Clinical Reviews in Allergy & Immunology (2024) 66:125–137
https://doi.org/10.1007/s12016-024-08990-8

REVIEW

From Skin to Solution: Exploring Epicutaneous Immunotherapy for Peanut Allergy—A Systematic Review and Meta-Analysis

Umm E Salma Shabbar Banatwala[1] · Muhammad Moiz Nasir[1] · Reema Javed[2] · Areeba Ahmed[3] · Syed Ali Farhan[4] · Ali Ajam[5]

Accepted: 16 March 2024 / Published online: 25 March 2024

Abstract

Peanut allergy is a leading cause of severe food reactions. This meta-analysis evaluates the efficacy and safety of epicutaneous immunotherapy (EPIT) compared to placebo for peanut-allergic individuals. After prospectively registering on PROSPERO, we searched three databases (PubMed, Google Scholar, and Cochrane CENTRAL) and 2 trial registries till September 2023. Analysis was conducted via RevMan where data was computed using risk ratios (RR). The Cochrane Risk of Bias tool and GRADE criteria were used to appraise and evaluate the evidence. From 4927 records, six multicenter randomized placebo-controlled trials comprising 1453 participants were included. The 250 µg EPIT group had a significant increase in successful desensitization compared to placebo (RR: 2.13 (95% C.I: 1.72, 2.64), $P < 0.01$, $I^2 = 0\%$), while the 100 µg EPIT group did not (RR: 1.54 (95% C.I: 0.92, 2.58), $P = 0.10$, $I^2 = 0\%$) (moderate certainty evidence). Moreover, there was a significant increase in local (RR: 1.69 (95% C.I: 1.06, 2.68), $P = 0.03$, $I^2 = 89\%$) and systemic adverse events (RR: 1.75 (95% C.I: 1.14, 2.69), $P = 0.01$, $I^2 = 0\%$) with EPIT. Additionally, individuals administered EPIT have an increased probability of requiring rescue medications like epinephrine (RR: 1.91 (95% C.I: 1.12, 3.28), $P = 0.02$, $I^2 = 0\%$) and topical corticosteroids (RR: 1.49 (95% C.I: 1.29, 1.73), $P < 0.01$, $I^2 = 0\%$) to treat adverse events. The association of adverse events post-treatment including anaphylaxis (RR: 2.31 (95% C.I: 1.00, 5.33), $P = 0.05$, $I^2 = 36\%$), skin/subcutaneous disorders like erythema or vesicles (RR: 0.93 (95% C.I: 0.79, 1.08), $P = 0.33$, $I^2 = 0\%$), and respiratory disorders like dyspnea or wheezing (RR: 0.94 (95% C.I: 0.77, 1.15), $P = 0.55$, $I^2 = 0\%$) with EPIT is inconclusive. EPIT, although effective in desensitization, is linked to an increased risk of adverse events. PROSPERO registration: CRD42023466600.

Keywords Allergen desensitization · Epicutaneous immunotherapy · Immunotherapy for allergy · Peanut allergy · Peanut protein

Introduction

The prevalence of food allergy has become an escalating concern for families, clinicians, and policymakers since it affects millions worldwide [1]. Reports suggest that over 10% of individuals in Western countries experience some form of food allergy, with children being the most vulnerable

Key Messages

- Peanut allergy can cause fatal food reactions and is usually not outgrown, unlike other food allergies.
- Epicutaneous immunotherapy improves desensitization to peanut protein but is associated with a variety of adverse events.
- Epicutaneous immunotherapy exhibits no significantly increased risk of anaphylaxis. However, the calculated *P*-value of 0.05 warrants caution.

✉ Umm E Salma Shabbar Banatwala
salmabanatwala@gmail.com

[1] Dow University of Health Sciences, Karachi, Pakistan

[2] Department of Dermatology, Al-Mustafa Hospital and Rajput General Hospital, Karachi, Pakistan

[3] Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[4] Department of Plastic and Reconstructive Surgery, Ohio State University, Columbus, OH, USA

[5] Department of Rheumatology and Immunology, Ohio State University, Columbus, OH, USA

[2]. At its core, food allergy represents the immune system's reaction to proteins in food [1]. Notably, shellfish, cow's milk, eggs, and peanuts are the most common culprits behind such allergic responses [1, 3]. While many children outgrow milk and egg allergies, the persistence of peanut or nut allergies throughout life poses a significant challenge, with only one in five children managing to outgrow the condition and tolerate peanuts later in life [4].

Peanut allergy is the leading cause of fatal food reactions, including anaphylaxis, even in individuals with a history of mild reactions [5]. The global prevalence of peanut allergy is rising, particularly in developed nations, affecting 25% of children with food allergies making it a significant health concern [6]. Presently, researchers have identified 18 peanut allergens, with Ara h1, Ara h2, and Ara h3 being the most common ones [7, 8]. These allergens induce the production of specific immunoglobulin E (IgE) antibodies in exposed individuals, triggering an allergic reaction [7]. The resulting symptoms may manifest as pruritus, urticaria, rash, swelling of the lips and tongue, angioedema, syncope, and abdominal cramps, leading to potentially life-threatening situations [9].

Managing peanut allergy primarily revolves around avoiding peanuts altogether [4]. However, the omnipresence of trace amounts of peanut or peanut protein in food makes complete avoidance virtually impossible, presenting a constant challenge for those affected by the allergy. A possible preventive measure in dealing with peanut allergy is the early exposure of peanuts among high-risk infants (infants with severe eczema, or a family history of peanut allergy) which can reduce the risk of developing peanut allergy [10, 12]. Immunotherapy offers another avenue for improving the condition. Oral immunotherapy constitutes the daily ingestion of peanut allergen, gradually increasing the doses over several months to enhance allergen tolerance [13]. The downsides of oral immunotherapy include logistic pitfalls such as missed patient appointments and an increased risk of anaphylaxis and gastrointestinal events [14, 15].

Epicutaneous immunotherapy (EPIT) has also demonstrated the ability to enhance allergen tolerance. In EPIT, the allergen is delivered through multiple applications to the skin, via dermal patches also known as "peanut patches," where it is taken up by the skin's dendritic cells and migrates towards the lymph nodes. Since the allergen is exposed to non-vascularized skin layers, systemic absorption is avoided contributing to the intervention's safety profile [16]. Recently, multiple randomized controlled trials have investigated the safety and efficacy of EPIT for peanut allergy providing an array of evidence. While various systematic reviews and meta-analyses [17–19] have examined the use of EPIT for diverse allergies or compared different treatments for peanut-specific allergies such as oral or sublingual immunotherapy, none has specifically analyzed the use of EPIT for peanut allergies.

In light of the mounting evidence and the need to consolidate existing knowledge, this systematic review and meta-analysis was undertaken to comprehensively assess the safety and efficacy of EPIT specifically for peanut allergy.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [20] and was registered on PROSPERO, an international prospective register of systematic reviews (CRD42023466600).

Eligibility Criteria

Double-blind randomized control trials studying the effects of EPIT on individuals with peanut allergies were included. Any review articles, editorials, case reports, or non-randomized trials were excluded. We placed no restrictions on the age of the population or the age of diagnosis of peanut allergy. Studies enrolling participants with a clinically diagnosed peanut allergy with a current allergic status through skin prick tests, positive provocation tests, or heightened IgE levels were included. Since we investigated the efficacy and safety of EPIT, the intervention had to be a peanut patch in one group and a placebo in the other group. Our outcomes to investigate were (1) desensitization to peanut protein, (2) incidence of anaphylaxis, (3) local adverse events (any patch site skin reaction such as erythema, infiltration, papules, or vesicles), (4) systemic adverse events (defined according to the World Allergy Organization's grading system of side effects [21] and further included anaphylaxis, skin and subcutaneous, immune system, eye, infectious, gastrointestinal, and respiratory disorders), (5) any serious adverse events related to systemic adverse events (anaphylaxis, death, disability, life-threatening events, or events requiring immediate medical intervention), certain specific adverse events after treatment such as (6) skin and subcutaneous tissue disorders (urticaria, eczema, generalized pruritus, dermatitis limited to or exceeding the limits of the patch application area), (7) infections (upper and lower respiratory tract infections, nasopharyngitis, gastroenteritis, ear infections, conjunctivitis, pneumonia, tonsillitis, varicella, oral herpes, cellulitis, hand-foot-and-mouth disease, pharyngitis, impetigo, sinusitis, bronchitis, infectious diarrhea, giardiasis, lice infestation, and vulvar infections), (8) respiratory disorders (sneezing, nasal congestion, rhinorrhea, respiratory infections, laryngeal symptoms, and wheezing), and (9) eye disorders (eye swelling, periorbital edema, increased lacrimation, eye pruritus, ocular hyperemia, eye irritation, eye discharge, and conjunctivitis), along with the (10) use of epinephrine, (11) use of corticosteroids, and (12) changes in serum-specific IgE and immunoglobulin G4 (IgG4) levels after treatment.

Desensitization to peanut protein was defined and based on the initial eliciting dose used in each study. The criteria to assess desensitization for each study are described in Table 1. Systemic adverse events can be further described as any acute system allergic reactions that are not associated with the food challenge. All adverse events were noted as a result of exposure to the treatment. Some of these were directly related to the study drug and some to accidental ingestion of peanuts or any other allergen.

Data Sources and Literature Search

A systematic literature search across prominent databases such as PubMed (MEDLINE), Google Scholar, Cochrane CENTRAL, and clinical trial registries such as ClinicalTrials.gov and the International Clinical Trials Registry was conducted for relevant studies from inception to September 2023 without any language restrictions. Trial registries were searched to find data that has not been reported in peer-reviewed literature. An assessment of protocols published in trial registries sheds light on selective reporting biases.

The search strategy employed specific and pertinent keywords such as "epicutaneous immunotherapy" and "peanut allergy". The detailed search strategy is mentioned in Supplementary Table S1. Additionally, the references of each of the retrieved studies were examined to identify other studies that conformed to our inclusion criteria. Two of the study authors (U.S.B and M.M.N) independently searched through the literature. The screening process began by assessing the studies based on their title and abstract, allowing for a preliminary evaluation of their relevance. Subsequently, those studies that passed the initial screening underwent a comprehensive examination, with their full texts retrieved and critically appraised. The assessment closely followed the predetermined inclusion and exclusion criteria, ensuring that only the most suitable articles were ultimately selected. All the selected studies were imported to EndNote X9 (Thomson Reuters, Toronto, Ontario, Canada), and duplicates were identified and removed.

Data Extraction

In order to extract data, an extraction sheet was designed for this review on Excel (Microsoft, USA). Two of the study authors (U.S.B and M.M.N) independently extracted data from the selected studies. To avoid errors, the same two authors reviewed each other's extraction. In case of any disagreement, a third author made the final decision (S.A.F). Data extracted included (1) study and population characteristics (including the number of patients randomized, number of patients lost at follow-ups, age, type of study, study duration, and baseline IgE and IgG4 levels), (2) the EPIT dose, (3) previous medical history of participants, and (4) outcomes, including baseline and post-intervention values.

Risk of Bias Assessment

Two authors (U.S.B and M.M.N) independently assessed the quality of the included randomized controlled trials using the Cochrane Risk of Bias tool for randomized controlled trials [22]. This assessment involved categorizing each trial as having either a low, high, or unclear risk of bias. For trials to be considered as having a low risk of bias, they must meet specific criteria. Random sequence generation; adequate allocation concealment and blinding of participants, treatment administrators, and outcome assessors; and unbiased and complete reporting are crucial factors in determining the level of bias. Trials that effectively implement these measures are classified as having a low risk of bias, indicating a higher level of methodological rigor and reliability in their findings.

The certainty of evidence was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [23]. This included an assessment of the overall risk of bias, imprecision (95% confidence interval (CI) relative to the clinical significance threshold), inconsistency (I^2 cutoff of 50%), indirectness (study population), and publication bias. Although no formal calculations were made to assess the publication bias due to the limited number of included studies, a visual inspection of funnel plots for each outcome was performed.

Data Synthesis and Statistical Analysis

Outcomes were analyzed based on the intention-to-treat population. For continuous outcomes, when the data was provided with a median and range, approximation methods were used to determine the mean and standard deviation [24]. On the other hand, for dichotomous outcomes, we used the risk ratio (RR) for analysis. Data were analyzed using the RevMan software (Review Manager version 5.3.5, The Nordic Cochrane Centre, Copenhagen). Effect sizes and 95% C.I for the intervention were calculated using a random-effects or fixed-effects model depending upon the heterogeneity score across studies. When the observed heterogeneity was greater than 50%, the random-effects model was adopted. In other circumstances, the fixed-effects model was preferred to control invariant omitted variables. Forest plots were generated to evaluate the effect of EPIT on each of the outcomes. Leave-one-out sensitivity analysis was conducted to assess if any single study disproportionately influenced the results and resulted in an increase in heterogeneity. Heterogeneity was assessed using the Cochrane Q statistic; $P < 0.1$ indicates significant heterogeneity. Heterogeneity across the trials was also evaluated by the I^2 test, and the scale was set as a value < 25% which means low risk, 25–75% means moderate risk, and > 75% means high risk. A P-value of < 0.05 was considered significant in all cases.

Table 1 Baseline characteristics of included trials and participants

Author (years)	Trial design	Study location	Duration of study (weeks)	Dose of EPIT (μg)	Number of participants		Mean age (SD) (years)		Mean peanut-specific IgE (SD) (kU/L)		Mean peanut-specific IgG4 (SD) (mg/L)		Medical history	How was the primary outcome (desensitization) defined?
					EPIT	PBO	EPIT	PBO	EPIT	PBO	EPIT	PBO		
Greenhawt et al (2023) [25]	Phase 3	USA, Canada, Australia, and Europe	52	250	244	118	2.5 (0.26)	2.4 (0.26)	13.4 (11.46)	14.8 (8.7)	0.4 (0.22)	0.4 (0.17)	Asthma, eczema, allergic rhinitis, and food allergies other than peanut	Post-treatment eliciting dose greater than 1000 mg (baseline eliciting dose > 10 mg) or 300 mg (baseline eliciting dose ≤ 10 mg)
Pongracic et al (2022) [26]	Phase 3	USA and Canada	26	250	294	99	7.2 (2.2)	7.2 (2.3)	190.5 (212.4)	227.5 (286.90	1.2 (1.7)	1.5 (3.1)	Asthma, eczema, allergic rhinitis, and allergies other than peanut	NR
Fleischer et al (2019) [27]	Phase 3	Australia, Canada, Germany, and USA	52	250	238	118	7 (0.56)	7 (0.74)	77.9 (31.85)	101 (37.57)	0.69 (0.22)	0.74 (0.22)	Asthma, eczema, allergic rhinitis, and allergies other than peanut	Post-treatment eliciting dose greater than 1000 mg (baseline eliciting dose > 10 mg) or 300 mg (baseline eliciting dose ≤ 10 mg)
Jones et al (2017) [28]	Phase 2	USA	52	100 or 250	49	25	8.4 (2.31) and 7.7 (1.89)	8.5 (2.87)	84.6 (39.37) and 92.1 (37.31)	58.0 (39.30)	0.6 (0.44) and 0.5 (0.55)	1.1 (1.29)	Asthma, eczema, and allergies other than peanut	Post-treatment eliciting dose 10-fold greater than baseline eliciting dose

Table 1 (continued)

Author (years)	Trial design	Study location	Duration of study (weeks)	Dose of EPIT (μg)	Number of participants		Mean age (SD) (years)		Mean peanut-specific IgE (SD) (kU/L)		Mean peanut-specific IgG4 (SD) (mg/L)		Medical history	How was the primary outcome (desensitization) defined?
					EPIT	PBO	EPIT	PBO	EPIT	PBO	EPIT	PBO		
Sampson et al (2017) [29]	Phase 2b	North America and Europe	52	50, 100, or 250	112	56	10 (1.48), 12 (1.30), and 11.5 (1.30)	11 (0.98)	83.0 (39.35), 66.1 (34.56), and 79.9 (33.63)	68.5 (36.09)	0.7 (0.24), 0.4 (0.02), and 0.6 (0.11)	0.5 (0.19)	NR	Post-treatment eliciting dose is > 1000 mg or 10-fold greater than the baseline eliciting dose
Jones et al (2016) [30]	Phase 1	USA	3	50, 100, 250, or 500	80	20	24.7 (11.56)	22.2 (9.18)	22.73 (29.24)	36.50 (38.18)	NR	NR	Asthma, eczema, and allergic rhinitis	NR

PBO placebo, *EPIT* epicutaneous immunotherapy, *NR* not reported

Since sufficient data according to dose was available for the first outcome, i.e., desensitization to peanut protein, we planned to perform a subgroup analysis to identify the effect of the dosage of EPIT on desensitization to peanut protein. Due to limited data, subgroups were not created for the remaining outcomes.

Results

Search Results and Patient Characteristics

The initial search result produced 4927 studies, which, after removing duplicated publications (such as meeting abstracts, presentations, and protocols) ($n = 4846$), previously published review articles ($n = 124$), and studies outside the scope of this research ($n = 16$), yielded six multicenter trials [25–30] for the final quantitative and qualitative analysis (Fig. 1). Of note, eight articles were excluded since they were long-term follow-ups or extensions of the original trial.

The characteristics of the included studies are summarized in Table 1. Most of these trials were conducted in the USA ($n = 5$), followed by Canada ($n = 3$) and Europe ($n = 3$). A few of these trials ($n = 3$) were simultaneously conducted across continents. In most of the trials ($n = 4$), the duration of intervention was 52 weeks. The total number of participants included in our analysis was 1453 ($n = 1017$ in EPIT and $n = 436$ in placebo). Most of the participants were children with a mean age of 10 years and had a reported history of peanut allergy. In just one study [30], the population included young adults as well (mean age between 22.2 and 24.7). It is worth noting that most participants experienced disorders of the atopic triad (atopic dermatitis, asthma, and allergy). Four of the included trials specified the type of allergic disorders and noted four allergic disorders among the study population. Among the included studies, all the EPIT patches came from the same company (Viaskin, DBV Technologies) that designed and supported the trials. Our literature search did not reveal any studies utilizing EPIT patches from any other company. Dosages for EPIT varied from 50 to 250 μg with the most commonly used dose being the 250 μg one. Three studies reported using the 100 μg dose, while two reported using the 50 μg dose. Lastly, one study reported the use of 500 μg dosages.

Baseline peanut-specific IgE levels differed greatly between studies and ranged from a mean of 13.4 to 227.5 kU/L with the REALISE trial [26] reporting the highest levels. On the other hand, baseline peanut-specific IgG4 levels were similar between the studies with the highest reported by the REALISE trial [26] (1.2 and 1.5 mg/L in the placebo and intervention groups, respectively).

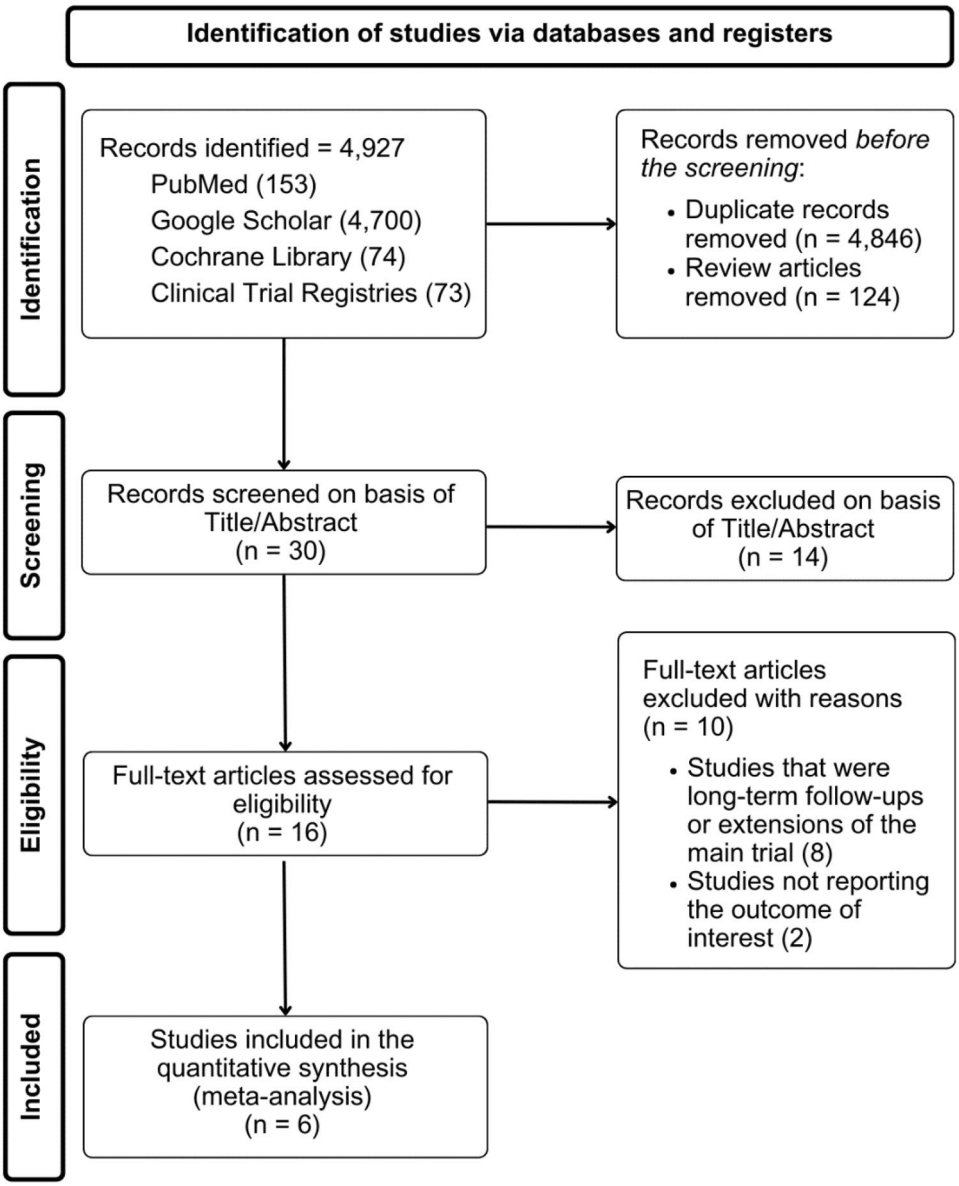


Fig. 1 PRISMA flowchart of the database literature search. A total of 4927 articles were yielded from 3 databases and 2 trial registries, which were then subjected to screening for duplication and evaluated on the basis of title, abstract, and full-text review matching. A total of six studies were finally selected for inclusion

Outcome data for each study is presented in Supplementary Tables S2 and S3.

Quality Assessment

All the studies assessed using the Cochrane Risk of Bias tool 1.0 showed an overall low risk of bias. All studies demonstrated adequate allocation concealment, randomized treatment allocation, blinding of participants and outcome assessors, and complete reporting of outcomes (Supplementary Figs. S1A, B). One study [30] had a high risk of bias for the "other bias" category due to the small study duration. A "high risk" was allocated since a small study duration of just 3 weeks may not allow for the emergence of treatment-related adverse events or allow sufficient time to explore the efficacy of the treatment. Another study [25] had a high risk of reporting bias since its protocol mentioned evaluating quality of life, but this was not reported in the study.

The GRADE assessment was performed to evaluate the certainty of the evidence for each outcome as shown by Supplementary Table S4.

Results of Meta-Analysis

Desensitization

This outcome was reported by four different studies [25, 27–29] with two different doses of EPIT 100 µg and 250 µg, and therefore, a subgroup analysis was performed (Fig. 2). When compared to placebo, 100 µg dose of EPIT showed no

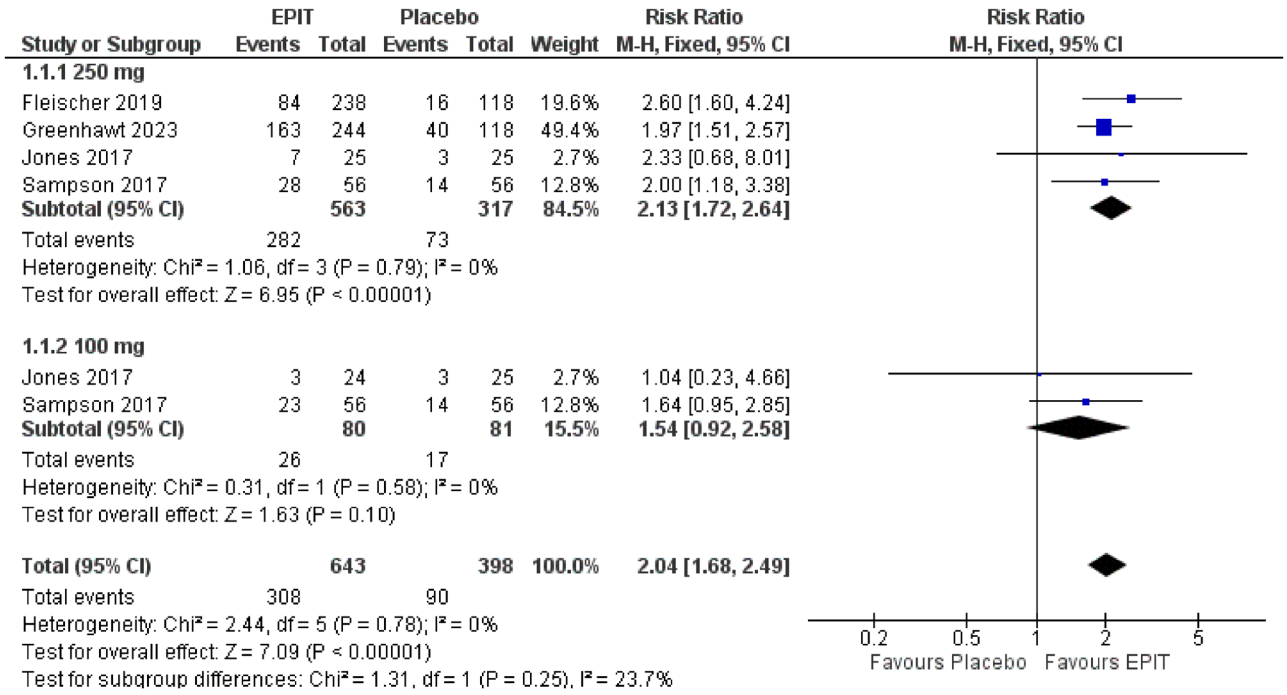


Fig. 2 Forest plot showing desensitization to peanut allergy after epicutaneous immunotherapy (EPIT) versus placebo for peanut allergy. The figure illustrates that the high dose of EPIT demonstrates significant desensitization

conclusive difference in desensitization (RR: 1.54 (95% C.I: 0.92, 2.58), $P = 0.10$, $I^2 = 0\%$), whereas the patient cohort administered 250 µg of EPIT demonstrated a significant benefit in achieving successful desensitization (RR: 2.13 (95% C.I: 1.72, 2.64), $P < 0.01$, $I^2 = 0\%$) (P-interaction = 0.25). No significant statistical heterogeneity was observed overall ($I^2 = 0\%$, $P = 0.78$) although clinically, due to the varying dose of EPIT, heterogeneity is present between the included studies prompting us to initially create the subgroups. Certainty assessment concluded no serious risk of bias, inconsistency, indirectness, or publication bias. However, moderately serious imprecision yielded an overall certainty of evidence for this outcome as moderate.

Anaphylaxis

This outcome was reported by five of the included trials [25–27, 29, 30]. A total of 36 events (3.9%) occurred among the 912 participants allocated to EPIT while five events (1.2%) occurred among 411 participants receiving placebo. The study by Jones et al. [28] reported zero events of anaphylaxis in either group. Pooled analysis of the studies (Fig. 3) indicated a non-significant increase in the incidence of anaphylaxis in subjects receiving EPIT, compared to placebo (RR: 2.31 (95% C.I: 1.00, 5.33), $P = 0.05$, $I^2 = 36\%$]; however, of note, this result indicates a trend towards harm. Certainty assessment yielded no

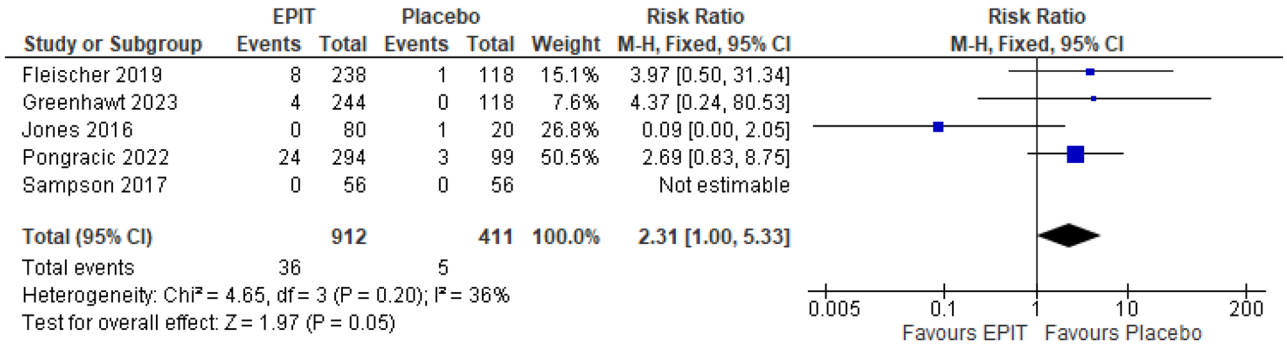
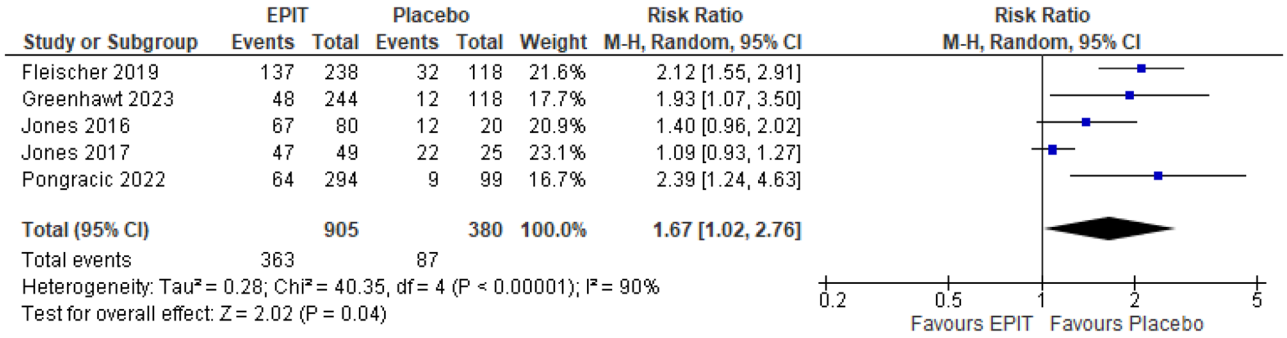


Fig. 3 Forest plot showing the incidence of anaphylaxis to peanut allergen after epicutaneous immunotherapy (EPIT) versus placebo for peanut allergy

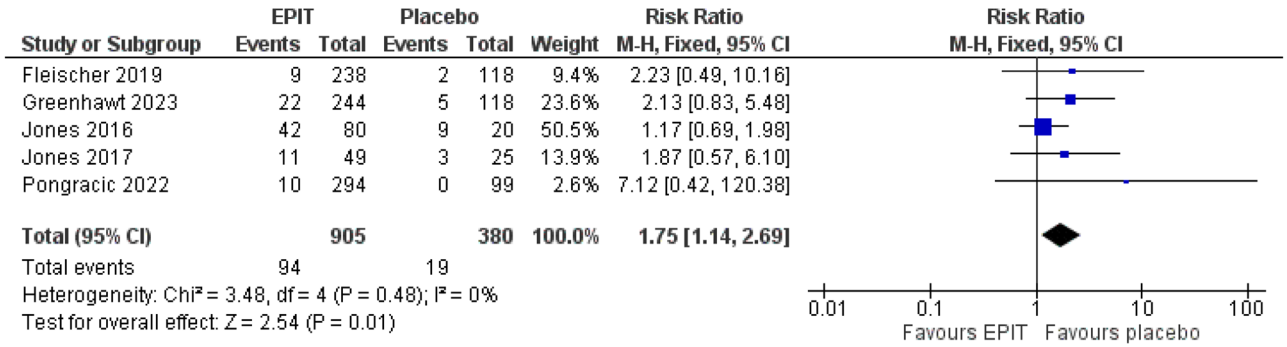
serious inconsistency, indirectness, imprecision, or publication bias. However, a moderately serious overall risk of bias resulted in an overall certainty of evidence for this outcome as moderate.

Adverse Events

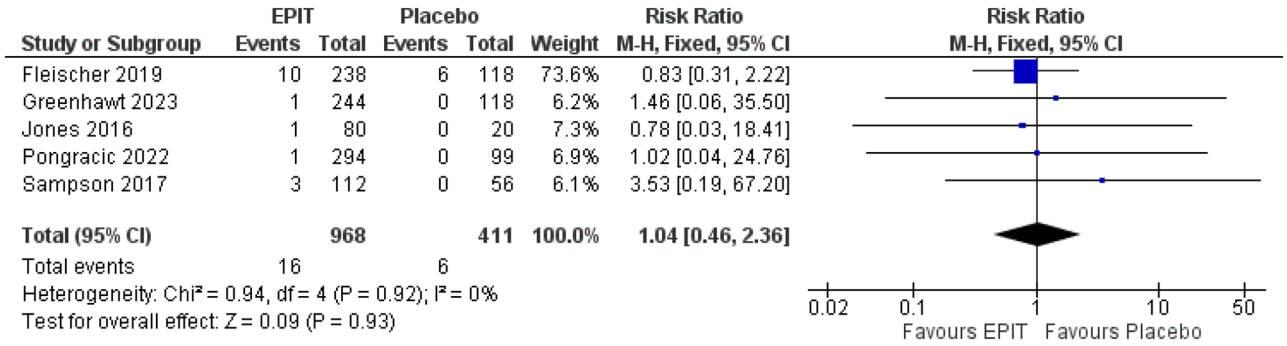
Pooled analysis (Fig. 4) showed that when compared to placebo, patients receiving EPIT had a significantly high risk of local adverse events (RR: 1.67 (95% C.I: 1.02, 2.76), $P = 0.04$, $I^2 = 90\%$], and systemic adverse events (RR: 1.75 (95% C.I: 1.14, 2.69), $P = 0.01$, $I^2 = 0\%$). The high heterogeneity for the local adverse events outcome fell to 23% upon excluding the trial by Jones et al. [28]. The high heterogeneity may be attributed to the use of Tegaderm covering on the application site since this study was the only one reporting its use. However, this association is unclear. After removing this study, the risk of local adverse events



(a)



(b)



(c)

Fig. 4 Forest plots showing **a** local adverse events, **b** systemic adverse events, and **c** serious adverse events after epicutaneous immunotherapy (EPIT) versus placebo for peanut allergy

remained significant (RR: 1.86 (95% C.I: 1.44, 2.39), $P < 0.01$). All trials reported serious adverse events; however, no significant serious adverse events were observed in patients receiving EPIT (RR: 1.04 (95% C.I: 0.46, 2.36), $P = 0.93$, $I^2 = 0\%$]. None of the trials reported any incidence of allergy-associated mortality (Supplementary Table S3). Upon assessment of certainty, the evidence for local adverse events has low certainty, while the evidence for systemic and serious adverse events has a moderate level of certainty.

Skin and Subcutaneous Tissue Disorders

This outcome was reported by three studies [25, 27, 30]. A total of 183 skin disorders (32.6%) were reported among 562 individuals receiving EPIT while 94 events (36.7%) were reported among 256 individuals assigned to the placebo group. Analysis (Fig. 5) indicated no significant effect between EPIT use and any ensuing skin reaction (RR: 0.93 (95% C.I: 0.79, 1.08), $P = 0.33$, $I^2 = 0\%$). Overall, the certainty of evidence for this outcome is moderate.

Infection and Respiratory Disorders

Only four studies reported infection [25–27, 30] (Supplementary Fig. S2) and three reported respiratory disorders [25–27] (Supplementary Fig. S3). There was no significant effect of the intervention on infections (RR: 0.99 (95% C.I: 0.88, 1.12), $P = 0.88$, $I^2 = 32\%$) or respiratory disorder (RR: 0.94 (95% C.I: 0.77, 1.15), $P = 0.55$, $I^2 = 0\%$). Overall, the certainty of evidence for this outcome is moderate.

Eye Disorders

Two trials [25, 27] reported eye disorders post-treatment with 7.1% of individuals in the EPIT and 6.4% of individuals in the placebo group experiencing this condition. Our analysis (RR: 1.10 (95% C.I: 0.62, 1.96), $P = 0.74$, $I^2 = 47\%$) suggested that there is no conclusive effect of EPIT on eye disorders (Supplementary Fig. S4). Overall, the certainty of evidence for this outcome is moderate.

Use of Epinephrine

In the EPIT groups, 64 individuals (6.7%) reported using epinephrine while 15 from the placebo group (3.4%) reported using it. Two of the included studies reported that neither group required epinephrine [28, 30]. Pooled data (Fig. 6) from the six studies [25–30] indicated that individuals administered EPIT had a significantly increased probability of using epinephrine compared to placebo (RR: 1.91 (95% C.I: 1.12, 3.28), $P = 0.02$, $I^2 = 0\%$). Overall, the certainty of evidence for this outcome is moderate.

Use of Corticosteroids

Two of the trials [25, 26] reported the use of corticosteroids (Supplementary Fig. S5A, B). There is no conclusive evidence that EPIT leads to an increased risk of requiring systemic or inhaled corticosteroids (RR: 0.98 (95% C.I: 0.72, 1.32), $P = 0.88$, $I^2 = 0\%$) while the risk of needing topical corticosteroids is significantly higher with the EPIT group (RR: 1.49 (95% C.I: 1.29, 1.73), $P < 0.01$, $I^2 = 0\%$). Overall, the certainty of evidence for this outcome is moderate.

Serum Peanut-Specific IgE Levels

Changes in serum IgE levels differed across the trials. The EPITOPE trial [25] demonstrated an increase in peanut-specific IgE levels from the baseline to 3 months in both the EPIT and placebo groups. However, at 12 months, the peanut IgE levels decreased from baseline in EPIT participants whereas they increased in the placebo group (median change: −0.71 and 2.03 kU/l, respectively). The REALISE trial [26] investigated IgE levels until 6 months and reported no appreciable increase in these levels for the placebo group. This trial stated that although the levels rose for the EPIT group until 3 months and then decreased for the remaining 3 months, the overall decrease was not below the baseline level. On the other hand, the PEPITES [26] and VIPES trials [29] reported a similar trend for both the placebo and EPIT groups over 12 months with respect to the relative change in IgE levels (increase at 3 months and then

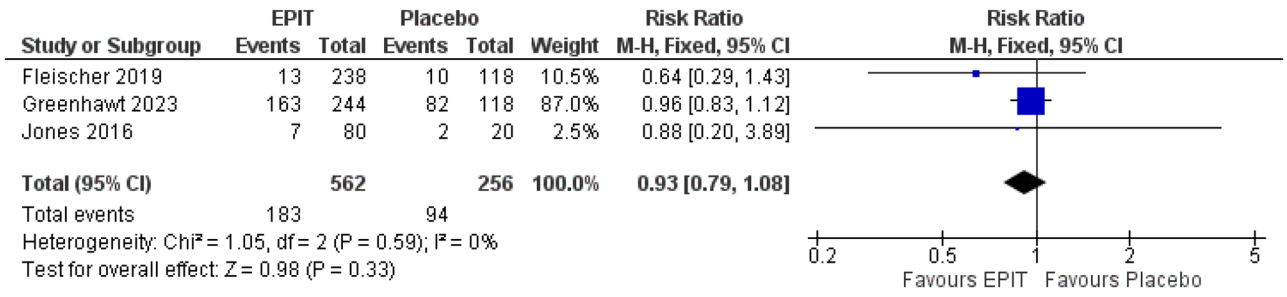


Fig. 5 Forest plot showing the incidence of skin and subcutaneous disorders after epicutaneous immunotherapy (EPIT) versus placebo for peanut allergy

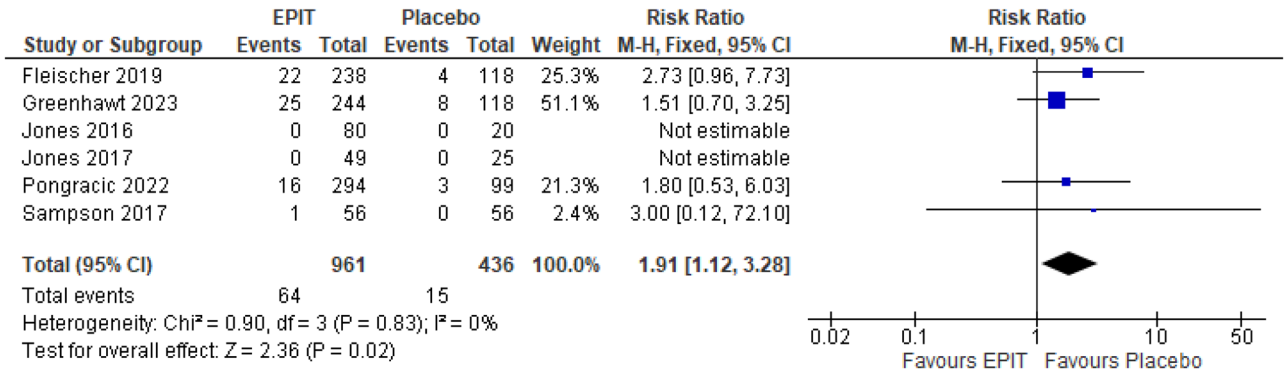


Fig. 6 Forest plot showing the need of rescue medications such as epinephrine to peanut allergen exposure after epicutaneous immunotherapy (EPIT) versus placebo for peanut allergy

decrease). However, at 3 months, the EPIT groups had a larger increase in IgE levels. Moreover, the CoFAR trial [28] reported no significant differences between the two groups. Due to the absence of original data for this outcome, a meta-analysis was not performed.

Figure 7 shows the median change in peanut-specific IgE levels over time in the EPIT group as reported by graphs from the various included trials (according to their dosage). The 100 µg EPIT dose in the CoFAR trial [28] reported the greatest change in peanut IgE levels at 3 months while the least change was reported by the EPITOPE trial which investigated the 250 µg dose [25]. From 3 to 6 months, the median change in IgE levels varied across the trials while after 6 months, most trials demonstrated a further decrease in IgE levels.

Serum Peanut-Specific IgG4 Levels

The EPITOPE trial [25] reported an increase in IgG4 levels for both groups over the 12 months; however, the increase in the EPIT group was steeper and greater than for the placebo group. According to the VIPES, REALISE, and PEPITES trials [26, 27, 29], the placebo group did not demonstrate much difference over the course of the study whereas IgG4 levels increased consistently for the EPIT group. Lastly, the CoFAR study [28] mentioned that changes in IgG4 levels were significant ($P < 0.01$) between the groups and a large increase was noted in the EPIT group. Due to the absence of original data for this outcome, a meta-analysis was not performed.

Discussion

This systematic review and meta-analysis provides valuable insight into the usage of EPIT for peanut allergy. Our results show that the efficacy of EPIT in patients with peanut allergy in our study concurs with the efficacy reported in previous meta-analyses for other food allergies. de Silva et al. [19] mentioned that EPIT probably increased the proportion of individuals able to tolerate peanut protein during treatment. However, they reported no increases in anaphylaxis and did not include outcomes such as infections and respiratory disorders along with the use of rescue medications in their analysis due to their scarcity. The meta-analysis by Xiong et al. [17] demonstrated that desensitization by EPIT for peanut allergy has a substantial benefit but did not find a significant association with any treatment-related adverse events or systemic adverse events. Additionally, they reported that the use of rescue medication was similar in both groups. On the other hand, our study which had a narrower inclusion criteria and focused solely on EPIT with peanut allergy has demonstrated a significant association between EPIT with these outcomes (moderate-certainty evidence).

Although our included trials did not mention any long-term outcomes, long-term follow-up publications of included trials can be discussed. Brown-Whitehorn et al. in their clinical communication [31] examined the longer-lasting effect of EPIT in desensitized patients of the VIPES trial and found that sustained unresponsiveness (unresponsiveness or lack of remission for 2 or more years) to peanut protein after long-term therapy with EPIT may be achievable for some patients with the allergy. Similarly, the PEPITES open-label extension called the PEOPLE study [32] reported that 77.8% of the participants demonstrated sustained unresponsiveness until 38 months and had an eliciting dose greater than 1000 mg of peanut protein. Since data on sustained unresponsiveness is scarce, we could not include the outcome in our analysis. A sample analysis of the participants in the PEPITES study conducted by Bastin et al. [33] concluded that immunologic biomarker trajectories with EPIT are similar to those with other immunotherapy modalities indicating similar immunologic changes. Another study based on the PEPITES and PEOPLE trial by DunnGalvin et al. [34] investigating the food allergy quality of life changes after

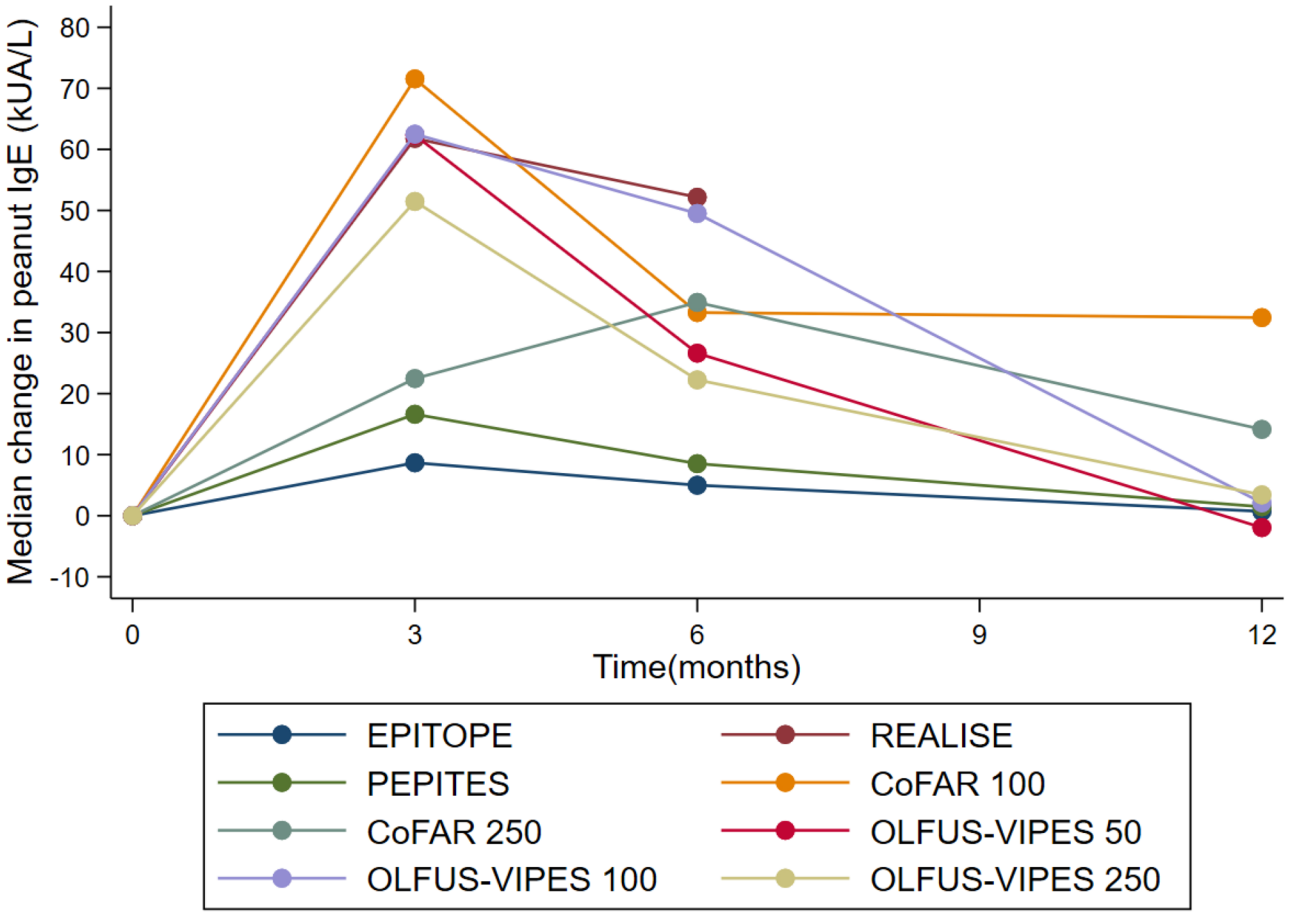


Fig. 7 Graphical representation of the median change in peanut-specific IgE levels (kU/L) in the intervention groups as reported by the various trials

treatment with EPIT concluded that EPIT is associated with significant quality of life improvements.

Our systematic review and meta-analysis considered two dosages of EPIT (100 and 250 µg) among the 4 (50, 100, 250, and 500 µg) which were used across studies to investigate desensitization. According to the analysis, the higher dosage group (250 µg) demonstrated significantly greater desensitization compared to placebo while the lower dosage group (100 µg) did not offer any significant difference. Due to the limited evidence for the remaining dosage groups, we could not carry out an analysis specific to them.

Most participants in our analysis were children. Although few children outgrow peanut allergy, peanut allergy is still a concern for adults. None of the studies investigated the ability of EPIT to induce desensitization in adults although one of them investigated its safety in the adult population. Since early exposure to the allergen has the greatest ability to induce desensitization [10, 11], it is unclear if EPIT may be of any benefit to adults.

It is pertinent to highlight that the included study by Pongracic et al. [26] pointed to an association between mutations in the filaggrin gene and local skin reactions resulting from EPIT administration. This mutation may result in reduced or no filaggrin protein which can result in a skin barrier defect. Such mutations are genetic risk factors for atopic dermatitis [35]. Since local adverse events were significantly associated with EPIT, prior screening for this mutation can help decide if peanut allergy-affected individuals should opt for this treatment.

There are multiple strengths of this review. Firstly, this review was conducted using multicenter randomized double-blind placebo-control trials, most with a low risk of bias which proves the reliability of our results. Moreover, there was low heterogeneity between our studies for most outcomes. Furthermore, the certainty of evidence for the majority of outcomes was moderate. This review is the first meta-analysis investigating the safety and efficacy of EPIT for peanut allergy specifically and includes a variety of outcomes while providing a dose-based analysis on desensitization. There are a few limitations to this review that the authors would like to highlight. Firstly, all the EPIT patches came from the same company (Viaskin, DBV Technologies) which was also involved in designing the trials. Secondly, outcome data on serum peanut-specific IgE and IgG4

levels were not quantifiable. These outcomes showed considerable variation across the studies. Another limitation is that there was limited data available to differentiate between the cause of the adverse events. Therefore, it is unclear if the adverse events were triggered by the application of the product or by accidental exposures to peanut or any other allergen. Moreover, data specific to each age bracket (i.e., pediatric and young adult) was not available, and therefore, the efficacy of EPIT in different age groups could not be investigated. Additionally, due to a lack of data, we could not investigate the quality of life after use of EPIT, an outcome which is integral for clinical trials in food allergy [36]. Lastly, we could not establish if EPIT led to sustained or prolonged unresponsiveness after initial treatment due to limited data.

Although multiple immunotherapy routes are present (oral, epicutaneous, and sublingual), studies comparing these therapies with each other are rare. A cost-effectiveness analysis by Shaker et al. [37] reported that EPIT costs less than oral immunotherapy and is associated with fewer episodes of anaphylaxis but also has lower quality-adjusted life years. Future trials should compare these therapies directly with each other in order to establish a superior treatment. Additionally, future studies should report outcomes such as prolonged unresponsiveness, serum peanut-specific IgE, and IgG4 levels for a quantifiable analysis and investigate epicutaneous peanut patches from other companies. Moreover, while our analysis shows a non-significant association between EPIT and anaphylaxis, with a *P*-value of 0.05, we recommend caution. By including additional studies, this association can be further clarified.

Conclusion

In conclusion, EPIT for peanut allergy is effective in inducing desensitization to peanut protein. Unfortunately, this treatment is significantly associated with local and systemic adverse events and the need for rescue medication such as epinephrine and topical corticosteroids. As for respiratory disorders, infections, and skin disorders, there are no significantly increased risks of them after EPIT. EPIT exhibits no significant effect on the risk of anaphylaxis; however, the calculated *P*-value of 0.05 warrants caution. EPIT should be administered keeping in mind the adverse events and genetic predisposition reported in this study. There is no evidence that EPIT protects people with peanut allergies from allergic reactions, but EPIT increases the threshold of reactivity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12016-024-08990-8.

Acknowledgements The authors are thankful for the assistance in data representation provided by Shagufta Shabbar, PhD Scholar, Department of Economics at the Institute of Business Administration, Pakistan.

Author Contributions 1. Umm E Salma Shabbar Banatwala: idea conception, literature search, data extraction, data analysis, and manuscript writing. 2. Muhammad Moiz Nasir: data extraction, data analysis, and manuscript writing. 3. Reema Javed: manuscript writing and editing. 4. Areeba Ahmed: manuscript editing and revision. 5. Syed Ali Farhan: manuscript editing and revision. 6. Ali Ajam: final revision.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval This study does not require ethical approval since there was no direct interaction with humans or animals. Data from published trials has been used in this analysis.

Consent to Participate Due to the nature of this study, informed consent from participants was not required as this study is a meta-analysis that includes trials that had these participants.

Competing Interests The authors declare no competing interests.

References

1. Lopez CM, Yarrarapu SNS, Mendez MD (2023) Food allergies. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing [cited 2023 Jul 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482187/
2. Loh W, Tang MLK (2018) The epidemiology of food allergy in the global context. Int J Environ Res Public Health [Internet]. [cited 2023 Jul 26];15(9):2043. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6163515/
3. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM et al (2019) Prevalence and severity of food allergies among us adults. JAMA Netw Open 2(1):e185630
4. Patel R, Koterba AP (2023) Peanut allergy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing [cited 2023 Jul 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK538526/
5. Bock SA, Muñoz-Furlong A, Sampson HA (2001) Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 107(1):191–193
6. Krogulska A, Wood RA (2020) Peanut allergy diagnosis: moving from basic to more elegant testing. Pediatr Allergy Immunol 31(4):346–357
7. Palladino C, Breiteneder H (2018) Peanut allergens. Mol Immunol [Internet]. [cited 2023 Jul 26]; 100:58–70. Available from: https://www.sciencedirect.com/science/article/pii/S0161589018301226
8. Who/iuis allergen nomenclature home page [Internet]. [cited 2023 Jul 26]. Available from: http://www.allergen.org/index.php
9. Dougherty JM, Alsayouri K, Sadowski A (2023) Allergy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing [cited 2023 Jul 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK545237/
10. Shroba J, Rath N, Barnes C (2019) Possible role of environmental factors in the development of food allergies. Clin Rev Allergy Immunol 57(3):303–311
11. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF et al (2015) Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 372(9):803–813
12. Eimear O, Hilary T, Andrew C, Andrew L, Sindher S, Sharon CR (2022) Current insights: a systemic review of therapeutic options for peanut allergy. Curr Opin Allergy Clin Immunol

[Internet]. [cited 2023 Jul 26];22(3):188–193. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9178908/
13. Bégin P, Chan ES, Kim H, Wagner M, Cellier MS, Favron-Godbout C et al (2020) CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy. Allergy Asthma Clin Immunol 16:20
14. Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S et al (2019) Oral immunotherapy for peanut allergy (Pace): a systematic review and meta-analysis of efficacy and safety. Lancet 393(10187):2222–2232
15. Fiocchi A, Artesani MC, Fierro V, Riccardi C, Dahdah L, Mennini M (2020) Oral immunotherapy for peanut allergy: the con argument. World Allergy Organ J [Internet]. [cited 2023 Jul 26];13(8):100445. Available from: https://www.sciencedirect.com/science/article/pii/S1939455120303483
16. Wang J, Sampson HA (2018) Safety and efficacy of epicutaneous immunotherapy for food allergy. Pediatr Allergy Immunol 29(4):341–349
17. Xiong L, Lin J, Luo Y, Chen W, Dai J (2020) The efficacy and safety of epicutaneous immunotherapy for allergic diseases: a systematic review and meta-analysis. Int Arch Allergy Immunol 181(3):170–182
18. Sun J, Hui X, Ying W, Liu D, Wang X (2014) Efficacy of allergen-specific immunotherapy for peanut allergy: a meta-analysis of randomized controlled trials. Allergy Asthma Proc 35(2):171–177
19. de Silva D, Rodríguez Del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A et al (2022) Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy 77(6):1852–1862
20. Page MJ, McKenzie JE, Bossuyt PM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 29(372):n71
21. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ et al (2007) Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (Wao) taskforce: recommendations for immunotherapy clinical trials. Allergy [Internet]. [cited 2023 Jul 26];62(3):317–324. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2006.01312.x
22. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors) (2022) Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022). Cochrane. www.training.cochrane.org/handbook. Accessed 25 Oct 2023
23. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J et al (2011) GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol [Internet]. 64(4):383–394. https://linkinghub.elsevier.com/retrieve/pii/S0895435610003306. Accessed 30 Oct 2023
24. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14:135
25. Greenhawt M, Sindher SB, Wang J, O'Sullivan M, Du Toit G, Kim EH, Albright D et al (2023) Phase 3 trial of epicutaneous immunotherapy in toddlers with peanut allergy. N Engl J Med 388(19):1755–1766. https://doi.org/10.1056/NEJMoa2212895
26. Pongracic JA, Gagnon R, Sussman G, Siri D, Oriel RC, Brown-Whitehorn TF, Green TD et al (2022) Safety of epicutaneous immunotherapy in peanut-allergic children: REALISE randomized clinical trial results. The Journal of Allergy and Clinical Immunology: In Practice 10(7):1864–1873.e10. https://doi.org/10.1016/j.jaip.2021.11.017
27. Fleischer DM, Greenhawt M, Sussman G, Bégin P, Nowak-Wegrzyn A, Petroni D, Beyer K et al (2019) Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy. JAMA 321(10):946–955. https://doi.org/10.1001/jama.2019.1113
28. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, Henning AK et al (2017) Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 139(4):1242–1252.e9. https://doi.org/10.1016/j.jaci.2016.08.017
29. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, Cheema AS et al (2017) Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity. JAMA 318(18):1798–1809. https://doi.org/10.1001/jama.2017.16591
30. Jones SM, Agbotounou WK, Fleischer DM, Burks AW, Pesek RD, Harris MW, Martin L, Thebault C, Ruban C, Benhamou PH (2016) Safety of epicutaneous immunotherapy for the treatment of peanut allergy: a phase 1 study using the Viaskin patch. J Allergy Clin Immunol 137(4):1258–1261.e10. https://doi.org/10.1016/j.jaci.2016.01.008
31. Brown-Whitehorn TF, de Blay F, Spergel JM, Green TD, Peillon A, Sampson HA, Campbell DE (2021) Sustained unresponsiveness to peanut after long-term peanut epicutaneous immunotherapy. The Journal of Allergy and Clinical Immunology: In Practice 9(1):524–526. https://doi.org/10.1016/j.jaip.2020.08.017
32. Fleischer DM, Shreffler WG, Campbell DE, Green TD, Anvari S, Assa'ad A, Bégin P, et al (2020) Long-term, open-label extension study of the efficacy and safety of epicutaneous immunotherapy for peanut allergy in children: PEOPLE 3-year results. J Allergy Clin Immunol 146(4):863–874. https://doi.org/10.1016/j.jaci.2020.06.028
33. Bastin M, Carr WW, Davis CM, Fleischer DM, Lieberman JA, Mustafa SS et al (2023) Immune response evolution in peanut epicutaneous immunotherapy for peanut-allergic children. Allergy [Internet]. 78(9):2467–2476. https://onlinelibrary.wiley.com/doi/10.1111/all.15709. Accessed Nov 2023
34. DunnGalvin A, Fleischer DM, Campbell DE, O'B Hourihane J, Green TD, Sampson HA et al (2021) Improvements in quality of life in children following epicutaneous immunotherapy (Epit) for peanut allergy in the pepites and people studies. JACI: In Practice [Internet]. 9(1):216–224.e1. https://linkinghub.elsevier.com/retrieve/pii/S221321982030831X. Accessed Nov 2023
35. Gupta J, Margolis DJ (2020) Filaggrin gene mutations with special reference to atopic dermatitis. Current Treatment Options in Allergy 7(3):403–413. https://doi.org/10.1007/s40521-020-00271-x
36. (2020) Home • core outcome measures for food allergy [Internet]. European Cooperation in Science and Technology (COST). https://comfa.eu/. Accessed Dec 2023
37. Shaker M, Greenhawt M (2019) Estimation of health and economic benefits of commercial peanut immunotherapy products: a cost-effectiveness analysis. JAMA Network Open 2(5):e193242