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The Association between Barrett's Esophagus and *Helicobacter pylori* Infection: A Meta-Analysis

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Abstract

Objective—The effect of *Helicobacter pylori* on Barrett's esophagus is poorly understood. We conducted a meta-analysis to summarize the existing literature examining the effect that *H pylori* has on Barrett's esophagus.

Design—We performed a comprehensive search to identify studies pertaining to the association between *H pylori* and Barrett's esophagus. We conducted meta-regression analyses to identify sources of variation in the effect of *H pylori* on Barrett's esophagus.

Results—Our analysis included a total of 49 studies that examined the effect of *H pylori* on Barrett's esophagus and 7 studies that examined the effect of *cag A* positivity on Barrett's esophagus. Overall, *H pylori,* and even more so *cag A,* tended to be protective for Barrett's esophagus in most studies; however there was obvious heterogeneity across studies. The effect of *H pylori* on Barrett's esophagus varied by geographic location and in the presence of selection and information biases. Only 4 studies were found without obvious selection and information bias, and these showed a protective effect of *H pylori* on Barrett's esophagus (Relative Risk = 0.46 [95% CI: 0.35, 0.60]).

Conclusions—Estimates for the effect of *H pylori* on Barrett's esophagus were heterogeneous across studies. We identified selection and information bias as potential sources of this heterogeneity. Few studies without obvious selection and information bias have been conducted to examine the effect of *H pylori* on Barrett's esophagus, but in these, *H pylori* infection is associated with a reduced risk of Barrett's esophagus.

Background

The incidence of esophageal adenocarcinoma has steadily increased over the past three decades in developed countries, while the five-year survival rate continues to be low (only 16% in the US and 10% in Europe).[1,2] Barrett's esophagus, which is estimated to affect less than 2% of the general population,[3–5] is considered to be the precancerous lesion for esophageal adenocarcinoma.[6–8] Yet little is known about the etiological process leading to Barrett's esophagus.

Helicobacter pylori has been implicated as a risk factor for precancerous lesions in the stomach which affect the acid producing parietal cells.[9–11] However, inconsistent evidence

exists regarding the effect of *H pylori* on gastroesophageal reflux disease, the primary putative risk factor for Barrett's esophagus and esophageal adenocarcinoma, and the current evidence regarding the effect of *H pylori* on Barrett's esophagus remains poorly understood. Some previous studies have reported that *H pylori* is a risk factor for Barrett's esophagus,[12–14] while other studies have reported that *H pylori* has no effect on Barrett's esophagus[15–16] and others still report a protective effect.[17–19] Previous meta-analyses, using small subsets of studies on this topic, failed to investigate sources of the heterogeneity of effects across studies.[20–22] To better understand the conflicting results, we conducted a meta-analysis to evaluate potential sources of heterogeneity for estimates of the effect of *H pylori* on Barrett's esophagus, and to summarize the effect that *H pylori* has on Barrett's esophagus within homogeneous patient groups.

Methods

We conducted a meta-analysis to summarize the effect that various factors have on Barrett's Esophagus.[4, 12–19, 23–62] However, the study presented here focuses on the analyses examining the effect of *H pylori* on Barrett's Esophagus.

A. Data sources

Sources of studies included the literature databases Medline (PubMed and Ovid) and Science Citation Index.[63] Studies were searched from the inception of each database through December 31, 2010 using the keywords 'Barrett's esophagus,' 'Barrett's metaplasia' or 'Barrett's oesophagus,' and '*Helicobacter pylori' or 'Campylobacter pylori.* Two collaborators used information from the references' titles and abstracts to identify potentially eligible studies from the literature database searches. We supplemented these searches with backward citation tracking of eligible primary studies, reviews of Barrett's esophagus, and hand-searches of conference proceedings published in Gut and Gastroenterology.

B. Study selection

All eligible studies satisfied the following inclusion criteria:

1. Barrett's esophagus could be used as an outcome in the analysis.
2. Relevant information was provided to allow the estimation of a relative risk (risk ratio or odds ratio) and a variance measure for the association between *H pylori* and Barrett's esophagus.
3. The individual was used as the unit of analysis for estimating the relative risk.
4. Information must have been available in English or Spanish (at least as an abstract).
5. A sample size of more than 4 subjects for each comparison group was utilized.[64] Therefore, case reports were not included.

We excluded studies based on the following criteria:

1. The study was not conducted on humans.
2. Barrett's esophagus was not mentioned in the abstract.
3. The results came from a review article.

When data from multiple reports were identified, we included only the report with the most complete relevant data.

C. Data extraction

All potentially eligible studies were randomly assigned to two of the three primary data extractors for independent preliminary screening. Each extractor first reviewed the report to confirm eligibility, and if ineligible, provided the primary reason for ineligibility. The two assigned primary extractors then independently extracted relevant data from studies judged to be eligible.

We created an extraction database to collect relevant information regarding each eligible study such as citation information; how *H pylori* and Barrett's esophagus were measured; the measure of effect and confidence intervals; sample sizes; study location (geographic location, country, etc); design (cross-sectional, basic control or population-based case-control); characteristics of the study population (e.g. prevalence of the modifiable risk factor); comparison group (endoscopic patients, asymptomatic patients; gastroesophageal reflux disease patients; etc); data analyses conducted (adjustment for confounding, etc); likelihood for selection and information bias; and other potential sources of heterogeneity across studies.

Selection bias was considered likely if the comparison group without Barrett's esophagus did not represent the base population (in terms of the distribution of the exposure) from which the cases of Barrett's esophagus came. The base population was defined as those who, if they developed Barrett's esophagus, would be a case with Barrett's esophagus in the study. For example, if Barrett's esophagus cases were chosen from patients undergoing an upper endoscopic examination at clinic A in Los Angeles, CA, then the base population would be individuals who, if they had Barrett's esophagus, would undergo an upper endoscopy examination at clinic A in Los Angeles, CA and would be identified as a case in the study. If the comparison group (without Barrett's esophagus) was chosen from those undergoing upper endoscopy examinations at clinic A in Los Angeles, CA, then it is likely that selection bias occurred since the distribution of *H pylori* in endoscopy patients is likely to differ from *H pylori* in the base population.

Information bias was suggested when the measurement of *H pylori* or Barrett's esophagus was likely to be inaccurate. Variables indicating how *H pylori* and Barrett's esophagus were measured included an indicator of incident (versus prevalent) measurement, methods used to measure or define *H pylori* (urea breath test, rapid urease test, culture, histology, serology, fecal test, etc), location of biopsy samples for *H pylori* measure (gastric biopsies, esophageal biopsies only, or no biopsies), whether the methods for *H pylori* measurement was consistent for Barrett's esophagus cases and the non-Barrett's comparison group, and whether Barrett's esophagus was diagnosed by first seeing Barrett's mucosa at endoscopy, and then histologically confirming intestinal metaplasia in biopsy specimens taken at the site where the Barrett's mucosa was observed.

D. Data cleaning and screening

Studies judged to be eligible by the two data extractors were then assigned to an additional screener for data cleaning and screening. When a discrepancy was observed between the two extractions, the third collaborator reviewed the original report to resolve the discrepancy and correct any errors.

E. Data analysis

The effect measures of interest were relative risks that compared the risk of Barrett's esophagus among individuals who tested positive for *H pylori* to the risk of Barrett's esophagus among individuals who tested negative for *H pylori*. We assumed that the

Barrett's esophagus was a rare outcome and therefore used proportions, risk ratios, or odds ratios from eligible studies to estimate this relative risk.

We examined the distribution of the measures of effect using visual and tabular displays and tests of homogeneity to reveal systematic variation in the relative risks of *H pylori* on Barrett's esophagus across studies.[64] Furthermore, we investigated potential publication bias by using funnel plots.[65]

We conducted meta-regression analyses to identify factors that influence variation in the estimated relative risks across studies within the pool of available data (previously described under data extraction) and to define subgroups for which the effect of *H pylori* on Barrett's esophagus did not show observable residual heterogeneity in the measure of effect across studies. The relative risk estimates were then modeled by the fixed effects of factors that had the greatest potential to explain variation in effects and for which there was sufficient data and variation across studies. Quality scoring, which has well-described methodological shortcomings,[66–68] was not included in this meta-analysis. Instead we examined whether specific characteristics of data quality could predict variation in the measure of effect across studies. We also examined the association between Barrett's esophagus and *cag A* positive strains of *H pylori*.

Results

A total of 2,661 abstracts were screened for preliminary eligibility. Of these, 2,487 were judged to be ineligible. Data extraction was performed on the remaining 174 studies, 40 of which were subsequently judged to be ineligible and 134 eligible for the effect of any factor on Barrett's esophagus; 49 of these pertained to the effect of *H pylori* on Barrett's esophagus and were included in this anlaysis. [4, 12–19, 23–62] The most common reasons for ineligibility were lack of reported data to estimate a relevant measure of effect (46%) and sources of data exclusively coming from review articles (41%).

The included studies utilized populations from around the world, including Europe (51%), the United States (20%), Canada, Japan, Malaysia, China, Peru, Chile, Pakistan and Australia. The pooled overall random effects estimate of the relative risk was 0.73 (95% CI 0.60, 0.88). However, heterogeneity was observed both in the visual graph of the measures of effect across studies and the test for heterogeneity ($p<0.0001$). Figure 1 illustrates the distribution of the estimated effect of *H pylori* on Barrett's esophagus across the 49 studies that specifically examined this effect. The funnel plot did not suggest that publication bias was a major concern.

Most of the 49 studies (92%) which examined the effect of *H pylori* on Barrett's esophagus used convenience comparison groups or other populations which would not be likely to estimate the true distribution of *H pylori* in the base population from which the cases of Barrett's esophagus arose (Table 1), and therefore were considered to have biased estimates of effect due to selection bias. Misclassification of *H pylori* and Barrett's esophagus (information bias) was also common; 33% of studies did not specifically state that they diagnosed Barrett's esophagus by histologically confirming intestinal metaplasia in biopsy specimens taken at the site where the Barrett's mucosa was observed at endoscopy, and 14% (n=7) diagnosed *H pylori* histologically but did not use a biopsy sample from either the antrum or the corpus of the stomach to measure *H pylori* (6 of these 7 studies only measured *H pylori* in the esophagus or gastro-esophageal junction). The pooled estimate for the studies that used gastric biopsies was 0.66 (95% CI: 0.53, 0.83); test for heterogeneity $p<0.0001$) while the estimate from studies that measured *H pylori* only in the esophagus or gastro-esophageal junction was 1.39 (95% CI: 0.52, 3.52; test for heterogeneity $p>0.0001$).

In weighted meta-regression analyses using all 49 studies, selection bias, *H pylori* infection measured only using a biopsy sample from the stomach, and study location were identified as sources of heterogeneity. As illustrated in Figure 2, the effect within the group of 4 studies with appropriate measurement of *H pylori* and without a likely source of selection bias was consistently protective for BE; the random effects summary estimate for the relative risk was 0.46 (95% CI: 0.35, 0.60).[4,17,25,51] Likewise, the effect of *H pylori* on BE was consistently protective in studies conducted in the United States; 0.46 (95% CI: 0.40, 0.53), (heterogeneity test p=0.50) (Figure 3). Strongly protective measures of effect (RR = 0.01 and 0.04) were reported for the two studies from Japan. Residual heterogeneity was observed for all other strata of these variables; effect estimates ranged from 0.25 to 5.14 for studies conducted outside of the United States or Japan with a likely source of selection bias which used gastric biopsy samples from the antrum or corpus to measure *H pylori*.

We also examined the effect of *cag A* positivity on Barrett's esophagus. Data from the subgroup of 7 studies which examined the effect of *cag A* positivity on BE, suggested a protective effect of *cag A* on BE in all but 1 study (Table 2, Figure 4).[17,25,29,49,52,56,69] The pooled random estimate for the relative risk in these 7 studies was 0.38 (95% CI: 0.19, 0.78), but the relative risk for the study by Ferrández et al. (estimated to be 1.5 [95% CI: 0.93, 2.46]) differed greatly from the other studies.[29]

Discussion

In the current analysis we examined the effect of *H pylori* on Barrett's esophagus across 49 studies. Our analyses suggest that *H pylori* tended to be protective for Barrett's esophagus. However, heterogeneity was easily observable across studies, and the effect varied in the presence of selection bias, with the use of esophageal tissue instead of gastric tissue to diagnose *H pylori*, and in different geographic locations.

The effect of information bias through inaccurate measurement of *H pylori* using tissue from the esophagus instead of the stomach was observed to be a source of heterogeneity. Studies that defined *H pylori* exclusively from esophageal biopsies were more likely to find a positive association between *H pylori* and Barrett's esophagus, whereas the rest of the studies that measured *H pylori* using gastric biopsies tended to show a protective association between *H pylori* and Barrett's esophagus. Since the occurrence of *H pylori* in the esophagus would not likely reflect the occurrence of *H pylori* in the stomach, a person's true *H pylori* status is likely to be misclassified when tissue from the esophagus is used.

A strong protective effect of gastric *H pylori* on Barrett's esophagus was observed without observable heterogeneity within the subgroup of 4 studies without a likely source of selection or information bias 0.46 (95% CI: 0.35, 0.60), where the definitions of Barrett's esophagus as well as *H pylori* adhere to internationally accepted standards.[70] However, 45 of the 49 studies had obvious sources of selection bias (some with information bias as well), so only 4 studies were used to estimate this measure of effect.[4,17,25,51] Additional studies are needed with appropriately chosen comparison groups. For example, for case-control studies, the controls should be chosen to represent the exposure distribution of the base population from which the cases arose. Endoscopy patients, healthy blood donors, and patients with conditions positively or negatively associated with *H pylori* would not be appropriate comparison groups. Controls from identified catchment populations from which the cases arose would be the most appropriate choice.

The effect of *cag A* positive *H. pylori* on Barrett's esophagus also tended to be protective. Only one of the seven studies examining the association between *cag A* and Barrett's esophagus did not show a protective effect. In the study by Ferrández et al which used healthy blood donors as controls, the relative risk was estimated to be 1.5 (95% CI: 0.93,

2.46).[29] Blood donors typically are healthier in many ways and younger than most populations and therefore may have led to selection bias since they may have a lower prevalence of *H pylori* than the base population from which the cases arose. On the other hand, the protective effect observed in 5 of the 6 other studies was also likely affected by selection bias.

Potential candidates for sources of heterogeneity for the effect of *H pylori* on Barrett's esophagus include corpus inflammation and atrophy. Some evidence suggests these factors may modify the effect of *H pylori* on related disease outcomes such as symptomatic GERD and erosive esophagitis.[71] However, existing studies examining the effect of *H pylori* on Barrett's esophagus did not evaluate effect modification by type or distribution of gastritis on the risk of Barrett's esophagus. Figure 5 illustrates possible mechanisms whereby *H pylori* may decrease the risk for Barrett's esophagus. *H pylori* infection's hypothesized protective effect on Barrett's esophagus may occur due to its association with multifocal atrophic gastritis and the resulting damaging effect it has on the acid producing parietal cells.[9–11] With a loss of parietal cells, the esophagus is less likely to be exposed to the harmful effects of gastric acid and acid reflux, erosive esophagitis and then Barrett's esophagus is less likely to occur. Also in this hypothesized protective pathway for Barrett's esophagus, both a low intake of fruits and vegetables and older age is associated with *H pylori* infection,[72–746] while younger age is associated with lower calorie consumption and increased physical activity, both leading to a lower risk for obesity.[75,76] With a lower risk for obesity, lower visceral fat and lower insulin levels both may lead to a reduction in Barrett's esophagus (Figure 5).[77–80] Using this figure, after eliminating intermediates and controlling for age and dietary factors such as fruit and vegetable consumption, there may be no remaining potential confounders for the effect of *H pylori* on Barrett's esophagus. Therefore, age and dietary factors such as fruit and vegetable intake should be controlled for, yet only 3 (7%) of the studies adjusted for age,[17,19.34] and only 1 adjusted for a relevant dietary factor (Corley, et al).[17]

Two previous meta-analyses have reported a protective effect of *H pylori* on Barrett's esophagus across only 5 and 9 studies.[20,21] These summary measures of effect were reported in the presence of heterogeneous effects without searching for sources of the variation of effects across studies. As noted by Wang et al in a more recent meta-analysis, the reported protective summary measure of effect may have been affected by the types of subjects used as the comparison group.[22] Wang et al limited their meta-analysis of the effect of *H pylori* on Barrett's esophagus to studies which used "normal healthy subjects as controls," which included blood donors in 3 studies and endoscopy controls in 9 studies.[22] As we discussed previously, the use of blood donors as controls is likely to lead to a biased (higher) estimate of effect due to selection bias. Likewise, the prevalence of *H pylori* infection among endoscopy patients would not likely represent the prevalence of *H pylori* in the base population from which the cases arose. The current meta-analysis is the first to examine the effect of selection and other biases on the observed effect of *H pylori* on Barrett's esophagus across studies.

Conclusion

Our meta-analysis of 49 studies suggests that *H pylori* infection is associated with a reduced risk of Barrett's esophagus. However, the effect is heterogeneous across studies. We identified methodological issues such as selection and information bias as potential sources of heterogeneity. In total, we found four studies without obvious selection and information bias and these showed a protective effect of *H pylori* on Barrett's esophagus.

Acknowledgments

Statement of Interests

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55:74–108. [PubMed: 15761078]
2. El-Serag HB, Mason AC, Petersen N, Key CR. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut. 2002; 50:368–72. [PubMed: 11839716]
3. Zagari RM, Fuccio L, Wallander MA, et al. Gastro-oesophageal reflux symptoms, oesphagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut. 2007; 57:1354–59. [PubMed: 18424568]
4. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterol. 2005; 129:1825–31.
5. Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA. Prevalence of columnar-lined (Barrettt's) Esophagus comparison of population-based clinical and autopsy findings. Gastroenterol. 1990; 99:918–22.
6. Shaheen NJ, Richter JE. Barrett's oesophagus. Lancet. 2009; 373:850–61. [PubMed: 19269522]
7. Spechler SJ. Clinical practice. Barrett's Esophagus. N Engl J Med. 2002; 346:836–42. [PubMed: 11893796]
8. Cook MB, Wild CP, Everett SM, et al. Risk of mortality and cancer incidence in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. 2007; 16:2095–96.
9. Correa P. The epidemiology of gastric cancer. World J Surg. 1991; 15:228–34. [PubMed: 2031359]
10. Correa P. The human model of gastric carcinogenesis. Cancer Res. 1988; 48:3554–60. [http://cancerres.aacrjournals.org/cgi/reprint/48/13/3554]. [PubMed: 3288329]
11. Fischbach LA, Correa P, Feldman M, Fontham E, Priest EL, Goodman KJ, Jain R. Increased Reflux Symptoms after Calcium Carbonate Supplementation and Successful *Helicobacter pylori* Treatment: Results from a Randomized Clinical Trial in a Population with a High Prevalence of Multifocal Atrophic Gastritis. Dig Dis Sci. 2003; 48:1487–94. [PubMed: 12924641]
12. Henihan RD, Stuart RC, Nolan N, et al. Barrett's esophagus and the presence of *Helicobacter pylori*. Am J Gastroenterol. 1998; 93:542–6. [PubMed: 9576445]
13. Loffeld RJ, Ten Tije BJ, Arends JW. Prevalence and significance of *Helicobacter pylori* in patients with Barrett's esophagus. Am J Gastroenterol. 1992; 87:1598–1600. [PubMed: 1442681]
14. Meng X, Scheer MA, Tsang TK. GERD, Barrett's esophagus and *Helicobacter pylori* infection. Gastroenterol. 2008; 134:A443.
15. Csendes A, Smok G, Cerda G, Burdiles P, Mazza D, Csendes P. Prevalence of *Helicobacter pylori* infection in 190 control subjects and in 236 patients with gastroesophageal reflux, erosive esophagitis or Barrett's esophagus. Dis Esophagus. 1997; 10:38–42. [PubMed: 9079272]
16. Peng S, Cui Y, Xiao YL, et al. Prevalence of erosive esophagitis and Barrett's esophagus in the adult Chinese population. Dis of the Esophagus. 2009; 41:1011–17.
17. Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, et al. *Helicobacter pylori* infection and the risk of Barrett's oesophagus: a community-based study. Gut. 2008; 57:727–33. [PubMed: 17895354]
18. Fassan M, Rugge M, Parente P, Tieppo C, Rugge M, Battaglia G. The role of *Helicobacter pylori* in the spectrum of Barrett's carcinogenesis. Cancer Prev Res. 2009; 2:94.
19. Sonnenberg A, Lash R, Genta R. A national study of *Helicobacter pylori* infection in gastric biopsy specimens. Gastroenterology. 2010; 139:1894–1901. [PubMed: 20727889]

20. Rokkas T, Pistiolas D, Sechopoulous P, et al. Relationship between *Helicobacter pylori* infection and esophageal neoplasia: a meta-analysis. Clin Gastroenterol Hepatol. 2007; 5:1413–7. [PubMed: 17997357]
21. Gisbert JP, Pajares JM. Prevalence of *Helicobacter pylori* infection in gastroesophageal reflux disease and Barrett's esophagus. Med Clin (Barc). 2002; 119:217–23. [PubMed: 12200010]
22. Wang C, Yuan Y, Hunt RH. *Helicobacter pylori* infection and Barrett's esophagus: a systematic review and meta-analysis. Am J Gastroenterol. 2009; 104:494–500.
23. Abbas Z, Hussainy AS, Ibrahim F, Jafri S, Shaikh H, Khan AH. Barrett's oesophagus and *Helicobacter pylori*. J Gastroenterol Hepatology. 1995; 10:331–3.
24. Abouda GF, Cotton JC, Dillon JF. Prevalence of *Helicobacter pylori* virulence factors in patients with reflux oesophagitis and Barrett's oesophagus. Gut. 2003; 52:A411.
25. Anderson LA, Murphy SJ, Johnston BT, Watson RG, Ferguson HR, Bamford KB. Relationship between *Helicobacter pylori* infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. Gut. 2008; 57:734–9. [PubMed: 18025067]
26. Blaser MJ, Perez-Perez GL, Lindenbaum J, et al. Association of infection due to *Helicobacter pylori* with specific upper gastrointestinal pathology. Reviews Inf Dis. 1991; 13(Suppl 8):S704–8.
27. Chacaltana A, Urday C, Ramon W, Rodríguez C, Espinoza J, Velarde H. [Prevalence, clinical-endoscopic characteristics and predictive factors of Barrett's Esophagus in endoscopic screening for gastric cancer]. Rev Gastroenterol Peru. 2009; 29:24–32. [PubMed: 19424405]
28. El-Serag HB, Sonnenberg A, Jamal MM, Kunkel D, Crooks L, Feddersen RM. Characteristics of intestinal metaplasia in the gastric cardia. Am J Gastroenterol. 1999; 94:622–7. [PubMed: 10086641]
29. Ferrández A, Benito R, Arenas J, García-González MA, Sopeña F, Alcedo J. CagA-positive *Helicobacter pylori* infection is not associated with decreased risk of Barrett's esophagus in a population with high *H. pylori* infection rate. BMC Gastroenterol. 2006; 6:7. [PubMed: 16483364]
30. Goldblum JR, Richter JE, Vaezi M, Falk GW, Rice TW, Peek RM. *Helicobacter pylori* infection, not gastroesophageal reflux, is the major cause of inflammation and intestinal metaplasia of gastric cardiac mucosa. Am J Gastroenterol. 2002; 97:302–11. [PubMed: 11866266]
31. Hackelsberger A, Günther T, Schultze V, Manes G, Dominguez-Muñoz JE, Roessner A. Intestinal metaplasia at the gastro-oesophageal junction: *Helicobacter pylori* gastritis or gastro-oesophageal reflux disease? Gut. 1998; 43:17–21. [PubMed: 9771400]
32. Hirota WK, Loughney TM, Lazas DJ, Maydonovitch CL, Rholl V, Wong RK. Specialized intestinal metaplsia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. Gastroenterol. 1999; 116:277–285.
33. Inomata Y, Koike T, Ohara S, et al. Preservation of gastric acid secretion may be important for the development of gastroesophageal junction adenocarcinoma in Japanese people, irrespective of the *H pylori* infection status. Am J Gastroenterol. 2006; 101:926–933. [PubMed: 16573782]
34. Johansson J, Håkansson HO, Mellblom L, Kempas A, Johansson KE, Granath F. Risk factors for Barrett's oesophagus: a population-based approach. Scand J Gastroenterol. 2007; 42:148–56. [PubMed: 17327933]
35. Jonaitis L, Kriukas D, Sakalauskas L, Janciauskas D, Kupcinskas L. Prevalence of *H-pylori* among patients with erosive esophagitis and Barrett's esophagus among routinely endoscoped patients in high *H-pylori* prevalence area. Helicobacter. 2008; 13:440–1.
36. Kala Z, Dolina J, Marek F, Izakovicova Holla L. Polymorphisms of glutathione S-transferase M1, T1 and P1 in patients with reflux esophagitis and Barrett's esophagus. J Hum Genet. 2007; 52:527–34. [PubMed: 17476458]
37. Kiltz U, Baier J, Schmidt WE, Adamek RJ. Barrett's metaplasia and *Helicobacter pylori infection* (letter). Am J Gastroenterol. 1999; 94:1985–6. [PubMed: 10406284]
38. Laheij RJ, Van Rossum LG, De Boer WA, Jansen JB. Corpus gastritis in patients with endoscopic diagnosis of reflux oesophagitis and Barrett's oesophagus. Aliment Pharmacol Ther. 2002; 16:887–91. [PubMed: 11966496]
39. Lam KD, Phan JT, Garcia RT, Trinh H, Nguyen H, Nguyen K. Low proportion of Barrett's esophagus in Asian Americans. Am J Gastroenterol. 2008; 103:1625–30. [PubMed: 18557711]

40. Loffeld RJ, Werdmuller BF, Kuster JG, Pérez-Pérez GI, Blaser MJ, Kuipers EJ. Colonization with cagA-positive *Helicobacter pylori* strains inversely associated with reflux esophagitis and Barrett's esophagus. Digestion. 2000; 62:95–9. [PubMed: 11025356]
41. Loffeld RJ, van der Putten AB. *Helicobacter pylori* and gastro-oesophageal reflux disease: a cross-sectional epidemiological study. Neth J Med. 2004; 62:188–91. [PubMed: 15460497]
42. Lord RV, Frommer DJ, Inder S, Tran D, Ward RL. Prevalence of *Helicobacter pylori* infection in 160 patients with Barrett's oesophagus or Barrett's adenocarcinoma. Aust NZ J Surg. 2000; 70:26–33.
43. Martinek J, Hucl T, Spicak J. The prevalence of *Helicobacter pylori* infection in some disease of the esophagus, stomach and duodenum – a retrospective analysis. Cesk Slov Gastroenterol Hepatol. 2003; 57:228–32.
44. Monkemuller K, Neumann H, Nocon M, et al. Serum gastrin and pepsinogens do not correlate with the different grades of severity of gastro-oesophageal reflux disease: a matched case-control study. Aliment Pharm Ther. 2008; 28:491–6.
45. Nandurkar S, Talley NJ, Martin CJ, Ng TH, Adams S. Short segment Barrett's oesophagus: prevalence, diagnosis and associations. Gut. 1997; 40:710–5. [PubMed: 9245922]
46. Newton M, Bryan R, Burnham WR, Kamm MA. Evaluation of *Helicobacter pylori* in reflux oesophagitis and Barrett's oesophagus. Gut. 1997; 40:9–13. [PubMed: 9155568]
47. Paull G, Yardley JH. Gastric and esophageal *Campylobacter pylori* in patients with Barrett's esophagi. Gastroenteroloy. 1988; 95:216–8.
48. Peng S, Xiong LS, Xiao YL, et al. Prompt upper endoscopy is an appropriate initial management in uninvestigated patients with typical reflux symptoms. Am J Gastroenterol. 2010; 105:1947–52. [PubMed: 20354508]
49. Rajendra S, Ackroyd R, Robertson IK, Ho JJ, Karim N, Kutty KM. *Helicobacter pylori*, ethnicity, and the gastroesophageal reflux disease spectrum: a study from the East. Helicobacter. 2007; 12:177–83. [PubMed: 17309756]
50. Rajendra S, Kutty K, Karim N. Ethnic differences in the prevalence of endoscopic esophagitis and Barrett's esophagus: the long and short of it all. Dig Dis Sci. 2004; 49:237–42. [PubMed: 15104363]
51. Rex DK, Cummings OW, Shaw M, Cumings MD, Wong RK, Vasudeva RS. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. Gastroenterol. 2003; 125:1670–7.
52. Rugge M, Russo V, Busatto G, et al. The phenotype of gastric mucosa coexisting with Barrett's oesophagus. J Clin Pathol. 2001; 54:456–60. [PubMed: 11376019]
53. Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, Eskes SA, Meuwissen SG. *Helicobacter pylori* and the efficacy of omeprazole therapy for gastroesophageal reflux disease. Am J Gastroenterol. 1999; 94:884–7. [PubMed: 10201451]
54. Sirigu F, Capeccioni S, Dessì A, Masia AM. *Helicobacter pylori* in Barrett's esophagus and in normal or inflamed esophageal mucosa: a retrospective study. Riv Eur Sci Med Farmacol. 1994; 16:131–4. [PubMed: 7480972]
55. Toruner M, Soyikan I, Ensari A, Kuzu I, Yurdaydin C, Ozden A. Barrett's esophagus: prevalence and its relationship with dyspeptic symptoms. J Gastroenterol Hepatol. 2004; 19:535–40. [PubMed: 15086597]
56. Vicari JJ, Peek RM, Falk GW, et al. The seroprevalence of cagA-positive *Helicobacter pylori* strains in the spectrum of gastroesophageal reflux disease. Gastroenterology. 1998; 115:50–7. [PubMed: 9649458]
57. Vieth M, Masoud B, Meining A, Stolte M. *Helicobacter pylori* infection: protection against Barrett's mucosa and neoplasia? Digestion. 2000; 62:225–231. [PubMed: 11070405]
58. Watari J, Morichi K, Tanabe H, et al. Differences in genetic instability and cellular phenotype among Barrett's, cardiac and gastric intestinal metaplasia in a Japanese population with *Helicobacter pylori*. Histopathology. 2009; 55:261–9. [PubMed: 19723140]
59. Werdmuller BF, Loffeld RJ. *Helicobacter pylori* infection has no role in pathogenesis of reflux esophagitis. Dig Dis Sci. 1997; 42:103–5. [PubMed: 9009123]

60. Weston AP, Badr AS, Topalovski M, Cherian R, Dixon A, Hassanein RS. Prospective evaluation of the prevalence of gastric *Helicobacter pylori* infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. Am J Gastroenterol. 2000; 95:387–94. [PubMed: 10685740]
61. White NM, Gabril M, Ejeckam G, et al. Barrett's esophagus and cardiac intestinal metaplasia: two conditions within the same spectrum. Can J Gastroenterol. 2008; 22:369–75. [PubMed: 18414711]
62. Zaninotto G, Portale G, Parenti A, Lanza C, Costantini M, Molena D. Role of acid and bile reflux in development of specialized intestinal metaplasia in distal oesophagus. Dig Liver Dis. 2002; 34:251–7. [PubMed: 12038808]
63. Kuper H, Nicholson A, Hemingway H. Searching for observational studies: what does citation tracking add to PubMed? A case study in depression and coronary heart disease. BMC Med Res Methodol. 2006; 6:4. [PubMed: 16483366]
64. Greenland, S. Meta-analysis. In: Rothman, KJ.; Greenland, S., editors. Modern Epidemiology. 2. Philadelphia, PA: Lippincott-Raven Publishers; 1998. p. 643-73.
65. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000; 53:1119–29. [PubMed: 11106885]
66. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. Am J Epidemiol. 1994; 140:290–6. [PubMed: 8030632]
67. Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics. 2001; 2:463–71. [PubMed: 12933636]
68. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999; 282:1054–60. [PubMed: 10493204]
69. Vaezi MF, Falk GW, Peek RM, Vicari JJ, Goldblum JR, Perez-Perez GI. CagA-positive strains of *Helicobacter pylori* may protect against Barrett's esophagus. Am J Gastroenterol. 2000; 95:2206–11. [PubMed: 11007219]
70. Sampliner RE. The Practice Parameters Committee of The American College of Gastroenterology. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's Esophagus. Am J Gastroenterol. 1998; 93:1028–32. [PubMed: 9672324]
71. El-Serag HB, Sonnenberg A, Jamal MM, Inadomi JM, Crooks LA, Feddersen EM. Corpus gastritis is protective against reflux oesophagitis. Gut. 1999; 45:181–5. [PubMed: 10403728]
72. Goodman KJ, Correa P, Tengana Aux HJ, DeLany JP, Collazos T. Nutritional factors and *Helicobacter pylori* infection in Colombian children. J Pediatr Gastroenterol Nutr. 1997; 25:507–15. [PubMed: 9360204]
73. Moujaber T, MacIntryre CR, Backhouse J, Gidding H, Quinn H, Gilbert GL. The seroepidemiology of *Helicobacter pylori* infection in Australia. Int J Infect Dis. 2008; 12:500–4. [PubMed: 18400542]
74. Lehours P, Yilmaz O. Epidemiology of *Helicobacter pylori* infection. Helicobacter. 2007; 12(Suppl 1):1–3. [PubMed: 17727452]
75. Flood VM, Burlutsky G, Webb KL, Wang JJ, Smith WT, Mitchell P. Food and nutrient consumption trends in older Australians: a 10-year cohort study. Eur J Clin Nutr. 2010; 64:603–13. [PubMed: 20234384]
76. Chang UJ, Hong YH, Suh HJ, Jund EY. Lowering the energy density of parboiled rice by adding water rich vegetables can decrease total energy intake in a parboiled rice-based diet without reducing satiety on healthy women. Appetite. 2010; 55:338–42. [PubMed: 20654665]
77. Jacobson BC, Chan AT, Giovannucci El, et al. Body mass index and Barrett's oesophagus in women. Gut. 2009; 58:1460–6. [PubMed: 19336423]
78. Abrams JA. Obesity and Barrett's oesophagus: more than just reflux. Gut. 2009; 58:1437–8. [PubMed: 19834111]
79. Sugerman HJ. Increased intra-abdominal pressure and GERD/Barrett's esophagus. Gastroenterology. 2007; 133:2075. [PubMed: 18054589]
80. Corley DA, Kubo A, Levin TR, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. Gastroenterology. 2007; 133:34–41. [PubMed: 17631128]

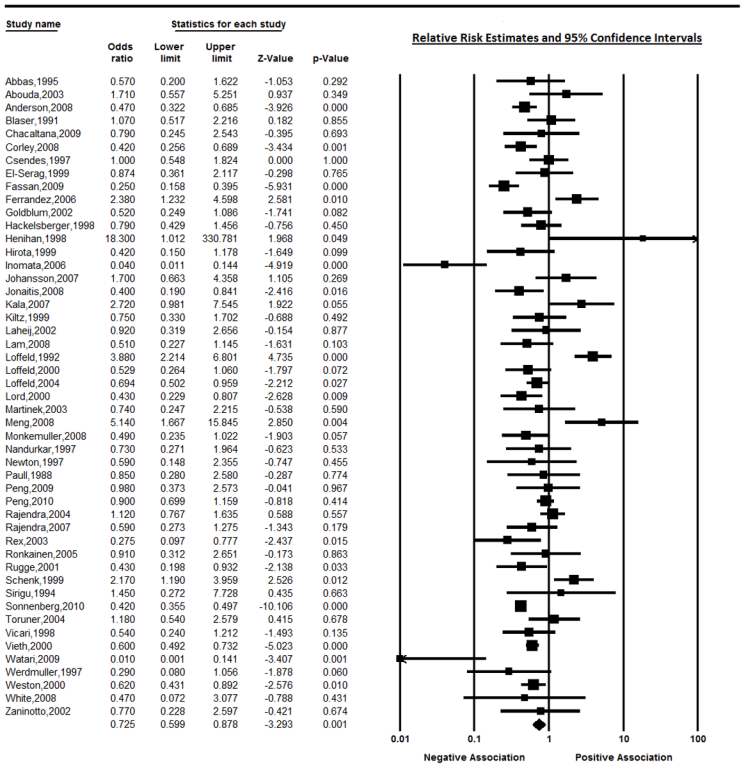

Figure 1.
Estimates of the effect of *H pylori* on Barrett's esophagus using estimates from all available studies.

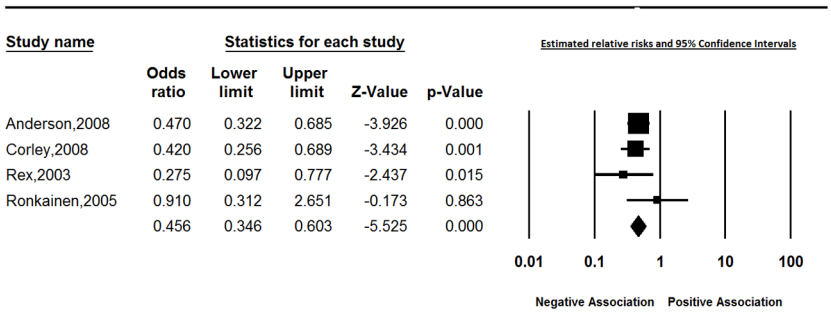

Figure 2.
Estimates of the effect of *H pylori* on Barrett's esophagus in studies with appropriate measurement of *H pylori* and without a likely source of selection bias..

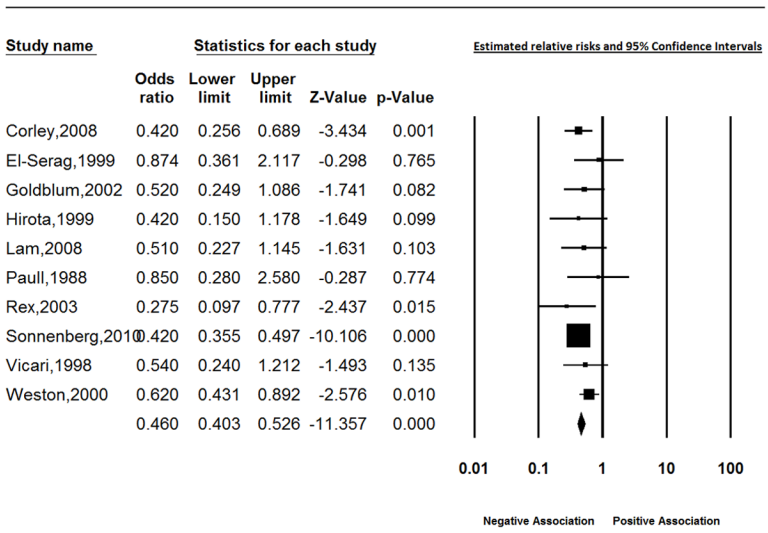

Figure 3.
Estimates of the effect of *Helicobacter pylori* on Barrett's esophagus using estimates from studies in the United States.

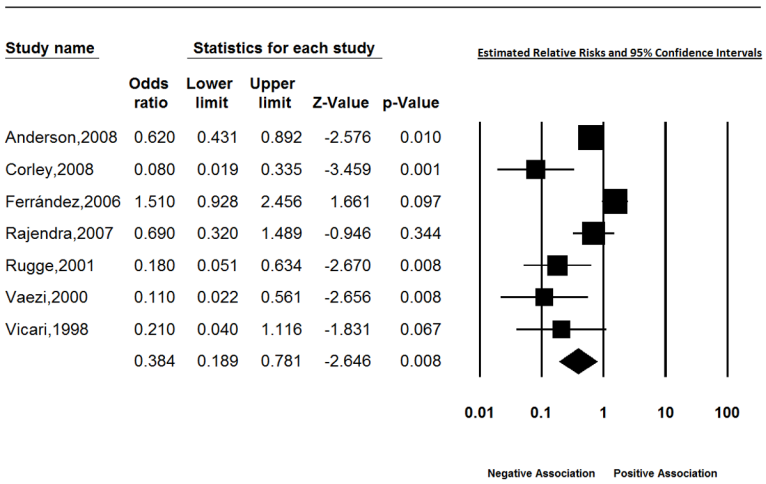

Figure 4.
Estimated effect of *Cag A status* on Barrett's esophagus.

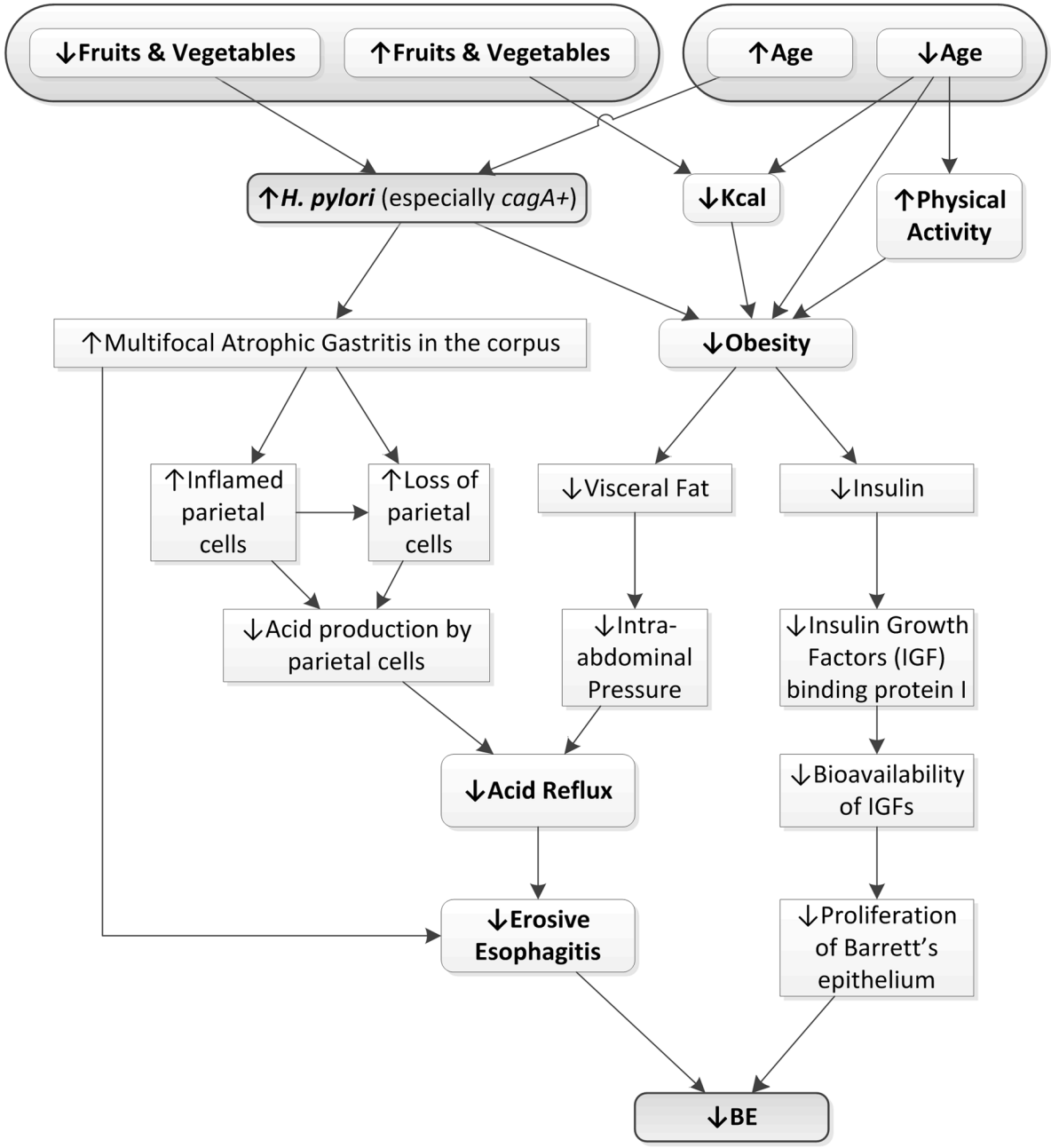

Figure 5.
The putative pathways involving *Helicobacter pylori* and a decreased risk for Barrett's Esophagus.

Table 1

Summary of studies with estimates for the effect of *Helicobacter pylori* on Barrett's esophagus

1st Author's Last Name, Year	Country	Observed Study Design*	Gold Standard Measure of BE Reported?	Measure of *H pylori*	Comparison Group without BE†	Selection Bias?	Factors Adjusted†	N	Relative Risk (95% CI)
Abbas Z, 1995	Pakistan	Case-control	No (prevalent)	Rapid urease, histology	Endoscopy patients with reflux esophagitis	Likely	None	58	0.57 (0.20, 1.62)
Abouda G, 2003	UK	Case-control	No (prevalent)	Rapid urease, serology	Endoscopy patients without GERD	Likely	None	85	1.71 (0.56, 5.28)
Anderson L, 2008	Ireland	Population-based Case-control	Yes (newly diagnosed)	Serology	Random sample from General Practice Master Index	Unlikely	None	468	0.47 (0.32, 0.68)
Blaser M, 1991	Canada	Case-control	Not specified	Serology/histology	Healthy hospital or military employees, blood donors, and elderly nursing home residents.	Likely	None	116	1.07 (0.52,2.23)
Chacaltan, 2009	Peru	Case-control	Yes (prevalent)	Histology	Asymptomatic military personnel without erosive esophagitis, and peptic ulcer disease	Likely	None	922	0.79 (0.25, 2.59)
Corley D, 2008	USA	Population-based Case-control	Yes (prevalent)	Serology	Random sample from Kaiser Permanente HMO	Unlikely	Age, gender, location, BMI, ethnicity, smoking, education, multivitamins	591	0.42 (0.26, 0.70)
Csendes A, 1997	Chile	Case-control	No (prevalent)	Histology	Endoscopy patients with dyspepsia, but no GERD	Likely	None	290	1.00 (0.55, 1.83)
El-Serag H, 1999	USA	Case-control	Yes (prevalent)	Histology	Endoscopy patient with erosive esophagitis	Likely	None	108	0.87 (0.36, 2.11)
Fassan M, 2009	Italy	Case-control	Not specified	Histology	Patients with dyspepsia	Likely	None	420	0.25 (0.16, 0.40)
Ferrández A, 2006	Spain	Case-control	Yes (prevalent)	Serology, rapid urease, histology, PCR	Healthy blood donors	Likely	None	317	2.38 (1.23, 4.59)
Goldblum J, 2002	USA	Case-control	Yes (newly diagnosed)	Rapid urease, histology, culture	Endoscopy VA patients without GERD	Likely	None	130	0.52 (0.25, 1.09)
Hackelsberger A, 1998	Germany	Case-control	Yes (prevalent)	Rapid urease, histology	Endoscopy patients	Likely	None	363	0.79 (0.43, 1.46)
Henihan R, 1998	Ireland	Case-control	Yes (prevalent)	Histology (esophagus)	Reflux esophagitis	Likely	None	122	18.3 (1.01,329.99)
Hirota W, 1999	USA	Cross-sectional	Yes (prevalent)	Histology (esophagus)	Endoscopy patients	Likely	None	842	0.42 (0.15, 1.18)
Inomata Y, 2008	Japan	Case-control	Yes (prevalent)	Serology, rapid urease, histology	Endoscopy patients with esophagitis	Likely	None	227	0.40 (0.19, 0.84)
Johansson J, 2007	Sweden	Case-control	Yes (prevalent)	Histology (gastrooesphageal junction)	Endoscopy patients (*H pylori* was not measured for the population controls)	Likely	Age, gender, BMI, heartburn, smoking and alcohol	519	1.7 (0.7, 4.6)
Jonaitis L, 2008	Lithuania	Case-control	Yes (prevalent)	Rapid urease	Endoscopy patients with esophagitis	Likely	None	227	0.40 (0.19, 0.84)
Kala Z, 2007	Czech Republic	Case-control	No (prevalent)	Rapid urease	Endoscopy patients with esophagitis	Likely	None	86	2.72 (0.98, 7.54)
Kiltz U, 1999	Germany	Case-control	Yes (prevalent)	Rapid urease, serology	Endoscopy patients	Likely	None	355	0.75 (0.33, 1.70)
Laheij R, 2002	Netherlands	Cross-sectional	No (prevalent)	Rapid urease, histology, culture	Endoscopy patients without reflux esophagitis	Likely	Gender, corpus gastritis	551	0.92 (0.30, 2.50)

1st Author's Last Name, Year	Country	Observed Study Design*	Gold Standard Measure of BE Reported?	Measure of *H pylori*	Comparison Group without BE†	Selection Bias?	Factors Adjusted†	N	Relative Risk (95% CI)
Lam K, 2008	USA	Case-control (nested within a Cross-sectional study)	Yes (prevalent)	Serology	Asymptomatic endoscopy patients	Likely	None	269	0.51 (0.32, 0.68)
Loffeld R, 1992	Netherlands	Case-control	Yes (prevalent)	Histology (esophagus)	Healthy blood donors	Likely	None	469	3.88 (2.21, 6.79)
Loffeld R, 2000	Netherlands	Case-control	No (newly diagnosed)	Serology	Endoscopy patients	Likely	None	490	0.53 (0.26, 1.06)
Loffeld R, 2004	Netherlands	Case-control	No (prevalent)	Histology	Endoscopy patients	Likely	None	4154	0.69 (0.50, 0.96)
Lord R, 2000	Australia	Case-control	Yes (prevalent)	Histology	Endoscopy patients	Likely	None	305	0.43 (0.23, 0.81)
Martinek J, 2003	Czech Republic	Case-control	Not Specified	Histology, rapid urease	Endoscopy patients	Likely	None	290	0.74 (0.25. 2.24)
Meng X, 2008	Not stated	Case-control	Not Specified	PCR	Endoscopy patients with dyspepsia	Likely	None	132	5.14 (1.67, 15.87)
Monkemuller K, 2008	Germany	Case-control	Yes (prevalent)	Histology	Non-erosive reflux disease patients with heartburn	Likely	None	194	0.94 (0.23, 1.00)
Nandurkar S, 1997	Australia	Cross-sectional	Yes (prevalent)	Histologyof biopsy tissue from the gastrooesphageal junction	Endoscopy patients	Likely	None	158	0.73 (0.27, 1.98)
Newton M, 1997	England	Case-control	Yes (prevalent)	Histology, rapid urease	Asymptomatic endoscopy patients	Likely	None	41	0.59 (0.15, 2.39)
Paull G, 1988	USA	Case-control	Yes (prevalent)	Histology	Endoscopy patients	Likely	None	51	0.85 (0.28, 2.58)
Peng S, 2009	China	Case-control	Yes (prevalent)	Rapid urease	Endoscopy patients with esophagitis	Likely	None	137	0.98 (0.37, 2.55)
Peng, 2010	China	Case-control	Yes (prevalent)	Rapid urease	Endoscopy patients with uninvestigated reflux symptoms	Likely	None	469	0.90 (0.70, 1.16)
Rajendra S, 2004	Malaysia	Case-control	Yes (prevalent)	Rapid urease, histology	Symptomatic endoscopy patients	Likely	None	1864	1.12 (0.77, 1.64)
Rajendra S, 2007	Malaysia	Case-control	Yes (prevalent)	Serology	Endoscopy patients without GERD	Likely	None	108	0.59 (0.27, 1.26)
Rex D, 2003	USA	Case-control	Yes (newly diagnosed)	Rapid urease	Asymptomatic Colonoscopy patients	Unlikely	None	812	0.27 (0.10, 0.77)
Ronkainen J, 2005	Sweden	Cross-sectional	Yes (prevalent)	Serology, histology, culture	Random sample of the adult population	Unlikely	None	1000	0.91 (0.31, 2.63)
Rugge M, 2001	Italy	Case-control	Yes (prevalent)	Histology	Endoscopy patients with non-ulcer dyspepsia	Likely	None	106	0.43 (0.20, 0.94)
Schenk B, 1999	Netherlands	Case-control	No (prevalent)	Histology	Endoscopy patients with GERD	Likely	None	137	2.17 (1.19, 3.96)
Sirigu F, 1994	Italy	Case-control	Yes (prevalent)	Histology	Age and gender matched endoscopy patients	Likely	None	82	1.45 (0.27, 7.67)
Sonnenberg A, 2010	USA	Cross-sectional	Yes (prevalent)	Histology	Endoscopy patients	Likely	Age, sex, state of residence and insurance type	78985	0.42 (0.35, 0.49)
Toruner M, 2004	Turkey	Case-control	Yes (prevalent)	Histology	Endoscopy patients	Likely	None	335	1.18 (0.54, 2.58)
Vicari J, 1998	USA	Case-control	No (prevalent)	Serology, histology	Endoscopy patients without GERD	Likely	None	105	0.54 (0.24, 1.21)
Vieth M, 2000	Germany	Case-control	No (prevalent)	Histology	Endoscopy patients with non-ulcer dyspepsia	Likely	None	1766	0.60 (0.49, 0.73)
Watari J, 2009	Japan	Case-control	Yes (prevalent)	Histology, culture	Patients with gastric metaplasia	Likely	None	140	0.01 (0.001, .20)

1st Author's Last Name, Year	Country	Observed Study Design*	Gold Standard Measure of BE Reported?	Measure of *H pylori*	Comparison Group without BE†	Selection Bias?	Factors Adjusted†	N	Relative Risk (95% CI)
Werdmuller B, 1997	Netherlands	Case-control	Not specified	Histology, culture, serology, rapid urease	Endoscopy patients with GERD	Likely	None	412	0.29 (0.08, 1.06)
Weston A, 2000	USA	Case-control	Yes (prevalent)	Histology	Endoscopy patients with GERD	Likely	None	506	0.62 (0.43, 0.89)
White N, 2008	Canada	Case-control	Yes (prevalent)	Histology (esophagus)	Endoscopy patients	Likely	None	68	0.47 (0.07, 3.00)
Zaninotto G, 2002	Italy	Case-control	Yes (prevalent)	Histology	Endoscopy patients with GERD	Likely	None	66	0.77 (0.23, 2.58)

*If not specified, studies are not population-based. Study design observed by data extraction may differ from the study design reported in the manuscript.

†BMI= body mass index; GERD = Gastroesophageal reflux disease

Table 2

Summary of studies with estimates for the effect of CagA + *Helicobacter pylori* on Barrett's esophagus

1st Author's Last Name, Year	Country	Observed Study Design	Gold Standard Measure of BE Reported?	Comparison Group without BE[†]	Selection Bias?	Factors Adjusted[†]	N	Measure of Effect (95% CI)
Anderson L, 2008	Ireland	Population-based Case-control	Yes	General Practice Master Index from 4 general practices in the region matched by age and gender	Likely, since age and gender were not adjusted for in the analysis	None	468	0.62 (0.43, 0.89)
Corley D, 2008	USA	Population-based Case-control	Yes	Kaiser Permanente members in Northern California	Unlikely	Age, gender, location, BMI, ethnicity, smoking, education, multivitamins	516	0.08 (0.02, 0.35)
Ferrández A, 2006	Spain	Case-control	Yes	Healthy blood donors	Likely	None	317	1.51 (0.93, 2.46)
Rajendra S, 2007	Malaysia	Case-control	Yes	Endoscopy patients without GERD and without acid suppression therapy	Likely	None	108	0.69 (0.32, 1.49)
Rugge M, 2001	Italy	Case-control	Yes	Endoscopy patients	Likely	None	54	0.18 (0.05, 0.62)
Vicari J, 1998	USA	Case-control	No	Endoscopy patients with Non-ulcer dyspepsia	Likely	None	41	0.21 (0.04, 1.13)
Vaezi M, 2000	USA	Case-control	No	Endoscopy patient without symptomatic GERD	Likely	None	143	0.11 (0.02, 0.52)

[*] If not specified, studies are not population-based.

[†] BMI = body mass index; GERD = Gastroesophageal reflux disease