

Online Resource 1 - Supplementary Tables and Figures

SN Comprehensive Clinical Medicine

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

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Table S1. Search sources, dates, and record counts

Source	Last search	Records	Search-concept summary
Embase (Ovid)	3 August 2026	Structural/remodeling search: 3,886; histologic-response search: 1,131; combined unique within Embase: 4,588	EoE terms combined with stricture, stenosis, narrowing, dilation/dilatation, fibrostenosis, fibrosis, remodeling, distensibility, EndoFLIP, or food impaction; separate histologic-response/persistent-eosinophilia block.
MEDLINE/PubMed	3 August 2026	Structural search: 1,197; histologic-response search: 477; combined: 1,508	EoE terms combined with structural/remodeling or histologic-response concepts; no date limit.
Cochrane CENTRAL	3 August 2026	398	Combined structural/remodeling and histologic-response search; CENTRAL Trials.
Scopus	3 August 2026	Main search: 483	EoE, histologic-response/persistent-activity, and structural/remodeling concepts.
Google Scholar via Publish or Perish	3 August 2026	Focused: 56; structural: 15; 69 unique	Focused histologic-response and structural searches.
Scopus citation searching	3 August 2026	Forward citations: 420; backward references: 184	Citation searching from nine sentinel studies.

Note: The complete line-by-line search histories are retained in the review archive. The counts reproduce the reviewer-verified search log and PRISMA totals.

Table S2. Classification of included reports and cohort independence

Report	Category	Dataset	Independence/overlap	Decision
Aceves et al., 2010	Longitudinal tissue-remodelling	UCSD/Rady pediatric paired-biopsy cohort	Aceves dataset; probable partial overlap with Rajan	Include
Rajan et al., 2016	Longitudinal tissue-remodelling	UCSD/Rady pediatric long-term topical-corticosteroid cohort	Rajan dataset; probable partial overlap with Aceves and possible overlap with Collins	Include
Carlson et al., 2017	Longitudinal physiologic remodelling	Northwestern EoE-FLIP registry	Independent report-defined dataset	Include
Dellon et al., 2016 (EREFS)	Longitudinal endoscopic remodelling	UNC prospective EREFS cohort	Same underlying cohort as Dellon pull-sign companion report	Include
Dellon et al., 2016 (pull sign)	Companion publication	UNC prospective EREFS cohort	Companion to Dellon EREFS; do not count as a second study	Include as companion
Park et al., 2024	Longitudinal endoscopic remodelling	Korean single-center treated EoE cohort	Independent report-defined dataset	Include
Pehrsson et al., 2023	Longitudinal biomarker remodelling	Amsterdam four-food elimination diet cohort	Independent report-defined dataset	Include, narrative only
Sharlin et al., 2026	Longitudinal molecular/endoscopic remodelling	PPI-treated paired-biopsy cohort	Independent report-defined dataset	Include, narrative only
Runge et al., 2017	Primary longitudinal clinical fibrostenosis	UNC clinicopathologic database, 2001-2014	Use instead of overlapping Gee report for dilation outcome	Include
Kim et al., 2020	Primary longitudinal caliber outcome	Northwestern severe-stricture cohort	Independent report-defined dataset	Include, narrative only
Snyder et al., 2024	Primary longitudinal caliber outcome	Mayo structured-esophagram cohort	Independent report-defined dataset	Include, narrative only
Starling et al., 2024	Primary longitudinal clinical fibrostenosis	CHOP childhood-to-adult cohort	Independent for structural-event meta-analysis; possible partial overlap with CHOP component of Kennedy	Include
Thel et al., 2025	Primary longitudinal clinical fibrostenosis	UNC pediatric cohort	Independent for structural-event meta-analysis	Include
Kennedy et al., 2026	Primary longitudinal physiologic fibrostenosis	CHOP and Children's Hospital Colorado prospective FLIP cohort	Independent outcome; possible partial CHOP overlap with Starling	Include
Schoepfer et al., 2026	Primary longitudinal clinical fibrostenosis	Swiss EoE Cohort Study	Independent for structural-event and dilation meta-analyses	Include
Collins et al., 2019	Longitudinal clinical fibrostenosis (narrative)	UCSD/Rady pediatric longitudinal registry	Possible/probable overlap with Aceves/Rajan	Include, narrative only

Table S3. Detailed outcome extraction

Study	Outcome domain	Raw data	Adjusted/model estimate	Synthesis
Aceves 2010	Biopsy fibrosis	Response: fibrosis 1.6 → 0.67; nonresponse: 2.3 → 2.4	No adjusted estimate	Narrative only; small cohort and nonstandard response threshold.
Rajan 2016	Biopsy fibrosis	Mean fibrosis score 1.03 when <15 eos/hpf vs 2.59 when active; maximal fibrosis 23% vs 53% of observed time	Correlation eosinophilia-fibrosis $r=0.53$, $P<.001$	Narrative; possible overlap with Aceves/Collins.
Carlson 2017	FLIP distensibility	DP improvement ≥ 2 mm: 5/7 responders vs 3/11 nonresponders	RR 2.62 (approx. 95% CI 0.90-7.66)	Not pooled; very small study and no significant association.
Dellon EREFS 2016	Fibrostenotic EREFS	Post-treatment score: 0.63±0.71 responders vs 1.24±0.99 nonresponders; stricture 4/38 vs 13/29	Unadjusted MD -0.61	Poolable with Park for exploratory EREFS analysis.
Dellon pull-sign 2016	Pull sign	At follow-up: 5/25 responders vs 26/33 nonresponders	No adjusted effect	Companion; narrative only.
Park 2024	Fibrostenotic EREFS	Post-treatment score: 0.27±0.46 responders vs 0.88±0.64 nonresponders	Unadjusted MD -0.61	Poolable with Dellon; small retrospective sample.
Pehrsson 2023	ECM biomarkers	Remission $n=10$ vs no remission $n=19$; lower CTX-III/net fibrolysis in remission; fibrosis progression linked to PRO-C3/PRO-C6	No common adjusted effect	Narrative; exploratory biomarker multiplicity.
Sharlin 2026	Endoscopic fibrosis/molecular remodeling	Rings 7/10 → 4/10 vs 9/9 → 9/9; strictures 5/10 → 2/10 vs 6/9 → 6/9	No adjusted comparative effect	Narrative; small translational cohort.
Runge 2017	Subsequent dilation	Any dilation 14/27 vs 21/28; adjusted predicted number 1.6 vs 4.6	Adjusted HR 0.48 (0.24-0.99); OR any 0.14 (0.03-0.67); rate OR 0.13 (0.03-0.63)	HR pooled with Schoepfer dilation.
Kim 2020	Caliber improvement	59/66 reached ≥ 13 mm; 43/66 reached ≥ 15 mm	Adjusted OR ≥ 13 mm 16.56 (1.85-148.60); ≥ 15 mm 34.97 (6.45-189.49)	Narrative; exposure classified by time of maximum diameter.
Snyder 2024	Diameter change	Annual maximum-diameter change: inactive +0.8 mm (IQR 0-5.3) vs active 0.0 (-0.4-0.6), $P=.019$	No adjusted effect	Narrative; disease status assessed near final esophagram.
Starling 2024	Subsequent stricture	5/55 control vs 15/50 no control	Adjusted HR 0.29 (0.095-0.936); unadjusted HR 0.232 (0.084-0.64)	Included in structural-event meta-analysis.
Thel 2025	Subsequent fibrostenosis	Second follow-up: 5/52 response vs 17/61 nonresponse	Adjusted HR 0.48 (0.13-1.81); unadjusted HR 0.37 (0.14-0.99)	Included in structural-event meta-analysis.
Kennedy 2026	Distensibility slope	Resolved inflammation +1.41 mm/year vs continuous active +0.16 mm/year	Time-by-group interaction $P=.003$	Narrative; no compatible second FLIP slope study.
Schoepfer 2026	New stricture/dilation	New stricture 7/93 controlled vs 12/58 active; dilation 41/93 vs 30/58	Active vs control HR: stricture 3.16 (1.09-9.17); dilation 1.40 (0.86-2.31)	Inverted for control-vs-active meta-analyses.

Study	Outcome domain	Raw data	Adjusted/model estimate	Synthesis
Collins 2019	Rings/strictures	1/59 continuous, 5/65 intermittent, 2/22 nonresponders; mixed prevalent/incident endpoint	No adjusted effect	Narrative only; overlapping UCSD/Rady cohort risk.

Table S4. Cohort-overlap assessment

Reports	Assessment	Analytic implication
Aceves 2010 ↔ Rajan 2016	Probable partial overlap	Same UCSD/Rady pediatric database, investigators, topical corticosteroid setting, and lamina propria outcomes. Do not pool their fibrosis estimates.
Aceves/Rajan ↔ Collins 2019	Possible to probable partial overlap	Same continuously accruing UCSD/Rady pediatric program and overlapping long-term follow-up. Treat findings as a cohort family.
Dellon EREFS ↔ Dellon pull sign	Same cohort/companion reports	Prospective UNC enrollment in the same period; use one statistical unit and retain distinct outcomes narratively.
Runge 2017 ↔ Gee 2025	High/substantial overlap	Same UNC database and near-identical baseline dilation/topical-steroid framework. Gee excluded from independent synthesis.
Runge ↔ Dellon EREFS/pull sign	Possible partial overlap	UNC enrollment periods overlap; outcome cohorts and inclusion criteria differ. Avoid combining potentially duplicated outcomes.
Thel 2025 ↔ other UNC reports	Low to possible overlap	Pediatric diagnosis makes major overlap with predominantly adult Runge/Dellon cohorts unlikely, but identifiers are unavailable.
Starling 2024 ↔ Kennedy 2026	Possible partial overlap	Kennedy includes a CHOP component during years overlapping the CHOP database used by Starling; outcomes are not pooled together.
Snyder 2024 ↔ Lee 2012	Possible Mayo overlap; Lee excluded	Both use Mayo patients/esophagram methods. Excluding Lee prevents duplicate quantitative contribution.
Starling, Thel, Schoepfer	No identified overlap	Distinct CHOP/University of Pennsylvania, UNC pediatric, and Swiss national cohorts; independent units for structural-event pooling.
Runge, Schoepfer	No identified overlap	Distinct UNC and Swiss cohorts; independent units for dilation pooling.

Table S5. ROBINS-I judgments

Study	Confounding	Selection	Exposure classification	Deviations	Missing data	Outcome measurement	Reported result	Overall	Notes
Aceves 2010	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Small selected paired-biopsy sample; nonrandom response; probable cohort overlap.
Rajan 2016	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Longitudinal but selected tissue availability; time-varying treatment and disease activity; overlap risk.
Carlson 2017	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Very small registry sample; heterogeneous treatment; no confounder adjustment.
Dellon EREFS/pull sign	Serious	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Serious	Prospective assessment but nonrandom response and short follow-up; same cohort in two reports.
Park 2024	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Small retrospective treated subset; heterogeneous therapy and limited adjustment.
Pehrsson 2023	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Serious	Exploratory biomarker multiplicity, small sample, no adjusted response-outcome model.
Sharlin 2026	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Serious	Small translational cohort; multiple molecular outcomes; no adjusted comparative effect.
Runge 2017	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate	Response precedes future dilation; adjusted models, but residual confounding remains.
Kim 2020	Serious	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Histologic remission defined by time of maximum diameter, creating time-dependent/reverse-causation risk.
Snyder 2024	Serious	Moderate	Serious	Moderate	Serious	Low	Moderate	Serious	Disease status near second esophagram; incomplete disease-status data and temporal ambiguity.
Starling 2024	Serious	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Sustained control requires surviving/remaining under observation for repeated EGDs; immortal-time/time-varying exposure concern.
Thel 2025	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Follow-up response precedes outcome and adjusted models used; residual confounding and selection remain.
Kennedy 2026	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate	Moderate	Prospective repeated measures and mixed models; nonrandom treatment and variable follow-up.

Study	Confounding	Selection	Exposure classification	Deviations	Missing data	Outcome measurement	Reported result	Overall	Notes
Schoepfer 2026	Serious	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious	At-least-one remission classification is time-dependent and can induce immortal-time bias; adjusted models partly mitigate confounding.
Collins 2019	Serious	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious	Response trajectory defined across follow-up; mixed prevalent/incident endpoint and overlap risk.

Table S6. Full-text exclusions

Report	Standardized exclusion reason	Detail
Beppu et al., 2015 — MMP-2/MMP-14	No eligible histologic-response comparator	All paired treated participants were successful histologic responders.
Lee et al., 2012 — esophageal diameter after topical corticosteroids	No eligible histologic-response comparator	Single pre/post treated cohort without responder versus nonresponder data.
Lieberman et al., 2012 — dietary therapy and subepithelial fibrosis	No eligible histologic-response comparator	Fibrosis reversal was analyzed by treatment type/continuous eosinophil change rather than threshold-defined response groups.
Lucendo et al., 2011 — prolonged fluticasone and collagen/cytokines	No eligible histologic-response comparator	Single paired treatment cohort without responder versus nonresponder analysis.
Kagalwalla et al., 2012 — epithelial-mesenchymal transition	No eligible histologic-response comparator	Treatment-responsive cohort did not provide a persistent-active comparator meeting the PECO.
Yoon et al., 2021 — reversibility of endoscopic features	No eligible histologic-response comparator	Pre/post treatment endoscopic changes were not reported by achieved histologic response.
Thakkar et al., 2022 — long-term PPI efficacy	No eligible histologic-response comparator	Long-term analysis was restricted to initial PPI responders.
Navarro et al., 2021 — PPI reversal of endoscopic fibrosis	No eligible histologic-response comparator	Pre/post EREFS changes were reported by treatment and among responders, without a directly extractable responder-versus-nonresponder structural comparison.
Gee et al., 2025 — endoscopic response and future dilation	Wrong exposure/comparator; overlapping report	Primary exposure was endoscopic EREFS response; concordant combined endoscopic-plus-histologic subgroups do not isolate the prespecified histologic exposure and substantially overlap Runge.
Ruffner et al., 2024 — persistent esophageal changes after remission	Wrong comparator	Histologic-remission patients were compared with non-EoE controls rather than persistent histologic activity.
Bon et al., 2022 — close follow-up and stricture formation	Wrong exposure	Exposure was follow-up intensity/care gaps rather than achieved histologic response.
LaFata et al., 2026 — surveillance timing and outcomes	Wrong exposure	Exposure was timing of surveillance endoscopy after remission rather than responder versus persistent-active status.
Cotton et al., 2022 — EREFS treatment-response threshold	Ineligible timing/outcome structure	Histology and structural EREFS were concurrent; no responder-specific longitudinal structural change or subsequent fibrostenotic event was reported.
Hoelz et al., 2025 — desmoglein-1/periostin in remission	Ineligible timing/outcome structure	Molecular findings were contemporaneous with histologic status rather than a subsequent longitudinal structural outcome.
Almazan et al., 2025 — EndoFLIP DI and histology	Cross-sectional/no eligible longitudinal outcome	Distensibility and histology were correlated at the same assessment without longitudinal response-to-outcome sequence.
Al-Mulaabed et al., 2026 — pediatric mechanical properties by disease stage	Cross-sectional/no eligible longitudinal outcome	Mechanical properties were compared across disease stages/treatments without eligible longitudinal response groups.

Report	Standardized exclusion reason	Detail
Eindor-Abarbanel et al., 2026 — proteomic remodeling	Cross-sectional/no eligible longitudinal outcome	Proteomic remodeling was assessed cross-sectionally in suspected/active disease.
Moosavi et al., 2023 — esophageal compliance	Cross-sectional/no eligible longitudinal outcome	FLIP compliance and tissue remodeling were assessed cross-sectionally.
Carlson et al., 2024 — C2D2 FLIP composite	Wrong temporal direction	Baseline structural physiology predicted future histologic response; the structural measure preceded rather than followed response classification.
Santacroce & Di Sabatino, 2025 — fast versus slow fibrosers	Not original participant research	Ideas-and-opinions article without original eligible cohort data.

Figure S1. Unadjusted risk-ratio sensitivity analysis for subsequent fibrostenotic structural events using reported event counts from Starling et al. [21], Thel et al. [22], and Schoepfer et al. [24]. Values below 1 favor histologic control.

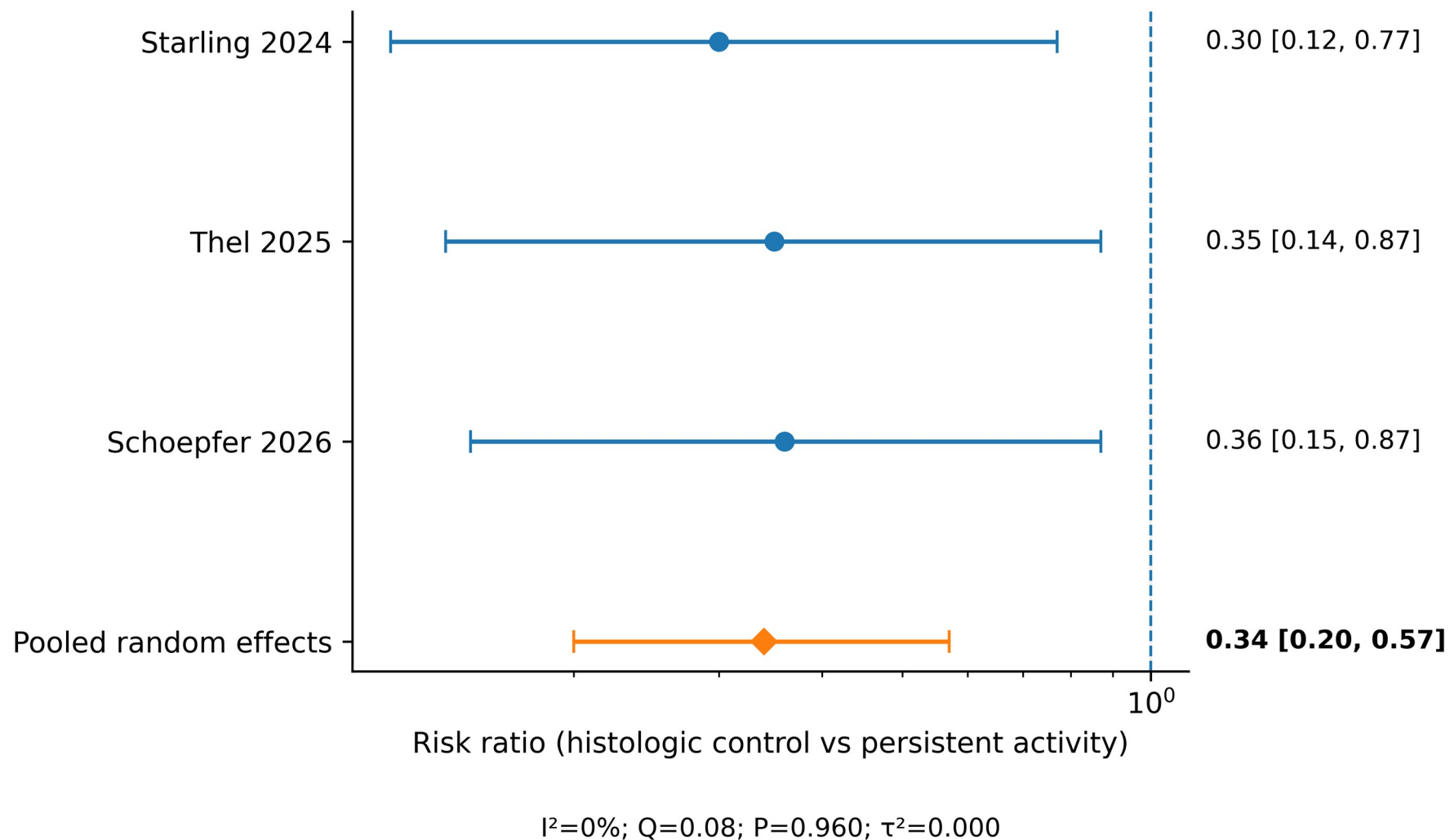


Figure S2. Random-effects meta-analysis of adjusted hazard ratios for subsequent esophageal dilation from Runge et al. [18] and Schoepfer et al. [24]. Values below 1 favor histologic control; CI, confidence interval; HR, hazard ratio.

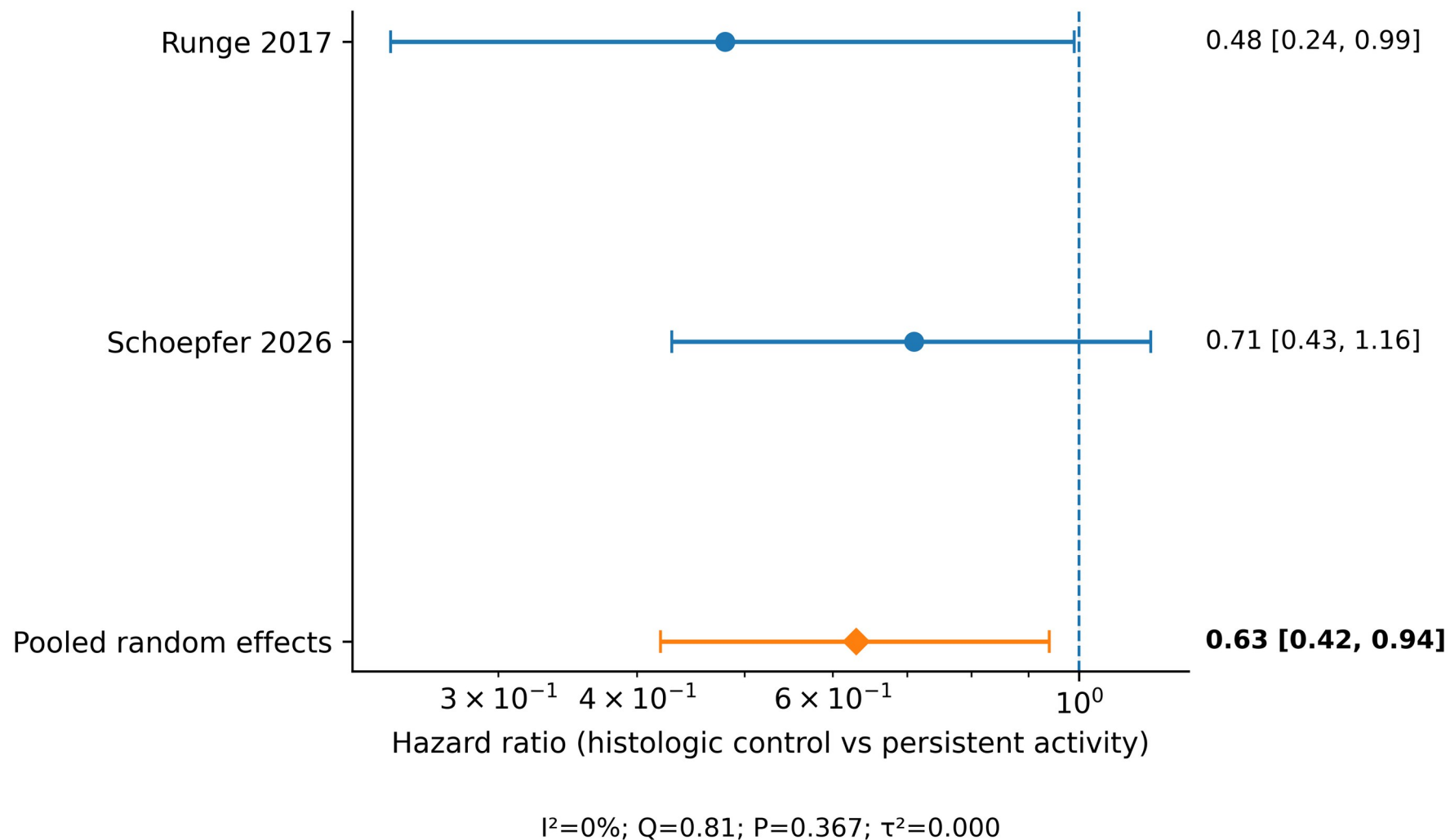


Figure S3. Random-effects meta-analysis of mean differences in post-treatment fibrostenotic EREFS from Dellon et al. [13] and Park et al. [15]. Negative values favor histologic response; CI, confidence interval; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; MD, mean difference.

