

Long-term assessment of esophageal remodeling in patients with pediatric eosinophilic esophagitis treated with topical corticosteroids

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Background: Eosinophilic esophagitis (EoE) is a chronic T_H2 inflammatory disease characterized by tissue remodeling that leads to esophageal strictures and food impactions. Effects of therapy on long-term remodeling in patients with pediatric eosinophil-associated diseases have not been previously described.

Objective: We sought to understand the long-term control of esophageal remodeling in patients with EoE.

Methods: We assessed endoscopic and histologic remodeling and TGF- β 1 expression in esophageal biopsy specimens from children (n = 32) with EoE treated with topical corticosteroids (TCSs) over 10 years (mean, 4.5 years). We used standardized EoE scoring tools to gauge endoscopic and symptom features. **Results:** Seven hundred thirty-eight biopsy specimens from 246 endoscopic procedures were evaluated over 10 years. Four hundred eighty-six biopsy specimens had adequate lamina propria for evaluation of subepithelial remodeling. The severity of epithelial esophageal eosinophilia correlated with epithelial remodeling (basal zone hyperplasia, desquamation, and dilated intercellular spaces; $P < .0001$), lamina propria eosinophilia ($P < .0001$), and fibrosis ($P < .0001$). Sixteen subjects were initial responders (<15 eosinophils/high-power field) to TCSs.

Responders and nonresponders spent 54% and 97% of their total disease duration with active EoE ($P < .001$) and 23% and 53% ($P < .02$) with maximal fibrosis scores, respectively.

Responders had lower endoscopy scores during their disease duration ($P = .013$). Having less than 15 eosinophils/high-power field at any time correlated with lower fibrosis and endoscopic severity. TGF- β 1⁺ cell counts decreased in responders at the first biopsy, but this was not sustained. Symptoms did not correlate with other disease features.

Conclusions: Children with EoE have substantial esophageal remodeling, which associates with inflammation and can improve in a sustainable manner with TCSs. Although endoscopic features correspond to histologic features, symptoms did not correlate with inflammation or fibrosis. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Eosinophilic esophagitis, remodeling, fibrosis, topical corticosteroid, TGF- β 1

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Supported by National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) grant AI092135 (to S.S.A.); an ART/APFED HOPE Award (to S.S.A.); Department of Defense grant FA100044 (to D.H.B. and S.S.A.); NIH/NIAID grants AI 107779, AI 70535, and AI 72115 (to D.H.B.); the Hearst Foundation (to R.D.); and CEGIRS U54AI117804 (to S.S.A.) as part of the Rare Diseases Clinical Research Network, an initiative of the Office of Rare Diseases Research, NCATS; this consortium is funded through collaboration between NCATS, NIAID, and NIDDK. This project was also partially supported by NIH grant ULRR031980 for years 1 and 2, CTSA funding and/or UL1TR0001000 during year 3 and beyond of CTSA funding (support of the EoE database).

Disclosure of potential conflict of interest: R. Dohil has a patent for oral viscous budesonide and receives royalties from this patent and has stock/stock options with Meritage Pharma. D. H. Broide has received research support from the National Institutes of Health (NIH). S. S. Aceves has received research support from the NIH/National Institute of Allergy and Infectious Diseases (NIAID) and the Department of Defense, is a member of the medical advisory boards for Food Allergy Research and Education and the American Partnership for Eosinophilic Disorders, has a patent for Oral Viscous Budesonide and receives royalties from this patent, has stock/stock options in Meritage Pharma, and has received travel support from the NIH/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 12, 2014; revised April 15, 2015; accepted for publication May 14, 2015.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2015.05.045>

Eosinophilic esophagitis (EoE) is a chronic inflammatory T_H2 disease of increasing prevalence and incidence that is associated with substantial tissue remodeling, including fibrosis and angiogenesis.^{1,2} Remodeling is believed to be the underpinning of EoE complications that include dysmotility, strictures, narrowing, and food bolus impactions.^{3,4} Remodeling includes histologic changes of epithelial basal zone hyperplasia and dilated intercellular spaces, as well as subepithelial angiogenesis, fibrosis, and smooth muscle hyperplasia/hypertrophy.⁵ Natural history studies in adults demonstrate that EoE is a progressive fibrostenotic disease, which almost uniformly leads to stricture formation, and increasing stricture risk is proportional to longer untreated disease duration.^{6,7} In children and adults EoE is a chronic disorder with spontaneous remission occurring in a minority of patients.⁸⁻¹⁰ Although longitudinal studies assessing endoscopic and symptomatic fibrostenosis in adults have been published,^{7,11} there have been no long-term systematic histologic assessments of remodeling in patients with EoE. Indeed, eosinophil-associated tissue remodeling and its clinical effects have been difficult to study in the past because of a paucity of human tissue for analysis. In this regard EoE offers a novel opportunity to understand the relationship between histologic and molecular tissue remodeling with clinical disease features.

Chronic management with either medications or food elimination is required to maintain EoE remission.^{9,11} Disease control is important for the patient's quality of life, as well as for decreasing complications.^{12,13} Adult studies show that increasing use of esophageal topical corticosteroids (TCSs) over a 5-year time period associates with fewer episodes of food impactions.¹¹ Although this type of data has not been published in the pediatric

Abbreviations used

EGD:	Esophagogastroduodenoscopy
EoE:	Eosinophilic esophagitis
FS:	Fibrosis score
hpf:	High-power field
LP:	Lamina propria
PPI:	Proton pump inhibitor
TCS:	Topical corticosteroid
UCSD/RCHSD:	University of California San Diego/Rady Children's Hospital—San Diego

EoE population, it is clear that children also need prolonged dietary elimination, TCSs, or both.^{9,14} In children short-term TCSs, dietary elimination, or both can control both inflammation and fibrosis.^{15–17} However, whether TCSs can sustainably control remodeling is not clear. In addition, the duration and degree of inflammatory control to avoid the onset of fibrosis are not clear.¹⁸ The notion that prolonged fibrotic control implies control of esophageal narrowing is a hypothesis that has not been proved. These issues are particularly salient for children, many of whom will likely require lifelong therapy and for whom prevention of stricture over their lifetime is a key component of disease management.

To begin to understand the relationships between long-term TCS therapy, esophageal remodeling, and clinical course, we analyzed 738 biopsy specimens from 32 pediatric patients with EoE over a maximum of 10 years. To our knowledge, this is the largest cohort of pediatric biopsy specimens studied in the context of esophageal remodeling and fibrosis over time, as well as the first study to assess tissue remodeling in the setting of any eosinophil-associated disease in children over long treatment times. Our current data suggest that control of epithelial eosinophilia correlates with control of lamina propria (LP) eosinophilia and fibrosis in children and that endoscopic and histologic features are better controlled both in initial responders to esophageal TCS therapy and in those children who had epithelial eosinophilia of less than 15 eosinophils/high-power field (hpf) at any given point in their disease course. Although epithelial inflammation and endoscopic features correlated with fibrosis, symptoms did not. Given the number of years of follow-up and the large number of endoscopic/histologic features studies, these data have potentially important clinical implications for EoE control and progression and point to the need for additional therapeutic strategies to control chronic esophageal eosinophilia.

METHODS**Patients with EoE and biopsies**

Subjects were selected from the University of California San Diego/Rady Children's Hospital—San Diego (UCSD/RCHSD) EoE database who met the following criteria: (1) EoE defined as 15 or more eosinophils/hpf on hematoxylin and eosin staining at $\times 400$ magnification on light microscopy; (2) the presence of typical symptom and endoscopic features; (3) semi-continuously prescribed esophageal TCSs; (4) adequate (defined as ≥ 3 eosinophils/hpf) LP in at least 3 specimens over time, including the baseline biopsy specimen; and (5) treatment follow-up at UCSD/RCHSD for a minimum of 12 months. A total of 32 subjects met the criteria and were analyzed. Subjects' characteristics are listed in [Table I](#). All studies were approved by the UCSD/RCHSD Institutional Review Board.

Immunostaining and histologic assessment

Hematoxylin and eosin–stained, formalin-fixed, paraffin-embedded specimens from 3 esophageal levels (proximal, middle, and distal; 2–3 biopsy specimens per level) were evaluated by a single pathologist blinded to the therapy (R.O.N.). The numbers of epithelial and LP eosinophils, severity of basal zone hyperplasia, presence/absence of dilated intercellular spaces and desquamation, and LP fibrosis severity were quantified by using our previously published pathology scoring tool.¹⁹ The epithelial remodeling score was generated by adding basal zone hyperplasia severity (0–3) to the presence or absence of dilated intercellular spaces and desquamation (0 = absent, 1 = present). LP fibrosis was scored as 0 to 3 based on the density of collagen bundles. The average epithelial remodeling score and LP fibrosis score (FS) is reported.

Tissue sections (5 μ m) were deparaffinized, hydrated, and immunostained, as previously described, for anti-TGF- $\beta 1$ antibody (1:400; Santa Cruz Biochemicals, Santa Cruz, Calif).² The mean of the peak numbers of TGF- $\beta 1^{+}$ cells from 3 to 5 hpfs were quantified and reported as cells per square millimeter by using ImagePro software (ImagePro; Media Cybernetics, Bethesda, Md). All images were analyzed under identical light microscopic conditions, including magnification, gain, camera position, and background illumination.

Endoscopy and symptom score

Endoscopy and symptom scores were generated as previously described.¹⁹ Features of pallor/lichenification, plaques, concentric rings/strictures/narrowing, and friability were graded as present/absent (0/1) at each esophageal level for total endoscopy score (maximum = 12). Symptoms of heartburn/regurgitation, nausea/vomiting, dysphagia, abdominal pain, and nocturnal awakening were graded 0 to 3 by the subjects and their parents for the total symptom score.

Statistical analysis

All statistical analyses and graphing were done with GraphPad Prism software (GraphPad Software, San Diego, Calif). Comparisons between 2 groups were done with an unpaired *t* test for continuous/Gaussian variables; the Mann-Whitney test was used for nonparametric variables. Comparisons within a group were done as paired *t* tests or Wilcoxon matched pairs tests for continuous/Gaussian variables or noncontinuous variables, respectively. A *P* value of less than .05 was considered significant.

RESULTS**Clinical characteristics**

One hundred twelve subjects from the EoE database were screened for the presence of biopsy specimens with adequate LP to assess remodeling features in at least 3 instances when followed clinically for at least 12 months and prescribed semicontinuous TCS therapy with fluticasone or oral viscous budesonide as routine clinical care. Thirty-two subjects met all of the required criteria. Three subjects, all nonresponders, had their diagnostic biopsies performed at an outside facility. Twenty-nine (91%) subjects were male, 26 (81%) were atopic (defined as a positive serum IgE level or skin prick test response to foods or aeroallergen), and 26 (81%) were white. The mean age at diagnosis was 6 years (range, 13 months to 17 years). Proton pump inhibitor (PPI) monotherapy failed in 20 (63%) subjects. Nine of the subjects were given a diagnosis before the EoE consensus recommendations of PPI monotherapy and before our current understanding of PPI-responsive esophageal eosinophilia.^{20–22}

We evaluated 246 endoscopic procedures with 738 biopsies in the study time period ([Table I](#)). In total, 486 biopsy specimens were evaluated for remodeling. The remainder were excluded

TABLE I. Subjects' characteristics

Age at diagnosis (y)	Sex	Total disease duration (y)	Duration of disease analyzed (y)	Total no. of EGDs	EGDs that were analyzed	EGDs during TCS use (%)	EGDs during PPI use (%)	Responder
1.08	M	7.50	5.50	11	7	67	86	Yes
1.25	M	3.92	3.92	8	7	33	43	No
1.42	M	9.17	6.33	11	4	100	75	Yes
1.42	M	5.92	5.92	7	6	100	17	Yes
1.42	M	1.00	1.00	3	3	50	33	No
2.25	M	5.67	1.75	9	4	67	75	No
2.42	M	8.75	7.50	15	8	100	88	No
2.92	M	12.25	10.00	12	6	20	0	No
3.17	M	7.42	7.33	8	6	60	33	No
3.42	M	7.08	5.67	12	8	100	100	Yes
3.50	M	8.17	6.33	10	3	0	33	Yes
4.00	F	4.08	4.08	6	5	75	100	Yes
4.08	M	4.75	1.75	9	3	100	67	Yes
4.42	F	9.25	7.67	18	8	100	75	No
4.75	M	5.58	4.00	17	7	83	71	Yes
4.92	M	1.33	1.33	3	3	100	0	Yes
4.92	M	9.42	5.92	13	5	100	100	No
5.08	M	8.83	3.83	20	9	100	100	No
5.25	M	12.83	5.50	14	4	67	25	Yes
6.58	M	2.67	2.67	4	4	100	75	No
6.75	M	6.00	6.00	8	4	100	50	Yes
6.83	F	9.75	8.75	11	5	75	40	No
7.17	M	4.67	4.67	7	5	100	100	Yes
7.83	M	1.33	1.33	4	4	100	50	Yes
8.08	M	6.17	4.17	11	6	100	50	No
8.75	M	8.08	6.00	13	4	100	100	Yes
9.33	M	4.08	3.50	7	5	50	100	Yes
9.33	M	8.50	7.17	10	3	50	67	Yes
10.75	M	2.42	2.42	5	5	100	20	No
13.67	M	4.17	1.75	8	4	100	75	No
16.58	M	1.25	0.92	4	3	50	33	No
17.08	M	1.25	0.67	4	3	100	67	No
5.95 (mean)		6.04 (mean)	4.54 (mean)	9.44 (mean)	5.03 (mean)	79.58 (mean)	60.23 (mean)	

F, Female; M, male.

because of a lack of adequate LP. These biopsies covered a maximum of 10 years and a mean of 4.5 years of follow-up. There were 4.7 procedures per subject done during TCS treatment (range, 3-8 procedures). Overall, 63% and 80% of the biopsy specimens were procured on reported adherence with prescribed PPIs and TCSs, respectively (Table I). The initial dose of TCS was 110 to 220 μ g, 2 puffs swallowed twice daily, for fluticasone propionate or 0.5 to 2 mg/d for oral viscous budesonide. Repeat biopsies were done in the subjects for changes in prescribed or self-instituted TCS dose, nonadherence to the prescribed regimen, or routine surveillance follow-up.

Baseline histologic and endoscopic features

Baseline epithelial eosinophil count per hpf in the total cohort was 81 (95% CI, 66-95). Our standardized histology scoring tool includes an epithelial remodeling score encompassing basal zone hyperplasia severity plus the presence/absence of dilated intercellular spaces plus the presence/absence of desquamation (maximum, 5). The baseline mean epithelial remodeling score was 3.2 (95% CI, 2.8-3.6). The mean number of LP eosinophils per hpf was 23 (95% CI, 13-32), FS was 2.7 (maximum, 3; 95% CI, 2.5-2.9), and the mean number of TGF- β 1⁺ cells was 1332/mm² (95% CI, 1127-1537/mm²; Table II).

There were no differences in baseline histologic findings by age. Children 0 to 3 years old had epithelial remodeling, LP fibrosis, and TGF- β 1⁺ cell counts that were similar to those of children in all the older age groups (Fig 1, A-C). However, there were significant differences in baseline total esophagogastroduodenoscopy (EGD) scores in children by age. Children who were older than 10 years had EGD scores that were almost twice as high (mean score, 10; 95% CI, 4.49-15.51) as children who were less than 10 years old (mean EGD score, 5.3; 95% CI, 4.05-6.6; $P = .017$; Fig 1, D).

In adults the validated endoscopic EoE Endoscopic Reference Score (EREFS) system uses concentric rings, narrowing, and strictures as esophageal remodeling features.²³ EREFS is not validated in children. Our prior work suggests that in children LP remodeling features correlates with endoscopic linear furrows.¹⁹ By using rings, narrowing/strictures, and/or furrows, 21 (65%) subjects had endoscopic remodeling, with furrows in 21 (65%), rings in 3 (9%), and strictures in 1 (3%, Table II). Baseline endoscopic features reflective of inflammation (pallor and plaques) also occurred in the majority of subjects.

Longitudinal features in the total cohort

It is not possible to know exactly when esophageal inflammation reasonably started by using symptom criteria in children. For

TABLE II. Baseline histologic, endoscopic and symptom scores in responders versus nonresponders

Category	Age (y)	Epithelial eosinophils/hpf	Epithelial remodeling (range, 0-5)	LP eosinophils/hpf	Fibrosis (range, 0-3)	TGF- β 1 ⁺ (cells/mm ²)	Symptom score (0-14)	EGD features	EGD score (range, 0-15)
Responders	5.25	86	3	120	3	745	2	Pa, F	6
	1.42	100	3.33	18	2.66	2032	0	Pa, F, Pl	8
	3.42	70	4	27	2.66	1650	0	Pa, F	4
	1.42	80	4	62	3	2284	2	Pa, F, Pl	9
	9.33	50	3	13	1	983	7	Pa, F	6
	1.08	50	4	26	2.33	1330	4	Pa, F, Pl	9
	3.50	16	1.33	40	2	946	2	Normal	0
	8.75	150	3	4	2.5	1386	2	Normal	0
	9.33	80	3.33	7	2.66	1416	2	Pa, F	6
	7.17	50	0	8	3	710	0	Pa, R	2
	6.75	28	3	4	3	535	5	Pa, F	6
	4.08	15	1.33	5	2.3	464	4	Pa, F	4
	4.75	120	3.67	15	2.66	481	4	Pa, F, Pl	9
	7.83	95	3	2	3	1494	1	Pa, Pl	6
	4.00	58	3.67	18	3	2062	7	Pl	2
	4.92	110	2.33	13	3	2437	5	Pa, F, Pl	7
Mean	5.19	72.38	2.87	23.88	2.61	1309	2.94		5.25
Nonresponders	2.92	115	3.33	50	3	1651	4	Pa, F, Pl	9
	13.67	54	4	25	2	905	2	Pa, F, R, Pl, S	15
	2.42	100	1.67	10	1.5	1573	2	Pa, Pl	2
	5.08	40	ND	ND	ND	ND	ND	ND	ND
	4.42	100	4.67	25	3	1252	0	Pa, F	6
	8.08	100	2.67	7	3	1443	0	Pa, F, Pl	9
	2.25	40	4	1	3	2093	9	Normal	0
	6.83	89	4	7	3	1154	2	Pa, F, Pl	9
	4.92	50	3.33	34	3	1187	4	Pa, F	6
	3.17	100	ND	ND	ND	ND	ND	ND	ND
	10.75	80	4.33	45	3	816	2	Pa, F, Pl	9
	6.58	50	4	27	3	1317	4	Pa, F	6
	16.58	95	3.33	9	3	878	1	Pa, F, Pl	7
	17.08	150	2.67	1	3	1714	6	Pa, F, R	9
	1.25	60	ND	ND	ND	ND	ND	ND	ND
	1.42	200	4.67	35	3	1690	10	Pl	2
Mean	6.71	88.9	3.59	21.23	2.81	1359	3.54		6.85

F, Furrows; ND, not done; Pa, pallor; Pl, plaques; R, rings; S, stricture.

this reason, we defined EoE initiation as the time of first histologic evidence of esophageal eosinophilia. All of the subjects could be evaluated through their third endoscopy (2.6 years), and 44% could be evaluated through their fifth endoscopy (4.1 years, Fig 2). To have sufficient numbers of subjects per group over time (Fig 2), we combined endoscopic procedures into instances such that endoscopies 4 and 5 were evaluated together (mean, 4.1 years) and endoscopies 6 to 8 were evaluated together (mean, 5.6 years).

We analyzed the relationship between epithelial inflammation and histologic remodeling longitudinally over time. The severity of peak epithelial eosinophilia correlated positively with epithelial remodeling over the entire disease duration ($r = 0.76$, $P < .0001$) and in most instances (overall = longitudinal over the entire disease and instance = at each endoscopy, Table III). Epithelial eosinophilia also correlated with LP fibrosis ($r = 0.53$, $P < .001$) and eosinophilia ($r = 0.54$, $P < .001$) both longitudinally and at multiple instances (Table III). The severity of the mean epithelial eosinophilia correlated even more strongly with epithelial remodeling over time (see Table E1 in this article's Online Repository at www.jacionline.org). Fibrotic severity depended on disease duration and inflammatory severity. Generally, subjects of all ages and disease durations had lower FSs if they had less

than 15 epithelial eosinophils (Fig 3). The overall mean FS over time in the children with less than 15 eosinophils/hpf was 1.03 compared with an FS of 2.59 in children with 15 eosinophils/hpf or more ($P < .0001$). TGF- β 1 cell counts correlated with epithelial eosinophilia in the overall group only in the baseline biopsy specimen (Table III). Fibrosis correlated most strongly with epithelial remodeling (see Table E2 in the article's Online Repository at www.jacionline.org).

Longitudinal effects of therapies in addition to TCSs

Because PPI therapy can alter esophageal eosinophilia and its effects on remodeling are unknown, we compared the degree of esophageal eosinophilia and remodeling between those subjects receiving or not receiving PPIs at any given instance (see Fig E1 in this article's Online Repository at www.jacionline.org). This analysis demonstrated that the presence of PPIs did not have significant effects on eosinophilia or remodeling. We also completed a subgroup analysis by using only those subjects (63%) in whom PPI monotherapy failed and found that this subgroup analysis was essentially identical to the analysis of the entire cohort longitudinally at each instance (see Fig E1, left panel) and over the overall timeframe (see Fig E1, right panel,

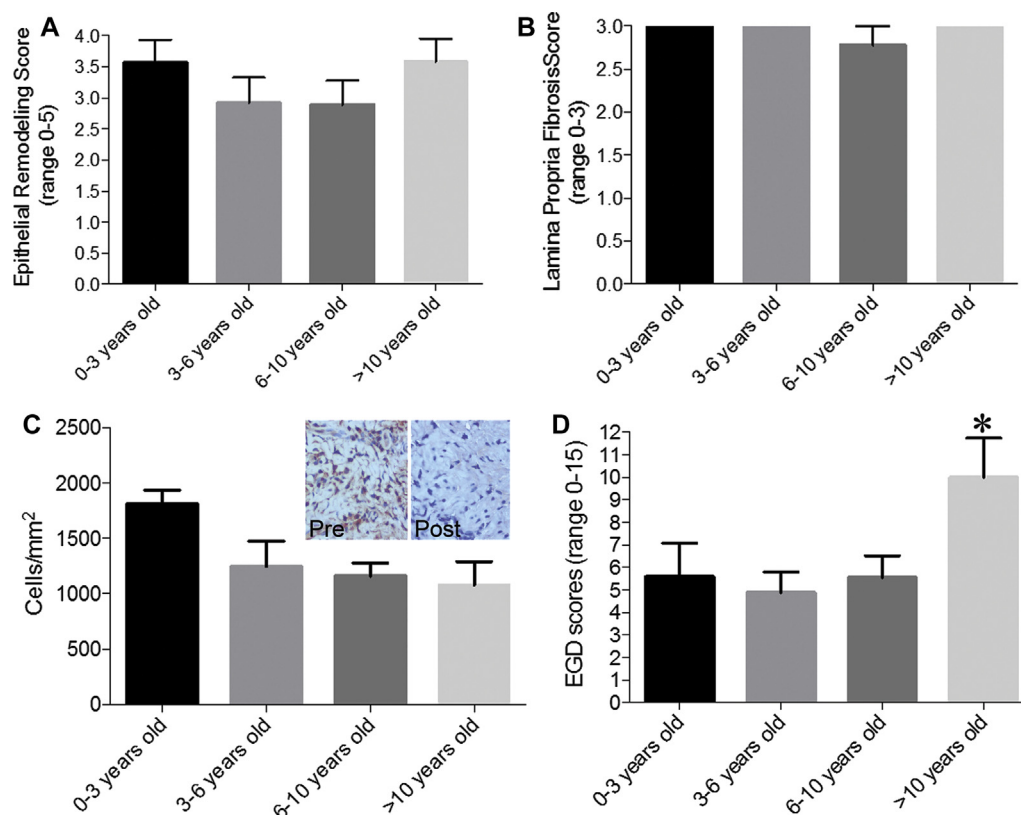


FIG 1. Esophageal remodeling features broken down by age: **A**, epithelial remodeling; **B**, LP FSs; **C**, TGF- $\beta 1^+$ cells; and **D**, EGD scores by age group.

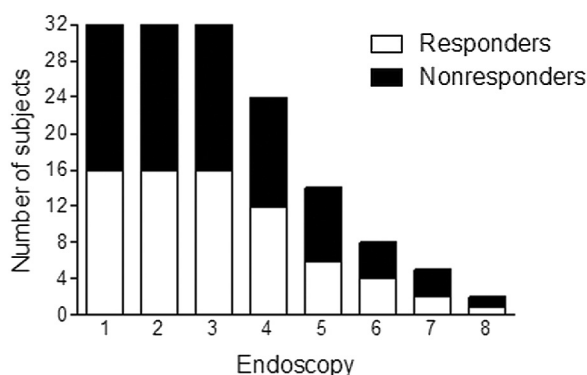


FIG 2. Number of study subjects by endoscopy. Open bars represent responders, and solid bars represent nonresponders.

and see Fig E2 in this article's Online Repository at www.jacionline.org.

We excluded time points in the study period when subjects were receiving oral corticosteroids (8 instances), dietary elimination (1 instance), or biologic therapy (4 instances). A secondary analysis that included these instances showed that overall epithelial eosinophilia and LP fibrosis were higher in those subjects who received other therapy in addition to TCSs. This likely reflects the difficulty in controlling their disease. In addition, there were no substantial changes in these data when these additional instances were added (see Fig E3 in this article's Online Repository at www.jacionline.org).

Effects of TCSs on histologic features: Responders versus nonresponders

To compare subjects with active inflammation despite TCS therapy with those with controlled inflammation, we separated the subjects into responders and nonresponders based on their initial histologic response of less than 15 (responders) or 15 or more (nonresponders) eosinophils/hpf. Based on these criteria, 16 subjects were responders, and 16 were nonresponders. Subjects were kept in their initial category for each instance evaluated over 10 years. No baseline symptoms or histologic or endoscopic features predicted initial responders from nonresponders (Tables I and II).

Responders and nonresponders had equivalent numbers of biopsy specimens to evaluate with 4.6 EGDs per subject (range, 3-8 EGDs) in responders over a mean of 4.7 years, whereas nonresponders had 4.8 EGDs (range, 3-8 EGDs) per subject over a mean of 4.3 years. It is important to note that nonresponders still had decreases in their eosinophil counts at a number of time points. They also had improvements in their symptoms and EGD scores (Fig 4).

Responders had significantly more substantial decreases in their epithelial eosinophilia and remodeling compared with nonresponders longitudinally over time ($P < .0001$; Fig 4, A and B, right panel) and at multiple instances over the study period (Fig 4, A and B, left panel). As a group, initial responders had fluctuating epithelial eosinophilia despite stated adherence to prescribed esophageal TCSs (Fig 4, A, left panel). Initial control of epithelial eosinophilia was maintained in 10 (62.5%) responders over 1.9 years when analyzing all of the biopsy specimens, even if

TABLE III. Correlation coefficients when comparing epithelial eosinophilia with epithelial feature scores, LP eosinophil counts, LP FSs, and TGF- β 1 cell counts

Time (y)	Epithelial remodeling	LP eosinophils	Fibrosis	TGF- β 1 ⁺ cells
0	$r = 0.08, P = .68$	$r = -0.03, P = .89$	$r = 0.19, P = .3$	$r = 0.38, P = .04$
1.2	$r = 0.85, P < .0001$	$r = 0.81, P < .0001$	$r = 0.77, P < .0001$	$r = 0.33, P = .06$
2.6	$r = 0.85, P < .0001$	$r = 0.65, P = .0002$	$r = 0.58, P = .002$	$r = 0.12, P = .50$
4.1	$r = 0.71, P < .0001$	$r = 0.46, P = .004$	$r = 0.42, P = .012$	$r = -0.33, P = .045$
5.6	$r = 0.90, P < .0001$	$r = 0.61, P = .039$	$r = 0.62, P = .035$	$r = -0.53, P = .041$
Overall	$r = 0.76, P < .0001$	$r = 0.54, P < .001$	$r = 0.53, P < .001$	$r = 0.06, P = .47$

LP was not available. The average time to recurrence of epithelial eosinophilia to greater than 15 eosinophils/hpf in responders was 2.8 years. Nonresponders had nonsignificant improvements in their epithelial eosinophil counts initially (Fig 4, A, left panel), and 4 time points from 4 subjects had less than 15 epithelial eosinophils/hpf. As a group, the lowest epithelial eosinophil count per hpf in the nonresponders was 62, which occurred at 1.21 years (Fig 4, A). Responders and nonresponders spent 46% and 2% of their disease duration, respectively, with histologic control of esophageal eosinophilia ($P < .0001$). The reported rates of medication adherence were similar between responders (88%) and nonresponders (84%, $P = .47$) over the 10 years, suggesting that medication use might not account for differences in therapeutic response. We also found that accounting for PPI use at any instance in responders and nonresponders did not significantly change any of the inflammatory or remodeling parameters, except epithelial eosinophil counts at baseline in nonresponders and LP eosinophils at year 4.1 in responders (data not shown).

At multiple instances over time and longitudinally over the study period, responders had fewer LP eosinophils ($P = .05$) and lower FSs ($P = .01$) than nonresponders (Fig 4, C and D, left panel for each instance and right panel overall). There was a significant correlation between LP eosinophil counts and fibrosis ($r = 0.54$, $P < .0001$) among responders. Responders and nonresponders spent 23% and 54% of their time, respectively, at a maximal FS of 3 ($P = .025$). An FS of greater than 2 correlated with an epithelial eosinophil count of 78 eosinophils/hpf and an LP eosinophil count of 20 eosinophils/hpf, whereas an FS of less than 2 correlated with epithelial and LP eosinophil counts of 29 and 6 eosinophils/hpf, respectively. Fibrosis went together with inflammation and seemed not to be significantly affected by TCSs outside of inflammatory control because subjects receiving or not receiving TCSs 75% or greater or less than 75% of the time did not have significantly different FSs (see Fig E4 in this article's Online Repository at www.jacionline.org), and subjects with less than 50 eosinophils/hpf over time had significantly lower FSs (see Fig E5 in this article's Online Repository at www.jacionline.org). Consistent with this, subjects who had more than 50 eosinophils/hpf over their disease duration had significantly higher FSs and EGD scores than subjects who had less than 15 or 15 to 50 eosinophils/hpf overall (see Fig E5). The time to the first EGD was longer in this cohort of subjects than in our previously published cohorts, and as such, the current data show that pediatric responders can have control of many remodeling features, including fibrosis for more than 1 year, while successfully treated with TCSs.

TGF- β 1-expressing cell counts were lower at the first EGD after TCSs in responders ($P = .05$; Fig 4, E) but not over the entire disease duration. TGF- β 1 counts were lower in responders than nonresponders for 2.6 years. Unexpectedly, TGF- β 1 counts increased in responders to greater than those seen in

nonresponders at year 4.1 of therapy. In responders the numbers of TGF- β 1⁺ cells correlated with the FS ($r = 0.32$, $P = .01$), but this was not the case in nonresponders.

We also assessed the potential effect of atopy in our subjects. Of the 32 subjects, 84% had some atopic disease. Twenty-two subjects had allergic rhinitis (11 responders and 11 nonresponders), 9 had asthma (3 responders and 6 nonresponders), 8 had eczema (3 responders and 5 nonresponders), and 13 had food allergies (5 responders and 8 nonresponders). Because there were more nonresponders who had asthma, food allergies, or both, we assessed potential differences in disease control in these subjects. Asthmatic patients had significantly higher baseline epithelial eosinophil counts than nonasthmatic subjects (see Fig E6 in this article's Online Repository at www.jacionline.org). There were no other differences in inflammatory parameters in asthmatic patients or patients with food allergy at baseline or overall (data not shown).

Effects of TCSs on endoscopy and symptoms

EGD scores decreased in proportion to epithelial remodeling ($r = 0.73$, $P < .0001$) and the LP FS ($r = 0.58$, $P < .0001$) in responders. At multiple instances and over the disease duration, responders had significantly lower EGD scores than nonresponders (mean, 2.8 vs 4.0; $P < .01$; Fig 4, F). By using furrows, strictures, rings, or narrowing as endoscopic signs of remodeling, responders and nonresponders spent 44% and 27%, respectively, of their disease duration with an endoscopically unremodeled esophagus ($P = .04$). Four children had strictures or rings, 3 of whom had these findings at baseline. One subject was a responder whose strictures reversed on therapy. The other 3 were nonresponders, and among them, 1 had improvement, 1 had no improvement, and 1 progressed to narrowing despite therapy. The 2 patients who had no improvement of progression to strictures spent 100% of their time during the study period at an FS of 3. Symptoms were not consistently different among the responders or nonresponders at any instances or overall (Fig 4, G).

Results using shifting groups for responders and nonresponders

For the purposes of this study, responders were defined as those subjects who responded initially to therapy. However, epithelial eosinophil counts fluctuated from one biopsy specimen to the next. For this reason, we reanalyzed the longitudinal data by allowing subjects to shift categories (ie, responder to nonresponder and *vice versa*) at any given instance. By using this analysis, 62.5% of subjects were responders over the 10 years of follow-up, and it was evident that decreases in epithelial eosinophilia associated with decreases in epithelial remodeling, LP eosinophilia, and FS (Fig 5, A-D). In subjects who had less than

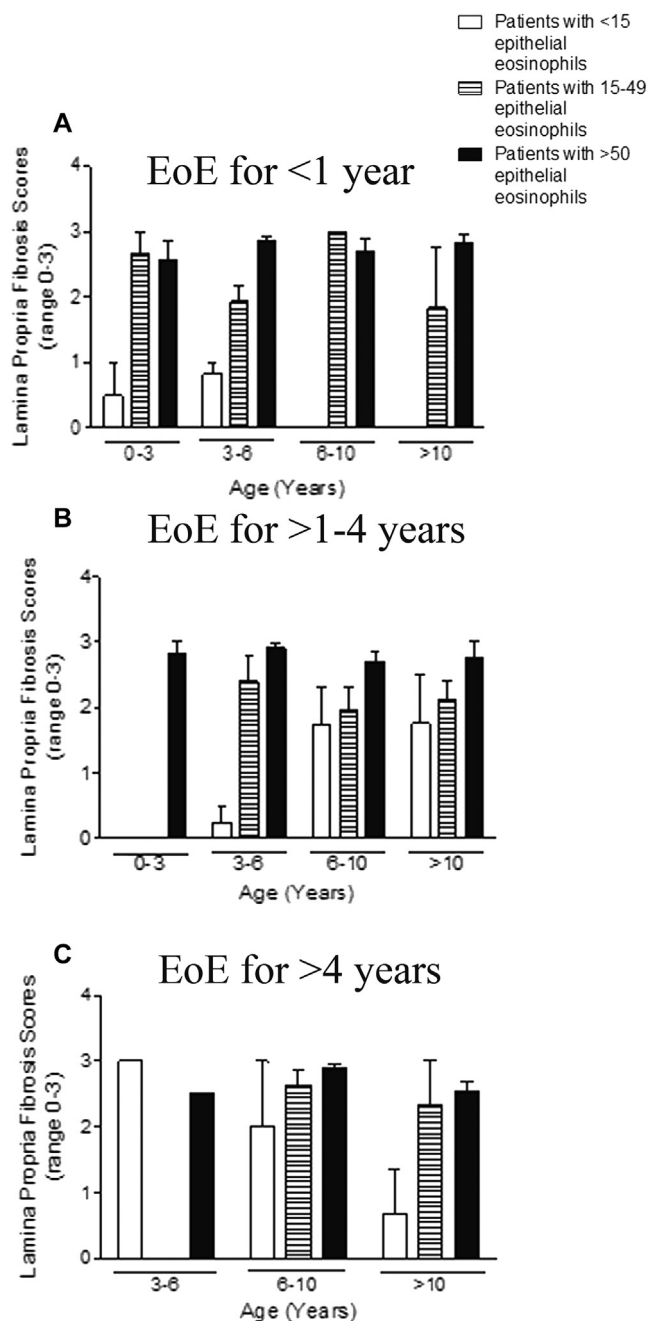


FIG 3. Fibrosis by age and disease duration. FSs in children 0 to 3, greater than 3 to 6, greater than 6 to 10, and greater than 10 years old by disease duration of less than 1 year (there were no subjects in the 6- to 10-year-old and >10-year-old groups, with eosinophils <15 per hpf **A**); disease duration of greater than 1 to 4 years (there were no subjects in the <15 or 15-49 eosinophils/hpf 0 to 3-year-old group, **B**); and disease duration of greater than 4 years (there were no subjects in the 3- to 6-year-old, 15-49 eosinophils/hpf group; **C**).

15 eosinophils/hpf, the overall average epithelial remodeling score was 0.36, the LP eosinophil count was 3, and the FS was 1.2 compared with 2.4 ($P < .0001$), 17 ($P < .0001$), and 2.5 ($P < .0001$), respectively, in the group with 15 or more eosinophils/hpf. TGF- $\beta 1^+$ cell numbers were lower in the group with less than 15 eosinophils/hpf for only the first 2 instances (Fig 5, E). Esophageal epithelial eosinophil counts of less than 15

eosinophils/hpf corresponded to lower endoscopy scores (Fig 5, F). In contrast, symptoms did not reflect other disease features, even in this analysis (Fig 5, G).

DISCUSSION

The concept of tissue remodeling and eosinophil-associated fibrosis has been established in patients with asthma, hyper-eosinophilic syndrome, and more recently, EoE.²⁴ EoE allows a unique opportunity to study histologic remodeling in the context of clinical features over long time frames because management requires repeated tissue assessment.¹ The natural history and potential of therapy to sustain fibrotic control in patients with eosinophil-associated diseases is not clear, especially in children. However, this is conceptually important because fibrosis appears to be an integral mechanism to strictures. Herein we report a number of novel findings based on data from more than 400 esophageal biopsy specimens obtained over 10 years in 32 children with EoE.

First, we show that epithelial inflammation is concordant with epithelial remodeling, LP eosinophilia, and fibrosis in children both longitudinally and at multiple time points over a maximum of 10 years of treatment. This information is important because fibrostenosis is essentially universal in untreated adults and because the theory that epithelial inflammatory control corresponds to fibrotic control has previously been only an assumption.

Second, we demonstrate that histologic EoE control by TCSs in pediatric patients might help to mitigate disease complications of strictures and food impactions because only 1 subject progressed to esophageal narrowing.

Third, our data suggest that there are likely to be intrinsic differences at the genetic/molecular level between patients who do and do not respond completely to therapy because responders and nonresponders reported adherence to medications in the majority of instances. This underscores the need for additional data on maintenance regimens and additional or complementary therapeutic options in patients with EoE.

The most severe disease complication in patients with EoE is stricture formation, which is driven by tissue remodeling.^{1,6,7,10} In adults risk factors for food impactions and strictures include esophageal rigidity, untreated disease duration, and less frequent use of TCSs.^{3,6,7,11} In our cohort of responders, those who used TCSs 75% of the time or more trended toward lower FSs. In adults fibrosis can be difficult to reverse once established.^{25,26} Children have more inflammation and less fibrostenosis, and our data suggest that long-term EoE control can keep fibrosis at a lower severity. Initially decreasing eosinophil counts to less than 15 resulted in an FS of 1 (normal using our FS). Because none of the responders had the onset of stricture, whereas 2 nonresponders had no improvement or progression of narrowing, our data suggest that the goal in children of preventing esophageal fibrostenosis can be accomplished when epithelial inflammation is controlled.

Our study also shows that there is recurrence of eosinophilia despite continued therapy. This aligns with recently published adult data from Kuchen et al¹¹ showing that most adults with EoE had histologic disease activity of more than 10 eosinophils/hpf over a 5-year treatment period despite chronic TCS therapy, which underscores the importance of continuous follow-up in patients with EoE. In our current study 4 nonresponders shifted to responders in 4 instances, 2 of which were due to increased medication dose or compliance. Responders had recurrence of esophageal

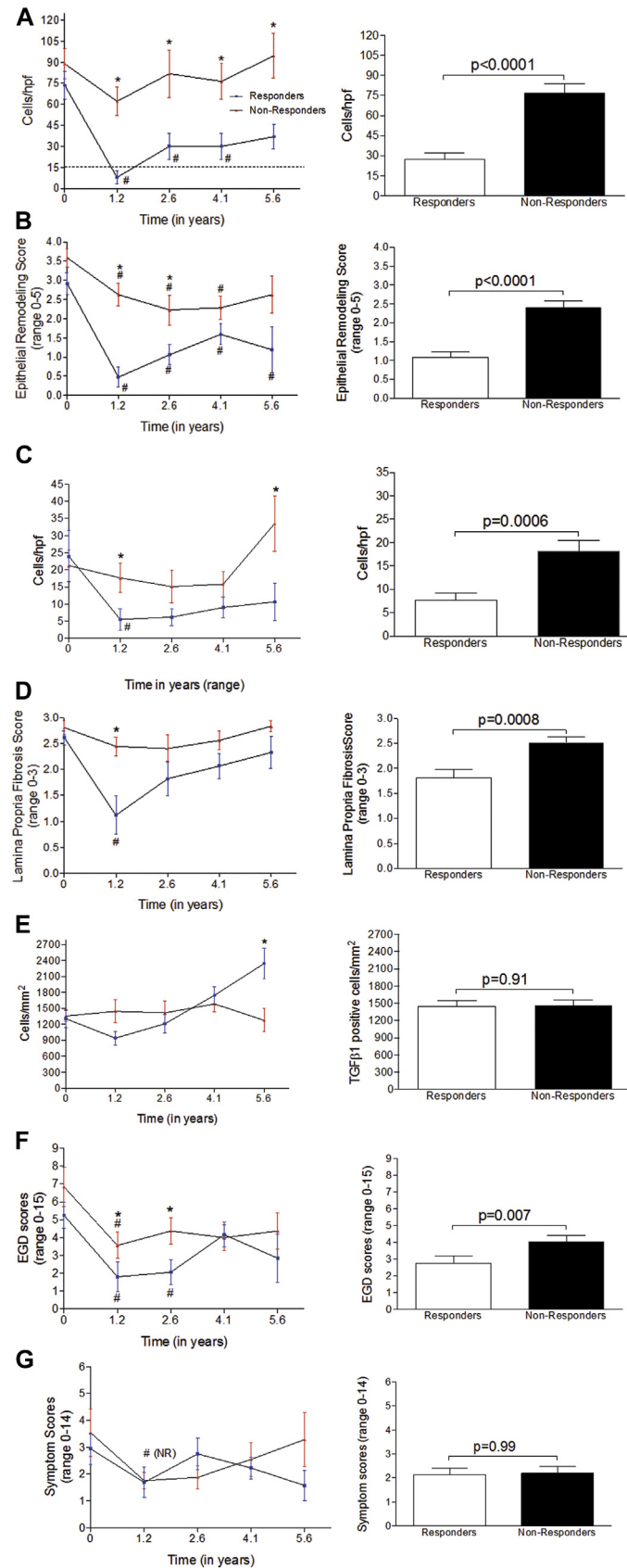


FIG 4. Histologic remodeling, endoscopic features, and subjects' symptoms over 10 years. Line graphs of responders (blue error bars) and nonresponders (red error bars) over mean times of 1.2, 2.6, 4.1, and 5.6 years (left panels) and cumulative findings over 10 years (right panels) for epithelial eosinophils (A), epithelial remodeling (B), LP eosinophils (C), LP fibrosis (D), TGF- $\beta 1^+$ cells (E), endoscopy scores (F), and symptoms (G) are shown. *Statistically significant between groups. #Statistically significant from baseline.

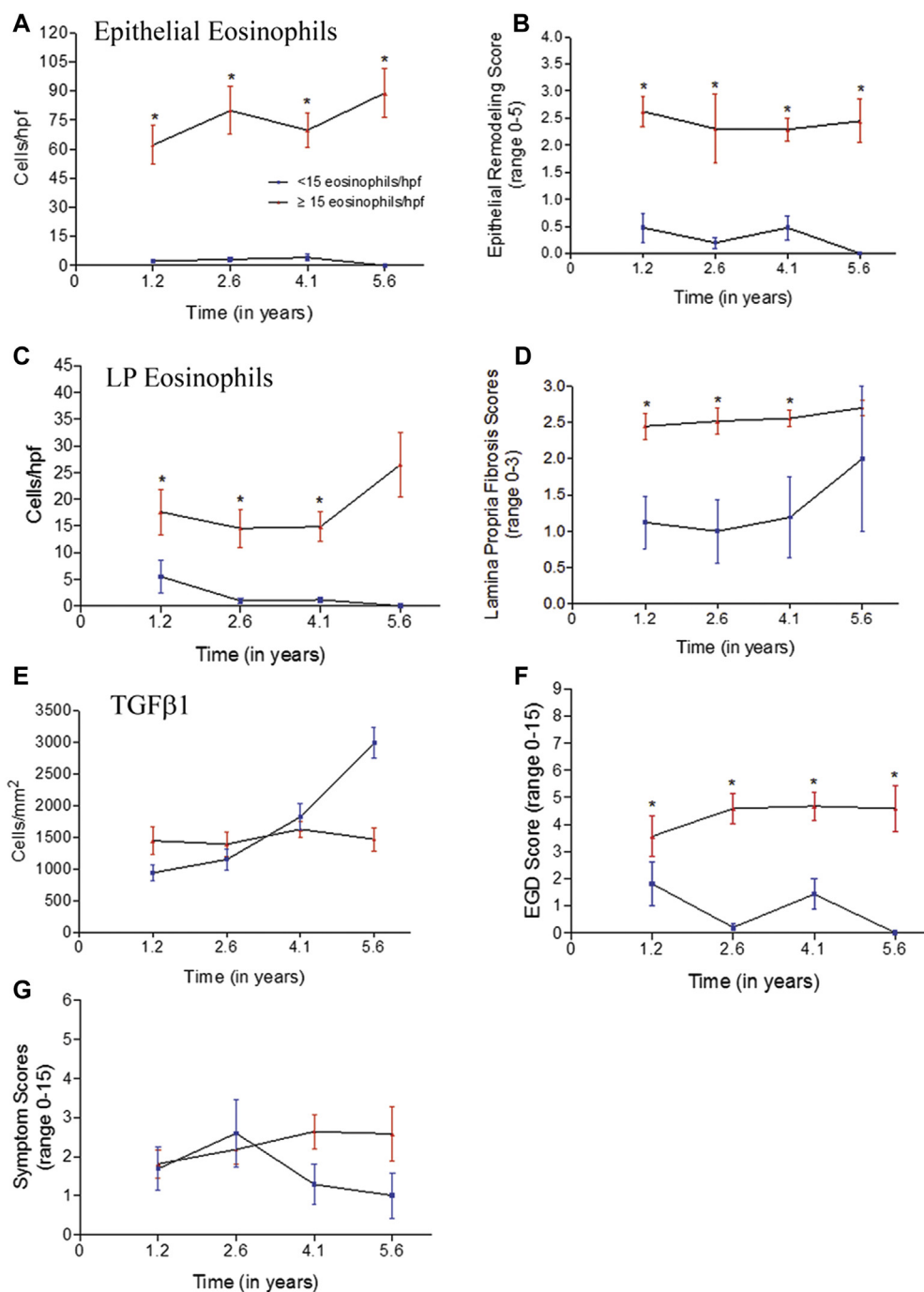


FIG 5. Histologic remodeling, endoscopic features, and symptoms among subjects with less than 15 and 15 or more eosinophils/hpf at each time point. Line graphs of subjects with less than 15 (blue error bars) and greater than 15 (red error bars) eosinophils/hpf over mean times of 1.2, 2.6, 4.1, and 5.6 years for epithelial eosinophils (A), epithelial remodeling (B), LP eosinophils (C), LP fibrosis (D), TGF- β 1⁺ cells (E), endoscopy scores (F), and symptom scores (G) are shown. *Statistically significant between groups.

eosinophilia; 6 stopped their medications, but 9 had no change in their medications. The reasons for recurrence of epithelial inflammation are not clear but could include intermittent medication adherence, worsening acid-induced eosinophilia, accumulation of allergic triggers, seasonality, onset of TCS resistance, age and maturation of other systems (eg, hormonal axes during puberty), and/or differential penetration of TCSs in the inflamed versus

less inflamed esophagus. However, what does seem clear is that there are distinct EoE phenotypes, including persistent, transient, and perhaps even intermittent responders. Further understanding of the degree of inflammatory control necessary to prevent complications will be important in guiding management.

There are inherent limitations in our study. We did not study other treatments, such as an elimination diet and limitation to TCS

use, which could introduce potential bias in the population. However, we wanted to study a more homogenous population. Indeed, we had a very high percentage of male subjects (91%), and this also can help with population homogeneity. Because this was not a prospective randomized trial and because holding EoE therapy would not be medically advised, this study cannot include an untreated natural history cohort. As such, the persistent nonresponder group functions as the closest approximation to a natural history cohort that we have available. Because nonresponders still had some decreases in remodeling features and inflammation in certain instances, TCSs are having a partial effect in this population. In addition, our overall cohort might be biased toward a more severe phenotype. In general, the presence of LP, a requirement for evaluation in this study, was associated with higher epithelial eosinophil counts. In addition, it was rare to have an FS of 0 to 1 on the biopsy specimens we were able to evaluate. As such, in children the mere absence of LP in a biopsy specimen with no or low epithelial eosinophilia might imply a nonfibrotic esophagus. This coupling of epithelial inflammation and LP fibrosis in children might allow for surrogate markers of fibrosis that occur in the epithelium. Despite the retrospective nature of our study, it is the first of its kind to assess longitudinal remodeling in children with EoE.

Although we saw alignment between epithelial inflammation and fibrosis, as well as endoscopic features, we did not find alignment with TGF- β 1 levels except early in the disease course and only in responders. Although there were initial decreases in TGF- β 1⁺ cell counts among responders, this was not sustained, and in fact, responders progressed to having more TGF- β 1⁺ cells than nonresponders at later time points. These increases did associate with increasing FS but might also reflect a shift in the cellular compartment of cells that produce TGF- β 1. For example, it is possible that early in the disease course inflammatory cells make TGF- β 1 but that later in the course TGF- β 1 is produced by regulatory cells in responders. There might also be a shift in profibrotic molecules during the disease. For example, levels of CXCL18 and fibroblast growth factor 9 have been reported to be increased in adults with EoE.²⁵

In conclusion, studies to date in pediatric and adult populations demonstrate that EoE is a chronic disease that recurs on removal of therapy,^{8,9,26} but the history of tissue remodeling has not been systematically studied in adults or children. The current study demonstrates that esophageal remodeling can be improved with long-term TCSs. Our data suggest that childhood or shorter disease duration offers an important window for controlling fibrostenotic complications. Larger and longer studies are needed to clearly distinguish EoE phenotypes both on the therapeutic and molecular levels.

We thank Tom Yang and Loan Duong for technical assistance.

Clinical implications: Long-term esophageal remodeling is associated with eosinophilia in pediatric patients with EoE and can be improved after esophageal TCS therapy.

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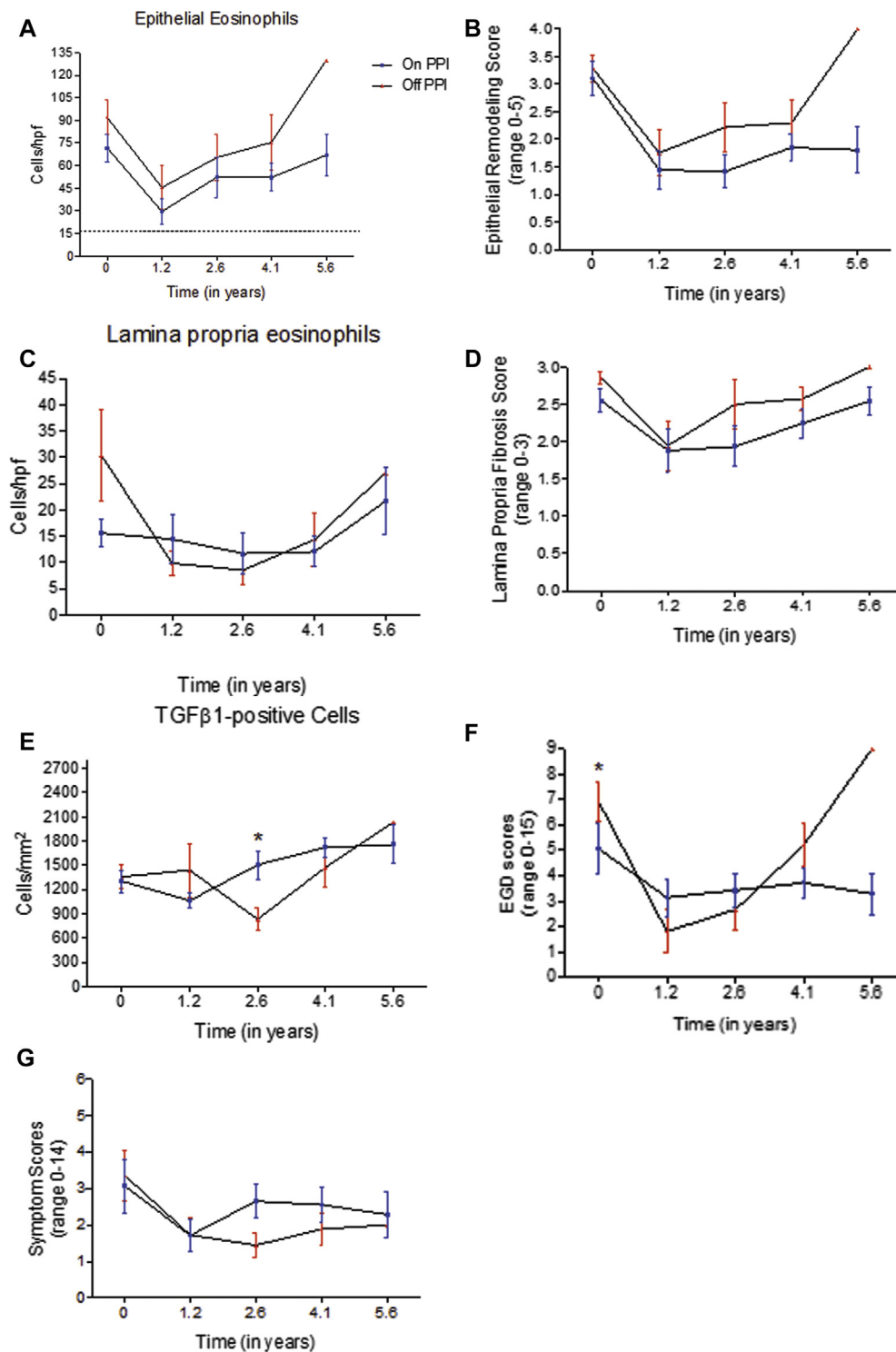


FIG E1. PPI use does not significantly alter inflammation or fibrosis in patients with long-term EoE. Epithelial eosinophil counts (**A**) and remodeling (**B**) and LP eosinophil counts (**C**), FSs (**D**), TGF- β 1⁺ cell counts (**E**), EGD (**F**), and symptom score (**G**) in subjects receiving and not receiving PPIs through a mean of 4.5 years are shown. * $P < .05$.

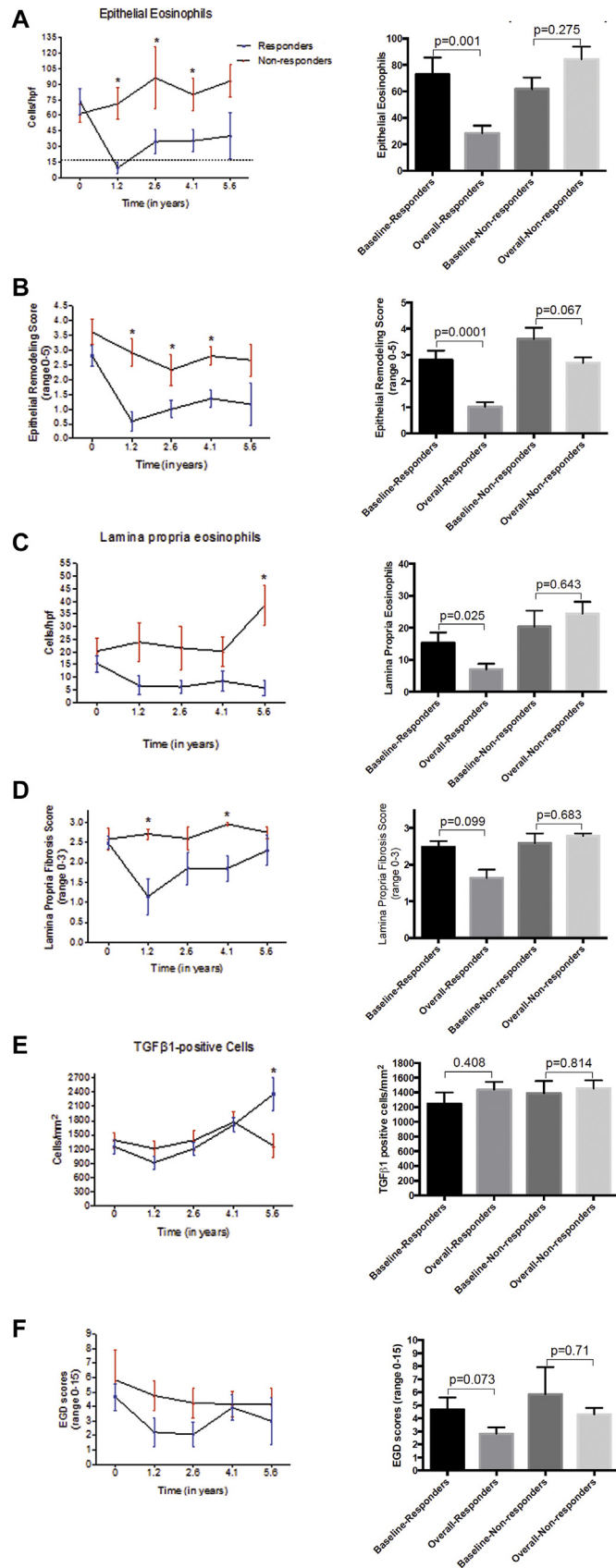


FIG E2. The subgroup of patients in whom PPI monotherapy failed have similar findings as the total cohort. Epithelial eosinophil counts (**A**) and remodeling (**B**) and LP eosinophil counts (**C**), FSs (**D**), TGF- β 1⁺ cell counts (**E**), and EGD scores (**F**) in the subgroup of subjects in whom PPI monotherapy failed are shown. Line graphs (*left panel*) represent differences at each instance, and bar graphs (*right panel*) represent baseline versus average control over the entire time period in responders and nonresponders. * $P < .05$ between responders and nonresponders.

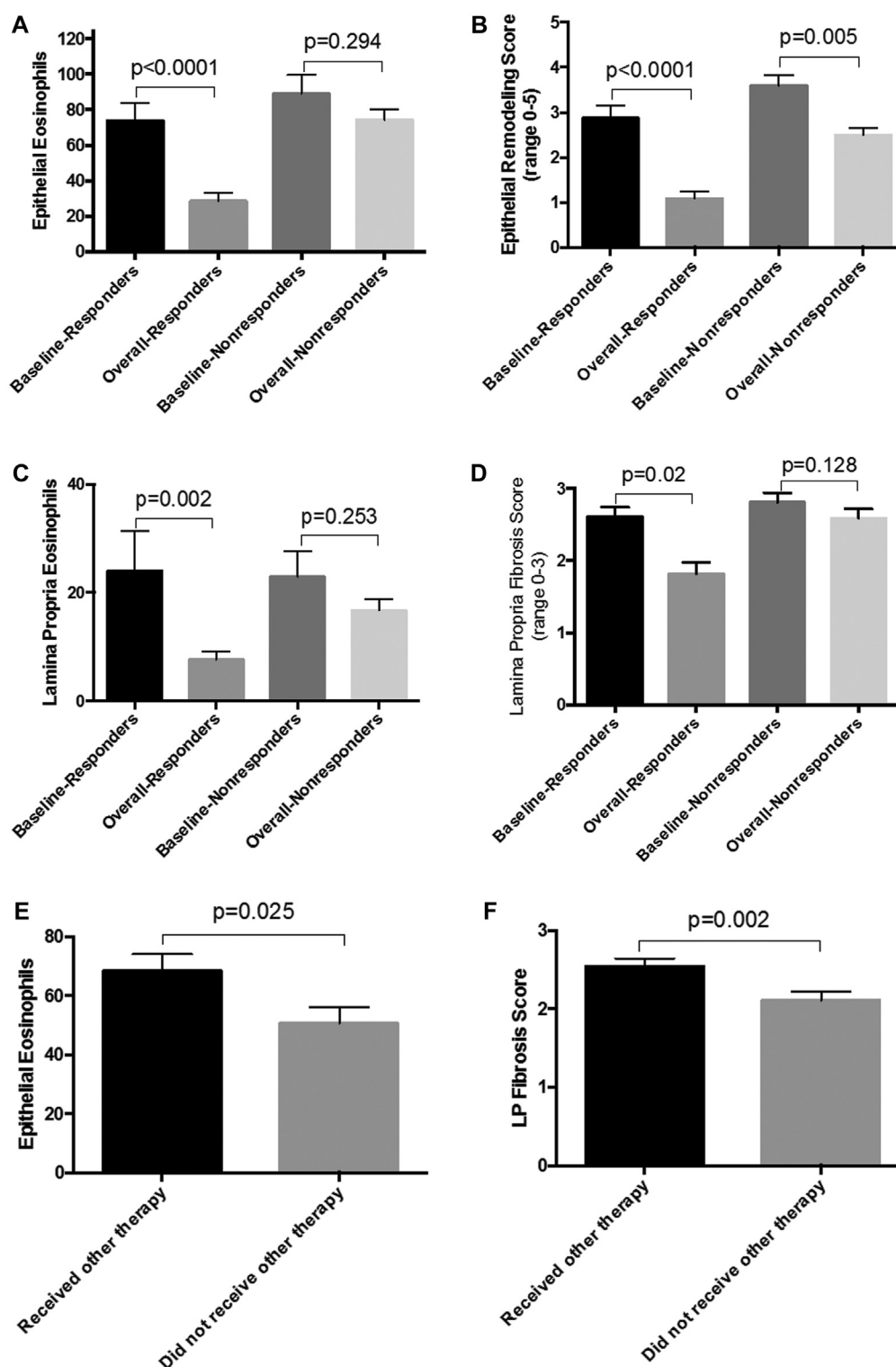


FIG E3. Effects of other therapies in addition to TCSs on long-term remodeling features. Epithelial eosinophil counts (A) and remodeling (B) and LP eosinophil counts (C) and FSs (D) in all subjects receiving any therapy (including TCSs, oral corticosteroids, elimination diet, and/or biologics) during the study time period are shown. Epithelial eosinophil counts (E) and LP FSs (F) in subjects who did versus did not receive other therapies in addition to TCSs. Bars represent mean data $\pm$ SEMs for all subjects on all therapies through the entire study period.

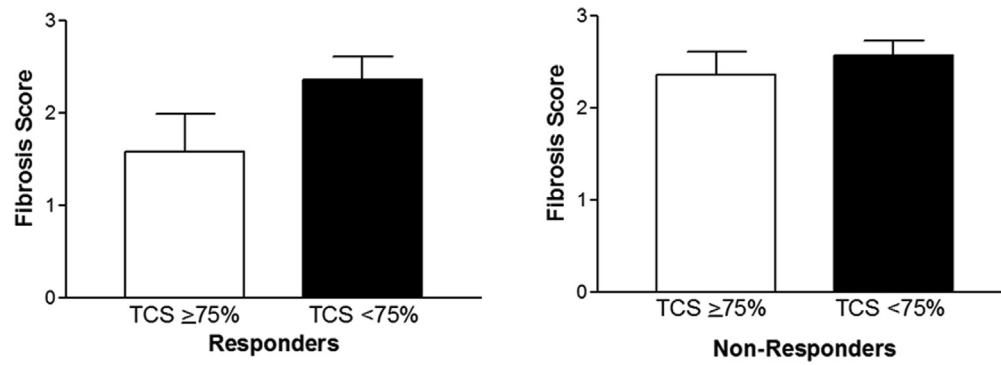


FIG E4. FSs in responders (*left*) and nonresponders (*right*) filtered by TCS use. Bars represent mean data $\pm$ SEMs for all subjects through the entire study period.

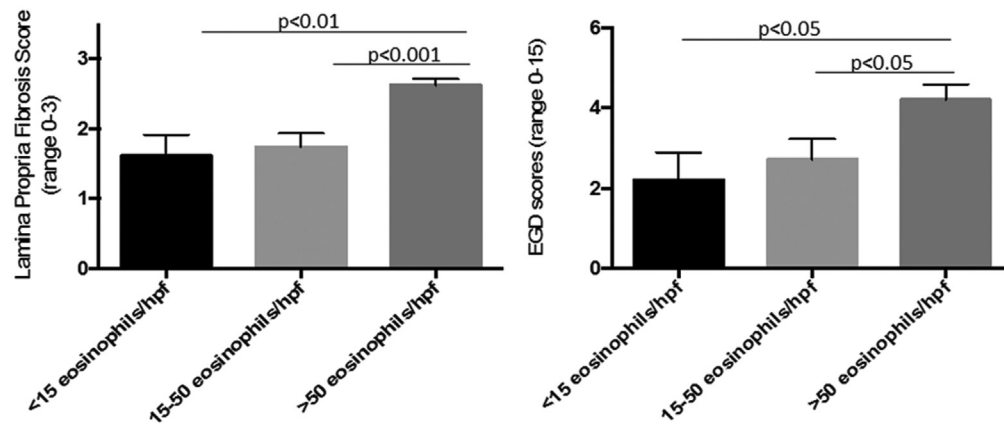


FIG E5. Overall FS and EGD scores are lower when inflammation is better controlled. Final FSs and final EGD scores in subjects who have less than 15, 15 to 50, or more than >50 eosinophils/hpf over their disease duration are shown. Bars represent mean data $\pm$ SEMs for all subjects through the entire study period.

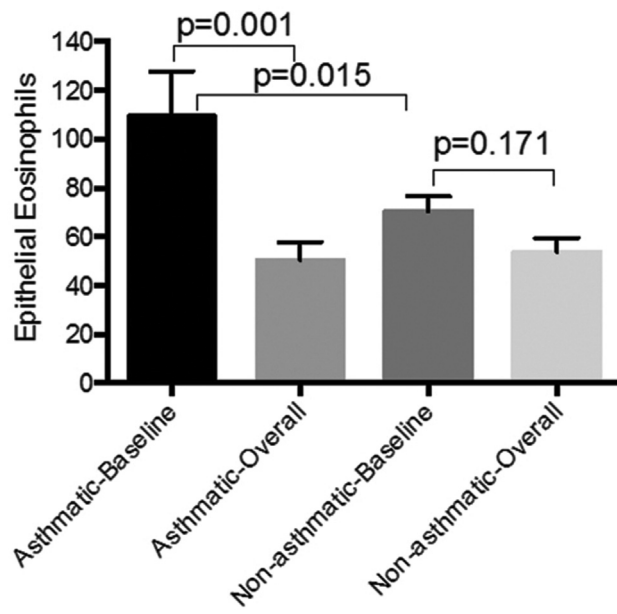


FIG E6. Asthmatic patients have higher epithelial eosinophil counts than those without asthma. Graphs show means $\pm$ SEMs of baseline epithelial eosinophils in the total population with and without asthma.

TABLE E1. Correlation coefficients when comparing mean epithelial eosinophil count with LP FSs, epithelial remodeling scores, LP eosinophil counts, TGF- β 1 cell counts, epithelial eosinophilia, EGD scores, and symptom scores

Time (y)	Epithelial remodeling score	LP eosinophil count	LP FS	TGF- β 1 cell count	EGD score	Symptom score
0	$r = 0.36, P = .0587$	$r = 0.19, P = .3249$	$r = 0.32, P = .09$	$r = 0.21, P = .275$	$r = 0.31, P = .0981$	$r = -0.07, P = .725$
1.21	$r = 0.87, P < .0001$	$r = 0.80, P < .0001$	$r = 0.79, P < .0001$	$r = 0.33, P = .063$	$r = 0.72, P < .0001$	$r = 0.30, P = .098$
2.58	$r = 0.86, P < .0001$	$r = 0.63, P = .0002$	$r = 0.59, P = .0013$	$r = 0.17, P = .3576$	$r = 0.65, P < .0001$	$r = -0.12, P = .504$
4.05	$r = 0.73, P < .0001$	$r = 0.52, P = .0012$	$r = 0.49, P = .0022$	$r = -0.30, P = .0632$	$r = 0.70, P < .0001$	$r = 0.37, P = .0221$
5.56	$r = 0.94, P < .0001$	$r = 0.75, P = .0062$	$r = 0.56, P = .0614$	$r = -0.51, P = .0515$	$r = 0.86, P < .0001$	$r = 0.40, P = .1385$
Overall	$r = 0.82, P < .0001$	$r = 0.60, P < .0001$	$r = 0.59, P < .0001$	$r = 0.07, P = .4212$	$r = 0.67, P < .0001$	$r = 0.22, P = .006$

TABLE E2. Correlation coefficients when comparing LP FSs with epithelial remodeling scores, LP eosinophil counts, TGF- β 1 cell counts, epithelial eosinophilia, EGD scores, and symptom scores

Time (y)	Epithelial remodeling score	LP eosinophil count	TGF- β 1 cell count	Epithelial eosinophilia	EGD score	Symptom score
0	$r = 0.25, P = .19$	$r = 0.03, P = .88$	$r = 0.21, P = .27$	$r = 0.19, P = .3$	$r = 0.15, P = .444$	$r = 0.05, P = .797$
1.21	$r = 0.82, P < .0001$	$r = 0.71, P < .0001$	$r = 0.47, P < .014$	$r = 0.77, P < .0001$	$r = 0.88, P < .0001$	$r = 0.21, P = .294$
2.58	$r = 0.79, P < .0001$	$r = 0.61, P = .0008$	$r = 0.09, P = .65$	$r = 0.58, P = .0015$	$r = 0.55, P = .003$	$r = -0.30, P = .125$
4.05	$r = 0.57, P = .0002$	$r = 0.34, P = .0427$	$r = -0.03, P = .83$	$r = 0.41, P = .0116$	$r = 0.36, P = .0298$	$r = 0.23, P = .175$
5.56	$r = 0.64, P = .0319$	$r = 0.30, P = .349$	$r = -0.30, P = .21$	$r = 0.62, P = .035$	$r = 0.44, P = .146$	$r = 0.16, P = .617$
Overall	$r = 0.64, P < .0001$	$r = 0.44, P < .0001$	$r = 0.18, P = .035$	$r = 0.53, P < .0001$	$r = 0.54, P < .0001$	$r = 0.10, P = .24$