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Development and Validation of a Symptom-Based Activity Index for Adults with Eosinophilic Esophagitis

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Submission for **Gastroenterology**

Development and Validation of a Symptom-Based Activity Index for Adults with Eosinophilic Esophagitis

Running head: adult EEsAI Patient Reported Outcome Instrument

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Abbreviations used in this paper: AMS score, avoidance, modification and slow eating score; ANOVA, analysis of variance; DSQ, dysphagia symptom questionnaire; EoE, eosinophilic esophagitis; EEsAI, eosinophilic esophagitis activity index; EGD, esophagogastroduodenoscopy; EndoFLIP®, Endolumenal Functional Lumen Imaging Probe; EREFS, EoE Endoscopic Reference Score; FDA, US Food and Drug Administration;

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GERD, gastro-esophageal reflux disease; IQR, interquartile range; MDQ-30, Mayo Dysphagia Questionnaire 30-Day; PatGA, patient global assessment; PGA, physician global assessment; PRO, patient-reported outcome; TS, trouble swallowing; VDQ, visual dysphagia question.

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ABSTRACT

BACKGROUND & AIMS: Standardized instruments are needed to assess the activity of eosinophilic esophagitis (EoE), to provide endpoints for clinical trials and observational studies. We aimed to develop and validate a patient-reported outcome (PRO) instrument and score, based on items that could account for variations in patients' assessments of disease severity. We also evaluated relationships between patients' assessment of disease severity and EoE-associated endoscopic, histologic, and laboratory findings.

METHODS: We collected information from 186 patients with EoE in Switzerland and the US (69.4% male; median age, 43 years) via surveys (n = 135), focus groups (n = 27), and semi-structured interviews (n = 24). Items were generated for the instruments to assess biologic activity based on physician input. Linear regression was used to quantify the extent to which variations in patient-reported disease characteristics could account for variations in patients' assessment of EoE severity. The PRO instrument was prospectively used in 153 adult patients with EoE (72.5% male; median age, 38 years), and validated in an independent group of 120 patients with EoE (60.8% male; median age, 40.5 years).

RESULTS: Seven PRO factors that are used to assess characteristics of dysphagia, behavioral adaptations to living with dysphagia, and pain while swallowing accounted for 67% of the variation in patients' assessment of disease severity. Based on statistical consideration and patient input, a 7-day recall period was selected. Highly active EoE, based on endoscopic and histologic findings, was associated with an increase in patient-assessed disease severity. In the validation study, the mean difference between patient assessment of EoE severity and PRO score was 0.13 (on a scale from 0 to 10).

CONCLUSIONS: We developed and validated an EoE scoring system based on 7 PRO items that assesses symptoms over a 7-day recall period. Clinicaltrials.gov number: NCT00939263.

KEYWORDS: disease activity measurement, esophagus, patient reported outcome, marker

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a young disease, as only a little more than two decades have passed, since this condition has been recognized as its own standing entity.[1,2] Some years ago, a panel of international experts defined EoE as "a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation".[3] The prevalence of EoE is currently estimated at 1/2,000 in the pediatric and adult population of the United States and Europe.[4,5,6,7] Most adult patients suffer from dysphagia. However, patients may also report refractory heartburn and/or chest pain, which is centrally located and does not adequately respond to acid-suppressive medications.[8,9,10]

A standardized and validated patient-reported outcome (PRO) instrument assessing symptom severity in patients with EoE is urgently needed to define meaningful endpoints for clinical trials and to follow disease evolution in observational studies. Until now, EoE symptoms in adult patients have been evaluated in clinical trials using different PRO instruments. For example, Alexander *et al.* used the Mayo Dysphagia Questionnaire 30-Day (MDQ-30) version and found that swallowed fluticasone improved histologic characteristics, but not symptoms of EoE in adult patients.[11] The MDQ-30 version has been validated in a group of patients presenting with dysphagia and thoracic pain due to various gastrointestinal diseases, but not specifically due to EoE.[12] An *ad hoc*-constructed symptom assessment instrument was used by Straumann *et al.* in a placebo controlled study to evaluate the efficacy of budesonide in adult EoE patients.[13,14] Dellon *et al.* developed the dysphagia symptom questionnaire (DSQ), a 3-item electronic PRO administered daily to assess the frequency of dysphagia caused by eating solid food and relief strategies during the dysphagia episodes.[15] This DSQ was evaluated in a group of 35 adolescent and adult EoE patients with clinically and histologically active disease.[15] Of note, none of these three instruments fulfill all the criteria currently required for an EoE PRO instrument. The assessment of dysphagia is particularly challenging, as it depends not only on disease severity, but also on consistencies of foods consumed, and on behavioral adaptation

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strategies to living with dysphagia. Thus, any PRO instrument assessing dysphagia must take these factors into account.

Given the lack of standardized, validated PRO instruments, the results of clinical trials performed in EoE cannot be easily compared. This might also explain why different therapeutic trials document various degrees of association between patient-reported symptoms and endoscopic and histologic findings.[11,13,14] The current situation poses a major challenge for regulatory approval of EoE therapies.[16,17]

In this paper, we describe the process of development and validation of a PRO instrument for adult EoE patients. The study was carried out in accordance with the US Food and Drug Administration (FDA) guidelines.[16]

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PATIENTS AND METHODS

Study overview

The adult EEsAI study was carried out in three phases, which are illustrated in **supplementary Figure 5**. During the 1st phase, a comprehensive list of relevant items to be potentially incorporated into the PRO, endoscopy, histology, and blood biomarker instruments was generated. During the 2nd phase, the prototypes of standardized instruments were evaluated in a first patient group. Data derived from the PRO instrument were used to derive a symptom severity score. During the 3rd phase, the PRO instrument and PRO score were validated in a second group of adult EoE patients.

Item generation

We first established a conceptual framework for instruments to assess symptoms, behavioral adaptations, and biologic activity of adult EoE patients (**Figure 1**). For the item generation, a review of the literature and the existing instruments to assess clinical, endoscopic, histologic, and biochemical EoE activity was carried out, and expert opinion was provided using the Delphi technique (telephone conferences and emails). The Delphi technique allows geographically dispersed experts to reach a consensus on a particular complex task.[18] A Delphi group of adult EoE gastroenterologists (N = 9), allergists (N = 2), and pathologists (N = 2) from Switzerland and the United States contributed a list of items that they thought best in reflecting endoscopic [N = 6 items], histologic [N = 7 items], and biochemical activity [N = 5 items]).

For the PRO instrument item generation, patient input was obtained by a mixed methods approach using open-ended patient symptom surveys (N = 135 patients), focus groups (N = 27 patients) as well as semistructured patient interviews (N = 24 patients). The qualitative methods of the development of the PRO instrument are described in detail in the supplementary section (**Appendix 1** includes **supplementary Tables 1** to **8** and **supplementary Figures 1** to **4**) according to the consolidated criteria for reporting qualitative research guidelines.[19,20]

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Item reduction and formatting of the instruments assessing biologic activity

Delphi group members ranked each provided item assessing biologic EoE activity from 0 (not important) to 5 (very important). The number of items was then reduced by rank order from 7 to 5 items, and from 5 to 3 items for histology and blood biomarkers, respectively. The number of items (N = 6) for endoscopy did not change. The generated instruments were distributed to the Delphi group, and multiple Delphi rounds were conducted to minimize interobserver variability, establish clear definitions and to ensure that the final instruments reflect the consensus opinion.

PRO instrument

The EEsAI instruments were developed in such a way that PROs are assessed separately from items measuring biologic activity.[21,22,23,24] The PRO instrument included items on symptom severity and behavioral adaptations, which were recalled over 24 hours, 7 days, and 30 days, to determine the optimal recall period.

The PRO instrument contained 5 domains: a general domain to assess socio-demographic characteristics, two symptom domains to address symptoms dependent and independent of food intake, a co-morbidities domain and a medication domain. The PRO instrument consisted of 45 items. The domain addressing symptoms while eating or drinking includes items on duration, frequency and severity of dysphagia, time required for meal intake, dysphagia upon consuming liquids, and pain when swallowing. The Visual Dysphagia Question (VDQ) addressed the severity of dysphagia when consuming food of 8 distinct consistencies. The 8 food consistencies and examples of foods to illustrate those consistencies were as follows: 1) solid meat (such as steak, chicken, turkey, lamb), 2) soft foods (such as pudding, jelly, apple sauce), 3) dry rice or sticky Asian rice, 4) ground meat (hamburger, meatloaf), 5) fresh white untoasted bread or similar foods (such as doughnut, muffin, cake), 6) grits, porridge (oatmeal), or rice pudding, 7) raw fibrous foods (such as apple, carrot, celery), and 8) French fries. The examples were chosen based on foods that are consumed in the United States, Europe, and Canada. The behavioral adaptations (avoidance, modification and slow eating [AMS] of various foods) were also assessed in the

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context of consuming 8 distinct food consistencies. A domain addressing symptoms independent of eating or drinking included items on chest pain, heartburn, and acid regurgitation. The last two items were reproduced from the MDQ-30 with the permission of the copyright owners.[12]

Patients were asked to provide a Patient Global Assessment (PatGA) of EoE severity on an 11-point Likert scale, where a score of 0 is defined as 'no symptoms' and a score of 10 is defined as 'most severe symptoms'. The PatGA was used as a main outcome parameter for every recall period. The PRO instrument was first created in English. Translation of the PRO instrument into German and French was performed in accordance with the World Health Organization guidelines for translation and adaptation of instruments.[25]

Instruments assessing endoscopic, histologic, and laboratory findings

The instrument for physicians consisted of 5 domains: a general domain for physician and patient characteristics, a gastro-esophageal reflux (GERD) domain, an anti-eosinophil treatment domain, a blood biomarker domain, and an endoscopy domain. The instrument also incorporated the physician global assessment of EoE severity (PGA) item. The PGA took into account patients' symptoms (based on history taking), endoscopic, histological, and biochemical findings. The PGA was assessed on an 11-point Likert scale, where a score of 0 was defined as 'inactive EoE' and a score of 10 was defined as 'most active EoE'. The endoscopy domain of the physician instrument was designed based on the EoE Endoscopic Reference Score (EREFS) classification and grading system.[26]

The histopathology instrument contained three domains: a general domain for pathologists and two domains assessing EoE-associated histologic features in the distal and proximal esophagus. 'Distal' was defined as section of the esophagus 5 cm above the gastroesophageal junction, while 'proximal' was defined as section spanning the top 1/2 of the esophagus.

The detailed overview of the physician and histopathology instruments can be found in **supplementary Table 9**.

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Study population

The study was registered on clinicaltrials.gov (NCT00939263) and was approved by local institutional review boards and ethics committees. All authors had access to the study data and reviewed and approved the final manuscript. Between April, 2011 and December, 2012 (evaluation group) and May, 2013, and July, 2014 (validation group), EoE patients were recruited in 1 ambulatory care clinic and 7 hospitals in Switzerland and the United States. Adult EoE patients (≥ 17 years of age) in need of an esophagogastroduodenoscopy (EGD) for initial diagnosis, for confirming a suspected diagnosis, or for monitoring previously-diagnosed EoE were invited to participate in the study. Patients provided informed consent to participate in the study. EoE was diagnosed by investigators at all centers using published diagnostic criteria.[3] EoE patients with concomitant GERD were also included if they were under a continued proton-pump inhibitor therapy at the time of EGD. All patients underwent a standardized physical examination by a physician. EGD was performed and at least 8 biopsies were obtained (4 from the proximal and 4 from the distal esophagus). Endoscopic findings were assessed according to the endoscopy atlas created by Hirano *et al*.[26] Levels of blood eosinophils were also measured. Patients completed the PRO instrument before the EGD. Gastroenterologists completed the instrument for physicians, while pathologists completed the histopathology instrument.

Histologic evaluation was performed by the local center pathologist. Five-µm sections were cut from paraffin blocks and hematoxylin & eosin stained for examination by light microscopy. The area of a high power field and percentage of the area covered by tissue were noted to allow for calculation of peak eosinophil counts/mm^2. To determine the peak eosinophil count, at least 5 levels of every esophageal biopsy specimen were surveyed under low power, and the eosinophils in the most densely infiltrated area were counted under high power examination.

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Construction of the visual dysphagia question and avoidance, modification and slow eating scores

The data obtained from the VDQ and AMS items were used to create a composite score. A sample calculation of the VDQ and AMS scores is provided in **Appendix 2**.

Data handling and statistical analysis

Data were double-entered by two researchers into EpiData database (version 3.1, the EpiData Association, Odense, Denmark) and imported into Stata (version 13, College Station, Texas, USA) for analysis. Descriptive results are presented as frequencies and corresponding percentages of the group total or median plus interquartile range (IQR). We used multivariable linear regression analysis and analysis of variance (ANOVA) models to identify redundant information and to obtain an equation for constructing a PRO score. In these analyses, the PatGA was used as the outcome, and responses to specific items in the instrument as predictors. These analyses allowed us to quantify the extent to which included items explained the variability in PatGA. The variables included in the final models were chosen on the basis of their relative contribution to the explanatory power of the models, coherence of parameter estimates and expert opinion. We evaluated the fit of the models using the coefficient of determination (R^2). To validate the EEsAI PRO instrument, a second group of adult EoE patients was included, and the EEsAI PRO score was calculated based on the regression coefficients. The R^2 was calculated to assess the relationship between EEsAI PRO score and the PatGA. A Bland-Altman plot was used to evaluate the agreement between the calculated EEsAI PRO score and the PatGA.

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RESULTS

Patient characteristics

153 and 120 adult EoE patients were recruited for evaluation and validation phase, respectively. The characteristics of these patients are shown in **Table 1**. Age at inclusion, sex, ethnicity, and education level were comparable between the two groups. When compared to the patients in the evaluation group, the patients in the validation group were more likely to have EoE symptom onset > 5 years before inclusion into the study (67.2% *vs.* 52.9%), to experience self-reported food allergies (50% *vs.* 30.1%) and to receive EoE-specific therapies in the last 12 months before inclusion into the study (85.8% *vs.* 58.8%); however, they were less likely to have concomitant GERD (15% *vs.* 30.7%) and be treated with proton-pump inhibitor therapy (32.5% *vs.* 55.6%).

Predominant EoE symptoms (evaluation group)

Table 2 illustrates the predominant symptoms of patients in the evaluation group, reported over the past 24 hours, 7 days and 30 days. When recalled over the last 24 hours, 7 days, and 30 days, the median PatGA assessed on the 11-point Likert scale (range 0 - 10) was 1 (IQR 0 – 3), 2 (IQR 1 - 4) and 2 (IQR 1 - 4), respectively. Forty-one (27.5%), 91 (59.5%), and 126 (82.4%) patients reported trouble swallowing in the past 24 hours, 7 days and 30 days, respectively. Overall, except for the meal duration, which remained relatively constant over the time periods examined, patients were more likely to experience dysphagia and pain events with increasing length of the recall period.

Assessing dysphagia severity and behavioral adaptations when ingesting foods of different consistencies

The symptoms of patients in the evaluation group were analyzed for a 24-hour, 7-day and 30-day recall period. The data of the VDQ and AMS recalled over a 7-day recall period are shown in **supplementary Table 10**. Generally, the severity of perceived dysphagia increased with increasing food consistency. For instance, 21 (13.7%) patients reported that they expected to experience severe difficulties when eating solid meat, and 11 (7.2%)

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patients reported the same when eating foods included in a 'Raw foods' category. In contrast, 5 (3.3%) and 6 (3.9%) patients reported that they expected to experience severe difficulties when consuming foods of the 'Soft foods' and 'Grits and porridge' categories, respectively. Increased time required to eat a certain food item was the most common complaint for EoE patients. For example, 103 (67.3%) patients experienced this phenomenon when eating solid meat, followed by 65 (42.5%) when eating ground meat, and 54 (35.3%) when eating bread. Food avoidance and food modification were less frequently reported for 'soft foods' and were mostly associated with high consistency foods, such as meat, and 'Raw foods', such as vegetables. Similar trends were observed, when data for the 24-hour and 30-day recall periods were analyzed (data not shown).

Choosing the appropriate symptom recall period: patient input

Patients participating in the focus groups (n = 27) were asked to choose the best time period to reliably recall their symptoms. The majority of patients indicated that 7 day-period is the best recall period (19/27, 70.4%), followed by 14-day (5/27, 18.5%), 30-day (2/27, 7.4%), and 24- hour (1/27, 3.7%) periods.

Development of the PRO score

We modeled the PatGA recalled over 24-hour, 7-day and 30-day periods by evaluating its strength and significance of association with the items of the PRO instrument. The following seven items were chosen for inclusion in the PRO instrument based on their contribution to the explanatory power of the models, coherence of parameter estimates and expert opinion: frequency of trouble swallowing, duration of trouble swallowing, pain when swallowing, VDQ, as well as 3 AMS questions. As the answers to VDQ and 3 AMS items were scored to derive VDQ and AMS scores, respectively, the resulting 5 variables were used for the purposes of analyses presented below.

Frequency of trouble swallowing, duration of trouble swallowing, severity of pain when swallowing, VDQ and AMS scores positively correlated with the PatGA for three recall periods. The data for the 7-day recall period are shown in **supplementary Figure 6**. We used multivariable linear regression analysis and ANOVA models to evaluate the

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contribution of chosen PRO variables to the PatGA. The results of these analyses are depicted in **Table 3**. In general, the increasing severity of PRO variables mostly showed a positive and significant relationship with the PatGA for three recall periods examined. For example, for the 7-day recall period, if a patient experienced daily episodes of trouble swallowing, the predicted PatGA increased by 2.61, when compared to 1.3 and 2.29 for trouble swallowing episodes experienced 1 - 3 and 4 - 6 times/week, respectively. If, in addition, the duration of those trouble swallowing episodes was > 5 minutes, the predicted PatGA increased by another 0.53.

Although the contribution of 5 PRO variables to the PatGA was similar, when the 7-day and 30-day recall periods were examined, the contribution of these variables was quite different, when the 24-hour recall period was evaluated. For instance, for patients with a highest VDQ score quartile (score ranging from 7.6 to 10 – patients experiencing severe difficulties eating various foods), the predicted PatGA increased 6.19 for a 24-hour recall period, when compared to the increase of only 1.96 and 1.57 for the 7-day and 30-day recall periods, respectively. As such, for a 24-hour recall period, the VDQ score contributed ~ 3 - 4 times more to the predicted PatGA, when compared to the same VDQ score for the 7-day and 30-day recall periods. On the other hand, the coefficients for the highest values of the AMS score were quite similar with 2.19 for the 24-hour, 2.15 for the 7-day, and 1.91 for the 30-day periods.

The regression model with 5 variables of the EEsAI PRO instrument explained 72% (R^2 = 0.72), 67% and 58% of the variability in PatGA for the 24-hour, 7-day and 30-day recall periods, respectively. Since R^2 can be made artificially high by including a large number of independent variables that have an apparent effect purely by chance, only 5 independent variables that had a large effect were included into the model. Since the EEsAI PRO score for a 24-hour recall period was strongly influenced by a response to the VDQ, and the frequency of the events, such as pain and dysphagia, was also the lowest for the 24-hour recall period, we judged the 24-hour recall period to be less reliable for assessing EoE severity. Based on these statistical considerations and patient input, we concluded that a 7-

ACCEPTED MANUSCRIPT

day recall period represents the best choice for assessing patient-reported EoE severity by the means of the EEsAI PRO score.

Relationship between patient-assessed EoE severity and biologic EoE activity

We observed a positive association between endoscopic/histologic alterations and PatGA, which is illustrated by means of box plots in **Figure 2**. We did not find a correlation between PatGA and peripheral blood eosinophil counts (r = 0.045, *P* = 0.67).

Validation of the score as well as practicability and content validity of the instrument

To validate the PRO score obtained during the evaluation phase, we calculated it for every EoE patient recruited in the validation group and compared it with the PatGA. The plot in **Figure 3A** shows that the EEsAI PRO score for the 7-day recall period predicted 65% of the variability in PatGA, which closely compares with the 67% of variability in PatGA explained by the EEsAI PRO score in the evaluation group. The Bland-Altman plot (**Figure 3B**) evaluates the agreement between the calculated EEsAI PRO score and the PatGA. A mean difference of only 0.13 between PatGA and EEsAI PRO score was observed. The upper and lower 95% limits of agreement were 3.04 and -2.79, respectively. Two versions of the validated 7-day EEsAI PRO score are shown in **Table 4**: 1) the original PRO score that ranges from 0 to 8.52 and the 2) 'user-friendly' EEsAI PRO score that ranges from 0 to 100.

To evaluate the practicability and content validity of the validated EEsAI PRO instrument, we again contacted the 27 patients that participated in the focus groups. First, we evaluated the time patients needed to complete the EEsAI PRO instrument. When completing the instrument for the first time, patients required a median of 8 min (IQR 7 - 9 minutes, range 4 - 10 min). When asked "How difficult was it for you to complete this questionnaire?", patients responded with a median of 1 (IQR 0 - 2, range 0 - 6; 11-point Likert scale where 0 stands for 'no difficulties at all', 10 stands for 'very difficult'). To evaluate content validity, patients were asked the Likert scale question: "Does this questionnaire measure the complaints you have had / you currently have due to EoE?" Patents responded with a median of 8 (IQR 7 - 9, range 4 - 10; 10 stands for 'perfectly', 0 stands for 'not at all').

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DISCUSSION

Eosinophilic esophagitis is a young disease, and, so far, no validated PRO instruments reliably assessing disease activity have been approved by regulatory authorities in US and Europe.

In this article, we describe the process of development and validation of the adult EEsAI PRO instrument that assesses EoE symptom severity. We developed the EEsAI PRO instrument according to FDA guidelines.[16] Patient surveys, focus groups, and semi-structured interviews were used to gain patient input to inform PRO instrument development. The resulting PRO instrument was evaluated in the first group of adult EoE patients. As gold-standard, we used patient assessment of disease severity (PatGA) to develop the EEsAI PRO instrument score. Based on statistical considerations and expert input, seven PRO items were selected. These items explained 67% of the total variability in the PatGA over a 7 day recall period. The EEsAI PRO instrument was validated in a second group of patients, and these seven items explained 65% of the variability in PatGA.

Assessment of dysphagia is a challenge, because this symptom depends not only on the severity of the disease, but also on the consistency of the ingested foods. Moreover, patients suffering from dysphagia rapidly develop behavioral adaptation strategies. The EEsAI PRO instrument assesses dysphagia caused by eating foods of different consistencies (VDQ) and takes into account behavioral adaptation strategies. The food consistencies of the VDQ are well-defined, and the foods used to illustrate those consistencies are frequently eaten in Western countries. As the VDQ includes items on various food groups, the EEsAI PRO instrument can be used to assess dysphagia in individuals with, among others, vegetarian dietary patterns, food intolerances, and in patients on elimination diets. Based on patient input, the EEsAI PRO instrument is a content-valid measure of EoE symptom severity and easy to complete.

PRO must be assessed in a defined recall period, but its choice depends on the following factors: 1) intended use of the instrument (conceptual framework), 2) the ability of the patient to remember the required information, 3) the extent to which the patient with a certain illness is burdened when completing the instrument, 4) the nature of the disease and the

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symptoms, and 5) the study design.[27] The choice of a short recall period may lead to underestimation of symptom severity, when symptoms have a day-to-day fluctuation, or else may place undue burden on the patient, if patients are too ill to frequently complete the questionnaire. However, a long recall period may over- or underestimate the true health status of the patient. Based on patient preferences and statistical considerations presented in this study, the 7-day symptom recall period appears to be most suitable for this chronic condition.

In the recent years, several PRO instruments have been developed to assess EoE symptom severity. The Straumann Dysphagia Index does not assess dysphagia caused by eating food of different consistencies and does not take into account behavioral adaptations to living with dysphagia.[13,14] The MDQ-30 Day version assesses dysphagia due to various esophageal diseases, but it has not been developed for EoE specifically.[11,12] Using the DSQ, Dellon *et al.* recently evaluated dysphagia to solid food in a group of 35 adolescent and adult EoE patients.[15] However, the term 'solid food' was not defined in the manuscript. In our study, we noted important differences in dysphagia severity and behavioral adaptations to dysphagia when patients consumed 'solid food' of different consistencies. For example, 75% of patients expected to experience dysphagia due to consumption of solid meat, whereas only 17% of patients expected to experience dysphagia when eating grits or porridge. Standardizing the assessment of dysphagia by ingestion of a defined test meal is one way of avoiding the complexities associated with the definition of 'solid food'. However, such an approach may not be entirely practical and may raise ethical concerns associated with the exposure of the patients to the risk of food bolus impactions.[28] The VDQ can be thought of as a 'hypothetical test meal' that potentially avoids the ethical issues associated with the ingestion of a defined test meal. In contrast to findings reported by Dellon *et al.*[15], we found that patients frequently reported behavioral adaptations to dysphagia, such as food modification, food avoidance, and slow eating. For example, 67% of EoE patients reported eating solid meat slower than other people eating this type of food. We conclude that the EEsAI PRO instrument is the first to assess dysphagia caused by eating foods of distinct consistencies and also takes into account behavioral adaptations.

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We observed a positive relationship between endoscopic and histologic alterations and patient-assessed EoE severity. We suspect that patients are to a lesser extent sensitive to mild endoscopic/histologic alterations when compared to moderate/severe ones. This relative lack of sensitivity to mild EoE alterations may explain why the positive correlations between EoE symptom severity and endoscopic and histologic findings have been documented in some,[13,14,29] but not other studies[11,30] in both adult and pediatric patients. The observed inconsistencies in the correlations between PRO and biologic items may also be related to the fact that dysphagia and behavioral adaptations in these studies has not been assessed in the context of the various food consistencies. Lastly, the assessment of endoscopic and histologic alterations in adult EoE has not been standardized in these studies. The recent work by Hirano *et al.* represents an important milestone in standardizing the assessment of endoscopic alterations in EoE.[26] At present, the presumed pathophysiological mechanisms leading to EoE symptoms involve mucosal inflammation that is associated with dysmotility and/or mechanical restriction due to subepithelial fibrosis. We have yet to assess the relationship between symptom severity as captured by the EEsAI PRO instrument and the esophageal compliance that can be measured by the Endolumenal Functional Lumen Imaging Probe (EndoFLIP).[31,32] For the purposes of clinical trials, it seems prudent to include both PRO and biologic endpoints as untreated eosinophil-predominant esophageal inflammation is associated with the generation of esophageal strictures that ultimately lead to symptoms.[31,33]

Our study has several strengths, but some limitations as well. We present data of the first international multicenter study to develop and validate an activity index for adult EoE patients. We followed the recommendations of the FDA for PRO instrument development.[16] While the DSQ applies a scoring algorithm that involves giving a discrete arbitrarily-chosen value to each item response,[15] the scores for individual items of the EEsAI PRO instrument are based on the regression coefficients of the linear regression modeling using PatGA (the current 'gold-standard' for patient-perceived symptom severity) as the outcome. The EEsAI PRO instrument is the first EoE-specific instrument designed to assess dysphagia caused by eating 8 different food consistencies and behavioral adaptations to living with dysphagia. As

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such, the validated EEsAI PRO instrument can be used to measure EoE symptom severity in patients that do not eat certain food categories, such as vegetarians or patients on specific elimination diets. The EEsAI PRO instrument is validated, content-valid, and easy to complete.

As for limitations, the EEsAI PRO instrument was evaluated and validated for adult patients only (≥ 17 years of age). The EEsAI PRO instrument is about to be used in an upcoming randomized placebo-controlled clinical trials that will provide data on the responsiveness. We also evaluated and validated the PRO instrument for a 24-hour recall period, in case completion of the PRO instrument on daily basis might be preferred in certain studies. These data will be published elsewhere. The development of an electronic PRO (hand-held device) will certainly make the instrument even more 'user-friendly'.

In summary, we report on the development and validation of the adult EEsAI PRO instrument to assess EoE symptom severity over a 7-day recall period. The EEsAI PRO instrument is content-valid and is easy to complete. The development and validation of an instrument for standardized assessment of EoE symptom severity is a matter of paramount importance for guiding clinical decision making and for defining the outcome parameters for clinical trials as well as epidemiologic studies.

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FIGURE LEGEND

Figure 1: Conceptual framework for development of EEsAI instruments. The components of the flow chart outlined with a dashed line, such as EndoFlip or mucosal biomarkers, were not, as of yet, evaluated for the purposes of the EEsAI study.

Abbreviations: EndoFlip®, Endolumenal Functional Lumen Imaging Probe.

Figure 2: The relationship between endoscopic / histologic activity and patient-assessed EoE severity. The box contains the 25^{th} - 75^{th} percentile of values, the horizontal line in the middle of the box represents the median.

Figure 3: A. The correlation plot between the EEsAI PRO score and the PatGA in the validation group. **B.** The Bland-Altman plot for the agreement between the EEsAI PRO score and the PatGA in the validation group. The grey box indicates the 95 % limits of agreement.

Abbreviation: PatGA, patient global assessment; EEsAI, eosinophilic esophagitis activity index; PRO, patient-reported outcome.

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Table 1: Patient characteristics.

Characteristic	Evaluation group Frequency	%	Validation group Frequency	%
Number of patients	153	(100.0)	120	(100.0)
Males	111	(72.5)	73	(60.8)
Age at inclusion (median, IQR, range)	38	(29 - 46; 17 - 71)	40.5	(31 - 49; 19 - 80)
Ethnicity				
White	148	(96.7)	114	(95.0)
Non-white	5	(3.3)	6	(5.0)
Education				
Compulsory schooling	2	(1.3)	1	(0.8)
Vocational training	38	(24.8)	33	(27.5)
Upper secondary education	67	(43.8)	54	(45.0)
University education	46	(30.1)	32	(26.7)
EoE symptoms onset				
1 to 3 months ago	1	(0.7)	0	(0.0)
4 to 11 months ago	8	(5.2)	2	(1.7)
1 to 5 years ago	63	(41.2)	38	(31.7)
more than 5 years ago	81	(52.9)	80	(66.6)
Allergic diseases / Allergies				
Asthma	53	(34.6)	42	(35.0)
Rhinoconjunctivitis	92	(60.1)	72	(60.0)
Eczema	18	(11.8)	34	(28.3)
Food allergy	46	(30.1)	60	(50.0)
Gastro-esophageal reflux disease (GERD)	47	(30.7)	18	(15.0)
Diagnosis established				
Clinically	28	(59.6)	3	(16.7)
Endoscopically	11	(23.4)	6	(33.3)
Based on pH-metric studies	1	(2.1)	2	(11.1)
Clinically and endoscopically	7	(14.9)	5	(27.8)
Concomitant medications				
Proton-pump inhibitors	85	(55.6)	39	(32.5)
Histamine antagonists (H_2-receptor)	7	(4.6)	1	(0.8)
Histamine antagonists (H_1-receptor)	25	(16.3)	18	(15.0)
Inhaled corticosteroids for asthma	4	(2.6)	4	(3.3)
β2-adrenergic agonists for asthma	20	(13.1)	2	(1.7)
Leukotriene receptor antagonists for asthma	4	(2.6)	1	(0.8)
EoE-specific treatments in the last 12 months	90	(58.8)	103	(85.8)
Hypo-allergenic diets	20	(13.1)	19	(15.8)
Swallowed topical corticosteroids	65	(42.5)	78	(65.0)
Esophageal dilation	30	(19.6)	26	(21.7)

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Table 2: Type and frequency of EoE-related symptoms assessed in the EEsAI PRO instrument over 3 recall periods (N = 153).

	Recall period							
Characteristic	***24 hours***			***7 days***			***30 days***	
Median symptom severity (IQR; range)	1	(0 - 3; 0 - 10)		2	(1 - 4; 0 - 10)		2	(1 - 4; 0 - 10)
Frequency of trouble swallowing								
Never	111	(72.5)	Never	62	(40.5)	Never	27	(17.6)
1 to 3 times / day	34	(22.2)	1 to 3 times / week	60	(39.2)	1 to 3 times / month	40	(26.1)
≥ 4 times / day	7	(4.6)	4 to 6 times / week	15	(9.8)	1 to 3 times / week	52	(34.0)
	--	--		--	--	4 to 6 times / week	19	(12.4)
	--	--	Daily	16	(10.5)	Daily	15	(9.8)
Not applicable	1	(0.7)		--	--		--	--
Intensity of trouble swallowing								
Everything was easy to swallow	111	(72.5)		53	(34.6)		26	(17.0)
Slight retching	22	(14.4)		69	(45.1)		73	(47.7)
Food stuck for ≤ 5 minutes	7	(4.6)		25	(16.3)		37	(24.2)
Food stuck for > 5 minutes	3	(2.0)		4	(2.6)		10	(6.5)
Impacted food had to be removed	6	(3.9)		0	(0.0)		3	(2.0)
Missing	4	(2.6)		2	(1.3)		4	(2.6)
Duration of trouble swallowing								
No troubles swallowing	107	(69.9)		56	(36.6)		26	(17.0)
< 15 seconds	24	(15.7)		45	(29.4)		49	(32.0)
16 to 59 seconds	8	(5.2)		29	(19.0)		34	(22.2)
1 to 5 minutes	3	(2.0)		18	(11.8)		28	(18.3)
> 5 minutes	10	(6.5)		5	(3.3)		16	(10.5)
Not applicable	1	(0.7)		--	--		--	--
Time required to eat a regular meal								
< 15 minutes	24	(15.7)		22	(14.4)		20	(13.1)
16 to 30 minutes	91	(59.5)		88	(57.5)		86	(56.2)
31 to 45 minutes	30	(19.6)		34	(22.2)		37	(24.2)
46 to 60 minutes	3	(2.0)		3	(2.0)		3	(2.0)
> 1 hour or refusal to eat	3	(2.0)		4	(2.6)		5	(3.3)
Not applicable	2	(1.3)		2	(1.3)		2	(1.3)
Frequency of pain when swallowing								
Never	137	(89.5)	Never	122	(79.7)	Never	106	(69.3)

ACCEPTED MANUSCRIPT

1 to 3 times / day	14	(9.2)	1 to 3 times / week	21	(13.7)	1 to 3 times / month	19	(12.4)
4 or more times / day	2	(1.3)	4 to 6 times / week	6	(3.9)	1 to 3 times / week	16	(10.5)
	--	--		--	--	4 to 6 times / week	9	(5.9)
	--	--	Daily	3	(2.0)	Daily	2	(1.3)
Missing	0	(0.0)	Missing	1	(0.7)	Missing	1	(0.7)

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Table 3: Linear regression coefficients, 95% confidence intervals (CI) and *P*-values for the models of Patient Global Assessment of the EoE activity (PatGA) recalled over the 24 hours, 7-days and 30-day periods. **Abbreviations:** Coef, coefficient; CI, confidence interval; VDQ, visual dysphagia question; AMS, avoidance, modification and slow eating.

	Recall period								
	24 hours			***7 days***			***30 days***		
Characteristic	Coef[a]	95% CI	*P*	Coef[a]	95 % CI	*P*	Coef[a]	95 % CI	*P*
Frequency of trouble swallowing			0.01			< 0.0001			0.0001
Never		ref.	ref.	Never		ref. ref.	Never	ref.	ref.
1 - 3 times / day	1.30	(0.50 - 2.09)		--	--	--	1 - 3 times / month	0.31 (-0.62 - 1.23)	
≥4 times / day	0.86	(-0.91 - 2.63)		1 - 3 times / week	1.30	(0.74 - 1.86)	1 - 3 times / week	1.28 (0.26 - 2.29)	
--	--	--	--	4 - 6 times / week	2.29	(1.40 - 3.18)	4 - 6 times / week	2.49 (1.26 - 3.73)	
--	--	--	--	Daily	2.61	(1.66 - 3.56)	Daily	2.46 (1.09 - 3.83)	
Duration of trouble swallowing			0.03			0.41			0.52
≤ 5 minutes	ref.	ref.		ref.	ref.		ref.	ref.	
> 5 minutes	1.64	(0.16 - 3.13)		0.53	(-0.76 - 1.83)		0.30	(-0.61 - 1.20)	
Pain when swallowing			0.10			0.0001			0.0001
No	ref.	ref.		ref.	ref.		ref.	ref.	
Yes	0.78	(-0.16 - 1.73)		1.27	(0.66 - 1.87)		1.17	(0.58 - 1.75)	
VDQ score			<0.0001			0.02			0.01
0	ref.	ref.		ref.	ref.		ref.	ref.	
0.1 - 2.5	0.14	(-0.66 - 0.93)		1.02	(0.22 - 1.81)		0.40	(-0.60 - 1.39)	
2.6 - 5.0	2.00	(1.02 - 2.98)		1.63	(0.69 - 2.56)		1.64	(0.50 - 2.78)	
5.1 - 7.5	3.22	(1.66 - 4.78)		1.81	(0.43 - 3.20)		1.62	(-0.05 - 3.29)	
7.6 - 10.0	6.19	(4.21 - 8.17)		1.96	(0.45 - 3.47)		1.57	(-0.23 - 3.37)	
AMS score			0.20			0.01			0.10
0	ref.	ref.		ref.	ref.		ref.	ref.	
0.1 - 2.5	-0.04	(-0.73 - 0.66)		-0.57	(-1.24 - 0.10)		-0.35	(-1.13 - 0.43)	
2.6 - 5.0	-0.16	(-1.16 - 0.85)		-0.06	(-0.98 - 0.86)		-0.42	(-1.43 - 0.59)	

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	5.1 - 7.5	0.20	(-1.34 - 1.73)		0.77	(-0.59 - 2.12)		0.39	(-1.15 - 1.93)	
	7.6 - 10.0	2.19	(0.28 - 4.10)		2.15	(0.46 - 3.84)		1.91	(0.01 - 3.81)	
Constant[b]		0.39	(-0.21 - 0.98)	0.20	0.38	(-0.14 - 0.89)	0.15	0.88	(0.20 - 1.55)	0.01
R^2[c]		**0.72**			**0.67**			**0.58**		

[a] The coefficient represents the change in the value of the predicted PatGA for each category change of the independent variable. For example, for a 7 day recall period, the predicted PatGA increased by 1.3 if the patient reported having frequency of trouble swallowing of 1 – 3 times a week (category 'never' was the reference category). Similarly, the predicted PatGA increased by 2.29 and 2.61 points, if instead of not having any trouble swallowing (never), the patient reported having frequency of trouble swallowing of 4 - 6 times/week and daily, respectively. In this analysis, with frequency of trouble swallowing, duration of trouble swallowing *etc*. as independent variables and predicted PatGA as the dependent variable, the adjusted regression coefficient for duration of trouble swallowing represents the amount of variation in predicted PatGA that is due to the effects of duration of trouble swallowing alone, after frequency of trouble swallowing has been taken into account. For example, for a 7 day recall period, if the patient experienced daily episodes of trouble swallowing (with predicted PatGA increase of 2.61 points), his/her predicted PatGA increased by another 0.53 points, if the duration of those trouble swallowing episodes was > 5 minutes.

[b] The constant represents the value of the predicted PatGA when all 5 values of independent variables are zero.

[c] The coefficient of determination, R^2, is a measure of the extent to which the regression model describes the observed data. The closer the R^2 is to 1, the more precise the regression model is. Since R^2 can be made artificially high by including a large number of independent variables that have an apparent effect purely by chance, only independent variables that have a large effect have been included in the model. This was also done to ensure that the statistical model is clinically meaningful and can be easily interpreted.

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Table 4: EEsAI PRO score for the 7-day recall period. The score based on regression coefficients that ranges from 0 to 8.52 is shown in column 1. For clinical ease of use, a total of the score based on the regression coefficients was set to 100 and values for each category adjusted accordingly. This score is shown in column 2. **Abbreviations:** VDQ, visual dysphagia question; AMS, avoidance, modification, and slow eating score.

Item		***Score (based on regression coefficients)***	***Score (total set to 100)***
Frequency of trouble swallowing	Never	0	0
	1-3 times/week	1.30	15
	4-6 times/week	2.29	27
	Daily	2.61	31
Duration of trouble swallowing	≤5 minutes	0	0
	>5 minutes	0.53	6
Pain when swallowing	No	0	0
	Yes	1.27	15
VDQ score	0	0	0
	0.1-2.5	1.02	12
	2.6-5.0	1.63	19
	5.1-7.5	1.81	21
	7.6-10.0	1.96	23
AMS score	0	0	0
	0.1-2.5	0	0
	2.6-5.0	0	0
	5.1-7.5	0.77	9
	7.6-10.0	2.15	25
Total		8.52	100

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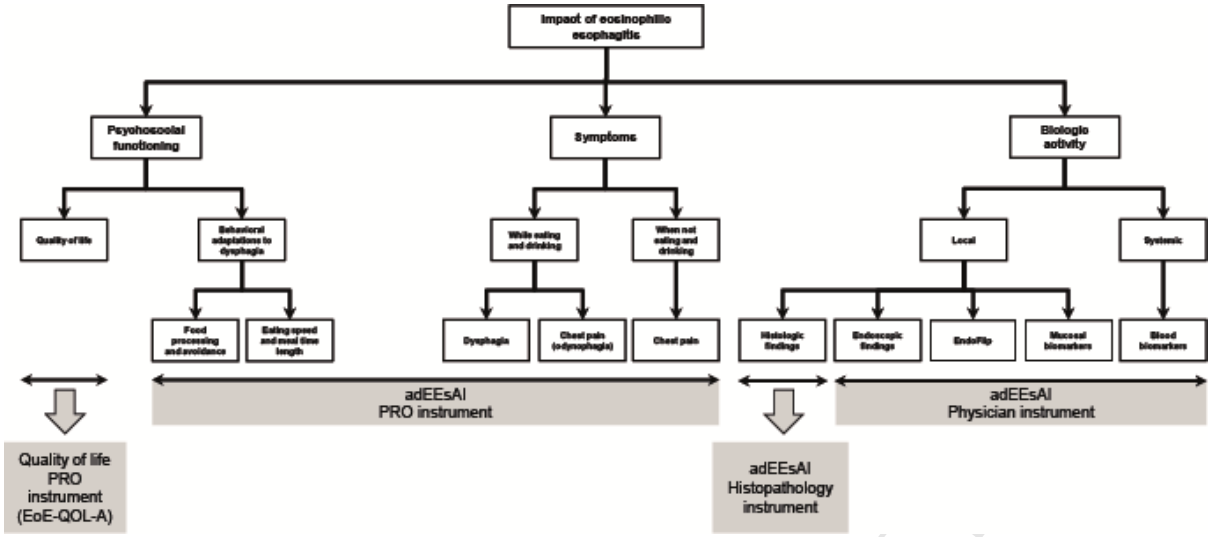

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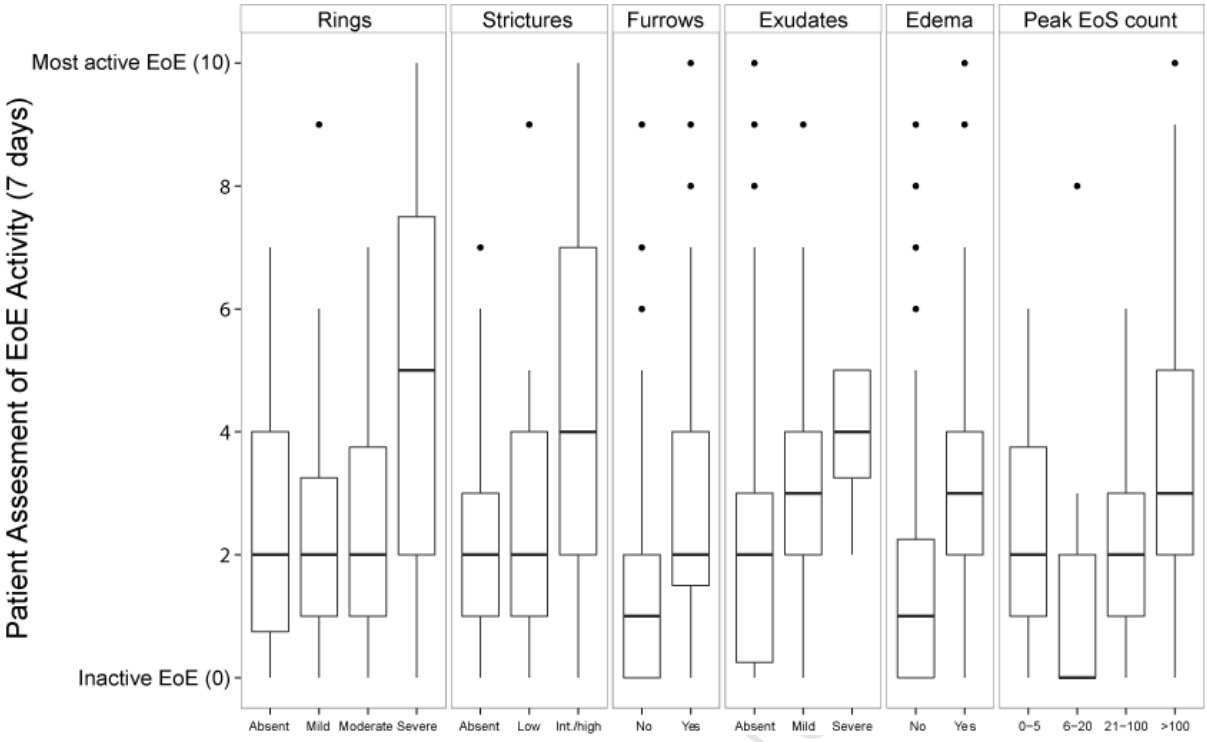

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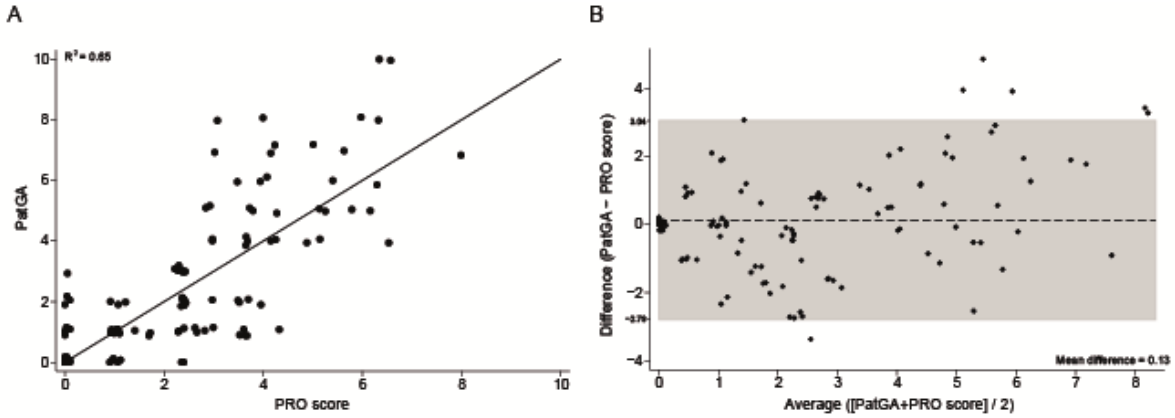

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APPENDIX 1

Development and Validation of a Symptom Activity Index for Adults with Eosinophilic Esophagitis: Qualitative Methods

This section describes in detail the qualitative methods used to develop and validate the EEsAI PRO instrument. Findings are reported according to the consolidated criteria for reporting qualitative research (COREQ).[19]

PATIENTS AND METHODS

The EEsAI study is registered under clinicaltrials.gov (NCT00939263) and approved by the institutional review boards and ethics committees of the participating centers. The qualitative work reported in this paper was conducted in Switzerland (Cantons of Bern and Solothurn) and at the Northwestern University, Chicago, USA. All participants provided written informed consent.

Research Team and Reflexivity

The research team was composed of experts in the field of EoE (AMS is a practicing male gastroenterologist, MD; AS is a practicing male gastroenterologist, MD; IH is a practicing male gastroenterologist, MD; NG is a practicing female gastroenterologist, MD), general internal medicine (Emily Kern, MD), mucosal immunology (ES is a female immunologist, PhD), veterinary medicine (EM is a female veterinarian, PhD), epidemiology (RP is a male epidemiologist; CK is a female pediatric pulmonologist and epidemiologist, MD, MSc; MZ is a male epidemiologist, PhD, PRO design (KK is a male PRO specialist, PhD; BS is a female PRO specialist, PhD), statistics (MC is a male statistician, PhD), and psychology (TT is a female psychologist, PhD; KM is a female psychologist, MSc) with specific expertise in qualitative research. NH is a female research assistant, BSc.

The interviewer TT, KM as well as BS were trained in qualitative methodology as part of university studies and research activities; interviewer EK as well as facilitators AMS and AS received training in qualitative research methodology for the purposes of this study. Those performing content analysis (ES, AMS, NH, and EM) received the training in qualitative research

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methodology for the purposes of this study. TT, CK, MZ, and ES have conducted research on various aspects of EoE for > 5 years, RP, MC, EM, and NH conducted EoE research for at least one year. KK, KM, and BS received a background training on various aspects of EoE related to this study specifically for the purposes of this study. AS, AMS, IH, and NG are experts and published extensively on EoE.

Patients participating in the survey had an established relationship with treating physicians (AS, IH, NG). Patients participating in the survey were informed about the purpose and research interest of the research team through a letter that described the purpose of the study. Patients that participated in the focus groups had an established relationship with the treating physician (AS), but no previous relationship with AMS and KM. Prior to the focus groups, patients were provided the information about the study and the research interests of AMS and AS. Patients participating in the face-to-face semistructured interviews had an established relationship with the treating physicians (IH, NG), but no previous relationship with EK.

Study design

Theoretical Framework

Given the fact that there is no single 'gold-standard' to gain patient input for PRO development, we chose a mixed methods approach by gathering patient's input by means of surveys, focus-groups, and individual interviews (**Supplementary Figure 1**). The content analysis was performed using a deductive category application approach described by Mayring.[20,34] This method allows separation of the data from the text and systematic reduction of the information.[20,34,35] We followed the COREQ guidelines when reporting the results of this study.[19]

Participant selection and setting

Diagnosis of EoE was established according to published criteria.[3] Patients with EoE and concomitant gastro-esophageal reflux disease that was under treatment with at least a standard-dose of proton pump inhibitors were included into the study.

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Patients participating in the survey: A total of 110 EoE patients in Switzerland (AS) and 287 EoE patients in Northwestern Medical Center, Chicago, USA (IH and NG) were addressed to participate in the study. EoE patients were sent questionnaires by mail. Patients completed these at a place of their choice and returned the completed questionnaires by mail.

Patients participating in the focus groups: Thirty-two EoE patients were approached during a routine clinical visit in EoE clinic, Olten County, Switzerland, and invited by AS to participate in the focus groups. Five patients declined the invitation. Twenty-seven EoE patients were interviewed in 3 focus groups (n = 9 for each focus group). Interviews were conducted at the EoE clinic in Olten, Switzerland. Except for the interviewer (KM) and two facilitators (AMS, AS), no one else was present at the time of the focus groups.

Patients participating in the individual patient interviews: A total of 30 patients were approached during a routine clinical visit at a university based gastroenterology practice and invited by IH and NG to participate in the face-to-face patient interviews. Six patients declined participation. Interviews were conducted in Northwestern Medical Center, Chicago, USA.

Data collection

Eosinophilic esophagitis symptom questionnaire used in the survey: The EoE symptom questionnaire consists of seven close-ended questions designed to address participants' age, sex, country of citizenship, education and current occupation and two open-ended questions assessing EoE-related symptoms and their severity (**supplementary Table 1**). For each open-ended question, we provided an example of the way an answer to this question might be given and a space of 4 lines for description of a single symptom or complaint. We also provided an 11-point Likert scale for patients to rank the severity of a given symptom (**supplementary Figure 2**). For each open-ended question, a space for description of up to 6 concerns or symptoms was provided. Patients were asked to write any other additional symptoms they might have experienced on a separate sheet of paper, if they were to run out of space. The questionnaire was developed in German (Olten County is located in the German-speaking part of Switzerland). The EoE symptom questionnaire in German was translated into US English as described by Acquadro *et al.*[36] During the pilot study, 15 study participants were asked to complete the

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questionnaires. Following the completion of the questionnaires, patients were interviewed to provide feedback. Patients judged the questionnaires to be appropriate to capture EoE-related symptoms and easy to complete.

Focus groups: Subjects participated in the focus group guided by an experienced psychologist (KM) to learn about the patient's symptoms and other experiences with EoE. AMS and AS were present as facilitators. *A priori* themes, such as symptoms during food intake or symptoms when not eating or drinking, behavioral adaptations to living with dysphagia, impairment in social and professional activities, experience with treatments and endoscopies, as well as other concerns were developed based on the existing literature, the experience of the research team or were adopted and/or reproduced directly from a study by Tufts *et al.* with permission of the senior investigator (IH).[1-4,8,37] The open-ended questions were constructed in German language, a translation of these questions into English is provided in **supplementary Table 2**. Three repeat focus groups were carried out in Swiss dialect of German language. The focus groups lasted between 1.5 and 2 hours. All sessions were audio-recorded, translated and transcribed in German, since Swiss dialect of German is not a written language. The research team reviewed transcriptions of the focus groups. The transcripts were analyzed by the lead investigator (AS) and the research team (ES, EM, NH). Field notes were taken by AS. Transcripts were not returned to participants for further comments. Since no new theme has arisen during the last two focus groups, no additional focus group interviews were carried out.

The patients participating in the focus group interviews for item generation were contacted at later time points to provide feedback about the best recall period to assess EoE symptoms, to assess the content validity and the practicability of the EEsAI PRO instrument.

Individual patient interviews: Twenty-four EoE patients, underwent individual face-to-face semistructured interviews guided by a trained physician (EK) to inquire about the symptoms and other experiences with EoE. No facilitator was present during the individual interviews. Interviews were conducted in English. The set of questions has been previously published by Taft *et al*.[37] An individual patient interview lasted between 50 to 60 minutes. Following the interview, patients underwent a debriefing with the interviewer, to better understand various reasons behind patients' responses. Field notes were taken by the interviewer after the

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individual patient sessions. All interviews and debriefing sessions were audio-recorded and transcribed. The transcripts were analyzed by the local investigators (EK, TT, IH, NG) and the research team in Switzerland (ES, NH, AMS).

Analysis and findings

Development and description of the code book: Based on the review of the existing literature and the proposals of the multidisciplinary research team, the conceptual model was developed (**supplementary Figure 3**), and the preliminary version of the codebook was derived.[1-4] The input from patients and the expert discussions were designed to elicit concepts related to patient experiences with EoE symptoms to inform an EoE symptom severity instrument development.

Data analysis: We conducted a computer-assisted content analysis according to Mayring using ATLAS.ti software, version 5.0 (ATLAS.ti, GmbH, Berlin, Germany).[20,34] We established definitions and coding rules for each main code category and its sub code categories prior to the coding (see development and description of the code book). The unit of analysis was defined as all words and sentences related to the description of a single symptom or a problem (written within the four lines provided per discomfort). The complete transcripts of surveys, focus groups, and individual patient interviews were read by 2 coders (AMS and ES). As questionnaires were completed in two languages, three coders with proficiency in English and German analyzed the material. Categories were discussed among coders until mutual agreement was reached. One researcher (ES) analyzed all the material using these code categories, and categories were revised or expanded, if necessary, in order to saturate the content of the material provided. As a formative check of reliability, we clarified definitions, as well as new and obsolete codes, until consensus about saturation was reached. The final codes were applied to all the text (**Supplementary Table 3**). As a part of summative check of reliability, the final matching of main code and sub code categories, as well as their validity, were discussed by a research team, and agreement was reached, when opinions differed. Given the fact that Taft *et al.* already described the impact that EoE has on several psychosocial domains, we specifically analyzed the

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transcripts of semistructured interviews for description of the physical complaints and those psychosocial domains related to adaptations to living with dysphagia.[37]

The socio-demographic data were entered in a database created in EpiData, version 3.1 (EpiData Association, Odense, Denmark). Descriptive analyses were performed using Stata, version 11.2 (Stata Corporation, Austin, Texas).

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RESULTS

Response rate, characteristics of the study population

Supplementary Table 4 provides an overview of the socio-demographic characteristics of the study sample overall which consists of patients having participated in the surveys, in the focus group interviews, and in the individual patient interviews. A total of 397 consecutive EoE patients were addressed by treating physicians to participate in the survey in Switzerland and the United States, respectively. Response rates were 19.2 % (55/287 patients) in the United States and 72.7 % (80/110 patients) in Switzerland. The results are based on the responses provided by 135 patients. Of a total of 617 statements, 467 (75.7 %) described symptoms while eating (a statement represents one answer written within the four lines provided per discomfort). Fifty-three patients (39.3%) reported only discomfort related to eating or drinking. For focus groups, 32 Swiss patients were invited with 5 patients declining participation (response rate of 84 %). For semistructured face-to-face interviews, 30 US patients were approached with 6 patients declining participation (response rate of 80%). All patients had confirmed EoE diagnosis at the time of participation in the study.

Qualitative Analysis

Major themes

Three key themes and two subthemes emerged: the definitions of dysphagia and dysphagia characteristics, dysphagia caused by different foods, pills and beverages, behavioral adaptations to living with dysphagia (two subthemes: strategies aimed to avoid impaction and strategies dealing with impaction, once it occurred). The key domains and their relationships are illustrated in **supplementary Figure 4**.

Definition of dysphagia and dysphagia characteristics

In **supplementary Table 5**, sample quotation of the description of dysphagia events and the specific characteristics of these events provided by the patients are shown. Participants described dysphagia in terms of difficulty swallowing, solids/liquids passing slowly or not smoothly, feeling of tightness, and most commonly as impaction events, characterized by food being stuck or lodged in the esophagus or else by choking on food. Dysphagia events were

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described by patients to be occurring in the throat and chest or esophagus. We were able to identify various characteristics and attributes of dysphagia, such as duration, frequency and severity of dysphagia events. The duration of dysphagia events ranges from a few seconds, to minutes, to many hours, especially if impacted food had to be removed by endoscopy. The frequency of dysphagia ranges from “infrequent” events, to those occurring a few times a week, and, finally, to those occurring “every day and every time one eats”. Patients often mentioned that various disease treatments diminished the frequency or the severity of the dysphagia events.

Dysphagia caused by eating different foods, pills and drinking beverages

Patients frequently described dysphagia events caused by eating certain foods, drinking beverages or swallowing pills. In **supplementary Table 6**, the sample quotation of the describing dysphagia events caused by eating foods, swallowing pills and drinking beverages is shown. Of all the foods causing dysphagia, meat was most frequently mentioned, followed by bread and rice. However, other foods, such as uncooked fruits and vegetables, ground meat, French fries and pasta also caused trouble swallowing in patients with EoE. Patients also described dysphagia caused by swallowing large pills. In addition, drinking liquids also caused dysphagia events. Patients were also likely to specify that alcoholic beverages were causing these events. Lastly, patients occasionally mentioned foods that do not cause dysphagia and are easy to swallow.

Patients also used various adjectives to describe foods that cause dysphagia, of these “solid” and “dense” were most frequent, but “heavy”, “tough” or “thick” were also used. Mostly these adjectives were used in the context of dysphagia caused by eating meat, although other foods were also mentioned. Similarly, adjectives “fibrous” and “course” were also frequently used to describe foods causing dysphagia; most frequently these adjectives were used to describe uncooked vegetables, but these were also occasionally used in the context of eating meat. Lastly, the adjective “dry” was frequently used to describe dry foods, such as popcorn and chips, that also caused dysphagia, but this adjective was also frequently used in the context of dysphagia events caused by eating meat.

Behavioral adaptations to living with dysphagia

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Over the years, patients have developed various strategies to avoid impaction events or to deal with them, especially to avoid going for emergency treatment. Examples of these strategies are shown in **supplementary Table 7**. The following strategies for avoiding impaction events were used by EoE patients: food avoidance, food processing, eating carefully / slowly and drinking liquids to wash down the food. Patients mostly avoided eating meat, although rice, bread and vegetables were also described as foods to be avoided. Patients also processed their foods to avoid food impaction events, of which the most common strategy was to cut meat in small pieces before consuming it. Other strategies involved peeling apples before eating them or eating foods with sauces to facilitate swallowing. Patients also described that eating slowly, carefully, taking smaller bites out of their foods and chewing carefully helped them to avoid impaction episodes. Patients also mentioned that eating quickly would lead to dysphagia episodes; we interpreted these statements as indication of eating slowly as strategy to avoid dysphagia. Lastly, many patients mentioned that they nearly always had something to drink during mealtimes. The strategies of dealing with impaction events were also frequently mentioned by the patients. For the purposes of coding, these strategies had to be used in the context of impaction events, described as foods “sticking” or “lodging itself” in the chest, esophagus or throat. These strategies included trying to induce “choking”, “coughing” or vomiting of impacted food. Waiting for impaction to resolve itself was also a very common strategy. Patients also used liquids to wash down impacted food. This strategy was different from the strategy of avoiding impaction by drinking liquids, which was defined as something occurring regularly when eating. Liquids were frequently described as either helping to resolve impaction events or not. Patients also used other strategies, like relaxing, walking and doing physical activity, such as jumping to trying to resolve the impaction event.

Other themes

Other themes identified in the process of our analysis included swallowing-associated pain, non-swallowing associated pain, allergic reactions related to food intake, gastro-esophageal reflux disease-like symptoms and treatments. In **supplementary Table 8**, the sample quotation for these themes is shown.

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Patients mentioned that swallowing and particularly episodes of impaction were associated with pain mostly occurring in the chest / esophagus, although sometimes also in belly / stomach. Characteristics of these swallowing-associated pain episodes, such as description of pain, frequency, duration or severity were also described. Similarly, non-swallowing associated pain (and its characteristics), defined for the purposes of coding as pain occurring outside the time of eating or drinking and not occurring at the time of impaction, was also mentioned by the patients. Patients also described allergic reactions related to food. For the purposes of coding, this was defined as itching, swelling or irritation of the mouth. Patients described this occurring when consuming fruits, dairy and wheat products, such as bread and beer. Lastly, patients mentioned experiencing gastro-esophageal reflux disease-like symptoms, including heartburn and acid regurgitation, often described as “reflux” or “acid reflux”.

As treatments, patients mentioned endoscopic desimpactions, dilation, as well as treatments with anti-acid / gastro-esophageal reflux medications and swallowed topical corticosteroids. Mostly patients mentioned treatment with medications and dilation in the context of feeling better after these treatments, although side-effects of corticosteroid intake, such as fungal infection, were also described. In case of food impactions requiring endoscopic removal, these were mentioned in the context of being unable to swallow one’s saliva and worrying, fearing or panicking during these extreme episodes. Other treatments were mentioned in connection with other allergic disorders, such as asthma.

Although assessing the themes related to psychosocial function lying outside of disease-modifying behavior was outside the scope of our study, patients mentioned that they were concerned, often panicking, when experiencing episodes of food impaction. Patients also mentioned that they were concerned about meal times both at home and when eating out, especially in the presence of company.

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Supplementary Table 1: Open-ended questions used in the patient survey to gain input on eosinophilic esophagitis-related symptoms.

Question	Wording of the question
Open-ended question 1: Discomfort while eating	Please describe any discomfort that you have experienced while eating or drinking that is due to eosinophilic esophagitis.
Open-ended question 2: Discomfort not related to eating or drinking	Please describe any discomfort related to eosinophilic esophagitis that occurs at times when you are not eating or drinking. In other words, symptoms that occur between meals.
Defining the question	*Please try to explain your symptoms as precisely and clearly as possible.*
Giving examples for the definition	*For example: If you have pain, where exactly is the pain? In your throat, stomach, chest, etc.? How long does the pain last? How intense is the pain? How often do you have pain, etc.?*
Explaining the procedure	*If you have more than 6 symptoms, please describe them in detail on a separate sheet of paper.*
Explaining the severity scoring for each symptom	*A score of 0 (not annoying) indicates that you don't have the symptom, while a score of 10 (very annoying) indicates that the symptom is very strong, almost unbearable.*
Giving an example how it would look like when being filled	**Supplementary Figure 2** (example for question 1)

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Supplementary Table 2: Semi-structured questions for focus groups. Abbreviation: EoE, eosinophilic esophagitis.

Question 1:	How would you describe to someone else what EoE is? [a]
Question 2:	How old were you when you were diagnosed with EoE?
Question 3:	What sources did you use to learn more about EoE? [a]
Question 4:	What symptoms did you have because of your EoE? Please describe first the symptoms that occurred during meal times and then the symptoms that occurred independent of meal times.
Question 5:	Have you avoided or do you avoid certain foods?
Question 6:	Have you modified/changed certain foods?
Question 7:	Have you eaten longer than other people? If yes, how long do you need to eat a meal?
Question 8:	What impact EoE has on your professional life?
Question 9:	What impact EoE has on your social life?
Question 10:	What impact EoE has on your activities, including sport, in your spare time?
Question 11:	What was your experience with endoscopies and foods that got stuck? [a]
Question 12:	Since being diagnosed with EoE, have you told anyone about it? [a]
Question 13:	Did you undergo allergy testing? [a]
Question 14:	What are your concerns regarding the long-lasting evolution of your EoE? Do you worry about cancer? Do you worry about new episodes of foods getting stuck? [a]
Question 15:	What have your experiences been with swallowed steroids? Diets? Stretching of the esophagus? [a]
Question 16:	What is the most difficult thing about having EoE? [a]
Question 17:	Compared to any other current medical problems you once had, where does EoE stand? [a]

[a] These questions were adopted or reproduced directly from a study by Tufts *et al.*[47] with permission of the senior investigator.

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Supplementary Table 3: Coding tree.

Main code	Sub codes
Dysphagia	• Definition, impaction • Definition, tightness • Definition, difficulty swallowing • Definition, solids / liquids passing slowly or not smoothly • Location, throat • Location, chest/esophagus • Duration • Frequency • Severity • Unable to swallow/build-up of saliva
Dysphagia caused by different foods, pills and beverages	• Description, compact / solid • Description, dry • Description, fibrous • Foods specified, meat • Foods specified, bread • Foods specified, pill • Foods specified, raw fibrous • Foods specified, rice • Foods specified, French fries • Foods specified, pasta • Other / unspecified • Beverages specified, alcohol-containing • Beverages, other / unspecified
Foods not causing dysphagia	
Strategies avoiding impaction	• Food avoidance • Food processing • Eat slowly / Trigger – hasty eating • Washing food down – helps • Washing food down – does not help
Strategy dealing with dysphagia event	• Choke / cough impacted food out • Vomit impacted food • Waiting until impaction resolves itself • Washing food down – helps • Washing food down – does not help • Other strategies mention / not specified
Swallowing-associated pain	• Location, throat • Location, chest/esophagus • Location, belly/stomach • Description, burning • Duration • Frequency • Severity • Circumstances, with food impaction • Circumstances, with food but no impaction • Circumstances, with beverages

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Non-swallowing-associated pain

- Circumstances
- Description
- Location, chest
- Location, belly/stomach
- Location, throat
- Duration
- Frequency
- Severity

Allergic manifestations

- Allergies related to food, location, throat
- Allergies related to food, location, esophagus
- Allergies related to food, duration of event
- Foods causing allergies
- Afflictions mentioned, allergic reactions not for food
- Symptom, itching/scratching/irritation
- Symptom, throat swelling
- Symptom, tightness

Treatments

- Anti-acid/GERD medications
- Dilation
- Endoscopic desimpaction
- Swallowed topical corticosteroids
- Diet
- Not specified
- Treatments for concomitant allergic diseases

Gastro-esophageal reflux disease-like symptoms

- Definition, heartburn
- Definition, acid regurgitation/reflux
- Definition, gastro-esophageal reflux disease
- Location, chest
- Circumstances
- Duration
- Frequency
- Severity
- Pain

Other concerns

- Symptoms, sweating
- Symptom, vomiting
- Symptom, problems breathing / choking
- Symptom, pressure on the chest
- Symptom, nausea
- Symptom, foreign body sensation
- Symptom, clearing ones throat
- Symptom, belching/gas/burping
- Overall duration of disease / symptoms

Psychological concerns

- Psychological factors, worry about potential impaction
- Psychological factors, feelings during impaction
- Psychological factors, reduced enjoyment of mealtimes
- Psychological factors, other

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Supplementary Table 4: Characteristics of the study population.

Source of input	**Patient survey**				**Focus Groups**		**Interviews**	
Provenience	**Switzerland**		**USA**		**Switzerland**		**USA**	
Patient numbers	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Responders	80	100	55	100	27	100	24	100
Sex								
Men	62	77.5	31	56.4	19	70.4	17	70.8
Women	18	22.5	24	43.6	8	29.6	7	29.2
Age at time of questionnaire completion (years)	43.4 ± 14.4		43.2 ± 10.6		45.8 ± 14.5		39.1 ± 11.4	
Education [1]								
Compulsory schooling [2]	1	1.2	0	0	0	0	0	0
Vocational training [3]	35	43.7	5	9.1	12	44.4	0	0
Upper second. education [4]	31	38.8	23	41.8	12	44.4	3	12.5
University education [5]	13	16.3	27	49.1	3	11.2	21	87.5
Migration								
No migration background	74	92.5	54	98.2	27	100	24	100
Migration background	6	7.5	1	1.8	0	0	0	0

Abbreviation: N = Number of individuals

[1] Education: Systems are different in Switzerland and the USA. We compared the different levels according the International Standard Classification of Education (ISCED).

[2] Basic education: in both countries 9 years (ISCED codes 1 - 2).

[3] Secondary education: high school; vocational training; apprenticeship; grammar school (leads in Switzerland to a “Maturity degree” and is the regular pathway to university education); teachers’ college (was in Switzerland the regular pathway to be a primary school teacher until very recently) (ISCED codes 3 - 4).

[4] First stage tertiary education: Switzerland: bachelor’s degree, or additional schooling, that leads to higher degrees/managerial jobs in specific professions, e.g. in economics, social work, engineer, journalist, etc. USA: some college but no degree, associate’s degree, bachelor’s degree (ISCED codes Switzerland: 5.1 - 5.6, 5.8; USA: 5.1 - 5.3).

[5] University education: University degree, e.g. master’s degree, doctorate degree, medicine/MD, law/JD/LLB (ISCED codes Switzerland: 5.7, 5.9 - 5.14, 6; USA: 5.4 - 5.8, 6).

[6] Migration background defined as: participant moved to Switzerland/USA after birth, or was not a Swiss/US citizen at the time of the questionnaire completion, or became Swiss/US citizen after birth.

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Supplementary Table 5: Dysphagia and its characteristics.

Definition of dysphagia			
Impaction	**Tightness**	**Difficulty swallowing**	**Solids/liquids passing slowly or not smoothly**
• There are times when I will eat sandwiches and bites will get stuck for about 30 seconds.	• When I eat red meat, I will occasionally have a feeling of tightness or impaction.	• Sometimes eating chicken or other meats is tough to swallow.	• When I eat chicken I feel it either slowly go down or get stuck in my throat.
• When taking medication sometimes the pills get temporarily stuck in my throat.	• When I eat red meat, I feel a tightness in my throat - often times I need to walk around and swallow continuously to allow swallowing the food.	• When eating sometimes just have a hard time swallowing. Throat does not clog but just closes enough to make eating and drinking difficult.	• Sometimes meat or very heavy foods do not go down smoothly.
• Sometimes when I eat bread or meat it will become lodged in my esophagus and takes a long time (> 5 min) to completely be swallowed (move down into stomach).	• Prior to treatment I would experience a painful and complete constriction of my throat, a complete choking sensation. Nothing would relieve it, only a few minutes for it to clean.	• Symptoms are better or less obvious now that I take Nexium a day. Don't seem to choke or have as much difficulty while swallowing after eating.	• Earlier, when I was experiencing symptoms, I had trouble swallowing. Things, especially sandwiches, would get "stuck" or slow down before getting to my stomach.
• When I eat rice, I have difficulty swallowing or sometimes it feels like it gets stuck in my throat.	• Sometimes when I eat, I feel a tightness in my upper chest, back of throat. I drink a lot of water virtually every time.	• I have trouble swallowing - very, very painful and many choking experiences.	• When I eat at every meal, it doesn't matter what type of food, I notice that the food goes down the esophagus somewhat slowly.
• Most of my symptoms are related to choking on foods - very painful.		• If I am very stressed or upset, I find some difficulty in swallowing liquids.	

Dysphagia characteristics			
Dysphagia duration	**Dysphagia frequency**	**Dysphagia severity**	**Dysphagia Location**
• When I eat food (various things) sometimes it gets stuck in my throat for a few seconds, then goes down.	• Tightness in my throat when eating hamburgers, sandwiches too quickly. Infrequent symptoms.	• Symptoms are better or less obvious now that I take a Nexium a day. Don't seem to choke or have as much difficulty while swallowing after eating.	• Esophagus: Sometimes when I eat bread or meat it will become lodged in my esophagus and takes a long time (more than 5 min) to completely be swallowed (move down into stomach).
• When I eat bread (or bagels) I feel a tightness in my throat / upper chest. It usually goes away after 20-30 seconds. I stop eating and focus on relaxing and may drink water to make it go away.	• Prior to treatment I would experience a painful and complete constriction of my throat, a complete choking sensation. Nothing would relieve it, only a few minutes for it to clean. This would happen relatively often 1 or two times per week after eating "dense" foods.	• Occasionally when I eat, I feel a tightness that is severe. I hope when I drink something that it will go away.	• Throat /Chest: Pork (especially pork chops) always cause tightness in throat / chest. It lasts 30+ seconds but my throat/chest will feel sore for a while.
• I have to take smaller bites, wait until it [food] goes down then I can eat again. It takes about 5 seconds between bites.	• Most frequently when I have a problem the food will get stuck for 10-20 seconds. Sometimes I try to get it down by swallowing water which may or may not work. There is a slight discomfort and tightness in my esophagus but I can always tell that it will go down and eventually it does go down by itself. I can usually start eating again after that. If I have a second incident during the same meal, I will stop eating. That occurs maybe 50% of the time.	• Most frequently when I have a problem the food will get stuck for 10-20 sec. Sometimes I try to get it down by swallowing water which may or may not work. There is a slight discomfort and tightness in my esophagus but I can always tell that it will go down and eventually it does go down by itself. I can usually start eating again after. If I have a second incident during the same meal, I will stop eating. I rate this symptom as a 4 [on a scale from 0 to 10] unless it reoccurs during the same meal, then it is a 6.	• Throat: Pieces of meat have severely gotten stuck in my throat producing the feeling of choking - but obviously not in the airways. Happens several times per year.
• When eating meat, I would have a problem if I swallowed too big of a bite. I would get stuck in my throat and sometimes be stuck for hours. 80% of the time it would only be stuck for a few minutes.	• My most recent symptom is various types of solid foods getting stuck in my throat. It will not go down with dry swallowing, but will go down with one to two drinks of liquid. It happens once or twice a week.		• Throat: Dry chicken (white meat) causes tightness in my throat / chest that lasts 10-20 seconds.

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Supplementary Table 6: Dysphagia caused by different foods, pills and beverages.

Meat	Pills	Bread	Other foods / unspecified
• Periodically meat will remain in my esophagus for several minutes and coughing or throwing up seem to be the only solution.	• Difficulty swallowing pills due to a history of dysphagia with larger pills. More a mental annoyance that I get concerned about swallowing pills. I take a “gummy” chewable multivitamin instead of a pill.	• Sometimes when I eat bread or meat it will become lodged in my esophagus and takes a long time (more than 5 minutes) to completely be swallowed (move down into stomach).	• When I eat items like crackers, peanuts, popcorn etc. - the material that’s finely chewed gets stuck in my throat. This material is not easily washed down with water.
• Sometimes eating chicken or other meats is tough to swallow.	• When I take pills, they must be very small or it will get stuck in my throat. Nothing like water helps, so I must try to throw up the pill.	• When I eat meat or breads, they are hard to pass down my esophagus. My passage becomes restricted and I am forced to wait until the food passes (30 min - 3 hours) or try to physically throw up the blockage.	• Earlier, when I was experiencing symptoms, I had trouble swallowing. Things, especially sandwiches, would get “stuck” or slow down before getting to my stomach. They would clear with liquids.
• Sometimes when I eat meat, I feel a scratch in my throat or a light tightness that remains until I wash it down with a fluid.	• Cannot swallow pills – that is how I first came across my problem, got stuff in my esophagus and had severe choking for several hours..	• When I eat food (various things) sometimes it gets stuck in my throat for a few seconds and then goes down (examples of foods may be bread).	• When I eat potato chips, sometimes chip fragments hang up in my throat. Generally, they pass naturally.
• When I eat meat too much too quickly I have to wait to let the food pass.			

Pasta	Raw fibrous foods	Rice	Ground meat
• When I eat bread or pasta, especially if I don’t chew it into small pieces, it gets stuck in my upper chest / just past throat and I wait 15 - 20 seconds for it to pass before I can drink water. It often causes tightness in my chest.	• When I eat carrots, I feel them stick at the top of my throat until I wash them down with water.	• When I eat rice, I have difficulty swallowing or sometimes it feels like it gets stuck in my throat.	• Tightness in my throat when eating hamburgers, sandwiches too quickly. Infrequent symptoms.
• If I eat pasta (wheat) with a thick sauce or lots of cheese it feels like a sticky lump in my throat and lasts 30+ seconds.	• Have to peel apples to eat.	• When I eat rice and it is dry it gets stuck so I stay away.	• In the past I have had tightness in my throat while eating various things like chicken, hot dogs, steak, hamburger, etc. Increases with fluid. Sometimes lasts 5 seconds to 10 min or until food passed through.

French Fries	Beverages	Alcoholic beverages
• Throat - I can’t swallow pills and certain foods may get stuck like French fries. There is no pain. I chew my food more than most and can’t drink liquids as fast (this is without stretching and medication – fluticasone).	• When I drink diet soda I sometimes get a painful lump in my chest - it feels like the liquid gets stuck.	• The difficulties swallowing have subsided in the past two years and do not currently exist. In the past, I had problems when eating rice, meat and drinking wine.
• French fries and peanuts are difficult to swallow and require water to wash down the food.	• When I drink liquids quickly, the liquid often catches in my throat.	• Sometimes, when drinking a glass of wine, it feels as if my esophagus narrows down.
• Beyond steak and French fries, I can’t identify certain foods as being special offenders.	• Several times per week, even water doesn’t go down smoothly.	• When I eat fast, bread, meat or while drinking alcohol, I sometimes get food stuck.

Description, dense / solid	Description, dry	Description, course / fibrous
• When I eat certain foods my throat ‘closes’ - “clogs” - so that I can’t swallow or eject it. Not certain what foods cause this but typically steak or heavier meats. Have to wait for clog to subside or have emergency treatment.	• When I eat chicken and it is dry, iIt sticks in my throat and I must drink and cough to get it moved.	• Coarse foods like raw vegetables like carrots, broccoli get stuck in my throat, so I avoid them. It is very difficult to dislodge food stuck in my throat, drinks or coughing don’t work much.
• Also could not eat solid anything for several	• When I eat rice and it is dry it gets stuck so I stay	• I also could no longer swallow fibrous vegetables,

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months.	avoid it.	such as, for example, spinach, beans, celery, etc.
• If I am off my meds, it feels like food gets caught in my throat with dense foods e.g. meats.	• When I eat dry food (lately corn chips), the food sometimes gets hung up in my throat. I have to wash it down with water.	

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Supplementary Table 7: Behavioral adaptation to living with dysphagia.

Strategies avoiding impaction

Food avoidance	Food processing	Eating slowly (Trigger, hasty eating)	Washing food down
• After 15+ esophageal dilations, I still have some problems eating. Always have to have water to wash food down. Have to chew a lot and still take small bites. Certain foods I still stay away from.	• When I eat steak, I have to cut it into tiny pieces for fear that it may get stuck in my throat.	• When I eat, at every meal, it doesn't matter what type of food, I notice that the food goes down the esophagus somewhat slowly. I have to take smaller bites, wait until it goes down then I can eat again. It takes about 5 seconds between bites. No pain at all.	• Always have water with me just in case. Have trouble with popcorn, nuts, corn, tough meat, thick cheeses, bread. Sweets go down easy, except caramel – too thick. Have not had peanut butter in over 15 years.
• I avoid the steak in pepper and all steak for that matter because I feel it is tough to swallow.	• Have to peel apples to eat.	• When going out to eat, have to be careful what I order, due to eating so slow and just being careful on food going down. Most of the time, I have to take at home half or three quarters of the meal because everyone else is done.	• Whenever I eat anything, I always have to have something to wash the food down.
• When I eat rice and it is dry it gets stuck so I avoid it.	• Eat only foods with sauces, so that I can easily swallow them.	• Always have a drink while eating and almost have to eat carefully, slowly.	• Always have to have water to wash the food down.
• Coarse foods like raw vegetables like carrots, broccoli get stuck in my throat, so I avoid them.			

Strategies dealing with impaction

Choke / cough / vomit impacted food out	Waiting until impaction resolves itself	Washing food down - helpful	Washing food down - not helpful	Other strategies mentioned / not specified
• If coughing and drinking doesn't dislodge food and I can't swallow my saliva, after 10min I panic and will try to induce vomiting to dislodge food.	• When I eat meat or breads, they are hard to pass down my esophagus. My passage becomes restricted and I am forced to wait until the food passes (30 min - 3 hours) or try to physically throw up the blockage. When blockage occurs I am subject to spit a lot of saliva.	• My most recent symptom is various types of solid foods getting stuck in my throat. It will not go down with dry swallowing, but will go down with one to two drinks of liquid. It happens once or twice a week. It will happen even with a breath mint that I've started to chew.	• When I take pills, they must be very small or it will get stuck in throat. Nothing like water helps, so I must try to throw up the pill.	• There are times when I will eat sandwiches and bites will get stuck for about 30 seconds. Repeated swallowing and walking tend to help.
• Periodically meat will remain in my esophagus for several minutes and coughing or throwing up seem to be the only solution.	• When I eat certain foods my throat "closes" - "clogs" - so that I can't swallow or eject it. Not certain what foods cause this but typically steak or heavier meats. Have to wait for clog to subside or have emergency treatment.	• When eating I use to feel like the food would not go all the way down & I had to drink something to wash the food down. Discomfort ended once food was washed down.	• When I eat items like crackers, peanuts, popcorn, etc. - the material that's finely chewed gets stuck in my throat. This material is not easily washed down with water.	• Food sticks near my neck, at the base of my throat. I have to slap my chest or jump up and down to move it.
• I have had 3 impactions that I now am aware of. I felt like I was chocking. My throat was tight. After several times throwing up, I felt better but was unable to eat. Afraid I couldn't swallow.	• I have had two total food impactions that have had to be removed by endoscopy. Both times not even liquids would go down and I had to spit up my swallowed saliva. Before going to the hospital, I tried the Heimlich and	• When I eat chicken and it is dry. It sticks in my throat and must drink and cough to get it moved.	• I have found that sucking on ice works better than liquid which can make it worse.	

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waited several hours to see if the food would go down on its own.

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Supplementary Table 8: Other themes.

Allergic reactions related to food	Swallowing-associated pain	Non-swallowing-associated pain	Gastro-esophageal reflux disease symptoms
• When I eat, most foods such as fruits, I feel my throat swelling, ears itching, throat itching as well.	• I have trouble swallowing - very, very painful and many choking experiences.	• Stomach upset. The pain can last several hours. The pain is about a 2 to 8 [on a 10 point scale] depending on the type of food, but it's annoying. The pain may last half an hour or longer. I avoid these foods.	• I sometimes experience heartburn and reflux as a result of the food that I eat.
• When I eat foods with my specific allergen (dairy), or foods that have residuals on them, I have trouble swallowing, and my throat feels swollen shut.	• When I drink diet soda I sometimes get a painful lump in my chest - it feels like the liquid gets stuck. It burns and is very painful.	• Prior to be diagnosed I used to get severe pain in the middle of my chest right at the bottom of my rib cage. The pain would last all day and was very annoying. Was very hard on me and my family.	• When lying down at bedtime or during sleep I am sometimes awakened with heartburn, reflux and stomach pain.
• … many fresh fruits and vegetables irritate my mouth, throat and stomach…	• Swallowing non-stick foods gives me pain in the chest.	• A reoccurring chest pain / cramp - comes on suddenly.	• I occasionally have acid reflux, mostly at night.
	• I have chest pain from food blockage when I eat the certain foods that block my esophagus. Pain is mild but goes away once food passes.		

Treatment

Endoscopic desimpaction	Dilations	Anti-acid/GERD medications	Swallowed topical corticosteroids
• Three times in the last 10 years I have gone to the hospital after many attempts at freeing meat - the only solution then (after several hours) is an upper endoscopy.	• About a year ago, I had an endoscopy and stretching, which helped for a few months.	• Before starting daily pepcid [Famotidine],) doses (20mg), I had trouble swallowing many types of meats and dry foods. Sometimes I would have to force the food up, or drink water to force the food down.	• I'm currently using the Fluticasone inhaler, so I don't have any symptoms recently.
• If food does get caught, there is a burning where my throat hits my stomach. I have been scoped in the ER 3x because of this issue. I have had 9 total upper GI's because of this.	• I have had my throat stretched twice in the past. The first time was a piece of steak lodged in my throat for 24 hrs. It was then removed prior to the first balloon dilatation. When it was lodged, no liquid would pass through.	• When I used to eat chicken or other drier cuts of meat, regardless of the size of bite I take on, how much I chew it up, I would have difficulty swallowing it and need to wash it down immediately with water. Since going on an anti-acid reflux regimen, I have not experienced this problem (only on exceptionally rare occasion).	• Before I regularly used Flovent [fluticasone], I occasionally was unable to swallow food - most often, meat - that was lodged in my throat. When it happened, I often had to go to the emergency room to dislodge the food.
• I have had two total food impactions that have had to be removed by endoscopy. Both times not even liquids would go down and I had to spit up my swallowed saliva.	• After 15+ esophageal dilations, still have some problems eating. Always have to have water to wash food down. Have to chew a lot and still take small bites. Certain foods I still stay away from.	• I used to get periodic (i.e. monthly) tightness in the center of my chest- a stabbing pain. It would last anywhere between 5-15 minutes. I have not experienced this since taking anti-acid medication daily.	• I can't swallow pills and certain foods may get stuck like French fries. There is no pain. I chew my food more than most and can't drink as fast (this is without stretchings and medication – fluticasone).

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Supplementary Figure 1: Patient input.

Supplementary Figure 2: Extract of the survey to gain patient input on EoE-related symptoms.

Supplementary Figure 3: Conceptual model of the study.

Supplementary Figure 4: Key domains of EoE-related symptoms.

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APPENDIX 2: The data obtained from the Visual Dysphagia Question (VDQ) were used to create a composite score. The degree of perceived difficulties when eating a given food consistency was graded between 0 for 'No difficulties' and 3 for 'Severe difficulties'. These grades for each food consistency were summed in the numerator of the score and divided by the maximum sum of grades that could be attained for each subject, which depending on the number of food consistencies consumed by a subject in a given recall period.

For the Avoidance, Modification and Slow Eating (AMS) score, answers to three items exploiting the pattern of behavioral adaptation were scored for each food consistency consumed by the subject. If patients recorded no behavioral changes, a score of 0 was assigned; when reporting eating slower than others, a score of 1 was assigned; when reporting the modification of certain food consistencies, a score of 2 was assigned; when reporting both eating slower than others and modifying certain food consistencies, a score of 3 was assigned; if the subject completely avoided one or several food consistencies due to EoE symptoms, a score of 5 was assigned. Scores for all consumed food consistencies were summed up in the numerator and divided by the maximum sum of scores that could be attained by a given subject.

The VDQ and AMS scores range from 0 to 10.

Below we provide a sample calculation of VDQ (A) and AMS (B) scores for a patient X, who reported that he/she ate all eight food consistencies and expected to experience moderate difficulties eating solid meat, mild difficulties eating dry rice, ground meat and fresh white untoasted bread and French fries, and no difficulties eating soft foods, grits/porridge/rice pudding and raw fibrous foods. In the past 7 days, the patient reported that he/she modified solid meat and French fries, but not other foods. The patient did not avoid any foods. However, the patient ate solid meat, ground meat, fresh white untoasted bread and French fries slower than other people eating these same foods, but not other foods. The verb 'modified' was illustrated with the following examples: put the food in the blender, cut it in small pieces, dunk it in liquid or mash it. The patient X had a VDQ score of 2.5 and an AMS score of 2.

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A. VDQ score:

$$VDQ = \frac{N_1 \times 1 + N_2 \times 2 + N_3 \times 3}{D \times 3} \times 10$$

Where:

1. N_1 = number of food consistencies graded with 'Mild difficulties'
2. N_2 = number of food consistencies graded with 'Moderate difficulties'
3. N_3 = number of food consistencies graded with 'Severe difficulties'
4. D = number of relevant food consistencies (different than 'Not applicable')

For patient X,

$N_1 = 4$
$N_2 = 1$
$N_3 = 0$
D = 8

$$VDQ = \frac{4 \times 1 + 1 \times 2 + 0 \times 3}{8 \times 3} \times 10 = 2.5$$

B. AMS score:

$$AMS = \frac{N_1 \times 1 + N_2 \times 2 + N_3 \times 3 + N_4 \times 5}{D \times 5} \times 10$$

Where:

1. N_1 = number of food consistencies with 'Yes' to 'Eating slowly' only
2. N_2 = number of food consistencies with 'Yes' to 'Modification' only
3. N_3 = number of food consistencies with 'Yes' to both 'Eating slowly' and 'Modification'
4. N_4 = number of food consistencies with 'Yes' to 'Avoidance' only
5. D = number of relevant food consistencies (different than 'Not applicable')

For patient X,
$N_1 = 2$ (ground meat and fresh white untoasted bread)
$N_2 = 0$
$N_3 = 2$ (solid meat and French fries)
$N_4 = 0$
D = 8

$$AMS = \frac{2 \times 1 + 0 \times 2 + 2 \times 3 + 0 \times 5}{8 \times 5} \times 10 = 2$$

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APPENDIX 3: SUPPLEMENTARY TABLES AND FIGURES.

Supplementary Table 9: Description of the physician and histology instruments.

	Physician instrument	***Histology instrument***
Derivation	Delphi	Delphi
Completed by	Physician and study coordinator (if applicable)	Pathologist
Number of items	39 close-ended items	22 close-ended items
Type of items	5 items: dichotomous scale 1 item: Likert scale 21 items: multiple non-hierarchical options 12 items: multiple hierarchical options	3 items: dichotomous scale 0 items: Likert scale 13 items: multiple non-hierarchical options 6 items use multiple hierarchical options
Average completion time	30 minutes	10 minutes (without histologic evaluation)
Overall assessment variable	Physician global assessment of EoE activity (11-point Likert scale)	
Domains	***1. EoE treatment strategies*** a. treatment with steroids b. elimination diets c. dilation ***2. Blood biomarkers*** a. eosinophil serum levels b. IgE c. IL-5 ***3. Endoscopic features*** a. endoscopic features described by Hirano *et al.*[34] with some modifications ***4. GERD*** a. presence of GERD b. GERD-like symptoms c. Barrett's esophagus d. hiatal herniation e. fundoplication surgery ***5. General*** a. qualification and experience of the participating gastroenterologists	***1. Distal esophagus*** a. eosinophil peak number b. distribution of eosinophils in a high power field c. percentage of high power field covered by the tissue d. sample orientation e. distribution of inflammation f. presence of abscesses g. basal layer enlargement h. lamina propria fibrosis ***2. Proximal esophagus*** same as above ***3. General*** a. qualification and experience of the participating pathologist

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Supplementary Table 10: Symptom severity and behavioral changes when eating foods of eight distinct consistencies as assessed by the visual dysphagia question (n = 153).

Characteristic	*Solid meat*		*Ground meat*		*Fresh bread*		*Dry rice*		*Raw food*		*French fries*		*Grits, porridge*		*Soft foods*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Difficulties eating																
No	37	24.2	81	52.9	69	45.1	69	45.1	85	55.6	89	58.2	127	83.0	141	92.2
Mild	56	36.6	37	24.2	45	29.4	52	34.0	39	25.5	39	25.5	13	8.5	6	3.9
Moderate	39	25.5	26	17.0	24	15.7	22	14.4	16	10.5	11	7.2	2	1.3	1	0.7
Severe	21	13.7	8	5.2	8	5.2	8	5.2	11	7.2	8	5.2	6	3.9	5	3.3
Don't know	0	0.0	0	0.0	6	3.9	1	0.7	1	0.7	4	2.6	4	2.6	0	0.0
Missing	0	0.0	1	0.7	1	0.7	1	0.7	1	0.7	2	1.3	1	0.7	0	0.0
Behavior																
Modification	23	15.0	6	3.9	7	4.6	5	3.3	10	6.5	7	4.6	0	0.0	1	0.7
Avoidance	17	11.1	13	8.5	11	7.2	16	10.5	18	11.8	7	4.6	5	3.3	1	0.7
Eating slower	103	67.3	65	42.5	54	35.3	51	33.3	47	30.7	36	23.5	9	5.9	8	5.2

The eight food consistencies and examples of foods to illustrate those are as follows: 1) solid meat (steak, chicken, turkey lamb), 2) soft foods (pudding, jelly, apple sauce), 3) dry rice or sticky Asian rice, 4) ground meat (hamburger, meatloaf), 5) fresh white untoasted bread or similar foods (doughnut, muffin, cake), 6) grits, porridge (oatmeal), or rice pudding, 7) raw fibrous foods (apple, carrot, celery) 8) French fries. The sample calculation of the visual dysphagia question and food avoidance, modification and slow eating scores are provided in **Appendix 2**.

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Supplementary Figure 5: Timetable for the adult EEsAI study.

Supplementary Figure 6: This figure illustrates the relationship between the Patient Global Assessment of EoE severity and the PRO components that were chosen for the construction of the PRO score. The data for 7-day recall period are shown. Abbreviations: TS, trouble swallowing.

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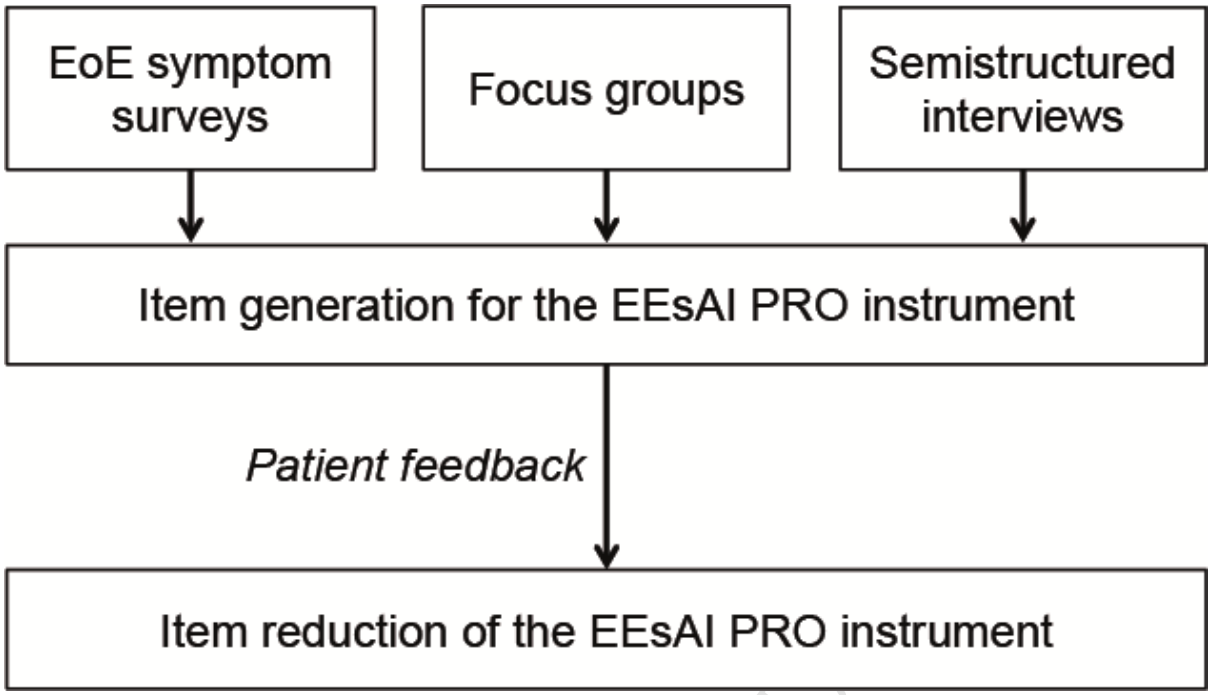

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QUESTIONS RELATING TO EOSINOPHILIC ESOPHAGITIS

DISCOMFORT WHILE EATING

Please describe any discomfort that you have experienced while eating or drinking that is due to eosinophilic esophagitis.

Please try to explain your symptoms as precisely and clearly as possible. For example: If you have pain, where exactly is the pain? In your throat, stomach, chest, etc.? How long does the pain last? How intense is the pain? How often do you have pain, etc.?

If you have more than 6 symptoms, please describe them in detail on a separate sheet of paper.

A score of 0 (not annoying) indicates that you don't have the symptom, while a score of 10 (very annoying) indicates that the symptom is very strong, almost unbearable.

Example:

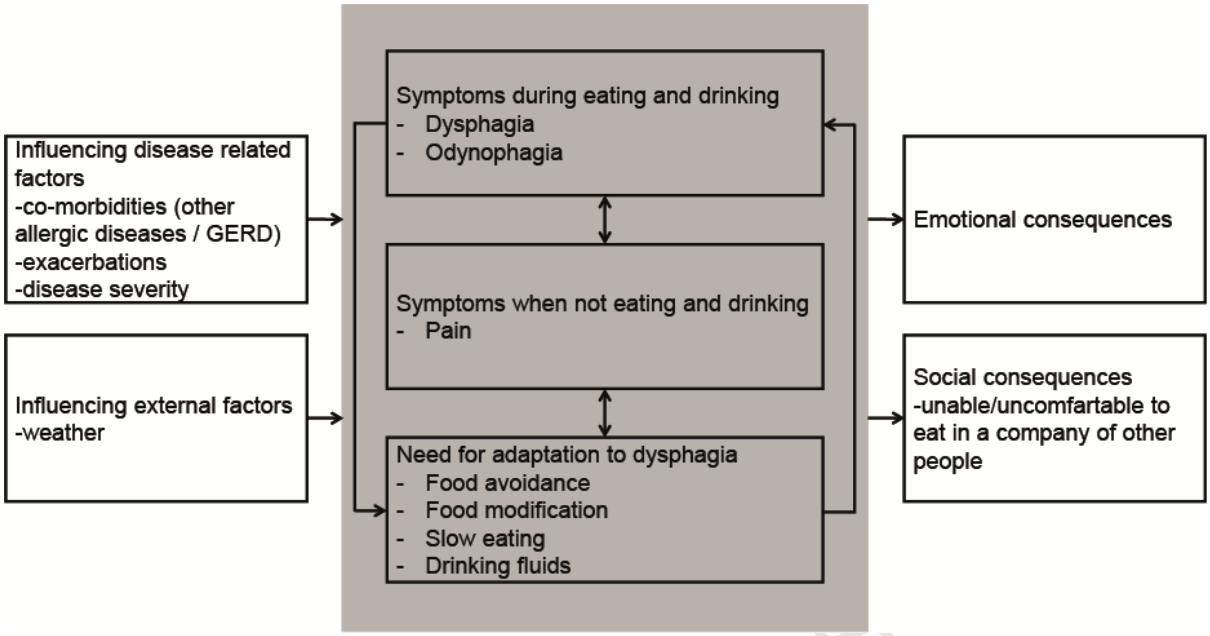
When I eat French fries, I feel a tightness in my throat that lasts 10-20 seconds; afterwards, I have to drink water to wash down the food.

	0	1	2	3	4	5	6	7	8	9	10	
Not annoying	☐	☐	☐	☐	☑	☐	☐	☐	☐	☐	☐	very annoying

	0	1	2	3	4	5	6	7	8	9	10	
Not annoying	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	very annoying

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT



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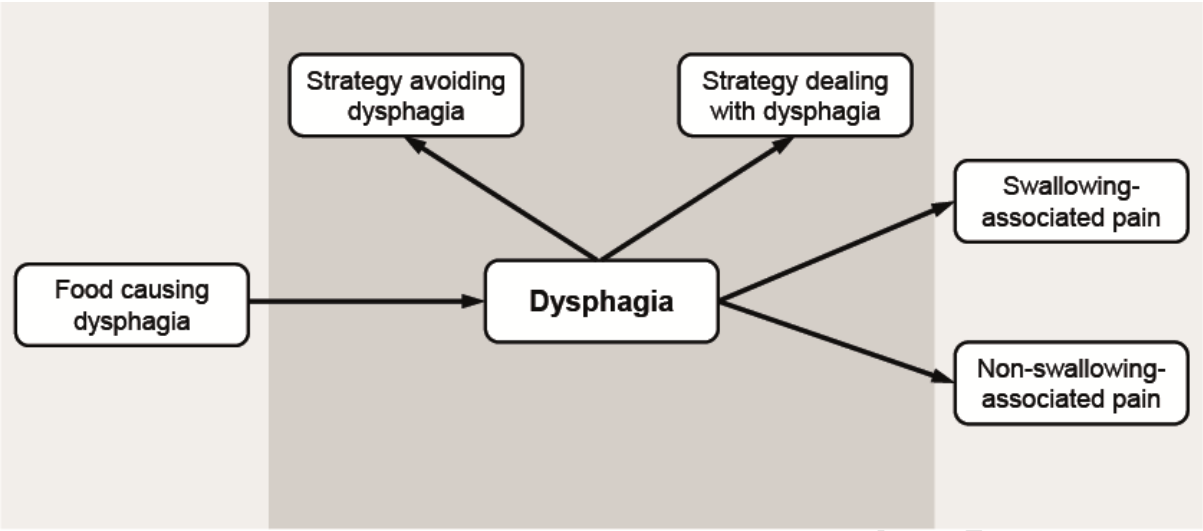

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Study phase	
Phase 1: Candidate item selection • Item generation • Item reduction • Instrument formatting/piloting	Patient Input Delphi process
Phase 2: EEsAI derivation • Removal of superfluous items • Item weighting	Group 1: 153 adult EoE patients
Phase 3: EEsAI validation • Score validation	Group 2: 120 adult EoE patients

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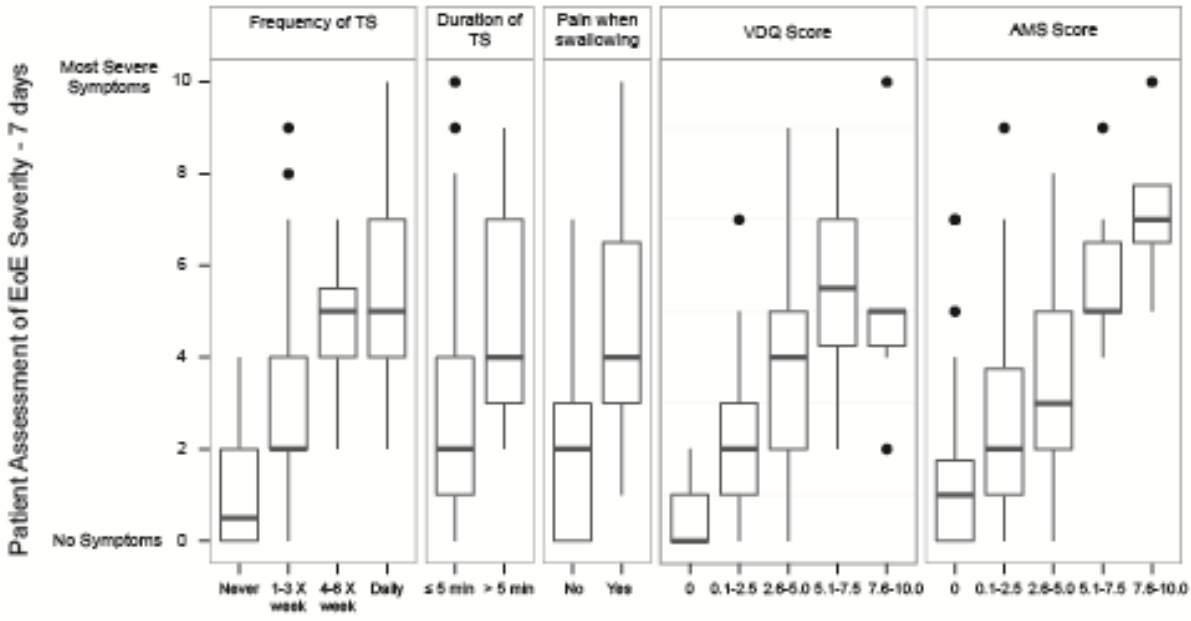

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