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Specific allergen immunotherapy for the treatment of atopic eczema (Review)

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[Intervention Review]

Specific allergen immunotherapy for the treatment of atopic eczema

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ABSTRACT

Background

Specific allergen immunotherapy (SIT) is a treatment that may improve disease severity in people with atopic eczema (AE) by inducing immune tolerance to the relevant allergen. A high quality systematic review has not previously assessed the efficacy and safety of this treatment.

Objectives

To assess the effects of specific allergen immunotherapy (SIT), including subcutaneous, sublingual, intradermal, and oral routes, compared with placebo or a standard treatment in people with atopic eczema.

Search methods

We searched the following databases up to July 2015: the Cochrane Skin Group Specialised Register, CENTRAL in the Cochrane Library (Issue 7, 2015), MEDLINE (from 1946), EMBASE (from 1974), LILACS (from 1982), Web of Science™ (from 2005), the Global Resource of EczemA Trials (GREAT database), and five trials databases. We searched abstracts from recent European and North American allergy meetings and checked the references of included studies and review articles for further references to relevant trials.

Selection criteria

Randomised controlled trials (RCTs) of specific allergen immunotherapy that used standardised allergen extracts in people with AE.

Data collection and analysis

Two authors independently undertook study selection, data extraction (including adverse effects), assessment of risk of bias, and analyses. We used standard methodological procedures expected by Cochrane.

Main results

We identified 12 RCTs for inclusion in this review; the total number of participants was 733. The interventions included SIT in children and adults allergic to either house dust mite (10 trials), grass pollen, or other inhalant allergens (two trials). They were administered subcutaneously (six trials), sublingually (four trials), orally, or intradermally (two trials). Overall, the risk of bias was moderate, with high loss to follow up and lack of blinding as the main methodological concern.

Our primary outcomes were 'Participant- or parent-reported global assessment of disease severity at the end of treatment'; 'Participant- or parent-reported specific symptoms of eczema, by subjective measures'; and 'Adverse events, such as acute episodes of asthma or anaphylaxis'. SCORing Atopic Dermatitis (SCORAD) is a means of measuring the effect of atopic dermatitis by area (A); intensity (B); and subjective measures (C), such as itch and sleeplessness, which we used.

For 'Participant- or parent-reported global assessment of disease severity at the end of treatment', one trial (20 participants) found improvement in 7/9 participants (78%) treated with the SIT compared with 3/11 (27%) treated with the placebo (risk ratio (RR) 2.85, 95% confidence interval (CI) 1.02 to 7.96; P = 0.04). Another study (24 participants) found no difference: global disease severity improved in 8/13 participants (62%) treated with the SIT compared with 9/11 (81%) treated with the placebo (RR 0.75, 95% CI 0.45 to 1.26; P = 0.38). We did not perform meta-analysis because of high heterogeneity between these two studies. The quality of the evidence was low.

For 'Participant- or parent-reported specific symptoms of eczema, by subjective measures', two trials (184 participants) did not find that the SIT improved SCORAD part C (mean difference (MD) -0.74, 95% CI -1.98 to 0.50) or sleep disturbance (MD -0.49, 95% CI -1.03 to 0.06) more than placebo. For SCORAD part C itch severity, these two trials (184 participants) did not find that the SIT improved itch (MD -0.24, 95% CI -1.00 to 0.52). One other non-blinded study (60 participants) found that the SIT reduced itch compared with no treatment (MD -4.20, 95% CI -3.69 to -4.71) and reduced the participants' overall symptoms (P < 0.01), but we could not pool these three studies due to high heterogeneity. The quality of the evidence was very low.

Seven trials reported systemic adverse reactions: 18/282 participants (6.4%) treated with the SIT had a systemic reaction compared with 15/210 (7.1%) with no treatment (RR 0.78, 95% CI 0.41 to 1.49; the quality of the evidence was moderate). The same seven trials reported local adverse reactions: 90/280 participants (32.1%) treated with the SIT had a local reaction compared with 44/204 (21.6%) in the no treatment group (RR 1.27, 95% CI 0.89 to 1.81). As these had the same study limitations, we deemed the quality of the evidence to also be moderate.

Of our secondary outcomes, there was a significant improvement in 'Investigator- or physician-rated global assessment of disease severity at the end of treatment' (six trials, 262 participants; RR 1.48, 95% CI 1.16 to 1.88). None of the studies reported our secondary outcome 'Parent- or participant-rated eczema severity assessed using a published scale', but two studies (n = 184), which have been mentioned above, used SCORAD part C, which we included as our primary outcome 'Participant- or parent-reported specific symptoms of eczema, by subjective measures'.

Our findings were generally inconclusive because of the small number of studies. We were unable to determine by subgroup analyses a particular type of allergen or a particular age or level of disease severity where allergen immunotherapy was more successful. We were also unable to determine whether sublingual immunotherapy was associated with more local adverse reactions compared with subcutaneous immunotherapy.

Authors' conclusions

Overall, the quality of the evidence was low. The low quality was mainly due to the differing results between studies, lack of blinding in some studies, and relatively few studies reporting participant-centred outcome measures. We found limited evidence that SIT may be an effective treatment for people with AE. The treatments used in these trials were not associated with an increased risk of local or systemic reactions. Future studies should use high quality allergen formulations with a proven track record in other allergic conditions and should include participant-reported outcome measures.

PLAIN LANGUAGE SUMMARY

Specific allergy immunotherapy for the treatment of atopic eczema

Background

At least one in seven children and one in 50 adults suffer from atopic eczema, a skin condition characterised by an itchy red rash. People with atopic eczema are allergic to things in the environment, such as house dust mites, and exposure to what they are allergic to may make their eczema worse. Specific allergen immunotherapy is a treatment that involves a course of injections or drops under the tongue containing the substance to which a person is allergic. The treatment can reduce the severity of a person's allergy and may therefore be able to reduce symptoms of atopic eczema. We evaluated whether specific allergen immunotherapy was better or worse than a standard treatment or placebo at improving disease severity and symptoms as assessed by participants, parents, or investigators.

Review question

Is specific allergen immunotherapy an effective treatment for people with atopic eczema?

Study characteristics

The evidence is current to July 2015. We found 12 studies, with 733 participants, which included both children and adults. Studies were conducted in specialist allergy centres in nine countries. The duration of trials ranged from four months to three years. Immunotherapy was administered to the participants in four different ways. Allergen manufacturers funded seven of the 12 studies.

Key results

We found no evidence from the studies in our review that SIT may be an effective treatment for atopic eczema, as rated by participants or parents for disease severity and symptoms. We found limited evidence that SIT may improve investigator-rated disease severity. Immunotherapy did not cause any more harm than a standard treatment or placebo.

Quality of the evidence

Overall, the quality of the evidence was low. We downgraded quality mainly due to the differing results between studies, lack of blinding in some studies, and that relatively few studies reported outcomes relevant to patients. Future studies should use high quality allergen formulations with a proven track record in other allergic conditions and should include participant-reported outcome measures.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Specific immunotherapy compared with no immunotherapy for atopic eczema

Patient or population: adults and children with atopic eczema and inhalant allergen sensitisation
Settings: specialist allergy centres in the UK (2 trials), Italy (3 trials), USA, Germany, Belgium, Poland, Columbia, and China
Intervention: specific allergen immunotherapy
Comparison: no immunotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No immunotherapy	Specific allergen immunotherapy				
Participant- or parent-reported global assessment of disease severity Follow-up: 6 to 12 months	See comments	See comments	Not estimable	44[a] (2)	⊕⊕◯◯ **low**[b]	Improvement in 7/9 participants (78%) in the immunotherapy group and 3/11 participants (27%) in the placebo group (RR 2.85, 95% CI 1.02 to 7.96; P = 0.04 (Warner 1978)) 8/13 participants (62%) in the immunotherapy group and 9/11 participants (81%) in the placebo group (RR 0.75, 95% CI 0.45 to 1.26; P = 0.38 (Glover 1992)) Due to unexplained statistical heterogeneity, we did not pool the data

Participant- or parent-reported specific symptoms of eczema Follow-up: 12 to 18 months SCORAD part C measured as a combination of 2 Visual Analogue Scales (1 for itch, 1 for sleep disturbance), each on a scale from 0, no specific symptoms, to 10, maximum specific symptoms	The mean SCORAD part C score ranged across control groups from **3.07 to 5.29** The mean SCORAD part C sleep severity score ranged across control groups from **0.8 to 2.31** (Di Rienzo 2014; Novak 2012)	The mean SCORAD part C score in the immunotherapy group was on average **0.74 lower (95% CI -1.98 to 0.50)** The mean SCORAD part C sleep severity score in the immunotherapy group was on average **0.49 lower (95% CI -1.03 to 0.06)** (Di Rienzo 2014; Novak 2012)	-	339[a] (6)	⊕○○○ **very low**[c]	Itch: SCORAD part C itch severity at the end of treatment: MD -0.24, 95% CI -1.00 to 0.52; I^2 = 0% for Di Rienzo 2014 and Novak 2012 Itch severity score: MD -4.20, 95% CI -3.69 to -4.71 for Sanchez 2012 Due to unexplained statistical heterogeneity, we did not pool the data
Adverse events - any systemic reaction Follow-up: 6 to 18 months	**Low-risk population**		**RR 0.78** (0.41 to 1.49)	492[a] (7)	⊕⊕⊕○ **moderate**[d]	-
	0 per 1000	**0 per 1000** (0 to 0)				
	Medium-risk population					
	71 per 1000	**55 per 1000** (29 to 106)				
	High-risk population					
	163 per 1000	**127 per 1000** (67 to 243)				
Investigator- or physician-rated global assessment of disease severity Follow-up: 1 to 3 years	**Low-risk population**		**RR 1.48** (1.16 to 1.88)	286[a] (7)	⊕○○○ **very low**[e]	-

	0 per 1000	**0 per 1000** (0 to 10)				
	Medium-risk population					
	471 per 1000	**697 per 1000** (546 to 885)				
	High-risk population					
	778 per 1000	**1151 per 1000** (903 to 1462)				
Investigator- or physician-rated eczema severity using a published scale Follow-up: 12 to 18 months	The mean SCORAD score ranged across control groups from **26.7 to 32.6** (Di Rienzo 2014; Novak 2012; Sanchez 2012)	The mean SCORAD score in the immunotherapy group was on average **5.79 lower (95% CI -7.92 to -3.66)** (Di Rienzo 2014; Novak 2012; Sanchez 2012)	-	435[a] (6)	⊕◯◯◯ **very low**[f]	-
Participant or parent-rated eczema severity using a published scale Follow-up: 12 to 18 months	See comment	See comment	Not estimable	184[a] (2)	⊕⊕◯◯ **low**[g]	SCORAD part C used as the specific eczema symptom score (Di Rienzo 2014; Novak 2012)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IQR:** interquartile range; **MD:** mean difference; **RR:** risk ratio; **SCORAD**: SCORing Atopic Dermatitis.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risks are based on the total control group risk across all included studies (medium risk population) and the included studies with the lowest (low risk population) and highest (high risk population) control group risks.

[a]The number of total participants did not include those that were lost to follow up. The number of total participants and trials included those that contributed to narrative synthesis.

[b]We downgraded the quality of the evidence by two levels because of unexplained heterogeneity (serious, -1) and imprecision (serious, -1). There was significant heterogeneity (I^2 = 83%) between the estimate of dichotomous effects in two studies (Glover 1992 and Warner 1978), and data were not pooled. The information size was small.

[c]We downgraded the quality of the evidence by three levels because of study limitations (serious, -1), imprecision (serious, -1), and unexplained heterogeneity (serious, -1). Two trials were non-blinded (Di Rienzo 2014; Sanchez 2012). Moderate proportions of participants were not analysed (losses to follow up). The information size was small. Most subgroups of estimate of treatment effects were not significant, with high heterogeneity displayed by itch (I^2 = 98%). We did not pool data from all studies because of different symptoms and different scoring systems reported.

[d]We downgraded the quality of the evidence by one level because of imprecision (serious, -1). The estimate of treatment effect relied largely on two studies (Novak 2012; Qin 2014). It is unclear whether the estimate obtained from a small number of adverse reactions to two different dust mite extracts can be generalised. Indeed, data from other populations suggest that specific allergen immunotherapy is generally associated with a small but significant risk of systemic adverse reactions.

[e]We downgraded the quality of the evidence by three levels because of study limitations (serious, -2) and imprecision (serious, -1). The estimate of treatment effect relied on two non-blinded studies. The information size was small.

[f]We downgraded the quality of the evidence by three levels because of study limitations (serious, -2) and imprecision (serious, -1). Two studies were non-blinded. Moderate proportions of participants were not analysed (losses to follow up). The information size was small.

[g]We downgraded the quality of the evidence by two levels because of study limitations (serious, -1) and imprecision (serious, -1). One study was non-blinded. Moderate proportions of participants were not analysed (losses to follow up). The information size was small. We did not include analyses of non-published scales in this summary table.

BACKGROUND

We have listed unfamiliar terms in the glossary of terms in Table 1.

Description of the condition

Atopic eczema (AE) is a chronic inflammatory skin condition that affects 15% to 30% of children and 2% to 10% of adults world wide (Odhiambo 2009; Williams 2006). The terms 'atopic eczema' and 'atopic dermatitis' are synonymous. Severe itching and patches of dry inflamed skin in varying locations depending on the age of the person characterise this condition (Akdis 2006). In infants, AE is usually found on the cheeks, forehead, or scalp. In childhood, AE usually involves the hands, feet, wrists, ankles, and the creases of the elbows and backs of the knees (Akdis 2006). In adults, AE causes dry scaly patches and large plaques of thickened (lichenified) skin in the flexural folds; the face and neck; the upper arms and back; and the backs of the hands, feet, fingers, and toes (Akdis 2006). Strictly speaking, the term 'atopic eczema' "should only refer to individuals who have the physical features of eczema plus evidence of specific immunoglobulin E (IgE) antibodies to common environmental allergens such as house dust mite" (Johansson 2004). We have used this strict definition throughout this review unless we have specified otherwise.

Several observations suggest that allergens may be important causes of atopic eczema. Firstly, direct exposure of the skin to environmental allergens, including perennial allergens like house dust mite, and seasonal allergens like pollen has been shown to increase the severity of atopic eczema (Capristo 2004; Purvis 2005; Schäfer 1999). Secondly, other diseases triggered by allergens are common in those with atopic eczema. For example, of those children who develop the condition during the first two years of life, an estimated 50% may develop asthma during subsequent years (Warner 2001). Finally, those with more severe AE have an increased risk of asthma and allergic rhinitis (Gustafsson 2000; Illi 2004).

Despite the current available topical treatment with emollients; corticosteroids; calcineurin inhibitors; and other treatments, such as antibiotics, people with atopic eczema often cannot keep their condition completely under control. In some cases, the medications used can cause more harm than benefit (Akdis 2006). Therefore, considering the atopic background of the disease and its possible correlation with allergen-triggering factors, some other types of treatment have been proposed, which include specific allergen immunotherapy (SIT) (Darsow 2012).

Description of the intervention

Specific allergen immunotherapy (SIT) is a treatment for allergic disease that involves the administration of an allergen in high doses in order to induce immune tolerance to that allergen and relieve symptoms (Calderon 2007). For example, in people with hay fever who are allergic to grass pollen, SIT may involve treatment with injections, drops, or tablets of grass pollen over a period of months in order to relieve symptoms (Calderon 2007; Wilson 2005). Specific allergen immunotherapy is the only treatment shown to provide longer-term benefit in allergic diseases after treatment has stopped (Durham 1999). It has been shown to be an effective treatment for allergic rhinitis and allergic asthma, although the treatment carries a risk of severe allergic reaction (Calderon 2007; CSM report 1986; Wilson 2005).

How the intervention might work

Specific allergen immunotherapy works by inducing changes in the immune response to the relevant allergen, so that in diseases caused by an abnormal response to that allergen, there may be an improvement in symptoms (Allam 2006). The specific immune changes caused by SIT include an increase in activity of suppressive components of the immune system (regulatory T cells) and an increase in antibodies (immunoglobulin G (IgG) antibodies) to the allergen (Bussmann 2007; Bussmann 2009; Maintz 2007). The presence of allergic sensitisation in those with AE and the relationship between AE and other allergic diseases suggest that allergic immune responses are an important part of the disease process in AE (Gustafsson 2000; Illi 2004; Warner 2001). It is therefore plausible that SIT might be able to reduce symptoms in people with AE by inhibiting abnormal immune responses to allergens.

Why it is important to do this review

Specific allergen immunotherapy is a disease-modifying treatment that reduces symptoms in people with other allergic conditions: allergic rhinitis, allergic conjunctivitis, and asthma (Abramson 2003; Calderon 2007; Dahl 2006; Didier 2007; Penagos 2008). Hence, SIT might be potentially effective in reducing AE. An evaluation of its effects on skin manifestations in the context of randomised controlled trials could provide an alternative treatment for people with AE.

The plans for this review were published as a protocol 'Specific allergen immunotherapy for the treatment of atopic eczema' (Calderon 2010).

OBJECTIVES

To assess the effects of specific allergen immunotherapy (SIT), including subcutaneous, sublingual, intradermal, and oral routes, compared with placebo or a standard treatment in people with atopic eczema.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults and children with atopic eczema (AE) and allergic sensitisation to an inhalant or food allergen. "Allergy needed to be proven using an objective test such as a positive skin prick test or high circulating levels of allergen-specific IgE antibody detected by a specific blood test for allergy called the radioallergosorbent test. Trials focusing on allergic rhinitis or asthma without eczema were excluded" (Calderon 2011). Where trials included participants with and without AE, we only included the trial if the results for the participants with AE were separately reported.

Types of interventions

High-dose immunotherapy with standardised allergen extracts for single allergen or mixed allergens administered by the sublingual (under the tongue), subcutaneous (under the skin), intradermal (into the skin), or oral route compared with placebo or a standard treatment, such as emollients, topical corticosteroids, or topical calcineurin inhibitors. We considered all appropriate allergens at all doses and all durations of treatment.

Types of outcome measures

Primary outcomes

1. Participant- or parent-reported global assessment of disease severity at the end of treatment, i.e. the proportion with good or excellent improvement at this time as reported in the trials (whether treatment was given for one, two, or three years, or other duration).
2. Participant- or parent-reported specific symptoms of eczema, by subjective measures such as itch or sleep disturbance (SCORing Atopic Dermatitis (SCORAD) part C).
3. Adverse events, such as acute episodes of asthma or anaphylaxis.

Secondary outcomes

1. Investigator- or physician-rated global assessment of disease severity at the end of treatment, i.e. the proportion with good or excellent improvement at this time as reported in the trials (whether treatment was given for one, two, or three years, or other duration).
2. Parent- or participant-rated eczema severity assessed using a published scale (e.g. Patient Oriented Eczema Measure (POEM)).
3. Investigator- or physician-rated eczema severity assessed using a published scale (e.g. SCORAD).
4. Use of other medication for treatment of eczema during the intervention period (e.g. topical/systemic corticosteroids, calcineurin inhibitors, or oral antihistamines).
5. Validated eczema-related quality of life scores (e.g. Dermatitis Family Impact Questionnaire, Children's Dermatology Life Quality Index) (Lewis-Jones 1995).

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 21 July 2015:

- the Cochrane Skin Group Specialised Register using the terms '(dermatitis or eczema) and (immuno* or allerg*)';
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2015, Issue 7, in the Cochrane Library using the search strategy in Appendix 1;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 2;
- EMBASE via Ovid (from 1974) using the strategy in Appendix 3;
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 4;
- the Global Resource of EczemA Trials. Centre of Evidence Based Dermatology, accessed at www.greatdatabase.org.uk, using the terms 'immuno* or allerg*' in the title or keywords of records and restricting to included studies only; and
- Web of Science™ (from 2005) using the strategy in Appendix 5.

Trials registers

We searched the following trials registers up to 3 August 2015 using the terms 'immunotherapy and (eczema or dermatitis)'.

- The International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (apps.who.int/trialsearch/).

- The Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

We created a database of first and last names of authors of potentially eligible studies and searched the Science Citation Index Expanded (SCI-EXPANDED, 1945 to the present) using these names in order to identify further relevant studies.

Reference lists

We checked the bibliographies of each included study and of published reviews for further reports of relevant trials.

Correspondence

We contacted the primary author of each included study to identify additional published and unpublished studies. We contacted allergen immunotherapy product manufacturers to request details of published or unpublished studies of allergen immunotherapy that included eczema as an outcome measure.

Conference proceedings

We searched the abstracts of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology meetings from 2010 to 2015.

Data collection and analysis

Some parts of the methods section of this review uses text that was originally published in other Cochrane Reviews co-authored by RB and MC (predominantly Boyle 2012 and Calderon 2011). We included a 'Summary of findings' table where we used the Grading of Recommendations Assessment, Development and Education (GRADE) approach to assess the quality of the evidence for the primary and secondary outcomes.

Selection of studies

Two authors, RB and MC or HT, independently checked titles and abstracts identified from the searches, looked at the full text of all studies of possible relevance for assessment, and decided which trials met the inclusion criteria. The authors resolved any disagreements by discussing issues with each other, and the planned recourse to a third author (HN) for arbitration did not prove necessary. We sought further information from trial authors when needed to confirm eligibility.

Data extraction and management

Two authors, RB and HT or LM, independently extracted data from included trials and entered data into a specially designed data extraction sheet, and the authors met to compare results. MC, RB, and HT wrote to all authors to request additional information as required. Two authors, RB and HT or LM, entered the data into Review Manager (RevMan).

Assessment of risk of bias in included studies

We assessed and documented the risk of bias in the included studies by concentrating on the following six parameters to assess quality: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Three authors, RB, HT, and HN, independently assessed risk of bias: we were not masked to study details. We met to resolve any disagreements, and the planned recourse to a fourth author, MC, for arbitration did not prove necessary.
The 'Risk of bias' tables, which are part of the 'Characteristics of included studies' tables, addressed each domain for each study.

Measures of treatment effect

For continuous data, we calculated individual and pooled statistics as mean differences (MD) where studies used the same outcome measure and reported them with a 95% confidence interval (CI) where possible. For dichotomous outcomes, we expressed results as a risk ratio (RR) with 95% CI, where possible. We were unable to express the result for dichotomous outcomes as number needed to treat (NNT) as we had originally planned.

Unit of analysis issues

We planned to analyse cross-over trials through the use of techniques appropriate for paired designs and data from parallel trials and cross-over trials as separate subgroups, since cross-over studies may not be appropriate for immunotherapy studies. Our search did not identify any cross-over trials.
We planned to list non-randomised controlled studies but did not discuss them further because we did not identify significant studies or data from non-randomised controlled studies.
Where studies reported more than one active intervention, we planned to combine the two active interventions and analyse them together, but we included no trials with more than one eligible active intervention. Where studies reported non-parametric statistics, we planned to include these in meta-analyses where possible, following the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We contacted authors when a paper did not present details about study design or descriptive statistics for outcomes (mean, standard deviation (SD)). If the authors did not respond within a reasonable time (six to eight weeks) to at least two separate written requests for information, we conducted the review based on available information.

Assessment of heterogeneity

We used the I^2 statistic to test for heterogeneity and assumed substantial statistical heterogeneity if the I^2 was greater than 50% (Higgins 2002). We used sensitivity or subgroup analysis to explore any statistical or clinical heterogeneity (see below). Quantitative analyses of outcomes were, wherever possible, on an intention-to-treat basis, i.e. participants were evaluated in the groups to which they were randomised, rather than according to the actual treatment that they received.

We gave consideration to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity and used a random-effects model.

Assessment of reporting biases

We planned to use funnel plots to assess publication bias graphically (if there were sufficient included studies) and Begg and Egger tests to assess it statistically (Begg 1994; Egger 1997); however, we did not have a sufficient number of included studies.

Data synthesis

We planned to combine appropriate data from individual studies in a meta-analysis only if heterogeneity measured by I^2 was less than 75% with the use of a random-effects model. Where meta-analyses were not applicable, we used a narrative synthesis of outcomes from relevant studies.

Subgroup analysis and investigation of heterogeneity

We planned five a priori subgroup analyses.

1. Immunotherapy type: sublingual and subcutaneous.
2. Allergen type: seasonal inhalant, perennial inhalant, food, and microbial.
3. Age of participants: up to four years, five to 11, 12 to 17, and 18 or over.
4. Immunotherapy regimens to be subdivided empirically into low, intermediate, and high dose therapy according to content of major allergen per dose (e.g. *Phleum* p5 for grass, Bet v1 for birch pollen, Fel d1 for cat, etc.):

    i) for subcutaneous immunotherapy, content of major allergen 1 mcg to 5 mcg, 6 mcg to 10 mcg, and greater than 11 mcg per four- to six-weekly maintenance injection doses; and

    ii) for sublingual immunotherapy, content of major allergen 1 mcg to 5 mcg, 6 mcg to 10 mcg, and greater than 11 mcg per daily maintenance sublingual dose (or equivalent if taken less frequently).

5. Severity of AE at randomisation: mild (SCORAD mean objective score of 0 to 15), moderate (SCORAD mean objective score of 16 to 40), and severe (SCORAD mean objective score of greater than 40).

Sensitivity analysis

We planned to undertake sensitivity analysis for the allocation of missing data by best and worst case analysis. If we had found significant heterogeneity between studies, we planned to explore possible reasons for this, which would have included risk of bias in the included studies. However, we did not perform posthoc sensitivity analyses because of the small number of studies that contributed to meta-analyses.

RESULTS

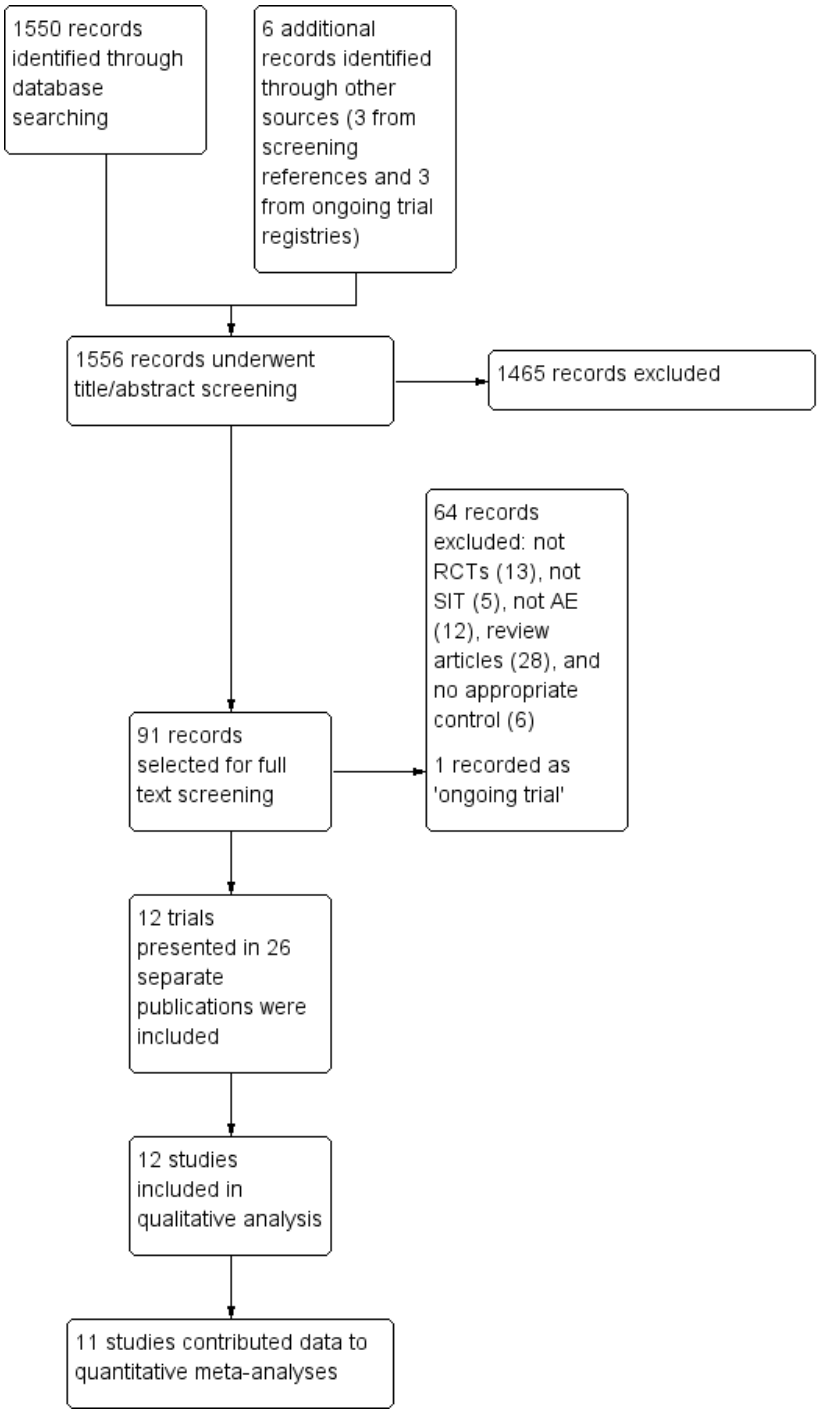
Description of studies

See the 'Characteristics of included studies', 'Characteristics of excluded studies', 'Characteristics of studies awaiting classification', and 'Characteristics of ongoing studies' tables.

Results of the search

The search identified 1550 references from electronic databases and six additional reports from other sources (three from screening references of review articles and three from ongoing trials registries), which gave a total of 1556 records (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Figure 1). We excluded 1465 references based on titles and abstracts. MC or HT and RB selected 91 records for which they screened the full text. We excluded 64 records and listed one as an ongoing study. Overall, 26 reports of 12 separate studies met the inclusion criteria (Di Rienzo 2014; Galli 1994; Glover 1992; Kaufman 1974; Leroy 1993; Luna-Pech 2013; Novak 2012; Pajno 2007; Qin 2014; Sanchez 2012; Silny 2006; Warner 1978). We contacted the authors of all of the 12 included trials for original data and clarification of methods; we received further details from the authors or their collaborators for four trials (Di Rienzo 2014; Novak 2012; Sanchez 2012; Warner 1978).

Figure 1. PRISMA flow diagram



Included studies

We included 12 studies, with a total of 733 participants.

Setting

Studies were conducted in specialist allergy centres in the UK (Glover 1992; Warner 1978), Italy (Di Rienzo 2014; Galli 1994; Pajno 2007), the USA (Kaufman 1974), Germany (Novak 2012), Belgium (Leroy 1993), Poland (Silny 2006), Columbia (Sanchez 2012), Mexico (Luna-Pech 2013), and China (Qin 2014).

Participants

Two trials studied adults (Novak 2012; Qin 2014), six studied children (Di Rienzo 2014; Galli 1994; Glover 1992; Luna-Pech 2013; Pajno 2007; Warner 1978), and four studied both children and adults (Kaufman 1974; Leroy 1993; Sanchez 2012; Silny 2006). Ten studies were restricted to people allergic to *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* (house dust mites) or both (Di Rienzo 2014; Galli 1994; Glover 1992; Leroy 1993; Luna-Pech 2013; Novak 2012; Pajno 2007; Qin 2014; Sanchez 2012; Warner 1978), one study was restricted to people allergic to house dust mites or grass pollen (Silny 2006), and one study was restricted to people allergic to a group of unspecified inhalant antigens (Kaufman 1974).

Interventions

The 12 included studies were all of specific allergen immunotherapy (SIT). Of these, six trials studied subcutaneous immunotherapy (SCIT) (Glover 1992; Kaufman 1974; Novak 2012; Sanchez 2012; Silny 2006; Warner 1978), four studied sublingual immunotherapy (SLIT) (Di Rienzo 2014; Luna-Pech 2013; Pajno 2007; Qin 2014), one studied intradermal immunotherapy (Leroy 1993), and one studied oral immunotherapy (Galli 1994).
Eight trials compared the intervention with a placebo (Glover 1992; Kaufman 1974; Leroy 1993; Luna-Pech 2013; Novak 2012; Pajno 2007; Silny 2006; Warner 1978), and four compared the intervention with a standard treatment (Di Rienzo 2014; Galli 1994; Qin 2014; Sanchez 2012). The duration of treatment was less than a year in one trial, Leroy 1993, and at least a year in Di Rienzo 2014, Galli 1994, Glover 1992, Kaufman 1974, Luna-Pech 2013, Novak 2012, Pajno 2007, Qin 2014, Sanchez 2012, Silny 2006, and Warner 1978.

Outcomes

With regard to our prespecified primary outcomes, two studies reported 'Participant- or parent-reported global assessment of disease severity at the end of treatment' (Glover 1992; Warner 1978), six studies reported 'Participant- or parent-reported specific symptoms of eczema, by subjective measures' (Di Rienzo 2014; Glover 1992; Leroy 1993; Novak 2012; Pajno 2007; Sanchez 2012), and seven studies reported 'Adverse events' (Di Rienzo 2014; Glover 1992; Novak 2012; Pajno 2007; Qin 2014; Sanchez 2012; Silny 2006).
With regard to our prespecified secondary outcomes, seven studies reported 'Investigator- or physician-rated global assessment of disease severity at the end of treatment' (Di Rienzo 2014; Galli 1994; Kaufman 1974; Leroy 1993; Qin 2014; Sanchez 2012; Silny 2006), two studies reported 'Parent- or participant-rated eczema severity assessed using a published scale' in the form of SCORing Atopic Dermatitis (SCORAD) part C (Di Rienzo 2014; Novak 2012), six studies reported 'Investigator- or physician-rated eczema severity assessed using a published scale' (Di Rienzo 2014; Luna-Pech 2013; Novak 2012; Qin 2014; Pajno 2007; Sanchez 2012), eight studies reported 'Use of other medication for treatment of eczema during the intervention period' (Glover 1992; Kaufman 1974; Luna-Pech 2013; Novak 2012; Pajno 2007; Qin 2014; Sanchez 2012; Silny 2006), and one study reported 'Validated eczema-related quality of life scores' (Novak 2012).
Three studies measured other outcomes: one measured total serum immunoglobulin E (IgE) levels, specific IgE levels, and skin prick test results (Glover 1992); another measured specific IgE levels and other serum inflammatory parameters associated with either allergic inflammation or its suppression, including eosinophilic cationic protein (ECP), soluble interleukin 2 receptor (sIL-2R), interferon gamma (IFN-gamma), or interleukins 4, 5, and 10 (Silny 2006); and a third measured specific serum IgG4 levels (Qin 2014).
Only two of the five publications that reported outcomes from the Pajno 2007 study contributed data to the review, because the other three publications did not report atopic eczema outcomes.

Excluded studies

We rejected the other 64 titles for the following reasons: not a randomised controlled trial (RCT) (13), not SIT (five), not atopic eczema (AE) (12), review articles (28), and no appropriate control (six). The reason we included these articles for the full text review stage is that from the title or abstract we could not exclude the possibility that they were RCTs of adults or children with AE and allergic sensitisation, but after assessment of the full text, we excluded them.

Studies awaiting classification

There were no studies awaiting classification.

Ongoing studies

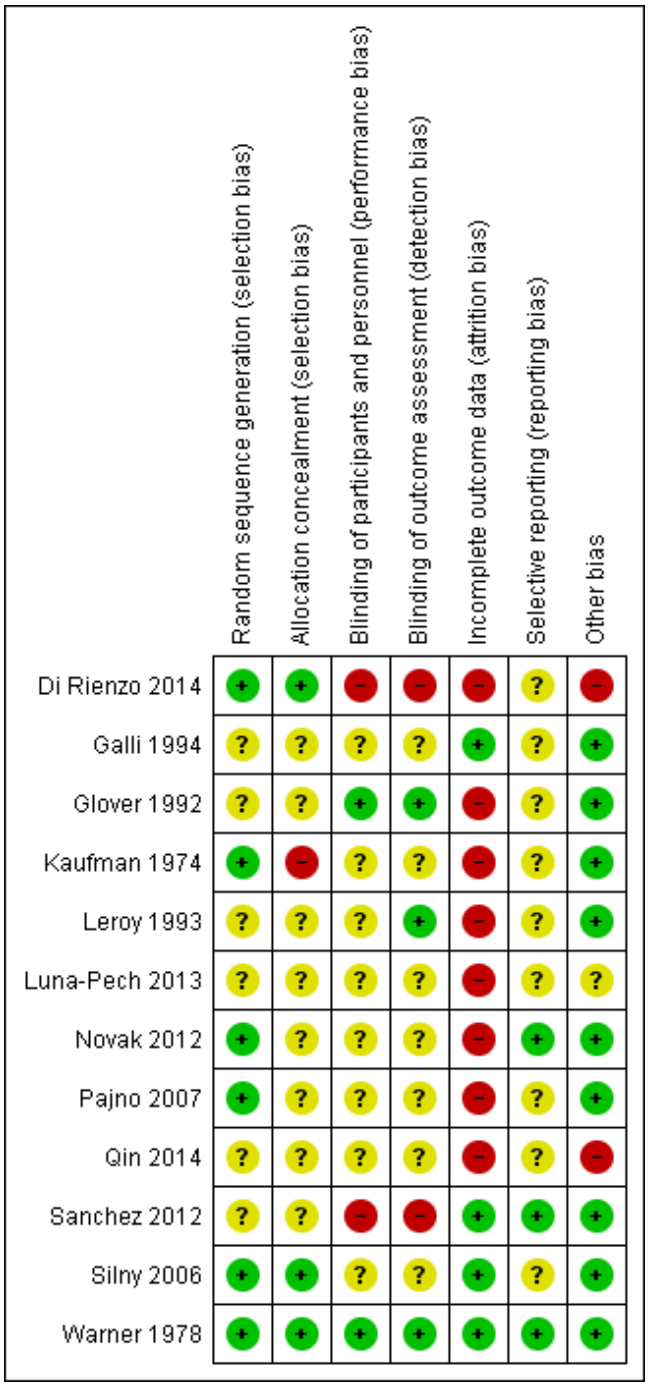
There was one ongoing trial with no outcome data available at the time of review (see the 'Characteristics of ongoing studies' table).

The contacts for the trial NCT00310492 did not respond to our request for further information.

Risk of bias in included studies

Full details are shown in the 'Characteristics of included studies' tables. Please see the 'Risk of bias' summary (review authors' judgements about each 'Risk of bias' item for each included study, Figure 2).

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study



Random sequence generation

There was a low risk of bias related to generation of randomisation sequence concealment in six studies, Di Rienzo 2014, Kaufman 1974, Novak 2012, Pajno 2007, Silny 2006, Warner 1978, and unclear risk in the following six studies: Galli 1994, Glover 1992, Leroy 1993, Luna-Pech 2013, Qin 2014, and Sanchez 2012.

Allocation

There was a low risk of bias related to allocation concealment in three studies (Di Rienzo 2014; Silny 2006; Warner 1978), high risk in one study (Kaufman 1974), and unclear risk in eight studies due to insufficient details provided (Galli 1994; Glover 1992; Leroy 1993; Luna-Pech 2013; Novak 2012; Pajno 2007; Sanchez 2012; Qin 2014).

Blinding

There was a low risk of bias related to blinding of participants and personnel in two studies (Glover 1992; Warner 1978), which were either double blinded or triple blinded; high risk in two studies (Di Rienzo 2014; Sanchez 2012), which were open label; and unclear risk in eight studies due to insufficient details provided (Galli 1994; Kaufman 1974; Leroy 1993; Luna-Pech 2013; Novak 2012; Pajno 2007; Qin 2014; Silny 2006).

There was a low risk of bias related to blinding of outcome assessors in three studies (Glover 1992; Leroy 1993; Warner 1978); high risk in two studies (Di Rienzo 2014; Sanchez 2012), which were open label; and unclear risk in seven studies (Galli 1994; Kaufman 1974; Luna-Pech 2013; Novak 2012; Pajno 2007; Qin 2014; Silny 2006), four of which were unclear regarding whether they included outcome assessors in the double blinding (Kaufman 1974; Novak 2012; Pajno 2007; Silny 2006).

Incomplete outcome data

There was a low risk of bias related to incomplete outcome data in four studies, Galli 1994, Sanchez 2012, Silny 2006, and Warner 1978, where loss to follow-up rates were low, and high risk in eight studies where loss to follow up rates were high (up to 51%) or postrandomisation exclusions were noted: Di Rienzo 2014, Glover 1992, Kaufman 1974, Leroy 1993, Luna-Pech 2013, Qin 2014, Novak 2012, and Pajno 2007.

Selective reporting

There was a low risk of bias related to selective reporting in three studies where the specified outcomes in the methodology were reported in the results, Novak 2012, Sanchez 2012, Warner 1978, and unclear risk in nine studies: Di Rienzo 2014, Galli 1994, Glover 1992, Kaufman 1974, Leroy 1993, Luna-Pech 2013, Pajno 2007, Qin 2014, and Silny 2006.

Other potential sources of bias

There was low risk of bias related to other sources in nine studies (Galli 1994; Glover 1992; Kaufman 1974; Leroy 1993; Novak 2012; Pajno 2007; Sanchez 2012; Silny 2006; Warner 1978), high risk in two studies where the manufacturer funded the study either partly or wholly and the authors were affiliated with the manufacturer (Di Rienzo 2014; Qin 2014), and unclear risk in one study where it was unclear whether the authors were affiliated with the manufacturer (Luna-Pech 2013).

Effects of interventions

See: **Summary of findings for the main comparison** Specific allergen immunotherapy versus no immunotherapy

See Summary of findings for the main comparison for the main comparison 'specific allergen immunotherapy versus no immunotherapy'.

Primary outcomes

1. Participant- or parent-reported global assessment of disease severity at the end of treatment

One study, Warner 1978, measured this outcome as whether the eczema was improved, there was no change, or it was worse as rated by the participants or parents. These data were available for 20 participants at the end of the treatment (nine active, 11 placebo), with improvement in 7/9 (78%) of the immunotherapy group and 3/11 (27%) in the placebo group (risk ratio (RR) 2.85, 95% confidence interval (CI) 1.02 to 7.96). Another study, Glover 1992, measured this outcome as whether the eczema was better, the same, or worse as rated by parents. These data were available for 24 participants, with improvement in 8/13 (62%) of those in the active treatment group and 9/11 (81%) in the placebo group (RR 0.75, 95% CI 0.45 to 1.26). We did not perform meta-analysis because of high heterogeneity between the two studies (I^2 = 83%). The high loss to follow-up rate and as-treated analysis in the study by Glover 1992 may have contributed to the significant heterogeneity. The quality of the evidence was low.

2. Participant- or parent-reported specific symptoms of eczema, by subjective measures

We used original data shared by the authors of two studies, Di Rienzo 2014 and Novak 2012, to calculate SCORing Atopic Dermatitis (SCORAD) part C scores at the end of treatment, and the components of SCORAD part C, which are itch measured by Visual Analogue Scales (VAS) and sleep disturbance measured by VAS, each on a scale from 0 to 10. Meta-analysis, with a total of 184 participants, showed no significant difference in SCORAD part C (mean difference (MD) -0.74, 95% CI -1.98 to 0.50; I^2 = 0%; Analysis 1.1) or severity of sleep disturbance (MD -0.49, 95% CI -1.03 to 0.06; I^2 = 0%; Analysis 1.1).

The authors of Sanchez 2012 provided original data that showed subjective symptom scores at the end of the treatment on a scale of 0 to 100, where higher scores meant more symptoms, and a component of the symptom score, which measured itching severity on a scale of 0 to 10, where higher scores also mean more symptoms. These data were available for 60 participants at the end of the treatment (31 active, 29 placebo), with a mean overall severity score of 37.3 (95% CI 32.4 to 42.1) in the immunotherapy group and 80.8 (95% CI 75.8 to 85.7) in the control group (P < 0.001) and a mean itch severity score of 3.2 (95% CI 2.3 to 4.0) in the immunotherapy group and 7.5 (95% CI 6.9 to 8.0) in the control group (P < 0.001). The difference between groups in change in itch severity score from baseline was also statistically significant (MD -4.20, 95% CI -3.69 to -4.71).

For itch severity, we did not meta-analyse data from these three studies because of extreme heterogeneity (I^2 = 98%), which was attributable to the open label study of Sanchez 2012. When we excluded this study from meta-analysis, combined data from Novak 2012 and Di Rienzo 2014 showed no significant difference in SCORAD part C itch severity (MD -0.24, 95% CI -1.00 to 0.52; I^2 = 0%).

One study, Glover 1992, reported symptoms in the form of itch score presented graphically that showed no significant difference between the active and placebo groups. One study, Leroy 1993, reported a mean itch score of 2.2 (or 33% reduction from baseline) after immunotherapy compared with 2.6 (or 19% reduction from baseline) in the control group. The authors did not comment on whether this difference was statistically significant and did not respond to our request for further data.

Other studies reported insufficient data, such as Pajno 2007, or did not measure this outcome, such as Galli 1994, Kaufman 1974, Luna-Pech 2013, Qin 2014, Silny 2006, and Warner 1978.

3. Adverse events

Seven studies reported local or systemic reactions to treatment (Di Rienzo 2014; Glover 1992; Novak 2012; Pajno 2007; Qin 2014; Sanchez 2012; Silny 2006).

In addition to individual studies, meta-analysis, with a total of 484 participants, showed no statistically significant increase in risk of local reactions (RR 1.27, 95% CI 0.89 to 1.81; I^2 = 25%; Analysis 1.2). Data from seven of the 12 studies contributed to this effect estimate (Di Rienzo 2014; Glover 1992; Novak 2012; Pajno 2007; Qin 2014; Sanchez 2012; Silny 2006).

In addition to individual studies, meta-analysis with a total of 492 participants showed no statistically significant increase in risk of systemic reactions (RR 0.78, 95% CI 0.41 to 1.49; I^2 = 0%; Analysis 1.2), with 18 events observed in the immunotherapy group and 15 in the control group. Data from four of 12 studies contributed to this effect estimate (Glover 1992; Novak 2012; Pajno 2007; Qin 2014). However, there were no systemic reactions reported in three studies (Di Rienzo 2014; Sanchez 2012; Silny 2006).

One study, Pajno 2007, with 48 participants, measured other adverse reactions and showed no statistically significant increase in risk of tiredness (RR 5.08, 95% CI 0.66 to 39.02; Analysis 1.2) or headache (RR 2.56, 95% CI 0.11 to 59.75; Analysis 1.2).

Secondary outcomes

1. Investigator- or physician-rated global assessment of disease severity at the end of treatment

Six studies reported investigator- or physician-rated global assessment of disease severity (Di Rienzo 2014; Galli 1994; Kaufman 1974; Qin 2014; Sanchez 2012; Silny 2006). Meta-analysis, with 262 participants, showed significant improvement in disease severity (RR 1.48, 95% CI 1.16 to 1.88; I^2 = 19%; Analysis 1.3).

One study, Leroy 1993, with 24 participants, reported improvement in 70% of all of the participants that used an investigator-rated index of disease severity at a threshold of 50% improvement. This was significant between the treatment and the placebo group (P < 0.003), but there were no separate data for the treatment and placebo group, so we could not include them in a meta-analysis.

Other studies did not measure this outcome (Glover 1992; Luna-Pech 2013; Novak 2012; Pajno 2007; Warner 1978).

2. Parent- or participant-rated eczema severity assessed using a published scale

None of the studies reported participant- or parent-rated eczema severity using a published scale, except for two studies that we have mentioned above, Di Rienzo 2014 and Novak 2012, which recorded SCORAD part C, which we included in this systematic review as a parent- or participant-rated specific eczema symptom (MD -0.74, 95% CI -1.98 to 0.50; I^2 = 0%; Analysis 1.1).

Participant- or parent-rated eczema severity assessed using a non-published scale

Although this was not a prespecified outcome, we felt it important to include. Four studies measured participant- or parent-rated eczema severity assessed using non-published Visual Analogue Scales (VAS) on a scale of 0 to 10 (0 = no symptoms, 10

= maximal symptoms). Meta-analysis of two studies (Di Rienzo 2014; Qin 2014), with a total of 158 participants, showed statistically significant lower end-of-treatment VAS scores (MD -1.12, 95% CI -1.92 to -0.32; I^2 = 0%; Analysis 1.4). We used original data shared by the authors of one study, Di Rienzo 2014, to conduct this analysis.

The other two studies only provided original data listed as illustrative text: Pajno 2007 reported a VAS that measured overall eczema symptoms with 10.7% improvement in the treatment group and 13.1% worsening in the placebo group (P = 0.07), but the study did not report absolute values. Leroy 1993 reported a VAS that measured participant general well-being with a significant improvement in the treatment group (P = 0.008) but not in the control group, but again, did not report absolute values. Authors of the latter two studies did not respond to our requests for original data for inclusion in a meta-analysis.

3. Investigator- or physician-rated eczema severity assessed using a published scale

Six studies reported 'Investigator- or physician-rated eczema severity assessed using a published scale' in the form of SCORAD (Di Rienzo 2014; Luna-Pech 2013; Novak 2012; Pajno 2007; Qin 2014; Sanchez 2012). Authors of two studies supplied original data for end-of-treatment SCORAD (Novak 2012; Sanchez 2012). Meta-analysis of three trials (Di Rienzo 2014; Novak 2012; Sanchez 2012), with 244 participants, showed significant improvement in end of treatment SCORAD (MD -5.79, 95% CI -7.92 to -3.66; I^2 = 0%; Analysis 1.5).

One study, Qin 2014, reported reduction ratios in SCORAD and classified scores as cure (greater than 90%), marked effect (60% to 89%), improvement (20% to 59%), and ineffective (less than 19%). The total efficacy (defined as percentage of participants with change in SCORAD $\geq$ 60%) was significantly greater in the specific allergen immunotherapy (SIT) group (77.78%) than in the control group (53.85%) (P < 0.05) and was included as a dichotomous 'Investigator- or physician-rated global assessment of disease severity at the end of treatment' outcome in a meta-analysis in this review (RR 1.48, 95% CI 1.16 to 1.88; I^2 = 19%; Analysis 1.3). Another study, Luna-Pech 2013, found a significant change in SCORAD between immunotherapy (-18.4 ± 6.5) and control (-6.6 ± 4.1) (P = 0.008). This effect was greater for participants with severe eczema at baseline. A further study, Pajno 2007, suggested greater SCORAD improvement with the SIT than in controls in graphical data (P < 0.001), but no numerical data were available. No data for end of treatment SCORAD scores from these three studies were available for inclusion in a meta-analysis.

One study, Glover 1992, reported no significant difference in a non-published scale that measured erythema, lichenification, and surface damage between the immunotherapy and the placebo groups. Another study, Galli 1994, reported no significant difference between treatment groups, using a non-published scale that measured severity of erythema, vesicles, fissuration, lichenification, and itching.

4. Use of other medication for treatment of eczema during the intervention period

One study, Silny 2006, with 20 participants, reported no statistically significant difference between the treatment groups in the use of topical steroids for mild to moderate flares of AE (RR 1.33, 95% CI 0.74 to 2.41; Analysis 1.6). Another study, Glover 1992, reported no significant difference in the use of topical steroids between the treatment groups. (There were no numerical data for meta-analysis.) One study, Sanchez 2012, reported a significant reduction in the use of topical steroids and tacrolimus during one year of immunotherapy (P = 0.02), but there was no such reduction in the control group.

Two studies reported the use of systemic steroids for AE. One study, Kaufman 1974, with 26 participants, required the use of systemic steroids in 8/16 participants (50%) in the immunotherapy group and 4/10 participants (40%) in the placebo group (P = 0.70). Another study, Sanchez 2012, with 60 participants, reported a significant increase in systemic steroid use in 12/29 participants (41%) in the control group compared with 4/31 participants (13%) in the immunotherapy group (P = 0.02). We did not perform meta-analysis because of the high heterogeneity (I^2 = 76%). The reason for high heterogeneity between these two studies was unclear.

Another study, Novak 2012, with 168 participants, reported a non-significant 32% difference in the median AUC (area under the curve) of medication score, a culmination of topical medication and overall consumption of systemic medication (19,330 in the immunotherapy group and 28,420 in the placebo group; P = 0.08). These data were not in a format suitable for incorporation into a meta-analysis.

One study, Pajno 2007, reported a significant decrease in the use of rescue medications (oral hydroxyzine and topical steroids, respectively) in the immunotherapy group. There were 171 occasions where rescue medications were used in the immunotherapy group compared with 346 occasions in the placebo group (P = 0.03). The rescue medications were used on 93 days in the immunotherapy group and 158 days in the placebo groups (P = 0.01).

One study, Luna-Pech 2013, reported significantly less use of rescue medications (not defined) in the treatment group compared with the control group, but no details were provided.

Another study, Qin 2014, reported an average daily drug score (one point for symptomatic use of levocetirizine hydrochloride tablet, mometasone furoate cream, or mupirocin ointment each day; and six points for every six-day course of clarithromycin for superinfection). Average daily drug score was lower in the treatment group (mean 0.5, standard deviation (SD) 0.4) than in the control group (mean 1.3, SD 0.7) (P < 0.01).

Other studies did not report this outcome (Di Rienzo 2014; Galli

1994; Leroy 1993; Warner 1978). None of the studies reported the use of oral antihistamines or calcineurin inhibitors as separate outcomes.

5. Validated eczema-related quality of life scores

One study, Novak 2012, reported a validated eczema-related quality of life score, the Dermatology Life Quality Index (DLQI), at the end of treatment. We used original data kindly provided by the trial authors to calculate DLQI at the end of treatment, which showed no difference between the treatment groups - a median of 3 (interquartile range (IQR) 1.0 to 8.0) for immunotherapy and a median of 3.5 (IQR 1.0 to 10.5) for placebo (P = 0.525).

Subgroup analyses

We undertook 16 planned subgroup analyses where data were available. We did not undertake further sensitivity analyses because of the small number of trials that contributed data to the analyses.

1. Immunotherapy type: sublingual and subcutaneous.
2. Allergen type: seasonal inhalant, perennial inhalant, food, and microbial.
3. Age of participants: up to four years, five to 11, 12 to 17, and 18 or over.
4. Immunotherapy regimens to be subdivided empirically into low, intermediate, and high dose therapy according to content of major allergen per dose (e.g. *Phleum* p5 for grass, Bet v1 for birch pollen, Fel d1 for cat, etc.):
   i) for subcutaneous immunotherapy, content of major allergen 1 mcg to 5 mcg, 6 mcg to 10 mcg, and greater than 11 mcg per four- to six-weekly maintenance injection doses; and
   ii) for sublingual immunotherapy, content of major allergen 1 mcg to 5 mcg, 6 mcg to 10 mcg, and greater than 11 mcg per daily maintenance sublingual dose (or equivalent if taken less frequently).
5. Severity of AE at randomisation: mild (SCORAD mean objective score of 0 to 15), moderate (SCORAD mean objective score of 16 to 40), and severe (SCORAD mean objective score of greater than 40).

First, we analysed our primary outcome measure 'Participant- or parent-reported global assessment of disease severity at the end of treatment'. Two studies reported dichotomous outcomes that we did not combine in meta-analyses because of significant heterogeneity (I^2 = 83%) (Glover 1992; Warner 1978). We did not perform subgroup analyses because both studies fell under the same subgroup categories (subcutaneous route, perennial allergen, and both children and adults). One study, Warner 1978, showed significant improvement in 7/9 participants (78%) in the immunotherapy group compared with 3/11 participants (27%) in the placebo group (P = 0.04). Another study, Glover 1992, showed significant improvement in 8/13 participants (62%) in the active group compared with 9/11 (81%) in the placebo group (P = 0.38).

Next, we analysed our primary outcome measure 'Participant- or parent-reported specific symptoms of eczema, by subjective measures' in nine subgroup analyses. We found no evidence that this outcome differed according to the following.

- Route of immunotherapy: SCORAD part C (subcutaneous: MD -0.62, 95% CI -2.18 to 0.93) (sublingual: MD -0.94, 95% CI -3.00 to 1.13) (test for subgroup differences: I^2 = 0%; Analysis 2.1). With regard to itch, meta-analysis was not possible due to extreme heterogeneity (I^2 = 99%) attributable to the study of Sanchez 2012. Without this study in the analysis, the test for subgroup difference between sublingual and subcutaneous immunotherapies and their controls was not significant (I^2 = 0%) for sleep disturbance (subcutaneous: MD -0.42, 95% CI -1.24 to 0.40) (sublingual: MD -0.54, 95% CI -1.27 to 0.19) (test for subgroup differences: I^2 = 0%; Analysis 2.2).
- Allergen type: SCORAD part C (seasonal inhalant: MD not estimable) (perennial inhalant: MD -0.74, 95% CI -1.98 to 0.50; Analysis 2.3) (food: MD not estimable) (microbial: MD not estimable). With regard to itch, meta-analysis was not possible due to extreme heterogeneity (I^2 = 99%) attributable to the study of Sanchez 2012. Without this study in the analysis, the test for subgroup differences for seasonal inhalant and perennial inhalant immunotherapies was not significant (I^2 = 0%) for sleep disturbance (seasonal inhalant: MD not estimable) (perennial inhalant: MD -0.49, 95% CI -1.03 to 0.06; Analysis 2.4) (food: MD not estimable) (microbial: MD not estimable).
- Participant age: SCORAD part C (up to four years: MD not estimable) (five to 11 years of age: MD not estimable) (12 to 17 years of age: MD not estimable) (18 years of age or over: (MD -0.62, 95% CI -2.18 to 0.93; Analysis 2.5); itch (up to four years of age: MD not estimable) (five to 11 years of age: MD not estimable) (12 to 17 years of age: MD not estimable) (18 years of age or over: MD -0.20, 95% CI -1.05 to 0.64; Analysis 2.6); or sleep disturbance (up to four years of age: MD not estimable) (five to 11 years of age: MD not estimable) (12 to 17 years of age: MD not estimable) (18 years of age or over: MD -0.42, 95% CI -1.24 to 0.40; Analysis 2.7).
- Severity at randomisation using original data from one study for the outcomes itch and sleep disturbance (Novak 2012). In the moderate severity subgroup, data were available for 37 participants (23 in the immunotherapy group and 14 in the placebo group): itch did not differ significantly between groups - with a median of 1.7 (IQR 0.3 to 3.5) for immunotherapy and 1.7 (IQR 0.5 to 3.7) for placebo (P = 0.96) - nor did sleep disturbance - with a median of 0.3 (IQR 0.1 to 2.8) for immunotherapy and 0.5 (IQR 0.3 to 1.5) for placebo (P = 0.53). In the severe subgroup, data were available for 109 participants (75 in the active group and 34 in the placebo group): itch did not differ significantly between groups - with a median of 2.0 (IQR 0.7 to 4.1) for immunotherapy and 2.9 (IQR 1.3 to 5.4) for placebo (P = 0.22) - nor did sleep disturbance - with a median of 1.1 (IQR 0.4 to 3.3) for immunotherapy and 1.9 (IQR 0.6 to

5.1) for placebo (P = 0.14). During treatment, we also calculated the change in itch in the moderate (MD 1.01, 95% CI -1.31 to 3.33) and severe subgroups (MD 0.10, 95% CI -1.38 to 1.58; Analysis 2.8) and sleep disturbance in the moderate (MD 0.38, 95% CI -1.32 to 2.09) and severe subgroups (MD -0.31, 95% CI -1.66 to 1.04; Analysis 2.9). We found no significant difference between the immunotherapy and control groups.

Last, we analysed our primary outcome 'Adverse events' in six subgroup analyses. We found evidence that this outcome differed significantly according to the following:

- route of immunotherapy: local reactions were greater in the immunotherapy group than the control group by the sublingual (RR 9.76, 95% CI 1.28 to 74.26) but not the subcutaneous route (RR 1.18, 95% CI 0.90 to 1.55) (test for subgroup differences: I^2 = 76%; Analysis 2.10).

We found no evidence that this outcome differed between the immunotherapy or control groups according to the following:

- route of immunotherapy: systemic reactions (subcutaneous: RR 0.82, 95% CI 0.34 to 2.00) (sublingual: RR 0.74, 95% CI 0.29 to 1.89) (test for subgroup differences: I^2 = 0%; Analysis 2.11);
- allergen type: local reactions (seasonal inhalant: RR not estimable) (perennial inhalant: RR 1.31, 95% CI 0.81 to 2.13; Analysis 2.12) (food: RR not estimable) (microbial: RR not estimable); systemic reactions (seasonal inhalant: RR not estimable) (perennial inhalant: RR 0.78, 95% CI 0.41 to 1.49; Analysis 2.13) (food: RR not estimable) (microbial: RR not estimable); and
- participant age: local reactions (up to four years: RR not estimable) (five to 11: RR not estimable) (12 to 17: RR not estimable) (18 years or over: RR 1.37, 95% CI 0.44 to 4.23; Analysis 2.14); systemic reactions (up to four years: RR not estimable) (five to 11: RR not estimable) (12 to 17: RR not estimable) (18 years or over: RR 0.74, 95% CI 0.38 to 1.47; Analysis 2.15).

There were no data available for other subgroup analyses of our primary outcomes.

DISCUSSION

Summary of main results

We identified 12 randomised controlled clinical trials of specific allergen immunotherapy (SIT) for the treatment of atopic eczema (AE), which included 733 participants with eczema and allergic sensitisation to an inhalant allergen. The studies were of children and adult participants allergic to house dust mite, grass pollen, and other inhalant allergens; and immunotherapy via subcutaneous, sublingual, oral, and intradermal routes. We judged nine studies to have a high risk of bias due to high rates of loss to follow up or postrandomisation exclusions, Di Rienzo 2014, Glover 1992, Kaufman 1974, Leroy 1993, Luna-Pech 2013, Novak 2012, Pajno 2007, Qin 2014, or non-blinded outcome assessment, Di Rienzo 2014, Sanchez 2012.

For our prespecified primary outcomes 'Participant- or parent-reported global assessment of disease severity at the end of treatment' (two studies, 44 participants, low quality evidence) and 'Participant- or parent-reported specific symptoms of eczema, by subjective measures' (six studies, 339 participants, very low quality evidence), SIT is not an effective treatment for AE (Summary of findings for the main comparison). However, the results for our secondary outcomes 'Investigator- or physician-rated global assessment of disease activity at the end of treatment' (seven studies, 286 participants) and 'Investigator- or physician-rated eczema severity assessed using a published scale (e.g. SCORing Atopic Dermatitis (SCORAD))' (six studies, 435 participants) indicated SIT was effective, although the quality of the evidence was low and very low for these two outcomes, respectively. Our other secondary outcomes 'Parent- or participant-rated eczema severity assessed using a published scale' (two studies, 184 participants) and 'Validated eczema-related quality of life scores' (one study, 168 participants) showed no difference with SIT.

For our primary outcome 'Adverse events', SIT was not associated with increased risk of local (seven studies, 484 participants) or systemic (seven studies, 492 participants, moderate evidence) adverse reactions. Also, SIT was not associated with an increased need for topical (one study, 20 participants) or systemic (two studies, 86 participants) corticosteroid use during the studies.

Three studies had more positive findings than the others. One, Sanchez 2012, reported a marked improvement in participant- or parent-reported symptoms and smaller but statistically significant improvements in investigator- or physician-reported global eczema severity and total SCORAD (a 5.8-point greater improvement) compared with untreated participants. Another, Qin 2014, reported a significantly greater investigator- or physician-rated global disease severity, defined as change in SCORAD $\geq$ 60% in SIT (77.78%) compared with the control (53.85%) (P < 0.05). A further study, Luna-Pech 2013, reported a significant change in investigator- or physician-rated global disease severity through assessment of SCORAD in SIT (mean -18.4, SD 6.5) compared with the control (mean -6.6, SD 4.1) (P = 0.008), with a greater effect in those with severe eczema at baseline. No original data were available for inclusion in meta-analyses.

Subgroup analyses identified a low confidence of effect that sublingual immunotherapy was associated with more local adverse reactions compared with subcutaneous immunotherapy. Other subgroup analyses did not identify a type of allergen, a participant age, or a severity of AE at randomisation with a different efficacy or safety profile, although these analyses were generally inconclusive due to the limited data available.

Overall completeness and applicability of evidence

Overall, we found low quality of evidence that specific allergen immunotherapy is effective in the treatment of atopic eczema. The varied disease severity scales and symptom scores used across the trials generally limited the meta-analyses. In those with comparable data, some outcomes were significant. Wide confidence intervals for many outcome measures reflected relatively small studies and varied methodologies. Several outcomes were based on analysis from a single trial, Novak 2012, with a large number of participants but high loss to follow up. Three trials, Di Rienzo 2014, Qin 2014, Sanchez 2012, had more positive findings than the others and showed a clear beneficial effect on participant- or parent-reported eczema symptoms and investigator- or physician-reported global eczema severity in the form of SCORAD. It is not clear why the findings of these trials differed, but there was a risk of detection bias due to lack of blinding of participants or investigators in at least two trials (Di Rienzo 2014; Sanchez 2012). We found that adverse reaction rates were not significantly increased with immunotherapy in the included studies, but other evidence suggests that SIT carries a significantly increased risk of severe allergic reactions (Calderon 2007). While this might suggest that the allergic sensitisation present in the trial participants is of little clinical relevance or that the allergen extracts used were of low potency, it may equally reflect the small number of trials and participants that contributed to the adverse events analyses.

Quality of the evidence

Our overall judgement of the quality of the body of evidence that contributed to the results of the review, using the Grading of Recommendations Assessment, Development and Education (GRADE) approach (Higgins 2011), was low. The reasons we downgraded were relatively few trials and participants, lack of blinding in at least two trials, wide confidence intervals, moderate risk of bias with high loss to follow up as the main concern, and significant heterogeneity between the estimate of treatment effects for a primary outcome.

Potential biases in the review process

The strengths of this review were the adherence to our published protocol and the repeated efforts to acquire original data from study authors in order to maximise opportunities for meta-analysis and clarify methodological uncertainties. The limited number of included studies did not allow formal assessment for publication bias. We analysed different outcome measures as separate analyses, which limited the opportunities to pool data from different studies that used different outcome assessment tools.

Agreements and disagreements with other studies or reviews

Three other systematic reviews of SIT for the treatment of AE have been undertaken. In one review (Bae 2013), the authors identified eight of the 12 trials included in this review but analysed the data in a different way, by pooling heterogeneous outcomes 'measured by any scoring systems', which may not be appropriate (Tam 2013). In contrast to our review, they found moderate evidence that SIT may be an effective treatment for AE both in all participants studied (odds ratio (OR) for improved eczema 5.35, 95% confidence interval (CI) 1.61 to 17.77) and in subgroup analyses of participants with severe eczema at randomisation (OR 3.13, 95% CI 1.31 to 7.47) and studies that used subcutaneous immunotherapy (OR 4.27, 95% CI 1.36 to 13.39). The different outcomes in their review are likely due to the unconventional approaches for extracting and combining data from the included trials. There was no registered protocol for their review, so we cannot confirm that the inclusion criteria and outcome measures were determined a priori.

In a systematic review that used the GRADE recommendations (Gendelman 2013), the authors identified five of the nine trials included in our review, and an additional two that we excluded (Ring 1982; Werfel 2006). The review did not perform meta-analyses. Similar to our review, they found only weak strength of recommendations for the use of SIT to treat AE. They also reported similar methodological shortcomings, including high losses to follow up.

In a similar systematic review on sublingual immunotherapy only that used the GRADE recommendations (Gendelman 2015), the authors identified three of the 12 trials included in our review and an additional two that we excluded (Cadario 2007; Mastrandrea 2000). The review did not perform meta-analyses. Similar to our study, they found only weak strength of recommendations for the use of sublingual immunotherapy to treat AE with a large placebo effect in two studies. They also reported similar methodological shortcomings, which included lack of blinding, lack of control, and lack of randomisation.

AUTHORS' CONCLUSIONS

Implications for practice

We found limited evidence that specific allergy immunotherapy (SIT) provides a treatment benefit for people with atopic eczema (AE) compared with placebo or no treatment, but due to methodological concerns in the included studies, this form of treatment cannot be recommended for AE at present.

Implications for research

The evidence to date is inconclusive, so more trials are needed to

clarify whether SIT is effective for the treatment of atopic eczema. Further large, well-blinded randomised controlled trials that use modern high quality allergen formulations with a proven track record in other allergic conditions and also evaluate patient-reported primary outcome measures are needed. If the treatment is found to be efficacious, identification of those most likely to benefit would be of great interest.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Di Rienzo 2014

Methods	Randomised, open label, controlled, parallel group trial Duration of study: 12 months
Participants	Country: Italy Age range: children (5 to 18 years) Total number: 57 Treatment group n: 30 (63% males) Control group n: 27 (63% males) Losses to follow up: 19 (33.3% of total) (7 in the treatment group and 12 in the control group) **Inclusion criteria** People (1) aged over 5 and less than 18; (2) with clinical history of chronic mild to moderate AD with no evidence of spontaneous remission at the age of 5 years, with or without intermittent moderate-severe or persistent mild-moderate rhinoconjunctivitis (Allergic Rhinitis and its Impact on Asthma criteria); (3) with sensitisation to *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae* or both diagnosed by prick test (wheal diameter greater than 3 mm) and by serum specific IgE; (4) aged over 3 years; (5) with positive atopy patch test to HDM extracts (a concomitant sensitisation to pollen allergens without exacerbations of AD during pollination was acceptable); and (6) with SCORAD baseline greater than 8, but 40 or less **Exclusion criteria** None specified
Interventions	Treatment: sublingual immunotherapy of SLITone® (50% *Dermatophagoides pteronyssinus* and 50% *Dermatophagoides farinae* standardised extracts) and pharmacological topical or systemic treatment or both as needed Updosing schedule: none Maintenance dose/frequency: 200 STU daily Manufacturer: ALK-Abelló, Milan, Italy Control: pharmacological topical or systemic treatment or both as needed only
Outcomes	• Change in SCORAD from baseline to any postbaseline time point • Change in VAS 0 to 10 of subjective cutaneous symptoms • Investigator judgement on efficacy from baseline to any postbaseline time point • Adverse events
Notes	Funding: ALK-Abelló Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer generated the randomisation list: 1 list into blocks of 10 per each centre

Di Rienzo 2014 (*Continued*)

Allocation concealment (selection bias)	Low risk	The randomisation number was assigned using a centralised procedure only after each investigator identified 1 participant who was eligible for recruitment. Investigators were not aware of the randomisation sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open label (not blinded)
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was open label (not blinded)
Incomplete outcome data (attrition bias) All outcomes	High risk	7 participants (23%) in the treatment group and 12 in the control group (44%) were lost to follow up. Postrandomisation exclusion from analyses were noted
Selective reporting (reporting bias)	Unclear risk	The outcomes were clearly stated, and the paper reported results for all of these outcomes. However, it was unclear if the trial was registered
Other bias	High risk	Senior authors listed their affiliations as the company that manufactures the SLIT drops, which is a significant conflict of interest. The manufacturer also funded the study

Galli 1994

Methods	Randomised, controlled, parallel group trial Duration of study: 3 years
Participants	Country: Italy Age range: children (0.5 to 12 years) Total number: 34 Treatment group n: 16 (43.8% males) Control group n: 18 (61.1% males) Losses to follow up: none reported **Inclusion criteria** People (1) with positive (greater than 2+) skin prick tests to *Dermatophagoides pteronyssinus* solutions or positive RAST® for anti *Dermatophagoides pteronyssinus* IgE or both; (2) with eczema diagnosed according to Hanifin and Rajka's criteria; and (3) aged between 0.5 to 12 years old **Exclusion criteria**

Galli 1994 (*Continued*)

	None specified
Interventions	Treatment: oral hyposensitisation therapy that contained major (Der p I and Der p II) and minor antigens of *Dermatophagoides pteronyssinus* in addition to conventional therapy Updosing schedule: hyposensitisation therapy was given in increasing dosages up to a final dose of 250 STU Maintenance dose/frequency: 3 times per week Manufacturer: not stated Control: conventional therapy only
Outcomes	• Investigator-rated global assessment of symptom improvement using an unpublished scale • Use of other medications for treatment of eczema during the intervention period
Notes	Funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details were provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details were provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details were provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details were provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no reported losses to follow up, and all participants were included in the analyses
Selective reporting (reporting bias)	Unclear risk	This was unclear
Other bias	Low risk	We neither detected nor suspected other sources of bias

Glover 1992

Methods	Randomised, controlled, parallel group trial Duration of study: maximum 12 months 6 weeks
Participants	Country: UK Age range: children (5 to 16 years) Total number: 26 Treatment group n: 13 (69.2% males) Control group n: 13 (38.4% males) Losses to follow up: 2 (7.7% of total) in the control group (1 refused to continue receiving injections, and 1 had an adverse reaction) **Inclusion criteria** People (1) with a positive skin prick reaction (wheal greater than 4 mm) to *Dermatophagoides pteronyssinus* 1.2% containing the same allergen preparation as used in the hyposensitising injection; (2) with severe atopic eczema unresponsive to adequate treatment with emollients, mild topical corticosteroids, icthammol paste bandage, systemic antihistamines, and appropriate elimination diet; and (3) aged between 5 to 16 years old **Exclusion criteria** None specified
Interventions	Treatment: subcutaneous injections of tyrosine-adsorbed glycerinated extract of *Dermatophagoides pteronyssinus* vaccine Updosing schedule: progressively increased every 6 weeks from 4, 10, 25, 60, 150 to a maximum of 400 Noon units Maintenance dose/frequency: 400 Noon units once monthly Manufacturer: Migen, Bencard (Brentford, UK) Control: subcutaneous injections of tyrosine suspension only
Outcomes	• Parent-reported global assessment of symptom improvement using diary cards. At the end of the study, parents were asked whether they thought that their child's eczema was the same, worse, or better than at the start of the study • Adverse events monitoring • Number of topical steroid courses • Investigator-reported erythema/lichenification/surface damage score on a non-published scale • Total serum IgE (measured by double antibody radioimmunoassay) and specific IgE to *Dermatophagoides pteronyssinus*, cat fur, dog hair, mixed glass pollens, hen's egg, and cow's milk with results expressed on a scale from 0 (negative) to 4 (very high) • Skin prick test to *Dermatophagoides pteronyssinus*, cat fur, dog hair, mixed grass, whole egg, and cow's milk
Notes	Funding: Beechams® Pharmaceuticals (supplied materials and funded cost of statistical analysis)

Risk of bias

Bias	Authors' judgement	Support for judgement

Glover 1992 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Participants were noted as randomly assigned. Details of randomisation were not provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details were provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was stated as double blind, and placebo injections were described as indistinguishable in colour and texture from the active injections and were administered in the same way
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessor for eczema severity scores was described as being unaware of whether the participant received active or placebo treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were not analysed for 2 out of 13 participants in the placebo group who stopped treatment prematurely
Selective reporting (reporting bias)	Unclear risk	Insufficient details were provided
Other bias	Low risk	We neither detected nor suspected other sources of bias

Kaufman 1974

Methods	Randomised, controlled, parallel group trial Duration of study: minimum of 2 years
Participants	Country: USA Age range: children and adults (2 to 47 years) Total number: 52 Treatment group n: 25; final treatment group n: 16 (56.2% males) Control group n: 27; final control group n: 10 (30% males) Losses to follow up: 26 (50% of total) (9 in the treatment group and 17 in the control group) **Inclusion criteria** People (1) with atopic dermatitis diagnosed by their paediatrician or internist (diagnosis was confirmed by physicians in the general dermatology clinic and again in the subspecialty atopic dermatitis clinic - the diagnosis was independently confirmed by a board-certified dermatologist and allergist, respectively); (2) with uncontrolled atopic dermatitis; and (3) with presence of at least 3 positive inhalant skin tests from a group of 19 antigens for scratch testing and skin pigmentation light enough for easy interpretation of wheat- and flare-type skin reactions **Exclusion criteria** None specified

Kaufman 1974 (*Continued*)

Interventions	Treatment: subcutaneous injections of water soluble alum-precipitated pyridine-extracted complex - a mix of appropriate concentrations of inhalant antigens to which the participant was sensitised, chosen from a panel of 10 inhalant agents Updosing schedule: Antigen concentration 10 PNU/ml Dose (volume in ml) • 1 (0.10) • 2 (0.15) • 3 (0.25) • 4 (0.40) • 5 (0.60) • 6 (0.90) Antigen concentration 100 PNU/ml Dose (volume in ml) • 7 (0.10) • 8 (0.15) • 9 (0.25) • 10 (0.40) • 11 (0.60) • 12 (0.90) Antigen concentration 1000 PNU/ml Dose (volume in ml) • 13 (0.10) • 14 (0.15) • 15 (0.25) • 16 (0.40) (every 3 weeks) • 17 (0.40) (every 3 weeks) Maintenance dose/frequency: once weekly for the first 16 doses and thereafter 3-weekly throughout the study period Manufacturer: Dome Laboratories Control: subcutaneous injections of buffered saline solution only without antigens
Outcomes	• Investigator-rated global assessment of symptom improvement supported by a scoring system on individual symptoms and signs • Use of systemic steroids
Notes	Funding: Dome Laboratories, West Haven (provided immunotherapy products)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using a flipping coin method
Allocation concealment (selection bias)	High risk	The randomisation procedure was not concealed from the person who prepared the study treatment for each participant as it

Kaufman 1974 (*Continued*)

		was the same nurse who did both procedures; therefore, the allocation sequence was open to manipulation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was reported that only the clinic nurse (who allocated and prepared the study treatments) was aware of treatment allocation. It was also reported that each participant only saw the syringe that was used for them
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	9 participants (36%) in the treatment group and 17 (63%) in the control group were lost to follow up. As-treated analyses were performed
Selective reporting (reporting bias)	Unclear risk	Insufficient details were provided
Other bias	Low risk	We neither detected nor suspected other sources of bias

Leroy 1993

Methods	Randomised, controlled, parallel group trial Duration of study: 4 months
Participants	Country: Belgium Age range: children and adults (17 to 64 years) Total number: 24 Treatment group n: 13 (58% males) Control group n: 11 (55% males) Losses to follow up: 1 (4.2% of total) participant in the treatment group was withdrawn because of failure to improve **Inclusion criteria** People with atopic dermatitis (1) diagnosed by the criteria of Hanifin and Rajka; (2) affecting more than 20% of body surface area and without significant spontaneous remission during the last 2 years; (3) of at least 2 years duration; (4) aged between 15 to 20 years old; and (5) resistant to environmental treatment and showing rapid release after discontinuation of systemic corticotherapy with total IgE greater than 20 kU/L and presence of specific IgE to *Dermatophagoides pteronyssinus* and positive skin prick test to that allergen **Exclusion criteria** Other treatments of 1) oral corticodepedence or systemic corticosteroids within the 2 months before the trial; 2) cytokine or immunosuppressive therapy (e.g. cyclosporine)

	; or 3) phototherapy of PUVA during the 6 weeks preceding the trial; or other disease whose treatment could affect the symptoms of AD, i.e. erythroderma; acute cutaneous infection; or immunodeficiency or hyper IgE syndrome or pregnancy
Interventions	Treatment: intradermal injections of autologous specific antibody and a glycerinated extract of *Dermatophagoides pteronyssinus* Maintenance dose/frequency and updosing schedule: twice-weekly injection of 100 µl allergen-antibody complex solution for the first 3 weeks, then weekly for the next 9 weeks and then twice during the 4th month (total amount of 240 µg of specific antibodies and 60 µg of allergens in the intervention group) Manufacturer: Bencard Ltd, Epsom, Surrey Control: intradermal injections of the carrier buffer
Outcomes	• Independent investigator clinical evaluation using Visual Analogue Scale. Itch was graded on a 4-point scale based on an interview with the participant • Proportion with local reactions/flare of dermatitis within 48 hours • Estimation of drug use, i.e. corticosteroid/antibiotic use
Notes	Funding: Baxter Healthcare Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details were provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details were provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was stated that the study blinded both the clinician who administered the injections and the clinician who assessed the participants
Incomplete outcome data (attrition bias) All outcomes	High risk	Noted data from the withdrawn participant was not analysed, and 1 participant who successfully completed the course of injections was not included for analysis because he no longer satisfied the entrance criteria at the time of the first injection
Selective reporting (reporting bias)	Unclear risk	This was unclear

Leroy 1993 (*Continued*)

Other bias	Low risk	We neither detected nor suspected other sources of bias

Luna-Pech 2013

Methods	Randomised, controlled, double blind, parallel group trial Duration of study: 12 months
Participants	Country: Mexico Age range: children (4 to 10 years) Total number: 68 participants Treatment group n: 34; dropout rate = 9% (n: 3) Control group n: 34; dropout rate = 18% (n: 6) **Inclusion criteria** Moderate to severe AD and monosensitised to *Dermatophagoides pteronyssinus* **Exclusion criteria** Unknown
Interventions	Treatment: sublingual immunotherapy to *Dermatophagoides pteronyssinus* Updosing schedule: unknown Manufacturer: unknown Control: sublingual placebo tablet
Outcomes	• Change in SCORAD • Rescue medications • Number to treat in order to gain benefit from the intervention
Notes	Funding: none declared The authors did not respond to our request for further information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The abstract provided insufficient details
Allocation concealment (selection bias)	Unclear risk	The abstract provided insufficient details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was stated as double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear whether outcome assessors were included in the double blinding

Luna-Pech 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	9% of participants in the treatment group and 18% in the placebo group were lost to follow up. Reasons for these were not available. It was unclear whether there were post-trandomisation exclusions from analyses
Selective reporting (reporting bias)	Unclear risk	The outcomes were clearly stated, and results for all of these outcomes were reported. However, it was unclear if the trial was registered. The abstract may not have included other outcomes
Other bias	Unclear risk	It was unclear whether the authors were affiliated with the manufacturer

Novak 2012

Methods	Randomised, controlled, parallel group trial Duration of study: 18 months
Participants	Country: Germany Age range: adults (18 to 66 years) Total number: 168 Treatment group n: 112 (55% males) Control group n: 56 (50% males) Losses to follow up: 55 (33% of total) - 37 in the treatment group (11 due to adverse events - 4 of those adverse events considered likely to be due to study medication; 3 due to protocol violation; 23 due to participant withdrawal, non-compliance, or loss to follow-up) and 18 in the placebo group (3 due to adverse events - 1 of those adverse events considered likely to be due to study medication; 2 due to protocol violation; 13 due to participant withdrawal, non-compliance, or loss to follow up) **Inclusion criteria** People with (1) eczema diagnosed by Hanifin and Rajka criteria; (2) at least 2 exacerbations of eczema or permanent skin lesions during the past 2 months, aggravation of eczema by exposure to HDM during the heating period (September to February); (3) duration of condition > 2 years; (4) positive SPT to *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Def f) with a wheal diameter of $\geq$ 4 mm, a negative control reaction, and specific IgE for Der p or Der f in a RAST® class of $\geq$ 3; and (5) stable environmental control - i.e. people were to have implemented encasing strategies for bedding and mattresses for > 6 months **Exclusion criteria** (1) Previous specific immunotherapy with HDM; (2) photopheresis within 3 months prior to the study; (3) immunosuppression within 1 month prior to the study; or (4) pregnant or nursing women
Interventions	Treatment: subcutaneous injections of depigmented, polymerised mite extract Updosing schedule: increasing progressively every 6 weeks from 2, 5, 20, to 50 DPP Maintenance dose/frequency: up to 50 DPP every 6 weeks

	Manufacturer: LETI Pharma GmbH, Germany Control: subcutaneous injections of tyrosine suspension
Outcomes	**Primary outcomes** • Total SCORAD scores over the 18-month treatment period, reported as improvement in AUC of SCORAD • Use of basic medications over the 18-month treatment period **Secondary outcomes** • DLQI evaluated for the whole treatment period and for the heating period from September to February • Adverse reactions
Notes	Funding: LETI Pharma GmbH, Germany The study excluded some participants with premature study termination from analysis potentially because of non-medical reasons whilst including others in the analysis. The study authors used imputation for missing data to account for the high loss to follow up rate during the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised random numbers were used
Allocation concealment (selection bias)	Unclear risk	Insufficient details were provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was stated as double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear whether outcome assessors were included in the double blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	37 participants (33%) in the treatment group and 18 (32%) in the placebo group were lost to follow up. Postrandomisation exclusion from analyses were noted
Selective reporting (reporting bias)	Low risk	The outcomes reported were consistent with those described in the registered trial
Other bias	Low risk	We neither detected nor suspected other sources of bias

Pajno 2007

Methods	Randomised, controlled, parallel group trial Duration of study: 18 months
Participants	Country: Italy Age range: children (5 to 16 years) Total number: 56 Treatment group n: 28 (53.6% males) Control group n: 28 (42.8% males) Losses to follow up: 8 (14.3% of total) (2 in the treatment group due to worsening of symptoms and 6 in the control group: 1 moved out of the area, 3 were non-compliant with the protocol, and 2 were lost to follow up) **Inclusion criteria** Children (1) aged between 5 to 16 years old; (2) with a clinical history of chronic AD without evidence of spontaneous improvement at age 5 years; (3) with a SCORAD of 8 or greater; (4) with an IgE-mediated sensitisation to HDM assessed by positive skin prick test (wheal greater than 3 mm) and positive CAP-RAST® assay (class III or greater); (5) for whom if a positive or suggestive history of food allergy in the previous years with positive skin tests were reported, fully tolerated those foods at enrolment, as confirmed by a double blind, placebo-controlled food challenge; and (6) with a FEV_1 greater than 80% of predicted value **Exclusion criteria** (1) Any previous course of immunotherapy; (2) bronchial asthma requiring regular treatment with inhaled steroids; (3) acute persistent food allergy; or (4) severe systemic disorders (e.g. cystic fibrosis, diabetes, coeliac disease) or malignancies
Interventions	Treatment: sublingual therapy (vial 3) containing 4.3 ug/mL Der p I and 3.5 ug/mL Der f I glycerinated solution. The dose reached was 3.3 mcg Der p I and 2.7 mcg Der f I per week Updosing schedule: 15 days. 1 drop from the first vial (100 RAST® units/mL) every day up to 5 drops then repeating the steps with vial 2 (1000 RAST® units/mL) and then vial 3 (10,000 RAST® units/ mL) Maintenance dose/frequency: 5 drops (250 mcl) from vial 3 (10,000 RAST® units per/ mL), 3 times a week for 18 months Manufacturer: not stated Control: sublingual therapy of placebo solution
Outcomes	• VAS 0 to 10 recorded by parent at baseline and 18 months - 'how was the eczema in the last month?' scored from 0, no symptoms at all, to 10, very severe symptoms • The change in SCORAD versus baseline assessed before randomisation and then after 3, 6, 9, 12, 15, and 18 months of treatment • The use of medications (1 point for each dose of oral hydroxyzine or topical steroid (fluticasone ointment) and 2 points for each dose of oral clarithromycin in the 6-day course. The latter was given only in the case of superinfection)
Notes	Funding: Stallergenes

Risk of bias

Bias	Authors' judgement	Support for judgement

Pajno 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	A computer-generated code was used
Allocation concealment (selection bias)	Unclear risk	Insufficient details were provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was stated to be double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear whether outcome assessors were included in the double blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	8 participants were not included in the analyses: 6 in the control and 2 in the intervention group. Postrandomisation exclusion from analyses were noted
Selective reporting (reporting bias)	Unclear risk	This was unclear
Other bias	Low risk	We neither detected nor suspected other sources of bias

Qin 2014

Methods	Randomised, controlled, parallel group trial Duration of study: 12 months
Participants	Country: China Age range: adults (18 to 46 years) Total number: 107 Treatment group n: 58 (56.9% males) Control group n: 49 (61.2% males) Losses to follow up: 23 (21% of total) (13 in the treatment group and 10 in the control group) **Inclusion criteria** (1) Clinical history of chronic AD over 2 years; (2) moderate AD, diagnosed according to Hanifin and Rajka criteria; and (3) sensitisation to *Dermatophagoides farinae*, assessed by positive skin prick test (skin wheal area $\geq$ 50% of the positive control) **Exclusion criteria** (1) Any active, acute, or chronic obstructive pulmonary disease, except for asthma and allergic rhinitis; (2) forced expiratory volume in 1s $\leq$ 70% of predicted value; (3) people who had disorders with respect to drug absorption, distribution, metabolism, and excretion; and (4) all contraindications for SLIT or the researchers did not think the person was suitable for the study

Qin 2014 (*Continued*)

Interventions	Treatment: sublingual *Dermatophagoides farinae* drops administered at home plus pharmacotherapy (i.e. oral levocetirizine hydrochloride and topical mometasone furoate cream) Updosing schedule: increasing drops of 1 ug/ml, 10 ug/ml, 100 ug/ml, 333 ug/ml, and 1000 ug/ml in the first 5 weeks Maintenance dose/frequency: 2 drops of 1000 ug/ml daily Manufacturer: Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd Control: only pharmacotherapy (i.e. oral levocetirizine hydrochloride and topical mometasone furoate cream)
Outcomes	Follow-up at 1, 3, 6, 9, and 12 months: • Total efficacy measured as ratio of SCORAD reduction ratio ≥ 60% • VAS 0 to 10 on overall AD symptoms • Adverse events documented daily • Drug score documented daily • *Dermatophagoides farinae*-specific serum IgG4 at 1, 6, and 12 months
Notes	Funding: none declared The authors did not respond to our request for further information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The paper provided insufficient details
Allocation concealment (selection bias)	Unclear risk	The paper provided insufficient details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The paper provided insufficient details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The paper provided insufficient details
Incomplete outcome data (attrition bias) All outcomes	High risk	13 participants (22%) in the treatment group and 10 (20%) in the placebo group were lost to follow up. It was unclear whether there were postrandomisation exclusion from analyses
Selective reporting (reporting bias)	Unclear risk	The outcomes were clearly stated, and results for all of these outcomes were reported. However, it was unclear if the trial was registered

Qin 2014 (*Continued*)

Other bias	High risk	2 authors listed their affiliations as the company that manufactures the SLIT drops, which is a significant conflict of interest

Sanchez 2012

Methods	Randomised, open label, controlled, parallel group trial Duration of study: 12 months
Participants	Country: Columbia Age range: children and adults (3 to 25 years) Total number: 65 Treatment group n: 32; final treatment group n: 31 (52% males) Control group n: 33; final control group n: 29 (48% males) Losses to follow up: 5 (7.7% of total) due to moving out of the area (1 in the treatment group and 4 in the control group) **Inclusion criteria** People with atopic dermatitis (1) diagnosed by the criteria of Hanifin and Rajka; (2) of at least 2 years' duration; (3) aged over 3 years; (4) with a SCORAD baseline over 15; and (5) with IgE sensitisation to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* **Exclusion criteria** 1) Administration of immune suppressors or biological agents in the last 3 months; 2) significant improvement of symptoms in the last 6 months; or 3) systemic diseases that contraindicated the use of immunotherapy
Interventions	Treatment: subcutaneous injections of depigmented polymerised mites extract (0.5 ml Der f/Der p, 50 DPP) and pharmacotherapy Maintenance dose/frequency and updosing schedule: a first injection of 2 separate refracted doses (0.2 ml and 0.3 ml), then monthly single 0.5 ml doses Manufacturer: LETI laboratories, Madrid, Spain Control: pharmacotherapy only
Outcomes	• SCORAD at 0, 3, 6, 9, and 12 months • SS consisting of 3 questions (A. How was the eczema last week?, B. Over the last week, how much has your skin been a problem in your daily activities or sleep?, C. How severe was the itching during the last week?); the average score was expressed as a percentage at 0, 3, 6, 9, and 12 months • Use of rescue mediations (steroids and topical tacrolimus) • Adverse effects - local and systemic reactions • Total IgE and specific IgE and IgG4 levels
Notes	Funding: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Sanchez 2012 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Participants were noted as randomly assigned, but no details of randomisation were provided
Allocation concealment (selection bias)	Unclear risk	Insufficient details were provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open label (not blinded)
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was open label (not blinded)
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in the treatment group (3%) and 4 in the placebo group (12%) were lost to follow up because they moved to other cities
Selective reporting (reporting bias)	Low risk	Outcomes were clearly stated with results reported for all of these outcomes. However, the trial was not registered
Other bias	Low risk	We neither detected nor suspected other sources of bias

Silny 2006

Methods	Randomised, controlled, parallel group trial Duration of study: 12 months
Participants	Country: Poland Age range: children and adults (5 to 40 years) Total number: 20 Treatment group n: 10 (70% males) Control group n: 10 (80% males) Losses to follow up: none reported **Inclusion criteria** People with atopic dermatitis and monovalent sensitisation to airborne allergens (house dust mites or grass pollens) - confirmed by clinical symptoms, skin prick tests, and specific serum IgE levels **Exclusion criteria** None specified
Interventions	Treatment: subcutaneous injections of aluminium hydroxyzine-adsorbed allergen preparations with *Dermatophagoides pteronyssinus* (50%), *Dermatophagoides farinae* (50%), or grass pollens (100%) Manufacturer: Allergopharma-Nexter

Silny 2006 (*Continued*)

	Control: subcutaneous injections of placebo (0.0125 or 0.125 mg/ml of histamine)
Outcomes	• Clinical score (point index of severity and extensiveness of skin inflammation) • Serum concentration of total and allergen specific IgE • Serum concentration of immunological parameters, i.e. ECP, sIL-2R, IFN-gamma, Il-4, Il-5, Il-10
Notes	Funding: Allergopharma-Nexter and unspecified university

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	It was stated that the sponsor (Allergopharma-Nexter) undertook random sequence generation
Allocation concealment (selection bias)	Low risk	It was stated that the sponsor (Allergopharma-Nexter) undertook allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was stated as double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear whether the study included outcome assessors in the double blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no reported losses to follow up, which resulted in all participants included in the analyses
Selective reporting (reporting bias)	Unclear risk	This was unclear
Other bias	Low risk	We neither detected nor suspected other sources of bias

Warner 1978

Methods	Randomised, controlled, parallel group trial Duration of study: 12 months
Participants	Country: UK Age range: children (5 to 14 years) Total number: 56 Treatment group n: 28; final treatment group n: 27 (77.7% males) Control group n: 28; final treatment group n: 24 (75.0% males)

	Losses to follow up: 5 (8.9% of total) (1 in the treatment group and 4 in the control group) **Inclusion criteria** People (1) with moderate to severe atopic dermatitis; (2) aged between 5 to 14 years old; and (3) with a positive bronchial provocation test to *Dermatophagoides pteronyssinus* defined as a fall in peak expiratory flow rate of greater than 20% from baseline within 20 minutes of challenge **Exclusion criteria** People on (1) long-term oral steroids or (2) who had hyposensitisation in the previous 3 years
Interventions	Treatment: subcutaneous injections of tyrosine-absorbed *Dermatophagoides pteronyssinus* Updosing schedule: 4, 10, 25, 60, 150, and 400 Noon units - weekly injections for 6 weeks Maintenance dose/frequency: 400 Noon units every 8 weeks Manufacturer: Migen (Bencard, UK) Control: subcutaneous injections of tyrosine suspension only
Outcomes	• Participant completed a daily diary card of night cough, night wheeze, day wheeze, and day activity, graded 0 to 5, and recorded each dose of drugs taken for asthma. At 2-monthly clinic visits, the diary cards were checked, and the participants and parents were asked whether the asthma (allergic rhinitis, eczema) was better, unchanged, or worse • Adverse events recorded by investigators using participant diary cards
Notes	Funding: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed via a numbers table
Allocation concealment (selection bias)	Low risk	A third party (pharmacy) conducted the allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial authors confirmed that participants, their parents, study personnel, and outcome assessors were all blind to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial authors confirmed that participants, their parents, study personnel, and outcome assessors were all blind to treatment allocation

Warner 1978 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	There was 1 (3.6%) withdrawal from treatment in the active group and 4 (14.3%) in the control group. We included all available data in the analyses
Selective reporting (reporting bias)	Low risk	The trial authors confirmed that they used no other relevant outcome measures in the trial
Other bias	Low risk	We neither detected nor suspected other sources of bias

AD: atopic dermatitis
AUC: area under curve
CAP-RAST®: immunoCAP Specific IgE blood test
DLQI: Dermatology Life Quality Index
DPP: DePigmented and Polymerize
ECP: eosinophil cationic protein

FEV_1 : forced expiratory volume in 1 second
HDM: house dust mite
IFN: interferon
IgE: immunoglobulin E
IL: interleukin
n: number
PNU: protein nitrogen unit
PUVA: psoralen combined with ultraviolet A
RAST®: radioallergosorbent test
SCORAD: SCORing Atopic Dermatitis
sIL-2R: soluble interleukin 2 receptor
SPT: skin prick test
SS: subjective score
STU: standard therapeutic units
VAS: Visual Analogue Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ariano 2009	This was not about atopic eczema
Brunetti 2005	This was not a randomised controlled trial
Businco 1997	This was not about immunotherapy

(*Continued*)

Bussman 2007	This was a review article
Cadario 2007	This was not a randomised controlled trial
Canonica 2009	This was a review article
Compalati 2010	This was a systematic review protocol
D'Souza 1973	This was not about atopic eczema
Darsow 2005	This was a review article
Derkach 2015	There was no appropriate control
Finegold 2009	This was a review article
Gendelman 2011	This was a review article
Gendelman 2013	This was a review article
Gendelman 2014	This was a review article
Gendelman 2015	This was a review article
Horak 2009	This was not a randomised controlled trial
Incorvaia 2009	This was a review article
Jacquemin 1995	This was not about specific allergen immunotherapy
Juji 2003	This was not a randomised controlled trial
Larenas-Linnemann 2008	This was a review article
Larenas-Linnemann 2009	This was a review article
Lee 2015	This was a review article
Leung 2015	This was a review article
Margona 2015	This was a review article
Mastrandrea 2000	This was not a randomised controlled trial
Melamed 2010	This was not about atopic eczema
Mihara 2008	This was a review article
Minelli 2010	This was not about atopic eczema

(*Continued*)

Mohapatra 2010	This was a review article
Nahm 2008	This was not a randomised controlled trial
Niebuhr 2007	This was a review article
Niebuhr 2008	This was a review article
Noh 2000	This was not a randomised controlled trial
Novak 2007	This was a review article
Ong 2010	This was a review article
Ozdemir 2009	This was a review article
Panzani 1995	This was not about atopic eczema
Passalacqua 2012	This did not have atopic eczema outcomes separately reported
Pereira 2013	This was a review article
Petrova 2001	This was not a randomised controlled trial
Pons-Guiraud 1986	This was not about atopic eczema
Ring 1982	This was not a randomised controlled trial
Roos 2004	This was a review article
Schiavino 2006	This was not about atopic eczema
Senti 2009	This was not a randomised controlled trial
Shi 2010	There was no appropriate control
Slavyanskaya 2014	There was no appropriate control
Slavyanskaya 2014b	There was no appropriate control
Smolkin 2000	This was a review article
Stiller 1993	This was not about immunotherapy
Stiller 1994	This was not about immunotherapy
Strannegard 1982	This was not about immunotherapy

(*Continued*)

Tammaro 2009	This was not about atopic eczema
Tonnel 2004	This was not about atopic eczema
Van Wijk 2008	This was a review article
Wen 1992	This was not a randomised controlled trial
Werfel 2006	This was not a randomised controlled trial; it was a dose-response study
Werfel 2007	This was a review article
Werfel 2008	This was a review article
Zachariae 1985	There was no appropriate control
Zheng 2011	There was no appropriate control
Zolkipli 2014	This was not about treatment for atopic eczema
Zolkipli 2014b	This was not about treatment for atopic eczema
Zolkipli 2015	This was not about treatment for atopic eczema

The reason we included these articles for the full text review stage is that from the title or abstract, we could not exclude the possibility that they were randomised controlled trials of adults or children with atopic eczema and allergic sensitisation, but we excluded them after full text review.

Characteristics of ongoing studies *[ordered by study ID]*

NCT00310492

Trial name or title	Multicenter, randomized, double-blind, placebo-controlled parallel group study to demonstrate the efficacy of a 12-month subcutaneous specific immunotherapy with ALK-depot SQ milbenmischung in patients with atopic dermatitis and proven IgE-mediated sensitization to house dust mites
Methods	Randomised, controlled, parallel group trial Duration of study: 12 months
Participants	Country: Germany Age range: adults (15 to 55 years) **Inclusion criteria** (1) Positive specific IgE to house dust mites; (2) atopic dermatitis according to Hanifin/Rajka; (3) chronic course of atopic dermatitis; and (4) SCORAD larger than 25 points **Exclusion criteria**

NCT00310492 (*Continued*)

	(1) Erythrodermia; (2) systemic treatment with GCs or immunosuppressive agents in the previous 4 weeks; (3) history of specific immunotherapy with mites; (4) UV radiation; and (5) group 4 topical corticosteroids (European classification)
Interventions	Treatment: subcutaneous injections with ALK-depot SQ mites Updosing schedule: 16 injections to 100,000 SQ-U Manufacturer: ALK-Abelló A/S Control: placebo injections
Outcomes	**Primary outcome measures** • Changes from baseline in SCORAD and topical medication consumption **Secondary outcome measures** • Changes from baseline in SCORAD intensity score, Eczema Area Severity Index score, and change in topical medication consumption **Other outcome measures** • SCORAD extent criteria, index, subjective symptoms, Investigator's Global Assessment score, oral rescue medication, exacerbation of atopic dermatitis, DLQI, and treatment expectation questionnaire
Starting date	April 2006
Contact information	Alexander Kapp; Hanover Medical School
Notes	Also registered as EudraCT 2005-004675-37

AD: atopic dermatitis
AE: atopic eczema
APT: atopy patch testing
DLQI: Dermatology Life Quality Index
GCs: glucocorticoids
HDM: house dust mite
HIV: human immunodeficiency virus
IgE: immunoglobulin E
SCORAD: SCORing Atopic Dermatitis
SPT: skin prick test
SQ: standardised quality
SQ-U: standardised quality units
UV: ultraviolet
UVA: ultraviolet A
UVB: ultraviolet B
VAS: Visual Analogue Scale

DATA AND ANALYSES

Comparison 1. Immunotherapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant- or parent-reported specific symptoms of eczema	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 SCORAD part C	2	184	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.98, 0.50]
1.2 Severity of sleep disturbance	2	184	Mean Difference (IV, Random, 95% CI)	-0.49 [-1.03, 0.06]
2 Adverse events	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Any local reaction	7	484	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.89, 1.81]
2.2 Any systemic reaction	7	492	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.41, 1.49]
2.3 Tiredness	1	48	Risk Ratio (M-H, Random, 95% CI)	5.08 [0.66, 39.02]
2.4 Headache	1	48	Risk Ratio (M-H, Random, 95% CI)	2.56 [0.11, 59.75]
3 Investigator- or physician-rated global disease severity	6	262	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.16, 1.88]
4 Participant- or parent-rated eczema severity using a non-published scale	2	158	Mean Difference (IV, Random, 95% CI)	-1.12 [-1.92, -0.32]
5 Investigator-rated eczema severity assessed using a published scale	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Total SCORAD	3	244	Mean Difference (IV, Random, 95% CI)	-5.79 [-7.92, -3.66]
6 Use of other medications for eczema	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Planned subgroup analyses: immunotherapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by route of immunotherapy	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Subcutaneous immunotherapy	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Sublingual immunotherapy	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by route of immunotherapy	2		Mean Difference (IV, Random, 95% CI)	Totals not selected

2.1 Subcutaneous immunotherapy	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Sublingual immunotherapy	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by allergen type	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Perennial inhalant	2	184	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.98, 0.50]
4 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by allergen type	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Perennial inhalant	2	184	Mean Difference (IV, Random, 95% CI)	-0.49 [-1.03, 0.06]
5 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by participant age	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 18 years or over	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Participant- or parent-reported specific symptoms of eczema - itch severity by participant age	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 18 years or over	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by participant age	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 18 years or over	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Participant- or parent-reported specific symptoms of eczema - itch severity by severity at randomisation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Moderate (SCORAD mean objective score 16 to 40)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Severe (SCORAD mean objective score > 40)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by severity at randomisation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Moderate (SCORAD mean objective score 16 to 40)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Severe (SCORAD mean objective score > 40)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Adverse events: any local reaction by route of immunotherapy	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Subcutaneous	5	320	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.90, 1.55]
10.2 Sublingual	2	164	Risk Ratio (M-H, Random, 95% CI)	9.76 [1.28, 74.26]

11 Adverse events: any systemic reaction by route of immunotherapy	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Subcutaneous	5	328	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.34, 2.00]
11.2 Sublingual	2	164	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.29, 1.89]
12 Adverse events: any local reaction by allergen type	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Perennial inhalant	6	464	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.81, 2.13]
13 Adverse events: any systemic reaction by allergen type	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Perennial inhalant	6	472	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.41, 1.49]
14 Adverse events: any local reaction by participant age	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 18 years or over	2	275	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.44, 4.23]
15 Adverse events: any systemic reaction by participant age	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 18 years or over	2	275	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.38, 1.47]

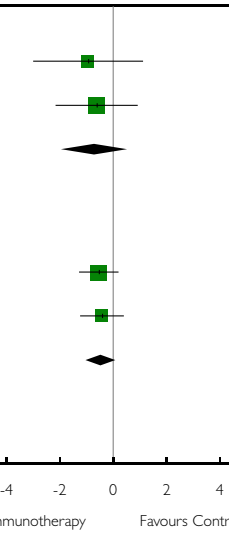
Analysis 1.1. Comparison 1 Immunotherapy versus control, Outcome 1 Participant- or parent-reported specific symptoms of eczema.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 1 Immunotherapy versus control

Outcome: 1 Participant- or parent-reported specific symptoms of eczema

Study or subgroup	Favours Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 SCORAD part C							
Di Rienzo 2014	23	2.1304 (2.599)	15	3.07 (3.4942)		36.2 %	-0.94 [-3.00, 1.13]
Novak 2012	98	4.6653 (4.3373)	48	5.29 (4.5845)		63.8 %	-0.62 [-2.18, 0.93]
Subtotal (95% CI)	**121**		**63**			**100.0 %**	**-0.74 [-1.98, 0.50]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%							
Test for overall effect: Z = 1.16 (P = 0.24)							
2 Severity of sleep disturbance							
Di Rienzo 2014	23	0.2609 (0.5408)	15	0.8 (1.3732)		55.9 %	-0.54 [-1.27, 0.19]
Novak 2012	98	1.8929 (2.1617)	48	2.31 (2.474)		44.1 %	-0.42 [-1.24, 0.40]
Subtotal (95% CI)	**121**		**63**			**100.0 %**	**-0.49 [-1.03, 0.06]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%							
Test for overall effect: Z = 1.75 (P = 0.080)							

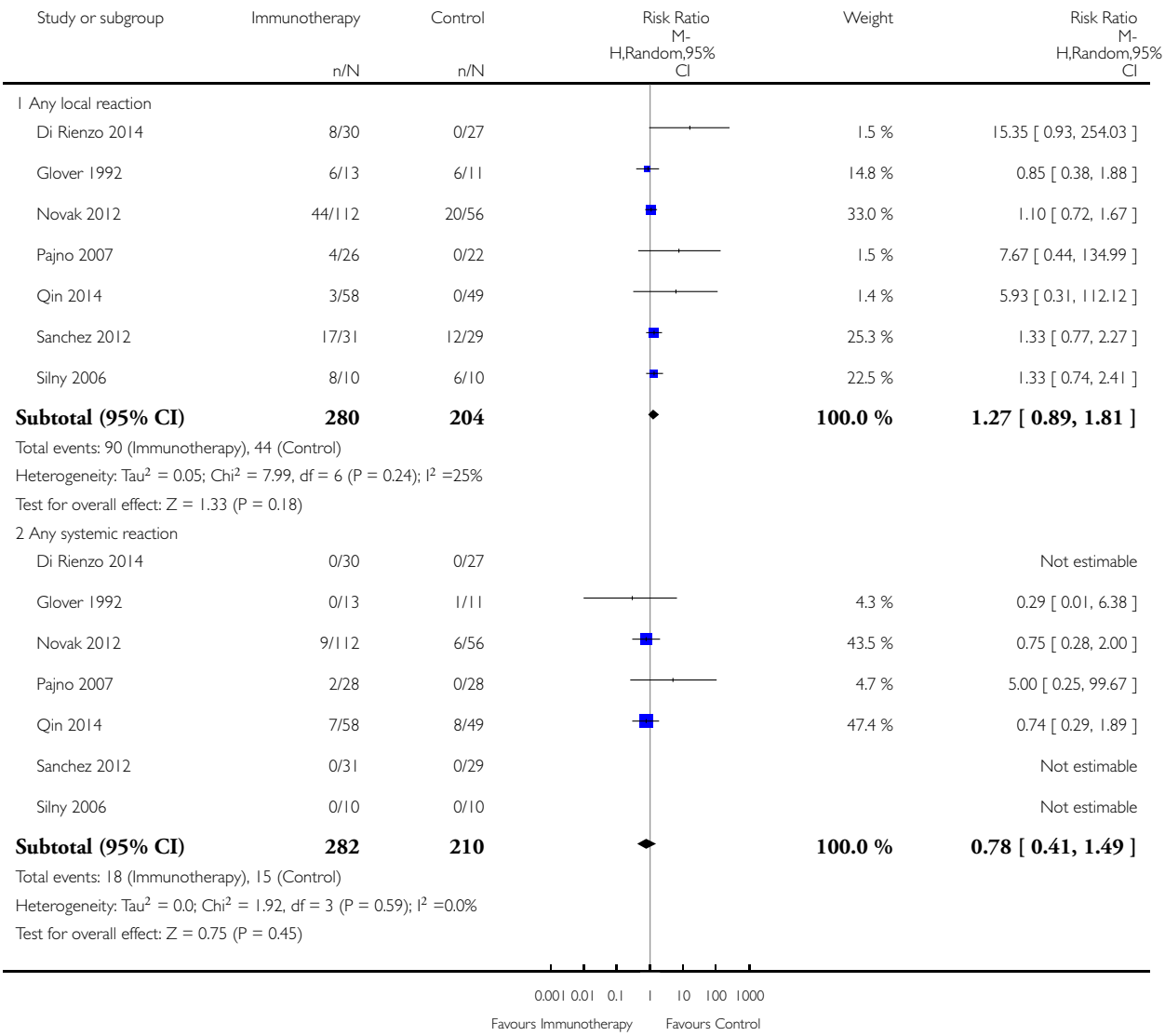


Analysis 1.2. Comparison 1 Immunotherapy versus control, Outcome 2 Adverse events.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 1 Immunotherapy versus control

Outcome: 2 Adverse events



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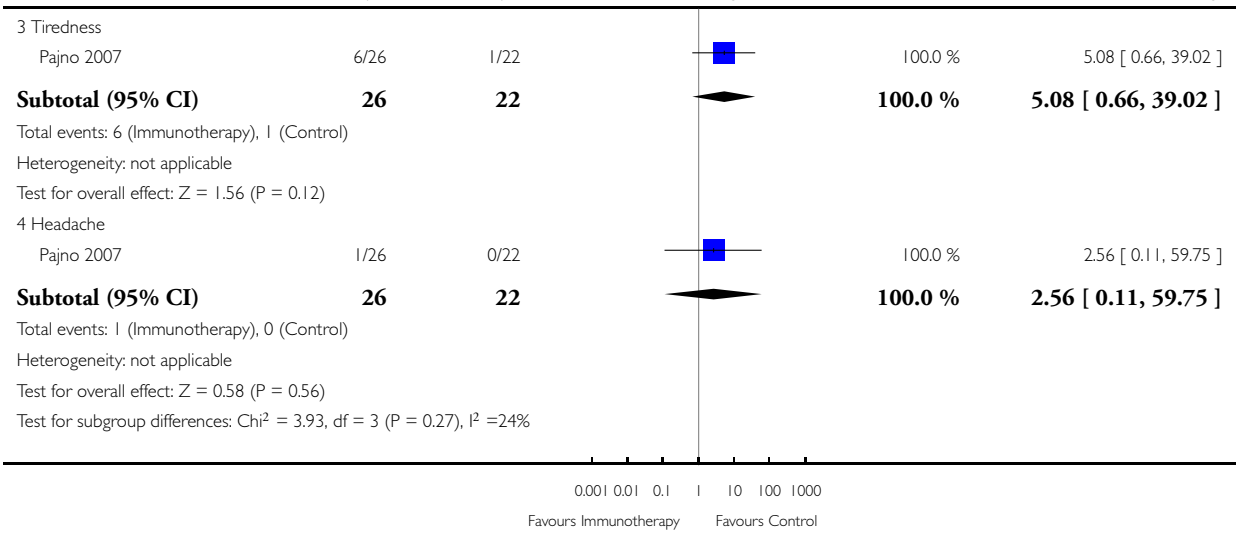
Study or subgroup	Immunotherapy n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Tiredness					
Pajno 2007	6/26	1/22		100.0 %	5.08 [0.66, 39.02]
Subtotal (95% CI)	**26**	**22**		**100.0 %**	**5.08 [0.66, 39.02]**
Total events: 6 (Immunotherapy), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.56 (P = 0.12)					
4 Headache					
Pajno 2007	1/26	0/22		100.0 %	2.56 [0.11, 59.75]
Subtotal (95% CI)	**26**	**22**		**100.0 %**	**2.56 [0.11, 59.75]**
Total events: 1 (Immunotherapy), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Chi^2 = 3.93, df = 3 (P = 0.27), I^2 =24%					



Analysis 1.3. Comparison 1 Immunotherapy versus control, Outcome 3 Investigator- or physician-rated global disease severity.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 1 Immunotherapy versus control

Outcome: 3 Investigator- or physician-rated global disease severity

Study or subgroup	Immunotherapy n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Di Rienzo 2014	20/23	9/15		22.1 %	1.45 [0.93, 2.26]
Galli 1994	10/16	11/18		16.7 %	1.02 [0.60, 1.74]
Kaufman 1974	13/16	4/10		8.3 %	2.03 [0.92, 4.50]
Qin 2014	35/45	21/39		33.1 %	1.44 [1.04, 2.01]
Sanchez 2012	22/31	12/29		19.0 %	1.72 [1.05, 2.79]
Silny 2006	7/10	0/10		0.8 %	15.00 [0.97, 231.84]
Total (95% CI)	**141**	**121**		**100.0 %**	**1.48 [1.16, 1.88]**

Total events: 107 (Immunotherapy), 57 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.17$, df = 5 (P = 0.29); $I^2 = 19\%$

Test for overall effect: Z = 3.18 (P = 0.0015)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Immunotherapy versus control, Outcome 4 Participant- or parent-rated eczema severity using a non-published scale.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 1 Immunotherapy versus control

Outcome: 4 Participant- or parent-rated eczema severity using a non-published scale

Study or subgroup	Immunotherapy		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Di Rienzo 2014	29	3.414 (2.784)	22	4.59 (2.806)		26.5 %	-1.18 [-2.73, 0.37]
Qin 2014	58	6.1 (2.16)	49	7.2 (2.67)		73.5 %	-1.10 [-2.03, -0.17]
Total (95% CI)	**87**		**71**			**100.0 %**	**-1.12 [-1.92, -0.32]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 2.75 (P = 0.0060)

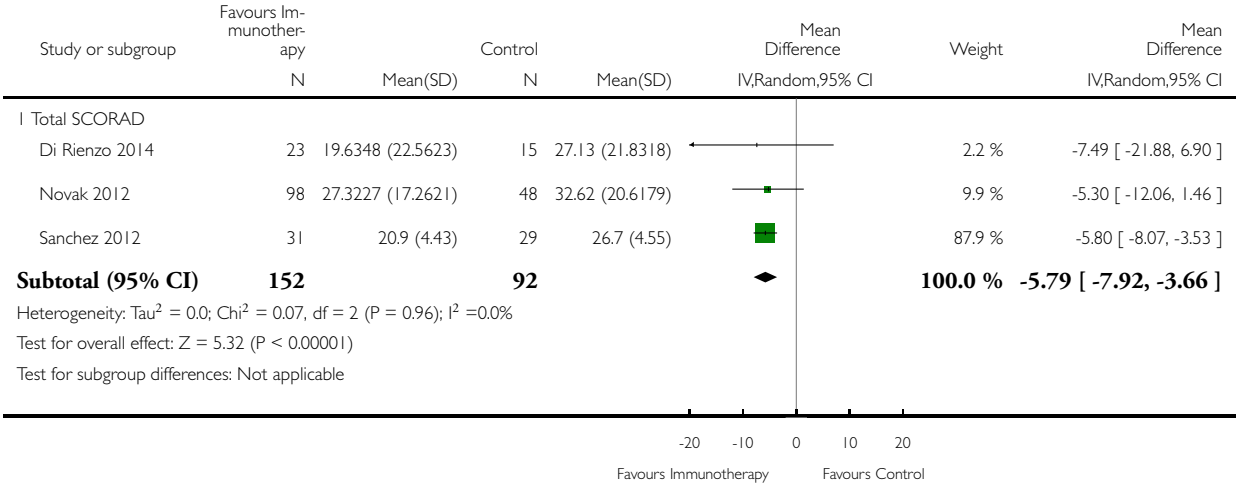
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Immunotherapy versus control, Outcome 5 Investigator-rated eczema severity assessed using a published scale.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 1 Immunotherapy versus control

Outcome: 5 Investigator-rated eczema severity assessed using a published scale

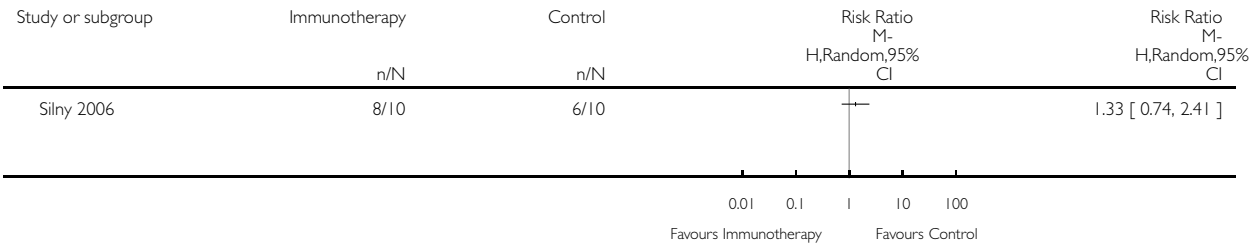


Analysis 1.6. Comparison 1 Immunotherapy versus control, Outcome 6 Use of other medications for eczema.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 1 Immunotherapy versus control

Outcome: 6 Use of other medications for eczema



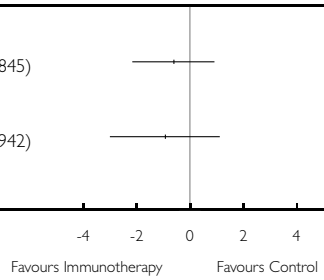
Analysis 2.1. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 1 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by route of immunotherapy.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 1 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by route of immunotherapy

Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Subcutaneous immunotherapy						
Novak 2012	98	4.6653 (4.3373)	48	5.29 (4.5845)		-0.62 [-2.18, 0.93]
2 Sublingual immunotherapy						
Di Rienzo 2014	23	2.1304 (2.599)	15	3.07 (3.4942)		-0.94 [-3.00, 1.13]



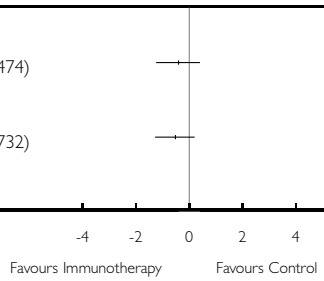
Analysis 2.2. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 2 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by route of immunotherapy.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 2 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by route of immunotherapy

Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Subcutaneous immunotherapy						
Novak 2012	98	1.8929 (2.1617)	48	2.31 (2.474)		-0.42 [-1.24, 0.40]
2 Sublingual immunotherapy						
Di Rienzo 2014	23	0.2609 (0.5408)	15	0.8 (1.3732)		-0.54 [-1.27, 0.19]

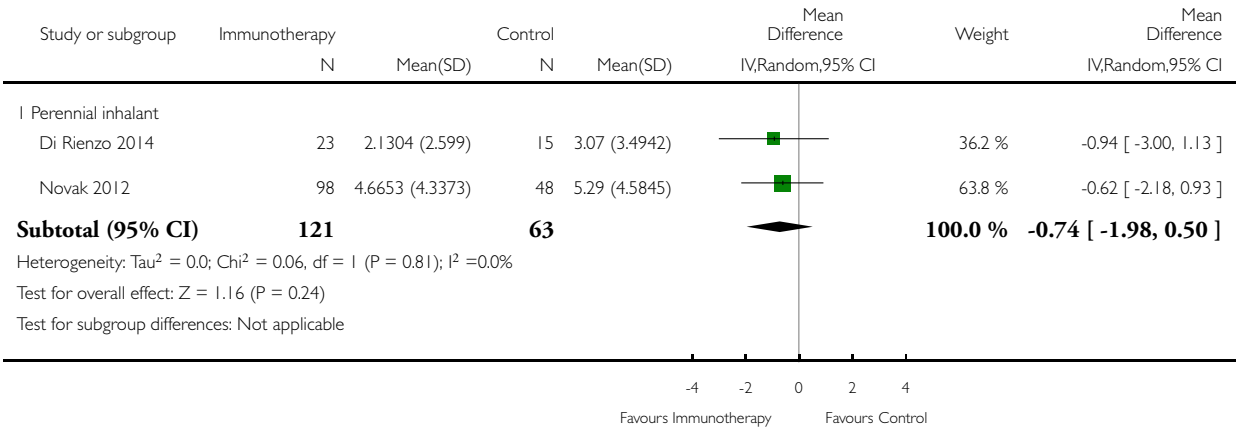


Analysis 2.3. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 3 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by allergen type.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 3 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by allergen type



Analysis 2.4. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 4 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by allergen type.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 4 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by allergen type

Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Perennial inhalant							
Di Rienzo 2014	23	0.2609 (0.5408)	15	0.8 (1.3732)		55.9 %	-0.54 [-1.27, 0.19]
Novak 2012	98	1.8929 (2.1617)	48	2.31 (2.474)		44.1 %	-0.42 [-1.24, 0.40]
Subtotal (95% CI)	**121**		**63**			**100.0 %**	**-0.49 [-1.03, 0.06]**

Heterogeneity: Tau² = 0.0; Chi² = 0.05, df = 1 (P = 0.83); I² =0.0%

Test for overall effect: Z = 1.75 (P = 0.080)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 5 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by participant age.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 5 Participant- or parent-reported specific symptoms of eczema - SCORAD part C by participant age

Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 18 years or over						
Novak 2012	98	4.6653 (4.3373)	48	5.29 (4.5845)		-0.62 [-2.18, 0.93]

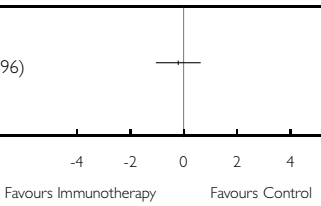
Analysis 2.6. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 6 Participant- or parent-reported specific symptoms of eczema - itch severity by participant age.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 6 Participant- or parent-reported specific symptoms of eczema - itch severity by participant age

Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 18 years or over						
Novak 2012	98	2.7724 (2.5204)	48	2.98 (2.3996)		-0.20 [-1.05, 0.64]



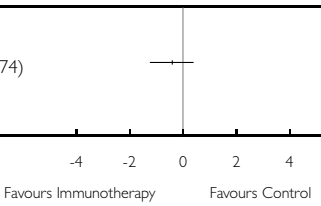
Analysis 2.7. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 7 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by participant age.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 7 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by participant age

Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 18 years or over						
Novak 2012	98	1.8929 (2.1617)	48	2.31 (2.474)		-0.42 [-1.24, 0.40]



Analysis 2.8. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 8 Participant- or parent-reported specific symptoms of eczema - itch severity by severity at randomisation.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 8 Participant- or parent-reported specific symptoms of eczema - itch severity by severity at randomisation

Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Moderate (SCORAD mean objective score 16 to 40)						
Novak 2012	23	2.5 (3.2927)	14	1.49 (3.605)		1.01 [-1.31, 3.33]
2 Severe (SCORAD mean objective score > 40)						
Novak 2012	75	3.0441 (3.3939)	34	2.95 (3.767)		0.10 [-1.38, 1.58]

Analysis 2.9. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 9 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by severity at randomisation.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 9 Participant- or parent-reported specific symptoms of eczema - severity of sleep disturbance by severity at randomisation

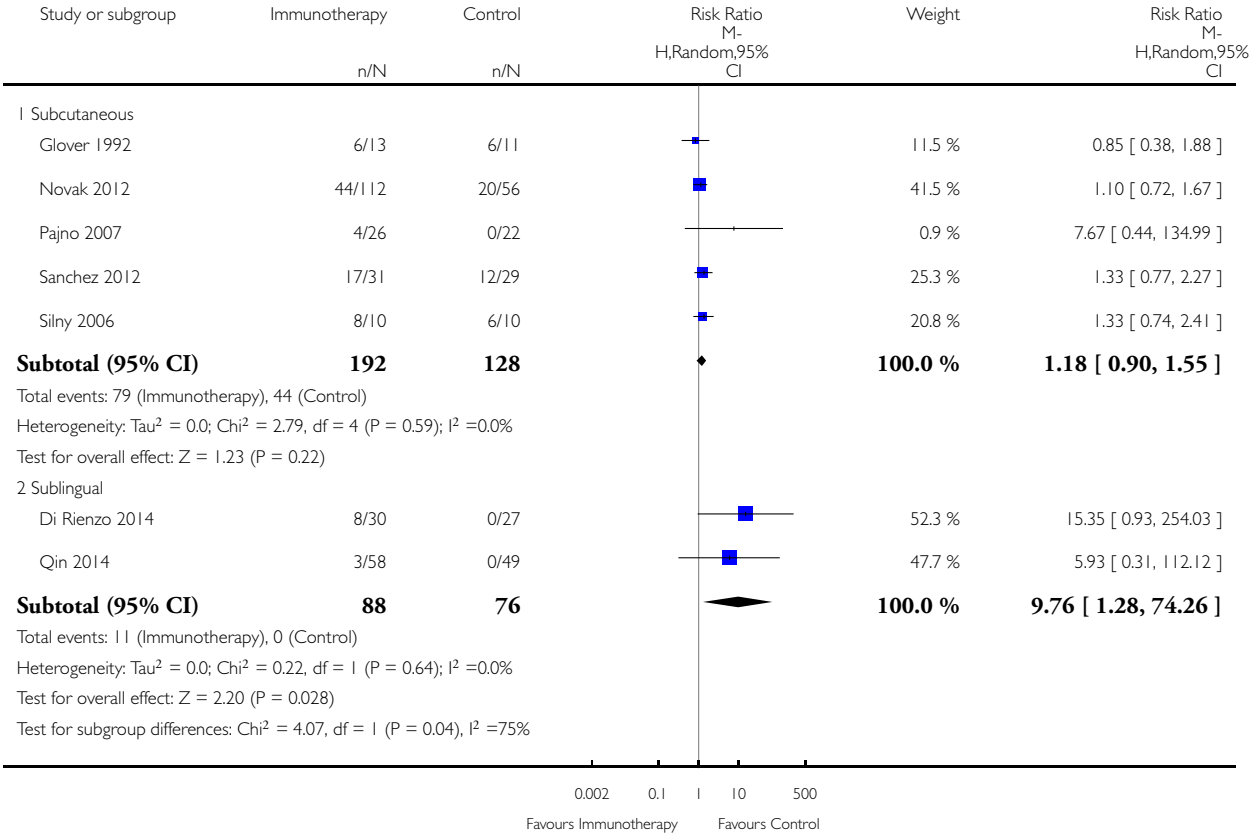
Study or subgroup	Immunotherapy N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Moderate (SCORAD mean objective score 16 to 40)						
Novak 2012	23	1.6571 (2.5785)	14	1.27 (2.5537)		0.38 [-1.32, 2.09]
2 Severe (SCORAD mean objective score > 40)						
Novak 2012	75	2.6412 (3.3808)	34	2.95 (3.3225)		-0.31 [-1.66, 1.04]

Analysis 2.10. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 10 Adverse events: any local reaction by route of immunotherapy.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 10 Adverse events: any local reaction by route of immunotherapy

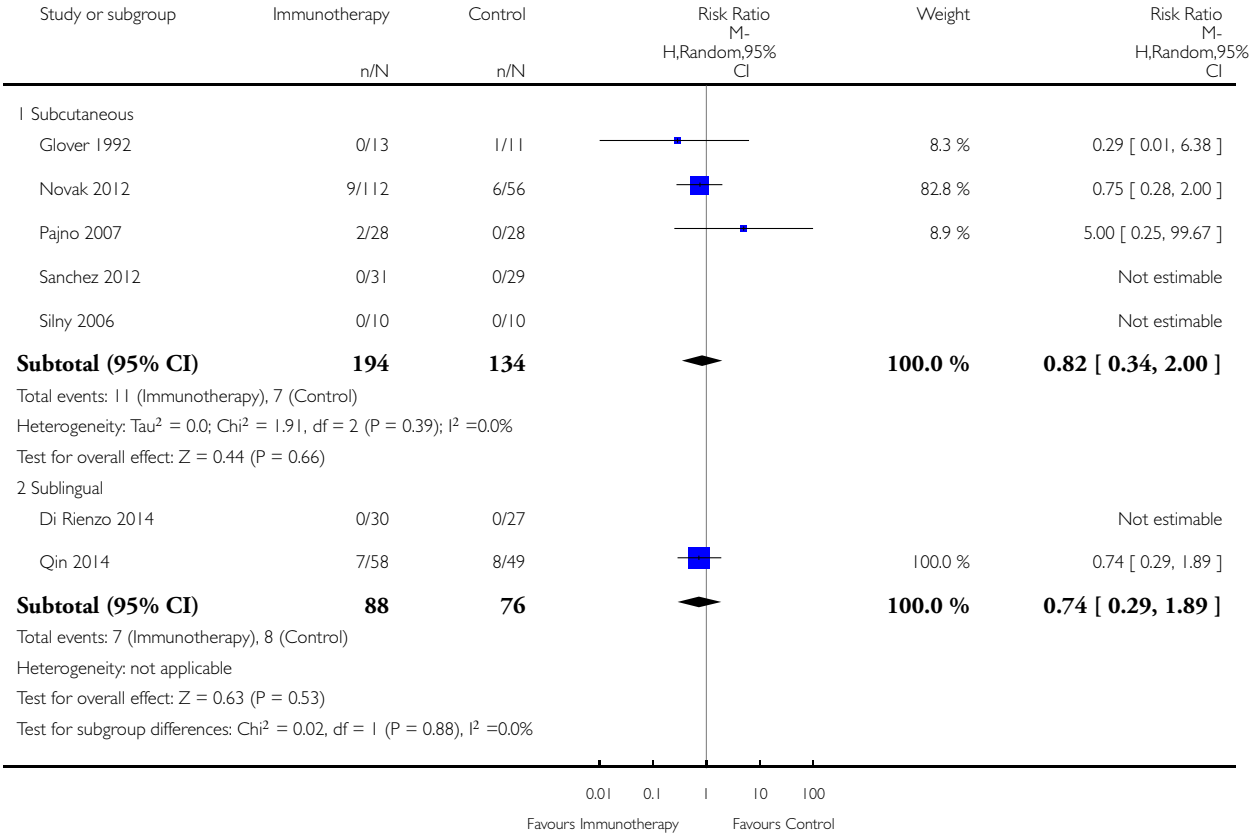


Analysis 2.11. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 11 Adverse events: any systemic reaction by route of immunotherapy.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 11 Adverse events: any systemic reaction by route of immunotherapy



Analysis 2.12. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 12 Adverse events: any local reaction by allergen type.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 12 Adverse events: any local reaction by allergen type

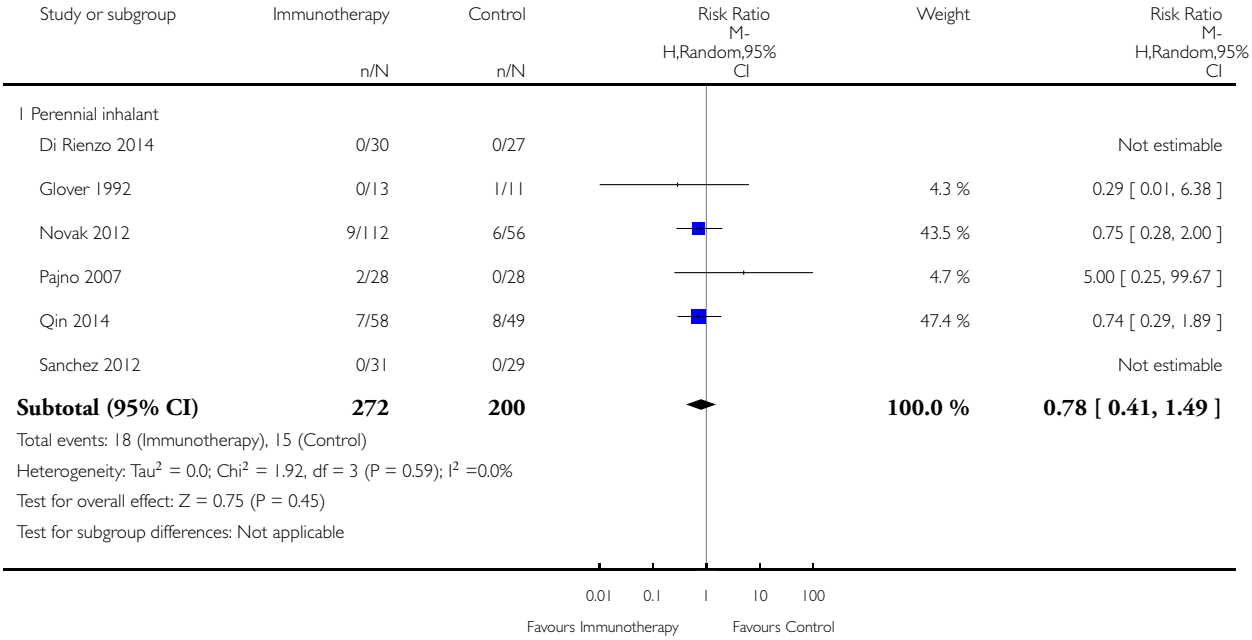
Study or subgroup	Immunotherapy n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Perennial inhalant					
Di Rienzo 2014	8/30	0/27		2.8 %	15.35 [0.93, 254.03]
Glover 1992	6/13	6/11		21.8 %	0.85 [0.38, 1.88]
Novak 2012	44/112	20/56		37.9 %	1.10 [0.72, 1.67]
Pajno 2007	4/26	0/22		2.7 %	7.67 [0.44, 134.99]
Qin 2014	3/58	0/49		2.6 %	5.93 [0.31, 112.12]
Sanchez 2012	17/31	12/29		32.1 %	1.33 [0.77, 2.27]
Subtotal (95% CI)	**270**	**194**		**100.0 %**	**1.31 [0.81, 2.13]**
Total events: 82 (Immunotherapy), 38 (Control)					
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.04$, df = 5 (P = 0.15); $I^2 = 38\%$					
Test for overall effect: Z = 1.09 (P = 0.28)					
Test for subgroup differences: Not applicable					

Analysis 2.13. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 13 Adverse events: any systemic reaction by allergen type.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 13 Adverse events: any systemic reaction by allergen type

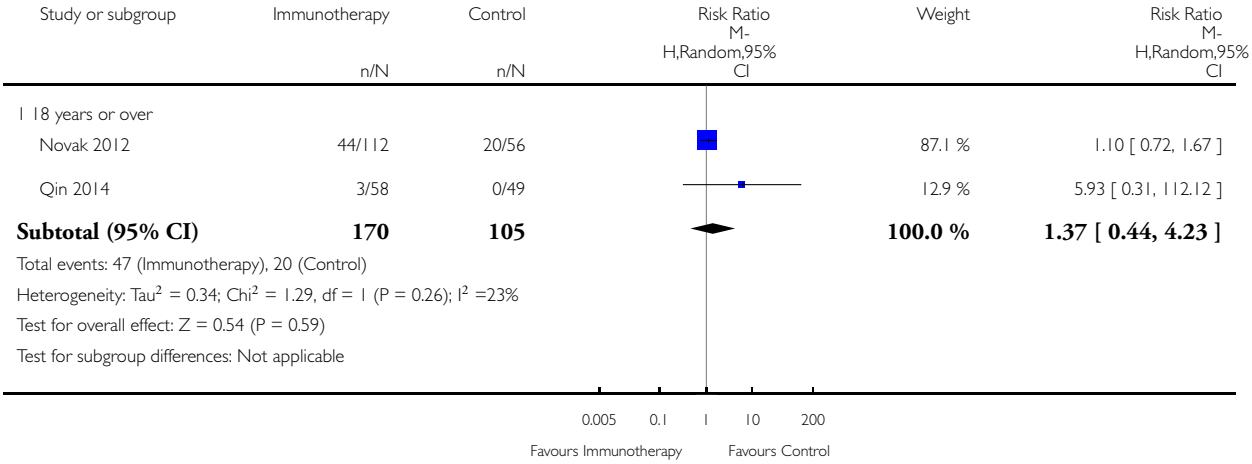


Analysis 2.14. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 14 Adverse events: any local reaction by participant age.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 14 Adverse events: any local reaction by participant age

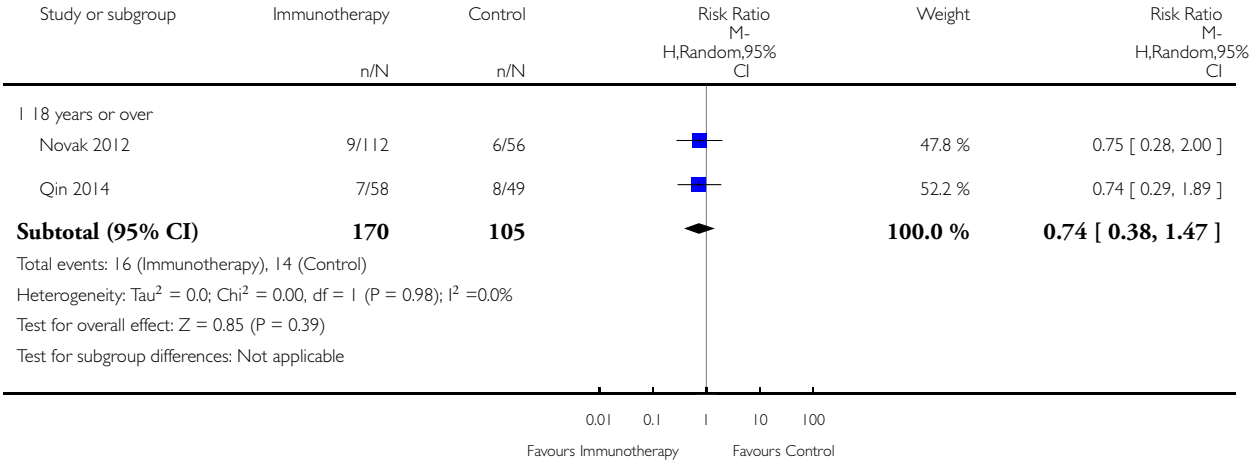


Analysis 2.15. Comparison 2 Planned subgroup analyses: immunotherapy versus control, Outcome 15 Adverse events: any systemic reaction by participant age.

Review: Specific allergen immunotherapy for the treatment of atopic eczema

Comparison: 2 Planned subgroup analyses: immunotherapy versus control

Outcome: 15 Adverse events: any systemic reaction by participant age



ADDITIONAL TABLES

Table 1. Glossary of unfamiliar terms

Term	Definition
Anaphylaxis	A serious, life-threatening allergic reaction
Fissuration	Formation of tears in the skin
Intradermally	Into the skin (dermis), below the epidermis
Lichenification	Thickening and hardening of the skin
Monovalent	1 kind of antibody
Perennial	Long-lasting continually
Photopheresis	A form of apheresis and photodynamic therapy
Sublingual	Under the tongue

Table 1. Glossary of unfamiliar terms (*Continued*)

Vesicles	Fluid-filled cavities

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) search strategy

#1 (atopic dermatitis)
#2 (atopic eczema)
#3 (neurodermatitis)
#4 (eczema)
#5 MeSH descriptor Dermatitis explode all trees
#6 MeSH descriptor Eczema explode all trees
#7 MeSH descriptor Neurodermatitis explode all trees
#8 MeSH descriptor Dermatitis, Atopic explode all trees
#9 (dermatitis)
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 (besnier* prurigo)
#12 (season* or spring or summer or perennial or pollen or grass* or birch or tree* or weed*)
#13 (mite* or dust* or cat* or dog* or bacteri* or fung* or food* or egg* or peanut* or milk)
#14 (dematophagoides or allergen* or poacea or malassezia or staphylococcus aureus)
#15 MeSH descriptor Pyroglyphidae explode all trees
#16 MeSH descriptor Allergens explode all trees
#17 MeSH descriptor Pollen explode all trees
#18 MeSH descriptor Poaceae explode all trees
#19 MeSH descriptor Malassezia explode all trees
#20 MeSH descriptor Staphylococcus aureus explode all trees
#21 MeSH descriptor Desensitization, Immunologic explode all trees
#22 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#23 (#10 OR #11)
#24 (desensitization or immunotherapy or immunomodulatory or hyposensitisation)
#25 (immune therapy) or (immunologic response) or (dose response relationship)
#26 MeSH descriptor Immunotherapy explode all trees
#27 MeSH descriptor Dose-Response Relationship, Immunologic explode all trees
#28 (specific and allergen and immunotherapy)
#29 (#21 OR #24 OR #25 OR #26 OR #27 OR #28)
#30 (#23 AND #22 AND #29)

Appendix 2. Medline (Ovid) search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (humans and animals)).sh.
10. 8 not 9
11. exp Eczema/ or eczema.mp.
12. exp Dermatitis, Atopic/
13. atopic eczema.mp.
14. atopic dermatitis.mp.
15. exp Dermatitis/
16. neurodermatitis.mp. or Neurodermatitis/
17. (besnier$ and prurigo).mp.
18. (season$ or spring or summer or perennial or pollen or grass$ or birch or tree$ or weed$).mp.
19. (mite$ or dust$ or cat$ or dog$ or bacteri$ or fung$ or food$ or egg$ or peanut$ or milk).mp.
20. dermatophagoides.mp. or exp Pyroglyphidae/
21. allergens.mp. or exp Allergens/
22. exp Pollen/ or pollen.mp.
23. poacea.mp. or Poaceae/
24. Malassezia.mp. or exp Malassezia/
25. exp Staphylococcus aureus/ or staphylococcus aureus.mp.
26. exp Desensitization, Immunologic/ or desensitization.mp.
27. immunotherapy.mp. or exp Immunotherapy/
28. immunomodulatory.mp.
29. immune therapy.mp.
30. immunologic response.mp.
31. hyposensitisation.mp.
32. exp Dose-Response Relationship,Immunologic/
33. dose response relationship.mp.
34. specific allergen immunotherapy.mp.
35. 11 or 16 or 13 or 17 or 12 or 15 or 14
36. 25 or 21 or 20 or 22 or 18 or 24 or 19 or 23
37. 27 or 33 or 32 or 28 or 26 or 30 or 29 or 31 or 34
38. 36 and 35 and 37 and 10

[1-10: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 3. EMBASE (Ovid) search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp.
6. (singl$ adj blind$).mp.
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. eczema.mp. or exp ECZEMA/
15. exp DERMATITIS/ or dermatitis.mp.
16. atopic dermatitis.mp. or exp atopic dermatitis/
17. atopic eczema.mp.
18. neurodermatitis.mp. or exp NEURODERMATITIS/
19. besnier$ prurigo.mp.
20. (season$ or spring or summer or perennial or pollen or grass$ or birch or tree$ or weed$).mp.
21. (mite$ or dust$ or cat$ or dog$ or bacteri$ or fung$ or food$ or egg$ or peanut$ or milk).mp.
22. dermatophagoides.mp. or exp DERMATOPHAGOIDES/
23. pyroglyphidae.mp. or exp PYROGLYPHIDAE/
24. allergens.mp. or exp allergen/
25. exp POLLEN/ or pollen.mp.
26. poaceae.mp. or exp POACEAE/
27. poacea.mp.
28. exp MALASSEZIA/ or malassezia.mp.
29. exp Staphylococcus aureus/ or staphylococcus aureus.mp.
30. exp desensitization/
31. immunotherapy.mp. or exp IMMUNOTHERAPY/
32. immunomodulatory.mp.
33. immune therapy.mp. or exp immunotherapy/
34. immunologic response.mp.
35. hyposensitisation.mp.
36. dose response relationship.mp.
37. exp dose response/
38. specific allergen immunotherapy.mp.
39. 14 or 15 or 16 or 17 or 18 or 19
40. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
41. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
42. 13 and 39 and 40 and 41

Appendix 4. LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Words] and (dermatitis or eczema or eccema) [Words]
In LILACS we searched using the Controlled clinical trials topic-specific query filter.

Appendix 5. Web of Knowledge search strategy

We searched the Science Citation Index Expanded (SCI-EXPANDED) 2005 to present
Topic=(eczema)
Refined by: Topic=(trial) AND Topic=(specific allergen immunotherapy)
Databases=SCI-EXPANDED Timespan=2005-to present
OR

Topic=(eczema)
Refined by: Topic=((randomised controlled trial) or (randomized controlled trial)) AND Topic=(immuno*)
Databases=SCI-EXPANDED Timespan=2005-to present

CONTRIBUTIONS OF AUTHORS

MC was the contact person with the editorial base at the protocol stage; and RB, at the review stage. MC and RB designed the study and co-wrote the protocol. HN, HW, and SD reviewed earlier drafts of the protocol and provided comments. RB co-ordinated contributions from the co-authors. HT, MC, LM, and RB screened papers against eligibility criteria, appraised the quality of papers, extracted data, and sought additional information form original authors. HT, RB, and HN assessed the risk of bias. HT, LM, and RB entered data into Review Manager (RevMan) and analysed and interpreted data. HT and RB wrote the final draft of the review with contributions from all authors.

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DECLARATIONS OF INTEREST

Herman Tam: nothing to declare.

Moises A Calderon: nothing to declare.

Logan Manikam: nothing to declare.

Helen Nankervis: nothing to declare.

Ignacio García Núñez: nothing to declare.

Hywel C Williams: nothing to declare.

Stephen Durham: "I have received research funding for immunotherapy trials in hay fever (but not eczema) via Imperial College from ALK-Abelló, Denmark; Merck, USA; and BioTech Tools, Belgium; all are manufacturers of allergy vaccines (research in relation to

vaccines for hay fever, not for eczema). I have acted as a paid advisor for Merck, USA, a manufacturer of allergy vaccines (in relation to allergy vaccines for hay fever, not for eczema). I have received consultancy fees via Imperial College from Circassia, UK; Stallergenes, France; and Biomay, Austria (in relation to vaccines for hay fever, not for eczema)."

Robert J Boyle: nothing to declare.

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Internal sources

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- The University of Malaga, Spain.

External sources

- The National Institute for Health Research (NIHR), UK.

The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

HT and LM joined as a co-authors.

Types of interventions: we specified allergen formulations as standardised allergen extracts for single allergen or mixed allergens and included intradermal and oral routes of immunotherapy because of recent evidence that these routes may be effective for allergen immunotherapy in general (Anagnostou 2014; Rotiroti 2012).

Types of outcome measures: we clarified the primary outcome 'Participant- or parent-reported specific symptoms of eczema' by subjective measures such as itch and sleep disturbance (SCORing Atopic Dermatitis (SCORAD) part C).

Types of outcome measures: although not one of our prespecified outcomes, we analysed 'Participant- or parent-rated eczema severity assessed using a non-published scale' because we thought it was important to include it as a subcategory. Six studies reported this outcome in the form of Visual Analogue Scales.

Types of outcome measures: for consistency, we added 'physician-rated' to the third secondary outcome.

Measures of treatment effect: we amended the measure of treatment effect in continuous data to be expressed as mean differences where possible. We planned to express dichotomous outcomes as number needed to treat (NNT), where appropriate, with a 95% confidence interval (CI) and the baseline risk to which it applies but did not because we identified no suitable findings to which a NNT might be applied, since the review findings were either negative or inconclusive.

Unit of analysis issues: we planned to use techniques appropriate for paired designs and data from parallel trials and cross-over trials as separate subgroups to analyse cross-over trials, since cross-over studies may not be appropriate for immunotherapy studies. Our search did not identify any cross-over trials.

We did not list non-randomised controlled studies because we did not identify significant studies or data from non-randomised controlled studies.

Where studies reported more than one active intervention, we planned to combine the two active interventions and analyse them together, but we included no trials with more than one eligible active intervention. Where studies reported non-parametric statistics, we planned to include these in meta-analyses where possible, following the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, there were no relevant studies.

Assessment of reporting biases: we planned to use funnel plots to assess publication bias graphically (if there were sufficient included studies) and to use Begg and Egger tests (Begg 1994; Egger 1997) to assess it statistically; however, we did not have a sufficient number of included studies.

Sensitivity analysis: we planned to undertake sensitivity analysis for the allocation of missing data by best and worst case analysis. If we had found significant heterogeneity between studies, we planned to explore possible reasons for this, which would have included risk of bias in the included studies. However, we did not perform posthoc sensitivity analyses because of the small number of studies that contributed to meta-analyses.

Appendices: we updated the search strategy for ongoing trial databases to identify relevant trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Allergens [*therapeutic use]; Dermatitis, Atopic [*therapy]; Dermatophagoides farinae; Dermatophagoides pteronyssinus; Desensitization, Immunologic [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Animals; Child; Humans