

# CLINICAL—ALIMENTARY TRACT

## Efficacy of Dietary Interventions for Inducing Histologic Remission in Patients With Eosinophilic Esophagitis: A Systematic Review and Meta-analysis

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this questionnaire, successful learners will be able to distinguish the different dietary therapies used in the treatment of EoE, identify remission rates of each dietary options and recognize some important methodological aspects of systematic reviews and meta-analyses.

**BACKGROUND & AIMS:** Various dietary interventions have been used to treat patients with eosinophilic esophagitis (EoE), yielding varied results. This systematic review assesses the efficacy of different dietary therapies in inducing disease remission. **METHODS:** We performed a systematic search of the MEDLINE, EMBASE, and SCOPUS databases for studies investigating the efficacy of dietary interventions (reducing infiltration by immune cells <15 eosinophils/high-power field in esophageal biopsies) for pediatric and adult patients with EoE. Summary estimates, including 95% confidence intervals (CI), were calculated for exclusive feeding with amino acid-based elemental formulas, allergy test result-directed food elimination diets, and 6-food elimination diets (SFED). A fixed- or random-effects model was used depending on heterogeneity ( $I^2$ ); publication bias risks were assessed by means of funnel plot analysis. **RESULTS:** The search yielded 581 references; of these, 33 were included in the quantitative summary. We analyzed data on a total of 1317 patients with EoE (1128 children and 189 adults) who received different dietary treatments. Elemental diets were effective for 90.8% of cases (95% CI, 84.7%–95.5%;  $I^2 = 52.3\%$ ), SFED for 72.1% (95% CI, 65.8%–78.1%;  $I^2 = 0$ ), and allergy test result-directed food elimination for 45.5% of cases (95% CI, 35.4%–55.7%;  $I^2 = 75.1\%$ ). Additional strategies (elimination of cow's milk, gluten-free diets, and 4-food elimination diet) were also evaluated. Adults vs children had no significant differences in remission after dietary interventions (67.2% vs 63.3%). **CONCLUSIONS:** Dietary interventions are effective in producing histologic remission in patients with EoE. Elemental diets and SFEDs were the most effective, achieving <15 eosinophils/high-power field in 90.8% and 72.1% of patients, respectively.

**Keywords:** Esophagus; Inflammation; Immune Regulation; Therapy.

of other causes of esophageal eosinophilia, especially gastroesophageal reflux disease.<sup>1</sup> First characterized as a distinctive clinicopathologic disorder 20 years ago,<sup>2</sup> EoE has come to be recognized as the most prevalent cause of chronic esophageal symptoms among children and young adults,<sup>3,4</sup> with an estimated prevalence of 43–56.7 cases/100,000 inhabitants in both America and Europe, affecting pediatric and adult patients alike.<sup>5–10</sup> As a consequence, EoE poses a large burden to health care systems, involving multidisciplinary teams that include gastroenterologists, dietitians, and allergists in the management of the disease.

From its earliest descriptions, the origin of EoE has been linked to allergy; indeed, both pediatric and adult patients commonly present concurrent family and/or personal atopic conditions, such as asthma, rhinitis, conjunctivitis, eczema, and IgE-mediated food allergies.<sup>1,11</sup> Food sensitization identified by positive results in skin prick tests (SPTs) is also commonly described in patients of all ages.<sup>12–14</sup> The definitive categorization of EoE as a characteristic manifestation of food allergy came when researchers documented disease remission after feeding a series of pediatric patients exclusively with an amino acid-based elemental formula lacking any antigenic capacity, followed by disease recurrence after subjects resumed a normal diet.<sup>15</sup>

According to consensus guidelines, the treatment of EoE consists primarily of medical (corticosteroid) or dietary therapy,<sup>1</sup> the latter encompassing several approaches to avoid putative food triggers for EoE. Besides elemental diet, both skin allergy testing-directed food elimination and empirical restriction of the most common food antigens

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder characterized by symptoms of esophageal dysfunction and histologic evidence of eosinophil-predominant inflammation in esophageal mucosal biopsies, which persists after the exclusion

**Abbreviations used in this paper:** CI, confidence interval; EoE, eosinophilic esophagitis; hpf, high-power field; SFED, 6-food elimination diet; SPT, skin prick test.

from the diet have been used by different researchers with varied results. As a result, a commonly accepted algorithm for treating patients is currently lacking, and a wide variability, in both standard of care of EoE patients and adherence to proposed guidelines, has been documented in clinical practice.<sup>10,16</sup>

In the short time since EoE was first described, an increasing number of publications have focused on dietary treatment of pediatric and adult EoE patients. Such research has renewed the interest in food restrictions as a drug-free alternative to topical steroids, which still constitute the most widely utilized therapy for EoE in patients of all ages.<sup>10,16</sup>

However, the efficacy of the various dietary treatment modalities assayed in EoE patients has yet to be systematically analyzed in order to provide clinicians with useful evidence for making decisions concerning the complex management of EoE.

The aim of our study was to conduct a systematic review and meta-analysis on the efficacy and consistency of the available dietary treatment alternatives in inducing histologic remission of EoE in children and adults.

## Methods

### Selection of Studies

Source studies were identified by systematically searching in 3 major bibliographic databases (PUBMED, EMBASE, and Scopus) for the period up to June 2013. To this end, a pre-determined protocol was used in accordance with the quality of reporting meta-analyses of observational studies in epidemiology.<sup>17,18</sup>

Comprehensive search criteria were used to identify articles dealing with dietary treatments for EoE. We consulted the thesauri for MEDLINE (MESH) and EMBASE (EMTREE) using the following search strategy: eosinophilic esophagitis AND (diet OR dieta\* OR diete\*). For the Scopus database, only free text searches with truncations were carried out. The search was not restricted with regard to date or language of publication.

We also examined the reference lists from retrieved articles and abstracts of conference proceedings to identify relevant studies. Abstracts books of the annual Digestive Diseases Week, American College of Gastroenterology Meeting, and the United European Gastroenterology Week for the period 2004 to 2013 were also examined. Three reviewers (AA, JG-C, and AJL) independently screened the database search for titles and abstracts. If any of the reviewers believed that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

### Inclusion Criteria

Randomized controlled trials, observational prospective and retrospective studies, and case series reports were included if data on histologic efficacy or effectiveness after dietary treatment were provided. Studies evaluating any kind of dietary intervention were included, including elemental diets, allergy testing-directed elimination diets, empirical 6-food elimination diets (SFEDs), and modified empirical SFEDs, as well as any kind of food exclusion, after which a histologic evaluation was undertaken. Studies providing objective

quantitative data on diet efficacy in terms of histologic response were included (EoE remission was considered to be a peak eosinophil count <15 eosinophils/high-power field [hpf] in esophageal biopsies)<sup>1,19</sup> after dietary treatment.

### Exclusion Criteria

Studies using dietary intervention simultaneously with another therapeutic alternative capable of reducing esophageal inflammation (topical and systemic steroids and/or immunomodulatory drugs) were excluded. Review articles on the treatment of EoE that did not provide original data on dietary therapy, clinical guidelines, and consensus documents were excluded. Studies not carried out on humans were excluded. Studies providing duplicated information were excluded (ie, repeated abstracts presented at different congresses or abstracts published later as a full paper). Subsets of cases or controls from a previously published article by the same authors were excluded.

### Quality Assessment

Cohort studies, case series, and case reports were evaluated for quality only if the article described all patients, the type of dietary strategy assessed, and any additional therapeutic interventions. Likewise, peak eosinophil counts had to be specifically stated in the text as well as the time frames and the clinic or clinics in which the study was carried out. Quality assessment was checked with a specific evaluation form for observational studies developed by our group and based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.<sup>20</sup>

The study was considered to be at low risk for bias if each of the bias items could be categorized as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Two investigators (AA and AJL) independently gave each eligible study an overall rating of high, low, or unclear risk of bias, and if disagreements emerged, a third reviewer (JG-C) was consulted.

### Data Extraction

Three reviewers (AA, AJL, and JG-C) independently extracted relevant information from each eligible study using a standardized data extraction sheet and then proceeded to cross check the results. The data extracted included the trial study areas, the last name of the first author, publication year, type of dietary intervention assessed, age and sex of study participants, sample size, methodological design, and study period, whenever possible. At the same time, data on the key outcomes, including eosinophil count reduction to <15 eosinophils/hpf, were extracted from all included studies. Disagreements between reviewers about data extraction were resolved through discussion. The authors of the various studies were contacted by e-mail for additional information if necessary.

### Statistical Analysis

Response percentages for dietary intervention were summarized with the aid of a fixed- or random-effects meta-analysis weighted for the inverse variance following DerSimonian and Laird's method. Summary estimates, including 95% confidence

intervals (CI), were calculated for the rate of reduction of peak eosinophil counts to <15 eosinophils/hpf.

Heterogeneity between studies was assessed by means of a  $\chi^2$  test (Cochran Q statistic) and quantified with the  $I^2$  statistic. If  $P < .1$  and/or  $I^2 > 50\%$ , there was significant heterogeneity and a random-effects model was used. Generally,  $I^2$  was used to evaluate the level of heterogeneity, assigning the categories low, moderate, and high to  $I^2$  values of 25%, 50%, and 75%, respectively.<sup>21</sup> Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed through Begg-Mazumda's rank test.<sup>22</sup>

For the primary outcomes, planned subgroup analyses were performed based on the types of diets used (elemental diet, allergy testing-directed elimination diet, empirical SFED, cow's milk elimination, and gluten-free diet) and age (adults vs children).

A sensitivity analysis was performed with regard to quality (risk of bias) and type of document (full-length article vs abstract presented at conference proceedings). All calculations were made with StatsDirect statistical software version 2.7.9 (StatsDirect Ltd, Cheshire, UK).

## Results

The search strategy yielded 581 references; 481 documents were excluded after examining the title and abstract because they did not fulfill the inclusion criteria. Of the remaining 100 references, 13 abstracts were excluded

either because they were subsequently published as full papers or because they had been presented multiple times at different conferences. For the remaining 87 references that were considered to be potentially relevant, the full text was retrieved for detailed evaluation. Of these, 54 were excluded because they did not include data on the histologic response after treatment. In the end, 33 studies were included in the meta-analysis (Figure 1).

The major characteristics of each study are summarized in Table 1. Of the 33 documents, 23 were full-text articles and 10 were abstracts. Overall, data from 1317 patients (1128 children and 189 adults) receiving any kind of dietary therapy were retrieved, with the size of the various study populations ranging from 1 to 470 cases in the largest series. The 33 documents included in our meta-analysis globally assessed 47 dietary therapeutic assays, with several assessing more than one dietary intervention.

Overall effectiveness in inducing histologic remission of EoE (defined as the reduction of peak eosinophil counts to <15 eosinophils/hpf) for any dietary intervention was 66.3% (95% CI, 56.9%–75%), with no significant differences between pediatric and adult patients (67.2% vs 63.6%), although the higher number of studies carried out in children is noteworthy (Table 2).

An analysis of the efficacy and concordance of each individual dietary intervention in achieving EoE remission will be described.

### Elemental Diet

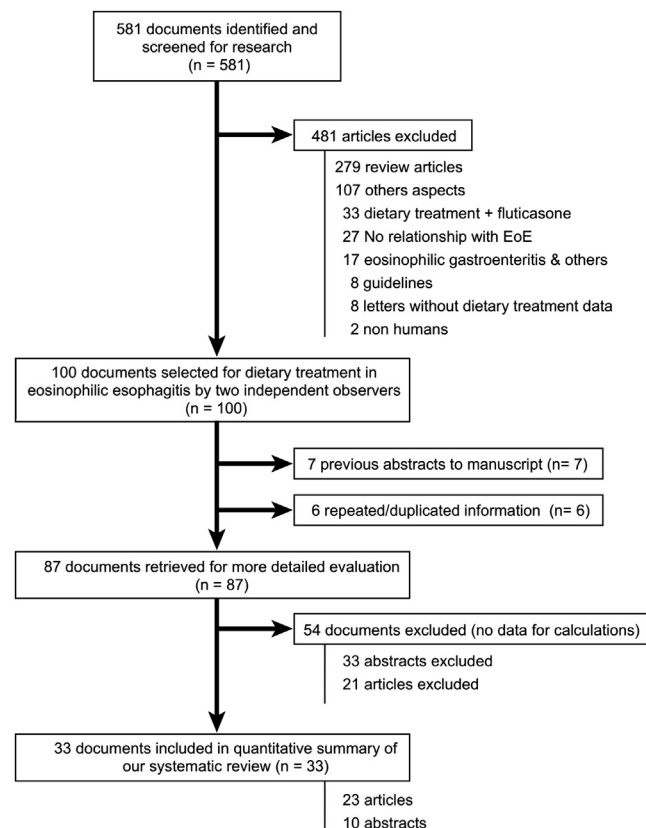
Thirteen studies, including a total of 429 EoE patients (411 children and 18 adults), evaluated the efficacy of exclusive feeding with an amino acid-based elemental diet. Of these, 12 studies were carried out on children and only 1 on adult patients. The overall efficiency of elemental diet in achieving histologic remission of EoE was 90.8% (95% CI, 84.7%–95.5%). Although data for adults are limited, the response rate was very high in both children and adults (90.4% vs 94.4%, respectively), with a moderate homogeneity ( $I^2=52.3\%$ ) among results from different studies (Table 2 and Figure 2).

### Allergy Testing-Directed Food Elimination

The strategy of eliminating foods that gave a positive result in skin allergy tests was assessed in 14 different studies (only 2 of which included adults) carried out on 626 patients (594 children and 32 adults). Overall efficacy was 45.5% (95% CI, 35.4%–55.7%), but with a wide variability regarding the response rate ( $I^2=75.1\%$ ). The 2 studies carried out on adult patients showed a significantly lower response rate of only 26.6%<sup>41</sup> and 35%<sup>54</sup> (Table 2 and Figure 3).

### Six-Food Elimination Diet

The combined efficacy documented in the 7 studies evaluating SFED (4 of them developed in pediatric populations and 3 in adult patients) was 72.1% (95% CI,



**Figure 1.** Flowchart for process of identifying studies that were included and excluded in the systematic review.

**Table 1.** Demographics and Characteristics of Studies Included in Our Systematic Revision and Meta-Analysis

First author, publication year	Dietary treatment	Population	No. of included patients	Design	Period	% Male
Full papers						
Kelly, 1995 <sup>15</sup>	Elemental diets	Children	10	Prospective	1992–1994	60
Siafakas, 2000 <sup>23</sup>	Allergy testing–direct elimination diets	Children	1	Case report	2000	100
De Agustín, 2002 <sup>24</sup>	Elemental diets	Children	2	Case report	2002	100
Liacouras, 2005 <sup>25</sup>	Elemental diets and allergy testing–direct elimination diets	Children	247	Retrospective	1994–2004	66
Arriola-Pereda, 2006 <sup>26</sup>	Allergy testing–direct elimination diets	Children	2	Case report	2006	0
Kagalwalla, 2006 <sup>27</sup>	SFED	Children	35	Retrospective	2003–2005	74
Quaglietta, 2007 <sup>28</sup>	Allergy testing–direct elimination diets and gluten-free diet	Children	17	Prospective	2005–2006	70.6
Kagalwalla, 2007 <sup>29</sup>	SFED	Children	1	Case report	2006	100
Ooi, 2008 <sup>30</sup>	Gluten-free diet	Children	2	Retrospective	1999–2007	50
Verzegnassi, 2007 <sup>31</sup>	Gluten-free diet	1 Child/2 adults	3	Case report	2006	33
Ferreira, 2008 <sup>32</sup>	Elemental diets	Children	1	Case report	2008	100
Leslie, 2010 <sup>33</sup>	Gluten-free diet	Children	4	Retrospective	2000–2007	50
Rizo Pascual, 2011 <sup>34</sup>	Elemental diets and allergy test	Children	14	Prospective	2001–2009	82.3
Basiliou, 2011 <sup>35</sup>	Elemental diets and allergy test	Children	3	Case report	2005	66.7
Abu-Sultaneh, 2011 <sup>36</sup>	Elemental diets and Soy- free diet	Children	2	Case report	2003–2008	50
Gonsalves, 2012 <sup>37</sup>	SFED	Adults	50	Prospective	2006–2010	50
Kagalwalla, 2012 <sup>38</sup>	Elemental diets, allergy testing–direct elimination diets, cow's-milk elimination diets	Children	111	Retrospective	2006–2011	NR
Peterson, 2013 <sup>39</sup>	Elemental diets	Adults	18	Prospective	2009–2011	55.5
Henderson, 2012 <sup>40</sup>	Elemental diets, allergy testing–direct elimination diets, and SFED	Children	98	Retrospective	1999–2011	75.5
Molina-Infante, 2012 <sup>41</sup>	Allergy testing–direct elimination diets	Adults	22	Prospective	—	77.3
Spergel, 2012 <sup>42</sup>	Elemental diets and allergy testing–direct elimination diets	Children	470	Retrospective	2000–2011	NR
Al-Hussaini, 2013 <sup>43</sup>	Elemental diets, allergy testing–direct elimination diets, gluten-free diet	Children	14	Prospective	2009–2012	64.3
Lucendo, 2013 <sup>44</sup>	SFED	Adults	67	Prospective	2008–2010	82.1
Abstracts						
Kewalramani, 2009 <sup>45</sup>	Allergy testing–direct elimination diets	Children	13	Prospective	NR	NR
Alonso-Llamazares, 2010 <sup>46</sup>	Milk elimination diet	Adults	1	Case report	2010	0
Hiremath, 2010 <sup>47</sup>	Elemental diets	Children	13	Retrospective	NR	70
Johnson, 2010 <sup>48</sup>	Gluten-free diet	Adults	2	Retrospective	2009	NR
Muir, 2010 <sup>49</sup>	SFED	Children	13	Prospective	NR	84.6
Maggadottir, 2012 <sup>50</sup>	Milk elimination diet	Children	1	Case report	2012	0
Costable, 2012 <sup>51</sup>	Gluten-free diet	Adults	1	Case report	2012	0
Kalach, 2013 <sup>52</sup>	Allergy testing–direct elimination diets	Children	49	Retrospective	NR	NR
Gonsalves, 2013 <sup>53</sup>	FFED	13 Adults/15 children	28	Prospective	NR	64.3
Wolf, 2013 <sup>54</sup>	Allergy testing–direct elimination diets and SFED	Adults	22	Retrospective	2006–2012	46

FFED, 4-food elimination diet; NR, not reported.



**Table 2.** Summary of Histologic Remission Rates and 95% CIs for the Different Dietary Treatment Options Published for Children and Adults With Eosinophilic Esophagitis<sup>a</sup>

Dietary treatment	Overall effect, %	n	Children, %	n	Adult, %	n
All	66.3 (56.9–75)	47	67.2 (55.9–77.5)	36	63.6 (47.8–77.9)	10
Elemental diets	90.8 (84.7–95.5)	13	90.4 (83.5–95.5)	12	94.4 (17/18)	1
Allergy testing–direct elimination diets	45.5 (35.4–55.7)	14	47.9 (36.8–59.1)	12	32.2 (17.8–48.7)	2
SFED	72.1 (65.8–78.1)	7	72.8 (62.5–82)	4	71.3 (61.7–80)	3
FFED	53.4 (35.7–70.6)	2	60 (9/15)	1	46.2 (6/13)	1
Gluten-free diet	58.7 (23.1–89.7)	7	45.5 (2.6–93.8)	4	88.8 (50.5–99.1)	2
Milk elimination diet	68.2 (47.8–85.6)	3	66.3 (44.7–84.8)	2	100 (1/1)	1
Others (soy-free diet)	100 (1/1)	1	100 (1/1)	1	—	—
Subgroups according to quality						
Medium/high to high	68.7 (57.8–78.7)	34	69.8 (56.4–81.6)	27	66.8 (48.7–82.7)	6
Low to medium/low	59 (37.5–78.7)	13	58.5 (32.2–82.3)	9	55.6 (27.5–81.8)	4
Subgroups according to type of publication						
Article	68.8 (57.7–79)	35	69.2 (56.4–80.8)	30	69.4 (48.4–86.8)	4
Abstract/poster	53.1 (45.2–60.9)	12	54.8 (45.5–64)	6	48.8 (34.4–63.2)	6
Subgroups according to design						
Prospective	62.4 (49.3–74.7)	16	61.2 (42.7–78.2)	11	65.5 (46.4–82.4)	5
Retrospective	61.3 (49.9–72.1)	31	69.4 (55.9–81.5)	25	59.4 (32.8–83.2)	5

<sup>a</sup>Subgroup analysis is provided according to quality assessment and document type.

65.8%–78.1%). Combined results from 197 patients (75 children and 122 adults) were extremely homogenous ( $I^2 = 0\%$ ), regardless of the age of the population being assessed (72.8% and 71.3% for children and adults, respectively) (Table 2 and Figure 4). Remarkably, this dietary treatment strategy was the only one assessed in more adults than children.

### Other Diet-Based Therapeutic Modalities

Data on additional EoE treatment modalities based on dietary modifications were also retrieved, including

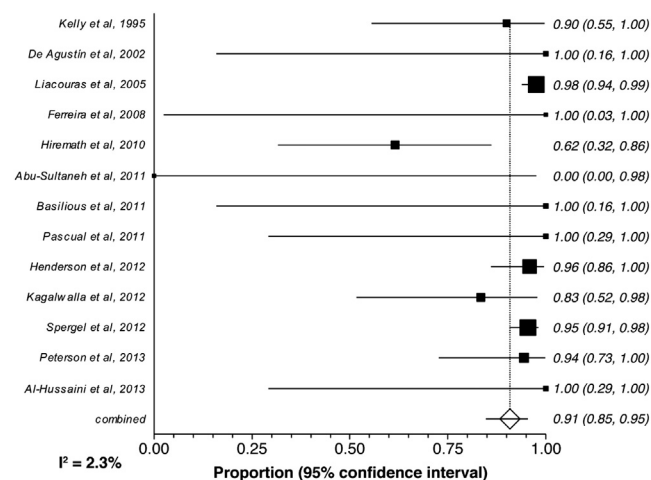
data from studies on gluten-free diets, cow's milk elimination diet, and empiric 4-food elimination diet. Summaries of overall efficiency in inducing remission of eosinophilic infiltration are presented in Table 2. However, because studies assessing these dietary treatments are still scarce, making conclusions from them can be risky. For example, although the overall efficacy of a gluten-free diet in achieving histologic remission of EoE was 58.7%, the remission rate ranged from 23.1% to 85.6% ( $I^2 = 67.2\%$ ).

### Publication Bias

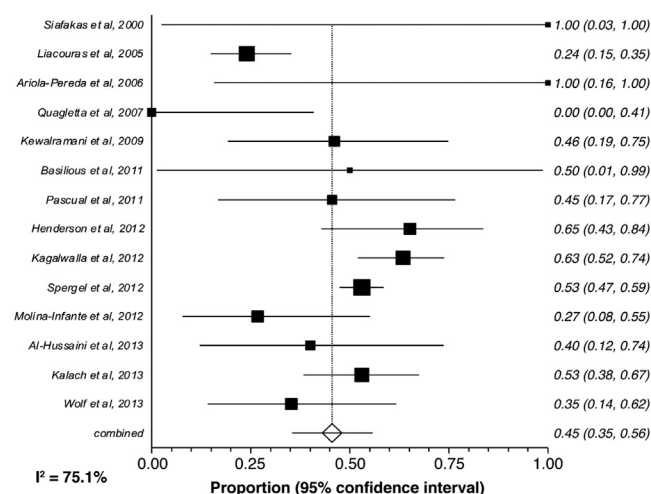
The funnel plot showed no obvious asymmetry (Figure 5). The Begg-Mazumdar's rank test likewise indicated no evidence of publication bias ( $P = .193$ ).

### Subgroup Analysis

Finally, an analysis of subgroups categorized according to quality and type of document was carried out (Table 2). Most of the selected studies were considered to be at least acceptable in quality, although the efficacy of the dietary treatment was higher in studies of high/high-mild quality compared with that found in low/low-mild quality studies (68.7% vs 59%, respectively). Regarding the type of publication, dietary treatment also exhibited higher efficacy rates in research published as full papers than those in abstracts (68.8% vs 53.1%, respectively). Finally, the overall efficacy rates of prospective studies were slightly lower from those with a retrospective fashion and case reports (62.4% vs 68.2%, respectively); in contrast, efficacy of dietary treatment in adult patients was higher in prospective studies compared with the remaining designs (65.5% vs 59.4%, respectively).



**Figure 2.** Overall combined effects of elemental diet for inducing histologic remission of EoE. Percentage of clinical improvement after following an elemental diet was extracted from each article/abstract and 95% CIs were calculated using the exact binomial method. A random-effects model was used to calculate the overall effect size. The  $I^2$  of 52.3% indicates that intra-study differences (heterogeneity) account for only 2.3% of the variability in the overall effect size.

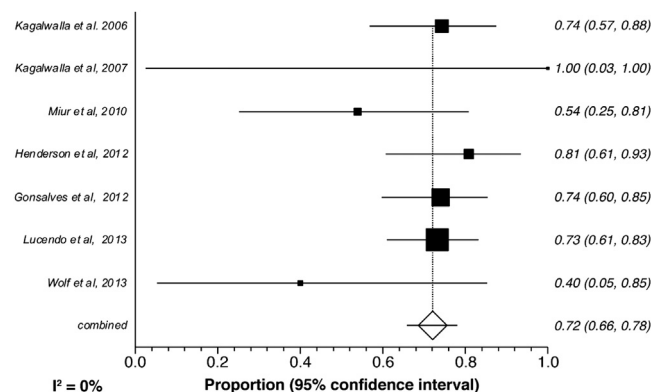


**Figure 3.** Overall effect size of allergy testing-directed food elimination for inducing histologic remission of EoE.

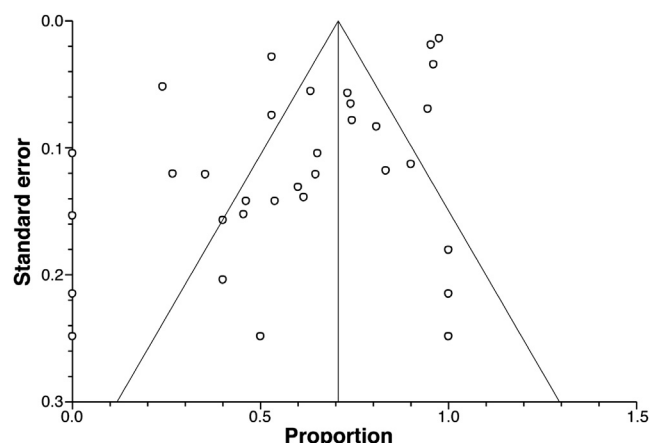
## Discussion

This meta-analysis of 33 published documents demonstrates that dietary treatment is an effective, drug-free therapy for achieving remission of eosinophilic infiltration in EoE patients. Additionally, our results show that the various dietary treatment strategies are associated with varied efficacy rates, ranging from 90.8% for elemental diets to 45.5% for allergy testing-directed food elimination.

Exclusive feeding with an elemental diet, which was first used in 1995,<sup>15</sup> has been assessed in 429 patients recruited for 13 different studies, yielding an overall combined efficacy of >90% in inducing disease remission. Despite its obvious success, the multiple drawbacks of elemental diets, which include the need to avoid all table food, its unpleasant taste, and high cost, and the psychological effects produced by the social limitations that this diet entails, have probably contributed to the fact that this dietary intervention has been restricted almost exclusively to pediatric patients. In fact, no research on adults was available until 2013,<sup>39</sup> with the reported remission rates being comparable with those documented in children.



**Figure 4.** The efficacy of SFEDs in inducing histologic remission (<15 eosinophils/hpf) in patients with EoE.



**Figure 5.** Begg funnel plot of studies on the efficacy of dietary treatment for inducing histologic remission in patients with EoE. The solid line in the center is the natural logarithm of pooled remission rates, and the 2 oblique lines are pseudo 95% confidence limits.

The drawbacks of elemental diets for long-term use led investigators to try to identify and remove from the diet specific food allergens based on skin allergy testing results in an attempt to improve the feasibility of dietary therapy for a greater number of patients. The high efficacy rates reported by Spergel and colleagues,<sup>55</sup> who in 2002 identified potential food triggers for EoE by using a combination of SPTs and atopy patch tests, have not been universally reproduced by other authors.<sup>34,41,56–58</sup> In our meta-analysis, we combined data from 626 patients, most of them children, and found that the combined effectiveness did not reach 50%. In fact, there was a wide range of variation in remission rates reported in the individual studies, with the only study carried out on adult patients showing disease remission in only 32.2% of treated patients.<sup>41</sup>

In 2006, Kagalwalla et al<sup>27</sup> proposed the empiric SFED in an attempt to overcome the limitations of allergy testing in directing food elimination, as well as to make dietary therapy more palatable. This approach consists of eliminating those intact food proteins most commonly associated with food allergies in children as well as those most commonly reported to cause mucosal injury in children with EoE,<sup>27</sup> including milk protein, soy, eggs, wheat, peanuts/treenuts, and seafood. This list has been modified in subsequent studies to also include those foods with a positive SPT result<sup>37,40</sup> or according to regional allergy sensitization patterns.<sup>44</sup> The results for the 7 studies that evaluated an SFED were extremely homogeneous, with a combined efficacy rate of 72.1%. All of the studies on SFED in children and adults have revealed a major role as causative food allergens for cow's milk, wheat, eggs, and soy/legumes, with a minor role for nuts and fish/seafood. Therefore, a 4-food elimination diet, including the common food triggers mentioned, could improve patient adherence to dietary restrictions and reduce both the number of endoscopies and the overall time necessary for completing the food reintroduction process.<sup>53</sup>

One relevant finding of our meta-analysis was the varied consistency of results from each dietary treatment option. Results from SFED showed a great deal of homogeneity (with  $I^2 = 0\%$ ), which indicate that the results are widely generalizable. For elemental diet-based studies, the homogeneity was moderate ( $I^2 = 52.3\%$ ). In contrast, results from studies assessing allergy testing-based food elimination proved highly heterogeneous ( $I^2 = 75.1\%$ ), calling into question whether this treatment should be recommended to EoE patients. Statistical heterogeneity was only one component of variability across these particular studies; the most important was actually the diversity of allergy testing methods used. In this context, there is a great deal of controversy with regard to the use of allergy testing for managing EoE patients. Although measurements of serum-specific IgE and SPTs rely on standardized methodologies, the use of atopy patch tests to assess food allergies has yet to be standardized or validated.<sup>1</sup> In any case, the wide variability in remission rates reported among the individual studies questions the universal reproducibility of skin allergy testing in directing dietary treatment for EoE, as has been previously addressed by several authors.<sup>34,56,58</sup> A growing body of evidence points to the involvement of a cell-mediated delayed hypersensitivity reaction instead of a predominantly IgE-mediated mechanism as the pathophysiologic cause of EoE.<sup>59</sup> Retrospective analyses have shown that food-specific IgE serum measurements and SPTs were neither sensitive nor specific methods for predicting EoE food triggers in adult patients.<sup>37,44</sup>

In addition to these 3 major dietary treatment options, other dietary interventions have proven effective in achieving histologic remission of EoE. The newest strategy is empirical elimination of cow's milk,<sup>38,46,50</sup> a treatment strategy that has yet to be fully assessed, but with a combined effectiveness of 68.2%. However, this surprisingly high figure might be influenced by the inclusion of patients with a particular allergic background, that is, those undergoing desensitization for a previously identified IgE-mediated cow's milk allergy. Additional studies are necessary to confirm these initial results, not least of all because of the extremely small sample size used: to date, only 19 patients following this treatment have been discussed in literature. Gluten-free diets have also been evaluated in 17 EoE patients,<sup>28,30,31,33,43,48,51</sup> with a combined efficacy rate of 58.7% in reducing peak eosinophil counts to  $<15$  eosinophils/hpf, but with wide heterogeneity among the different studies. Again, bias in patient selection (specifically favoring the inclusion of subjects with both EoE and celiac disease) might have influenced this result.

After achieving EoE remission through a given dietary strategy, it is then essential to undertake food reintroduction for proper dietary management of EoE patients. This has the double aim of selectively identifying foods that cause EoE by documenting disease recurrence after sequential food reintroduction, and also improving patient adherence to a less restrictive diet. Available research has demonstrated that one or several different foods can be

responsible for EoE<sup>37,44,60</sup> and, although data are still limited, it seems clear that continuous avoidance of foods that trigger EoE allows for a prolonged, drug-free remission of the disease.<sup>44,61</sup> Food-reintroduction protocols generally entail repeated endoscopies with biopsies, which are not always well accepted by patients and should be performed under sedation. For this reason, the search for noninvasive markers of esophageal inflammation activity is of the utmost importance for facilitating the use of dietary therapies in more EoE patients. Unfortunately, surrogate biochemical markers, including serum levels of eosinophil-derived granular proteins, have proven of little utility in monitoring disease activity.<sup>62</sup> However, a novel minimally invasive string test has been shown to accurately reflect mucosal eosinophilic inflammation by measuring eosinophil-derived proteins in luminal secretions,<sup>63</sup> but more research is needed to validate this method of monitoring EoE activity in clinical practice.

The results of our meta-analysis affirm that SFED seems to be the best dietary approach for treating EoE patients and that it should be considered for both children and motivated adult patients; not only is it highly effective in achieving disease remission, it also avoids the many disadvantages of elemental diets. Until better and more accurate food allergy testing capable of identifying specific food triggers is available, or until genetic profiling can accurately predict individual responses to diet, the unreliability of skin allergy testing limits the use of this method to experienced centers where it has proven to be efficient.

The strength of our research lies with the fact that it compiles the results of an exhaustive literature search in 3 major databases and in abstracts books of the 3 major Gastroenterology Congresses, recovered studies were critically appraised according to their methodologic aspects, and different investigators independently extracted the data from the studies included. The possibility of not recovering all the relevant information published on dietary treatment of EoE patients should be considered as one of the limitations of our study, along with a risk of bias that remains despite having excluded any such publication bias by means of a funnel plot analysis. In addition, no randomized controlled trials on dietary interventions for EoE are available, with most of the data coming from observational studies. The effectiveness of dietary intervention on symptomatic improvement was not analyzed in our research; when reported, clinical data were not structurally or objectively assessed in most of studies. The absence of a reliable and validated score to assess symptoms of EoE patients and difficulties in registering EoE-related symptoms in pediatric populations contribute to reporting eosinophils peak count as the more commonly used study end point. Additionally, the variations in diagnostic criteria for EoE along the near 20 year-period covered by our systematic review (regarding eosinophils count threshold and exclusion of proton pump inhibitor-responsive esophageal eosinophilia<sup>64</sup>) were not taken into account. Finally, the different dietary treatment strategies have been evaluated mostly in pediatric patients, with the exception of SFED, so some caution should be taken when interpreting combined

results from this meta-analysis in adults, especially for allergy testing-directed food exclusion, elimination of cow's milk, and gluten-free diets.

In conclusion, our research has demonstrated that dietary modifications are an effective treatment alternative for inducing histologic remission of EoE, reinforcing the idea that this strategy should be considered as a first-line therapy in both children and adults affected by the disease. Additional research is needed to assess the many aspects related to dietary treatment that require clarification, including the sustained effect of dietary restriction in maintaining EoE remission, changes in esophageal fibrosis, aspects associated with adherence to the diet, and quality of life issues.

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#### Conflicts of interest

The authors disclose no conflicts.