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# Association Between Histologic Response and Subsequent Fibrostenotic Complications in Treated Eosinophilic Esophagitis: A Systematic Review and Meta-analysis

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## Abstract

Persistent eosinophilic inflammation is considered a driver of fibrostenotic remodeling in eosinophilic esophagitis (EoE), but the structural significance of histologic control is uncertain. We assessed whether post-treatment histologic response is associated with fewer fibrostenotic complications. MEDLINE/PubMed, Embase, CENTRAL, Scopus, and Google Scholar were searched from inception to 3 August 2026, with forward and backward citation searching. Longitudinal comparative studies of treated EoE reporting structural outcomes by histologic-response status were eligible. Adjusted estimates were prioritized and clinically compatible outcomes were pooled with random-effects models. Sixteen reports representing 15 datasets were included. Histologic control was associated with a lower hazard of subsequent stricture or fibrostenosis across three independent cohorts (hazard ratio 0.34, 95% confidence interval 0.17–0.67; $I^2$=0%). A raw-event sensitivity analysis was concordant (risk ratio 0.34, 95% confidence interval 0.20–0.57). Two cohorts showed a lower hazard of subsequent dilation (hazard ratio 0.63, 95% confidence interval 0.42–0.94; $I^2$=0%). Two short-term cohorts showed lower post-treatment fibrostenotic endoscopic scores among responders (mean difference − 0.61, 95% confidence interval − 0.93 to -0.29). Biopsy fibrosis, esophageal caliber, molecular remodeling, and distensibility findings were directionally supportive but unsuitable for pooling. All datasets had moderate or serious risk of bias. Histologic control was associated with fewer subsequent fibrostenotic events and dilations in treated EoE. Histologic remission is a clinically relevant treatment target, although the evidence remains observational and susceptible to residual confounding and time-dependent exposure bias.

## Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation. Histologic activity is commonly defined by a peak eosinophil count of at least 15 eosinophils per high-power field (eos/hpf), and post-treatment counts below this threshold are widely used to define response [1, 2]. This threshold is practical and reproducible, but it captures mucosal inflammatory activity rather than the full clinical consequences of the disease.

The principal long-term concern in EoE is progression from mucosal inflammation to structural disease. Fibrosis, rings, focal strictures, diffuse narrowing, reduced esophageal caliber, and impaired distensibility contribute to dysphagia, food impaction, and the need for dilation. Natural-history studies have linked diagnostic delay and untreated disease duration with fibrostenotic phenotypes, supporting a biologically plausible inflammation-remodeling sequence [3, 4]. Endoscopic severity can be standardized with the EoE Endoscopic Reference Score (EREFS), while functional lumen imaging probe measurements provide an objective assessment of esophageal distensibility [5, 6]. Histologic fibrosis and profibrotic signaling provide complementary tissue-level measures, although adequate lamina propria is not consistently obtained in routine biopsies.

The relation between inflammatory control and structural outcome is clinically important because symptoms, histology, and remodeling may be discordant. Dysphagia may improve after dilation without a change in inflammation, and patients may reduce symptoms by avoiding solid foods, eating slowly, or modifying meal behavior. Conversely, eosinophilia may improve before established rings or strictures resolve. A single post-treatment endoscopy can therefore show histologic response with persistent fibrostenotic features, whereas a longer observation period may be required to determine whether inflammatory control alters the subsequent risk of stricture formation or repeated dilation.

Available studies address different points along this pathway. Some compare subsequent incident strictures, composite fibrostenosis, or dilation after histologic response has been established. Others assess short-term changes in endoscopic rings and strictures, biopsy fibrosis, molecular remodeling, esophageal diameter, or distensibility at the same follow-up interval used to classify response. Combining these outcomes indiscriminately would obscure clinically meaningful differences in timing, measurement, and reversibility. In addition, several reports originate from the same institutional cohorts, creating a risk of double-counting participants if publications are treated as independent studies.

We conducted a systematic review and meta-analysis to determine whether post-treatment histologic response, compared with persistent histologic activity, is associated with fewer subsequent fibrostenotic complications in children and adults with treated EoE. Separate syntheses were planned for clinically distinct outcome domains. Adjusted estimates were prioritized, short-term concurrent remodeling outcomes were distinguished from later clinical events, and overlapping institutional cohorts were mapped before quantitative analysis.

## Methods

# Protocol and reporting

The review protocol was registered prospectively in PROSPERO (CRD420261468375). Reporting followed the PRISMA 2020 statement [7]. The registered title, population, exposure, comparator, and primary outcome were retained. Because histologic response is an achieved post-treatment state rather than an assigned intervention, the review was framed as a population-exposure-comparator-outcome question.

Reviewer-verified eligibility decisions, extracted values, risk-of-bias judgments, analytic results, and PRISMA counts were treated as final for this report.

## Eligibility criteria

We included longitudinal comparative human studies of children or adults with confirmed EoE who received pharmacologic, dietary, biologic, or combination treatment; underwent post-treatment histologic assessment; and had an eligible structural outcome reported or calculable by histologic-response status. The preferred exposure was a peak count < 15 eos/hpf, compared with persistent activity ≥ 15 eos/hpf. Studies using a clearly defined alternative threshold or longitudinal disease-control trajectory were retained but analyzed according to the authors' definition. Eligible outcomes were incident or progressive stricture, narrowing, fibrostenosis, subsequent dilation, dilation frequency or time to dilation, esophageal caliber or diameter, FLIP/EndoFLIP distensibility, biopsy-based fibrosis or remodeling, endoscopic fibrostenotic features, and profibrotic biomarkers. Case reports, noncomparative series, cross-sectional studies without longitudinal structural assessment, nonhuman studies, and reports without an eligible responder-versus-nonresponder comparison were excluded. Studies in which the primary exposure was treatment type, surveillance frequency, endoscopic response, or baseline structural severity were excluded unless the prespecified histologic comparison was separately extractable.

## Protocol clarification

The protocol specified that histologic classification should precede a subsequent structural outcome, while also allowing longitudinal remodeling outcomes analyzed in relation to histologic response. We therefore included paired pre/post studies when structural change was measured longitudinally and reported by achieved response, but excluded purely cross-sectional contemporaneous associations. Short-term studies in which post-treatment histology and structural assessment occurred at the same procedure were analyzed separately and did not contribute to the primary long-term clinical meta-analyses. This operational clarification preserved the protocol's remodeling outcomes without treating concurrent endoscopic or tissue findings as evidence of prevention of a later complication.

## Information sources and search strategy

MEDLINE/PubMed, Embase via Ovid, the Cochrane Central Register of Controlled Trials, Scopus, and Google Scholar were searched from inception to 3 August 2026. Search concepts combined controlled vocabulary and free-text terms for EoE, histologic response or persistent eosinophilia, and fibrostenotic or remodeling outcomes, including stricture, stenosis, narrowing, dilation or dilatation, fibrosis, remodeling, diameter, distensibility, FLIP, and food impaction. No date restriction was applied. Forward and backward citation searching was performed in Scopus from nine sentinel studies. Search results were retained in their original exported formats. Database-specific counts, search dates, and concept summaries are provided in Online Resource 1 (Table S1); complete line-by-line strategies were preserved in the review archive.

## Record management and study selection

All database and citation-search exports were combined and deduplicated using DOI, PMID, normalized title, and bibliographic fields, followed by manual review of uncertain matches. Counts from database/search-engine identification and citation searching were retained as separate PRISMA pathways before global deduplication. Two reviewers independently screened titles and abstracts and assessed full-text reports against the prespecified criteria. Each excluded full text received one primary standardized reason. Disagreements were resolved by consensus. Reports were linked at the dataset level before the number of included studies was determined; companion publications were retained as reports but were not counted as independent datasets.

# Data extraction

Two reviewers independently extracted data using a prespecified form. Extracted items included study design, setting, recruitment period, sample size, age group, treatment, baseline fibrostenotic phenotype, definition and timing of histologic response, follow-up duration, structural outcome definition, event counts, group means and variance measures, adjusted and unadjusted estimates, covariates, and information required for risk-of-bias assessment. When an article reported several histologic thresholds, the threshold closest to < 15 eos/hpf was prioritized. When several structural outcomes were available, clinically distinct endpoints were retained separately rather than combined into an investigator-created composite. Numerical data were taken from the report's tables, text, figures, and supplementary material as available; no unreported values were imputed.

## Cohort overlap

Potential participant overlap was assessed using institution, investigator group, recruitment period, age range, treatment setting, eligibility criteria, and sample characteristics. Reports arising from the same cohort were classified as companion publications when they measured different outcomes. For each outcome-specific meta-analysis, only one independent statistical unit from a potentially overlapping cohort was used. When overlap was probable but the exact number of shared participants could not be established, the reports were kept in separate narrative domains or the report providing the most direct prespecified exposure and adjusted longitudinal estimate was selected.

### Risk of bias

Risk of bias was assessed independently by two reviewers using ROBINS-I across confounding, selection, exposure classification, deviations from intended treatment, missing data, outcome measurement, and selective reporting domains [8]. An overall judgment was assigned for each dataset. Particular attention was given to confounding by baseline fibrostenotic severity, diagnostic delay, adherence, treatment selection, prior dilation, and follow-up intensity; selection requiring repeat endoscopy or adequate lamina propria; and time-dependent definitions of histologic control that could introduce immortal-time bias.

## Statistical analysis

Hazard ratios (HRs) were preferred for time-to-event outcomes; risk ratios (RRs) for binary outcomes; and mean differences (MDs) for continuous outcomes measured on the same scale. Adjusted estimates were prioritized for the primary analyses. Effect estimates and confidence limits were transformed to the log scale and pooled using inverse-variance random-effects models with restricted maximum likelihood estimation of between-study variance. Estimates reported in the opposite direction were inverted before pooling. For raw-event sensitivity analysis, responder and nonresponder event counts were used without continuity correction because no contributing study had a zero cell. Heterogeneity was summarized using Cochran's Q, tau-squared, and $I^2$ [9]. Results were not pooled when outcome definitions, measurement scales, timing, or cohort independence were incompatible. Publication-bias tests and funnel plots were not performed because each synthesis included fewer than 10 studies. No meta-regression or subgroup analysis was undertaken because the number of studies per outcome was insufficient. Analyses were conducted in Python 3.13 using NumPy and SciPy. Statistical tests were two-sided, and 95% confidence intervals (CIs) were reported.

### Results

## Study selection

The searches identified 8,081 records: 7,477 from database and search-engine searches and 604 from citation searching. After 2,806 duplicate occurrences were removed, 5,275 unique records underwent title and abstract screening. Of these, 5,239 were excluded. Thirty-six reports were sought, retrieved, and assessed in full text; 20 were excluded. The most frequent full-text reason was absence of an eligible histologic-response comparator. Other exclusions reflected the wrong exposure, ineligible temporal structure, cross-sectional design, or absence of original participant data. Sixteen reports representing 15 report-defined datasets were included because the two Dellon 2016 publications arose from the same prospective University of North Carolina (UNC) cohort and were treated as companion reports (Fig. 1; Online Resource 1, Table S6).

## Study characteristics

Included reports were published between 2010 and 2026 and enrolled pediatric and adult cohorts from the United States, Switzerland, the Netherlands, and South Korea (Table 1) [10–25]. The evidence consisted of retrospective cohorts, prospective observational cohorts, paired pre/post treatment studies, a dietary-trial biomarker substudy, and translational paired-biopsy analyses. No eligible randomized comparison assigned participants to histologic response or persistent activity. Sample sizes ranged from 16 to 166 participants, and follow-up ranged from 6 weeks to a mean of 11.4 years.

Table 1
Characteristics of included datasets

| Study | Country | Design | Sample | Treatment | Histologic response | Follow-up | Structural outcomes |
|---|---|---|---|---|---|---|---|
| Aceves 2010 | USA | Retrospective paired-biopsy cohort | 16 children (9 response, 7 nonresponse) | Swallowed budesonide ≥ 3 months | ≤ 7 eos/hpf vs persistent high counts | ≥ 3 months | Lamina propria fibrosis; TGF-β1; pSmad2/3; vascular activation |
| Rajan 2016 | USA | Retrospective longitudinal cohort | 32 children (16 initial responders, 16 nonresponders) | Topical corticosteroids | < 15 vs ≥ 15 eos/hpf; repeated activity | Mean 4.5 years (up to 10) | Fibrosis score; epithelial remodeling; endoscopic severity; TGF-β1 |
| Carlson 2017 | USA | Prospective registry pre/post study | 18 adults (7 histologic response) | PPI, topical steroid, diet | < 15 vs ≥ 15 eos/hpf | Mean 14.6 weeks | FLIP distensibility plateau; EREFS rings/stricture |
| Dellon EREFS 2016 | USA | Prospective pre/post cohort | 67 adults (38 response, 29 nonresponse) | Mostly topical steroids; some diet | < 15 vs ≥ 15 eos/hpf | 6–8 weeks | Fibrostenotic EREFS; rings; stricture |
| Park 2024 | South Korea | Retrospective pre/post cohort | 30 treated adults (22 response, 8 nonresponse) | PPI and/or steroids | < 15 vs ≥ 15 eos/hpf | 6–8 weeks | Fibrostenotic EREFS |
| Pehrsson 2023 | Netherlands | Prospective dietary trial biomarker substudy | 29 adults (10 remission, 19 no remission) | Four-food elimination diet | < 15 vs ≥ 15 eos/hpf | 6 weeks | Serum extracellular-matrix remodeling biomarkers; EREFS fibrosis change |
| Sharlin 2026 | USA | Prospective paired-biopsy translational cohort | 19 adults (10 response, 9 nonresponse) | PPI ≥ 8 weeks | < 15 vs ≥ 15 eos/hpf | ≥ 8 weeks | Rings; strictures; remodeling/fibrosis transcriptome |
| Runge 2017 | USA | Retrospective cohort | 55 (27 response, 28 nonresponse) | Baseline dilation then topical steroids | < 15 vs ≥ 15 eos/hpf | Median 19 months | Subsequent dilation occurrence, number, rate, and time |
| Kim 2020 | USA | Retrospective severe-stricture cohort | 66 adults (55 complete histology) | Medical/diet therapy plus serial dilation | Remission < 15 eos/hpf by maximum diameter | Variable | Achievement of ≥ 13 mm and ≥ 15 mm diameter |
| Snyder 2024 | USA | Retrospective serial-esophagram cohort | 78; activity comparison 15 inactive vs 33 active | Heterogeneous routine care | Inactive/remission vs active (> 15 eos/hpf or untreated) | Median 2.6 years | Maximum/minimum esophageal diameter change |
| Starling 2024 | USA | Longitudinal childhood-to-adult cohort | 105 | Heterogeneous chronic therapy | ≥ 2 consecutive EGDs < 15 eos/hpf | Mean 11.4 years | Incident stricture/narrowing; food impaction |
| Thel 2025 | USA | Retrospective pediatric cohort | 166 | Heterogeneous routine care | < 15 vs ≥ 15 eos/hpf at follow-up EGDs | Mean 4.7 years | Fibrostenosis: stricture, narrowing, or dilation |
| Kennedy 2026 | USA | Prospective two-center longitudinal cohort | 112 children; 300 endoscopies | Heterogeneous routine care | Continuous remission, continuous inflammation, resolved, variable | Median 11 months (2–54) | FLIP distensibility slope; fibrostenotic complications |
| Schoepfer 2026 | Switzerland | Prospectively collected national cohort | 151 adults (93 controlled, 58 continuously active) | Stable PPI, topical steroid, or diet | ≥ 1 visit < 15 vs all visits ≥ 15 eos/hpf | Median 56 months | New stricture; dilation; impaction; composite complications |

Abbreviations: EGD, esophagogastroduodenoscopy; eos/hpf, eosinophils per high-power field; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; FLIP, functional lumen imaging probe; PPI, proton pump inhibitor; TGF-β1, transforming growth factor-beta 1.

| Study | Country | Design | Sample | Treatment | Histologic response | Follow-up | Structural outcomes |
|---|---|---|---|---|---|---|---|
| Collins 2019 | USA | Longitudinal pediatric registry | 146 (59 continuous, 65 intermittent, 22 nonresponders) | Heterogeneous chronic therapy | Remission at > 75%, 25–75%, or < 25% of follow-up | 2–13 years | Rings/strictures; endoscopic phenotype |

Abbreviations: EGD, esophagogastroduodenoscopy; eos/hpf, eosinophils per high-power field; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; FLIP, functional lumen imaging probe; PPI, proton pump inhibitor; TGF-β1, transforming growth factor-beta 1.

Treatments included swallowed topical corticosteroids, proton pump inhibitors, elimination diets, dilation combined with anti-inflammatory therapy, and heterogeneous routine-care regimens. Most studies defined response as < 15 eos/hpf, although Aceves et al. used a residual count of ≤ 7 eos/hpf and several long-term cohorts used response trajectories. Starling et al. required at least two consecutive endoscopies in remission, Schoepfer et al. classified participants according to at least one remission episode versus continuously active disease, Kennedy et al. modeled repeated disease-activity patterns, and Collins et al. defined continuous, intermittent, and nonresponse according to the proportion of follow-up spent in remission.

Outcome domains included subsequent stricture or composite fibrostenosis, subsequent dilation, post-treatment fibrostenotic EREFS, biopsy fibrosis and profibrotic signaling, extracellular-matrix biomarkers, FLIP distensibility, and esophageal diameter on endoscopy or structured esophagram. Long-term clinical outcomes and short-term remodeling measures were analyzed separately (Online Resource 1, Table S3).

## Report and cohort overlap

The included literature contained several institutional report families (Online Resource 1, Tables S2 and S4). Aceves, Rajan, and Collins arose from the University of California San Diego/Rady Children's Hospital program and probably shared some participants, although the degree of overlap could not be reconstructed [10, 11, 25]. They were therefore not combined in a single quantitative analysis. The two Dellon 2016 reports arose from the same UNC prospective cohort: one reported EREFS and the other the biopsy pull sign [13, 14]. They were counted as two reports but one dataset. The Runge and Gee dilation cohorts had substantial overlap; Gee was excluded because its primary exposure was endoscopic response, whereas Runge isolated the prespecified histologic exposure and reported adjusted longitudinal estimates. Possible overlap between the Children's Hospital of Philadelphia component of Kennedy and the childhood-to-adult cohort of Starling did not affect pooling because the reports contributed to different outcome domains. The primary structural-event meta-analysis used three clearly independent cohorts: Starling, Thel, and Schoepfer [21, 22, 24].

## Subsequent structural events

Three independent cohorts contributed adjusted HRs for incident stricture or composite fibrostenosis [21, 22, 24]. Starling followed 105 patients diagnosed in childhood for a mean of 11.4 years and reported that a period of sustained histologic control was associated with less subsequent stricture development. Thel followed 166 children for a mean of 4.7 years and related histologic response at the second follow-up endoscopy to later fibrostenosis, defined as stricture, narrowing, or dilation. Schoepfer analyzed 151 treated adults in a prospectively maintained national cohort over a median of 56 months and compared patients with at least one remission episode with those who remained continuously active.

Across these cohorts, histologic control was associated with a lower hazard of subsequent structural events (pooled HR 0.34, 95% CI 0.17–0.67; Q = 0.35, P = 0.837; $I^2$=0%; $tau^2$=0; Fig. 2). The Schoepfer estimate was originally reported for ongoing activity versus disease control and was inverted before pooling. A sensitivity analysis using directly reported event counts was concordant (pooled RR 0.34, 95% CI 0.20–0.57; Q = 0.08, P = 0.960; $I^2$=0%; Online Resource 1, Figure S1). The small number of cohorts precluded meaningful assessment of whether the association differed by age, treatment, duration of remission, or structural endpoint definition.

## Subsequent dilation

Runge et al. and Schoepfer et al. contributed adjusted time-to-dilation estimates [18, 24]. In Runge, 55 patients with an incident EoE diagnosis underwent baseline dilation, received topical corticosteroids, and were classified at a subsequent endoscopy as 27 histologic responders and 28 nonresponders. Over a median follow-up of 19 months, responders required fewer subsequent dilations while achieving a similar increase in esophageal diameter. Schoepfer evaluated new dilation as one component of the treated long-term disease course.

Histologic control was associated with a lower hazard of subsequent dilation (pooled HR 0.63, 95% CI 0.42–0.94; Q = 0.81, P = 0.367; $I^2$=0%; $tau^2$=0; Online Resource 1, Figure S2). Runge also reported adjusted predicted numbers of 1.6 dilations among responders and 4.6 among nonresponders and lower odds of any subsequent dilation. The pooled estimate should be interpreted as a distinct clinical outcome from incident stricture because dilation is influenced by baseline caliber, local practice, symptom burden, prior mechanical therapy, and clinician threshold for repeat intervention.

## Short-term endoscopic fibrostenosis

Dellon et al. and Park et al. reported compatible post-treatment fibrostenotic EREFS means after short treatment intervals [13, 15]. Responders had lower fibrostenotic scores than nonresponders (pooled MD -0.61, 95% CI -0.93 to -0.29; $I^2$=0%; Online Resource 1, Figure S3). This analysis was secondary because histologic and endoscopic status were assessed concurrently after approximately 6–8 weeks and both cohorts were nonrandomized. The result indicates less residual ring/stricture burden among responders at follow-up but does not establish prevention of a later event. In the companion pull-sign report from the same UNC dataset, the sign persisted at follow-up in 5 of 25 responders and 26 of 33 nonresponders [14]. The pull-sign result was not added to the EREFS meta-analysis because it was a different outcome from the same participants (Table 2).

Table 2
Outcome-specific quantitative syntheses

| Outcome | Effect measure | Contributing studies | Pooled estimate (95% CI) | $I^2$ | Interpretation |
|---|---|---|---|---|---|
| Subsequent stricture/fibrostenosis | Adjusted HR | Starling 2024; Thel 2025; Schoepfer 2026 | 0.34 (0.17–0.67) | 0% | Primary analysis; values < 1 favor histologic control |
| Subsequent stricture/fibrostenosis | Unadjusted RR | Starling 2024; Thel 2025; Schoepfer 2026 | 0.34 (0.20–0.57) | 0% | Raw-event sensitivity analysis |
| Subsequent esophageal dilation | Adjusted HR | Runge 2017; Schoepfer 2026 | 0.63 (0.42–0.94) | 0% | Two-study analysis; clinically heterogeneous |
| Post-treatment fibrostenotic EREFS | Mean difference | Dellon 2016; Park 2024 | -0.61 (-0.93 to -0.29) | 0% | Secondary short-term analysis; response minus nonresponse |

Abbreviations: CI, confidence interval; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; HR, hazard ratio; RR, risk ratio.

## Tissue remodeling and molecular outcomes

Biopsy-based studies were directionally consistent with lower remodeling burden during histologic control. In Aceves et al., fibrosis scores decreased from 1.6 to 0.67 among nine budesonide responders but remained essentially unchanged among seven nonresponders (2.3 to 2.4) [10]. Reductions in transforming growth factor-beta 1, phosphorylated Smad2/3, and vascular activation also occurred among responders. In the longer UCSD/Rady cohort, mean fibrosis scores were 1.03 during histologic control and 2.59 during active disease; initial responders spent less observed time with maximal fibrosis and had lower endoscopic severity [11]. These studies were not pooled because participant overlap was probable, thresholds differed, and repeated longitudinal summaries could not be converted to a common independent effect estimate.

Pehrsson et al. assessed extracellular-matrix turnover during a 6-week four-food elimination diet and identified biomarker differences according to remission status [16]. Sharlin et al. reported paired endoscopic and transcriptomic changes after proton pump inhibitor therapy, including improvement in rings and strictures and attenuation of fibrosis-associated pathways among responders [17]. Neither report provided a compatible adjusted responder-versus-nonresponder effect suitable for quantitative synthesis. The molecular findings were therefore treated as supportive mechanistic evidence rather than clinical event data.

## Distensibility and esophageal caliber

Repeated FLIP studies supported a relationship between disease control and structural physiology, although their measurements and analytic approaches were incompatible. Carlson et al. studied 18 adults without interval dilation and reported a distensibility-plateau improvement of at least 2 mm in 5 of 7 responders and 3 of 11 nonresponders [12]. Kennedy et al. evaluated 300 endoscopies in 112 children and found the greatest increase in esophageal distensibility among participants whose inflammation resolved (+ 1.41 mm/year), compared with persistently active disease (+ 0.16 mm/year; time-by-group P = 0.003) [23]. Kennedy also found that lower baseline distensibility predicted later dilation, but that prognostic association was not a histologic-response effect and was not pooled.

Among 66 adults with severe strictures, Kim et al. found histologic remission strongly associated with achieving esophageal diameters of at least 13 mm and 15 mm, although remission was classified by the time of maximum diameter and therefore did not clearly precede the outcome [19]. In Snyder's serial-esophagram cohort, annual maximum-diameter change was greater in inactive than active disease (+ 0.8 vs 0.0 mm/year; P = 0.019) [20]. These studies were not combined because one used achievement of diameter thresholds during serial dilation and the other used annual continuous change on standardized esophagrams. Collins et al. reported rings or strictures in 1 of 59 continuous responders, 5 of 65 intermittent responders, and 2 of 22 nonresponders, but the endpoint combined prevalent and incident findings and the cohort probably overlapped other UCSD/Rady reports [25].

## Risk of bias

Three datasets were judged at moderate overall risk of bias and the remainder at serious risk (Online Resource 1, Table S5). No dataset was judged low risk. The principal concerns were residual confounding, selection of patients with repeated endoscopy or adequate lamina propria tissue, heterogeneous treatment and follow-up, time-dependent classification of remission, potential immortal-time bias, and uncertain participant overlap. The long-term event studies provided adjusted estimates, but adjustment sets differed and could not eliminate confounding by baseline structural severity, diagnostic delay, adherence, prior dilation, or intensity of surveillance.

## Discussion

In this systematic review of treated EoE, histologic control was consistently associated with a lower fibrostenotic burden across clinical, endoscopic, physiologic, and tissue-remodeling domains. The strongest quantitative evidence came from three independent long-term cohorts, in which histologic control was associated with an approximately two-thirds lower hazard of subsequent stricture or composite fibrostenosis. A separate two-study synthesis showed a lower hazard of subsequent dilation. The concordant raw-event analysis and the directionally consistent observations for fibrosis, distensibility, caliber, molecular remodeling, and endoscopic fibrostenosis support a coherent association between inflammatory control and structural outcome.

The primary structural-event analysis and the secondary remodeling analyses address related but noninterchangeable questions. Incident strictures, composite fibrostenosis, and future dilation are clinically consequential events that occur after an exposure classification and are most relevant to prevention. In contrast, post-treatment EREFS, lamina propria fibrosis, transcriptomic pathways, diameter, and FLIP measurements describe the structural state or its change over a shorter interval. A concurrent association can reflect common response to treatment, less severe baseline disease, or partial reversibility; it cannot by itself establish that histologic remission prevented a subsequent complication. Separating these domains avoided assigning the same causal interpretation to outcomes with different temporal structures.

The findings are biologically coherent. Eosinophil-rich inflammation can promote transforming growth factor-beta signaling, fibroblast activation, extracellular-matrix deposition, angiogenesis, smooth-muscle dysfunction, and loss of wall compliance [10, 11, 17]. Repeated or sustained disease activity would therefore be expected to increase fixed narrowing and reduce distensibility over time. Conversely, suppression of inflammation may prevent further matrix deposition and permit partial reversal of inflammatory edema, epithelial remodeling, and early fibrotic change. The improvement in biopsy fibrosis and remodeling mediators among responders, together with longitudinal gains in distensibility and caliber, supports this model. Nevertheless, these observations do not demonstrate complete reversal of established collagen deposition or a mature fixed stricture.

The distinction between a single histologic response and sustained disease control also deserves emphasis. The included long-term cohorts used different exposure definitions: response at a specified follow-up endoscopy, two consecutive remissions, at least one remission episode, or a trajectory across repeated examinations. A single response may indicate treatment sensitivity but may not represent durable suppression. Conversely, trajectory definitions may better reflect cumulative inflammatory exposure but can use future information and introduce immortal-time or classification bias. The available evidence therefore supports the clinical relevance of control, but it does not define the duration, depth, or frequency of remission required to alter fibrostenotic risk.

These results have practical implications for care. Histologic remission appears relevant not only as a trial endpoint but also as a marker associated with later structural outcomes. Symptom improvement alone may be insufficient because dysphagia can be modified by behavioral adaptation and mechanical dilation, while persistent eosinophilia may continue to drive remodeling. The findings support treatment strategies that assess histology after induction and maintain anti-inflammatory control rather than relying solely on symptoms. They may be particularly relevant to patients with a narrow-caliber esophagus, early rings, prior food impaction, or a history of dilation, in whom prevention of further structural progression is a major treatment objective.

Histologic control should not be viewed as a substitute for evaluation and treatment of existing fibrostenosis. Patients with fixed narrowing may continue to require dilation despite mucosal remission, and the lower pooled hazard of subsequent dilation does not imply that mechanical therapy can be withheld when clinically indicated. Dilation and anti-inflammatory treatment address different components of disease: dilation increases lumen caliber, whereas pharmacologic or dietary therapy targets inflammatory activity. The Runge cohort is informative in this respect because responders underwent fewer later dilations while attaining a similar increase in caliber, suggesting that inflammatory control may reduce repeat intervention after initial mechanical management.

The magnitude of the pooled associations should be interpreted cautiously. Histologic response was not randomized, and responders may differ from nonresponders in adherence, baseline disease severity, treatment selection, diagnostic delay, access to follow-up, or other prognostic factors. Treatment could also be intensified in patients with more severe structural disease, creating confounding by indication. Several studies defined control using future information, such as two consecutive remissions or at least one remission episode during follow-up. Such definitions can introduce time-dependent or immortal-time bias. The Schoepfer estimate required inversion from active-versus-controlled disease, and the pooled dilation estimate combined cohorts with different baseline phenotypes and outcome ascertainment.

The absence of observed statistical heterogeneity should not be overinterpreted. Each meta-analysis contained only two or three studies, providing little power to detect inconsistency. The structural-event studies differed in age, duration of follow-up, remission definition, and whether the outcome was stricture alone or a composite including narrowing and dilation. Similarly, dilation depends on local practice and baseline caliber. The pooled estimates summarize the available compatible evidence, but they should not be read as evidence that the effect is identical across pediatric and adult disease, treatment classes, or stages of fibrostenosis.

This review has several strengths. The search was broad, incorporated both forward and backward citation searching, and covered structural outcomes assessed by endoscopy, esophagram, FLIP, and histology. The exposure was restricted to achieved histologic status rather than receipt of a particular treatment, aligning the synthesis with a clinically important treat-to-target question across therapies. Reports were mapped to underlying datasets before analysis, adjusted estimates were prioritized, and outcome domains were not forced into a single composite meta-analysis. The raw-event sensitivity analysis yielded a result consistent with the adjusted structural-event synthesis.

Limitations arise from both the evidence base and the available reporting. All included datasets were observational, most were small, and outcome definitions and response trajectories varied. Long-term data were concentrated in a small number of tertiary centers, limiting generalizability to community practice and more diverse populations. Potential overlap could not be excluded within the UCSD/Rady, UNC, and Children's Hospital of Philadelphia report families. Missing variance data and incompatible scales prevented quantitative synthesis of several mechanistically important outcomes. The protocol's temporal criterion required operational clarification to accommodate paired pre/post remodeling studies; these short-term concurrent assessments were kept separate from the primary long-term clinical analyses. Formal assessment of small-study effects and meta-regression were not possible.

Future studies should classify histologic response at prespecified landmark times and then follow participants prospectively for incident strictures, dilation, food impaction, diameter, and FLIP-defined biomechanics. Repeated-measures or time-varying exposure models are needed to quantify cumulative inflammatory control without using future information to define the exposure. Studies should report baseline caliber, diagnostic delay, previous food impaction and dilation, treatment adherence, treatment changes, and surveillance frequency, and should use standardized definitions of stricture, narrowing, and fibrostenosis. Individual-participant-data analyses across established EoE cohorts would help resolve overlap, harmonize response trajectories, and determine whether sustained remission offers greater structural protection than a single response assessment.

In conclusion, post-treatment histologic control was associated with fewer subsequent fibrostenotic events and a lower need for dilation in treated EoE. Directionally consistent endoscopic, tissue, caliber, and distensibility findings support histologic remission as a clinically meaningful treatment target. Because the evidence remains observational and at moderate or serious risk of bias, the pooled estimates should be interpreted as associations rather than causal effects.

## Declarations

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**Conflicts of interest/Competing interests**

The authors declare that they have no conflicts of interest or competing interests.

**Ethics approval**

Not applicable. This systematic review and meta-analysis analyzed data from previously published studies and did not involve direct participation of human subjects.

**Consent to participate**

Not applicable.

**Written Consent for publication**

Not applicable.

**Availability of data and material**

All aggregate data used in the analyses are provided in the article and Online Resource 1. The deduplicated bibliographic library and study-level extraction dataset are available from the corresponding author on reasonable request.

**Code availability**

The analytic code used for the meta-analyses is available from the corresponding author on reasonable request.

**Authors' contributions**

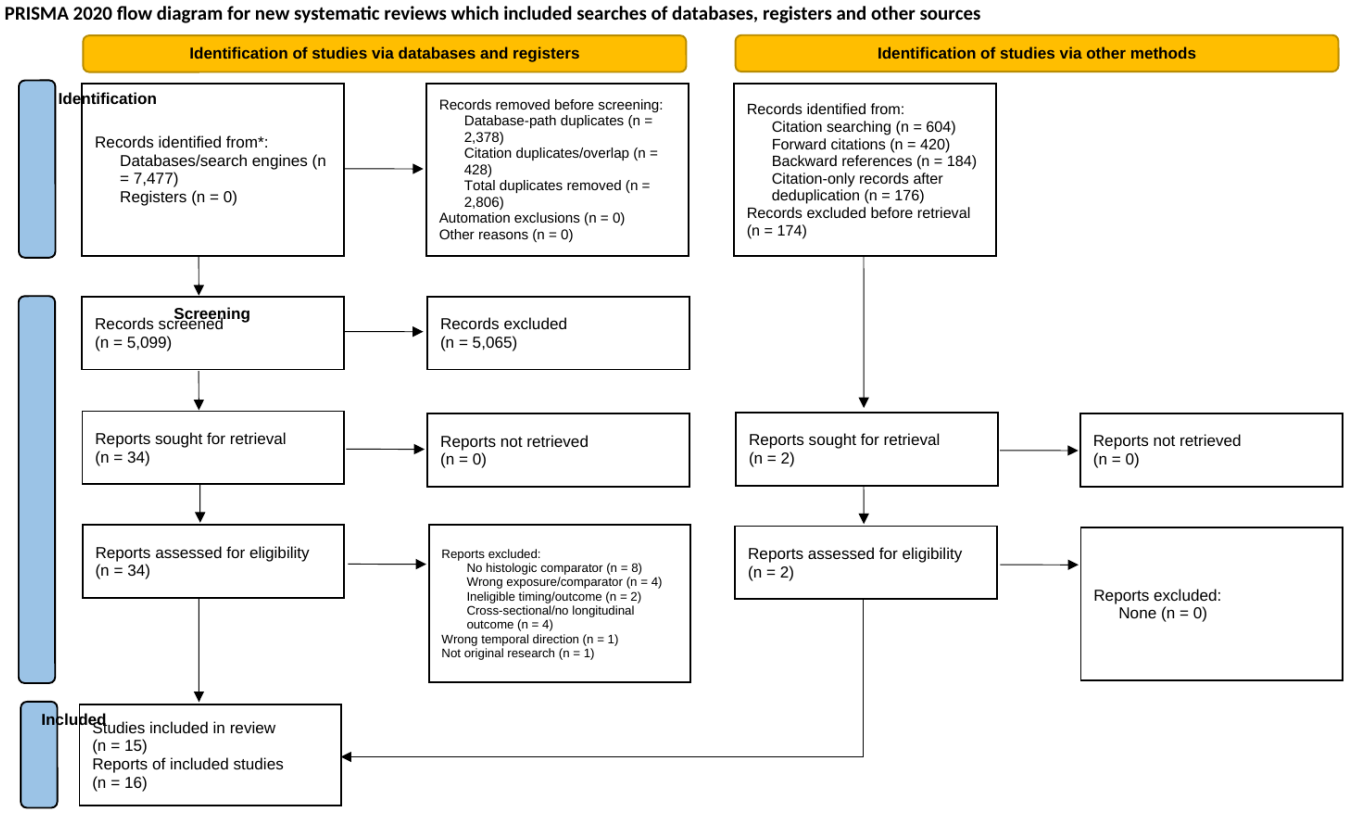
Yamen Shayah: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing. Mohd Diya Masmoum: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing. MHD Rasheed Awad: Data curation, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing.

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## Figures




*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

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**Figure 1**

PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion. The database/search-engine pathway yielded 14 included reports and the citation-search pathway yielded 2 included reports; the 16 reports represented 15 datasets. Adapted from Page et al. [7]

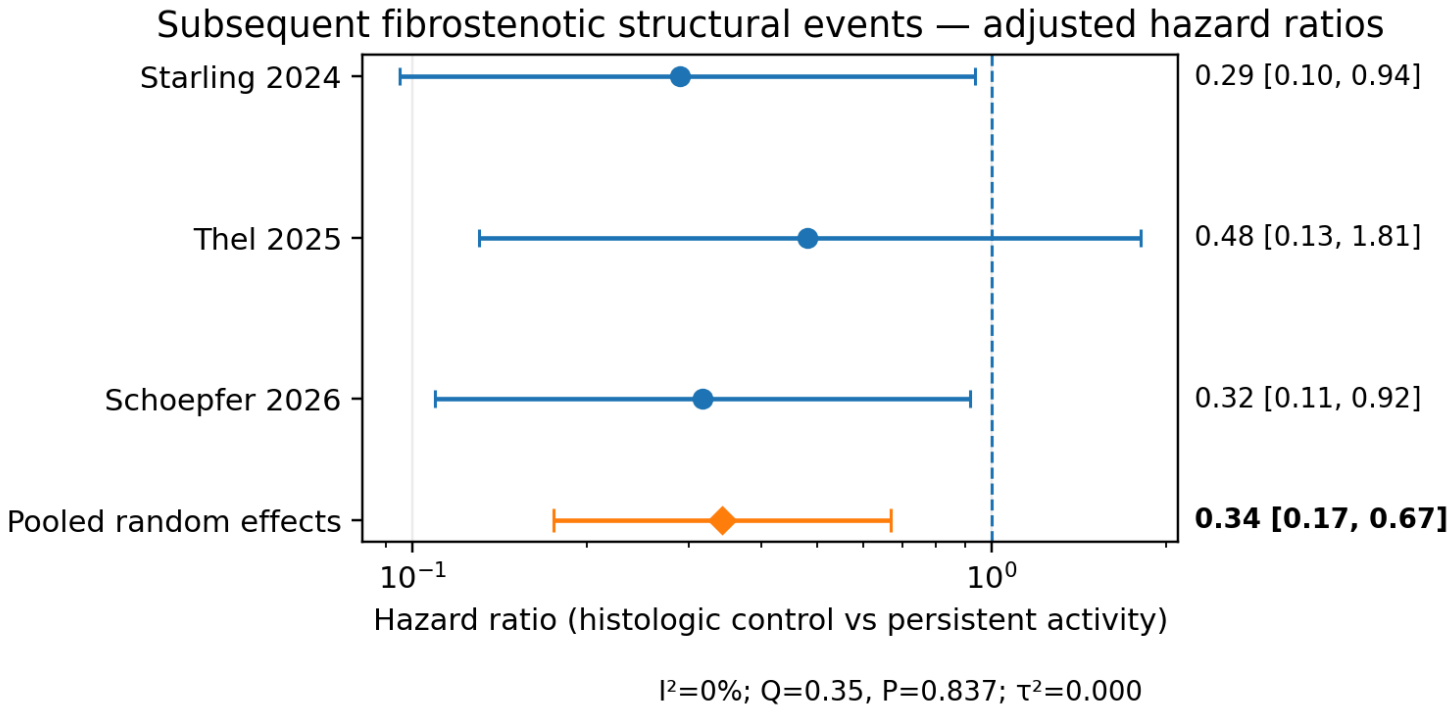



**Figure 2**

Random-effects meta-analysis of adjusted hazard ratios for subsequent stricture or composite fibrostenotic structural events from Starling et al. [21], Thel et al. [22], and Schoepfer et al. [24]. Values below 1 favor histologic control; CI, confidence interval; HR, hazard ratio

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SNCCMEoEOnlineResource1.pdf