Eradication Therapy to Prevent Gastric Cancer in *Helicobacter pylori*–Positive Individuals: Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies

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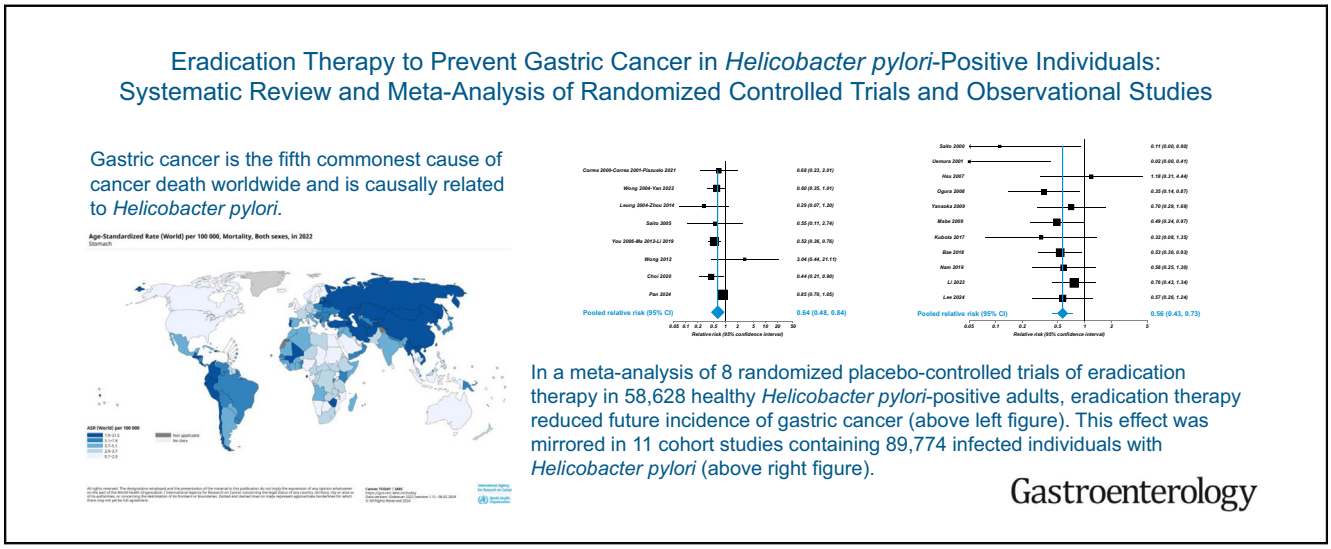

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BACKGROUND & AIMS: Screening for, and treating, *Helicobacter pylori* in the general population or patients with early gastric neoplasia could reduce incidence of, and mortality from, gastric cancer. We updated a meta-analysis of randomized controlled trials (RCTs) examining this issue. **METHODS:** We searched the literature through October 4, 2024, identifying studies examining effect of eradication therapy on incidence of gastric cancer in *H pylori*–positive adults without gastric neoplasia at baseline or *H pylori*–positive patients with gastric neoplasia undergoing endoscopic mucosal resection (EMR) in either RCTs or observational studies. The control arm received placebo or no eradication therapy in RCTs and no eradication therapy in observational studies. Follow-up was ≥2 years. We estimated relative risks (RR) of gastric cancer incidence and mortality. **RESULTS:** Eleven RCTs and 13 observational studies were eligible. For RCTs, RR of gastric cancer was lower with eradication therapy in healthy *H pylori*–positive individuals (8 RCTs, 0.64; 95% confidence interval [CI], 0.48–0.84) and *H pylori*–positive patients with gastric neoplasia undergoing EMR (3 RCTs, 0.52; 95% CI, 0.38–0.71). RR of death from gastric cancer was lower with eradication therapy in healthy *H pylori*–positive individuals (5 RCTs, 0.78; 95% CI, 0.62–0.98). In observational studies, RR of future gastric cancer was lower with eradication therapy in *H pylori*–positive subjects without gastric neoplasia at baseline (11 studies, 0.56; 95% CI, 0.43–0.73) and *H pylori*–positive patients with gastric neoplasia undergoing EMR (2 studies, 0.19; 95% CI, 0.06–0.61). **CONCLUSIONS:** This meta-analysis provides further evidence that administering eradication therapy prevents gastric cancer in *H pylori*–positive individuals, with consistency in results among studies of different design.

Keywords: Gastric Cancer; *Helicobacter pylori*; Meta-Analysis; Eradication Therapy; Mortality.

Abbreviations used in this paper: **CI, confidence interval; EMR, endoscopic mucosal resection; FIT, fecal immunochemical test; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; RCT, randomized controlled trial; RR, relative risk.**

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Gastric adenocarcinoma is the fifth most common cancer globally, with more than 968,000 cases annually.[1] Observational studies have shown that *Helicobacter pylori* is associated strongly with gastric adenocarcinoma,[2–5] and population-based randomized controlled trials (RCTs) have suggested that this association may be causal.[6] This raises the possibility that implementing strategies involving testing for, and treating, *H pylori* in the general population could reduce the incidence of, and mortality from, gastric adenocarcinoma. Some guidelines have recommended such screening strategies to reduce gastric cancer risk,[7,8] but others have not.[9] No country has, as yet, instituted a national population-based program to screen for and treat *H pylori* although there have been some regional programs, for example, in Matsu Islands, Taiwan, and Bhutan,[10,11] and Japan's national health insurance reimburses treatment of *H pylori* for endoscopically confirmed gastritis.[12]

This inaction relates, in part, to the extent and quality of the evidence. We have conducted a previous systematic review and meta-analysis of RCTs,[13,14] and this suggested that, although screening for and treating *H pylori* in the general population was effective in reducing future incidence of gastric adenocarcinoma, the quality of the evidence was low. The main issue was that the number of incident gastric cancer events was modest and, therefore, the estimate of effect was not robust. Since then, however, there have been further population-based trials addressing this question,[15,16] and so we have updated our systematic review and meta-analysis of the RCT evidence.

In this update, we have also included data from cohort studies evaluating whether *H pylori* eradication therapy reduces risk of subsequent gastric cancer, as this is the highest quality observational data, which is less prone to bias than data from case-control studies.[17] Others have shown that evaluating both RCT and observational data can give a richer picture of the direction and strength of effect of an intervention,[18] as observational studies often include a more broadly representative sample of the population.[19] Updating the meta-analysis in this way may, therefore, improve the quality of the evidence, which will provide support to future guidelines and policy makers.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Gastric cancer is the fifth most common cause of cancer death worldwide and is associated with *Helicobacter pylori*. *H pylori* eradication therapy may reduce incidence of gastric cancer but no country has adopted screening because quality of evidence is low.

NEW FINDINGS

In a meta-analysis of randomized controlled trials and observational studies there was consistent evidence that *H pylori* eradication therapy prevents gastric cancer.

LIMITATIONS

Due to low numbers of events in many of the studies, heterogeneity may have been underestimated. Only 2 of the studies were conducted outside East Asia so these results may not apply to other regions.

CLINICAL RESEARCH RELEVANCE

Countries at high risk of gastric cancer should consider adopting population screening and treatment programs for *H pylori* as a means of preventing gastric cancer.

BASIC RESEARCH RELEVANCE

Incidence of gastric cancer varies worldwide and this is not explained by prevalence of *H pylori* alone. Factors contributing to gastric cancer development in *H pylori* infection require further study.

Methods

Search Strategy and Study Selection

We updated our previous systematic review and meta-analysis examining the impact of *H pylori* eradication therapy on the future incidence of gastric cancer,[13,14,20,21] but expanded our search to include observational studies. We searched MEDLINE (January 1, 1946–October 4, 2024), EMBASE and EMBASE Classic (January 1, 1947–October 4, 2024), and the Cochrane central register of controlled trials to identify potential studies. In addition, we searched clinicaltrials.gov for unpublished trials, or supplementary data for potentially eligible studies. We also searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2024. Finally, we performed a recursive search, using the bibliographies of all obtained articles.

Eligible RCTs examined the effect of at least 7 days of eradication therapy on subsequent occurrence of gastric cancer in *H pylori*–positive individuals who were otherwise healthy, or in *H pylori*–positive patients with gastric neoplasia, including dysplasia or early gastric cancer, that was suitable for endoscopic mucosal resection (EMR), compared with placebo or no eradication therapy. Eligible observational studies recruited *H pylori*–positive subjects without gastric neoplasia at baseline, or *H pylori*–positive patients with gastric neoplasia that was suitable for EMR. The exposed group received a recognized *H pylori* eradication regimen, and the nonexposed group received no eradication therapy for *H pylori*. Studies had to recruit adults (≥18 years). In all studies, irrespective of design, a minimum follow-up duration of 2 years was required, and at least 2 gastric cancers had to occur during follow-up (Supplementary Table 1). We extracted all endpoints at the last point of follow-up that they were reported.

The search strategy is provided in the Supplementary Materials. All abstracts identified by the search were assessed for eligibility, independently, by 2 investigators (YY and ACF). We obtained all potentially relevant papers in full, evaluating them in detail, using predesigned forms, to assess eligibility, again independently, according to our predefined criteria. Any disagreements were resolved between investigators by arbitration by a third investigator (PM). There were no language restrictions. We translated foreign language papers, where required. For fully published studies that did not report data concerning subsequent occurrence of gastric cancer, wherever possible, we contacted the first or senior author to obtain supplementary data. Where we found multiple articles for a single study, only the data from the latest publication from each

eligible study were extracted. Ethical approval was not required.

Outcome Assessment

Our primary outcome in RCTs was the effect of *H pylori* eradication therapy, compared with placebo or no eradication therapy, on the subsequent occurrence of gastric cancer. Our primary outcome in observational studies was the effect of *H pylori* eradication therapy, compared with no eradication therapy, on the subsequent occurrence of gastric cancer. Secondary outcomes in RCTs included the effect of eradication therapy on gastric cancer–related mortality or all-cause mortality.

Data Extraction

Two investigators (YY and ACF) extracted all data independently as dichotomous outcomes (presence or absence of gastric cancer). We also extracted the following data for each trial: country, number of centers, method used to confirm *H pylori* infection, type of *H pylori* eradication regimen used (including dose and schedule of individual drugs within it), duration of treatment, eradication rate, duration of follow-up, method to ascertain incident cases of gastric cancer, mortality from gastric cancer, and mortality from other causes. For each observational study we extracted: country, number of centers, method used to confirm *H pylori* infection, type of *H pylori* eradication regimen used (including dose and schedule of individual drugs within it), duration of treatment, eradication rate, where reported, duration of follow-up, and method to ascertain incident cases of gastric cancer.

The shortest duration of follow-up in the RCTs we identified was $\geq$4 years and, therefore, dropout rates were relatively high. As a result, data were extracted from RCTs using a modified intention-to-treat analysis. Individuals found to be ineligible after randomization (eg, heathy individuals in whom a gastric cancer was detected at baseline, patients with gastric neoplasia who underwent surgery rather than EMR, or any study participants who were found to be *H pylori*-negative), were excluded, as were those who did not receive the intervention to which they were assigned. Due to the relatively rare nature of the outcome of interest, we kept all subjects lost to follow-up in the denominator for the study, assuming they had not developed gastric cancer.

Quality Assessment and Risk of Bias

We performed this at the study level. Risk of bias was assessed by 2 investigators independently (PM and ACF), using the Cochrane risk of bias tool for RCTs,[22] and the ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions) tool for observational studies.[23] We resolved disagreements by arbitration by a third investigator (YY). For RCTs, we recorded the method used to generate the randomization schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes. For observational studies we recorded whether there was evidence of bias due to confounding or selection of participants preintervention, whether there was evidence of bias due to the classification of the intervention itself, and whether there was evidence of bias due to deviation from intended interventions, missing data, measurement of outcomes, or selection of the reported results postintervention. We assessed the overall quality of the evidence of RCTs using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[24]

Data Synthesis and Statistical Analysis

Data were pooled using a random effects model,[25] to give a more conservative estimate of the effect of *H pylori* eradication therapy on future incidence of gastric cancer, allowing for heterogeneity between studies. The impact of eradication therapy, compared with placebo or no eradication therapy, was expressed as a relative risk (RR) of occurrence of gastric cancer with 95% confidence intervals (CIs). We calculated the number needed to treat (NNT) in RCTs, with a 95% CI, using the formula NNT = 1/(assumed control risk $\times$ (1 – RR)).

Heterogeneity, which occurs due to variation between individual study results arising because of differences in participants or methodology, was assessed using both the χ^2 test, with a P value $<$.10 used to define a significant degree of heterogeneity, and the I^2 statistic. The latter ranges between 0% and 100%, with values of 25%–49% considered low, 50%–74% moderate, and $\geq$75% high heterogeneity.[26]

We used Review Manager version 5.4.1 (RevMan for Windows 2014, the Nordic Cochrane Centre, Copenhagen, Denmark) to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. We assessed the latter for evidence of asymmetry, and, therefore, possible publication bias or other small study effects, using the Egger test,[27] if there were $\geq$10 eligible studies included in the meta-analysis, in line with previous recommendations.[28]

Because one of the studies was a cluster-randomized trial,[15] with patients assigned to treatment strategy by village, rather than randomized individually, we used the cluster size and the intracluster correlation coefficient (personal communication: Dr W-Q Li, 2024). This reduced the size of the trial to its "effective sample size" before any data pooling was carried out.[29] If clustering is ignored, a "unit of analysis error" can occur,[30] which would overestimate the effect of eradication therapy in the study, and also mean the study's weight in the meta-analysis was artificially high.

Results

The updated search strategy identified 941 new citations. After reviewing the titles and abstracts, 89 articles that appeared potentially eligible for inclusion were retrieved and evaluated (Supplementary Figure 1). The agreement between investigators for trial eligibility was excellent (kappa statistic = 0.81). One new trial and 1 updated report from a prior eligible RCT were combined with the existing 10 RCTs, reported in 16 articles, from the previous meta-analyses,[13,14,20,21] and 12 observational studies, reported in 13 articles, were also identified. There was 1 further RCT comparing the effect of a strategy of inviting individuals eligible for biennial fecal immunochemical tests (FIT) for colorectal cancer screening to provide both a FIT and a stool sample for *H pylori* antigen testing, with eradication therapy offered to infected individuals, vs providing a FIT alone.[16] This could not be included in the meta-analysis of RCTs because the *H pylori*

infection status of individuals providing a FIT alone was not known. However, we included data from individuals providing both a FIT and an *H pylori* stool antigen test as an observational study, according to whether or not they received eradication therapy.

Finally, therefore, 24 studies were included, reported in 32 separate articles, all of which were published in English. Of these, 14 articles,[6,15,31–42] reporting data from 8 separate RCTs, compared *H pylori* eradication therapy with placebo or no eradication therapy in 58,628 healthy *H pylori*–positive individuals. Seven recruited healthy people from the community without gastric neoplasia at baseline and 1 South Korean RCT recruited healthy first-degree relatives of patients with gastric cancer.[42] Three RCTs, reported in 4 articles,[43–46] compared *H pylori* eradication therapy with placebo or no eradication therapy in 1841 *H pylori*–positive patients with gastric neoplasia that was suitable for EMR. Eleven observational studies compared *H pylori* eradication therapy with no eradication therapy in 89,774 *H pylori*–positive subjects without gastric neoplasia at baseline.[16,47–56] Finally, 2 observational studies, reported in 3 articles, compared *H pylori* eradication therapy with no eradication therapy in 269 *H pylori*–positive patients with gastric neoplasia that was suitable for EMR.[57–59] Characteristics of eligible and included RCTs are provided in Table 1 and observational studies in Table 2.

All RCTs in healthy populations were conducted in East Asia, with the exception of 1 study conducted in a Colombian community,[31–33] who were previously shown to be at high risk of gastric cancer in epidemiologic studies.[60–62] The longest duration of follow-up in the RCTs in healthy populations we identified was 26.5 years,[35,36] and the shortest duration was $\geq$4 years.[37] We classified 5 trials as being at low risk of bias,[15,35,39–42] 1 trial was at unclear risk,[37] and 2 trials were at high risk of bias.[6,31–34] One was high risk of bias due to the fact that no placebo comparator was used for the active eradication therapy regimen and, therefore, this part of the trial was unblinded.[31–33] The other was considered high risk due to inconsistencies in data reporting at various points of follow-up.[6,34] All RCTs in *H pylori*–positive patients with gastric neoplasia that was suitable for EMR were conducted in East Asia. The longest duration of follow-up in these RCTs was 10 years,[43,44] and the shortest duration was 5.9 years.[46] We classified 1 trial as unclear risk of bias for completeness of outcomes data.[46] This was because a relatively large number of patients were excluded after randomization, leading to a slight imbalance between treatment arms. Two trials were at high risk of bias,[43–45] both because no placebo comparator was used for the active eradication therapy regimen and, therefore, this part of the trial was unblinded. Assessment of risk of bias of individual RCTs is provided in Supplementary Table 2.

All observational studies in *H pylori*–positive subjects without gastric neoplasia at baseline were conducted in East Asia, except for 1 study from the United States.[56] The longest duration of follow-up in the observational studies was 9.5 years,[52] and the shortest duration was 2 years.[47] Risk of bias was judged as moderate in 6 of the observational studies,[16,47–49,53,56] and serious in the remainder. Both observational studies in *H pylori*–positive patients with gastric neoplasia that was suitable for EMR were conducted in East Asia, with mean durations of follow-up of 4.3 years and 5 years, respectively. Risk of bias was judged as moderate in 1,[57,58] and serious in the other. Assessment of risk of bias of all observational studies is provided in Supplementary Table 3.

Effect of Eradication Therapy in RCTs

When data were pooled from the 8 RCTs conducted in healthy *H pylori*–positive individuals,[6,15,31–42] there were 258 (0.87%) gastric cancers occurring among 29,782 infected subjects who received eradication therapy, compared with 351 (1.2%) in 28,846 individuals who received placebo or no eradication therapy. The RR of subsequent occurrence of gastric cancer with eradication therapy vs placebo or no eradication therapy was 0.64 (95% CI, 0.48–0.84), with low heterogeneity between studies ($I^2 = 35\%$; $P = .15$) (Figure 1, Supplementary Figure 2). The NNT was 228 (95% CI, 158–514). Restricting the analysis to the 5 trials at low risk of bias did not change the risk estimate (RR = 0.65; 95% CI, 0.46–0.91; $I^2 = 57\%$; $P = .05$). In this analysis, 1 RCT from China with 22.3 years of follow-up contributed 24.8% weight to the meta-analysis,[38–40] and the cluster-randomized trial from China contributed 35.6% weight. We evaluated the overall GRADE quality of evidence for population-based RCTs as "moderate" as we downgraded 1 point for heterogeneity (Supplementary Table 4).

In the 3 RCTs in *H pylori*–positive patients with gastric neoplasia that was suitable for EMR,[43–46] there were 54 (5.9%) future gastric cancers occurring in 910 patients randomized to eradication therapy, compared with 106 (11.4%) in 931 patients receiving placebo or no eradication therapy (RR = 0.52; 95% CI, 0.38–0.71; $I^2 = 0\%$; $P = .99$) (Figure 1). The NNT was 18 (95% CI, 14–30). There were too few RCTs in either of these analyses to assess for publication bias. There was no heterogeneity between the effect in the general population compared with that in those having EMR for gastric neoplasia (subgroup heterogeneity $P = .33$; $I^2 = 0\%$). In this analysis, the Japanese RCT with 10 years of follow-up contributed 41.6% weight to the meta-analysis.[43,44]

When we pooled data from all 11 RCTs containing both healthy *H pylori*–positive individuals and *H pylori*–positive patients with gastric neoplasia that was suitable for EMR, reported in 18 articles,[6,15,31–46] there were 312 (1.0%) gastric cancers occurring among 30,692 infected subjects who received eradication therapy, compared with 457 (1.5%) in 29,777 individuals who received placebo or no eradication therapy. The RR of subsequent occurrence of gastric cancer with eradication therapy vs placebo or no eradication therapy was 0.61 (95% CI, 0.49–0.75; Figure 1), with low heterogeneity between studies ($I^2 = 29\%$; $P = .17$) and no evidence of publication bias, or other small study effects (Egger test; $P = .15$).

There were 5 RCTs conducted in healthy *H pylori*–positive individuals, which provided data on mortality from

Table 1. Characteristics of RCTs of Eradication Therapy vs Placebo or No Eradication Therapy in the Prevention of Future Gastric Cancer in Healthy *H pylori*–Positive Individuals or *H pylori*–Positive Patients With Gastric Neoplasia Undergoing EMR at Baseline

Healthy *H pylori*–positive individuals							
Study	Method used to confirm presence of *H pylori*	Sample size (no. receiving *H pylori* eradication therapy), characteristics of participants, and location	*H pylori* eradication therapy regimen used	Eradication rate[a]	Last point of follow-up	Method of ascertainment of gastric cancer cases	Risk of bias
Correa 2000,[31] Correa 2001,[32] and Piazuelo 2021[33]	Histology	852 (437) healthy individuals, mean age 51.1 y (range, 29–69 y), 46.1% male, 2 communities in Colombia	Bismuth subsalicylate 262 mg, amoxicillin 500 mg, and metronidazole 375 mg tid for 2 wk	58.0%	20 y	Histology from upper gastrointestinal endoscopy at 3, 6, 12, 16, and 20 y	High
Leung 2004[6] and Zhou 2014[34]	Histology and rapid urease testing	552 (276) healthy individuals, mean age 52.0 y (range, 35–75 y), 47.8% male, 11 villages in China	Omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg bid ± for 1 wk	55.6%	10 y	Histology from upper gastrointestinal endoscopy at 2, 5, 8, and 10 y	High
Wong 2004[35] and Yan 2022[36]	Histology and rapid urease testing	1630 (817) healthy individuals, mean age 42.2 y (range, 35–65 y), 54.0% male, 7 villages in China	Omeprazole 20 mg, co-amoxiclav 750 mg, and metronidazole 400 mg bid for 2 wk	83.7%	26.5 y	Histology from upper gastrointestinal endoscopy at 26.5 y or, if diagnosed before 7.5 y, review of clinical records and pathology specimens	Low
Saito 2005[37]	Not reported	692 (379) healthy individuals, mean age not reported (range, 20–59 y), proportion male not reported, 145 centers in Japan	Lansoprazole 30 mg, amoxicillin 1.5 g, and clarithromycin 400 mg od for 1 wk	74.4%	≥4 y	Histology from upper gastrointestinal endoscopy at ≥4 y	Unclear
You 2006,[38] Ma 2012,[39] and Li 2019[40]	Serologic testing	2258 (1130) healthy individuals, mean age 46.8 y (range, 35–64 y), 50.0% male, 13 villages in China	Omeprazole 20 mg and amoxicillin 1 g bid for 2 wk	73.2%	22.3 y	Histology from upper gastrointestinal endoscopy, or from clinical, laboratory, or pathologic data	Low
Wong 2012[41]	^{13}Carbon-urea breath testing	513 (255) healthy individuals, mean age 53.0 y (range, 35–64 y), 46.4% male, 12 villages in China	Omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg bid for 1 wk	63.5%	5 y	Histology from upper gastrointestinal endoscopy at 5 y	Low

Table 1. Continued

Healthy *H pylori*–positive individuals							
Study	Method used to confirm presence of *H pylori*	Sample size (no. receiving *H pylori* eradication therapy), characteristics of participants, and location	*H pylori* eradication therapy regimen used	Eradication rate[a]	Last point of follow-up	Method of ascertainment of gastric cancer cases	Risk of bias
Choi 2020[42]	Histology and rapid urease testing	1826 (912) healthy first-degree relatives of gastric cancer patients, mean age 48.8 y (range, 40–65 y), 49.5% male, 1 center in South Korea	Lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg bid for 1 wk	60.4%	9.2 y	National cancer database to confirm all cases of gastric cancer diagnosed at upper gastrointestinal endoscopy	Low
Pan 2024[15,b]	^{13}Carbon-urea breath testing	102,330 (52,026) healthy individuals, mean age 42.4 y, 47.7% male, 980 villages in China	Omeprazole 20 mg bid, tetracycline 750 mg and metronidazole 400 mg tid, and bismuth citrate 300 mg bid for 10 d	62.1%	11.8 y	Cancer registry and monthly reporting of all gastric cancer cases by village doctors, with 6-monthly case validation	Unclear
H pylori–positive patients with gastric neoplasia undergoing EMR at baseline							
Study	Method used to confirm presence of *H pylori*	Sample size (no. receiving *H pylori* eradication therapy), characteristics of participants, and location	*H pylori* eradication therapy regimen used	Eradication rate[a]	Last point of follow-up	Method of ascertainment of gastric cancer cases	Risk of bias
Fukase 2008[43] and Kato 2012[44]	Histology and rapid urease testing	544 (272) patients, median age 68.5 y (range, 20–79 y), 76.4% male, 51 centers in Japan	Lansoprazole 30 mg, amoxicillin 750 mg, and clarithromycin 200 mg bid for 1 wk	74.9%	10 y	Histology from 1-yearly upper gastrointestinal endoscopy	High
Choi 2018[45]	Histology and rapid urease testing	901 (444) patients, mean age 60.4 y (range, 20–75 y), 67.7% male, 1 center in South Korea	Omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg bid for 1 wk	81.3%	6 y	Histology from upper gastrointestinal endoscopy	High
Choi 2018[46]	Histology and rapid urease testing	396 (194) patients, mean age 59.8 y (range, 18–75 y), 75.3% male, 1 center in South Korea	Rabeprazole 10 mg, amoxicillin 1 g, and clarithromycin 500 mg bid for 1 wk	80.4%	5.9 y	Histology from upper gastrointestinal endoscopy at 3 months and 3 y	Unclear

bid, twice daily; od, once daily; tid, 3 times daily.
[a]True intention-to-treat analysis, with all dropouts assumed to have failed eradication therapy.
[b]Cluster-randomized trial; trial size reduced to its effective sample size. Supplementary information obtained from the authors.

Table 2. Characteristics of Observational Studies of Eradication Therapy vs No Eradication Therapy in the Prevention of Future Gastric Cancer in *H pylori*–Positive Subjects Without Gastric Neoplasia at Baseline or *H pylori*–Positive Patients With Gastric Neoplasia Undergoing EMR at Baseline

	H pylori–positive subjects without gastric neoplasia at baseline						
Study	Method used to confirm presence of *H pylori*	Sample size (no. receiving *H pylori* eradication therapy), characteristics of participants, and location	*H pylori* eradication therapy regimen used	Eradication rate	Mean duration of follow-up	Method of ascertainment of gastric cancer cases	Risk of bias
Saito 2000[47]	Histology and serology	64 (32) patients with gastric adenoma, mean age 79.2 y (range, 68–90 y), 54.7% male, 1 center in Japan	Omeprazole 20 mg, amoxycillin 1 g, and clarithromycin 400 mg od for 1 wk	100%	2 y	Histology from 6-monthly upper gastrointestinal endoscopy	Moderate
Uemura 2001[48]	Histology or rapid urease testing, or serology	1246 (253) patients with duodenal ulcer, benign gastric ulcer, gastric hyperplasia, or functional dyspepsia, mean age 52.3 y, 57.3% male, 1 center in Japan	Not reported	Not reported	7.8 y	Histology from upper gastrointestinal endoscopy	Moderate
Hsu 2007[49]	Histology or rapid urease testing	618 (362) patients with duodenal ulcer, benign gastric ulcer, or functional dyspepsia, mean age 53.6 y, 68.6% male, 1 center in Taiwan	Not reported	78.2%	6.4 y	Histology from 1- to 3-yearly upper gastrointestinal endoscopy and cancer registry	Moderate
Ogura 2008[50]	Culture or more than 2 of histology, rapid urease testing, ^{13}Carbon-urea breath testing, or serology	708 (404) patients with previous gastroduodenal disease, gastroduodenal symptoms, abnormal barium meal, or abnormal serum pepsinogen, mean age 62.4 y, 56.5% male, 1 center in Japan	Lansoprazole 30 mg, amoxycillin 750 mg or 1 g, and clarithromycin 400 mg or metronidazole 250 mg bid for 1 wk	100%	3.2 y	Histology from 1-yearly upper gastrointestinal endoscopy	Serious
Mabe 2009[51]	Rapid urease testing	4133 (3781) patients with duodenal ulcer or benign gastric ulcer, mean age 52.9 y, 71.7% male, 82 centers in Japan	Lansoprazole 30 mg or omeprazole 20 mg, amoxicillin 750 mg, and clarithromycin 200 mg or 400 mg bid for 1 wk	64.8%	5.6 y	Histology from 1-yearly upper gastrointestinal endoscopy	Serious

Table 2. Continued

H pylori–positive subjects without gastric neoplasia at baseline							
Study	Method used to confirm presence of *H pylori*	Sample size (no. receiving *H pylori* eradication therapy), characteristics of participants, and location	*H pylori* eradication therapy regimen used	Eradication rate	Mean duration of follow-up	Method of ascertainment of gastric cancer cases	Risk of bias
Yanaoka 2009[52]	Serologic testing	4129 (473) factory workers attending a health check-up, mean age 49.8 y, 100% male, no. of centers not reported, Japan	Omeprazole 20 mg and amoxicillin 750 mg or 500 mg bid for 2 wk, or omeprazole 20 mg, amoxicillin 750 mg, and clarithromycin 200 mg bid for 1 wk	87.2%	9.3 y	Barium X-ray and/or serum pepsinogen screening with upper gastrointestinal endoscopy in screen positives	Serious
Kubota 2017[53]	Not reported	694 (326) patients attending gastric cancer screening, mean age and proportion male not reported, no. of centers not reported, Japan	Not reported	Not reported	2.5 y	1-yearly upper gastrointestinal endoscopy	Moderate
Bae 2018[54]	Serologic testing	24,289 (4535) healthy asymptomatic individuals attending gastric cancer screening, median age 49 y, 62.3% male, 1 center in South Korea	Lansoprazole 30 mg, pantoprazole 40 mg, or omeprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg bid for 1–2 wk	86.0%	6.4 y	Upper gastrointestinal endoscopy during follow-up	Serious
Nam 2019[55]	Histology or rapid urease testing	5110 (2050) healthy individuals attending a comprehensive health check-up, mean age 53.2 y, 59.8% male, 1 center in South Korea	Omeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1 g bid for 1 wk	82.1%	5.5 y	Upper gastrointestinal endoscopy during follow-up	Serious
Li 2023[56,a]	Stool antigen test, Carbon-urea breath test, histology, or rapid urease testing	36,193 (28,484) health plan members undergoing screening for *H pylori* infection, mean age 56.2 y, 46.1% male, 1 healthcare maintenance organization in USA	PPI, amoxicillin, and clarithromycin, or PPI, metronidazole and clarithromycin, or PPI, amoxicillin and metronidazole, or bismuth, metronidazole, and tetracycline for 10 d to 2 wk	Not reported	Mean follow-up duration not reported but 45% had follow-up of 7 y or more	Healthcare maintenance organization cancer registry	Moderate

Table 2. Continued

H pylori–positive subjects without gastric neoplasia at baseline							
Study	Method used to confirm presence of *H pylori*	Sample size (no. receiving *H pylori* eradication therapy), characteristics of participants, and location	*H pylori* eradication therapy regimen used	Eradication rate	Mean duration of follow-up	Method of ascertainment of gastric cancer cases	Risk of bias
Lee 2024[16,a]	Stool antigen testing	12,142 (8809) participants in a colorectal cancer screening program, mean age not reported (range, 50–69 y), 40.4% male, 51 centers in Taiwan	Esomeprazole 40 mg od and amoxicillin 1 g bid for d 1 to 5, then esomeprazole 40 mg od and clarithromycin 500 mg and metronidazole 500 mg bid for d 6–10	90.4%	5.7 y	Cancer registry	Moderate
H pylori–positive patients with gastric neoplasia undergoing EMR at baseline							
Study	Method used to confirm presence of *H pylori*	Sample size (no. receiving *H pylori* eradication therapy), characteristics of participants, and location	*H pylori* eradication therapy regimen used	Eradication rate	Mean duration of follow-up	Method of ascertainment of gastric cancer cases	Risk of bias
Uemura 1997[57] and Uemura 2000[58]	Serologic testing	132 (65) patients, mean age 69 y (range, 44–85 y), 73.5% male, 1 center in Japan	Omeprazole 20 mg and clarithromycin 400 mg od for 2 wk	100%	5 y	Histology from 6-monthly upper gastrointestinal endoscopy	Moderate
Kim 2014[59]	2 or more of histology, rapid urease testing, or serology	156 (68) patients, mean age and proportion male not reported, 1 center in South Korea	Pantoprazole 40 mg, omeprazole 20 mg, or rabeprazole 10 mg, amoxicillin 1 g, and clarithromycin 500 mg bid for 1 wk	72.1%	4.3 y	1-yearly upper gastrointestinal endoscopy	Serious

PPI, proton pump inhibitor.
[a]Supplementary information obtained from the authors.

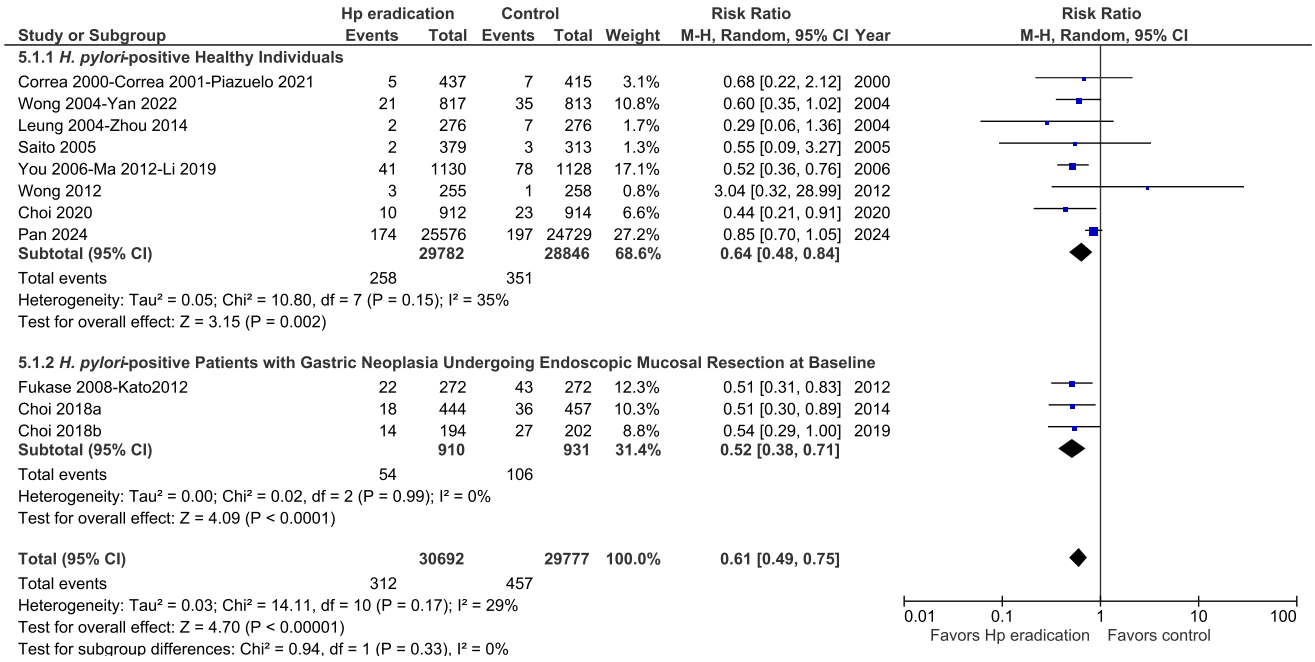

Figure 1. Forest plot of RCTs of *H pylori* eradication therapy: effect on subsequent occurrence of gastric cancer in healthy *H pylori*–positive individuals or *H pylori*–positive patients with gastric neoplasia undergoing EMR.

gastric cancer in 56,606 subjects.[6,15,34–36,38–40,42] Follow-up in these 5 trials ranged from 9.2 years to 26.5 years. Overall, there were 124 deaths (0.43%) due to gastric cancer among 28,730 infected subjects randomized to eradication therapy, compared with 156 (0.56%) deaths in 27,876 participants allocated to placebo or no eradication therapy. The RR of death from gastric cancer with eradication therapy compared with placebo or no eradication therapy was 0.78 (95% CI, 0.62–0.98; Figure 2), with no heterogeneity between studies ($I^2 = 0\%$; $P = .65$). The NNT was 812 (95% CI, 470–8935).

There were 5 RCTs that reported all-cause mortality among 7079 healthy *H pylori*–positive individuals according to treatment allocation.[3––33,35,36,38-42] Follow-up in these 5 RCTs ranged from 5 years to 26.5 years. In total, 420 (11.8%) of 3551 infected subjects receiving eradication therapy were dead at the last point of follow-up, compared with 426 (12.1%) of 3528 individuals receiving placebo or no eradication therapy. The RR of death from any cause at last point of follow-up with eradication therapy compared with placebo or no eradication therapy was 0.98 (95% CI, 0.87–1.11; Figure 3), with no heterogeneity between studies (I^2=0%; $P = .49$).

Effect of Eradication Therapy in Observational Studies

When data were pooled from the 11 observational studies conducted in *H pylori*–positive subjects without gastric neoplasia at baseline,[16,47–56] there were 146 (0.29%) gastric cancers occurring among 49,957 infected subjects who received eradication therapy, compared with 277 (0.70%) in 39,817 individuals who received no eradication therapy. The RR of subsequent occurrence of gastric cancer with eradication therapy vs no eradication therapy was 0.56 (95% CI, 0.43–0.73; Figure 4, Supplementary Figure 3), with no heterogeneity between studies ($I^2 = 0\%$; $P = .60$) but, again, evidence of publication bias, or other small study effects (Egger test; $P = .055$).

When only the 2 observational studies conducted in *H pylori*–positive patients with gastric neoplasia that was

Figure 2. Forest plot of RCTs of *H pylori* eradication therapy: effect on subsequent mortality from gastric cancer in healthy *H pylori*–positive individuals.

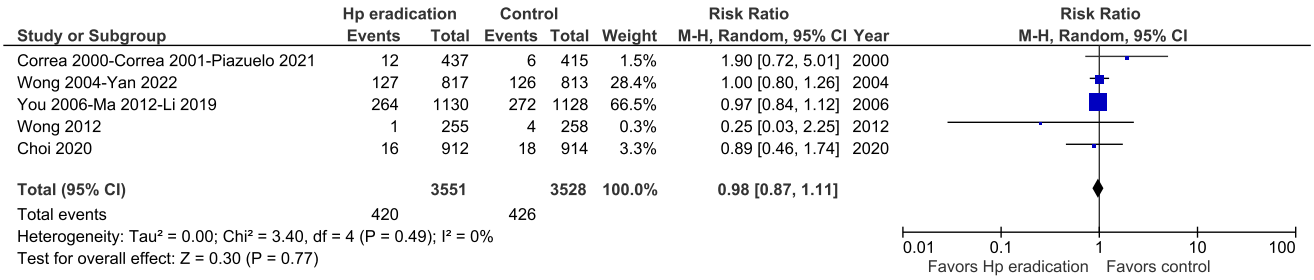

Figure 3. Forest plot of RCTs of *H pylori* eradication therapy: effect on subsequent all-cause mortality in healthy *H pylori*–positive individuals.

suitable for EMR were included,[57–59] there were 3 gastric (2.6%) cancers occurring in 114 patients receiving eradication therapy, compared with 24 (15.5%) of 155 patients who did not receive eradication therapy (RR = 0.19; 95% CI, 0.06–0.61; Figure 4). There was moderate heterogeneity between the effect in *H pylori*–positive patients without gastric neoplasia at baseline compared with that in those having EMR for gastric neoplasia (subgroup heterogeneity $P = .08$; $I^2 = 68\%$).

When we pooled data from all 13 observational studies, reported in 14 articles,[16,47–59] there were 149 (0.30%) gastric cancers occurring among 50,071 infected subjects who received eradication therapy, compared with 301 (0.75%) in 39,972 individuals who received no eradication therapy. The RR of subsequent occurrence of gastric cancer with eradication therapy vs no eradication therapy was 0.53 (95% CI, 0.41–0.68; Figure 4), with no heterogeneity between studies ($I^2 = 0\%$; $P = .45$) but with evidence of publication bias, or other small study effects (Egger test; $P = .015$).

Discussion

We updated our previous meta-analyses examining the impact of *H pylori* eradication therapy on future incidence of gastric cancer and mortality in both *H pylori*–positive individuals without gastric cancer at baseline and *H pylori*–positive patients with gastric neoplasia that was suitable for EMR at baseline. This increased the number of *H pylori*–positive participants included in population-based RCTs from 8323 to 58,628, increasing the robustness of the effect size and the GRADE quality of the evidence from "weak" in our previous systematic review to "moderate." On this occasion, we also included data from observational studies for both groups of subjects. When data were pooled from RCTs conducted among healthy *H pylori*–positive individuals without gastric cancer at baseline, there was a 36% relative risk reduction for future gastric cancer and a 22% reduction in the relative risk of mortality from gastric cancer, but no effect on all-cause mortality. In RCTs conducted among those with gastric neoplasia that was suitable

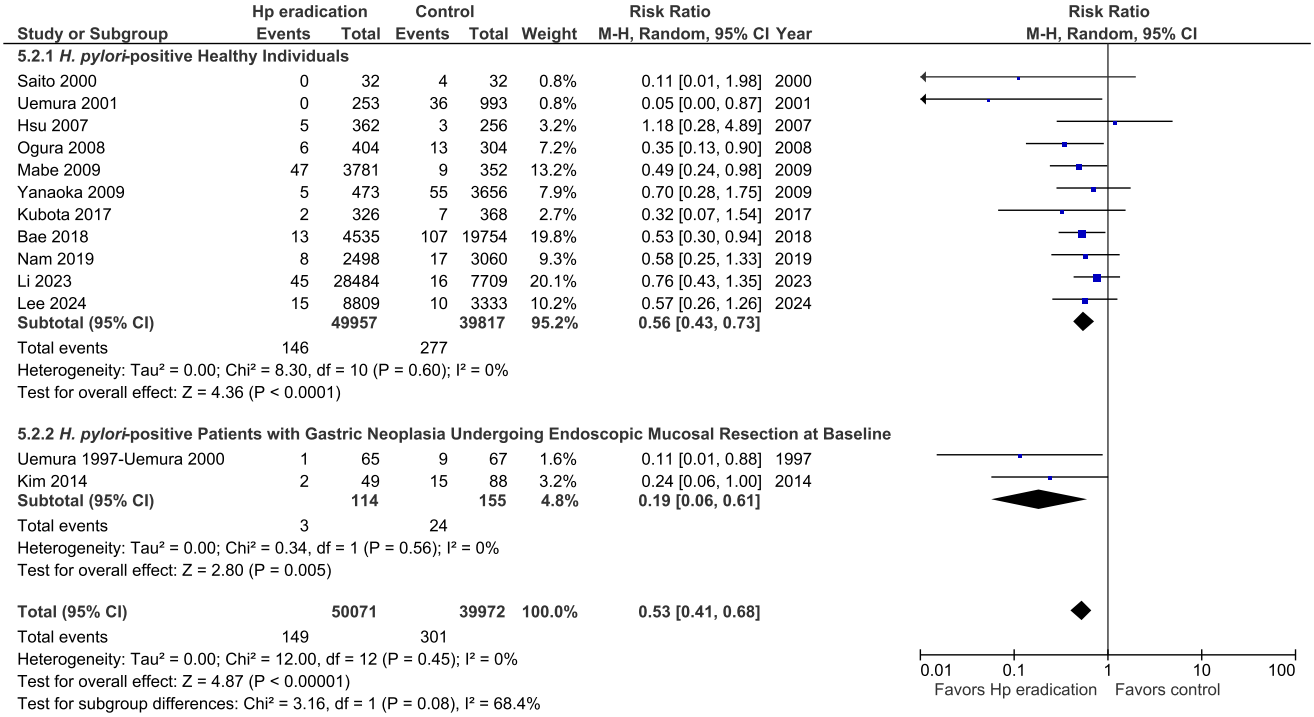

Figure 4. Forest plot of observational studies of *H pylori* eradication therapy: effect on subsequent occurrence of gastric cancer in *H pylori*–positive subjects without gastric neoplasia at baseline or *H pylori*–positive patients with gastric neoplasia undergoing EMR.

for EMR at baseline, there was a 48% relative risk reduction for future gastric cancer. When all RCTs were pooled together, irrespective of the population under study, there was a 39% reduction in the relative risk of future incidence of gastric cancer occurring among those receiving eradication therapy, compared with those receiving placebo or no eradication therapy. When data from observational studies were pooled, there was a 44% reduction in the relative risk of gastric cancer occurring among *H pylori*–positive subjects without gastric neoplasia at baseline receiving eradication therapy, compared with those receiving no eradication therapy, and an 81% relative risk reduction in *H pylori*–positive patients with gastric neoplasia that was suitable for EMR at baseline who received eradication therapy, compared with those who did not, although CIs around this latter estimate were wide. Finally, when data from all observational studies was pooled there was a 47% reduction in the RR of gastric cancer occurring among infected individuals receiving eradication therapy, compared with those receiving no eradication therapy.

This updated meta-analysis included data from a recent cluster-randomized trial, recruiting more than 100,000 healthy *H pylori*–positive individuals.[15] Once we had corrected this to its effective sample size, this meant we included data from RCTs recruiting almost 60,000 healthy *H pylori*–positive individuals without gastric neoplasia at baseline in our analyses examining risk of future incidence of gastric cancer and gastric cancer–related mortality. Broadening our inclusion criteria to observational studies meant that we included data from a further 90,000 *H pylori*–positive individuals, allowing us to replicate the results seen in RCTs, albeit in these less rigorously conducted studies, but with a possibly more representative general population. To ensure as similar populations as possible in the observational studies, we only included studies that compared gastric cancer incidence in *H pylori*–positive adults receiving eradication therapy with the incidence among infected patients who did not receive eradication therapy. Studies that compared gastric cancer incidence among patients with successful eradication therapy with patients with unsuccessful eradication therapy were ineligible. We contacted authors of 3 studies to obtain supplementary data to maximize the number of studies eligible for inclusion.[15,16,56] Finally, by using a random effects model and a modified intention-to-treat analysis, we minimized the possibility that the effect of eradication therapy on the future incidence of gastric cancer, or gastric cancer–related mortality, has been overestimated.

Only 2 of the studies were conducted outside East Asia,[31,56] meaning that we have very limited data assessing the effect of eradicating *H pylori* on gastric cancer incidence outside this region. In terms of the quality assessment of the RCTs we identified, only 5 trials were at low risk of bias, all of which recruited healthy *H pylori*–positive individuals without gastric neoplasia at baseline,[35,39–42] and all of the observational studies were at moderate or serious risk of bias. The RCTs at low risk of bias showed a similar effect on reducing the incidence of gastric adenocarcinoma, suggesting study quality did not impact the conclusions of the review. Our previous meta-analysis was published in 2020,[14] and this update included 1 new trial and 1 extended report from a prior eligible RCT.[15,36] A search of clinicaltrials.gov and the UK Clinical Study Registry reveals 3 ongoing trials in this area, which are being conducted in the UK (ISRCTN71557037), South Korea (NCT02112214), and China (NCT01133951), which are due to report in 2026, 2029, and 2032, respectively. Finally, we examined the effect of *H pylori* eradication therapy, rather than successful eradication of *H pylori*, on the future incidence of gastric cancer due to the way individual RCTs reported data.

In the largest trial conducted, to date, which recruited more than 100,000 healthy infected individuals in China, the effect of eradication therapy in terms of preventing future incidence of gastric cancer was not significant, once we corrected the cluster-randomized design to its effective sample size.[15] This RCT used an active treatment in both arms, with the comparator consisting of a combination of omeprazole and bismuth because it was considered unethical to provide placebo or no treatment. However, bismuth is thought to have bactericidal effects,[63] and this is supported by the fact that 15% of the control arm were *H pylori*-negative post-treatment. This, together with the fact that the eradication rate in the arm receiving eradication therapy was only 72.9%, could have attenuated the difference in effect between the eradication therapy arm of the trial and the control arm. In addition, no endoscopic screening was undertaken at trial entry to exclude individuals with gastric cancer at baseline, meaning this RCT may have included prevalent, as well as incident, cases.

Another trial from Taiwan, published only recently, was unable to be included in the meta-analysis of RCTs.[16] This compared the effect of a strategy of inviting individuals eligible for FIT for colorectal cancer screening to provide both a FIT and a stool sample for *H pylori* antigen testing vs providing a FIT alone, and so the infection status of individuals providing a FIT only was unknown. However, we were able to contact the authors to obtain extra data for infected individuals according to treatment status for this RCT and included it as an observational study. Due to the low numbers of events in many of the studies included in this review, heterogeneity between them may have been underestimated.[64] In addition, where events of interest are rare, meta-analyses are also vulnerable to sparse data bias, which can lead to inflation of summary estimates.[65]

Due to changing global population demographics, it is estimated that the number of incident cases of gastric cancer will increase from 968,000 in 2022 to 1.8 million in 2050, and mortality from gastric cancer will increase from 660,000 in 2022 to 1.3 million in 2050.[66] Our results provide further support for screening for and treating *H pylori* to reduce the future incidence of gastric cancer in healthy infected individuals from populations at moderate to high risk of gastric cancer. They also provide additional evidence that, among *H pylori*–positive patients with dysplasia or early gastric cancer that is suitable for EMR, eradication therapy reduces the incidence of metachronous gastric cancer. The latter observation is likely to be only of relevance in populations where endoscopic screening for gastric

cancer is carried out, such as Japan and South Korea, in whom these types of lesions are most likely to be detected.

Given that most *H pylori* is acquired in childhood,[67,68] and that after successful eradication reinfection is unlikely, irrespective of country of residence,[10,69] any screening program would only need to be conducted once in each individual's lifetime. Several economic modeling studies have suggested this would be cost-effective,[70–75] and our previous meta-analysis estimated that there would be approximately 9 million disability-adjusted life years gained globally if such a screening program were to be implemented.[14] Although earlier screening for, and treatment of, *H pylori* may give the greatest chance of preventing stepwise progression from atrophy to intestinal metaplasia, to dysplasia, to cancer,[76] our data demonstrate that eradication therapy reduces future incidence of gastric cancer significantly, even among patients with dysplasia or early gastric cancer that is suitable for EMR. This contrasts with the point of no return theory,[77,78] where it is proposed that eradication of *H pylori* cannot reverse the changes in the gastric mucosa, although trials of eradication therapy conducted specifically in infected patients with gastric atrophy or intestinal metaplasia that report gastric cancer incidence would be required to disprove this.

Therefore, in summary, this updated systematic review and meta-analysis provides further evidence that administering *H pylori* eradication therapy to healthy infected individuals and infected patients with dysplasia or early gastric cancer that is suitable for EMR leads to significant reductions in the future incidence of gastric cancer and gastric cancer–related mortality, although not in all-cause mortality. There was consistency between the results of RCTs and observational studies. Thus, the increased sample size and confirmation of an effect in studies of different designs increases our confidence in the interpretation of the results. However, due to a scarcity of studies from other countries, these results may not apply to regions other than East Asia. There remain ongoing RCTs, and we will continue to update this work as the results of these are reported. In the meantime, countries at moderate to high risk of gastric cancer should consider adopting population-based screening and treatment programs for *H pylori* as a means of preventing gastric cancer.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.12.033.

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Conflicts of interest

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Data Availability

Study data will be made available to other investigators on reasonable request.