Helicobacter

Helicobacter ISSN 1523-5378

Effects of *Helicobacter pylori* Eradication on Gastroesophageal Reflux Disease

Bingbing Qian[1], Shijie Ma[1], Li Shang, Juan Qian and Guoxin Zhang

Department of Gastroenterology, First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Keywords
Eradication, gastroesophageal reflux disease, *H. pylori*, meta-analysis.

Reprint requests to: Prof. Guoxin Zhang, 300 Guangzhou Road, Department of Gastroenterology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China. E-mail: guoxinz@njmu.edu.cn.

[1]These authors contributed to this paper equally.

Abstract

Background and Aims: *Helicobacter pylori* infection appears to be a protective factor for gastroesophageal reflux disease (GERD). However, *H. pylori* is associated with the subtype of esophageal carcinoma, and long-term proton-pump inhibition usage would cause gastric atrophy in patients with persistent *H. pylori* infection, which is a precancerous lesion. The relationship between *H. pylori* infection and GERD is still unclear. We aimed to confirm whether the eradication of *H. pylori* would worsen or improve symptomatic or endoscopic GERD.

Methods: A systematic review of the published data was undertaken, and a meta-analysis was performed to determine the effect of *H. pylori* eradication on the occurrence of symptomatic (heartburn, acid regurgitation) and endoscopically proven erosive (esophagitis) GERD in patients with or without pre-existing GERD.

Results: A total of 11 articles met the inclusion criteria and thus were included in the meta-analysis. There was no significant difference in the frequency of symptomatic or endoscopically proven erosive GERD after the eradication between patients with *H. pylori* eradicated and those with persistent infection, regardless of follow-up period, location, or the baseline disease.

Conclusion: *H. pylori* eradication does not aggravate the clinical outcomes in terms of short-term and long-term posteradication occurrence of GERD. There is no association between *H. pylori* eradication and the development of GERD in the patients with different diseases, even those with GERD.

Gastroesophageal reflux disease (GERD) is a complex disorder defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [1]. The etiology of GERD is multifactorial, and both increased gastric acid secretion and decreased lower esophageal sphincter pressure play important roles. As *Helicobacter pylori* infection may reduce gastric acid secretion in a substantial proportion of individuals [2], *H. pylori* infection is reported to be inversely associated with the development of GERD. A large community-based study of *H. pylori* and GERD showed that both self-described symptomatic GERD and endoscopically proven erosive GERD were inversely associated with *H. pylori* infection [3], in agreement with previous studies [4]. It has been also reported that with the widespread utilization of eradication therapy, the falling prevalence of *H. pylori* infection has been paralleled with an increase in the occurrence of GERD and its complications [5]. Therefore, *H. pylori* infection appears to be a ''protective'' factor for GERD, although this notion has never been confirmed by well-designed, population-based data.

Current guidelines, including the Asia-Pacific Consensus on the Management of GERD [6] and Maastricht III Consensus Report [7], recommend maintenance therapy with antisecretory medications such as proton-pump inhibitors (PPI) to be used for resolving the symptoms and healing erosive esophagitis patients with GERD. However, it has been indicated that long-term PPI therapy for GERD affects the pattern of gastritis within the stomach and increases the risk of progression of gastric atrophy and intestinal metaplasia to gastric cancer in the presence of *H. pylori* infection [7]. Moreover, persistent *H. pylori* infection has been

reported to be associated with the development of a subtype of esophageal squamous cell carcinoma [8]. Thus, eradication of *H. pylori* infection in patients with GERD may produce an overall benefit despite the putative ''protective effect'' for GERD.

A number of studies have evaluated the effects of *H. pylori* eradication in patients with or without GERD on the symptomatic or endoscopic reflux disease but produced inconsistent and inconclusive results [9–20]. Previously, a few meta-analyses of the associations between *H. pylori* and GERD have demonstrated marked heterogeneity, and thus, the nature of this relation is uncertain [21,22]. Therefore, there is insufficient evidence to support eradication therapy as an optimum management strategy for patients with GERD. Consequently, whether patients with GERD should be tested and treated for *H. pylori* infection and the consequences of *H. pylori* eradication (i.e., the effect of *H. pylori* eradication on the progression of GERD) remain undefined.

To further elucidate whether the eradication of *H. pylori* infection worsens or improves GERD, symptomatically or endoscopically, we performed a meta-analysis that included more recently published randomized controlled trials (RCTs) with a higher quality in study design and more sample sizes than those that were included in previous meta-analyses. In addition, this meta-analysis also determined whether the eradication of *H. pylori* infection provokes the development of GERD.

Methods

Literature Search

A computer-assisted search of the literature was performed. This search included the Medline and Embase databases and also the bibliographies of all relevant citations published in English up to January 2010. Cochrane review articles were also reviewed.

The initial search was performed by combining the keywords ''GERD/gastro-esophageal reflux, disease/gastro-oesophageal reflux disease/GORD/GERD,'' with ''*Helicobacter pylori*/Hp/*H. pylori*'', and ''eradication/cure/therapy/treatment''.

Inclusion Criteria

Studies included in this meta-analysis must be classified as RCTs with a follow-up period of at least 6 months. The quality of the RCTs must be scored as ≥3, as assessed by a scaling system developed by Jadad et al. [23], which classifies the RCTs with scores ranging between 0 and 5. The eradication treatment must have been clearly described. All enrolled participants must have had the same disease or the same symptom, i.e., peptic ulcer disease (PUD), GERD, or dyspepsia, in the study. All groups must have been similar in all important characteristics except the treatment regimens. The occurrence of GERD after treatment must have been available in patients with *H. pylori* infection eradicated and those with persistent *H. pylori* infection. The articles must have been published in full in peer-reviewed medical journals; all abstracts, review articles, commentaries, and book chapters were excluded. If more than one article was published by the same authors using the same case series, we only included the article that reported the data with the largest number of cases.

Data Extraction

A standard data collection and report form was created and used to extract the data from each publication, including first author's name, year of publication, country in which the study was carried out, sample sizes, Jadad scores, baseline diseases, follow-up time, heartburn, reflux symptom, and/or reflux esophagitis present at the end of trials, relapse time of GERD symptoms (i.e., GERD symptoms returned to the baseline score) and/or reflux esophagitis, and 24-hour esophageal pH before and after treatment.

Final article selection and data entry were carried out independently by both the authors, and disagreements

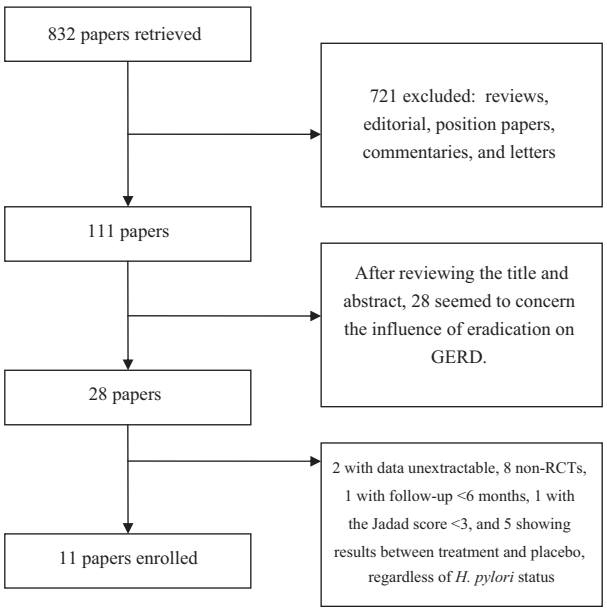

Figure 1 Flow chart of the study selection process for the systematic review.

were resolved by a third investigator. The selection process is shown in Fig. 1.

Statistical Methods

The meta-analysis was conducted by using the Review Manager 4.2.8. Analysis was performed between patients with *H. pylori* eradicated and those with persistent *H. pylori* infection. Odds ratio (OR) and 95% confidence interval (CI) for each of the parameters (i.e., heartburn, regurgitation, symptomatic GERD, and erosive GERD) were estimated for each study. We examined heterogeneity using χ^2 tests ($p < .1$ was considered significant). We used a random effects model if the χ^2 tests were significant; otherwise, we used a fixed effects model. To enhance the confidence of the results of the statistics when the number of combined studies was lacking, we used the I^2 metric, which describes the proportion of variability across studies that is because of score heterogeneity. If $I^2 = 0$, there is no heterogeneity. $I^2 > 50\%$ is considered to be indicative of heterogeneity. Larger values indicate greater heterogeneity.

Results

Description of Studies

As shown in Fig. 1, our initial search identified 832 papers that were published by January 2010. Of these papers, 721 publications were excluded which were reviews, editorials, position papers, comments, and

Table 1 Detailed characteristics of the 16 studies included in the meta-analysis

Study	Publication date	Baseline disease	No. of cases	Follow-up (months)	Jadad score	Region
Befrits et al. [9]	2000	DU	165	24	5	Europe
Bytzer et al. [10]	2000	DU	276	24	6	Europe
Fallone et al. [11]	2000	DU	98	12	6	North America
Vakil et al. [12]	2000	DU	242	6	5	North America
Schwizer et al. [13]	2001	GERD	70	6	4	Europe
Laine and Sugg [14]	2002	DU	1165	8	4	North America
Malfertheiner et al. [15]	2002	PU	1497	6	5	Multinational
Wu et al. [16]	2002	RE	25	6	5	Asia
Kupcinskas et al. [17]	2004	DU	255	12	6	Europe
Ott et al. [18]	2005	Dyspepsia	157	12	5	South America
Jonaitis et al. [19]	2008	GU	88	12	3	Europe

DU, duodenal ulcer; PU, peptic ulcer; RE, reflux esophagitis; GERD, gastroesophageal reflux disease.

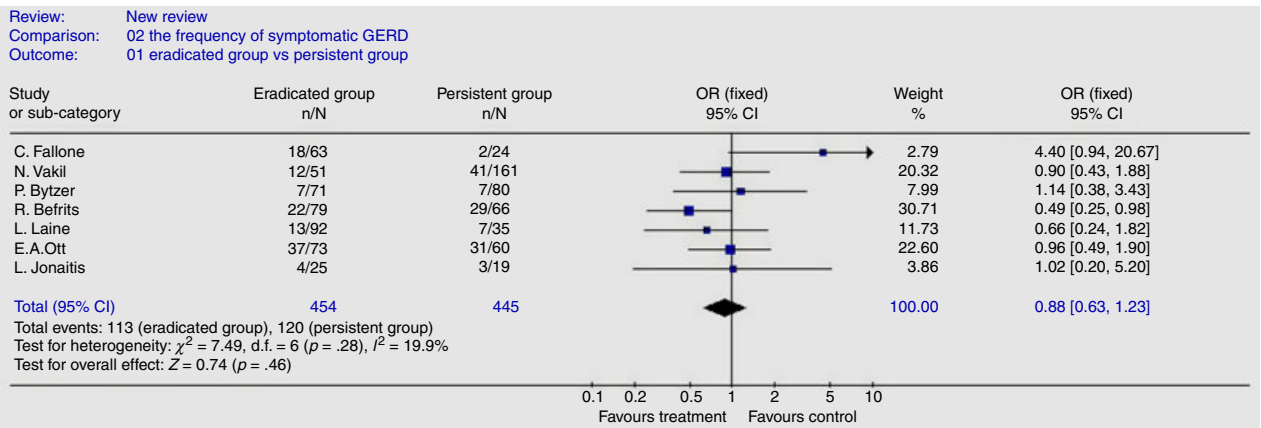

Figure 2 The frequency of symptomatic gastroesophageal reflux disease after treatment between patients with *Helicobacter pylori* infection eradicated and those with persistent *H. pylori* infection reported in seven randomized controlled trials.

letters. After the titles and the abstracts were reviewed, 28 articles were considered to concern the influence of eradication on GERD. With further careful screening, 17 articles were eventually excluded: eight were not RCTs, five did not report the results between patients with *H. pylori* infection eradicated and those with persistent *H. pylori* infection, one followed patients for fewer than 6 months, one had a Jadad score of <3, and two had data unextractable because of the rank sum test used as the statistical method. Therefore, 11 RCTs fulfilled the inclusion criteria and were included for the planned meta-analysis [9–19].

The 11 RCTs recruited 4038 patients (intention-to-treat), most involved patients in Europe (Table 1). Patients were treated for PUD, GERD, and dyspepsia at baseline in eight, two, and one RCTs, respectively.

Effect of *H. pylori* Eradication on GERD Symptoms, Reflux Symptom, and Erosive Esophagitis

Seven RCTs reported the frequency of symptomatic GERD at the end of trials [9–12,14,18,19] and showed no significant difference in the occurrence of symptomatic GERD between patients with *H. pylori* eradicated and those with persistent infection (OR = 0.88, 95%CI: 0.63–1.23, p = .46) (Fig. 2).

Four RCTs reported heartburn symptom as the most prominent symptom, after no fewer than a 6-month

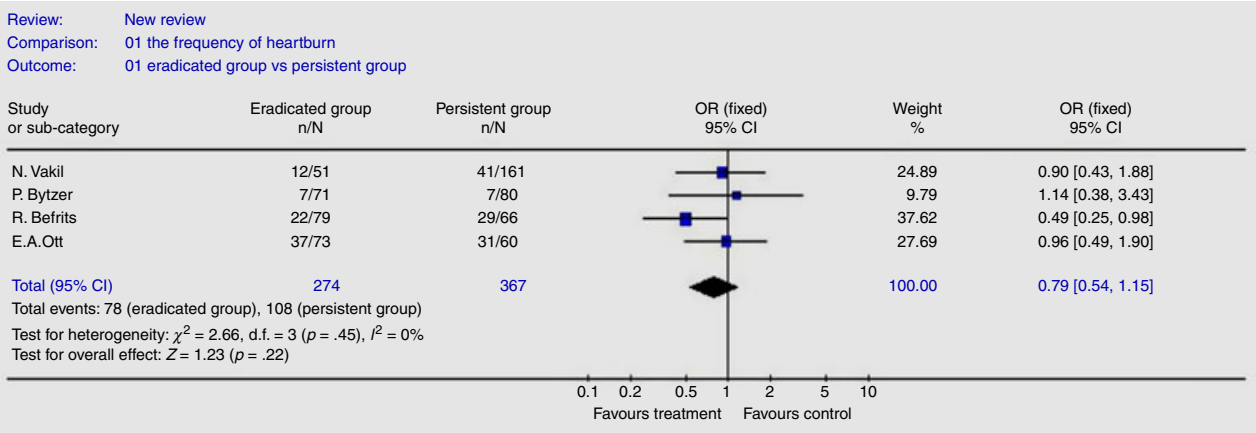

Figure 3 The frequency of heartburn symptom after treatment between patients with *Helicobacter pylori* infection eradicated and those with persistent *H. pylori* infection reported in four randomized controlled trials.

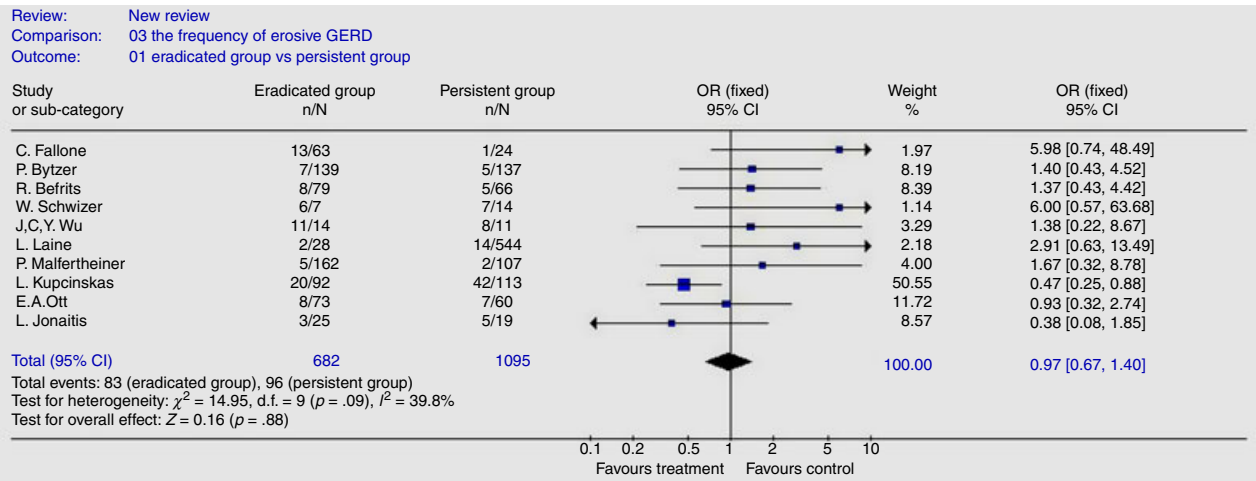

Figure 4 The frequency of erosive esophagitis after treatment between patients with *Helicobacter pylori* infection eradicated and those with persistent *H. pylori* infection reported in 10 randomized clinical trials.

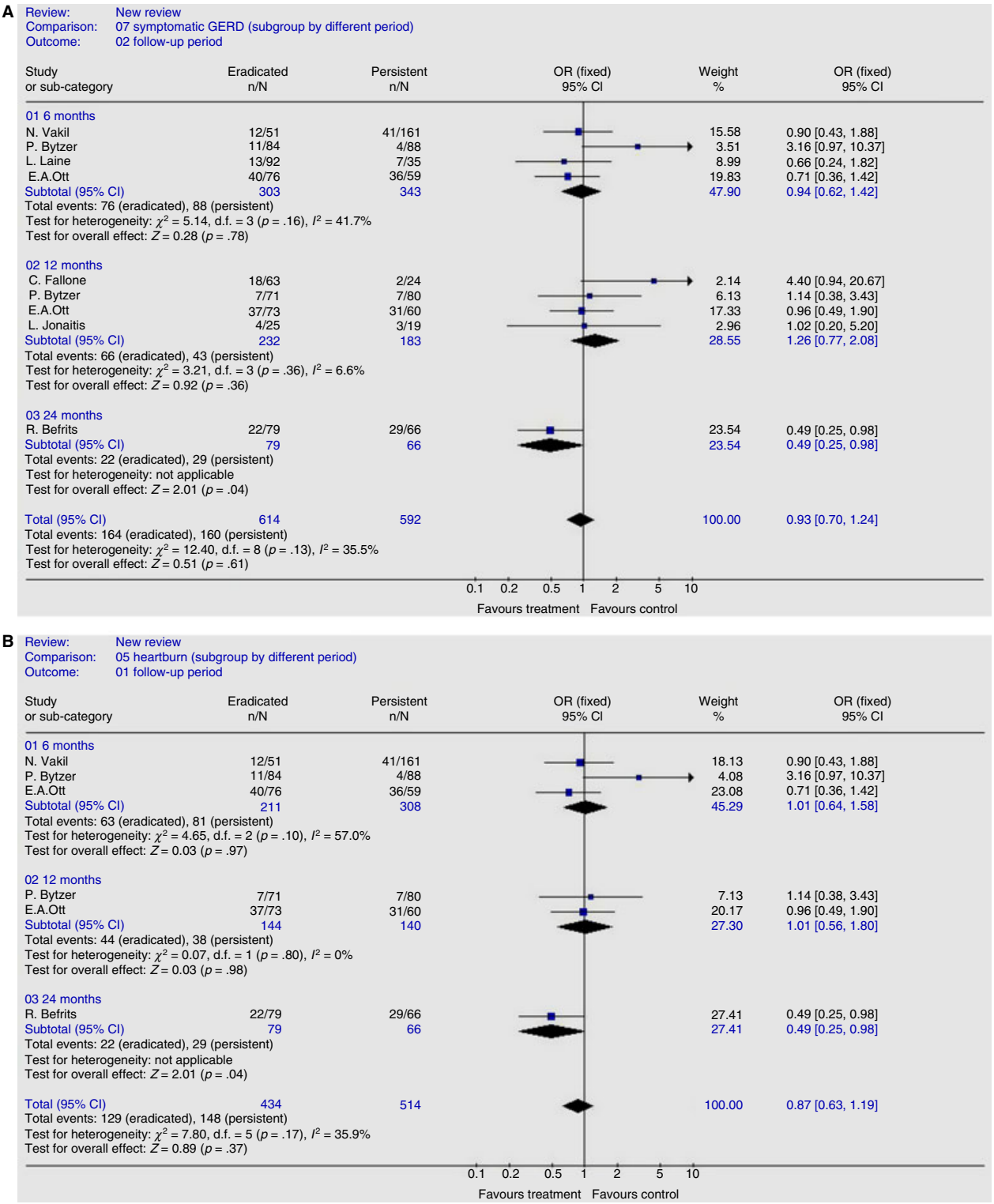

Figure 5 The frequency of gastroesophageal reflux disease symptoms (*A*), heartburn symptom (*B*), and erosive esophagitis (*C*) between patients with *Helicobacter pylori* infection eradicated and those with persistent *H. pylori* infection at follow-up of 6, 12, and 24 months.

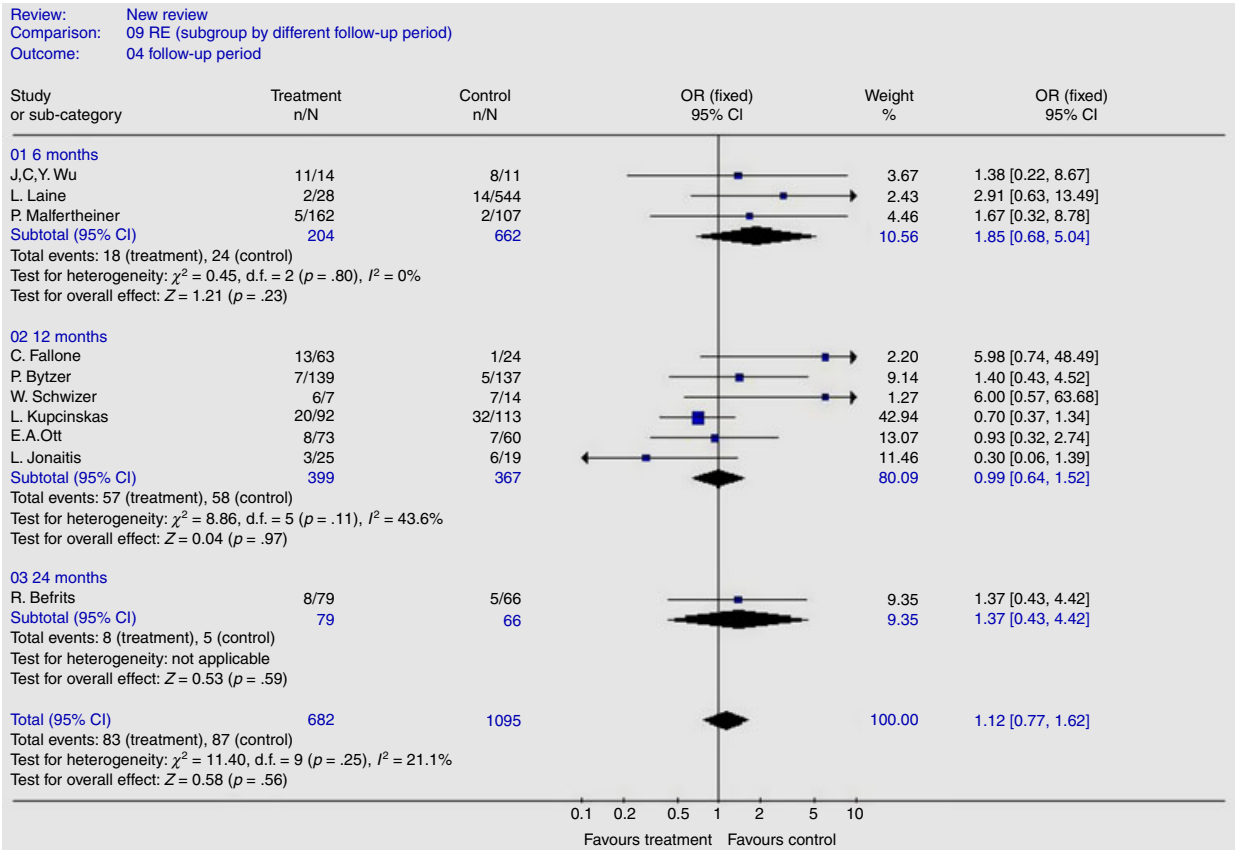

Figure 5 (*Continued*).

follow-up [9,10,12], and pooled data showed no significant difference in the frequency between the two groups (OR = 0.79, 95%CI: 0.54–1.15, $p = .22$) (Fig. 3). Because not all the included trials used a 4-point ordinal scoring system to record the symptoms, it was impossible for us to perform further subgroup analysis focusing on the severity of the symptoms. The frequency of erosive esophagitis was similar between the two groups after treatment (OR = 0.97, 95%CI: 0.67–1.40; $p = .88$) (Fig. 4).

There was no significant difference between the two groups in the frequency of GERD symptoms present at 6 months (OR = 0.94, 95%CI: 0.62–1.42, $p = .78$) or at 12 months (OR = 1.26, 95%CI: 0.77–2.08, $p = .36$) of the follow-up. Only one study followed up the patients for 24 months, with an OR (95%CI) of 0.49 (95%CI: 0.25–0.98) (Fig. 5A). Test of heterogeneity was not significant for the meta-analysis ($p = .13$, $\lambda^2 = 12.4$, d.f.: 8, $I^2 = 35.5\%$) (Fig. 5A). Similarly, there was no significant difference between the two groups in the frequency of heartburn symptom presented at 6 months (OR 1.01, 95%CI: 0.64–1.58, $p = .97$) or at 12 months (OR 1.01, 95%CI: 0.56–1.80, $p = .98$) (Fig. 5B).

The frequency of erosive esophagitis was similar between the two groups at the 6-month (OR = 1.85, 95%CI: 0.68–5.04; $p = .23$) and 12-month follow-up (OR = 0.99, 95%CI: 0.64–1.52; $p = .97$) (Fig. 5C). As the presence or absence, not the severity, of erosive esophagitis was recorded, according to the Savary–Miller (SM) system or LA classification, there were insufficient data available for further subgroup analysis.

Subgroup Analyses on the Effect of *H. pylori* Eradication on GERD Symptoms and Erosive Esophagitis, in Relation to the Baseline Disease and Country of Patient Residency

Based on subgroup analysis by the baseline disease, there was no significant difference in the frequency of GERD symptoms at the end of the treatment between the two groups for patients with PUD (OR = 0.86, 95%CI: 0.59–1.25, $p = .43$) and dyspepsia (OR = 0.96, 95%CI: 0.49–1.90) (Fig. 6A). The test of heterogeneity was not significant for the meta-analysis ($p = .28$, $\lambda^2 = 7.49$, d.f.: 6, $I^2 = 19.9\%$). Similar results were in heartburn symptom and erosive esophagitis (Fig. 6B,C).

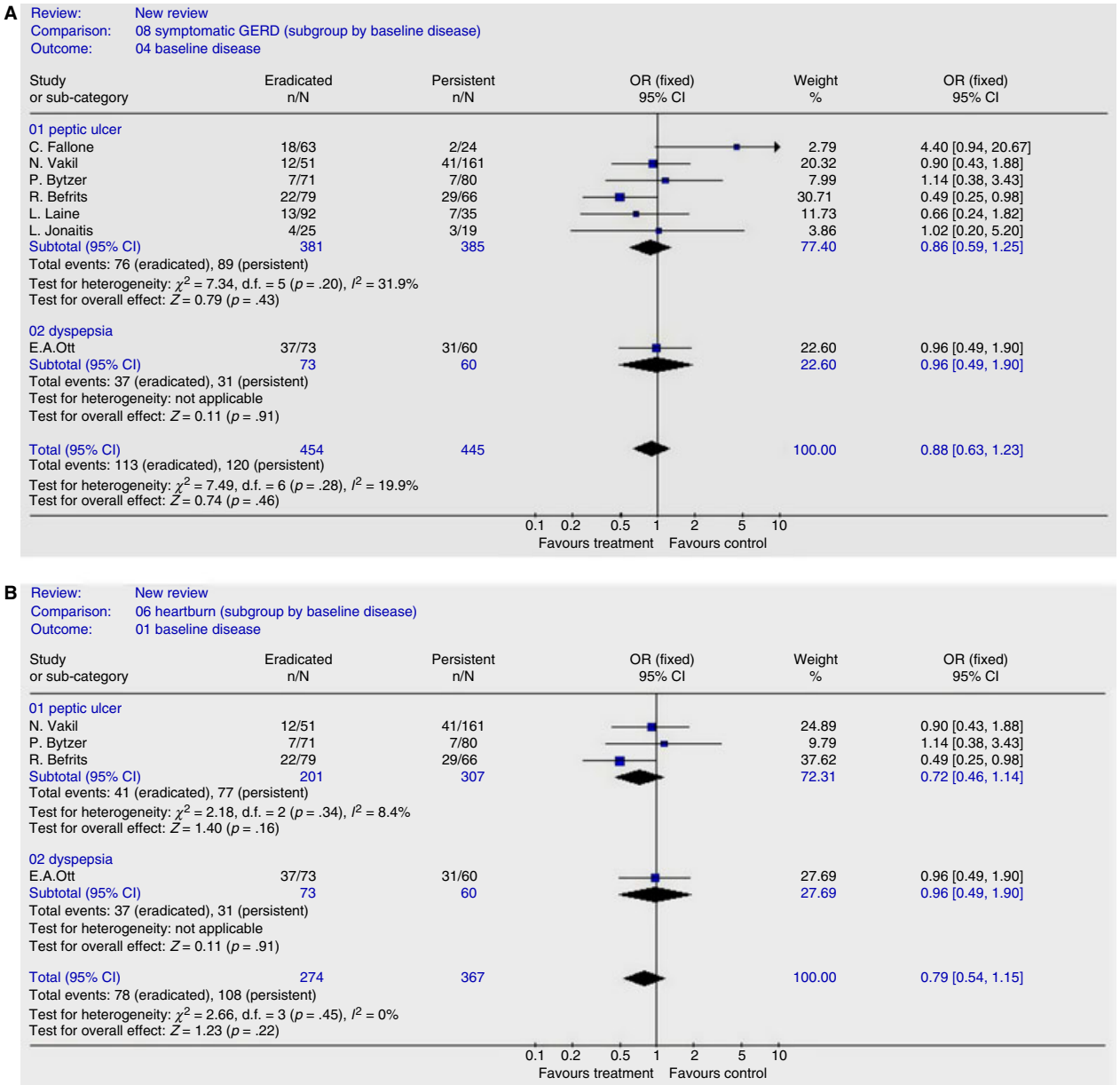

Figure 6 The frequency of symptomatic gastroesophageal reflux disease (GERD) (*A*), heartburn symptom (*B*), and erosive esophagitis (*C*) after treatment between patients with *Helicobacter pylori* infection eradicated and those with persistent *H. pylori* infection, in relation to the baseline diseases such as peptic ulcer disease, dyspepsia, and GERD.

When studies including patients in Europe and the United States were analyzed, there was no significant difference in the frequency of GERD symptoms between the two groups at the end of treatment (OR = 0.85, 95%CI: 0.73–1.00; p = .04) (Fig. 7A). The test of heterogeneity was not significant for the meta-analysis (p = .56, λ^2 = 4.84, d.f.: 6, I^2 = 0%).

In studies involving patients in Europe and the Unites States, the frequencies of reflux symptom and erosive esophagitis were also similar between the two groups (Fig. 7B,C).

Effect of *H. pylori* Eradication on 24-hour Esophageal pH

There were only two studies evaluating the effect of *H. pylori* eradication on 24-hour esophageal pH. Wu et al. [16] showed similar esophageal acid exposure time

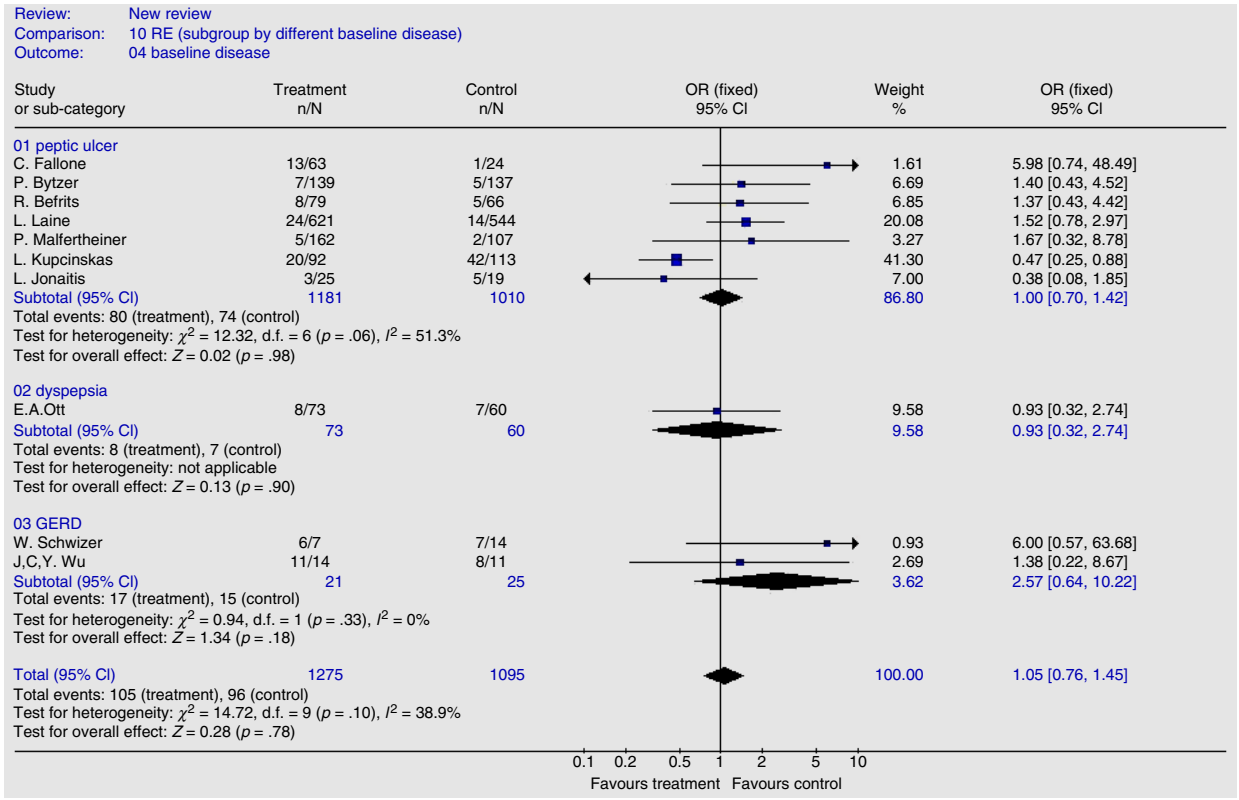

Figure 6 (*Continued*).

at pH < 4 and DeMeester scores at the baseline and the endpoint between case and control groups. However, the total percentages of time at pH < 2 and pH < 3 were increased in the eradication therapy group. The author concluded that *H. pylori* eradication increases esophageal acid exposure and may adversely affect the clinical course. In contrast, Schwizer et al. [13] showed no significant differences between the two groups.

Effect of *H. pylori* Eradication on the Time to Relapse of GERD Symptoms

Two studies explored this issue. Moayyedi et al. [20] showed that GERD symptoms relapsed in 83% of patients with *H. pylori* eradicated and those with persistent infection, suggesting that *H. pylori* status after treatment had no impact on the recurrence of GERD symptoms. However, Schwizer et al. [13] reported that GERD symptoms relapsed faster in infected patients than in the negative controls.

Discussion

A considerable number of studies have investigated the effect of *H. pylori* eradication on GERD in patients with or without GERD; while some reported that eradication halted the progression of reflux symptoms, others failed to confirm this observation [9–20]. In the present meta-analysis, we included 11 well-designed RCTs, with large sample sizes and balanced baseline characteristics, and demonstrated that *H. pylori* eradication had no significant effect on the occurrence of either symptomatic or erosive GERD in patients, which was consistent with the previous meta-analyses. Moreover, the present meta-analysis further demonstrated that all pre-existing reflux symptoms did not regress after *H. pylori* eradication, regardless of the length of follow-up period (up to 24 months), populations (European or Americans), and the baseline diseases (PUD, GERD, and dyspepsia).

The first systematic review of 28 studies by Raghunath et al. [21] in 2004 showed that *H. pylori* eradication did not provoke GERD in patients with DU, but it did not have sufficient data to draw a firm conclusion on the impact of *H. pylori* eradication in patients with reflux esophagitis. Recently, another meta-analysis [22] of seven RCTs and five cohort studies published before February 2007 also showed no association between *H. pylori* eradication and the development of GERD. However, these two meta-analyses limited the possibility of selection heterogeneity. For example, they used

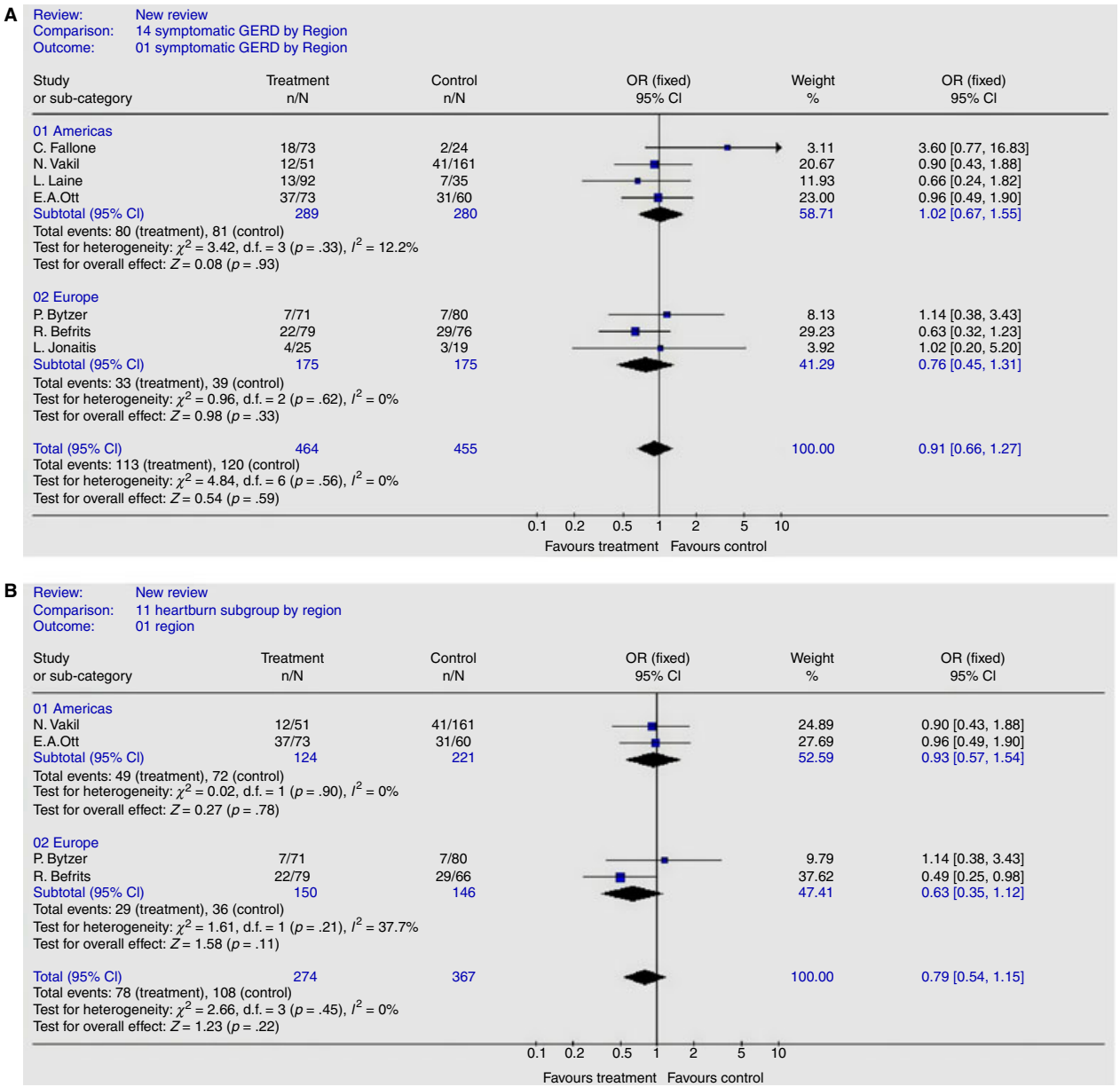

Figure 7 The frequency of gastroesophageal reflux disease symptoms (*A*), heartburn symptom (*B*), and erosive esophagitis (*C*) after treatment between patients with *Helicobacter pylori* infection eradicated and those with persistent *H. pylori* infection in studies in different countries.

different inclusion criteria that allow both RCTs and observational studies to be included in the meta-analysis, and the RCTs included both low- and high-quality clinical trials. They did not analyze the changes (reflux symptoms severity, healing, and relapse) in patients with GERD; analysis of these changes in patients with GERD would provide the strategic data on how to manage GERD patients with *H. pylori* infection. They also did not subanalyze according to geographic regions, the diversity of which may be linked to many possible biases, including different lifestyles and genes. Finally, these meta-analyses did not include recent well-designed RCTs that were published between 2007 and 2010, which are the main source data for meta-analysis.

A few limitations of this meta-analysis should be mentioned. First, possible selection bias existed because unpublished data and articles published in a language other than English were not included. Furthermore, we cannot rule out the possibility that some are missing, as

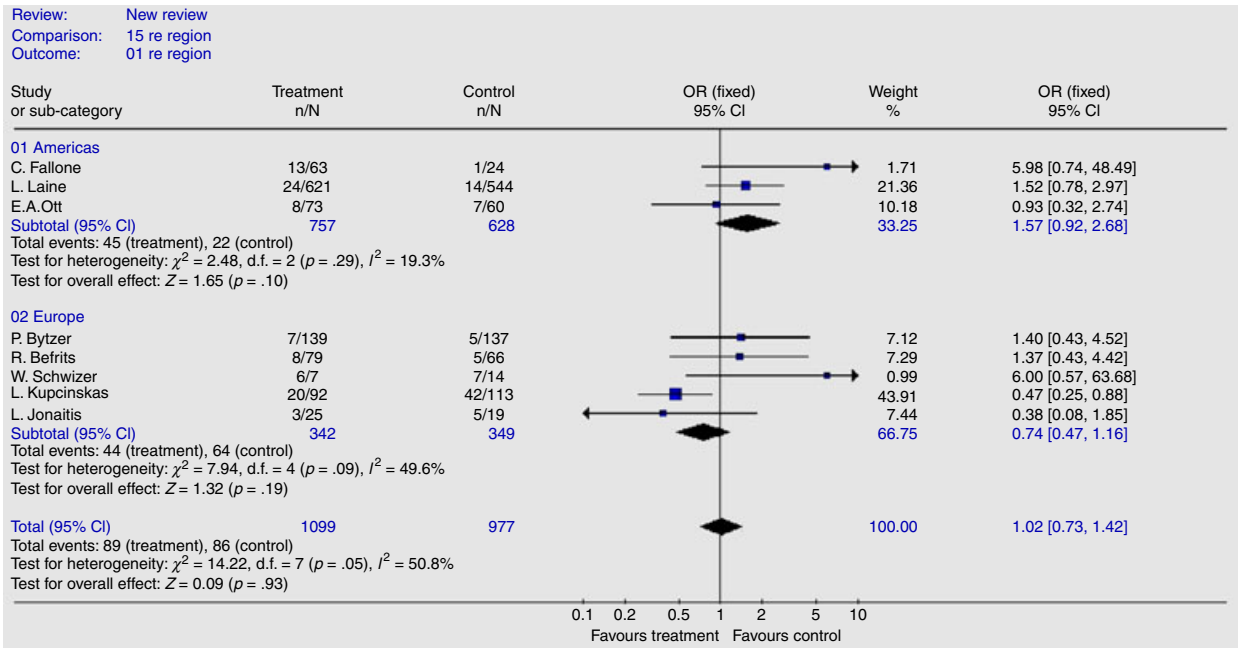

Figure 7 (*Continued*).

some trials were not initially designed to aim at the effect of *H. pylori* eradication on GERD. Second, as studies with similar designs and comparable outcome measures were virtually lacking, we were unable to determine the effects of *H. pylori* eradication on the severity of reflux esophagitis, the healing time or the relapse time of reflux symptoms, GERD questionnaire score changes, and the cost-effectiveness. Third, many trials we included did not follow up with the patients for a longer period, and thus monitoring the long-term effect of the effects of *H. pylori* eradication on the development of GERD needs to be continued. Fourth, the subanalysis on the effects of *H. pylori* eradication on the efficacy of PPI therapy for GERD was not performed because of the inclusion of only one relevant publication [16]. The conclusions of this analysis are thus limited in this regard. Lastly, we determined the effects of *H. pylori* eradication on the development of GERD based on the presence or absence of *H. pylori* infection after treatment, not on the initial treatment regimens. However, we believe that this approach is more accurate and generally accepted because most currently recommended treatment regimens for *H. pylori* eradication cannot achieve eradication rates of 90%.

In conclusion, eradication does not aggravate the clinical outcomes in terms of short-term and long-term posteradication occurrence of GERD. There is no association between *H. pylori* eradication and the development of GERD in patients with different diseases, even those with GERD.

Acknowledgements and Disclosures

This work was supported by the Natural Science Funds of China (No. 81072032 and 30770992). The authors thank Medjaden Bioscience Limited for proofreading the manuscript.

References

1 Vakil N, Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroentrol* 2006;101:1900–20.
2 Sharma P, Vakil N. Review article: *Helicobacter pylori* and reflux disease. *Aliment Pharmacol Ther* 2003;17:297–305.
3 Cullen D, Hawkey G, Greenwood D, et al. *Helicobacter Pylori* and gastroesophageal reflux disease: a Community-Based Study. *Helicobacter* 2008;13(5):352–60.
4 Graham DY. The changing epidemiology of GERD: geography and *Helicobacter pylori*. *Am J Gastroenterol* 2003;98:1462–70.
5 Katelaris PH. Gastro-oesophageal reflux disease and *Helicobacter pylori*. *Minerva Gastroenterol Dietol* 2003;49:235–41.
6 Fock KM, Talley NJ. Asia-Pacific consensus on the management of gastroesophageal reflux disease: update. *J Gastroenterol Hepatol* 2008;23:8–22.
7 Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007;56:772–81.
8 Ye W, Held M, Lagergren J, et al. *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous-cell

carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004;96(5):387–96.
9 Befrits R, Sjostedt S, Odman B, et al. Curing *Helicobacter pylori* infection in patients with duodenal ulcer does not provoke gastroesophageal reflux disease. *Helicobacter* 2000;5(4):202–5.
10 Bytzer P, Aalykke C, Rune S, et al. Eradication of *Helicobacter pylori* compared with long-term acid suppression in duodenal ulcer disease. *Scand J Gastroenterol* 2000;10:1023–32.
11 Fallone CA, Barkun AN, Friedman G, et al. Is *Helicobacter pylori* eradication associated with gastroesophageal reflux disease? *Am J Gastroenterol* 2000;95(4):914–20.
12 Vakil N, Hahn B, McSorley D. Recurrent symptoms and gastro-oesophageal reflux disease in patients with duodenal ulcer treated for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000; 14(1):45–51.
13 Schwizer W, Thumshirn M, Dent J, et al. *Helicobacter pylori* and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001;357(9270):1738–42.
14 Laine L, Sugg J. Effect of *Helicobacter pylori* eradication on development of erosive esophagitis and gastroesophageal reflux disease symptoms: a *post hoc* analysis of eight double blind prospective studies. *Am J Gastroenterol* 2002;97:2992–7.
15 Malfertheiner P, Dent J, Zeijlon L, et al. Impact of *Helicobacter pylori* eradication on heartburn in patients with gastric or duodenal ulcer disease – results from a randomized trial programme. *Aliment Pharmacol Ther* 2002;16(8):1431–42.
16 Wu JC, Chan FKL, Wong SKH, et al. Effect of *Helicobacter pylori* eradication on oesophageal acid exposure in patients with reflux oesophagitis. *Aliment Pharmacol Ther* 2002;16:545–52.
17 Kupcinskas L, Jonaitis L, Kiudelis G. A 1 year follow-up study of the consequences of *Helicobacter pylori* eradication in duodenal ulcer patients: unchanged frequency of erosive oesophagitis and decreased prevalence of non-erosive gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2004;16(4): 369–74.
18 Ott EA, Mazzoleni LE, Edelweiss MI, et al. *Helicobacter pylori* eradication does not cause reflux oesophagitis in functional dyspeptic patients: a randomized, investigator-blinded, placebo-controlled trial. *Aliment Pharmacol Ther* 2005;21: 1231–9.
19 Jonaitis L, Kiudelis G, Kupčinskas L. Gastroesophageal reflux disease after *Helicobacter pylori* eradication in gastric ulcer patients: a one-year follow-up study. *Medicina (Kaunas)* 2008;44(3):211–5.
20 Moayyedi P, Bardhan C, Young L, et al. *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001;121(5):1120–6.
21 Raghunath AS, Hungin APS, Wooff D, et al. Systematic review: the effect of *Helicobacter pylori* and its eradication on gastro-oesophageal reflux disease in patients with duodenal ulcers or reflux oesophagitis. *Aliment Pharmacol Ther* 2004;20(7):733–44.
22 Yaghoobi M, Farrokhyar F, Yuan Y, et al. Is there an increased risk of GERD after *Helicobacter pylori* eradication?: a meta-analysis. *Am J Gastroenterol* 2010;1:734–40.
23 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.