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# Comparison of viscous budesonide and fluticasone in the treatment of patients with eosinophilic esophagitis: a systematic review and meta-analysis

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## Abstract

**Background** Steroids are an important pharmacologic treatment in patients with eosinophilic esophagitis (EoE). Fluticasone and budesonide are the 2 main steroid medications used in EOE treatment, but current United States (US) guidelines do not recommend one agent over the other. In this study, we conducted a meta-analysis to compare important patient outcomes when both agents are used.

**Methods** A comprehensive search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus was performed from each database's inception to March 29th, 2023. Two independent reviewers systematically identified trials that compared the effect of budesonide vs. fluticasone in the management of EoE. A meta-analysis was performed using a fixed-effects model. The primary outcome was the histologic response (defined as an eosinophil count <15 per high-power field) which reflects the response to treatment.

**Results** Three studies met our inclusion criteria and were included in the analysis, with a total of 272 patients. All studies were carried out in the US and 1 was a randomized controlled trial. Our meta-analysis showed no statistically significant difference with the use of budesonide compared to fluticasone in achieving a histologic response (odds ratio 1.29, 95% confidence interval 0.77-2.14; P=0.34; $I^2$=0%).

**Conclusion** Our systematic review and meta-analysis indicated no difference between budesonide and fluticasone in achieving a histologic response in patients with EoE.

**Keywords** Eosinophilic esophagitis, steroids, treatment, fluticasone, budesonide

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## Introduction

Unlike other areas of the gastrointestinal tract, the esophagus is normally devoid of eosinophils [1,2]. Eosinophilic esophagitis (EoE) is a chronic condition characterized by eosinophilic infiltration of the esophagus. This condition can affect both pediatric and adult populations [3]. The first case of EoE was not described until 1978; however, it was thought to be a variant of eosinophilic gastroenteritis and was not recognized as its own distinct entity until the 1990s [4,5].

The initial cases led to a subsequent rise in research, which in turn led to an increased awareness of this condition and refinement of the diagnostic criteria. Subsequently, a significant increase in incidence and prevalence have been observed [6,7], with a current estimated prevalence of 52.2 cases per 100,000 persons [8] and an incidence of 10 cases per 100,000 persons [7] in the United States (US). Because of the increasing incidence and prevalence of EoE, healthcare costs have also increased, with total costs recently estimated at $503 million to $1.36 billion per year in the US [9].

Treatment of EoE is multimodal, consisting primarily of dietary restriction (i.e., elimination diet) and pharmacologic therapy [10]. As with other conditions that have an allergic component, corticosteroids play a crucial role in treatment. Topical steroids are generally preferred to systemic steroids, as they deliver the drug directly to the affected tissue (esophageal mucosa) and are associated with fewer systemic side-effects [10,11]. The 2 most commonly used steroid agents are budesonide and fluticasone [12]. Steroid therapy is an effective treatment modality and the majority of patients achieve a symptomatic benefit, while a histologic response is seen in 50-90% [13,14].

Current treatment guidelines are clear about the indication for steroids in EoE. The British Society of Gastroenterology recommends orodispersible budesonide as the preferred formulation. However, this therapy is not currently approved in the US. Moreover, current US guidelines do not recommend one form of corticosteroid over another. We conducted a meta-analysis to compare budesonide and fluticasone and determine whether one of them was associated with better outcomes.

## Materials and methods

This meta-analysis and systematic review were reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. A specific protocol was developed to conduct this meta-analysis and to specify methods, databases to use, eligibility criteria and outcomes of interest. A comprehensive search of Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Ovid Cochrane Database of Systematic Reviews was performed from each database's inception to March 29th, 2023.

### Eligibility criteria

We included studies that involved patients of any age, diagnosed with EoE, and we did not specify any gender for inclusion. Our metanalysis included randomized clinical trials and comparative studies (prospective or retrospective). The included studies compared EoE patients treated with budesonide vs. fluticasone. Our exclusion criteria included patients with esophageal or gastric cancer, esophageal varices, active gastrointestinal bleed, pregnancy, and previous esophageal surgery.

### Study selection and data extraction

Two authors (LN and MK) screened titles and abstracts of identified citations in duplicate, in an independent and blinded manner. Any disagreement was resolved by reference to a third author (SH). Authors assessed full-text eligibility and extracted information from eligible studies.

### Quality assessment

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence of each outcome [16]. Evidence from randomized controlled trials (RCTs) is considered to be of high certainty initially, and it can be downgraded subsequently to moderate, low, or very low certainty, as a result of risk of bias, inconsistency, imprecision, indirectness, or publication bias. Evidence from observational studies starts as low certainty and can be downgraded for the same reasons as RCTs, but can also be upgraded if a large effect and/or dose-response relationship exist. We created a summary of our findings using GradePro in the Supplementary Table 1 [17].

### Risk of bias

We conducted the risk of bias assessment for the RCTs using the Cochrane Risk of Bias Tool for Randomized Controlled Trials [18], and for observational studies using the Newcastle-Ottawa scale [19]. The risk of bias findings is summarized in the Supplementary Table 2.

### Statistical analysis

For dichotomous outcomes, we calculated the relative effect of therapies using odds ratios (ORs) and 95% confidence intervals (CIs). For outcomes reported as incidence rate, we calculated the relative effect of therapies using rate ratios and 95%CIs. For continuous outcomes, we calculated the relative effect of therapies using the mean difference (MD) and 95%CIs. We calculated incidence ratios when there were no comparative data for an outcome. We used RevMan (Revman 5.3) to conduct random-effects meta-analyses for risk ratios and rate ratios. When we could not perform a meta-analysis, we summarized the results narratively.

## Results

### Study selection

The initial search retrieved 647 studies, of which 444 were included for screening by 2 authors after duplicate removal. Following full-text screening, we identified 3 studies eligible for data abstraction to answer the question addressed in this systematic review (Fig. 1). The reasons for exclusion at full-text review were ineligible study design, study population, sample size less than 10 patients, or not enough information to determine an effect estimate.

### Study characteristics

All studies included in the final analysis were published between 2016 and 2019 and conducted in the US. A total of

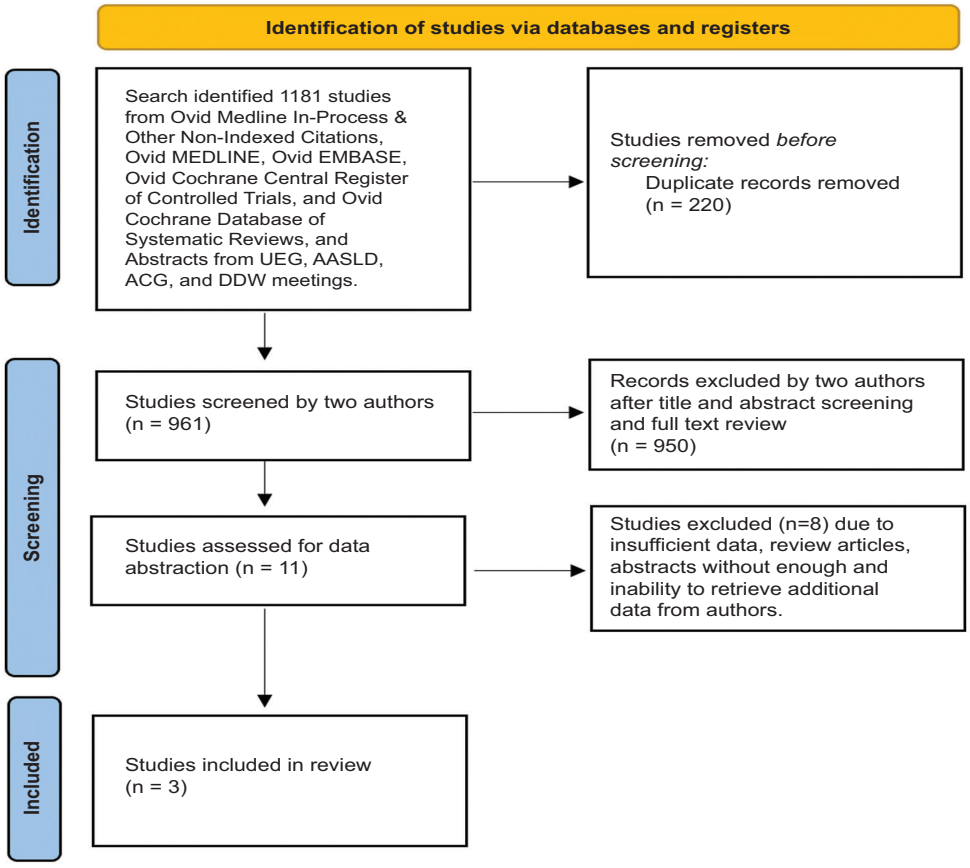


**Figure 1** Flowchart outlining the search process

272 patients were included, of whom 140 received budesonide and 132 fluticasone. One study was a double-blinded clinical trial [20], and the other 2 were observational studies [21,22]. Table 1 summarizes the studies included in our review.

### Eosinophil counts pre- and post-treatment

Two studies reported the eosinophilic counts pre and post treatment in the budesonide and fluticasone groups. We did not conduct a metanalysis on this outcome. In the budesonide group, Delon *et al* reported a decline in the mean eosinophilic count post-treatment from 72.6 to 14.7 eos/high-power field (hpf), while Fable *et al* reported a decline from 45 to 12 eos/hpf. In the fluticasone group, the mean eosinophilic count declined post treatment from 76.9 to 20.9 eos/hpf in the study by Delon *et al*, while Fable *et al* reported an eosinophilic count decline from 48 to 30 eos/hpf in this group. Broadly speaking, a greater response was seen in the budesonide groups.

### Histologic response

Histologic response was defined as a total eosinophil count <15 eos/hpf. Three studies reported the histological response in the budesonide and fluticasone groups. There was no statistically significant difference between budesonide and fluticasone in achieving a histologic response, with a pooled odds ratio of 1.29 (95%CI 0.77-2.14), P=0.34, and no heterogeneity in the results ($I^2$=0%) (Fig. 2).

### Side-effects

One study by Delon *et al* compared the side-effects in both groups. They reported 10 adverse events in the budesonide group with no serious adverse events. The side-effects were reported as 8 cases of esophageal candidiasis and 2 oral candidiasis. The fluticasone group had 15 adverse events with 1 serious adverse event, which was food impaction requiring an urgent intervention with endoscopy. The other side-effects in the fluticasone group were: 10 cases of esophageal candidiasis, 1 oral candidiasis, 1 food impaction, 2 sore throat, 1 chest pain, and 1 pneumonia.

### Publication bias

We performed funnel plot analyses for the included studies comparing budesonide to fluticasone for patients with EoE, which revealed no significant publication bias as shown by a symmetrical funnel plot (Fig. 3).

**Table 1** Included studies baseline information and patient characteristics

| Study [ref.], year, country, design | Study selection | Patient characteristics |
|---|---|---|
| Albert *et al* [21], 2016<br>Country: USA Study design: Retrospective | Objective:<br>To determine the response to 2 topical steroids (fluticasone and budesonide), compare their efficacy, and examine patient characteristics which could predict non-response to topical steroids.<br>Inclusion criteria:<br>patients>1 year of age who were diagnosed with EoE, as defined by most recent consensus guidelines.<br>Exclusion criteria:<br>Individuals that did not receive at least an 8-week trial of high-dose PPI prior to index endoscopy; diagnosed with proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE); had been previously treated with swallowed topical steroids; did not complete an 8-week course of topical corticosteroids after diagnosis of EoE; or did not have an EGD with esophageal biopsies before or after 8 weeks of corticosteroid treatment. | n=75<br>Age: 33 (range 2-64) years<br>Sex: 84% male<br>Ethnicity: 76% Caucasian<br>Treatment: fluticasone was used in 63% of patients, and the remaining 37% were treated with budesonide |
| Fable *et al* [22], 2017<br>County: USA<br>Study design: Retrospective | Objective:<br>To compare endoscopic and histologic outcomes after swallowed fluticasone propionate (FP) vs. oral viscous budesonide therapy in children with EoE<br>Inclusion criteria:<br>Age 1 to 20, documented EoE by endoscopic biopsy, treated with fluticasone or budesonide between 2010 and 2015.<br>Exclusion criteria:<br>Individuals with various comorbidities, including inflammatory bowel disease, celiac disease and *Helicobacter pylori* gastritis. | n=68<br>Age: 11±5 years<br>Sex: 81% male<br>Ethnicity: 72% Caucasian<br>Treatment: fluticasone was used in 29% of patients, and the remaining 71% were treated with budesonide. |
| Dellon *et al* [20], 2019<br>County: USA<br>Study design: Randomized Clinical Trial | Objective:<br>To determine whether budesonide is more effective than fluticasone for improving esophageal eosinophil counts and symptoms of dysphagia for adult patients with EoE who did not respond to PPI therapy.<br>Inclusion criteria:<br>Patients aged 16-80 years. New diagnosis of EoE as per consensus guidelines at the time of the study design. Patients had to have dysphagia or other symptoms of esophageal dysfunction, persistent esophageal eosinophilia (>15 eosinophils in at least 1 high-power field [eos/hpf]) after 8 weeks of treatment with a twice daily PPI, and other competing causes of esophageal eosinophilia excluded.<br>Exclusion criteria:<br>Concomitant eosinophilic gastroenteritis; swallowed/topical steroids for EoE or systemic steroids for any condition within the 4 weeks before baseline endoscopy; inability to pass a standard 9-mm upper endoscope due to esophageal narrowing or stricturing; previous esophageal surgery; esophageal or gastric cancer; esophageal varices, inability to stop anticoagulation, or active gastrointestinal bleeding; medical instability that precluded endoscopy; inability to read or understand English; or pregnancy. | n=129<br>Budesonide group<br>Age: 36.2±19.1<br>Fluticasone group<br>Age: 39.0±14.5<br>Budesonide group sex: 62% male<br>Fluticasone group sex: 69% male<br>Budesonide group ethnicity: 97% white<br>Fluticasone group ethnicity: 98% white<br>Treatment:<br>The fluticasone group included 65 patients and the budesonide group 64 |

*EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; hpf, high-power field*

## Discussion

Although EoE was previously known as a rare condition, it has become increasingly prevalent. In addition to its growing economic burden, EoE imposes a major burden on the patient and has been associated with a negative impact on health-related quality of life in both children and adults [23]. Symptoms in adults range from dysphagia, heartburn and abdominal pain to food impaction. Advanced disease carries a risk of more serious complications due to remodeling of the tissue, including esophageal rigidity, and strictures [24].

Early and effective medical therapy (e.g., corticosteroids) is instrumental in preventing recurrence of symptoms and complications of the disease, as well as alleviating the

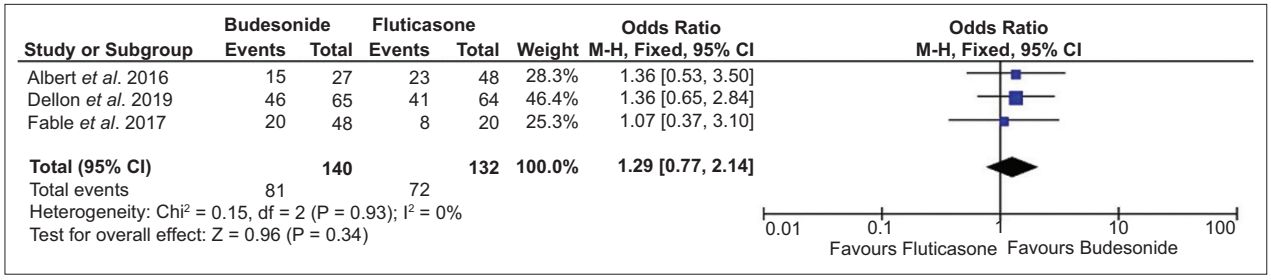


**Figure 2** Forest plot comparing Budesonide to Fluticasone in achieving histologic response
*CI, confidence interval*

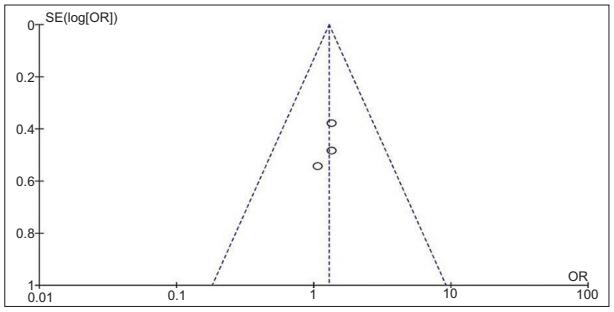


**Figure 3** Funnel plot of all included studies in the meta-analysis

economic burden and the negative impact on the quality of life. Eosinophils have a deleterious effect on the esophagus due to their degranulation; thus, reducing esophageal eosinophil counts to fewer than 15 eos/hpf is the primary goal of therapy [25]. Steroid therapy is used to achieve the goal of reducing eosinophil counts. British guidelines demonstrate a preference for orodispersible budesonide over other steroid formulations. While this therapy has not been approved for use in the US, viscous formulations are the preferred preparations. The American College of Gastroenterology gives a strong recommendation for treatment with topical steroids. However, they do not recommend one steroid over the other, and there is no FDA-approved swallowed steroid for treatment [26]. In our study, we conducted a systemic review and meta-analysis designed to determine which agent was associated with a better histological response. Our meta-analysis found no significant difference in histologic response between patients treated with budesonide or fluticasone.

Multiple studies have been conducted in an attempt to determine which agent is superior. The studies we analyzed had mixed results, suggesting either that budesonide was superior to fluticasone [22], or that there was no significant difference between the treatments [20,21]. Notably, no significant difference was found between these agents in an RCT [18]. In addition to the limitation of their retrospective designs, 2 of the studies noted that the dose of steroids prescribed was lower than in current practice and compliance could not be measured retrospectively. Either of these limitations may have interfered with the results.

Moreover, 1 retrospective study that suggested budesonide was superior took place within a pediatric population (age range 1-20 years), so the results do not apply to older adult populations. Therefore, our analysis was consistent with the current literature in that one agent was not found to be definitively superior over the other in regard to their efficacy in inducing a histologic response. These studies indicate that larger sample size and future RCTs are needed to determine whether there is a significant difference in the efficacy of these treatment modalities.

There may be other differences between the medications, such as their ability to control symptoms or achieve improvement in endoscopic findings (e.g., trachealization, furrows). However, these comparisons could not be analyzed in our study. Further studies are needed to better illustrate the efficacy of each agent, both in inducing a histologic response and in controlling the symptoms of the disease. When choosing between the 2 medications, factors such as availability, tolerability, cost and ease of administration should be considered. Monoclonal antibodies are also a component of the treatment of EoE [27]. These drugs may have a greater role as further studies are completed.

The strengths of this meta-analysis include a comprehensive search of multiple databases by 2 independent reviewers, while our study is the first meta-analysis to compare treatment with fluticasone and budesonide for EoE. Limitations of this meta-analysis include the low number of included studies, variability in study type (2 retrospective studies and 1 RCT), and variability in the ages of the patient population among the studies analyzed, which were accounted for in the risk of bias judgement. The insufficient data did not allow us to run an analysis for secondary outcomes, such as clinical response and adverse events. Confounding variables (e.g., use of proton pump inhibitors, adherence to elimination diet) were not available for analysis and thus could not be assessed. Other variables not included, and thus not assessed, included duration of disease remission and rate of relapse. In addition, there may be a discrepancy between the clinical and histologic response in patients with EoE, and data on the clinical response were not available. Ideally, the clinical response should have also been assessed and compared to the histologic response.

In conclusion, this systematic review and meta-analysis showed that neither agent was superior in inducing a histologic response in patients with EoE. Future RCTs are needed to validate the conclusions of this study and determine whether there is superiority among these agents in regard to symptom control and endoscopic improvement.

**Summary Box**

**What is already known:**

- Proton pump inhibitors and topical steroids (e.g., budesonide and fluticasone) are the first line of treatment for eosinophilic esophagitis (EoE) in the United States
- Some studies compared both topical steroids, but there was no clear answer as to whether either would be superior to the other. However, British guidelines demonstrate a preference for orodispersible budesonide over other steroid formulations

**What the new findings are:**

- Neither of the topical steroids (fluticasone and budesonide) was superior to the other in achieving a histological response in EoE patients
- The 2 medications had similar side-effect profiles
- There is a shortage of evidence on this subject, and further studies are needed to directly compare these medications

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**Supplementary Table 1** GRAGE Pro Summary of findings

Budesonide compared to Fluticasone in Achieving Histological Response in Patients with Eosinophilic Esophagitis (EoE)

Patients: Eosinophilic esophagitis

Comparison: Budesonide vs. Fluticasone in achieving histological response in patients with EoE

| Outcome № of participants (studies) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | | | Difference | | |
| Histological response № of participants: 129 (1 RCT) | OR 1.36 (0.53 to 2.84) | 64.1% | 70.8% (48.6 to 83.5) | 6.7% more (15.5 fewer to 19.4 more) | ⊕⊕⊕⊕ High | |
| Histological response № of participants: 143 (2 observational studies) | OR 1.22 (0.60 to 2.48) | 45.6% | 50.5% (33.5 to 67.5) | 5.0% more (12.1 fewer to 21.9 more) | ⊕⊕◯◯ Low | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **OR:** odds ratio

**GRADE Working Group grades of evidence High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Supplementary Table 2** Risk of bias for included studies

A: Risk of bias in the included randomized clinical trial

| Study, year [ref.] | Random Sequence | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome | Incomplete Outcome | Selective | Other Bias |
|---|---|---|---|---|---|---|---|
| | Generation (Selection bias) | (Selection bias) | (Performance bias) | Assessment (Detection bias) | Data (Attrition bias) | Reporting of Outcomes (Reporting bias) | |
| Dellon *et al*, 2019 [20] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |

B: Risk of bias in the included non-randomized clinical trial

| Study | Selection | | | | Comparability | Outcome | | |
|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort? | Selection of the non- exposed cohort? | Ascertainment of exposure? | Demonstration that outcome of interest was not present at start of study? | Comparability of cohorts on the basis of the design or analysis? | Assessment of outcome? | Was follow- up long enough for outcome s to occur? | Adequacy of follow up of cohorts? |
| Albert *et al*, 2016 [21] | * | - | * | - | ** | * | * | * |
| Fable *et al*, 2017 [22] | * | - | * | * | ** | * | * | * |

The * are part of the NOS score, they are questions to assess risk of bias and if a study meets the criteria, it gets a star, so basically it is the numbers of stars the study got in that category

**Search strategies**

- OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid
  MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present - Search Strategy:

1 (Eosinophilic esophagitis or EoE).mp. (3365)
2 (treat* or therap*).mp. (9466922)
3 (fluticasone or budenoside).mp. (4677)
4 1 and 2 and 3 (159)
5 (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo).ab. or drug therapy.fs. or (randomly or trial or groups).ab. (5137543)
6 epidemiologic studies/or exp case control studies/or exp cohort studies/or Cross-sectional studies/(3080326)
7 case control.tw. (133200)
8 (cohort adj (study or studies)).tw. (262863)
9 cohort analy$.tw. (9916)
10 (Follow up adj (study or studies)).tw. (51100)
11 (Observational adj (study or studies)).tw. (129015)
12 (longitudinal or retrospective or cross sectional).tw. (1233516)
13 or/6-12 (3436203)
14 (registr* or database).mp. (664317)
15 5 or 13 or 14 (7743616)
16 4 and 15 (128)

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- Embase <1974 to 2023 March 29> - Search Strategy:

1 (Eosinophilic esophagitis or EoE).mp. (6092)
2 (treat* or therap*).mp. (11390897)
3 (fluticasone or budenoside).mp. (18583)
4 1 and 2 and 3 (1713)
5 random*.ab. or random*.ti. or (clinical adj trial*).hw,ab,ti. or exp 'health care quality'/ (4983953)
6 exp disease course/or risk:.mp. or diagnos:.mp. or follow-up.mp. or ep.fs. or outcome.tw. (13440497)
7 5 or 6 (14497434)
8 4 and 7 (1641)
9 limit 8 to human (1603)

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- Cochrane - Search Strategy:

Search Name: EOE
Date Run: 15/04/2019 19:50:03
ID Search Hits
#1 (Eosinophilic esophagitis or EoE) AND (treat or therapy) AND (Steroid or fluticasone or budenoside) (Word variations have been searched) 63 6