TITLE: Functional Heartburn Overlaps With Irritable Bowel Syndrome More Often than GERD.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE
- Typical reflux syndrome (heartburn with/without regurgitation) is reportedly associated with irritable bowel syndrome (IBS).
- Previous studies documented a greater overlap between functional dyspepsia and FH compared with NERD and HR, suggesting a common pathogenetic background.
- A study distinguishing functional heartburn (FH) from gastroesophageal reflux disease (GERD) by means of impedance-pH monitoring, and concerning their association with IBS is lacking.

WHAT IS NEW HERE
- IBS and anxiety occur significantly more often in FH than in reflux-related heartburn (GERD+HE).
- HE shows intermediate characteristic between GERD and FH especially in term of response to PPI treatment.

ABSTRACT

OBJECTIVES: We aimed to evaluate the prevalence of irritable bowel syndrome (IBS) in patients with typical reflux symptoms as distinguished into gastroesophageal reflux disease (GERD), hypersensitive esophagus (HE), and functional heartburn (FH) by means of endoscopy and multichannel intraluminal impedance (MII)-pH monitoring. The secondary aim was to detect pathophysiological and clinical differences between different sub-groups of patients with heartburn.

METHODS: Patients underwent a structured interview based on questionnaires for GERD, IBS, anxiety, and depression. Off-therapy upper-gastrointestinal (GI) endoscopy and 24 h MII-pH monitoring were performed in all cases. In patients with IBS, fecal calprotectin was measured and colonoscopy was scheduled for values >100 mg/kg to exclude organic disease. Multivariate logistic regression analysis was performed to identify independent risk factors for FH.

RESULTS: Of the 697 consecutive heartburn patients who entered the study, 454 (65%) had reflux-related heartburn (GERD+HE), whereas 243 (35%) had FH. IBS was found in 147/454 (33%) GERD/HE but in 187/243 (77%) FH patients (P<0.001). At multivariate analysis, IBS and anxiety were independent risk factors for FH in comparison with refl ux-related heartburn (GERD+HE).

CONCLUSIONS: IBS overlaps more frequently with FH than with GERD and HE, suggesting common pathways and treatment. HE showed intermediate characteristic between GERD and FH.

KEY WORDS;

INTRODUCTION

Gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS) are gastrointestinal (GI) disorders affecting a large part of the general population, with relevant impact on quality of life and health-care costs (1,2). To date, population- and clinical based studies have reported a certain degree of overlap between GERD and IBS, which cannot be explained solely by chance (3–7).

In IBS patients, the overall mean prevalence of GERD is 38%, ranging from 11 to 79%, whereas in GERD patients the overall mean prevalence of IBS is 36%, ranging from 8 to 71% (8). It is worth noting that the available literature displays a high heterogeneity in terms of both criteria and diagnostic procedures employed to establish the presence of GERD and IBS. In particular, most of the available data were collected in the context of epidemiological studies, which were conducted using heartburn-centered questionnaires; only few studies included endoscopic evaluation but nonpathophysiological investigations.

Formerly, GERD was subdivided into erosive reflux disease (ERD) and non-ERD (NERD) on the basis of presence or absence of esophageal mucosa erosions at endoscopic examination (9), ERD representing no more than 30% of the GERD population (9).

Recently, the definition of NERD has been revised and currently a link between heartburn and reflux as shown by an abnormal acid-exposure time (AET) at reflux monitoring is recommended for diagnosis (10). Moreover, patients with a close temporal relationship between heartburn and reflux episodes at reflux monitoring have been defined as hypersensitive esophagus (HE) (9) and are currently considered overlapping with but separately from GERD (9,10). Patients with proton-pump inhibitor (PPI)-refractory heartburn and normal findings at multichannel intraluminal impedance and pH (MII-pH) monitoring have been defined as functional heartburn (FH) (11–14), a functional GI disorder distinct from GERD (9,10).

Symptoms of IBS have not yet been assessed in patients with reflux symptoms as distinguished into GERD, HE, and FH. Recently, it has been reported that patients with

GERD (15,16) as well as patients with IBS (17,18) have increased levels of anxiety, in turn associated with increased perception of symptoms and reduced quality of life (19). Again, the prevalence of anxiety in patients with reflux symptoms as clearly distinguished into GERD, HE, and FH has not yet been assessed.

Our aim was to assess the prevalence of IBS as well as anxiety and depression in patients with typical reflux symptoms subdivided into GERD, HE, and FH by means of upper-GI endoscopy and MII-pH monitoring. Secondary aim was to compare the clinical characteristics of FH and HE with those of GERD. Finally, we evaluated whether clinical features may distinguish between PPI responders and non-responders GERD patients.

METHODS

Study subjects

Throughout 2014–2015, we prospectively enrolled consecutive patients with typical reflux symptoms (i.e., heartburn and/ or regurgitation) presenting to the outpatient esophageal pathophysiology centers at the Universities of Genoa, Pisa, and Padua.

The inclusion criteria were as follows: age higher than 18 years; complaints of heartburn with/without regurgitation at least twice a week for 6 months in the previous year.

The exclusion criteria were as follows: pregnancy (excluded by urine analysis) or breastfeeding; eating disorders; history of thoracic, esophageal, or gastric surgery; underlying psychiatric illness; use of non-steroid anti-inflammatory drugs or aspirin; peptic ulcer at a previous endoscopy, manometric diagnosis of achalasia, or scleroderma.

All patients signed an informed consent. Th e study was designed and carried out in accordance with Th e Helsinki Declaration (Sixth revision, Seoul 2008).

All patients underwent a structured interview by a distinct investigator, including a questionnaire for GERD (GERDQ) (20)

and for IBS symptoms (RIIIAQ) (21,22), a detailed medical history with recording of height, weight, and body mass index, current assumption of medications, smoking, alcohol, and coffee consumption. Symptom severity and the efficacy of PPI therapy were evaluated with a global visual analog scale from 0 (complete symptom relief) to10 (no relief at all). Th e visual analog scale has been used as a self-assessment tool for symptom measure and has been adopted for evaluation of visceral symptoms in many trials (23,24). All patients were inquired for previous PPI treatment and were defined as responders when symptoms relief was >50% from baseline (25).

The study questionnaires included the Hospital Anxiety and Depression Scale (26). The Hospital Anxiety and Depression Scale is a self-assessment measure of the severity of anxiety and depression mood. Th is scale contains 14 questions: 7 to assess

anxiety and 7 to assess depression. The scoring system employs a 4-grade Likert scale from 1 to 3, giving a possible score of 0–21 for each parameter. According to Snaith and Zigmond (26), a score of 11 or more is regarded as diagnostic of anxiety or depression.

Upper-GI endoscopy

All patients underwent upper endoscopy aft er 4-week wash-out from PPIs or H2-blockers. All endoscopies were performed with standard devices by expert endoscopists. The gastroesophageal junction was determined by the most proximal extent of the gastric mucosal folds. Hiatal hernia was defined as a distance between the diaphragmatic hiatus and the gastroesophageal junction >2 cm. During endoscopy two biopsies were routinely collected from the antrum, one from the angulus, and two from the corpus to detect Helicobacter pylori infection.

According to the Los Angeles Classification, presence of esophageal mucosal breaks defined ERD which was classified into four grades (from A to D) (27). Patients with negative endoscopy underwent stationary esophageal manometry and off -therapy 24-h MII-pH monitoring. Patients were only allowed to take alginates, on as-needed basis, as rescue therapy for controlling heartburn before MII-pH monitoring (28).

Esophageal MII-pH monitoring

MII-pH monitoring was preceded by esophageal manometry after PPI withdrawal lasting from at least 2 weeks. Achalasia and scleroderma esophagus constituted exclusion criteria. Th e MII-pH catheter adopted allowed monitoring changes in intraluminal impedance at 3, 5, 7, 9, 15 and 17 cm, and in intraluminal pH 5 cm, respectively above the manometrically defined lower esophageal sphincter (Sandhill Scientifi c, Highland Ranch, CO). All patients consumed foods and beverages exclusively during three standard meals (lunch at 1 pm, dinner at 8 pm, and breakfast at 8 am of the next day) on the basis of a Mediterranean diet (29), without consumption of alcohol and coff ee, to reduce variability due to alimentary habits.

They were instructed to indicate the beginning and ending times of meals with the apposite button on the data logger. The patients were requested also to remain in the upright position during the day and to indicate the recumbent period during night-time (max 8 h) with the apposite button. Each patient was instructed to press the "event marker" button, on the MII-pH data logger, whenever they experienced reflux symptoms during the recording period.

MII-pH data analysis

At the end of the recording period, MII-pH tracings were reviewed manually in order to ensure an accurate detection and classification of reflux episodes using 5-min operative windows. Meal periods were excluded from the analysis. Impedance and pH data were used to determine the number and type of reflux episodes as well as the AET (%) in each patient. In particular, a distal esophageal AET was defi ned as the total time with pH below 4, divided by the total time of monitoring, and was considered as normal if less than 4.2% of 24 hours (29). Reflux events were characterized from different standpoints: physical, chemical, and proximal extension. AET, and correlation between symptoms and reflux episodes expressed with symptom index (SI; positive if >50%) and SAP (symptom association probability; positive if >95%) were evaluated for each patient, as previously described (30,31).

All endoscopy-negative patients were stratified into three groups by means of MII-pH analysis as follows: "NERD" (abnormal AET; "hypersensitive esophagus" (normal AET, positive SI/SAP); "FH" (normal AET, negative SI/SAP). According to Rome IV (10), ERD and NERD patients were then considered as GERD and, together with HE constituted the reflux-related heartburn (RRH) population.

Irritable bowel syndrome

All patients who recorded a positive diagnosis for IBS were evaluated with dosage of the fecal level of calprotectin. When calprotectin values were higher than 100 mg/kg, colonoscopy was scheduled to exclude organic disease. Patients with IBS were classified into three subcategories: IBS with prevalent constipation, IBS with prevalent diarrhea, and mixed IBS with alternating bowel habits (21).

Statistical analysis

Results are presented as mean and standard deviation or absolute frequency and percentage. At univariate analysis, continuous and categorical variables were evaluated with analysis of variance and $\chi 2$ -test, respectively, with Bonferroni's correction for multiple comparisons. Variables considered were clinical characteristics, i.e., age, gender, body mass index, smoking, consumption of alcohol, consumption of coffee, diagnosis of anxiety, and/or depression, diagnosis of IBS. Endoscopic criteria included presence of hiatal hernia and H. pylori positivity. Following univariate analysis, two multivariate logistic regressions analyses were performed in order to identify independent risk or protective factors for HE vs. GERD diagnosis, and HE vs. FH diagnosis. An additional multivariate logistic regression analysis was performed in order to evaluate a population of RRH composed by GERD and HE population as compared with FH patients. Multiple logistic regression was performed to evaluate those variables associated with response/nonresponse to PPI treatment in RRH patients. A P value <0.05 was considered significant. Analyses were performed using STATA statistical software, release13 (STATA, College Station, TX).

RESULTS

Clinical and endoscopic characteristics

The clinical and endoscopic characteristics of the 697 patients who met inclusion criteria were as follows: male/female ratio, 283/414; mean age (±s.d.), 49.8 (±14); mean body mass index (±s.d.), 25.2 (±2.6).

No patient was excluded after esophageal manometry. In all, 147 of 697 patients (21.1%) were regular smokers, 483/697 (69.3%) were used to take at least a cup of coff ee daily, and 263/697 (37.7%) reported a consumption of 2-to-3 alcohol units per day. Hiatal hernia was found in 369/697 (52.9%) patients. Helicobacter pylori (H. pylori) resulted positive in 65/697 (9.3%). All patients reported heartburn (100%), 418/697 (60%) had regurgitation, 144/697 (20.7%) had chest pain, 264/697 (37.9%) had dyspepsia, and 75/697 (10.8%) complained of belching. All patients were treated with a full dosage of PPI for a mean period of 12.8±4.6 weeks. The symptom relief during PPI therapy was >50% in 284/697 (40.7%) patients.

Th e overall prevalence of IBS in our population was 334/697 (47.9%). In 51/334 (15.3%) patients with IBS the level of calprotectin was higher than 100 mg/kg (mean value 142.4±67.3). These latter patients underwent lower endoscopy: in 49/51 (96%) the endoscopy showed no abnormal changes; in 2/51 (4%) small polyps were detected and removed during the procedure. Histological analysis revealed the presence of adenomatous tissue in them. These findings did not change the final diagnosis and all 51 colonoscopies were considered negative. Th e three subcategories of IBS were distributed as follows: 148/334 (44.4%) had IBS with prevalent constipation; 95/334 (28.4%) had IBS with alternating bowel habits, and 91/334 (27.2%) had frequent diarrhea (IBS with prevalent diarrhea). Anxiety was diagnosed in 307 of 697 (44%) patients whereas depression was diagnosed in 67 of 697 (9.6%) patients.

Reflux esophagitis was found in 94/697 (13.5%) patients. These patients were sub-grouped by means of Los Angeles Classification: 59 patients with A grade, 21 patients

with B grade, 9 patients with C grade, and 5 patients with D grade. No other complications of GERD were recorded.

Univariate and multivariate analysis

The MII-pH study was well-tolerated by all subjects and no technical failures occurred. According to MII-pH data, 142 of 603 (23.5%) endoscopy-negative patients were classified as NERD, and 218 of 647 (36.2%) cases as HE. Overall, 454 (65%) patients were classified as GERD and HE, whereas 243 (35%) were classified as FH. Overall, the IBS diagnosis occurred in 147 of 454 (33%) patients with GERD and HE as compared with 187 of 243 (77%) patients with FH (p <0.001). Anxiety was diagnosed in 103 of 454 (23%) GERD/HE cases as compared with 204 of 243 (84%) FH cases (p<0.001). Depression was diagnosed in 25 of 454 (6%) GERD/HE cases as compared with 42 of 243 (17%) FH cases (p <0.001). Coffee consumption was reported by 324 of 454 (71.4%) GERD/HE patients and by 159 of 243 (65.4%) FH patients (p=0.045). Smoking was reported by 90 of 454 (19.8%) GERD/HE cases and by 57 of 243 (23.5%) FH cases (p=0.268). Hiatal hernia was present in 274 of 454 (62%) GERD/HE patients and in 87 of 243 (36%) FH patients (p <0.001). H. pylori was found in 32 of 454 (7%) GERD/HE patients and in 33 of 243 (13.6%) FH cases (p=0.008). Mean age did not significantly differ between GERD/HE (49.6±14.5 years) and FH (50.2±13.1 years; p=0.105).

Results of the univariate analysis concerning multiple comparisons among GERD, HE, and FH are reported in **Table 1**. GERD patients were more often male than HE and FH patients. Presence of hiatal hernia was associated with GERD and HE. IBS and anxiety were more prevalent in HE and in FH than in GERD. Depression was rare, slightly more frequent in FH.

At multivariate analysis, exploring HE vs. GERD it was shown that female sex, IBS, and H. pylori infection were associated with HE, whereas the presence of hiatal hernia and anxiety diagnosis resulted in association with GERD (p<0.05; **Table 2**).

At multivariate analysis, exploring HE vs. FH it was shown that smoking habits, H. pylori infection, IBS, and anxiety diagnosis were associated to FH, whereas the presence of hiatal hernia resulted in association with HE (p<0.05; **Table 3**).

An additional multivariate analysis explored the differences between FH patients and the population of patients with RRH, i.e., GERD and HE. Th is analysis confirmed that smoking habits, H. pylori infection, IBS, and anxiety diagnosis were associated with FH whereas the presence of hiatal hernia resulted associated with RRH (p<0.05). All details are reported in **Table 4**. Finally, at multivariate analysis we found that smoking habit was significantly associated with PPI response (OR 1.99, CI 95% 1.15–3.43; p=0.013) whereas alcohol consumption was significantly more frequent in PPI-unresponsive patients (OR 0.626, CI 95% 0.41–0.95; p=0.028). No other difference between PPI responders and non-responders was found at multivariate analysis (**Table 5**). Moreover, the prevalence of PPI responders was 161/236 (68.2%) in GERD and 122/218 (56%) in HE, as compared with 0/243 in FH (p<0.017; **Figure 1**).

DISCUSSION

Heartburn and IBS origin from different regions of the GI tract, but it has been noted that they may both occur in the same patient. Large population-based studies have used validated questionnaires to investigate a possible association between GERD and IBS, and have found that refl ux symptoms can affect a considerable proportion of patients with IBS (6), or vice versa (32).

However, these studies were not performed with the state-of-the-art method to distinguish RRH from reflux-unrelated heartburn as population and patients' selection were mainly based on questionnaires and endoscopic findings only (8). Recent studies based on MII-pH monitoring have shown the importance of a careful categorization of heartburn patients via pathophysiological investigations to distinguish GERD and HE from FH (9,33–35). Thus, to the best of our knowledge, this is the first prospective study in which a large population of patients with heartburn has been distinguished into

GERD, HE, and FH by means of MII-pH monitoring, and the relationship of these distinct disorders with IBS and anxiety has been carefully investigated. In the present large series, we found that IBS occurs significantly more oft en in FH, i.e., reflux-unrelated heartburn (77% of cases) than in GERD/HE, i.e., RRH (33% of cases) as well as anxiety occurs significantly more often in FH (84% of cases) than in RRH (23% of cases). Moreover, we confirmed that GERD and HE causes heartburn in more than two-thirds of patients properly investigated by MII-pH monitoring (11–14), whereas in PPI refractory patients reflux is not the cause of the symptom in more than half of cases (60% of PPI non-responder had FH) (36,37). From a multivariate analysis, we observed that IBS diagnosis was more frequently associated with HE when compared with GERD. Similarly, IBS was an independent risk factor for FH when compared with HE. Overall, anxiety and IBS diagnosis were risk factors for FH compared with RRH (GERD and HE).

In line with these results, a more frequent association of IBS with FH than with GERD and HE is in keeping with a previous study showing that FH has more in common with functional dyspepsia than with NERD (11): possible common pathways for functional GI disorders have been acknowledged (8,38), which in turn could explain the reported efficacy of visceral pain modulators for both FH and IBS (9,21,39).

Furthermore, HE showed to have intermediate characteristics between GERD and FH. Recently, Rome IV underlined that HE is a rare example of functional disorder that shows a better response to PPI treatment compared with other functional esophageal disorders (10). In line with this assumption, in our population HE patients showed slightly but significantly lower response rate to PPI (56%) compared with GERD (68%); interestingly, anxiety was more prevalent in PPI non-responders RRH patients, suggesting that PPI responsiveness could be affected by anxiety (40). In conclusion, we found that IBS and anxiety occur in nearly two thirds of FH patients, suggesting a common pathophysiological mechanism including visceral hypersensitivity and central neural mechanisms justifying prescription of visceral pain modulators for

these patients. In terms of clinical findings and PPI responsiveness, HE shows intermediate characteristic between GERD and FH.

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TABLE PAGES

Table 1: Clinical and endoscopic characteristics of patients (univariate analyses).

	GERD (*n*=236)	HE (*n*=218)	FH (*n*=243)
Age, years (mean; s.d.)	51.8 (14.3)	47.2 (14.3)	50.2 (13.1)
P=0.001 for GERD vs. HE, P=0.266 for GERD vs. FH, **P=0.001 for HE vs. FH**			
Female sex, *n* (%)	100 (42.4%)	145 (66.5%)	169 (69.5%)
P=0.001 for GERD vs. HE and FH, P=0.550 for HE vs. FH			
BMI (mean; s.d.)	25.1 (3.3)	24.1 (4.4)	24 (4.1)
P=0.001 for GERD vs. HE, **P=0.001 for GERD vs. FH**, P=0.999 for HE vs. FH			
Smoking (%)	57 (24.2%)	33 (15.1%)	57 (23.5%)
P=0.022 for GERD vs. HE, P=0.943 for GERD vs. FH, P=0.033 for HE vs. FH			
Coffee (%)	178 (75.4%)	146 (67%)	159 (65.4%)
P=0.059 for GERD vs. HE, P=0.022 for GERD vs. FH, P=0.063 for HE vs. FH			
Alcohol (%)	89 (37.7%)	85 (39%)	89 (36.6%)
P=0.854 for GERD vs. HE, P=0.880 for GERD vs. FH, P=0.669 for HE vs. FH			
Hiatal hernia (%)	178 (75.4%)	104 (47.7%)	87 (35.8%)
P=0.001 for GERD vs. HE and FH, **P=0.013 for HE vs. FH**			
H. pylori infection (%)	23 (9.7%)	9 (4.1%)	33 (13.6%)
P=0.031 for GERD vs. HE, P=0.245 for GERD vs. FH, **P=0.001 for HE vs. FH**			
IBS, diagnosis (%)	42 (17.8%)	105 (48.2%)	187 (77%)
P=0.001 for GERD vs. HE and FH, **P=0.001 for HE vs. FH**			
Anxiety, diagnosis (%)	25 (10.6%)	78 (35.8%)	204 (84%)
P=0.001 for GERD vs. HE and FH, **P=0.001 for HE vs. FH**			
Depression, diagnosis (%)	12 (5.1%)	13 (6%)	42 (17.3%)
P=0.838 for GERD vs. HE, **P=0.001 for GERD vs. FH**, **P= 0.001 for HE vs. FH**			

Legend: BMI=body mass index; FH=functional heartburn; GERD=gastroesophageal reflux disease; HE=hypersensitive esophagus; IBS=irritable bowel syndrome.

Results expressed as mean and s.d., or absolute frequency and percentage (%).

Bold values indicate statistical significance.

Table 2: Variables associated with hypersensitive esophagus on the basis of multivariate logistic regression analysis as compared with GERD.

	OR (95% CI)	*P* value
Age	**0.973 (0.957–0.989)**	**0.001**
Female sex	**2.722 (1.706–4.344)**	**0.001**
BMI	0.974 (0.919–1.032)	0.373
IBS diagnosis	**2.749 (1.679–4.503)**	**0.001**
Smoking	0.624 (0.349–1.114)	0.111
Coffee	0.689 (0.417–1.139)	0.146
Alcohol	1.089 (0.684–1.733)	0.720
Hiatal hernia	**0.326 (0.207–0.514)**	**0.001**
Helicobacter pylori	**2.887 (1.608–5.182)**	**0.001**
Anxiety diagnosis	**0.306 (0.121–0.775)**	**0.012**
Depression diagnosis	0.398 (0.147–1.076)	0.069

Legend: BMI=body mass index; 95%CI=95% confidence interval; GERD=gastroesophageal reflux disease; IBS=irritable bowel syndrome; OR=odds ratio.

Bold characters indicate statistical significance.

Table 3: Variables associated with hypersensitive esophagus on the basis of multivariate logistic regression analysis as compared with functional heartburn.

Study variable	OR (95% CI)	*P* value
Age	**0.977 (0.961–0.993)**	**0.005**
Female sex	0.919 (0.562–1.504)	0.738
BMI	1.004 (0.952–1.059)	0.871
IBS	**0.468 (0.289–0.756)**	**0.002**
Smoking	**0.431 (0.238–0.780)**	**0.005**
Coffee	1.031 (0.631–1.684)	0.903
Alcohol	1.265 (0.787–2.031)	0.331
Anxiety diagnosis	**0.134 (0.083–0.219)**	**0.001**
Hiatal hernia	**1.704 (1.082–2.685)**	**0.022**
Helicobacter pylori	**0.289 (0.117–0.713)**	**0.007**
Depression diagnosis	0.716 (0.347–1.477)	0.365

Legend: BMI=body mass index; 95%CI=95% confidence interval; IBS=irritable bowel syndrome; OR=odds ratio.

Bold characters indicate statistical significance.

Table 4: Variables associated with functional heartburn on the basis of multivariate logistic regression analysis compared with reflux-related heartburn, comprising GERD and hypersensitive esophagus

Study variable	OR (95% CI)	P value
Age	1.013 (0.998–1.028)	0.083
Female sex	1.282 (0.824–1.993)	0.271
BMI	0.983 (0.936–1.033)	0.501
IBS	**2.841 (1.838–4.391)**	**0.001**
Smoking	**1.798 (1.072–3.016)**	**0.026**
Coffee	0.883 (0.562–1.387)	0.589
Alcohol	0.827 (0.534–1.282)	0.395
Anxiety diagnosis	**10.797 (6.884–16.933)**	**0.001**
Hiatal hernia	**0.404 (0.266–0.612)**	**0.001**
Helicobacter pylori	**2.096 (1.058–4.155)**	**0.034**
Depression diagnosis	1.271 (0.683–2.366)	0.450

Legend: BMI=body mass index; 95%CI=95% confidence interval; IBS=irritable bowel syndrome; OR=odds ratio.

Bold characters indicate statistical significance.

Table 5: Variables associated with PPI responsiveness in the population of reflux-related heartburn, comprising GERD and hypersensitive esophagus

	Multivariate OR (95%CI)	*P* value
Age	1.014 (0.999–1.029)	0.076
Female sex	0.843 (0.550–1.291)	0.431
Anxiety, diagnosis	0.614 (0.370–1.019)	0.059
Depression, diagnosis	0.473 (0.205–1.093)	0.080
IBS, diagnosis	0.957 (0.605–1.515)	0.853
BMI (s.d.)	1.019 (0.968–1.073)	0.470
Smoking	**1.992 (1.155–3.435)**	**0.013**
Coffee	1.017 (0.638–1.619)	0.945
H. pylori infection	1.253 (0.569–2.759)	0.576
Hiatal hernia	1.336 (0.891–2.005)	0.161
Alcohol	**0.626 (0.412–0.951)**	**0.028**

Legend: BMI=body mass index; FH=functional heartburn; GERD, gastroesophageal reflux disease; HE, hypersensitive esophagus; IBS, irritable bowel syndrome; PPI, proton-pump inhibitor.

Bold characters indicate statistical significance.

FIGURE PAGE

Figure 1: PPI response rate in GERD, HE and FH.
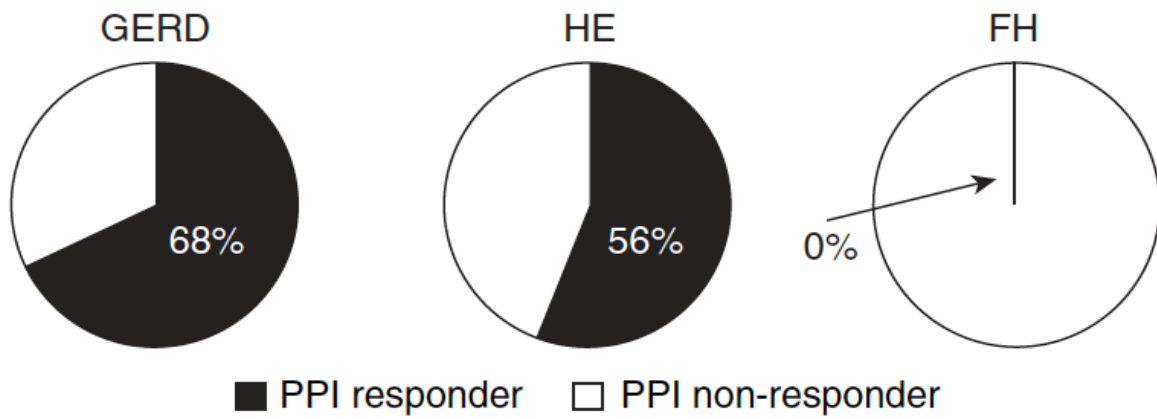
Legend: FH=functional heartburn; GERD, gastroesophageal reflux disease; HE=hypersensitive esophagus; PPI=proton-pump inhibitor.