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TITLE PAGE

Title: Systematic review with meta-analysis: Association of *Helicobacter pylori* infection with gastro-oesophageal reflux and its complications.

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SUMMARY

Background: Conflicting results exist on the association between *Helicobacter pylori* (*H. pylori*) infection and gastro-oesophageal reflux (GOR), and its complications, such as erosive oesophagitis (EO) and Barrett's oesophagus (BO).

Aims: To explore the association of *H. pylori* infection with GOR symptoms and their complications.

Methods: We searched Embase, PubMed, Web of Science, and Scopus databases (through December 2020) for relevant articles. Regarding the association between *H. pylori* and GOR symptoms (heartburn, regurgitation, or reflux), we included observational studies comparing the prevalence of GOR symptoms between *H. pylori*-positive and negative individuals. Concerning the association between *H. pylori* and complications of GOR, we included studies comparing prevalence of EO or BO between *H. pylori*-positive and negative individuals.

Results: In total, 36 papers were eligible. Based on seven cross-sectional surveys, *H. pylori* infection was associated with a lower odds of GOR symptoms (odds ratio [OR] 0.74, 95% confidence interval [CI] 0.61–0.90). However, in four case-control studies, *H. pylori* infection was not associated with odds of GOR symptoms (OR 1.10, 95% CI 0.85–0.1.43). In 26 cross-sectional studies in patients with GOR symptoms, the OR for EO was 0.70 (95% CI 0.58–0.84) in *H. pylori*-positive versus negative cases. Based on nine cross-sectional studies in subjects with GOR complications, no significant association was found between *H. pylori* infection and either endoscopically-diagnosed (OR 1.84, 95% CI 0.67–5.02) or histologically-confirmed (OR 0.85, 95% CI 0.60–1.20) BO.

Conclusions: *H. pylori* infection appears to be associated with a decreased odds of GOR symptoms and EO. In contrast, *H. pylori* infection did not seem to affect the odds of BO in patients with GER complications.

Keywords: *Helicobacter pylori,* gastro-oesophageal reflux, erosive reflux disease, Barrett's oesophagus

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is one of the most common gastrointestinal disorders, particularly in western countries. Approximately 15% of the general population is affected by gastro-oesophageal reflux (GOR) symptoms, with a detrimental impact on quality of life among individuals who experience them, as well as a significant economic burden for the community.[1] The chronic nature of GOR symptoms can lead to the development of complications, mainly in the distal oesophagus, such as erosive oesophagitis (EO) or Barrett's oesophagus (BO), the precancerous condition for oesophageal adenocarcinoma.[2] Although the majority of patients who undergo endoscopic evaluation due to GOR symptoms demonstrate normal oesophageal mucosa, and are usually labelled as having non-erosive reflux disease (NERD), EO is found in up to 30% of GORD patients, and between 3% and 14% are found to have histologically-confirmed BO.[3,4] Many factors have been associated with an increased risk of GORD, and its complications, including alcohol consumption, presence of hiatus hernia, and obesity.[5-7]

Due to its pivotal role in gastric inflammation and carcinogenesis, *Helicobacter pylori* (*H. pylori*) infection has also been evaluated as a possible factor related to oesophageal diseases. Infection with this bacterium has been inversely associated with GORD and BO, particularly the cagA+ strain, as it is thought that the resultant chronic gastritis reduces total acid production and, therefore, acid reflux.[8-10] Numerous studies have been conducted to assess the relationship between *H. pylori* infection and GOR with conflicting results, questioning whether *H. pylori* infection truly protects against the development of GOR and its complications. For instance, some studies alluded to a protective effect of *H. pylori* infection against GOR symptoms,[11,12] but others have not shown this effect.[13,14] Conflicting results were also reported concerning the relationship between BO and *H. pylori* by two meta-analyses; Wang *et al.* found no clear

association between *H. pylori* infection and BO pooling data from 12 case-control studies,[15] whereas Fischbach *et al.* reported that *H. pylori* might be protective for BO.[16]

A considerable amount of data has been published in the interim, and a more recent meta-analysis by Erőss *et al*. concluded that *H. pylori* infection was associated with a reduced risk of BO.[17] However, most of the studies included in this meta-analysis used control groups recruited opportunistically, or populations that would not be likely to provide a true background prevalence of *H. pylori.* To overcome these issues, we conducted a contemporaneous systematic review and meta-analysis of observational studies to examine the association between *H. pylori* infection and the presence of GOR symptoms. We also aimed to evaluate the association between *H. pylori* infection and GOR complications, specifically EO and BO.

METHODS

Study Protocol

This systematic review and meta-analysis was performed according to the meta-analyses of observational studies in epidemiology (MOOSE) guideline.[18] The protocol was registered online in PROSPERO (CRD42020209577 and CRD42018109780).

Information Sources and Search Strategy

We searched the published literature from inception to 31st December 2020 using Embase, PubMed, Web of Science, and Scopus, without language restrictions. The full search strategy is provided in the Supplement. We also performed a hand search of the reference lists of relevant review articles and the retrieved papers to capture additional studies.

Inclusion and Exclusion Criteria

We had two separate aims. The first was to determine the association between *H. pylori* infection and GOR symptoms in the general population. We included observational studies (cross-sectional surveys, or cohort or case-control studies) recruiting ≥100 unselected adults (aged ≥18 years old) that compared prevalence of GOR symptoms between *H. pylori*-positive and negative individuals. We chose this minimum sample size to maximise precision of estimates arising from individual studies. Hospital-based studies enrolling only symptomatic subjects were excluded. The second was to examine the association between *H. pylori* infection and complications of GOR, including EO and BO, in patients with GOR symptoms undergoing upper endoscopy. To examine this issue, we included observational studies (cross-sectional

surveys, or cohort or case-control studies) recruiting ≥100 unselected adults (aged ≥18 years old) that compared prevalence of GOR complications (EO or BO) between *H. pylori*-positive and negative individuals. When assessing the association between *H. pylori* infection and EO, we included studies recruiting patients with GOR symptoms undergoing upper endoscopy that reported the prevalence of EO according to presence or absence of *H. pylori* infection. The diagnosis of EO had to be based on characteristic endoscopic findings including mucosal breaks, such as erosions or ulceration. When assessing the association between *H. pylori* infection and BO, we included studies recruiting patients with GOR symptoms undergoing upper endoscopy that reported the prevalence of BO according to presence or absence of *H. pylori* infection. The diagnosis of endoscopic BO had to be according to the presence of columnar-lined oesophagus (proximal displacement of the squamo-columnar junction above the upper end of the gastric folds or gastro-oesophageal junction), whereas a definition of histologically-confirmed BO required the presence of specialised intestinal metaplasia on biopsies obtained from a columnar-lined oesophagus. Studies in which endoscopy was conducted on patients presenting with gastrointestinal complaints other than GOR symptoms, were excluded. Surveys conducted on subjects undergoing upper endoscopy for a health check-up or screening were, however, eligible for inclusion.

In all studies, the diagnosis of GOR symptoms could be based on a questionnaire or clinical assessment (according to presence of heartburn, regurgitation, or reflux). The diagnosis of *H. pylori* infection had to be based on one or more of serology, rapid urease test, histology, culture, or urease breath test. To be eligible, studies had to report available data on the number of *H. pylori*-positive cases, according to presence or absence of GOR symptoms and/or their complications.

Study Selection and Data Extraction

Two independent investigators (SA and AH) screened the identified titles and abstracts for potential suitability. Full texts of potentially relevant articles were examined in more detail for final assessment of suitability for inclusion, according to the pre-defined eligibility criteria. Any discrepancies were resolved by mutual consensus between the reviewers. If agreement was not reached, a third author (MZ or LHE) adjudicated. Data were extracted by two authors (SA and AH) onto a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA) for final analysis. The following data were extracted: publication year, country, total number of participants, mean age of participants, number of men and women recruited, number with or without GOR symptoms, method used to confirm presence or absence of GOR symptoms (questionnaire or clinical assessment), whether the Montreal criteria for GOR were fulfilled (defined according to the reporting of at least weekly GOR symptoms),[19] the method used to diagnose *H. pylori* infection, whether there was a history of GORD treatment (acid-suppressive therapy), or a history of treatment for *H. pylori*. In studies recruiting adults from the general population, we recorded the number of individuals reporting GOR symptoms, according to *H. pylori* infection status. In studies where patients with GOR symptoms underwent upper endoscopy, we recorded the number diagnosed with and without EO following endoscopy, and the number with BO, according to the presence or absence of *H. pylori* infection. We recorded the data related to different classifications of EO (Los Angeles[20] or Savary-Miller classification[21]), if available. In addition, we extracted the data pertaining to short-segment BO (SSBO, length ≤3cm) or long-segment BO (LSBO, >3cm), if available. Non-English articles were translated using Google Translate. Where there were duplicate publications, we included the study providing the most comprehensive details.

Risk of Bias Assessment

The quality of the included studies was assessed using the Newcastle–Ottawa scale (NOS) for non-randomised studies.[22,23] The NOS adapted for cross-sectional studies assesses quality based on the selection of the study groups (domains including representativeness of the sample, sample size, non-respondents, and ascertainment of the exposure; maximum five scores), the comparability of the groups (maximum two scores), and the assessment of the outcome of interest (domains including outcome assessment, and statistical test; maximum three scores). The NOS for case-control studies assesses quality based on the selection of the study groups (domains including case definition, representativeness of the cases, selection of controls, and definition of controls; maximum four scores), the comparability of the groups (maximum two scores), and the ascertainment of the exposure (domains including exposure ascertainment, ascertainment method for cases and controls, and non-response rate; maximum three scores). In both cases, studies with higher scores have a lower risk of bias and higher overall quality.

Study Outcomes and Statistical Analysis

We compared the prevalence of GOR symptoms and complications (EO and BO) between *H. pylori*-positive and negative individuals using pooled odds ratios (ORs) with 95% confidence intervals (95% CIs). For studies investigating the association between *H. pylori* infection and GOR symptoms, the denominator was all included subjects and we conducted separate analyses according to study type (cross-sectional or case-control). For studies investigating the association between *H. pylori* infection and EO, the denominator was all patients undergoing endoscopy with GOR symptoms. For studies investigating the association between *H. pylori* infection and BO, the denominator was all subjects with either BO or EO, but

we performed a *post hoc* analysis including all patients undergoing endoscopy with GOR symptoms in order not to underestimate any protective effective effect of *H. pylori* on development of BO among all patients with GOR symptoms. A random-effects model was used to pool data to give more conservative estimates. Heterogeneity between studies was assessed by the I^2 statistic with a cut-off of 50%, and the chi-squared test with a p-value <0.10, considered as a threshold for a statistically significant degree of heterogeneity. Publication bias was evaluated using the Egger's test,[24] where there were sufficient studies identified (≥10), in line with previous recommendations.[25] Meta-regression was applied to explore the potential influence of publication year on the outcomes, with a p-value <0.05 considered statistically significant. Sensitivity analyses were performed separately by excluding studies where comparison groups were not matched by age and sex, studies recruiting patients with a history of acid suppression and/or *H. pylori* eradication therapy, and studies where GOR symptoms were not defined as per the Montreal criteria, to examine their potential effects on the results of the meta-analysis.

Regarding the association between *H. pylori* infection and presence of EO, we performed a subgroup analysis according to different EO grades in patients with EO at upper endoscopy. In this regard, we classified EO grades as mild to moderate (Los Angeles A+B or Savary-Miller 1+2) or severe (Los Angeles C+D or Savary-Miller 3+4). Concerning the association between *H. pylori* infection and presence of BO, we performed a subgroup analysis based on endoscopic diagnosis and histologic confirmation of BO. We also explored the association between *H. pylori* infection and length of BO by categorising this as either SSBO or LSBO. In addition, we performed a subgroup analysis according to the method used to confirm *H. pylori* infection, where reported. All statistical analyses were done using the R package 'meta' (https://cran.r-project.org/package=meta).

RESULTS

Search Results, Study Selection, and Characteristics

The initial search recovered 10,662 publications, and 4,603 remained after removing duplicates. After appraising the title or abstract, 4,485 articles were excluded due to not meeting the inclusion criteria. Full texts of the remaining 118 articles were evaluated for eligibility. Finally, 36 eligible papers were included (Figure 1),[11-14,26-57] of which 8 studies investigated the association between *H. pylori* infection and GOR symptoms,[14,26-32] 16 studies evaluated the association between *H. pylori* infection and EO,[13,33-47] two studies assessed the association between *H. pylori* infection and BO,[48,49] three studies investigated the association between *H. pylori* infection and both GOR symptoms and EO,[11,12,50] and seven studies evaluated the association between *H. pylori* infection and both EO and BO.[51-57] Agreement between investigators for eligibility judging was excellent (Kappa statistic=0.92). All but one paper was published in English.[54] None of the identified studies were of a cohort design. Baseline characteristics of the included articles are summarised in Tables S1-S4. The results of the quality assessment of the studies have been represented in Tables S5-S8.

H. pylori infection and GOR symptoms

In total, 11 studies assessed the association between *H. pylori* infection and GOR symptoms,[11,12,14,26-32,50] of which seven were cross-sectional,[11,12,14,26-28,50] and four were case-control.[29-32] Analysis of the seven cross-sectional studies (Table 1), including a total of 28,990 subjects, showed that *H. pylori* infection was associated with a 26% decrease in the odds of GOR symptoms (OR 0.74, 95% CI 0.61–0.90) (Figure 2), but with significant heterogeneity between

studies (I^2=84%, p<0.001). When the analysis was restricted to two studies,[11,12] involving a total of 22,527 subjects, without a prior history of acid suppression and/or *H. pylori* treatment results were similar (OR 0.69, 95% CI 0.59–0.82). When the analysis was restricted to five studies,[12,14,27,28,50] including a total of 17,120 patients, which defined presence of GOR symptoms according to the Montreal definition, a similar result was obtained again (OR 0.76, 95% CI 0.61–0.94). Subgroup analysis showed that there was no significant association between *H. pylori* infection and GOR symptoms when either serology was used to define the infection (OR 0.64, 95% CI 0.41–1.00) or when other tests were used (OR 0.78, 95% CI 0.59–1.03).

Analysis of the four case-control studies (Table 2), containing a total of 6,024 individuals, demonstrated that *H. pylori* infection was not associated with an increased odds of GOR symptoms (OR 1.10, 95% CI 0.85–0.1.43) (Figure 3). There was borderline significant heterogeneity between studies (I^2=55%, p=0.079). Again, when the analysis only included three studies,[29-31] including a total of 1,300 cases, which defined GOR symptoms as per the Montreal definition, no significant association was found between *H. pylori* infection and GOR symptoms (OR 0.89, 95% CI 0.48–1.68). Finally, subgroup analysis showed that there was no significant association between *H. pylori* infection and GOR symptoms according to either serology (OR 1.03, 95% CI 0.52–2.07) or urease breath test (OR 1.06, 95% CI 0.79-1.43).

H. pylori infection and EO

Twenty-six cross-sectional studies,[11-13,33-47,50-57] including a total of 27,081 patients with GOR symptoms who underwent upper endoscopy, compared the prevalence of EO according to *H. pylori* infection status (Table 3). After these studies were pooled, patients with GOR symptoms infected by *H. pylori* infection had a 30% lower odds of EO than *H. pylori*-negative

patients with GOR symptoms (OR 0.70, 95% CI 0.58–0.84) (Figure 4). Again, significant heterogeneity was detected between studies (I^2=87%, p<0.001). Egger's test did not detect any significant publication bias (p=0.76). Meta-regression analysis indicated that the observed association between *H. pylori* infection and EO was not affected by publication year (β=-0.015, p=0.36). When the analysis was restricted to nine studies,[11-13,37,44,45,47,52,57] involving a total of 5,833 subjects without a history of acid suppression and/or *H. pylori* treatment, the inverse association between *H. pylori* infection and EO remained (OR 0.51, 95% CI 0.35–0.76). However, when only the 11 studies,[12,13,33,34,36,42,46,47,50,56,57] containing 4,174 patients, that defined presence of GOR symptoms as per the Montreal definition there was no significant association between *H. pylori* infection and EO (OR 0.70, 95% CI 0.47–1.05). Subgroup analyses according to grade of EO demonstrated that *H. pylori* exposure was associated with a 71% and a 53% reduction in odds of either mild/moderate (OR 0.29, 95% CI 0.21–0.41) or severe EO (OR 0.47, 95% CI 0.25–0.88), respectively. Finally, subgroup analysis showed that there was a significant inverse association between *H. pylori* infection and EO according to serology (OR 0.49, 95% CI 0.29–0.81) and other tests (OR 0.80, 95% CI 0.64–0.99).

H. pylori infection and BO

Nine cross-sectional studies,[48,49,51-57] including a total of 14,786 patients diagnosed with complications of GOR at upper endoscopy, compared the prevalence of BO according to *H. pylori* infection status (Table 4). Three studies diagnosed BO according to the presence of columnar-lined oesophagus at endoscopy,[48,52,54] and six studies confirmed the presence of specialised intestinal metaplasia histologically.[49,51,53,55-57] According to the analysis, no significant association was found between *H. pylori* infection and BO in subjects with GOR

complications, either endoscopically-diagnosed (OR 1.84, 95% CI 0.67–5.02), with significant heterogeneity between studies (I^2=93%, p<0.001), or histologically-confirmed (OR 0.85, 95% CI 0.60–1.20) with no statistical heterogeneity detected (Figure 5). Similarly, when we included all patients undergoing endoscopy with GOR symptoms from seven studies,[51-57] irrespective of the presence of EO, again no significant association was found between *H. pylori* infection and BO in subjects with GOR symptoms, either endoscopically-diagnosed (OR 0.79, 95% CI 0.42–1.48), or histologically-confirmed (OR 0.94, 95% CI 0.64–1.36). Analysis by segment length showed no association between *H. pylori* infection and either SSBO (OR 2.41, 95% CI 0.78–7.47) or LSBO (OR 0.46, 95% CI 0.19–1.13) in two studies.[48,52]

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis that has attempted to examine the potential association between *H. pylori* infection and GOR symptoms and its complications, such as EO and BO, comprehensively. Analysis of cross-sectional surveys, but not case-control studies, showed that *H. pylori* exposure was associated with a reduced odds of GOR symptoms. This finding was also supported by subgroup analyses restricted to cross-sectional studies including subjects without prior history of acid suppression and/or *H. pylori* eradication therapy. Analysis of 26 studies indicated that among patients with GOR symptoms, the odds of EO was significantly lower in *H. pylori*-positive than in *H. pylori*-negative cases. Again, this association remained when we restricted the analysis to the studies recruiting patients without a history of acid suppression and/or *H. pylori* eradication. Subgroup analysis demonstrated an association between *H. pylori* infection and reduced odds of EO irrespective of severity. Finally, we found no significant association between presence or absence of *H. pylori* infection and presence of BO among patients with GOR complications, based on nine studies, or among patients with GOR symptoms in seven studies, and no effect according to segment length or whether BO was endoscopically-diagnosed or histologically-confirmed.

According to our results, it appears that *H. pylori* infection may provide a protective effect against GOR symptoms, although this effect was not observed in case-control studies, and attenuated when symptoms become more frequent according to the Montreal criteria, or as the complications of GOR symptoms become more severe. The reasons for this are unclear, but there are potential explanations. Previous studies have reported that the corpus-predominant gastritis induced by *H. pylori* infection, especially by CagA-positive strain, leads to diminished gastric acid output and, consequently, a reduction in the damaging effect of gastric acid on the

oesophagus.[58,59] *H. pylori* infection may also be associated with decreased gastric production of leptin or ghrelin and, accordingly, reduced gastric acid secretion.[60,61] Moreover, it has been shown that *H. pylori* DNA can systemically downregulate the pro-inflammatory responses, such as via type 1 interferon and interleukin-12 cytokines,[62] potentially leading to a reduced risk of EO. However, more studies need to be done to confirm these hypotheses.

The relationship between *H. pylori* infection and BO has been evaluated by prior meta-analyses, which alluded to an inverse association,[15-17] which is not in agreement with the results of our study. One of the major limitations of these meta-analyses was the use of inappropriate control groups in the included study, which consisted of healthy individuals and/or patients with any upper gastrointestinal complaints. In the present study, we considered either patients with complications of GOR or GOR symptoms as the comparator, in order not to overestimate the magnitude of the effect of *H. pylori* infection. This may explain the inconsistency between our findings and the results of these previous meta-analyses.

There are some limitations of the present study. We relied on raw data from the studies, due to a lack of reporting of adjusted estimates of association in sufficient studies, meaning that we reported unadjusted ORs. These do not consider potential confounding. There was variability in the criteria used to define presence of GOR symptoms, according to both frequency and severity of symptoms. However, we tried to resolve this issue as much as possible by performing subgroup analyses restricted to studies using the Montreal criteria. When only these studies were included, the significant difference in the prevalence of GOR symptoms among *H. pylori*-negatives versus positives remained. There was a lack of information on prior history of acid suppression and/or *H. pylori* eradication therapy in most of the studies, which we attempted to address by a subgroup analysis excluding studies that did not report this information. With

respect to the different diagnostic criteria for BO, we conducted a subgroup analysis to explore the association between *H. pylori* infection and BO based on endoscopically-diagnosed, as well as histologically-confirmed, BO. Although there was no significant association in either analysis, there was statistical heterogeneity when only studies using endoscopically-diagnosed BO were analysed, but not for histologically-confirmed BO; inter-observer variation among endoscopists may have contributed to this. Another limitation was the variety of methods used to determine the presence of *H. pylori* infection. Furthermore, 95% CIs were wide for some of the pooled estimates, likely relating to the small sample sizes in these analyses. Finally, significant heterogeneity was observed between studies in many of our analyses, which could be explained by the above-mentioned differences between the individual papers, as well as the variations in the geographical location.

For this systematic review and meta-analysis, we conducted a comprehensive literature search of different databases using several keywords, as well as a recursive search of the references of the eligible studies in any language to reduce the likelihood of omitting any relevant articles. We also used strictly defined eligibility criteria, which were determined *a priori*, and performed judging of eligibility and data extraction in duplicate, and independently. In addition, quality assessment was conducted for the individual studies. We also performed several subgroup analyses to assess the consistency of our results and to control for potential confounders. Finally, we assessed for publication bias, where applicable.

In conclusion, this systematic review and meta-analysis has demonstrated that *H. pylori* infection is associated with a decreased odds of both GOR symptoms and EO. We did not detect any significant reduction in the odds of BO, in patients with GOR complications or GOR symptoms with *H. pylori* infection, in contrast to the findings among those with EO versus those

without. It appears this inverse association between *H. pylori* infection and GOR attenuates as the complications get more severe, from GOR symptoms, through EO, and BO. Further studies are needed to clarify the mechanisms of these inverse associations, as well as to gain consensus on the approach to eradication of *H. pylori* infection in patients with GOR symptoms.

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CONTRIBUTORS

MZ, LHE and AF contributed in study design. SA and AH contributed in data collection. MZ contributed in data analysis. MZ, SA, AH, LHE and AF contributed in drafting the manuscript. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

We declare no competing interests.

DATA SHARING

No additional data are available.

ETHICS APPROVAL

Not required.

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Table 1. Characteristics of cross-sectional studies reporting prevalence of gastro-oesophageal reflux symptoms according to *Helicobacter pylori* (*H. pylori*) infection status.

Study	Country	Total sample size	Number of *H. pylori* positive subjects (% with GOR symptoms)	Number of *H. pylori* negative subjects (% with GOR symptoms)	Newcastle–Ottawa scale score (out of 10)
Minatsuki 2013[11]	Japan	10837	3472 (19.4)	7365 (24.2)	5
Miyamoto 2008[26]	Japan	241	151 (5.3)	90 (32.2)	5
Nam 2017[12]	Korea	11690	5760 (12.1)	5930 (17.8)	8
Pandeya 2012[27]	Australia	1316	302 (53.3)	1014 (57)	5
Wang 2019[50]	China	2844	1143 (15.0)	1701 (18.9)	6
Zagari 2008[28]	Italy	1033	596 (44.8)	437 (43.7)	9
Zou 2011[14]	China	1029	738 (4.9)	291 (4.1)	4

Table 2. Characteristics of case-control studies reporting prevalence of gastro-oesophageal reflux (GOR) symptoms according to *Helicobacter pylori* (*H. pylori*) infection status.

Study	Country	Total sample (n)	Number of *H. pylori* positive subjects (% with GOR symptoms)	Number of *H. pylori* negative subjects (% with GOR symptoms)	Newcastle–Ottawa scale score (out of 9)
Bor 2001[30]	Turkey	100	79 (46.8)	21 (61.9)	6
Corley 2008[29]	USA	256	59 (25.4)	197 (33.5)	6
Harvey 2004[32]	England	4724	1560 (28.1)	3164 (25.2)	4
Nordenstedt 2007[31]	Norway	944	350 (55.1)	594 (47.0)	6

Table 3. Characteristics of cross-sectional studies reporting prevalence of erosive oesophagitis (EO) in patients with gastro-oesophageal reflux symptoms according to *Helicobacter pylori* (*H. pylori*) infection status.

Author	Country	Total sample (n)	Number of *H. pylori* positive patients (% with EO)	Number of *H. pylori* negative patients (% with EO)	Number of *H. pylori* positive EO patients (% with severe EO*)	Number of *H. pylori* negative EO patients (% with severe EO*)	Newcastle–Ottawa scale score (out of 10)
Ang 2005[45]	Singapore	533	141 (61.7)	392 (58.7)	NA	NA	5
Bayrakçi 2008[36]	Turkey	133	58 (19.0)	75 (16.0)	NA	NA	6
Chourasia 2011[37]	India	118	56 (58.9)	62 (80.6)	NA	NA	5
Csendes 1997[51]	Chile	136	40 (65.0)	96 (57.3)	NA	NA	4
Csendes 1998[52]	Chile	189	106 (36.8)	83 (45.8)	NA	NA	4
Dore 2016[53]	Italy	3384	1325 (38.3)	2059 (42.9)	NA	NA	5
Fujiwara 2005[44]	Japan	253	96 (55.2)	157 (70.7)	NA	NA	5
Jonaitis 2004[33]	Lithuania	104	73 (43.8)	31 (67.7)	32 (6.3)	21 (14.3)	5
Kim 2006[54]	Korea	222	79 (55.7)	143 (50.3)	NA	NA	4
Ko 2017[39]	Korea	2992	1815 (13.6)	1177 (17.2)	NA	NA	6
Koek 2008[55]	Belgium	392	77 (24.7)	315 (46.0)	21 (4.8)	143 (8.4)	6

Labenz 2004[38]	Germany	5289	1432 (43.0)	3857 (47.7)	NA	NA	5
Liu 2006[43]	China	206	45 (64.4)	161 (49.7)	29 (6.9)	80 (11.3)	4
Malfertheiner 2005[40]	Germany, Austria, and Switzerland	6215	1607 (47.4)	4608 (53.9)	NA	NA	5
Manes 1999[13]	Italy	202	97 (41.2)	105 (66.7)	40 (7.5)	70 (4.3)	6
Minatsuki 2013[11]	Japan	2455	672 (11.9)	1783 (36.6)	NA	NA	5
Nam 2017[12]	Korea	1752	696 (32.8)	1056 (57.8)	NA	NA	8
Pieramico 2000[46]	Italy	122	51 (47.1)	71 (42.3)	NA	NA	5
Rasmi 2009[41]	Iran	154	116 (51.7)	38 (65.8)	NA	NA	4
Ronkainen 2005[35]	Sweden	369	109 (19.3)	260 (29.6)	NA	NA	7
Sharifi 2014[56]	Iran	702	204 (43.6)	498 (36.1)	NA	NA	7
Wang 2019[50]	China	492	171 (53.8)	321 (55.8)	NA	NA	6
Wu 1999[47]	Hong Kong	106	33 (63.6)	73 (61.6)	NA	NA	5
Wu 2000[57]	Hong Kong	225	77 (57.1)	148 (64.9)	44 (13.6)	96 (32.3)	5
Wu 2007[34]	Hong Kong	224	61 (32.8)	163 (55.8)	20 (5.0)	91 (18.7)	6
Zentilin 2003[42]	Italy	112	35 (37.1)	77 (40.3)	NA	NA	5

*We classified erosive oesophagitis grades as ‘mild to moderate’ (Los Angeles A+B or Savary-Miller 1+2) or severe (Los Angeles C+D or Savary-Miller 3+4).

Table 4. Characteristics of cross-sectional studies reporting Barrett's oesophagus (BO) in patients with gastro-oesophageal reflux complications according to *Helicobacter pylori* (*H. pylori*) infection status.

Author	Country	Total sample (n)	Number of *H. pylori* positive patients (% with BO)	Number of *H. pylori* negative patients (% with BO)	Number of *H. pylori* positive BO patients (% with long-segment)	Number of *H. pylori* positive BO patients (% with long-segment)	Newcastle–Ottawa scale score (out of 10)
Csendes 1997[51]	Chile	181	46 (43.5)	135 (59.3)	NA	NA	4
Csendes 1998[52]	Chile	247	135 (71.1)	112 (66.1)	96 (10.4)	74 (13.5)	4
Dore 2016[53]	Italy	1523	966 (8.5)	763 (8.0)	NA	NA	5
Kim 2006[54]	Korea	147	56 (21.4)	91 (20.9)	NA	NA	4
Koek 2008[55]	Belgium	194	20 (5.0)	174 (16.7)	NA	NA	6
Peng 2009[49]	China	137	36 (19.4)	101 (19.8)	NA	NA	6
Sharifi 2014[56]	Iran	303	101 (11.9)	202 (10.9)	NA	NA	5
Usui 2020[48]	Japan	11914	2080 (84.8)	9834 (57.5)	1764 (0.3)	5655 (1.1)	6
Wu 2000[57]	China	140	44 (0)	96 (6.3)	NA	NA	5

*We categorised Barrett's oesophagus as short-segment (length ≤3cm) or long-segment (length >3cm)

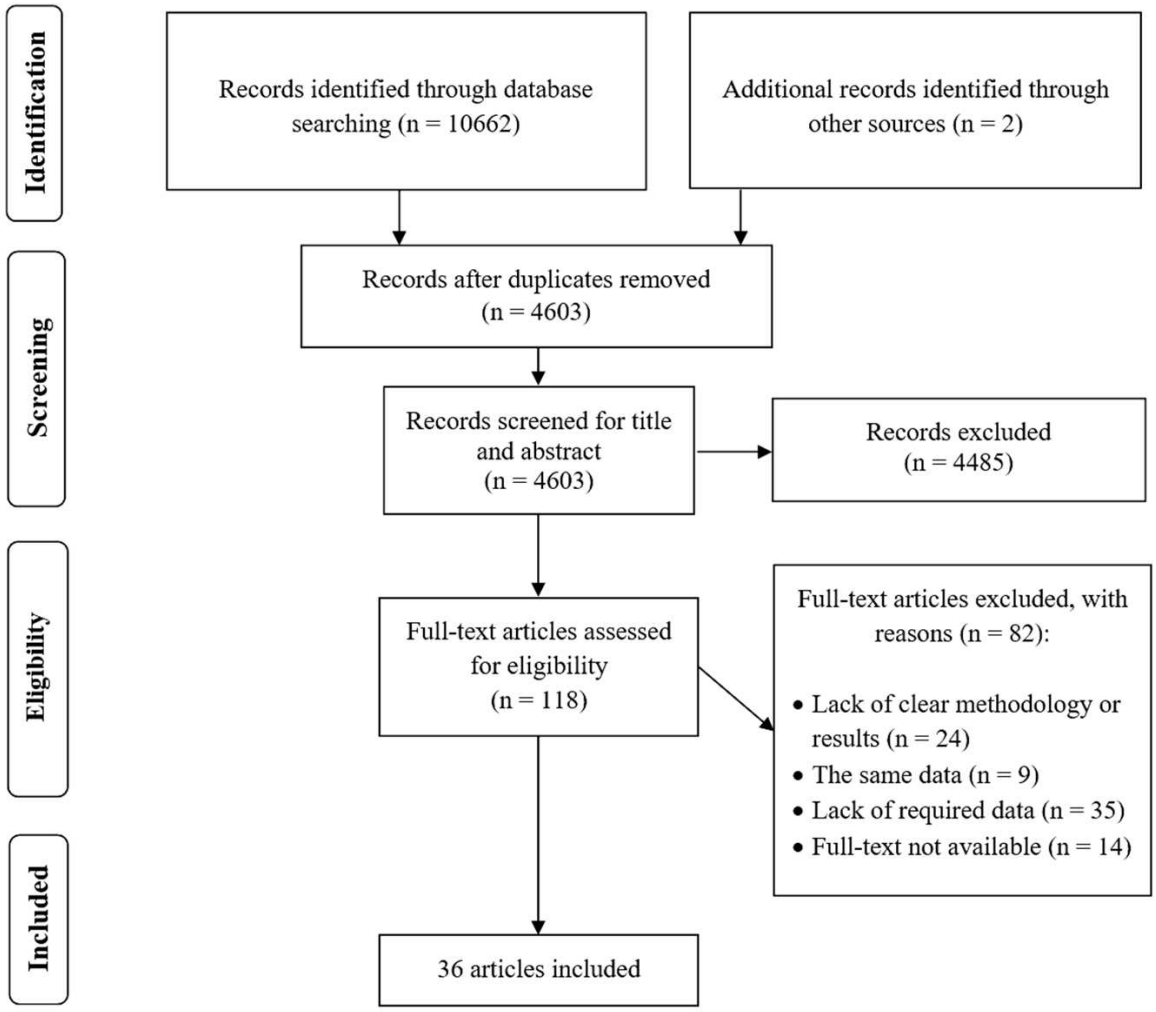

Figure 1. PRISMA flow diagram

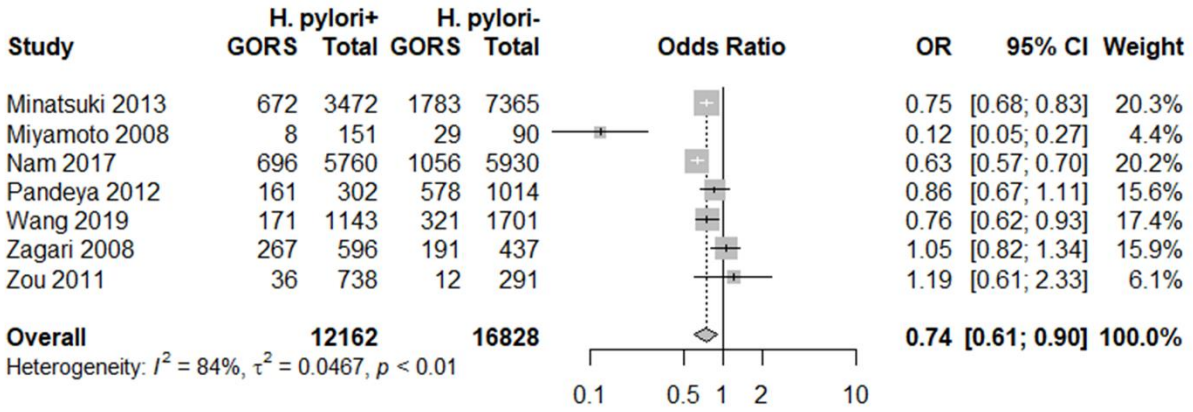

Figure 2. Forest plot of odds of gastro-oesophageal reflux symptoms (GORS) according to *Helicobacter pylori* (*H. pylori*) infection status in cross-sectional studies.

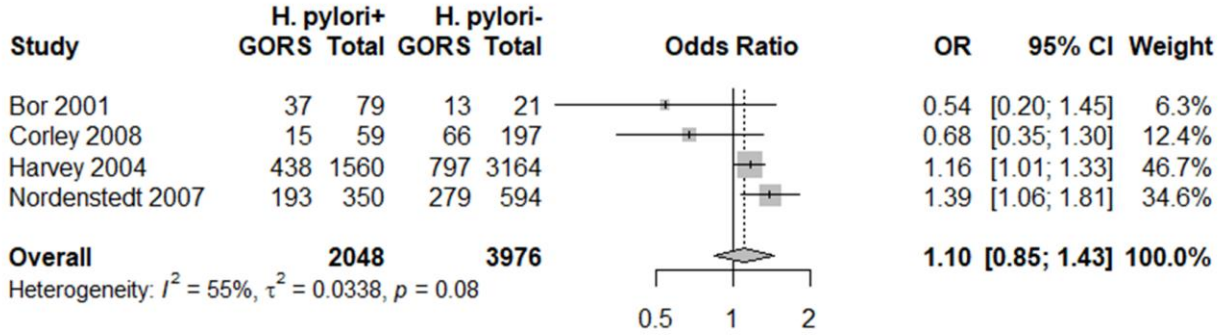

Figure 3. Forest plot of odds of gastro-oesophageal reflux symptoms (GORS) according to *Helicobacter pylori* (*H. pylori*) infection status in case-control studies.

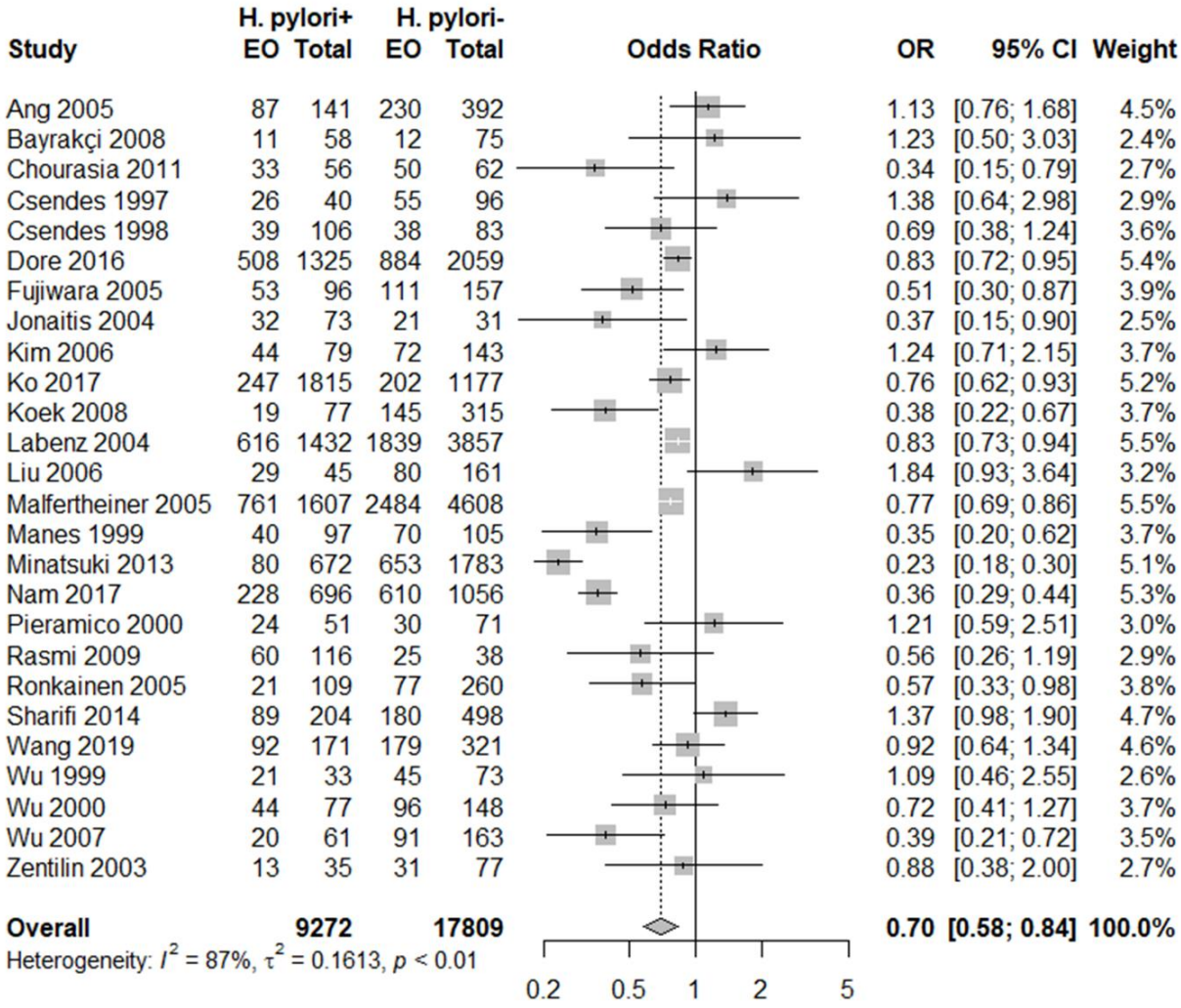

Figure 4. Forest plot of odds of erosive oesophagitis (EO) according to *Helicobacter pylori* (*H. pylori*) infection status in patients with gastro-oesophageal reflux symptoms.

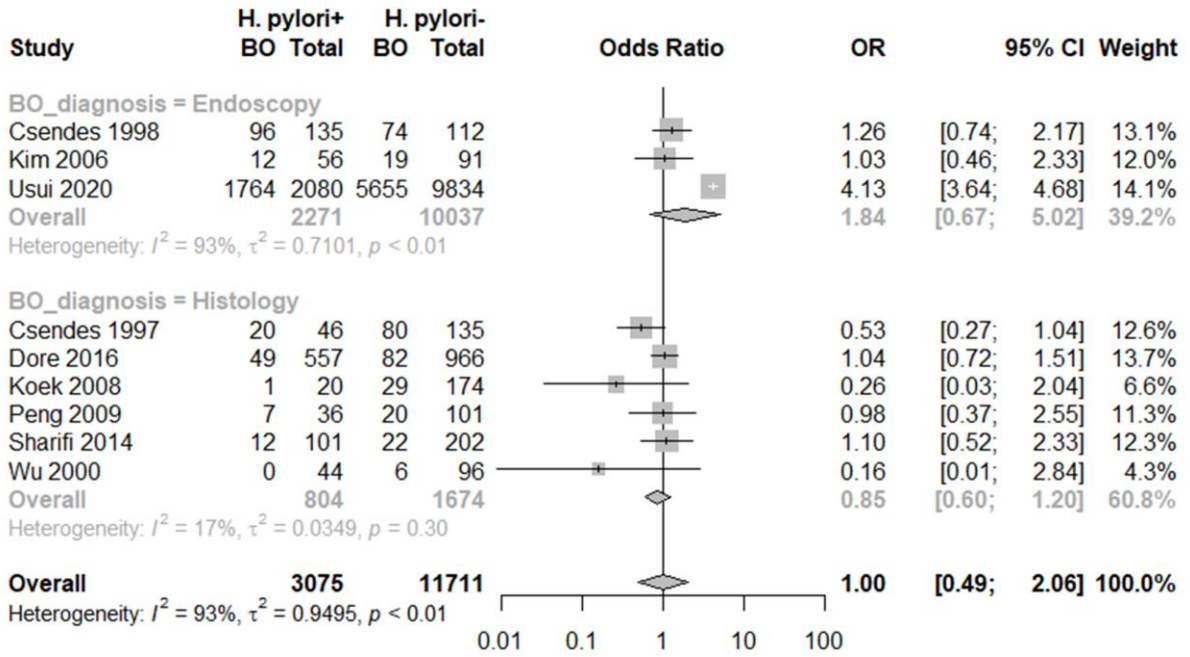

Figure 5. Forest plot of odds of Barrett's oesophagus (BO) according to *Helicobacter pylori* (*H. pylori*) infection status in patients with complications of gastro-oesophageal reflux.