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Association of Barrett's esophagus with *Helicobacter pylori* infection: a meta-analysis

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Abstract

Background and Aims: Barrett's esophagus (BE) is the only recognized precursor for esophageal adenocarcinoma. *Helicobacter pylori* (*H. pylori*) infection is a major contributing factor towards upper gastrointestinal diseases, but its relationship with BE remains controversial. Some previous studies suggested that *H. pylori* infection negatively correlated with BE, while others did not. This may be attributed to the difference in the selection of control groups among studies. The present meta-analysis aims to clarify their association by combining all available data from well-designed studies.

Methods: The *PubMed*, *EMBASE*, and *Cochrane Library* databases were searched. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled by a random-effects model. Heterogeneity was evaluated using the Cochran's Q test and I^2 statistics. Meta-regression, subgroup, and leave-one-out sensitivity analyses were employed to explore the sources of heterogeneity.

Results: Twenty-four studies with 1,354,369 participants were included. Meta-analysis found that patients with BE had a significantly lower prevalence of *H. pylori* infection than those without (OR = 0.53, 95% CI = 0.45–0.64; $p < 0.001$). The heterogeneity was statistically significant ($I^2 = 79\%$; $p < 0.001$). Meta-regression, subgroup, and leave-one-out sensitivity analyses did not find any source of heterogeneity. Meta-analysis of 7 studies demonstrated that CagA-positive *H. pylori* infection inversely correlated with BE (OR = 0.25, 95% CI = 0.15–0.44; $p = 0.000$), but not CagA-negative *H. pylori* infection (OR = 1.22, 95% CI = 0.90–1.67; $p = 0.206$). Meta-analysis of 4 studies also demonstrated that *H. pylori* infection inversely correlated with LSBE (OR = 0.39, 95% CI = 0.18–0.86; $p = 0.019$), but not SSBE (OR = 0.73, 95% CI = 0.30–1.77; $p = 0.484$).

Conclusion: *H. pylori* infection negatively correlates with BE. More experimental studies should be necessary to elucidate the potential mechanisms in future.

Keywords: Barrett's esophagus, esophageal adenocarcinoma, gastroesophageal reflux disease, *Helicobacter pylori*, meta-analysis

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Introduction

Barrett's esophagus (BE), a precancerous lesion of esophageal adenocarcinoma (EAC), is defined as the squamous epithelium replaced by specialized intestinal metaplasia (IM).[1] It is often asymptomatic and can only be diagnosed by endoscopy.[2] Risk factors of BE include age greater than 50 years, male, smoking, white race, gastroesophageal reflux disease (GERD), high body mass index (BMI), and hiatal hernia.[3] Its prevalence is approximately 10% to 15% in patients with GERD.[4,5]

Helicobacter pylori (*H. pylori*), a gram-negative microaerophilic bacterium, influences at least 50% of the world's population.[6] At present, *H. pylori* is the most common causative agent of infection-associated cancers, accounting for 5.5% of the global cancer burden.[7] The importance of *H. pylori* in upper gastrointestinal pathology is undoubted, because it can lead to gastric and duodenal ulcers, mucosa-associated tissue lymphoma, non-Hodgkin's lymphoma of the stomach, and gastric adenocarcinoma.[8] Nevertheless, the relationship between

H. pylori and esophagus diseases, especially BE, remains controversial.[9] Some studies have reported that *H. pylori* is a risk factor for BE,[10,11] while others have inferred that *H. pylori* has a protective effect on BE[12,13] and that *H. pylori* infection may not be associated with BE.[14,15] Until now, several meta-analyses have explored their association. However, among these meta-analyses, not all control subjects have undergone endoscopy, which may cause missed diagnoses of GERD or peptic ulcer, thereby overestimating or underestimating the effect of *H. pylori* infection on BE. Therefore, we have comprehensively collected the most recent data from well-designed studies and conducted a meta-analysis to analyze the correlation between *H. pylori* and BE.

Methods

The meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The PRISMA checklist is shown in **Supplementary Material**.

Registration

The meta-analysis was registered in **PROSPERO** with a registration number of CRD42021241042.

Literature search

All relevant papers regarding the prevalence of *H. pylori* infection in patients with and without BE were searched in the *PubMed*, *EMBASE*, and *Cochrane Library* databases. The search was performed using the following terms: ('Helicobacter pylori' OR 'H pylori' OR 'H. pylori' OR 'Helicobacter' OR 'Campylobacter Pylori') AND ('Barrett esophagus' OR 'Barrett' OR 'Barrett metaplasia' OR 'Barrett oesophagus'). The last search was conducted on November 11, 2021. There was no language restriction.

Selection criteria

Inclusion criteria were as follows: (1) observational (case-control or cross-sectional) studies, (2) all participants should undergo upper gastrointestinal endoscopy, (3) studies should compare the prevalence of *H. pylori* infection between participants with and without BE, and (4) *H. pylori* infection should be confirmed by histology, rapid urease test, culture, stool antigen test, and/or serology.

Exclusion criteria were as follows: (1) duplicated studies; (2) reviews and meta-analyses; (3) case reports; (4) guidelines, consensus, or reports; (5) editorials, comments, letters, or notes; (6) experimental or animal studies; (7) studies which did not explore the association between *H. pylori* infection and BE; (8) participants had peptic ulcer or gastric cancer; (9) participants in control groups did not undergo upper gastrointestinal endoscopy; (10) participants in control groups had GERD; (11) overlapping participants among studies; and (12) absence of relevant data.

Data extraction

The following data were extracted from the included studies: first author, publication year, country, study design, number of participants in case and control groups, the prevalence of *H. pylori* infection in the 2 groups, methods and biopsy sites for detecting *H. pylori* infection, diagnostic criteria for BE, diagnostic timing of BE, whether age and gender were matched between participants with and without BE, whether participants with a history of *H. pylori* eradication therapy were excluded, whether participants who used proton pump inhibitors (PPIs) within at least 2 weeks before detection of *H. pylori* infection were excluded, and the prevalence of *H. pylori* infection according to the segment lengths of BE and status of cytotoxin-associated gene A (CagA).

Study quality assessment

The quality of included case-control studies was assessed by the Newcastle-Ottawa Scale (NOS), which includes study selection (4 points), comparability (2 points), and exposure (3 points). The maximum NOS score is 9. A score of 0–3, 4–6, and 7–9 represents low, moderate, and high quality, respectively.

The quality of included cross-sectional studies was assessed with 11 items formulated by the Agency for Healthcare Research and Quality (AHRQ), which are answered with "yes", "no", or "unclear". The maximum AHRQ score is 11. A score of 0–3, 4–7, and 8–11 represents low, moderate, and high quality, respectively.

Statistical analyses

All statistical analyses were performed using Review Manager software (Version 5.4, Cochrane collaboration, the Nordic Cochrane Center, Copenhagen, Denmark) and Stata software (Version 12.0, Stata Corp, College Station, USA). We pooled the odds ratios (ORs) and 95% confidence intervals (CIs) by using a random-effects model. Forest plots were constructed for a visual display of ORs of individual studies. The Cochrane Q test and I^2 statistics were employed to assess the heterogeneity. $I^2 > 50\%$ and/or $p < 0.1$ were considered to have statistically significant heterogeneity. Leave-one-out sensitivity analyses were assessed by sequentially omitting 1 study each time. Subgroup analyses were performed according to study design (case-control vs cross-sectional), publication year (before 2010 vs after 2010), region (Asia vs Europe vs America), country (Eastern vs Western), methods for detecting *H. pylori* (histology/rapid urease test vs serology vs $\geqslant 2$ diagnostic methods), sample size ($<10{,}000$ vs $>10{,}000$), number of biopsy sites for detecting *H. Pylori* (1 vs $\geqslant 2$), diagnostic criteria for BE (IM vs CM), diagnostic timing of BE (newly vs previously diagnosed), whether age and gender were matched between patients with and without BE (matched vs unmatched), participants with a history of *H. pylori* eradication therapy (excluded vs not excluded), and participants who used PPIs within at least 2 weeks before detection of *H. pylori* infection (excluded vs not excluded). The interaction between subgroups was tested. Meta-regression analyses were also employed according to the variables mentioned above. Publication bias among the included studies was checked by the Egger test. $p < 0.1$ was considered as a statistically significant publication bias. In addition, the prevalence of *H. pylori* infection according to different segment lengths of BE (LSBE vs SSBE) and status of CagA (CagA-positive vs CagA-negative) were also compared.

Results

Study selection

Our initial search identified 2,422 studies from the *PubMed, EMBASE*, and *Cochrane Library* databases, and 1 study from hand-searching. Finally, 24 studies with 1,354,369 participants were included (Figure 1). Notably, 2 of them had

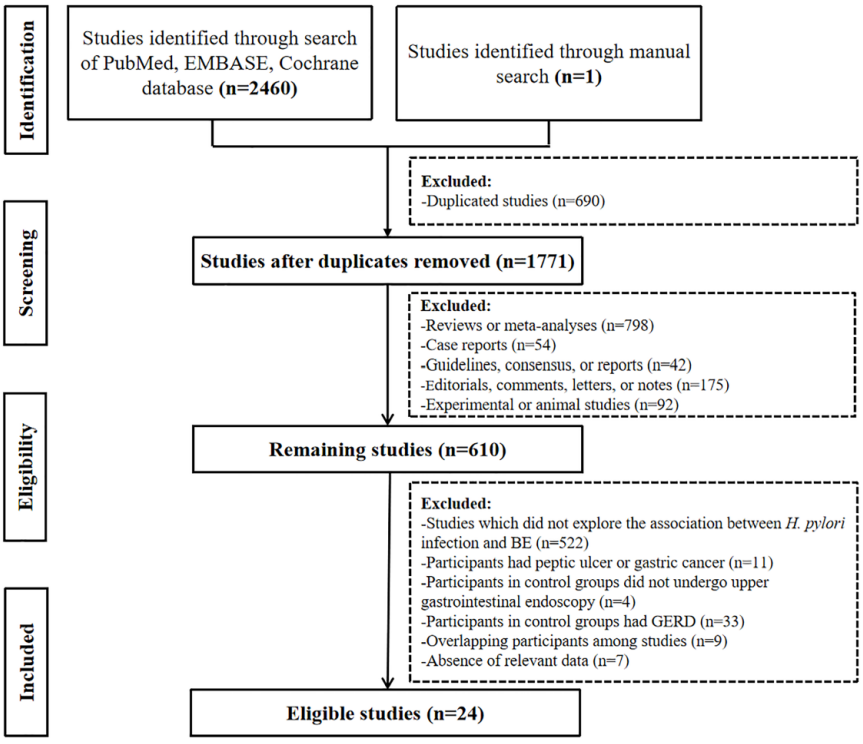

Figure 1. A flowchart of study inclusion.

overlapping participants, but explored different variables. One had a larger sample size, but just provided the data in LSBE participants;[16] and the other had a smaller sample size, but specifically compared the prevalence of *H. pylori* infection according to different segment lengths of BE.[17]

Study characteristics

Characteristics of the included studies were shown in Table 1. Among them, 14 studies were case-control studies, and 9 were cross-sectional studies. They were published between 1988 and 2020. Five studies were performed in Asia,[16,19,22,25,27] 11 in Europe,[20,23,26,28–30,32–34,36,37] and 7 in America.[12,18,21,24,31,35,38]

Study quality

Among the case-control studies, 8 and 6 were of moderate and high quality, respectively (Supplementary Table 1). Among the cross-sectional studies, 3 and 6 were of moderate and high quality, respectively (Supplementary Table 2).

Meta-analyses in overall patients

Meta-analysis demonstrated a significantly lower prevalence of *H. pylori* infection in patients with BE than those without (OR = 0.53, 95% CI = 0.45–0.64; $p < 0.001$). The heterogeneity was statistically significant (I^2=79%; $p < 0.001$) (Figure 2).

Results of sensitivity analyses were shown in Supplementary Table 3. After omitting each study, the heterogeneity remained statistically significant.

Results of subgroup analyses were shown in Table 2. Regardless of study design, publication year, region, country, diagnostic methods of *H. pylori* infection, sample size, number of biopsy sites for detecting *H. pylori*, diagnostic criteria for BE, diagnostic timing of BE, age and gender matched between 2 groups, participants with a history of *H. pylori* eradication therapy, and participants who used PPIs within at least 2 weeks before detection of *H. pylori* infection, meta-analyses demonstrated a significantly lower prevalence of *H. pylori* infection in patients with BE than those without. The interaction between subgroups was only significant in the subgroup analysis according to the sample size ($p = 0.002$), but not in others.

Table 1. Summary of baseline characteristics of the prevalence of *H. pylori* infection in patients with and without BE.

First author	Country	Study design	BE on endoscopy		Prevalence of *H. pylori* infection		Methods for detection of *H. pylori*	Biopsy sites for detecting *H. pylori*	Diagnostic criteria for BE	Diagnostic timing of BE	Age and gender matched between 2 groups	Exclusion criteria for participants	
			BE	No BE	BE	No BE						History of *H. pylori* eradication therapy	Using PPIs within at least 2 weeks before detection of *H. pylori* infection
Turner *et al.*[18]	USA	Cross-sectional	52186	1207207	2332/52186	126351/1207207	H	Antral, corpus, and angus	IM	NA	No	No	No
Zhang *et al.*[19]	China	Case-control	40	40	15/40	23/40	H, R	Esophageal and antral	CM	NA	No	No	No

(Continued)

Table 1. (Continued)

First author	Country	Study design	BE on endoscopy		Prevalence of *H. pylori* infection		Methods for detection of *H. pylori*	Biopsy sites for detecting *H. pylori*	Diagnostic criteria for BE	Diagnostic timing of BE	Age and gender matched between 2 groups	Exclusion criteria for participants	
			BE	No BE	BE	No BE						History of *H. pylori* eradication therapy	Using PPIs within at least 2 weeks before detection of *H. pylori* infection
Xu *et al.*[20]	UK	Cross-sectional	38	202	3/38	34/202	R, S	NA	IM	NA	No	No	No
Tan *et al.*[21]	USA	Cross-sectional	329	1856	68/329	606/1856	H	Antral, corpus, and cardia	IM	Previously	No	No	No
Chen *et al.*[22]	China	Case-control	161	644	42/148	261/588	R	Antral	IM	NA	Yes	No	Yes
Dore *et al.*[23]	Italy	Cross-sectional	133	1772	49/131	669/1772	H, R, U	Antral and corpus	IM	Newly	No	No	Yes
Rubenstein *et al.*[12]	USA	Case-control	150	177	25/150	46/177	S	NA	IM	Newly	No	No	No
Sonnenberg *et al.*[24]	USA	Cross-sectional	2510	76475	144/2510	9356/76475	H	Antral, corpus, and angus	IM	Previously	No	No	No
Abe *et al.*[16]	Japan	Case-control	36	108	4/36	80/108	H, S, R	Antral, corpus	CM	Newly	Yes	Yes	Yes
Rajendra *et al.*[25]	Malaysia	Case-control	55	53	29/55	32/53	H, S, R	Antral, corpus, and cardia	IM	Previously	No	Yes	Yes
§Inomata *et al.*[17]	Japan	Case-control	36	80	3/36	57/80	H, S, R	Antral, corpus	IM	NA	No	Yes	Yes
Loffeld *et al.*[26]	Netherlands	Cross-sectional	307	5341	55/179	1550/3975	H, C	Antral	NA	Previously	No	No	No
Rajendra *et al.*[27]	Malaysia	Case-control	123	1741	46/123	604/1741	H, R	Antral and corpus	IM	NA	No	Yes	Yes
Ackermark *et al.*[28]	Netherlands	Cross-sectional	51	62	21/51	39/62	S	NA	IM	NA	No	No	No
Laheij *et al.*[29]	Netherlands	Cross-sectional	23	528	6/23	281/528	H, C, R	Antral and corpus	CM	NA	No	Yes	No

(Continued)

Table 1. (Continued)

First author	Country	Study design	BE on endoscopy		Prevalence of *H. pylori* infection		Methods for detection of *H. pylori*	Biopsy sites for detecting *H. pylori*	Diagnostic criteria for BE	Diagnostic timing of BE	Age and gender matched between 2 groups	Exclusion criteria for participants	
			BE	No BE	BE	No BE						History of *H. pylori* eradication therapy	Using PPIs within at least 2 weeks before detection of *H. pylori* infection
Rugge *et al.*[30]	Italy	Case-control	53	53	19/53	36/53	H, S, P	Antral, corpus, and incisural	IM	NA	Yes	Yes	Yes
Vaezi *et al.*[31]	USA	Case-control	83	60	28/83	25/60	H, S	Antral, corpus	CM	Previously	No	Yes	No
Loffeld *et al.*[32]	Netherlands	Cross-sectional	36	454	14/36	248/454	H, S, R, C	Antral	CM	Newly	No	Yes	Yes
Vieth *et al.*[33]	Germany	Case-control	1054	712	562/1054	468/712	H	Antral and corpus	IM	Previously	No	No	No
Kiltz *et al.*[34]	Germany	Case-control	35	320	8/35	91/320	R, S	Antrum and corpus	CM	Previously	No	Yes	No
Vicari *et al.*[35]	USA	Case-control	48	57	15/48	26/57	H, S	Antral, fundus, and cardia	CM	Previously	No	No	No
Werdmuller *et al.*[36]	Netherlands	Case-control	13	399	3/13	204/399	H, R, C, S	Antral	NA	NA	No	No	No
Newton *et al.*[37]	UK	Case-control	16	25	4/16	9/25	H, R	Antral and fundus	CM	Previously	No	No	Yes
Paull *et al.*[38]	USA	Case-control	26	26	10/26	11/26	H	Gastric and esophageal	CM	Previously	Yes	No	No

§Study only in the analysis for BE segment length.
BE, Barrett's esophagus; C, culture; CM, columnar metaplasia; H, histology; IM, intestinal metaplasia; PCR, polymerase chain reaction; PPIs, proton pump inhibitors; S, serology; SA, stool antigen; R, rapid urease test; U, urea breath test.

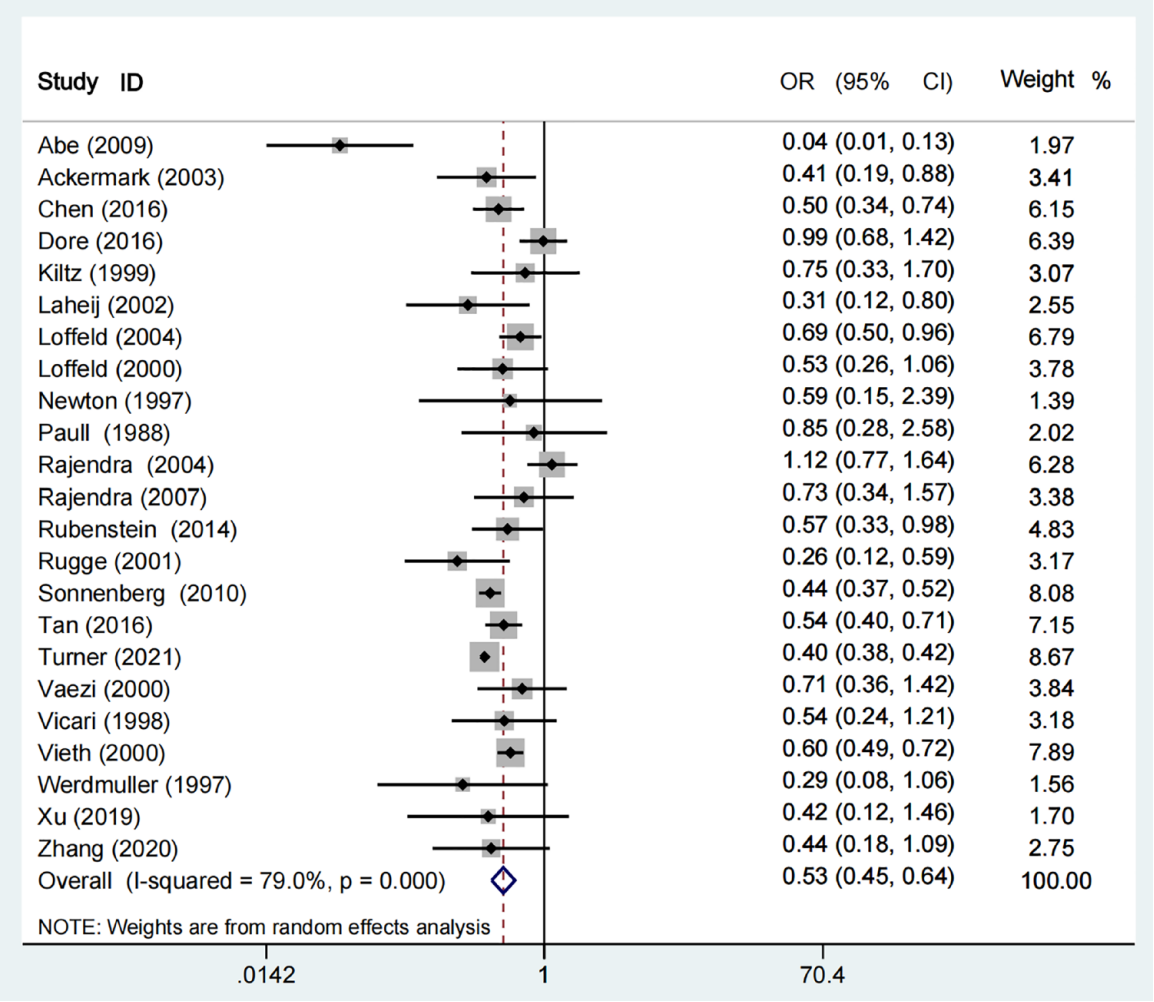

Figure 2. Forest plots showing the association of *H. pylori* infection with BE.

Meta-regression analyses did not find any source of heterogeneity (Supplementary Table 4). Egger test showed significant evidence of publication bias ($p = 0.043$).

Meta-analyses regarding association of CagA status with BE

Seven studies compared the prevalence of *H. pylori* infection according to different status of CagA (Supplementary Table 5). There was a significantly lower prevalence of CagA-positive *H. pylori* infection in patients with BE than those without BE (OR = 0.25, 95% CI = 0.15–0.44; $p = 0.000$). The heterogeneity was not statistically significant ($I^2 = 42\%$; P = 0.111) (Supplementary Figure 1). By contrast, the prevalence of CagA-negative *H. pylori* infection was statistically similar between patients with and without BE (OR = 1.22, 95% CI = 0.90–1.67; $p = 0.206$). The heterogeneity was not statistically significant ($I^2 = 0\%$; $p = 0.881$) (Supplementary Figure 2).

Meta-analyses regarding association of H. pylori *with BE segment lengths*

Four studies compared the prevalence of *H. pylori* infection according to different segment lengths of BE (Supplementary Table 6). There was a significantly lower prevalence of *H. pylori* infection in patients with LSBE than those without BE (OR = 0.39, 95% CI = 0.18–0.86; $p = 0.019$). The heterogeneity was statistically significant ($I^2 = 66\%$; $p = 0.033$) (Supplementary Figure 3). By contrast, the prevalence of *H. pylori* infection was statistically similar between patients with SSBE and those without BE (OR = 0.73, 95% CI = 0.30–1.77; $p = 0.484$). The heterogeneity was statistically

Table 2. Results of subgroup analyses regarding the association of *H. pylori* infection with BE.

Groups	No. Studies	OR (95%CI)	Heterogeneity		$P_{interaction}$
			I^2 (%)	*p* value	
Total	23	0.53 (0.45-0.64; $p < 0.001$)	79%	<0.001	
Study design					0.940
Case-control	14	0.53 (0.39–0.71; $p < 0.001$)	67%	<0.001	
Cross-sectional	9	0.52 (0.42–0.65; $p < 0.001$)	79%	<0.001	
Publication year					0.870
After 2010	8	0.51 (0.42–0.63; $p < 0.001$)	76%	<0.001	
Before 2010	15	0.53 (0.40–0.70; $p < 0.001$)	66%	<0.001	
Region					0.220
Asia	5	0.43 (0.20–0.93; $p = 0.030$)	88%	<0.001	
Europe	11	0.58 (0.46–0.73; $p < 0.001$)	39%	0.090	
America	7	0.46 (0.40–0.53; $p < 0.001$)	46%	0.080	
Country					0.580
Eastern	5	0.43 (0.20–0.93; $p = 0.030$)	88%	<0.001	
Western	18	0.54 (0.45–0.64; $p < 0.001$)	72%	<0.001	
Diagnostic methods of *H. Pylori*					0.900
Histology/RUT	6	0.48 (0.41–0.58; $p < 0.001$)	77%	<0.001	
Serology	3	0.50 (0.33–0.76; $p = 0.001$)	0%	0.770	
⩾ 2 diagnostic methods	14	0.53 (0.38–0.74; $p < 0.001$)	71%	<0.001	
Sample size					***0.002***
> 10000	2	0.40 (0.39–0.42; $p < 0.001$)	0%	0.330	
< 10000	21	0.56 (0.46–0.68; $p < 0.001$)	61%	<0.001	
Number of biopsy sites for detecting *H. Pylori*					0.610
1	4	0.58 (0.46–0.73; $p < 0.001$)	0%	0.400	
⩾ 2	16	0.54 (0.43–0.67; $p < 0.001$)	84%	<0.001	
Diagnostic criteria for BE					0.410
IM	12	0.56 (0.45–0.69; $p < 0.001$)	85%	<0.001	
CM	9	0.44 (0.27–0.73; $p = 0.001$)	64%	0.005	
Diagnostic timing of BE					0.450
Newly diagnosed	4	0.39 (0.15–0.98; $p < 0.001$)	89%	<0.001	

(Continued)

Table 2. (Continued)

Groups	No. Studies	OR (95%CI)	Heterogeneity		$P_{interaction}$
			I^2 (%)	*p* value	
Previously diagnosed	11	0.55 (0.48–0.63; $p<0.001$)	17%	0.280	
Age and gender matched between 2 groups					0.160
Matched	4	0.28 (0.10–0.76; $p<0.001$)	84%	<0.001	
Unmatched	19	0.58 (0.48–0.69; $p<0.001$)	79%	<0.001	
Participants with a history of *H. pylori* eradication therapy					0.570
Excluded	8	0.45 (0.25–0.81; $p=0.008$)	82%	<0.001	
Not excluded	15	0.54 (0.45–0.64; $p<0.001$)	75%	<0.001	
Participants who used PPIs within at least 2 weeks before detection of *H. pylori* infection					0.910
Excluded	8	0.50 (0.29–0.83; $p=0.008$)	83%	<0.001	
Not excluded	15	0.51 (0.44–0.60; $p<0.001$)	63%	<0.001	

BE, Barrett's esophagus; CM, columnar metaplasia; IM, intestinal metaplasia; OR, odds ratio; PPIs, proton pump inhibitors; RUT, rapid urease test.

significant ($I^2=76\%$; $p=0.005$) (Supplementary Figure 4). It is inappropriate to conduct meta-regression analyses to explore the sources of heterogeneity since only 4 studies were included.[39]

Discussion

This is an updated meta-analysis which more comprehensively searched relevant studies to explore the relationship between *H. pylori* infection and BE. Our study found that the prevalence of *H. pylori* infection was significantly lower in patients with BE than those without, suggesting that *H. pylori* infection is inversely related to BE.

Seven previous meta-analyses were performed to explore the relationship between *H. pylori* infection and BE. However, their conclusions were inconsistent. The meta-analysis by Wang *et al.*[40] demonstrated no association of *H. pylori* infection with BE; by comparison, 6 others reported a significantly lower prevalence of *H. pylori* infection in patients with BE than those without.[41–46]

Our current meta-analysis has several advantages as compared to previous ones. First, there was a more comprehensive collection of eligible studies by expanding the search strategy and updating the final search date. Second, a larger number of subgroup analyses were planned to further explore the association between *H. pylori* infection and BE according to the 12 prespecified co-variates. More importantly, the interaction between subgroups was also tested to infer whether the protective effect of *H. pylori* infection on BE differs among subgroups, which has not been performed in 7 previous meta-analyses yet. Third, meta-regression analyses, an important statistical method for analyzing the source of heterogeneity, were performed in our meta-analysis, but have not been done in previous meta-analyses yet. Fourth, the selection of eligible participants in our meta-analysis is more reasonable and rigorous. In details, all participants included should have undergone upper gastrointestinal endoscopy; all participants included should not have been diagnosed with gastric cancer or peptic ulcer; and the participants included in control groups should not have been diagnosed with GERD. Such considerations are very important to eliminate the effects of these potential confounding factors on the reliability of our findings. By comparison, these selection criteria have not been employed by previous meta-analyses yet. More importantly, a remarkable negative correlation between *H. pylori* infection and BE has been observed in all of our subgroup analyses, strengthening the robustness of our conclusion.

Currently, the pathogenesis of BE is primarily attributed to frequently transient lower esophageal sphincter (LES) relaxation, which leads to gastric acid reflux, resulting in esophageal mucosa injury.[47,48] The protective effect of *H. pylori* infection on BE may be explained by its secondary reduction in gastric acid secretion and reflux.

First, there are several possible mechanisms that *H. pylori* infection protects against BE by reducing gastric acid secretion, as follows: (1) fatty acids produced by *H. pylori* can directly inhibit parietal cell function, and then reduce gastric acid secretion;[49] (2) cytokines, such as TNF-α and IL-1ß, resulting from corpus-predominant gastritis caused by *H. pylori* infection, can also inhibit parietal cell function, thereby reducing gastric acid secretion;[50,51] (3) long-term colonization of *H. pylori* in stomach can cause atrophic gastritis, which reduces the number of parietal cell, further decreasing gastric acid secretion; and (4) ghrelin can protect gastric mucosa[52] and promote gastric acid secretion.[53] *H. pylori* infection causes corpus gastritis and/or gastric atrophic changes,[54,55] leading to the loss of ghrelin producing cells and reduction of plasma ghrelin concentrations, which finally aggravates gastric mucosal damage and reduces gastric acid secretion.

Second, there are some potential mechanisms that *H. pylori* infection protects against BE by reducing gastric acid reflux, as follows: (1) elevated serum gastrin levels in antrum-predominant *H. pylori* gastritis may increase LES pressure, and then reduce gastric acid reflux;[56] and (2) ghrelin may promote food intake.[57] A decreased level of ghrelin secondary to *H. pylori* infection is associated with a reduction of BMI with a lower intra-abdominal pressure which decreases gastric acid reflux.[58] In addition, bile acids in combination with low pH may induce oxidative stress and DNA damage in esophageal cells, resulting in the activation of anti-apoptotic pathways and increased inflammatory response on esophageal tissues.[59] By contrast, reduced bile acids reflux, which can result from increased LES pressure and decreased intra-abdominal pressure caused by *H. pylori* infection, may play an important role in the protective effect on BE.[60–63]

Third, *H. pylori* DNA may directly down-regulate the inflammatory stimulation of type 1 interferon and IL-12 on esophageal mucosa, and then delay the progression of BE.[64,65]

Our meta-analysis demonstrated a significant association of BE with CagA-positive *H. pylori* infection, but not CagA-negative *H. pylori* infection. CagA can encode a high-molecular-weight immunodominant antigen that can induce IL-8 production.[66–68] CagA-positive strains are also associated with enhanced local inflammatory response.[69,70] Hence, CagA-positive *H. pylori* infection induces more severe gastric inflammation and multifocal atrophic gastritis, finally resulting in a reduction of gastric acid secretion.[71,72]

Our meta-analysis also found a significant association of *H. pylori* infection with LSBE, but not SSBE. Unfortunately, there is no direct evidence used to explain this phenomenon. It seems obvious that SSBE has a lower degree of gastric acid exposure than LSBE.[73,74] Accordingly, it is hypothesized that SSBE may be less affected by a reduction of gastric acid secretion and reflux attributed to *H. pylori* infection compared with LSBE. It should be acknowledged that only 4 small studies explored the prevalence of *H. pylori* infection according to different segment lengths of BE. Thus, such statistical results may be unpowered.

Our meta-analysis had several other limitations. First, most of the included studies were retrospective, leading to the selection bias and recall bias. Second, the heterogeneity among studies was significant, in spite of leave-one-out sensitivity and meta-regression analyses. Third, 2 studies[29,37] performed biopsies at different sites to assess *H. pylori* infection and provided more than 1 *H. pylori* infection rate. Only the *H. pylori* infection in the antrum was selected for the present meta-analysis, which may underestimate the prevalence of *H. pylori* infection.[75,76] Forth, the absence of detailed information on race or ethnicity may compromise from estimating the prevalence of *H. pylori* infection in different racial or ethnic groups of BE patients. Fifth, the definitions of BE proposed by current practice guidelines and consensus are different among countries. IM is a required criterion for BE according to the American College of Gastroenterology clinical guideline published 2016,[77] but not the Chinese consensus published 2017.[78] Considering that currently available data regarding association of *H. pylori* with BE are from West, more well-designed studies should be conducted in China.

Our findings indicate an inverse relationship between *H. pylori* infection and BE. Accordingly, it appears that *H. pylori* eradication is not beneficial for the prevention of BE, which is contrary to the recommendations of current practice guidelines and consensus regarding management of *H. pylori* infection.[6] Indeed, other evidence also suggest the benefits of *H. pylori* infection on decreasing the risk of EAC,[79] especially Barrett's adenocarcinoma,[80] and allergic diseases.[81] Therefore, we should re-evaluate the necessity of eliminating this pathogen globally, especially in the West, where gastric adenocarcinoma and peptic ulcer disease are much less prevalent.

Conclusion

The current study suggests that *H. pylori* infection is inversely related to BE. More well-designed prospective cohort studies are required to confirm our findings in future, and experimental studies should also be necessary to elucidate the potential mechanisms.

Abbreviations

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; GERD, gastroesophageal reflux disease; BMI, body mass index; *H. pylori*, *Helicobacter pylori*; PPIs, proton pump inhibitors; CagA, cytotoxin-associated gene A; NOS, Newcastle-Ottawa Scale; AHRQ, Agency for Healthcare Research and Quality; ORs, odds ratios; CIs, confidence intervals; CM, columnar metaplasia; IM, intestinal metaplasia; LES, lower esophageal sphincter; TNF, tumor necrosis factor; IL, interleukin.

Declarations

Ethics approval and consent to participate

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The requirement for approval is waived due to the nature of this article.

Consent for publication

Not applicable.

Author contributions

Shaoze Ma: Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Xiaozhong Guo: Formal analysis; Validation; Writing – review & editing.

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Availability of data and materials

Full datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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