

Original Article

Probiotics improve efficacy and tolerability of triple therapy to eradicate *Helicobacter pylori*: a meta-analysis of randomized controlled trials

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Received February 1, 2015; Accepted April 2, 2015; Epub April 15, 2015; Published April 30, 2015

Abstract: Objective: Gastric colonization by *Helicobacter pylori* is linked to a host of diseases, but eradication rates have declined in recent years. Some experimental studies suggest that probiotics may inhibit growth of *H. pylori*. This investigation was conducted to assess the impact of probiotics on both efficacy and tolerability of triple therapy to eradicate *H. pylori*. Methods: PubMed, Web of Science, and the Cochrane Collaboration were searched for relevant articles published through August 31, 2014. All analytics relied on commercially available software (Stata 11). Results: Twenty-three studies (N = 3900) qualified for meta-analysis. Pooled *H. pylori* eradication rates for triple therapy used alone and with added probiotics were 1464/2026 (72.26%; 95% CI, 67.66%-74.13) and 1513/1874 (80.74%; 95% CI, 74.68%-82.76%), respectively (odds ratio [OR] = 0.58; 95% CI, 0.50-0.68). Loss of appetite was similar in both groups (OR = 0.94; 95% CI, 0.61-1.45), but most adverse events (nausea, diarrhea, epigastric pain, vomiting, taste distortion, and skin rash) were mitigated through addition of probiotics. Publication bias was not evident, as indicated by Begg's and Egger's tests. Conclusions: Probiotics may improve the efficacy of triple therapy in eradicating gastric *H. pylori* and alleviate most treatment-related adverse events.

Keywords: *Helicobacter pylori*, probiotics, triple therapy, adverse events, eradication

Introduction

One-half of the world's population is colonized by *Helicobacter pylori*. In developing countries, the prevalence is 80-90% [1]. *H. pylori* is not only responsible for digestive pathology such as gastritis, peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue lymphoma, but it is also implicated in non-digestive ailments, including cardiovascular problems, allergies, diabetes and its complications, neurologic or endocrine disorders, and hematologic disease [2]. Triple therapy, combining a proton-pump inhibitor (PPI) with two effective antibiotics, is generally administered as treatment, but eradication rates have declined in recent years. The eradication failure rate, which now exceeds 20% [3], is largely due to side effects of the traditional regimen (promoting non-compliance) and antibiotic resistance. Newer alternative therapies or adjunctive treatments are needed.

At present, some studies suggest that combining probiotics with triple-agent therapy may improve *H. pylori* eradication. Still, other researchers hold opposing views. To clarify the role of probiotics in this setting, a meta-analysis was performed.

Materials and methods

Literature search strategy

PubMed, Web of Science, and the Cochrane Collaboration were searched for relevant articles published through August 31, 2014. Our search included the following terms: probiotics, lactococcus, fermented milk, yogurt, bifidobacterium, yeasts, lactobacillus, *Clostridium butyricum*, *Bacillus subtilis*, saccharomyces, *Bacillus licheniformis*, *Helicobacter pylori*, and *H. pylori*.

Selection criteria

Inclusion criteria were as follows: 1) randomized controlled trials (RCTs) only; 2) subjects >

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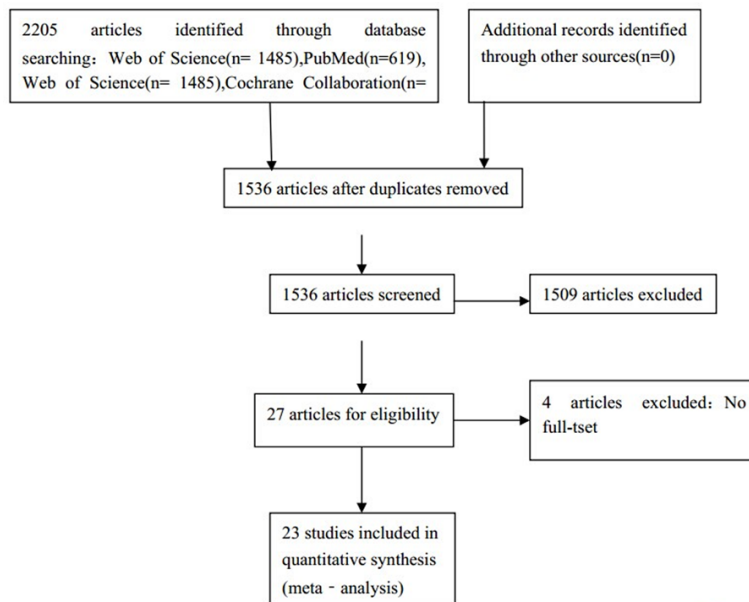


Figure 1. Identification process for eligible trial.

14 years old; 3) proven *H. pylori* colonization; 4) *H. pylori* treatment-naïve status; 5) confirmed eradication (at least 4 weeks post-treatment); 6) two-arm minimum randomization (triple therapy alone and with probiotics); and 7) publications in English. Exclusion criteria were as follows: (1) non-RCTs; (2) subjects < 14 years old; (3) sequential therapeutics; (4) articles not published in English; and (5) abstract-only reports.

Data extraction

All articles were independently screened by two researchers, who separately generated JADAD scores (based on randomization, blinding, and attrition). A third researcher served to resolve any scoring differences.

Statistical methods

Statistical calculations (including subanalyses) relied on commercially available software (Stata 11; StataCorp LP, College Station, TX, USA). Odds ratios (ORs) of eradication rates and side effects were determined through a fixed-effects model via Mantel-Haenszel method.

Results

Search results

Initial searches of the three electronic databases yielded 2205 entries that met our predefined

inclusion criteria, 669 of which were then excluded as duplicates (**Figure 1**). Another 1513 articles were excluded as non-original articles, comments, reviews, or non-RCTs. Ultimately, 23 citations [4-26] proved acceptable for this meta-analysis (**Figure 1**). The characteristics of 23 trials selected in the meta-analysis are summarized in detail (**Table 1**).

Eradication rates

A total of 23 articles qualified for this analysis, encompassing 3900 subjects given triple therapy, either without ($n = 2026$) or with probiotics ($n = 1874$). Using triple therapy alone, the eradication rate was 72.26% (1464/2026; 95% CI, 67.66%-74.13%), compared with a rate of 80.74% (1513/1874; 95% CI, 74.68%-82.76%) for combined triple-agent and probiotic therapy (Cochran's $\chi^2 = 20.61$; $P = 0.762$; $I^2 = 0.0\%$). A fixed-effects model was used, given no significant heterogeneity. The treatment groups without and with probiotics differed significantly (pooled OR = 0.58; 95% CI, 0.50-0.68; **Figure 2, Table 2**).

Side effects

Rates at which specific symptoms (i.e., nausea, diarrhea, epigastric pain, vomiting, taste distortion, and skin rash) occurred during eradication therapy were analyzed (**Table 3**), comparing incidences without and with added probiotics, respectively for nausea (11.86% vs. 7%; **Figure 3**), diarrhea (14.71% vs. 6.34%; **Figure 4**), epigastric pain (11.68% vs. 8.85%; **Figure 5**), vomiting (7.19% vs. 2.47%; **Figure 6**), taste distortion (18.50% vs. 12.26%; **Figure 7**), loss of appetite (15.08% vs. 15.94%; **Figure 8**), bloating (34.55% vs. 20.19%; **Figure 9**), constipation (7.14% vs. 4.23%; **Figure 10**), and skin rash (11.51% vs. 3.8%; **Figure 11**).

Subgroup analysis

Any failure to apply blinding was grounds for potential bias. In subgroup analysis, articles

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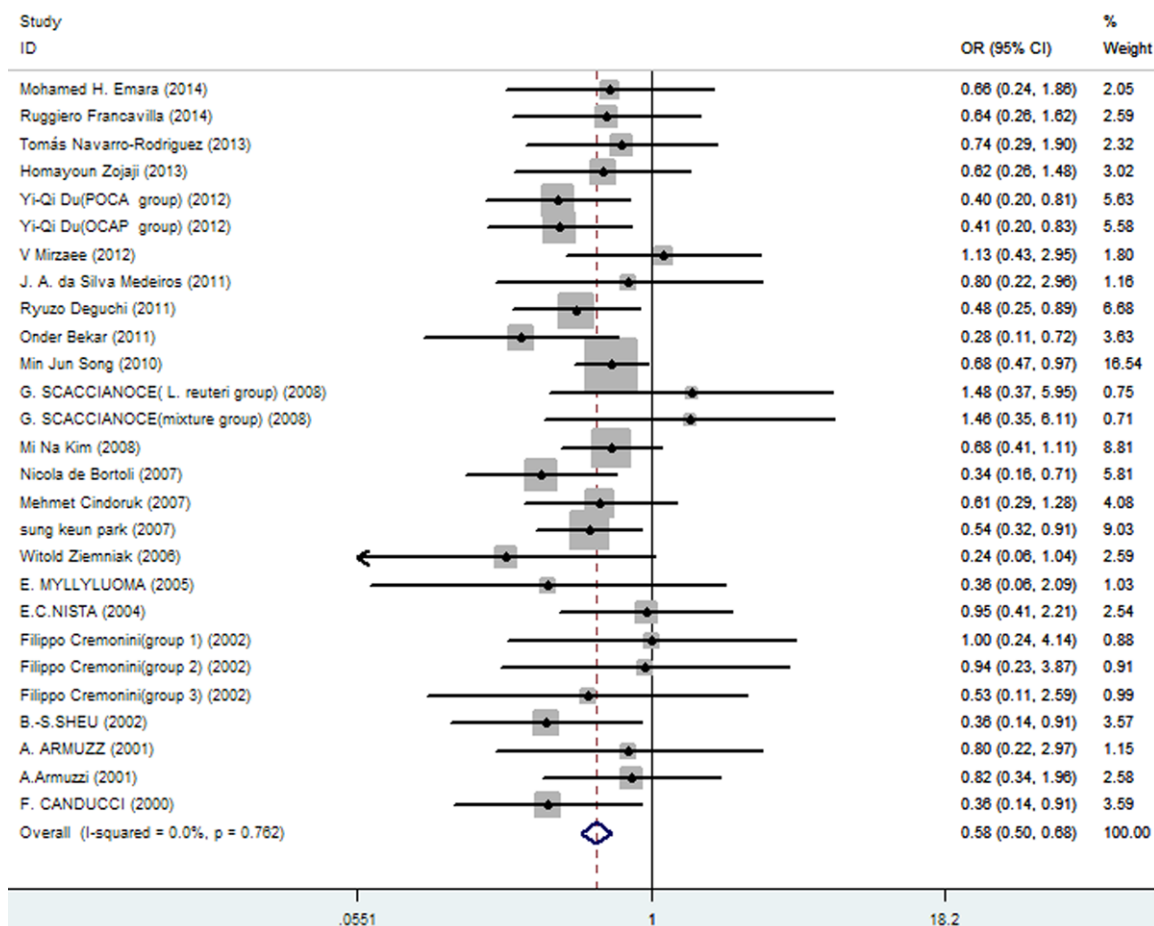


Figure 2. The effect of triple therapy group vs. triple therapy with probiotics group on eradication rates.

with JADAD scores of 5 (OR = 0.64; 95% CI, 0.47-0.88) and those with JADAD scores < 5 (OR = 0.57; 95% CI, 0.47-0.67) differed significantly (**Figure 12**). Furthermore, eradication rates differed significantly in subgroup analysis (**Figure 13**) of probiotics as follows: 1) lactobacillus: OR = 0.65 (95% CI, 0.44-0.95); 2) *S. boulardii*: OR = 0.67 (95% CI, 0.50-0.90); 3) mixed probiotics: OR = 0.53 (95% CI, 0.41-0.67); and 4) yogurt: OR = 0.48 (95% CI, 0.32-0.72).

Publication bias

No publication bias was evident on funnel plot (**Figure 13**), as confirmed by Begg's ($P = 0.532$) and Egger's ($P = 0.765$) tests (**Figure 14**).

Discussion

Marshall and Warren first discovered and successfully isolated *H. pylori* in 1982 [27], later confirming its link with gastritis, peptic ulcer,

gastric cancer and other digestive diseases [28]. This organism is also implicated in a host of non-digestive disorders (metabolic, autoimmune, infectious, and more) [29, 30]. As cited in the Maastricht 2-2000 Consensus Report, a 7-day course of triple therapy (clarithromycin, amoxicillin, and a PPI) is first-line choice to eradicate gastric colonization by *H. pylori*. However, eradication is often hampered by undesirable adverse effects and increasing antibiotic resistance, which likely account for a recently noted decline in the efficacy of this approach. On a global basis, eradication rates for first-line triple therapy and rescue regimens (for antibiotic resistance of varied patterns) a host of range from 55%-90% and 70%-90%, respectively [31-35].

In recent years, probiotics have proved beneficial in treating IBD [36], IBS [37], obesity [38], non-alcoholic fatty liver disease [39], colon

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Table 1. Characteristics of included studies

References	Year	Location	Total	triple therapy	Probiotic	Day	Blind	Placebo	Jaded scores
Mohamed H. Emara [4]	2014	Egypt	70	Omeprazole amoxicillin clarithromycin	Lactobacillus reuteri	14	double-blind	Y	5
Ruggiero Francavilla [5]	2014	Italy	100	PPI amoxicillin clarithromycin	Lactobacillus reuteri	7	double-blind	Y	5
Tomás Navarro-Rodríguez [6]	2013	Brazilian	107	Lansoprazole furazolidone, tetracycline	Lactobacillus acidophilus Lactobacillus rhamnosus ifidobacterium bifidum Streptococcus faecium	7	double-blind	Y	5
Homayoun Zojaji [7]	2013	Iran	160	omeprazole amoxicillin clarithromycin	saccaromyces boulardii	14	-	N	1
Yi-Qi Du [8]	2012	China	234	Omeprazole amoxicillin clarithromycin	Lactobacillus acidophilus Streptococcus faecalis Bacillus subtilis (B. subtilis)	7	open	N	3
V Mirzaee [9]	2012	Iran	102	Pantoprazole amoxicillin clarithromycin	probiotic yogur	7	-	Y	2
J. A. da Silva Medeiros [10]	2011	Portugal	62	Esomeprazole amoxicillin clarithromycin	L. acidophilus	8	double-blind	N	2
Onder Bekar [11]	2011	Turkey	82	Lansoprazole amoxicillin clarithromycin	kefir	14	double-blind	Y	5
Ryuzo Deguchi [12]	2011	Japan	229	Rabeprazole amoxicillin clarithromycin	yogurt (L. gasseri OLL2716)	7	-	N	2
Min Jun Song [13]	2010	Korea	661	Omeprazole amoxicillin clarithromycin	S. boulardii	7	-	N	3
Mi Na Kim [14]	2008	Korea	347	PPI amoxicillin clarithromycin	L. acidophilus HY 2177, L. casei HY 2743, B. longum HY 8001, S. thermophilus B-1	7	Open	N	3
G. SCACCIAOCE [15, 16]	2008	Italy	48	Lansoprazole amoxicillin clarithromycin	Lactobacillus plantarum L. reuteri Lactobacillus casei subsp. Rhamnosus Bifidobacterium infantis Bifidobacterium longum Lactobacillus salivarius Lactobacillus acidophilus Streptococcus termophilus Lactobacillus sporogenes (Lactobacillaceae)	7	open	N	3
sung keun park [16]	2007	Korea	352	Omeprazole amoxicillin clarithromycin	Bacillus subtilis, streptococcus faecium	7	-	N	3
Nicola de Bortoli [17]	2007	Italy	206	Esomeprazole amoxicillin clarithromycin	Lactobacillus plantarum, L. reuterii L. casei subsp. rhamnosus, Bifidobacterium infantis and B. longum, L. salivarius, L. acidophilus Streptococcus termophilus, L. sporogenes (Lactobacillaceae bif)	7	open	N	3
Mehmet Cindoruk [18]	2007	Turkey	124	Lansoprazole amoxicillin clarithromycin	S. boulardii	14	double-blind	Y	5
Witold Ziemniak [19]	2006	Poland	245	PPI amoxicillin clarithromycin	Lactobacillus acidophilus Lactobacillus rhamnosus	10	-	N	2
E. MYLLYLUOMA [20]	2005	Finland	47	Lansoprazole amoxicillin clarithromycin	LGG L. rhamnosus P. freudenreichii ssp. shermanii JS B. breve	7	double-blind	Y	5
E. C.NISTA [21]	2004	Italy	120	rabeprazole amoxicillin clarithromycin	B. clausii, Enterogermina	7	double-blind	Y	5
B. -S.SHEU [22]	2002	Taiwan	160	Lansoprazole amoxicillin clarithromycin	Lactobacillus-andBifidobacterium-containing yogurt	7	-	N	2
Filippo Cremonini [23]	2002	Italy	85	Rabeprazole clarithromycin tinidazole	Group 1 Lactobacillus casei subsp. rhamnosus (GG) Group 2 Saccharomyces boulardii Group 3 Lactobacillus acidophilus	7	Triple Blind	Y	5
A. ARMUZZ [24]	2001	Italy	60	Rabeprazole clarithromycin tinidazole	Lactobacillus GG	7	double-blind	Y	5
A. Armuzzi [26]	2001	Italy	120	Pantoprazole clarithromycin tinidazole	Lactobacillus GG	7	open	N	3
F. CANDUCCI [25]	2000	Italy	120	Rabeprazole amoxicillin clarithromycin	Lactobacillus acidophilus strain LB	7	open	N	3

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Table 2. Eradication rates of triple therapy group vs. triple therapy with probiotics group

Eradication rates of triple therapy group	Eradication rates of triple therapy with probiotics group	OR	95% CI	P value
1464/2026 (72.26%; 5% CI = 67.66%-74.13%)	1513/1874 (80.74%; 5% CI = 74.68%-82.76%)	0.58	0.50-0.68	0.000

Table 3. Side effects of triple therapy group vs. triple therapy with probiotics group

Side Effects	The incidence in the triple therapy group	The incidence in the triple therapy with probiotics group	OR	95% CI	P value
nausea	136/1374, (11.86%: 95% CI = 12.31%-25.39%)	97/1385 (7%: 95% CI = 6.53%-14.15%)	1.97	1.50-2.61	0.000
diarrhea	224/1523 (14.71%: 95% CI = 15.84%-26.80%)	97/1531 (6.34%: 95% CI = 5.07%-10.50%)	2.69	2.09-3.47	0.000
epigastric pain	84/719 (11.68%: 95% CI=9.48%-34.20%)	63/712 (8.85%: 95% CI = 6.22%-25.12%)	1.54	1.04-2.28	0.030
vomiting	46/640 (7.19%: 95% CI = 5.12%-17.36%)	16/648 (2.47%: 95% CI = 1.59%-3.87%)	2.84	1.66-4.86	0.000
taste distortion	183/989 (18.50%: 95% CI = 19.84%-46.43%)	123/1003 (12.26%: 95% CI = 6.18%-31.83%)	2.13	1.58-2.87	0.000
loss of appetit	46/305 (15.08%: 95% CI = 11.76%-17.68%)	51/320 (15.94%: 95% CI = 2.34%-28.73%)	0.94	0.61-1.45	0.786
bloating	142/411 (34.55%: 95% CI = 12.09%-51.53%)	84/416 (20.19%: 95% CI = 7.50%-31.96%)	2.17	1.57-3.01	0.000
constipation	46/644 (7.14%: 95% CI = 5.97%-17.08%)	27/638 (4.23%: 95% CI = 3.41%-12.96%)	1.84	1.12-3.04	0.016
skin rash	35/304 (11.51%: 5% CI = -4.30%-31.28%)	12/316 (3.8%: 95% CI = 1.84%-5.21%)	3.01	1.61-5.64	0.001

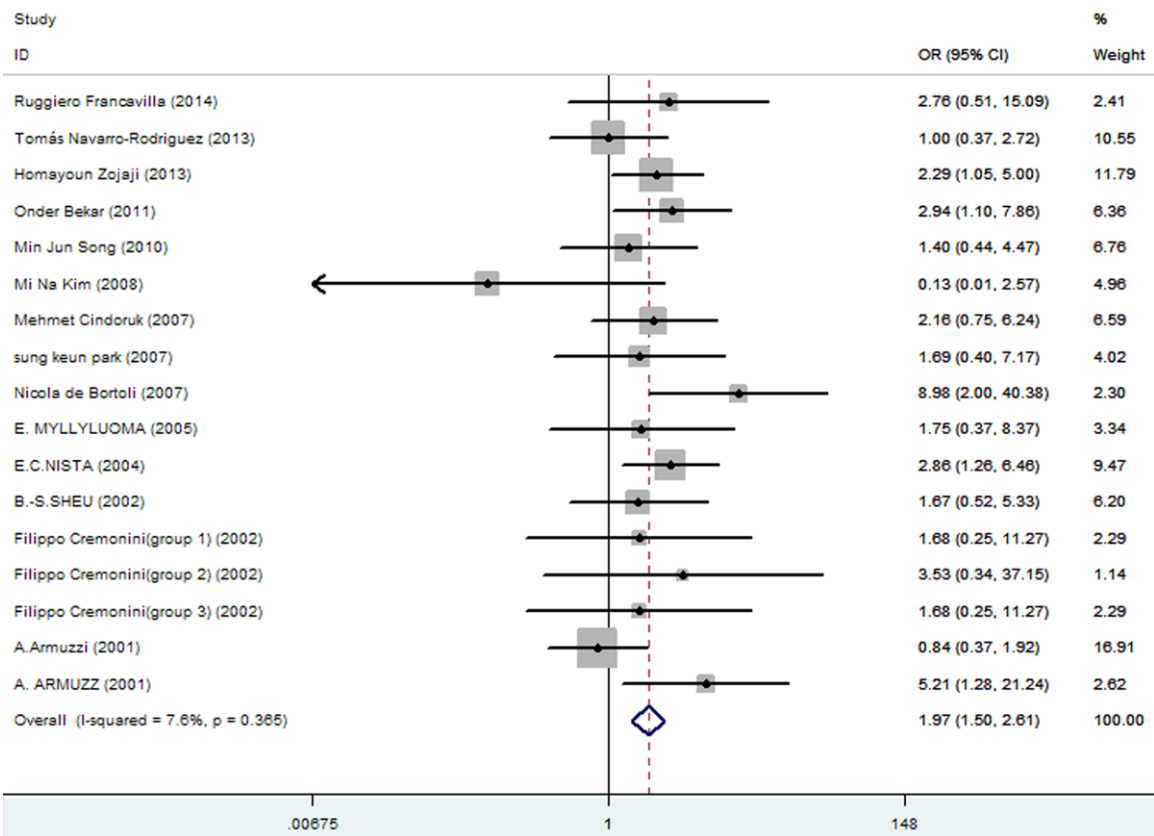


Figure 3. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of nausea.

cancer [40], and other diseases. Adjuvant use of probiotics in eradicating gastric *H. pylori* has thus become a topic of great interest. *In vitro* studies suggest that probiotics may inhibit acute membrane leakage induced by *H. pylori* [41]. Probiotics may also hinder adherence of

H. pylori to mammalian gastric mucosa, thus reducing or eliminating the organism [42], and various probiotics are known to inhibit *in vitro* growth of *H. pylori*. *Lactobacillus gasseri* OLL2716 (LG21) appears to suppress *H. pylori*-related IL-8 production in a gastric cell line and

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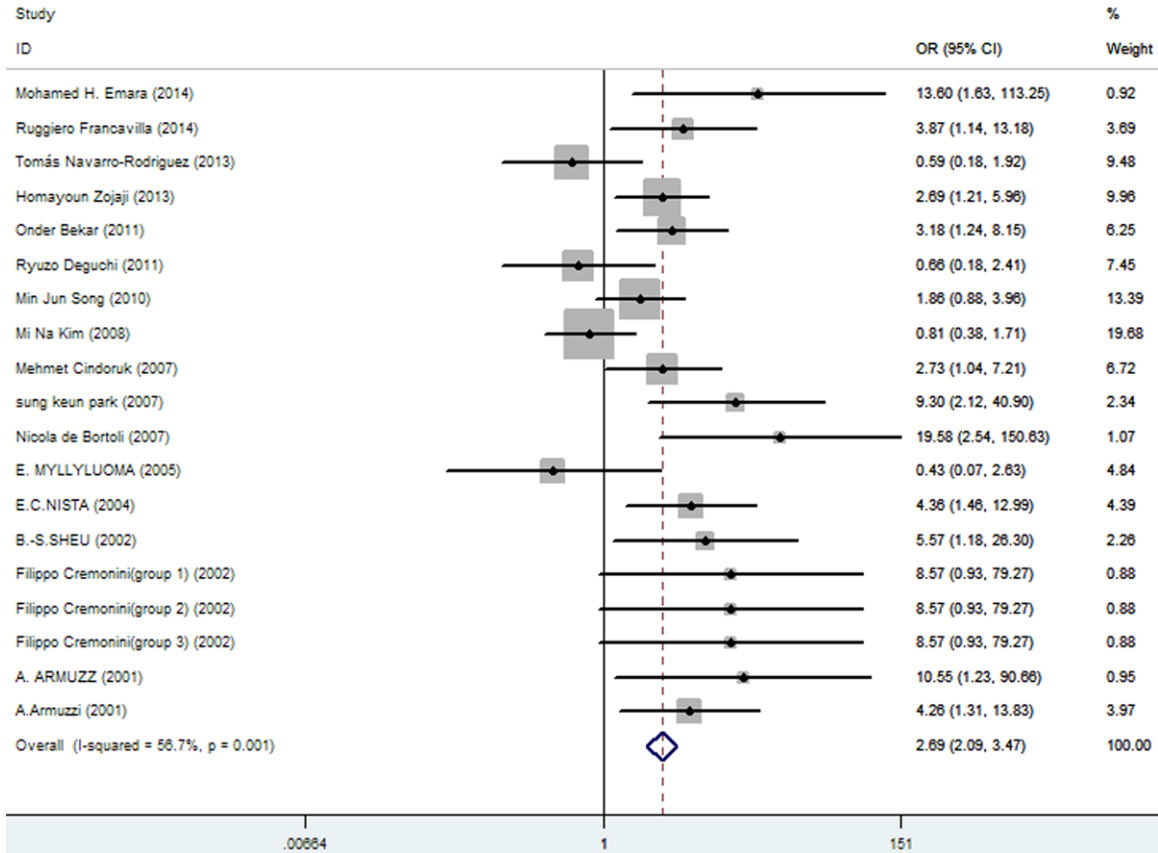


Figure 4. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of diarrhea.

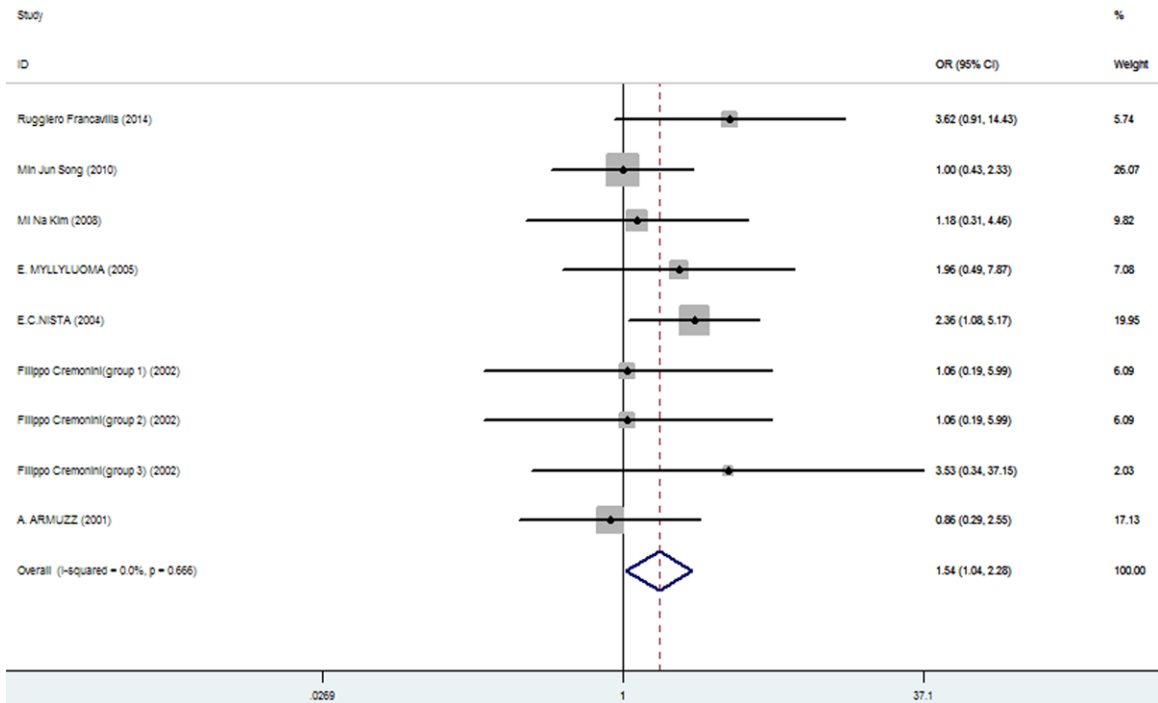


Figure 5. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of epigastric pain.

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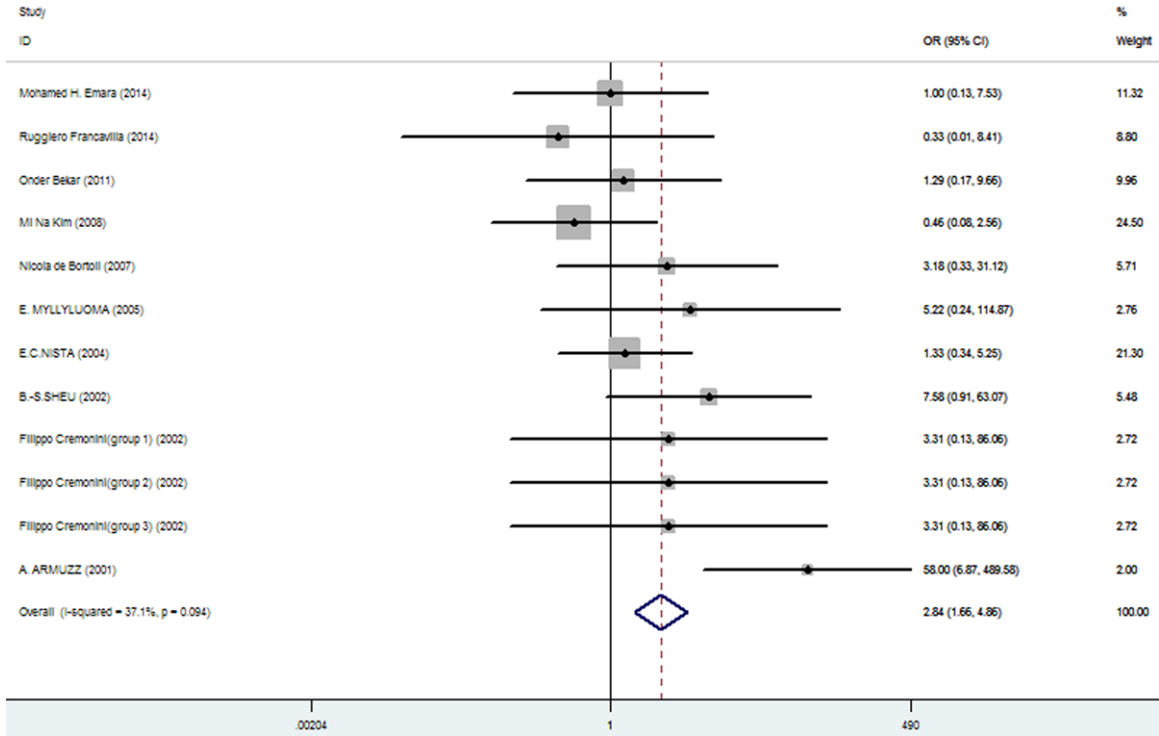


Figure 6. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of Vomiting.

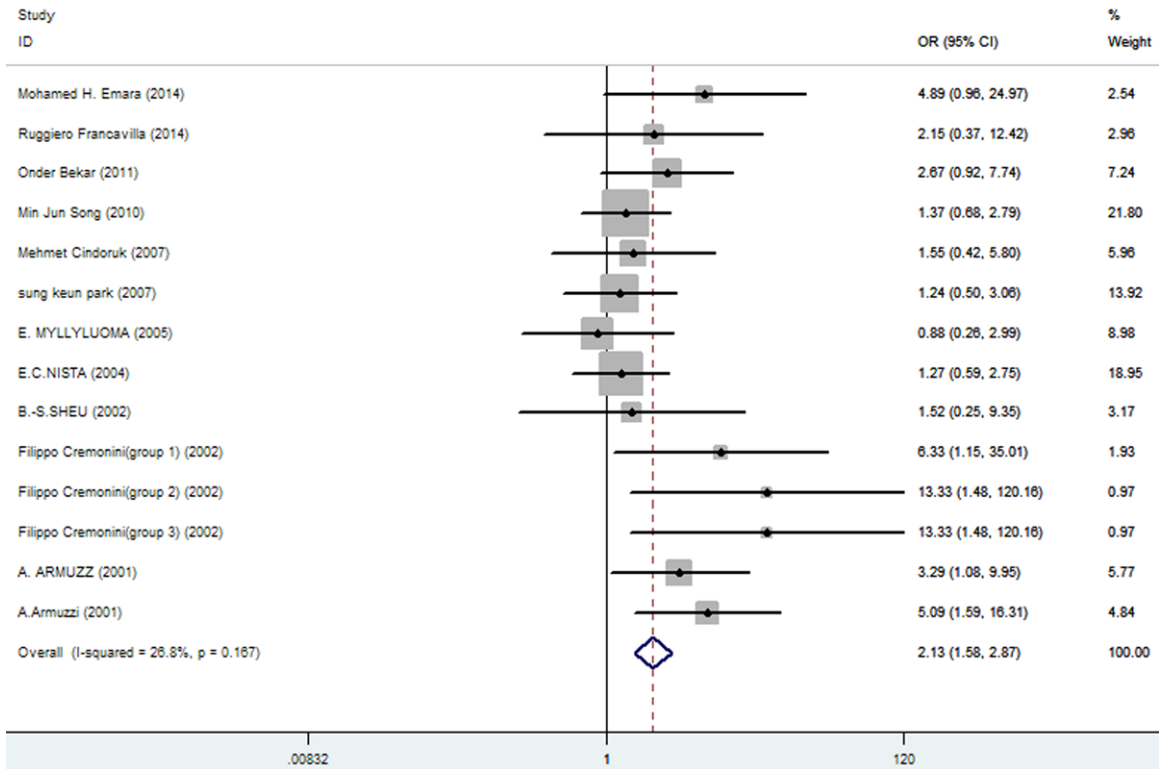


Figure 7. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of Taste distortion.

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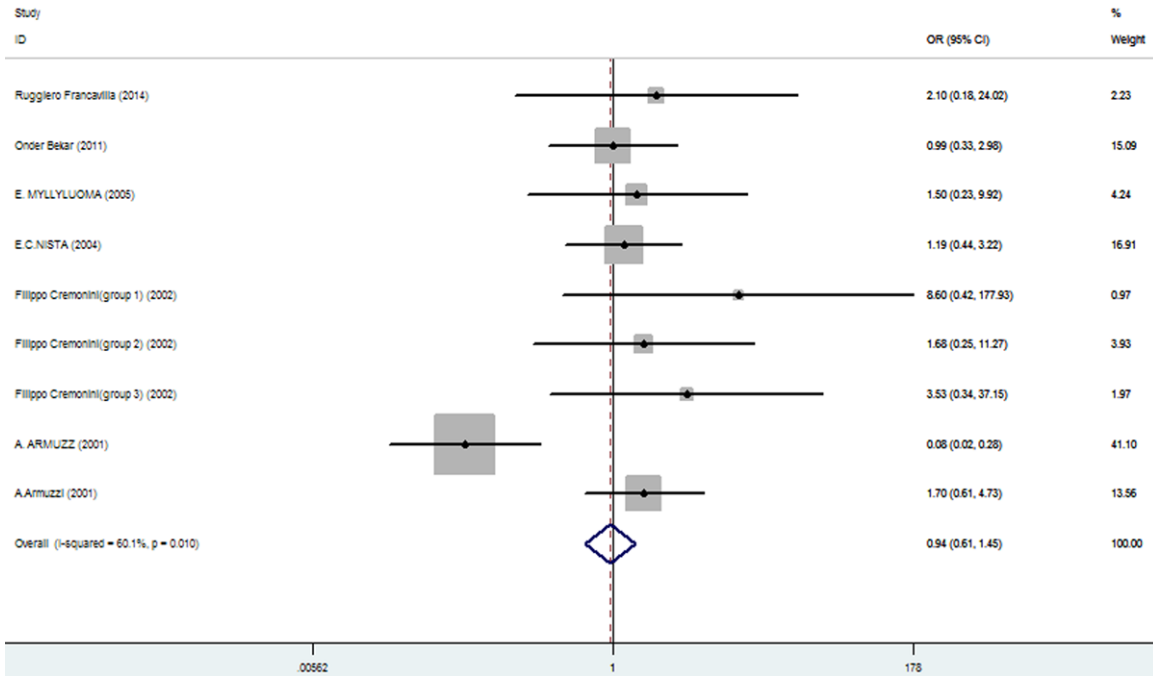


Figure 8. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of Loss of appetite.

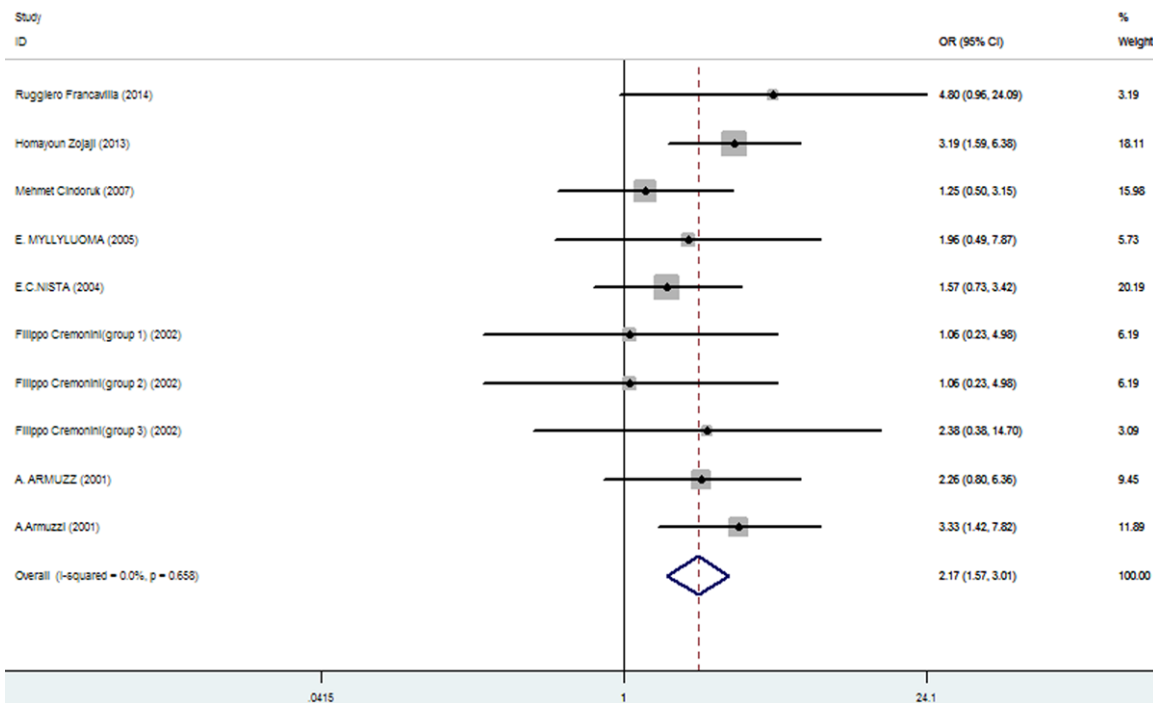


Figure 9. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of Bloating.

within gastric mucosa [43], whereas *in vitro* antagonism of strain *B. subtilis* 3 to *H. pylori* is due to secretion of antibiotic-like substances [44]. The neuraminidase activity of *S. boulardii*

selectively removes α (2-3)-linked sialic acid from surfaces of duodenal epithelial cells to prevent binding with *H. pylori* adhesin and thereby impede bacterial adherence [45]. *In*

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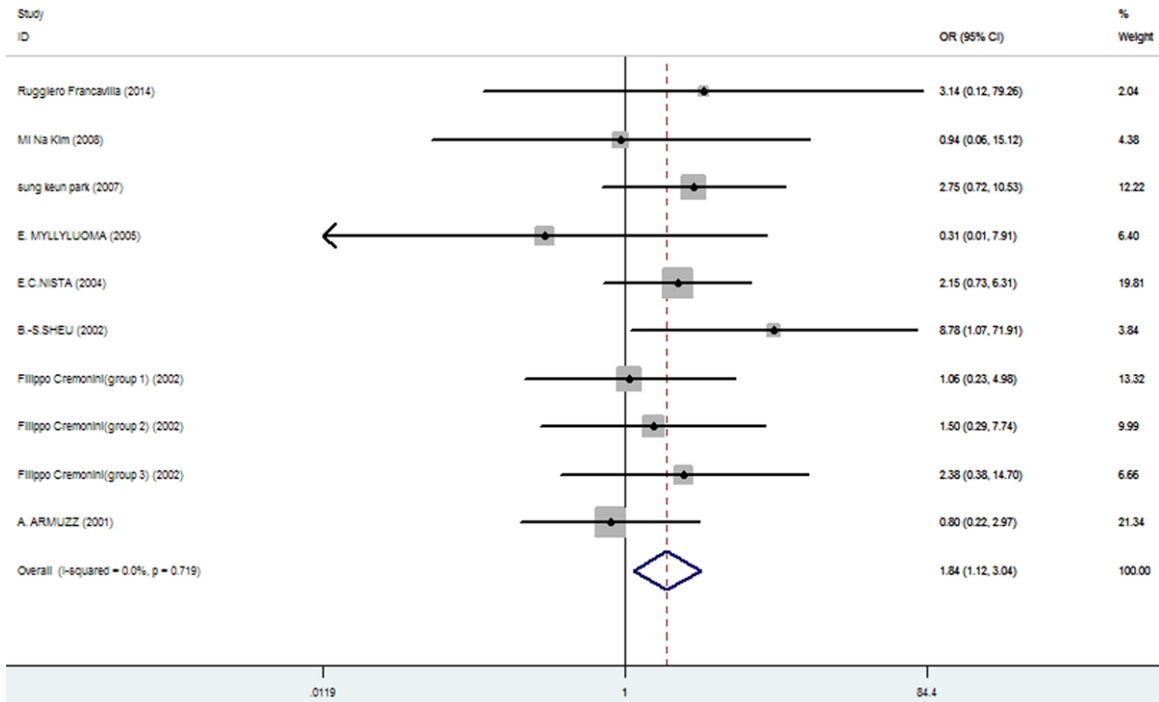


Figure 10. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of Constipation.

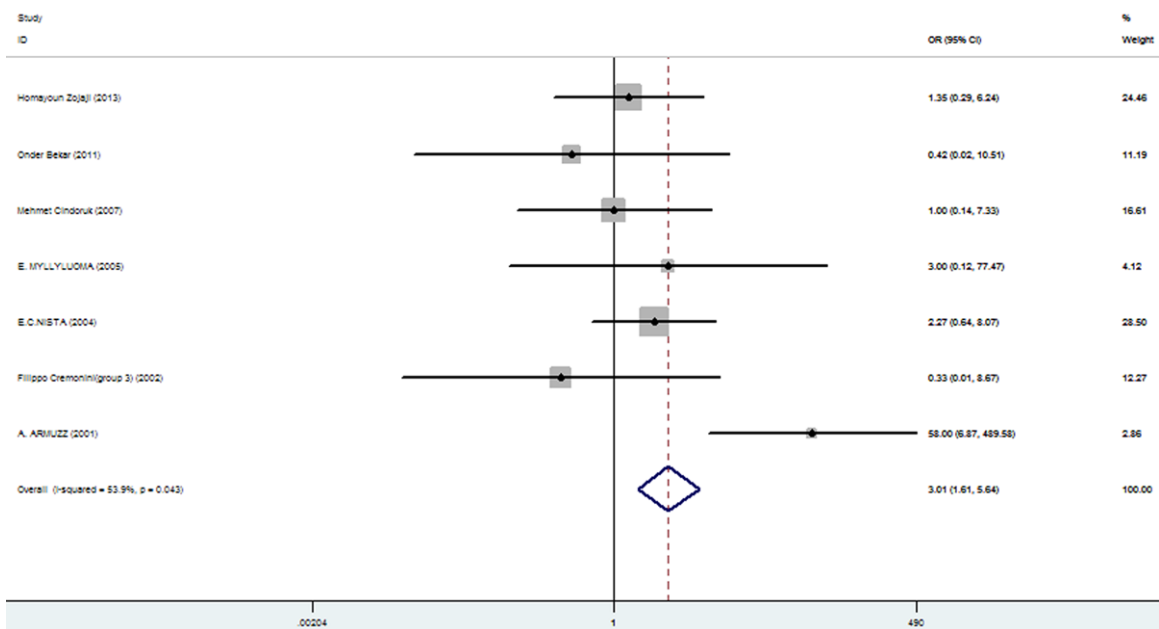


Figure 11. The effect of triple therapy group vs. triple therapy with probiotics group on the incidence of Skin rash.

vitro and *in vivo* experiments have shown that butyric acid-forming bacteria may inhibit *H. pylori* colonization as well, contributing to eradication [46]. Many clinical trials have concluded that probiotic supplementation may be a wise

strategy, enhancing the efficacy of anti-*H. pylori* therapy and reducing related adverse effects.

On the other hand, some researchers either hold opposing views [5-7, 9] or have expended

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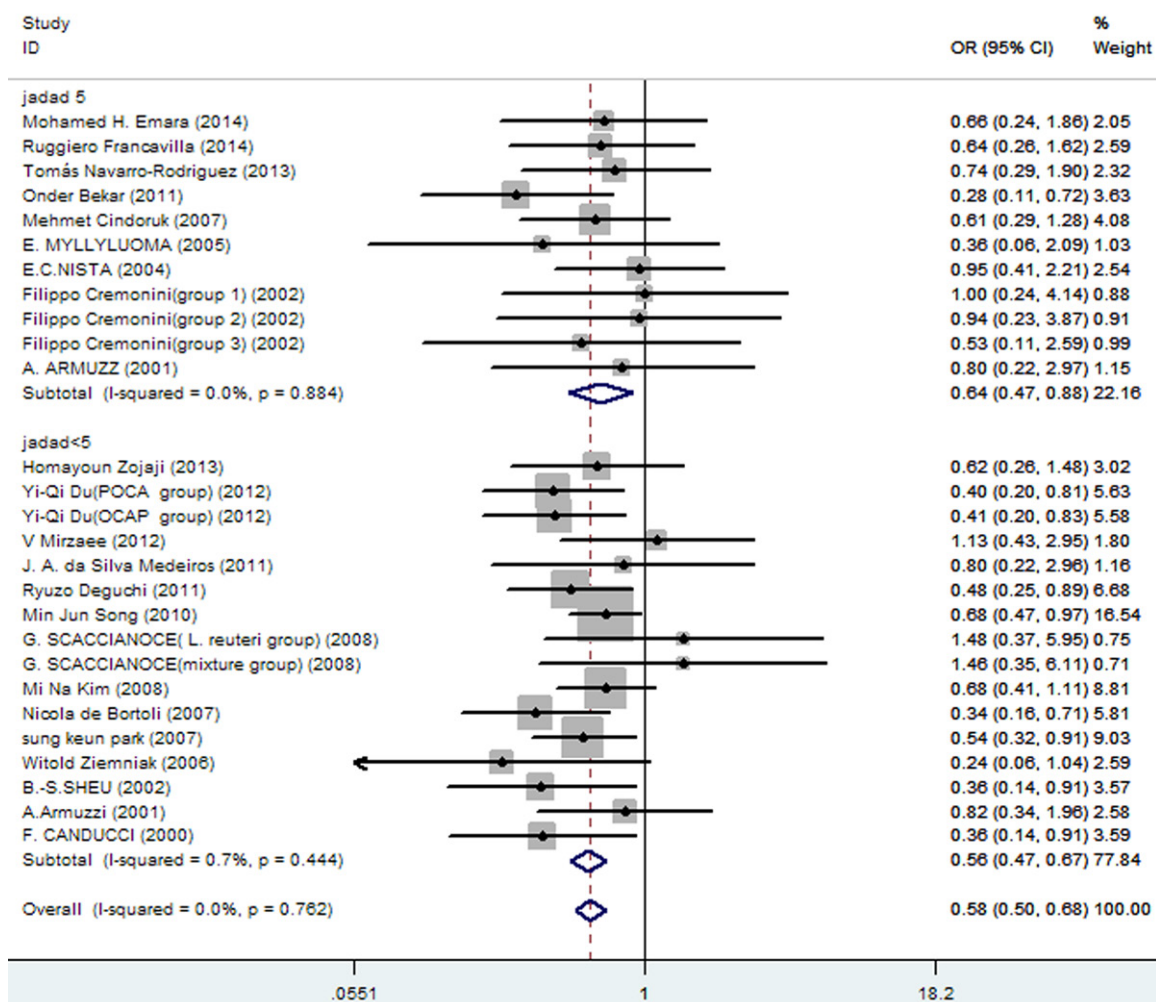


Figure 12. Meta-analysis of eradication rates by different score of JADAD.

less effort. An earlier meta-analysis by Tong et al [47] included both triple- and quadruple-agent regimens, albeit fewer adverse effects and probiotic subgroups were assessed. Another meta-analysis by Aarti Sachdeva et al [48] entailed some of summaries of articles, some with no full text. Still another conducted by Zhen-Hua Wang et al [49] had no data from Africa and South America.

This meta-analysis, drawn from 23 full-text reports of related global RCTs (to include South America [6] and Africa [4]) and involving a diversity of data on adverse effects, probiotic subgroups, and JADAD scores, is comparatively more robust. Our fixed-effects analytic model showed that probiotic supplementation of triple-agent therapy improved *H. pylori* eradica-

tion rates (OR = 0.58; 95% CI, 0.50-0.68), thus corroborating findings elsewhere [47, 50, 51]. Subgroup analysis further suggested that choice of probiotic is a factor in bettering *H. pylori* eradication rates. We also confirmed that addition of probiotics to triple-agent *H. pylori* eradication therapy alleviated most adverse effects, with loss of appetite as the exception. These results have important clinical implications and provide impetus for future research, although black and Australian populations have yet to be represented. Given the mounting evidence that probiotics are beneficial in this context, large-scale clinical studies are anticipated.

Disclosure of conflict of interest

None.

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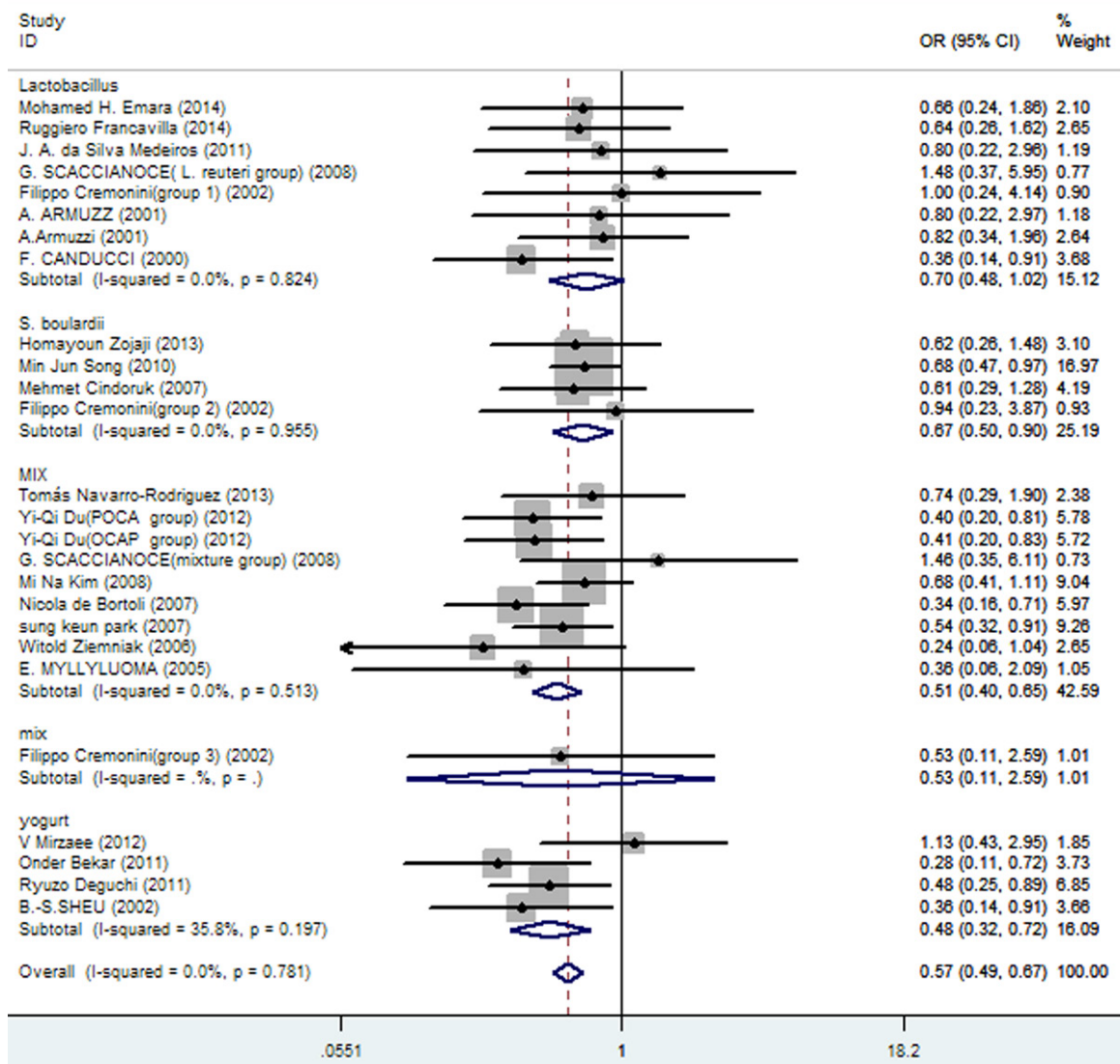


Figure 13. Meta-analysis of eradication rates by different probiotic preparations

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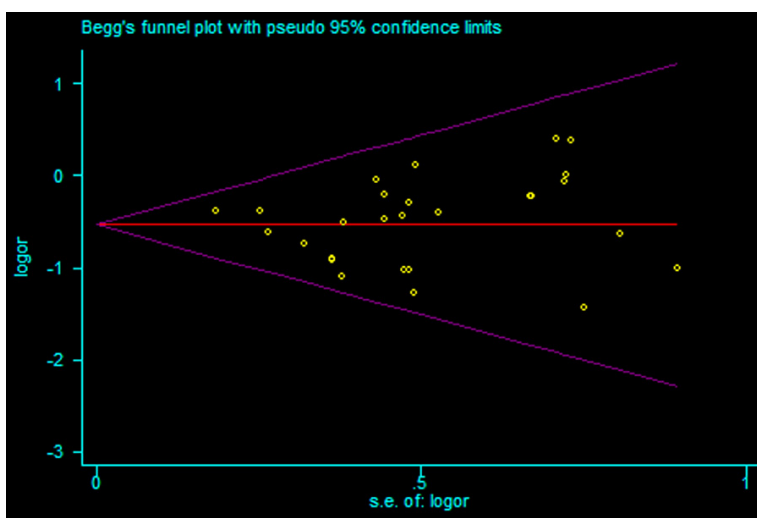


Figure 14. Funnel plot of included studies for eradication rates.

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