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Outcomes reported in randomized controlled trials for mixed and non-IgE-mediated food allergy: Systematic review

Bel Imam, Manal ; Stikas, Charalampos-Vlasios ; Guha, Payal ; Chawes, Bo L ; Chu, Derek ; Greenhawt, Matthew ; Khaleva, Ekaterina ; Munblit, Daniel ; Nekliudov, Nikita ; van de Veen, Willem ; Schoos, Ann-Marie M

Abstract: Background Mixed and non-IgE-mediated food allergy is a subset of immune-mediated adverse food reactions that can impose a major burden on the quality of life of affected patients and their families. Clinical trials to study these diseases are reliant upon consistent and valid outcome measures that are relevant to both patients and clinicians, but the degree to which such stringent outcome reporting takes place is poorly studied. Objective As part of the Core Outcome Measures for Food Allergy (COMFA) project, we identified outcomes reported in randomized clinical trials (RCT) of treatments for mixed or non-IgE-mediated food allergy. Design In this systematic review, we searched the Ovid, MEDLINE and Embase databases for RCTs in children or adults investigating treatments for food protein-induced enterocolitis syndrome, food protein-induced allergic proctocolitis, food protein-induced enteropathy and eosinophilic gastrointestinal disorders including eosinophilic esophagitis [EoE], eosinophilic gastritis and eosinophilic colitis published until 14 October 2022. Results Twenty-six eligible studies were identified, with 23 focused on EoE (88%). Most interventions were corticosteroids or monoclonal antibodies. All EoE studies assessed patient-reported dysphagia, usually using a non-validated questionnaire. Twenty-two of 23 EoE studies used peak tissue eosinophil count as the primary outcome, usually using a non-validated assessment method, and other immunological markers were only exploratory. Thirteen (57%) EoE studies reported endoscopic outcomes of which six used a validated scoring tool recently recommended as a core outcome for EoE trials. Funding source was not obviously associated with likelihood of an RCT reporting mechanistic versus patient-reported outcomes. Only 3 (12%) RCTs concerned forms of food allergy other than EoE, and they reported on fecal immunological markers and patient-reported outcomes.ConclusionsOutcomes measured in clinical trials of EoE and non-IgE-mediated food allergy are heterogeneous and largely non-validated. Core outcomes for EoE have been developed and need to be used in future trials. For other forms of mixed or non-IgE-mediated food allergies, core outcome development is needed to support the development of effective treatments.

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SYSTEMATIC REVIEW

WILEY

Outcomes reported in randomized controlled trials for mixed and non-IgE-mediated food allergy: Systematic review

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Abstract

Background: Mixed and non-IgE-mediated food allergy is a subset of immune-mediated adverse food reactions that can impose a major burden on the quality of life of affected patients and their families. Clinical trials to study these diseases are reliant upon consistent and valid outcome measures that are relevant to both patients and clinicians, but the degree to which such stringent outcome reporting takes place is poorly studied.

Objective: As part of the Core Outcome Measures for Food Allergy (COMFA) project, we identified outcomes reported in randomized clinical trials (RCT) of treatments for mixed or non-IgE-mediated food allergy.

Design: In this systematic review, we searched the Ovid, MEDLINE and Embase databases for RCTs in children or adults investigating treatments for food protein-induced enterocolitis syndrome, food protein-induced allergic proctocolitis, food protein-induced enteropathy and eosinophilic gastrointestinal disorders including eosinophilic esophagitis [EoE], eosinophilic gastritis and eosinophilic colitis published until 14 October 2022.

Results: Twenty-six eligible studies were identified, with 23 focused on EoE (88%). Most interventions were corticosteroids or monoclonal antibodies. All EoE studies assessed patient-reported dysphagia, usually using a non-validated questionnaire. Twenty-two of 23 EoE studies used peak tissue eosinophil count as the primary outcome, usually using a non-validated assessment method, and other immunological markers were only exploratory. Thirteen (57%) EoE studies reported endoscopic outcomes of which six used a validated scoring tool recently recommended as a core outcome for EoE trials. Funding source was not obviously associated with likelihood of an RCT reporting mechanistic versus patient-reported outcomes. Only 3 (12%) RCTs

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concerned forms of food allergy other than EoE, and they reported on fecal immunological markers and patient-reported outcomes.

Conclusions: Outcomes measured in clinical trials of EoE and non-IgE-mediated food allergy are heterogeneous and largely non-validated. Core outcomes for EoE have been developed and need to be used in future trials. For other forms of mixed or non-IgE-mediated food allergies, core outcome development is needed to support the development of effective treatments.

Systematic review registration: OSF public registry DOI:10.17605/OSF.IO/AZX8S

KEYWORDS
eosinophilic esophagitis, food protein-induced allergic proctocolitis, food protein-induced enterocolitis syndrome, food protein-induced enteropathy, non-IgE-mediated food allergy, outcome measures

1 | INTRODUCTION

Non-IgE-mediated food allergy is increasingly recognized and carries a significant health and quality of life burden to affected individuals.[1] This form of food allergy can be difficult to diagnose, and at least some forms of non-IgE-mediated food allergy appear to be overdiagnosed in some countries.[2] Non-IgE-mediated food allergies include food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP) and food protein-induced enteropathy (FPE). Eosinophilic gastrointestinal disorders (EGIDs; including eosinophilic esophagitis [EoE], eosinophilic gastritis and eosinophilic colitis) are by some classified as a mixed IgE/non-IgE-mediated food allergy.[3]

Non-IgE-mediated food allergy is characterized by dysregulated immunological reactions to dietary proteins that typically involve a delayed, likely cellular, immune response, which does not critically rely on IgE. These conditions are characterized specifically by a lack of immediate symptoms after exposure, and often their clinical presentation is almost exclusively gastrointestinal in nature. Few population-level studies have investigated the incidence and prevalence of non-IgE-mediated food allergy; however, the estimated incidence of EoE is 51 cases per 100,000 person-years, and the estimated incidence of FPIES is 15.4 cases per 100,000 person-years.[4,5] Additionally, the heterogeneity of how non-IgE-mediated food allergy can present clinically may impede accurate estimation of their true prevalence, in particular in response to specific allergens. According to the EuroPrevall study,[6] the incidence of non-IgE-mediated food allergy to cow's milk (CM) was below 1%, though the follow-up was limited to only four participating countries. While multiple clinical trials with robust outcomes are available for EoE, these are lacking in other non-IgE-mediated food allergic conditions, which hinders studying and further defining these disease processes.

Lack of harmonization in outcomes assessed in different studies, particularly those investigating intervention effectiveness, is a common problem. It is critical that the outcomes reported in trials are relevant to all stakeholders and put patients' needs at the centre of decision-making at the planning stage of clinical trials. For EoE, a core outcome set has been recently developed and reported by the COREOS group.[7] The group consisted of a panel of EoE experts and used data from previous reviews that reported on outcomes in EoE,[8–11] patient interviews and other relevant stakeholders. No such endeavour has been pursued yet in other non-IgE-mediated food allergies.

Key messages

- Most outcomes reported in clinical trials of mixed or non-IgE-mediated food allergy treatment are non-validated
- Core outcomes have been developed for eosinophilic esophagitis and should be used in future trials.
- Core outcome set development is needed for other forms of mixed and non-IgE-mediated food allergy.

Our systematic review aims to provide an updated overview on reported trial outcomes in mixed IgE/ non-IgE-mediated food allergies such as EoE, as well as the first systematic look at reported trial outcomes in other non-IgE-mediated food allergies. Secondary to that, the updated list of EoE trial outcomes will be commented on regarding alignment with the COREOS outcome set and relevance of funding status to nature of reported outcomes.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria, Information sources and search strategy

This review was conducted in accordance with a predefined search strategy available in the Supplementary Materials S1. We searched the Ovid MEDLINE and Embase databases on 14 October 2022 and limited the search to human studies published in English. We

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excluded conference abstracts and trial protocols, focusing on peer-reviewed published studies only. We applied filters to narrow the search down to randomized clinical trials in children and adults, with maximal sensitivity. The search terms included food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE), eosinophilic esophagitis (EoE), eosinophilic gastritis, eosinophilic colitis, allergic proctocolitis, eosinophilic gastrointestinal disorders (EGID) and non-immunoglobulin E. Trials that tested efficacy of interventions on active disease only were included. The full search strategy is provided as a Supplementary Material S1.

2.2 | Selection process

The records were exported into EndNote X9 (Clarivate Analytics). After removal of duplicate records, non-English language records, correspondence and conference abstracts, the records were imported into Rayyan QCRI for screening.[12] Two reviewers (PG and CS) independently screened the records for RCTs assessing mixed and non-IgE-mediated food allergy as per the search terms described above. Upon termination of screening, blinding was revoked, and conflicting decisions were resolved by a third reviewer (NAN). Any disagreements were resolved through discussion involving additional reviewers until consensus was reached.

2.3 | Data collection process

The data were extracted by four reviewers (PG, CS, NAN and MB) with one reviewer per record in a Microsoft Excel spreadsheet. The accuracy and data extraction were then assessed by the study supervisor (AMS) independently. In case of a published protocol in a clinical trial registry, the record was merged with the corresponding published study. If more than one publication was available for a single study, the outcomes were extracted separately from these records due to a possible temporal difference between the outcomes reported in each publication, however, the studies counted as one study in the different calculations in the result section. We did not contact study investigators and used no automation tools for data extraction.

We extracted disease type, study type, duration of the intervention, length of follow-up, population (age range and number of subjects), intervention (type of intervention, dosage and frequency of administration) and outcomes reported in the study. The outcomes were grouped into "immunological markers," "patient-reported outcomes" (PROs), "endoscopic outcomes" and "miscellaneous outcomes" along with the respective measurement tools. PROs were further subcategorized into general symptoms, dysphagia symptoms and quality of life (QoL). Immunological parameters were subcategorized into four major categories: eosinophil counts, antibodies, cytokines and other factors, and immune cell phenotyping.

2.4 | Data synthesis and reporting

We chose to report EoE findings separately to non-EoE findings since the bulk of the included studies was pertaining to EoE and EoE is not considered completely non-IgE mediated. As this systematic review was concerned with reporting the number and type of trial outcomes identified in the literature, data synthesis was kept to a minimum. Trials were reported by source of funding, population age and class of intervention, and trial outcomes were grouped by type, as outlined above. Finally, the number and proportion of trials that included each outcome type was reported for industry and non-industry funded trials, respectively. No bias risk assessment was calculated for the included trials since we merely reported on the measured outcomes and not measured efficacy of treatments.

3 | RESULTS

3.1 | Included studies

After removing duplicates and records not in English, we identified and screened 4026 potentially eligible records (Figure 1). Of these studies, 3854 were excluded in line with the inclusion criteria, leaving 172 reports sought for retrieval. Further 146 reports were excluded for the following reasons: published as conference abstracts ($n = 109$), represented secondary analyses within a study already included in the analysis ($n = 13$), non-relevant study design ($n = 16$) no intervention reported ($n = 3$); and non-relevant population ($n = 5$). Finally, 26 randomized clinical trials were included out of which 23 studies were focused on interventions for EoE; only 3 RCTs were found for interventions in pure non-IgE-mediated food allergies. For this reason, the EoE and non-EoE findings were reported in separate sections.

3.1.1 | Overview of EoE studies

Treatment duration in EoE studies varied from 2 to 36 weeks. Out of the 23 studies, 13 included only adult patients, 6 were paediatric trials, and 4 included a mixed population (Table 1). The most common pharmacological treatment in EoE studies was steroids; 14 out 23 studies (61%) compared steroids with either placebo (8/14),[13–20] a second steroid agent (4/14)[21–24] or PPIs (2/14).[25–26] Topical steroidal formulations – budesonide, fluticasone or mometasone – were trialled in all but one study; oral prednisolone efficacy was studied by Schaefer et al.[21]

The second most common intervention class among the EoE trials was immunotherapies; their efficacy was investigated in 6 out of 23 EoE studies (26%). The most common target for monoclonal antibody therapy was interleukins. Anti-IL-13 antibody infusions were administered in one study.[27] Two different anti-IL-5 antibodies were mentioned in the literature, mepolizumab[28] and reslizumab.[29] Dupilumab was the only anti-IL-4 antibody that was

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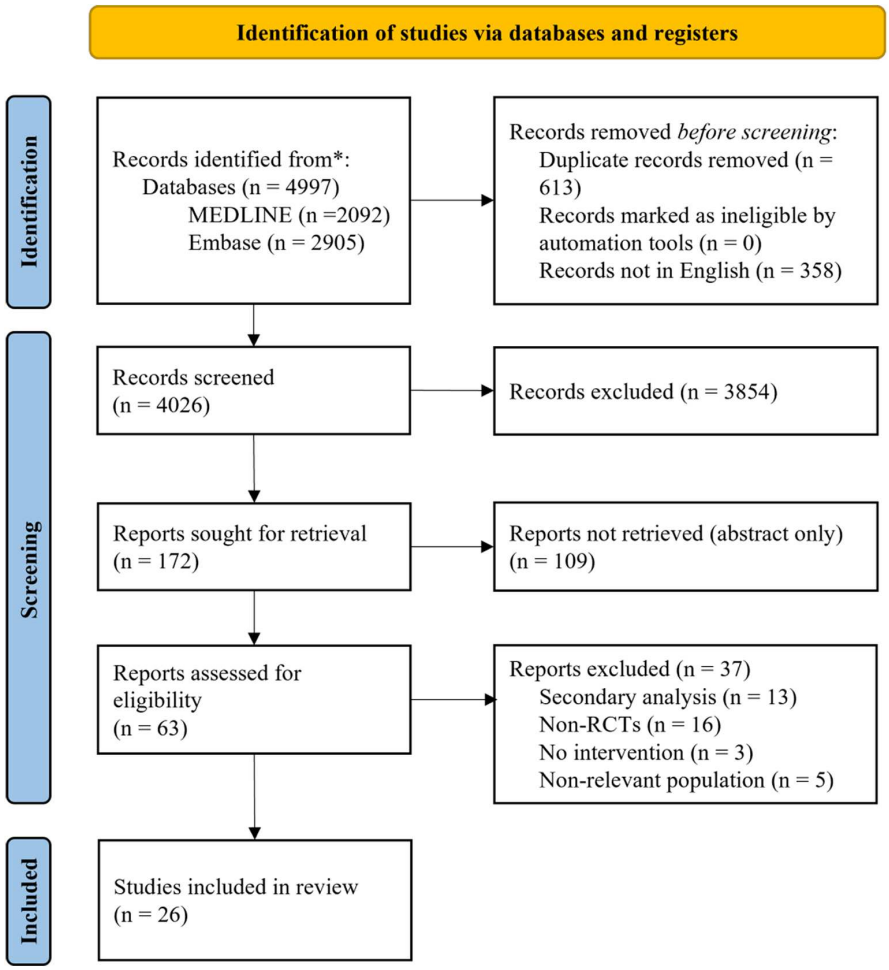

FIGURE 1 PRISMA flow chart of the search and screening process.

TABLE 1 Overview of EoE RCTs. Studies were grouped by intervention and population (adult/paediatric).

Intervention under investigation	Trial population (adult/paediatric)	
	Adult	Paediatric
Corticosteroids	Moawad et al 2013, Peterson et al 2010, Tytor et al 2021, **Dellon et al 2019**, Dellon, et al 2012*, Lucendo et al 2019*, Miehlke et al 2016*, Alexander et al 2012*, **Butz et al 2014*, Dellon, et al 2017*, Straumman et al 2010***	Dohil et al 2010*, Gupta et al 2015*, Scahefer et al 2008*
Immunotherapy	Rotherberg et al 2014, Hirano et al 2020, Straumann et al 2010, Clayton et al 2014	Spergel et al 2012*, Spergel et al 2020*
Other	de Rooij et al 2022*, Straumann et al 2013*	Lieberman et al 2018

Note: Studies in bold included children. Asterix denotes partial or complete industry funding.

mentioned in an EoE study.[30] Finally, Clayton et al. was the only study to look at anti-IgE antibody therapy[31] and epicutaneous immunotherapy was tested in one other study.[32] Other reported interventions included cromolyn,[33] prostanoid 2 receptor antagonist timapiprant[34] and amino acid-based formula feed.[35] Funding for the trials came from industry sources (e.g. pharmaceutical companies) and non-industry sources (e.g. public institutes, government bodies). Eighteen out of the 23 trials (78%) received either partial or full funding from industry sources; only four corticosteroid trials and the cromolyn paediatric study did not rely on any industry funding.

3.1.2 | Patient-reported outcomes in EoE studies

All the 23 trials in EoE included at least one PRO measure and all the trials reported adverse effects. Around 56% of the studies (13/23) used a single PROs questionnaire. Some studies, however, used more than one instrument to assess outcomes with maximum of four in Lucendo et al.[15] The identified PROs were classified into three domains, related to dysphagia, non-dysphagia symptoms or quality of life questionnaires (Figure 2). All trials regardless of funding status measured patient-reported dysphagia. Two trials used the Dysphagia Symptom Questionnaire (DSQ)[17,23]; DSQ was the only dysphagia

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scoring tool specifically validated for EoE patients.[36] Non-validated dysphagia scoring tools were used in 10 trials; these included Mayo dysphagia score,[19,24,25,27] Straumann Dysphagia Index (SDI),[30,35] Watson Dysphagia Scale[20] and custom dysphagia scores.[17,20,22,26,35]

Eleven out of the 18 industry funded studies (61%)[13–16,21,29–32,34–35] measured patient reported symptoms other than dysphagia versus 4 out of the 5 publicly funded trials (80%).[20,23,26,33] These outcomes included tools for adults such as Eosinophilic Esophagitis Activity Index (EEsAI),[15,23,30] age agnostic tools, for example, Patient Global Assessment (PGA),[15,29,34] as well as paediatric tools like Children's Health Questionnaire (CHQ),[29] and Paediatric Eosinophilic Esophagitis Symptom Score (PEESS).[32–33] The rest of the trials used custom clinical symptom scoring systems. QoL PROs were captured in 28% of industry funded RCTs[15,28,30,32,35] and 40% of non-industry funded RCTs.[20,23] The most common QoL outcome was the Adult Eosinophilic Esophagitis Quality of Life questionnaire (EoEQoL-A).[15,23,30,35]

3.2 | Immunological markers in EoE trials

Out of the 23 EoE studies, 22 studies investigated immunological parameters (Table 2).

3.2.1 | Eosinophil counts

Most of the EoE studies (96%, 22/23) used histological response as their primary outcome. The measure of response was peak and mean eosinophil counts per high power field (hpf) with a light microscope. The peak eosinophil count is determined by counting eosinophils in the area with the highest eosinophil density in a hpf at 400X by light microscopy, while the mean eosinophil count is determined by calculating the average of eosinophil counts in different fields.[37] Most studies specifically defined histological remission as their primary outcome which ranged from <1 to <5 eosinophils/hpf depending on the study. No trial used the Eosinophilic Esophagitis Histology Scoring System (EoEHSS), a recently validated tool for scoring biopsies in EoE.[38]

To assess eosinophil counts in oesophageal epithelium of the patients, biopsies were obtained during post-treatment oesophago-gastro-duodenoscopy. In most studies, specimens were obtained from proximal and distal oesophageal halves; only 4 studies included biopsies from upper, mid and distal oesophagus.[14–15,17,22]

Peripheral eosinophilia was examined in 8 studies.[15–16,18,21–22,28–29,34]

3.2.2 | Antibodies

Serum specific antibody levels were reported in two studies; serum total IgE levels were measured in both trials.[16,31] IgG4 levels against fat-free milk, wheat gluten, whole egg and mixed fresh peanut and almond were investigated in serum in one study.[31]

IgE measurement in biopsy specimens and immunoglobulin quantitation by class (IgM, IgA, IgG1, IgG2, IgG3 and IgG4) was performed in one study only.[31]

3.2.3 | Cytokines, chemokines and other factors

Six studies reported cytokine levels (biopsies and/or serum). Two of these studies analysed the level of TGFβ1 in oesophageal biopsies,[16,34] and one study additionally analysed its promoter genotype at the C-509 T SNP from peripheral blood samples.[13] One study assessed CCL7, CCL-18 and CCL-26 levels in blood.[22] Another study reported levels of IL-13 and TSLP detected by staining biopsy specimens.[34]

Besides cytokine measurements, serum eosinophil cationic protein (ECP)[16,22] and serum mast cell tryptase (MCT) were analysed.[22] MCT was additionally detected by immunostaining of biopsies.[16,31,33–34] Eosinophil-derived neurotoxin (EDN) was analysed by immunofluorescent staining on biopsy specimen and the results were compared with standards from a previous study[39] and assigned scores from 0 to 3 for intracellular and extracellular EDN deposition.[19]

3.2.4 | Immune cell phenotyping

Eosinophil peroxidase (EPX), chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2)[34] and CD3[16,34] were examined by indirect immunofluorescence on biopsy specimens. TGFβ1+ cells were detected from immunostained biopsies containing lamina propria.[13]

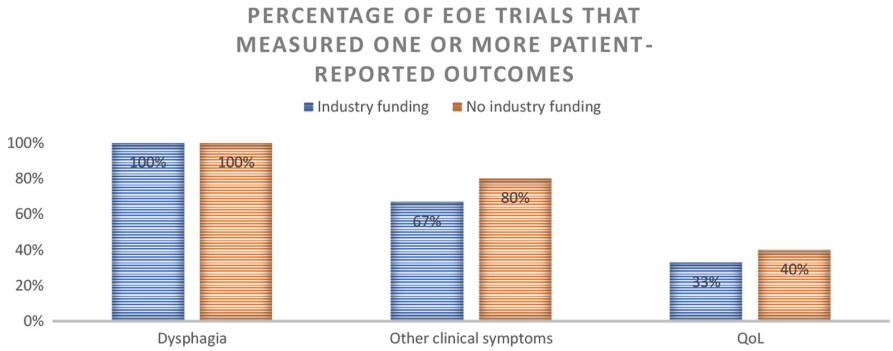

FIGURE 2 Percentage of industry-funded and non-industry-funded EoE RCTs that measured at least one PRO from one of the three domains: dysphagia, other symptoms and quality of life.

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TABLE 2 Immunological markers measured in 23 EoE studies.

Immunological marker	Origin	Number of trials	References
Peak eosinophil counts	Oesophageal biopsies	22	Dellon et al., 2017, Butz et al., 2014, Clayton et al., 2014, Alexander et al., 2012, Dellon et al., 2012, Dellon et al., 2019, Dohil et al., 2010, Gupta et al., 2015, Hirano et al., 2020, Lieberman et al., 2018, Lucendo et al., 2019, Moawad et al., 2013, Peterson et al., 2010, Rothenberg et al., 2014, Schaefer et al., 2008, Miehlke et al., 2016, Spergel et al., 2020, Spergel et al., 2012, Straumann et al., 2013, Straumann et al., 2010, Straumann et al., 2010, de Rooij et al., 2021
	Serum	2	Butz et al., 2014, Miehlke et al., 2016
Antibodies	Oesophageal biopsies	1	Clayton et al., 2014
	Blood	2	Clayton et al., 2014, Straumann et al, 2010
Cytokines and other factors	Oesophageal biopsies	5	Dohil et al., 2010, Straumann et al., 2013, Clayton et al., 2014, Lieberman et al., 2018, Alexander et al, 2012
	Blood	3	Dohil et al., 2010, Miehlke et al., 2016, Straumann et al, 2010
Immune cell phenotyping	Oesophageal biopsies	2	Dohil et al., 2010, Straumann et al., 2013
	Blood	2	Miehlke et al., 2016, Straumann et al., 2010

4 | ENDOSCOPIC OUTCOMES

Gross visual endoscopic outcomes (e.g. macroscopic findings, not including tissue analysis reported above) before and after the intervention were reported in 57% (13/23) of EoE studies. The most frequently used score to assess improvement in the endoscopic appearance was the EoE Endoscopic Reference Score (EREFS) first described in 2013 by Hirano et al.[40] This validated score[40] quantifies five key endoscopic findings: exudates (scored 0–2), oesophageal rings (scored 0–3), oedema (scored 0–1), furrows (scored 0–2) and strictures (scored 0–1). The EREFS ranges from 0 to 9, with higher scores indicating more severe endoscopic findings (Figure 3). Grades 1 and 2 for oedema as depicted in Figure 3 were collapsed into a single grade in the modified version. EREFS is one of the core outcomes discussed in the COREOS study.[7]

Of the 13 studies that included a visual endoscopic outcome measure, 6 (46%) used the EREFS as an assessment tool (Table 3), and of the studies published after 2013, 6/7 (86%) used the EREFS. Four trials used non-validated endoscopic scoring tools and 3 trials assigned no scoring to endoscopic findings.

4.1 | Non-EoE findings

Three (12%) of the 26 included trials concerned non-IgE-mediated food allergic conditions other than EoE.[41–43] All of them were performed exclusively among infants and children younger than 5 years old and no study included endoscopic outcome measures. One of the non-EoE studies was performed with industry funding, a formula-based RCT by Fox et al.[41] The other 2 non-EoE studies did not receive industry or public funding.

FPIES (food protein-induced enterocolitis syndrome): No RCTs were identified.

FPIAP (food protein-induced allergic proctocolitis): One RCT[41] investigated infants with FPIAP. The study included 71 children <13 months of age with cow's milk FPIAP, who were randomly assigned to a symbiotic or non-symbiotic containing amino acid-based formula for 8–26 weeks duration (sponsored by Nutricia).[41] The reported outcomes were fecal bacteria assessments, fecal immunological markers (sIgA, eosinophil cationic protein, calprotectin, alpha-1-antitrypsin), parent-reported outcomes (scales for skin, respiratory, gastrointestinal and general symptoms) and adverse events.

Other non-IgE-mediated food allergic conditions: One RCT included 39 children, who at a mean age of 2.5 months were diagnosed with cow's milk-induced enteropathy characterized by stools with blood, loose stools, gas, bloating and bowel movements, that is, not FPIES.[42] The children were randomized to introduction of milk-free rice cereal or pureed carrots as the first complementary food at age 6 months, and the reported outcomes were diary-based 2 weeks parent-reporting of gastrointestinal symptoms based on a validated dietary interview from the TRIGR study.[44] Another RCT examined 20 children aged 21–58 months, who had non-IgE-mediated allergic reactions to soy, which did not include FPIES.[43] The children were randomly assigned to a 1-week challenge with soya lecithin or placebo biscuits in a cross-over design with 1 week wash-out periods, and the reported outcomes were a parent-reported gastrointestinal symptom score on a Likert scale at week 4.[45]

5 | DISCUSSION

Mixed and non-IgE-mediated food allergic conditions are broadly recognized immune-mediated food reactions, and our review examined trials primarily on EoE as only 3 identified trials assessed treatment efficacy in other non-IgE-mediated conditions such as FPIES,

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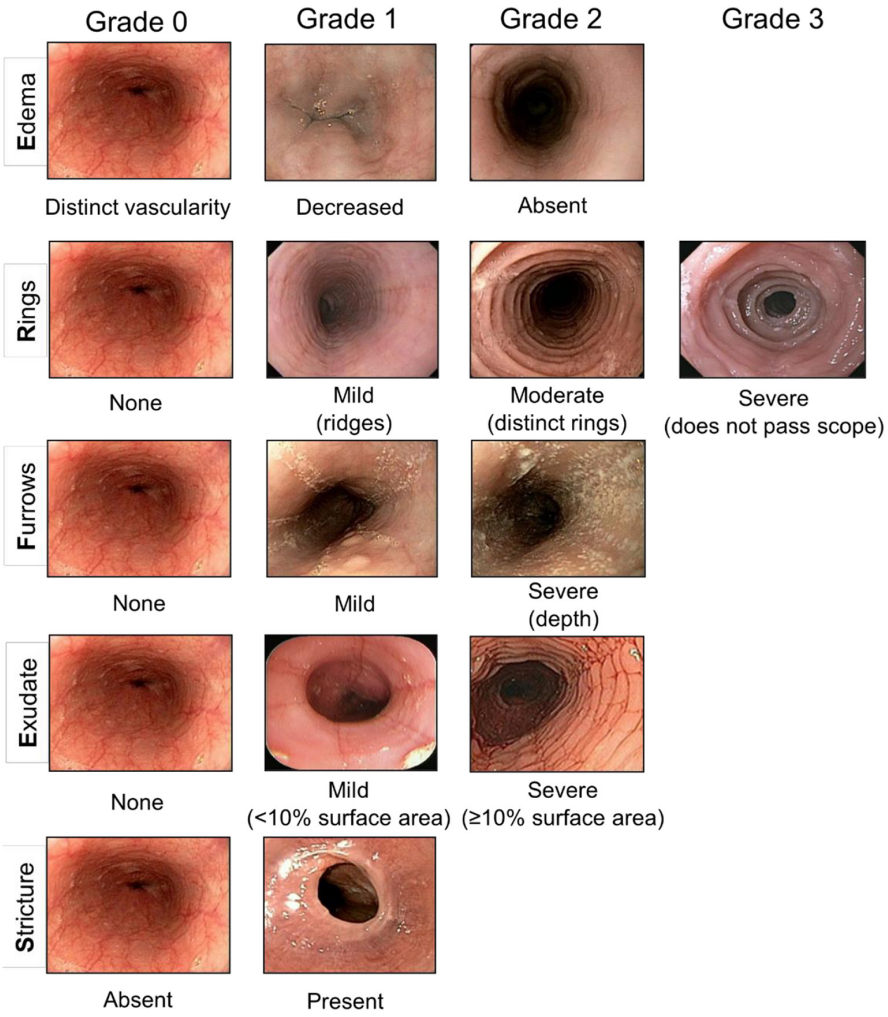

FIGURE 3 EoE Endoscopic Reference Score (EREFS) with reference pictures and their relative classification.[39] In the modified version of EREFS, oedema is graded as either 0 or 1.

TABLE 3 Endoscopic outcomes assessed in EoE studies.

Endoscopic outcome measure	Number of trials	References
EREFS.	6	Dellon et al., 2017; Dellon et al., 2019; Hirano et al., 2020; Lucendo et al., 2019; Tytor et al., 2021, de Rooij et al., 2022
Macroscopic description (e.g. furrows, oedema, concentric rings), but no score.	3	Alexander et al., 2012; Moawad et al., 2013; Straumann et al., 2010
The following endoscopic abnormalities were classified as either absent (0), mild (1), moderate (2) or severe (3): white exudates, furrows, oedema, fixed rings, crepe paper sign, short-segment stenosis, long-distance stenosis. Total score: 0–21.	1	Miehlke et al., 2016
Upper Gastrointestinal Endoscopy Score. Total score: 0–15.	1	Dohil et al., 2010
The global appearance of endoscopic abnormalities was assessed using a 10-cm visual analogue scale ranging from severe appearance to remission.	1	Straumann et al., 2013
Endoscopic findings were graded by means of a simple overall score: absent, minor (fine nodules, fine whitish reticular structures, furrows), moderate (bright white scale- or plaque-like structures, corrugated rings) or severe (mucosal lesions, fixed stenosis).	1	Straumann et al., 2010

FPIAP and FPE. Despite recognition and world-wide distribution, diagnosis of non-IgE-mediated food allergic conditions and their subsequent management is still challenging and not well-characterized, partly due to lack of firm diagnostic criteria. With emerging evidence on the topic, outcome measures used in the research settings are still very heterogenous. An agreed core outcome set for EoE trials was

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outlined in the recently published COREOS study,[7] yet no agreed core outcome exists for non-IgE-mediated food allergies. Many of the reviewed studies and/or clinical trials used individual and non-validated questionnaires.

All but one EoE trials analysed immunological parameters in oesophageal biopsy specimens. While tissue eosinophil count was the most frequently reported parameter, investigated in 22/23 studies, antibody and cytokine levels were only reported in 2/23 and 6/23 studies, respectively. Occasionally, individual studies mentioned other factors, such as eosinophil cationic protein and eosinophil-derived neurotoxin.[22] Histological remission measured with a peak eosinophil count cut-off was the primary trial outcome in all but one study regardless of their industry funding status. This shows that funding source appeared to play no role in determining the primary outcomes of EoE trials. Other immunological markers were confined to exploratory outcome status only. Funding source appeared to be associated with the range of markers that were measured in trials as only one publicly funded study measured additional immunological markers other than peak eosinophil count, whereas commercially funded studies did measure additional immunological outcomes.

Although there is considerable heterogeneity in the instruments used, all the EoE studies relied upon PROs. Dysphagia-related scoring systems were universally utilized. Funding appeared to make no significant difference in the likelihood that a trial measured other clinical symptoms (61% in industry funded vs. 80% in non-industry funded) or QoL outcomes (28% in industry funded vs. 40% in non-industry funded). It is apparent that beyond the utilization of tools like DSQ, there is a need in harmonization of the data collection and assessment of the existing instruments validity and reliability.

Six EoE studies used the EREFS to assess key endoscopic findings. The remaining 7 studies that reported visual endoscopic outcomes used non-validated endoscopic measure scores. While this highlights the need for a standardized approach for assessment of endoscopic findings, the EREFS has been used more in recent years, representing 86% of the included studies after 2013.

When we turn to the core EoE trial outcome set proposed by the COREOS group,[7] we observe that all but one recommended outcome were identified in our analysis (Table 4). Strikingly no identified trial reported an EoEHSS score. Most of the included RCTs did not use any of the standardized PRO measures outlined in COREOS; this discrepancy reveals the reliance of EoE trials thus far on non-standardized PRO outcomes and reiterates the significance of the COREOS study endeavour.

In contrast, non-EoE studies are less generalizable. Among the three trials that examined other non-IgE-mediated diseases than EoE, a single study on FPIAP examined immunological markers (i.e. calprotectin, secretory immunoglobulin A, ECP and alpha-1-antitrypsin).[41] Indeed, the lack of information on these disorders displays the need to perform further investigations, especially on additional population groups, and to adapt to a universal classification of measured outcomes.

This review highlights the scope and range of outcomes that have been assessed in non-IgE-mediated food allergy studies. There is a paucity of research regarding outcomes related to non-IgE-mediated food allergy outside of multiple interventional clinical trials for EoE, which itself is not entirely a non-IgE-mediated food allergy as much as it is a mixed IgE/non-IgE-mediated process. Within EoE research, there are established outcomes regarding tissue eosinophil counts, cytokine responses and symptom scores that serve as benchmarks to measure diet and pharmacologic interventions. However, in other non-IgE-mediated food allergic conditions, similar measures are lacking. Even within EoE, the markers being measured revolve around diagnosis, as opposed to prognosis or underlying immunopathology, though these are now well established and well replicated. Unlike the increasing number of trials in EoE and the published COREOS study, RCTs in other non-IgE-mediated food allergies, such as FPIES or FIAIP, are lacking and high-quality evidence regarding the importance of outcomes is absent. This represents an important unmet need to be addressed, which will facilitate guideline development for these conditions.

Our review has several limitations. First, our search was restricted to articles published in English, and therefore, outcomes described in other languages were not considered. Second, we did not include ongoing trials, and hence, different or new outcome measures could show importance when regarding studies that are currently underway. Third, there is a risk of ascertainment and selection bias, given the scarcity of studies that were identified, which was particularly pronounced for non-EoE conditions. Finally, non-IgE-mediated food allergy is a heterogeneous collection of multiple disease entities, all with rather diffuse diagnostic criteria, except for EoE. For example, some authors use macroscopic blood for FPIAP diagnosis, others include microscopic blood – some require exclusion of differential diagnoses, while others do not. The lack of firm diagnostic criteria for some non-IgE-mediated food allergies inevitably hinders outcomes measure development.

TABLE 4 List of suggested outcomes for EoE studies concluded by the COREOS study and number of studies that measured the suggested outcomes included in this systematic review.

COREOS study	Present review
Suggested outcome	Number of studies that measured the suggested outcome
N. Eos/hpf	22
EREFS	6
EoEHSS	0
DSQ	2
EEsAI	3
EoE-QoL	4
Peds-QL	1

Abbreviations: DSQ, Dysphagia Symptom Questionnaire; EEsAI, Eosinophilic Esophagitis Activity Index; EoEHSS, Eosinophilic Esophagitis Histologic Scoring System; EoE-QoL-A, Adult Eosinophilic Esophagitis Quality of Life Questionnaire; Eos/hpf, eosinophils per high power field; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; Peds-QL, Paediatric Quality of Life Inventory.

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6 | CONCLUSION

This review provides an up-to-date overview of the outcomes measured in mixed and non-IgE-mediated food allergy RCTs published until 2022 and the potential relevance of source of funding to outcome reporting. It compares outcomes reported in the COREOS study with outcomes identified in the literature. Additionally, it highlights the scarcity of data on diseases other than EoE. A generation of set of outcome measures for non-IgE-mediated food allergies other than EoE would ease the retrieval of useful information from trials on such conditions and lead to a better understanding of the treatment's efficacy and the patients' quality of life.

AUTHOR CONTRIBUTIONS

The guarantor of the study is AMS, from conception and design to conduct of the study and acquisition of data, data analysis and interpretation of data. MBI and C-VS have written the first draft of the manuscript. All co-authors have provided important intellectual input and contributed considerably to the analyses and interpretation of the data. All authors guarantee that the accuracy and integrity of any part of the work have been appropriately investigated and resolved and all have approved the final version of the manuscript. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication. No honorarium, grant or other form of payment was given to any of the authors to produce this manuscript.

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CONFLICT OF INTEREST STATEMENT

Matthew Greenhawt: is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Sanofi/Regeneron, Nutricia, Novartis, Aquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello and Prota, with all activity unrelated to vaccines/vaccine development or COVID-19 treatment; is an unpaid member of the scientific advisory council for the National Peanut Board and medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the *Annals of Allergy, Asthma, and Immunology*; and is member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, MedLearningGroup, RMEI Medical Education, and multiple state/local allergy societies. He received past research support ending in 2020 from the Agency for Healthcare Quality and Research (K08-HS024599). **Willem van de Veen**: is a consultant for Mabylon AG, Switzerland. Has received research grants from European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Promedica Stiftung, Switzerland, Novartis Freenovation, Switzerland, and EoE stiftung Switzerland. **Ann-Marie M Schoos**: is a consultant for ALK (ending in 2022). Has received research support from Sanofi Genzyme.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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