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Validation of the Oesophageal Hypervigilance and Anxiety Scale for Chronic Oesophageal Disease

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Abstract

Background—Oesophageal hypervigilance and anxiety can drive symptom experience in chronic oesophageal conditions, including gastro-oesophageal reflux disease, achalasia, and other functional oesophageal disorders. To date, no validated self-report measure exists to evaluate oesophageal hypervigilance and anxiety.

Aims—This study aims to develop a brief and reliable questionnaire assessing these constructs, the oesophageal hypervigilance and anxiety scale (EHAS).

Methods—Questions for the EHAS were drawn from four existing validated measures that assessed hypervigilance and anxiety adapted for the oesophagus. Patients who previously underwent high-resolution manometry testing at a university-based oesophageal motility clinic were retrospectively identified. Patients were included in the analysis if they completed the EHAS as well as questionnaires assessing symptom severity and health-related quality of life at the time of the high-resolution manometry.

Results—982 patients ages 18-85 completed the study. The EHAS demonstrates excellent internal consistency ($\alpha=0.93$) and split-half reliability (Guttman=0.87). Inter-item correlations indicated multicollinearity was not achieved, thus, no items were removed from the original 15-

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Statement of Interests

1. Authors declaration of personal interests: John Pandolfino has served as a speaker and consultant for Medtronic, Sandhill, and Torax, a consultant for Ironwood, and has a licensing agreement with Croston. Tiffany Taft has served as a speaker for Abbvie and Janssen.
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item scale. Principal components factor analysis revealed two subscales measuring symptom-specific anxiety and symptom-specific hypervigilance. Construct validity for total and subscale scores was supported by positive correlations with symptom severity and negative correlations with health-related quality of life.

Conclusions—The EHAS is a 15-item scale assessing oesophageal hypervigilance and symptom-specific anxiety. The EHAS could be useful in evaluating the role of these constructs in several oesophageal conditions in which hypersensitivity, hypervigilance, and anxiety may contribute to symptoms and impact treatment outcomes.

Introduction

Chronic conditions affecting the oesophagus, including gastro-oesophageal reflux disease (GERD), eosinophilic oesophagitis, achalasia, and functional oesophageal disorders, represent a substantial percentage of the current work load in gastroenterology practices.^{1, 2} In ambulatory settings, there are over 7 million diagnoses per year for GERD and over 1.1 million diagnoses for dysphagia.² In comparison, the overall number of diagnoses for ulcerative colitis and Hepatitis C were approximately 720,000 and 670,000 per year, respectively. Oesophageal disorders are associated with substantial morbidity and mortality.¹⁻³ Additionally, these conditions are associated with severe symptoms that substantially reduce quality of life and generate significant healthcare expenditures.⁴⁻⁹ The management of symptomatic oesophageal disorders is complex due to the complicated interaction of the brain and gut.^{10, 11}

While symptoms in the oesophagus can be directly related to underlying inflammatory (e.g., esophagitis) or motility (e.g., achalasia) issues, there is a significant disconnect between symptom severity and the underlying disease process,^{12, 13} indicating other processes likely influence symptom triggering and experience.¹⁰⁻¹⁵ Further, oftentimes patients continue to experience symptoms despite effective first-line treatments, leaving these patients with inadequate treatment outcomes.^{13, 16} The reason for this disconnect lies in the complexity of how oesophageal events are perceived and acted upon. Perception of oesophageal stimuli is a complex process dependent on both peripheral and centrally-mediated neurologic processes.¹⁷

Most of the current research focused on evaluating the correlation between physiologic abnormalities of the oesophagus and symptoms is hampered by the fact that these psychological stressors and cognitive factors have not been considered as important confounders and modulators of the symptom experience. Specifically, oesophageal hypersensitivity involves the perception of stimuli not normally perceived (i.e., allodynia) and the experience of pain and discomfort at higher intensity than would typically be perceived (i.e., hyperalgesia).¹⁸ Oesophageal hypersensitivity is mediated by a variety of factors, including peripheral sensory inputs (i.e., peripheral sensitization to noxious stimuli) and factors impacting central processing, such as enhanced synaptic transmission leading to central sensitization.^{19, 20}

Both increased emotional arousal or mood state²¹ and cognitive processes lead the individual to experience oesophageal sensations as frightening and develop an intolerance of

these symptoms and their perceived, feared consequences. Such cognitive and affective processes include selective attention to oesophageal sensations, heightened anxiety about symptoms and expectation of pain, and catastrophic thinking about the consequences of symptoms. Taken together, these cognitive-affective phenomena encompass oesophageal hypervigilance.^{14, 15}

We hypothesize that centrally mediated cognitive-affective processes, including altered visceral anxiety, hypervigilance, and symptom hypersensitivity are 1) drivers of symptom generation in oesophageal disease and 2) likely explain a substantial percentage of the disconnect between overt organic disease severity and symptom severity (Figure 1). Currently no validated self-report measure exists to evaluate oesophageal hypervigilance and anxiety. As such, we aim to develop a brief, reliable and valid questionnaire under the 2009 FDA guidelines for patient reported outcome development²².

Methods

Development of the Initial Oesophageal Hypervigilance and Anxiety Scale (EHAS)

Current FDA guidelines recommend a three-phase process for PRO development, the first of which involves patient interviews to formulate questionnaire items. Due to the number of existing validated measures of the hypothesized components of oesophageal hypervigilance and anxiety, we opted to draw items from four existing validated questionnaires, adapted for the oesophagus (Table 2): the Sullivan Pain Catastrophizing Scale (4 of 13 items),²³ the Visceral Sensitivity Index (2 of 15 items),²⁴ the McCracken Pain Vigilance and Awareness Scale (6 of 15),^{25, 26} the Rosenstiel & Keefe Coping Strategies Questionnaire (3 of 27 items).²⁷ The four scales were administered in their original form to a representative sample of 200 oesophageal patients. Principal components factor analysis identified factor loadings for each item and those with the highest correlations were selected for the EHAS. Items were reviewed by a clinical psychologist (LK) and gastroenterologist (JP) with expertise in oesophageal disease. Fifteen items were chosen for the initial measure, modified to better reflect oesophageal disease patient experiences, and given to participants in this study. A five-point Likert scale was used (0=Strongly Disagree to 4=Strongly Agree) with a reporting timeframe of the last month.

Subjects

Patients were retrospectively identified using a query of the Oesophageal Center at Northwestern Motility Laboratory Registry, which includes English-speaking patients 18-85 years old that were evaluated at Northwestern with high-resolution manometry (HRM). Based on guidelines for minimum sample size for scale development and factor analysis²⁸ a minimum of 300 individual responses (15 items × 20 questionnaire responses per item) was determined. However, due to the number of patients in the registry, we utilized all completed entries to meet standards for “excellent” sample size (e.g. 1000 subjects).

Patients were included if they completed the EHAS at the time of oesophageal manometry between 9/17/15 and 6/1/17. If patients completed more than one EHAS during the study period, only the first was included. Clinical details associated with HRM, e.g. indication for

manometry and previous foregut surgery, were also obtained from the patient registry. Oesophageal motility diagnoses were designated from ten supine swallows in accordance with the Chicago Classification v3.0.²⁹ Basic demographic information (age, gender) was also collected. A waiver of informed consent was obtained. The study protocol was approved by the Northwestern University Institutional Review Board.

Symptom Assessment

Symptoms were assessed by patient completion of written questionnaires at the time of HRM. These included:

Gastrooesophageal Reflux Questionnaire (GERDQ)—The GerdQ is a 6-item self-report measure used to support healthcare professionals in the diagnosis of GERD, assess the relative impact of GERD on patient's lives, and measure response to treatment over time.³⁰ Participants are asked questions regarding the frequency of their GERD symptoms over the past 7 days. Each question has 5 response options ranging in value from 0 to 3. Higher scores denote more symptoms.

Brief Oesophageal Dysphagia Questionnaire (BEDQ)—The BEDQ is a 10-item, recently validated self-report measure of oesophageal dysphagia that also assesses for food impactions.³¹ The frequency and difficulty with swallowing solid foods, soft foods, and liquids are rated on a 5-point Likert scale for 8 items over the past 30 days. An additional 2 items measure how many instances of food impaction lasting more than 30 minutes or requiring an emergency department visit occurred in the past year.

Quality of Life Assessment

Health related quality of life was assessed by patient completion of the following at time of HRM:

NIH PROMIS Global Health Scale—The PROMIS Global Health short form is a 10-item instrument representing degradations in multiple domains of health-related quality of life: overall physical health, mental health, social health, pain, fatigue, and overall perceived quality of life.^{32, 33} The scale yields an overall total score as well as a Global Physical Health (GPH) score and a Global Mental Health (GMH) score. T-scores are available for the GPH and GMH scales with a normative average of 50. Higher scores denote better HRQOL.

Northwestern Oesophageal Quality of Life Scale (NEQOL)—The NEQOL is a 14-item self-report measure assessing disease-specific health-related quality of life including social function, emotional distress, eating impact, sleep, and financial burden in patients with oesophageal symptoms over the past 2 weeks.⁶ Each question is rated on a 5-point Likert scale ranging from 4="Not True at all" to 0="Very True". Higher scores denote greater quality of life.

Statistical Analysis

Data were exported into SPSS v23 for Macintosh (Chicago, IL). Preliminary evaluation for normal distribution of the EHAS was performed using standardized cutoff scores of < 2.0 to

> -2.0 for skewness and kurtosis. Reliability was determined via measures of internal consistency (Cronbach α), split-half reliability (Guttman statistic), and multicollinearity (inter-item Pearson's correlation); items with a correlation >.80 are deemed redundant and evaluated for removal. Principal components factor analysis (PCFA) with Varimax rotation evaluated the EHAS scale structure. Eigenvalues greater than 1 are considered for subscale analyses. Construct validity of the EHAS is evaluated via Pearson's correlations with validated measures of symptom severity (GERDQ, BEDQ) and health related quality of life (PROMIS Global Health, NEQOL). Additional evaluation of construct validity was performed via independent samples t-Tests to compare patients measuring "Normal to High" to those measuring "Normal to Low" on the EHAS as determined via median split of the total EHAS score. Statistical significance is set at $P < .05$ for all analyses with the exception of t-Tests which used $P < .01$ (Bonferroni correction) to control for Type 1 error.

Results

The EHAS was completed by 982 individual patients (mean $\pm$ SD age 53 $\pm$ 15 years; 598, 61%, female) during the study period. Younger patients reported slightly higher EHAS scores ($r = -0.14$, $p < .01$) as did female participants (Mean (SD) = 30.7 (14.2) vs. 28.4 (15.6), $p = .024$). The most common indications for manometry were dysphagia in 53% and gastro-esophageal reflux (symptom evaluation or prior to anti-reflux surgery or hiatal hernia repair) in 32% (Table 1). 243 patients (27%) had foregut surgery prior to evaluation, most commonly fundoplication (91/243, 37%) or lower-oesophageal sphincter myotomy (66/243, 27%, with Heller's myotomy and 52/243, 21%, with per-oral endoscopic myotomy). Additionally, 29 patients (3%) previously underwent pneumatic dilation for therapy of achalasia. Motility diagnosis based on HRM are displayed in Table 1.

Data for each EHAS item and EHAS total score were normally distributed based on skewness and kurtosis cutoffs. The median total score was 30.0. Internal consistency of the EHAS is excellent (Cronbach $\alpha = 0.931$) as is split-half reliability (Guttman statistic = 0.873). Inter-item correlations range from $r = 0.210$ (Q2 and Q5) and $r = 0.758$ (Q9 and Q10) with all $p < .001$, indicating each question uniquely contributes to the EHAS score and is sufficiently associated with other items without achieving multicollinearity. As such, no items were removed from the original 15-item scale. PCFA produces two subscale scores: Scale 1 (9 items, eigenvalue = 7.72), measuring symptom-specific anxiety that accounts for 51.5% of the variance in EHAS score and Scale 2, measuring symptom-specific hypervigilance (6 items, eigenvalue = 1.28), accounting for 8.6% of variance in score. Both subscale scores are normally distributed. The rotated component matrix is presented in Table 2. Additional PCFA conducted for the symptom-specific anxiety and the symptom-specific hypervigilance subscales did not yield any additional delineation of EHAS items for scoring purposes.

Mean scores for each scale are presented in Table 3 and correlations between HRQOL, symptom severity, and the EHAS in Table 4. The EHAS demonstrates good construct validity for its total score and each subscale score as represented by moderate, significant correlations (Range: -0.31 to -0.70) with HRQOL and symptom severity. Patients who report greater oesophageal hypervigilance also report greater symptom severity and poorer

HRQOL. The relationships between symptom-specific anxiety and HRQOL is larger than hypervigilance for both the PROMIS QOL and NEQOL, while symptom-specific anxiety and hypervigilance are equally associated with symptom severity measured via the BEDQ and GERDQ.

To further understand the constructs evaluated by the EHAS, secondary analyses for patients scoring “low” versus “high” on the measure were performed. Patients scoring normal to high on the EHAS were younger in age (Mean (SD) = 50.5 (15.6) vs. 55.0 (14.9) years).

Significant associations exist for indications for HRM ($\chi^2 = 18.16$, $p < .001$), with patients undergoing HRM for chest pain more likely to score “normal to high” on the EHAS and those categorized as “other” more likely to score “normal to low”; no differences existed for dysphagia or reflux/hiatal hernia. Differences also existed for oesophageal diagnosis ($\chi^2 = 20.07$, $p = 0.018$), with those with distal oesophageal spasm and absent contractility more likely to score “normal to low” on the EHAS. No significant associations existed for patients foregut surgery status ($p = .05$) or gender ($p = .10$). Patients categorized as “normal to high” also scored significantly higher on the GERDQ (8.59 (4.8) vs. 5.30 (4.5)) and BEDQ (10.93 (10.8) vs. 5.89 (7.1), both $p < .001$) and significantly lower on the PROMIS QOL (14.79 (8.8) vs. 21.53 (9.7) and NEQOL (26.82 (13.1) vs. 43.71 (11.6), both $p < .001$). Female participants scored higher on symptom-specific anxiety (17.7 (9.6) vs. 16.1 (10.2), $p = .011$) but no differences exist by sex for symptom-specific hypervigilance (13.1 (5.8) vs. 12.5 (6.4), $p = .13$).

Discussion

Oesophageal symptom-specific anxiety and hypervigilance are potentially important confounders in the presentation and treatment of patients with chronic oesophageal disease. The Oesophageal Hypervigilance and Anxiety Scale represents the first step in empiric evaluation of this construct via a reliable and valid 15-item scale with two subscale scores for symptom-specific anxiety and symptom-specific hypervigilance. While statistically the subscale scores on the EHAS cannot be further reduced, items may be interpreted as those measuring cognitive processes such as catastrophizing and rumination versus compensatory coping behaviours and vigilance. As such, the EHAS can guide clinical interventions intended to reduce oesophageal hypervigilance and anxiety, including cognitive behavioral therapies and pharmacological agents. Overall, the EHAS demonstrates excellent reliability and appropriate construct validity to fulfill the first and second criteria for PRO development outlined by the FDA. The final step, cognitive interviews with representative patients to gauge question wording and understandability, is ongoing.

The EHAS is designed to assess hypervigilance and anxiety across oesophageal diagnoses. However, we found certain sub-populations may be more likely to score higher in these domains including younger patients and patients presenting with chest pain as their primary complaint. Conversely, we observed that patients with major disorders of peristalsis, including distal oesophageal spasm and absent contractility, were more likely to score lower on the EHAS. Future studies should aim to evaluate differences in oesophageal hypervigilance and anxiety across diagnoses to identify patient populations at greater risk of

their symptoms being exacerbated by these processes, and for referral to appropriate treatment.

Oesophageal hypersensitivity is likely moderated by symptom-specific anxiety and hypervigilance, with anxiety potentially having a greater impact on patient symptom experiences. Symptom anxiety is well studied in other groups, such as irritable bowel syndrome^{24, 34-38} and functional dyspepsia³⁹⁻⁴¹, and is associated with poorer patient outcomes. However, prior research has fallen short in its understanding of the psychological processes in oesophageal disease course, often focusing on depression, anxiety and somatization⁴²⁻⁴⁵ rather than investigating visceral sensitivity, patient perceptions and vigilance, and central arousal.

Oesophageal hypervigilance can be considered a specific form of interoceptive sensitivity to oesophageal symptoms that plays a role in the development and maintenance exacerbation of functional oesophageal symptoms. An oesophageal stimulus is perceived peripherally by afferent nerves in the vagus, primarily focused on mechanical sensation and reflex mediated responses, and spinal afferent pathways associated with pain and nociception. The processing of these signals in the brain is complex and although neuroimaging provides insight into structural and functional components, there is a paucity of information regarding the cognitive-evaluative and affective-motivational domain of oesophageal symptom perception and severity.⁴⁶ Oesophageal hypervigilance uniquely contributes to oesophageal hypersensitivity, and significantly increases disease burden and impairment in quality of life. These same processes often increase anxiety and may subsequently drive individuals to engage in behaviors aiming to prevent symptoms from occurring and/or to minimize the consequences of symptoms when they do occur.

In anxiety literature, these behaviors are referred to as safety behaviors, and often involve avoidance of various activities and result in significant disruption to one's daily life (e.g., elimination of certain foods, eating only in certain places or at specific times, excessive water consumption) and overall quality of life. As individuals continue to selectively attend to oesophageal sensations, they may begin to interpret even normal bodily or digestive sensations as symptoms, which can drive increased hypervigilance and the development of new and more drastic safety and avoidance behaviors since their current regimen appears insufficient. Additionally, as is often found in individuals with panic disorder, hypervigilance to symptoms can trigger the sympathetic nervous system response, which may drive symptom experience by aggravating oesophageal hypersensitivity. Unfortunately, hypervigilance and catastrophic thinking are reinforced both when symptoms do and when they do not occur. When they do not occur, individuals may attribute this to the effectiveness of their attentiveness to potential symptoms and to their attempts to avoid perceived triggers.
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Previous research in GERD finds perceptions of reflux symptoms are associated with psychosocial distress, reduced QOL and sensation of dysphagia among patients who are non-responsive to proton pump inhibitor (PPI) therapy who also have normal impedance-pH.¹² Among these PPI refractory patients, patient-reported symptom severity is associated with physiologic differences, as opposed to psychosocial factors. These results highlight the

delicate interplay between psychosocial factors and abnormal physiology in predicting symptom severity in GERD and should be further evaluated in other oesophageal patient groups using the EHAS. Additionally, the present study does not assess the relationship between the hypervigilance measured via the EHAS and established measures of visceral hypersensitivity which we suspect would be at least modest in size. Future studies may aim to evaluate this relationship and how it presents across the spectrum of oesophageal diseases.

While the present study has several strengths, including a large sample of well-defined oesophageal patients, limitations exist that should be considered in its interpretation. We do not know the racial and ethnic composition of the study sample, as such caution should be taken when applying the findings to minority groups. The data were retrospectively collected and may be prone to collection or abstraction error; future prospective studies with the EHAS can serve to correct this and further validate the measure, including in more diverse patient groups.

These findings demonstrate that the EHAS is a brief, easily administered, valid self-measure of oesophageal symptom specific anxiety and hypervigilant behavior. Measurement of oesophageal hypervigilance and anxiety is an essential component in the diagnosis and treatment of functional oesophageal disorders, but also an important factor to account for when assessing symptom severity among other oesophageal disorders. Thus, the EHAS should have significant utility in future research and in measuring symptom-based treatment outcomes across oesophageal conditions.

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Figure 1.
Potential Moderating Relationship Between Hypersensitivity, Anxiety, and Hypervigilance
in Oesophageal Symptom Reporting

Table 1

Clinical Characteristics of Study Sample

	n (%; n/982)
Indication for manometry	
Dysphagia	524 (53)
Reflux/Hiatal hernia	319 (32)
Chest pain	79 (8)
Other	60 (6)
Previous foregut surgery	
Fundoplication	91 (9)
Heller's myotomy	66 (7)
POEM	52 (5)
Pneumatic dilation	29 (3)
Gastric bypass	12 (1)
Gastrectomy	10 (1)
Adjustable gastric band placement	6 (1)
Other	6 (1)
Motility diagnosis *, no previous foregut surgery	
Type I achalasia	15 (2)
Type II achalasia	41 (4)
Type III achalasia	18 (2)
EGJ outflow obstruction	135 (14)
Hypercontractile oesophagus	18 (2)
Distal oesophageal spasm	5 (1)
Absent contractility	30 (3)
Fragmented peristalsis	6 (1)
Ineffective oesophageal motility	121 (12)
Normal motility	321 (33)
Motility diagnosis *, previous foregut surgery †	
Type I achalasia	21 (2)
Type II achalasia	9 (1)
Type III achalasia	16 (2)
EGJ outflow obstruction	44 (4)
Hypercontractile oesophagus	6 (1)
Distal oesophageal spasm	10 (1)
Absent contractility	60 (6)
Fragmented peristalsis	9 (1)
Ineffective oesophageal motility	50 (5)
Normal motility	47 (5)

* Based on Chicago Classification, version 3.0.²⁹

[†] Including previous pneumatic dilation. POEM – per-oral endoscopic myotomy. EGJ – esophagogastric junction

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Table 2

Rotated Component Matrix with Factor Loading for EHAS Demonstrating Two Subscales

EHAS Item	Factor 1	Factor 2	Source	Intervention Point
I can't seem to keep my symptoms out of my mind	.813		PCS	Rumination
I have a difficult time enjoying myself because cannot get my mind off the discomfort in my throat/chest/oesophagus.	.805		VSI	Rumination
These symptoms are awful and I feel that they overwhelm me.	.787		PCS	Catastrophizing
As soon as I awake, I worry that I will have discomfort in my throat/chest/oesophagus during the day.	.771		CSQ	Rumination
I often worry about problems in my throat/chest/oesophagus.	.699		VSI	Rumination
These symptoms are terrible and I think things are never going to get any better.	.683		CSQ	Catastrophizing
There's nothing I can do to reduce the intensity of the symptoms.	.681		PCS	Catastrophizing
When I feel discomfort in my throat/chest/oesophagus, it frightens me.	.646		CSQ	Catastrophizing
I anxiously want the symptoms to go away.	.617		PCS	Coping
I am quick to notice changes in location or extent of my oesophageal symptoms.		.874	PVAS	Vigilance
I am aware of sudden or temporary changes in my oesophagus		.830	PVAS	Vigilance
I notice my symptoms even if I am busy with another activity.		.669	PVAS	Vigilance
I focus on oesophageal sensations.		.573	PVAS	Rumination
I am very sensitive to oesophageal sensations such as heartburn or chest pain.		.533	PVAS	Vigilance
I keep track of my symptom level.		.516	PVAS	Coping

Factor 1: Symptom-specific Anxiety. Factor 2: Symptom-specific Hypervigilance

PCS: Pain Catastrophizing Scale.²³ VSI: Visceral Sensitivity Index.²⁴ CSQ: Coping Strategies Questionnaire.²⁷ PVAS: Pain Vigilance and Awareness Scale.²⁵

Table 3

Descriptive Statistics for EHAS Total, EHAS Subscales, Symptom Severity, and HRQOL Scales

Scale	Max Score	Mean (SD)	S.E.	Range
EHAS Total	60	29.79 (14.8)	0.49	0 – 60
EHAS Anxiety	36	17.08 (9.85)	0.32	0 – 36
EHAS Hypervigilance	24	12.85 (6.08)	0.20	0 – 24
PROMIS QOL	48	18.37 (9.84)	0.32	0 – 47
NEQOL	70	34.10 (15.07)	0.74	0 – 70
GERDQ	24	7.12 (4.94)	0.16	0 – 18
BEDQ	40	8.57 (9.53)	0.46	0 – 40

Table 4

Pearson's Correlations Between EHAS Total, Subscales, Symptom Severity, and HRQOL

	1	2	3	4	5	6	7
1 EHAS Total	-						
2 EHAS Anxiety	0.96**	-					
3 EHAS HV	0.87**	0.72**	-				
4 PROMIS QOL	-0.44**	-0.46**	-0.31**	-			
5 NEQOL	-0.69**	-0.70**	-0.55**	0.51**	-		
6 BEDQ	0.37**	0.34**	0.34**	-0.34**	-0.43**	-	
7 GERDQ	0.44**	0.42**	0.39**	-0.39**	-0.47**	0.41**	-

** P < .01