% CI, 1.050–1.211; $P=0.001$), and mixture of probiotics (RR =1.140; 95% CI, 1.086–1.197; $P<0.001$). There was no significant difference in heterogeneity between the groups ($P=0.938$).

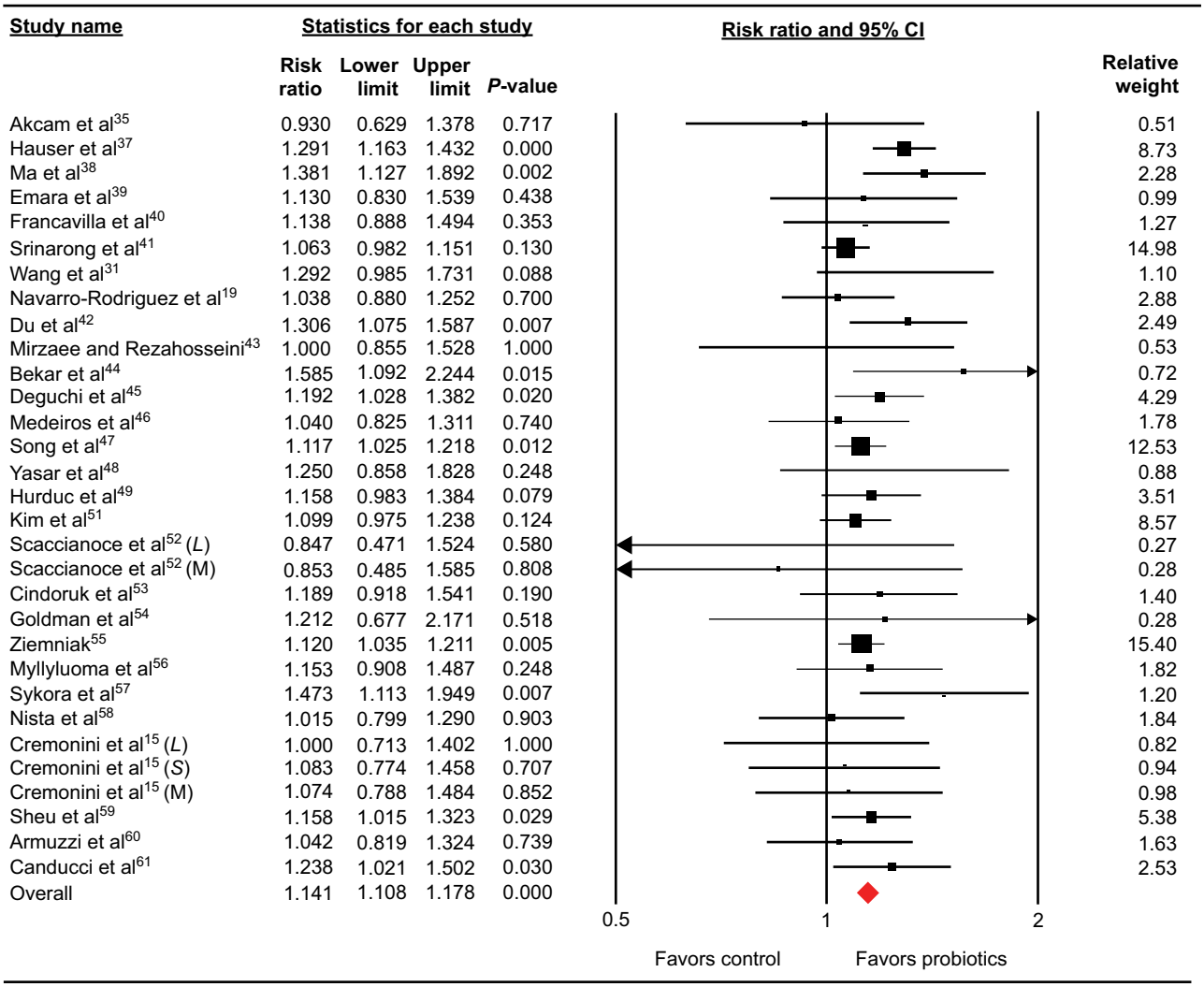

Figure 3 Forest plot evaluating the relative risk of *Helicobacter pylori* eradication associated with probiotic supplementation (intention-to-treat).
Abbreviation: CI, confidence interval; *L*, *Lactobacillus*; *S*, *Saccharomyces*; M, mixture of probiotics.

Subgroup analysis by ethnicity identified that probiotic supplementation improved the efficacy of triple therapy in both Asians (RR =1.132; 95% CI, 1.084–1.182; $P<0.001$) and non-Asians (RR =1.150; 95% CI, 1.101–1.200; $P<0.001$), with no significant difference based on ethnicity ($P=0.959$).

Subgroup analysis of the control group utilized identified a significant improvement in triple therapy efficacy in both the no treatment group (RR =1.149; 95% CI, 1.103–1.197; $P<0.001$) and placebo group (RR =1.130; 95% CI, 1.079–1.184; $P<0.001$), with no significant difference between the two groups ($P=0.636$).

Adverse events

A total of 18 of the studies (N=2,916 patients) reported on the incidence of nausea, 14 of the studies (N=1,703 patients) reported on the incidence of vomiting, 19 of the studies (N=2,554 patients) reported on the incidence of diarrhea, and 14 of the studies (N=2,537 patients) reported on the incidence of epigastric pain. There was a significant reduction in the risk of nausea (RR =0.606; 95% CI, 0.520–0.705; $P<0.001$), vomiting (RR =0.724; 95% CI, 0.533–0.985; $P=0.040$), diarrhea (RR =0.549; 95% CI, 0.391–0.771; $P=0.001$), and epigastric pain (RR =0.812; 95% CI, 0.727–0.907; $P<0.001$) with the addition of probiotics to standard triple therapy compared to triple therapy alone (Figures S1–S4).

Sensitivity analysis

Sensitivity analysis revealed similar overall effect sizes and RR estimates for *H. pylori* eradication rates after the removal of each individual study. *H. pylori* eradication rates ranged from 11.1% increase (RR =1.111; 95% CI, 1.078–1.144;

$P<0.001$) to 13.1% increase (RR =1.131; 95% CI, 1.098–1.165; $P<0.001$) (Figure S5).

Publication bias

Publication bias for *H. pylori* eradication rates was assessed utilizing both a funnel plot for qualitative analysis and Egger's and Begg's tests to quantitatively calculate the bias. There was no asymmetry on the funnel plot (Figure S6) and no significant publication bias calculated by either Egger's test ($P=0.784$) or Begg's test ($P=0.566$).

Discussion

H. pylori, a Gram-negative, spiral bacterium, was first discovered in 1982 by Warren and Marshall.[1] Over half of the world's population is colonized with *H. pylori*, which if left untreated potentially leads to chronic gastritis, gastric and duodenal ulcers, gastric cancer, and MALTomas.[2,4,5,7,22] *H. pylori* induces an initial inflammatory response (histological gastritis), followed by chronic inflammation and gastritis, causing damage to the epithelium and atrophy of the gastric lining.[2] Chronic inflammation leads to the production of reactive oxygen species (ROS), leading to DNA damage, which in turn leads to mutations, intestinal metaplasia and dysplasia, and further gastric pathology.[2]

Standard triple therapy remains the gold standard for eradicating *H. pylori*; however, more recent studies have shown a constant decline in *H. pylori* eradication rates, to as low as 50%.[12,23,24] This decline has been attributed to increased clarithromycin resistance and low medication compliance secondary to medication side effects.[13,14] Numerous alternative therapeutic regimens to enhance eradication rates have been proposed, including sequential therapy, which utilizes a dual 5-day therapy, with an initial 5-day regimen of amoxicillin and a proton pump inhibitor followed by 5 days of clarithromycin, metronidazole, and a proton pump inhibitor.[25] Lau et al[25] conducted a meta-analysis with 12 RCTs and 1,221 patients and revealed that sequential therapy improved eradication rates by 14.2%. Low medication compliance due to side effects has been deemed the most important factor in eradicating *H. pylori*, highlighting the need for novel treatments that increase medication tolerability and patient compliance.[17]

Probiotics, living commensal microorganisms naturally found in the host intestinal flora, exert a protective effect on the gastrointestinal tract.[26,27] Although the precise mechanism of probiotics has not been fully elucidated, numerous mechanisms have been proposed. Each probiotic strain has a unique mechanism of action that may be more or less effective in increasing *H. pylori* eradication and reducing the side effects. Previous studies have shown that probiotics significantly reduce the risk of antibiotic-associated side effects, including nausea, vomiting, diarrhea, and epigastric pain.[24,26] These commensal bacteria inhibit enteric pathogens and suppress pathogenic bacterial growth and invasion, ultimately improving intestinal barrier function.[28] Probiotics also modulate proinflammatory cytokines, which help maintain homeostasis and regulate immune responses.[28,29] *Lactobacillus* species have been shown to modify immune response by decreasing the levels of proinflammatory cytokines, stimulate mucin secretion, suppress bacterial growth, and inhibit *H. pylori* adhesion to the gastric epithelium.[14,20] Studies have shown that *Lactobacillus salavaris* reduces interleukin (IL)-8 secretion from the gastric epithelial cells, *Lactobacillus acidophilus* inactivates the Smad7 and NFκB inflammatory pathways, and *Lactobacillus bulgaricus* inhibits the activation of the TLR4 signaling pathway and IL-8 production.[20] *Lactobacilli* are also able to enhance the local IgA secretion and reduce specific anti-*H. pylori* IgG antibodies.[20] Additionally, strains of *Lactobacillus* are responsible for increasing mucin production.[20] Mucins protect the gastric epithelium, and *H. pylori* suppresses *MUC5AC* and *MUC1* gene expressions. *Lactobacillus plantarum* 299v increases MUC2 expression while *Lactobacillus rhamnosus* GG stimulates MUC3 gene expression.[20] Lactobacilli also secrete antibacterial substances, including lactic acid, hydrogen peroxidase, bactericines, and short-chain fatty acids.[14,20] *L. acidophilus* contains an autolysin, a proteinaceous compound, and antibacterial that is released after the cell lyses.[20] *Lactobacillus reuteri* produces reuterina that suppresses the growth of bacteria and also inhibits bacterial adhesion and colonization by binding of spiral bacterium to glycolipid protein receptors asialo-GMI and sulfatide.[20] *Bifidobacterium* acts by inhibiting DNA gyrase enzymes involved in bacterial cell division.[20] *Saccharomyces* contains neuroaminidase activity that removes the ligand for sialic acid-binding *H. pylori* adhesion to the gastric epithelium, α(2-3)-linked sialic acid.[20]

This current meta-analysis found that the addition of probiotics to the triple therapy is associated with a 13.8% increase in the chance of eradicating *H. pylori* infection compared to triple therapy alone, which is consistent with the results of a prior meta-analysis.[21] Additionally, probiotics have shown a significant decrease in side effects, including nausea, vomiting, epigastric pain, and diarrhea.

Despite the improvements in *H. pylori* eradication with adjunct probiotics, the use of probiotics as monotherapy has been shown to reduce bacterial load but not effective in

eradicating *H. pylori*.[30,31] Bhatia et al[32] discovered that *H. pylori* growth was inhibited in vitro if *L. acidophilius* was present. Michetti et al[33] was the first to study the effect of *L. acidophilus* in vivo, concluding that the probiotic decreased the density of the bacterial load, but complete eradication was unsuccessful. Wang et al studied adult patients taking multispecies probiotic therapies that included *L. acidophilus* and concluded a decrease in urea breath test values but not in complete *H. pylori* eradication.[31]

Although probiotic efficacy has been studied extensively with numerous RCTs, the side effect profile for probiotics is not well documented. The Agency for Healthcare Research and Quality conducted a comprehensive review of 622 studies on the safety of probiotic use, and reported that a majority of the published studies only state the presence or absence of one or more specific side effect, but lack specific details, and only a third provided vague statements indicating that the probiotics were well tolerated.[34] Case reports of sepsis, bacteremia, and fungemia with probiotic use have been reported; however, these adverse events are inconsistent and, when pooled together, are not statistically significant.[34]

Despite the significant and positive results from this meta-analysis, there are several limitations, mainly a result of the variation and heterogeneity of the included RCTs. Age, gender, ethnicity, and country of origin varied. The specific medications and dosage regimen, as well as diagnostic methods and any follow-up conducted, varied between studies. Similarly, the specific probiotic strain, dose, and treatment duration utilized were also slightly different. Additional RCTs are required to determine the best probiotic supplement for *H. pylori* eradication. Given the promise of probiotics in *H. pylori* eradication, further studies evaluating the bactericidal effects of different probiotic strains and potentially comparing the efficacy of probiotics alone vs probiotics in combination with triple therapy are warranted.

Despite the limitations discussed, this study identified that probiotic supplementation is associated with increased *H. pylori* eradication rates in adults and children, as well as Asians and non-Asians, compared to standard triple therapy alone. *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and mixtures of probiotics appear beneficial in *H. pylori* eradication. Furthermore, the reduction in antibiotic-associated side effects, such as nausea, vomiting, diarrhea, and epigastric pain, improves medication tolerance and patient compliance. Given the significant increase in *H. pylori* eradication rate and reduction in side effects, probiotics should be administered concurrently with standard triple therapy.

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Disclosure

The authors report no conflicts of interest in this work and have not accepted financial sponsorship in producing and presenting this article.

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Supplemenatary Materials

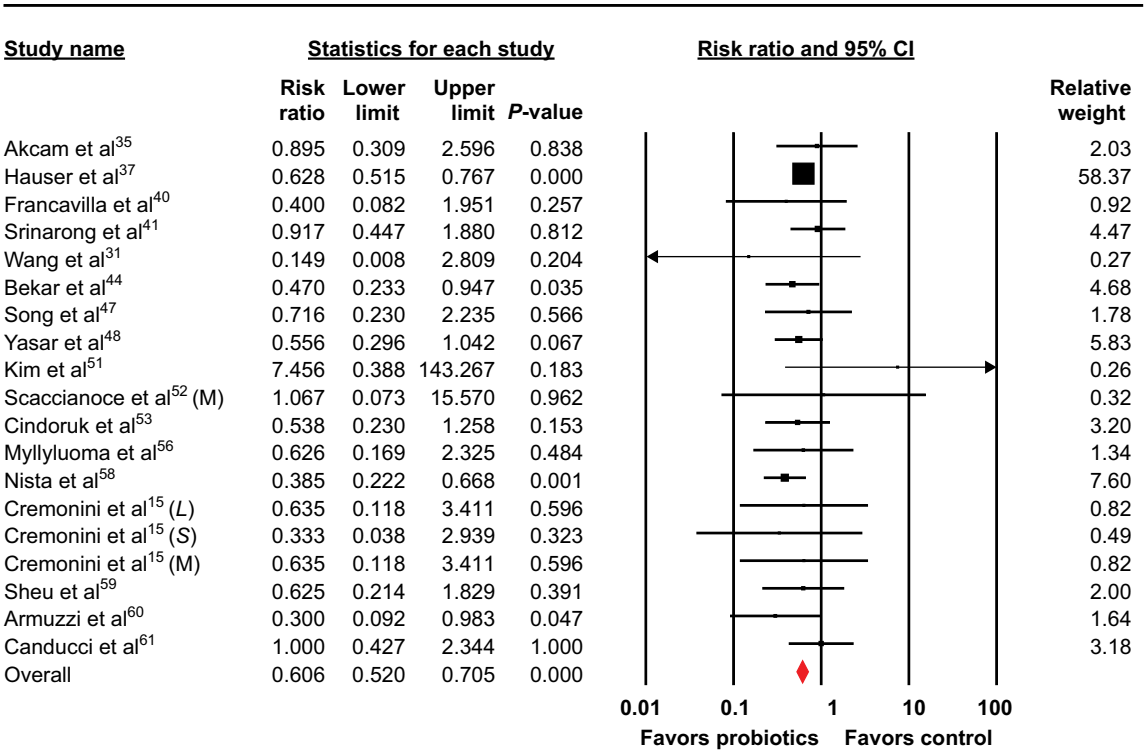

Figure S1 Forest plot evaluating the relative risk of nausea associated with probiotic supplementation.
Abbreviations: CI, confidence interval; *L*, *Lactobacillus*; *S*, *Saccharomyces*; M, mixture of probiotics.

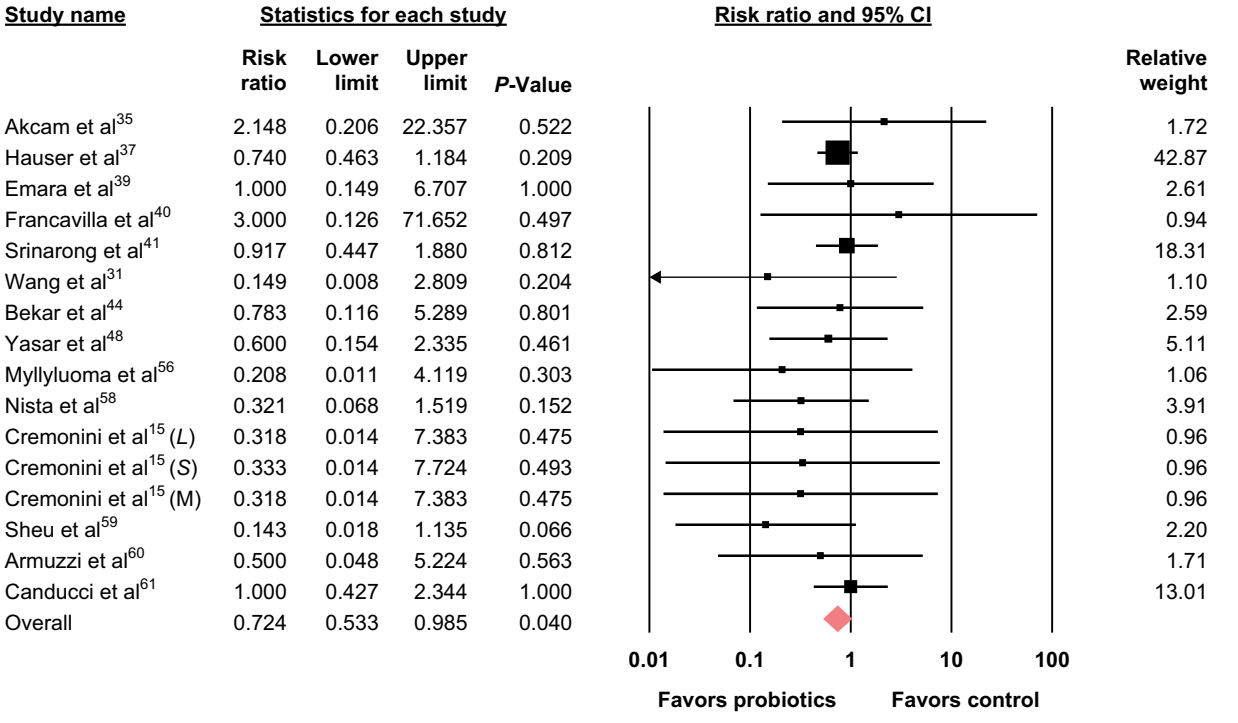

Figure S2 Forest plot evaluating the relative risk of vomiting associated with probiotic supplementation.
Abbreviations: CI, confidence interval; *L*, *Lactobacillus*; *S*, *Saccharomyces*; M, mixture of probiotics.

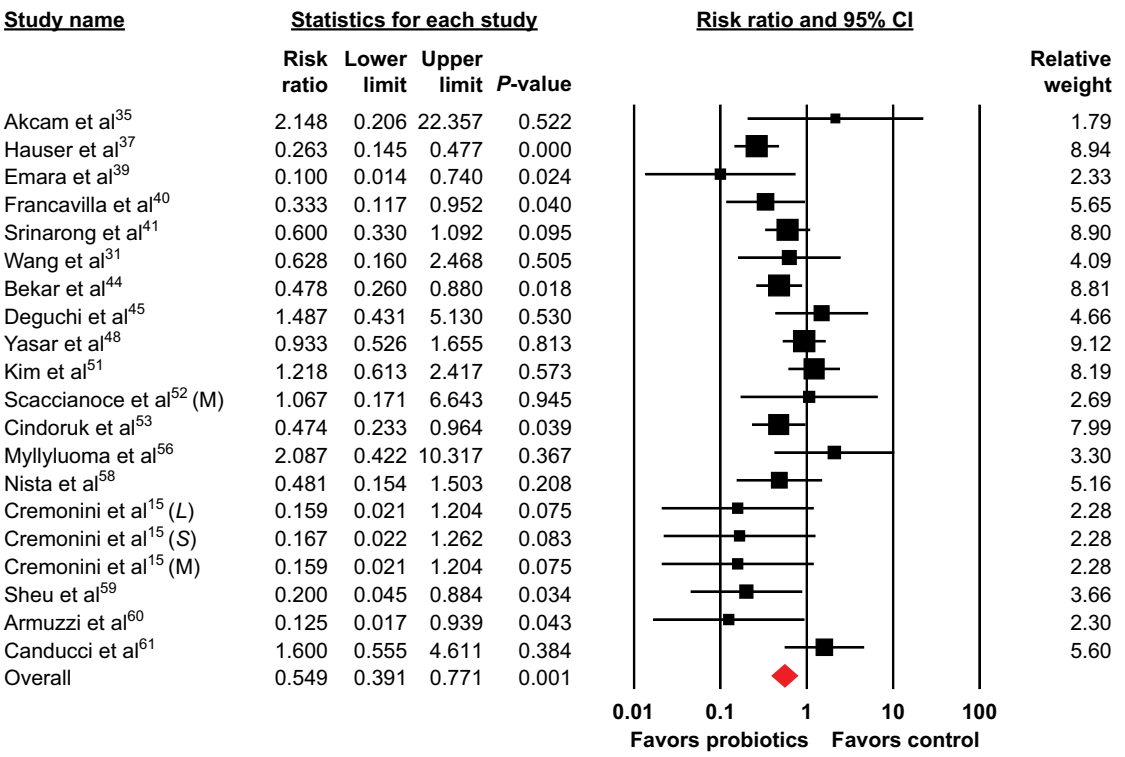

Figure S3 Forest plot evaluating the relative risk of diarrhea associated with probiotic supplementation.
Abbreviations: CI, confidence interval; *L*, *Lactobacillus*; *S*, *Saccharomyces*; M, mixture of probiotics.

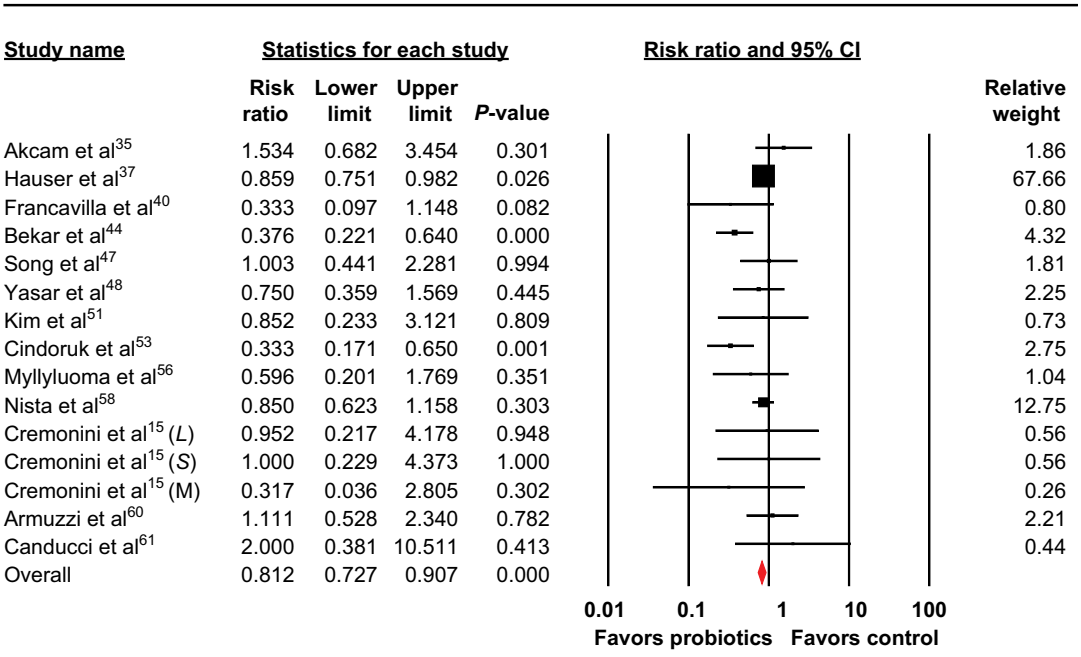

Figure S4 Forest plot evaluating the relative risk of epigastric pain associated with probiotic supplementation.
Abbreviations: CI, confidence interval; *L*, *Lactobacillus*; *S*, *Saccharomyces*; M, mixture of probiotics.

Study name	Statistics with study removed			
	Point	Lower limit	Upper limit	*P*-value
Akcam et al[35]	1.139	1.106	1.173	0.000
Bin et al[36]	1.137	1.104	1.171	0.000
Hauser et al[37]	1.127	1.092	1.163	0.000
Ma et al[38]	1.133	1.100	1.167	0.000
Emara et al[39]	1.138	1.104	1.172	0.000
Francavilla et al[40]	1.138	1.104	1.172	0.000
Srinarong et al[41]	1.150	1.114	1.187	0.000
Wang et al[31]	1.135	1.102	1.170	0.000
Navarro-Rodriguez et al[19]	1.140	1.107	1.175	0.000
Du et al[42]	1.133	1.100	1.167	0.000
Mirzaee and Rezahosseini[43]	1.138	1.105	1.172	0.000
Bekar et al[44]	1.135	1.102	1.169	0.000
Deguchi et al[45]	1.135	1.102	1.170	0.000
Medeiros et al[46]	1.139	1.106	1.173	0.000
Song et al[47]	1.140	1.105	1.176	0.000
Yasar et al[48]	1.137	1.104	1.171	0.000
Hurduc et al[49]	1.137	1.103	1.171	0.000
Szajewska et al[50]	1.139	1.106	1.173	0.000
Kim et al[51]	1.140	1.106	1.175	0.000
Scaccianoce et al[52] (*L*)	1.138	1.105	1.172	0.000
Scaccianoce et al[52] (M)	1.138	1.105	1.172	0.000
Cindoruk et al[53]	1.137	1.104	1.171	0.000
Goldman et al[54]	1.137	1.104	1.171	0.000
Ziemniak[55]	1.140	1.105	1.177	0.000
Myllyluoma et al[56]	1.137	1.104	1.172	0.000
Sykora et al[57]	1.134	1.101	1.168	0.000
Nista et al[58]	1.140	1.106	1.174	0.000
Cremonini et al[15] (*L*)	1.139	1.106	1.173	0.000
Cremonini et al[15] (*S*)	1.138	1.105	1.173	0.000
Cremonini et al[15] (M)	1.138	1.105	1.172	0.000
Sheu et al[59]	1.136	1.103	1.171	0.000
Armuzzi et al[60]	1.139	1.106	1.173	0.000
Canducci et al[61]	1.135	1.102	1.170	0.000
Overall	1.138	1.105	1.171	0.000

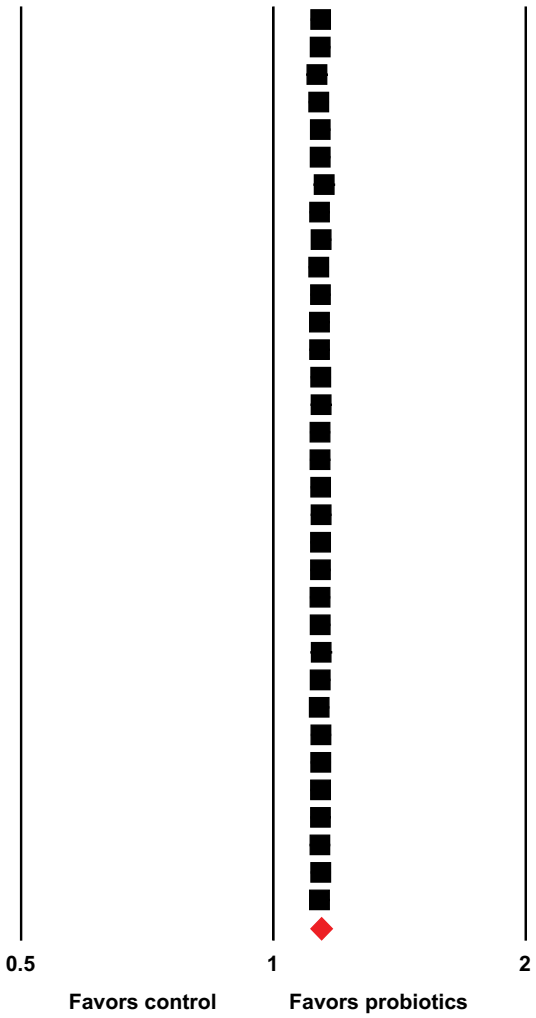

Figure S5 Sensitivity analysis evaluating the impact of removing each randomized control trial on the overall relative risk of *Helicobacter pylori* eradication with probiotic supplementation.

Abbreviations: CI, confidence interval; *L*, *Lactobacillus*; *S*, *Saccharomyces*; M, mixture of probiotics.

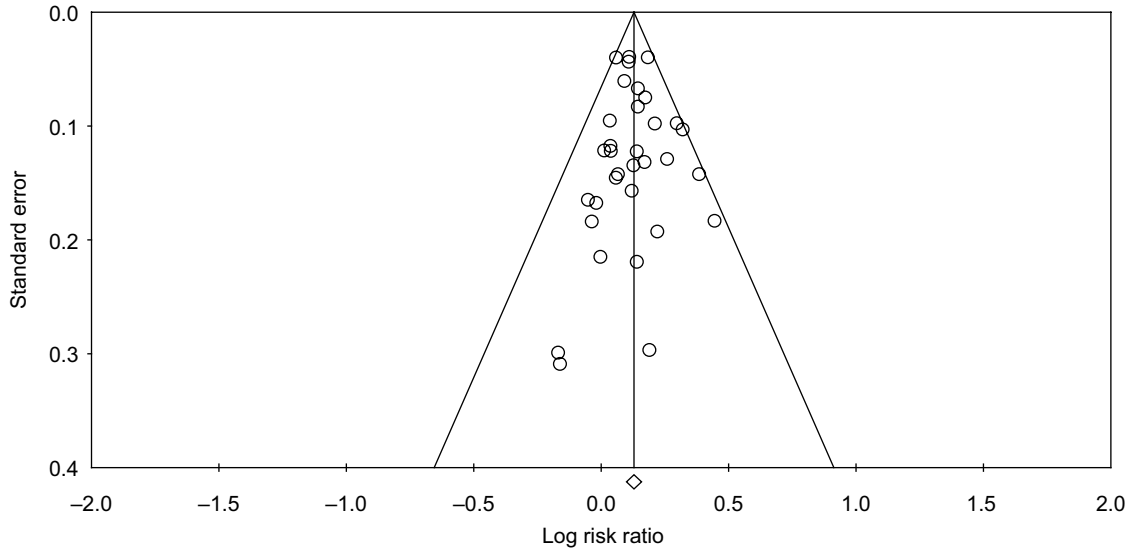

Figure S6 Funnel plot assessing publication bias (analyzing the effect of probiotics on the efficacy of triple therapy in the eradication of *Helicobacter pylori*).
Notes: Each circle represents a RCT included in the current meta-analysis. The diamond represents the overall result.
Abbreviation: RCT, randomized control trial.