

The Efficacy and Safety of Epicutaneous Immunotherapy for Allergic Diseases: A Systematic Review and Meta-Analysis

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Keywords

Epicutaneous immunotherapy · Food allergy · Grass-pollen allergy · Desensitization · Adverse reaction

Abstract

Objectives: To systematically review the effect and safety of epicutaneous immunotherapy (EPIT) for allergic diseases. **Methods:** We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, CQ VIP Database, Wanfang Data, and international trial register from their inception to July 29, 2019, without language restrictions, for randomized controlled trials (RCTs) that compared EPIT versus no EPIT for allergen-triggered allergic reactions. We assessed certainty of evidence by the GRADE approach. **Results:** Ten RCTs with 1,085 participants (aged from 10 months to 65 years) comparing EPIT with placebo for peanut, cow milk, or grass-pollen allergy met the eligibility criteria. A substantial benefit in terms of desensitization in EPIT group was more likely for peanut or cow milk protein allergy (risk ratio [RR] 2.34, 95% CI 1.69–3.23; $I^2 = 0\%$; high certainty evidence). EPIT increased local-treatment-related adverse events (L-TRAE; RR 1.56, 95% CI

1.03–2.36; $I^2 = 82\%$; moderate certainty evidence). But there were no significantly increased risk of any TRAEs (low certainty evidence) or systemic-TRAEs (S-TRAEs; very low certainty evidence) in EPIT group. The incidence rate of serious AEs, the use of rescue medications, and anaphylactic reactions stratified by organ systems including skin and mucosa, eyes and upper respiratory, lower respiratory, and gastrointestinal system in EPIT group were similar to placebo group. In subgroup analysis, desensitization of EPIT was significantly effective in peanut allergy (RR 2.29, 95% CI 1.64–3.21; $I^2 = 0\%$) and children <12 years (RR 2.85, 95% CI 1.92–4.24; $I^2 = 0\%$) with high certainty evidence. Only epicutaneous grass-pollen immunotherapy significantly increased the risk of S-TRAE (RR 4.65, 95% CI 1.10–19.64; $I^2 = 0\%$). **Conclusion:** The systematic review suggests that EPIT might induce desensitization in peanut allergy and an increased risk of local AEs. These findings should be interpreted with caution owing to the limited study and heterogeneity. More data in the older (children ≥ 12 years and adults) and other allergic diseases are needed.

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Introduction

Allergen-induced allergic diseases such as food allergy and respiratory allergy are emerging as a major public health problem [1–4]. The current standard of care is allergen avoidance and rapid administration of rescue medication on presentation of allergic symptoms [5, 6]. However, successful avoidance is complicating. Accidental exposures and unpredictable severe allergic reactions still occur, which may lead to morbidity and significant negative impacts on quality of life [7]. Recently, allergen immunotherapy (AIT) has been regarded as a curable treatment that could safely and feasibly result in desensitization and reduce risk of unintentional exposure [8]. Epicutaneous immunotherapy (EPIT) is a novel AIT for allergen-specific allergic diseases [9, 10]. This administration uses an allergen adsorbed patch to deliver allergen to the skin, where it is taken up by Langerhans cells (antigen-presenting cells) [10–12]. Compared with other AIT, this administration route is needle-free and self-administered. Besides, the newly published stimulated analysis showed that EPIT might be cost-effective [13]. Though the efficacy of allergen administration via the skin for the treatment of allergic disorders had been published in the early 20th century [14–16], this approach was not further pursued for several decades until a resurgence of interest occurred in recent years. Recently, multiple randomized controlled trials (RCTs) on EPIT have been completed, but no rigorous systematic synthesis of all relevant data is available to date. The latest review published in 2018 concluded that EPIT seemed effective and safe in rhino-conjunctivitis and food allergies [17]; however, quantitative support was lacking and evidence was conflicting.

Considering factors above, we incorporated studies comparing EPIT versus no EPIT till now and performed a systematic review and meta-analysis to figure out the safety and efficacy of EPIT for allergen-induced allergic diseases. This review should provide more evidence on the effects of EPIT as a novel AIT.

Method

Search Strategy

From the inception to July 29, 2019, we searched international trial register (ClinicalTrials, gov) and 6 electronic databases including PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Wanfang Data, China National Knowledge Infrastructure, and CQ VIP Database for published materials. We did not use any language restrictions. Search strategies as (epicutaneous immunotherapy OR EPIT OR transcutaneous immunotherapy) AND (allergy OR allergies OR hypersensitivities OR allergic

OR allergic reaction) were used. The corresponding Chinese key terms were used in Chinese databases. In addition, we reviewed the reference lists from retrieved articles to identify additional relevant studies.

Eligibility Criteria

RCTs that evaluated the effects of EPIT on children and adults with allergen-triggered allergies were considered. The specific criteria were listed as follows: (1) participants with a clinician-diagnosed allergy such as grass-pollen allergy, food allergy, or other allergen-induced allergic disorders with confirmation of allergic status through positive provocation tests, skin prick tests, or increased specific-immunoglobulin E (sIgE) level, (2) EPIT was supplied to the intervention group, (3) placebo or allergen avoidance was supplied to control group, and (4) at least one of the primary or secondary outcomes was reported.

Outcome Measures

Primary Outcome

1. Desensitization: the proportion of participants with good or excellent response to allergen extract after EPIT defined per each study (i.e., the passing of oral food challenge).
2. Participant- or parent-reported specific symptom scores of allergen-induced diseases.
3. Adverse event (AE): including any treatment-related AE (TRAE), local-TRAE (L-TRAE), and systemic-TRAE (S-TRAE). L-TRAE was defined as any patch site skin reaction including erythema, pruritus, swelling, and eczema. S-TRAE was defined in accordance with the World Allergy Organization's grading system of side-effects related to specific AIT [18].

Secondary Outcome

1. Anaphylactic reactions stratified by organ system in accordance with World Allergy Organization's guidelines on the assessment of anaphylaxis [6].
2. Serious AE (SAE): defined as death, life threatening, disability, or requiring urgent medical intervention or hospitalization.
3. The use of rescue medications.
4. Serum-specific IgE.
5. Serum-specific IgG4.

Data Collection

Two reviewers independently screened titles and abstracts and reviewed full-texts. Two reviewers independently extracted data and assessed risk of bias. Any disagreement was resolved through discussion with a third reviewer. Data extraction was performed using a self-designed data collection form. Authors were contacted to provide the missing information if required data were not reported in the original article.

Data Analysis

We tried to analyze outcomes by intention-to-treat as much as possible. For continuous outcomes, we pooled data using mean difference, or the standardized mean difference if the outcomes were measured with different scales. For dichotomous outcomes, risk ratio (RR) was used for analysis. Random-effects model or fixed-effects model was used depending on the heterogeneity across studies. We calculated 95% CI for each effect size estimate. $p < 0.05$ meant it was statistically significant. Heterogeneity in the

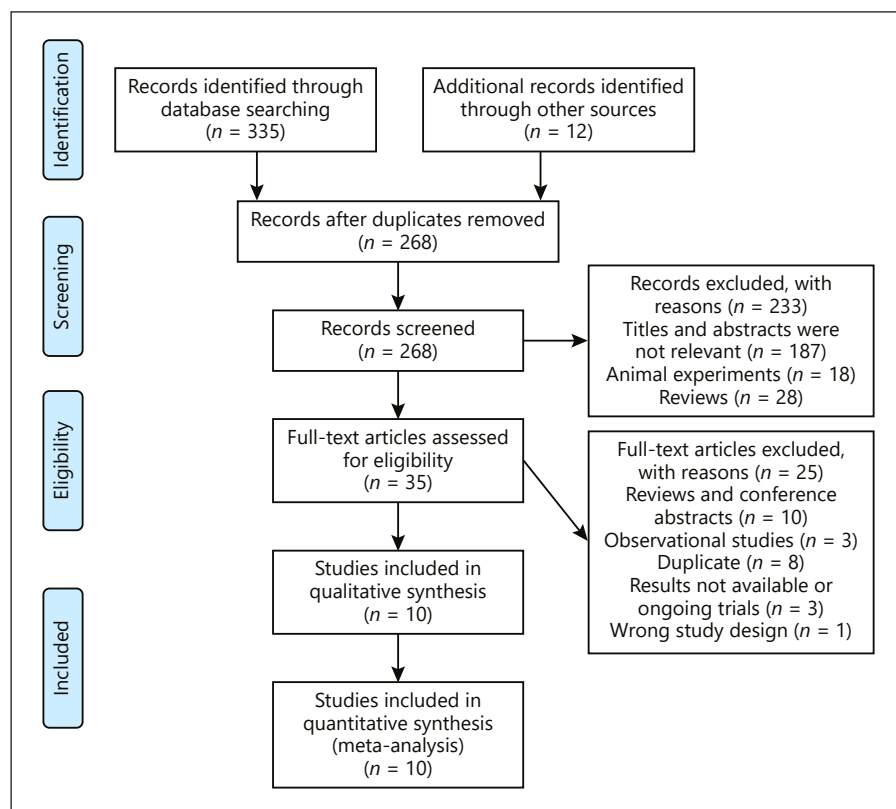


Fig. 1. Study flow diagram.

meta-analysis was estimated by the I^2 statistic. The heterogeneity was considered low if $I^2 < 50\%$ [19]. We would perform subgroup analyses for primary outcomes if data were sufficient. The factors included age, allergen types, pathomechanism, and intervention doses. Sensitivity analyses were performed to test the robustness of the findings by removing those studies rated as “high” or “unclear” risk of selection, performance, detection, and attrition bias. Begg’s test and Egger’s test were conducted to assess the potential publication bias of primary outcomes. Meta-analyses were conducted by Review Manager version 5.3 and STATA version 12.0. We also evaluated the quality of evidence using the GRADE approach. GRADE classified the certainty into high, moderate, low, and very low level.

Results

Literature Search

Three hundred and forty-seven records were obtained, of which 12 relevant studies were searched in the international trial registers. There were 256 records identified through database searching after 79 duplicates were removed. We screened 268 records, reviewed 35 in full-text, and included 10 RCTs [20–29] (Fig. 1). Among 12 relevant records searched in the international trial registers, 8 trials were regarded as duplicate records because of

available published papers. Two RCTs were ongoing but no data were available. One study had completed but results were not available. The last one was excluded for wrong study design that the trial compared the influence of EPIT for birch pollen allergy on different skin conditions without setting a blank control group.

Characteristics of Included Studies

Ten RCTs were included in different areas across the world including Australia, North America, and Europe. The characteristics of each trial were summarized in Table 1. Briefly, 1,085 participants (10 months to 65 years) diagnosed with food allergy (6 trials) and grass-pollen allergy (4 trials) [20, 21, 23, 24] were enrolled. Among the 6 trials about food allergy, 2 trials [22, 29] were on cow milk allergy and 4 trials [25–28] were on peanut allergy. They compared EPIT with placebo for varied treatment durations (48 h to 52 weeks). In all trials, the demographic characteristics of the intervention and placebo group were similar at baseline. But studies had varied dose of specific allergen for EPIT. Outcomes including desensitization, specific symptom scores, AEs, the use of rescue medications, serum-specific IgE (sIgE), and IgG4 were reported.

Table 1. Characteristics of included study

Author, years	Study design	geographic area	Participant sample size	age, years	diagnosis	baseline provocation test	Intervention and control		Outcomes
							treatment duration time*	intervention control	
Senti et al. [21], 2009	RCT	Zurich, Switzerland	37	18–65	Clinical-diagnosed grass pollen-induced rhinoconjunctivitis	Positive nasal provocation test	12 weeks	Grass pollen extract patch (21 µg Phl p 5)	Placebo SS, RM, TRAE, L-TRAE, SAE
Agostinis et al. [20], 2009	RCT	Milan, Italy	30	Children [†]	Clinical diagnosed seasonal allergic rhinoconjunctivitis	Not mentioned	12 weeks	Grass pollen extract patch	SS, RM
Dupont et al. [22], 2010	Bicenter RCT	Paris and Lille, France	18	10 months to 7 years	Clinical-diagnosed cow milk allergy	Positive OFC	12 weeks	Viaskin milk patch (1 mg)	Desensitization, RM, sIgE, L-TRAE, SAE
Senti et al. [23], 2012	RCT	Zurich, Switzerland	132	18–65	Clinical-diagnosed grass pollen-induced rhinoconjunctivitis	Positive conjunctival provocation test	83±3 days	Grass allergen extract patch (3, 15, 30 µg Phl p 5)	SS, RM, TRAE, S-TRAE, SAE
von Moos et al. [24], 2014	RCT	Zurich, Switzerland	97	18–65	Clinical-diagnosed grass pollen-allergic rhinoconjunctivitis	Positive conjunctival provocation test	48 h	Grass pollen extract patch (21 µg Phl p 5)	S-TRAE, SAE
Jones et al. [25], 2016	Multicenter RCT	USA	100	6–50	Clinical-diagnosed peanut allergy	Not mentioned	2 weeks	Viaskin peanut patch (20, 100, 250, and 500 µg)	sIgE, RM, TRAE, L-TRAE, S-TRAE, SAE
Sampson et al. [27], 2017	Multicenter RCT	North America and Europe	221	6–55	Clinical-diagnosed peanut allergy	Positive OFC	12 months	Viaskin peanut patch (50, 100, and 250 µg)	Desensitization, sIgE, IgG4, TRAE, SAE
Jones et al. [26], 2017	Multicenter RCT	USA	74	4–20	Clinical-diagnosed peanut allergy	Positive OFC	52 weeks	Viaskin peanut patch (100 and 250 µg)	Desensitization, sIgE, IgG4, RM, TRAE, L-TRAE, S-TRAE, SAE
Fleischer et al. [28], 2019	Multicenter RCT	Australia, Canada, Germany, and USA	356	4–11	Physician-diagnosed peanut allergy	Positive OFC	12 months	Viaskin peanut patch (250 µg)	Desensitization, sIgE, IgG4, TRAE, L-TRAE, S-TRAE, SAE
Spergel et al. [29], 2019	RCT	USA	20	4–17	Physician-diagnosed milk-induced Eosinophilic Esophagitis	Positive OFC	9 months	Viaskin milk protein patch (500 µg)	Desensitization, SS, L-TRAE, S-TRAE, SAE

* The duration of followed open-label phase was not included because there was no control group.

[†] 7.57 ± 3.67 years in placebo groups and 9.20 ± 4.22 years in active groups.

RCT, randomized controlled trial; OFC, oral food challenge; SS, symptoms scores; RM, rescue medication; sIgE, specific immunoglobulin E; TRAE, treatment-related adverse event; L-TRAE, local-treatment-related adverse event; S-TRAE, systemic-treatment-related adverse event; SAE, serious adverse event.

Quality of Individual Studies

Risk of bias of 10 included studies was assessed according to the Cochrane Handbook. Six studies [20, 22–26] reported inadequate description of randomization as well as blinding of participants and personnel for the characteristics of interventions. The same 6 studies also did not report the adequate method of allocation concealment except one [23] using a random-number table which was regarded as of high risk. The blinding of outcome assessment was applied in 4 studies [21, 27–29], other included studies remained unclear. In terms of incomplete outcome data, all studies were at low risk of bias for no data were missing. Four included studies had low risk in selective reporting [22, 26, 28, 29], while others had unclear risk. Other risks including potential source of bias were not found in all included studies (Fig. 2).

Meta-Analysis of Primary Outcomes Desensitization

Five studies reported the ability to tolerate allergic food (2 trials for cow milk protein and 3 trials for peanut) [22, 26–29]. Only one study [29] defined good response in milk-induced eosinophilic esophagitis (EOE) as eosinophil counts <15/hpf from the biopsy. Other 4 studies used oral food challenges as a primary measure of treatment efficacy. The pooled data suggested that EPIT could significantly raise the threshold of reactivity to peanuts or cow milk (RR 2.34, 95% CI 1.69–3.23; $I^2 = 0\%$) with low heterogeneity compared with placebo (high certainty evidence; Fig. 3).

Participant- or Parent-Reported Specific Symptom Scores of Allergen-Induced Diseases

Four studies reported specific symptom scores [20, 21, 23, 29]. Three studies reported participants who received epicutaneous grass-pollen immunotherapy had a markedly stronger symptom improvement than the placebo group. One study reported that the symptom scores of subjects with milk-induced EOE were similar in both groups at the end of the study [29]. However, no study described symptoms scores by mean and SD. Thus, we could not perform meta-analysis.

Adverse Events

Nine included studies reported the incidence of AEs.

Treatment-Related AEs

Six studies reported any TRAE [21, 23, 25–28]. Meta-analysis, with a total of 920 participants, showed that EPIT did not statistically significantly increase the risk of

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agostinis, 2010 (grass-pollen)	?	?	?	?	+	?	+
Dupont, 2010 (cow milk)	?	+	?	?	+	+	+
Fleischer, 2019 (peanut)	+	+	+	+	+	+	+
Jones, 2016 (peanut)	?	?	?	?	+	?	+
Jones, 2017 (peanut)	?	?	?	?	+	+	+
Moos, 2014 (grass-pollen)	?	?	?	?	+	?	+
Sampson, 2017 (peanut)	+	+	+	+	+	?	+
Senti, 2009 (grass-pollen)	+	+	+	+	+	?	+
Senti, 2012 (grass)	?	–	?	?	+	?	+
Spergel, 2019 (cow milk)	+	+	+	+	+	+	+

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

any TRAE (RR 1.48, 95% CI 0.81–2.72; $I^2 = 98\%$) with high heterogeneity compared with placebo (low certainty evidence; Fig. 4).

Local-TRAES

Six studies reported L-TRAES [21, 22, 25, 26, 28, 29]. Meta-analysis, with a total of 605 participants, showed that EPIT had statistically significant increase in risk of local reactions (RR 1.56, 95% CI 1.03–2.36; $I^2 = 82\%$) with high heterogeneity compared with placebo (moderate certainty evidence; Fig. 5).

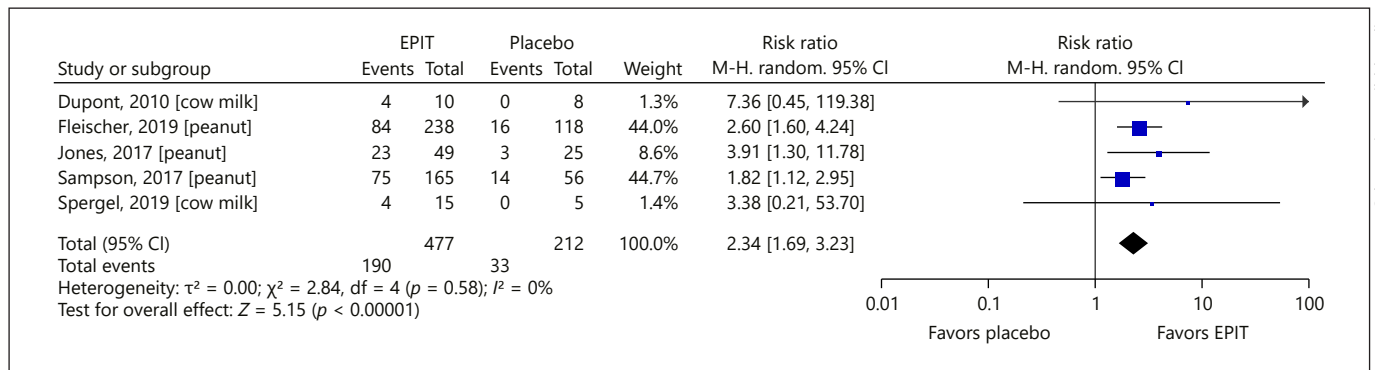


Fig. 3. RRs of desensitization following EPIT versus placebo. EPIT, epicutaneous immunotherapy; RR, risk ratio.

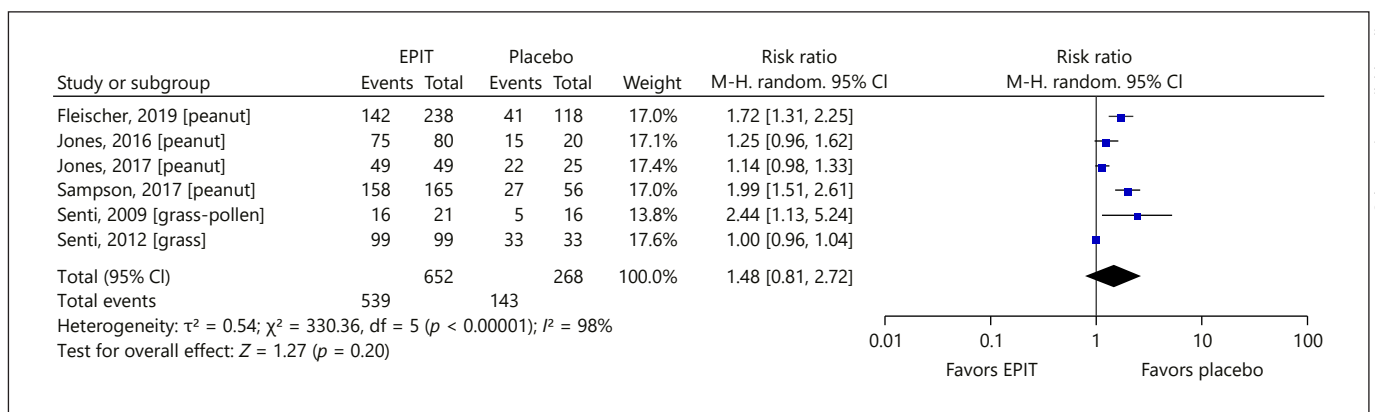


Fig. 4. Any treatment-related AEs with EPIT versus placebo. EPIT, epicutaneous immunotherapy; RR, risk ratio.

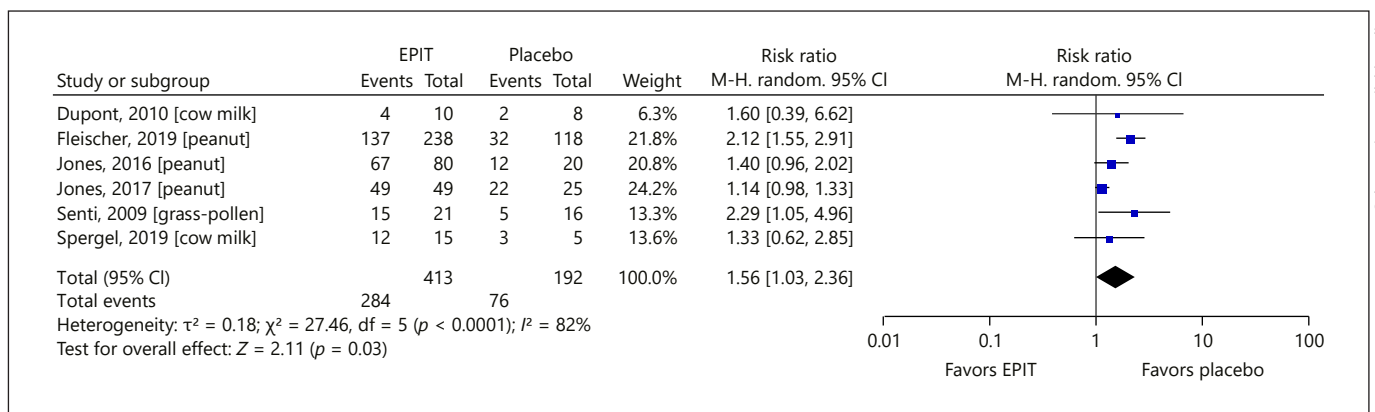


Fig. 5. Local treatment-related AEs with EPIT versus placebo. EPIT, epicutaneous immunotherapy; RR, risk ratio.

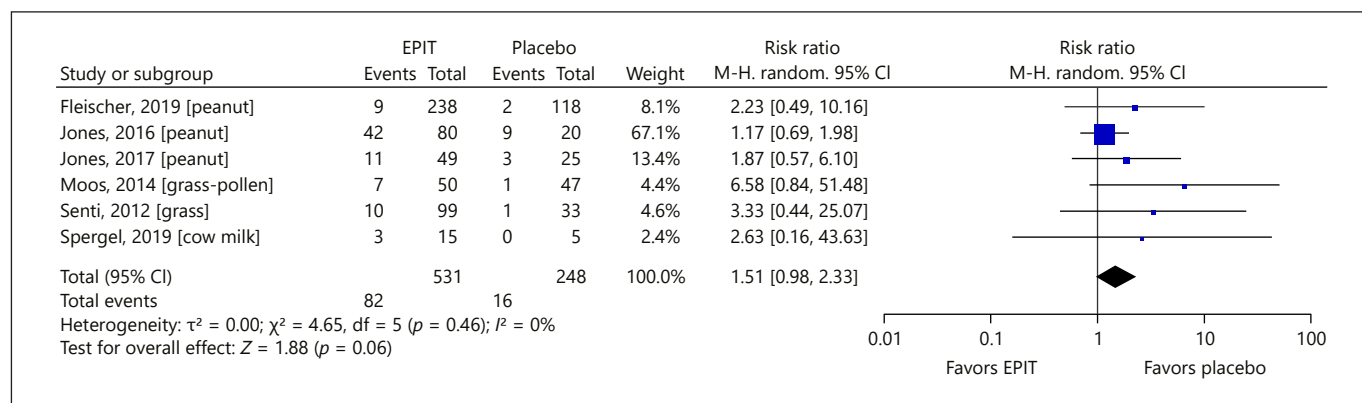


Fig. 6. Systemic treatment-related AEs with EPIT versus placebo. EPIT, epicutaneous immunotherapy; RR, risk ratio.

Table 2. Anaphylactic reactions stratified by organ systems

Organ systems	Sample size	RR (95% CI)	Grades of evidence
Skin and subcutaneous tissue disorders	531 participants	0.98 (0.54–1.78)	Low certainty
Eyes and upper respiratory disorders	431 participants	1.13 (0.40–3.21)	Moderate certainty
Lower respiratory disorders	431 participants	0.90 (0.28–2.83)	Moderate certainty
Gastrointestinal disorders	138 participants	1.28 (0.38–4.27)	Moderate certainty

RR, risk ratio.

Systemic-TRAEs

Six studies reported S-TRAEs [23–26, 28, 29]. Meta-analysis, with a total of 779 participants, showed that EPIT had no statistically significant increase in risk of systemic reactions (RR 1.51, 95% CI 0.98–2.33; $I^2 = 0\%$) with low heterogeneity compared with placebo (very low certainty evidence; Fig. 6).

Meta-Analysis of Secondary Outcomes

Anaphylactic Reactions Stratified by Organ Systems

Anaphylactic reactions stratified by organ systems were summarized in Table 2. There was no statistically significant increase in risk of skin and mucocutaneous, eyes and upper respiratory, lower respiratory, or gastrointestinal reactions.

Serious AEs

Nine studies reported SAEs [21–29]. Meta-analysis, with a total of 1,055 participants, showed that EPIT had no statistically significant increase in risk of SAEs (RR 0.81, 95% CI 0.34–1.92; $I^2 = 0\%$) with low heterogeneity compared with placebo (moderate certainty evidence; Fig. 7).

The Use of Rescue Medications

Seven trials reported the use of rescue medications. Two trials [20, 26] were removed for the author did not provide original data. One study reported the use of epinephrine and the other 4 studies reported the use of corticosteroids and antihistamines. The pooled data ($n = 643$) suggested that EPIT compared with placebo did not increase the risk of rescue medication uses (RR 2.13, 95% CI 0.64–7.13; $I^2 = 56\%$) with high heterogeneity compared with placebo (low certainty evidence; Fig. 8).

Serum sIgE

Five studies reported the results of sIgE [22, 25–28]. Only 2 trials reported that median sIgE levels increased numerically over the first 3–6 months in patients treated with peanut patches, followed by a gradual decrease to near baseline levels at month 12. The others reported no statistically significant increase of sIgE in EPIT compared with placebo group. Of the 5 trials, 2 studies [25, 26] did not provide original data and another 2 studies [27, 28] described sIgE level by median and interquartile range. Thus, we could not perform meta-analysis.

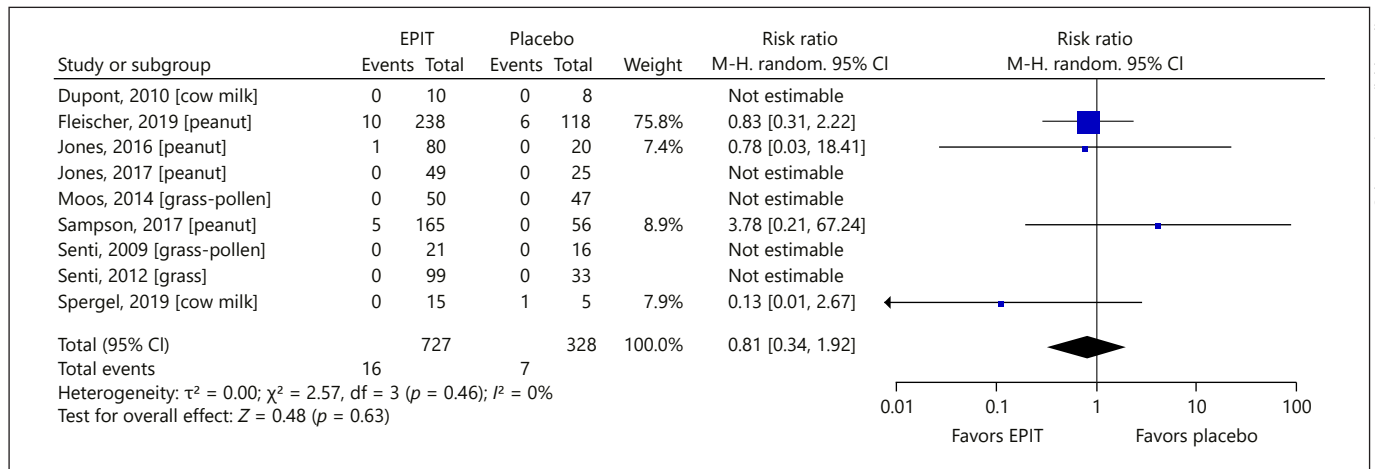


Fig. 7. SAEs with EPIT versus placebo. EPIT, epicutaneous immunotherapy; RR, risk ratio.

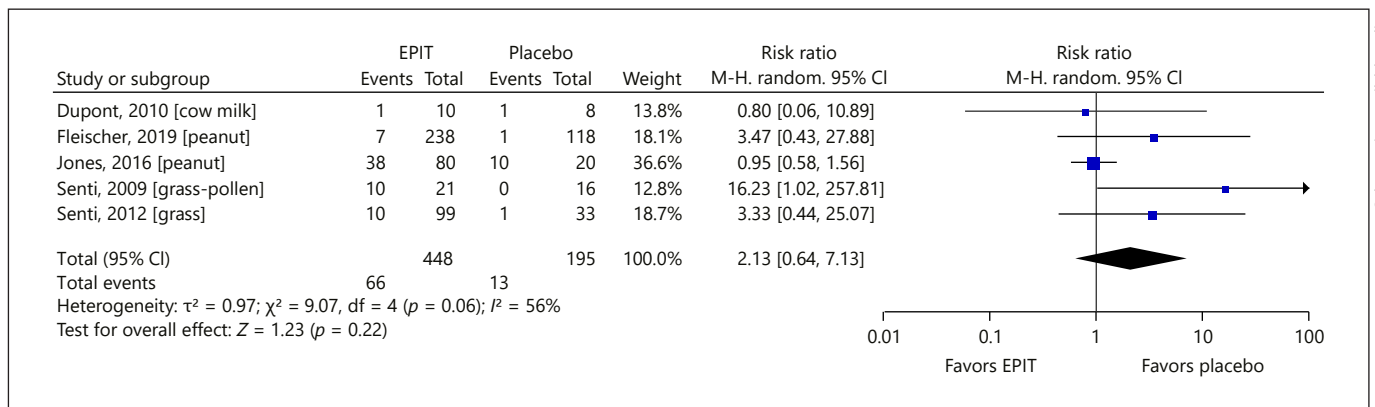


Fig. 8. The use of rescue medications with EPIT versus placebo. EPIT, epicutaneous immunotherapy; RR, risk ratio.

Serum-Specific IgG4

Three studies reported the results of serum IgG4 levels [26–28]. Peanut-specific IgG4 levels increased progressively in peanut EPIT group over the treatment duration time in the 3 studies. And significant increase of IgG4 levels was observed in peanut EPIT group compared with placebo as well. Of the 3 trials, one study [26] did not provide original data, one study [28] described IgG4 level by median and interquartile range, and the other [27] described IgG4 level by median and 95% CI. Thus, we could not perform meta-analysis.

Subgroup Analyses

We conducted subgroup analyses to investigate whether the effects of primary outcomes would differ according to allergen types, pathomechanism, age, and therapeutic dose (Table 3). However, because of limited data, the subgroup analyses based on therapeutic dose were not conducted. Subgroup analyses of desensitization based on allergen types (cow milk versus peanut) revealed that only epicutaneous peanut immunotherapy improved the tolerance to peanut significantly (RR 2.29, 95% CI 1.64–3.21; $I^2 = 4\%$). The subgroup analyses based on pathomechanism revealed that EPIT improved the tolerance to allergic food significantly in IgE-mediated peanut and cow milk allergy (RR 2.33, 95% CI 1.68–3.22; $I^2 = 0\%$). And sub-

Table 3. Subgroup analyses

	Sample size	RR (95% CI)	I^2 , %
<i>Desensitization</i>			
Allergen types			
Cow milk	2 RCTs; 38 participants	4.97 (0.70–35.41)	0
Peanut	3 RCTs; 651 participants	2.29 (1.64–3.21)	4
Age, years			
<12	4 RCTs; 540 participants	2.85 (1.92–4.24)	0
≥12	2 RCTs; 129 participants	1.09 (0.60–1.97)	0
Pathomechanism			
IgE mediated	4 RCTs; 669 participants	2.33 (1.68–3.22)	0
Non-IgE mediated	1 RCTs; 20 participants	3.38 (0.21–53.70)	Not estimable
<i>TRAE</i>			
Allergen types			
Grass pollen	2 RCTs; 169 participants	1.55 (0.13–18.49)	98
Peanut	4 RCTs; 751 participants	1.47 (1.06–2.05)	88
<i>L-TRAE</i>			
Allergen types			
Grass pollen	1 RCTs; 37 participants	2.29 (1.05–4.96)	Not estimable
Cow milk	2 RCTs; 38 participants	1.39 (0.71–2.71)	0
Peanut	3 RCTs; 530 participants	1.49 (0.85–2.61)	92
<i>S-TRAE</i>			
Allergen types			
Grass pollen	2 RCTs; 229 participants	4.65 (1.10–19.64)	0
Cow milk	1 RCTs; 20 participants	2.63 (0.16–43.63)	Not estimable
Peanut	3 RCTs; 530 participants	1.33 (0.84–2.10)	0
RCTs, randomized controlled trials; TRAE, treatment-related adverse event; L-TRAE, local-treatment-related adverse event; S-TRAE, systemic-treatment-related adverse event.			

group analyses based on the age of the population studied (children <12 vs. children ≥12 years old and adults) revealed that tolerance was significantly improved only for children <12 years (RR 2.85, 95% CI 1.92–4.24; $I^2 = 0\%$). Subgroup analyses also revealed that epicutaneous peanut immunotherapy was associated with increased risk of TRAE (RR 1.47, 95% CI 1.06–2.05; $I^2 = 88\%$). As for L-TRAE and S-TRAE, subgroup analyses revealed that only epicutaneous grass-pollen immunotherapy significantly increased the risk of L-TRAE (RR 2.29, 95% CI 1.05–4.96) and S-TRAE (RR 4.65, 95% CI 1.10–19.64; $I^2 = 0\%$).

Sensitivity Analysis

Sensitivity analyses were conducted for the primary outcomes by removing studies with high or unclear risk of selection, performance, detection, or attrition bias. Removing all studies with high or unclear risk of bias did not change the result of desensitization and S-TRAE. But, EPIT had significantly increased risk of TRAE (RR 1.87, 95% CI 1.56–2.26; $I^2 = 0\%$; 614 participants) and L-TRAE

(RR 2.02, 95% CI 1.54–2.65; $I^2 = 0\%$; 413 participants) with low heterogeneity (Fig. 9).

Publication Bias

The results of the Egger's test ($p = 0.24$) and Begg's test ($p = 0.81$) suggested that there was no statistically significant publication bias of desensitization. Egger's test ($p = 0.55$) and Begg's test ($p = 0.71$) for TRAE as well as Egger's test ($p = 1.00$) and Begg's test ($p = 0.99$) for L-TRAE suggested that there were no statistically significant publication bias of TRAE and L-TRAE as well. For S-TRAE, Egger's test ($p = 0.02$) and Begg's test ($p = 0.13$) suggested that there might be publication bias.

Discussion

This systematic review and meta-analysis suggested that EPIT might be effective in raising the threshold of reactivity to peanut or cow milk protein in patients with pea-

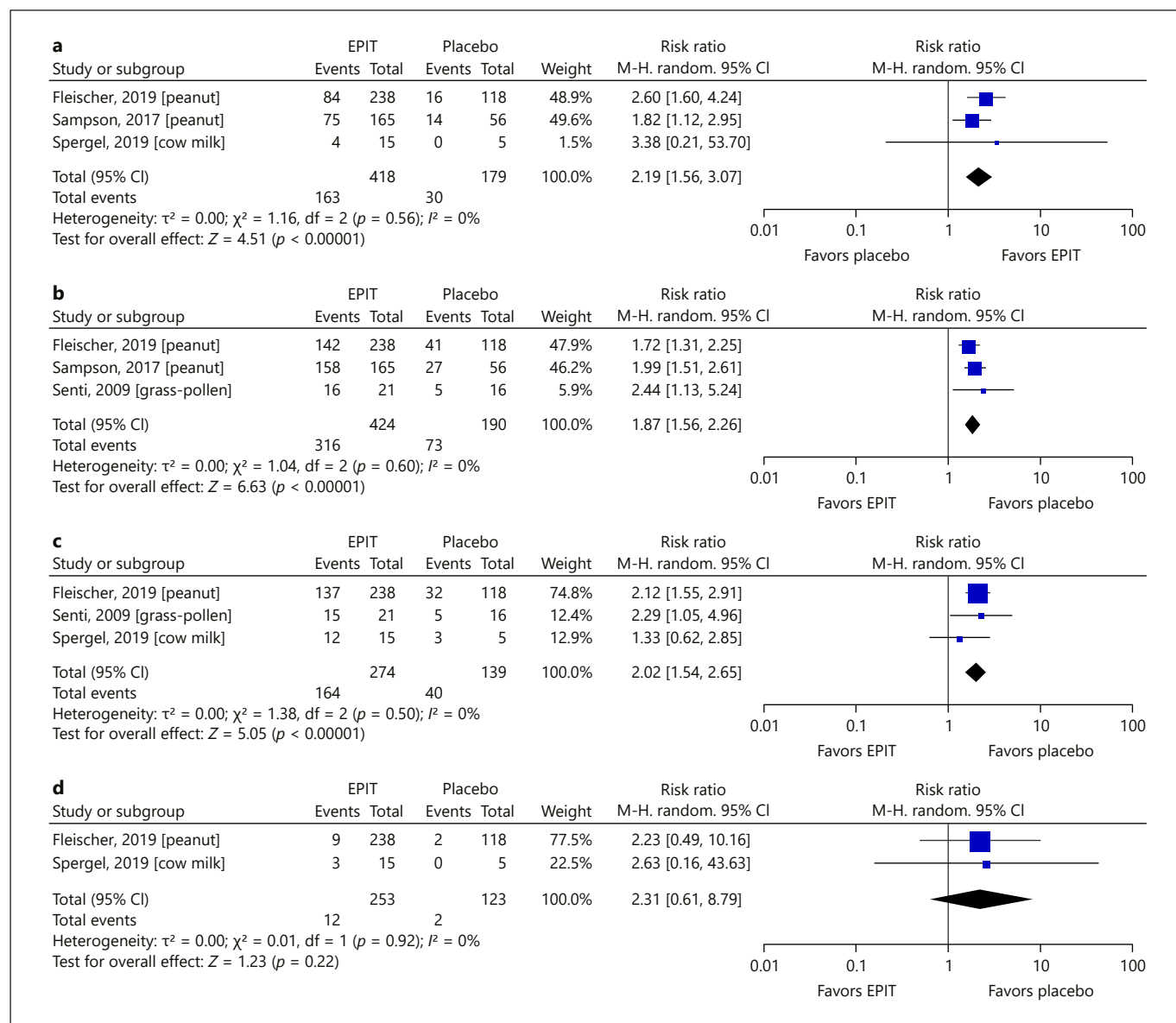


Fig. 9. Sensitivity analyses of (a) desensitization, (b) treatment-related AEs, (c) local treatment-related AEs, and (d) systemic treatment-related AEs. EPIT, epicutaneous immunotherapy; RR, risk ratio.

nut or cow milk allergy compared with placebo, with the greatest effect noted among the younger (<12 years) and peanut allergic participants. Our findings also indicated that EPIT could increase the chance of local skin reactions with moderate certainty evidence. However, there was very low certainty evidence that EPIT might not significantly increase the risk of S-TRAEs. There were low to moderate certainty evidence that compared with placebo patch, EPIT might not increase the chance of anaphylactic reactions, SAEs, and the use of rescue medications.

The efficacy of EPIT in patients with food allergy in our study agreed with other AIT. A recent meta-analysis enrolled 25 trials about oral immunotherapy (OIT) and 5 studies about sublingual immunotherapy (SLIT) for food allergy demonstrated a substantial benefit in terms of desensitization (RR 0.19, 95% CI 0.12–0.29), and its subgroup analysis based on the age also revealed a substantial benefit only for children (RR 0.19, 95% CI 0.12–0.30), but not for adults studies [30]. As for our study, subgroup analyses according to allergens revealed that only peanut-

allergic patients had significant treatment response with high certainty evidence. The result of cow milk allergic patients was insignificant, which may be due to small sample sizes and varied criteria for good treatment effect. Subgroup analysis also revealed different therapeutic response between the older (children ≥ 12 years and adults) and the younger (< 12 years), but the majority of participants were peanut allergic. Only children < 12 years had significant treatment response with high certainty evidence. The reason for the result remained unclear. Multicenter RCTs had confirmed the dose of EPIT had influence to its efficacy [27]. Studies in murine models have shown that higher doses and exposure to larger surface areas increase efficacy [31]. Therefore, factors such as possibly less immunologic plasticity in older patients and relatively lower dose on a per-weight/surface area may contribute to it. So, more studies are needed to optimize EPIT for the older. Because of unavailable original data, the clinical efficacy of EPIT for grass-pollen allergic diseases was unclear. Therefore, more studies on grass-pollen allergy are needed as well.

Epicutaneous immunization targeting the immunologically rich milieu of the skin could modulate the T cell response [32, 33]. Preclinical studies in mice and piglets reported EPIT could be effective in peanut induced eosinophilic gastrointestinal disorders [34, 35]. In our study, one trial [29] was about milk-induced EOE that is reported to be non-IgE-mediated food allergy and mainly associated with T cell response [36]. In this pilot study of pediatric patients with EOE given EPIT with Viaskin milk or placebo for 11 months, there was no significant difference between groups for the maximum eosinophil count at the end of the study. However, in the per-protocol analysis, the Viaskin milk patch group had lower eosinophil count and improvement in endoscopy scores on the reintroduction of milk compared to the placebo. At study completion, 47% of patients who continued open-label Viaskin milk for an additional 11 months had mean eosinophil count $< 15/\text{hpf}$. Therefore, EPIT might work on non-IgE-mediated diseases as well, but multicenter RCTs are needed to confirm this finding.

Though oral food challenges and specific symptom scores were used as the primary tool to determine clinical effect, it remained a surrogate measure. It could not predict a patient's future risk, frequency, and severity of allergic reactions in the real world. Therefore, the National Institute of Allergy and Infectious Diseases and FDA recommended patient-centered outcomes to estimate the effect of interventions for food allergies, such as the level of IgE antibodies, the risk of allergic reactions, and SAEs [5,

18]. Our review demonstrated the need for such approaches.

A meta-analysis focused on OIT and SLIT for food allergy demonstrated that the chance of local (RR 1.88, 95% CI 1.42–2.48) and systemic allergic reactions (RR 1.09, 95% CI 1.00–1.19) increased significantly. Another high-quality meta-analysis also suggested that current peanut OIT approaches increased the chance and frequency of allergic reactions, including anaphylaxis, need of epinephrine, and SAEs [37]. Our meta-analysis showed that EPIT might increase the risk of AEs especially in subjects with peanut allergy. But it was mainly associated with local skin reactions. No significant increase was observed in systemic reactions, anaphylactic reactions, or SAEs in EPIT group. But the risk of systemic reactions in EPIT was uncertain because the certainty of evidence was very low. Subgroup analysis of L-TRAE for peanut allergy suggested that EPIT did not significantly increase the risk of local reactions with high heterogeneity. The result might be related to different therapeutic dose and treatment time of EPIT. Subgroup analysis also suggested that only EPIT for grass-pollen allergy might significantly increase the risk of systemic reactions. But it was based on small sample, maybe the evidence was insufficient. Based on current evidences, comparing with OIT and SLIT for food allergy, EPIT is relatively safer. As for safety of EPIT for grass-pollen allergy, more studies are needed.

There are several strengths of this review. First, it is the first meta-analysis evaluating effects and safety of EPIT for allergic diseases that could provide rigorous evidence for EPIT as a novel AIT. Second, EPIT was better evaluated in clinical practice by comprehensive patient-important outcomes mentioned above. Third, all included studies are RCTs and 4 of them are multicenter RCTs, the high quality of included studies proves the reliability of this meta-analysis. There are several potential limitations need to be noted as well. First, despite including all available RCTs, the numbers and sample size of included studies were small. Second, the characteristics of the intervention had obvious clinical heterogeneity. Because of the widely ranged EPIT time and dose, it was difficult to make a subgroup analysis to explore the most appropriate intervention time and dose. Third, we could not obtain data from some studies that did not fully report all their data for all the study participants. We contacted authors for additional information on outcome data but did not receive satisfactory responses. Therefore, meta-analysis of 3 outcomes could not be conducted. The efficacy of EPIT could not be completely estimated. Fourth, it is another limitation of our study that the test drug of 5 studies re-

porting desensitization came from the same company (Viaskin, DBV Technologies). Rigorous RCTs using other company's product that evaluate patient-important outcomes are needed in the future.

Conclusion

The systematic review and meta-analysis provide high certainty evidence that EPIT could achieve desensitization in patients with peanut allergy, with the greatest effect noted in children <12 years. The efficacy of EPIT for cow milk allergy and grass-pollen allergy remains uncertain. EPIT might promote more local skin reactions with moderate certainty evidence. As for the systemic AEs, anaphylactic reactions, SAEs, and uses of rescue medication, there are no significantly increased risks of them after receiving EPIT with very low to moderate certainty. Because of limited numbers of studies and heterogeneity, these findings should be interpreted with caution. More well-designed RCTs with larger sample sizes need to be conducted to investigate the benefits and AEs of EPIT in the older (children ≥12 years and adults) and other allergic diseases.

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Author Contributions

L.X.: is responsible for conception, data search, inclusion and exclusion of studies, data extraction, assessment of methodological quality, data analysis, and writing the manuscript. J.L. and W.C.: are responsible for inclusion and exclusion of studies, data extraction, and data analysis. Y.L.: is responsible for data search, inclusion and exclusion of studies, assessment of methodological quality, and checking the data of the outcomes. J.D.: is responsible for supervision, interpretation of results, as well as checking the first and the final versions of the manuscript.

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