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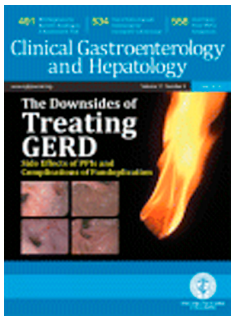

Long-Lasting Dissociation of Esophageal Eosinophilia and Symptoms Following Dilation in Adults with Eosinophilic Esophagitis

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Long-Lasting Dissociation of Esophageal Eosinophilia and Symptoms Following Dilation in Adults with Eosinophilic Esophagitis

Short title: Eosinophilia-Symptom Dissociation Post-Dilation

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Abbreviations: CEGIR, the Consortium of Gastrointestinal Eosinophilic Disease Researchers; EEsAI, symptom-based eosinophilic esophagitis activity index; EoEHSS, eosinophilic esophagitis histologic scoring system; EoE-QoL-A, adult eosinophilic esophagitis-specific quality of life; EREFS, endoscopic reference score; eos/hpf, peak esophageal eosinophil counts; IQR, interquartile range; PRO, patient-reported outcomes; RS, rings and stricture as detected by EREFS.

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Ekaterina Safroneeva (i) received consulting fees from AVIR Pharma, Inc., Aptalis Pharma, Inc., Celgene Corp., Novartis, AG, and Regeneron Pharmaceuticals Inc. E. King reports (ii) being a former employee of the Procter & Gamble Company and (iii) has stock and stock options in the Procter & Gamble Company. M. H. Collins is (i) a consultant for Allakos, Arena, Astra Zeneca, Calypso, Esocap, GSK, Receptos/BMS, Regeneron, Shire, a Takeda company, and Robarts Clinical Trials; and reports research grants from Receptos/BMS, Regeneron, and Shire, a Takeda Company. E. S. Dellon (i) received research funding from: Adare, Allakos, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos, Regeneron, Shire/Takeda; consulting fees from: Abbott, Adare, Aimmune, Allakos, Arena, AstraZeneca, Biorasi, Calypso, Celgene/Receptos, Eli Lilly, EsoCap, GSK, Gossamer Bio, Regeneron, Robarts, Salix, Shire/Takeda; and educations grants from: Allakos, Banner, Holoclara. G. W. Falk reports (i) grants and/or personal fees from Shire, ADARE/Ellodi, Regeneron, Allakos, Lucid, and Celgene. N. Gonsalves receives (i) consulting fees from Allakos and royalties from UpToDate. S. K. Gupta reports (i) personal fees from Allakos, Abbott, Receptos, QOL, and Shire. I. Hirano reports (i) research funding from: Adare, Allakos, GSK, Meritage, Celgene/Receptos, Regeneron, Shire/Takeda; consulting fees from: Adare, Allakos, Arena, AstraZeneca, Celgene/Receptos, Eli Lilly, EsoCap, GSK, Gossamer Bio, Regeneron, Shire/Takeda V. A. Mukkada reports (i) grants and/or personal fees from Shire Pharmaceutical. Alain M. Schoepfer received (i) consulting fees and/or speaker fees and/or research grants from Adare Pharmaceuticals, Inc., AstraZeneca, AG, Switzerland, Aptalis Pharma, Inc., Celgene Corp., Dr. Falk Pharma, GmbH, Germany, Glaxo Smith Kline, AG, Nestlé S. A., Switzerland, Novartis, AG, Switzerland, Receptos, Inc., and Regeneron Pharmaceuticals, Inc. J. M. Spergel reports (i) grants and/or personal fees from DBV Technologies, End Allergy Together, Food Allergy Research Education, Aimmune Therapeutics, UpToDate, Regeneron, and Shire. Barry K. Wershil received (i) consulting fees and/or speaker fees from Mead Johnson Nutrition, and Abbott Nutritionals. M. E. Rothenberg

reports (i) personal fees from Celgene, Astra Zeneca, Arena Pharmaceuticals, Adare Pharmaceuticals, GlaxoSmith Kline, Guidepoint and Suvretta Capital Management, and (iii) has an equity interest in Pulm One, Spoon Guru, ClostraBio, Serpin Pharm and Allakos, and royalties from reslizumab (Teva Pharmaceuticals), PEESSv2 (Mapi Research Trust) and UpToDate. M.E.R. is (iv) an inventor of patents owned by Cincinnati Children's Hospital. S. S. Aceves reports (i) being a consultant for Regeneron, Astra-Zeneca, Astellos, and AImmune and (iv) a UCSD patent licensed to Shire-Takeda Pharma and. G. T. Furuta reports (i) personal fees and/or grants from EnteroTrack, Shire/ Takeda and UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.

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ABSTRACT

Background and aims: Esophageal dilation improves dysphagia but not inflammation in eosinophilic esophagitis (EoE) patients. We investigated if dilation modifies the association between symptoms and esophageal eosinophil count (eos/hpf).

Methods: Adults enrolled in a multisite, prospective Consortium of Gastrointestinal Eosinophilic Disease Researchers OMEGA observational study (NCT02523118) completed the symptom-based EoE activity index (EEsAI) patient-reported outcome instrument and underwent endoscopy with biopsies. Patients were stratified based on dilation status as absent, performed ≤1 and >1 year before endoscopy. Assessments included Spearman's correlations of the relationship between symptoms and eos/hpf and linear regression with EEsAI as the outcome, eos/hpf as predictor, and interaction for dilation and eos/hpf.

Results: Amongst 100 patients (n=61 male, median age 37 years), 15 and 40 patients underwent dilation ≤1 year and >1 year before index endoscopy, respectively. In non-dilated patients, association between eos/hpf and symptoms was moderate (Rho=0.49, p-value<0.001); for 10 eos/hpf increase, the predicted EEsAI increased by 2.69 (p-value=0.002). In patients dilated ≤1 and >1 year before index endoscopy, this association was abolished (Rho=-0.38, p-value=0.157 for ≤1 year and Rho=0.02, p-value=0.883 >1 year); for 10 eos/hpf increase, the predicted EEsAI changed by -1.64 (p-value=0.183) and 0.78 (p-value=0.494), respectively). Dilation modifies association between symptoms and eos/hpf (p-value=0.005 and p-value=0.187 for interaction terms of eos/hpf and dilation ≤1 year and >1 year before index endoscopy, respectively).

Conclusion: In non-dilated EoE adults, eos/hpf correlates modestly with symptoms; this correlation was no longer appreciated in dilated patients, and the dilation effects lasted longer than one year. Dilation status should be considered in studies evaluating EoE treatment and for clinical follow-up.

Word count: 260

Key words: dysphagia, pain when swallowing, eosinophilic esophagitis histologic scoring system, endoscopic reference score, eosinophilic esophagitis-specific quality of life in adults, effect modification.

INTRODUCTION

In adults with eosinophilic esophagitis (EoE), dilation is frequently used to manage dysphagia symptoms.[1,2] Using a non-validated physician-reported dysphagia measure in adult EoE patients managed by dilation alone, Schoepfer *et al.* demonstrated that dysphagia improved for a median of 15 months; in a patient survey, 67% of patients reported that the effect of dilation on symptoms lasted for ≥12 months.[2] A recent systematic review suggested that dilation performed at study baseline perturbs association between treatment-induced changes in peak eosinophil counts (PEC) and symptoms.[3] Given the above data, however, the effects of dilation last much longer; hence, dilation performed well before the study baseline may still perturb the association between symptoms and PEC. In randomized clinical trials (RCTs), consideration of patients' dilation status is variable. This can be problematic, as trials are designed to assess improvements in dysphagia in conjunction with improvement in PEC and other biologic markers. Dellon *et al.* examined the efficacy of budesonide in improving symptoms and PEC, and the dilation history at baseline was not reported.[4] When examining efficacy of budesonide in inducing clinico-histologic remission, Lucendo *et al* excluded patients with dilation performed within eight weeks of screening.[5]

Data on the relationship between symptoms and biologic findings assessed using validated instruments are scarce.[6,7,8,9] A single study documented effect modification of dilation on the relationship between PEC and symptoms performed within a few months of RCT baseline.[10]

We examined long-term effect modification of dilation on the relationship between biologic findings, including centrally read histology, and validated patient-reported outcome (PRO) measures in adult EoE patients enrolled into the Consortium of Gastrointestinal Eosinophilic Disease Researchers (CEGIR) prospective, multi-center, observational OMEGA study.[11,12]

METHODS AND PATIENTS

Upon entry into the CEGIR OMEGA study (ClinicalTrials.gov NCT02523118), adults with EoE completed PRO measures and underwent endoscopy with biopsy sampling between February 2016 and March 2018 in 14 centres across the United States.[11] Of the 392 patients of ≥18 years of age enrolled into the study, 100 patients with baseline histologic assessment and a known history regarding dilation status completed the symptom-based eosinophilic esophagitis activity index (EEsAI) (**Supplementary Figure 1**). Patients were consented/assented into the central (Cincinnati) and local institutional review board− and National Institutes of Health−approved protocol.

PRO measures

The EEsAI 7-day recall period version and the EoE-specific quality of life in adults (EoE-QoL-A) the 24-item version applicable for all patients [score ranges from 0 (very good) to 96 (very poor)] instruments were used in this study.[8,9] Ninety-six patients, two patients, and two patients completed the EEsAI on the day, within seven and 20 days of endoscopy, respectively.

Histologic evaluation

CEGIR core pathologists (MHC, KEC, NA, and G-YY) reviewed scanned, whole slide images of esophageal biopsy specimens (×400 magnification) obtained during endoscopy. Maximum of proximal and distal PEC were used for analyses. To calculate the EoE Histologic Scoring System (EoEHSS) expressed as ratio, all the features were first scored from 0-24 for grade (severity) and from 0-24 for stage (extent) and then divided by maximum possible value of EoEHSS that could be obtained based on the features available.[6]

Data handling and statistical analysis

Statistical analyses were performed using SAS software (version 9.4; Cary, NC, USA). Data distributions were evaluated using QQ plots. Demographic and clinical characteristic of adults with EoE were summarized as frequencies and percentages, or medians and interquartile ranges (IQRs). The Wilcoxon rank-sum test was used to compare dilated and non-dilated patients. EEsAI, endoscopy, and histology data were matched by date for each

participant. The pairwise relationship between EEsAI, EoE-QoL-A, endoscopic severity assessed using the EoE Endoscopic Reference Score (EREFS scored 0-18, higher score indicates a more severe endoscopic disease), PEC per high-power field (eos/hpf; hpf=0.27 mm^2), and components of EoEHSS were analyzed with non-parametric correlations (Spearman's rho) stratified by dilation (absence, performed ≤12 and >12 months prior to endoscopy). The following definitions to interpret the Spearman's correlation coefficients were applied: 0.0-0.3, weak; >0.3-<0.7 moderate; 0.7 or higher, strong relationship.

Linear regression analysis in the overall population and the non-dilated patients was performed with EEsAI as the outcome and either eos/hpf or EREFS as predictors. Residual analysis indicated normality assumptions were met. As dilation might act as an effect modifier (measures of association might differ in dilated and non-dilated patients), we included an interaction term for dilation with biologic findings. Dilation was ordered as follows: no dilation (reference category), ≤12 and >12 months prior to endoscopy. We evaluated the fit of the models using the coefficient of determination (R^2) in non-dilated patients. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

One hundred adult EoE patients with baseline histologic assessment and a known dilation history completed the EEsAI (**Supplementary Figure 1**). Overall, median EEsAI, EoE-QoL-A, EoEHSS, and PEC were similar between non-dilated and dilated patients (**Table 1**). Total proximal and distal EREFS score was higher in dilated than in non-dilated patients (p-value=0.037), which was mostly driven by the difference in distal EREFS score (distal: p-value=0.012; proximal: p-value=0.318). Dilated patients were more likely to have rings and strictures, when compared to non-dilated patients (distal: p-value<0.001; proximal: p-value=0.013; distal and proximal: p-value<0.001), but they had comparable edema, furrows, and exudate score. At index endoscopy, dilated patients tended to be older than non-dilated patients (p-value=0.070). Dilated patients tended to be diagnosed with EoE later in life (p-value=0.051), had longer disease duration (time interval from first symptom onset until endoscopy, p-value=0.023) and diagnostic delay (time interval from first symptom onset until diagnosis, p-value=0.009) than patients without dilation.

Correlation between PEC, EoEHSS, EEsAI, and EoE-QoL-A stratified on dilation status

We observed moderate positive associations between peak eos/hpf and EEsAI in 45 non-dilated patients (Rho=0.49, p-value<0.001), but no significant association between these parameters in 40 (Rho=0.02, p-value=0.883) and 15 (Rho=-0.38, p-value=0.157) subjects dilated >12 and ≤12 months prior to endoscopy, respectively (**Figure 1A**). The relationship between components of the EEsAI and eos/hpf is shown in **Supplementary Figure 2**. Similarly, we observed moderate positive association between the EoEHSS and EEsAI score in non-dilated patients (Rho=0.47, p-value=0.001) and no significant association between these parameters in patients dilated >12 (Rho=0.18, p-value=0.274) and ≤12 (Rho=-0.13, p-value=0.663) months prior to endoscopy (**Figure 2A**). When examining the relationships between EEsAI and EREFS (**Figure 1B**), we observed no significant association between symptoms and EREFS in non-dilated patients and in patients dilated >12 months prior to

endoscopy, but we observed a moderate negative association between symptoms and EREFS in patients dilated ≤12 months prior to endoscopy.

To evaluate if the relationship described above could also be observed using a different PRO instrument, we examined the relationship between EoE-QoL-A and eos/hpf. The relationship between components of the EEsAI and EoE-QoL-A score in 96 patients is shown in **Supplementary Figure 3**. We observed no significant association between EoE-QoL-A and eos/hpf in 39 non-dilated patients (p-value=0.160) and 37 patients dilated >12 months prior to endoscopy (p-value=0.362), but we found moderate negative association between EoE-QoL-A and eos/hpf in 15 patients dilated ≤12 months prior to endoscopy (p-value=0.019) (**Supplementary Figure 4A**). Similar findings were observed when the relationships between EoE-QoL-A and EREFS were examined (**Supplementary Figure 4B**).

Variation in EEsAI with PEC by dilation status

Using linear regression analyses, we found a significant interaction between dilation and eos/hpf indicating that slopes of the line between EEsAI and peak eos/hpf change depending on dilation status. When compared to the non-dilated group with a slope of 2.69, the slope for patients dilated ≤12 months prior to endoscopy was significantly decreased (difference in slopes: -4.33; 95% confidence interval [CI] -7.30, -1.36; p-value=0.005). There was no significant change in slope between the non-dilated group and the group dilated >12 months prior to endoscopy (difference in slopes: -1.90; 95% CI -4.75, 0.94; p-value=0.187). In non-dilated patients, EEsAI showed a positive relationship with the peak eos/hpf. For example, for a 10-cell increase in eos/hpf in non-dilated patients, the predicted EEsAI increased by 2.69 (p-value=0.002). For a 10-cell increase in eos/hpf in patients dilated ≤12 and >12 months prior to endoscopy, the predicted EEsAI decreased by 1.64 (p-value=0.183) and increased by 0.78 (p-value=0.494), respectively (**Table 2**). This relationship between predicted EEsAI and eos/hpf is illustrated by displaying the prediction lines and 95% confidence bands for each line (**Figure 3**). Using single variable linear regression in non-dilated patients (**Supplementary Table 1**) we found that variation in eos/hpf explained 19% of EEsAI variation.

Variation in EEsAI with EREFS by dilation status

We observed significant interaction between dilation and EREFS indicating that the slopes of the line between EEsAI and EREFS differed with the dilation status. Compared to the non-dilated patients, the slope of the line for patients dilated within 12 months of endoscopy significantly decreased (difference in slopes: -3.43; 95% CI, -6.41, -0.46; p-value=0.024); no significant difference between slopes in the non-dilated patients and patients dilated >12 months prior to endoscopy (difference in slopes: -0.42; 95% CI, -2.25, 1.40; p-value=0.646) was observed. The predicted EEsAI increases by 1.88 for 1-unit increase in EREFS in non-dilated patients (p-value=0.068). The predicted EEsAI decreased by 5.31 (p-value=0.004) and 2.30 (p-value=0.097) for one-unit increase in EREFS in patients dilated ≤12 and >12 months prior to endoscopy, respectively (**Table 2**, **Figure 3**). In non-dilated patients, variation in EREFS explained 7% of EEsAI variation (**Supplementary Table 1**).

DISCUSSION

In this observational cohort study of adults with EoE, we found that dilation performed within 12 months of the endoscopy modifies the relationship between biologic findings and symptom severity. In non-dilated patients, we identified a statistically significant moderate positive association between PEC and symptom severity. The association trended negative in patients dilated within 12 months of index endoscopy, although it did not reach statistical significance. We found a positive weak correlation between EREFS and symptom severity in non-dilated patients that did not reach statistical significance but a statistically significant negative moderate association between these parameters in patients dilated within 12 months of index endoscopy. No association between symptoms and biologic findings was observed in patients dilated >12 months prior to endoscopy. The direction of the associations between symptoms and biologic findings was consistent irrespective of whether the relationship between symptoms and PEC or symptoms and EREFS was examined. In non-dilated patients, variation in PEC explained 19% of the variation in symptom severity. Our study makes the following impactful conclusions: 1) dilation modifies the relationship between symptoms and biologic findings, and dilation effects may last > 12 months; 2) consideration should be given to dilation impact on baseline symptom assessment in RCTs; and 3) in clinical practice, symptoms should not be used to monitor therapy response for at least 12 months after dilation.

The dissociation between validated PRO measures-assessed symptoms and PEC in the RCTs of adults with EoE is a matter of concern.[4,13,14,15] Many studies including phase II RCT assessing the budesonide efficacy do not provide information on subjects' dilation status, and although dysphagia symptom questionnaire (DSQ)-assessed symptoms were significantly improved in budesonide vs placebo, no association (spearman rho=0.03) between PEC and symptoms was observed.[14] Knowing patients' dilation status is important for RCT design and clinical practice, as dilation may hold the key for dissociation between improvement in symptoms and PEC observed in some studies. In RCTs of anti-inflammatory therapies, dilation status in the past 12-24 months should be considered.[2] Demonstrating

symptom improvement that reflects improvement in PEC in dilated patients might prove futile, and symptom severity in the dilated patients at study baseline is not reflective of their inflammation.[2,5,10] Although dilated patients benefit from anti-eosinophil therapies, physicians should not rely on symptoms for monitoring treatment response in recently dilated patients.[16] Kinetics of post-dilation symptom severity on and off anti-eosinophil treatment, and dilation characteristics including dilator type, diameter achieved in a single session, and number of sessions, merit careful examination. Although symptoms were shown to be not useful at detecting histologic remission in EoE patients dilated (area under the curve [AUC]=0.52) and not dilated (AUC=0.63) in the past 12 months, similar analyses should be repeated in patients that never underwent dilation.[17] Given moderate association between symptoms and PEC in non-dilated patients, it is likely that symptoms are not sensitive enough to detect histologic remission in these patients. Further studies should evaluate the utility of histologic remission as treatment target.

There was no overlap between CEGIR OMEGA and the budesonide vs. fluticasone RCT study populations.[10] Although the analyses performed are similar, the data are complimentary, as patient populations examined differ.[10] Whilst incident EoE cases with no prior therapy except failed proton-pump inhibitors were recruited into the RCT, prevalent cases with diverse clinical presentation and treatments were recruited into the OMEGA. In the RCT, the association between EEsAI/DSQ-assessed symptoms and PEC (cross-sectional) and the treatment-induced changes in DSQ and PEC was examined, and the effect modification of dilation performed within few months of study baseline was reported. We only examined cross-sectional data, and not only confirmed the effect modification of dilation performed within 12 months of index endoscopy, but also concluded that dilation effects may last > 12 months.

Our results should be interpreted with certain considerations in mind. We observed no significant modification of the relationship between EoE-QoL-A and biologic findings based on dilation status. Only limited information about dilation characteristics was collected. The modification effect of dilation remains after adjusting for dietary, swallowed topical

corticosteroid, and proton-pump inhibitor therapy use. Given the limited sample size and the cross-sectional nature of the study, the in-depth analysis of the interaction of anti-eosinophil therapies with dilation could not be performed. As these therapies affect both symptoms and inflammation, we do not expect to observe such an interaction. The study describes 25% subset of the cohort, as remaining enrolled patients were excluded due to missing data. The study findings are susceptible to bias, since they are based on a small number of patients. Despite limitations our study had several strengths, particularly its prospective design, the inclusion of multiple sites, the use of a central pathology evaluation process and validated instruments for assessment of clinical endpoints.

In conclusion, dilation modifies the association between histologic activity and symptom severity, and the effects of dilation last longer than 12 months. Future studies evaluating EoE treatments should consider dilation status, and investigators should make decisions regarding stratified randomization based on the planned sample size. Study population characteristics, such as stricture prevalence, should be considered, especially when demonstrating both symptom and PEC improvement is of interest. In clinical practice, symptoms should not be used to monitor response to medical treatments in patients dilated within at least 12 months of index endoscopy if not longer.

TABLES

Table 1: Patient characteristics.

Characteristics	Median, IQR, or Frequency (%) n=100 (All)	Median, IQR, or Frequency (%) n=45 (Non-dilated group)	Median, IQR, or Frequency (%) n=55 (Dilated group)
Age (years) at index endoscopy	37.4 (27 to 46)	32.6 (23.5 to 45.1)	38.4 (31.1 to 46.7)
Age (years) at diagnosis[a]	32.0 (22 to 41)	30.0 (19.0 to 39.0)	35.5 (28.0 to 41.0)
Age (years) at first endoscopy[b]	31.0 (20 to 39)	30.0 (19.5 to 41.0)	32.2 (24.0 to 39.0)
Age (years) at first symptom onset[c]	23.5 (15 to 34)	22.2 (16.0 to 38.0)	26.2 (12.6 to 33.8)
Disease duration (years)[d]	9.7 (4 to 19)	7.1 (3.8 to 12.4)	10.2 (7.1 to 22.7)
Diagnostic delay (years)[e]	4.0 (1 to 13)	3.0 (0.9 to 29.9)	8.9 (0.1 to 40.0)
Male	61 (61.0%)	25 (55.6%)	36 (65.5%)
White	94 (94.0%)	42 (93.3%)	52 (94.5%)
Peak eos/hpf	18.0 (2 to 51)	18.0 (2.0 to 48)	19.0 (2.0 to 52)
EoEHSS (grade+stage)	0.7 (0.3 to 0.9)	0.7 (0.3 to 0.9)	0.6 (0.3 to 1.0)
EREFS (proximal+distal)	5 (2 to 8)	3 (2 to 7)	5 (3 to 9)
EREFS (proximal)	2 (1 to 4)	2 (1 to 3)	3 (1 to 4)
EREFS (distal)	3 (1 to 5)	2 (1 to 3)	3 (2 to 5)
RS (proximal+distal)	2 (0 to 4)	1 (0 to 6)	3 (0 to 8)
RS (proximal)	1 (0 to 2)	1 (0 to 3)	1 (0 to 4)
RS (distal)	1 (0 to 2)	0 (0 to 3)	2 (0 to 4)
EEF (proximal+distal)	3 (1 to 4)	3 (0 to 8)	3 (0 to 8)
EEF (proximal)	1 (0 to 2)	1 (0 to 3)	1 (0 to 4)
EEF (distal)	2 (0 to 3)	1 (0 to 5)	2 (0 to 5)
EEsAI PRO score	27 (12 to 42)	27 (12 to 43)	27 (12 to 39)
Frequency of trouble swallowing			
Never	43 (43.0%)	18 (40.0%)	25 (45.5%)
1-3 times/week	39 (39.0%)	17 (37.8%)	22 (40.0%)
4-6 times/week	13 (13.0%)	6 (13.3%)	7 (12.7%)
Daily	5 (5.0%)	4 (8.9%)	1 (1.8%)
Pain when swallowing	17 (17.0%)	8 (17.8%)	9 (16.4%)
Visual dysphagia question	1.7 (0 to 6)	2.1 (0.4 to 3.3)	1.4 (0 to 3.3)
Avoidance, modification, slow eating (median (range))	1.7 (0 to 6)	1.8 (0.3 to 3.2)	1.5 (0.5 to 2.9)
EoE-QoL-A score	27.0 (15 to 48)	27.0 (15.0 to 51.0)	26.5 (16.0 to 47.5)
Impact of diet/eating	6.0 (3 to 10)	7.0 (3.0 to 11.0)	5.0 (3.0 to 9.0)

Social impact	4.0 (1 to 8)	4.0 (1.0 to 8.0)	3.0 (0.0 to 8.0)
Emotional impact	7.0 (3 to 13)	7.0 (3.0 to 13.0)	7.0 (3.0 to 11.0)
Disease anxiety	6.0 (3 to 12)	6.0 (3.0 to 11.0)	7.0 (4.0 to 12.0)
Swallowing anxiety	4.0 (1 to 6)	4.0 (1.0 to 8.0)	4.0 (2.0 to 6.0)
Anti-eosinophil therapy (at index endoscopy)			
None	4 (4.0%)	1 (2.2%)	3 (5.5%)
Monotherapy with diets	21 (21.0%)	11 (24.4%)	10 (18.2%)
Monotherapy with proton-pump inhibitors	11 (11.0%)	5 (11.1%)	6 (10.9%)
Monotherapy with swallowed topical corticosteroids	28 (28.0%)	14 (31.1%)	14 (25.5%)
Mixed treatments	36 (36.0%)	14 (31.1%)	22 (40.0%)
Dilation	55	NA	55
≤1 year prior index endoscopy	15 (15%)	NA	n=15 Median time (years) from dilation date to index endoscopy, IQR, range 0.59 (0.40 to 0.86), 0.11 to 0.996
>1 year prior to index endoscopy	40 (40%)	NA	n=40 Median time (years) from dilation date to index endoscopy, IQR, range 3.49 (1.95 to 4.11), 1.05 to 19.3

[a] Data available in 39/45 non-dilated and 50/55 dilated patients.

[b] Data available in 44/45 non-dilated and 53/55 dilated patients.

[c] Data available in 38/45 non-dilated and 44/55 dilated patients.

[d] The disease duration is defined as the time interval between the first symptom onset and index endoscopy (data available in 38/45 non-dilated and 44/55 dilated patients).

[e] The diagnostic delay is defined as the time interval between the first symptom onset and diagnosis (data available in 32/45 non-dilated and 41/55 dilated patients).

Abbreviations: EEsAI, eosinophilic esophagitis activity index; eos/hpf, esophageal eosinophilia per high-power field; EoE-QoL-A, adult eosinophilic esophagitis-specific quality of life; EREFS, endoscopic reference score; IQR, interquartile range; RS, rings and stricture score.

Table 2. Linear regression coefficients, 95% confidence intervals, and p-values for the models of EEsAI PRO as outcome in all patients.

Model with eos/hpf as predictor	Coefficient [95% CI]	p-value[b]
[a]**coefficient for 10-cell increase in max eos/hpf in non-dilated patients**	2.69 (0.97, 4.40)	0.002
coefficient for 10-cell increase in max eos/hpf in patients dilated > 1 year prior to index endoscopy	0.78 (-1.48, 3.05)	0.494
coefficient for 10-cell increase in max eos/hpf in patients dilated ≤ 1 year prior to index endoscopy	-1.64 (-4.07, 0.79)	0.183
Model with EREFS as predictor	**Coefficient [95% CI]**	**p-value**
coefficient for unit increase in EREFS in non-dilated patients	1.88 (-0.14, 3.91)	0.068
coefficient for unit increase in EREFS in patients dilated > 1 year prior to index endoscopy	-2.30 (-5.03, 0.42)	0.097
coefficient for unit increase in EREFS in patients dilated ≤ 1 year prior to index endoscopy	-5.31 (-8.91, -1.71)	0.004

[a] The coefficient represents the change in the predicted EEsAI for 10-cell increase in max eos/hpf in non-dilated patients. For a 10-cell increase in eos/hpf score, the predicted EEsAI PRO increased by 2.69 in non-dilated patients.

[b] P-value is testing whether the slope of the regression line in each dilation group is different from zero.

Abbreviations: CI, confidence interval; eos/hpf, esophageal eosinophilia per high-power field; EEsAI, eosinophilic esophagitis activity index; EREFS, endoscopic reference score.

Supplementary Table 1. Single variable linear regression coefficients, 95% confidence intervals, and p-values for the models with EEsAI as outcome in non-dilated patients.

For model with eos/hpf as predictor	Coeff.	95% CI	p-value	R^2	Constant [95% CI]
Per 10-cell increase in max eos/hpf	2.69	(0.97, 4.41)	0.003	0.19	198.9 (117.2-280.5)
For model with EREFS as predictor	**Coeff.**	**95% CI**	**p-value**	**R^2**	**Constant [95% CI]**
Per 1-unit increase in EREFS	1.88	(-0.30, 4.06)	0.089	0.07	19.92 (8.05-31.79)

Abbreviations: coeff, coefficient; CI, confidence interval; eos/hpf, esophageal eosinophilia per high-power field; EEsAI, eosinophilic esophagitis activity index; EREFS, endoscopic reference score.

405 **FIGURES**

406 **Figure 1.** Scatter plots of EEsAI vs. eos/hpf (**A**), EEsAI vs. EREFS (**B**), EoE-QoL-A vs.
407 eos/hpf (**C**), and EoE-QoL-A vs. EREFS (**D**) in non-dilated patients (n=45), in patients dilated
408 >12 (n=40) and ≤12 (n=15) months prior to index endoscopy.

409 **Figure 2.** Scatter plots EEsAI vs. EoEHSS (**A**), EEsAI vs. EoEHSS grade (**B**), EEsAI vs.
410 EoEHSS stage (**C**) in non-dilated patients (n=45), and in patients dilated >12 (n=40) and ≤12
411 (n=15) months prior to index endoscopy.

412 **Figure 3.** The marginal effects plot of expected EEsAI in non-dilated patients (n=45), in
413 patients dilated >12 (n=40) and ≤12 (n=15) months prior to index endoscopy by eos/hpf (**A**)[a],
414 and by EREFS (**B**).

415 [a] In non-dilated patients with the peak eos/hpf of 50 and 100, values of predicted EEsAI of 33
416 and 47, respectively, are observed. In patients dilated <12 months of index endoscopy with
417 the peak eos/hpf of 50 and 100, values of predicted EEsAI of 20 and 12, respectively, are
418 observed.

419 **Abbreviations:** adult eosinophilic esophagitis-specific quality of life; EREFS, endoscopic
420 reference score; EEsAI, eosinophilic esophagitis activity index; EoE-QoL-A, eos/hpf,
421 eosinophils per high-power field; eosinophilic esophagitis Histologic Scoring System
422 (EoEHSS).

423 **Supplementary Figure 1.** Patient selection.

424 **Supplementary Figure 2.** Relationship between eos/hpf and EEsAI subcomponents
425 [frequency of trouble swallowing (box and whiskers plot[a]) (**A**), pain when swallowing (box and
426 whiskers plot) (**B**), VDQ (scatter plot) (**C**), and AMS (scatter plot) (**D**) in non-dilated patients
427 (n=45), in patients dilated >12 (n=40) and ≤12 (n=15) months prior to index endoscopy].

428 **Supplementary Figure 3. A.** Relationship[a] between EoE-QoL-A and EEsAI subcomponents
429 in all patients (n=91). In the trend test for each panel, p-values ≥0.008 or smaller were
430 observed. **B.** Scatter plots of EEsAI vs. EoE-QoL-A in non-dilated patients (n=39), in patients
431 dilated >12 (n=37) and ≤12 (n=15) months prior to index endoscopy.

432 [a] For each distribution, the box spans the values between the quartiles one and three
433 (interquartile range), and the median is marked by horizontal line inside the box. The
434 whiskers extend to the maximum of 1.5× the interquartile range beyond the box boundaries.
435 Data beyond the range of whiskers are outliers and presented as points.

436 **Supplementary Figure 4.** Relationship between eos/hpf and EoE-QoL-A subscales
437 (eating/diet impact (**A**), social impact (**B**), emotional impact (**C**), disease anxiety (**D**) and

swallowing anxiety (**E**)) in non-dilated patients (n=45), and in patients dilated >12 (n=40) and ≤12 (n=15) months prior to index endoscopy.

Abbreviations: adult eosinophilic esophagitis-specific quality of life; AMS, avoidance, modification, slow eating; EEsAI, eosinophilic esophagitis activity index; EoE-QoL-A, eos/hpf, eosinophils per high-power field; VDQ, visual dysphagia question.

443 STROBE Statement—checklist of items that should be included in reports of observational studies
444

	Item No.	Recommendation		Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	6		Adults enrolled in a multisite, prospective Consortium of Gastrointestinal Eosinophilic Disease Researchers OMEGA observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6		Abstract
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8		In adults with eosinophilic esophagitis (EoE), esophageal dilation is frequently used to manage symptoms of esophageal dysfunction but does not improve the underlying inflammatory diathesis. For example, using a non-validated physician-reported dysphagia measure in adult EoE patients managed by dilation alone, Schoepfer et al. demonstrated that dysphagia improved for a median of 15 months. These data were corroborated by the results of a patient survey, in which 67% of patients reported that the effect of dilation on symptoms lasted for 12 months or longer. Presently, in randomized clinical trials

				(RCTs), consideration of the dilation status of enrolled patients is variable. This can be problematic since the effects of dilation on symptoms may be prolonged, and trials are designed to assess improvements in dysphagia in conjunction with improvement in eos/hpf and other biologic markers. Dellon et al. examined the efficacy of budesonide oral suspension in improving symptoms and eos/hpf, and the history of dilation at baseline was not reported. When examining efficacy of budesonide in inducing clinical and histologic remission, Lucendo et al excluded patients with dilation performed within eight weeks of screening.
Objectives	3	State specific objectives, including any prespecified hypotheses	8	Since dilation improves symptoms without any effect on inflammation, we examined long-term effect modification of dilation on the relationship between biologic findings, including centrally read histology, and PROs assessed using validated measures in adult EoE patients
Methods				
Study design	4	Present key elements of study design early in the paper	9	Upon entry into the CEGIR OMEGA prospective, multi-

				center, observational study (ClinicalTrials.gov identification number NCT02523118) AND Cross-sectional data of these patients was analysed for the purposes of this study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9	…. adults with EoE completed PRO instruments and underwent endoscopy with biopsy sampling between February 2016 and March 2018 in 14 centres across the continental United States.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9, Supplementary Figure 1	Patients with EoE of 18 years of age or older were eligible. Patients with histology assessment, PRO assessment and known history of dilation were selected for the study.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10	Linear regression analysis in the overall population as well as in the non-dilated patients

				was performed with EEsAI as the outcome and either eos/hpf or EREFS score as predictors. Residual analysis indicated normality assumptions for the statistical models are appropriate. Given that we hypothesized that dilation might act as an effect modifier (measures of association might be different in the group of patients that were dilated and were not dilated), we included an interaction term for dilation with biologic findings. Dilation was ordered as follows: no dilation (reference category), ≤12 months, and >12 months prior to index endoscopy.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10	The description of the way PRO, histology and endoscopy data were collected is described on pages 9/10. The Wilcoxon rank-sum test was used to compare dilated and non-dilated patient groups. The differences in slopes between dilated and non-dilated patients was assessed using linear regression (interaction terms).
Bias	9	Describe any efforts to address potential sources of bias	9-10	The study was prospectively conducted. Validated measures were used to assess all the outcomes of the

				study (PRO, histology, endoscopy)
Study size	10	Explain how the study size was arrived at	9 Supplementary Figure 1	Patients with histology assessment, PRO assessment and known history of dilation were selected for the study.

445

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10	Quantitative variables were summarized as medians and interquartile ranges. Comparisons between groups were done using Wilcoxon rank-sum test (non-parametric).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding		Non-parametric correlations (Spearman's rho) and linear regression were used. Dilation groups were ordered as follows: no dilation (reference category for linear regression), ≤12 months, and >12 months prior to index endoscopy.
		(*b*) Describe any methods used to examine subgroups and interactions		Linear regression was used. The interaction of dilation and either eos/hpf or EREFS was examined.
		(*c*) Explain how missing data were addressed		No data imputation was used for missing values of outcome measures.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed		Not applicable.

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses		Residual analysis indicated normality assumptions for the statistical models are appropriate.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12, Supplementary Figure 1	Of the 392 patients, 176 had baseline histologic assessment, 122 completed EEsAI PRO. Of the 122, 100 had a history of dilation. Of the 100 patients with EEsAI PRO, 96 patients completed EoE-QoL-A instrument.
		(b) Give reasons for non-participation at each stage	12	Lack of data.
		(c) Consider use of a flow diagram	12, Supplementary Figure 1	The flow diagram is provided in Supplementary Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12, Table 1	Provided in table 1 and discussed in subsection Patient characteristic of the Results section
		(b) Indicate number of participants with missing data for each variable of interest	Supplementary Figure 1	216 were missing central histology assessment at the time of the start of the

				analyses 54 patients were missing EEsAI PRO completion 22 patients were missing the history of dilation 4 patients were missing EoE-QoL-A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		NA
		Cross-sectional study—Report numbers of outcome events or summary measures	12-15	100 outcomes events (EEsAI PRO as outcome)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15	Slope estimates (regression coefficients), interaction term esitimates and their 95% confidence intervals were provided.
		(*b*) Report category boundaries when continuous variables were categorized	12, Table1	Interquartile ranges were provided for continuous variables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity		Not applicable

446

		analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives	16	In this observational cohort study of adult patients with EoE, we found that dilation performed within 12 months of the index endoscopy modifies the relationship between biologic findings and symptom severity as assessed by EEsAI. In non-dilated patients, we identified a statistically significant moderate positive association between eos/hpf and symptom severity. The association tended negative in patients dilated within 12 months of index endoscopy, although it did not reach statistical significance. Similarly, we found a positive weak correlation between EREFS and symptom severity in non-dilated patients that did not reach statistical significance but a statistically significant negative moderate association between these parameters in patients dilated ≤12 months prior to index endoscopy. No association between symptoms and biologic findings was observed in patients that were dilated > 12 months prior to index endoscopy. Overall, the direction of the associations between symptoms and biologic findings was consistent

				irrespective of whether the relationship between symptoms and eos/hpf or symptoms and EREFS was examined. In non-dilated patients, variation in maximum of proximal and distal eos/hpf explained 19% of the variation in symptom severity. Given that dilation modifies the relationship between symptoms and biologic findings, consideration should be given to the impact of dilation on symptom assessment both in therapeutic studies and clinical practice.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18	Our results should be interpreted with a number of considerations in mind. We observed no significant modification of the slope and, therefore, the relationship between EoE-specific quality of life and biologic findings based on dilation status. Therefore, larger studies are needed to examine whether dilation modifies the association between EoE-QoL-A and biologic findings. We observed a negative association, when we examined the relationship between symptoms and biologic findings in 15 patients dilated ≤12 months prior to index endoscopy. Given the relatively small sample size, we were not able to adjust for confounding,

				such as the use of anti-inflammatory therapies and duration of treatment, and other factors responsible for symptom variation in EoE patients. In addition, only limited information about dilation characteristics was collected. Therefore, reasons for this negative association remain unexplained and larger studies are needed to elucidate the nature of the relationship between symptoms and biologic findings in recently dilated individuals.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18	In conclusion, dilation modifies the association between histologic activity and symptom severity, and the effects of dilation last for longer than 12 months. In non-dilated patients, the strength of the positive association between eos/hpf and symptom score was moderate, while no statistically significant association was observed in patients dilated prior to index endoscopy. The results of the current study in part corroborate the finding by Schoepfer and colleagues that previously showed that the effects of the dilation likely last approximately 12 months in adults with EoE (ref 2). In a secondary analyses of data from a RCT comparing oral

				viscous budesonide and fluticasone in a multi-dose inhaler in newly diagnosed EoE patients, Safroneeva et al. recently found that dilation performed ≤3 months prior to symptom assessment not only modifies the association between baseline eos/hpf and symptom severity (findings corroborated by this study), but also modifies the association between the change from baseline to end of treatment in eos/hpf and symptom severity (ref 10)
Generalisability	21	Discuss the generalisability (external validity) of the study results	18	Based on these findings, we suggest that futures studies evaluating treatments for EoE should consider dilation status, and, where appropriate, make decisions regarding stratified randomization in the context of the planned sample size. In addition, characteristics of the study population in terms of stricture prevalence should be considered, especially when demonstrating symptom improvement in conjunction with improvement in eos/hpf is of interest. In clinical practice, symptoms should not be used to monitor the benefit of medical treatments in patients that underwent dilation within at least 12 months prior to index

				endoscopy.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4	CEGIR (U54 AI117804) is part of the Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS. CEGIR is also supported by patient advocacy groups including American Partnership for Eosinophilic Disorders (APFED), Campaign Urging Research for Eosinophilic Diseases (CURED), and Eosinophilic Family Coalition (EFC). As a member of the RDCRN, CEGIR is also supported by its Data Management and Coordinating Center (DMCC) (U2CTR002818). This work is also supported by a grant given to Ekaterina Safroneeva by Swiss National Science Foundation (Project number: 32473B_185008). La Cache Chair for GI Allergy and Immunology Research (GTF).

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Figure 1

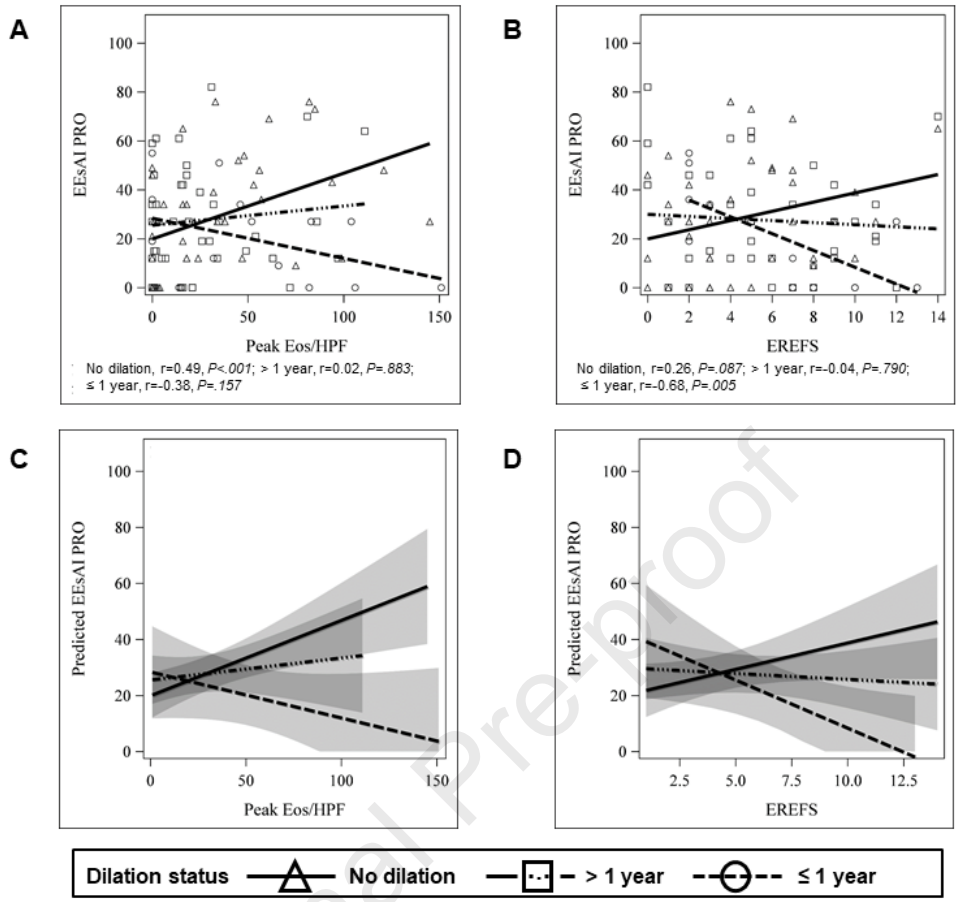
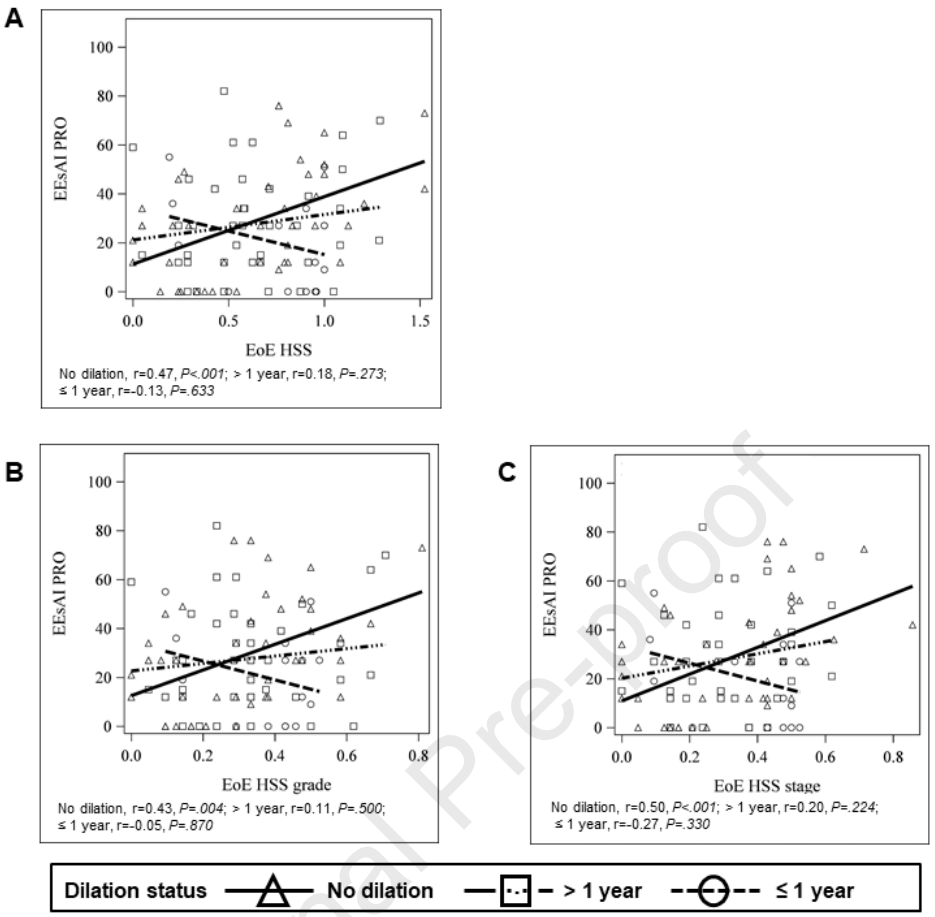
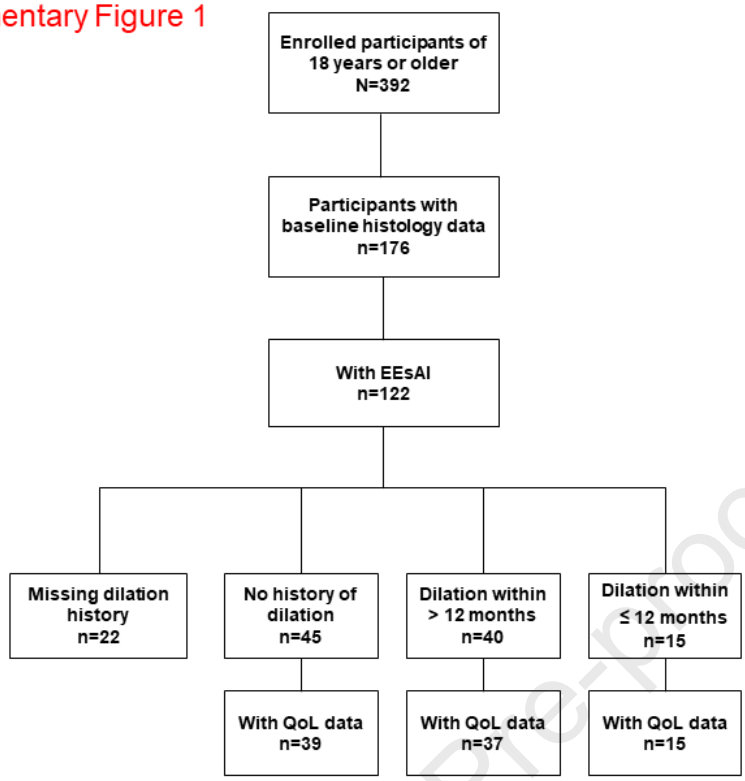


Figure 2

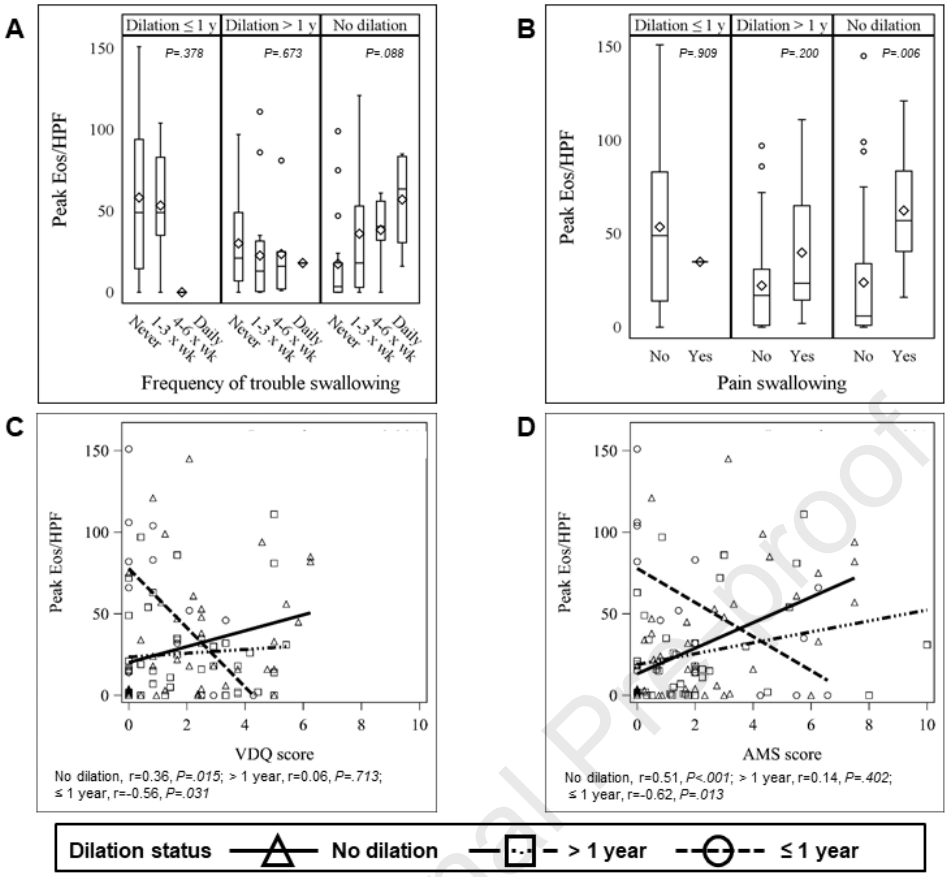


Supplementary Figure 1

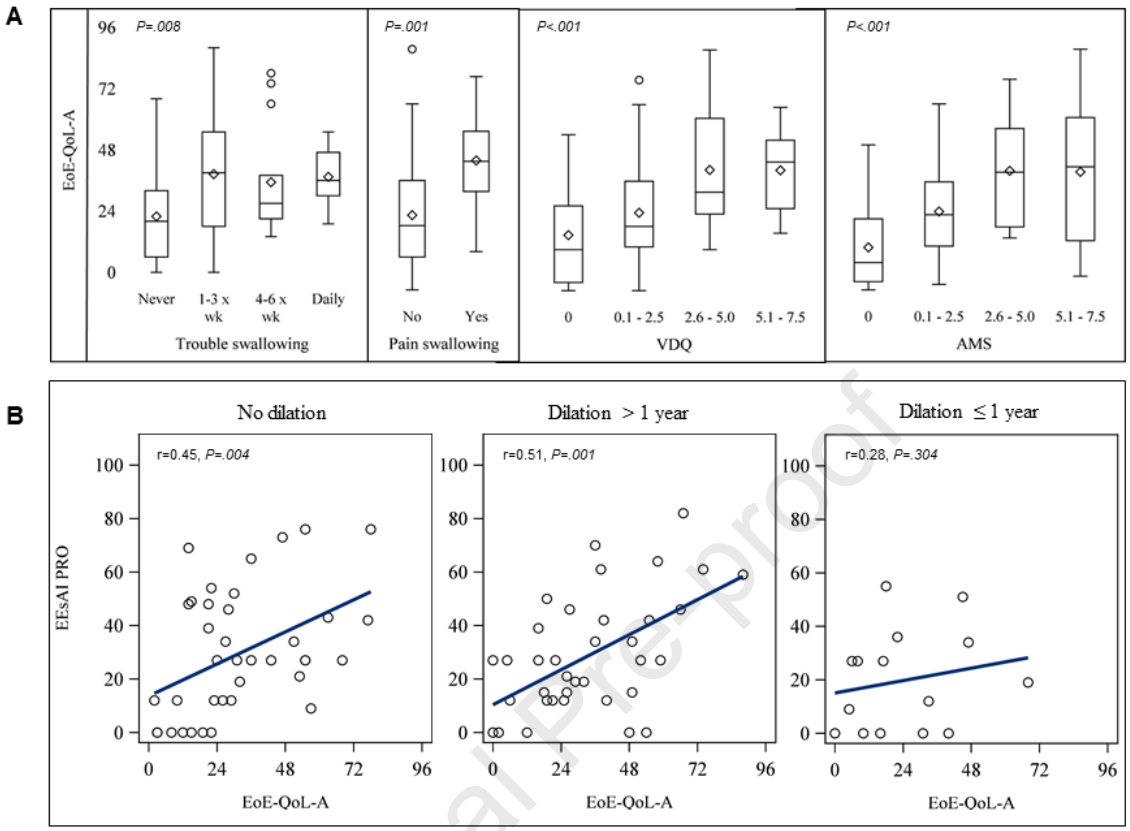


* The field for past dilation history is blank in medical history table.

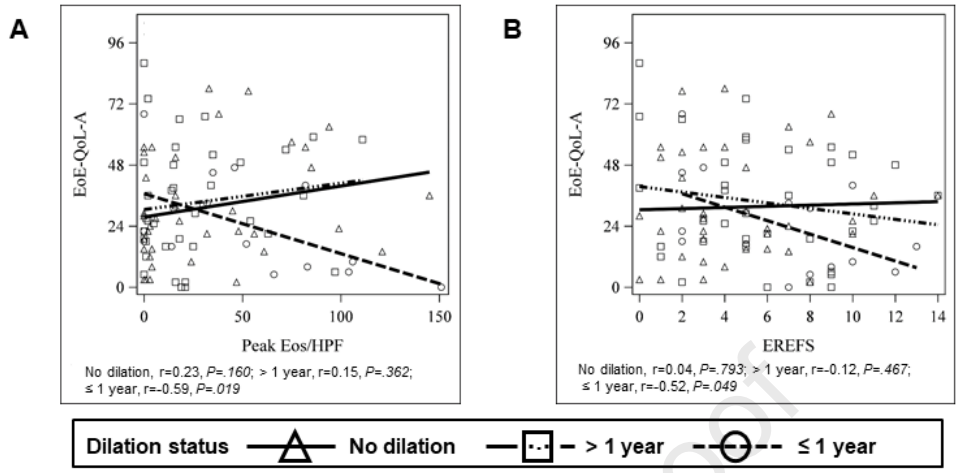
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



What You Need to Know

Background

As esophageal dilation improves dysphagia but not inflammation in eosinophilic esophagitis patients, it might mask the association between symptoms and biologic findings; literature on duration of that effect is limited.

Findings

In non-dilated adult patients, inflammation correlates modestly with symptoms; this correlation was no longer appreciated in dilated patients, and the dilation effects lasted longer than one year.

Implications for patient care

Symptoms should not be used to monitor therapy response for at least 12 months after dilation.