Published in final edited form as:
Gut. 2008 June ; 57(6): 727–733. doi:10.1136/gut.2007.132068.

Helicobacter Pylori Infection and the Risk of Barrett's Oesophagus: A Community-Based Study

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Abstract

Objective—Gastric colonization with the *Helicobacter pylori* bacterium is a proposed protective factor against oesophageal adenocarcinoma, but its point of action is unknown. We evaluated its associations with Barrett's oesophagus, a metaplastic change that is a probable early event in the carcinogenesis of oesophageal adenocarcinoma.

Design—A case-control study

Setting—The Kaiser Permanente Northern California population, a large health services delivery organization

Patients—Persons with a new Barrett's oesophagus diagnosis (cases) were matched to subjects with gastrooesophageal reflux disease (GORD) without Barrett's oesophagus and to population controls.

Main Measures—Subjects completed direct in-person interviews and antibody testing for *Helicobacter pylori* and its cagA protein.

Results—Serologic data were available on 318 Barrett's oesophagus cases, 312 GORD patients, and 299 population controls. Patients with Barrett's oesophagus were substantially less likely to have antibodies for *Helicobacter pylori* (odds ratio [OR] = 0.42, 95% confidence interval [CI] 0.26–0.70) than population controls; this inverse association was stronger among those with lower body mass indexes (BMI<25 OR=0.03, 95% CI 0.00 – 0.20) and those with cagA+ strains (OR=0.08, 95% CI 0.02–0.35). The associations were diminished after adjustment for GORD symptoms. The *H. pylori* status was not an independent risk factor for Barrett's oesophagus compared to the GORD controls.

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Statement of competing interests: none to declare

Conclusions—*Helicobacter pylori* infection and cagA+ status were inversely associated with a new diagnosis of Barrett's oesophagus. The findings are consistent with the hypothesis that *Helicobacter pylori* colonization protects against Barrett's oesophagus and that the association may be at least partially mediated through GORD.

Keywords

Barrett's esophagus; Barrett's oesophagus; helicobacter; GERD; GORD; esophageal adenocarcinoma; oesophageal adenocarcinoma

BACKGROUND

The incidence of oesophageal adenocarcinoma is rising more rapidly than that of any other malignancy in many countries, but relatively little is known about the carcinogenic sequence leading to cancer development.[1–4] Barrett's oesophagus, a metaplastic change in the oesophageal lining that is associated with damage from gastrooesophageal reflux (GORD), may be a precursor to oesophageal adenocarcinoma.[5] Persons with Barrett's oesophagus have a substantially increased risk of oesophageal adenocarcinoma; thus, the evaluation of risk factors for Barrett's oesophagus may provide information on early events in the carcinogenic pathway for oesophageal adenocarcinoma.[5]

Helicobacter pylori (*H. pylori*) is a bacterium that frequently colonizes the gastric lining. *H. pylori*, especially the cagA+ strain, is an established risk factor for stomach cancer.[6] In contrast, *H. pylori* may be inversely associated with the risk of developing oesophageal adenocarcinoma, although few studies exist.[7–10] The hypothesized links between *H. pylori*, Barrett's oesophagus, and oesophageal adenocarcinoma are intriguing for several reasons. The decreasing prevalence of *H. pylori* infection in many countries correlates with the recent marked increases in oesophageal adenocarcinoma incidence, and the prevalence of *H. pylori* infection is lower in demographic groups at higher risk of oesophageal adenocarcinoma, such as Caucasians.[11–14] If a potentially beneficial effect for *H. pylori* colonization were demonstrated, it would further inform the debate regarding the overall utility of routine *H. pylori* testing and eradication.[15]

Existing studies of the association between *H. pylori* and Barrett's oesophagus have been conflicting, possibly from the lack of ideal comparison groups. Almost all existing studies consist of series of endoscopy patients and lack a true non-endoscopy control population.[16–24] Since patients undergo endoscopy for a variety of indications, subjects referred for endoscopy (but who lack Barrett's oesophagus) may not represent the general population's prevalence of *H. pylori.* Patients with nonulcer dyspepsia or peptic ulcer disease, for example, may be more likely to be colonized with *H. pylori* than the general population.[25–27] Comparisons of Barrett's oesophagus vs. non-Barrett's oesophagus patients in endoscopic series, therefore, may suggest that Barrett's oesophagus patients have a lower prevalence of Helicobacter pylori when, in fact, it is the comparison group that has a higher than average prevalence. Case-control studies of the association between *H. pylori* and oesophageal adenocarcinoma may also be misleading: analyses using post-cancer diagnosis sera are potentially biased by the loss of antibody positivity over time or by treatment of *H. pylori* for gastrointestinal symptoms earlier in life;[28–30] these sera may thus not reflect the true infection status at the initiation of the carcinogenic pathway (such as when Barrett's oesophagus may develop).[31] The evaluation of new diagnoses of Barrett's oesophagus (at their first endoscopy that diagnosed Barrett's oesophagus), the use of population controls, and the evaluation of treatment histories for *H. pylori* would provide insights less susceptible to such biases.

We evaluated the associations between *Helicobacter pylori* antibody status and Barrett's oesophagus using a case-control study of all persons with a new diagnosis of Barrett's oesophagus in a non-referral, community-based population.

DESIGN AND METHODS

Study Population

We conducted a nested case-control study within the Kaiser Permanente, Northern California (KPNC) integrated health services delivery organization. Its membership contains approximately 3.3 million persons; the membership demographics closely approximate the underlying census population of Northern California.[32] Eligible subjects were all adult (ages 18–79 years) members who had at least 2 years of membership prior to their index date, met the case or control definitions outlined below, and understood spoken and written English. The population and GORD comparison groups were frequency matched to the Barrett's oesophagus cases by gender, age at the index date, and geographic region (each subject's home facility); controls were serially recruited coincident with case identification. The index date for cases was the date of Barrett's oesophagus diagnosis and for controls was the midpoint of each 2–3 month selection interval for the cases.

Case Definition

Cases were eligible KPNC members with a new Barrett's oesophagus diagnosis, using the International Classification of Disease, 9th revision (ICD-9) code 530.2 (which at KPNC is uniquely coded as "Barrett's esophagitis"), or the College of American Pathologists code 73330 ("Barrett's oesophagus"). A single board-certified gastroenterologist (DAC) then reviewed the endoscopy and pathology records of potentially eligible cases. Subjects were included if the endoscopist clearly described a visible length of columnar-type epithelium proximal to the gastrooesophageal junction/gastric folds, this area was biopsied, and the biopsies showed specialized intestinal epithelium.[5] Cases were serially enrolled (shortly after their diagnosis and record review) between October, 2002 and September, 2005. Pathology slides underwent a separate manual review by a gastrointestinal pathologist (GJR). The following patients were excluded: patients with only gastric-type metaplasia of the oesophagus on all pathologic evaluations; patients with columnar metaplasia without features of intestinal metaplasia on all pathology readings; patients without a biopsy of oesophageal origin; biopsies of only a mildly irregular squamocolumnar junction (i.e. an "irregular z-line"); and patients with a prior Barrett's oesophagus diagnosis. The index date for cases was the date of Barrett's oesophagus diagnosis.

Population Controls

Controls from the base population were randomly selected from the at-risk (no prior Barrett's oesophagus) members of the entire Northern California Kaiser Permanente membership roster using risk set sampling.[33]

GORD Comparison Group

GORD comparison group members were randomly selected from among persons with the following characteristics prior to their index date: a GORD-related diagnosis code (ICD-9 codes 530.11 [reflux esophagitis] or 530.81 [gastrooesophageal reflux]); a prescription for at least 90 days supply of a histamine-2 receptor antagonist or a proton pump inhibitor (medications used for treating GORD symptoms) in the previous year (from electronic pharmacy records); no prior Barrett's oesophagus; and an esophagogastroduodenoscopy close to the index date that did not demonstrate oesophageal columnar metaplasia of any type.

Exposure Measurements

All subjects completed: an in-person interview (most commonly at the subject's home) of medication use, GORD symptoms and medical history; a food frequency questionnaire; phlebotomy; and anthropometric measurements. Participants reported exposures in the year prior to the index date.

The body mass index used the equation (BMI = weight (kilograms)/height(meters)^2). GORD symptom frequency and severity were evaluated with a validated questionnaire.[34] GORD was defined as heartburn (a burning pain or discomfort behind the breastbone) or acid regurgitation (a bitter or sour-tasting fluid coming up into the throat or mouth). Severity was recorded as mild (could be ignored), moderate (could not be ignored, but didn't affect lifestyle), severe (could not be ignored and did affect lifestyle), or very severe (markedly affected lifestyle). Frequency was defined as never, less than once a month, once a month, once a week, several times a week, or daily.

H. pylori assays were blinded to the case status and run in mixed batches of cases and controls. These in-house ELISA assays have been used extensively in the Kaiser Permanente population and validated in different ethnic groups.[35–37] The assay sensitivity and specificity for a current, active infection (compared to histopathologic diagnosis) have been 94% and 91%, respectively. All subjects were also tested for antibodies to the *H. pylori* CagA protein (OraVax, Inc, Cambridge, MA).[38]

Confounding and Effect Modification

We evaluated the following as potential confounders: BMI, ethnicity (Caucasian vs. non-Caucasian), smoking, recent alcohol use, aspirin or nonsteroidal anti-inflammatory drug (NSAID) use (including over-the-counter use from the interview), a comorbidity index (the DxCg score, which creates a predictive comorbidity score based on demographic data, medical coding, and pharmacy utilization),[39,40] calorie intake, waist circumference, socioeconomic data (grade level and household income), and multivitamin use. We evaluated for non-response bias (differences between participants vs. eligible non-participants) using available information from electronic databases (BMI, smoking status, ethnicity, age, gender, DxCg score, GORD diagnosis) on eligible subjects. In addition, contacted subjects who declined an in-person interview were asked to complete a brief telephone interview for several risk factors.

Statistical Analysis

We utilized standard analytic techniques for case-control studies including unconditional logistic regression and the binomial distribution.[33,41–43] Confounders were incorporated if their inclusion altered the odds ratio for the main effects by >10% (education level or multivitamin use), they were a frequency matched variable (gender, age, and medical facility) or if published data suggested potential associations (ethnicity, BMI and smoking status). We evaluated for effect modification (e.g. differences in the associations by gender or BMI) by evaluating cross product terms in the logistic regression model and contrasting stratum specific odds ratios.[43] The attributable fraction calculations utilized maximum likelihood estimates from the logistic regression models.[44]

The study and analyses were approved by the institutional review board and all subjects provided written informed consent. Analyses used the STATA statistical package (version 8, STATA Corporation, College Station, TX).

RESULTS

Study Population

We interviewed 953 subjects; serologic data were available for 929 subjects (97% of interviewed subjects): 318 Barrett's oesophagus cases, 312 GORD patients, and 299 controls. The interviewed subjects represented 57% of all living, eligible subjects able to be contacted by phone and 43% of all potentially eligible subjects. Reasons for non-participation included: declined to participate (33%), unable to contact (18%), severe physical or mental disorders (5%) (primarily excluded by their physician prior to contact), or deceased (1%). The general subject characteristics are provided in Table 1. Equivocal *H. pylori* assays were found in 24 subjects; after their exclusion, there were 309 Barrett's oesophagus cases, 301 GORD patients, and 295 controls for the main analyses. Among the cases, the length of the Barrett's segment was <3 centimeters in 117 subjects (37%), ≥3 centimeters in 150 subjects (47%), and the length was not reported in 51 subjects (16%).

Helicobacter pylori antibody status

The prevalences of H. pylori infection were 11.7%, 9.6%, and 22.7% in the Barrett's oesophagus cases, GORD patients, and controls, respectively. There was an inverse association between a positive *H. pylori* antibody status and the risk of Barrett's oesophagus (Table 2) (OR 0.42, 95% CI 0.26–0.70) compared with the population controls. There were no differences between subjects with a long segment of Barrett's oesophagus (≥3 centimeters) (OR=0.37, 95% CI 0.19–0.70) vs. subjects with shorter segments (OR=0.45, 95% CI 0.22–0.91). The *H. pylori* status was not an independent risk factor for Barrett's oesophagus compared to the GORD controls (Table 2).

CagA+ status

The risk of Barrett's oesophagus was substantially lower among subjects with a cagA+ *H. pylori* antibody status (OR=0.08, 95% CI 0.02–0.35) (compared to the population controls) (Table 2). There was a weaker inverse association among subjects who were *H. pylori* antibody positive but cagA antibody negative (OR=0.61, 95% CI 0.35–1.04).

Mediation by GORD Symptoms

The absence of *H. pylori* has been hypothesized to increase the risk of GORD, which may, in turn, directly increase the risk of Barrett's oesophagus. We evaluated whether the association between *H. pylori* antibody status and Barrett's oesophagus was potentially mediated through GORD symptoms by contrasting logistic models with and without the inclusion of GORD symptoms. If GORD is in the causal pathway between *H. pylori* and Barrett's oesophagus, then "adjusting" for GORD symptoms in the logistic model should diminish or eliminate any association between *H. pylori* and Barrett's oesophagus. Adjustment for GORD symptom severity (among persons with at least weekly GORD symptoms) decreased the association between a positive *H. pylori* antibody and Barrett's oesophagus from OR=0.42 (95% CI 0.26–0.70) to OR=0.71 (95% CI 0.36–1.38); adjustment for GORD symptom frequency alone decreased the association to OR=0.54 (95% CI 0.30–0.98) (Table 3).

Attributable Fraction

The attributable fraction for any H. pylori infection (i.e. the proportion of Barrett's oesophagus in the population theoretically independently attributable to the absence of any *H. pylori* infection, if we assume the associations are causal) was 32.9% (95% CI 12.5%, 48.6%). The attributable fraction for a cagA+ H. pylori infection was 82.0% (95% CI 33.0%, 95.0%). These estimates are adjusted for the listed potential confounders.

Supplemental Analyses

The inverse association for a positive H. pylori antibody was stronger among subjects with lower BMIs (BMI<25 OR=0.03, 95% CI 0.00 – 0.20) than among those with higher BMIs (BMI≥30 OR=0.43, 95% CI 0.20–0.91), p-value on interaction term p=0.16 (comparisons used population controls).

There was no evidence of confounding by caloric intake, smoking status, alcohol use, aspirin use, nonsteroidal anti-inflammatory agents, household income, or comorbidity status (DxCg score). The exclusion of educational status or multivitamin use had a small influence, thus these were included in the main models. A fully adjusted model for *H. pylori* antibody status (containing all the listed factors plus age, gender, facility, and ethnicity) (OR=0.42, 95% CI 0.25, 0.69) was very similar to a model that contained only the bivariate association between case status and *H. pylori* antibody status (OR=0.46, 95% CI 0.30, 0.72).

Although Barrett's oesophagus itself is asymptomatic, and GORD symptoms are not typically treated with effective *H. pylori* eradication regimens, we evaluated for the possibility of reverse causation whereby gastrointestinal symptoms (prior to the Barrett's oesophagus diagnosis) resulted in taking medications that decreased H. pylori prevalence at the time of the Barrett's oesophagus diagnosis. The pharmacy database included a total of 57 subjects (a combination of cases and controls) who had received effective two or three drug anti- *H. pylori* antibiotic regimens prior to their index dates. Barrett's oesophagus cases were not significantly more likely to have received treatment (p=0.16) and an analysis that adjusted for prior treatment status also did not alter the main association between *H. pylori* and Barrett's oesophagus (OR=0.42, 95% CI 0.26–0.69).

The evaluation for non-response bias utilized available electronic medical data on all subjects (see methods). Participants did not differ significantly from non-participants by gender, smoking status, or BMI (using electronic data). Participants were somewhat less likely to be Asian or Hispanic, more likely to have an electronic GORD diagnosis (63% vs. 52%), slightly older (62 years vs. 59 years), and had a slightly higher comorbidity score (3.1 vs. 2.7, p<0.01). Similar relationships were seen in analyses confined to the population controls and for aspirin/NSAID use (among population controls who participated in a brief telephone interview).

DISCUSSION

To our knowledge, this is the first study of the association between *Helicobacter pylori* antibody status and Barrett's oesophagus in a large community-based population; there were several findings. First, there was a strong inverse association between the presence of antibodies against *H. pylori* and Barrett's oesophagus, for comparisons with the population controls. Second, *H. pylori* infection did not have an inverse association for Barrett's oesophagus compared with GORD patients; this suggests that, among patients who have GORD, *H. pylori* is not an additional risk factor for Barrett's oesophagus. Third, the association between *H. pylori* and Barrett's oesophagus among the population controls was diminished after adjustment for GORD symptom severity. These analyses suggest that, if the associations are causal, a portion of the risk for Barrett's oesophagus may be associated with the absence of *Helicobacter pylori* and this association may be at least partly mediated through *H. pylori's* associations with GORD.

This study extends the findings of previous analyses, which found that persons without *Helicobacter pylori* colonization were more likely to develop oesophageal adenocarcinoma. [7–10] Some prior studies also suggested an increased risk of Barrett's oesophagus in patients without *Helicobacter pylori*, but these almost exclusively consisted of endoscopy studies that contrasted patients with Barrett's oesophagus with patients referred for other gastrointestinal

problems, possibly contributing to the conflicting results.[16,23,45–47] In addition, no prior study to our knowledge evaluated for prior treatment of *H. Pylori.*

The mechanism through which the absence of *Helicobacter pylori* colonization is associated with Barrett's oesophagus is unknown, but there are several potential possibilities. First, *Helicobacter pylori* infection, in particular the more virulent cagA+ strain, may suppress acid production and lead to gastric atrophy; this may lower the risk of Barrett's oesophagus and oesophageal adenocarcinoma (both or which are directly associated with GORD).[7,38,48–50] Epidemiologic data linking an absence of *H. pylori* and GORD, however, are somewhat conflicting, likely due to patient selection, the use of different comparison groups, and the lack of population-based studies.[24,51,52] A recent large (604 patients) cross-sectional study of endoscopy patients actually suggested an increased risk of Barrett's oesophagus and GORD among patients with *H. pylori*.[16] Randomized trials of *H. pylori* treatment have not demonstrated increased GORD symptoms after eradication, though eradication in adulthood may not have a similar effect on gastric acid production as the life-long absence of *H. pylori*, since most *H. pylori* infections start in childhood.[53–55] Our results suggest some of the association between *H. pylori* and Barrett's oesophagus is mediated through GORD symptoms; if it was entirely mediated through GORD symptoms we might expect the association to be abolished rather than only diminished. However, this is also consistent with the imperfect correlation between GORD symptoms and GORD-induced reflux damage, and the lack of reflux symptoms among a portion of persons with documented Barrett's oesophagus or oesophageal adenocarcinoma.[56–60] Second, the presence of H. pylori may enhance gastric emptying (thereby decreasing acid reflux) in younger persons.[61,62] Third, the absence of *H. pylori* may increase ghrelin levels,[63–65] a peptide that increases appetite and facilitates fat storage, and lead to weight gain,[66] a risk factor for both GORD and for oesophageal adenocarcinoma.[67,68] Although our finding that the absence of *H. pylori* was more strongly associated with Barrett's oesophagus at lower BMI's does not provide general support for this hypothesis, it is possible that an increased risk of GORD at higher BMI's unrelated to *H. pylori* infection may dilute the association between *H. pylori* and Barrett's oesophagus among obese patients. The biologic role of *H. pylori* is complex, given the positive associations between *H. pylori* infection and the risks of gastric cancer and peptic ulcer disease.[6,69]

There are several strengths of this analysis. First, the subjects came from a diverse population base that closely approximates the region's census demographics; thus, the results can likely be generalized to similar large populations.[32] Second, this is the first study to use only patients with serially identified new diagnoses of Barrett's oesophagus and the study identified essentially all patients with a new diagnosis within the population. Prevalent or referral cases may represent patients with a different clinical course, patients compliant with follow-up, or persons who initiated medical or behavioral changes after their diagnosis. [70] In particular, patients may have *H. pylori* identified and treated at the time of endoscopy. Given *H. pylori* antibody titers can fall after treatment, the use of only new diagnoses decreases the potential for bias.[28,29] Third, the GORD comparison group provided information on the risk of Barrett's oesophagus among patients with GORD. Fourth, we were able to stratify by length of Barrett's oesophagus; the analyses confined to long segments of Barrett's oesophagus minimize the chance of misclassifying persons with hiatal hernias or irregular gastrooesophageal junction boundaries as having Barrett's oesophagus. Finally, the data was of high quality and contained information for multiple potential confounders including socioeconomic status and treatment in recent years for *H. Pylori*. Measurements used trained personnel, a systematic protocol, an established laboratory, validated questionnaires, direct review of pathology and endoscopic examinations, and comprehensive pharmacology databases.

There are several potential limitations of this analysis. First, case-control studies cannot definitively establish cause and effect.[33] Second, observational studies are subject to bias. Although analyses of multiple variables provided little evidence of confounding, we cannot exclude incomplete control of confounding and we cannot exclude a component of reverse causation whereby patients with Barrett's oesophagus had been previously treated for *H. pylori* in the more distant past, thereby decreasing their antibody titers and the study's use of new diagnoses of Barrett's oesophagus should decrease the effect of interventions associated with the endoscopy itself. Similarly, although cases should be representative of new diagnoses of Barrett's oesophagus, as with most chronic diseases, the date the Barrett's oesophagus first developed is unknown. Patients diagnosed with Barrett's oesophagus may differ from subjects with undiagnosed Barrett's oesophagus. However, since *H. pylori* colonization most commonly begins in childhood, it is unlikely that the Barrett's oesophagus preceded the exposure. Third, the presence of nonresponders may lead to bias; however, the electronic data suggested that nonresponders were, on average, somewhat healthier than the responders, with slightly lower comorbidity scores. This finding, combined with the lack of major confounding factors in the primary analyses, would suggest the effect of nonresponse, if any, may be to bias the results towards the null (making the population controls more similar to the cases). Fourth, the number of cagA+ subjects was small in some analyses, decreasing the precision of these estimates, particularly the analyses of mediation by GORD symptoms.

In summary, in a community-based population, there were inverse associations between the presence of *H. pylori* antibodies and a first diagnosis of Barrett's oesophagus. The associations for Barrett's oesophagus were stronger for the cagA positive strain, but were present also for cagA negative strains. The attributable fraction analyses suggest that, if the associations are causal, a substantial portion of the risk for Barrett's oesophagus may be associated with the absence of *Helicobacter pylori.* These data are consistent with the hypothesis that the absence of *Helicobacter pylori* infection may be linked to the risk of oesophageal adenocarcinoma, with Barrett's oesophagus as a potential intermediary step. Future studies are needed to evaluate whether the absence of *H. pylori* infection is associated with an increased risk of Barrett's oesophagus progressing to oesophageal adenocarcinoma and whether interventions that eradicate *H. pylori* infection modify the subsequent risk of developing oesophageal adenocarcinoma.

Acknowledgements

Funding Sources: United States National Institutes of Health RO1 DK63616 and K08 DK02697. The study sponsor reviewed the protocol, but did not participate in the collection, analysis, or interpretation of the data.

Abbreviations

GORD
: Gastroosophageal reflux disease

BMI
: body mass index

KPNC
: Kaiser Permanente, Northern California

CI
: confidence interval

ICD-9
: International Classification of Disease, 9th revision

NSAID

nonsteroidal anti-inflammatory drug

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Table 1

Characteristics of study groups

	Barrett's Oesophagus Cases	GORD controls	Population controls
	Number or Mean (% or standard deviation)	Number or Mean (% or standard deviation)	Number or Mean (% or standard deviation)
Number of subjects	318	312	299
Age (years)			
20–39	9 (3)	12 (4)	9 (3)
40–59	120 (38)	113 (36)	101 (34)
60–79	189 (59)	187 (60)	189 (63)
Race			
White	276 (87)	250 (80)	254 (85)
Black	4 (1)	20 (6)	16 (5)
Hispanic	25 (8)	20 (6)	11 (4)
Asian	3 (1)	7 (2)	8 (3)
Others	8 (3)	13 (4)	9 (3)
Unknown	2 (1)	2 (1)	1 (0)
Gender			
Male	232 (73)	215 (69)	206 (69)
Smoking status (Ever smoked)	210 (66)	184 (59)	164 (55)
GORD			
Any GORD	297 (93)	293 (94)	180 (60)
At least weekly	256 (81)	230 (74)	84 (28)
Mean body mass index (kg/m^2)	29.5 (±6.1)	28.8 (±5.3)	29.5 (5.8)

Eligible Barrett's oesophagus cases were frequency matched to control groups by gender, age (by 5 year age groups) and center of diagnosis.

Table 2

Antibody status for *Helicobacter pylori* infection, cagA antibody status, and the risk of Barrett's oesophagus.

		Number of Subjects	Odds Ratio[1] (95% Confidence Interval)	Odds Ratio[1] (95% Confidence Interval)
Helicobacter pylori Antibody Status	CagA+ Antibody Status	Barrett's Oesophagus/GORD/Controls	Barrett's Oesophagus vs. Controls	Barrett's Oesophagus vs. GORD patients
Negative	Negative	263/259/225	1.00	1.00
	Positive	10/13/3	1.95 (0.48–7.83)	0.78 (0.30–2.00)
Positive	Negative	31/19/44	0.61 (0.35–1.04)	1.66 (0.89–3.13)
	Positive	5/10/23	0.08 (0.02–0.35)	0.30 (0.06–1.45)
All *H. Pylori* Positive subjects[2]		36/29/67	0.42 (0.26–0.70)	1.24 (0.71–2.18)

[1] Adjusted for gender, age, home facility location, body mass index, ethnicity, smoking status, educational status and multivitamin use

[2] These include both cagA positive and cagA negative subjects.

Table 3

Association between *Helicobacter pylori* infection and Barrett's Oesophagus: evaluation of mediation by GORD symptoms. This analysis evaluates whether the association between *Helicobacter pylori* and Barrett's oesophagus (for Barrett's oesophagus cases vs. population controls) is potentially mediated by the frequency or severity of GORD symptoms.

		Number of Subjects	**Odds Ratio[1] (95% Confidence Interval)**	**Odds Ratio[1] (95% Confidence Interval)**	**Odds Ratio[1] (95% Confidence Interval)**
Helicobacter pylori Antibody Status	CagA+ Antibody Status	Barrett's Oesophagus/GORD/Controls	Barrett's Oesophagus vs. Controls (Without GORD in model)	Barrett's Oesophagus vs. Controls (With GORD *frequency* in model)[2]	Barrett's Oesophagus vs. Controls (With GORD *severity* in model)[2]
Negative	Negative	263/225	1.00	1.00	1.00
Positive	Negative	31/44	0.61 (0.35–1.04)	0.80 (0.42–1.51)	1.29 (0.60–2.80)
	Positive	5/23	0.08 (0.02–0.35)	0.08 (0. 15–0.45)	0.08 (0.12–.49)
All *H. Pylori* Positive subjects[3]		36/67	0.42 (0.26–0.70)	0.54 (0.30–0.98)	0.71 (0.36–1.38)

[1] Adjusted for gender, age, home facility location, body mass index, ethnicity, smoking status, educational status and multivitamin use

[2] The GORD severity analysis compared severity among persons with at least weekly GORD to persons with no GORD symptoms. Severity was recorded as mild (could be ignored), moderate (could not be ignored, but didn't affect lifestyle), severe (could not be ignored and did affect lifestyle), or very severe (markedly affected lifestyle). Frequency was defined as never, less than once a month, once a month, once a week, several times a week, or daily.

[3] These include both cagA positive and cagA negative subjects.