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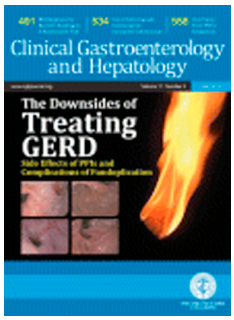

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Sex impacts disease activity but not symptoms or quality of life in adults with eosinophilic esophagitis

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Abbrevation:

EEsAI: symptom-based eosinophilic esophagitis Activity Index

EoE: Eosinophilic esophagitis

Eos/hpf: Eosinophils per high-power field

EREFS: Endoscopic reference score

GERD: Gastroesophageal reflux disease

EoE-QoL-A: Eosinophilic esophagitis-specific quality of life in adults

PEC/hpf: Peak eosinophil count per high power field

PPI: Proton pump inhibitor

PRO: Patient-reported outcome

SEECS: Swiss eosinophilic esophagitis cohort study

STC: Swallowed topical corticosteroids

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Abstract:

Background: Eosinophilic esophagitis (EoE) has a strong male predominance that appears at least partially due to genetic susceptibility. However, data regarding sex-related differences in patients with EoE are scarce.

Methods: We analyzed prospectively collected data from adults enrolled into the Swiss EoE cohort study (SEECS). Patients with and without dilation in the past 12 months completed patient-reported EoE activity index (EEsAI) and EoE-specific QoL (EoE-QoL-A) and underwent endoscopy with biopsies. We used linear regression with EEsAI or EoE-QoL-A as the outcome, eosinophils per high power field, rings and strictures, current therapy use, and disease duration as predictors.

Results: A total of 266 patients (77% male, median age at diagnosis 35.8 years, median disease duration 10.4 years) were seen during 408 visits. Men had a longer diagnostic delay (62 vs. 36 months, p = 0.022), had higher endoscopic disease activity (EREFS median 3.0, IQR 1.0-6.0 vs. EREFS median 2.0, IQR 0.0-4.0, p = 0.010), more microabscesses (25% vs. 13%, p = 0.025) and more often fibrosis of the lamina propria (mild/moderate 74.7% vs. 61.5%, severe 9.1% vs. 5.8%, p = 0.047) than women. When adjusting for objective measures of disease activity, disease duration and current therapy use, we did not observe differences in EEsAI or EoE-QoL-A between women and men.

Conclusions: Male EoE patients had higher endoscopic and histologic disease activity than female patients. When adjusting for biologic activity and therapy use we did not identify differences in symptom severity or EoE-specific QoL between male and female EoE patient.

KEY WORDS: esophagus; sex; gender; eosinophilic esophagitis

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease of the esophagus with three times higher prevalence in males than in females[1]. This difference is not only explained by gender-associated differences in lifestyle and exposure to environmental factors[2], but also by sex-specific differences in molecular signatures of biomarkers for EoE.[3,4] In addition to anatomical differences, such as a shorter esophageal length in females[5], there exist disparities in esophageal function also exist. Males more frequently suffer from abnormal esophageal acid exposure[6] and have less Langerhans cells in the esophageal epithelium indicating sex-associated differences in mucosal immunity[7].

Despite the heterogeneity in usage of terms sex and gender in the literature, sex and gender are increasingly recognized as important modifiers of clinical manifestations, progression and treatment responses in different diseases[8]. However, in EoE the data on sex-specific differences with respect to disease characteristics, disease course and complications are limited[9-11].

The aim of this study was to investigate sex-specific differences in clinical characteristics as well as in endoscopic and histologic findings in adult EoE patients enrolled into the Swiss EoE cohort.

Methods

Patients and Swiss EoE Cohort

We analyzed prospectively obtained data from the Swiss Eosinophilic Esophagitis Cohort Study (SEECS)[12]. Briefly, SEECS is a nation-wide cohort study, into which adult EoE patients are continuously recruited starting in 2016. For the purposes of inclusion into SEECS, patients are required to have a history of symptoms of esophageal dysfunction and ≥15 esophageal eosinophils per high-power field (eos/hpf). Other causes of esophageal

eosinophilia are excluded. Whether patients had a concomitant gastroesophageal reflux disease (GERD) or not was defined by the treating physician. However, since the physician was asked about the grading of GERD on the Savary-Miller classification, only patients with at least a minimal endoscopic activity could be diagnosed with concomitant GERD. Data are collected in multiple hospitals throughout Switzerland.

Patients with a complete screening, enrollment, and follow-up visit questionnaires (if available) were included in the study. Patients are typically seen once a year for clinical, endoscopic and histologic assessment. At the same visit, patients and physicians complete the screening / enrollment / follow-up questionnaires for patients and physicians, respectively.

Although there exists a distinctive difference between the term sex and gender, these terms have not been used unequivocally in the literature and there is rather a widespread inconsistency regarding the following definitions: Sex is a biological construct and relates to disease prevalence, phenotype and genetic response to treatment. On the other hand, gender is a social construct influencing disease perception, help-seeking behavior and risk exposure. For the sake of simplicity and improved readability, we used terms related to sex in the manuscript. We aimed to employ an accurate distinction between the terms throughout the manuscript. However, there frequently is a continuum or even substantial overlap between the two connotations, thus whenever dubious the term sex was used throughout our manuscript.

SEECS has been approved by ethics committees in all participating centers in Switzerland (leading ethics committee CER-VD 148/15). All participants provided written informed consent.

To asses symptom severity and EoE-specific quality of life (QoL), we used validated patient-reported outcome (PRO) instruments Eosinophilic Esophagitis Activity Index (EEsAI, 7-day recall period, ranges from 0 to 100 with higher number indicating greater symptom severity) and EoE-specific QoL in adults (EoE-QoL-A, 7-day recall period, ranges from 0 to 96 with

higher values indicating worse quality of life), respectively[13,14]. To assess endoscopic disease activity, we used EoE Endoscopic Reference Score (EREFS scored 0-16, higher score indicates a more severe endoscopic disease; exudates 0 – 2, rings 0 – 3, edema 0 – 1, furrows 0 – 1, strictures 0 – 1, scored separately for each proximal and distal esophagus)[15]. In the absence of a histologic score to be used by pathologists not specializing in EoE in daily practice, histologic activity in the SEECS is assessed using a standardized protocol that takes into account not only the peak eosinophil count (proximal peak eosinophil and distal peak eosinophil count), but also basal layer enlargement, presence of eosinophil abscesses, and lamina propria fibrosis. The lamina propria fibrosis was graded semi quantitatively based on evaluation of deposition of extracellular matrix using H&E staining. We used the same method as in the study for the development of EEsAI PRO[13].

Statistics

Data were retrieved from the database of the SEECS at the Institute of Social and Preventive Medicine at University of Lausanne, Switzerland. All statistical analyses were performed by the cohort statistician (JBR) using the statistical program Stata (version 16.1, College Station, Texas, USA). Quantitative data distribution was analyzed using Normal-QQ-Plots. Results of quantitative data are presented as median, interquartile range, as well as minimum and maximum values. Categorical data were summarized as the percentage of the group total. For quantitative data at a patient level, differences in distribution between two groups were evaluated using the Wilcoxon-Mann-Whitney rank test. For categorical outcomes at a patient level, differences in observed frequencies between groups were compared using the chi-squared test, or the exact Fisher test for groups with a small number of observations ($n<5$). At a visit level, the dependency between the observations must be considered when groups are compared, since a patient may have several visits. Consequently, for each characteristic, a univariate logistic regression is performed with the sex as dependent variable taking into

account the fact that each patient defines a cluster. This allows to have intragroup correlation, but the observations are independent across groups. Patient characteristics and therapies use ever in life were analysed per patients. Disease activity, therapy use at the time of index endoscopy, symptoms and quality of life were analysed on a visit level.

We performed a multivariable linear regression with either EEsAI PRO or EoE-QoL-A as outcomes to identify differences in PRO measures between male and female adult EoE patients. The models were fitted at a visit level and, therefore, coefficients, confidence intervals, and p-values were corrected by considering each patient as a cluster. The following parameters were used as predictors (per visit data): (i) rings and stricture part of EREFS score (RS) proximal and distal (ranges 0 to 8), (ii) natural logarithm (maximum value of proximal and distal peak eosinophilic count divided by 10) (logPEC_10), disease duration (defined as time from onset of first symptoms to the time of diagnosis, in years, continuous variable); therapy use at the time of index endoscopy (when using EEsAI as outcome: monotherapy with either swallowed topical corticosteroids, PPI or diet and mixed therapy; when using EoE-QoL-A as outcome, all possible therapy combinations were examined separately). We evaluated the fit of the models using the coefficient of determination (R^2). We performed a multivariable logistic regression with either histologic remission (defined as <15 peak eosinophil count) or need for dilation at index endoscopy with the same predictors mentioned on the above. The models were fitted at a visit level and, therefore, odds ratios, confidence intervals, and p-values were corrected by considering each patient as a cluster. A p-value of < 0.05 was considered significant.

Since dilation modifies association between symptoms and disease activity [16] and symptom relief following dilation has been shown to last at least 12 month[17] we chose a 12 month cutoff between visit and antecedent dilation and excluded visits from patients that had undergone dilation in the last 12 months from the analyses of symptoms and EoE-QoL-A.

RESULTS

In total, 266 SEECS patients (77% male) seen during 408 visits were analyzed; of these, 261 SEECS patients (77% male) without dilation in the past 12 months were seen during 379 visits (Supplementary Figure 1). The median age at the last visit was 42 years (range 17.9 – 83 .1 years), and the median age at diagnosis was 36 years (range 8.4 – 79.0 years).

The patient characteristics are shown in **Table 1**. There was no difference regarding age, presence of family history of EoE and presence of atopic disease between male and female patients. Males had a longer diagnostic delay (62 vs. 36 months, p = 0.022), a longer disease duration (11.6 vs. 9.0 months, p = 0.013) and had a higher education level than females. Although there was no difference between medication use (swallowed topical corticosteroids (STC) and PPI) ever in life and number of dilations patients underwent ever in life, female patients were more likely to use elimination diet (16.4% vs. 7.8%, p = 0.047) to treat the EoE over the course of their disease.

Clinical findings (per visit) are summarized in **Table 2**. Compared to females, males had higher EREFS scores and higher histologic activity with more abscesses (25% vs. 13%, p = 0.025) and higher rates of fibrosis of the lamina propria (absent, mild/moderate or severe 16.2% vs. 32.7%, 74.7% vs. 61.5% and 9.1% vs. 5.8%, respectively, p = 0.047). However, there was no difference in peak eosinophilic count/hpf (median 17.5, IQR 2.0-72.0 vs. median 13.0, IQR 0.0-50.0). The relationship between patient-reported outcomes and peak eosinophil counts and patient-reported outcomes and EREFS are shown in **Figure 1 A and B** and **Figure 2 A and B**, respectively.

Variation in EEsAI and EoE-QoL-A

To analyze variation in EEsAI, we excluded visits of patients that underwent dilation in the last 12 months. In the multivariable linear regression model with EEsAI score (7-day recall period) as outcome (**Table 3**), we found that for one point increase in RS component of EREFS score, the predicted EEsAI increased by 2.02 (p-value=0.004). For a 10-unit increase in natural log-transformed eos/hpf, the predicted EEsAI increased by 1.73 (p-value=0.068). In patients on a single anti-inflammatory therapy (either swallowed topical corticosteroids, PPI, or diets), the predicted EEsAI decreased by 5.63 (p-value=0.033). When adjusting for inflammation assessed as peak eos/hpf, rings and strictures, current medication use, and disease duration, we observed no difference in predicted EEsAI between male and female patients with EoE (coefficient = 2.267, p = 0.334).

Using multivariable linear regression with EoE-QoL-A as outcome, we observed no difference in predicted EEsAI between male and female patients with EoE (coefficient = 2.723, p-value = 0.313) (**Table 3**). Except for RS component of EREFS score (coefficient = 1.11, p-value = 0.09), we observed no relationship between EoE-QoL-A and inflammation assessed as peak eos/hpf, current medication use, and disease duration.

In a multivariable linear regression with EEsAI score and EoE-QoL-A as outcome using 24 months as dilation cut off, the results were similar.

Likelihood of attaining histologic remission and undergoing dilation

We performed a multivariable logistic regression with histologic remission < 15 eosinophils/high-power field and dilation at the time of index endoscopy. There was no difference between female and male patients in the analyzed outcomes (**Table 4**). Patients on anti-eosinophil monotherapy were 3.32 times more likely to be in histologic remission than patients without therapy. The odds of finding patients in histologic remission were decreased for every unit increase in rings and strictures score perhaps indicative of a more complex disease course. The likelihood of undergoing dilation was 1.4 times higher for every unit

increase in rings and strictures score and 1.6 times higher for every 10-year increase in disease duration (OR=1.05, p-value < 0.0001).

DISCUSSION

In this nation-wide cohort study of adult EoE patients, we investigated whether male and female EoE patients differ with respect to clinical presentation, perception of symptoms and disease course. The following key findings emerge: 1) males have higher endoscopic and histologic disease activity compared to females; 2) when adjusted for disease activity, disease duration, and current therapy use, symptom burden and EoE-specific QoL were not different between males and females; and 3) when adjusting for disease activity, disease duration, and current therapy use, the likelihood of attaining histologic remission and undergoing dilation were not different between male and female patients with EoE.

Our multivariable linear regression analysis indicates that severity of symptoms appears to be independent of sex unlike that of inflammatory bowel disease[18-20] and irritable bowel syndrome, as females with these conditions are more likely to report higher gastrointestinal symptom severity than males[21]. In a recent survey of 71812 persons in United States, females with GERD were also more likely to report their symptoms compared to males[22]. Females were also reported to have a lower pain threshold upon esophageal distention[23] and experienced more heartburn despite having less frequent esophageal ulceration[22,24] when compared to males. Therefore, data on symptom severity in EoE do not appear to mirror that for other gastro-intestinal conditions.

Aside from symptoms, one of the most important identified outcome in EoE patients is quality of life (QoL)[25]. In our cohort study, we found no difference in EoE-specific QoL between male and female patients after correcting for disease activity, disease duration, and therapy use. Our data are congruent with those by Lucendo and colleagues[26], who showed no

difference in overall EoE-specific QoL between men and women in a study of 170 Spanish EoE patients. However, in patients with other gastrointestinal diseases, such as inflammatory bowel disease, female patients are more like to have a lower general and disease-specific health-related QoL than male patients[27-29]. Overall, female patients are more likely to report their concerns and to be more diligent regarding their health, both potentially resulting in higher disease burden and lower quality of life[19,24]. Whilst the jury is still out on whether general health-related QoL might differ between male and female EoE patients, EoE-specific QoL does not appear to differ between sexes.

In line with the results by Moawad et al[11], we showed that males with EoE have a longer diagnostic delay than females. Generally, in a given disease with sex-related discrepancies in prevalence, a longer diagnostic delay due to misdiagnosis and under-recognition is typically observed in the underrepresented sex[30]. However, our findings clearly indicate, that the opposite holds true in EoE, i.e. that males are prone to experience a longer delay to diagnosis than females. This might be explained by the fact that males under-use medical care [31] and consequently defer seeking a doctor's attention. As our data are limited to the total diagnostic delay, studies ascertaining the influence of sex on diagnostic delay attributed to patients and physicians are needed, especially as EoE symptoms at presentation might differ between sexes[9,10]. Despite having a longer diagnostic delay than females, males were just as likely to experience food bolus impactions requiring endoscopic removal as female enrolled into SEECS. This result is in agreement with findings by Moawad et al.[11], but differs from the findings from Sperry et al.[9] and Lynch et al.[10]. However, given that our findings are based on a limited number of bolus impactions, the results must be interpreted with caution.

In our cohort, female EoE patients used dietary interventions more often than male patients, potentially owing to the fact that women more readily believe in being able to influence their disease themselves[32] as well as due to the fact that women with children more

commonly shoulder most of housework and, hence, more likely to cook regularly when compared to men[33].

In patients with EoE symptoms are not very accurate in detecting biologic remission, with area under the curve of 0.6, which means that approximately 1/3 of patients in clinical remission still have signs of endoscopic and histologic activity[34]. Given clinical nature of SEECS that includes many patients in clinical remission on swallowed topical corticosteroids, we are likely in the range of symptom severity, where patients' symptoms likely do not accurately differentiate between severity of biologic activity, even if on the whole, male EoE patients have more severe biologic disease than female patients.

This is the largest study that evaluated whether males and females with EoE differ with respect to clinical presentation, perception of symptoms, and EoE-specific quality of life. Nevertheless, the results of our study are interpreted with some limitations in mind. Majority of the patients included into SEECS were not a newly diagnosed patients, as nearly 100% of patients were already treated according to widely accepted therapeutic guidelines prior to inclusion into the study[35]. Therefore, we could not reliably adjust for treatment duration and years of untreated disease. Given that studies with longitudinal design are better suited for examining effects of therapy on symptoms and EoE-specific QoL, it is likely that these could not be optimally assessed in our analyses of cross-sectional data. We observed no differences with regards to clinical, endoscopic, and histologic activity in patients with and without follow up. Our analyses by encounter number might have enriched visits of persons with severe disease. However, in a linear regression analysis, we observed that the only criterion leading to enrichment in visit frequency in patients with multiple visits was eosinophil inflammation. Despite limitations our study had several strengths, particularly the nation-wide catchment area making the data representative, its prospective design, large sample size, the inclusion of multiple sites, and the use of validated instruments for assessment of symptoms, EoE-specific QoL, and endoscopic activity.

In summary, we demonstrate in a large prospective cohort of EoE patients that male sex is associated with higher endoscopic and histologic disease activity, but similar symptom burden and EoE-specific QoL as well as likelihood of attaining histologic remission when adjusted for disease activity, disease duration, and therapy use.

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TABLE AND FIGURE LEGENDS

Table 1: Patient characteristics (per patient data)

Table 2: Disease activity and clinical findings (per visit data)

Table 3: Multivariable linear regression coefficients, 95% confidence intervals (CI) and *P*-values for the models with EEsAI PRO 7-day recall period and the EoE-QoL-A as outcome. **Abbreviations:** EEsAI, symptom-based eosinophilic esophagitis activity index; EoE-QoL-A, eosinophilic esophagitis -specific quality of life in adults.

Table 4: Multivariable logistic regression for histologic remission (<15 eosinophils/high-power field), and dilation at the time of endoscopy (n=408 visits). Odds ratios and p-values are computed by considering each patient as a cluster.

Figure 1: Relationship between peak eosinophilic count and EEsAI score (**A**) and peak eosinophilic count and EoE-QoL-A (**B**). **Abbreviations:** EEsAI, symptom-based eosinophilic esophagitis activity index; EoE-QoL-A, eosinophilic esophagitis -specific quality of life in adults.

Figure 2: Relationship between EEsAI score and different components of the EREFS Score (**A**) and EoE-QoL-A score and different components of the EREFS score (**B**) when stratified by sex. For each distribution, the box spans the values between the quartiles 1 and 3 (interquartile range), and the median is marked by horizontal line inside the box. The whiskers extend to the maximum of 1.59 the interquartile range beyond the box boundaries. Data beyond the range of whiskers are outliers and presented as points. P-values for trend tests are provided in the boxes. **Abbreviations:** EEsAI, symptom-based eosinophilic esophagitis activity index; EoE-QoL-A, eosinophilic esophagitis -specific quality of life in adults; EREFS, endoscopic reference score.

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	All patients	Males	Females	p-value (chi2 or Wilcoxon)
Number of patients	**266**	**205 (77.1%)**	**61 (22.9%)**	
Diagnosis at last follow-up				
EoE only	218 (82.0%)	163 (79.5%)	54 (90.2%)	0.058
EoE and GERD	48 (18.0%)	42 (20.5%)	5 (9.8%)	
Age at...				
...first symptoms (median, IQR, range)	28.3, 18.3 – 41.0, 0.9 – 77.0	28.2, 18.3 – 40.9, 2.1 – 64.8	28.8, 18.7 – 41.9, 0.9 – 77.0	0.74
...diagnosis (median, IQR, range)	35.8, 27.2 – 46.6, 8.4 – 79.0	36.1, 28.4 – 46.6, 10.6 – 75.7	32.1, 23.5 – 46.2, 8.4 – 79.0	0.191
...last visit (median, IQR, range)	41.7, 32.4 – 52.7, 17.9 – 83.1	42.2, 34.3 – 53.5, 18.7 – 80.1	41.3, 30.0 – 51.1, 17.9 – 83.1	0.178
Diagnostic delay[a] (*months)*				
(median, IQR, range)	57.5, 18.0 – 123.0, 0.0 – 477.0	62.0, 20.0 – 145.0, 0.0 – 477.0	36.0, 13.0 – 81.0, 0.0 – 270.0	**0.022**
Disease duration				
(median, IQR, range)	10.4, 6.7 – 18.5, 0.2 – 48.9	11.6, 7.0 – 19.1, 0.4 – 48.9	9.0, 6.1 – 13.6, 0.2 – 29.7	**0.013**
ISCED 2011 education levels[b]				
Level 2 or less	11 (4.1%)	9 (4.4%)	2 (3.3%)	<**0.001**
Level 3, 4 or 5	90 (33.8%)	56 (27.3%)	34 (55.7%)	
Level 6 or higher	165 (62.0%)	140 (68.3%)	25 (41.0%)	
Family history of EoE				
Yes	59 (25.2%)	42 (23.2%)	17 (32.1%)	0.191
Atopic disease ever in life				
Yes	191 (74.9%)	147 (74.2%)	44 (77.2%)	0.651
Oral allergy syndrome	80 (31.4%)	60 (30.3%)	20 (35.1%)	0.493
Neurodermitis	26 (10.2%)	20 (10.1%)	6 (10.5%)	0.926
Asthma	89 (34.9%)	68 (34.3%)	21 (36.8%)	0.727
Rhinoconjunctivitis	139 (54.5%)	106 (53.5%)	33 (57.9%)	0.560
Swallowed topical corticosteroids ever				
Yes	188 (70.7%)	150 (73.2%)	38 (62.3%)	0.101
Elimination diet ever				
Yes	26 (9.8%)	16 (7.8%)	10 (16.4%)	**0.047**
Proton-pump inhibitor therapy ever				
Yes	73 (27.4%)	60 (29.3%)	13 (21.3%)	0.221
Dilation ever				
Yes	108 (40.6%)	84 (41.0%)	24 (39.3%)	0.820
Bolus impaction ever				
Yes	108 (41.5%)	89 (44.3%)	19 (32.2%)	0.689

[a] Definition diagnostic delay: Date of first symptoms to diagnosis
[b] ISCED Level: International Standard Classification of Education Level: Level 2 or less is a lower secondary education or less; Level 3-5 is up to short-cycle tertiary education; Level 6 or higher is at least a Bachelor's or equivalent.

	All Visits	Males	Females	p-value
Number of visits	**408**	**322 (78.9%)**	**86 (21.1%)**	
Age, in years	•	•	•	•
(median, IQR, range)	40.6, 31.6 – 51.4, 17.9 – 83.1	40.6, 32.3 – 51.9, 18.1 – 80.1	40.9, 29.9 – 51.1, 17.9 – 83.1	0.608
Disease duration, in years	•	•	•	•
(median, IQR, range)	10.7, 6.7 – 18.6, 0.2 – 48.9	11.2, 6.8 – 19.0, 0.4 – 48.9	9.9, 6.5 – 17.1, 0.2 – 29.7	0.093
Peak eosinophil count per high power field		•	•	•
(median, IQR, range)	16.0, 1.0 – 63.5, 0.0 – 290.0	17.5, 2.0 – 72.0, 0.0 – 270.0	13.0, 0.0 – 50.0, 0.0 – 290.0	0.104
Abscesses	•	•	•	•
Absent	317 (77.7%)	242 (75.2%)	75 (87.2%)	**0.025**
Present	91 (22.3%)	80 (24.8%)	11 (12.8%)	
Fibrosis of the lamina propria	•	•	•	•
Mild/Moderate	171 (71.8%)	139 (74.7%)	32 (61.5%)	**0.047**
Severe	20 (8.4%)	17 (9.1%)	3 (5.8%)	•
EREFS (proximal + distal)	•	•	•	•
(median, IQR, range)	3.0, 1.0 – 6.0, 0.0 – 14.0	3.0, 1.0 – 6.0, 0.0 – 14.0	2.0, 0.0 – 4.0, 0.0 – 12.0	**0.010**
RS (proximal + distal)	•	•	•	•
(median, IQR, range)	1.0, 0.0 – 2.0, 0.0 – 7.0	1.0, 0.0 – 2.0, 0.0 – 7.0	1.0, 0.0 – 2.0, 0.0 – 6.0	0.078
EEsAI PRO, last 7 days	•	•	•	•
(median, IQR, range)	13.5, 0.0 – 27.0, 0.0 – 63.0	12.0, 0.0 – 27.0, 0.0 – 63.0	15.0, 12.0 – 34.0, 0.0 – 63.0	0.385
Pain when swallowing (last 7 days)	•	•	•	•
Present	54 (13.2%)	40 (12.4%)	14 (16.3%)	0.382
Avoidance, modification, slow eating (last 7 days)	•	•	•	•
(median, IQR, range)	0.4, 0.0 – 1.4, 0.0 – 7.3	0.3, 0.0 – 1.3, 0.0 – 6.0	0.7, 0.0 – 2.0, 0.0 – 7.3	**0.027**
EoE-QoL-A	•	•	•	•
(median, IQR, range)	14.8, 7.0 – 26.0, 0.0 – 72.0	14.0, 7.0 – 25.0, 0.0 – 64.0	16.0, 5.0 – 27.0, 0.0 – 72.0	0.178
•	•	•	•	•
Impact of diet/eating	2.0, 0.0 – 5.0, 0.0 – 16.0	2.0, 0.0 – 4.0, 0.0 – 15.0	2.5, 1.0 – 6.0, 0.0 – 16.0	0.113
Social impact	2.0, 0.0 – 4.0, 0.0 – 15.0	2.0, 0.0 – 4.0, 0.0 – 13.0	2.0, 0.0 – 5.0, 0.0 – 15.0	0.080
Emotional impact	2.0, 1.0 – 6.0, 0.0 – 23.0	2.0, 1.0 – 6.0, 0.0 – 23.0	3.0, 1.0 – 7.0, 0.0 – 21.0	0.182
Disease anxiety	5.0, 2.0 – 8.0, 0.0 – 20.0	5.0, 2.0 – 7.5, 0.0 – 20.0	4.0, 0.0 – 9.0, 0.0 – 18.0	0.977

Swallowing anxiety	2.0, 0.0 – 4.0, 0.0 – 12.0	2.0, 0.0 – 3.0, 0.0 – 11.0	2.0, 0.0 – 5.0, 0.0 – 12.0	0.185
Symptoms of GERD in the past 7 days				
Heartburn	14 (3.4%)	11 (3.4%)	3 (3.5%)	0.974
Regurgitation	2 (0.5%)	1 (0.3%)	1 (1.2%)	0.351
Treatment for EoE	•	•	•	•
Diets	38 (9.3%)	28 (8.7%)	10 (11.6%)	0.507
Proton-pump inhibitors	92 (22.5%)	78 (24.2%)	14 (16.3%)	0.181
Swallowed topical corticosteroids	262 (64.2%)	211 (65.5%)	51 (59.3%)	0.374
Swallowed topical corticosteroids AND proton-pump inhibitors	36 (8.8%)	32 (9.9%)	4 (4.7%)	0.331
Swallowed topical corticosteroids AND diets	12 (2.9%)	11 (3.4%)	1 (1.2%)	0.328
Dilation >1 year prior to index endoscopy	172 (42.2%)	136 (42.2%)	36 (41.9%)	0.963

EEsAI PRO 7-day recall period	Coef[a]	Coef. (95% CI)	p-value
Female	2.27	2.27 (-2.34 – 6.88)	0.334
Rings + Strictures (proximal + distal)	2.02	2.02 (0.66 – 3.39)	0.004
Logarithm of Peak eos. Count per high power field, divided by 10	1.73	1.73 (-0.13 – 3.58)	0.068
Disease Duration (per year)[b]	0.07	0.07 (-0.14 – 0.28)	0.493
Therapy class			
No therapy		0 (ref.)	
Monotherapy	-5.63	-5.63 (-10.81 – -0.46)	0.033
Corticosteroids and PPI	-2.70	-2.70 (-11.37 – 5.96)	0.540
Corticosteroids and diet	-4.72	-4.71 (-14.01 – 4.58)	0.319
Constant[c]	17.00	10.73-23.28	< 0.01
R^{2d}	0.08		
EoE-QoL-A			
Female	2.72	2.72 (-2.58 – 8.02)	0.313
Rings + Strictures (proximal + distal)	1.11	1.11 (-0.17 – 2.40)	0.090
Logarithm of Peak eos. Count per high power field, divided by 10	1.05	1.05 (-0.67 – 2.77)	0.232
Disease Duration (per year)	-0.08	-0.09 (-0.28 – 0.11)	0.380
Therapy class			
No therapy		0 (ref.)	
Corticosteroids only	-2.85	-2.85 (-8.12 – 2.43)	0.289
PPI only	1.99	1.99 (-4.45 – 8.42)	0.543
Diet only	-0.05	-0.04 (-6.20 – 6.11)	0.989
Corticosteroids and PPI	-3.15	-3.15 (-9.56 – 3.26)	0.335
Corticosteroids and diet	3.75	3.75 (-4.35 – 11.85)	0.363
Constant[c]	16.65	10.69-22.61	< 0.01
R^{2d}	0.06		

Multivariable linear regression for EEsAI PRO 7-day recall period (A) and EoE-QoL-A (B) in patients did not undergo dilation in the last 12 months (n = 379).. Confidence intervals and p-values are computed by considering each patient as a cluster.

a) The coefficient represents the change in the value of the predicted EEsAI, resp. QoL for each category change of the independent variable. For example, for a 7 day recall period, the predicted EEsAI increased by 2.3 if the patient has a female gender.

b) Disease duration: Date of first symptoms to date of last visit

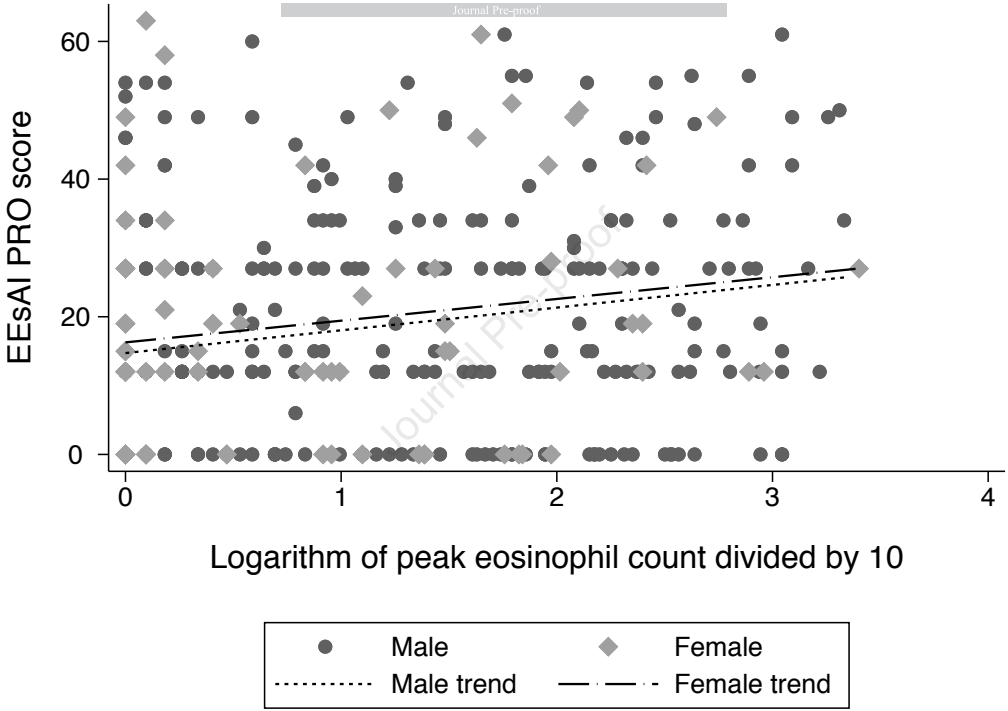
c) The constant represents the value of the predicted EEsAI or QoL, resp., when all values of independent variables are zero.

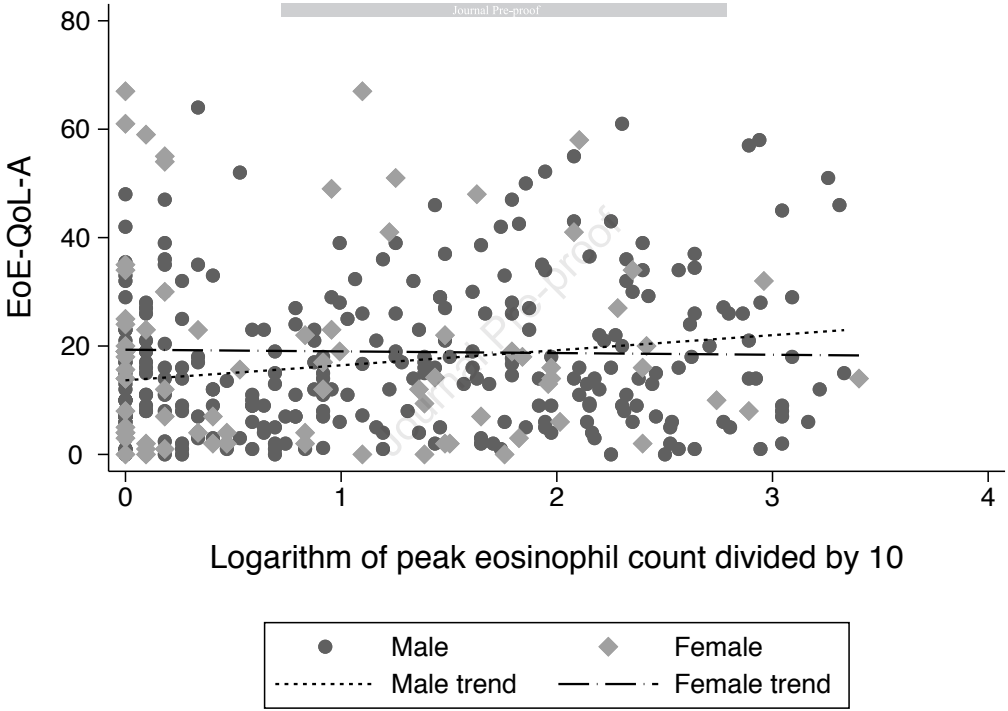
d) The coefficient of determination, R2, is a measure of the extent to which the regression model describes the observed data. The closer the R2 is to 1, the more precise the regression model is. Since R2 can be made artificially high by including a large number of independent variables that have an apparent effect purely by chance,

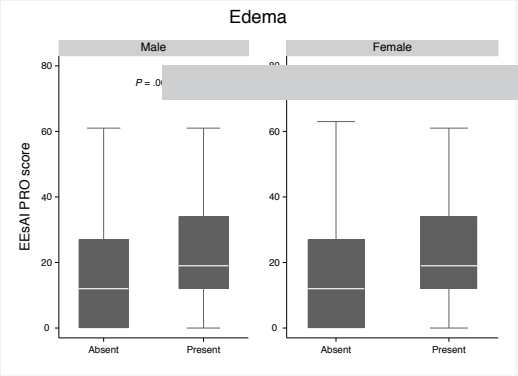
Table 4

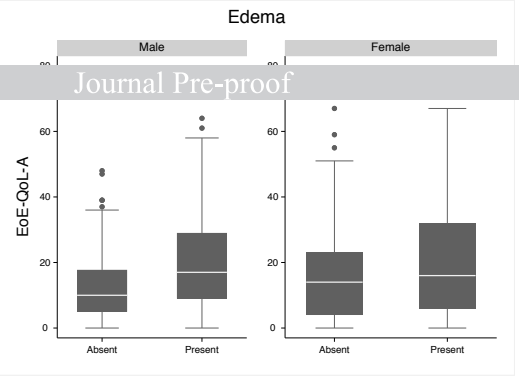
Model with histologic remission as outcome	**Odds ratio**	**95% CI**	**p-value**
Female	1.143	0.674 - 1.939	0.621
Rings + Strictures (proximal + distal)	0.568	0.464 - 0 .697	<0.0001
Disease duration (per year)[a]	1.020	0.994 - 1.046	0.128
Therapy class vs. no therapy			
Monotherapy	3.323	1.592 - 6.934	0.001
Corticosteroids and PPI	4.716	1.536 - 14.485	0.007
Corticosteroids and diet	2.421	0.580 - 10.101	0.225
Model with dilation at the time of index endoscopy	**Odds ratio**	**95% CI**	**p-value**
Female	1.642	0.900 - 3.000	0.106
Rings + Strictures (proximal + distal)	1.368	1.142 - 1.638	0.001
Natural logarithm of peak eos. count per hpf, divided by 10	0.951	0.724 - 1.251	0.720
Disease duration (per year)	1.046	1.020 - 1.072	<0.0001
Therapy class vs. no therapy			
Monotherapy	1.177	0.605 - 2.293	0.631
Corticosteroids and PPI	1.157	0.358 - 3.739	0.807
Corticosteroids and diet	0.318	0.043 - 2.373	0.264

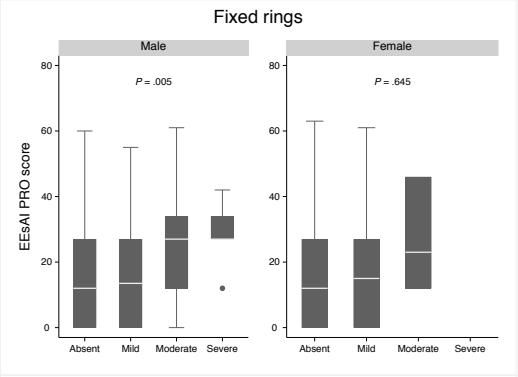
Multivariable logistic regression for histologic remission (<15 eosinophils/high-power field), dilation at the time of endoscopy, and strictures. Odds ratios and p-values are computed by considering each patient as a cluster.

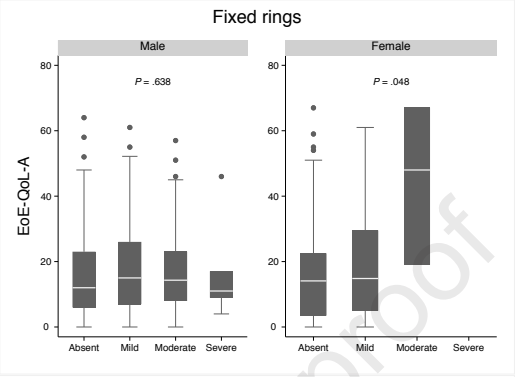


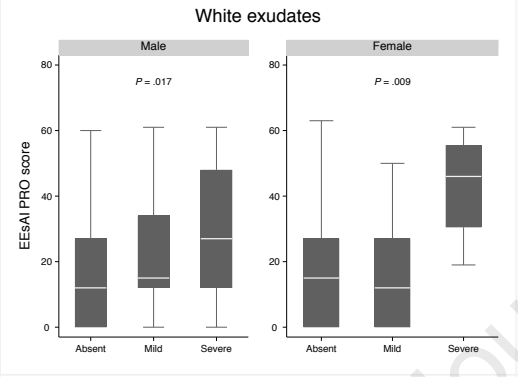


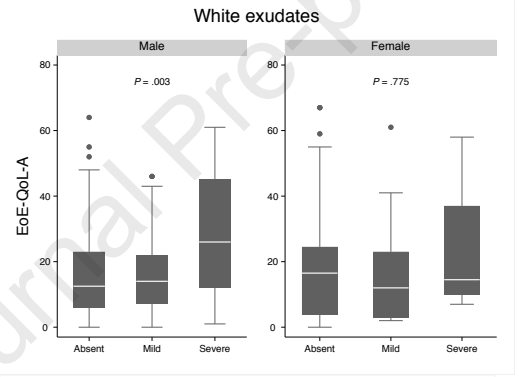


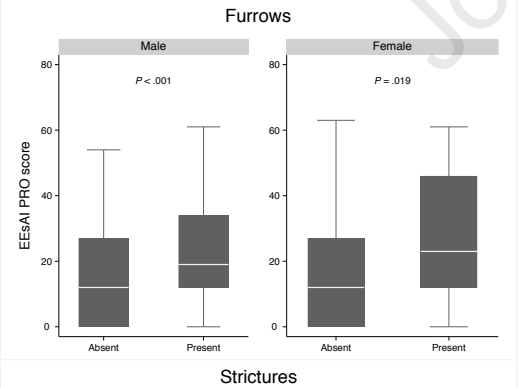


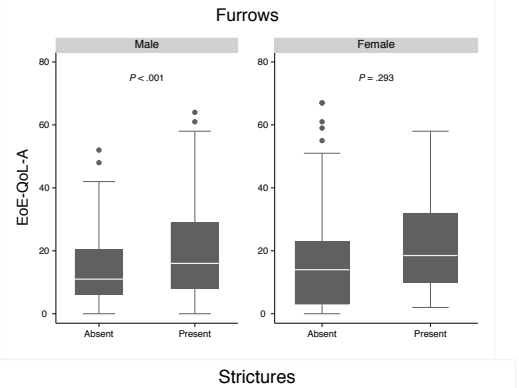


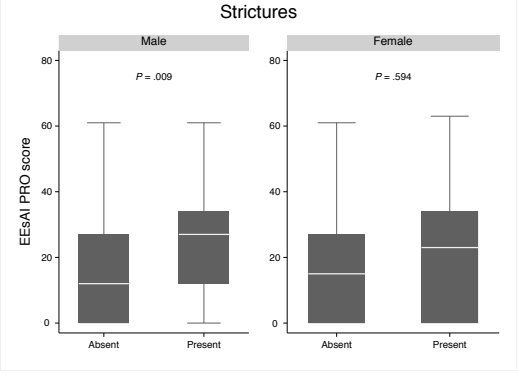


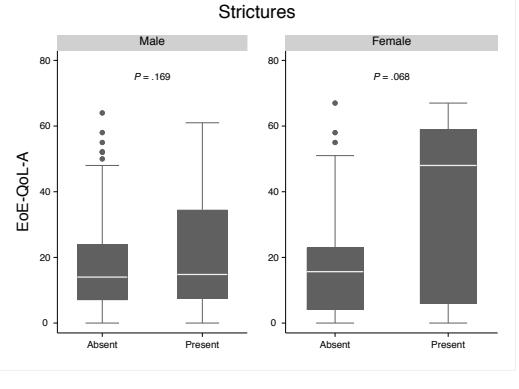












What you need to know

BACKGROUND

Sex may influence disease perception, treatment response and disease course in most diseases. In most gastrointestinal diseases women report a lower quality of life and higher symptom burden than men.

FINDINGS

In adults with eosinophilic esophagitis (EoE), when adjusting for disease activity and therapy use, quality of life and symptom burden do not differ between women and men.

IMPLICATIONS FOR PATIENT CARE

Sex does not affect disease perception and has no influence on the disease course in EoE patients.