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Risk factors associated with functional esophageal disorders (FED) versus gastroesophageal reflux disease (GERD)

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Abstract

Introduction Despite the high prevalence of typical symptoms of gastroesophageal reflux disease (GERD), approximately 30% of patients have functional esophageal disorders (FED) on ambulatory reflux monitoring, which may include reflux hypersensitivity (RH; defined as physiologic acid exposure but temporally correlated symptoms of reflux), or functional heartburn (FH; defined as physiologic acid exposure and negative symptom correlation). There are limited epidemiological data characterizing these conditions. We investigated demographic and socioeconomic factors as well as medical comorbidities which may predispose to FED versus pathologic GERD.

Methods Adult patients with reflux symptoms for at least 3 months were studied with 24-h pH-impedance testing from 11/2019 to 3/2021. Participants were categorized into pathologic GERD, FH, or RH using pH-impedance data and reported symptom correlation. Demographic data, including age, gender, race/ethnicity, zip code, insurance status, and medical comorbidity data were retrospectively retrieved from the electronic medical record on all participants.

Results 229 patients were included. Non-Hispanic Asian ethnicity (OR 5.65; $p=0.01$), underweight BMI (OR 7.33; $p=0.06$), chronic pain (OR 2.33; $p<0.01$), insomnia (OR 2.83; $p=0.06$), and allergic rhinitis (OR 3.90; $p<0.01$) were associated with a greater risk for FED. Overweight BMI (OR 0.48; $p=0.03$) and alcohol use (OR 0.57; $p=0.06$) were associated with a decreased risk for FED.

Discussion This is the first report of a greater risk of FED in patients with underweight BMI, insomnia, chronic pain, allergic rhinitis, or of Asian or Hispanic ethnicities. The weak associations between female gender and anxiety are corroborated in other studies. Our findings enable clinicians to better screen patients with reflux for this disorder.

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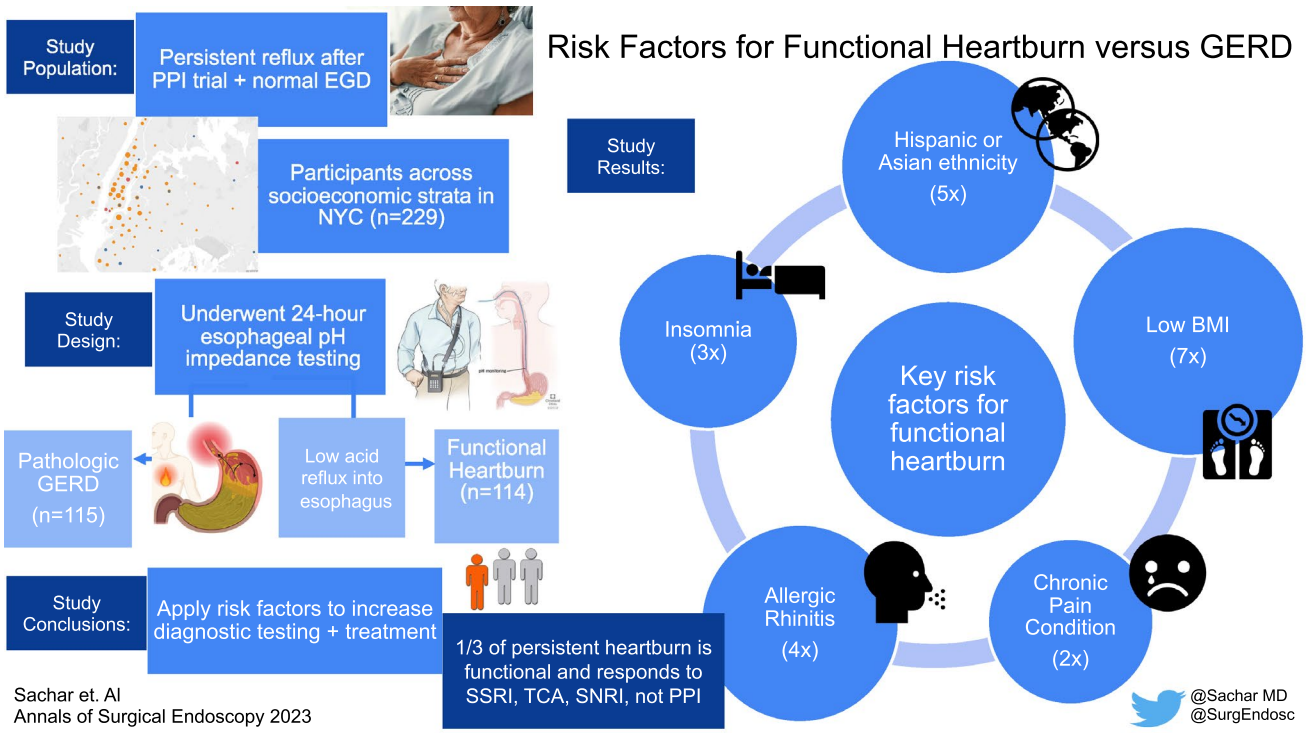
Graphical abstract



Keywords Functional esophageal disorder · Gastroesophageal reflux disease · Reflux hypersensitivity · Impedance testing · Ambulatory pH monitoring

More than 50% of patients with typical reflux symptoms, of heartburn, chest pain, or regurgitation have normal mucosal findings on endoscopy [1–4]. These patients are half as likely to respond to standard proton pump inhibitor (PPI) therapy as compared with patients who have erosive esophagitis [2, 5, 6], highlighting the importance of further testing to tailor therapy in patients with non-erosive acid reflux, and ambulatory reflux monitoring is used to characterize the length, frequency, and associated symptoms of esophageal acid exposure time (AET) over a 24–96 h period. These data obtained from pH monitoring allow us to categorize patients as having pathologic gastroesophageal reflux disease (GERD; defined as AET > 6%) or a functional esophageal disorder (FED; defined as AET < 4%). FED can be further stratified as reflux hypersensitivity (RH) if symptoms are temporally correlated with reflux events, or functional heartburn (FH) if a correlation between symptoms and reflux events is absent. Studies have shown that only 25–35% of all patients with symptoms of heartburn have pathologic non-erosive GERD, and up to 35% of these patients carry a diagnosis of FED. 15–20% of patients have FH, 10–15% of patients have RH [7–9].

Two studies to date have compared the demographic and psychiatric co-morbidities associated with FEDs versus pathologic GERD. One study found that female sex, irritable bowel syndrome (IBS), and *Helicobacter pylori* conferred a greater risk of RH, whereas the presence of a hiatal hernia and anxiety conferred a greater risk of pathologic GERD [10]. When comparing RH to FH, smoking, IBS, and anxiety were more associated with FH whereas hiatal hernia was more associated with RH [11]. Another study investigating comorbid psychiatric disorders found that depression had a stronger association with FH and anxiety was more strongly associated with pathologic GERD and RH [4]. There are limited data investigating the relationship between medical co-morbidities or socioeconomic factors and the development of FEDs versus pathologic GERD. Further characterization of the risk factors for pathologic non-erosive GERD and FEDs can help identify patients who may derive benefit from ambulatory reflux monitoring to elucidate the etiology of their symptoms and tailor subsequent management.

Methods

This was a retrospective cohort study of adults ≥ 18 years of age with reflux symptoms who received 24-h multichannel intraluminal pH-impedance testing between 11/25/2019 and 3/1/2021 at NYU Langone Health Center for Esophageal Health. Inclusion criteria were prior endoscopy without conclusive evidence of pathologic reflux and pH-impedance testing within the study window conducted off PPI therapy. Exclusion criteria were major disorders of esophageal motility (i.e., achalasia, distal esophageal spasm, hypercontractile esophagus) as defined by Chicago Classification version 4.0 and endoscopic evidence of Los Angeles grade C or D esophagitis, long-segment Barrett's esophagus, para-esophageal hernia, or prior reflux surgery, bariatric surgery, esophageal, or gastric malignancy. Patients with incomplete studies or incomplete pre-procedure symptom assessments were also excluded. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The study protocol was approved by the Institutional Review Board at NYU School of Medicine.

pH-impedance testing and study interpretation

Each patient undergoing pH impedance was asked to complete the GERD Health-Related Quality of Life (HRQL) and Esophageal Hypervigilance and Anxiety Scale (EHAS) surveys to define the frequency and intensity of symptoms prior to their procedure. Information on both typical symptoms including heartburn, regurgitation, chest pain, and atypical symptoms including cough, bloating, belching, nausea, and early satiety was collected; however, for the purposes of this study, symptom correlation calculations were based on typical and more specific symptoms of heartburn, regurgitation, chest pain, and cough.

24-h pH-impedance testing was performed according to standard protocol, and patients were asked to document meals, symptoms, and supine periods for the duration of the study. Recorded symptoms of interest included heartburn, regurgitation, chest pain, and cough. An acid exposure time (AET) of greater than 6% confirmed pathologic GERD, whereas an AET less than 4% confirmed a FED [12]. An AET between 4 and 6% was considered inconclusive; thus, accessory data such as the number of reflux episodes and reflux-symptom correlation informed whether esophageal reflux was considered pathologic [13]. The symptom index (SI) and the symptom-association probability (SAP) were used in addition to AET to interpret study results. SI is the percentage of reported symptoms (when recorded at least three times over the duration of the study) occurring within 2 min of a detected reflux event, with above 50% lending to positive symptom correlation [14–16]. SAP incorporates the total number of reported symptoms and reflux events, with a positive SAP > 95% indicating that the probability of symptom correlation occurring by chance is < 5% [17, 18]. A positive SI and/or a positive SAP confirmed positive symptom correlation. If FED was diagnosed, it was further classified as reflux hypersensitivity (RH) if there was a positive symptom correlation to acid reflux events or as functional heartburn (FH) if there was a negative symptom correlation to reflux events.

Data retrieval

Demographic data including age, gender, race/ethnicity, zip code, and insurance status were retrieved from each patient's electronic medical record. Socioeconomic variables were estimated from available demographic data. Median income estimates were based on zip code of each subject using available models [19, 20], and socioeconomic class estimates were based on median income estimates and insurance plan information. Low socioeconomic status (SES) was categorized as $25,000 or less, middle SES as $25,001–$150,000, and high SES as $150,000 and above. Subjects on Medicaid or the Essential Plan, New York State health insurance for working adults with lower incomes who do not qualify for Medicaid, were categorized as low socioeconomic status (SES) regardless of income.

Major medical comorbidities and comorbidities studied in relation to pathologic or functional reflux in literature were extracted from documented problem lists of the electronic medical record. These include history of anxiety or depression, chronic pain (headaches, lower back pain, and joint pain), asthma or non-asthmatic lung condition (chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis, pulmonary hypertension, sleep apnea), autoimmune condition, irritable bowel syndrome, inflammatory bowel disease, hypertension and/or hyperlipidemia, parathyroid and/or thyroid conditions, allergic rhinitis, insomnia, and polycystic ovarian syndrome. Patients with BMI < 18.5 were classified as underweight, 18.5–24.9 as normal weight, ≥ 25 as overweight, and ≥ 30 as obese. Alcohol use, tobacco use, and recreational drug use were also documented.

Data analysis

To compare participant characteristics and comorbidities by esophageal diagnosis, chi-square analysis and Fischer's exact tests were utilized. To compare the risk of functional esophageal disorder across all predictor participant

characteristics and medical comorbidities, univariable and multivariable logistic regression models were utilized. Based on the zip code location and esophageal disorder diagnosis of participants, population density maps were created. Odds ratios and 95% confidence intervals were computed. In all cases, $p < 0.05$ was required for statistical significance. All statistical analysis was performed using R Statistical Software version 4.1.1 (2021-08-10).

Results

During the 15-month period, a total of 391 participants underwent ambulatory pH-impedance testing. After excluding participants with incomplete studies or medical records, participants with studies performed on PPI, and participants with prior reflux or bariatric surgery, a total of 229 participants were included for analysis. 50% of participants ($n = 115$) met criteria for pathologic GERD and the remaining half ($n = 114$) met criteria for a FED, of which 82% ($n = 93$) had FH and 18% ($n = 21$) had RH. When comparing pathologic GERD to FED, there was no difference in

Table 1 Demographic & social history variables across GI disorder

Variable	Participants with pathologic GERD ($n = 115$)	Participants with FED ($n = 114$)	Total ($n = 229$)	*P* value
Age (years)[a]	46.99 (1.5)	47.71 (1.42)	47.35 (15.7)	0.73
Gender (female)[b]	61 (53.0%)	77 (67.54%)	138 (60.3%)	0.02
Ethnicity[b]				
Non-Hispanic White	98 (85.2%)	81 (71.1%)	179 (78.2%)	0.01
Non-Hispanic Black	2 (1.7%)	4 (3.5%)	6 (2.6%)	0.40
Non-Hispanic Asian	3 (2.6%)	14 (12.3%)	17 (7.4%)	< 0.01
Hispanic	7 (6.1%)	13 (11.4%)	20 (8.7%)	0.15
Other	5 (4.4%)	2 (1.8%)	7 (3.1%)	0.25
Socioeconomic status[b]				
Low	7 (6.8%)	12 (11.9%)	19 (9.3%)	0.21
Medium	89 (86.4%)	86 (85.2%)	175 (85.8%)	0.80
High	7 (6.8%)	3 (3.0%)	10 (4.9%)	0.21
Median income by zip code[b]				
$25,001–$75,000	36 (35.3%)	40 (35.1%)	76 (37.6%)	0.49
$75,001–$150,000	59 (57.8%)	57 (50%)	116 (57.4%)	0.90
$150,001 or above	7 (6.9%)	3 (2.6%)	10 (5.0%)	0.21
Health insurance plan[b]				
Medicaid + essential plan*	7 (6.2%)	12 (10.9%)	19 (8.5%)	0.21
Medicare	24 (21.2%)	15 (13.4%)	39 (17.5%)	0.14
Commercial	82 (72.6%)	83 (75.5%)	165 (74.0%)	0.62
Substance use[b]				
Ever alcohol use	66 (57.4%)	50 (43.9%)	106 (50.7%)	0.04
Ever smoker	28 (24.4%)	23 (20.2%)	51 (22.3%)	0.44
Drug use	10 (8.7%)	5 (4.4%)	15 (6.6%)	0.19
Symptom assessment**				
GERD HRQL score	25 (2.5)	24 (1.9)	25 (2.3)	0.88
EHAS score	37 (2.8)	39 (2.2)	38 (2.4)	0.40
Total impedance events	71 (3.5)	26 (2.5)	45 (3.1)	0.04

GERD gastroesophageal reflux disease, *FED* functional esophageal disorder, *GERD HRQL* GERD Health-Related Quality of Life, *EHAS* Esophageal Hypervigilance and Anxiety Scale

*The essential plan is New York State health insurance for working adults with lower incomes who do not qualify for Medicaid

**Symptom assessment scores were completed by 80% of all participants

[a]Continuous variables reported as mean (standard deviation)

[b]Categorical variables reported as frequency (percentage)

the GERD HRQL score (25 vs 24; $p=0.88$) or EHAS score (37 vs 39; $p=0.40$). There was a higher average number of impedance events in the pathologic GERD versus FED population (71 vs 26; $p=0.04$) (Table 1). No participants with FED had > 80 overall impedance events.

There was no difference in the baseline age or distribution of SES, median income, and health insurance plan between pathologic GERD versus FED (Table 1). There was a diverse geographic and socioeconomic distribution of participants with FED in the greater New York City area, with the majority of medium socioeconomic class located in Manhattan and Brooklyn (Supp. Fig. 1). Compared to pathologic GERD, a higher frequency of FED participants were of lower SES, though this trend was not statistically significant. A greater percentage of patients with FED vs GERD were female (68% vs 53%; $p=0.02$) and non-Hispanic Asian (12% vs. 3%; $p<0.01$). A greater percentage of GERD patients were non-Hispanic white (85% vs 71%; $p=0.01$) and reported a history of alcohol use (58% vs 44%; $p=0.04$) (Table 1).

Comorbid conditions are displayed in Table 2. A greater percentage of patients with GERD were overweight (43% vs 29%; $p=0.01$) or obese (17% vs 10%; $p=0.09$), while a greater percentage of patients with FED were underweight (9% vs 1%; $p<0.01$) or normal weight (53% vs 38%; $p=0.03$). Among patients with FED, chronic pain condition (37% vs 20%; $p<0.01$), insomnia (14% vs 4%; $p=0.05$), anxiety or depression (38% vs 27%; $p=0.08$), and allergic rhinitis (20% vs 6%; $p<0.01$) were more common (Table 2). The majority of these differences were persistent in univariate and multivariate logistic regression analyses (Table 3). On univariate analysis, female gender (OR 1.84; $p=0.03$), underweight BMI (OR 7.33; $p=0.06$), and insomnia (OR 2.83; $p=0.06$) were associated with a greater risk for FED, but were not statistically significant in multivariate analysis. On multivariable analysis, Asian ethnicity (OR 4.06; $p=0.05$), Hispanic ethnicity (OR 4.39; $p=0.01$), chronic pain condition (OR 2.37; $p<0.01$), allergic rhinitis (OR 3.29; $p=0.02$), anxiety, or depression (OR 1.90; $p=0.06$) was associated with greater risk of FED. Overweight BMI (OR 0.39; $p<0.01$), obesity (OR 0.23; $p\leq0.01$), and alcohol use (OR 0.53; $p=0.04$) were associated with a decreased risk of FED (Table 3).

There were no statistically significant differences in the distribution of other analyzed medical comorbidities (Table 2). When comparing FH to RH, a greater percentage of those with FH had a history of alcohol use (51% vs 24%; $p=0.04$; Supp. Table 1). In spite of not reaching statistical significance, a greater percentage of patients with RH (81% vs 67%; $p=0.15$) were female, had anxiety or depression

Table 2 Medical comorbidities across esophageal disorder type

Variable	All patients with pathologic GERD ($n=115$)	All patients with FED ($n=114$)	Total ($n=229$)	*P* value
BMI (kg/m^2)[a]	26.80 (0.61)	24.08 (0.4)	25.44 (5.7)	< 0.01
BMI (levels)[b]				
Underweight (%)[b]	1 (0.9%)	10 (8.8%)	11 (4.8%)	< 0.01
Normal weight (%)	44 (38.3%)	60 (52.6%)	106 (45.4%)	0.03
Overweight (%)	50 (43.5%)	33 (29.0%)	83 (36.2%)	0.02
Obese (%)	20 (17.4%)	11 (9.7%)	31 (13.5%)	0.09
Medical comorbidities[b]				
Anxiety/depression diagnosis (%)	31 (27.0%)	43 (37.7%)	74 (32.3%)	0.08
Diagnosis of chronic pain (%)	23 (20.0%)	42 (36.8%)	65 (28.4%)	< 0.01
Diagnosis of asthma (%)	25 (21.7%)	17 (14.9%)	42 (18.3%)	0.18
Autoimmune disorder (%)	19 (16.5%)	15 (13.2%)	31 (14.9%)	0.47
Non-asthmatic lung disease (%)	11 (9.6%)	10 (8.8%)	21 (9.2%)	0.84
Irritable bowel syndrome (%)	13 (11.3%)	8 (7.0%)	21 (9.2%)	0.26
Inflammatory bowel disease (%)	4 (3.5%)	3 (2.6%)	7 (3.1%)	0.71
Parathyroid or thyroid condition (%)	14 (12.2%)	21 (18.4%)	35 (5.3%)	0.19
Insomnia diagnosis (%)	5 (4.4%)	13 (11.4%)	18 (7.9%)	0.05
Polycystic ovarian syndrome (%)	1 (0.9%)	2 (1.8%)	3 (1.3%)	0.55
Allergic rhinitis (%)	7 (6.1%)	23 (20.2%)	30 (13.1%)	< 0.01
Hypertension/hyperlipidemia (%)	26 (22.6%)	27 (23.7%)	53 (23.1%)	0.85

BMI body mass index, *GERD* gastroesophageal reflux disease, *FED* functional esophageal disorder

[a]Continuous variables reported as mean (standard deviation)

[b]Categorical variables reported as frequency (percentage)

Table 3 Multivariable logistic regression of significant* variables on risk of functional esophageal disorder

Variable	Odds ratio	95% CI	*P* value**
Gender (female)	1.55	(0.83, 2.91)	0.17
Ethnicity			
Non-Hispanic Black	1.52	(0.22, 10.46)	0.67
Non-Hispanic Asian	4.06	(0.99, 16.68)	0.05
Hispanic	4.39	(1.36, 14.17)	0.01
Other	0.53	(0.08, 3.67)	0.53
BMI			
Underweight	5.26	(0.61, 45.25)	0.13
Overweight	0.39	(0.19, 0.77)	< 0.01
Obese	0.23	(0.09, 0.64)	< 0.01
Chronic pain condition	2.37	(1.18, 4.76)	0.01
Insomnia	2.07	(0.62, 6.88)	0.23
Allergic rhinitis	3.29	(1.19, 9.07)	0.02
Ever alcohol use	0.53	(0.29, 0.97)	0.04
Anxiety/depression	1.90	(0.99, 3.66)	0.06

BMI body mass index

*Variables displayed above were found to have significance or near significance in univariable logistic regression analysis

**Odds ratio for gender is compared with male; Odds ratio for ethnicity levels are compared with Non-Hispanic White; Odds ratio for BMI levels are compared with normal weight ($18.5 < \text{BMI} \leq 25$); Odds ratio for medical comorbidity variables are compared with negative disease status

(48% vs 38%; $p = 0.30$), a diagnosis of insomnia (19% vs 10%; $p = 0.22$), and a diagnosis of allergic rhinitis (33% vs 18%; $p = 0.10$) when compared to patients with FH (Supp. Table 1).

Discussion

In this retrospective cohort study across a heterogeneous population in New York City, we found low BMI, insomnia, chronic pain, allergic rhinitis, Asian race and Hispanic ethnicity, anxiety or depression, and female gender were associated with a greater risk of functional esophageal disorder versus pathologic GERD.

Many studies have shown a positive relationship between BMI and erosive GERD [21–23], but this is the first report of an inverse relationship between BMI and FED. One study found that high BMI was a risk factor for pathologic GERD but did not find an association between low BMI and FED; however, there was a significant proportion of overweight patients within this study cohort [22]. Another study did not find an association between BMI and either pathologic GERD or FED [11], though this study differed from ours as it excluded patients with eating disorders (which could exclude underweight patients) and was conducted in Italy with a less heterogeneous patient population.

This is the first report of an association between Asian race or Hispanic ethnicity and FEDs. Our findings regarding an increased risk of FED with female sex, and risk of GERD among Caucasian race and alcohol use have been previously validated in the literature. One study found that female sex was more associated with FED as compared to pathologic GERD [11]. GERD has been more associated with non-Hispanic white ethnicity compared to other races and ethnicities. Several studies have postulated that this is perhaps due to this population's better understanding of the terms "heartburn" and "reflux," and thus, more frequent reporting of symptoms. We found that alcohol use was more associated with GERD than FED, and more associated with FH over RH. A meta-analysis of 29 studies showed a dose–response association with alcohol use and GERD, likely due to direct mucosal damage, decreased lower esophageal peristalsis [24], and sensitized epithelial cells to gastric acid [25].

Our findings also revealed an association between allergic rhinitis, insomnia, and chronic pain with FED. Data on FED specifically are limited; however, there is evidence to support functional gastrointestinal disorders (FGID) and sleep changes. In a study on 1009 patients with FGID, sleep changes were associated with functional esophageal chest pain and heartburn symptoms, but not associated with functional globus, dysphagia, or regurgitation symptoms [26]. In a study comparing patients with functional dyspepsia to GERD diagnosed by endoscopic and impedance, sleep disturbances were commonly reported in functional dyspepsia patients, though experienced more frequently in patients with GERD [27]. Allergic rhinitis is an atopic disorder that has been associated with FGIDs [28], possibly due to the common pathway of excessive histamine release [29] and low-grade mucosal inflammation and immune activation [30]. Although a connection between FEDs and chronic pain has not been established, the use of neuromodulators for functional esophageal disorders is thought to target central sensitization and the altered processing of peripheral stimuli that may explain the incidence of other chronic pain disorders in patients with FEDs [31].

While associations between asthma, anxiety, IBS, and reflux disorders have been demonstrated in the literature, we did not find such associations in our study. Although our study found a borderline association between anxiety or depression and FED, three other studies found stronger associations between anxiety and FED [11, 31, 32]. In these studies, anxiety was assessed with a standardized survey and patients with underlying psychiatric illness were excluded, whereas in our study, anxiety and depression were grouped together, were clinician-reported,

and were not excluded due to other psychiatric illness. de Bortoli et al. found IBS was more prevalent in FED than GERD [11], with a prevalence of 50% and diagnoses based on negative endoscopy results, whereas our study had a 9% prevalence of IBS with diagnoses based on clinician reporting.

There are several limitations of our study. As this is a retrospective study, we are unable to assess causation (i.e., whether insomnia and low BMI are the results of functional symptoms or insomnia and low BMI-precipitated functional symptoms). Data regarding comorbid conditions relied on clinician-reported data obtained from retrospective chart review, rather than direct patient acquired data. Although only information on typical symptoms (heartburn, regurgitation, chest pain) and cough were utilized for symptom correlation, patients may have had concomitant functional dyspepsia symptoms (bloating, belching, nausea, early satiety). In addition, surrogate markers were utilized to extrapolate data regarding socioeconomic status (i.e., zip code and health insurance information), rather than patient-reported income and the additional factors that encompass socioeconomic status that have previously been linked to patient-related health outcomes. Although patients with normal AET can have symptoms secondary to non-acid reflux events (i.e., bile reflux), in our study, all patients with normal AET had less than 40 impedance events, considered normal range by the Lyon Consensus, and thus, non-acid reflux was likely non-contributory to symptomatology [11]. It is important to consider that symptom indices (SI, SAP) are patient reported and there is a great degree of variability in education level, socioeconomic status, and English fluency, which may influence categorization of patients into RH versus FH sub-groups. However, our study defined functional esophageal disease largely by overall esophageal acid exposure, and therefore, these results would remain similar in that respect. Given the importance of patient-reported symptoms in diagnosis, the possibility that patients misunderstand the meaning of "heartburn" and "reflux" is problematic and is a reminder to explore alternative etiologies for symptoms in certain populations. Although a strength of our demographics analysis was the diverse population residing within the areas in and around New York City, allowing for greater generalizability of our data, larger, multicenter studies are needed to better characterize this patient population.

In conclusion, we found that several disorders traditionally associated with GERD (allergic rhinitis, anxiety, and insomnia) are more associated with FEDs, perhaps due to hypersensitivity in the setting of atopy and central neural mechanisms predisposing to sleep difficulty. We found that comorbid chronic pain conditions and underweight BMI are significant risk factors for FED. High BMI and alcohol use may in fact be protective against FED, consistent with the literature showing the association between obesity and alcohol use with pathologic GERD.

Our results can be utilized by clinicians to refer at-risk patients to ambulatory pH testing, which is underutilized and recommended as a personalized approach in guiding treatment decisions for patients with reflux symptoms [10]. Current literature suggests that normal pre-operative acid exposure is a risk factor for poor surgical outcomes, particularly after Nissen fundoplication [33]. In addition, psychological comorbidity is common among GERD patients and may play a role in ongoing reflux symptoms despite medication management with acid suppression [32]. Our study results, suggest that there may be a subgroup of patients that may merit further consideration with regards to candidacy for an anti-reflux surgery. Therefore, further risk stratifying patients in the pre-operative setting or during medical evaluation can be crucial to medical and surgical outcomes. While several of our studied risk factors have not been associated in the literature with failure of medical GERD treatment, they may in fact be related, and these risk factors should be studied in relation to PPI failure in future studies. As participants with prior reflux surgery were excluded, we are unable to comment on whether these risk factors may be associated with surgical failure; however, future studies should also consider these factors. Nevertheless, at this point, it is accepted that both anti-reflux surgery and endoscopic treatment for GERD should be avoided in patients with functional heartburn and medical management should be the mainstay of therapy among this patient population.

Our findings better characterize these patients, contributing to the epidemiologic data of this relatively new condition and, thus, enabling clinicians to optimize their approach to testing and treatment.

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Declarations

Disclosures Moniyka Sachar, Marina Mautner Wizentier, Emma Risner, Hannah Asmail, Mathew Omara, Shreya Chablaney, Abraham Khan, Rita Knotts have no conflicts of interest or financial ties to disclose.

Informed consent Informed patient consent was obtained prior to publication of case.

References

1. Spechler SJ (1992) Epidemiology and natural history of gastro-oesophageal reflux disease. Digestion 51:24–29
2. Lind T, Havelund T, Carlsson R et al (1997) Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. Scand J Gastroenterol 32:974–979
3. Jones RH, Hungin AP, Phillips J et al (1995) Gastro-oesophageal reflux disease in primary care in Europe: clinical presentation and endoscopic findings. Eur J Gen Pract 1:149–154
4. Patel A, Sayuk GS, Gyawali CP (2016) Prevalence, characteristics, and treatment outcomes of reflux hypersensitivity detected on pH-impedance monitoring. J Neurogastroenterol Motil 28:1382–1390
5. Bate CM, Griffin SM, Keeling PW et al (1996) Reflux symptom relief with omeprazole in patients without unequivocal oesophagitis. Aliment Pharmacol Ther 10:547–555
6. Richter JE, Kovacs TO, Greski-Rose PA et al (1999) Lansoprazole in the treatment of heartburn in patients without erosive oesophagitis. Aliment Pharmacol Ther 13:795–804
7. Martinez SD, Malagon IB, Garewal HS et al (2003) Non-erosive reflux disease (NERD)—acid reflux and symptom patterns. Aliment Pharmacol Ther 17:537–545
8. Yamasaki T, Fass R (2017) Reflux hypersensitivity: a new functional esophageal disorder. J Neurogastroenterol Motil 23:495
9. Savarino E, Zentilin P, Tutuian R et al (2012) Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. J Gastroenterol 47:159–168
10. Roman S, Gyawali CP, Savarino E et al (2017) Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. J Neurogastroenterol Motil 29:1–5
11. de Bortoli N, Frazzoni L, Savarino EV, Frazzoni M, Martinucci I, Jania A, Tolone S, Scagliarini M, Bellini M, Marabotto E, Furnari M et al (2016) Functional heartburn overlaps with irritable bowel syndrome more often than GERD. Am J Gastroenterol 111:1711–1717
12. Gyawali CP, Kahrilas PJ, Savarino E et al (2018) Modern diagnosis of GERD: the Lyon Consensus. Gut 67:1351–1362
13. Savarino E, Bredenoord AJ, Fox M et al (2017) Advances in the physiological assessment and diagnosis of GERD. Nat Rev Gastroenterol Hepatol 14:665–676
14. Lam H, Breumelhof R, Roelofs JM et al (1994) What is the optimal time window in symptom analysis of 24-hour esophageal pressure and pH data? Dig Dis Sci 39:402–409
15. Herregods TV, Pauwels A, Tack J et al (2017) Reflux-cough syndrome: assessment of temporal association between reflux episodes and cough bursts. J Neurogastroenterol Motil 29:e13129
16. Wiener GJ, Richter JE, Copper JB et al (1988) The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol 83(4):358–361
17. Weusten BL, Roelofs JM, Akkermans LM et al (1994) The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 107:1741–1745
18. Ghillebert G, Janssens J, Vantrappen G et al (1990) Ambulatory 24 hour intraoesophageal pH and pressure recordings v provocation tests in the diagnosis of chest pain of oesophageal origin. Gut 31:738–744
19. United States Census Bureau (2019) American Community Survey 1-year estimates, table S1903 (2005–2019). https://data.census.gov/
20. United States Census Bureau (2014) American Community Survey 5-year estimates (2010–2014). https://data.census.gov/
21. Jacobson BC, Somers SC, Fuchs CS et al (2006) Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med 354:2340–2348
22. Savarino E et al (2011) Overweight is a risk factor for both erosive and non-erosive reflux disease. Dig Liver Dis 43:940–945
23. Berstad AR, Weberg R, Larsen IF et al (1986) Relationship of hiatus hernia to reflux oesophagitis a prospective study of coincidence, using endoscopy. Scand J Gastroenterol 21:55–58
24. Mayer EM, Grabowski CJ, Fisher RS (1978) Effect of graded doses of alcohol upon esophageal motor function. Gastroenterology 76:1133–1136
25. Barlow WJ, Orlando RC (2005) The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. Gastroenterology 128:771–778
26. Bouchoucha M, Mary F, Bon C et al (2018) Sleep quality and functional gastrointestinal disorders. A psychological issue. J Dig Dis 19:84–92
27. Vakil N, Wernersson B, Wissmar J et al (2016) Sleep disturbance due to heartburn and regurgitation is common in patients with functional dyspepsia. United Eur Gastroenterol J 4:191–198
28. Jones MP, Walker MM, Ford AC et al (2014) The overlap of atopy and functional gastrointestinal disorders among 23 471 patients in primary care. Aliment Pharmacol Ther 40:382–391
29. Schnedl WJ, Enko D (2021) Considering histamine in functional gastrointestinal disorders. Crit Rev Food Sci Nutr 61:2960–2967
30. Wouters MM, Vicario M, Santos J (2016) The role of mast cells in functional GI disorders. Gut 65:155–168
31. Dickman R, Maradey-Romero C, Fass R (2014) The role of pain modulators in esophageal disorders—no pain no gain. Neurogastroenterol Motil 26:603–610
32. Avidan B, Sonnenberg A, Giblovich H, Sontag SJ (2001) Reflux symptoms are associated with psychiatric disease. Aliment Pharmacol Ther 15:1907–1912
33. Campos GM, Peters JH, DeMeester TR et al (1999) Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg 3(3):292–300