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Six-Food Elimination Diet and Topical Steroids are Effective for Eosinophilic Esophagitis: A Meta-Regression

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Abstract

Background—Topical corticosteroids or six-food elimination diet are recommended as initial therapy for eosinophilic esophagitis (EoE).

Aims—We aimed to summarize published manuscripts that report outcomes of these therapies for EoE.

Methods—We performed a systematic review in MEDLINE, Web of Science, and Embase of published manuscripts describing topical fluticasone, topical budesonide, and six-food elimination diet as therapies for EoE. We conducted meta-analysis of symptom improvement and the change in peak mucosal eosinophil count, with heterogeneity between studies examined with meta-regression analysis.

Results—Systematic review yielded 51 articles that met inclusion criteria. Summary histologic response rates were 68.3% (95% prediction limits [PL] 16.2 to 96.0%) for fluticasone, 76.8% (95% PL 36.1 to 95.1%) for budesonide, and 69.0% (95% PL 31.9 to 91.4%) for six-food elimination diet. Corresponding decreases in eosinophil counts were 37.8 (95% PL 19.0 to 56.7), 62.5 (95% PL 125.6 to −0.67, and 44.6 (95% PL 26.5 to 62.7), respectively. Symptom response rates were 82.3% (95% PL 68.1 to 91.1%), 87.9% (95% PL 42.7 to 98.6%), and 87.3% (95% PL 64.5 to 96.3%), respectively. Meta-regression analyses decreased the initially large estimate of residual heterogeneity and suggested differences in histologic response rate associated with study populations' baseline eosinophil count and age.

Conclusions—The literature describing topical corticosteroids and six-food elimination diet consists of small studies with diverse methods and population characteristics. Meta-analysis with meta-regression shows initial histologic and symptomatic response rates on the same order of magnitude for topical corticosteroids and six-food elimination diet, but heterogeneity of study designs prevent direct comparison of modalities.

Keywords

eosinophilic esophagitis; meta-analysis; corticosteroids; dietary elimination therapy; outcomes

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Introduction

Eosinophilic esophagitis (EoE) is a clinicopathologic disease with a substantial healthcare burden [1,2]. Clinical guidelines suggest patients diagnosed with EoE, defined as the failure of esophageal eosinophilia to resolve after effective acid suppression, should receive a therapy with the aim of decreasing mucosal eosinophil counts, and recommend either topical corticosteroids (tCS) or the six-food elimination diet (SFED; removal of dairy, wheat, egg, soy, nuts, and seafood) as initial therapy [1,3]. However, there are no studies that directly compare these two treatment modalities.

In addition to SFED, other dietary approaches have been examined for therapy of EoE [4]. A four-food elimination diet, elemental diet, and allergy-test targeted elimination diets have been studied. Swallowed topical ciclesonide has also been studied as an alternative tCS for EoE [5]. These treatments are not addressed in this manuscript because the meta-regression techniques used here require a large number of studies for each modality.

Previously published systematic reviews and/or meta-analyses have considered tCS and SFED in isolation but have included studies that have been heterogeneous in design and outcomes [6–13]. Novel meta-regression techniques are particularly useful in such cases, as they can explore the high residual heterogeneity reported as a limitation in prior meta-analyses describing dietary and steroid therapies [6–13]. Such analysis can also give insight into differences in outcomes associated with study design or baseline population characteristics, but this has never been done for EoE. The most useful estimate for clinicians in describing a treatment to patients is its average effectiveness in a population of similar patients. The overall mean reported in classical fixed and random effects meta-analysis can produce biased estimates and erroneously narrow confidence intervals if there are systematic differences in populations or the treatments [14], and this limitation can be addressed by meta-regression.

Aims

The aims of this study were: 1) To perform a systematic review of studies that describe SFED and tCS as therapies for EoE; 2) To describe design features, outcomes reported, and characteristics of study populations for all included studies; and 3) To perform stratified meta-analysis and meta-regression analysis on groups of included studies with similarly specified outcomes.

Methods

We performed a systematic review of published manuscripts describing topical fluticasone, topical budesonide, and SFED as therapies for EoE, in accordance with the PRISMA guidelines [15]. Our search strategy was developed in consultation with a dedicated research librarian with expertise in systematic review methods. We searched MEDLINE, Web of Science, and Embase databases using search settings and filters as described in Table 1. The search was independently performed by two investigators (CCC and SE) who reviewed all titles and abstracts, and selected articles for detailed review and data extraction. For meta-analysis, we selected articles from those included in the systematic review that reported the

mean and standard deviation of eosinophil counts (eosinophils per high-powered field; eos/hpf) before and after treatment, or the proportion of patients with histologic response defined as a threshold of eos/hpf. We also performed meta-analyses of studies that reported the proportion of patients with improvement in symptoms or reported symptoms in a way that could be simplified into a dichotomous improvement variable (yes or no).

Heterogeneity between studies was examined in meta-regression analysis. Potential meta-regression moderators were selected a priori based on potential importance in describing differences in study populations or methods, as well as their availability in published manuscripts. Moderators included were study design as trial or cohort, proportion of male subjects, mean age, proportion with a PPI trial or pH/impedance testing to diagnose EoE, proportion of subjects with prior therapy, whether maximum eosinophil counts were reported overall or in the distal esophagus, and baseline mean maximum eosinophil count. Quantifying studies' risk of bias was not attempted to be quantified because studies could be subject to bias in different directions, while adjustment for risk of bias would assume all bias was in the same direction. Moderators were significance-tested using a bootstrap permutation method to estimate p [16]. Moderators with individual two-sided p value less than 0.2 were included for iterative reverse selection by maximum p value with a criterion for retention of p less than 0.05.

Meta-analyses were presented in forest plots. The summary estimate of the mean with 95% confidence limits was presented as a diamond and the 95% prediction limits (PL) were presented as brackets with a dotted line. Prediction limits include estimated residual heterogeneity between studies in addition to sampling error of the overall mean [17]. For analyses with one or more statistically significant meta-regression moderators, the predicted mean at common values of the moderator was presented beneath the overall random effects estimate and the studies were sorted in forest plots by descending value of the most statistically significant moderator. If no moderator was statistically significant, the studies were ordered by publication date.

Data for meta-analysis were abstracted from study text, tables, and figures. Parameters of interest were obtained from figures when possible and when estimates of interest were not present in text or tables. The outcome of histologic response was specified in several different ways: as a threshold, as a difference, and as a ratio. For meta-analysis of the difference and ratio, studies that did not provide the eosinophil counts at baseline and follow-up were excluded. Meta-analysis and meta-regression models were fit using mixed-effects models with the Hodges estimator of between-study variance. Statistical analysis was performed in R version 3.3.0 using the *metafor* package version 1.9 [18,19].

Results

The systematic review search in MEDLINE, Web of Science, and Embase databases yielded 1533 unique records (Figure 1). Of these, 193 full articles were considered pertinent based on the title or abstract, and 51 were selected for inclusion: 33 articles describing therapy with topical fluticasone [20–52], 17 articles describing therapy with topical budesonide [28,32–34,36,44,51,53–62], and 9 articles describing therapy with SFED [60,63–70].

Manuscripts started in year of publication in 2003 among studies of topical fluticasone, 2007 among studies of topical budesonide, and 2006 among studies of SFED. Four randomized trials described topical fluticasone therapy and five described topical budesonide therapy, and none described SFED.

Histologic response was reported as a proportion under a threshold of eos/hpf in the largest subset of studies included in systematic review [21,25,30,31,37,43,45–48,50,52–57,59–63,65–70]. The most common threshold was 15 eos/hpf, though two studies used thresholds of near but not 15 eos/hpf and were included with an adjustment term for the difference of reported threshold from 15 [46,52,57,60,62,71]. Without meta-regression moderators, the predicted overall mean proportion of patients with a threshold histologic response to topical fluticasone was 68.3% (95% PL 16.2 to 96.0%). Studies of topical fluticasone where diagnosis of EoE was confirmed for all subjects with a PPI trial or pH/Impedance testing had significantly higher proportions with histologic response (Figure 2a). The estimated proportion of patients with histologic response to topical budesonide was 76.8% (95% PL 36.1 to 95.1%) (Figure 2b). The estimated proportion of patients with histologic response to SFED was 69.0% (95% PL 31.9 to 91.4%). A significant meta-regression moderator was not identified in studies of threshold histologic response for SFED (Figure 2c).

A subset of studies that reported histologic response as the mean and standard deviations of eosinophils per HPF before and after treatment allowed meta-analysis of the mean difference [21,30,31,37,43,45,47,48,50,53–56,59,60,62,63,65–68,70]. The mean difference before and after therapy with topical fluticasone was a decrease of 37.8 eosinophils per HPF (95% PL 19.0 to 56.7). No meta-regression moderator was statistically significant for studies of mean difference of fluticasone (Figure 3a). The mean difference before and after therapy with topical budesonide was a decrease of 62.5 (95% PL 125.6 to −0.7). Studies of topical budesonide with a higher baseline peak eosinophil count per HPF had a significantly greater decrease in eosinophil count after treatment (Figure 3b). The mean difference before and after therapy with SFED was a decrease of 44.6 eosinophils per HPF (95% PL 26.5 to 62.7). As with studies of budesonide, studies of SFED with a higher baseline peak eosinophil count per HPF had a significantly greater decrease in eosinophil count before and after treatment (Figure 3c).

The subset of studies that reported individual peak eosinophil counts before and after treatment or the Pearson correlation coefficient between counts before and after treatment were included in a meta-analysis of the ratio of maximum esophageal eosinophils before treatment to the maximum after treatment [21,30,31,37,45,47,48,50,53,54,56,59,63,65–67]. The mean ratio before and after therapy with topical fluticasone was 0.20 (95% PL 0.03 to 1.49), with topical budesonide was 0.11 (95% PL 0.01 to 0.87), and with SFED was 0.10 (95% PL 0.02 to 0.39). No meta-regression moderators were statistically significant in analyses of the mean ratio (Supplemental Figures 1a–c).

The literature describing symptom response from tCS and SFED partially overlaps with the literature describing histologic response [21–23,27,37,39,40,45,47,54,56,62,63,65–68,70]. The proportion of patients with symptom improvement was 82.3% (95% PL 68.1 to 91.1%) among studies of topical fluticasone. The proportion of patients with symptom improvement

was 87.9% (95% PL 42.7 to 98.6%) among studies of topical budesonide. The proportion of patients with symptom improvement was 87.3% (95% PL 64.5 to 96.3%) among studies of SFED. No meta-regression moderators were statistically significant in analyses of the mean ratio (Figures 4a–c).

Discussion

Current guidelines recommend that either tCS or dietary elimination, typically with SFED, are acceptable first line treatments for EoE [1,3]. There have been no clinical studies directly comparing these modalities, and meta-analyses to date have been performed for each of the treatments in isolation without meta-regression. We therefore performed a meta-analysis with meta-regression of studies that examined the effects of topical fluticasone, topical budesonide, and SFED on peak mucosal eosinophil count and symptom response, based on data derived from the most inclusive systematic review of studies of tCS and SFED for EoE to date. We found that patients treated with all three therapies generally had improvement in symptoms and reduction in mean eosinophil count, but substantial uncertainty remains about which is most effective. Meta-regression analysis techniques showed studies' methods and characteristics of study populations could explain some of the hetereogeneity between studies and suggested differences in histologic response rate associated with study populations' baseline peak eosinophil counts and age.

The clinical implications of this work are that topical fluticasone, topical budesonide, and SFED are generally effective treatments for eosinophilic esophagitis, and response rates are roughly of the same order of magnitude. It is premature to conclude, however, that one of these therapies is most effective for eosinophil counts or symptom improvement given the currently available literature, and given the overlap of wide probability limits between the different treatment modalities. Prior meta-analysis with classical methods and stringent criteria for study inclusion (primarily with RCTs) were well designed to show that tCS or SFED were effective for initial therapy of EoE in highly selected clinical trial populations [8,11–13]. Our findings support these studies' conclusions, but caution the clinician that generalization of their estimates to particular populations that differ demographically or histologically from the included studies may not be appropriate.

We also found that there were substantial gaps in current knowledge describing EoE treatments. Only a few studies examined the effectiveness of maintenance therapy with a mucosal agent [25,72,73]. Very little is known about the longitudinal course of EoE patients under treatment, especially among patients on SFED, and what is known suggests relapse is common if treatments are stopped. Only two retrospective studies examined the effectiveness of second-line therapies, though at least a fifth to a third of patients fail to respond to first line therapies [34,51].

Our study is limited in that we did not directly compare the results of our analyses between tCS and dietary elimination. Our findings show that such an analysis would be problematic because study outcomes seem to vary non-randomly with factors other than the choice of therapy. For example, study results were correlated with subject age, baseline maximal eosinophil count, and the rigor of studies' diagnosis of EoE. In a direct comparison it would

be unclear whether outcomes differed because of effectiveness of the interventions or variability in these features. This study is also limited in that it provides no new primary data but rather summarizes and interprets existing literature. Additionally, the definition of symptom improvement varied widely between included studies, and this outcome is limited in that a standard symptom score is not reported in most of the studies. Conclusions about the effectiveness of SFED should be tempered by the absence of a randomized study and potential challenges of adherence to an elimination diet [74,75].

The strengths of the study include the rigorous and comprehensive systematic review, analysis of both threshold eosinophil count responses as well as absolute and relative change in counts, stratifying analysis by tCS type (fluticasone vs budesonide), and incorporating novel meta-regression methods. Moreover, we have included more studies and therefore more patients under treatment than other recent meta-analyses of EoE treatment.

In summary, this systematic review with meta-analysis using meta-regression techniques shows histologic response rates for tCS and SFED ranging from 68–77%, decreasing in eosinophil counts ranging from 38–63 eos/hpf, and symptom responses of 82–88%. Future studies should compare therapies to one another in a randomized study design, report symptoms and endoscopic findings using validated instruments, and report mucosal response as the proportion of subjects with a total esophageal peak eosinophil count under 15 using a standard area of high-power field [76]. For this purpose, validated symptom scores are available for adults and children [77,78], and a standardized endoscopic findings score has emerged [79]. In addition, future studies should examine the durability of each therapy in maintaining remission, and consider analyses stratified by baseline age and maximum eosinophil count. Until these data are available, the recommendation in guidelines that either dietary elimination or topical steroids could be considered as a first line treatment for EoE after non-response to PPIs, remains reasonable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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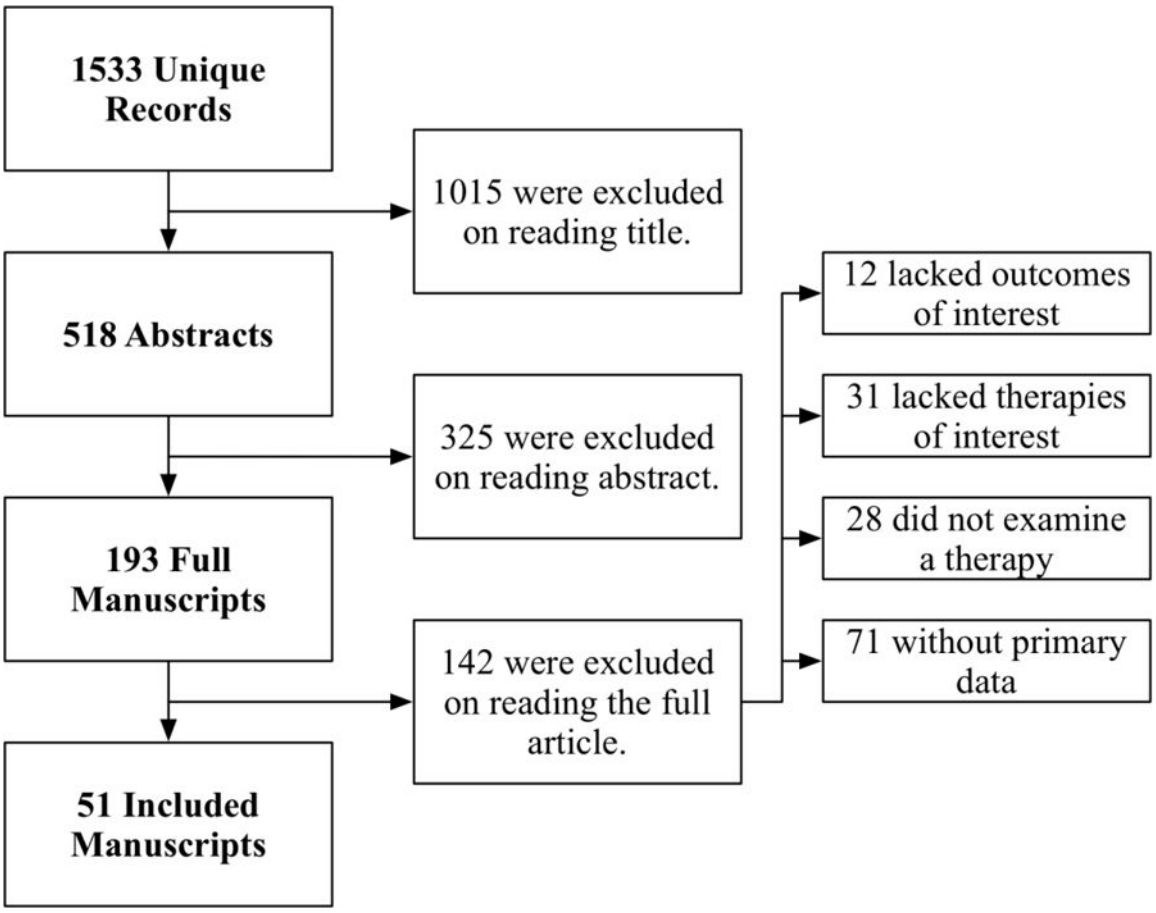
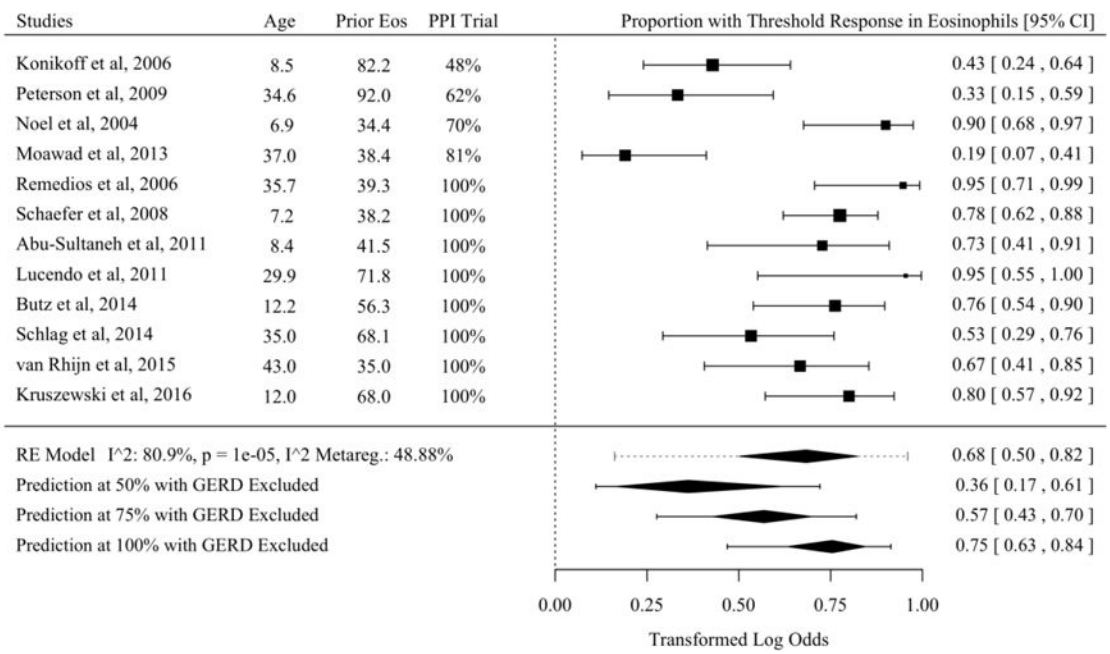


Figure 1.

Inclusion of 36 Articles for Meta-analysis and 51 Articles for Systematic Review from the 1533 Unique Articles Retrieved May 12, 2016 from MEDLINE, Web of Science, and Embase Search.

a



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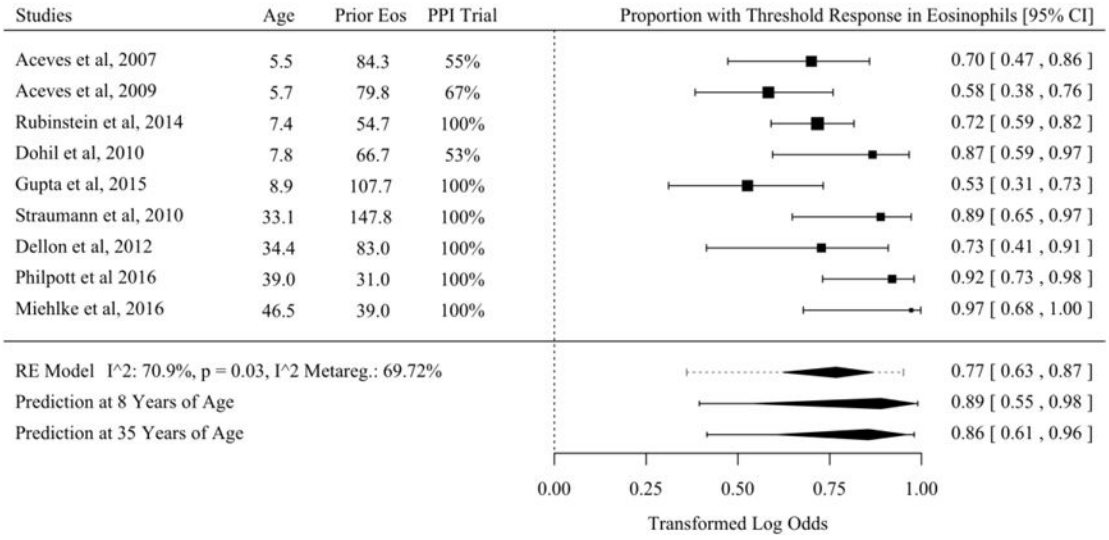


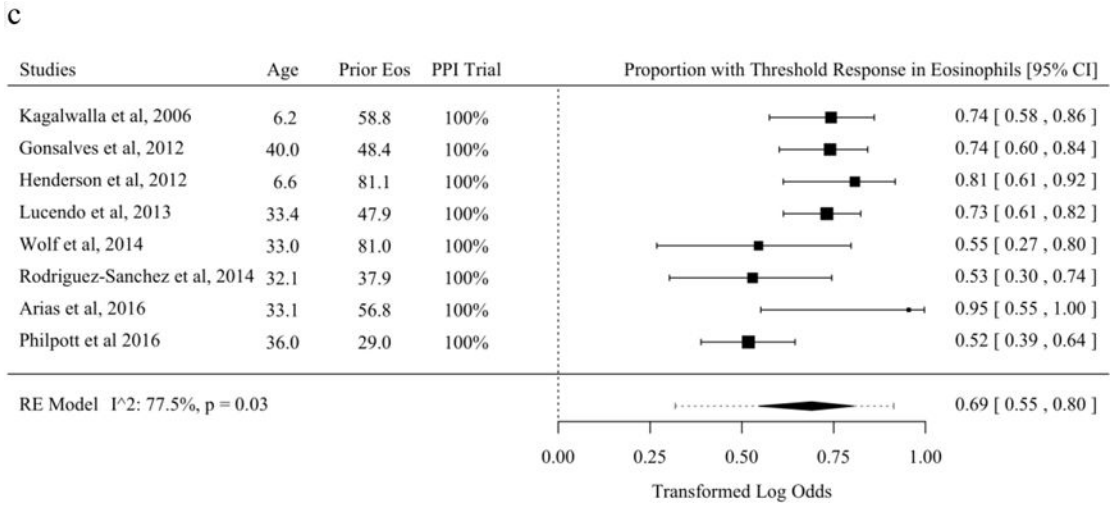
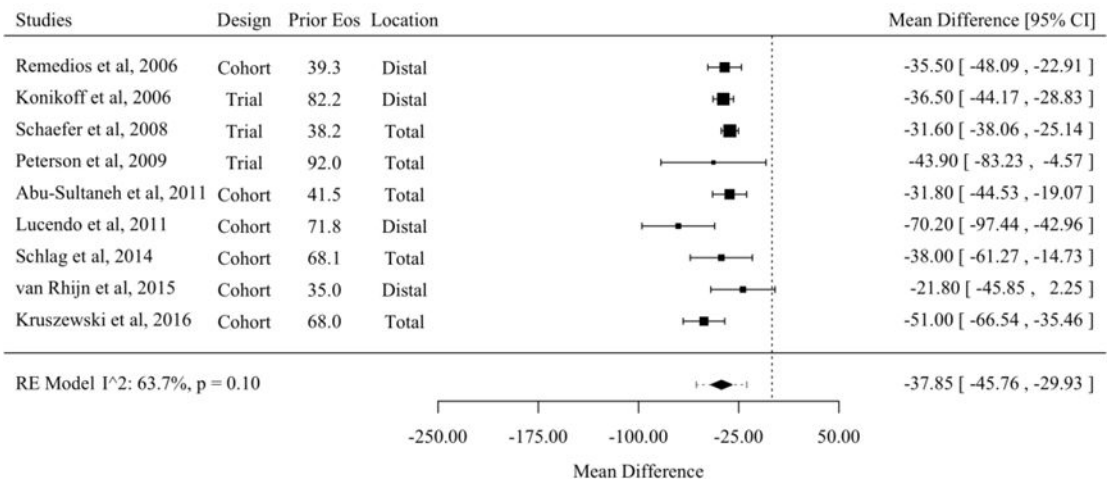


Figure 2.

Proportion of Subjects with Histologic Response Defined as a Threshold of Eosinophils per High-Power Field of or Near Fifteen After Therapy in Studies of Topical Fluticasone (A), Topical Budesonide (B), and Six-Food Elimination Diet (C) With Additional Study Details and Summary Estimates with 95% Prediction Limits. Studies are sorted in order of the statistically significant meta-regression moderator or by year if no moderator was significant at a threshold $p < 0.05$. Studies from systematic review that included the proportion of patients with response at a threshold of or near 15 eosinophils per high-power field without missing values for meta-regression variables were included.

a



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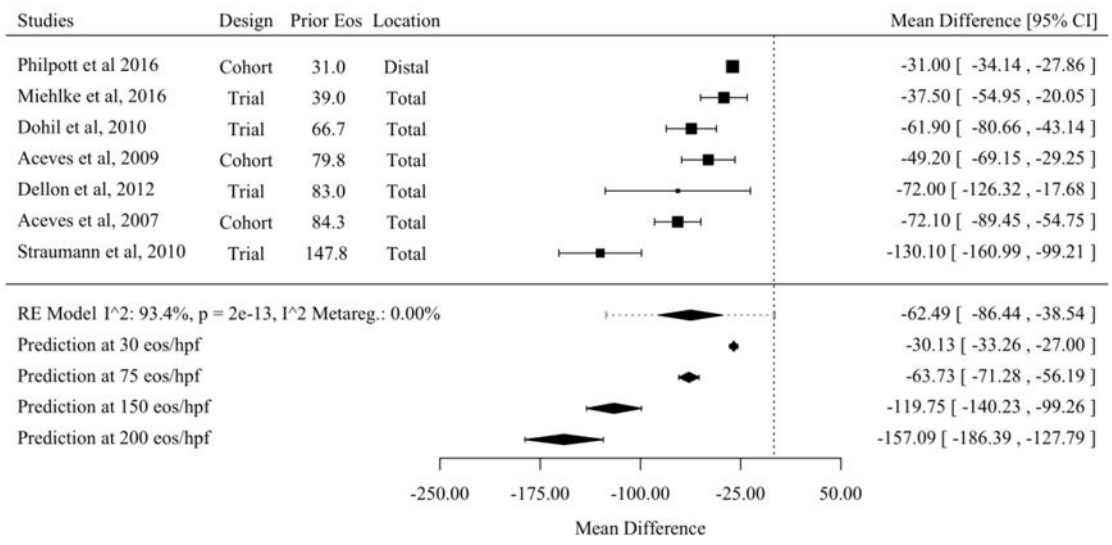

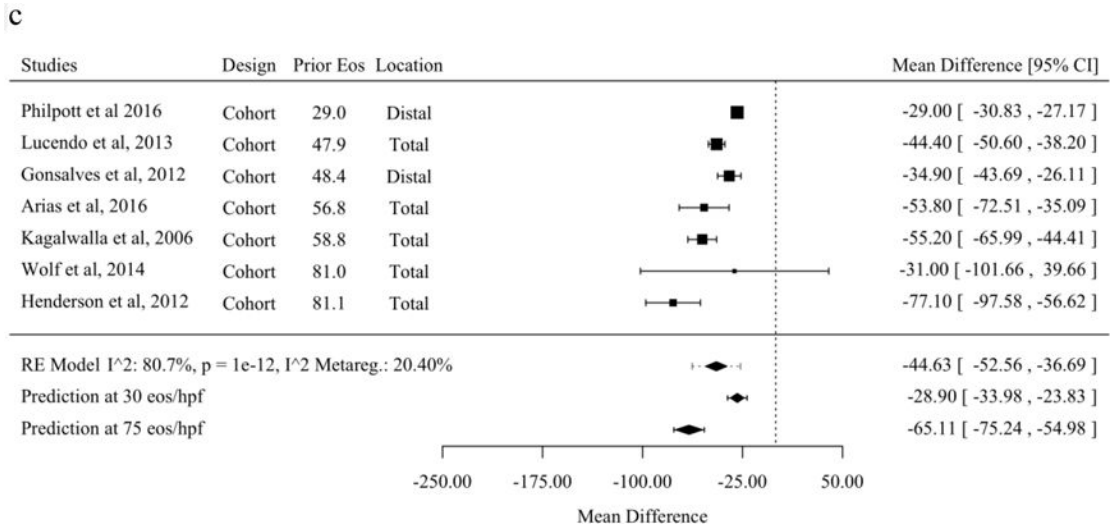

Figure 3.

Mean Difference for Eosinophils Before and After Therapy in Studies of Topical Fluticasone (A), Topical Budesonide (B), and Six-Food Elimination Diet (C) in Order of Publication Date or, if Present, Selected Meta-Regression Moderator. Studies are sorted in order of the statistically significant meta-regression moderator or by year if no moderator was significant at a threshold $p < 0.05$. Studies from systematic review that included the mean and standard deviation of eosinophils per high-power field before and after therapy without missing values for meta-regression variables were included.

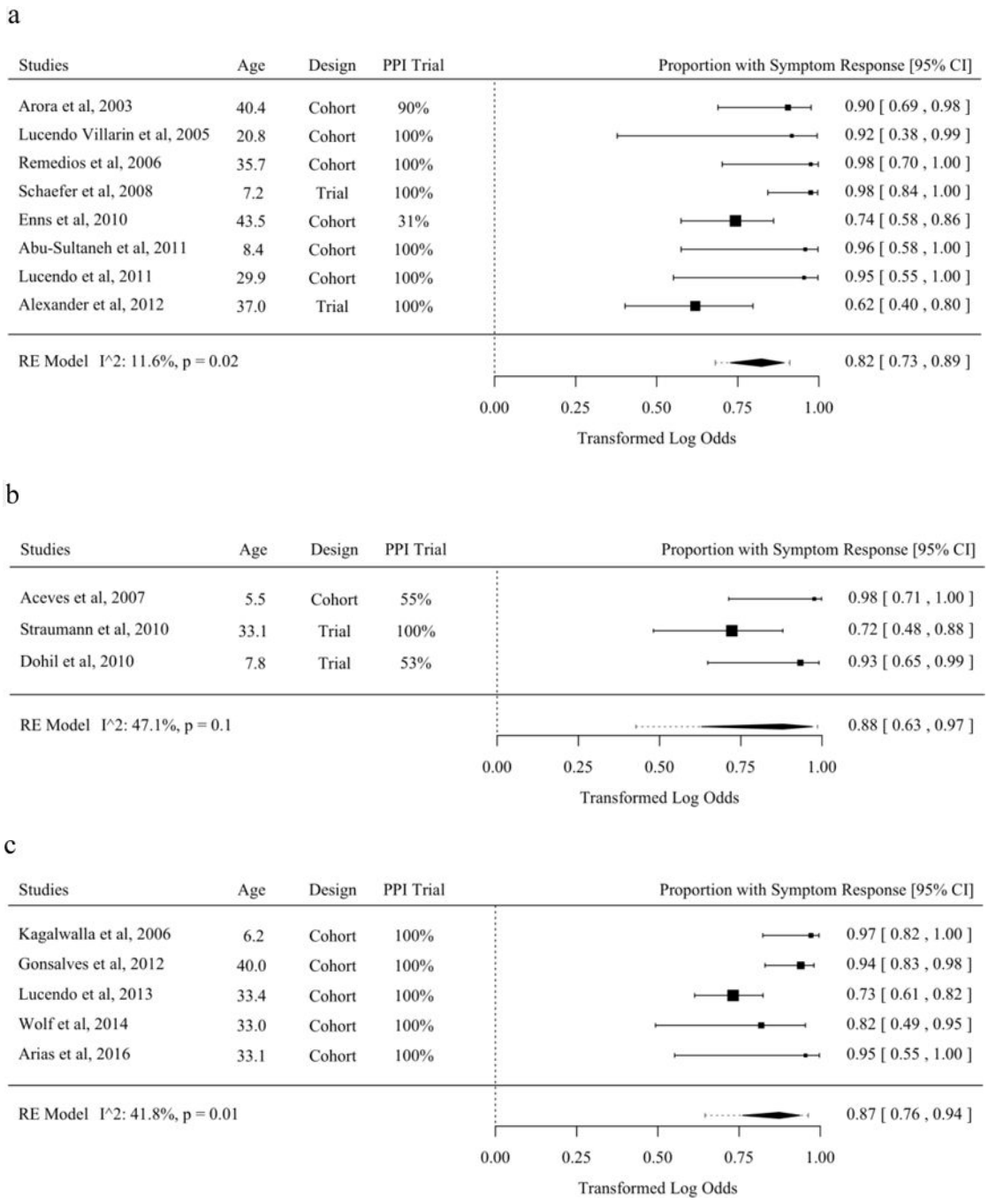

Figure 4.

Proportion of Patients with Symptom Response in Studies of Topical Fluticasone (A), Topical Budesonide (B), and Six-Food Elimination Diet (C) in Order of Publication Date or, if Present, Selected Meta-Regression Moderator. Studies are sorted in order of the statistically significant meta-regression moderator or by year if no moderator was significant at a threshold $p < 0.05$. Studies from systematic review that included the proportion of

patients with symptom response without missing values for meta-regression variables were included.

Table 1

Search Text, Filters, and Settings for MEDLINE, Embase, and Web of Science Searches.

	Search Text	Filters and Settings
MEDLINE search:	Eosinophili*[tw] AND Esophagitis[tw] AND (dilat*[tw] OR fluticasone[tw] OR budesonide[tw] OR ciclesonide[tw] OR steroid*[tw] OR diet[tw] OR diets[tw] OR dietary[tw] OR food*[tw])	Default
Embase search:	Eosinophili*:de,ti,ab AND Esophagitis:de,ti,ab AND (dilat*:de,ti,ab OR fluticasone:de,ti,ab OR budesonide:de,ti,ab OR ciclesonide:de,ti,ab OR steroid*:de,ti,ab OR diet:de,ti,ab OR diets:de,ti,ab OR dietary:de,ti,ab OR food*:de,ti,ab)	Embase, Embase and Medline; Reviews, Articles, and Conference Reviews.
Web of science search:	Eosinophili* AND Esophagitis AND (dilat* OR fluticasone OR budesonide OR ciclesonide OR steroid* OR diet OR diets OR dietary OR food*)	Articles, Reviews.
Criteria for study selection:	Journal articles that report measures of the effect of topical fluticasone, topical budesonide, or six-food elimination diet on eosinophil counts, adverse events, or symptoms.	

Table 2

The 51 Included Studies in Systematic Review and Their Study Design, Mean Characteristics, Therapies, Outcomes, and Adverse Events Reported.

Author and Year	Study Design	Age, Male, N	Therapies Described	Outcomes Reported	Adverse Events
			Studies of Topical Fluticasone		
Teitelbaum et al, 2002 *	Prospective cohort	8, 74%, 15	Topical fluticasone, specific elimination	Eos per HPF, other immune cells	13% candida
Arora et al, 2003	Retrospective cohort	40.4, 81%, 21	Topical fluticasone	Symptoms (binary †)	Not reported
Noel et al, 2004	Retrospective cohort	6.9, 75%, 20	Topical fluticasone	Symptoms (3 level §)	20% candida
Lucendo Villarín et al, 2005	Prospective cohort	20.8, 80% 5	Topical fluticasone	Symptoms (binary †), eos per HPF	Not reported
Konikoff et al, 2006	Randomized trial	8.5, 81%, 21	Topical fluticasone	Symptoms (specific ‡), eos per HPF	5% candida
Remedios et al, 2006	Prospective cohort	35.7, 32%, 19	Topical fluticasone	Eos per HPF	16% candida
Assa'ad et al, 2007 *	Retrospective cohort	6.2, 78.6%, 89	Topical fluticasone, specific elimination	EoE resolution	Not reported
Lucendo et al, 2007 *	Prospective cohort	36.2, 90%, 30	Topical fluticasone	Endoscopic findings	Not reported
Pasha et al, 2007 *	Retrospective cohort	44, 74%, 42	Topical fluticasone	Symptoms (binary †)	Not reported
Helou et al, 2008 *	Cross-sectional	34.9, 59%, 32	Topical fluticasone	Symptoms (MDQ)	Not reported
Schaefer et al, 2008	Randomized trial	7.2, 70%, 40	Topical fluticasone	Symptoms (specific ‡), eos per HPF	15% candida
Pentiuk et al, 2009 *	Cross-sectional	10.6, 89%, 14	Topical fluticasone	Symptoms (score °), eos per HPF	Not reported
Sayej et al, 2009	Prospective cohort	10.4, 59%, 15	Topical fluticasone	Eos per HPF	Not reported
Peterson et al, 2009	Randomized trial	34.6, 73%, 15	Topical fluticasone	Symptoms (score °), eos per HPF, endoscopic findings	Not reported
Enns et al, 2010	Retrospective cohort	43.5, 76%, 35	Topical fluticasone	Symptoms (binary †), endoscopic findings	Not reported
Abe et al, 2010 *	Retrospective cohort	38.5, 100%, 2	Topical fluticasone	Eos per HPF, endoscopic findings	Not reported
Abu-Sultaneh et al, 2011	Retrospective cohort	8.4, 45%, 11	Topical fluticasone	Symptoms (specific ‡), eos per HPF	Not reported
Lucendo et al, 2011	Prospective cohort	29.9, 90%, 10	Topical fluticasone	Symptoms (binary †), eos per HPF	Not reported
Alexander et al, 2012	Randomized trial	37.0, 86, 21	Topical fluticasone	Symptoms (binary †), eos per HPF	26% candida
Czaja-Bulsa et al, 2012	Retrospective cohort	9.2, 79%, 2	Topical fluticasone	Symptoms (binary †)	Not reported
Li et al, 2012 *	Prospective cohort	35.0, 88%, 8	Topical fluticasone + monteleukast	Symptoms (binary †)	Not reported
Moawad et al, 2013	Randomized trial	37.0, 90%, 21	Topical fluticasone	Symptoms (MDQ), eos per HPF, endoscopic findings	5% candida
Butz et al, 2014	Retrospective cohort	12.2, 79%, 21	Topical fluticasone	Eos per HPF, durability	0% AI

Author and Year	Study Design	Age, Male, N	Therapies Described	Outcomes Reported	Adverse Events
Schlag et al, 2014	Prospective cohort	35.0, 93%, 15	Topical fluticasone	Eos per HPF, serum ECP, symptoms (score °)	Not reported
van Rhijn et al, 2015	Prospective cohort	43.0, 67%, 15	Topical fluticasone	Eos per HPF, mucosal integrity	Not reported
Kruszewski et al, 2016	Prospective cohort	12.0, 63%, 20	Topical fluticasone	Symptoms (PedsQL), eos per HPF, endoscopic findings	Not reported
			Studies of Topical Budesonide		
Aceves et al, 2007	Retrospective cohort	5.5, 80%, 20	Topical budesonide	Symptoms (score °), eos per HPF	5% candida
Aceves et al, 2009	Retrospective cohort	5.7, 74%, 24	Topical budesonide	Eos per HPF	Not reported
Dohil et al, 2010	Randomized trial	7.8, 80%, 15	Topical budesonide	Symptoms (score °), eos per HPF, endoscopic findings	7% candida, 0% AI
Straumann et al, 2010	Randomized trial	33.1, 94%, 18	Topical budesonide	Symptoms (score °), eos per HPF, endoscopic findings	17% candida
Dellon et al, 2012	Randomized trial	34.4, 58%, 11	Topical budesonide	Symptoms (MDQ), eos per HPF, endoscopic findings	18% candida, 0% AI
Rubinstein et al, 2014	Retrospective cohort	7.4, 83%, 60	Topical budesonide	Eos per HPF	Not reported
Gupta et al, 2015	Randomized trial	8.5, 70%, 71	Topical budesonide	Symptoms (EoE CSS), eos per HPF	3% candida
Harel et al, 2015 *	Prospective cohort	10.6, 93%, 14	Topical budesonide	Adrenocorticotropin stimulation testing	43% AI
Miehlke et al, 2016	Randomized trial	46.5, 74%, 19	Topical budesonide	Symptoms (score °), eos per HPF	11% candida, 5% AI
			Studies of Six Food Elimination Diet		
Kagalwalla et al, 2006	Retrospective cohort	6.2, 74%, 35	Six food elimination, specific elimination	Symptoms (binary †), eos per HPF	Not reported
Gonsalves et al, 2012	Prospective cohort	40.0, 50%, 50	Six food elimination	Symptoms (SF-36), endoscopic findings, eos per HPF	Not reported
Henderson et al, 2012	Retrospective cohort	6.6, 77%, 26	Six food elimination, specific elimination	Symptoms (binary †), eos per HPF	Not reported
Lucendo et al, 2013	Prospective cohort	33.4, 82%, 67	Six food elimination	Symptoms (specific ‡), eos per HPF	Not reported
Colson et al, 2014 *	Retrospective cohort	6.5, 63%, 59	Six food + specific elimination	Symptoms (specific ‡), eos per HPF	Not reported
Rodriguez-Sanchez et al, 2014	Prospective cohort	32.1, 77%, 17	Six food elimination, specific elimination	Symptoms (VAS-EoE), endoscopic findings, eos per HPF	Not reported
Wolf et al, 2014	Retrospective cohort	33.0, 56%, 11	Six food elimination	Symptoms (binary †), eos per HPF, endoscopic findings	Not reported
Arias et al, 2016	Prospective cohort	33.1, 80%, 10	Six food elimination	Symptoms (score °), eos per HPF, gene expression	Not reported
			Studies of Multiple Included Therapies		
Lee et al, 2012 *	Prospective cohort	40, 27%, 11	Topical budesonide, topical fluticasone	Symptoms (MDQ), esophageal diameter	Not reported

Author and Year	Study Design	Age, Male, N	Therapies Described	Outcomes Reported	Adverse Events
Lieberman et al, 2012 *	Retrospective cohort	14.6, 78%, 9	Topical budesonide, topical fluticasone, specific elimination	Symptoms (binary †), eos per HPF	Not reported
Kuchen et al, 2014 *	Retrospective cohort	31, 76%, 206	Topical budesonide or topical fluticasone	Long-lasting bolus impactions	Not reported
Golekoh et al, 2015 *	Prospective cohort	12.9, 81%, 58	Topical fluticasone, topical budesonide	Adrenocorticotropin stimulation testing	10% AI
Wolf et al, 2015 *	Retrospective cohort	25.6, 70%, 221	Topical budesonide or topical fluticasone	Symptoms (binary †), eos per HPF, endoscopic findings	5% candida
Leung et al, 2015 *	Retrospective cohort	13.0, 78%, 100	Topical budesonide, topical fluticasone, multiple dietary	Eos per HPF, second-line therapies	Not reported
Philla et al, 2015	Prospective cohort	10.1, 71%, 14	Topical fluticasone, topical budesonide	Morning serum cortisol	0% AI
Philpott et al 2016	Prospective cohort	34, 84%, 82	Topical budesonide, six food elimination	Symptoms (binary †), eos per HPF	Not reported

*Study not included in meta-analysis because necessary estimates for outcome measures could not be taken from review of the published manuscript.

†, improvement or no improvement.

§, no improvement, partial improvement, complete improvement.

‡, individual symptoms such as dysphagia or abdominal pain.

°, the study reported an internally defined symptom score.

N, number; HPF, high-power field; MDQ, Mayo Dysphagia Questionnaire; AI, adrenal insufficiency; ECP, Eosinophil Cationic Protein.