Anxiety and Depression in Eosinophilic Esophagitis: A Scoping Review and Recommendations for Future Research

Tiffany H Taft 1
Livia Guadagnoli 1
Emily Edlynn 2

1 Northwestern University Feinberg School of Medicine, Division of Gastroenterology & Hepatology, Chicago, IL, USA; 2 Oak Park Behavioral Medicine LLC, Oak Park, IL, USA

Abstract: Eosinophilic esophagitis (EoE) is a rapidly emerging chronic disease with limited treatments. Impacting both children and adults, EoE and its treatments have the potential to significantly reduce psychological functioning, including increasing anxiety and depression. In this paper, we provide a scoping review of the scientific literature on anxiety and depression in both pediatric and adult patients. We aim to document the current state of research, identify knowledge gaps, recognize unique challenges that EoE patients may face as they relate to psychosocial function, and offer suggestions for future research directions. Based on the current review, both adult and pediatric patients with EoE are at risk for anxiety and depression symptoms, both due to the disease process and the prevailing dietary treatments. Significant gaps exist in the current understanding of anxiety and depression in EoE, providing ample opportunity for future studies to address this important issue.

Keywords: eosinophilic esophagitis, anxiety, depression, quality of life, scoping review

Introduction

Eosinophilic gastrointestinal disorders (EGIDs) are immune-mediated chronic diseases with the potential to impact the entirety of the digestive system. The most commonly diagnosed EGID, eosinophilic esophagitis (EoE), is characterized by chronic infiltration of the esophagus by eosinophils, normally absent in esophageal tissues. The diagnostic cutoff for EoE is greater than 15 eosinophils per high power field retrieved by biopsy. The prevailing theory is eosinophilic infiltration is due to exposure to environmental antigens, typically in foods, that triggers the allergic response. Structural changes may occur, including the presence of esophageal rings, furrows, exudates, and stricture. The most common symptom of EoE in adult patients is dysphagia, or difficulty swallowing, that may lead to food impaction. Other symptoms include heartburn and chest pain, which are the most common symptoms in children along with failure to thrive and poor appetite. Treatments for EoE are limited to swallowed, topical corticosteroids and elimination diets.

In addition to EoE, other EGIDs include eosinophilic gastritis (EG; impacting the stomach), eosinophilic gastroenteritis (EGE; impacting the stomach and small bowel) and eosinophilic colitis (EC; impacting the colon). These EGIDs are considered much rarer than EoE at the present time, and symptoms include nausea, vomiting, loss of appetite, abdominal pain, and diarrhea. Treatments are also limited to corticosteroids and dietary modification.
Currently, EoE is estimated to impact 10 to 57 per 100,000 people globally, with increasing incidence and prevalence rates. The estimated cost of EoE approaches $1 billion dollars annually, derived from outpatient visits, endoscopies, hospitalizations including emergency room visits, and medications. Additional costs are attributed to the need to follow special elimination diets, requiring patients to shop at specialty stores, or the use of expensive elemental formulas. Many patients are diagnosed with an EoE as a child, further adding to the extended burden of this disease.

As EoE has gained more attention in gastroenterology practice and research, the evaluation of their impact on mental well-being and health-related quality of life has also increased. However, significant gaps remain in the literature in our understanding of the relationships between EoE and these constructs, especially compared to other chronic digestive diseases such as inflammatory bowel disease and irritable bowel syndrome. As such, we aim to review the existing literature as it relates to two specific mental health concerns in patients with EoE: anxiety and depression, in both pediatric and adult patient populations. We also aim to provide suggestions for future lines of inquiry in anxiety and depression in EoE, as well as other potential aspects of mental health that may be impacted by these diseases.

Methods
A scoping review of studies published through July 2019 (no start date) in which participants had a diagnosis of at least one EGID type was performed via the online databases PubMed, PsycINFO, and Google Scholar following PRISMA guidelines (Figure 1).

Inclusion Criteria
We included all studies that met the following criteria: a) published in English in a peer-reviewed journal, b) participants were diagnosed with at least one EGID, and c) anxiety and/or depression was evaluated using standardized assessment tools. Studies that measured health-related quality of life were evaluated and included if anxiety or depression was part of the HRQOL assessment tool utilized.

Procedures
Articles were identified and stored in an EndNote database. Titles or abstracts were returned via the following keyword search combinations: eosinophilic gastrointestinal disorders, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis, anxiety, depression, psychosocial, psychological, mental health. Each unique abstract was examined by two raters (TT, LG) for inclusion criteria and any that were explicitly unmet (e.g., study of non-humans, no mention of anxiety or depression) were discarded. Inter-rater agreement was 100%. Reference lists of identified articles and book chapters were also reviewed for additional studies. Unpublished manuscripts, case reports, and dissertations are not included.

The majority of studies were published in the United States and Switzerland. Both adult and child/adolescent studies are included in this review and the findings are organized adult and pediatric studies. To date, no research evaluates anxiety and depression in non-EoE EGIDs. As such, this review is limited to EoE.

Adult Patients with EoE
General Findings
The literature search yielded only a handful of studies directly measuring anxiety or depression in adult EoE patients. Often times, anxiety and depression are included in studies evaluating other constructs such as HRQOL, social interactions, and disease stigmatization. As such, reviews of these patient outcomes are included within the context of how they are associated with anxiety and depression.

Anxiety and Depression
Few studies have evaluated the prevalence and impact of anxiety or depression in adult patients with EoE (Tables 1 and 2). A 2019 study sought to characterize a cohort of adult EoE patients through a retrospective medical record review, which included assessing the prevalence of several psychiatric comorbidities using ICD-9 and ICD-10 codes. Overall, 31% of patients had at least one psychiatric or neuropsychiatric comorbidity, with 12% of the sample demonstrating a diagnosis of depression, followed by anxiety, which was reported by 9.3% of patients. Further, the authors found these rates were significantly higher than the general hospital population, although comparable to the natural history of each respective disorder. Another study applied the Hospital Anxiety and Depression Scale-8 (HADS-8) to a cohort of Spanish patients with EoE. Results demonstrated that 31.1% and 9.8% reported anxiety and depression in the “probable-certain” range (score > 8), respectively. These
findings remained relatively stable at the 12-week re-test period.

Research suggests potential sex differences in adult patients with EoE, specifically with women reporting increased symptoms of anxiety and depression compared to men.\textsuperscript{12} These findings are consistent with research in the general population.\textsuperscript{13–15} However, more research is warranted before conclusive statements can be made.

**Illness Stigma**

Illness stigma may also impact anxiety and depression in adult patients with EoE. Greater internalized and perceived illness stigma was found to be significantly associated with increased anxiety and depression symptoms.\textsuperscript{12,16} Further, perceived and internalized stigma were each significant predictors of both anxiety and depression, even when controlling for variables such as disease severity, duration, and gender.\textsuperscript{12,16}

**Psychological Impact of EoE Treatment**

There are several options for EoE treatment, including pharmacological therapy, procedural intervention (e.g. balloon distention), and dietary modification, all of which have the potential of impacting an individual’s psychosocial functioning. In terms of medication, patients with EoE may report fear or worry about potential side effects,\textsuperscript{17} which can exacerbate an already stressful disease experience. Patients using dietary therapy may also experience negative impacts on their psychosocial functioning, in some cases even more so than those exclusively using medications.\textsuperscript{18} Dietary therapy requires adherence, which can be burdensome and inconvenient,\textsuperscript{17,19} and has been
found to negatively impact the emotional aspects of HRQOL in adult patients with EoE. Further, research has found that diet-related anxiety, such as worry about food being unavailable and time required to prepare foods, is associated with decreased dietary adherence for adult patients on the six-food elimination diet. In addition, anxiety and depression levels appear to be higher in patients identified as former users of the six-food elimination diet, compared to those who are actively using the diet, suggesting a relationship between emotional distress and dietary use, although directionality cannot be concluded.

### Social Impacts of EoE

Finally, EoE may impact patients’ social experience, which can in turn, affect emotional well-being. Patients with EoE report experiencing social embarrassment or distress due to their diagnosis, including negative experiences dining out or attending work interviews, worry about having a choking episode in public, and concern about having to hide the attack from others. Embarrassment and shame may contribute to perceived or internalized illness stigma, which can also negatively affect anxiety and depression symptoms in patients with EoE.

Interestingly, despite these findings, patients typically endorse feeling open to disclosing their illness to friends and family. The benefits of social support have been studied in a variety of chronic illnesses and are established as an important protective factor for prevention of adverse mental health outcomes and promotion of positive health behaviors. Thus, encouraging discussion about EoE and cultivating support from friends and family may aid as a buffer the potentially harmful outcomes.

### Relationship with HRQOL

While literature on anxiety and depression in adult patients with EoE is scarce, there has been progress in the field evaluating the impact of EoE on health-related quality of life (HRQOL). Research has consistently found that EoE patients experience reduced HRQOL, due to several facets of their disease, which has resulted in psychological and social implications. Notably, adult patients with EoE view HRQOL as one of the most important outcomes in long and short-term therapy, even when compared to reduction in biological and histological activity, underscoring HRQOL as an important facet of the overall EoE patient experience.

The demand for a better understanding of the impact of EoE on psychosocial functioning was augmented by the development of the Adult Eosinophilic Esophagitis Quality of Life (EoE-QOL-A) questionnaire, a tool to assess HRQOL specific to the EoE population. In addition to a total score, the EoE-QOL-A is comprised of several subscales, including emotional impact, social impact, eating/diet impact, choking anxiety, and disease anxiety, all of which have individual subscale scores, which allows for identification of specific underlying issues patients may be experiencing.

The emotional impact and choking and disease anxiety subscales are of particular interest, as it evaluates aspects.
The emotional impact subscale assesses the degree to which patients have felt like life is less enjoyable or felt helpless or isolated because of EoE, and was found to have the greatest influence on decreased HRQOL in a sample of patients with EoE in a recent study.[18]

In fact, a separate study found that disease anxiety and choking anxiety had the largest impacts on overall HRQOL in the EoE population.[11,20] EoE symptoms, such as dysphagia or food impaction, can produce a significant amount of fear and concern for patients,[17,18] and increased symptom severity is a significant predictor of both disease and choking anxiety.[27]

Further underscoring the association between emotional distress and HRQOL is the finding that increased scores on more general measures of anxiety and depression are significantly associated with decreases in HRQOL (as measured by the EoE-QOL-A).[11,26] However, some research suggests the correlation between anxiety and HRQOL is stronger than the relationship between HRQOL and depression.[11]

**Limitations and Future Research for Adults with EoE**

There is limited understanding of the role of anxiety and depression in adult patients with EoE. To our knowledge, there is one qualitative study evaluating these constructs, and while there is an increasing number of quantitative studies, the research is generally lacking in rigor and efficacy.

### Table 2 Relevant Studies Examining Anxiety in Adults with EoE

| Author Group | Year | Study Design | Sample Size | Assessments Used | Estimates Obtained |
|--------------|------|--------------|-------------|------------------|--------------------|
| Wang et al[19] | 2018 | Cross-sectional | 42 | NIH-PROMIS Anxiety Scale | Diet-related anxiety may impact SFED adherence: Anxiety higher in former users of SFED compared to current users. |
| Stern et al[18] | 2018 | Prospective | 167 | EoE-QOL-A | Anxiety (measured under QOL), is associated with symptom severity but not endoscopy or histology results. Prior food impaction influences choking anxiety. |
| Safroneeva et al[2] | 2018 | Cross-sectional | 109 | EoE-QOL-A | Anxiety (measured under QOL) is associated with patient treatment goals. |
| Lucendo et al[20] | 2018 | Cross-sectional | 170 | EoE-QOL-A | Disease anxiety and choking anxiety were the highest scoring domains of QOL. |
| Taft et al[17] | 2011 | Qualitative | 24 | Semi-Structured Interview | Disease anxiety and choking anxiety are important aspects of QOL. |
| Taft et al[26] | 2011 | Scale development | 201 | EoE-QOL-A | Disease anxiety and choking anxiety are 2 subscales on EoE-specific measure of QOL. |
| Lucendo et al[11] | 2014 | Prospective | 170 | Hospital Anxiety and Depression Scale | 31.1% of patients scored above the cutoff for anxiety. |
| Guadagnoli and Taft[12] | 2019 | Cross-sectional | 149 | NIH-PROMIS Anxiety Scale | Stigma internalization is positively correlated with increased anxiety. |
| Guadagnoli et al[16] | 2017 | Cross-sectional | 149 | NIH-PROMIS Anxiety Scale | Stigma perception is positively correlated with increased anxiety. |
| Leigh and Spergel[10] | 2019 | Retrospective chart review | 34 | ICD-9/ICD-10 | 9.3% Had diagnosis of anxiety. |
| Safroneeva et al[48] | 2018 | Cross-sectional | 98 | EoE-QOL-A | Symptoms severity was correlated with HRQOL scale and predicted HRQOL scores, including anxiety. |
Children and Adolescent Patients with EoE

General Findings

As the prevalence of EoE appears to be quickly growing, a better understanding of the impact of EoE on quality of life in children becomes more critical. The existing literature establishes a link between EoE and poorer HRQOL, with symptoms and disease status directly correlating with lower HRQOL. Within the larger body of research on HRQOL in EoE, evidence points to greater emotional and behavioral problems and worsened adjustment as children get older. Based on the scant studies of emotional symptoms within HRQOL, disease-specific symptoms such as epigastric pain and certain treatment options (e.g., food restrictions and g-tubes) may be most predictive of emotional symptoms.

In examining anxiety and depression specifically, however, the research is limited. Many studies of pediatric health-related quality of life collapse emotional symptoms on the PedsQL measure into one “psychosocial functioning” domain combined with school and social functioning, or include “worry” measured within the EoE module of the PedsQL.

Anxiety

Studies examining anxiety specifically suggest that youth with EoE do have higher rates of anxiety symptoms compared to healthy populations (Table 3). In the study of 705 patients, 15.5% reported anxiety and depression, with 19% of older patients (11–17 years) endorsing these symptoms compared to 9.3% of younger patients (<11 years). In a smaller cohort of 64 patients, reported rates of anxiety were 41% among children, but not stratified by age. These higher rates may be linked with symptoms and treatments unique to EoE, including worries about symptoms, dietary restrictions, and g-tubes. In the review by Klinnert et al clinical observations found patients with increased anxiety related to needing a G-tube and in those with comorbid food allergies which heightened fears about a life-threatening reaction. Qualitative interviews corroborate these concerns with anxieties traversing food reactions and choices, and having endoscopies. The common intervention of dietary restriction likely increases worry about foods (by children and their caregivers), as well as fears of embarrassment in social situations. The specific symptoms most often identified include worry about disease and symptoms, physical symptoms of anxiety and autonomic arousal, and school avoidance. It should be noted that...
a majority of studies including anxiety as a variable discuss anxiety at the symptom level rather than representing actual anxiety disorders. Some evidence shows that anxiety symptoms increase with age, suggesting the importance of developmental considerations.

Depression

Although anxiety has received more attention than depression in studying emotional symptoms in children and adolescents with EoE, results of studies to date suggest that mood is an important area in which to increase understanding (Table 4). When measured with anxiety symptoms, some evidence shows depression may also increase with age at higher rates than the general population. Depressive symptoms have been found to contribute to medical non-adherence in youth with EoE, and to be related to persistent epigastric pain and greater sleep disturbance. In one study, children and adolescents with EoE reported more symptoms on subscales of anhedonia, negative mood, and negative self-esteem compared to healthy controls. This early evidence base justifies depression and depressive symptoms as an important component of studying HRQOL in pediatric EoE.

Limitations and Suggestions for Future Research for Children with EoE

Data from the limited research of anxiety and depression in pediatric EoE populations indicate this area needs further study. Some limitations include the lack of standardized assessment tools, variability in study design, and the need for longitudinal follow-up to understand the trajectory of emotional symptoms over time.
further study to provide better understanding of the role of psychological symptoms across the developmental continuum of life with EoE, and to inform more holistic treatment interventions. Future research should more systematically not only include depression and anxiety as constructs, but should develop a more consistent approach to conceptualization and measurement. Associations between factors such as internalizing symptoms, sleep disturbance, and pain warrant more analysis. An improved understanding of how these symptoms interrelate would inform more effective clinical interventions, including behavioral health treatments potentially targeting pain and sleep in order to decrease internalizing symptoms. Finally, caregiver anxiety has been shown to be elevated, especially for those of younger children, due to worries about growth, nutrition, and avoiding harmful foods. As parent anxiety is known to increase the risk of child anxiety, this potential association also deserves more research in pediatric EoE. Screening for caregiver anxiety and providing appropriate referrals such as behavioral health interventions for caregivers could be an important part of treatment for pediatric EoE.

Conclusions
This scoping review of anxiety and depression studies in pediatric and adult patients with EoE demonstrates a significant gap in the existing literature and the necessity of more research to understand the true impacts of these mental health co-morbidities on patient outcomes. However, we can conclude that EoE does increase the risk of developing symptoms of anxiety and depression, which in turn may reduce HRQOL and treatment adherence. The lack of treatment options may be a driver of anxiety, especially in those patients who need to follow strict elimination diets indefinitely. Impacts on eating and food-specific anxieties are legitimate concerns that treating physicians and dietitians should actively monitor, including screening for restrictive behaviors beyond what would be considered reasonable (i.e. Avoidant Restrictive

| Author Group | Year | Study Design | Sample Size | Assessments Used | Estimates Obtained |
|--------------|------|--------------|-------------|------------------|-------------------|
| Chehade et al | 2018 | Cross-sectional | 705 | Self-Reported History of Anxiety or Depression | 24.0% in subjects ≥18 years of age, 9.0% in those 11–17 years of age, 9.3% in children <11 years of age |
| Hommel et al | 2012 | Cross-sectional | 96 | Behavior Assessment System for Children, 2nd Edition | Depressed patients being more likely (OR=7.27) to be non-adherent than non-depressed patients |
| Lynch et al | 2018 | Cross-sectional | 50 | Pediatric Quality of Life Scale for EoE | Caregivers of children with EoE and persistent pain reported significantly more depressive symptoms in their children compared to healthy controls |
| Case et al | 2017 | Cross-sectional | 20 | Revised Children’s Anxiety and Depression Scale, Pediatric Quality of Life Scale for EoE | 50% of participants reported high frequency anger and sadness related to special diets, measured by PedsQL-EoE Feelings subscale |
| Cortina et al | 2010 | Cross-sectional | 108 (Mothers & Children) | Children’s Depression Inventory | Children and adolescents with EoE reported greater overall depressive symptoms compared to controls, and more symptoms on three subscales: anhedonia, negative mood, negative self-esteem |
| Lynch et al | 2018 | Review | | | Higher rates of depressive symptoms in youth with EoE are associated with sleep problems and pain, all of which impact HRQOL (no study has yet examined these four constructs at once) |
Table 5 Common Screening Tools for Anxiety and Depression

| Measure Title                                      | Anxiety | Depression | Number of Items |
|---------------------------------------------------|---------|------------|-----------------|
| **Adults 18 years+**                              |         |            |                 |
| Hospital Anxiety and Depression Scale (HADS)      | ✓       | ✓          | 8               |
| Generalized Anxiety Disorder – 7 (GAD-7)          | ✓       | ✓          | 7               |
| Patient Health Questionnaire – 9 (PHQ-9)          | ✓       | ✓          | 9               |
| NIH-PROMIS Mental Health – Anxiety                | ✓       | ✓          | 7               |
| NIH-PROMIS Mental Heath – Depression              | ✓       | ✓          | 8               |
| Kessler 10                                        | ✓       | ✓          | 14              |
| **Children 17 years or Younger**                   |         |            |                 |
| Patient Health Questionnaire for Adolescents (PHQ-A) | ✓       | ✓          | 9               |
| Mood & Feelings Questionnaire – Short Form (MFQ-SF) | ✓       | ✓          | 13              |
| Childhood Anxiety Sensitivity Index (ASI)         | ✓       | ✓          | 16              |
| Screen for Child Anxiety-Related Disorders (SCARED)* | ✓       | ✓          | 41              |

Note: *Completed by parent.

Food Intake Disorder (ARFID)). ARFID is a condition defined by the Diagnostic and Statistical Manual for Mental Disorders – Fifth dition, generally applied to feeding issues in children. Recently ARFID specific to coping with digestive diseases has become a growing area of attention, including a 2019 case report of two children with EoE. We recommend gastroenterologists who treat EoE, and other EGIDs for that matter, conduct routine screens for anxiety and depression. There are several brief measures easily implemented in clinical practice such as the PROMIS mental health scales, the PHQ-9, and the GAD-7 (Table 5). In addition to screening, referral lines to mental health professionals specializing in health psychology, behavioral medicine, or psych-gastroenterology should be established so patients can be provided with resources once anxiety or depression symptoms are identified. Effective psychological interventions for anxiety and depression, such as cognitive behavioral therapy or acceptance and commitment therapy, while not formally evaluated in EoE, have been tested in other chronic digestive diseases and demonstrate sufficient efficacy.

Disclosure
The authors report no conflicts of interest in this work.

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