

Histological changes of gastric mucosa after *Helicobacter pylori* eradication: A systematic review and meta-analysis

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Abstract

AIM: To systematically review pathological changes of gastric mucosa in gastric atrophy (GA) and intestinal metaplasia (IM) after *Helicobacter pylori* (*H. pylori*) eradication.

METHODS: A systematic search was made of PubMed, Web of Science, EMBASE, ClinicalTrials.gov, OVID and the Cochran Library databases for articles published before March 2013 pertaining to *H. pylori* and gastric premalignant lesions. Relevant outcomes from articles included in the meta-analysis were combined using Review Manager 5.2 software. A Begg's test was applied to test for publication bias using STATA 11 software. χ^2 and I^2 analyses were used to assess heterogeneity. Analysis of data with no heterogeneity (P

> 0.1 , $I^2 < 25\%$) was carried out with a fixed effects model, otherwise the causes of heterogeneity were first analyzed and then a random effects model was applied.

RESULTS: The results of the meta-analysis showed that the pooled weighted mean difference (WMD) with 95%CI was 0.23 (0.18-0.29) between eradication and non-eradication of *H. pylori* infection in antral IM with a significant overall effect ($Z = 8.19$; $P < 0.00001$) and no significant heterogeneity ($\chi^2 = 27.54$, $I^2 = 16\%$). The pooled WMD with 95%CI was -0.01 (-0.04-0.02) for IM in the corpus with no overall effect ($Z = 0.66$) or heterogeneity ($\chi^2 = 14.87$, $I^2 = 0\%$) (fixed effects model). In antral GA, the pooled WMD with 95% CI was 0.25 (0.15-0.35) with a significant overall effect ($Z = 4.78$; $P < 0.00001$) and significant heterogeneity ($\chi^2 = 86.12$, $I^2 = 71\%$; $P < 0.00001$). The pooled WMD with 95% CI for GA of the corpus was 0.14 (0.04-0.24) with a significant overall effect ($Z = 2.67$; $P = 0.008$) and significant heterogeneity ($\chi^2 = 44.79$, $I^2 = 62\%$; $P = 0.0003$) (random effects model).

CONCLUSION: *H. pylori* eradication strongly correlates with improvement in IM in the antrum and GA in the corpus and antrum of the stomach.

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Key words: *Helicobacter pylori* eradication; Gastric atrophy; Intestinal metaplasia; Pathological changes; Gastric mucosa; Meta-analysis

Core tip: This study reports the results of a meta-analysis conducted on a large number of articles using an extensive and thorough method. The inclusion of only high-quality relevant articles resulted in the identification of a very strong correlation between the eradication of *Helicobacter pylori* infection and intestinal metaplasia of the antrum, and a strong correlation with gastric atrophy in both the antrum and the corpus of the stomach.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer in the world and the second leading cause of cancer-related deaths, accounting for 10.4%^[1]. The incidence and mortality of GC have fallen dramatically over the past 7 decades as a result of improved socioeconomic situations, sanitation, food preservation, as well as a decline in the incidence of *Helicobacter pylori* (*H. pylori*) infection^[2-4]. Despite these declines, however, GC cure rates have not changed^[4-6]. *H. pylori* infection has been known as a gastric carcinogen for over 10 years^[7], and is the main cause of GC^[8,9]. Infection triggers a multistep progression from chronic gastritis to gastric atrophy (GA), intestinal metaplasia (IM), dysplasia, and finally invasive cancer. *H. pylori* is a spiral-shaped, microaerophilic, Gram-negative bacterium measuring approximately 3.5×0.5 microns that is the cause for the most common chronic bacterial infection in humans, infecting 50% of the world population^[10,11].

H. pylori, which causes active chronic gastritis in all infected patients, leads to clinically relevant diseases, such as gastric and duodenal ulcers, mucosa associated lymphoid tissue lymphoma and GC, in 20% of infected carriers^[12-17]. Furthermore, meta-analyses have indicated that the infection confers a 2- to 3-fold increased risk of GC development^[18,19]. While the course of the infection depends on microbial virulence, host genetic factors and environmental factors, the clinical outcomes are determined by the type and intensity of gastritis, which can be categorized as either a simple benign gastritis, a duodenal ulcer phenotype, or a GC phenotype.

As *H. pylori* infection plays a causal role in the formation of GC, eradication of infection may play a role in GC prevention^[15,16]. After *H. pylori* eradication, neutrophils disappear and mononuclear cells slowly return to normal^[20]. However, the improvement in gastric mucosal lesions following eradication of *H. pylori* is not entirely clear. While the majority of studies have reported a reversal of atrophy, no reversal of IM has been shown. To further examine and resolve these discrepancies, a systematic review and meta-analysis was conducted to determine if the eradication of *H. pylori* infection eliminates the precancerous lesions of GA and IM.

MATERIALS AND METHODS

Search strategy

A systematic search of PubMed, Web of Science, EMBASE, ClinicalTrials.gov, OVID and the Cochrane Library databases was made to identify relevant review articles, editorials, and original studies published through

March 2013 using the following key words: *H. pylori* OR *Helicobacter pylori* (*H. pylori*) OR HP, eradication OR treatment OR cure OR therapy, gastric atrophy OR atrophic OR GA OR intestinal metaplasia, clinical test, English-language. Data were independently extracted from each study by two of the authors working independently and using a predefined form; disagreements were resolved by discussion with a third investigator.

Inclusion and exclusion criteria

Published reports were selected for inclusion in the meta-analysis according to the following criteria: (1) English language publication; (2) prospective and randomized controlled trials on *H. pylori* eradication; (3) studies of adults testing positive for the presence of *H. pylori* prior to treatment and eradication of the infection documented both by histology and carbon (C) 14 urea breath test (UBT) or 13 C-UBT (sensitivity, 100%; specificity, 96%)^[21]; (4) *H. pylori* eradication as the only treatment; and (5) gastric histology from at least three pathological specimens per sample processed for hematoxylin-eosin and modified Giemsa staining. Specimens were required to have been taken at baseline and at least 6 mo after treatment, evaluated separately for the antrum and corpus, and scored using the Sydney system^[22] or the updated Sydney system^[23]. Studies not meeting these criteria, those without data for retrieval, and duplicate publications were excluded from the meta-analysis.

Study quality and data extraction

The quality of included studies was assessed using the Risk of Bias table outlined in the Cochrane Reviewer's Handbook 5.0.1^[24]. This method evaluates biases originating from sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). Every facet was judged as either yes, no, or unclear. A judgment of "yes" indicated that the method described was clear and correct, the information was complete, and indicated a low likelihood of bias. A judgment of "no" indicated a high likelihood of bias due to improper use of methods, unused allocation concealment, incomplete information, or selective reporting bias. An "unclear" judgment indicated that an assessment of bias could not be obtained due to insufficient descriptions. Judgments were assigned by two of the authors working independently, and discrepancies were remedied through discussions with a third investigator to obtain a consensus.

The data extracted from each study included the following: general article information (author, publication date, journal name, *etc.*); data to calculate the value of the total effect (treatment number, effective number, *etc.*); clinical heterogeneity of the study (sex, age, concurrent disease, treatment regimen, *etc.*); methodological heterogeneity of the study (design type, randomized, blinded, follow-up, quantity of and processing methods

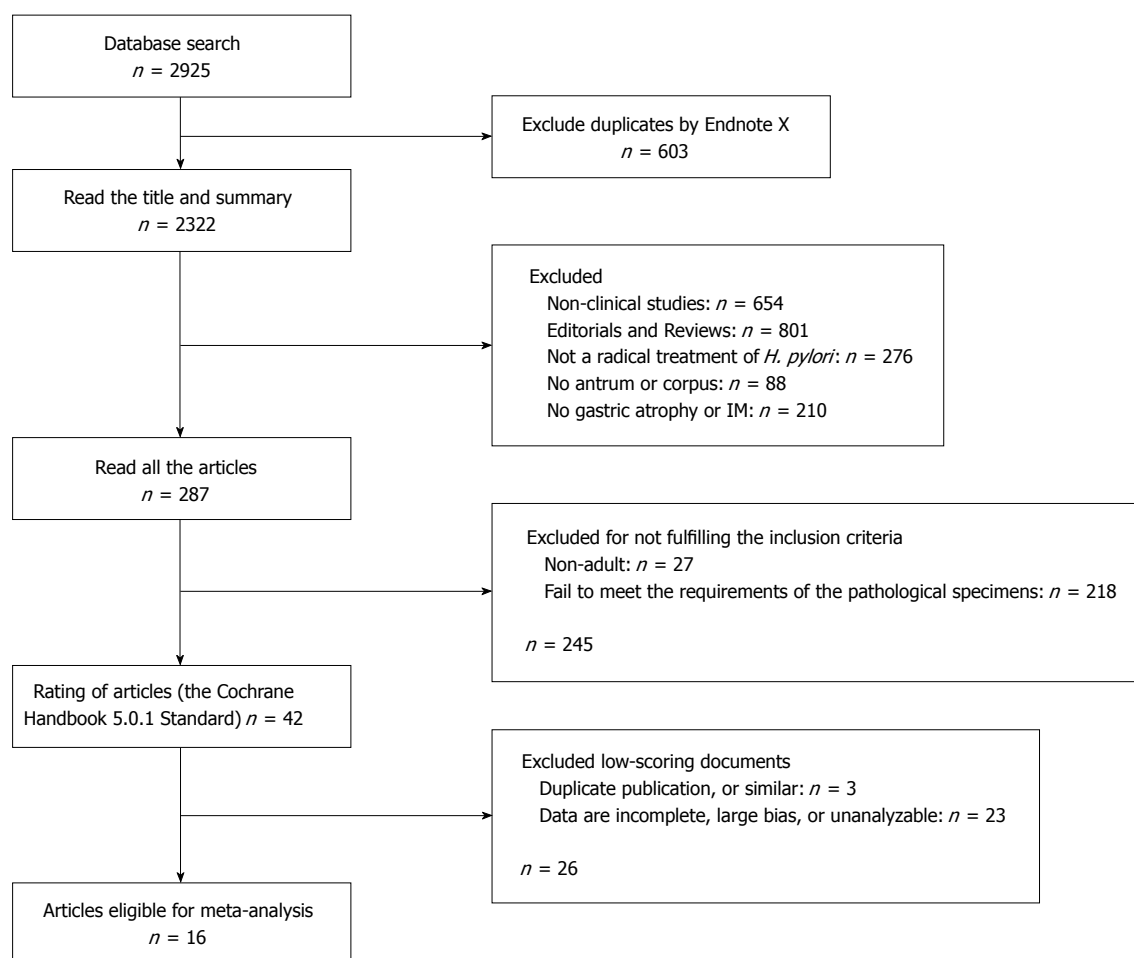


Figure 1 Flow diagram of the selection of included studies. *H. pylori*: *Helicobacter pylori*; IM: Intestinal metaplasia.

for pathological specimens, and methodology for histology scoring). Assessment of the degree of gastritis was performed according to the Sydney system^[22] or the updated Sydney system^[23]. For each graded variable, the following scores were assigned: 0 for absence and 1, 2 or 3 for mild, moderate or severe presence, respectively. The ultimate histology scores were used to weigh the severity of glandular atrophy or IM graded from 0 (normal) to 3 (markedly abnormal). Studies were reviewed and data extracted by two independent reviewers with knowledge of clinical medicine, epidemiology, and medical statistics, with discrepancies resolved through discussion. This process for data extraction was repeated to ensure accuracy.

Statistical analysis

Agreement on the selection of studies between the two reviewers was evaluated by the κ coefficient. Review Manager 5.2 and Begg's test with STATA 11 were used to perform the meta-analysis to compare continuous variables, such as histological scores before and after *H. pylori* eradication. The inverse variance of the weighted mean difference (WMD) and 95% CIs for gastric mucosal histology scores was estimated for each study. The chi-square test and *P*-value analysis were used to indicate the presence of heterogeneity, and the size of the heterogeneity

was tested with I^2 . If there was no heterogeneity, a fixed effects model was applied. In cases where heterogeneity was indicated ($P < 0.1$, $I^2 > 25\%$), causes for the heterogeneity were first analyzed; a random effects model was applied when the clinical and methodological heterogeneity could not be identified^[25] and subgroup analysis or sensitivity analysis was performed when the clinical or methodological heterogeneity was identified. In the presence of significant statistical heterogeneity, sensitivity analyses were performed to examine sample size, follow-up duration, number of biopsy samples, *etc.* To perform these analyses, meta-analyses were repeated following the exclusion of each individual study one at a time, in order to assess the overall effect of each study on the pooled WMD^[26]. Overall effects were considered as statistically significant with a *P*-value < 0.05 . Funnel plots were constructed to assess the likelihood of publication bias^[27].

RESULTS

Search results

The selection of studies included in the meta-analysis is described in a flow chart shown in Figure 1. The initial search strategy yielded 2925 citations. Of these, 1034

Table 1 Main characteristics of the 16 studies selected for meta-analysis

Ref.	Author, year (country)	Study arms, <i>n</i>		Follow-up in year	Medication	Histologic parameters			
		Eradicated	Not eradicated			GA		IM	
						Antrum	Corpus	Antrum	Corpus
[28]	Annibale B, 2000 (Italy)	25	7	0.5	BAM	Yes	Yes	Yes	Yes
		15	15	0.5	BAM				
		15	15	1	BAM				
[29]	Wamura C, 2004 (Japan)	107	118	1	L/A/C	Yes	Yes	Yes	Yes
		107	118	2	L/A/C				
		107	118	3	L/A/C				
[30]	Annibale B, 2002 (Italy)	8	0	0.5-1	BAM	Yes	Yes	Yes	Yes
		32	0	0.5-1	BAM				
[31]	Kamada T, 2005 (Japan)	20	233	1	O/L/A/C	Yes	Yes	Yes	Yes
		1767		1	O/L/A/C				
[32]	Tucci A, 1998 (Italy)	10	0	1	BAM	Yes	No	Yes	No
		8	2 (lost)	1	BAM				
[33]	Sung JJ, 2000 (China)	226	245	1	OAC	Yes	Yes	Yes	Yes
[34]	Ito M, 2002 (Japan)	22	22	5	PPI/A/C	Yes	Yes	Yes	Yes
[35]	Lahner E, 2005 (Italy)	38	36	6.7	B-BTI	Yes	Yes	Yes	Yes
[36]	Toyokawa T, 2009 (Japan)	241	19	5	PPI/A/C	Yes	Yes	Yes	Yes
[37]	Ohkusa T, 2001 (Japan)	115	48	1-1.25	PPI/A/C	Yes	Yes	Yes	Yes
[38]	Iacopini F, 2003 (Italy)	10	0	1	OMC	Yes	No	Yes	No
[39]	Kamada T, 2003 (Japan)	37	8	3	OMC	Yes	No	No	No
[40]	Lu B, 2005 (China)	92	62	3	O/LAC	Yes	No	Yes	No
[41]	Ruiz B, 2001 (Colombia)	29	21	1	BAM	Yes	No	No	No
[42]	Yoshio O, 2004 (Japan)	59	0	1	O/A/C	Yes	Yes	Yes	Yes
[43]	Yamada T, 2003 (Japan)	87	29	0.83-4.17	PPI/A/C	Yes	Yes	Yes	Yes

A: Amoxicillin; B: Bismuth subcitrate; B-BTI: Bismuth-based triple regimen; C: Clarithromycin; GA: Gastric atrophy; IM: Intestinal metaplasia; L: Lansoprazole; M: Metronidazole; O: Omeprazole; PPI: Proton pump inhibitor; BAM: Bismuth subcitrate, Metronidazole and Amoxicillin; OMC: Omeprazole, Metronidazole and Clarithromycin.

were rejected as duplicates or the title suggested that the articles were not appropriate, and a further 1604 were excluded after initial review (editorials, review articles, animal experiments, non-English language, *etc.*). Of the remaining 287 candidate articles, 245 did not fully meet the inclusion criteria and were excluded. A quality assessment of the 42 remaining papers led to elimination of a further 26 articles, leaving 16 studies eligible for the meta-analysis^[28-43]. Initial agreement between the reviewers for the selection of relevant articles was high ($\kappa = 0.96$).

Characteristics of included studies

The main characteristics of the 16 articles included in the meta-analysis are shown in Table 1. With the exception of one randomized control study^[35], all studies were single-center observational studies conducted in different parts of the world, mostly Japan and Italy. All the papers gave data for the four histological parameters evaluated (GA and IM separately for gastric corpus and antrum). *H. pylori* eradication in these studies consisted of a standard therapy with proton pump inhibitors, bismuth-based triple regimens, or dual regimens for 1-2 wk. Two studies enrolled patients with early gastric cancer who underwent endoscopic mucosal resection without recurrence^[33,34]. Histological scores were calculated twice in one study, as *H. pylori* eradication occurred at different time points in two different groups^[36]. Another study calculated the histological scores of both the lesser and greater parts of the antrum and corpus before and after *H. pylori* eradication^[31]. Initial agreement between the re-

viewers for the data extraction was high ($\kappa = 0.95$).

Intestinal metaplasia

Results of the analyses indicated no publication bias for reports on the effects of *H. pylori* eradication on IM in the antrum and corpus. The pooled WMD in the gastric antrum before and after *H. pylori* eradication with 95%CI was 0.23 (0.18-0.29) with a significant overall effect ($P < 0.05$) (Figure 2A). For IM in the corpus, the pooled WMD with 95%CI was -0.01 (-0.04-0.02) with no significant overall effect (Figure 2B). There was no significant heterogeneity among any of these trials, therefore fixed effects models were used.

Gastric atrophy

Results of the analyses indicated no publication bias for reports on the effects of *H. pylori* eradication on GA in the antrum and corpus. The pooled WMD in the gastric antrum before and after *H. pylori* eradication with 95%CI was 0.25 (0.15-0.35) with a significant overall effect ($P < 0.05$) (Figure 3A). For GA in the corpus, the pooled WMD with 95%CI was 0.14 (0.04-0.24) with a significant overall effect ($P < 0.05$) (Figure 3B). There was significant heterogeneity among these trials, therefore random effects models were applied and multiple sensitivity analyses were performed. These analyses showed that the pooled WMD was not influenced by individual trials, thus no studies were excluded from the meta-analysis. These results indicate that the eradication of *H. pylori* aids in the reversal of both GA and IM in the antrum, but only reversal of GA, and not IM, was

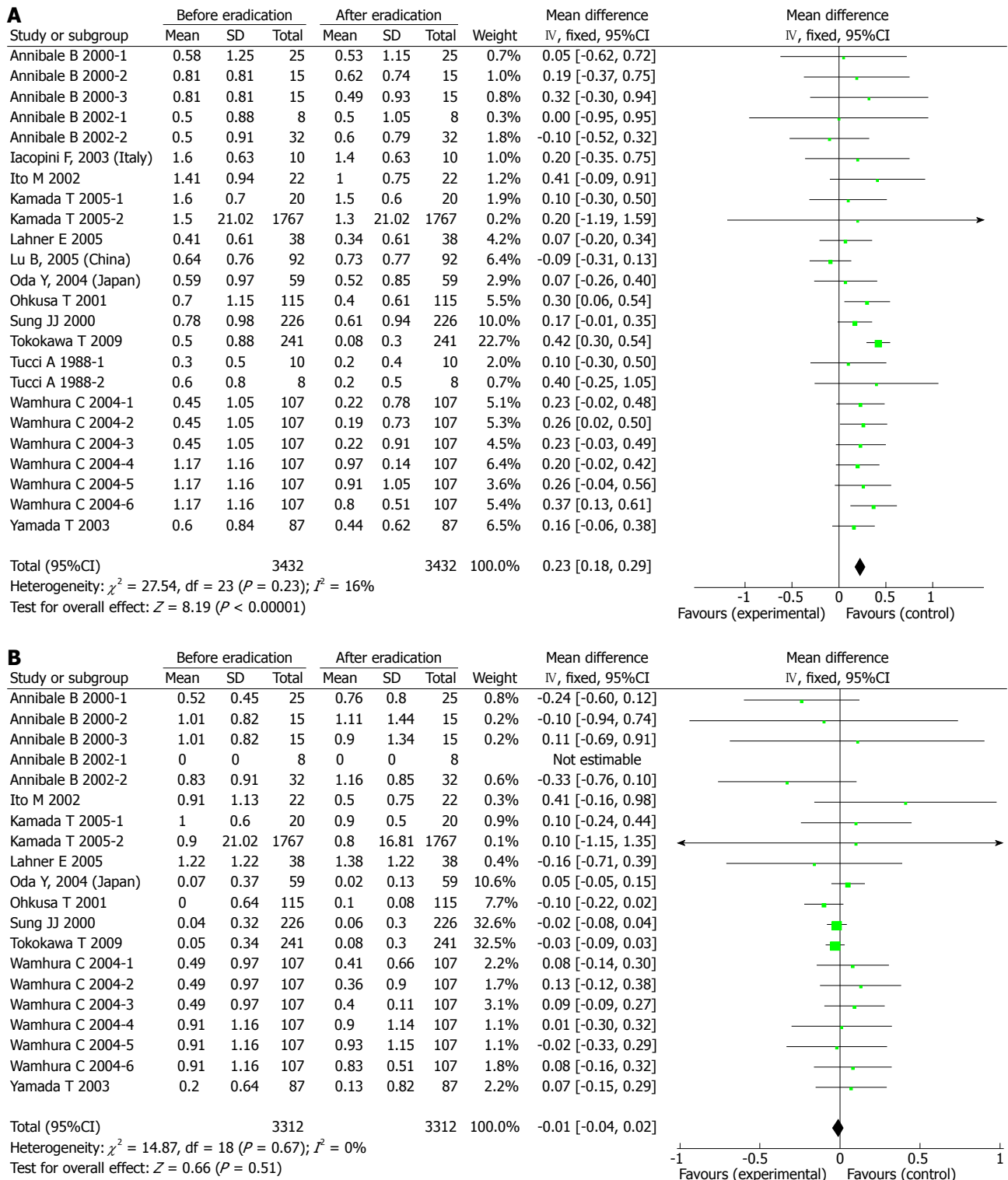


Figure 2 Forest plot comparing intestinal metaplasia in the antrum (A) and the corpus (B).

observed in the corpus.

DISCUSSION

Despite the numerous reports on the improvement of gastric mucosal lesions following *H. pylori* eradication^[44-55], some inconsistencies still remain^[48,51,56]. Thus, it is still disputed whether the pathology of gastric mucosa, par-

ticularly GA and IM, improves after curing of the *H. pylori* infection. In this meta-analysis, data from relevant published studies were pooled with an effort to determine if GA and IM of the stomach are reversible after *H. pylori* eradication, and therefore whether therapeutic intervention is possible, or if efforts should be more appropriately directed at prevention.

The results of this study indicated that *H. pylori* eradi-

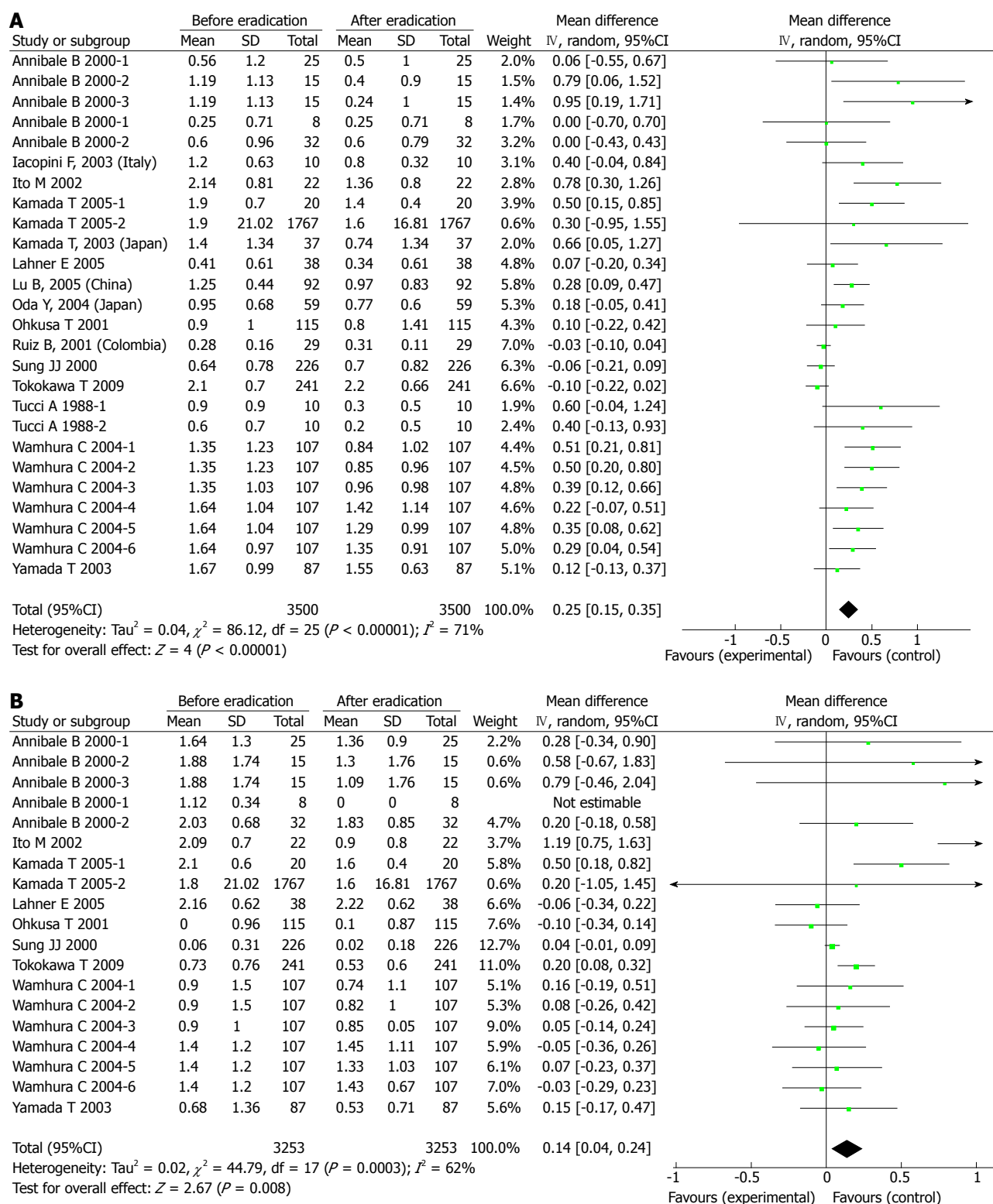


Figure 3 Forest plot comparing gastric atrophy in the antrum (A) and the corpus (B).

cation did indeed have beneficial long-term effects on gastric pathologies, such as halting the progression of pre-neoplastic lesions in the antrum and corpus. More specifically, IM in the antrum and GA in both the antrum and corpus showed regression after eradication of *H. pylori*, although this effect was not seen in IM of the gastric corpus. The interpretation of this finding is not

clear, but histological changes occurring after *H. pylori* eradication may play a role^[44].

The results reported here differ from similar previously published meta-analyses^[45,57]. There are several reasons that may explain this discrepancy. First of all, the previous analyses included a limited number of studies, whereas our analysis included 16 comparatively high-quality scor-

ing studies. Second, the analysis by Rokkas *et al.*^[45] used the odds ratio as a statistical index, which may not be as precise as WMD for continuous variables. Additionally, there were errors in the analysis reported by Wang *et al.*^[57], which may have led to an incorrect conclusion.

The results of the current meta-analysis should be considered more reliable as a result of the extensive and thorough measures employed. For articles that merely reported results in chart format, the authors were contacted to obtain the raw data. Failure to obtain the raw data resulted in exclusion of the study to ensure reliability of the included data. Articles reporting varying treatment durations for the same group of patients were included as a separate set of data in the analysis, while taking into account the fact that medications had not been changed during the full course of treatment. Sensitivity analyses were performed to exclude the effects of different treatment courses, resulting in more accurate results^[29]. Furthermore, data from articles that segregated results according to outcome were analyzed separately on the basis of the numbers of patients with successful eradication therapy in two groups^[28,30-32], and only the patients with successful eradication were included in the analysis. Lastly, random effects models were used, which result in wider confidence intervals and, thus, a more conservative estimate of treatment effects.

The meta-analysis reported here is not without limitations. One inherent weakness involves the methodological flaws of the included studies, dependent on factors such as number of biopsy samples taken, method for histological classification of findings, sample size, and duration of follow-up. To alleviate such influences and unify the method of histological evaluation of biopsy samples, we selected only reports employing the updated Sydney system and had greater than three pathological samples of every specimen that were stained by hematoxylin-eosin methods. Another weakness is the inability to retrieve unpublished studies or published abstracts, due to the absence of a specific searching mechanism. However, we maximized the chances of detecting such studies by going through the references of the selected articles. Furthermore, although we used medical subject heading terms and keywords, some studies may have been missed, particularly studies in which the association of *H. pylori* infection with GA or IM was not the primary research question.

In conclusion, this study illustrates a very strong correlation between the eradication of *H. pylori* infection and improvement in IM in the gastric antrum but not in the corpus, in addition to a strong correlation with GA in both the antrum and the corpus. However, the follow-up periods of the analyzed studies are relatively short compared to the long process of mucosal carcinogenesis. Therefore, more high quality clinical studies with longer follow-up periods are necessary to assess the long-term benefit and whether the eradication of *H. pylori* infection delays disease progression.

COMMENTS

Background

Gastric cancer (GC) is the fourth most common cancer in the world and the second leading cause of cancer-related deaths. Overall GC incidence and mortality have fallen dramatically over the past 7 decades, but despite that decline, the cure rates for GC have not changed. Therapeutic eradication of *Helicobacter pylori* (*H. pylori*) infection is one factor contributing to these declines; however, this association is still debated.

Research frontiers

Although *H. pylori* eradication has been reported to improve gastric mucosal lesions, there are many studies with contradictory results. A clear understating of the role *H. pylori* eradication plays in the incidence and progression of GC will help guide therapies towards effective treatment or prevention.

Innovations and breakthroughs

The results of this meta-analysis indicate that there is a very strong correlation between *H. pylori* infection and improvement in intestinal metaplasia in the antrum, but not the corpus, of the stomach. Furthermore, a strong correlation between *H. pylori* infection and improvement in gastric atrophy in the antrum and corpus was identified.

Applications

The results of this study confirm the association between *H. pylori* eradication and improvements in gastric pathologies. Although additional high quality clinical studies with longer follow-up periods are necessary to assess the long-term benefit of treatments, the findings implicate a viable treatment option for patients with intestinal metaplasia and gastric atrophy.

Terminology

Intestinal metaplasia is the transformation (metaplasia) of epithelium, usually of the stomach or the esophagus, to a type that bears some resemblance to the intestine, as seen in Barrett's esophagus. Chronic *H. pylori* infection in the stomach and gastroesophageal reflux disease are seen as the primary instigators of metaplasia and subsequent adenocarcinoma formation.

Peer review

This article presents a well-designed meta-analysis of high quality studies evaluating the effect of *H. pylori* eradication on intestinal pathologies, namely intestinal metaplasia and gastric atrophy in the antrum and corpus of the stomach. The analyses show a strong correlation with improvement of intestinal metaplasia in the antrum, and gastric atrophy in the antrum and corpus, following eradication of *H. pylori* infection.

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