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Epicutaneous immunotherapy for food allergy: a systematic review and meta-analysis

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Abstract

Background There is ongoing debate about the safety and efficacy of epicutaneous immunotherapy (EPIT) in treating food allergies. The systematic review and meta-analysis aimed to evaluate the safety and efficacy of EPIT.

Methods We systematically searched international trial registers (ClinicalTrials.gov), PubMed, Embase, the Cochrane Central of Controlled Trials (CENTRAL), and Web of Science from the inception of the database until June 25, 2023. Two authors independently screened potential studies based on the following criteria: food allergy, epidermal immunotherapy, and randomized controlled trials(RCTs). The risk-of-bias assessment was performed using the Cochrane risk-of-bias 2 (ROB 2) tool. The primary outcomes included desensitization, local adverse events, systemic adverse events, and quality of life. Secondary outcomes included epinephrine utilization, topical medication utilization, and severe adverse events. We assessed certainty of evidence by the GRADE approach.

Results Ten studies involving 1970 participants were included. Ten high-quality RCTs focusing on peanut allergy and cow's milk allergy were included in the analysis. The meta-analysis revealed that EPIT promoted desensitization in patients with food allergy (*RR* 2.11, 95% *CI* 1.72–2.58; $I^2 = 0\%$, high certainty), particularly in aged ≤ 11 years (*RR* 3.84, 95% *CI* 2.39–6.26; $I^2 = 34\%$). Additionally, treatment duration ≥ 52 weeks was found to increase immune tolerance (*RR* 3.37, 95% *CI* 2.39–4.75; $I^2 = 13\%$). Patients who undergo EPIT treatment not only raised the local adverse reactions (*RR* 1.63, 95% *CI* 1.10–2.41; $I^2 = 82\%$, low certainty) but also raised systemic adverse reactions (*RR* 1.52, 95% *CI* 1.01–2.28; $I^2 = 0\%$, high certainty).

Conclusion After EPIT treatment, patients with food allergy can effectively increase their immune tolerance to food. However, it also significantly increases mild-to-moderate anaphylaxis. There is limited data on the impact of EPIT on quality of life and other food allergic diseases, indicating a need for further research.

Keywords Food allergy, Epicutaneous immunotherapy, Systematic reviews, Meta-analyses

Introduction

The prevalence of food allergy has been steadily increasing in industrialized countries over the past three decades, highlighting a growing concern as it affects no less than 2–4% of individuals with such sensitivities [1–3]. The unpredictable allergic reactions that can result from unintentional contact with allergenic foods have a considerable detrimental effect on both patients and their families [4, 5]. The impact of food allergies on patients encompasses not only the economic burden of healthcare but also the physical impairment caused by

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allergic reactions and the psychological strain of constantly avoiding allergenic foods [6–9].

Avoidance of allergen exposure and preparation for potential allergic reactions are the current strategies for managing food allergies [10]. Nevertheless, this poses a major challenge for individuals, as they must be watchful of all foods that are allergic and any potential risks, which can be difficult for them and their families [11, 12]. Therefore, it is imperative to explore a safe and effective treatment method. Epicutaneous immunotherapy (EPIT) is a method of inducing immune tolerance and alleviating allergy-related symptoms through the epidermal delivery system. Despite early reports of successful cases of epidermal immunotherapy for food allergy in the early twentieth century, this therapeutic approach has not undergone further development [13, 14]. In recent years, the increasing prevalence of life-threatening food allergies has rekindled interest in epidermal immunotherapy. To date, several RCTs investigating epidermal immunotherapy for food allergy have been published; however, a comprehensive systematic synthesis of relevant data is yet to be conducted. Notably, certain findings from these studies suggest limited efficacy of EPIT in the treatment of food allergy [15]. Therefore, it is imperative to conduct a systematic review of EPIT for food allergy. The chief purpose of this review is to appraise the effectiveness and safety of EPIT in comparison to non-EPIT for managing food sensitivity.

Methods

This systematic review and meta-analysis is registered in PROPSPERO database (ID: CRD42023438950). This study protocol is reported following the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [16].

Search strategy

From inception until June 25, 2023, we conducted an exhaustive search of international trial registry (ClinicalTrials.gov), PubMed, Embase, CENTRAL, and Web of Science. The literature search was initiated on June 25th and concluded on the same day. At first, the search strategy came into being in the MeSH database journals of PubMed and then applied to the other databases (a complete list of search terms is provided in Appendix 1). To avoid missing any potential studies, we meticulously reviewed the references of all included research literature and reviews. No linguistic restrictions were imposed, and non-English literature was translated into English literature using Google Translate.

Eligibility criteria

We included RCTs that investigated the effects of EPIT in both pediatric and adult populations with food allergies. The eligible literature must have met the following criteria

1. Population: Individuals with physician-diagnosed food allergies or a convincing clinical history of food allergies, such as peanut, milk, nuts, and other food allergies.
2. Intervention and comparison: The intervention group received EPIT alone; the control group received placebo patches and avoided allergen exposure.
3. Outcome:

   Primary outcome

   1) Desensitization: The response rate of participants who exhibited positive reactivity to the allergenic food following EPIT intervention was measured (i.e., the ability to consume food containing the allergen safely).
   2) Local adverse reactions: Local adverse reactions refer to skin responses that occur at the patch application site, such as pruritus, erythema, and swelling.
   3) Systemic adverse reactions: The definition of systemic adverse reactions was consistent with the grading system for adverse effects established by the World Allergy Organization [17, 18].
   4) Quality of life (QOL)

   Secondary outcomes

   1) Serious adverse events
   2) Epinephrine utilization
   3) Topical medication utilization (i.e., active amelioration of symptoms of local adverse reactions)
   4) Allergic reaction of organ systems
   5) Immune results (i.e., IgE, IgG4, and skin prick test)
4. Study types: All RCTs were selected in these four databases.

Data collection

Two authors (X. X., S. C.) identified potential studies through a meticulous examination of headings and abstracts, followed by a comprehensive review of full

texts based on the predetermined eligibility criteria to select the required articles. A self-designed data extraction form was utilized. The following information was extracted: Basic information (first author, year of publication, contact information of author), type of RCT, characteristics of participants (age, gender, location, duration, dose of intervention group, diagnostic criteria), and outcomes (variables, change values for continuous data). If we had different opinions about data selected, we resolved them through discussion. If not, J. H. made a judgement to solve it. If the data extraction results were consistent after the two authors independently extracted four papers, this extraction template was used for subsequent papers.

Data analysis

For this meta-analysis, we used intention-to-treat analyses to combine data (RevMan 5.4). Due to the inevitable methodological and clinical heterogeneity of each study, we directly used the random-effects model for analysis. For binary variables, analyzing data involved calculating the risk ratio (RR) and the 95% confidence interval (95% CI). For continuous variables, no data analysis was performed because the included data could not be combined. The subgroup analysis was performed for four primary outcomes based on age, study population, length of treatment, and type of anaphylactogen. The sparse data and the cumulative analysis of the data in the meta-analysis increased the risk of random errors. We used trial sequential analysis to assess the statistical robustness of the available evidence and to avoid type 1 and type 2 errors. We performed trial sequential analyses on all outcomes, in order to calculate the required information size (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries. A more comprehensive explanation of trial sequential analysis can be found in the Sequential Analysis manual [19].

GRADE assessment

The qualitative grading of the results from each analysis was conducted in accordance with the GRADE guidelines [20]. In the event of risks associated with publication bias, study limitations, inconsistencies, indirectness, or imprecision, we address them by downgrade. Therefore, the quality of evidence was divided into four levels (very low, low, moderate, high) to indicate the level of confidence in the accuracy of the effect estimates.

Results

Literature search results

Our search yielded a total of 3765 potentially relevant records, with 15 being registered in the international trial registry. After removing 1401 duplicates, a total of 2349 records were identified using document management software (EndNote 20). Following title and abstract screening, we excluded 2297 irrelevant records and proceeded to conduct full-text screening of 67 articles. Eventually, after meticulous evaluation, we selected 10 RCTs for inclusion in our study [15, 21–29]. Among the initially identified 15 relevant records in the international trial registers, we discovered that 8 published papers were duplicated. Additionally, three studies were ongoing, while one had completed but lacked available data. Furthermore, three experiments had completed; however, no relevant data or published literature was accessible (Fig. 1).

Characteristics of included studies

The systematic reviews and meta-analysis comprised a total of 10 studies, with the study populations predominantly sourced from Europe, North America, and Oceania (Table 1). Ten RCTs encompassed a sample size of 1870 individuals ranging in age from 3 months to 55 years. Of the 10 studies, 6 focused solely on children [15, 24–26, 28, 29], while the remaining 4 included both children and adults [21–23, 27]. In terms of allergen types, two studies were conducted on cow's milk allergy using EPIT doses of 500 μg and 1 mg, respectively [15, 25]. The remaining eight studies focused on peanut allergy with EPIT doses ranging from 20 to 500 μg [21–24, 26–29]. Efficacy and safety outcomes were compared between EPIT and non-EPIT across varying durations, ranging from 2 weeks to 1 year.

Assessing risk of bias and grading the evidence

The RoB 2 tool for randomized trials was employed to assess the risk of bias in the 10 studies included. Out of these, five studies [15, 21, 22, 26, 27] were deemed to have a low risk, whereas the other five [23–25, 28, 29] were identified as having some concerns (Appendix 2). Although the sample size of some included studies was small, the RoB 2 assessment results indicated low-moderate risk in each domain. Therefore, the methodological and reporting quality of the included studies was high. With the exception of two studies that lacked previously published protocols, the remaining eight studies [21–25, 27–29] had established experimental protocols on international trial registers. The results of these eight experiments were reported in accordance with a preexisting protocol. The certainty of the evidence as assessed using GRADE is presented in Table 2.

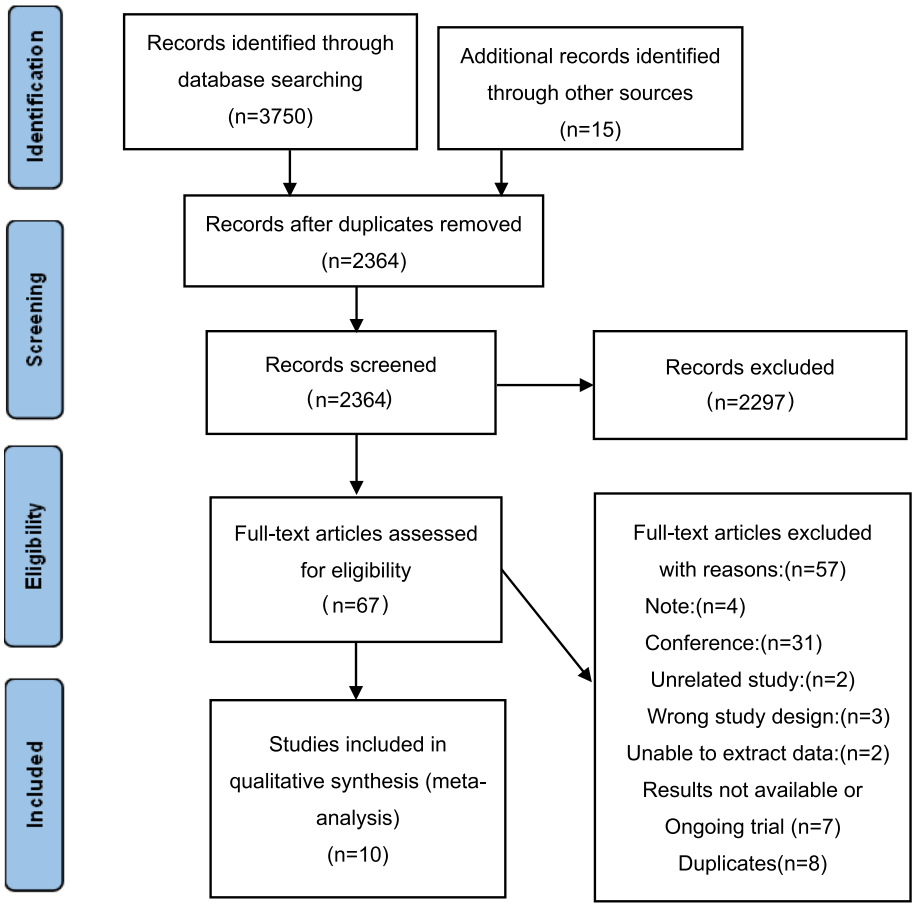

Fig. 1 Flowchart for study selection

Primary outcomes

Desensitization

Seven studies (1120 participants) reported data on desensitization [15, 22–25, 27, 29]. One study confirmed a positive response by demonstrating a decrease in eosinophil count to less than 15 eos/hpf [24]. Six studies showed an increase in threshold in participants with food allergy after active treatment [15, 22–24, 27, 29]. The meta-analysis revealed that the group receiving EPIT exhibited increased tolerance to food allergy compared with non-EPIT (*RR* 2.11, 95% *CI* 1.72–2.58; $I^2 = 0\%$, high certainty) (Fig. 2).

Local adverse reactions

Seven studies reported local adverse reactions, most of which were mild and confined to the site of application [15, 21, 22, 24, 25, 28, 29]. The pooled data (1305 participants) suggested that EPIT compared with non-EPIT increased risk of local adverse reaction (*RR* 1.63,95% *CI* 1.10–2.41; $I^2 = 82\%$, low certainty) (Fig. 3).

Systemic adverse reactions

Systemic adverse reactions were reported in 6 studies (1305 participants) [21, 22, 24, 25, 28, 29]. Systemic adverse effects were mild to moderate. Compared with non-EPIT, EPIT had clear evidence to increase risk of systemic adverse reactions (*RR* 1.52, 95% *CI* 1.01–2.28; $I^2 = 0\%$, high certainty) (Fig. 4).

Quality of life

Only two [25, 26] RCTs reported the impact of EPIT on QOL of participants, both utilizing self-evaluation and parental proxy evaluation. One was evaluated using the Food Allergy Quality of Life Questionnaires scale, while the other underwent assessment with the PedsQL EoE Module scale [30]. Data pooling was not possible due to incomplete information provided in one of the articles [25]. Nonetheless, both studies demonstrated that EPIT had a positive impact on the QOL of participants.

Secondary outcome

Epinephrine utilization

Epinephrine use was reported in 5 studies comprising 1150 participants [21, 22, 25, 28, 29]. Compared with

Table 1 Description of the included studies ($n = 10$)

	Methods	Country	Participants			Intervention	Comparison	Duration	Outcomes
	Design		Age (years)	Counts	Diagnose				
Dupont et al., 2010	Bicenter RCT	France	3 months–15 years	18	Clinical diagnosis	Viaskin (1 mg)	Placebo	3 months	DE, LAR, ES, SAE, TMS, IgE
Jones et al., 2016	RCT	America	6–50	100	Clinical diagnosis	Viaskin (20, 100, 250, 500 μg)	Placebo	2 weeks	LAR, SAR, ES, TMS, IgE, SPT, SAE
Jones et al., 2017	Multicenter RCT	America	4–25	75	Clinical diagnosis	Viaskin (100, 250, 500 μg)	Placebo	52 weeks	DE, LAR, SAR, ES, SAE, IgE, IgG4, SPT
Sampson et al., 2017	Multicenter RCT	North America, Europe	6–55	221	Clinical diagnosis	Viaskin (50, 250, 500 μg)	Placebo	12 months	DE, ES, SAE, IgE, IgG4, SPT
Fleischer et al., 2019	Multicenter RCT	Australia, Canada, Germany, Ireland, USA	4–11	356	Physician diagnosis	Viaskin 250 μg	Placebo	12 months	DE, LAR, SAR, SAE
Spergel et al., 2020	RCT	USA	4–17	20	Physician diagnosis	Viaskin (500 μg)	Placebo	9 months	DE, LAR, SAR, SAE, QOL
Scurlock et al., 2021	Multicenter RCT	USA	4–25	69	Clinical diagnosis	Viaskin (100, 250 μg)	Placebo	52 weeks	DE, IgE, IgG4, SPT
DunnGalvin et al., 2021	Multicenter RCT	USA, Europe, Canada, Australia	4–11	356	Physician diagnosis	Viaskin 250 μg	placebo	12 months	QOL
Pongracic et al., 2021	Multicenter RCT	Canada, USA	4–11	393	Physician diagnosis	Viaskin 250 μg	Placebo	6 months	LAR, SAR, ES, SAE, IgE, IgG4
Greenhawt et al., 2023	Multicenter RCT	USA, Canada, Australia Europe	1–3	362	Physician diagnosis	Viaskin (100, 250 μg)	Placebo	12 months	DE, LAR, SAR, ES, TMS, SAE

DE Desensitization, *LAR* Local adverse reactions, *SAR* Systemic adverse reactions, *SAE* Serious adverse events, *ES* Epinephrine use, *TMS* Topical medication use, *SPT* Skin prick test

Table 2 Summary of results according to GRADE

Outcome	Sample size	Risk radio (95% *CI*)	Absolute effect (95% *CI*)	Certainty of the evidence
Desensitization	1120 (7 RCTs)	2.11 (1.72–2.58)	Two-hundred thirty-eight more per 1000 (154 more to 339 more)	High
Local adverse reaction	1393 (7 RCTs)	1.63 (1.10–2.41)	One-hundred forty-seven more per 1000 (23 more to 330)	Low[a]
Systemic adverse reaction	1305 (6 RCTs)	1.52 (1.01–2.28)	Twenty-six more per 1000 (0 fewer to 63 more)	High
Epinephrine utilization	1150 (5 RCTs)	1.62 (0.86–3.04)	Twenty-one more per 1000 (5 fewer to 71 more)	Moderate[c]
Topical medication utilization	873 (4 RCTs)	1.39 (1.13–1.71)	One-hundred fifty-four more per 1000 (51 more to 281 more)	High
Serious adverse reaction	1544 (8 RCTs)	1.10 (0.45–2.67)	Three more per 1000 (15 fewer to 45 more)	Low[c,d]
Respiratory/ENT	757 (4 RCTs)	0.96 (0.79–1.15)	Eleven fewer per 1000 (58 fewer to 42 more)	Moderate[c]
Gastrointestinal disorders	400 (3 RCTs)	1.19 (0.76–1.86)	Seventy-one more per 1000 (90 fewer to 322 more)	Moderate[c]
Eye disorders	739 (3 RCTs)	1.02 (0.57–1.81)	One more per 1000 (27 fewer to 50 more)	Moderate[c]
Immune system disorders	719 (2 RCTs)	2.13 (0.78–5.81)	One-hundred twenty-four more per 1000 (24 fewer to 530 more)	Moderate[c]
Psychiatric disorders	377 (2 RCTs)	0.76 (0.24–2.44)	Six fewer per 1000 (19 fewer to 35 more)	Moderate[c]

ENT ear, nose, and throat, *CI* Confidence interval. Explanations: [a]Due to high heterogeneity, it was downgraded by two grades. [b]Due to moderate heterogeneity, it was downgraded by one grade. [c]Due to the fact that confidence intervals do not exclude the possibility of no effect, it was downgraded by one grade. [d]Due to the scatter of the point estimates, it was downgraded by one grade

non-EPIT, EPIT had no clear evidence for an increased risk in the use of epinephrine (*RR* 1.62, 95% *CI* 0.86–3.04; $I^2 = 0\%$, moderate certainty) (Fig. 5).

Topical medication utilization

Three studies, comprising 873 participants, documented the utilization of topical agents for treatment

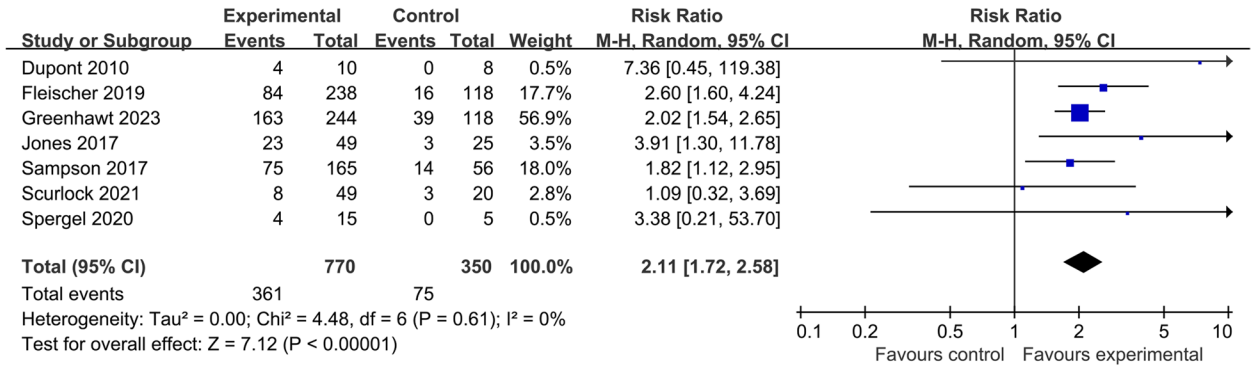

Fig. 2 Desensitization events with EPIT versus non-EPIT

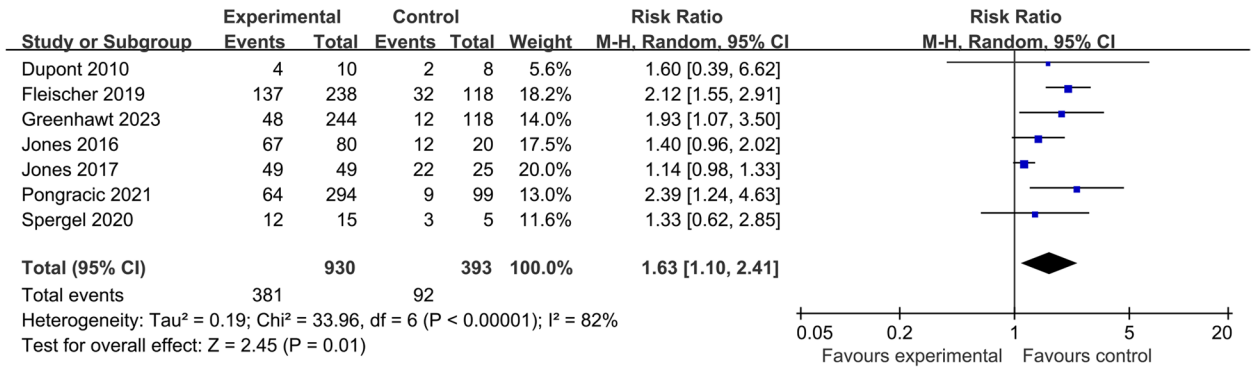

Fig. 3 Local adverse reaction events with EPIT versus non-EPIT

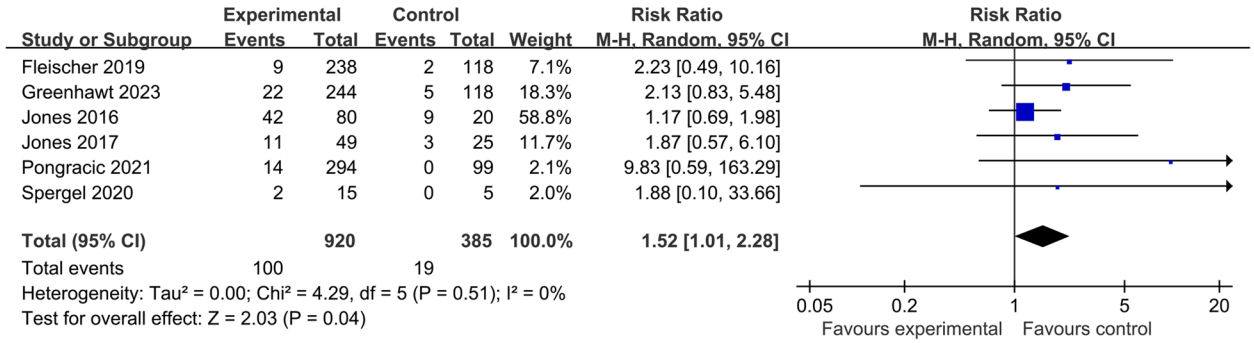

Fig. 4 Systemic adverse reaction events with EPIT versus non-EPIT

[15, 21, 28, 29]. Topical therapy entails administering steroid hormones locally to ameliorate adverse reactions. The meta-analysis suggests that EPIT had statistically significant increase risk in the use of topical agents (*RR* 1.39, 95% *CI* 1.13–1.71; $I^2 = 13\%$, moderate certainty) (Fig. 6).

Serious adverse events

Serious adverse events were defined as those resulting in death, posing a threat to life, requiring hospitalization or emergency medical intervention, or necessitating hospitalization as a preventive measure against such occurrences. Serious adverse events were reported in 8 studies comprising1544 participants [15, 21–25, 28, 29]. No deaths were reported in any of the study participants of the included studies. Compared with non-EPIT, EPIT had no clear evidence for an increased risk in serious adverse events (*RR* 1.10, 95% *CI* 0.45–2.67; $I^2 = 32\%$, low certainty (Fig. 7).

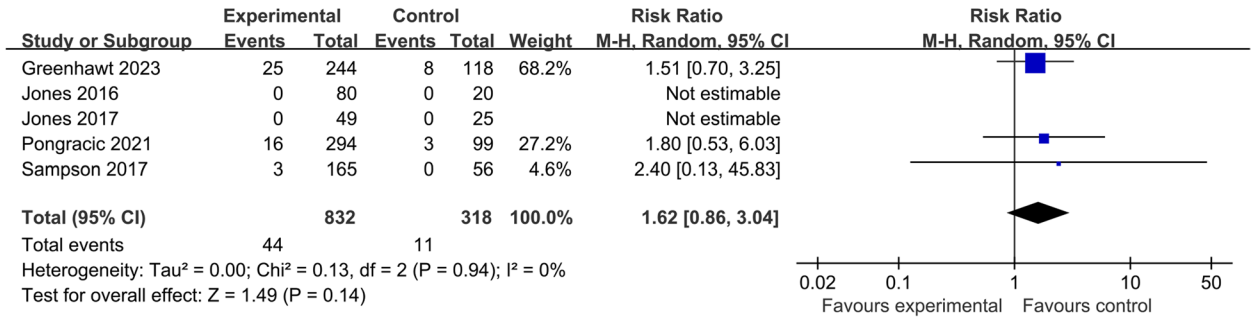

Fig. 5 The use of epinephrine with EPIT versus non-EPIT

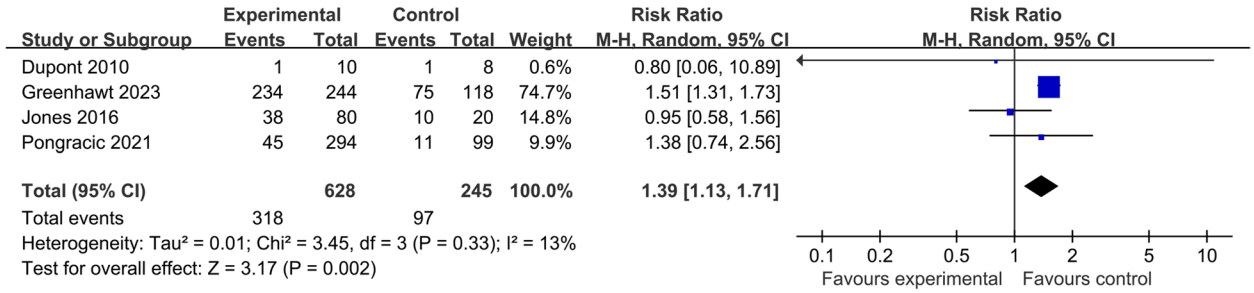

Fig. 6 The use of topical medication with EPIT versus non-EPIT

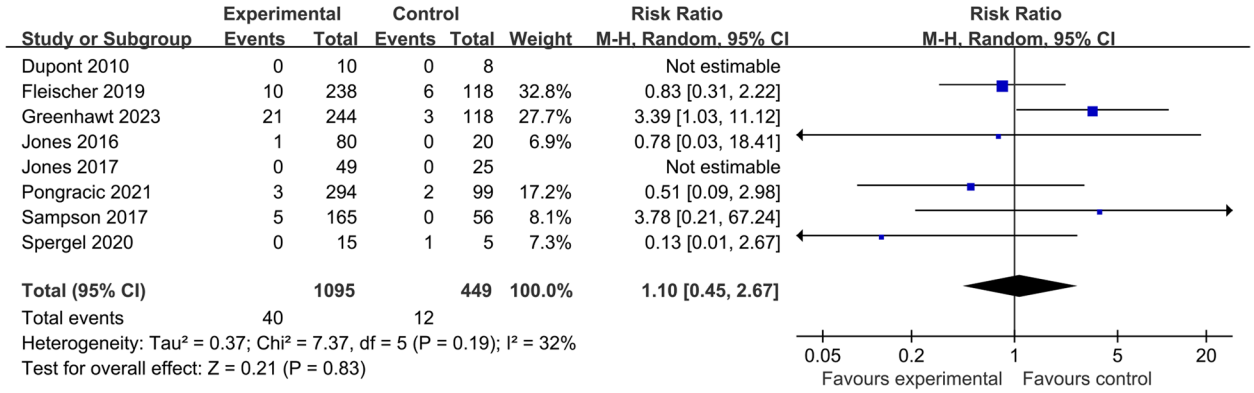

Fig. 7 Serious adverse reaction events with EPIT versus non-EPIT

Allergic reaction of organ systems

The outcome of allergic reactions caused by EPIT in multiple organ systems is summarized in Table 3. Compared with non-EPIT, EPIT had no clear evidence for an increased risk in the adverse reactions of organ system.

Table 3 Allergic reaction of organ systems

Organ system	Sample size	Risk radio (95% *CI*)	I^2
Respiratory/ENT	757 participants	0.96 (0.79–1.15)	0%
Gastrointestinal disorders	400 participants	1.19 (0.76–1.86)	13%
Eye disorders	739 participants	1.02 (0.57–1.81)	0%
Immune system disorders	719 participants	2.13 (0.78–5.81)	34%
Psychiatric disorders	377 participants	0.76 (0.24–2.44)	0%

Results of immunization

The immunological results of EPIT treatment investigated in this study encompassed alterations in serum levels of immunoglobulin (IgE, IgG4) and wheal size of skin prick test. These immune results were expressed

in various ways, with most of them being expressed as medians, which could not be combined.

Trial sequential analysis

The results of the trial sequential analysis showed sufficient information to draw conclusions except for severe side effects, allergic reactions of organ systems, and the epinephrine utilization. The size of the information required by the boundary was ignored for eye diseases, psychiatric diseases, and respiratory diseases because too little information was used. The results of the trial sequential analysis are presented in Appendix 3.

Subgroup analysis

A subgroup analysis was conducted on the primary outcomes to explore potential variations in treatment efficacy based on allergen type, age, study population, and duration of treatment. The results are presented in Table 4. For allergen types, the EPIT treatment of peanut could significantly improve immune tolerance to peanut (*RR* 3.37, 95% *CI* 2.39–4.75; $I^2=13\%$); EPIT treatment of peanut increased the risk of local adverse reactions (*RR* 3.09, 95% *CI* 2.23–4.29; $I^2=0\%$) and also increased the risk of systemic adverse reactions (*RR* 2.00, 95% *CI* 1.13–3.53; $I^2=0\%$). Subgroup analysis based on age demonstrated a significant enhancement in immune tolerance among children aged 11 years or younger (*RR* 3.84, 95% *CI* 2.39–6.16; $I^2=34\%$). For the study population, children had an increased risk of local adverse reactions (*RR* 2.96, 95% *CI* 2.11–4.14; $I^2=0\%$), while mixed populations (children and adults) were also likely to experience such reactions (*RR* 4.07, 95% *CI* 1.48–11.19; $I^2=0\%$). Children also raised the risk of systemic adverse reactions (*RR* 2.51, 95% *CI* 1.15–5.48; $I^2=0\%$). For the duration of treatment, treatment duration ≥ 52 weeks was associated with improved tolerance to food allergy (*RR* 3.37, 95% *CI* 2.39–4.75; $I^2=13\%$); treatment duration ≥ 52 weeks had an increased risk of local adverse reactions (*RR* 3.10, 95% *CI* 1.88–5.13; $I^2=24\%$), while treatment duration < 52 weeks was also likely to experience such reactions (*RR* 2.87, 95% *CI* 1.63–5.04; $I^2=0\%$). Treatment duration ≥ 52 weeks also raised the risk of systemic adverse reactions (*RR* 2.22, 95% *CI* 1.08–4.54; $I^2=0\%$).

Table 4 Subgroup analysis

	Sample size	RR (95% *CI*)	I^2
Desensitization			
Allergen type			
Milk	38	7.12 (0.80–63.45)	0%
Peanut	1082	3.37 (2.39–4.75)	13%
Age			
> 11 years	147	1.11 (0.48–2.58)	0%
≤ 11 years	935	3.84 (2.39–6.16)	34%
Duration of treatment			
≥ 52 weeks	1082	3.37 (2.39–4.75)	13%
< 52 weeks	38	7.12 (0.80–63.45)	0%
Local adverse reactions			
Allergen type			
Milk	38	2.29 (0.51–10.17)	0%
Peanut	1285	3.09 (2.23–4.29)	0%
Population			
Children only	1149	2.96 (2.11–4.14)	0%
Adult and children	174	4.07 (1.48–11.19)	0%
Duration of treatment			
≥ 52 weeks	792	3.10 (1.88–5.13)	24%
< 52 weeks	531	2.87 (1.63–5.04)	0%
Systemic adverse reactions			
Allergen type			
Milk	20	2.04 (0.08–49.68)	Not applicable
Peanut	1285	2.00 (1.13–3.53)	0%
Population			
Children only	1131	2.51 (1.15–5.48)	0%
Adult and children	174	1.57 (0.71–3.51)	0%
Duration of treatment			
≥ 52 weeks	792	2.22 (1.08–4.54)	0%
< 52 weeks	513	1.76 (0.68–4.56)	3%

Discussion

This systematic review and meta-analysis revealed that EPIT can enhance immune tolerance to food compared to placebo, particularly in children aged ≤ 11 years. According to the subgroup analysis, EPIT raised the response threshold in individuals with peanut allergy, but not in those with cow's milk allergy. EPIT, with a treatment duration of at least 52 weeks, can also raise the threshold for response to food allergy. However, EPIT treatment also increased local adverse reactions, and the high heterogeneity of local adverse reactions may be attributed to factors such as the type of food, length of treatment, and study population. The reason for the high heterogeneity of local adverse reaction may also be attributed to the use of improved topical medication. Topical agents could alleviate local symptoms. However, some studies did not report the use of topical drugs; this may have contributed to the variability in localized adverse reactions. Compared to placebo, EPIT treatment had clear evidence to raise risk of systemic adverse reactions. There were no statistically significant differences

in epinephrine use, severe adverse reactions between the EPIT and control groups. Only two RCTs mentioned QOL.

EPIT can achieve the immunological goal of desensitization and result in an increase in the allergy threshold, although the increase is smaller than that of oral immunotherapy (OIT) [3, 31]. But EPIT did not increase the response threshold in milk-allergic individuals. Given the limited sample size, the available evidence regarding the efficacy of EPIT for milk allergy may be insufficient, necessitating further multicenter clinical studies to validate this finding. The primary achievement of desensitization is observed in children aged 11 or younger, with age being a critical factor. In individuals over 11 years old, the immune efficacy of EPIT decreases, similar to the better results observed in OIT for younger children [32, 33]. So far, although no definite conclusion has been reached regarding the cause of this phenomenon, the reasons for this phenomenon may be described as follows. In the Viaskin epidermal delivery system, water-dissolved allergens are absorbed into the dermis [34]. Within the epidermis and dermis, dendritic cells that ingest allergens migrate to local lymph nodes to elicit an immune response [35, 36]. However, the cuticle of elderly skin is thicker, and the epidermis is drier, making it difficult for allergens dissolved in water to penetrate the skin. Another meta-analysis also suggested that the relative dose of allergen (ug/kg) was related to the desensitization effect [37]. The longer EPIT is used, the better the desensitization effect, which has been verified in other experiments [38]. Therefore, in the clinical management of children aged 11 or younger, an extended duration of EPIT treatment is correlated with a heightened probability of achieving desensitization.

Compared to non-EPIT, EPIT treatment induces mild-to-moderate anaphylactic reactions without a concurrent increase in the incidence of severe adverse events or the need for epinephrine. Therefore, EPIT has a good safety profile. In contrast to OIT, this result indicates that while raising the threshold, more allergic and adverse reactions are also added, which puts more burden on the participants [33]. Considering the potential risks and profits of EPIT for enhancing immune tolerance in those with food allergies, it is essential to consider the patient's value of expectations. Patients who possess high expectations for enhancing their immune tolerance and are not excessively concerned about the physical burden, risk of serious side effects, or cost may be appropriate candidates for OIT. Conversely, patients who cannot endure the physical burden and associated risks of immunotherapy may be better suited for EPIT.

We assert that this systematic review is the most comprehensive research on this theme to date. Ten studies we included were RCTs, with seven of them being high-quality multicenter studies. Additionally, subgroup analyses of the primary outcome based on study characteristics were performed, along with an investigation into the sources of high heterogeneity in local adverse effects.

There are some limitations of this review. Firstly, publication bias and random errors resulting from the design, conduct, measurement, and analysis of the results may lead to an overstatement of intervention effectiveness in studies with relatively small sample sizes. To address this issue, we performed the trial sequential analysis. Secondly, data on serum immune results (median, SD) were not available from some studies. No satisfactory answers were given when the authors were asked for extra data. Thirdly, due to the restriction of study type to RCTs, other potential study types (i.e., cohort study, non-randomized controlled study) were not included. In subsequent studies, these potential study types will be included.

Conclusion

This systematic review and meta-analysis provides high-certainty evidence that EPIT effectively enhances immune tolerance in patients with food allergy, particularly in children aged 11 years or younger. There is low to high certainty evidence that EPIT causes mild-to-moderate side effects. So EPIT have a good safety profile. Future studies need to devote more attention to the impact of EPIT on the QOL of patients and their families and increase the RCTs of EPIT on other food allergies.

Abbreviations

EPIT	Epicutaneous immunotherapy
RCTs	Randomized controlled trials
QOL	Quality of life
ROB2	Risk of bias 2
OIT	Oral immunotherapy
SD	Standard deviation
RR	Relative risk
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02727-6.

Additional file 1: Appendices. Appendix 1: Search strategy. Appendix 2: Risk-of-bias diagram of the included studies. Appendix 3: Trial sequential analysis

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Authors' contributions

XX answered for study design and writing the manuscript. JH collected and interpreted the data. SC and GH devised data extraction form. All authors participated in modifying the manuscript.

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Data availability
All data supporting the conclusion can be found in the study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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