Risk factors for erosive and non-erosive gastroesophageal reflux disease and Barrett’s esophagus in Northern Sardinia

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ABSTRACT
Objective: Gastroesophageal reflux disease (GERD) and esophageal adenocarcinoma have been increasing. We studied the relationship of conventional risk factors and Helicobacter pylori infection in patients with erosive and non-erosive GERD and Barrett’s esophagus.

Materials and methods: This was a retrospective study of dyspeptic patients undergoing upper endoscopy between 2002 and 2013. Following endoscopy, those with previously undiagnosed GERD were sub-grouped into non-erosive GERD (NERD), erosive GERD (eGERD), or Barrett’s esophagus. H. pylori status was confirmed by 2 positive tests.

Results: About 5156 patients were included, GERD was present in 65.6% including 1992 with NERD and 1392 with eGERD. About 1772 dyspeptic patients without symptoms of reflux and/or esophagitis served as controls. A hiatal hernia increased the risk of both eGERD and NERD. eGERD was more prevalent among the obese (OR = 1.72, p < 0.001), men (OR = 1.38, p < 0.001) and current smokers. Helicobacter pylori infection was significantly more common among those with NERD (OR = 1.17 versus 1.01, p = 0.046). Logistic regression analysis for eGERD and NERD using age, gender, body mass index, H. pylori infection, hiatal hernia, and smoking showed that overweight and hiatal hernia were significant risk factors for eGERD, and female gender for NERD. Male gender, eGERD and age > 50 years were the major risk factors for Barrett’s esophagus.

Conclusions: The epidemiology of eGERD and NERD suggests differences in pathogenesis, and prevention and treatment strategies should be separately examined in men and women.

Introduction
Gastroesophageal reflux occurs normally, especially post-prandially.[1] Reflux is considered pathologic when is associated with regular symptoms or visible esophageal mucosal injury. Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications such as Barrett’s esophagus.[2,3] Erosive esophagitis (eGERD) is diagnosed in patients who have endoscopic evidence of esophageal erosions with (or without) symptoms of GERD. Those with normal-appearing esophageal mucosa are said to have non-erosive GERD (NERD). Clinical gastroesophageal reflux disease typically occurs as sequelae of reflux of acid gastric content, the severity of which correlates with the esophageal acid exposure especially with the esophageal acid load.[1,3] Factors influencing the ability of the stomach to make acid such as gender, smoking, or Helicobacter pylori infection can affect the incidence and severity of GERD and its complications such as Barrett’s esophagus and esophageal adenocarcinoma.[4–8] Helicobacter pylori is a common chronic infection and causes progressive gastric mucosal inflammation. When H. pylori involves the gastric corpus, it acts like a biologic antisecretory agent by reducing the ability of the stomach to secrete acid.[3] In contrast, when the H. pylori infection is largely restricted to the gastric antrum, the infection is associated with high and prolonged acid secretion, an increased risk of duodenal ulcer, as well as an increased risk of symptomatic GERD.[9,10] Thus, both the presence of H. pylori infection and its location within the stomach are important factors related to the presence or absence of GERD. eGERD and NERD seems to have different pathophysiological and clinical features.[11] For example, studies have shown that 30–50% of NERD patients display esophageal acid exposure within the physiological range.[12] Overall, the results of epidemiologic studies have suggested that between 50% and 70% of patients with GERD have NERD.[12] It is possible that some of the recent studies overestimated the prevalence of NERD including healed erosive esophagitis subjects because of the large usage of PPIs.[12]

Although it is often assumed that NERD and eGERD represent a continuous disorder, differences in relation to epidemiological features, pathophysiological characteristics, and responses to treatment have been demonstrated.[12] For example, the evaluation of esophageal sensitivity in patients...
with NERD demonstrated a reduced compliance for painful stimuli.[13–16]

This study evaluated previously undiagnosed and untreated (i.e., naive) patients referred to a tertiary care system because of symptoms suggestive of GERD. The primary outcome was to investigate the relationship among eGERD, NERD, and Barrett’s esophagus and the presence of traditional risk factors for GERD (i.e., hiatal hernia, obesity, age, gender, and smoking habits), and H. pylori infection. Data were analyzed for the entire cohort and separately for those with eGERD, NERD, and those with Barrett’s esophagus.

Methods

Setting

This was a single-center retrospective study of patients undergoing upper endoscopy in a tertiary GI clinic in Sassari, Italy, from January 2002 to December 2013.

Eligibility criteria

Patients were referred to the endoscopy by family physicians and/or specialists for any reason (dyspeptic or reflux symptoms, follow-up, etc.). All patients were from Northern Sardinia, and each one was evaluated at the time of endoscopy by a gastroenterologist using a standard form (see Supplemental material). A medical history was obtained comprising chief complaint and all associated symptoms and treatments. Demographic data including age and gender, cigarette smoking, and the height and weight were collected for each participant. Body mass index (BMI) was calculated using the formula weight (kg)/height (m)^2. A standardized questionnaire for GERD symptoms was not available.

Exclusion criteria

In order to collect treatment-naïve subjects, those receiving PPIs, histamine two receptor antagonists and/or antacids for any reason, bismuth compounds, antibiotics, or probiotics during the 4 weeks before EGD, and those with previous endoscopy and/or a diagnosis of reflux disease were excluded. For patients who underwent multiple EGDs within the study period, only the results from the first endoscopy were included. The absence of gastric biopsies and/or dysphagia. Patients were further characterized on the basis of endoscopic findings as having eGERD, NERD, or Barrett’s esophagus. Esophagitis severity was graded using the Los Angeles classification which is based on the location and extent of erosions. Barrett’s esophagus was defined by the presence of a typical pink salmon-color columnar-lined esophagus, observed by endoscopy and confirmed by the pathologist as esophageal biopsies showing intestinal-type epithelium with goblet cells with or without dysplasia. Short and long Barrett’s segments were pooled as Barrett’s esophagus. When present, the degree (absent, low, and high grade) of dysplasia was not categorized. A hiatal hernia was diagnosed when the squamocolumnar junction was displaced at least 2 cm above the diaphragmatic hiatus.[11] Helicobacter pylori status was assessed by at least two tests: histology (at least four gastric biopsy specimens were taken: two from the antrum, one from the angulus and one from the corpus) plus rapid urease test (RUT) and/or 13Carbon-urea breath test (13C-UBT) as previously described.[11] Patients with neither GERD symptoms nor esophagitis were used as the control group.

Ethical considerations

The protocol was approved by the Local Ethics Committee (Protocol no. 2099/CE, 2014).

Statistical analysis

Patients were considered positive for H. pylori when the microorganism was detected at least in two tests (one gastric biopsy and 13C-UBT or RUT). Because both the presence of H. pylori infection and its location within the stomach are important for acid secretion and symptomatic GERD,[9,10] active gastritis, intestinal metaplasia, follicular gastritis, and atrophy were reported when observed on biopsy according to the site. Patients were categorized into (i) patients with chronic active gastritis with H. pylori infection; (ii) patients with gastritis and metaplasia and/or atrophy in the antrum and/or in the corpus positive for H. pylori infection; (iii) and with gastritis with metaplasia and/or atrophy in the antrum and/or in the corpus negative for H. pylori infection. The presence of corpus atrophy with normal antral mucosa was considered possibly related to autoimmune gastritis. Overweight and obesity were defined as a BMI of 25.0–29.9 or greater than 30 kg/m^2, respectively. Subjects without GERD or Barrett’s esophagus were considered as the comparator group for the analyses. Patients were stratified into groups based on gender and decade of initial diagnosis of reflux disease. The prevalence of eGERD or NERD was calculated for each age decade and expressed as absolute numbers and proportions. Unadjusted (crude) odds ratios (ORs) along with their respective 95% confidence intervals (CIs) were calculated to estimate the strength of associations with demographic, BMI, smoking, and H. pylori infection. Thereafter, a logistic regression analysis was carried out to calculate adjusted ORs. Hosmer–Lemeshow goodness-of-fit test was used to assess the adequacy of fitting in the regression analysis. All the statistical analyses were conducted by using SPSS Statistical Package (version 16.0, SPSS Inc., Chicago, IL) and the results were considered significant when p values were less than 0.05.

Results

The study variables of GERD

Among a total of 6380 patients, 5156 were included in the analysis. In 73 patients (1.4% of cases), there was discrepancy...
between the two tests for *H. pylori* and they were excluded from the analysis. Sixty-nine were between 16 and 17 years old.

There were 3384 with reflux disease (mean age 48.8 ± 17.3 years; male 50.5 ± 17.3, female 48.0 ± 17.2) and 1772 without (mean age 48.9 ± 18.3 years). Among those with GERD, 1392 had eGERD and 1992 NERD. The distribution of eGERD according to age was bimodal with peaks in the 30–39 and 60–69 age groups (Figure 1). Having a hiatal hernia notably increased the risk of both eGERD and NERD. eGERD was more frequent among men and NERD among women (43% versus men 31%;  \( p < 0.001 \) ) (Table 1). However, the prevalence of reflux disease was higher among women in the elderly (age > 69) (\( p = 0.002 \)) (Figure 1). Data about BMI and smoking habit were missing in 2747 and 2239 patients, respectively, because variables were added to the records later; however, around 3000 cases were available for both analyses. eGERD was more prevalent among the obese (41% in obese versus 31% in non-obese, respectively, OR =1.72, \( p < 0.001 \)) (Table 1). Ex-smokers had a lower prevalence of eGERD than current smokers (Table 1). NERD was significantly more common than eGERD among those with an active *H. pylori* infection (OR =1.17; 95% CI =1.02–1.35) (Table 1). Metaplasia and/or atrophy in the corpus was present in 14 out 130 (11%) with *H. pylori* infection; and in 69 out 577 (12%) without infection. Because the numbers were too small, sub-analysis was not able to find any difference about GERD and the site of metaplasia and/or atrophy. For this reason, patients were stratified as shown in Table 1. There was no relationship between age and presence of eGERD or NERD.

All the study variables were included in a logistic regression analysis and overweight, hiatal hernia, and smoking remained with a statistically significant trend for eGERD; for NERD, gender and overweight (Table 2).

**Barrett esophagus and risk factors**

We compared those with and without Barrett’s esophagus in relation to gender, age, smoking status, BMI, presence of hiatal hernia, and *H. pylori* infection. There were a total of 133 individuals with newly diagnosed Barrett’s esophagus. The majority also had eGERD (OR =24) (Table 3). Hiatal hernia was more frequent in those with Barrett’s esophagus than in those without (\( p < 0.046 \)) and, as expected,[17] Barrett’s was significantly more common among men than women (4% versus 1.8%; \( p < 0.0001 \)). An inverse correlation between atrophic changes (intestinal metaplasia) due to *H. pylori* infection and Barrett’s esophagus was not detected (Table 3). No overweight or obese patients had Barrett’s esophagus. A history of tobacco use in the past was present in 3.8% of Barrett’s patients versus 1.7% of current smokers. A significant difference was observed in regard to age older than 50 years (\( p = 0.012 \)). The magnitude of the OR was not reduced in the logistic regression analysis for Barrett’s esophagus for having eGERD, male sex, or age older than 50 years (Table 4).

**Discussion**

Infrequent episodes of reflux are a normal daily physiological phenomenon usually without clinically significant consequences and typically asymptomatic. However, when the normal
Table 1. Unadjusted odds ratio and 95% confidence interval for \( H. \text{ pylori} \) infection and other study variables among patients with reflux disease (GERD) with (eGERD) and without (NERD) esophagitis undergoing upper endoscopy.

| Variable                          | Total     | eGERD no. (%) | OR \(^a\) (95% CI) \(^b\) | NERD no. (%) | OR (95% CI) | NO GERD\(^d\) no. (%) |
|----------------------------------|-----------|---------------|-----------------------------|--------------|-------------|------------------------|
| **H. pylori status**             |           |               |                             |              |             |                        |
| No Hp infection                  | 2585      | 702 (27)      | Reference                   | 975 (38)     | Reference   | 908 (35)               |
| Active Hp infection\(^c\)      | 1864      | 478 (26)      | 0.91 (0.76–1.08)            | 773 (42)     | 1.17 (1.02–1.35)*    | 613 (33)               |
| Chronic gastritis and metaplasia Hp pos\(^d\) | 130 | 30 (23) | 0.69 (0.44–1.09) | 44 (34) | 0.73 (0.49–1.10) | 56 (43) |
| Chronic gastritis and metaplasia Hp neg\(^e\) | 577 | 182 (32) | 1.21 (0.96–1.51) | 200 (35) | 0.96 (0.77–1.19) | 195 (34) |
| Total patients                   | 5156      | 1392 (27)     |                             | 1992 (39)    |             | 1772 (34)             |
| **Gender**                       |           |               |                             |              |             |                        |
| Women\(^f\)                      | 3402      | 798 (24)      | Reference                   | 1453 (43)    | Reference   | 1151 (34)             |
| Men                              | 1754      | 594 (34)      | 1.38 (1.19–1.59)**          | 539 (31)     | 0.89 (0.77–1.03)**   | 621 (35)               |
| **Body Mass Index (kg/m\(^2\))**|           |               |                             |              |             |                        |
| BMI <25                          | 1385      | 434 (31)      | Reference                   | 464 (34)     | Reference   | 487 (35)              |
| BMI ≥25                          | 1024      |               |                             |              |             |                        |
| BMI 25.0–29.9                    | 727       | 270 (37)      | 1.49 (1.19–1.86)**          | 253 (35)     | 1.30 (1.04–1.63)*    | 204 (28)               |
| BMI ≥30                          | 297       | 121 (41)      | 1.72 (1.26–2.35)**          | 97 (33)      | 1.29 (0.93–1.78)     | 79 (27)                |
| Missing                          | 2747      |               |                             |              |             |                        |
| **Age**                          |           |               |                             |              |             |                        |
| <50 years                        | 2643      | 731 (28)      | Reference                   | 1008 (38)    | Reference   | 904 (34)              |
| ≥50 years                        | 2513      | 661 (26)      | 0.94 (0.82–1.08)            | 984 (39)     | 1.02 (0.89–1.16)     | 868 (35)               |
| **Hiatal hernia**                |           |               |                             |              |             |                        |
| No\(^g\)                         | 2881      | 679 (24)      | Reference                   | 1109 (39)    | Reference   | 1093 (38)             |
| Yes                              | 2275      | 713 (31)      | 1.69 (1.47–1.95)**          | 883 (39)     | 1.28 (1.13–1.46)**   | 679 (30)               |
| **Smoking**                      |           |               |                             |              |             |                        |
| No\(^h\)                         | 1893      | 590 (31)      | Reference                   | 708 (37)     | Reference   | 595 (31)              |
| Yes                              | 708       | 257 (36)      | 1.26 (1.01–1.56)*           | 245 (35)     | 1.00 (0.81–1.24)     | 206 (29)               |
| Ex-smokers                       | 316       | 103 (33)      | 0.98 (0.73–1.32)            | 107 (34)     | 0.85 (0.63–1.13)     | 106 (33)               |
| Missing                          | 2239      |               |                             |              |             |                        |

\(^a\) Odds ratio.  
\(^b\) Confidence interval.  
\(^c\) Reference group.  
\(^d\) No symptoms or findings of esophagitis at the endoscopy.  
\(^e\) Active Hp infection: chronic active gastritis with \( H. \text{ pylori} \) infection.  
\(^f\) Gastritis with metaplasia and/or atrophy in the antrum with \( H. \text{ pylori} \) infection.  
\(^g\) Gastritis with metaplasia and/or atrophy without \( H. \text{ pylori} \) infection.  
\(^h\) \( p < 0.05 \).  
\(^i\) \( p < 0.001 \).  

Table 2. Logistic regression analysis for risk factors studied for patients with esophageal reflux disease with (eGERD) and without (NERD) esophagitis.

| Covariates                        | OR\(^a\) | eGERD OR \(^b\) 95% CI  | \( p \) Value | OR\(^a\) | NERD OR \(^b\) 95% CI  | \( p \) Value |
|-----------------------------------|----------|--------------------------|---------------|----------|--------------------------|---------------|
| **Age**                           |          |                          |               |          |                          |               |
| <50 years                         | 1.00     |                          |               | 1.00     |                          |               |
| ≥50 years                         | 0.850    | (0.678–1.065)            | 0.158         | 1.059    | (0.844–1.327)            | 0.622         |
| **Gender**                        |          |                          |               |          |                          |               |
| Women                             | 1.00     |                          |               | 1.00     |                          |               |
| Men                               | 1.128    | (0.900–1.414)            | 0.295         | 0.620    | (0.488–0.787)            | <0.0001       |
| **BMI**                           |          |                          |               |          |                          |               |
| BMI <25                           | 1.00     |                          |               | 1.00     |                          |               |
| BMI ≥25                           | 1.640    | (1.308–2.057)            | <0.0001       | 1.327    | (1.057–1.665)            | 0.015         |
| **H. pylori**                     |          |                          |               |          |                          |               |
| No Hp infection                   | 1.00     |                          |               | 1.00     |                          |               |
| Active Hp infection\(^c\)        | 0.988    | (0.788–1.255)            | 0.922         | 1.049    | (0.827–1.330)            | 0.694         |
| Chronic gastritis and metaplasia Hp pos\(^d\) | 0.989 | (0.717–1.365) | 0.947 | 0.739 | (0.524–1.040) | 0.083 |
| Chronic gastritis and metaplasia Hp neg\(^e\) | 0.721 | (0.352–1.479) | 0.373 | 0.730 | (0.360–1.484) | 0.385 |
| **Hiatal hernia**                 |          |                          |               |          |                          |               |
| No\(^g\)                          | 1.00     |                          |               | 1.00     |                          |               |
| Yes\(^h\)                         | 1.460    | (1.169–1.823)            | 0.001         | 1.078    | (0.857–1.356)            | 0.520         |
| **Smoker**                        |          |                          |               |          |                          |               |
| No\(^i\)                          | 1.00     |                          |               | 1.00     |                          |               |
| Yes\(^j\)                         | 1.392    | (1.085–1.787)            | 0.009         | 1.131    | (0.875–1.463)            | 0.346         |
| Ex-smokers                        | 0.929    | (0.646–1.335)            | 0.691         | 0.874    | (0.595–1.284)            | 0.492         |

\(^a\) Odds ratio.  
\(^b\) Confidence interval.  
\(^c\) Active Hp infection: chronic active gastritis with \( H. \text{ pylori} \) infection.  
\(^d\) Gastritis with metaplasia and/or atrophy in the antrum with \( H. \text{ pylori} \) infection.  
\(^e\) Gastritis with metaplasia and/or atrophy in the antrum without \( H. \text{ pylori} \) infection.  
Bold values are statistically significant.
anti-reflux mechanisms fail, refluxate can cause symptoms and/or mucosal damage.[3]

_Helicobacter pylori_ infection is typically acquired in childhood and clinical disease only occurs after a long latent period during which gastric damage occurs silently. The recent trend for a decline in the incidence of both gastric and duodenal ulcer in Western societies [3,17] has been associated with a decrease in the prevalence of _H. pylori_ infection. At the same time, the prevalence of adenocarcinoma of the esophagus has been noted to be increasing in both United States and in several European countries.[17,18] This trend has led several investigators to examine the prevalence of _H. pylori_ in patients with GERD. Although duodenal ulcer has previously been linked to GERD, the overall increase in GERD and Barrett’s esophagus has been linked to the average increase in acid secretion related to the change in the prevalence of _H. pylori_ infections and to the pattern of gastritis among those with the infection.[19]

Worldwide, _H. pylori_ positive patients are less likely to have symptomatic GERD, and when GERD is present, the severity of esophagitis is typically less that among those without the infection.[20] A meta-analysis evaluating the association between _H. pylori_ infection and GERD reported significant heterogeneity.[21] The prevalence of _H. pylori_ infection among those with GERD was lower in the Far East than in North America with equivocal results in Europe.[21] The mean prevalence of _H. pylori_ in GERD subjects was of 38.2% compared with 49.5% in subjects without GERD.[21] The pooled OR was 0.6 (95% CI: 0.47–0.78) (i.e., the odds of an _H. pylori_ infection in individuals with GERD was only 60% of those without GERD).[21] Our results are similar as the OR for eGERD was 0.69, and 0.73 for NERD in patients with active chronic gastritis with metaplasia _H. pylori_ positive. According to our observation, a study from mainland Italy involving 202 consecutive patients reported a higher _H. pylori_ prevalence among patients with NERD than among patients with eGERD or normal subjects.[22] A multivariate analysis of elderly and very elderly patients from Southern Italy demonstrated that older age, a large hiatus hernia, and male gender were independent risk factors for severe esophagitis, whereas _H. pylori_ infection, gastric atrophy, NSAID use, and the presence of hiatus hernia were not.[23] In contrast, a study with 638 subjects conducted at the University of Padua reported no significant relation between _H. pylori_ infection and either GERD or NERD.[24] However, Raghunath et al. [21] in their meta-analysis found that geographical location was a strong contributor to the heterogeneity among studies.

Obesity is a known risk factor for GERD, erosive esophagitis, and esophageal adenocarcinoma.[25,26] Prior studies have reported a significant correlation between BMI and waist circumference with intragastric pressure and the gastroesophageal pressure gradient.[27] Obesity has also been associated with the disruption of the esophagogastric junction leading to a hiatal hernia and increased esophageal acid pressure.

### Table 3

Unadjusted odds ratio and 95% confidence interval for Barrett’s esophagus among patients with esophageal reflux disease with (eGERD) and without (NERD) esophagitis undergoing upper endoscopy.

| Covariates Total | BARRETT No. (%) | OR* (95% CI)** | p Value |
|------------------|-----------------|----------------|---------|
| **GERD diagnosis** |                 |                |         |
| No Hp infection | 1772 2 (0.11) | Reference |         |
| Active Hp infection | 2585 61 (2.4) | Reference |         |
| Chronic gastritis and metaplasia Hp pos | 1984 47 (2.5) | 1.07 (0.73–1.57) | 0.729  |
| Chronic gastritis and metaplasia Hp neg | 577 21 (3.6) | 1.56 (0.94–2.59) | 0.080  |
| Total patients | 5156 131 (2.5) | 2.33 (1.66–3.33) | 0.0001 |
| **Diagnosis** |                 |                |         |
| Women | 3402 60 (1.8) | Reference |         |
| Men | 1754 71 (4) | 2.35 (1.66–3.33) | 0.0001 |
| **Body Mass Index (kg/m²)** |                 |                |         |
| BMI <25 | 1385 31 (2.2) | Reference |         |
| BMI ≥25 | 1024 27 (2.6) | 1.18 (0.70–1.99) | 0.528  |
| Missing | 2747 |                |         |
| Age |                  |                |         |
| <50 years | 2643 53 (2) | Reference |         |
| ≥50 years | 2513 78 (3.1) | 1.57 (1.10–2.23) | <0.012 |
| **Hiatal hernia** |                 |                |         |
| No | 2881 62 (2.2) | Reference |         |
| Yes | 2275 69 (3.0) | 1.42 (1.00–2.01) | <0.046 |
| **Smoking** |                 |                |         |
| No | 1893 46 (2.4) | Reference |         |
| Yes | 708 12 (1.7) | 0.69 (0.36–1.31) | 0.258  |
| **Ex-smoker** |                 |                |         |
| Missing | 316 12 (3.8) | 1.58 (0.83–3.03) | 0.159  |

*Odds ratio.  
**Confidence interval.  
*aFace of _H. pylori_ infection.  
*bActive Hp infection: chronic active gastritis with _H. pylori_ infection.  
*cGastritis with metaplasia and/or atrophy in the antrum without _H. pylori_ infection.  
*dGastritis with metaplasia and/or atrophy in the antrum with _H. pylori_ infection.  
**Gastritis with metaplasia and/or atrophy in the antrum without _H. pylori_ infection.  

Bold values are statistically significant.
Table 4. Logistic regression analysis for risk factors associated with Barrett’s esophagus.

| Covariates                      | Reference | OR* (95% CI)b | p Value |
|---------------------------------|-----------|---------------|---------|
| Diagnosis                       | Reference |               |         |
| eGERD                           | 24.1 (5.8–100.2) | <0.0001       |         |
| NERD                            | 1.02 (0.143–7.307) | <0.982       |         |
| **H. pylori status**            | Reference |               |         |
| No Hp infectionc                | 0.677 (0.333–1.766) | 0.533       |         |
| Active Hp infectiond            | 0.000 (0.0–0.0) | 0.997       |         |
| Chronic gastritis and metaplasia Hp neg* | 0.0767 (0.347–1.320) | 0.252       |         |
| Chronic gastritis and metaplasia Hp pos* | 0.000 (0.0–0.0) | 0.997       |         |
| Gender                          | Reference |               |         |
| Smoker                          | Reference |               |         |
| Body Mass Index (kg/m²)         | Reference |               |         |
| BMI <25c                        | Reference |               |         |
| BMI 25.0–29.9                   | 0.618 (0.316–1.212) | 0.162       |         |
| BMI ≥30                         | 0.970 (0.422–2.228) | 0.943       |         |
| Age ≥50 years                  | Reference |               |         |
| Hiatal hernia                   | Reference |               |         |
| No                              | Reference |               |         |
| Yes                             | 1.061 (0.595–1.890) | <0.842     |         |
| Smoking                         | Reference |               |         |
| No                              | Reference |               |         |
| Yes                             | 0.447 (0.199–1.002) | 0.059       |         |
| Ex-smoker                       | 1.152 (0.511–2.595) | 0.733       |         |

*Odds ratio.  
bConfidence interval.  
Active Hp infection: chronic active gastritis with *H. pylori* infection.  
Gastritis with metaplasia and/or atrophy in the antrum with *H. pylori* infection.  
Gastritis with metaplasia and/or atrophy in the antrum without *H. pylori* infection.  
Bold values are statistically significant.

In our cohort, obese individuals were significantly more likely to have eGERD than those not obese (41% versus 31%) and this remained statistically significant in the logistic regression analysis.

The presence of hiatal hernia is currently considered as an important factor in the pathogenesis of GERD, since it adversely influences several mechanisms underlying gastroesophageal reflux (decreased sphincter pressure, transient sphincter relaxation, esophageal clearance, and the position of the acid pocket). The presence of a hiatal hernia has been associated with more severe reflux disease and mucosal damage. In our patients, having a hiatal hernia notably increased the risk of eGERD and NERD with an OR of 1.69 and of 1.28, respectively.

Of interest, men had a lower likelihood to have NERD, but a greater risk of GERD than women (i.e., men GERD was more often erosive than in women). Despite a large body of research in this field, surprisingly, there are only scant data addressing the different manifestations of GERD in women and men. A few studies suggest that the usual clinical presentation of GERD is similar in men and in women, although there is a trend toward a higher frequency and slightly increased severity of symptoms in women compared with men; the endoscopic findings, however, appear to differ between sexes with more erosive GERD in men as seen here. Although some authors have suggested that this is the result of different symptom sensitivities and/or different patterns of health-seeking behavior between the sexes, neither hypothesis has been confirmed.

Ex-smokers had a lower prevalence of eGERD than current smokers. pH monitoring data have shown that smoking increases esophageal acid exposure both by increasing acid secretion and by reducing lower esophageal sphincter pressure predisposing to strain-induced reflux. Finally, smoking decreases salivation that prolongs acid clearance.

Although there are few population-based studies such as improving the knowledge about characteristics and risk factors of reflux disease, some limitations need to be taken into account. First, it was a retrospective study setting out to analyze the relation between *H. pylori* and traditional risk factors for erosive and non-erosive reflux diseases and Barrett’s esophagus. A relatively large database of 5156 patients was included. The inherent danger of a large database is the trap of “data dredging” in the statistical analyses particularly if the study design is not structured or focused. Stacking multiple variables against each other produces many statistical results which are not necessary clinically meaningful. Given the nature of our method of characterization of subjects into NERD, eGERD, and Barrett’s esophagus, some may have been misclassified. In addition, data about duration of GERD symptoms (>5 years) considered a risk factor for Barrett’s esophagus are missing. The paucity of other important covariates (such as history and duration of alcohol, NSAID and PPI uses or misuses, amount of tobacco consumption, and data about central abdominal obesity) in the model could make weaker study findings. However, given the large number of patients in the cohort studied, we are confident that the extent of errors would be limited.

In conclusion, the findings support the hypothesis that NERD and eGERD are two distinct entities and NERD is not simply a step prior in the pathogenesis and progression to eGERD. Within NERD, there is a significant subgroup of patients where typical risk factors for reflux are absent (e.g., overweight) and other like *H. pylori* play a pivotal role. Therapeutic modalities focus on acid suppression as they do in erosive disease. Other therapeutic strategies should be considered in NERD which will require a broader perspective.

**Disclosure statement**

The authors report no conflict of interest.

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