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ESOPHAGUS

Psychological Processes, Not Physiological Parameters, Are Most Important Contributors to Symptom Severity in Patients With Refractory Heartburn/Regurgitation Symptoms

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BACKGROUND & AIMS: Physiological and psychological factors have been found to influence esophageal symptom reporting. We aimed to evaluate which of these factors are associated with 3 reflux symptom severity outcomes (ie, Total Reflux, Heartburn, and Sleep Disturbance) through a traditional statistical and a complementary machine-learning approach. **METHODS:** Consecutive adult patients with refractory heartburn/regurgitation symptoms underwent standard 24-hour pH-impedance monitoring and completed questionnaires assessing past and current gastrointestinal and psychological health. In the traditional statistical approach, hierarchical general linear models assessed relationships of psychological and physiological variables (eg, total number of reflux episodes) with reflux severity scores. Mediation analyses further assessed pathways between relevant variables. In the machine-learning approach, all psychological and physiological variables were entered into 11 different models and cross-validated model performance was compared among the different models to select the best model. **RESULTS:** Three hundred ninety-three participants (mean [SD] age, 48.5 [14.1] years; 60% were female) were included. General psychological functioning emerged as an important variable in the traditional statistical approach, as it was significantly associated with all 3 outcomes and mediated the relationship between childhood trauma and both Total Reflux and Heartburn Severity. In the machine-learning analyses, general psychological variables (eg, depressive symptoms) were most important for Total Reflux and Sleep Disturbance outcomes, and symptom-specific variables, like visceral anxiety, were more influential for Heartburn Severity. Physiological variables were not significant contributors to reflux symptom severity outcomes in our sample across reflux classifications and statistical methodology. **CONCLUSIONS:** Psychological processes, both general and symptom-specific, should be considered as another important factor within the multifactorial processes that impact reflux symptom severity reporting across the reflux spectrum.

Keywords: Gastroesophageal Reflux Disease; Functional Heartburn; Health Psychology; Anxiety; Depression.

Gastroesophageal reflux disease (GERD) is a chronic esophageal disorder with an estimated prevalence of 10%–30% in the adult Western population[1] and significant impact on quality of life.[2] The standard of care for GERD treatment is the use of proton pump inhibitors (PPIs),[3] which reduce stomach acid production. It is well established that PPIs are highly effective in healing esophagitis, but less effective in symptom control, especially in the absence of erosive lesions.[4] Per the Lyon Consensus,[5] patients with GERD can be stratified into the following 4 classifications based on the results of a 24-hour pH monitoring and multichannel intraluminal impedance (pH-MII): true GERD, borderline GERD, reflux hypersensitivity, and functional heartburn (see Supplementary Table 1 for Lyon Consensus parameters).

Despite several physiological mechanisms explaining the pathogenesis of GERD, anywhere from 30% to 96% of patients with refractory heartburn/regurgitation symptoms present with normal reflux parameters.[6,7] Even in cases of abnormal acid exposure (ie, true GERD), research indicates that there is a disconnection between the presence of acid and the reported symptom experience.[8] Indeed, studies evaluating the relationship between reflux characteristics and symptom perception in PPI nonresponders found a heterogeneous impedance reflux profile and, remarkably, symptoms were not associated with the majority of reflux events.[8–11] These findings suggest there are processes outside of physiological or pathological acid reflux that likely contribute to esophageal symptom perception in patients with GERD.

Research in the field of psychogastroenterology consistently demonstrates that psychological factors are significantly and independently associated with esophageal

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Abbreviations used in this paper: **ASE, average squared error; BAQ, Body Awareness Questionnaire; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IAS, Illness Attitudes Scale; PASS, Pain Anxiety Symptom Scale; pH-MII, pH monitoring and multichannel intraluminal impedance; PHQ-9, Patient Health Questionnaire-9; PPI, proton pump inhibitor; VSI, Visceral Sensitivity Index.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Psychological and physiological factors contribute to symptom reporting in patients with refractory heartburn/regurgitation symptoms. However, research evaluating which of these factors is most associated with symptom severity is lacking.

NEW FINDINGS

In a large sample of patients with refractory heartburn/regurgitation symptoms, psychological symptoms were significantly associated with reflux symptom severity, and physiological reflux variables (eg, number of reflux episodes) were not.

LIMITATIONS

The cross-sectional design limits the ability to make directional/causational claims. The heterogenous sample increases ecological validity but results in less standardization, although some variables were controlled for statistically.

CLINICAL RESEARCH RELEVANCE

Psychological symptom assessment should be included in research on patients with refractory heartburn/regurgitation symptoms, particularly when symptom severity is a main outcome. The current study supports further evaluation of brain–gut behavioral therapy in patients across the reflux spectrum, with psychological symptoms serving as potential target mechanisms.

BASIC RESEARCH RELEVANCE

The current study supports further evaluating the role of psychological symptoms in visceral (esophageal) perception. Specifically, future research should assess how psychological processes, both general and disease-specific, influence both frequency and intensity of visceral sensations.

symptom perception across esophageal diseases (ie, GERD, achalasia, and eosinophilic esophagitis), while controlling for physiological variables (eg, altered motility, sphincter pressure, and reflux events).[12,13] In GERD specifically, Yadlapati et al[6] found that psychosocial distress is associated with symptom severity in PPI nonresponders with normal pH-MII profiles. Although previous research often included PPI nonresponders only, a recent study observed that esophageal hypervigilance and symptom-specific anxiety are present across the different GERD phenotypes,[14] suggesting psychological processes may be important to esophageal symptom perception universally, regardless of physiological indicators of reflux. In addition to current psychological functioning, early life adversity, such as childhood trauma, influences development of the brain and gut separately, as well as their interaction via the brain–gut axis.[15] Although most research has focused on bowel and gastroduodenal disorders (eg, irritable bowel syndrome[16] and functional dyspepsia[17]), there is also evidence to suggest a relationship between childhood trauma and unexplained chest pain,[18] warranting investigation of this relationship in other esophageal conditions.

The poor symptom-reflux association in GERD, coupled with the potentially universal role of psychological processes in esophageal symptom severity reporting, underscores the importance of identifying factors that impact reflux symptom severity and their similarities and/or differences across reflux classifications. Our first aim (aim 1) was to investigate which factors, psychological and physiological, are associated with self-reported reflux symptom severity (frequency and intensity), including severity of GERD symptoms overall, of heartburn specifically, and of sleep disturbance, in a cohort of patients with GERD. We hypothesized that psychological variables are more strongly associated with reflux symptom severity compared with physiological reflux variables. Aim 2 was to further explore the nature of the associations from aim 1 using mediation analysis. We hypothesized that psychological variables would mediate the relationship between self-reported childhood trauma and reflux symptom severity outcomes. Our third aim (aim 3) was to explore whether the relationships from aim 1 differ across esophageal reflux classifications and by PPI status at the time of testing. We hypothesized that these relationships would not differ across reflux classifications and PPI status. We will take both a classic statistical approach and a complementary machine-learning approach to investigate our research questions.

Methods

Participants

Consecutive adult patients with refractory heartburn/regurgitation symptoms (eg, heartburn or regurgitation) who underwent 24-hour pH-MII between 2009 and 2014 at a tertiary care center were prospectively included in the study. Demographic (age and gender) and clinical (weight [in kilograms], height [in centimeters], body mass index, and PPI status at the time of pH-MII [on/off]) information was collected at time of enrollment. All patients included were referred for pH-MII due to refractory heartburn/regurgitation symptoms, meaning they continued to have symptoms after completing at least 12 weeks of PPI (twice per day) treatment. All patients had undergone a clinical evaluation, which did not identify other disorders (eg, motility disorders) as a major candidate underlying pathology, and an esophagogastroduodenoscopy during the previous 6 months that failed to explain their symptoms. Participants were excluded if they had exclusively atypical symptoms (eg, cough) without also having heartburn/regurgitation, dyspepsia as a primary symptom, an esophageal motility disorder (eg, achalasia), or a history of esophageal surgery. Participants provided demographic and clinical information and completed psychological questionnaires at the clinic visit. Subjects with a majority of questionnaires missing (n = 21) or with incomplete pH-MII testing reports (n = 84) were excluded from analysis. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Leuven (approval number S51450).

Patient-Reported Outcomes

Reflux symptom severity. The ReQuest is a 6-item self-report questionnaire assessing reflux symptom severity and is composed of 7 dimensions, including acid, upper abdominal/stomach, lower abdominal/digestive, nausea, general well-being, sleep disturbance, and other symptoms.[19] The current study used the total reflux severity score, the acid dimension, and the sleep disturbance dimension of the ReQuest as our 3 outcome variables (see Supplementary Table 2 for detailed scoring information).[19] The inclusion of specific heartburn and sleep dimensions, in addition to the total reflux symptom severity, underscores the multifaceted nature of heartburn/regurgitation symptoms. The outcome variables will be labeled as "Total Reflux Severity," "Heartburn Severity," and "Sleep Disturbance" to reflect their respective score/dimension.

Psychological questionnaires. Participants completed 13 questionnaires to assess psychosocial functioning (see Supplementary Table 2 for list of questionnaires and their description). The questionnaires evaluated several aspects of psychosocial health, including history of childhood trauma, personality traits (eg, trait anxiety or Big Five personality dimensions), as well as current general (eg, depressive and various anxiety symptoms) and body and illness-specific (eg, bodily awareness or gastrointestinal [GI]-specific anxiety) psychosocial functioning.

24-Hour pH Monitoring and Multichannel Intraluminal Impedance Recording and Analysis

The pH-MII recording was performed according to current clinical practice and details are provided in Supplementary Item 1. Patients on PPI were standardized to PPI twice per day without prokinetics or reflux inhibitors (eg, baclofen) for pH-MII. At the completion of the testing period, objective reflux parameters were evaluated and patients were classified into the following 4 categories based on the Lyon Consensus[5] (see Supplementary Table 1): true GERD, borderline GERD, reflux hypersensitivity, and functional heartburn. The total number of reflux events and the acid exposure time were chosen as the reflux parameters of interest. The total number of reflux events reflects the sum of the acidic and nonacidic reflux events during upright and recumbent position. Meanwhile, the total 24-hour esophageal acid exposure time (percent time) is defined as the total time period with esophageal pH $<$ 4 divided by the total monitoring time.

Statistical Analysis

The first approach to data analysis was a traditional statistical method, with the goal of using a hierarchical general linear model to evaluate the psycho- and physiological variables most associated with reflux symptom severity (aim 1), mediation analyses to further explore the nature of these relationships (aim 2), and moderation analyses to examine whether relationships differ by reflux classification and PPI status (aim 3). The predetermined α level was set at .05 for all tests. A flow diagram illustrating the statistical methods used is available in Supplementary Figure 1. All statistical analyses were performed in SAS software, version 9.4 (SAS Institute, Cary, NC). The full SAS code for our analyses is available at https://github.com/labgas/proj_reflux_database_1.

Missing data. A 3-step multiple imputation[20] was applied to handle missing questionnaire data. In the first step, we conducted scale-level imputations with the purpose of generating a set of placeholder scale scores for each questionnaire of interest. In the second step, item-level imputations were generated while using the placeholder scale scores as auxiliary variables. Finally, the placeholder scale scores were removed and new scale scores were computed for each questionnaire using the imputed item-level scores. More information regarding the multiple imputation procedure is available in Supplementary Item 2.

Data transformations. The distributions of the 3 dependent variables (ie, Total Reflux Severity, Heartburn Severity, and Sleep Disturbance) and relevant independent variables (eg, psychological questionnaires or reflux variables) were examined to assess normality and identify which variables needed to be transformed. All 3 dependent variables, as well as the independent variables of childhood trauma questionnaire, total number of reflux episodes, and total volume exposure were identified as non-normally distributed and were transformed using Box-Cox transformation.

Principal component analysis. Due to the high number of independent variables and potential for multicollinearity, principal component analysis with varimax rotation was carried out on all psychological questionnaires, except for the childhood trauma questionnaire, to reduce the number of psychological variables into a smaller number of orthogonal components capturing a high enough amount of the variance. The number of components was identified based on a Scree plot and the criterion of eigenvalue $>$1.0. The childhood trauma questionnaire was not included in the analysis, as childhood trauma is a historical event, which differs from the other psychological questionnaires assessing current self-reported psychological functioning. In addition, the childhood trauma questionnaire was used to test our aim 2 hypothesis that psychological variables will mediate the relationship between childhood trauma and reflux symptom severity outcomes (see "Mediation Analysis" for further details on aim 2).

General linear model. Hierarchical general linear models were performed to assess the primary question of which factors, psychological and physiological, are most associated with reflux symptom severity (aim 1). We estimated 3 independent models, with Total Reflux Severity, Heartburn Severity, and Sleep Disturbance set as the outcome variable, respectively. Step order was the same for all three models. Childhood trauma (Childhood Trauma Questionnaire) was entered in step 1, as it is considered a historical event that occurred earlier in time. In addition, in order to test aim 2 hypotheses, we needed to first assess the independent effects of childhood trauma on our 3 reflux symptom severity outcomes. The 5 psychological components determined in the principal component analysis were entered in step 2 to test the additive effects of these psychological variables, and to determine whether there is cause for subsequent mediation analyses. For example, if childhood trauma was significant in step 1, but then became nonsignificant after the psychological components were entered in step 2, it would be cause to further investigate potential mediation. Finally, relevant reflux testing variables, including total number of reflux events, total volume exposure, reflux classification, and PPI status, were entered in step 3. This allowed us to assess whether these further explained any

variance in the model and to control for the potential effects of clinical variables, such as PPI status, on outcomes.

Mediation analysis. For aim 2, mediation analyses were applied to evaluate our hypotheses that psychological variables would mediate the relationship between childhood trauma and reflux symptom severity outcomes. Our data are cross-sectional, making it difficult to establish temporal precedence of childhood trauma. However, it is plausible to assume childhood trauma temporally preceded the other variables, as other research has done.[16] The mediation analyses were conducted using the PROCESS macro (version 2.13) for SAS, which is a general linear model–based method of testing mediation (as opposed to a structural equation model–based method, to which path analysis commonly refers). To test the mediation (indirect) pathway, the relationship between the independent variable and mediator variables (path a) and the relationship between the mediator variables and the outcome variable (path b) are assessed for significance. In addition, the direct pathway (path c') between the independent and dependent variable is assessed. If the entire indirect pathway is significant, but the direct pathway is not significant, there is mediation. For all models, childhood trauma was set as the independent variable and mediator variables included the independent variables significant in the general linear model that corresponds to that outcome variable (eg, Total Reflux Severity). If multiple significant independent variables were identified in the general linear model, parallel mediation analyses were conducted, meaning the significant independent variables from the general linear model were all applied as mediator variables in parallel in a single mediation model. For example, if general psychological health, pain coping, and social functioning were significantly associated with Total Reflux Severity in the general linear model, the subsequent mediation analysis would include all 3 variables as parallel (as opposed to serial) mediator variables in 1 model.

Moderation analysis. General linear models were performed to assess whether the effects of psychological and physiological factors on reflux symptom severity differed by esophageal reflux classification (ie, true GERD, borderline GERD, reflux hypersensitivity, and functional heartburn) and PPI status at the time of testing (on/off PPI). First, we evaluated the moderating effect of reflux classification on the relationship between psychophysiological variables and Total Reflux Severity, Heartburn Severity, and Sleep Disturbance, respectively. For each model, childhood trauma, the 5 psychological components, total number of reflux events, total volume exposure, and PPI status were entered into the model as independent variables. The interaction effect with reflux classification was entered for each independent variable. This process was then repeated with PPI status as the moderating variable. However, in these models the independent variable "PPI status" was replaced with "reflux classification."

Machine Learning Analysis

In addition to the classical statistical approach mentioned above, we adopted a complementary data-driven machine learning approach with the aim of maximizing predictive performance in terms of explained variance in the target variables.

All machine learning analyses were performed in SAS Enterprise Miner 15.1 software (SAS Institute) according to the SEMMA (sample, explore, modify, model, and assess) process developed by SAS and implemented in Enterprise Miner.[21–23] See Supplementary Item 3 for a detailed outline of the SEMMA process.

The same standardized Box-Cox transformed ReQuest scores served as the target variables in both our general linear model and machine learning analyses for model performance comparison purposes. Rather than reducing the dimensionality of the psychological questionnaire variables by principal component analysis as in the general linear models, we entered the individual questionnaire scores into the machine learning models as individual input variables. Next, 11 models were selected. An overview of the configurations of the different models is shown in Supplementary Table 3. We used 8-fold cross-validation, as this is an economical and valid internal validation method.[24] Cross-validated model performance (criterion: average squared error [ASE]) was compared between the different models to select the best model.

Results

Descriptive Results

Three hundred ninety-three patients (mean [SD] age 48.38 [14.17] years; 60% were female) were included and classified as 98 true GERD, 85 borderline GERD, 77 reflux hypersensitivity, and 133 functional heartburn (see Supplementary Figure 2 for a CONSORT [Consolidated Standards of Reporting Trials] diagram of participant inclusion). In total, 38% of patients were on PPIs and 53% were off PPIs at the time of pH-MII, and 36 patients (9%) were missing data for PPIs. Sample characteristics for demographic, clinical, and questionnaire data are presented in Supplementary Table 4.

Principal Component Analysis

Principal component analysis produced the following 5 components (Supplementary Table 5): component 1 (8 items, eigenvalue = 3.32) composed of items measuring health-related/symptom-specific anxiety, component 2 (5 items, eigenvalue = 3.13) composed of items measuring general psychological functioning, component 3 (5 items, eigenvalue = 2.64) measuring personality, component 4 (2 items, eigenvalue = 1.76) measuring pain coping, and component 5 (2 items, eigenvalue = 1.29) measuring social functioning. The components were labeled health anxiety, general psychological health, personality, pain coping, and social functioning, respectively.

General Linear Model

Total Reflux Severity. Childhood trauma was significant in the first step ($R^2 = .01$, $F_{1,\ 391} = 4.37$; $P = .04$), although it only accounted for a small percentage (1%) of the explained variance in Total Reflux Severity scores. Childhood trauma was not significant in the final model ($\beta = .04$, $P = .39$), indicating potential mediation. The final model was statistically significant ($R^2 = .27$, $F_{13,\ 379} = 10.93$; $P < .0001$). General psychological health ($\beta = .45$; $P < .0001$), pain coping ($\beta = -.10$; $P = .02$), and social functioning ($\beta = .10$; $P = .03$) components remained significantly associated with Total Reflux Severity, even while controlling for

Table 1. Hierarchical General Linear Model Evaluating Influence of Past and Current Psychological Factors on Total Reflux Severity

Variable	R^2	β	SE	*P* value	95% Confidence limits
Model 1	.01	—	—	.04	—
Childhood trauma	—	.11	.05	.04*	0.00, 0.20
Model 2	.25	—	—	<.0001	—
Childhood trauma	—	.04	.05	.37	–0.05, 0.13
Factor 1: Health anxiety	—	.01	.04	.75	–0.07, 0.10
Factor 2: General psychological health	—	.47	.04	<.0001*	0.38, 0.56
Factor 3: Personality	—	.06	.05	.18	–0.03, 0.15
Factor 4: Pain coping	—	–.11	.04	.02*	–0.20, –0.02
Factor 5: Social functioning	—	.09	.04	.04*	0.00, 0.18
Model 3	.27	—	—	<.0001	—
Childhood trauma	—	.04	.05	.39	–0.05, 0.13
Factor 1: Health anxiety	—	.01	.04	.85	–0.80, 0.10
Factor 2: General psychological health	—	.45	.04	<.0001*	0.36, 0.54
Factor 3: Personality	—	.05	.05	.26	–0.38, 0.14
Factor 4: Pain coping	—	–.10	.04	.02*	–0.19, –0.02
Factor 5: Social functioning	—	.10	.04	.03*	0.01, 0.18
Total no. of reflux events	—	.04	.07	.61	–0.10, 0.17
Total volume exposure	—	–.08	.07	.22	–0.22, 0.05
Classification					
Functional heartburn	—	–.15	.14	.29	–0.44, 0.13
Reflux hypersensitivity	—	.18	.15	.24	–0.12, 0.47
Borderline GERD	—	–.16	.14	.27	–0.44, 0.12
True GERD	—	.00	—	—	—
PPI use					
Off PPI	—	–.13	.10	.21	–0.34, 0.08
Missing	—	–.15	.17	.36	–0.48, 0.17
On PPI	—	.00	—	—	—

*$P < .05$, significant.

relevant physiological variables. See Table 1 for an overview of the results.

Heartburn Severity. Childhood trauma was significant in the first step ($R^2 = .01$, $F_{1, 391} = 4.30$; $P = .04$), although again, it only accounted for a small percentage (1%) of the explained variance in Heartburn Severity scores. Childhood trauma was not significant in the final model ($\beta = .08$, $P = .11$), indicating potential mediation. The final model was statistically significant ($R^2 = .13$, $F_{13, 379} = 4.29$; $P < .0001$). General psychological health ($\beta = .21$; $P < .0001$), social functioning ($\beta = .14$; $P = .003$), and reflux classification ($P = .002$) were significantly associated with Heartburn Severity scores. For reflux classification, post-hoc analyses revealed the reflux hypersensitivity group reported the highest Heartburn Severity, and the score was significantly higher than both the functional heartburn and borderline GERD groups. Furthermore, the true GERD group had a significantly higher score compared with the borderline GERD group. See Table 2 for an overview of the results.

Sleep Disturbance. The first model was not significant ($R^2 = .01$, $F_{1, 391} = 3.66$; $P = .06$), indicating no significant association between childhood trauma and Sleep Disturbance. The final model was statistically significant ($R^2 = .20$, $F_{13, 379} = 7.40$; $P < .0001$) and demonstrated that general psychological health ($\beta = .40$; $P < .0001$) and personality ($\beta = .10$; $P = .043$) were significantly associated with Sleep Disturbance scores. See Table 3 for an overview of the results.

Mediation Analyses

Total Reflux Severity. A path diagram of the mediation analyses is represented in Figure 1. The direct effect of childhood trauma on Total Reflux Severity became nonsignificant (direct effect = 0.04; 95% CI, –0.05 to 0.13) when psychological and reflux variables were entered into the model, meaning there is a possibility the significant relationship between childhood trauma and Total Reflux Severity in the first model can be explained by 1 or more of the significant variables entered into the final model (general psychological health, pain coping, and social functioning). The indirect effect of childhood trauma through general psychological health on Total Reflux Severity was significant (indirect effect = 0.08; 95% CI, 0.03 to 0.13), meaning there is a significant path from childhood trauma to general psychological health, and from general psychological health to Total Reflux Severity. Findings suggest that general psychological health mediates the relationship between childhood trauma and Total Reflux Severity. Pain coping and social functioning were not significant mediator variables.

Table 2. Hierarchical General Linear Model Evaluating Influence of Past and Current Psychological Factors on Heartburn Severity

Variable	R^2	β	SE	*P* value	95% Confidence limits
Model 1	.01	—	—	.039	—
Childhood trauma	—	.10	.05	.04*	0.01, 0.20
Model 2	.09	—	—	<.0001	—
Childhood trauma	—	.09	.05	.08	–0.01, 0.19
Factor 1: Health anxiety	—	.01	.05	.82	–0.09, 0.11
Factor 2: General psychological health	—	.23	.05	<.0001*	0.13, 0.33
Factor 3: Personality	—	.09	.05	.09	–0.12, 0.18
Factor 4: Pain coping	—	–.01	.05	.87	–0.10, 0.09
Factor 5: Social functioning	—	.13	.05	.01*	0.03, 0.22
Model 3	.13	—	—	<.0001	—
Childhood trauma	—	.08	.05	.11	–0.02, 0.18
Factor 1: Health anxiety	—	.00	.05	.96	–0.10, 0.10
Factor 2: General psychological health	—	.21	.05	<.0001*	0.11, 0.31
Factor 3: Personality	—	.07	.05	.18	–0.03, 0.16
Factor 4: Pain coping	—	–.01	.05	.87	–0.10, 0.09
Factor 5: Social functioning	—	.14	.05	.003*	0.05, 0.24
Total no. of reflux events	—	.02	.07	.78	–0.13, 0.17
Total volume exposure	—	–.00	.07	.99	–0.15, 0.15
Classification					
Functional heartburn	—	–.34	.16	.03*	–0.65, –0.32
Reflux hypersensitivity	—	.07	.16	.65	–0.24, 0.40
Borderline GERD	—	–.41	.16	.01*	–0.72, –0.11
True GERD	—	.00	—	—	—
PPI use					
Off PPI	—	–.19	.11	.10	–0.41, 0.04
Missing	—	–.25	.18	.16	–0.61, 0.10
On PPI	—	.00	—	—	—

*$P < .05$, significant.

Heartburn Severity. A path diagram of the mediation analyses is represented in Figure 2. The direct effect of childhood trauma on Heartburn Severity became nonsignificant (effect = 0.09; 95% CI, −0.01 to 0.19) when additional psychological and reflux variables were entered into the model, indicating the initial significant relationship between from childhood trauma to Heartburn Severity may be explained through 1 or more of the other significant variables in the final model (general psychological health and social functioning). The indirect effect of childhood trauma on general psychological health was significant (effect = 0.037; 95% CI, 0.02 to 0.07). Thus, findings suggest that general psychological health mediates the relationship between childhood trauma and Heartburn Severity. Social functioning was not a significant mediator variable.

Sleep Disturbance. No mediation analyses were performed for the outcome variable Sleep Disturbance, as there was no significant association between childhood trauma and sleep disturbance in the general linear models.

Moderation Analyses

There was a significant interaction effect between social functioning and reflux classification for Heartburn Severity ($F = 2.90$; $P = .035$) and Sleep Disturbance ($F = 4.88$; $P = .003$) scores. There was no significant interaction effect between reflux classification and any of the independent variables for Total Reflux Severity. In addition, there was no significant interaction effect between PPI status and any independent variables for Total Reflux Severity, Heartburn Severity, or Sleep Disturbance.

Machine Learning

Total Reflux Severity. An overview of the predictive performance of the different machine learning models is shown in Supplementary Table 6.

The gradient boosting models showed the best cross-validated predictive performance, with GradBoost Tuned #4 having the lowest ASE (0.103), explaining 88% of the variance in Total Reflux Severity score. Figure 3A shows a comparison of the correlation between the observed and predicted values for both the general linear model and Gradient Boosting model to illustrate the difference in performance.

Variables are ranked in order of their variable worth, which is a measure of how much a variable contributes to the model prediction. Thus, variables with higher variable

Table 3. Hierarchical General Linear Model Evaluating Influence of Past and Current Psychological Factors on Sleep Disturbance

Variable	R^2	β	SE	*P* value	95% Confidence limits
Model 1	.01	—	—	.06	—
Childhood trauma	—	.10	.05	.06	–0.00, 0.20
Model 2	.19	—	—	<.0001	—
Childhood trauma	—	.06	.05	.24	–0.04, 0.16
Factor 1: Health anxiety	—	.05	.05	.29	–0.04, 0.14
Factor 2: General psychological health	—	.41	.05	<.0001*	0.31, 0.50
Factor 3: Personality	—	.11	.05	.03*	0.01, 0.20
Factor 4: Pain coping	—	.02	.05	.60	–0.07, 0.11
Factor 5: Social functioning	—	–.02	.05	.69	–0.11, 0.07
Model 3	.20	—	—	<.0001	—
Childhood trauma	—	.05	.05	.28	–0.04, 0.15
Factor 1: Health anxiety	—	.05	.05	.25	–0.04, 0.15
Factor 2: General psychological health	—	.40	.05	<.0001*	0.31, 0.50
Factor 3: Personality	—	.10	.05	.04*	0.00, 0.19
Factor 4: Pain coping	—	.02	.05	.65	–0.07, 0.11
Factor 5: Social functioning	—	–.01	.05	.85	–0.10, 0.08
Total no. of reflux events	—	–.02	.07	.78	–0.16, 0.12
Total volume exposure	—	.05	.07	.48	–0.09, 0.19
Classification					
Functional heartburn	—	–.20	.15	.19	–0.50, 0.10
Reflux hypersensitivity	—	–.10	.16	.63	–0.38, 0.23
Borderline GERD	—	–.30	.15	.08	–0.55, 0.04
True GERD	—	.00	—	—	—
PPI use					
Off PPI	—	.04	.11	.70	–0.17, 0.26
Missing	—	.12	.17	.50	–0.22, 0.46
On PPI	—	.00	—	—	—

*$P < .05$, significant.

worth are deemed to be more important in predicting the outcome compared with variables with lower worth. The most important variables were depressive symptoms (Patient Health Questionnaire-9 [PHQ-9]; variable worth = 0.21), followed by illness behavior (Illness Attitudes Scale subscale [IAS]; variable worth = 0.165), post-traumatic stress symptoms (PTSD-ZIL; variable worth = 0.128), GI-specific anxiety (Visceral Sensitivity Index [VSI]; variable worth = 0.117), pain catastrophizing (Pain Coping and Cognition List subscale; variable worth = 0.114), and pain anxiety (Pain Anxiety Symptom Scale [PASS]; variable worth = 0.109). The reflux variables had a considerably lower worth (ranging from 0.004 for PPI intake to 0.046 for total number of reflux episodes). An overview of the worth for all variables is provided in Table 4.

Heartburn Severity. An overview of the predictive performance of the different machine learning models is shown in Supplementary Table 7.

The gradient boosting models again showed the best cross-validated predictive performance, with GradBoost Tuned #2 having the lowest ASE (0.129), explaining 87% of the variance in Heartburn Severity score. Figure 3B shows a comparison of the correlation between the observed and predicted values for both the general linear model and gradient boosting model.

The most important variables were GI-specific anxiety (VS; variable worth = 0.074), illness behavior (IAS subscale;

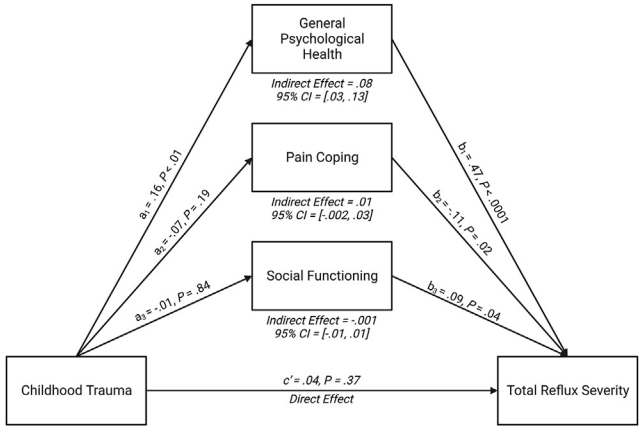

Figure 1. Path diagram of the indirect effect of childhood trauma on Total Reflux Severity through general psychological functioning.

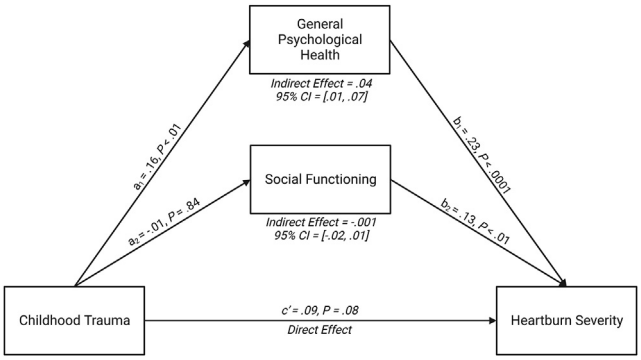

Figure 2. Path diagram of the indirect effect of childhood trauma on Heartburn Severity through general psychological functioning.

variable worth = 0.067), body awareness (Body Awareness Questionnaire [BAQ]; variable worth = 0.067), pain anxiety (PASS; variable worth = 0.066), depressive symptoms (PHQ-9; variable worth = 0.065), and catastrophizing (Pain Coping and Cognition List subscale; variable worth = 0.061), but the difference in worth between the variables was much smaller than in the Total Reflux Severity model, indicating a less pronounced distinction in variable importance. Similar to the model for Total Reflux Severity, however, the reflux variables had lower variable worth, ranging from 0.004 (PPI status) to 0.043 (total number of reflux episodes). An overview of the worth for all variables is provided in Table 4.

Sleep Disturbance. An overview of the predictive performance of the different machine learning models is shown in Supplementary Table 8.

Like for the other 2 reflux symptom severity outcomes, the gradient boosting models showed the best cross-validated predictive performance, with GradBoost Tuned #3 having the lowest ASE (0.118), explaining 86% of the variance in Sleep Disturbance score. Figure 3C shows a comparison of the correlation between the observed and predicted values for both the general linear model and Gradient Boosting model.

Two variables stood out in terms of importance, depressive symptoms (PHQ-9; variable worth = 0.191) and post-traumatic stress symptoms (PTSD-ZIL; variable worth = 0.176), followed by illness behavior (IAS subscale; variable worth = 0.096), pain anxiety (PASS; variable worth = 0.096), trait anxiety (*State-Trait Anxiety Inventory*; variable worth = 0.080), and body awareness (BAQ; variable worth = 0.076). Again, the reflux variables had a lower worth, ranging from 0.002 (PPI status) to 0.052 (total number of reflux episodes). An overview of the worth for all variables is provided in Table 4.

Discussion

The current study sought to determine which processes, both psychological and physiological, are associated with symptom severity (frequency and intensity) in a cohort of consecutive patients with refractory heartburn/regurgitation symptoms. Psychological symptoms emerged as the most important contributors to reflux symptom severity. In the traditional statistical approach, the general psychological health component was significantly and independently associated with all 3 outcome variables and mediated the relationship between childhood trauma and severity scores for both Total Reflux Severity and Heartburn Severity. For both Total Reflux Severity and Sleep Disturbance, results from the machine-learning approach complemented these findings. Indeed, depressive symptoms (PHQ-9) had the highest variable worth for both outcomes, followed by illness behaviors (IAS illness behavior subscale) and post-traumatic stress symptoms (PTSD-ZIL) for Total Reflux Severity, with the latter 2 being the same, albeit in reverse order, for Sleep Disturbance.

Consistent with our findings, prior research demonstrates psychological symptoms, including depression, anxiety, and post-traumatic stress, are associated with reflux symptom severity.[25–27] Indeed, psychological processes are believed to impact the brain–gut axis, particularly its central components,[28] leading to enhanced esophageal symptom perception and reporting.[6,29,30] Similar patterns are observed as it pertains to sleep functioning. The psychological symptoms present in our study, namely depressive and post-traumatic stress symptoms, have previously been associated with significant sleep disturbance, which can subsequently influence other aspects of quality of life.[31–33] However, as our data are cross-sectional, future research should investigate whether modulating psychological symptoms impacts both reflux and sleep-related severity in the context of GERD.

Unlike Total Reflux Severity and Sleep Disturbance, the traditional and machine-learning approaches demonstrated somewhat conflicting findings for Heartburn Severity. Although general psychological health and social functioning were the significant components in the general linear model, GI-specific anxiety (VSI) emerged as the most important variable in the machine-learning approach, followed by illness behaviors (IAS subscale), body awareness (BAQ), pain anxiety (PASS), and depressive symptoms (PHQ-9). The machine-learning findings are consistent with recent research suggesting esophageal-specific processes, such as esophageal hypervigilance and anxiety, are important indicators of symptom severity across esophageal conditions, including GERD,[6,14] dysphagia,[12] and eosinophilic esophagitis.[13] When contrasting the traditional approach with the machine-learning approach for Heartburn Severity, we find that 3 of the 5 most important variables in the machine-learning analysis can be categorized as body- or illness-related (eg, GI-specific anxiety, body awareness, and pain anxiety) and were present in the health anxiety component, yet health anxiety was not significant in the final hierarchical general linear model. There are several potential reasons for these conflicting findings, including the dimension reduction from the principal component analysis, the linear vs nonlinear nature of the models, and the cross-validation in the machine learning approach that was not used in the general linear models.

Interestingly, general psychological symptoms, namely depressive and post-traumatic stress symptoms, were the variables with the highest importance for Total Reflux

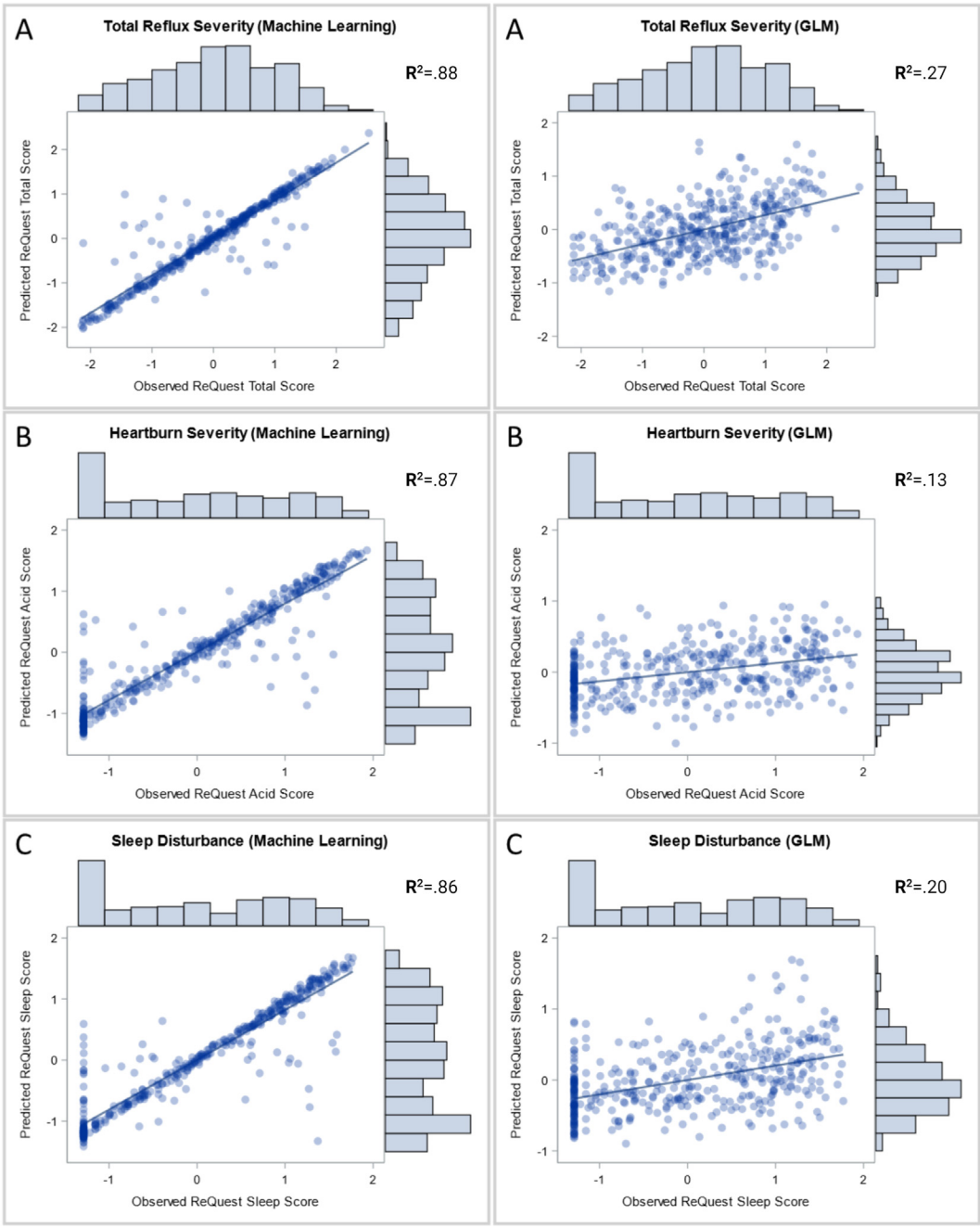

Figure 3. Performance comparison between machine learning models and general linear models (GLM) for Total Reflux Severity, Heartburn Severity, and Sleep Disturbance. Comparison of the correlation between the observed and predicted values for the best-performing machine learning model (*left*) and the general linear model (*right*). All variables are Box-Cox transformed and *z*-scored. (*A*) Comparison of the gradient boosting model (GradBoost #4) to the general linear model for Total Reflux Severity. (*B*) Comparison of the gradient boosting model (GradBoost #2) to the general linear model for Heartburn Severity. (*C*) Comparison of the gradient boosting model (GradBoost #3) to the general linear model for Sleep Disturbance.

Severity scores, and body- and illness-related processes, such as GI-specific anxiety, body awareness, and pain anxiety, were most important for Heartburn Severity (in the machine-learning approach). One reason for these differences between outcomes may be that Total Reflux Severity is a composite score of several dimensions, including abdominal/stomach, nausea, sleep disturbance, and "other" symptoms, and Heartburn Severity is more narrowly focused on esophageal pain or discomfort. Thus, the multifactorial nature of the Total Reflux Severity score may lend itself to be impacted more by general psychological factors that also impact other bodily-related processes captured by the Total Reflux Severity score (eg, depression impacts sleep and anxiety can impact nausea), although the symptom-specific nature of Heartburn Severity was most influenced by GI-specific anxiety.

Table 4. Ranking of Psychological and Physiological Variables by Variable Worth for Total Reflux Severity, Heartburn Severity, and Sleep Disturbance

	Total Reflux Severity		Heartburn Severity		Sleep Disturbance	
Rank	Variable	Worth	Variable	Worth	Variable	Worth
1	PHQ-9	0.210	VSI	0.074	PHQ-9	0.191
2	IAS – Illness behavior	0.165	IAS – Illness behavior	0.067	PTSD-ZIL	0.176
3	PTSD-ZIL	0.128	BAQ	0.067	IAS – Illness behavior	0.096
4	VSI	0.117	PASS	0.066	PASS	0.096
5	PCCL – catastrophizing	0.114	PHQ-9	0.065	STAI – trait	0.080
6	PASS	0.109	PCCL – catastrophizing	0.061	BAQ	0.076
7	PCCL – internal pain control	0.076	ASI	0.058	PCCL – catastrophizing	0.063
8	STAI – trait	0.074	PTSD-ZIL	0.054	VSI	0.057
9	NEO – neuroticism	0.063	IAS – health anxiety	0.049	ASI	0.057
10	ASI	0.056	PCCL – internal pain control	0.049	Total no. of reflux events	0.052
11	NEO – agreeableness	0.052	NEO – conscientiousness	0.047	NEO – neuroticism	0.046
12	Total no. of reflux events	0.046	NEO – agreeableness	0.046	NEO – agreeableness	0.045
13	BAQ	0.045	Total no. of reflux events	0.043	PCCL – external pain control	0.042
14	LSAS	0.042	LSAS	0.043	LSAS	0.041
15	NEO – conscientiousness	0.038	STAI – trait	0.041	NEO – extraversion	0.041
16	NEO – extraversion	0.038	CTQ	0.040	CTQ	0.036
17	Reflux classification	0.033	Reflux classification	0.040	PCCL – internal pain control	0.036
18	PCCL – pain coping	0.031	NEO – openness	0.034	PCCL – pain coping	0.036
19	CTQ	0.030	NEO – extraversion	0.030	Total volume exposure	0.033
20	PCCL – external pain control	0.030	NEO – neuroticism	0.029	NEO – openness	0.031
21	IAS – health anxiety	0.028	Total volume exposure	0.028	NEO – conscientiousness	0.028
22	Total volume exposure	0.026	PCCL – pain coping	0.028	IAS – health anxiety	0.028
23	NEO – openness	0.020	PCCL – external pain control	0.025	Reflux classification	0.022
24	PPI use	0.004	PPI use	0.003	PPI use	0.002

CTQ, Childhood Trauma Questionnaire; LSAS, Liebowitz Social Anxiety Scale; PCCL, Pain Coping and Cognition List; STAI, State-Trait Anxiety Inventory.

Reflux classification was also significantly associated with Heartburn Severity. Despite normal reflux parameters, patients in the reflux hypersensitivity group reported the highest level of Heartburn Severity, which was significantly higher than all other classifications, aside from true GERD. Reflux hypersensitivity is considered a disorder of gut–brain interaction and as such, lacks abnormal acid exposure. Although the pathophysiological mechanisms are not completely understood, symptoms are believed to be the result of esophageal hypersensitivity, leading patients to perceive normal acid reflux episodes as painful.[34] Findings suggest that although classifications differ physiologically (eg, presence of abnormal acid), patient perception of symptoms does not follow a similar pattern. Instead, patients with normal levels of acid reflux may report similar and even in some cases higher levels of heartburn compared with those with pathological acid. One reason for these findings may be that esophageal hypersensitivity can be influenced by both peripheral and central mechanisms.[34]

Mediation analyses demonstrated that although childhood trauma was weakly but significantly associated with Total Reflux and Heartburn Severity, its effect was mediated by general psychological functioning. Similarly, research in irritable bowel syndrome suggests that processes such as GI-specific anxiety and/or depression mediate the effects of abuse (childhood sexual and/or physical abuse) on symptom severity.[16] Specific to the esophagus, 1 study found that childhood emotional trauma was a risk factor for unexplained chest pain, however, the relationship became nonsignificant when controlling for depression.[18] Although

our findings may suggest future exploration of the relationships among trauma, psychological processes, and reflux symptoms, it is important to note that childhood trauma explained only a small percentage (1%) of variance in both of our outcomes. Thus, although significant, the effect of childhood trauma on symptom severity may be less meaningful compared with other variables.

Overall, moderation analyses indicated a clear lack of moderation by both PPI use and reflux classification for all outcomes. Indeed, findings suggest associations of psychological and physiological factors with reflux symptom severity were similar regardless of reflux classification or PPI status at the time of testing. The only significant finding was the effect on social functioning by reflux classification for Heartburn Severity and Sleep Disturbance. Our findings challenge the widely held belief that psychological symptoms are more important to consider in functional heartburn and reflux hypersensitivity, where there is a lack of reflux/physiological indicators to "explain" symptoms, and less important in GERD, where symptoms are believed to be reflux-related. The lack of differences across the spectrum of reflux classification is consistent with more recent research in the field of psychogastroenterology, which has found that psychological processes are consistent across GERD presentations.[6,14] This provides further evidence that psychological processes are important to consider in patients across reflux classifications, not just in patients who lack physiological indicators of disease (eg, functional heartburn).

Reflux parameters, including total number of reflux episodes and acid exposure time, were not significantly associated with symptom severity for any of the 3 outcomes in general linear models and, consistently, their variable worth was low in machine learning models. It is plausible that additional physiological factors, such as proximal extent and the chemical or volume composition of the refluxate, can contribute to symptom perception.[35,36] However, we limited the reflux variables to the total number of reflux episodes and total volume exposure, as these are less impacted by PPI use at the time of testing, and are hence valid across the entire sample, including the on and off PPI groups. Prior research has demonstrated a disconnection between reflux parameters and symptom reporting, resulting in a majority of reflux events not correlated with symptom reporting, even in patients with abnormal reflux parameters.[8] Thus, central processes may help to explain esophageal symptom perception. In laboratory-based studies using healthy adults, the mechanisms of stress and fear-learning on esophageal perception have been evaluated. One study found that intravenously administered corticotropin-releasing hormone resulted in increased sensitivity to esophageal mechanical distention.[37] Furthermore, other studies have demonstrated that fear of visceral sensations can be established through associative fear learning and results in altered perception (ie, increased intensity) and generalization of fear towards other intensities.[38,39] Meanwhile, questionnaire-based research in esophageal patients has found that GI-specific processes, such as esophageal hypervigilance and symptom-specific anxiety, are significantly and independently associated with illness severity reporting, however, studies are cross-sectional so causal claims cannot be made.[12–14] This previous literature coupled with the results of our current study underscore the need for continued research into the role of psychological factors in esophageal symptom perception.

Clinical Implications

Results from our study and other research in psychogastroenterology suggest that there is a need to adequately assess psychological symptoms in the context of GERD diagnosis and management across the reflux classification spectrum, particularly for refractory reflux patients and/or patients reporting elevated levels of psychological distress. In addition to widely used general psychological questionnaires (eg, PHQ-9), several validated measures[29,40,41] exist to evaluate esophageal-specific psychological functioning and quality of life that can be easily administered in a clinic visit. It is important to note that the stronger association between psychological processes (eg, GI-specific anxiety and depressive symptoms) and reflux symptom severity reporting does not negate a potential role of physiological processes, and vice versa. Instead, GERD pathophysiology should be viewed as multifactorial[3] and approached through a biopsychosocial lens that considers all relevant factors.[42] Brain–gut behavior therapies have been shown to reduce reflux symptom severity as well as comorbid psychological symptoms (eg, GI-specific anxiety),[43–45] although access to a clinician trained in brain–gut behavior therapy may be limited. The current study supports further evaluation of brain–gut behavioral therapy in patients across the GERD spectrum.

Limitations

Our study is limited by the cross-sectional design, whereby it is not possible to make directional or causal claims. Although it is plausible to assume childhood trauma temporally preceded the other variables, this is not the case for the psychological and physiological reflux variables. It is therefore conceivable that psychological symptoms may not only impact esophageal symptoms, but vice versa. The patients in this study were seen at a tertiary care center, which implies that most of the patients already had multiple steps of treatment for their symptoms. Thus, results may not generalize to reflux patients seen in other contexts (ie, primary care). Furthermore, the database included patients with a different PPI use status at the time of testing (eg, on/off PPI), although we controlled for this in our statistical model and relationships were not moderated by PPI status. In addition, although we did not have information on specific comorbidities (eg, other medications used or motility abnormalities), all patients had undergone an esophagogastroduodenoscopy that failed to explain the symptoms during the preceding 6 months. Although motility disorders were not formally excluded by manometry in all patients, clinical evaluation did not identify this as a major candidate underlying pathology. Furthermore, all medications altering GI

motility (eg, prokinetics and baclofen) are normally interrupted for pH-MII. Aside from the VSI (ie, GI-specific anxiety questionnaire), the disease-specific psychological questionnaires were mostly related to chronic (musculoskeletal) pain or general bodily anxiety (eg, IAS health anxiety subscale and BAQ), not GI-specific symptoms. As discussed, esophageal-specific anxiety and hypervigilance are important contributors to esophageal symptom perception. Although we did not have access to these esophageal-specific measures in this study, future research should focus on assessing esophageal-specific processes and their influence on esophageal symptom perception.

Conclusions

Psychological processes, both general and illness-specific, should be considered as another factor within the multifactorial processes (eg, reflux parameters, esophagogastric junction pressure, and hypersensitivity) that influence symptom reporting in patients with refractory heartburn/regurgitation symptoms. Psychological symptoms should be routinely screened for in patients with refractory heartburn/regurgitation symptoms across the reflux classification spectrum, but particularly in refractory patients or those demonstrating elevated levels of psychological distress. Future research and clinical practice should include the role of esophageal-specific measures, such as esophageal hypervigilance and GI-specific anxiety.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.06.019.

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Data Availability
Individual participant data will not be shared.