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Sublingual immunotherapy for allergic rhinitis (Review)

Radulovic S, Calderon MA, Wilson D, Durham S

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[Intervention Review]

Sublingual immunotherapy for allergic rhinitis

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ABSTRACT

Background

This is an update of a Cochrane Review first published in *The Cochrane Library* in Issue 2, 2003.

Allergic rhinitis is a common condition which can significantly impair quality of life. Immunotherapy by injection can significantly reduce symptoms and medication use but its use is limited by the possibility of severe systemic adverse reactions. Immunotherapy by the sublingual route is therefore of considerable interest.

Objectives

To evaluate the efficacy and safety of sublingual immunotherapy for allergic rhinitis in adults and children.

Search methods

We searched the Cochrane ENT Group Trials Register; CENTRAL (2010, Issue 3); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; *m*RCT and additional sources for published and unpublished trials. The date of the most recent search was 14 August 2009.

Selection criteria

Randomised, double-blind, placebo-controlled trials of sublingual immunotherapy in adults or children. Primary outcome measures were symptom and medication scores. We also collected adverse event data.

Data collection and analysis

Two independent authors selected studies and assessed risk of bias. One author extracted data which was rechecked by two other authors. We used the standardised mean difference (SMD) with a random-effects model to combine data.

Main results

We included a total of 60 randomised controlled trials in the review. Forty-nine were suitable for pooling in meta-analyses (2333 SLIT, 2256 placebo participants). Overall, we found a significant reduction in symptoms (SMD -0.49; 95% confidence interval (CI) -0.64 to -0.34, P < 0.00001) and medication requirements (SMD -0.32; 95% CI -0.43 to -0.21, P < 0.00001) in participants receiving sublingual immunotherapy compared to placebo. None of the trials included in this review reported severe systemic reactions or anaphylaxis, and none of the systemic reactions reported required the use of adrenaline.

Authors' conclusions

This updated review reinforces the conclusion of the original 2003 Cochrane Review that sublingual immunotherapy is effective for allergic rhinitis and has been proven to be a safe route of administration.

PLAIN LANGUAGE SUMMARY

Sublingual immunotherapy for allergic rhinitis (including hay fever)

Allergic rhinitis is characterised by red, itchy eyes, a blocked and runny nose, and sneezing. The most common causes of allergic rhinitis are different pollens (grass and tree), house dust mites, mould and animal dander. Allergic rhinitis can be intermittent (such as hay fever) or persistent (all year round). The treatment of allergic rhinitis depends on its severity and duration, and is usually based on the use of antihistamines and nasal corticosteroids. If these drugs cannot control symptoms immunotherapy is recommended. Immunotherapy involves the administration of gradually increasing doses of the allergen over a period of time to desensitise the patient. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms.

In reviewing 60 trials we found a significant reduction in symptom and medication scores in patients treated with sublingual immunotherapy compared to placebo. There were no serious adverse reactions reported in the included trials and no patient needed the use of adrenaline. This updated Cochrane Review therefore reinforces the conclusions of the earlier review in confirming the efficacy and safety of sublingual immunotherapy.

BACKGROUND

This is an update of a Cochrane Review first published in *The Cochrane Library* in Issue 2, 2003.

Allergic rhinitis is a common condition, affecting between 10% and 40% of people worldwide. The typical clinical features are sneezing, watery rhinorrhoea, nasal blockage, itchy, watery eyes and itchy throat. In clinical trials the severity of allergic rhinitis is usually assessed by numerical validation of nasal and eye symptoms, which takes into account subjective intensity, and whether the condition interferes with everyday life or school and work performance.

The ARIA guidelines (ARIA 2001; ARIA 2008) recommend allergen avoidance as first-line treatment, followed by pharmacotherapy aimed at symptom control (mainly antihistamines and topical nasal corticosteroids). For patients with more severe disease, who do not respond to usual therapy, specific immunotherapy is recommended.

Subcutaneous injection immunotherapy has been used for decades. The exact mechanism of action is not fully understood, but involves changes in serum antibody levels (Jutel 1995; Rossi 2004) and a number of cellular changes, including alteration of the T cell response, from Th2 to Th1 (Wachholz 2002). More recent work suggests that regulatory mechanisms could also play an important role (Francis 2003; Jutel 2003). This immunomodulation results in significant reductions in symptoms and medication requirements (Calderon 2010).

Though proven to be efficacious, the subcutaneous route can be uncomfortable and time-consuming. Local adverse events such as injection site itch or swelling are fairly common and, although rare, systemic reactions can be severe. For this reason alternative routes for the delivery of immunotherapy, with a better safety profile, were sought. In the last two decades attention has focused on the sublingual route.

A Cochrane Review of sublingual immunotherapy for allergic rhinitis was published in 2003 (Wilson 2003) and included 22 randomised, placebo-controlled trials identified up to September 2002. Analysis of symptom and medication scores proved sublingual immunotherapy to be efficacious. Adverse events reported in these trials were minor and local, and no systemic reactions were reported.

Research in the field of sublingual immunotherapy has continued since 2002, resulting in the publication of many additional studies with increased numbers of participants. This review updates the original to give a more comprehensive evaluation of the efficacy and safety of sublingual immunotherapy.

OBJECTIVES

To evaluate the efficacy of sublingual immunotherapy compared with placebo in:

1. reducing symptoms and/or medication requirements during naturally occurring allergic rhinitis;
2. altering immunological markers in blood and immunological markers and allergen sensitivity in target organs (nose, eye, skin).

To evaluate the safety of sublingual immunotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, placebo-controlled clinical trials.

Types of participants

Studies with participants of any age (children and adults). All patients had a history of allergic rhinitis, with or without allergic conjunctivitis, and with or without allergic asthma. In all studies the allergen was clearly identified. Patients' sensitivity was proven by positive skin prick tests and/or high specific IgE to a particular allergen. The existence of other clinically relevant sensitivities was one of the exclusion criteria in the majority of studies.

We excluded trials dealing with asthma only from the review.

Types of interventions

Included studies were those investigating the efficacy and safety of sublingual immunotherapy. We analysed all trials regardless of treatment dose, duration, or whether the allergen was swallowed or spat out.

Types of outcome measures

Primary outcomes

- Symptom scores, however recorded (either daily or weekly, via symptom score diaries, visual analogue scales, number of well days or overall assessment).
- Medication scores referring to the use of relevant anti-allergic medications, however recorded and scored.

Secondary outcomes

- Measurement of serum IgE and IgG (total and specific).
- Assessment of allergen sensitivity (eye, nose or skin).
- Quality of life.
- Adverse event reports.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 14 August 2009 following original searches in September 2002.

Electronic searches

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2009, Issue 3); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI (China National Knowledge Infrastructure); *m*RCT (Current Controlled Trials); ICTRP (International Clinical Trials Registry Platform) and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised

controlled trials and controlled clinical trials (as described in *The Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1, Box 6.4.b. (Handbook 2008)).

CENTRAL search strategy

#1 MeSH descriptor Immunotherapy explode all trees
#2 MeSH descriptor Desensitization, Immunologic explode all trees
#3 MeSH descriptor Allergens explode all trees with qualifiers: AD,IM
#4 immunotherap*
#5 ((allergen* OR immunologic*) AND (hyposensitiz* OR hyposensitis* OR desensitiz* OR desensitis*))
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Administration, Sublingual explode all trees
#8 (SUBLINGUAL* OR ORAL* OR TONGUE OR MUCOSA)
#9 (#7 OR #8)
#10 (#6 AND #9)
#11 SLIT
#12 (#10 OR #11)
#13 MeSH descriptor Rhinitis, Allergic, Perennial explode all trees
#14 MeSH descriptor Rhinitis, Allergic, Seasonal explode all trees
#15 MeSH descriptor Rhinitis explode all trees
#16 rhinti*
#17 MeSH descriptor Hypersensitivity explode all trees
#18 allerg* OR hypersensitiv*
#19 ((#15 OR #16) AND (#17 AND #18))
#20 (perennial:ti OR persistent:ti OR nonseasonal:ti OR nose:ti OR nasal:ti OR cat:ti OR fur:ti OR hair*:ti OR dander:ti OR dust*:ti OR mite*:ti OR pet*:ti OR dog*:ti OR cockroach*:ti OR seasonal:ti OR intermittent:ti OR spring:ti OR summer:ti OR pollen:ti OR grass*:ti OR birch:ti OR ragweed:ti OR tree*:ti OR weed*:ti OR mugwort:ti OR willow:ti OR alder:ti)
#21 ((#17 OR #18) AND #19)
#22 (hayfever OR "hay fever" OR pollenosis OR pollinosis OR SAR OR PAR)
#23 (#13 OR #14 OR #19 OR #21 OR #22)
#24 (#12 AND #23)

Search strategies for other key databases including PubMed are shown in Appendix 1.

Searching other resources

We scanned reference lists of identified studies for further trials. We searched PubMed, TRIPdatabase, NHS Evidence - ENT and Audiology, and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials. We sought abstracts from conference proceedings via the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

We identified additional trials through discussion with specialist allergists, or other professionals with an interest in the area.

We used papers written in English and other languages; translations were performed by the Cochrane ENT Group.

Data collection and analysis

Selection of studies

Two authors (SR and MC) independently screened the search results and selected studies which appeared to meet the review inclusion criteria. We obtained all such studies in full text for further assessment. Any disagreements about which studies to include in the review were resolved by further discussion with the other two authors (SRD and DW) where necessary.

Data extraction and management

We extracted data from the included studies onto a standard form, covering study type and methodology, number and description of participants, details of type, dosage, schedule, duration of sublingual immunotherapy used, as well as the results, types, timing and method of outcome measures. One author (SR) extracted all data and values were checked by MC and SRD.

Where published manuscripts did not report data sufficiently or in suitable format for meta-analysis we sought further information directly from the authors.

As all the authors were previously familiar with the content of most of the studies, we did not remove the study author names before assessment and data extraction.

Assessment of risk of bias in included studies

Three authors (SR, MC and DW) assessed the identified studies separately and compared the results.

For the original 2003 review, quality assessment of the trials was performed using the Jadad scale (Moher 1998). For the 2010 update, all the originally included studies were re-assessed by SR and MC, and scored again with the Jadad scale. We only included double-blind, placebo-controlled trials with a Jadad score > 3/5 in the review.

For the 2010 update, two authors (SR and MC) also assessed all included studies for risk of bias using the Cochrane Collaboration 'Risk of bias' tool as guided by *The Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2008).

The following were taken into consideration:

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We described each of these domains as reported in the trial and then assigned a judgement about the adequacy of each entry. This involved answering a pre-specified question whereby a judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias.

Data synthesis

Apart from adverse events, all the outcome data analysed were continuous. The most common way of recording data was through daily diary cards, recording and scoring symptoms (nasal, eye or less frequently chest) and medication use (antihistamine tablets, nasal sprays, eye drops). The data were subsequently totalled and averaged.

A wide range of different scoring systems and scales were employed by trial authors for both primary and secondary outcomes. This creates problems of significant heterogeneity but is unavoidable.

The outcome data extracted from the included studies were entered into RevMan 5 by SR and MC for the statistical analysis (RevMan 2008). A wide variety of scoring systems were used therefore we performed the analysis using the standardised mean difference (SMD) (the difference in means between two treatment groups, immunotherapy and placebo, in units of pooled standard deviation).

We used random-effect models for statistical analysis of the overall efficacy of sublingual immunotherapy. We presented the results as SMDs with the 95% confidence intervals (CI).

We analysed heterogeneity between studies using the Chi^2 test, with a P value of < 0.1 indicating the significant heterogeneity between studies, and the I^2 statistic which describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error. We used the threshold values recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (0% to 40%: might not be important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity).

We carried out subgroup analysis according to the review protocol as follows:

1. seasonal versus perennial allergens;
2. children versus adults;
3. dosage of major allergen (< 5 mcg of major allergen protein versus 5 to 20 mcg versus > 20 mcg;
4. duration of immunotherapy (< 6 months versus 6 to 12 months versus 12 months, to cover pre-seasonal, perennial and prolonged treatment);
5. sublingual spit versus sublingual swallow; and
6. sublingual drops versus tablets.

We analysed adverse events (AE) as discontinuous data, therefore we present only descriptive analysis.

RESULTS

Description of studies

The original 2003 version of this review included 22 studies; the 2010 update includes 60 studies.

Results of the search

The updated searches in 2009 identified 628 papers of potential interest. We discarded 498 papers after reading the abstracts (review articles or descriptive studies, papers investigating other routes of immunotherapy or not investigating allergic rhinitis). We therefore evaluated 130 papers in detail. Among these, 12 references were matched to studies already included or excluded from the review and these are grouped under the 'primary' reference for the study.

Following this evaluation we discarded another 68 papers.

Included studies

We thus identified 62 papers as potentially appropriate for the review and meta-analysis. We identified two studies as ongoing (Ingels 2002; O'Hehir 2005).

A total of 60 studies are now included in the 2010 update of this review, of which 49 studies are included in the updated meta-analyses. Eleven studies that did not contain efficacy data eligible for meta-analysis contained useful adverse event data.

Allergen

Most trials were performed with grass pollen (23 studies). Other allergens used were *Parietaria* (five trials), ragweed (two trials), trees (nine trials: two olive, three cypress, two birch pollen, two mixed trees), house dust mite (eight trials) and cat (one trial).

One of the trials investigated the efficacy of grass and birch pollen immunotherapy.

Participants

Thirty-four studies were performed in adults and 15 investigated efficacy and safety in children.

Treatment duration

Treatment lasted for less than six months in 17 studies; six to 12 months in 16 studies and longer than 12 months in 16 studies.

Dose of allergen

Of the 49 studies, 32 reported the major allergen dose in a manner suitable for meta-analysis. The rest of the trials either did not provide the sufficient data or reported the cumulative dose (weekly, monthly or a total cumulative dose over the complete treatment). Eight trials used daily doses of less than 5 mcg, in 12 studies the dose was between 5 and 20 mcg per day, and 12 papers reported a daily dose of more than 20 mcg.

Allergen reactivity

Nine trials reported data on skin sensitivity, but only six (skin prick test after treatment) could be included in the meta-analysis. Seven trials reported data eligible for meta-analysis of nasal reactivity. Data on conjunctival reactivity were not sufficient for meta-analysis.

Excluded studies

At the 2010 update we excluded 14 further studies. We also excluded three studies that had been previously included in the original 2003 review and which did not satisfy the new risk of bias assessment criteria (D'Ambrosio 1996; Mungan 1999; Quirino 1996). Two formerly excluded studies (Clavel 1998; Sabbah 1994) are now included in the review. These two studies did not contain sufficient efficacy data, but they satisfied the review inclusion criteria and their adverse event data were analysed. A total of 24 studies are excluded from this updated version of the review (see Characteristics of excluded studies). Studies listed as excluded are those which satisfied the majority but not all of our inclusion criteria.

Risk of bias in included studies

All included studies were double-blind, placebo-controlled trials of parallel-group design. Concealment of treatment allocation was considered adequate in all studies, based on statements made by the original authors. Blinding of study subjects and investigators was almost universally maintained by the use of identical placebo preparations. It should, however, be noted that most investigators reported high levels of minor oral side effects (tingling, itching and

swelling beneath the tongue) in actively treated subjects, which could influence blinding.

Full risk of bias assessments can be found in the Characteristics of included studies table. A 'Risk of bias' summary of our judgements about each risk of bias item for each included study is presented in Figure 1 and as a graph in Figure 2.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

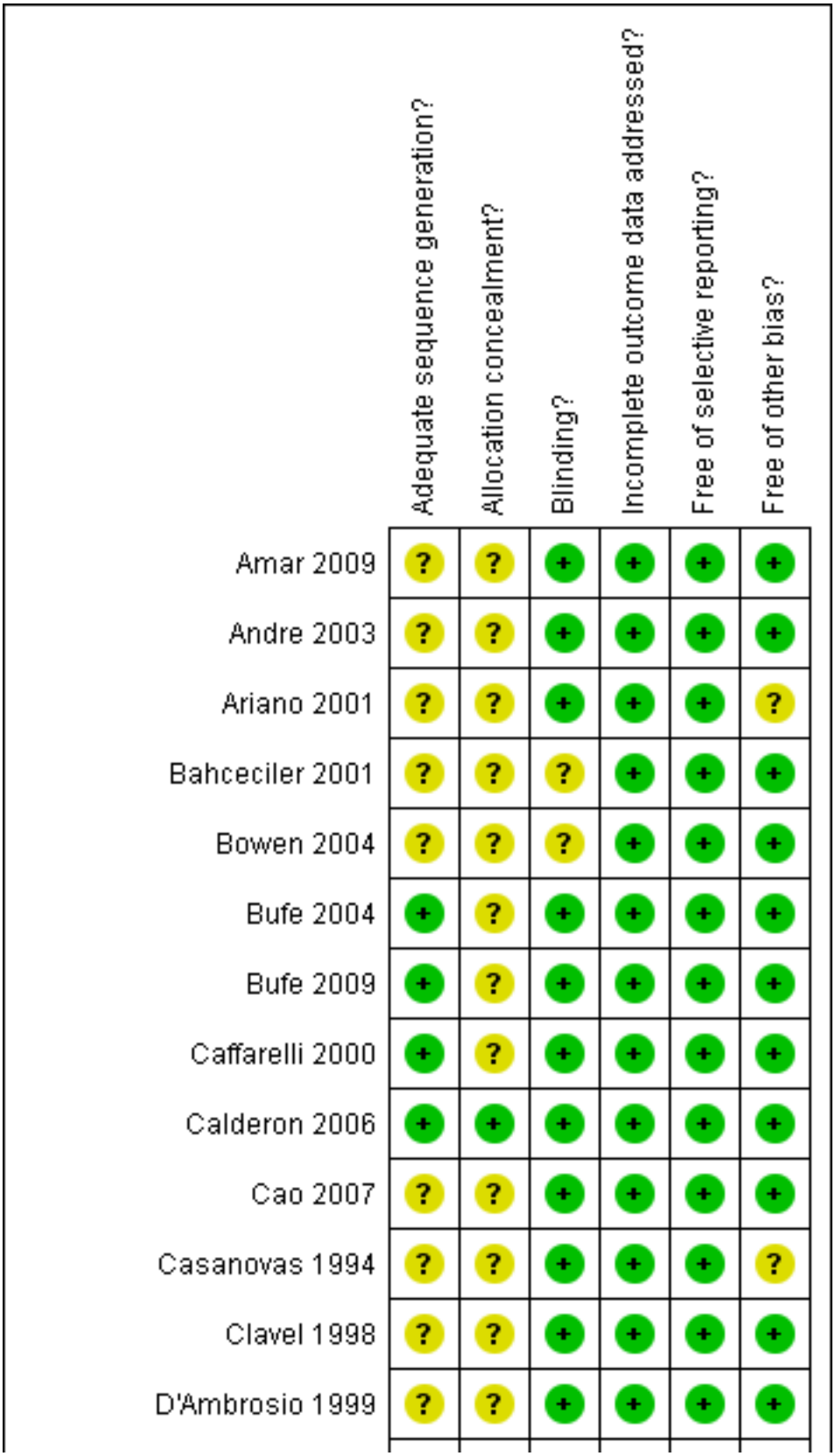


Figure 1. (Continued)

Figure 1. (Continued)

Figure 1. (Continued)

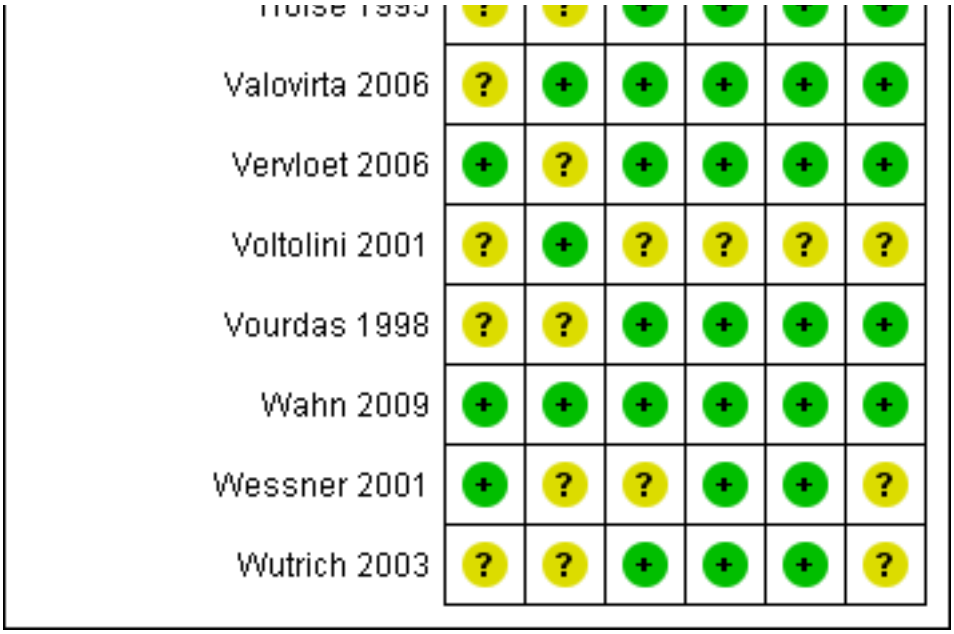
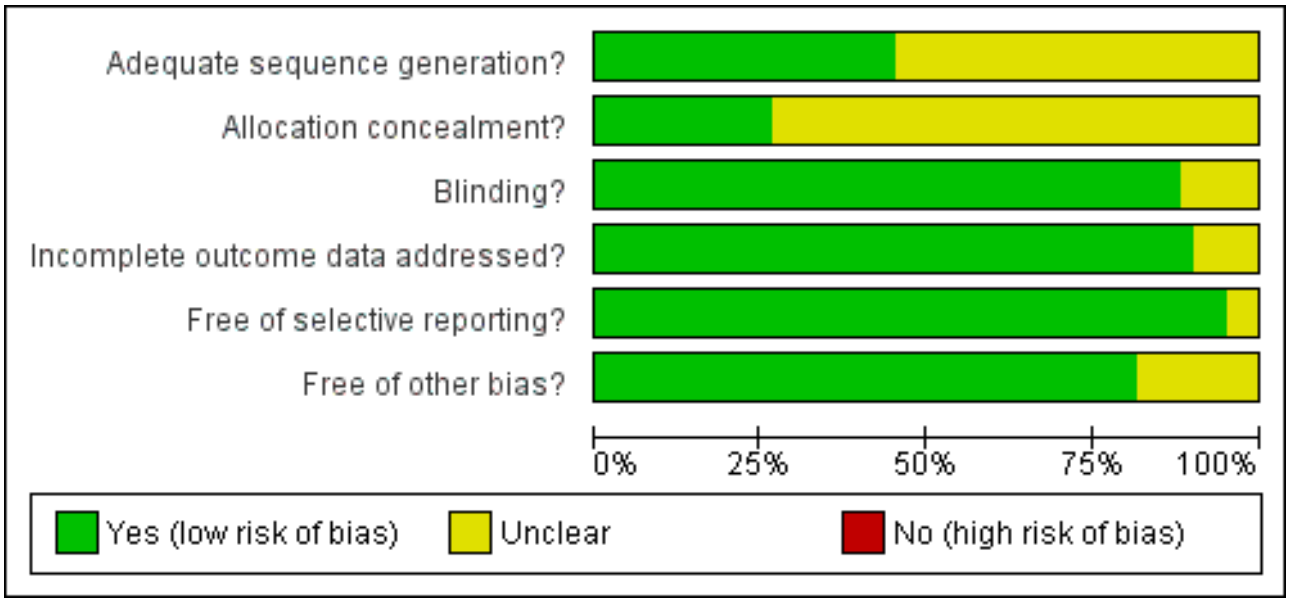


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

Symptom scores

A total of 49 studies were included in the meta-analysis. In total 2333 active (sublingual immunotherapy - SLIT) and 2256 placebo patients were included. The combined standardised mean difference (SMD) following sublingual immunotherapy (SLIT) was SMD -0.49 (95% confidence interval (CI) -0.64 to -0.34) favouring active treatment (P < 0.00001). There was significant heterogeneity between the studies (Chi^2 = 256.76, P < 0.00001, I^2 = 81%) (Analysis 1.1).

Subgroup analysis: seasonal and perennial allergens

We performed the first subgroup analysis in the two biggest subgroups: seasonal (39 trials) and perennial allergens (10 trials).

In the seasonal allergens group there were 2081 participants in the SLIT and 2003 in the placebo group. The combined SMD was -0.34 (95% CI -0.44, -0.25, P < 0.00001). Significant heterogeneity between studies was indicated (Chi^2 = 68.54, P = 0.002, I^2 = 45%) (Analysis 2.1).

The perennial allergen studies involved 252 SLIT and 253 placebo patients, with SMD -0.93 (95% CI -1.69 to -0.17, P = 0.02). Significant heterogeneity between studies was indicated (Chi^2 115.91, P < 0.00001, I^2= 92%) (Analysis 3.1).

Subgroup analysis: age

We performed the age subgroup analysis for adults and children in eight studies. In studies with a mixed population the participants were considered as adults if the median age was ≥ 20, otherwise they were not included in the age subgroup analysis.

Thirty-four studies were performed in adults, 1631 participants received SLIT and 1566 placebo. The combined SMD was -0.44 (95% CI -0.56 to -0.31, P < 0.00001). Significant heterogeneity was indicated between studies (Chi^2 77.81, P = 0.0001, I^2 = 58%) (Analysis 4.1).

Fifteen studies were identified in children; 702 participants were included in the SLIT and 690 in the placebo group. The combined SMD was -0.52 (95% CI -0.94 to -0.10, P = 0.02). Highly significant heterogeneity between studies was indicated (Chi^2 = 177.60, P < 0.00001, I^2 = 92%) (Analysis 5.1).

Subgroup analysis: treatment duration

Seventeen trials reported treatment duration for less than six months; 890 patients received SLIT and 882 received placebo treatment. The combined SMD in this group was -0.54 (95% CI -0.86 to -0.21, P = 0.001). There was an indication of highly significant heterogeneity between these trials (Chi^2 157.82 , P = 0.00001, I^2 = 90%) (Analysis 6.1).

In 16 studies the treatment duration was between six and 12 months; 867 participants were in the SLIT and 869 in the placebo group. The SMD in this group was -0.31 (95% CI -0.46 to -0.16, P < 0.0001). A significant level of heterogeneity was indicated (Chi^2 = 25.47, P = 0.04, I^2 = 41%) (Analysis 7.1).

Treatment lasted for longer than 12 months in 16 studies; 580 received SLIT and 509 placebo. The SMD was -0.63 (95% CI -0.92 to -0.34, P < 0.0001). Significant heterogeneity among the studies was indicated (Chi^2 = 74.88, P < 0.00001, I^2 = 80%) (Analysis 8.1).

Subgroup analysis: major allergen dose

Major allergen content < 5 mcg

Eight trials in this group reported symptom score results; 141 patients received SLIT and 134 placebo. The SMD was -0.32 (95% CI -0.69 to 0.05, P = 0.09). Significant heterogeneity was shown between studies (Chi^2 = 15.18, P = 0.03, I^2= 54%) (Analysis 9.1).

Major allergen content 5 to 20 mcg

There were 12 studies included in this subgroup, with 1006 patients receiving SLIT and 966 placebo. The SMD was -0.34 (95% CI -0.45 to -0.24, P < 0.00001). A lack of heterogeneity between studies was indicated (Chi^2 was 13.52, P = 0.26, I^2= 19%) (Analysis 10.1).

Major allergen content > 20 mcg

There were 12 studies in this subgroup, with 541 receiving SLIT and 500 placebo. The SMD in this group was -0.33 (95% CI -0.49 to -0.17, P < 0.0001). No significant heterogeneity between studies was demonstrated (Chi^2 = 15.19, P = 0.17, I^2 = 28%) (Analysis 11.1).

Subgroup analysis: individual allergens

It was possible to perform individual subgroup analysis for one perennial (house dust mite) and four seasonal (grass pollen, *Parietaria*, ragweed, tree) allergens because they were investigated in more than one study.

Nine studies investigated house dust mite, with 232 patients in the SLIT and 232 in the placebo group. The SMD was -0.97 (95% CI -1.80 to -0.13, P = 0.02). There was an indication of highly significant heterogeneity between studies (Chi^2 = 110.42, P < 0.00001, I^2 = 93%) (Analysis 13.1).

Twenty-three studies were performed with grass pollen allergen. There were 1549 in the SLIT and 1464 patients in the placebo group. The combined SMD was -0.35 (95% CI -0.45 to -0.24, P < 0.00001). Significant heterogeneity was indicated among studies (Chi^2 = 39.58, P = 0.01, I^2 = 44%) (Analysis 14.1).

There were only two studies investigating ragweed, involving 85 participants in the SLIT and 90 in the placebo group. The SMD was -0.44 (95% CI -0.74 to -0.14, P = 0.004). There was no heterogeneity shown between the studies (Chi^2 = 0.00, P = 0.96, I^2 = 0%) (Analysis 15.1).

Parietaria was investigated in five trials, with 74 patients in the SLIT and 77 in the placebo group. The SMD was -0.36 (95% CI -0.69 to -0.04, P = 0.03). There was no heterogeneity shown between studies (Chi^2 = 2.95, P = 0.57, I^2 = 0%) (Analysis 16.1).

Nine different studies involved trees (two mixed trees, two birch, two olive and three cypress); 197 participants received SLIT and 183 placebo. The SMD was -0.42 (95% CI -0.77 to -0.06, P = 0.02). Significant heterogeneity was indicated among studies (Chi^2 = 20.17, P = 0.01, I^2 = 60%) (Analysis 17.1).

Subgroup analysis: medication preparation

Sublingual tablets

Sublingual tablets were used in 11 studies, with 945 participants in the SLIT and 936 in the placebo group. The SMD in this subgroup was -0.48 (95% CI -0.58 to -0.38, P < 0.00001). A significant level of heterogeneity between studies was indicated (Chi^2 = 39.07, P < 0.0001, I^2 = 74%) (Analysis 20.1).

Sublingual drops

There were 35 studies included in this subgroup, with 1270 patients receiving SLIT and 1194 placebo. The SMD was -0.35 (95% CI -0.42 to -0.28, P < 0.00001). Highly significant heterogeneity between studies was indicated (Chi^2 = 436.12, P < 0.00001, I^2 = 92%) (Analysis 21.1).

Three studies used both drops and tablets and were not included in the analysis.

Medication scores

Thirty-eight trials reported medication score results, with a total of 1737 patients in the SLIT group and 1642 in the placebo group. The combined SMD was -0.32 (95% CI -0.43 to -0.21, P < 0.00001). Significant heterogeneity was indicated (Chi^2 = 73.32, P = 0.0003, I^2 = 50%) (Analysis 1.2).

Subgroup analysis: seasonal and perennial allergens

In the seasonal allergens group 32 trials reported medication score, with 1557 patients receiving SLIT and 1457 placebo. The SMD was -0.30 (95% CI -0.41 to -0.19, P < 0.00001). Significant heterogeneity among studies was indicated (Chi^2 = 55.80; P = 0.004, I^2 = 44%) (Analysis 2.2).

Six studies with perennial allergens involved 180 SLIT and 185 placebo patients. The SMD was -0.43 (95% CI -0.89 to 0.02, P = 0.06). Significant heterogeneity between studies was indicated (Chi^2 = 17.21, P = 0.004, I^2 = 71%) (Analysis 3.2).

Subgroup analysis: age

Twenty-six studies which were performed in adults reported the medication score; 1168 participants received SLIT and 1067 placebo. The combined SMD was -0.40 (95% CI -0.53 to -0.26, P < 0.00001). Significant heterogeneity was indicated (Chi^2 = 47.76, P = 0.004, I^2= 48%) (Analysis 4.2).

Twelve studies in children reported the medication score; 569 patients in the SLIT and 575 in the placebo group. The combined SMD was -0.16 (95% CI -0.32 to 0.00, P = 0.06). Heterogeneity was non-significant (Chi^2 = 17.31, P = 0.10, I^2 = 36%) (Analysis 5.2).

Subgroup analysis: treatment duration

Fifteen out of 17 trials with a treatment duration of less than six months reported medication scores; 694 participants received SLIT and 672 placebo. The SMD was -0.32 (95% CI -0.45 to -0.18, P < 0.00001). A lack of heterogeneity between studies was indicated (Chi^2 = 19.09; P = 0.16, I^2 = 27%) (Analysis 6.2).

Medication score was reported in 13 studies with a treatment duration between six and 12 months. A total of 705 active and 693 placebo participants took part in these trials. The SMD was -0.31 (95% CI -0.50 to -0.12, P = 0.002). A significant level of heterogeneity was indicated (Chi^2 = 26.90, P = 0.008, I^2 = 55%) (Analysis 7.2).

Treatment lasted for longer than 12 months in 10 studies reporting medication scores; 338 patients received SLIT and 277 placebo. The SMD was -0.34 (95% CI -0.64 to -0.04, P = 0.03). Significant heterogeneity among the studies was indicated (Chi^2 = 27.13, P = 0.001, I^2 = 67%) (Analysis 8.2).

Subgroup analysis: major allergen dose

Major allergen content < 5 mcg

Six trials in this group reported medication score; 110 patients received SLIT and 109 placebo. The SMD was -0.59 (95% CI -0.94 to -0.24, P = 0.0008). A lack of heterogeneity between studies was indicated (Chi^2 = 7.43, P = 0.19, I^2 = 33%) (Analysis 9.2).

Major allergen content 5 to 20 mcg

Eleven studies were included in this subgroup analysis, with total of 992 patients receiving SLIT and 948 placebo. The SMD was -0.21 (95% CI -0.35 to -0.07, P = 0.003). Significant heterogeneity between studies was indicated (Chi^2 = 19.84, P = 0.03, I^2 = 50%) (Analysis 10.2).

Major allergen content > 20 mcg

Ten studies from this group reported medication scores; 360 participants in the SLIT and 301 in the placebo group. The SMD in this group was -0.22 (95% CI -0.43 to 0.00, P = 0.05). Significant heterogeneity between studies was indicated (Chi^2 = 15.70, P = 0.07, I^2 = 43%) (Analysis 11.2).

Subgroup analysis: individual allergens

As with symptom scores, we performed meta-analysis for medication scores for one perennial (house dust mite) and four seasonal (grass pollen, *Parietaria*, ragweed, tree) allergens.

Medication scores were reported in five trials involving house dust mite; 95 patients received SLIT and 94 received placebo. The SMD was -0.52 (95% CI -1.09 to 0.05, P = 0.07). Highly significant heterogeneity was indicated between studies (Chi^2 test = 12.92, P = 0.01, I^2 = 69%) (Analysis 13.2).

Seventeen studies were performed with grass pollen allergen. There were 1201 patients in the SLIT and 1107 in the placebo group. The combined SMD was -0.23 (95% CI -0.37 to -0.10, P = 0.0008). Significant heterogeneity among studies was indicated (Chi^2 = 34.55, P = 0.005, I^2 = 54%) (Analysis 14.2).

Medication scores were also reported in two studies investigating ragweed, involving 85 patients in the SLIT and 90 in the placebo group. The SMD was -0.30 (95% CI -0.60 to 0.00, P = 0.05). No heterogeneity was shown between studies (Chi^2 0.82, P = 0.37, I^2 = 0%) (Analysis 15.2).

Parietaria was investigated in five trials, with 74 patients in the SLIT and 77 in the placebo group. The SMD was -0.62 (95% CI -1.00 to -0.24, P = 0.001). No heterogeneity was shown between studies (Chi^2 = 5.30, P = 0.26, I^2 = 25%) (Analysis 16.2).

Nine different studies involved trees, with 197 participants receiving SLIT and 183 placebo. The SMD was -0.38 (95% CI -0.62 to -0.13, P = 0.002). There was a lack of significant heterogeneity among studies (Chi^2 = 10.24, P = 0.25, I^2 = 22%) (Analysis 17.2).

Subgroup analysis: medication preparation

Sublingual tablets

Sublingual tablets were used in nine trials, with 799 participants in the SLIT group and 779 in the placebo group. The SMD was -0.33 (95% CI -0.46 to -0.20, P < 0.00001). Highly significant heterogeneity was shown between studies (Chi^2 = 50.39, P < 0.00001, I^2 = 84%) (Analysis 20.2).

Sublingual drops

Medication score was reported in 27 studies using sublingual drops; 865 SLIT and 788 placebo participants took part in these trials. The SMD was -0.01 (95% CI -0.05 to 0.04, P = 0.74). A significant level of heterogeneity was indicated (Chi^2 = 82.89, P < 0.00001, I^2 = 69%) (Analysis 21.2).

Specific serum antibodies

Fourteen studies reported increases in serum-specific IgE levels in a manner suitable for the meta-analysis, with 675 participants in the SLIT and 659 in the placebo group. The combined SMD was 0.27 (95% CI -0.01 to 0.55, P = 0.05). Significant heterogeneity was indicated between studies (Chi^2 = 68.63, P < 0.00001, I^2 = 81%) (Analysis 12.1).

Total serum-specific IgG was measured in three studies, with 286 participants in the SLIT and 304 in the placebo group. The combined SMD was 0.95 (95% CI 0.78 to 1.12, P < 0.00001). There was no significant heterogeneity between studies (Chi^2 = 1.01, P = 0.60, I^2 = 0%) (Analysis 12.2).

Serum-specific IgG4 was measured in 13 trials, with a total number of 588 in the SLIT and 599 in the placebo group. The total SMD was 0.46 (95% CI 0.29 to 0.63, P < 0.00001). Highly significant heterogeneity was indicated (Chi^2 = 174.24, P < 0.00001, I^2 = 93%) (Analysis 12.3).

Allergen sensitivity

Six studies included skin reactivity data (skin prick test or early phase reaction) that were eligible for the meta-analysis; 183 participants were in the SLIT and 148 in the placebo group. The SMD was 0.12 (95% CI -0.26 to 0.51, P = 0.53). Significant heterogeneity was indicated among studies (Chi^2 was 12.47, P = 0.03, I^2 = 60%) (Analysis 18.1).

The results of nasal reactivity were reported in 10 studies, but only seven were suitable for meta-analysis. The analysis involved 111 participants in the SLIT and 109 participants in the placebo group. The SMD was 0.32 (95% CI -0.13 to 0.78, P = 0.17). Highly significant heterogeneity was indicated between studies (Chi^2 = 16.39, P = 0.01, I^2 = 63%) (Analysis 18.2).

We identified only one study each assessing conjunctive and bronchial provocation tests which were eligible for meta-analysis, therefore we could not perform these analyses.

Adverse events

We included 60 studies in our systematic review and all were analysed for safety results. Adverse events were the only discontinuous data analysed in our review.

Twenty-five studies reported data in a manner not suitable for our analysis (insufficient data, adverse events reported by system organ classification, data expressed in percentages, etc.) (Table 1).

Six studies with 125 participants in the SLIT and 126 in the placebo group reported no adverse events during the trials (Table 2).

Twenty-two studies reported different local and systemic reactions as a total number of single adverse events during the whole trial, hence we analysed these data.

Twenty-five studies reported different local events. Buccal pruritus was reported in 21 trials: 1126 participants experienced a total number of 1798 events in the SLIT group and 1075 participants experienced 492 events in the placebo group. Labial oedema was reported in 11 studies, with 604 participants/55 events in the SLIT group and 526 participants/7 labial swelling episodes in the placebo group.

Bucco-lingual oedema was reported in eight trials, with 648 participants/143 events in the SLIT group, and 606 participants/2 episodes in the placebo group. Throat irritation was reported in 10 trials, including 770 participants in the SLIT and 747 in the placebo group, with 243 and 29 episodes respectively. Local adverse events were also reported as oral non-specified in three and local non-specified in three trials (Table 3).

Systemic reactions were reported by 18 studies (Table 4). Rhinitis was reported in 16 trials, with 965 participants/1403 events in the SLIT group and 912 participants/1034 events in the placebo group. Conjunctivitis alone was reported by eight trials, with 262 participants and 774 conjunctivitis episodes in the SLIT and 238 participants and 786 events in the placebo group. Cough was reported in eight trials: 337 participants treated with SLIT experienced 313 events and 304 participants in the placebo group reported 211 episodes of cough. Gastro-intestinal symptoms were described by 20 trials with 630 participants in the SLIT and 561 in the placebo group, with 88 and 10 events respectively. None of the studies reported anaphylaxis.

Fifteen studies reported adverse events which led to treatment discontinuation. In the SLIT group, 41 out of 824 patients and 12 out of 861 placebo participants were withdrawn because of adverse events. Troublesome local reactions were the most common cause, although systemic reactions were described (Table 5).

Five studies reported adverse events by their severity, but not all of them considered the link with the treatment. The majority of adverse events were mild to moderate and did not require any treatment. None of the reactions required the administration of adrenaline.

Quality of life

Quality of life was reported by three studies, but assessment in those studies differed greatly and we considered that these data could not be included in our analysis.

DISCUSSION

This systematic review of sublingually administered allergen immunotherapy (SLIT) represents an update of a review first published in *The Cochrane Library* in 2003 (Wilson 2003). The original review included data from 22 randomised controlled trials (979 patients) and demonstrated the efficacy of this form of treatment based on meta-analysis of symptom severity scores (standardised mean difference (SMD) -0.42; 95% confidence interval (CI) -0.69 to -0.15). Ongoing research in this area has been considerable and this review has now been updated to include studies published since 2003. The number of studies included has almost trebled to 60 (with 49 being suitable for pooling in meta-analyses) and the number of patients in meta-analysis has increased over four-fold, reflecting a trend towards larger, better designed and more powerful trials.

The overall results of the meta-analysis differ little from those seen in 2003, with the overall effect for symptom scores (SMD -0.49; 95% CI -0.64 to -0.34) being of a similar magnitude, with tighter confidence intervals reflecting the greatly increased number of study subjects. The same is true for the analysis of medication scores, with SMD -0.32 (95% CI -0.43 to -0.21). These data continue to support the clinical efficacy of sublingual immunotherapy for allergic rhinitis.

In contrast to the original review, the greater number of studies has allowed more meaningful analyses of some of the pre-determined subgroups. In particular there are now 15 studies looking exclusively at children, some of which are large studies in their own right (Bufe 2009; Wahn 2009). The treatment effect within this subgroup of trials appears to be similar to that seen in adults, especially when considering symptom scores. SLIT represents a

particularly attractive alternative to injection immunotherapy in this patient group and our findings are entirely consistent with those reported elsewhere (Calderon 2008).

The protocol for the original review reflected the then classification of aero-allergens into seasonal and perennial. The ARIA classification (ARIA 2008) now uses the terms intermittent and persistent but for this review this change makes no difference. In this meta-analysis there does appear to be a greater effect with perennial allergens (predominantly house dust mite) when compared to seasonal allergens although this is based on fewer studies. More studies of perennial rhinitis are needed to confirm or exclude this possibility.

It is not possible to differentiate between different doses on the basis of this meta-analysis. The difficulty in determining dose in terms of micrograms of major allergen, and standardising this information across a range of studies utilising allergen extracts from different sources, was acknowledged in the original review and remains problematic.

Although the difference is small, this review has shown a trend in symptom score reduction in trials which lasted for longer than 12 months, when compared with shorter treatment periods. Indeed, SLIT is now given for longer time periods (over 12 months in 32% of included studies compared with 19% in 2003), and more recent studies have shown that treatment for longer than 12 months provides consistent clinical improvement in symptom and medication scores (Dahl 2008; Durham 2010). These data are encouraging and should be taken into consideration in future recommendations or guidelines for the use of SLIT in allergic rhinitis.

Looking at the total effect and SMD (95% CI) of sublingual immunotherapy for individual allergens, house dust mite appears to be more effective than treatment with other types of allergen, and even more effective than treatment with grass pollen. However, the majority of these trials are small, with five (out of nine) trials involving fewer than 20 participants. Heterogeneity in this group is amongst the highest in all the meta-analyses; when comparing P values for the overall effect, the level of significance appears to be lower than for the majority of other allergens. We therefore conclude that this finding should be interpreted with caution.

This review has shown that SLIT provokes significant changes in terms of allergen-specific IgG and IgG4 antibodies, which coincide with a clinical response in terms of symptom and medication scores. These findings are in complete concordance with the findings of the previous SLIT review (Wilson 2003), as well as injection immunotherapy (Calderon 2007). Unfortunately, changes detected in IgG and IgG4 values were not supported by changes in allergen sensitivity, and meta-analysis of data for skin and nasal reactivity after treatment showed no difference between the immunotherapy and placebo group. The exact role of IgG and IgG4 is still not completely clear. Although they are likely to have a certain 'protective' role, there is still an ongoing debate as to whether this increase in (particularly) IgG4 is just a consequence of exposure to a high dose of allergen or the real immunomodulatory effect of sublingual immunotherapy. This review could not draw a definitive conclusion and only further mechanistic studies can enable us to answer this question.

This review explored the possible differences between different sublingual preparations (i.e. sublingual drops versus tablets). Although tablets proved to be more effective in terms of medication scores, and had similar efficacy in terms of symptoms, overlapping confidence intervals and the substantial heterogeneity between studies did not allow us to draw any firm conclusions. It seems both preparations are similarly effective.

An increasing number of studies report quality of life as a primary or secondary outcome measure as is the case in clinical trials in general. Nevertheless, there were big differences in quality of life scoring systems such that we were unable to analyse these data by meta-analysis.

It was acknowledged in the original review that many of the studies included were small, early publications that did not conform to the CONSORT (1996) guidelines for the publication of randomised controlled trials (Begg 1996; Moher 2001). The methodological quality of the studies included on this occasion has been scrutinised more closely using the new Cochrane criteria, including assessment of randomisation and allocation concealment.

The possible confounder of publication bias that exists in all meta-analysis (Calderon 2008; Nieto 2009) was acknowledged in the original review and has again been addressed on this occasion through extensive consultation with those active in the field of SLIT research. We are confident that no data have been excluded purely on the basis of negative outcome.

Funnel plot evaluations for the two main outcomes (Figure 3; Figure 4) showed that the plots were reasonably symmetrical and there did not appear to be a paucity of smaller trials with small or absent symptom reduction effect.

Figure 3. Funnel plot of comparison: 1 SLIT versus placebo - all, outcome: 1.1 Allergic rhinitis symptom scores.

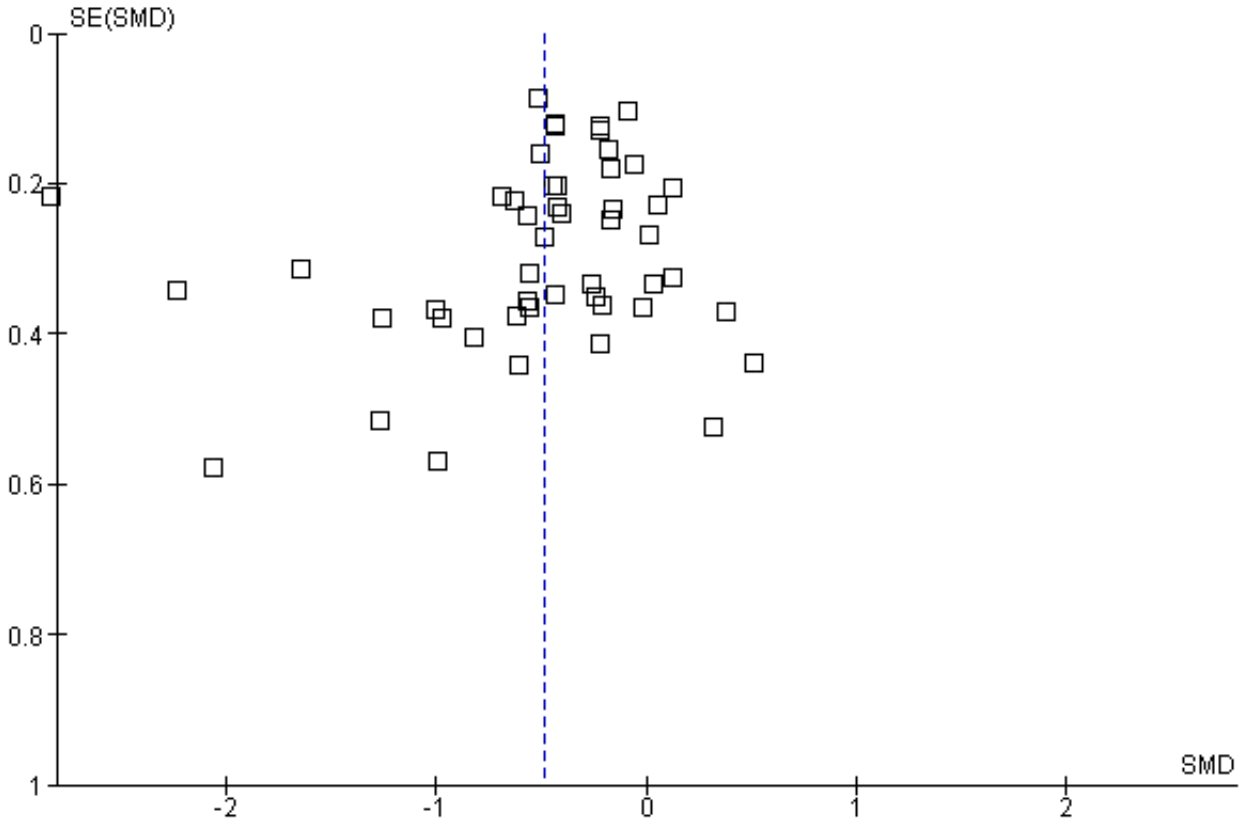
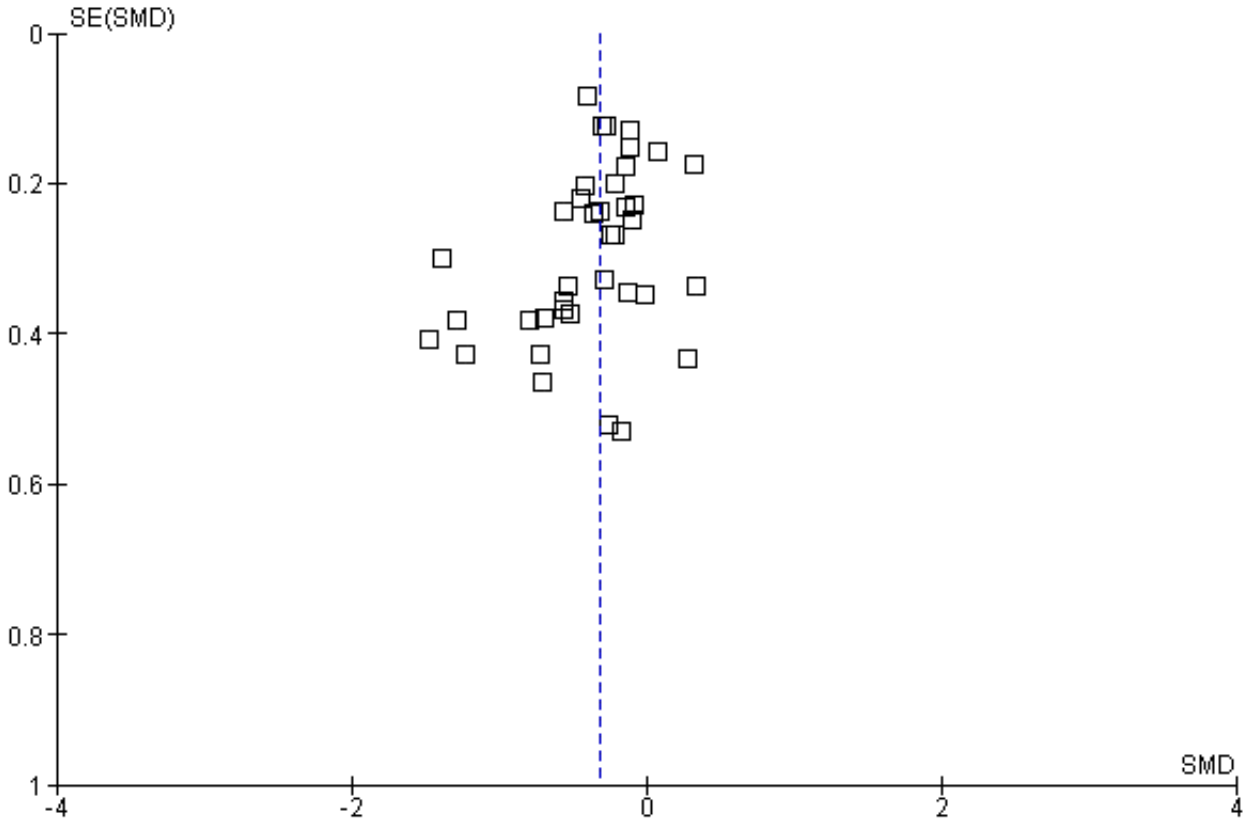


Figure 4. Funnel plot of comparison: 1 SLIT versus placebo - all, outcome: 1.2 Medication scores.



In the current review we withdrew three studies (D'Ambrosio 1996; Mungan 1999; Quirino 1996) that had been included in the 2003 review as they did not satisfy the new Cochrane criteria for randomised, double-blind studies.

Heterogeneity between studies was acknowledged as a significant problem in the last review, and is a known problem in systematic reviews. This results largely from methodological and clinical heterogeneity (i.e. differences in scoring systems, sample sizes, type and dose of allergen, age groups, etc.) used across studies. Selection of the studies for this review was defined in our protocol and studies which satisfied our criteria were chosen. The method used by The Cochrane Collaboration for assessing heterogeneity has however changed and can now be expressed as an I^2 statistic. It remains the case that studies in this field are heterogeneous and data are expressed in a wide variety of different ways. However, certain subgroup analyses (e.g. seasonal allergens, individual allergens, subgroup analysis for major allergen content) have shown the significant reduction in heterogeneity even though these groups were prespecified by a protocol. This means that there will always be a degree of interpretation required when amalgamating studies in meta-analysis and further subgroup analysis could be performed in order to address better the problem of heterogeneity. Despite this, there is remarkable consistency in the outcomes of related systematic reviews (Casale 2009; Cox 2006; Wilson 2005).

Adverse events

Although considered as a secondary outcome, we felt analysis of adverse events to be crucial as a low incidence confers advantage on SLIT as an alternative to injection immunotherapy. Adverse event data were, by their nature, non-continuous. Authors mainly reported data as total number of events for a number of patients, rather than number of certain events per patient. Some papers reported their most common events as a percentage of total events, or as a percentage of patients who experienced particular events. These were therefore not suitable for meta-analysis and we were able to perform only descriptive analysis. A further problem is that unlike for the subcutaneous route there is currently no internationally standardised methodology for reporting local adverse events of sublingual immunotherapy.

With these reservations, local reactions are again shown to be common and reported much more frequently in SLIT recipients than in those receiving placebo. These are clearly unavoidable but are usually seen as an inconvenience and cause little distress and have no lasting effect, though rarely these adverse events were distressing enough to warrant withdrawal of treatment.

Systemic reactions were again largely confined to the upper respiratory tract and associated organs (rhinitis, conjunctivitis or rhinoconjunctivitis) and were more frequent in the SLIT than in the placebo groups. Asthma or wheeze was no more likely in SLIT recipients than in placebo recipients. Gastrointestinal effects (non-specified) were rare but more apparent in SLIT recipients and were largely confined to paediatric trials. None were considered serious.

There were no reports in clinical trials of severe systemic reactions or anaphylaxis and none of the systemic reactions needed the use of adrenaline. No fatalities were reported.

This review evaluates a large number of double-blind, placebo-controlled studies which, in total, give us a large number of doses. No incidences of life-threatening reactions were reported in the studies analysed. We conclude that SLIT remains a safe treatment with an extremely low incidence of significant side effects. Systemic adverse events were predominantly mild to moderate and their causality was unlikely to be related to SLIT. We have been unable to correlate adverse events with allergen dose.

There are no reports of fatalities following sublingual immunotherapy. Six isolated cases of severe reactions have been reported independently of clinical trials and all involved deviation from current recommended practice according to international guidelines (Antico 2006; Blazowski 2008; de Groot 2009; Dunsky 2006; Eifan 2007). Numbers are too few to allow identification of risk factors for severe systemic reactions, whereas it can be noted that five out of six occurred in young females, five out of six had asthma, and two out of six had previously experienced severe reactions during subcutaneous immunotherapy. These data should be viewed in the context of the number of doses of sublingual immunotherapy that have been prescribed and administered worldwide.

Since the original systematic review in 2003 SLIT has become established as an effective and low-risk alternative to allergen injection immunotherapy, which carries a significant morbidity and a requirement for delivery within specialist centres capable of meeting CSM recommendations. SLIT is recommended to be initiated in secondary care and the first dose taken under medical supervision whereas maintenance treatment is recommended to be self-administered in the patient's home.

Only two studies in the original review compared injection immunotherapy with sublingual immunotherapy directly (Mungan 1999; Quirino 1996). In the current review only one study compared injection immunotherapy versus SLIT. Although comparison of those two treatment options was not the objective of this review, the search process enabled us to identify papers comparing the efficacy of these treatment options. We found very few such papers: there appears to be insufficient data available to draw any conclusions and more definitive head-to-head trials are needed.

A Cochrane Review of allergen injection immunotherapy, which included 51 trials with 2871 participants (Calderon 2007), showed a SMD of -0.73 (95% CI -0.97 to -0.5) for symptom scores compared to placebo and a SMD of -0.57 (95% CI -0.82 to -0.33) for medication scores. Although the SMDs are numerically different, the confidence intervals overlap with those for SLIT, indicating no apparent difference between the two therapies on this basis. However, it is not correct to perform a direct statistical comparison between these two meta-analyses. These data raise the importance of future double-blind, double-dummy trials that directly compare these two routes of immunotherapy.

Injection immunotherapy exerts its long-lasting effects through modulation of the response of the immune system upon allergen exposure, altering from an allergic response to one of immune tolerance as evidenced by alterations in Th cell cytokine profiles, numbers of effector cells at target sites and changes in humoral responses, including increases in putative blocking IgG4 class antibodies (Wilson 2001). In the 2003 review there were only six studies that reported immunological outcomes, in terms of immunoglobulin levels, that were suitable for meta-analysis but available data did suggest consistent increases in allergen-specific IgG4 during SLIT treatment. Eleven studies (doubling the number of subjects) in the current review contained data on IgG4 levels and a consistent and significant two-fold increase in IgG4 levels was observed. The role of allergen-specific IgG4 antibodies remains controversial but the evidence points towards similar immunological mechanisms underlying the two forms of therapy. Further discussion on mechanisms is outside the scope of this review.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review and meta-analysis is more powerful than the original review published in 2003, with over four times the number of patients. The data again strongly support the efficacy of sublingual immunotherapy compared with placebo in terms of a reduction in rhinitis symptom scores and anti-allergic medication requirements. Furthermore, the data now more strongly support the use of sublingual immunotherapy in children and in allergic rhinitis due to all aero-allergens.

Sublingual immunotherapy is now established as a viable alternative to allergen injection immunotherapy, with a significantly lower risk profile and, on the basis of meta-analyses, little difference in overall efficacy.

Implications for research

The optimum dose and duration of therapy remains an unanswered question and it is unlikely that meta-analysis will provide the answers. Ongoing clinical trials of prolonged therapy and increasing use of standardised tablet products may do.

The mechanism of action of both injection and sublingual immunotherapy remain under investigation, and injection immunotherapy has been proven to lead to long-term changes in the immunological response to allergen that may persist for years following discontinuation.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Amar 2009

Methods	Randomised DBPC trial
Participants	Adults 58 participants randomised 53 participants analysed Timothy grass monotherapy 19; losses to f/u 0 Mixed grass 17; losses to f/u 3 Placebo 17; losses to f/u 2
Interventions	10 months SLIT Monotherapy: timothy grass 680 mcg/ml Phl p5 Multiple allergen group: timothy grass, maple, ash, juniper, American elm, cottonwood, kochia, ragweed, sagebrush, Russian thistle Daily maintenance dose 19 mcg Phl p5; cumulative monthly dose 571 mcg Phl p5
Outcomes	Symptom scores, medication scores, titrated skin prick tests, titrated nasal challenge, allergen-specific IgE and IgG4
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Amar 2009 *(Continued)*

Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	This was not stated in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. Caramelised sugar was added to placebo and timothy grass monotherapy extract in order to mimic the colour of the active treatment groups.
Incomplete outcome data addressed? All outcomes	Low risk	Additional information was sought and obtained from the authors
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Andre 2003

Methods	Randomised DBPC trial
Participants	Adults and children Age range 7 to 55 years 55 active (22 m); losses to f/u 12 55 placebo (23 m); losses to f/u 6
Interventions	7.5 months Pre-seasonal (start at March) SLIT Sublingual drops and tablets Standardised ragweed extract Dose: 100 IR/ml solution = 1 tablets = 160 mcg of Amb a 1 Maintenance dose 1, 2 or 3 tablets 3 times a week, depending on patient's tolerance Cumulative dose over maintenance phase: 1300 to 30,500 Max maintenance dose 480 mcg/day 3 times a week
Outcomes	Symptom scores based on diary cards (nose, eyes) Medication scores Global assessment Skin prick test Allergen-specific IgE and IgG4
Notes	Jadad scale 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	It was not stated

Andre 2003 *(Continued)*

Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Ariano 2001

Methods	Randomised DBPC trial
Participants	Adults 10 active (5 m) 10 placebo (4 m)
Interventions	8 months SLIT 250,000U RAST
Outcomes	Diary scores Nasal provocation
Notes	Jadad scale 3/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	This was not stated
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	All patients completed the study
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Bahceciler 2001

Methods	Randomised DBPC trial

Bahceciler 2001 *(Continued)*

Participants	8 active (4 m) 7 placebo (4 m) Children
Interventions	5 months SLIT 0.56 mg DP 0.98 mg DF
Outcomes	Diary scores SPT Total IgE
Notes	Jadad scale 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	This was not stated in the paper
Blinding? All outcomes	Unclear risk	Investigators and patients were blinded to treatment but how this was done was not stated
Incomplete outcome data addressed? All outcomes	Low risk	All participants completed treatment
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Bowen 2004

Methods	Randomised DBPC trial
Participants	Adults and children 43 active; loses to follow up 15 40 placebo; losses to follow up 11
Interventions	3.5 months SLIT, 2 weeks pre-seasonal Sublingual drops Dose 116 mcg Amb 1/100 IR Max dose: 314 mcg Amb 1
Outcomes	Symptom scores (rhinitis and conjunctivitis) Number of days with asthma symptoms Medication score Overall evaluation Levels of ragweed-specific IgE and IgG4

Bowen 2004 *(Continued)*

	Adverse events description
Notes	Jadad scale 5/5 15 patients asthma; 9 in treatment and 6 in placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	This was not stated in paper
Blinding? All outcomes	Unclear risk	Investigators and patients were blinded to treatment but how this was done was not stated
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Bufe 2004

Methods	Randomised DBPC trial
Participants	Children 83 active; losses to follow up 15 78 placebo; losses to follow up 14
Interventions	1 year Pre-seasonal period: Sublingual drops Maintenance dose 2500 AU˜ 9.1 mcg Cumulative dose 2,625,000 AU (9.6 mg of Phl p 5)
Outcomes	Clinical symptoms assessed by questionnaire in a structured interview by an independent person by phone at 6 different points (nose, eye and lung symptoms) Visual analogue scale recorded by patients Medication score (medication index)
Notes	Jadad scale 5/5 Asthma symptoms 68; 35 in treatment and 33 in placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Block-wise randomisation was performed

Bufe 2004 *(Continued)*

Allocation concealment?	Unclear risk	Not stated in paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Bufe 2009

Methods	Randomised DBPC trial
Participants	Children Active: 126 (83 male); data analysed for 117 participants; withdrawn 12 Placebo: 127 (83 male); data analysed for 121 participants; withdrawn 7
Interventions	6 months 8 to 23 weeks pre-seasonal (mean 17.1 weeks) Sublingual tablets grass pollen (*Phleum pratense*) Daily dose 75000 SQ; 15 mcg Phl p 5
Outcomes	Symptom score Medication score Specific IgE, IgG4 and IgE blocking factor Adverse events
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomisation was performed by stratification according to trial centre
Allocation concealment?	Unclear risk	Not stated in paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group and reasons for attrition/exclusions where reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section

Bufe 2009 *(Continued)*

Free of other bias?	Low risk	No other sources of bias were detected or suspected

Caffarelli 2000

Methods	Randomised DBPC trial
Participants	Children 24 active (12 m); losses to follow up 0 20 placebo (13 m); losses to follow up 4
Interventions	3.5 months All pre-seasonal Sublingual tablets - allergoid (mixture 33% *Holcus lanatus*; 33% *Phleum pratense*, 33% *Poa pratense*) Max dose of allergen: 1000 AU Cumulative dose 37,250 AU
Outcomes	Symptom scores on daily dairy cards (nasal, eye and bronchial symptoms) Medication score Adverse events description ECP
Notes	Jadad scale 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Children were randomly assigned by a computer-generated list to receive either grass-pollen allergoid oral soluble tablets or placebo
Allocation concealment?	Unclear risk	Stated in a paper that neither the investigators nor the patients were aware of the treatment assignments, but no details were provided in the paper
Blinding? All outcomes	Low risk	Placebo tablets were indistinguishable from active treatment
Incomplete outcome data addressed? All outcomes	Low risk	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Attrition and exclusions were reported, the numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Calderon 2006

Methods	Randomised DBPC trial
Participants	Adults Active 9 (6 male); withdrawn 0

Calderon 2006 *(Continued)*

	Placebo 11 (6 male); withdrawn 0
Interventions	28 days; all pre-seasonal Sublingual tablet Grass pollen (*Phleum pratense*) 75000 SQ-T Daily dose 15 mcg Phl p 5
Outcomes	Adverse events
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Participants were randomly assigned by a computer-generated list
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	All randomised patients completed the trial and the adverse events were reported
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Cao 2007

Methods	Randomised DBPC trial
Participants	Children Active 139 Placebo 139 Age range 4 to 18
Interventions	SLIT drops *Dermatophagoides farinae* 25 weeks
Outcomes	Rhinitis symptom score Medication score for rhinitis Asthma symptom scores Lung function tests Skin sensitivity Mite-specific IgE and IgG4
Notes	Full paper published in Chinese, but authors have provided data for total symptom and medication scores for rhinitis

Cao 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	Not stated in paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Casanovas 1994

Methods	Randomised DBPC trial
Participants	Adults 9 active (3 m) 6 placebo (1 m) Minimum age 18
Interventions	2 months pre-seasonal SLIT Dose n/s
Outcomes	Diary scores SPT
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	Not stated in paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants excluded were accounted for along with patients followed to designated follow-up periods

Casanovas 1994 *(Continued)*

Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	Insufficient information to assess whether an important risk of bias exists. Small number of patients across each trial group.

Clavel 1998

Methods	Randomised DBPC trial
Participants	Adults 62 active 58 placebo Age range 27 +/- 10 years
Interventions	6 months SLIT 5 mixed grasses (orchard grass, meadow grass, rye grass, sweet vernal grass, timothy grass) Cumulative dose 2.6 mg timothy grass Updosing period 25 days
Outcomes	Daily dairy: symptom scores Medication scores Specific IgE and IgG4 Adverse events
Notes	Jadad scale 3/5. Data insufficient for meta-analysis. Included in the systematic review only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised, but it details were not provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. Placebo consisted of glycerol-saline diluent.
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data for each main outcome completed and attrition and exclusions were reported; the numbers in each intervention group and reasons for attrition/exclusions were reported
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

D'Ambrosio 1999

Methods	Randomised DBPC trial
Participants	Adults

D'Ambrosio 1999 *(Continued)*

	14 active (7 m) 16 placebo (7 m)
Interventions	9 months SLIT 12.77 mcg Parj 1 0.12 mcg/day solution of standardised extract
Outcomes	Diary scores Ig
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were provided in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Dahl 2006a

Methods	Randomised DBPC trial Multicentre
Participants	Adults 74 active (53 m); dropped out 13 40 placebo (24 m); dropped out 8
Interventions	3 to 3.5 months SLIT Sublingual tablet Grass pollen 75000 SQ-T daily Plp p5 15 mcg Pre-seasonal 10 to 14 weeks
Outcomes	Asthma symptom score (pre-seasonal and in season) Asthma medication score (pre-seasonal and in season) Rhinoconjunctivitis symptom scores and medication score; all reported through daily diaries Number of well days Adverse events reports
Notes	Jadad scale 5/5 All patients had mild to moderate seasonal asthma and rhinoconjunctivitis

Dahl 2006a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	The allocation sequence was generated by the sponsoring company and blinded for the investigators
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Dahl 2006b

Methods	Randomised DBPC trial; multicentre
Participants	Adults 316 active (179 m); losses to f/u 42 318 placebo (193 m); losses to f/u 46
Interventions	12 months SLIT Sublingual tablet Grass pollen 75 000 SQ-T Phl p 5 15 mcg Daily
Outcomes	Rhinoconjunctivitis symptom score Medication score Global assessment Adverse events
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	The allocation sequence was generated by the sponsoring company and blinded for the investigators
Allocation concealment?	Low risk	Central allocation

Dahl 2006b *(Continued)*

Blinding? All outcomes	Low risk	Unblinded efficacy and safety assessments on subject level were available only for a biostatistician at the Contract Research Organization. All personnel associated with the study and participants remained blinded.
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were completed for each main outcome. Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

de Blay 2003

Methods	Randomised DBPC trial; multicentre study
Participants	Adults and children 61 active 57 placebo Mean age 24.9 +/- 7.6 29 mild persistent
Interventions	10 months SLIT (8 months pre-season) Drops 3 grass pollen extract: *Dactylis glomerata*, *Phleum pratense* and *Lolium perenne* Average cumulative dose: 2.75 mg
Outcomes	Clinical score Rhinitis score Conjunctivitis score Rescue medication score
Notes	Jadad scale 3/5 ITT 104 patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but not stated in the paper how was it done
Allocation concealment?	Unclear risk	Not stated in paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section

de Blay 2003 *(Continued)*

Free of other bias?	Low risk	No other sources of bias were detected or suspected

Di Rienzo 2006

Methods	Randomised DBPC trial
Participants	Adults 19 active; losses to f/u 1 15 placebo; losses to f/u 1
Interventions	4 months SLIT Drops *Juniperus ashei* extract Maintenance 8 drops of 300 IR/ml Dose of major allergen 70 mcg/ml of Jun a1 at 100 IR conc
Outcomes	Symptom score Medication score Quality of life Adverse events
Notes	Jadad scale 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised, but the details about randomisation were not provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Placebo treatment consisted of identical vials containing only the diluent (a glycero-saline solution)
Incomplete outcome data addressed? All outcomes	Low risk	Participants excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Didier 2007

Methods	Randomised DBPC trial Multicentre
Participants	Adults (age range 18 to 45 years) Active 155 (ITT 136)

Didier 2007 *(Continued)*

	Active discontinued 22 Placebo 156 (ITT 148) Placebo discontinued 10
Interventions	Sublingual tablets mixed grass (orchard, meadow, perennial rye, sweet vernal, timothy grass) 4 months pre-seasonal and co-seasonal treatment Mean dosage 25 mcg/ml of the group 5 major allergens
Outcomes	Symptom score Quality of life Grass pollen specific IgE
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomisation list utilised
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Both investigators and participants were blinded to allocation. To maintain the blinding, patients took 2 tablets per day during the first 5 days of titration and 1 tablet per day from day 6 until the end of treatment.
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were completed for each main outcome. Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Drachenberg 2001

Methods	Randomised DBPC trial
Participants	Children and adults 49 active (28 m): 21 birch, 28 grass/rye pollen 19 placebo (9 m)
Interventions	6 months SLIT SL drops 27 days of updosing phase maintenance dose: 16 drops of 100,000 SOU/ml for both allergens Cumulative dose of major allergen For grass pollen: Phl p 1: 1913.6 mcg For birch pollen: Bet v 1: 1535.23 mcg
Outcomes	Combined symptom/medication score Titrated SPTs Adverse events

Drachenberg 2001 *(Continued)*

Notes	Jadad scale 5/5 Placebo group 19 Active treatment: Grass/rye 28 Birch 21

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation in blocks
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	The placebo consisted of the allergen-free solution
Incomplete outcome data addressed? All outcomes	Low risk	Participants excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Dubakiene 2003

Methods	Randomised DBPC trial
Participants	Adults 59 active; losses to f/u 12 60 placebo; losses to f/u 7 3 trees
Interventions	4 months SLIT 15 days updosing Sublingual drops tree pollen (birch, hazel, alder) Maintenance dose 2500 AU/ day Bet v 1 13 mcg/day
Outcomes	Rhinoconjunctivitis Clinical Index Score (combined from symptom and medication score) Adverse events
Notes	Jadad scale 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation in blocks of 4 was performed (2 SLIT and 2 placebo)
Allocation concealment?	Unclear risk	Not reported

Dubakiene 2003 *(Continued)*

Blinding? All outcomes	Unclear risk	Investigators and patients were blinded to treatment but how this was done was not stated in the paper
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were analysed
Free of selective reporting?	Unclear risk	Not reported in the abstract
Free of other bias?	Unclear risk	This paper has not been published

Durham 2006

Methods	Randomised DBPC trial
Participants	Adults 141 active (84 m) 136 placebo (89 m)
Interventions	18 weeks No updosing phase Sublingual tablets 75,000 SQ-T 15 mcg Phl p 5
Outcomes	Rhinoconjunctivitis symptom score Medication score Post-treatment specific IgE levels Post-treatment specific IgG Number of well days
Notes	Jadad scale 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	The allocation sequence was generated by the sponsoring company and blinded for the investigators (computer-generated schedule)
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. Tablet similar in taste, smell and appearance.
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were completed for each main outcome. Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Feliziani 1995

Methods	Randomised DBPC trial
Participants	Adults 18 active 16 placebo
Interventions	3 months SLIT Dose n/s in mcg Maintenance dose 20 BU daily 3 times a day
Outcomes	Diary scores Rhinoconjunctivitis symptom score Medication scores for rhinoconjunctivitis Asthmatic symptoms Overall symptoms Overall drug consumption
Notes	Jadad scale 4/5 The data published in previous review reporting overall symptom and medication score

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Treatments were coded according to a key unknown to the clinician and to the patient and they were assigned randomly to each patient
Allocation concealment?	Unclear risk	Not reported in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Grosclaude 2002

Methods	Randomised DBPC trial
Participants	Children and adults 47 active: 15; 16; 16 (29 m) 15 placebo (11 m)
Interventions	8 months SLIT 5 mixed grasses pollen tablets and drops 5 months pre-seasonal

Grosclaude 2002 *(Continued)*

	3 different updosing regimens 18 days updosing Maintenance 300 IR 3 times a day, drops Average cumulative dose 18,000 IR; 0.88 mg Lol p 1
Outcomes	Adverse events
Notes	Jadad scale 3/5 The study included in the review but not the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised, but no details were provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	The placebo consisted of tablets (cellulose, magnesium stearate, lactose) and drops (glycerinated saline) that were indistinguishable from active treatment
Incomplete outcome data addressed? All outcomes	Low risk	Participants excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Guez 2000

Methods	Randomised DBPC trial
Participants	Adults and children 36 active (14 m) 36 placebo (15 m)
Interventions	24 months SLIT Sublingual drops 2.2 mg D.Pt 1.7 mg D.f
Outcomes	Diary scores SPT Ig
Notes	Jadad scale 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Guez 2000 *(Continued)*

Adequate sequence generation?	Unclear risk	Patients were randomised, but details were not provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	The placebo preparation was identical to active treatment in terms of composition, appearance, presentation, taste and colour, but did not contain allergens
Incomplete outcome data addressed? All outcomes	Low risk	Participants excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Hirsch 1997

Methods	Randomised DBPC trial
Participants	Children 15 active (10 m) 15 placebo (10 m)
Interventions	12 months SLIT cumulative dose 570 mcg Derp 1
Outcomes	Diary scores SPT
Notes	Jadad scale 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Subjects were randomised according to a code provided by the manufacturer
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow-up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Hordijk 1998

Methods	Randomised DBPC trial
Participants	Adults 27 active (14 m) 30 placebo (13 m)
Interventions	SLIT drops mixed grasses 3 months pre-seasonal Dose n/s
Outcomes	Diary scores Ig
Notes	Jadad scale 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Stratified randomisation
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. The placebo consisted of the non-active ingredients.
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Ibanez 2007

Methods	Randomised DBPC trial
Participants	Children Active 45 (28 male); withdrawn 2 Placebo 15 (12 male); withdrawn 0
Interventions	28 days (pre-seasonal) Grass pollen (*Phleum pratense*) Sublingual tablet 75,000 SQ-T Daily dose 15 mcg Phl p 5
Outcomes	Adverse events

Ibanez 2007 *(Continued)*

Notes	This paper involves 2 studies performed with the identical study protocols

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised, but no details were provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Unclear risk	A placebo tablet similar in taste, smell and appearance was used
Incomplete outcome data addressed? All outcomes	Unclear risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Unclear risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	2 studies were pooled

Ippoliti 2003

Methods	Randomised DBPC trial
Participants	Children Active 47 (28 m); losses to f/u 0 Placebo 39 (22 m); losses to f/u 0
Interventions	6 months Sublingual drops Dose: 2.4 mcg/ml of Der p 1 and 1.2 mcg/ml of Der p2 per week
Outcomes	Symptom scores from diary cards Expression of CD40 on B cells Serum IL-13, ECP, prolactin Adverse events description
Notes	Jadad scale 3/5 33 children with rhinoconjunctivitis 18 in treatment 15 in placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised, but the full details were not provided

Ippoliti 2003 *(Continued)*

Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Placebo consisted of the same glycerine/phenol diluent used in active group
Incomplete outcome data addressed? All outcomes	Unclear risk	It is not clear if any patients lost during follow up occurred
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Khinchi 2004

Methods	Randomised, double-blind, double-dummy, placebo-controlled trial
Participants	Active SLIT 23; losses to f/u 9 Active SCIT 24; losses to f/u 5 Placebo 19; losses to f/u 9
Interventions	2 years Bet v 1 SLIT drops Max dose: SLIT 49.2 mcg every second day SCIT 3.38 mcg monthly
Outcomes	Symptom scores Medication score Adverse events
Notes	Jadad scale 4/5 3 groups of patients: SLIT, SCIT and placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomisation was performed by minimisation based on disease severity during the baseline season, gender and age
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	All study personal and participants were blinded to treatment assignment for the 2-year duration of treatment in the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section

Khinchi 2004 *(Continued)*

Free of other bias?	Low risk	No other sources of bias were detected or suspected

Kleine-Tebbe 2006

Methods	Randomised DBPC trial
Participants	Adults Active 63; no losses to f/u Placebo 21; no losses to f/u
Interventions	4 weeks SLIT tablets Grass pollen 25,000 SQ-T, 75,000 SQ-T, 150,000 SQ-T, 300,000 SQ-T, 500,000 SQ-T, 750,000 SQ-T, 1,000,000 SQ-T and placebo 100,000 SQ-T correspond to 20 mcg Phl p 5
Outcomes	Adverse events
Notes	Jadad scale 5/5 Study included in review, but not meta-analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Computer-generated randomisation list was provided by a manufacturer
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	All randomised subjects received intervention and all completed the trial
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

La Rosa 1999

Methods	Randomised DBPC trial
Participants	Children 20 active (13 m) 21 placebo (12 m) Losses to f/u 4
Interventions	24 months SLIT

La Rosa 1999 *(Continued)*

	52.5 mg Parj1
Outcomes	Rhinitis symptom scores Medication score Ig SPT Conjunctival
Notes	Jadad scale 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Lima 2002

Methods	Randomised DBPC trial
Participants	Adults 28 active 28 placebo
Interventions	12 to 18 months SLIT 900 mcg Phlp5 per month
Outcomes	Diary scores Ig
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation to active or placebo treatment was performed by the manufacturer of the grass pollen vaccine using a system of computer-generated random numbers in blocks of 12

Lima 2002 *(Continued)*

Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	The treatment schedule and assessments were performed double-blind, with treatment allocations kept in sealed envelopes by the principal investigator
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were completed for each main outcome. Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Malling 2005

Methods	Randomised DBPC trial
Participants	Adults 5 updose groups: 2500, 25,000, 75,000, 125,000, 375,000 SQ-T
Interventions	SLIT tablets Maximum dose 375000 SQ-T
Outcomes	*Phleum pratense* specific: IgE, IgA and IgG Adverse events description - local and systemic
Notes	Jadad scale 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised, but no details were provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Data completed for each main outcome, including attrition and exclusions from the analysis. Attrition and exclusions were reported, the numbers in each intervention group and reasons for attrition/exclusions where reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Marcucci 2005

Methods	Randomised DBPC trial
Participants	Children Active 13 (6 m); losses to f/u 0 Placebo 11 (10m); losses to f/u 0
Interventions	12 months SLIT Sublingual drops Maintenance dose: 0.8 mcg of mite allergen group 1 and 0.4 mcg of mite allergen group 2
Outcomes	Symptom scores for rhinitis and asthma Medication scores Nasal tryptase Nasal IgE Specific nasal challenge test Nasal ECP Sputum ECP Sputum tryptase Serum IgE
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised, but no details about randomisation provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	The placebo preparation was identical to active treatment in terms of composition, appearance, presentation, taste and colour, but did not contain allergens
Incomplete outcome data addressed? All outcomes	Low risk	Participants excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Nelson 1993

Methods	Randomised DBPC trial
Participants	Adults 20 active (7 m) 21 placebo (6 m)
Interventions	65 days SLIT drops

Nelson 1993 *(Continued)*

	450-900 Feld1 units
Outcomes	Cat room scores Ig Titrated SPT
Notes	Jadad scale 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised, but the details were not provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. Those randomised to the placebo group received histamine phosphate (1 mg/ml histamine base in 50% glycerine with caramelised sugar for colour).
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were completed for each main outcome. Attrition and exclusions were reported; the numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Ott 2009

Methods	Randomised DBPC trial
Participants	Adults Total mean age 33.3+/- 10.4 yrs (7.9 to 64.7) Active total 142 Active full analysis set (FAS) 123 Active ITT 99 Active per protocol 58 Active losses to f/u 43 Placebo total 67 Placebo full analysis set (FAS) 60 Placebo ITT 46 Placebo per protocol 33 Placebo losses to f/u 21
Interventions	3 consecutive grass pollen seasons SLIT grass pollen (mixture of 5 grasses; orchard, meadow, perennial rye, sweet vernal and timothy grass) Sublingual drops Rush updosing of 30, 90, 150 and 300 IR at 20 minutes intervals, followed by a daily intake of 300 IR for the duration of pollen season 300 IR/ml = 21 mcg/ ml og Phl p 5 major allergen

Ott 2009 *(Continued)*

Outcomes	Symptom score Medication score Combined symptom/medication score Specific IgE and IgG4 Compliance Safety
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were stated
Blinding? All outcomes	Low risk	Investigators and patients were blinded to treatment
Incomplete outcome data addressed? All outcomes	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Pajno 2003

Methods	Randomised DBPC trial
Participants	Children 15 active (7 m); losses to f/u 1 15 placebo (6 m); losses to f/u 2
Interventions	13 months SLIT *Parietaria* pollen Sublingual drops Maintenance dose 5 drops of 10 BU/ ml sol Cumulative dose of major allergen 20.3 mcg Par j 1 ˜ 0.15 mcg/day
Outcomes	Total symptom score Chest symptom score Nose symptom score Medication score Early and late-phase skin reaction
Notes	Active group: SLIT+ fluticasone Placebo group: placebo + fluticasone Control group: asthma medications as needed only

Pajno 2003 *(Continued)*

	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	The randomisation to the active, placebo or control group was obtained by means of a computer-generated key-code
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment. The placebo was indistinguishable from the active treatment in appearance, colour and taste.
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	A second drug other than SLIT was considered in the study design

Palma Carlos 2006

Methods	Randomised DBPC trial
Participants	Adults Active 17; loss to follow up 4 Placebo 16; loss to follow up 9
Interventions	24 months sublingual tablets Allergoid mixture (33% *Holcus lanatus*, 33% *Phleum pratense*, 33% *Poa pratensis*)
Outcomes	Symptom score Medication score Nasal reactivity (allergen nasal challenge) Adverse events
Notes	Major allergen protein dose not possible to measure as this is an allergoid

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were stated in the paper
Blinding? All outcomes	Unclear risk	Investigators and patients were blinded to treatment but how this was done was not stated

Palma Carlos 2006 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	39.4% of participants withdrew during follow up

Panzner 2008

Methods	Randomised DBPC trial
Participants	Adults and children Total mean age 19.5 Age range 7 to 50 years Active sublingual 20 (11 m) Placebo sublingual 15 (9 m)
Interventions	Sublingual and supralingual drops 6 grasses: oat grass (*Arrhenatherum elatius*), orchard grass (*Dactylis glomerata*), fescue (*Festuca sp.*), rye grass (*Lolium sp.*), timothy grass (*Phleum pratense*) and rye (*Secale cereale*) 1 year Updosing scheme from 1 to 10 drops. Maximal dose 10 drops of 10,000 JSK/ml (1.265 mcg of Lol p1)
Outcomes	Symptom scores (nasal, ocular and bronchial) Medication scores Skin prick tests Grass pollen specific IgE and IgG
Notes	Mixed grasses drops were delivered sublingually or supralingually. Only sublingual immunotherapy data were used for the purpose of this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Central randomisation. The randomisation key was generated by the GraphPad Software.
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Passalacqua 1998

Methods	Randomised DBPC trial
Participants	Adults 10 active (3 m) 10 placebo (4 m)
Interventions	24 months SLIT Tablets Dose n/s
Outcomes	Diary scores
Notes	Jadad scale 4/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random codes were used
Allocation concealment?	Unclear risk	It was not stated in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Passalacqua 1999

Methods	Randomised DBPC trial
Participants	Adults 15 active (10 m) 15 placebo (3 m)
Interventions	6 months SLIT 16 mcg Parj1
Outcomes	Diary scores Nasal challenge
Notes	Jadad scale 5/5

Passalacqua 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	It was not stated in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Passalacqua 2006

Methods	Randomised DBPC trial
Participants	Adults 34 active (11 m); losses to f/u 6 34 placebo (11 m); losses to f/u 6
Interventions	25 months SLIT allergoid Soluble tablets 1000 AU
Outcomes	Symptom score Medication score Quality of life questionnaire Adverse events
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A computer-generated list was used
Allocation concealment?	Unclear risk	Not stated in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed?	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.

Passalacqua 2006 *(Continued)*

All outcomes

Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Peter 2009

Methods	Randomised DBPC trial
Participants	Adults Active 176; lost to f/u unknown Placebo 189; lost to f/u unknown
Interventions	SLIT drops Grass pollen mixture (*Lolium perenne*, *Phleum pratense* and *Poa pratensis*) 16 weeks pre-seasonal
Outcomes	Clinical index score Symptom score Medication score Specific IgE for grass pollen mixture Specific IgE for Phl p 1 and Phl p 5 Specific IgG and IgG4 for grass pollen mixture Specific IgG and IgG4 for Phl p 1 and Phl p 5
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were provided in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Unclear risk	No details were provided in the paper
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Pfaar 2008

Methods	Randomised DBPC trial
Participants	Adults Active 49; losses to f/u 7 Placebo 55; losses to f/u 7
Interventions	Sublingual immunotherapy with 6 grasses pollen mixture (*Holcus lanatus*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis* and *Festuca elatior*) Sublingual drops Dose escalation was performed at the day 1 of the treatment, with doubling of a dose every 60 minutes. Initial dose, 1 drop, 2 drops, 4 drops (100%), corresponding to 10, 20 and 40 mcg of the group 5 grass allergen The group 5 allergen content of the maintenance dose was 40 mcg (ELISA) and 20 mcg (CREATE) Once daily
Outcomes	Symptom score Medication score Specific IgE Specific IgG1 and IgG4 Compliance Adverse events
Notes	A block randomisation was performed, and there was a stratification procedure with respect to asthma

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A block randomisation was performed, and there was a stratification procedure with respect to asthma
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were completed for each main outcome. Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Pradalier 1999

Methods	Randomised DBPC trial
Participants	Adults 63 active (29 m) 63 placebo (36 m)
Interventions	5 months pre-seasonal SLIT drops and tablets

Pradalier 1999 *(Continued)*

	Cumulative dose 0.935 mg Phlp5 Daily maintenance dose ~ 8.5 mcg
Outcomes	Diary scores SPT Ig
Notes	Jadad scale 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were provided in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Rolinck-Werninghaus 2004

Methods	Randomised DBPC trial
Participants	Children Age range 3 to 14 Active 49 (30 m); losses to f/u 11 Placebo 48 (35 m); losses to f/u 11
Interventions	32 months SLIT sublingual drops Mixed grasses (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense* and *Poa pratensis*) Maintenance dose: 5 drops of 1000 STU/ml solution 3 times a week Cumulative dose 188 mcg of major allergens The potency in STU; 1000 STU equivalent to 25 BU (2.5 mcg of major allergens) Study started in January 1999
Outcomes	Symptom scores (nasal, eyes, lung) Medication scores Total IgE, specific IgE and IgG4 Skin prick test Conjunctival provocation test Nasal provocation test

Rolinck-Werninghaus 2004 *(Continued)*

	Lung function test Exhaled nitric oxide concentrations SCORAD Adverse events descriptions
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation was conducted for age and history of asthma in consecutive order at inclusion
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Rőder 2007

Methods	Randomised DBPC trial
Participants	Children Age range 6 to 18 Active 108 (91 ITT); losses to follow up 26 Placebo 96 (77 ITT); losses to follow up 24
Interventions	Sublingual drops - mixed grasses 5 grasses extract (*Lolium perenne*, *Phleum pratense*, *Dactylis glomeratein*, *Anthoxatum odoratum*, *Holcus lanatus*) Treatment duration 2 years. Maintenance dose 21 mcg of Lol p 5 twice a week.
Outcomes	Symptom score Percentage of symptom-free days Percentage of medication-free days Quality of life evaluation Safety
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Rőder 2007 *(Continued)*

Adequate sequence generation?	Low risk	A computer-generated randomisation list stratifying for symptom score and participating general practice was utilised
Allocation concealment?	Low risk	A pharmacist allocated medication in accordance with a computer-generated randomisation list stratifying for symptom score and participating general practice. Participants, parents, investigators and caregivers were unaware of the group assignment and could not make a distinction between verum and placebo treatment.
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Sabbah 1994

Methods	Randomised DBPC trial
Participants	Children and adults Age range 13 to 51 Active 29 Placebo 29
Interventions	Sublingual drops - 5 grass pollen extracts or placebo The updosing phase duration was 40 days. It started with 1 drop of 1 IR/ml up to 10 drops on day 10, while on days 11 to 20, 1 to 10 drops of 10 IR/ml were given. Finally, from days 20 to 40, the patients took 1 to 20 drops of 100 IR/ml. Once this dose of 20 drops was reached, maintenance treatment was continued every day for 30 days and then every 2 days for the following 30 days. The cumulative dosage received by the patients was therefore 4500 IR.
Outcomes	Symptom scores Medication scores Safety
Notes	Study included in review, but not meta-analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised, but no details were provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment

Sabbah 1994 *(Continued)*

Incomplete outcome data addressed? All outcomes	Unclear risk	No details were provided in the paper
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Sanchez 2001

Methods	Randomised DBPC trial
Participants	Adults 40 participants Mean age: 24.5 years old Male 16 and female 24 Active 20 patients Placebo 20 patients
Interventions	SLIT: active therapy contained an aqueous extract of the major cat allergen Fel d 1 (CBF-Leti). Five vials were provided containing: 0.00032, 0.0016, 0.008, 0.04, 0.02 and 1 HEP equivalent/mL. Saline solution, glycerine 50% and phenol 0.4% was used as vehicle. SLIT was provided daily and kept under the tongue during 3 minutes. After 1 year of treatment the cumulative dose was 3.6 µg of Fel d 1. Placebo: saline solution, glycerine 50% and phenol 0.4%
Outcomes	Symptom scores Medication scores Skin prick tests Nasal provocation tests IgE and IgG4 Eosinophil cationic protein
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were provided in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Unclear risk	No details were provided in the paper
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section

Sanchez 2001 *(Continued)*

Free of other bias?	Low risk	No other sources of bias were detected or suspected

Smith 2004

Methods	Randomised DBPC trial
Participants	Adults 44 active treatment for 2 years (21 m) 45 active treatment then placebo (22 m) 45 placebo in both years (27 m)
Interventions	2 years SLIT from February until 31 July each year Sublingual drops and tablets for maintenance Mixed grasses (orchard, meadow, rye, sweet vernal and timothy grass) 100 IR contained 24 mcg Lolp1 and 14 mcg Dacg5 Cumulative annual dose 26.100 IR 6264 mcg Lolp1 3654 mcg Dacg5
Outcomes	Symptom scores; daily diary Medication scores; dairy cards Conjunctival provocation threshold Skin tests Specific IgE and IgG4 Side effects reported by patients
Notes	Jadad scale 5/5 Participants were randomised into 3 groups Active treatment for 2 years Active treatment for a year, then placebo and placebo for 2 years Treatment every year from February until 31 July

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	Authors stated that groups were checked for homogeneity regarding demographics, symptom scores and relevant clinical parameters
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. Placebo tablets and drops were physically identical to active medication.
Incomplete outcome data addressed? All outcomes	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Tari 1990

Methods	Randomised DBPC trial
Participants	Adults 34 active 32 placebo
Interventions	18 months SLIT 2340 drops of 5BU/ml mcg dose n/s
Outcomes	Diary scores Ig
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised, but further details were not provided
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	The placebo contained only the phosphate buffered physiological solution
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Tonnel 2004

Methods	Randomised DBPC trial
Participants	Adults and children 15 active (8 m); losses to f/u 5 17 placebo (10 m); losses to f/u 9
Interventions	24 months SLIT Der p 1 and Der f 1 50/50 drops and tablets Progression phase for 2 weeks Max dose 100 IR tablet Mean cumulative dose 47500 IR 1.28 mg Der p1 1.47 mg Der f 1
Outcomes	Symptom scores

Tonnel 2004 *(Continued)*

	Medication scores Skin prick tests Nasal provocation test Levels of specific IgE and IgG4 Adverse events reports and descriptions
Notes	Jadad scale 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A random computer-generated code was used
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Blinding was done using solutions and tablets of identical appearance
Incomplete outcome data addressed? All outcomes	Low risk	Attrition and exclusions were reported. The numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Troise 1995

Methods	Randomised DBPC trial
Participants	Adults 15 active (6 m) 16 placebo (6 m)
Interventions	10 months SLIT *Parietaria* extract 6.3 mcg Parj1
Outcomes	Diary scores
Notes	Jadad scale 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	It was not specified in the paper

Troise 1995 *(Continued)*

Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods. The specified outcomes in the methodology were reported in the results section.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Valovirta 2006

Methods	Randomised DBPC trial
Participants	Children 35 active Dose group one 33 patients (19 m); losses to f/u 1 Dose group 2: 32 patients (13 m); losses to f/u 7 33 placebo (18 m); losses to f/u 6
Interventions	18 months SLIT Group 1: accumulated weekly dose 3.6 mcg Bet v 1/ Aln g 1/ Cor a 1 Group 2: accumulated weekly dose 30 mcg of Bet v 1/ Aln g 1/ Cor a 1 5 weeks updosing schedule
Outcomes	Symptom score Medication score
Notes	Jadad scale 5/5 2 treatment groups Mixed tree pollen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	The study was conducted under double-blind conditions. There was no difference in colour and viscosity between the study drug and placebo. All blinding procedures were performed by the Quality Assurance Department at ALK-Abello A/S.
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data for each main outcome completed, including attrition and exclusions from the analysis. Attrition and exclusions were reported; the numbers in each intervention group and reasons for attrition/exclusions were reported.

Valovirta 2006 *(Continued)*

Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Vervloet 2006

Methods	Randomised DBPC trial
Participants	Adults 38 active (22 m); losses to f/u 2 38 placebo (17 m); losses to f/u 4
Interventions	4 months SLIT Sublingual drops Ultra rush treatment Maintenance dose 300 IR daily Dose of major allergen 228 mcg Jun a 1
Outcomes	Symptom scores Medication scores Adverse events reports
Notes	Jadad scale 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomisation in blocks was used
Allocation concealment?	Unclear risk	No details were provided in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Voltolini 2001

Methods	Randomised DBPC trial
Participants	Adults 15 active (7 m)

Voltolini 2001 *(Continued)*

	15 placebo (4 m)
Interventions	Rush pre-seasonal and co-seasonal maintenance 445 mcg Bet v 1 Tree pollen extract
Outcomes	Diary scores Ig SPT
Notes	Jadad scale 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Low risk	No details were provided in the paper
Blinding? All outcomes	Unclear risk	Investigators and participants were blinded to treatment assignment for the duration of the study. Placebo was prepared as saline solution in vials with exactly the same appearance, colour and taste, but without allergens, in order to guarantee the double-blind design of the trial.
Incomplete outcome data addressed? All outcomes	Unclear risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Unclear risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Vourdas 1998

Methods	Randomised DBPC trial
Participants	Children 34 active (25 m) 32 placebo (24 m)
Interventions	6 months SLIT per year for 2 years 4.05 mg Olee 1 Olive pollen extract solution
Outcomes	Diary scores SPT
Notes	Jadad scale 3/5

Risk of bias

Vourdas 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised but how this was done was not stated
Allocation concealment?	Unclear risk	No details were provided in the paper
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. The placebo was a glycerinated phenolated saline solution with an appearance similar to that of the active agent.
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Wahn 2009

Methods	Randomised DBPC trial
Participants	Children Active 131 (65.6% male); withdrawn 8 Placebo 135 (63.0% male); withdrawn 8
Interventions	< 6 months Sublingual tablets Mixed grasses (*Dactylis glomerata*, *Poa pratensis*, *Lolium perenne*, *Anthoxanthum odoratum*, *Phleum pratense*) Daily dose 300 IR; 20 mcg of group 5 major allergens
Outcomes	Symptom score Medication score Timothy grass specific IgE Grass pollen specific IgG4 Adverse events
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	The randomisation list was stratified by study centre and organised in blocks
Allocation concealment?	Low risk	Central allocation
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study. Excipients used in both active and placebo tablets include lactose, sodium stearate and sodium croscarmellose.

Wahn 2009 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Outcome data for each main outcome completed, including attrition and exclusions from the analysis. Attrition and exclusions were reported; the numbers in each intervention group and reasons for attrition/exclusions were reported.
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Low risk	No other sources of bias were detected or suspected

Wessner 2001

Methods	Randomised DBPC trial
Participants	22 active; losses to f/u 8 23 placebo; losses to f/u 5
Interventions	12 months SLIT drops maintenance dose 2000 AU per day 8 mcg major allergen per day
Outcomes	Symptom scores Daily cards Nasal provocation tests
Notes	Jadad scale 5/5 The study was performed for 2 years Only first year was performed as a DBPC trial; in the second year all participants received verum therapy for another year Data analysed only for the first year

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomisation blocks of 4 containing 2 of each treatment
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Unclear risk	No details were provided
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	The study has not been published after its presentation at a meeting in 2001

Wutrich 2003

Methods	Randomised DBPC trial
Participants	Children Age range 4 to 11 years Active 14 (7 m); losses to f/u 2 Placebo 14 (9 m); losses to f/u 0
Interventions	24 months SLIT Sublingual drops Mixed grasses (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*) Build-up phase 30 days - cumulative dose of major allergen was 1.88 mcg Maintenance phase - cumulative dose of major allergen 6 mcg The first year the cumulative dose was 67.88 mcg and 139.88 mcg of major allergen in total
Outcomes	Conjunctival provocation test Skin prick test Symptom scores - diary cards Medication scores - diary cards
Notes	Jadad scale 5/5 4 children were not included in data analysis because of their incomplete diary cards

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomised
Allocation concealment?	Unclear risk	No details were provided
Blinding? All outcomes	Low risk	Investigators and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? All outcomes	Low risk	Participants lost to follow up or excluded were accounted for along with patients followed to designated follow-up periods
Free of selective reporting?	Low risk	The specified outcomes in the methodology were reported in the results section
Free of other bias?	Unclear risk	Small number of patients across each trial group

DBPC = double-blind, placebo-controlled; f/u= follow up; mcg = microgram; ITT = intention-to-treat; m = male; n/s = not specified; SCIT = subcutaneous (injection); immunotherapy; SL = sublingual; SLIT = sublingual immunotherapy; SPT = skin prick test

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

Study	Reason for exclusion
Bernardis 1996	Not randomised
Black 2002	Insufficient data available for the review

Study	Reason for exclusion
Corthay 1996	Insufficient data available for the review
D'Ambrosio 1996	Open study design; not a randomised DBPC trial
Donato 1997	Prospective study; not a randomised DBPC trial
Feliziani 1993	Not randomised
Gammeri 2004	Not placebo-controlled
Gozalo 1997	Not randomised, controlled or blinded
Hansen 2004	Other outcomes investigated (food allergy)
Horak 1998	No symptom data. Not seasonal exposure.
Inal 2009	Insufficient data available for the review
Karakoc 2003	Not randomised, not blinded and not placebo-controlled
Mitsch 1996	Open study
Mungan 1999	Not a randomised DBPC trial
Nanda 2004	SCIT trial
Okubo 2008	Additional data not available
Quirino 1996	Not truly randomised
Radjenovic 2004	Not DBPC trial; prospective parallel-group study
Russello 2004	Not blinded
Sabbah 1993	Duplicate study (same as Sabbah 1994)
Tonnel 2002	Data published in Tonnel 2004
Troise 2009	Insufficient data available for the review
Van Niekerk 1987	Not sublingual immunotherapy
Yuksel 1999	This study does not investigate outcomes evaluated by this review

DBPC = double-blind, placebo-controlled; SCIT = subcutaneous immunotherapy

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

Ingels 2002

Trial name or title	A placebo controlled, double-blind, randomized study to assess efficacy of sublingual immunotherapy in patients with grass pollen allergy through assessment of its immunological effects on the mucosal tissue of the nose

Ingels 2002 *(Continued)*

Methods	Randomised, placebo-controlled, double-blind
Participants	Expected 38
Interventions	Sublingual immunotherapy with Oralgen Further procedures: Nasal biopsy Nasal washing PNIF
Outcomes	Decrease of IgE specific cells and Th2 mediator release Increase in Th 1 mediator release Rescue medication Determining the effects on decongestion Assessment of treatment compliance
Starting date	Study start 2002
Contact information	—
Notes	—

O'Hehir 2005

Trial name or title	A trial of immunological outcomes of sublingual immunotherapy for house dust mite (*D. pteronyssinus*)
Methods	Randomised, placebo-controlled, double-blind
Participants	Expected enrolment 30
Interventions	Sublingual immunotherapy for house dust mite
Outcomes	Immunoregulatory cytokine production and T cell phenotype and function Symptom diary Medication use Visual analogue score Disease-specific rhinoconjunctivitis Quality of life questionnaire
Starting date	November 2005
Contact information	Allesandra Sandrini MD, PhD a.sandrini@alfred.org.au +61 3 9276 2000 ext 2350
Notes	—

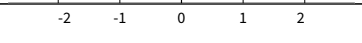
DATA AND ANALYSES

Comparison 1. SLIT versus placebo - all

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	49	4589	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-0.64, -0.34]
2 Medication scores	38	3379	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.43, -0.21]

Analysis 1.1. Comparison 1 SLIT versus placebo - all, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	3.8 (4.9)	17	3.7 (2.7)		1.87%	0.03[-0.63,0.68]
Andre 2003	48	2.3 (1.4)	51	3.1 (2.1)		2.4%	-0.45[-0.84,-0.05]
Ariano 2001	10	1.8 (1.8)	10	5.4 (1.6)		1.1%	-2.06[-3.19,-0.93]
Bahceciler 2001	8	0.5 (0.4)	7	0.4 (0.4)		1.24%	0.31[-0.71,1.34]
Bowen 2004	37	4 (2.5)	39	5 (2.5)		2.29%	-0.43[-0.88,0.03]
Bufe 2004	68	1.5 (0.8)	64	1.6 (1)		2.52%	-0.06[-0.4,0.28]
Bufe 2009	117	2.7 (2.4)	121	3.2 (2.1)		2.67%	-0.22[-0.48,0.03]
Caffarelli 2000	17	4.2 (3.7)	17	5.9 (3.8)		1.81%	-0.44[-1.12,0.24]
Cao 2007	85	0.7 (0.9)	91	2.6 (0.5)		2.35%	-2.85[-3.27,-2.43]
Casanovas 1994	9	5.5 (3.6)	6	11 (7.1)		1.12%	-1[-2.11,0.12]
D'Ambrosio 1999	14	509 (514.2)	16	897.1 (678.2)		1.71%	-0.62[-1.36,0.12]
Dahl 2006a	61	2.1 (1.7)	32	3.3 (2.2)		2.32%	-0.63[-1.07,-0.19]
Dahl 2006b	282	2.4 (1.6)	286	3.4 (2.2)		2.79%	-0.52[-0.69,-0.35]
de Blay 2003	33	20.6 (15.9)	42	23.5 (18.8)		2.28%	-0.17[-0.62,0.29]
Di Rienzo 2006	18	0.4 (0.3)	14	0.8 (0.5)		1.69%	-0.98[-1.72,-0.23]
Didier 2007	136	3.6 (3)	148	4.9 (3.2)		2.7%	-0.43[-0.67,-0.2]
Drachenberg 2001	37	29.5 (24.2)	12	36.4 (30.4)		1.87%	-0.26[-0.92,0.39]
Dubakiene 2003	47	0.5 (0.3)	53	0.6 (0.4)		2.41%	-0.42[-0.82,-0.03]
Durham 2006	131	2.5 (2.1)	129	3 (2.1)		2.69%	-0.23[-0.47,0.02]
Feliziani 1995	18	109.7 (92.5)	16	215.8 (114.2)		1.74%	-1[-1.72,-0.28]
Guez 2000	36	2.3 (1.9)	36	3.2 (2.4)		2.26%	-0.41[-0.88,0.06]
Hirsch 1997	12	1 (1.1)	10	0.5 (0.5)		1.49%	0.5[-0.35,1.36]
Hordijk 1998	35	3.2 (3.1)	36	5.1 (3.6)		2.24%	-0.57[-1.04,-0.09]
La Rosa 1999	16	1.2 (1.7)	17	1.6 (1.6)		1.81%	-0.24[-0.93,0.44]
Lima 2002	28	2494 (2326)	28	2465 (1537)		2.14%	0.01[-0.51,0.54]
Marcucci 2005	13	412.9 (332.6)	11	517.3 (548.2)		1.58%	-0.23[-1.03,0.58]
Nelson 1993	20	12.2 (8.7)	21	18.7 (13.6)		1.93%	-0.56[-1.18,0.07]
Ott 2009	123	-1 (4.5)	60	1.3 (4.5)		2.57%	-0.51[-0.83,-0.2]
Pajno 2003	14	4 (5.2)	13	10 (8.7)		1.61%	-0.82[-1.62,-0.03]
Palma Carlos 2006	17	31.2 (32.6)	16	55.9 (50.5)		1.78%	-0.57[-1.27,0.13]
Panzner 2008	20	111.4 (114.9)	15	321.6 (211.2)		1.7%	-1.26[-2,-0.52]
Passalacqua 1998	10	59.6 (27.8)	9	109.1 (45.7)		1.26%	-1.27[-2.28,-0.26]
Passalacqua 1999	15	189 (113)	15	191 (108)		1.75%	-0.02[-0.73,0.7]
Passalacqua 2006	28	1.8 (0.2)	28	2.2 (0.2)		1.95%	-1.65[-2.26,-1.04]



Favours SLIT — Favours Placebo

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Peter 2009	176	0.7 (0.5)	189	0.8 (0.5)		2.74%	-0.09[-0.3,0.11]
Pfaar 2008	42	146.2 (123)	48	236.2 (133.6)		2.34%	-0.69[-1.12,-0.27]
Pradalier 1999	63	2.3 (1.6)	63	2.7 (2)		2.5%	-0.18[-0.53,0.17]
Rolinck-Werninghaus 2004	39	13.7 (23.1)	38	12.7 (21.7)		2.3%	0.05[-0.4,0.49]
Rőder 2007	91	2.5 (1.5)	77	2.7 (1.7)		2.58%	-0.18[-0.49,0.12]
Smith 2004	45	2.6 (2.5)	51	2.3 (1.7)		2.4%	0.12[-0.28,0.52]
Tari 1990	30	8 (1.5)	28	12 (2)		1.84%	-2.24[-2.91,-1.58]
Tonnel 2004	10	2.7 (2.1)	12	4.1 (2.2)		1.48%	-0.61[-1.47,0.25]
Troise 1995	15	87 (76)	16	102 (58)		1.76%	-0.22[-0.92,0.49]
Valovirta 2006	27	1.5 (1.4)	29	2.2 (1.4)		2.12%	-0.49[-1.03,0.04]
Vervloet 2006	19	2.7 (1.6)	19	2.4 (2.1)		1.9%	0.13[-0.51,0.76]
Voltolini 2001	15	130 (154)	15	83 (79)		1.73%	0.37[-0.35,1.1]
Vourdas 1998	34	1.1 (1.6)	32	1.4 (2)		2.23%	-0.17[-0.65,0.32]
Wahn 2009	131	3.3 (2.9)	135	4.5 (2.9)		2.69%	-0.43[-0.68,-0.19]
Wessner 2001	14	0.3 (0.3)	18	0.5 (0.4)		1.75%	-0.56[-1.27,0.16]
Total ***	**2333**		**2256**			**100%**	**-0.49[-0.64,-0.34]**

Heterogeneity: Tau²=0.2; Chi²=256.76, df=48(P<0.0001); I²=81.31%

Test for overall effect: Z=6.35(P<0.0001)

Analysis 1.2. Comparison 1 SLIT versus placebo - all, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	0.4 (1.2)	17	0.1 (0.2)		1.92%	0.33[-0.33,0.99]
Andre 2003	48	2.4 (3.1)	51	4 (4.2)		3.46%	-0.42[-0.82,-0.02]
Ariano 2001	10	2.5 (2.1)	10	5.3 (4.9)		1.17%	-0.71[-1.62,0.2]
Bahceciler 2001	8	1.3 (1)	7	1.6 (1.3)		0.97%	-0.26[-1.28,0.76]
Bowen 2004	37	1.1 (1.6)	39	1.3 (1.2)		3.07%	-0.15[-0.6,0.3]
Bufe 2004	68	0.2 (0.2)	64	0.2 (0.2)		3.93%	0.31[-0.03,0.66]
Bufe 2009	117	2.1 (3.5)	121	2.5 (3)		4.78%	-0.12[-0.38,0.13]
Caffarelli 2000	17	8.1 (6.4)	17	9 (6.9)		1.86%	-0.13[-0.81,0.54]
Cao 2007	85	0 (0.1)	91	0.2 (1.9)		4.37%	-0.12[-0.42,0.17]
Casanovas 1994	9	1.7 (2.5)	6	2.1 (2.2)		0.94%	-0.17[-1.21,0.86]
D'Ambrosio 1999	14	48.1 (46.6)	16	124.4 (121)		1.59%	-0.79[-1.54,-0.04]
Dahl 2006a	61	2.4 (3.9)	32	4.2 (4.1)		3.2%	-0.45[-0.88,-0.02]
Dahl 2006b	282	1.5 (1.9)	286	2.4 (2.5)		5.62%	-0.4[-0.57,-0.24]
de Blay 2003	33	3.5 (5.4)	42	7.6 (8.2)		2.96%	-0.57[-1.03,-0.1]
Di Rienzo 2006	18	3.2 (0.7)	14	4.9 (1.5)		1.44%	-1.48[-2.28,-0.68]
Drachenberg 2001	37	12.5 (18.7)	12	23.8 (26.4)		1.91%	-0.54[-1.2,0.12]
Dubakiene 2003	47	0.1 (0.2)	53	0.2 (0.2)		3.5%	-0.22[-0.61,0.17]
Durham 2006	131	1.4 (2.1)	129	2 (2.4)		4.88%	-0.28[-0.52,-0.03]
Feliziani 1995	18	24.1 (25.7)	16	75.9 (50.3)		1.59%	-1.29[-2.04,-0.54]
Guez 2000	36	4.1 (5.5)	36	6.1 (6.8)		2.96%	-0.32[-0.79,0.15]
Hordijk 1998	35	0.2 (0.4)	36	0.3 (0.5)		2.94%	-0.36[-0.83,0.11]
La Rosa 1999	16	2.3 (3.9)	17	2.4 (4)		1.82%	-0.02[-0.7,0.66]
Lima 2002	28	2334 (2616)	28	2837 (2052)		2.58%	-0.21[-0.74,0.31]

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Marcucci 2005	13	21.9 (30.5)	11	67.5 (83.8)		1.35%	-0.72[-1.56,0.11]
Ott 2009	123	-0.3 (11.6)	60	-0.9 (2.5)		4.25%	0.07[-0.24,0.38]
Pajno 2003	14	10.3 (7.3)	13	26.3 (16.5)		1.35%	-1.23[-2.07,-0.4]
Palma Carlos 2006	17	15.4 (33)	16	44.6 (65.1)		1.77%	-0.56[-1.26,0.14]
Passalacqua 1999	15	42 (49.5)	15	83 (65)		1.62%	-0.69[-1.43,0.05]
Passalacqua 2006	28	110 (44)	28	166 (35)		2.24%	-1.39[-1.98,-0.8]
Pradalier 1999	63	1.8 (2.3)	63	2.1 (2.7)		3.88%	-0.14[-0.49,0.21]
Rolinck-Werninghaus 2004	39	2.5 (3.6)	38	2.9 (3.9)		3.09%	-0.08[-0.53,0.36]
Tonnel 2004	10	18.2 (22.4)	12	12.6 (16.1)		1.32%	0.28[-0.57,1.12]
Troise 1995	15	17 (21)	16	33 (33)		1.69%	-0.56[-1.28,0.16]
Valovirta 2006	27	2.9 (3.4)	29	3.9 (4.6)		2.57%	-0.24[-0.77,0.28]
Vervloet 2006	19	3.4 (3.9)	19	4.7 (5)		2%	-0.29[-0.93,0.35]
Voltolini 2001	15	22 (30)	15	39 (34)		1.66%	-0.52[-1.25,0.21]
Vourdas 1998	34	1.4 (3.4)	32	1.8 (3.9)		2.84%	-0.1[-0.59,0.38]
Wahn 2009	131	0.6 (0.6)	135	0.8 (0.6)		4.9%	-0.3[-0.54,-0.06]
Total * **	**1737**		**1642**			**100%**	**-0.32[-0.43,-0.21]**
Heterogeneity: Tau²=0.05; Chi²=73.32, df=37(P=0); I²=49.54%							
Test for overall effect: Z=5.77(P<0.0001)							

Comparison 2. SLIT versus placebo - seasonal allergen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	39	4084	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.44, -0.25]
2 Medication scores	32	3014	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.41, -0.19]

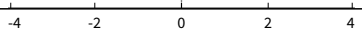
Analysis 2.1. Comparison 2 SLIT versus placebo - seasonal allergen, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	3.8 (4.9)	17	3.7 (2.7)		1.59%	0.03[-0.63,0.68]
Andre 2003	48	2.3 (1.4)	51	3.1 (2.1)		3.09%	-0.45[-0.84,-0.05]
Ariano 2001	10	1.8 (1.8)	10	5.4 (1.6)		0.63%	-2.06[-3.19,-0.93]
Bowen 2004	37	4 (2.5)	39	5 (2.5)		2.65%	-0.43[-0.88,0.03]
Bufe 2004	68	1.5 (0.8)	64	1.6 (1)		3.64%	-0.06[-0.4,0.28]
Bufe 2009	117	2.7 (2.4)	121	3.2 (2.1)		4.62%	-0.22[-0.48,0.03]
Caffarelli 2000	17	4.2 (3.7)	17	5.9 (3.8)		1.5%	-0.44[-1.12,0.24]
Casanovas 1994	9	5.5 (3.6)	6	11 (7.1)		0.65%	-1[-2.11,0.12]
D'Ambrosio 1999	14	509 (514.2)	16	897.1 (678.2)		1.32%	-0.62[-1.36,0.12]
Dahl 2006a	61	2.1 (1.7)	32	3.3 (2.2)		2.78%	-0.63[-1.07,-0.19]

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Dahl 2006b	282	2.4 (1.6)	286	3.4 (2.2)		5.73%	-0.52[-0.69,-0.35]
de Blay 2003	33	20.6 (15.9)	42	23.5 (18.8)		2.64%	-0.17[-0.62,0.29]
Di Rienzo 2006	18	0.4 (0.3)	14	0.8 (0.5)		1.3%	-0.98[-1.72,-0.23]
Didier 2007	136	3.6 (3)	148	4.9 (3.2)		4.86%	-0.43[-0.67,-0.2]
Drachenberg 2001	37	29.5 (24.2)	12	36.4 (30.4)		1.6%	-0.26[-0.92,0.39]
Dubakiene 2003	47	0.5 (0.3)	53	0.6 (0.4)		3.11%	-0.42[-0.82,-0.03]
Durham 2006	131	2.5 (2.1)	129	3 (2.1)		4.76%	-0.23[-0.47,0.02]
Feliziani 1995	18	109.7 (92.5)	16	215.8 (114.2)		1.37%	-1[-1.72,-0.28]
Hordijk 1998	35	3.2 (3.1)	36	5.1 (3.6)		2.51%	-0.57[-1.04,-0.09]
La Rosa 1999	16	1.2 (1.7)	17	1.6 (1.6)		1.48%	-0.24[-0.93,0.44]
Lima 2002	28	2494 (2326)	28	2465 (1537)		2.21%	0.01[-0.51,0.54]
Ott 2009	123	-1 (4.5)	60	1.3 (4.5)		3.94%	-0.51[-0.83,-0.2]
Pajno 2003	14	4 (5.2)	13	10 (8.7)		1.17%	-0.82[-1.62,-0.03]
Palma Carlos 2006	17	31.2 (32.6)	16	55.9 (50.5)		1.44%	-0.57[-1.27,0.13]
Panzner 2008	20	111.4 (114.9)	15	321.6 (211.2)		1.31%	-1.26[-2,-0.52]
Passalacqua 1999	15	189 (113)	15	191 (108)		1.38%	-0.02[-0.73,0.7]
Peter 2009	176	0.7 (0.5)	189	0.8 (0.5)		5.25%	-0.09[-0.3,0.11]
Pfaar 2008	42	146.2 (123)	48	236.2 (133.6)		2.87%	-0.69[-1.12,-0.27]
Pradalier 1999	63	2.3 (1.6)	63	2.7 (2)		3.55%	-0.18[-0.53,0.17]
Rolinck-Werninghaus 2004	39	13.7 (23.1)	38	12.7 (21.7)		2.71%	0.05[-0.4,0.49]
Rőder 2007	91	2.5 (1.5)	77	2.7 (1.7)		4.04%	-0.18[-0.49,0.12]
Smith 2004	45	2.6 (2.5)	51	2.3 (1.7)		3.08%	0.12[-0.28,0.52]
Troise 1995	15	87 (76)	16	102 (58)		1.41%	-0.22[-0.92,0.49]
Valovirta 2006	27	1.5 (1.4)	29	2.2 (1.4)		2.16%	-0.49[-1.03,0.04]
Vervloet 2006	19	2.7 (1.6)	19	2.4 (2.1)		1.66%	0.13[-0.51,0.76]
Voltolini 2001	15	130 (154)	15	83 (79)		1.36%	0.37[-0.35,1.1]
Vourdas 1998	34	1.1 (1.6)	32	1.4 (2)		2.45%	-0.17[-0.65,0.32]
Wahn 2009	131	3.3 (2.9)	135	4.5 (2.9)		4.77%	-0.43[-0.68,-0.19]
Wessner 2001	14	0.3 (0.3)	18	0.5 (0.4)		1.39%	-0.56[-1.27,0.16]
Total ***	**2081**		**2003**			**100%**	**-0.34[-0.44,-0.25]**

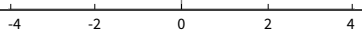
Heterogeneity: Tau²=0.03; Chi²=68.54, df=38(P=0); I²=44.56%

Test for overall effect: Z=7.16(P<0.0001)



Analysis 2.2. Comparison 2 SLIT versus placebo - seasonal allergen, Outcome 2 Medication scores.

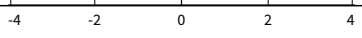
Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	0.4 (1.2)	17	0.1 (0.2)		2.09%	0.33[-0.33,0.99]
Andre 2003	48	2.4 (3.1)	51	4 (4.2)		4.01%	-0.42[-0.82,-0.02]
Ariano 2001	10	2.5 (2.1)	10	5.3 (4.9)		1.24%	-0.71[-1.62,0.2]
Bowen 2004	37	1.1 (1.6)	39	1.3 (1.2)		3.5%	-0.15[-0.6,0.3]
Bufe 2004	68	0.2 (0.2)	64	0.2 (0.2)		4.64%	0.31[-0.03,0.66]
Bufe 2009	117	2.1 (3.5)	121	2.5 (3)		5.84%	-0.12[-0.38,0.13]
Caffarelli 2000	17	8.1 (6.4)	17	9 (6.9)		2.03%	-0.13[-0.81,0.54]
Casanovas 1994	9	1.7 (2.5)	6	2.1 (2.2)		0.99%	-0.17[-1.21,0.86]



Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
D'Ambrosio 1999	14	48.1 (46.6)	16	124.4 (121)		1.72%	-0.79[-1.54,-0.04]
Dahl 2006a	61	2.4 (3.9)	32	4.2 (4.1)		3.66%	-0.45[-0.88,-0.02]
Dahl 2006b	282	1.5 (1.9)	286	2.4 (2.5)		7.12%	-0.4[-0.57,-0.24]
de Blay 2003	33	3.5 (5.4)	42	7.6 (8.2)		3.36%	-0.57[-1.03,-0.1]
Di Rienzo 2006	18	3.2 (0.7)	14	4.9 (1.5)		1.55%	-1.48[-2.28,-0.68]
Drachenberg 2001	37	12.5 (18.7)	12	23.8 (26.4)		2.09%	-0.54[-1.2,0.12]
Dubakiene 2003	47	0.1 (0.2)	53	0.2 (0.2)		4.06%	-0.22[-0.61,0.17]
Durham 2006	131	1.4 (2.1)	129	2 (2.4)		5.99%	-0.28[-0.52,-0.03]
Feliziani 1995	18	24.1 (25.7)	16	75.9 (50.3)		1.72%	-1.29[-2.04,-0.54]
Hordijk 1998	35	0.2 (0.4)	36	0.3 (0.5)		3.33%	-0.36[-0.83,0.11]
La Rosa 1999	16	2.3 (3.9)	17	2.4 (4)		1.98%	-0.02[-0.7,0.66]
Lima 2002	28	2334 (2616)	28	2837 (2052)		2.89%	-0.21[-0.74,0.31]
Ott 2009	123	-0.3 (11.6)	60	-0.9 (2.5)		5.09%	0.07[-0.24,0.38]
Pajno 2003	14	10.3 (7.3)	13	26.3 (16.5)		1.44%	-1.23[-2.07,-0.4]
Palma Carlos 2006	17	15.4 (33)	16	44.6 (65.1)		1.92%	-0.56[-1.26,0.14]
Passalacqua 1999	15	42 (49.5)	15	83 (65)		1.75%	-0.69[-1.43,0.05]
Pradalier 1999	63	1.8 (2.3)	63	2.1 (2.7)		4.57%	-0.14[-0.49,0.21]
Rolinck-Werninghaus 2004	39	2.5 (3.6)	38	2.9 (3.9)		3.53%	-0.08[-0.53,0.36]
Troise 1995	15	17 (21)	16	33 (33)		1.83%	-0.56[-1.28,0.16]
Valovirta 2006	27	2.9 (3.4)	29	3.9 (4.6)		2.88%	-0.24[-0.77,0.28]
Vervloet 2006	19	3.4 (3.9)	19	4.7 (5)		2.19%	-0.29[-0.93,0.35]
Voltolini 2001	15	22 (30)	15	39 (34)		1.79%	-0.52[-1.25,0.21]
Vourdas 1998	34	1.4 (3.4)	32	1.8 (3.9)		3.21%	-0.1[-0.59,0.38]
Wahn 2009	131	0.6 (0.6)	135	0.8 (0.6)		6.02%	-0.3[-0.54,-0.06]
Total * **	**1557**		**1457**			**100%**	**-0.3[-0.41,-0.19]**

Heterogeneity: Tau^2=0.04; Chi^2=55.8, df=31(P=0); I^2=44.44%

Test for overall effect: Z=5.35(P<0.0001)

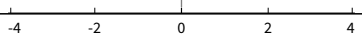


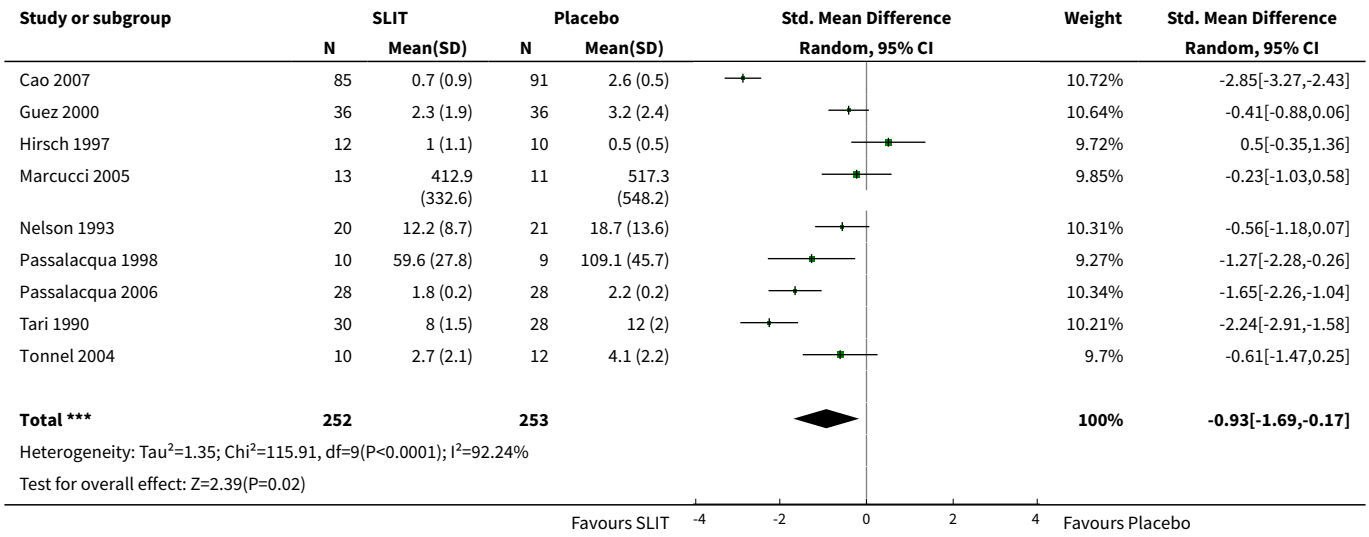
Comparison 3. SLIT versus placebo - perennial allergen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	10	505	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.69, -0.17]
2 Medication scores	6	365	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.89, 0.02]

Analysis 3.1. Comparison 3 SLIT versus placebo - perennial allergen, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	0.5 (0.4)	7	0.4 (0.4)		9.23%	0.31[-0.71,1.34]



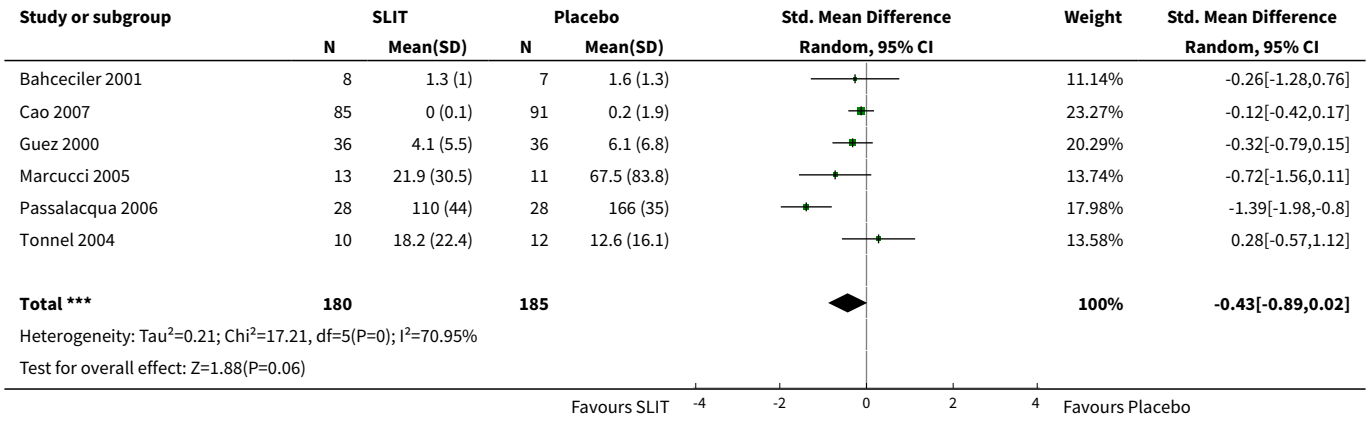


Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Cao 2007	85	0.7 (0.9)	91	2.6 (0.5)		10.72%	-2.85[-3.27,-2.43]
Guez 2000	36	2.3 (1.9)	36	3.2 (2.4)		10.64%	-0.41[-0.88,0.06]
Hirsch 1997	12	1 (1.1)	10	0.5 (0.5)		9.72%	0.5[-0.35,1.36]
Marcucci 2005	13	412.9 (332.6)	11	517.3 (548.2)		9.85%	-0.23[-1.03,0.58]
Nelson 1993	20	12.2 (8.7)	21	18.7 (13.6)		10.31%	-0.56[-1.18,0.07]
Passalacqua 1998	10	59.6 (27.8)	9	109.1 (45.7)		9.27%	-1.27[-2.28,-0.26]
Passalacqua 2006	28	1.8 (0.2)	28	2.2 (0.2)		10.34%	-1.65[-2.26,-1.04]
Tari 1990	30	8 (1.5)	28	12 (2)		10.21%	-2.24[-2.91,-1.58]
Tonnel 2004	10	2.7 (2.1)	12	4.1 (2.2)		9.7%	-0.61[-1.47,0.25]
Total ***	**252**		**253**			**100%**	**-0.93[-1.69,-0.17]**

Heterogeneity: Tau^2=1.35; Chi^2=115.91, df=9(P<0.0001); I^2=92.24%

Test for overall effect: Z=2.39(P=0.02)

Analysis 3.2. Comparison 3 SLIT versus placebo - perennial allergen, Outcome 2 Medication scores.



Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	1.3 (1)	7	1.6 (1.3)		11.14%	-0.26[-1.28,0.76]
Cao 2007	85	0 (0.1)	91	0.2 (1.9)		23.27%	-0.12[-0.42,0.17]
Guez 2000	36	4.1 (5.5)	36	6.1 (6.8)		20.29%	-0.32[-0.79,0.15]
Marcucci 2005	13	21.9 (30.5)	11	67.5 (83.8)		13.74%	-0.72[-1.56,0.11]
Passalacqua 2006	28	110 (44)	28	166 (35)		17.98%	-1.39[-1.98,-0.8]
Tonnel 2004	10	18.2 (22.4)	12	12.6 (16.1)		13.58%	0.28[-0.57,1.12]
Total ***	**180**		**185**			**100%**	**-0.43[-0.89,0.02]**

Heterogeneity: Tau^2=0.21; Chi^2=17.21, df=5(P=0); I^2=70.95%

Test for overall effect: Z=1.88(P=0.06)

Comparison 4. SLIT versus placebo - adults

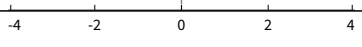
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	34	3197	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.56, -0.31]
2 Medication scores	26	2235	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.53, -0.26]

Analysis 4.1. Comparison 4 SLIT versus placebo - adults, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	3.8 (4.9)	17	3.7 (2.7)		2.3%	0.03[-0.63,0.68]
Andre 2003	48	2.3 (1.4)	51	3.1 (2.1)		3.83%	-0.45[-0.84,-0.05]
Ariano 2001	10	1.8 (1.8)	10	5.4 (1.6)		1.02%	-2.06[-3.19,-0.93]
Bowen 2004	37	4 (2.5)	39	5 (2.5)		3.42%	-0.43[-0.88,0.03]
Casanovas 1994	9	5.5 (3.6)	6	11 (7.1)		1.04%	-1[-2.11,0.12]
D'Ambrosio 1999	14	509 (514.2)	16	897.1 (678.2)		1.96%	-0.62[-1.36,0.12]
Dahl 2006a	61	2.1 (1.7)	32	3.3 (2.2)		3.54%	-0.63[-1.07,-0.19]
Dahl 2006b	282	2.4 (1.6)	286	3.4 (2.2)		5.67%	-0.52[-0.69,-0.35]
de Blay 2003	33	20.6 (15.9)	42	23.5 (18.8)		3.41%	-0.17[-0.62,0.29]
Di Rienzo 2006	18	0.4 (0.3)	14	0.8 (0.5)		1.94%	-0.98[-1.72,-0.23]
Didier 2007	136	3.6 (3)	148	4.9 (3.2)		5.15%	-0.43[-0.67,-0.2]
Drachenberg 2001	37	29.5 (24.2)	12	36.4 (30.4)		2.3%	-0.26[-0.92,0.39]
Dubakiene 2003	47	0.5 (0.3)	53	0.6 (0.4)		3.84%	-0.42[-0.82,-0.03]
Durham 2006	131	2.5 (2.1)	129	3 (2.1)		5.08%	-0.23[-0.47,0.02]
Feliziani 1995	18	109.7 (92.5)	16	215.8 (114.2)		2.03%	-1[-1.72,-0.28]
Guez 2000	36	2.3 (1.9)	36	3.2 (2.4)		3.34%	-0.41[-0.88,0.06]
Hordijk 1998	35	3.2 (3.1)	36	5.1 (3.6)		3.29%	-0.57[-1.04,-0.09]
Lima 2002	28	2494 (2326)	28	2465 (1537)		2.98%	0.01[-0.51,0.54]
Nelson 1993	20	12.2 (8.7)	21	18.7 (13.6)		2.43%	-0.56[-1.18,0.07]
Ott 2009	123	-1 (4.5)	60	1.3 (4.5)		4.51%	-0.51[-0.83,-0.2]
Palma Carlos 2006	17	31.2 (32.6)	16	55.9 (50.5)		2.11%	-0.57[-1.27,0.13]
Panzner 2008	20	111.4 (114.9)	15	321.6 (211.2)		1.95%	-1.26[-2,-0.52]
Passalacqua 1998	10	59.6 (27.8)	9	109.1 (45.7)		1.23%	-1.27[-2.28,-0.26]
Passalacqua 1999	15	189 (113)	15	191 (108)		2.04%	-0.02[-0.73,0.7]
Passalacqua 2006	28	1.8 (0.2)	28	2.2 (0.2)		2.5%	-1.65[-2.26,-1.04]
Peter 2009	176	0.7 (0.5)	189	0.8 (0.5)		5.39%	-0.09[-0.3,0.11]
Pfaar 2008	42	146.2 (123)	48	236.2 (133.6)		3.62%	-0.69[-1.12,-0.27]
Pradalier 1999	63	2.3 (1.6)	63	2.7 (2)		4.21%	-0.18[-0.53,0.17]
Smith 2004	45	2.6 (2.5)	51	2.3 (1.7)		3.81%	0.12[-0.28,0.52]
Tonnel 2004	10	2.7 (2.1)	12	4.1 (2.2)		1.56%	-0.61[-1.47,0.25]
Troise 1995	15	87 (76)	16	102 (58)		2.08%	-0.22[-0.92,0.49]
Vervloet 2006	19	2.7 (1.6)	19	2.4 (2.1)		2.38%	0.13[-0.51,0.76]
Voltolini 2001	15	130 (154)	15	83 (79)		2.01%	0.37[-0.35,1.1]
Wessner 2001	14	0.3 (0.3)	18	0.5 (0.4)		2.05%	-0.56[-1.27,0.16]
Total * **	**1631**		**1566**			**100%**	**-0.44[-0.56,-0.31]**

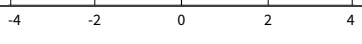
Heterogeneity: Tau^2=0.06; Chi^2=77.81, df=33(P<0.0001); I^2=57.59%

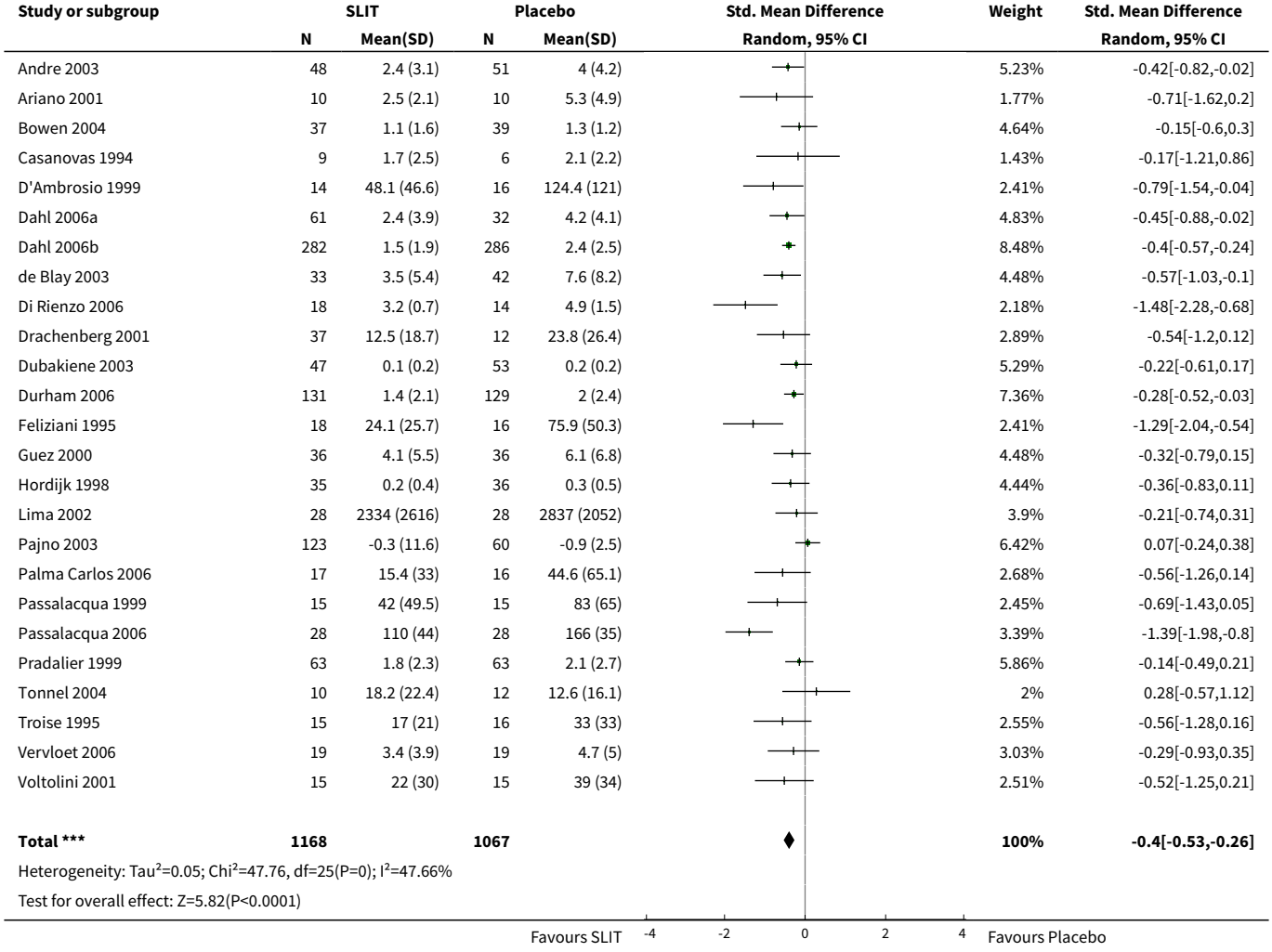
Test for overall effect: Z=6.9(P<0.0001)



Analysis 4.2. Comparison 4 SLIT versus placebo - adults, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	0.4 (1.2)	17	0.1 (0.2)		2.9%	0.33[-0.33,0.99]





Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Andre 2003	48	2.4 (3.1)	51	4 (4.2)		5.23%	-0.42[-0.82,-0.02]
Ariano 2001	10	2.5 (2.1)	10	5.3 (4.9)		1.77%	-0.71[-1.62,0.2]
Bowen 2004	37	1.1 (1.6)	39	1.3 (1.2)		4.64%	-0.15[-0.6,0.3]
Casanovas 1994	9	1.7 (2.5)	6	2.1 (2.2)		1.43%	-0.17[-1.21,0.86]
D'Ambrosio 1999	14	48.1 (46.6)	16	124.4 (121)		2.41%	-0.79[-1.54,-0.04]
Dahl 2006a	61	2.4 (3.9)	32	4.2 (4.1)		4.83%	-0.45[-0.88,-0.02]
Dahl 2006b	282	1.5 (1.9)	286	2.4 (2.5)		8.48%	-0.4[-0.57,-0.24]
de Blay 2003	33	3.5 (5.4)	42	7.6 (8.2)		4.48%	-0.57[-1.03,-0.1]
Di Rienzo 2006	18	3.2 (0.7)	14	4.9 (1.5)		2.18%	-1.48[-2.28,-0.68]
Drachenberg 2001	37	12.5 (18.7)	12	23.8 (26.4)		2.89%	-0.54[-1.2,0.12]
Dubakiene 2003	47	0.1 (0.2)	53	0.2 (0.2)		5.29%	-0.22[-0.61,0.17]
Durham 2006	131	1.4 (2.1)	129	2 (2.4)		7.36%	-0.28[-0.52,-0.03]
Feliziani 1995	18	24.1 (25.7)	16	75.9 (50.3)		2.41%	-1.29[-2.04,-0.54]
Guez 2000	36	4.1 (5.5)	36	6.1 (6.8)		4.48%	-0.32[-0.79,0.15]
Hordijk 1998	35	0.2 (0.4)	36	0.3 (0.5)		4.44%	-0.36[-0.83,0.11]
Lima 2002	28	2334 (2616)	28	2837 (2052)		3.9%	-0.21[-0.74,0.31]
Pajno 2003	123	-0.3 (11.6)	60	-0.9 (2.5)		6.42%	0.07[-0.24,0.38]
Palma Carlos 2006	17	15.4 (33)	16	44.6 (65.1)		2.68%	-0.56[-1.26,0.14]
Passalacqua 1999	15	42 (49.5)	15	83 (65)		2.45%	-0.69[-1.43,0.05]
Passalacqua 2006	28	110 (44)	28	166 (35)		3.39%	-1.39[-1.98,-0.8]
Pradalier 1999	63	1.8 (2.3)	63	2.1 (2.7)		5.86%	-0.14[-0.49,0.21]
Tonnel 2004	10	18.2 (22.4)	12	12.6 (16.1)		2%	0.28[-0.57,1.12]
Troise 1995	15	17 (21)	16	33 (33)		2.55%	-0.56[-1.28,0.16]
Vervloet 2006	19	3.4 (3.9)	19	4.7 (5)		3.03%	-0.29[-0.93,0.35]
Voltolini 2001	15	22 (30)	15	39 (34)		2.51%	-0.52[-1.25,0.21]
Total * **	**1168**		**1067**			**100%**	**-0.4[-0.53,-0.26]**

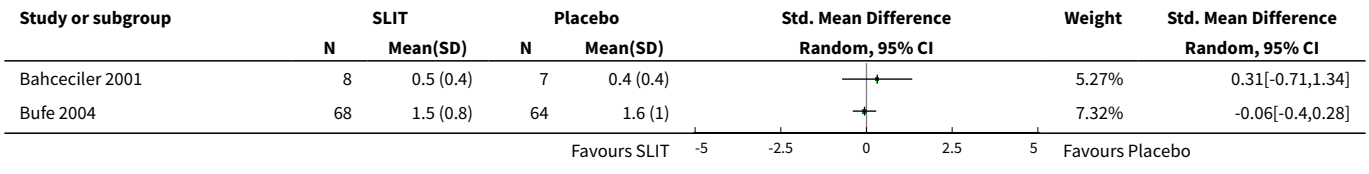
Heterogeneity: Tau²=0.05; Chi²=47.76, df=25(P=0); I²=47.66%

Test for overall effect: Z=5.82(P<0.0001)

Comparison 5. SLIT versus placebo - children

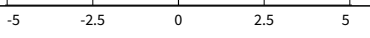
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	15	1392	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.94, -0.10]
2 Medication scores	12	1144	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.32, 0.00]

Analysis 5.1. Comparison 5 SLIT versus placebo - children, Outcome 1 Allergic rhinitis symptom scores.



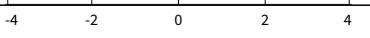
Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	0.5 (0.4)	7	0.4 (0.4)		5.27%	0.31[-0.71,1.34]
Bufe 2004	68	1.5 (0.8)	64	1.6 (1)		7.32%	-0.06[-0.4,0.28]

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bufe 2009	117	2.7 (2.4)	121	3.2 (2.1)		7.48%	-0.22[-0.48,0.03]
Caffarelli 2000	17	4.2 (3.7)	17	5.9 (3.8)		6.39%	-0.44[-1.12,0.24]
Cao 2007	85	0.7 (0.9)	91	2.6 (0.5)		7.13%	-2.85[-3.27,-2.43]
Hirsch 1997	12	1 (1.1)	10	0.5 (0.5)		5.82%	0.5[-0.35,1.36]
La Rosa 1999	16	1.2 (1.7)	17	1.6 (1.6)		6.37%	-0.24[-0.93,0.44]
Marcucci 2005	13	412.9 (332.6)	11	517.3 (548.2)		5.98%	-0.23[-1.03,0.58]
Pajno 2003	14	4 (5.2)	13	10 (8.7)		6.03%	-0.82[-1.62,-0.03]
Rolinck-Werninghaus 2004	39	13.7 (23.1)	38	12.7 (21.7)		7.07%	0.05[-0.4,0.49]
Röder 2007	91	2.5 (1.5)	77	2.7 (1.7)		7.39%	-0.18[-0.49,0.12]
Tari 1990	30	8 (1.5)	28	12 (2)		6.43%	-2.24[-2.91,-1.58]
Valovirta 2006	27	1.5 (1.4)	29	2.2 (1.4)		6.84%	-0.49[-1.03,0.04]
Vourdas 1998	34	1.1 (1.6)	32	1.4 (2)		6.97%	-0.17[-0.65,0.32]
Wahn 2009	131	3.3 (2.9)	135	4.5 (2.9)		7.5%	-0.43[-0.68,-0.19]
Total * **	**702**		**690**			**100%**	**-0.52[-0.94,-0.1]**
Heterogeneity: Tau^2=0.59; Chi^2=177.6, df=14(P<0.0001); I^2=92.12%							
Test for overall effect: Z=2.43(P=0.02)							



Analysis 5.2. Comparison 5 SLIT versus placebo - children, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	1.3 (1)	7	1.6 (1.3)		2.3%	-0.26[-1.28,0.76]
Bufe 2004	68	0.2 (0.2)	64	0.2 (0.2)		11.99%	0.31[-0.03,0.66]
Bufe 2009	117	2.1 (3.5)	121	2.5 (3)		15.85%	-0.12[-0.38,0.13]
Caffarelli 2000	17	8.1 (6.4)	17	9 (6.9)		4.74%	-0.13[-0.81,0.54]
Cao 2007	85	0 (0.1)	91	0.2 (1.9)		13.92%	-0.12[-0.42,0.17]
La Rosa 1999	16	2.3 (3.9)	17	2.4 (4)		4.63%	-0.02[-0.7,0.66]
Marcucci 2005	13	21.9 (30.5)	11	67.5 (83.8)		3.3%	-0.72[-1.56,0.11]
Pajno 2003	14	10.3 (7.3)	13	26.3 (16.5)		3.29%	-1.23[-2.07,-0.4]
Rolinck-Werninghaus 2004	39	2.5 (3.6)	38	2.9 (3.9)		8.73%	-0.08[-0.53,0.36]
Valovirta 2006	27	2.9 (3.4)	29	3.9 (4.6)		6.94%	-0.24[-0.77,0.28]
Vourdas 1998	34	1.4 (3.4)	32	1.8 (3.9)		7.85%	-0.1[-0.59,0.38]
Wahn 2009	131	0.6 (0.6)	135	0.8 (0.6)		16.47%	-0.3[-0.54,-0.06]
Total * **	**569**		**575**			**100%**	**-0.16[-0.32,0]**
Heterogeneity: Tau^2=0.03; Chi^2=17.31, df=11(P=0.1); I^2=36.46%							
Test for overall effect: Z=1.91(P=0.06)							



Comparison 6. SLIT versus placebo < 6 months

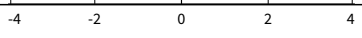
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	17	1772	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.86, -0.21]
2 Medication scores	15	1366	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.45, -0.18]

Analysis 6.1. Comparison 6 SLIT versus placebo < 6 months, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	0.5 (0.4)	7	0.4 (0.4)		4.23%	0.31[-0.71,1.34]
Bowen 2004	37	4 (2.5)	39	5 (2.5)		6.3%	-0.43[-0.88,0.03]
Caffarelli 2000	17	4.2 (3.7)	17	5.9 (3.8)		5.48%	-0.44[-1.12,0.24]
Cao 2007	85	0.7 (0.9)	91	2.6 (0.5)		6.4%	-2.85[-3.27,-2.43]
Casanovas 1994	9	5.5 (3.6)	6	11 (7.1)		3.93%	-1[-2.11,0.12]
Dahl 2006a	61	2.1 (1.7)	32	3.3 (2.2)		6.35%	-0.63[-1.07,-0.19]
Di Rienzo 2006	18	0.4 (0.3)	14	0.8 (0.5)		5.24%	-0.98[-1.72,-0.23]
Dubakiene 2003	47	0.5 (0.3)	53	0.6 (0.4)		6.48%	-0.42[-0.82,-0.03]
Durham 2006	131	2.5 (2.1)	129	3 (2.1)		6.89%	-0.23[-0.47,0.02]
Feliziani 1995	18	109.7 (92.5)	16	215.8 (114.2)		5.33%	-1[-1.72,-0.28]
Hordijk 1998	35	3.2 (3.1)	36	5.1 (3.6)		6.23%	-0.57[-1.04,-0.09]
Nelson 1993	20	12.2 (8.7)	21	18.7 (13.6)		5.69%	-0.56[-1.18,0.07]
Peter 2009	176	0.7 (0.5)	189	0.8 (0.5)		6.96%	-0.09[-0.3,0.11]
Pradalier 1999	63	2.3 (1.6)	63	2.7 (2)		6.62%	-0.18[-0.53,0.17]
Vervloet 2006	19	2.7 (1.6)	19	2.4 (2.1)		5.65%	0.13[-0.51,0.76]
Voltolini 2001	15	130 (154)	15	83 (79)		5.32%	0.37[-0.35,1.1]
Wahn 2009	131	3.3 (2.9)	135	4.5 (2.9)		6.89%	-0.43[-0.68,-0.19]
Total ***	**890**		**882**			**100%**	**-0.54[-0.86,-0.21]**

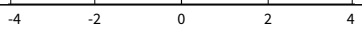
Heterogeneity: Tau^2=0.39; Chi^2=157.82, df=16(P<0.0001); I^2=89.86%

Test for overall effect: Z=3.19(P=0)



Analysis 6.2. Comparison 6 SLIT versus placebo < 6 months, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	1.3 (1)	7	1.6 (1.3)		1.68%	-0.26[-1.28,0.76]
Bowen 2004	37	1.1 (1.6)	39	1.3 (1.2)		6.9%	-0.15[-0.6,0.3]
Caffarelli 2000	17	8.1 (6.4)	17	9 (6.9)		3.58%	-0.13[-0.81,0.54]
Cao 2007	85	0 (0.1)	91	0.2 (1.9)		12.04%	-0.12[-0.42,0.17]
Casanovas 1994	9	1.7 (2.5)	6	2.1 (2.2)		1.63%	-0.17[-1.21,0.86]
Dahl 2006a	61	2.4 (3.9)	32	4.2 (4.1)		7.32%	-0.45[-0.88,-0.02]



Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Di Rienzo 2006	18	3.2 (0.7)	14	4.9 (1.5)		2.64%	-1.48[-2.28,-0.68]
Dubakiene 2003	47	0.1 (0.2)	53	0.2 (0.2)		8.38%	-0.22[-0.61,0.17]
Durham 2006	131	1.4 (2.1)	129	2 (2.4)		14.7%	-0.28[-0.52,-0.03]
Feliziani 1995	18	24.1 (25.7)	16	75.9 (50.3)		2.97%	-1.29[-2.04,-0.54]
Hordijk 1998	35	0.2 (0.4)	36	0.3 (0.5)		6.48%	-0.36[-0.83,0.11]
Pradalier 1999	63	1.8 (2.3)	63	2.1 (2.7)		9.83%	-0.14[-0.49,0.21]
Vervloet 2006	19	3.4 (3.9)	19	4.7 (5)		3.91%	-0.29[-0.93,0.35]
Voltolini 2001	15	22 (30)	15	39 (34)		3.11%	-0.52[-1.25,0.21]
Wahn 2009	131	0.6 (0.6)	135	0.8 (0.6)		14.84%	-0.3[-0.54,-0.06]
Total * **	**694**		**672**			**100%**	**-0.32[-0.45,-0.18]**
Heterogeneity: Tau²=0.02; Chi²=19.09, df=14(P=0.16); I²=26.65%							
Test for overall effect: Z=4.53(P<0.0001)							

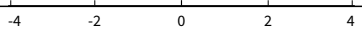
Comparison 7. SLIT versus placebo 6 to 12 months

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	16	1736	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.46, -0.16]
2 Medication scores	13	1398	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.50, -0.12]

Analysis 7.1. Comparison 7 SLIT versus placebo 6 to 12 months, Outcome 1 Allergic rhinitis symptom scores.

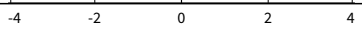
Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	3.8 (4.9)	17	3.7 (2.7)		4.04%	0.03[-0.63,0.68]
Andre 2003	48	2.3 (1.4)	51	3.1 (2.1)		8%	-0.45[-0.84,-0.05]
Ariano 2001	10	1.8 (1.8)	10	5.4 (1.6)		1.58%	-2.06[-3.19,-0.93]
Bufe 2004	68	1.5 (0.8)	64	1.6 (1)		9.47%	-0.06[-0.4,0.28]
Bufe 2009	117	2.7 (2.4)	121	3.2 (2.1)		12.18%	-0.22[-0.48,0.03]
D'Ambrosio 1999	14	509 (514.2)	16	897.1 (678.2)		3.34%	-0.62[-1.36,0.12]
Dahl 2006b	282	2.4 (1.6)	286	3.4 (2.2)		15.32%	-0.52[-0.69,-0.35]
de Blay 2003	33	20.6 (15.9)	42	23.5 (18.8)		6.78%	-0.17[-0.62,0.29]
Didier 2007	136	3.6 (3)	148	4.9 (3.2)		12.86%	-0.43[-0.67,-0.2]
Drachenberg 2001	37	29.5 (24.2)	12	36.4 (30.4)		4.05%	-0.26[-0.92,0.39]
Hirsch 1997	12	1 (1.1)	10	0.5 (0.5)		2.6%	0.5[-0.35,1.36]
Marcucci 2005	13	412.9 (332.6)	11	517.3 (548.2)		2.87%	-0.23[-1.03,0.58]
Passalacqua 1999	15	189 (113)	15	191 (108)		3.5%	-0.02[-0.73,0.7]
Troise 1995	15	87 (76)	16	102 (58)		3.57%	-0.22[-0.92,0.49]
Vourdas 1998	34	1.1 (1.6)	32	1.4 (2)		6.29%	-0.17[-0.65,0.32]

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Wessner 2001	14	0.3 (0.3)	18	0.5 (0.4)		3.52%	-0.56[-1.27,0.16]
Total ***	**867**		**869**			**100%**	**-0.31[-0.46,-0.16]**
Heterogeneity: Tau²=0.03; Chi²=25.47, df=15(P=0.04); I²=41.11%							
Test for overall effect: Z=4.08(P<0.0001)							



Analysis 7.2. Comparison 7 SLIT versus placebo 6 to 12 months, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	0.4 (1.2)	17	0.1 (0.2)		5.71%	0.33[-0.33,0.99]
Andre 2003	48	2.4 (3.1)	51	4 (4.2)		9.89%	-0.42[-0.82,-0.02]
Ariano 2001	10	2.5 (2.1)	10	5.3 (4.9)		3.56%	-0.71[-1.62,0.2]
Bufe 2004	68	0.2 (0.2)	64	0.2 (0.2)		11.1%	0.31[-0.03,0.66]
Bufe 2009	117	2.1 (3.5)	121	2.5 (3)		13.2%	-0.12[-0.38,0.13]
D'Ambrosio 1999	14	48.1 (46.6)	16	124.4 (121)		4.79%	-0.79[-1.54,-0.04]
Dahl 2006b	282	1.5 (1.9)	286	2.4 (2.5)		15.2%	-0.4[-0.57,-0.24]
de Blay 2003	33	3.5 (5.4)	42	7.6 (8.2)		8.58%	-0.57[-1.03,-0.1]
Drachenberg 2001	37	12.5 (18.7)	12	23.8 (26.4)		5.7%	-0.54[-1.2,0.12]
Marcucci 2005	13	21.9 (30.5)	11	67.5 (83.8)		4.08%	-0.72[-1.56,0.11]
Passalacqua 1999	15	42 (49.5)	15	83 (65)		4.87%	-0.69[-1.43,0.05]
Troise 1995	15	17 (21)	16	33 (33)		5.06%	-0.56[-1.28,0.16]
Vourdas 1998	34	1.4 (3.4)	32	1.8 (3.9)		8.26%	-0.1[-0.59,0.38]
Total ***	**705**		**693**			**100%**	**-0.31[-0.5,-0.12]**
Heterogeneity: Tau²=0.06; Chi²=26.9, df=12(P=0.01); I²=55.39%							
Test for overall effect: Z=3.13(P=0)							



Comparison 8. SLIT versus placebo > 12 months

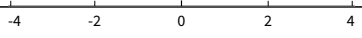
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	16	1089	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-0.92, -0.34]
2 Medication scores	10	615	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.64, -0.04]

Analysis 8.1. Comparison 8 SLIT versus placebo > 12 months, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Guez 2000	36	2.3 (1.9)	36	3.2 (2.4)		6.9%	-0.41[-0.88,0.06]
La Rosa 1999	16	1.2 (1.7)	17	1.6 (1.6)		5.74%	-0.24[-0.93,0.44]
Lima 2002	28	2494 (2326)	28	2465 (1537)		6.6%	0.01[-0.51,0.54]
Ott 2009	123	-1 (4.5)	60	1.3 (4.5)		7.64%	-0.51[-0.83,-0.2]
Pajno 2003	14	4 (5.2)	13	10 (8.7)		5.19%	-0.82[-1.62,-0.03]
Palma Carlos 2006	17	31.2 (32.6)	16	55.9 (50.5)		5.67%	-0.57[-1.27,0.13]
Panzner 2008	20	111.4 (114.9)	15	321.6 (211.2)		5.46%	-1.26[-2,-0.52]
Passalacqua 1998	10	59.6 (27.8)	9	109.1 (45.7)		4.2%	-1.27[-2.28,-0.26]
Passalacqua 2006	28	1.8 (0.2)	28	2.2 (0.2)		6.13%	-1.65[-2.26,-1.04]
Pfaar 2008	42	146.2 (123)	48	236.2 (133.6)		7.11%	-0.69[-1.12,-0.27]
Rolinck-Werninghaus 2004	39	13.7 (23.1)	38	12.7 (21.7)		7%	0.05[-0.4,0.49]
Rőder 2007	91	2.5 (1.5)	77	2.7 (1.7)		7.68%	-0.18[-0.49,0.12]
Smith 2004	45	2.6 (2.5)	51	2.3 (1.7)		7.23%	0.12[-0.28,0.52]
Tari 1990	34	8 (1.5)	32	12 (2)		6.06%	-2.25[-2.87,-1.62]
Tonnel 2004	10	2.7 (2.1)	12	4.1 (2.2)		4.85%	-0.61[-1.47,0.25]
Valovirta 2006	27	1.5 (1.4)	29	2.2 (1.4)		6.55%	-0.49[-1.03,0.04]
Total * **	**580**		**509**			**100%**	**-0.63[-0.92,-0.34]**

Heterogeneity: Tau^2=0.27; Chi^2=74.88, df=15(P<0.0001); I^2=79.97%

Test for overall effect: Z=4.21(P<0.0001)



Analysis 8.2. Comparison 8 SLIT versus placebo > 12 months, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Guez 2000	36	4.1 (5.5)	36	6.1 (6.8)		11.55%	-0.32[-0.79,0.15]
La Rosa 1999	16	2.3 (3.9)	17	2.4 (4)		8.77%	-0.02[-0.7,0.66]
Lima 2002	28	2334 (2616)	28	2837 (2052)		10.74%	-0.21[-0.74,0.31]
Ott 2009	123	-0.3 (11.6)	60	-0.9 (2.5)		13.65%	0.07[-0.24,0.38]
Pajno 2003	14	10.3 (7.3)	13	26.3 (16.5)		7.17%	-1.23[-2.07,-0.4]
Palma Carlos 2006	17	15.4 (33)	16	44.6 (65.1)		8.6%	-0.56[-1.26,0.14]
Passalacqua 2006	28	110 (44)	28	166 (35)		9.92%	-1.39[-1.98,-0.8]
Rolinck-Werninghaus 2004	39	2.5 (3.6)	38	2.9 (3.9)		11.8%	-0.08[-0.53,0.36]
Tonnel 2004	10	18.2 (22.4)	12	12.6 (16.1)		7.08%	0.28[-0.57,1.12]
Valovirta 2006	27	2.9 (3.4)	29	3.9 (4.6)		10.72%	-0.24[-0.77,0.28]
Total * **	**338**		**277**			**100%**	**-0.34[-0.64,-0.04]**

Heterogeneity: Tau^2=0.15; Chi^2=27.13, df=9(P=0); I^2=66.83%

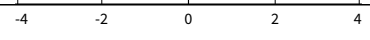
Test for overall effect: Z=2.23(P=0.03)

Comparison 9. Major allergen content < 5 mcg

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	8	275	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.69, 0.05]
2 Medication scores	6	219	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.94, -0.24]

Analysis 9.1. Comparison 9 Major allergen content < 5 mcg, Outcome 1 Allergic rhinitis symptom scores.

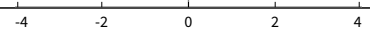
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
D'Ambrosio 1999	14	509 (514.2)	16	897.1 (678.2)		12.21%	-0.62[-1.36,0.12]
Hirsch 1997	11	1 (1.1)	10	0.5 (0.5)		10.19%	0.51[-0.36,1.39]
Marcucci 2005	13	412.9 (332.6)	11	517.3 (548.2)		11.14%	-0.23[-1.03,0.58]
Pajno 2003	14	4 (5.2)	13	10 (8.7)		11.36%	-0.82[-1.62,-0.03]
Panzner 2008	20	111.4 (114.9)	15	321.6 (211.2)		12.17%	-1.26[-2,-0.52]
Passalacqua 1999	15	189 (113)	15	191 (108)		12.56%	-0.02[-0.73,0.7]
Rolinck-Werninghaus 2004	39	13.7 (23.1)	38	12.7 (21.7)		17.66%	0.05[-0.4,0.49]
Troise 1995	15	87 (76)	16	102 (58)		12.71%	-0.22[-0.92,0.49]
Total ***	**141**		**134**			**100%**	**-0.32[-0.69,0.05]**
Heterogeneity: Tau^2=0.15; Chi^2=15.18, df=7(P=0.03); I^2=53.87%							
Test for overall effect: Z=1.69(P=0.09)							



Favours treatment — Favours control

Analysis 9.2. Comparison 9 Major allergen content < 5 mcg, Outcome 2 Medication scores.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
D'Ambrosio 1999	14	48.1 (46.6)	16	124.4 (121)		15.12%	-0.79[-1.54,-0.04]
Marcucci 2005	13	21.9 (30.5)	11	67.5 (83.8)		12.92%	-0.72[-1.56,0.11]
Pajno 2003	14	10.3 (7.3)	13	26.3 (16.5)		12.9%	-1.23[-2.07,-0.4]
Passalacqua 1999	15	42 (49.5)	15	83 (65)		15.37%	-0.69[-1.43,0.05]
Rolinck-Werninghaus 2004	39	2.5 (3.6)	38	2.9 (3.9)		27.74%	-0.08[-0.53,0.36]
Troise 1995	15	17 (21)	16	33 (33)		15.96%	-0.56[-1.28,0.16]
Total ***	**110**		**109**			**100%**	**-0.59[-0.94,-0.24]**
Heterogeneity: Tau^2=0.06; Chi^2=7.43, df=5(P=0.19); I^2=32.73%							
Test for overall effect: Z=3.34(P=0)							



Favours treatment — Favours control

Comparison 10. Major allergen content 5 to 20 mcg

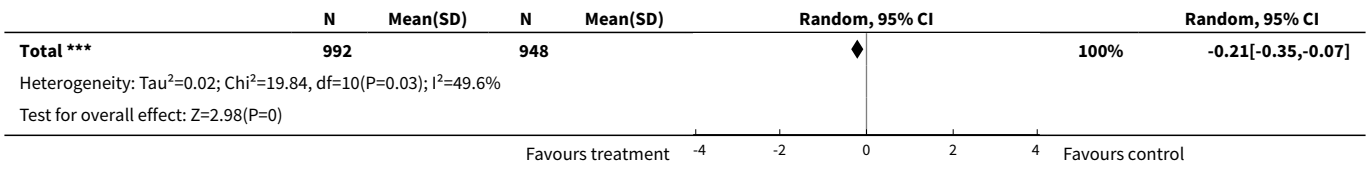
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	12	1972	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.45, -0.24]
2 Medication scores	11	1940	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.35, -0.07]

Analysis 10.1. Comparison 10 Major allergen content 5 to 20 mcg, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	3.8 (4.9)	17	3.7 (2.7)		2.48%	0.03[-0.63,0.68]
Bufe 2004	68	1.5 (0.8)	64	1.6 (1)		7.99%	-0.06[-0.4,0.28]
Bufe 2009	117	2.7 (2.4)	121	3.2 (2.1)		12.63%	-0.22[-0.48,0.03]
Dahl 2006a	61	2.1 (1.7)	32	3.3 (2.2)		5.2%	-0.63[-1.07,-0.19]
Dahl 2006b	282	2.4 (1.6)	286	3.4 (2.2)		21.66%	-0.52[-0.69,-0.35]
Drachenberg 2001	37	29.5 (24.2)	12	36.4 (30.4)		2.49%	-0.26[-0.92,0.39]
Dubakiene 2003	47	0.5 (0.3)	53	0.6 (0.4)		6.17%	-0.42[-0.82,-0.03]
Durham 2006	131	2.5 (2.1)	129	3 (2.1)		13.46%	-0.23[-0.47,0.02]
Guez 2000	36	2.3 (1.9)	36	3.2 (2.4)		4.63%	-0.41[-0.88,0.06]
Pradalier 1999	63	2.3 (1.6)	63	2.7 (2)		7.67%	-0.18[-0.53,0.17]
Wahn 2009	131	3.3 (2.9)	135	4.5 (2.9)		13.51%	-0.43[-0.68,-0.19]
Wessner 2001	14	0.3 (0.3)	18	0.5 (0.4)		2.1%	-0.56[-1.27,0.16]
Total ***	**1006**		**966**			**100%**	**-0.34[-0.45,-0.24]**
Heterogeneity: Tau^2=0.01; Chi^2=13.52, df=11(P=0.26); I^2=18.61%							
Test for overall effect: Z=6.35(P<0.0001)							

Analysis 10.2. Comparison 10 Major allergen content 5 to 20 mcg, Outcome 2 Medication scores.

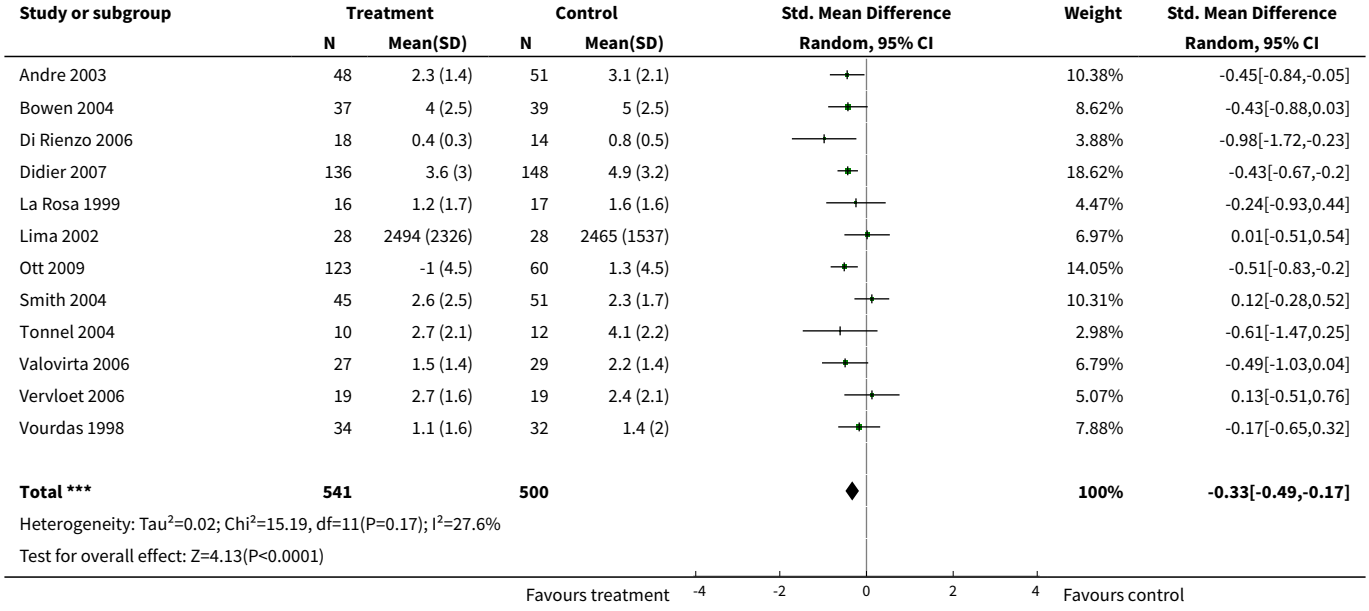
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	0.4 (1.2)	17	0.1 (0.2)		3.68%	0.33[-0.33,0.99]
Bufe 2004	68	0.2 (0.2)	64	0.2 (0.2)		9.16%	0.31[-0.03,0.66]
Bufe 2009	117	2.1 (3.5)	121	2.5 (3)		12.23%	-0.12[-0.38,0.13]
Dahl 2006a	61	2.4 (3.9)	32	4.2 (4.1)		6.91%	-0.45[-0.88,-0.02]
Dahl 2006b	282	1.5 (1.9)	286	2.4 (2.5)		15.94%	-0.4[-0.57,-0.24]
Drachenberg 2001	37	12.5 (18.7)	12	23.8 (26.4)		3.67%	-0.54[-1.2,0.12]
Dubakiene 2003	47	0.1 (0.2)	53	0.2 (0.2)		7.8%	-0.22[-0.61,0.17]
Durham 2006	131	1.4 (2.1)	129	2 (2.4)		12.63%	-0.28[-0.52,-0.03]
Guez 2000	36	4.1 (5.5)	36	6.1 (6.8)		6.27%	-0.32[-0.79,0.15]
Pradalier 1999	63	1.8 (2.3)	63	2.1 (2.7)		8.98%	-0.14[-0.49,0.21]
Wahn 2009	131	0.6 (0.6)	135	0.8 (0.6)		12.73%	-0.3[-0.54,-0.06]



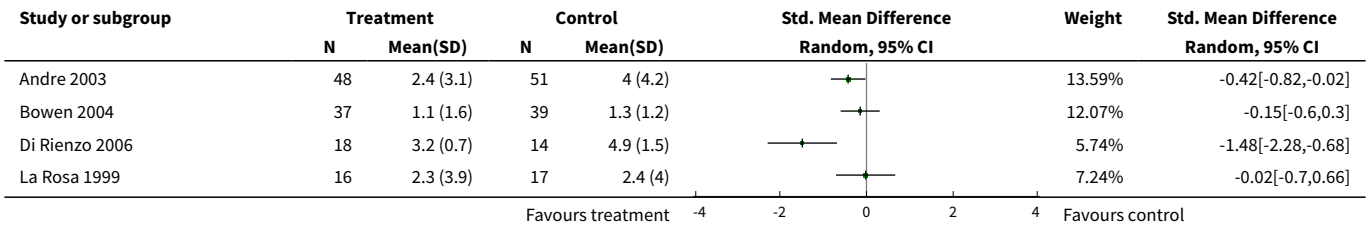
Comparison 11. Major allergen content > 20 mcg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	12	1041	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.49, -0.17]
2 Medication scores	10	661	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.43, 0.00]

Analysis 11.1. Comparison 11 Major allergen content > 20 mcg, Outcome 1 Allergic rhinitis symptom scores.



Analysis 11.2. Comparison 11 Major allergen content > 20 mcg, Outcome 2 Medication scores.



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Lima 2002	28	2334 (2616)	28	2837 (2052)		10.18%	-0.21[-0.74,0.31]
Ott 2009	123	-0.3 (11.6)	60	-0.9 (2.5)		16.61%	0.07[-0.24,0.38]
Tonnel 2004	10	18.2 (22.4)	12	12.6 (16.1)		5.27%	0.28[-0.57,1.12]
Valovirta 2006	27	2.9 (3.4)	29	3.9 (4.6)		10.17%	-0.24[-0.77,0.28]
Vervloet 2006	19	3.4 (3.9)	19	4.7 (5)		7.93%	-0.29[-0.93,0.35]
Vourdas 1998	34	1.4 (3.4)	32	1.8 (3.9)		11.21%	-0.1[-0.59,0.38]
Total ***	**360**		**301**			**100%**	**-0.22[-0.43,0]**
Heterogeneity: Tau²=0.05; Chi²=15.7, df=9(P=0.07); I²=42.69%							
Test for overall effect: Z=1.94(P=0.05)							

Favours treatment -4 -2 0 2 4 Favours control

Comparison 12. SLIT versus placebo - immunoglobulins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IgE levels - post-treatment	14	1334	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.01, 0.55]
2 IgG levels - post-treatment	3	590	Std. Mean Difference (IV, Random, 95% CI)	0.95 [0.78, 1.12]
3 IgG4 levels- post-treatment	13	1187	Mean Difference (IV, Fixed, 95% CI)	0.46 [0.29, 0.63]

Analysis 12.1. Comparison 12 SLIT versus placebo - immunoglobulins, Outcome 1 IgE levels - post-treatment.

Study or subgroup	Placebo N	Placebo Mean(SD)	SLIT N	SLIT Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	24.3 (32.2)	17	11.6 (16.6)		6.28%	0.48[-0.19,1.14]
Bowen 2004	35	41.1 (36.8)	39	25.5 (27.5)		7.72%	0.48[0.02,0.94]
Bufe 2004	68	63.3 (113.6)	64	47.8 (93.5)		8.57%	0.15[-0.19,0.49]
D'Ambrosio 1999	14	19.3 (24.7)	16	22.2 (20.3)		5.92%	-0.13[-0.84,0.59]
Durham 2006	133	99.5 (129.4)	130	40.7 (53.1)		9.14%	0.59[0.34,0.84]
Guez 2000	36	48.2 (59)	36	40.5 (52.3)		7.73%	0.14[-0.33,0.6]
Hirsch 1997	15	75.7 (26.6)	15	48.3 (29.7)		5.65%	0.95[0.19,1.71]
Lima 2002	28	415 (317)	28	246 (275)		7.2%	0.56[0.03,1.1]
Marcucci 2005	13	38 (32.4)	11	19.5 (16.1)		5.22%	0.68[-0.15,1.51]
Peter 2009	189	43863 (106216)	176	140862 (254114)		9.34%	-0.5[-0.71,-0.29]
Pradalier 1999	63	244 (459)	63	144 (231)		8.51%	0.27[-0.08,0.62]
Rolinck-Werninghaus 2004	37	88.8 (24)	36	72.2 (33.9)		7.69%	0.56[0.09,1.03]
Tonnel 2004	10	116.8 (228.1)	12	61 (59)		5.12%	0.34[-0.51,1.18]
Troise 1995	15	10.5 (5.7)	16	13.7 (5.7)		5.91%	-0.55[-1.27,0.17]
Total ***	**675**		**659**			**100%**	**0.27[-0.01,0.55]**

Favours SLIT -10 -5 0 5 10 Favours Placebo

Study or subgroup	Placebo N	Placebo Mean(SD)	SLIT N	SLIT Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Heterogeneity: Tau²=0.2; Chi²=68.63, df=13(P<0.0001); I²=81.06%							
Test for overall effect: Z=1.92(P=0.05)							

Favours SLIT -10 -5 0 5 10 Favours Placebo

Analysis 12.2. Comparison 12 SLIT versus placebo - immunoglobulins, Outcome 2 IgG levels - post-treatment.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Durham 2006	95	0.1 (0.1)	99	0 (0)		32.15%	1.05[0.75,1.36]
Peter 2009	176	6.5 (8.4)	189	0.9 (2.6)		62.37%	0.92[0.7,1.13]
Troise 1995	15	34.6 (7.9)	16	28.1 (10.1)		5.48%	0.7[-0.03,1.42]
Total ***	**286**		**304**			**100%**	**0.95[0.78,1.12]**
Heterogeneity: Tau²=0; Chi²=1.01, df=2(P=0.6); I²=0%							
Test for overall effect: Z=10.92(P<0.0001)							

Favours placebo -4 -2 0 2 4 Favours SLIT

Analysis 12.3. Comparison 12 SLIT versus placebo - immunoglobulins, Outcome 3 IgG4 levels- post-treatment.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Amar 2009	19	0.5 (0.8)	17	0.4 (0.9)		9.39%	0.08[-0.48,0.64]
Bowen 2004	35	6 (10)	39	0.4 (0.7)		0.27%	5.54[2.23,8.85]
Bufe 2004	68	65 (105.3)	64	22.6 (21.4)		0%	42.42[16.84,68]
D'Ambrosio 1999	14	2.6 (0.4)	16	2.6 (0.7)		18.4%	0.01[-0.39,0.41]
de Blay 2003	53	0.8 (0.9)	51	0.3 (0.3)		44.48%	0.54[0.28,0.8]
Guez 2000	36	4.8 (1.8)	36	5 (2.3)		3.27%	-0.2[-1.15,0.75]
Lima 2002	28	8.6 (8.3)	28	2.6 (3.1)		0.28%	6[2.73,9.27]
Peter 2009	176	995.6 (1736)	189	208.5 (719.5)		0%	787.11[510.88,1063.34]
Pradalier 1999	63	8.7 (10.9)	63	6.8 (4.5)		0.35%	1.9[-1.01,4.81]
Rolinck-Werninghaus 2004	37	1.2 (0.8)	36	0.9 (0.9)		21.69%	0.28[-0.09,0.65]
Tari 1990	34	10.7 (3.8)	32	2.8 (2)		1.4%	7.93[6.47,9.39]
Tonnel 2004	10	7.4 (4.3)	12	5.3 (1.7)		0.37%	2.12[-0.72,4.96]
Troise 1995	15	27.8 (8.2)	16	28.2 (7.1)		0.1%	-0.4[-5.82,5.02]
Total ***	**588**		**599**			**100%**	**0.46[0.29,0.63]**
Heterogeneity: Tau²=0; Chi²=174.24, df=12(P<0.0001); I²=93.11%							
Test for overall effect: Z=5.26(P<0.0001)							

Favours placebo -10 -5 0 5 10 Favours SLIT

Comparison 13. SLIT v placebo - house dust mite

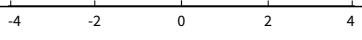
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	9	464	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-1.80, -0.13]
2 Medication scores	5	189	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.09, 0.05]

Analysis 13.1. Comparison 13 SLIT v placebo - house dust mite, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	0.5 (0.4)	7	0.4 (0.4)		10.36%	0.31[-0.71,1.34]
Cao 2007	85	0.7 (0.9)	91	2.6 (0.5)		11.88%	-2.85[-3.27,-2.43]
Guez 2000	36	2.3 (1.9)	36	3.2 (2.4)		11.8%	-0.41[-0.88,0.06]
Hirsch 1997	12	1 (1.1)	10	0.5 (0.5)		10.86%	0.5[-0.35,1.36]
Marcucci 2005	13	412.9 (332.6)	11	517.3 (548.2)		11%	-0.23[-1.03,0.58]
Passalacqua 1998	10	59.6 (27.8)	9	109.1 (45.7)		10.4%	-1.27[-2.28,-0.26]
Passalacqua 2006	28	1.8 (0.2)	28	2.2 (0.2)		11.5%	-1.65[-2.26,-1.04]
Tari 1990	30	8 (1.5)	28	12 (2)		11.37%	-2.24[-2.91,-1.58]
Tonnel 2004	10	2.7 (2.1)	12	4.1 (2.2)		10.84%	-0.61[-1.47,0.25]
Total * **	**232**		**232**			**100%**	**-0.97[-1.8,-0.13]**

Heterogeneity: Tau^2=1.49; Chi^2=110.42, df=8(P<0.0001); I^2=92.76%

Test for overall effect: Z=2.26(P=0.02)

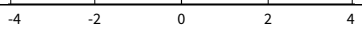


Analysis 13.2. Comparison 13 SLIT v placebo - house dust mite, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Bahceciler 2001	8	1.3 (1)	7	1.6 (1.3)		15.38%	-0.26[-1.28,0.76]
Guez 2000	36	4.1 (5.5)	36	6.1 (6.8)		25.16%	-0.32[-0.79,0.15]
Marcucci 2005	13	21.9 (30.5)	11	67.5 (83.8)		18.38%	-0.72[-1.56,0.11]
Passalacqua 2006	28	110 (44)	28	166 (35)		22.88%	-1.39[-1.98,-0.8]
Tonnel 2004	10	18.2 (22.4)	12	12.6 (16.1)		18.2%	0.28[-0.57,1.12]
Total * **	**95**		**94**			**100%**	**-0.52[-1.09,0.05]**

Heterogeneity: Tau^2=0.28; Chi^2=12.92, df=4(P=0.01); I^2=69.05%

Test for overall effect: Z=1.79(P=0.07)

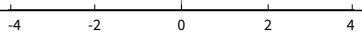


Comparison 14. SLIT versus placebo - grass pollen

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	23	3013	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.45, -0.24]
2 Medication scores	17	2308	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.37, -0.10]

Analysis 14.1. Comparison 14 SLIT versus placebo - grass pollen, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	3.8 (4.9)	17	3.7 (2.7)		2.19%	0.03[-0.63,0.68]
Bufe 2004	68	1.5 (0.8)	64	1.6 (1)		5.33%	-0.06[-0.4,0.28]
Bufe 2009	117	2.7 (2.4)	121	3.2 (2.1)		6.98%	-0.22[-0.48,0.03]
Caffarelli 2000	17	4.2 (3.7)	17	5.9 (3.8)		2.05%	-0.44[-1.12,0.24]
Dahl 2006a	61	2.1 (1.7)	32	3.3 (2.2)		3.96%	-0.63[-1.07,-0.19]
Dahl 2006b	282	2.4 (1.6)	286	3.4 (2.2)		8.98%	-0.52[-0.69,-0.35]
de Blay 2003	33	20.6 (15.9)	42	23.5 (18.8)		3.75%	-0.17[-0.62,0.29]
Didier 2007	136	3.6 (3)	148	4.9 (3.2)		7.4%	-0.43[-0.67,-0.2]
Drachenberg 2001	19	25.2 (19.9)	7	37.4 (37)		1.33%	-0.47[-1.34,0.41]
Durham 2006	131	2.5 (2.1)	129	3 (2.1)		7.22%	-0.23[-0.47,0.02]
Feliziani 1995	18	109.7 (92.5)	16	215.8 (114.2)		1.88%	-1[-1.72,-0.28]
Hordijk 1998	35	3.2 (3.1)	36	5.1 (3.6)		3.55%	-0.57[-1.04,-0.09]
Lima 2002	28	2494 (2326)	28	2465 (1537)		3.09%	0.01[-0.51,0.54]
Ott 2009	123	-1 (4.5)	60	1.3 (4.5)		5.82%	-0.51[-0.83,-0.2]
Palma Carlos 2006	17	31.2 (32.6)	16	55.9 (50.5)		1.97%	-0.57[-1.27,0.13]
Panzner 2008	20	111.4 (114.9)	15	321.6 (211.2)		1.79%	-1.26[-2,-0.52]
Pfaar 2008	42	146.2 (123)	48	236.2 (133.6)		4.1%	-0.69[-1.12,-0.27]
Pradalier 1999	63	2.3 (1.6)	63	2.7 (2)		5.19%	-0.18[-0.53,0.17]
Rolinck-Werninghaus 2004	39	13.7 (23.1)	38	12.7 (21.7)		3.86%	0.05[-0.4,0.49]
Röder 2007	91	2.5 (1.5)	77	2.7 (1.7)		5.99%	-0.18[-0.49,0.12]
Smith 2004	45	2.6 (2.5)	51	2.3 (1.7)		4.43%	0.12[-0.28,0.52]
Wahn 2009	131	3.3 (2.9)	135	4.5 (2.9)		7.23%	-0.43[-0.68,-0.19]
Wessner 2001	14	0.3 (0.3)	18	0.5 (0.4)		1.9%	-0.56[-1.27,0.16]
Total ***	**1549**		**1464**			**100%**	**-0.35[-0.45,-0.24]**
Heterogeneity: Tau^2=0.03; Chi^2=39.58, df=22(P=0.01); I^2=44.42%							
Test for overall effect: Z=6.27(P<0.0001)							

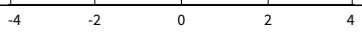


Analysis 14.2. Comparison 14 SLIT versus placebo - grass pollen, Outcome 2 Medication scores.

Study or subgroup	SLIT N	SLIT Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Amar 2009	19	0.4 (1.2)	17	0.1 (0.2)		3.23%	0.33[-0.33,0.99]
Bufe 2004	68	0.2 (0.2)	64	0.2 (0.2)		7.13%	0.31[-0.03,0.66]
Bufe 2009	117	2.1 (3.5)	121	2.5 (3)		8.94%	-0.12[-0.38,0.13]
Caffarelli 2000	17	8.1 (6.4)	17	9 (6.9)		3.13%	-0.13[-0.81,0.54]
Dahl 2006a	61	2.4 (3.9)	32	4.2 (4.1)		5.64%	-0.45[-0.88,-0.02]
Dahl 2006b	282	1.5 (1.9)	286	2.4 (2.5)		10.87%	-0.4[-0.57,-0.24]
de Blay 2003	33	3.5 (5.4)	42	7.6 (8.2)		5.18%	-0.57[-1.03,-0.1]
Drachenberg 2001	19	9.6 (19.9)	7	24.3 (31.4)		2.02%	-0.61[-1.5,0.27]
Durham 2006	131	1.4 (2.1)	129	2 (2.4)		9.16%	-0.28[-0.52,-0.03]
Feliziani 1995	18	24.1 (25.7)	16	75.9 (50.3)		2.66%	-1.29[-2.04,-0.54]
Hordijk 1998	35	0.2 (0.4)	36	0.3 (0.5)		5.13%	-0.36[-0.83,0.11]
Lima 2002	28	2334 (2616)	28	2837 (2052)		4.45%	-0.21[-0.74,0.31]
Ott 2009	123	-0.3 (11.6)	60	-0.9 (2.5)		7.8%	0.07[-0.24,0.38]
Palma Carlos 2006	17	15.4 (33)	16	44.6 (65.1)		2.97%	-0.56[-1.26,0.14]
Pradalier 1999	63	1.8 (2.3)	63	2.1 (2.7)		7.02%	-0.14[-0.49,0.21]
Rolinck-Werninghaus 2004	39	2.5 (3.6)	38	2.9 (3.9)		5.44%	-0.08[-0.53,0.36]
Wahn 2009	131	0.6 (0.6)	135	0.8 (0.6)		9.22%	-0.3[-0.54,-0.06]
Total * **	**1201**		**1107**			**100%**	**-0.23[-0.37,-0.1]**

Heterogeneity: Tau^2=0.04; Chi^2=34.55, df=16(P=0); I^2=53.69%

Test for overall effect: Z=3.36(P=0)



Comparison 15. SLIT versus placebo - ragweed

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	2	175	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.74, -0.14]
2 Medication scores	2	175	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.60, -0.00]

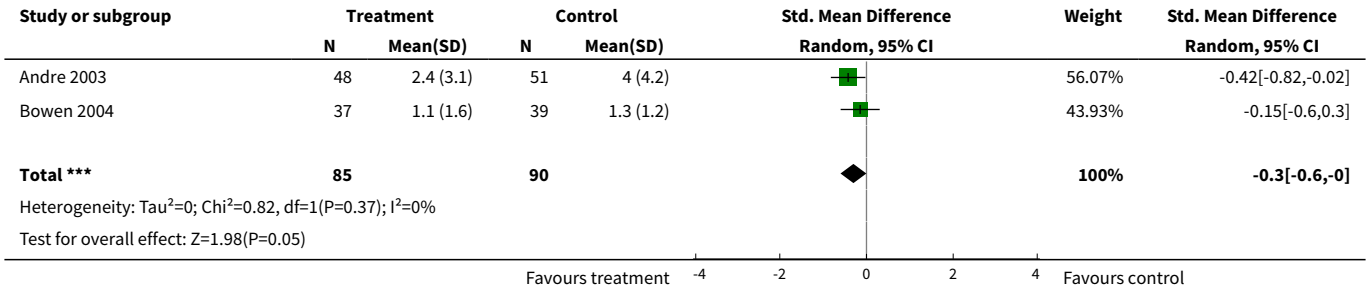
Analysis 15.1. Comparison 15 SLIT versus placebo - ragweed, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Andre 2003	48	2.3 (1.4)	51	3.1 (2.1)		56.53%	-0.45[-0.84,-0.05]
Bowen 2004	37	4 (2.5)	39	5 (2.5)		43.47%	-0.43[-0.88,0.03]
Total * **	**85**		**90**			**100%**	**-0.44[-0.74,-0.14]**

Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.96); I^2=0%

Test for overall effect: Z=2.86(P=0)

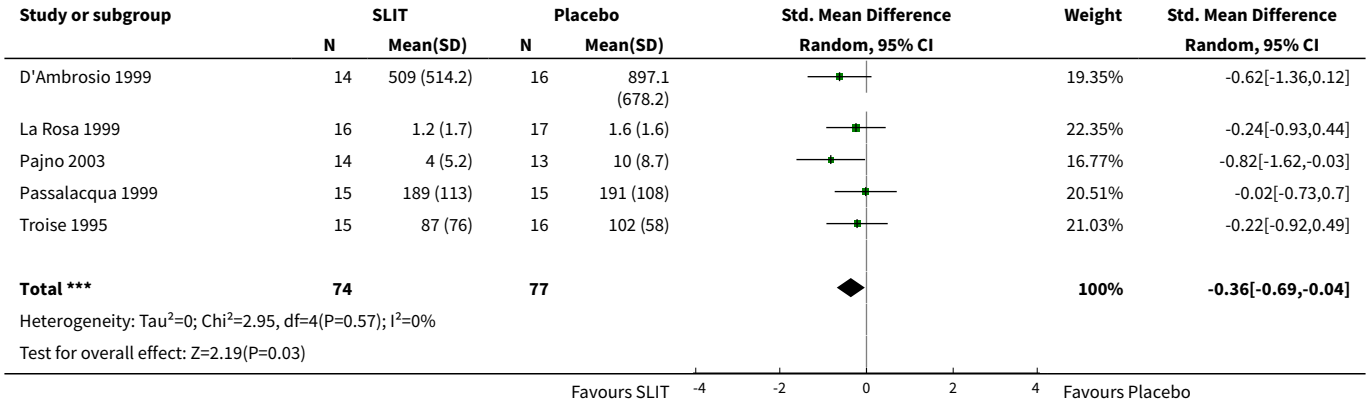
Analysis 15.2. Comparison 15 SLIT versus placebo - ragweed, Outcome 2 Medication scores.



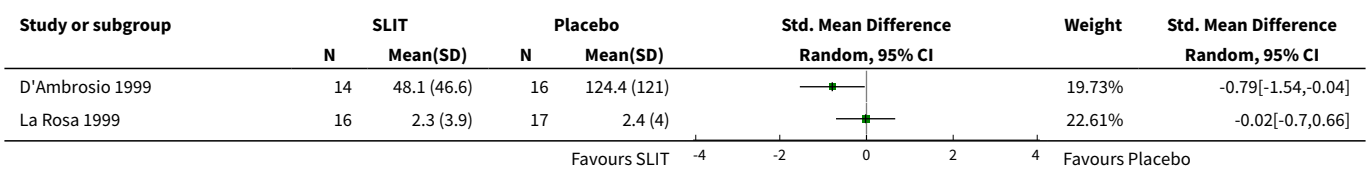
Comparison 16. SLIT versus placebo - Parietaria

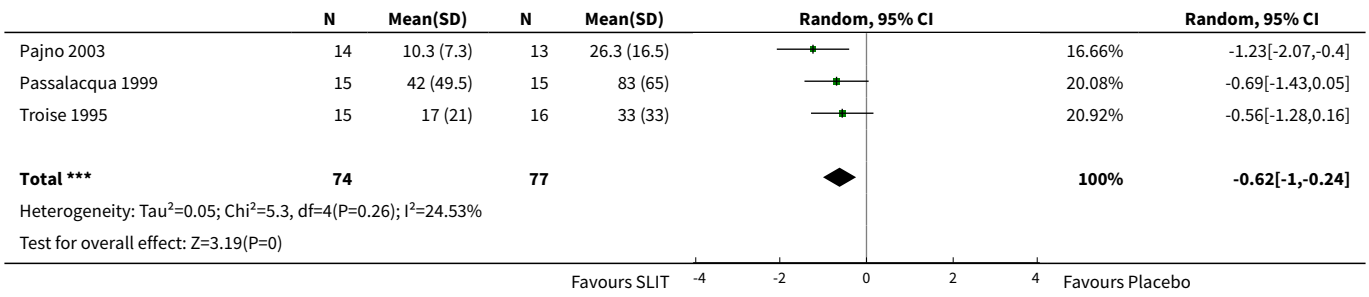
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	5	151	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.69, -0.04]
2 Medication scores	5	151	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-1.00, -0.24]

Analysis 16.1. Comparison 16 SLIT versus placebo - Parietaria, Outcome 1 Allergic rhinitis symptom scores.



Analysis 16.2. Comparison 16 SLIT versus placebo - Parietaria, Outcome 2 Medication scores.

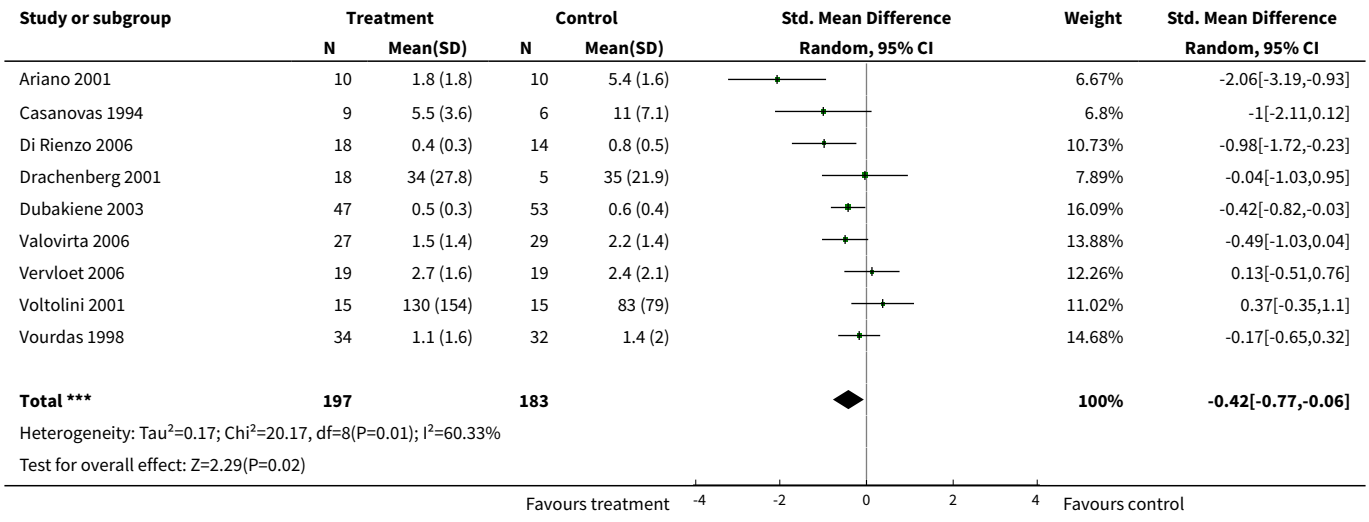




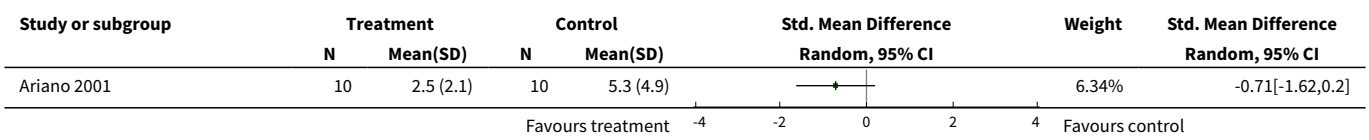
Comparison 17. SLIT versus placebo - tree

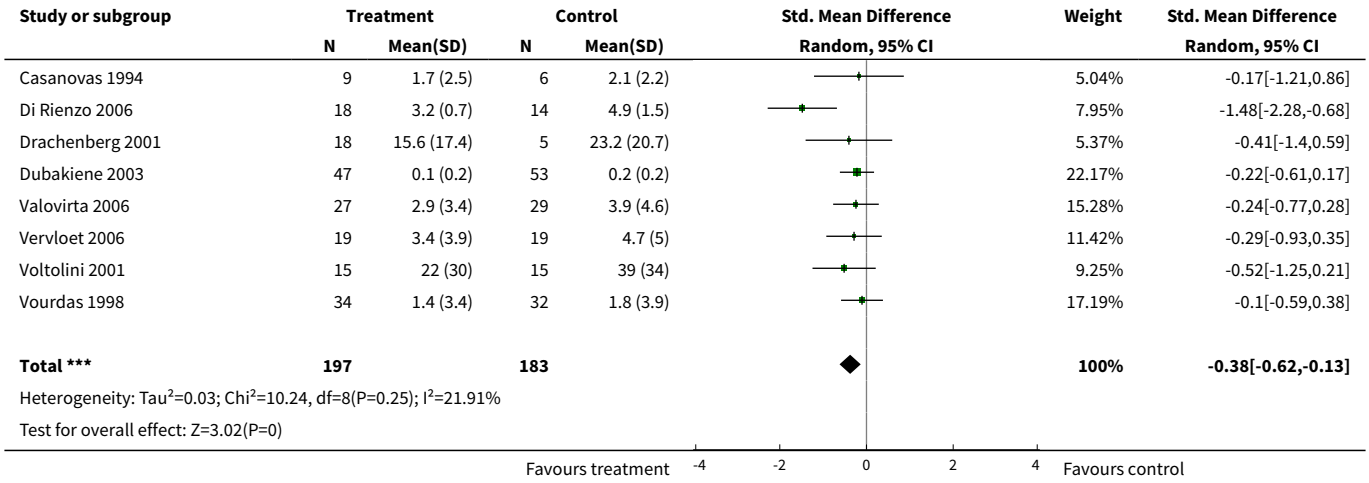
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	9	380	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.77, -0.06]
2 Medication scores	9	380	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.62, -0.13]

Analysis 17.1. Comparison 17 SLIT versus placebo - tree, Outcome 1 Allergic rhinitis symptom scores.



Analysis 17.2. Comparison 17 SLIT versus placebo - tree, Outcome 2 Medication scores.

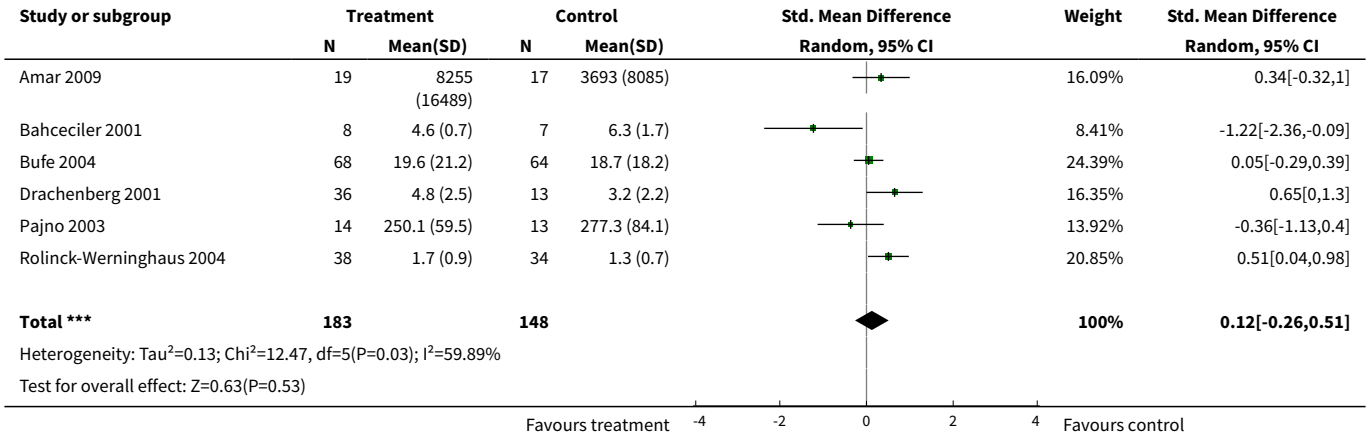




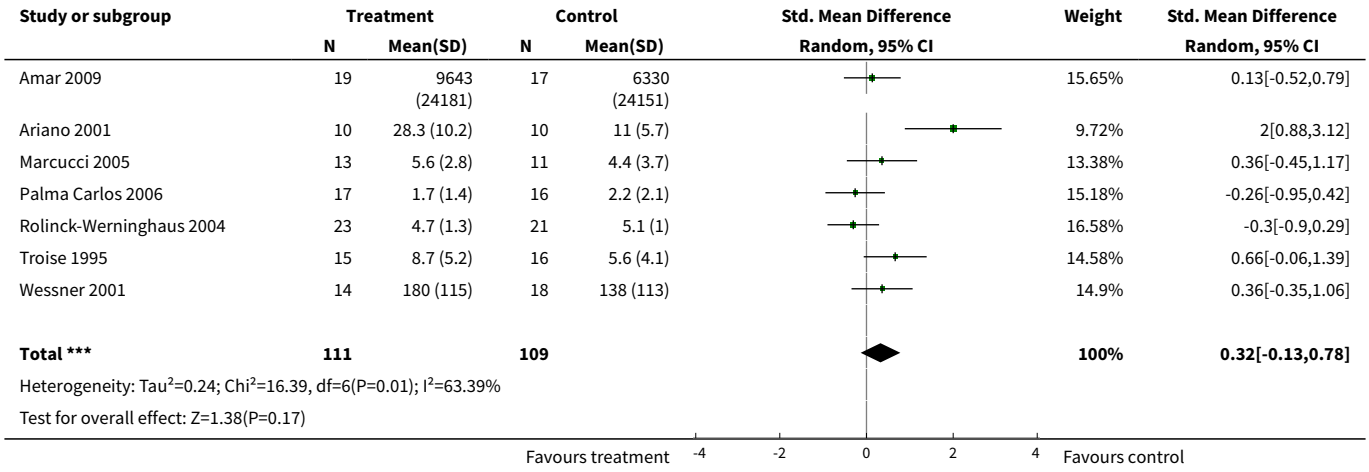
Comparison 18. Allergen sensitivity

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Skin reactivity after treatment	6	331	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.26, 0.51]
2 Nasal reactivity after treatment	7	220	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-0.13, 0.78]

Analysis 18.1. Comparison 18 Allergen sensitivity, Outcome 1 Skin reactivity after treatment.



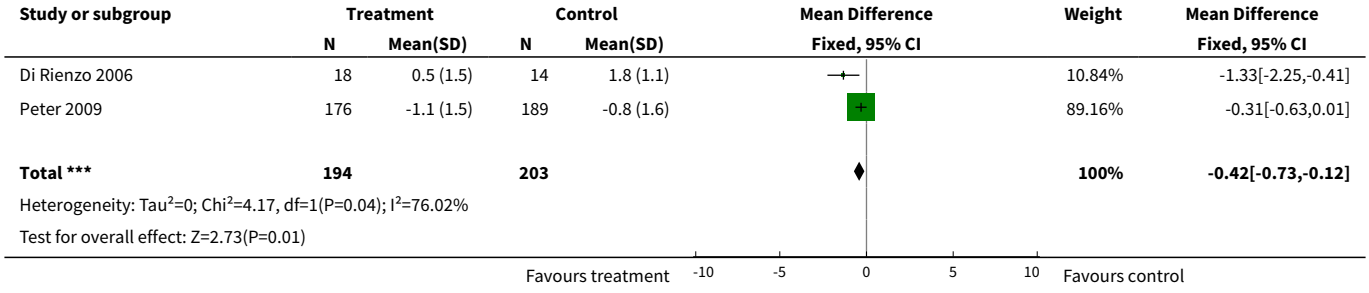
Analysis 18.2. Comparison 18 Allergen sensitivity, Outcome 2 Nasal reactivity after treatment.



Comparison 19. Quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adults	2	397	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.73, -0.12]

Analysis 19.1. Comparison 19 Quality of life, Outcome 1 Adults.



Comparison 20. SLIT versus placebo - tablets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	11	1881	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.58, -0.38]
2 Medication scores	9	1578	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.46, -0.20]

Analysis 20.1. Comparison 20 SLIT versus placebo - tablets, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	Experimental		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bufe 2009	117	2.7 (2.4)	121	3.2 (2.1)		2.99%	-0.5[-1.08,0.08]
Caffarelli 2000	17	4.2 (3.7)	17	5.9 (3.8)		0.16%	-1.7[-4.22,0.82]
Dahl 2006a	61	2.1 (1.7)	32	3.3 (2.2)		1.3%	-1.2[-2.07,-0.33]
Dahl 2006b	282	2.4 (1.6)	286	3.4 (2.2)		9.93%	-1[-1.32,-0.68]
Didier 2007	136	3.6 (3)	148	4.9 (3.2)		1.9%	-1.35[-2.07,-0.63]
Durham 2006	131	2.5 (2.1)	129	3 (2.1)		3.82%	-0.48[-0.99,0.03]
Palma Carlos 2006	17	31.2 (32.6)	16	55.9 (50.5)		0%	-24.71[-53.9,4.48]
Passalacqua 1998	10	59.6 (27.8)	9	109.1 (45.7)		0%	-49.5[-83.97,-15.03]
Passalacqua 1999	15	189 (113)	15	191 (108)		0%	-2[-81.1,77.1]
Passalacqua 2006	28	1.8 (0.2)	28	2.2 (0.2)		77.84%	-0.36[-0.47,-0.25]
Wahn 2009	131	3.3 (2.9)	135	4.5 (2.9)		2.05%	-1.26[-1.96,-0.56]
Total ***	**945**		**936**			**100%**	**-0.48[-0.58,-0.38]**
Heterogeneity: Tau^2=0; Chi^2=39.07, df=10(P<0.0001); I^2=74.41%							
Test for overall effect: Z=9.51(P<0.0001)							

Analysis 20.2. Comparison 20 SLIT versus placebo - tablets, Outcome 2 Medication scores.

Study or subgroup	SLIT		placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bufe 2009	117	2.1 (3.5)	121	2.5 (3)		2.57%	-0.4[-1.23,0.43]
Caffarelli 2000	17	8.1 (6.4)	17	9 (6.9)		0.09%	-0.9[-5.37,3.57]
Dahl 2006a	61	2.4 (3.9)	32	4.2 (4.1)		0.6%	-1.8[-3.53,-0.07]
Dahl 2006b	282	1.5 (1.9)	286	2.4 (2.5)		13.32%	-0.9[-1.26,-0.54]
Durham 2006	131	1.4 (2.1)	129	2 (2.4)		5.85%	-0.63[-1.18,-0.08]
Palma Carlos 2006	17	15.4 (33)	16	44.6 (65.1)		0%	-29.19[-64.71,6.33]
Passalacqua 1999	15	42 (49.5)	15	83 (65)		0%	-41[-82.35,0.35]
Passalacqua 2006	28	110 (44)	28	166 (35)		0%	-56[-76.82,-35.18]
Wahn 2009	131	0.6 (0.6)	135	0.8 (0.6)		77.57%	-0.19[-0.34,-0.04]
Total ***	**799**		**779**			**100%**	**-0.33[-0.46,-0.2]**
Heterogeneity: Tau^2=0; Chi^2=50.39, df=8(P<0.0001); I^2=84.12%							
Test for overall effect: Z=4.84(P<0.0001)							

Comparison 21. SLIT versus placebo - drops

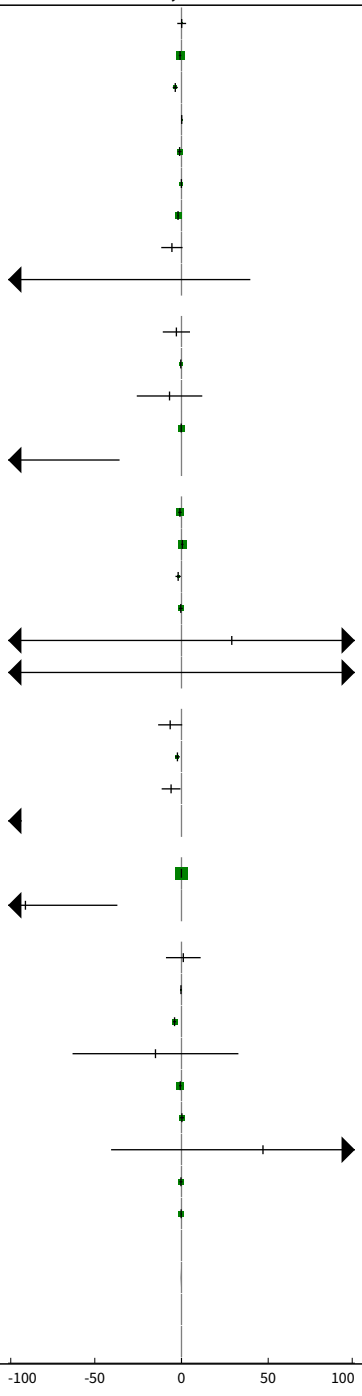
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allergic rhinitis symptom scores	35	2464	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.42, -0.28]
2 Medication scores	27	1653	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.05, 0.04]

Analysis 21.1. Comparison 21 SLIT versus placebo - drops, Outcome 1 Allergic rhinitis symptom scores.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Amar 2009	19	3.8 (4.9)	17	3.7 (2.7)		0.07%	0.12[-2.43,2.67]
Andre 2003	48	2.3 (1.4)	51	3.1 (2.1)		0.87%	-0.82[-1.53,-0.11]
Ariano 2001	10	1.8 (1.8)	10	5.4 (1.6)		0.21%	-3.58[-5.04,-2.12]
Bahceciler 2001	8	0.5 (0.4)	7	0.4 (0.4)		2.81%	0.13[-0.27,0.53]
Bowen 2004	37	4 (2.5)	39	5 (2.5)		0.35%	-1.08[-2.2,0.04]
Bufe 2004	68	1.5 (0.8)	64	1.6 (1)		4.94%	-0.05[-0.35,0.25]
Cao 2007	85	0.7 (0.9)	91	2.6 (0.5)		9.99%	-1.99[-2.2,-1.78]
Casanovas 1994	9	5.5 (3.6)	6	11 (7.1)		0.01%	-5.52[-11.66,0.62]
D'Ambrosio 1999	14	509 (514.2)	16	897.1 (678.2)		0%	-388.06[-815.82,39.7]
de Blay 2003	33	20.6 (15.9)	42	23.5 (18.8)		0.01%	-2.94[-10.79,4.91]
Di Rienzo 2006	18	0.4 (0.3)	14	0.8 (0.5)		5%	-0.4[-0.7,-0.1]
Drachenberg 2001	37	29.5 (24.2)	12	36.4 (30.4)		0%	-6.9[-25.79,11.99]
Dubakiene 2003	47	0.5 (0.3)	53	0.6 (0.4)		21.13%	-0.16[-0.3,-0.02]
Feliziani 1995	18	109.7 (92.5)	16	215.8 (114.2)		0%	-106.1[-176.5,-35.7]
Guez 2000	36	2.3 (1.9)	36	3.2 (2.4)		0.44%	-0.9[-1.9,0.1]
Hirsch 1997	12	1 (1.1)	10	0.5 (0.5)		0.89%	0.47[-0.23,1.17]
Hordijk 1998	35	3.2 (3.1)	36	5.1 (3.6)		0.18%	-1.92[-3.47,-0.37]
La Rosa 1999	16	1.2 (1.7)	17	1.6 (1.6)		0.36%	-0.4[-1.5,0.7]
Lima 2002	28	2494 (2326)	28	2465 (1537)		0%	29[-1003.65,1061.65]
Marcucci 2005	13	412.9 (332.6)	11	517.3 (548.2)		0%	-104.35[-475.32,266.62]
Nelson 1993	20	12.2 (8.7)	21	18.7 (13.6)		0.01%	-6.52[-13.46,0.42]
Ott 2009	123	-1 (4.5)	60	1.3 (4.5)		0.22%	-2.34[-3.74,-0.94]
Pajno 2003	14	4 (5.2)	13	10 (8.7)		0.01%	-6[-11.43,-0.57]
Panzner 2008	20	111.4 (114.9)	15	321.6 (211.2)		0%	-210.25[-328.41,-92.09]
Peter 2009	176	0.7 (0.5)	189	0.8 (0.5)		39.5%	-0.05[-0.15,0.06]
Pfaar 2008	42	146.2 (123)	48	236.2 (133.6)		0%	-90[-143.03,-36.97]
Rolinck-Werninghaus 2004	39	13.7 (23.1)	38	12.7 (21.7)		0%	1.05[-8.95,11.05]
Rőder 2007	91	2.5 (1.5)	77	2.7 (1.7)		1.91%	-0.29[-0.77,0.19]
Tari 1990	30	8 (1.5)	28	12 (2)		0.52%	-4[-4.91,-3.09]
Troise 1995	15	87 (76)	16	102 (58)		0%	-15[-62.82,32.82]
Valovirta 2006	27	1.5 (1.4)	29	2.2 (1.4)		0.81%	-0.7[-1.43,0.03]
Vervloet 2006	19	2.7 (1.6)	19	2.4 (2.1)		0.31%	0.24[-0.94,1.42]
Voltolini 2001	15	130 (154)	15	83 (79)		0%	47[-40.59,134.59]
Vourdas 1998	34	1.1 (1.6)	32	1.4 (2)		0.56%	-0.31[-1.2,0.58]
Wessner 2001	14	0.3 (0.3)	18	0.5 (0.4)		8.89%	-0.19[-0.41,0.03]
Total ***	**1270**		**1194**			**100%**	**-0.35[-0.42,-0.28]**

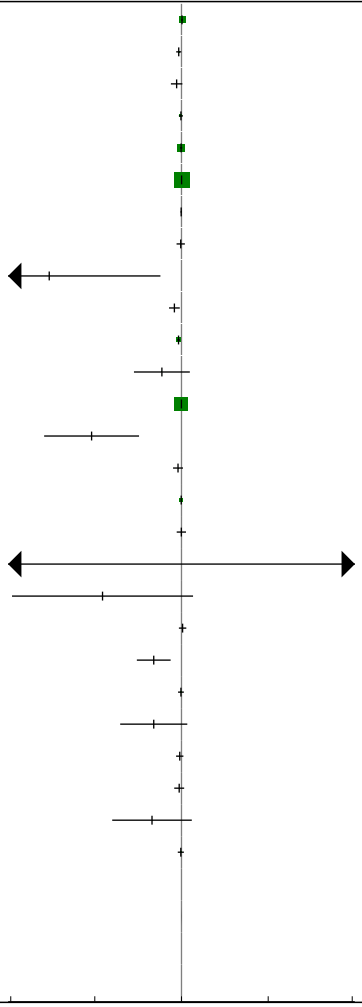
Heterogeneity: $Tau^2=0$; $Chi^2=436.12$, df=34(P<0.0001); $I^2=92.2\%$

Test for overall effect: Z=10.39(P<0.0001)



Analysis 21.2. Comparison 21 SLIT versus placebo - drops, Outcome 2 Medication scores.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Amar 2009	19	0.4 (1.2)	17	0.1 (0.2)		0.68%	0.3[-0.25,0.85]
Andre 2003	48	2.4 (3.1)	51	4 (4.2)		0.1%	-1.59[-3.05,-0.13]
Ariano 2001	10	2.5 (2.1)	10	5.3 (4.9)		0.02%	-2.8[-6.1,0.5]
Bahceciler 2001	8	1.3 (1)	7	1.6 (1.3)		0.15%	-0.32[-1.49,0.85]
Bowen 2004	37	1.1 (1.6)	39	1.3 (1.2)		0.5%	-0.21[-0.86,0.44]
Bufe 2004	68	0.2 (0.2)	64	0.2 (0.2)		49.28%	0.06[-0,0.12]
Cao 2007	85	0 (0.1)	91	0.2 (1.9)		1.33%	-0.17[-0.57,0.23]
Casanovas 1994	9	1.7 (2.5)	6	2.1 (2.2)		0.04%	-0.44[-2.84,1.96]
D'Ambrosio 1999	14	48.1 (46.6)	16	124.4 (121)		0%	-76.27[-140.39,-12.15]
de Blay 2003	33	3.5 (5.4)	42	7.6 (8.2)		0.02%	-4.09[-7.18,-1]
Di Rienzo 2006	18	3.2 (0.7)	14	4.9 (1.5)		0.29%	-1.7[-2.55,-0.85]
Drachenberg 2001	37	12.5 (18.7)	12	23.8 (26.4)		0%	-11.3[-27.41,4.81]
Dubakiene 2003	47	0.1 (0.2)	53	0.2 (0.2)		41.63%	-0.04[-0.11,0.03]
Feliziani 1995	18	24.1 (25.7)	16	75.9 (50.3)		0%	-51.84[-79.2,-24.48]
Guez 2000	36	4.1 (5.5)	36	6.1 (6.8)		0.03%	-2[-4.86,0.86]
Hordijk 1998	35	0.2 (0.4)	36	0.3 (0.5)		5.66%	-0.15[-0.34,0.04]
La Rosa 1999	16	2.3 (3.9)	17	2.4 (4)		0.03%	-0.08[-2.76,2.6]
Lima 2002	28	2334 (2616)	28	2837 (2052)		0%	-503[-1734.49,728.49]
Marcucci 2005	13	21.9 (30.5)	11	67.5 (83.8)		0%	-45.53[-97.73,6.67]
Ott 2009	123	-0.3 (11.6)	60	-0.9 (2.5)		0.05%	0.64[-1.49,2.77]
Pajno 2003	14	10.3 (7.3)	13	26.3 (16.5)		0%	-16[-25.74,-6.26]
Rolinck-Werninghaus 2004	39	2.5 (3.6)	38	2.9 (3.9)		0.07%	-0.31[-1.98,1.36]
Troise 1995	15	17 (21)	16	33 (33)		0%	-16[-35.35,3.35]
Valovirta 2006	27	2.9 (3.4)	29	3.9 (4.6)		0.05%	-1[-3.11,1.11]
Vervloet 2006	19	3.4 (3.9)	19	4.7 (5)		0.03%	-1.32[-4.18,1.54]
Voltolini 2001	15	22 (30)	15	39 (34)		0%	-17[-39.95,5.95]
Vourdas 1998	34	1.4 (3.4)	32	1.8 (3.9)		0.07%	-0.38[-2.14,1.38]
Total ***	**865**		**788**			**100%**	**-0.01[-0.05,0.04]**
Heterogeneity: Tau^2=0; Chi^2=82.89, df=26(P<0.0001); I^2=68.63%							
Test for overall effect: Z=0.33(P=0.74)							



ADDITIONAL TABLES

Table 1. Adverse events: data not suitable for analysis *(Continued)*

Study ID	Sublingual immunotherapy N	Placebo N	Additional comments
Bowen 2004	43	40	Report by SOC
Casanovas 1994	9	6	Grading according to EAACI
Cao 2007	85	91	Insufficient data

Table 1. Adverse events: data not suitable for analysis *(Continued)*

Dahl 2006a	61	32	AE reported as percentage of patients
de Blay 2003	33	42	AE reported as percentage of patients
Di Rienzo 2006	19	15	Insufficient data
Drachenberg 2001	49	19	AE reported as difference between SLIT and placebo group (P values)
Dubakiene 2003	59	60	Insufficient data
Durham 2006			AE reported by severity
Feliziani 1995	18	16	Insufficient data
Guez 2000	36	36	Insufficient data
Hirsch 1997	15	15	Insufficient data
Hordijk 1998	27	30	AE reported SOC
Ippoliti 2003	47	39	Insufficient data
Lima 2002	28	28	Data reported in percentages
Malling 2005	36	11	Trial design Data reported in percentages
Marcucci 2005	13	11	Insufficient data
Mungan 1999	15	11	Insufficient data
Ott 2009	142	67	Insufficient data
Palma Carlos 2006	17	16	Insufficient data
Panzner 2008	20	15	Insufficient data
Passalacqua 1998	10	10	Insufficient data
Sanchez 2001	20	20	Insufficient data
Tari 1990	34	32	Insufficient data
Voltolini 2001	15	15	Insufficient data

Table 2. No adverse events reported *(Continued)*

Study ID	Sublingual immunotherapy	Placebo
	N	N
Ariano 2001	10	10

Table 2. No adverse events reported *(Continued)*

Bahceciler 2001	8	7
D'Ambrosio 1999	14	16
Passalacqua 1998	15	15
Passalacqua 1999	15	15
Pradalier 1999	63	63

Table 3. Adverse events - local reactions *(Continued)*

Type of reaction	No of studies reported the event	Sublingual immunotherapy		Placebo	
		Total No of patients	Total No of events	Total No of patients	Total No of events
Labial oedema	11	604	55	536	7
Buccal pruritus	21	1126	1798	1075	492
Bucco- lingual oedema	8	648	143	606	2
Throat irritation	10	770	243	747	29
Oral - non-specified	3	68	143	71	24
Non-specified	3	119	7	116	3

Table 4. Adverse events - systemic reactions *(Continued)*

Type of reaction	No of studies reported the event	Sublingual immunotherapy		Placebo	
		Total No of patients	Total No of events	Total No of patients	Total No of events
Urticaria	8	204	7	199	9
Pruritus/rash	10	363	13	222	9
Conjunctivitis	8	262	774	238	786
Rhinitis	16	965	1403	912	1034
Rhino-conjunctivitis	6	184	60	176	58
Asthma/wheezing	15	488	51	450	42
Cough	8	337	313	304	211
Gastro-intestinal	20	630	88	561	10

Table 4. Adverse events - systemic reactions *(Continued)*

Headache	6	535	70	548	68
Anaphylaxis	6	291	0	288	0
Systemic - non-specified	5	330	4	36	0

Table 5. Adverse events leading to treatment discontinuation *(Continued)*

Study ID	Sublingual immunotherapy			Placebo		
	N	n	AE description	N	n	AE description
Andre 2003	53	4	Sublingual burning Oral pruritus, vomiting, headache Pruritus, lingual oedema, gastralgia, diarrhoea Asthma and gastralgia	53	1	Gastralgia
Dahl 2006b	316	5	Angioedema on the base of the tongue Inferior lip angioedema pharyngeal hyperemia, cough, mild dyspnoea Pharynx oedema, voice changes Swelling throat Angioedema of lips	318	0	Not applicable
Durham 2006	141	8	Not described	136	1	Not described
Khinchi 2004	23	3	Pain in fingers and visible veins Gastrointestinal complaints Itching in the mouth	24	1	Pain and weakness in both arms
La Rosa 1999	20	4	Not described	21	1	Not described
Lima 2002	28	1	Troublesome local side effects	28	0	Not applicable
Malling 2005	12	1	Sting and blisters in the mouth	11	1	Mouth itching
Pajno 2003	15	1	Systemic reaction (abdominal pain, shortness of breath, wheezing)	15	0	Not applicable
Pradalier 1999	63	2	Worsening symptoms Marked reactions	63	2	Worsening symptoms Marked reactions

Table 5. Adverse events leading to treatment discontinuation *(Continued)*

Rolinck-Werninghaus 2004	49	1	Acute asthma exacerbation needed hospitalisation	48	3	Not described
Smith 2004	44	7	4 patients with systemic but not life-threatening AE	45	-	Insufficient data
Tonnel 2004	15	1	Itching/burning of the mouth	17	1	Respiratory tract infection
Vervloet 2006	38	1	Gastric pain and vomiting	38	0	Not applicable
Vourdas 1998	33	1	Worsening of allergic disease	29	0	Not applicable
Voltolini 2001	15	1	Exacerbation of rhinitis and OAS	15	1	Dyspnoea

APPENDICES

Appendix 1. Search strategies

PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
#1 "IMMUNOTHERAPY" [MeSH] OR "DESENSITIZATION, IMMUNOLOGIC" [MeSH] #2 ("Allergens/administration and dosage"[Mesh] OR "Allergens/immunology"[Mesh]) #3 ALLERGEN* [tiab] OR IMMUNOLOGIC [tiab]) AND (HYPOSENSITIZ* [tiab] OR HYPOSENSITIS* [tiab] OR DESENSITIZ* [tiab] OR DESENSITIS* [tiab]) #4 #1 OR #2 OR #3 #5 "ADMINISTRATION, SUBLINGUAL" [Mesh] #6 (SUBLINGUAL* [tiab] OR ORAL* [tiab] OR TONGUE [tiab] OR MUCOSA [tiab]) #7 #5 OR #6 #8 #4 AND #7 #9 (SLIT [tiab] OR (SUBLINGUAL* [tiab] AND IMMUNOTHERAP* [tiab])) #10 #8 OR #9 #11 ((((("rhinitis, allergic, perennial"[Mesh]) OR ("rhinitis, allergic, seasonal"[Mesh]) OR ((("rhinitis"[Mesh]) OR (rhinit*[tiab])) AND (allerg*[tiab] OR "hypersensitivity"[Mesh])) OR ((((("rhinitis"[Mesh]) OR (rhinit*[tiab])) OR (allerg*[tiab] OR "hypersensitivity"[Mesh])) AND ((perennial[ti] OR persistent[ti] OR nonseaosnal[ti] OR nose[ti] OR nasal[ti] OR cat*[ti] OR fur[ti] OR hair*[ti] OR dander[ti] OR dust*[ti] OR mite*[ti] OR pet*[ti] OR dog*[ti] OR cockroach*[ti]) OR (seasonal[ti] OR intermittent[ti] AND spring[ti] OR summer[ti] OR pollen[ti] OR grass*[ti] OR birch[ti] OR ragweed[ti] OR tree*[ti] OR weed*[ti] OR mugwort[ti] OR willow[ti] OR alder[ti])))) OR (hayfever[tiab] OR "hay fever"[tiab] OR pollenosis[tiab] OR pollinosis[tiab] OR SAR [tiab] OR PAR [tiab]))	1 IMMUNOTHERAPY/ or IMMUNOLOGICAL TOLERANCE/ or exp IMMUNOMODULATING AGENT/ or exp IMMUNOSUPPRESSIVE TREATMENT/ 2 ((ALLERGEN* or IMMUNOLOGIC) and (HYPOSENSITIZ* or HYPOSENSITIS* or DESENSITIZ* or DESENSITIS*)).tw. 3 1 or 2 4 (SUBLINGUAL* or ORAL* or TONGUE or MUCOSA).tw. 5 4 and 3 6 (SLIT or (SUBLINGUAL* and IMMUNOTHERAP*)).tw. 7 6 or 5 8 exp Allergic Rhinitis/ 9 Rhinitis/ 10 Rhinit*.tw. 1110 or 9 12 exp Hypersensitivity/ 13 allerg*.tw. 14 13 or 12 15 11 and 14 16 (perennial or persistent or nonseasonal or nose or nasal or cat* or fur or hair* or dander or dust* or mite* or pet* or dog* or cockroach*).ti. 17 (seasonal or intermittent or spring or summer or pollen or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti. 18 17 or 16 19 11 or 14 20 18 and 19	S1 (MH "Rhinitis, Allergic, Perennial") or (MH "Rhinitis, Allergic, Seasonal") S2 (MH "Rhinitis") S3 TX rhinit* S4 S2 or S3 S5 TX allerg* S6 (MH "Hypersensitivity") S7 S5 or S6 S8 S4 and S7 S9 TI perennial or persistent or nonseasonal or nose or nasal or cat* or fur or hair* or dander or dust* or mite* or pet* or dog* or cockroach* S10 TI seasonal or intermittent or spring or summer or pollen or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder S11 S9 or S10 S12 S5 OR S6 S13 S11 and S12 S14 TX hayfever OR "hay fever" OR pollenosis OR pollinosis OR SAR S15 S1 or S8 or S13 or S14 S16 (MH "Immunotherapy")

(Continued)

#12 #10 AND #11	21 (hayfever or "hay fever" or pollenosis or pollinosis or SAR).tw. 22 15 or 8 or 20 or 21 23 22 and 7	S17 (MH "Desensitization, Immunologic") S18 TX (ALLERGEN* OR IMMUNOLOGIC*) and TX (HYPOSENSITIZ* OR HYPOSENSITIS* OR DESENSITIZ* OR DESENSITIS*) S19 S16 or S17 or S18 S20 (MH "Administration, Sublingual") S21 TX SUBLINGUAL* OR ORAL* OR TONGUE OR MUCOSA S22 S20 or S21 S23 S19 and S22 s24 TX SLIT OR TX (sublingual AND immunotherap*) S25 S23 OR S24 S26 S15 AND S25

Web of Science	BIOSIS Previews/CAB Abstracts (Ovid)	mRCT
#1 TS=rhiniti* #2 TS=(allerg* OR hypersensitivty) #3 #2 AND #1 #4 TI=(perennial or persistent or nonseasonal or nose or nasal or cat* or fur or hair* or dander or dust* or mite* or pet* or dog* or cockroach*) #5 TI=(seasonal or intermittent or spring or summer or pollen or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder) #6 #5 OR #4 #7 #6 AND #2 #8 TS=(hayfever OR "hay fever" OR pollenosis OR pollinosis OR SAR OR PAR) #9 #3 OR #7 OR #8 #10 TS=((ALLERGEN* OR IMMUNOLOGIC*) AND (HYPOSENSITIZ* OR HYPOSENSITIS* OR DESENSITIZ* OR DESENSITIS*)) #11 TS=(immunotherap*) #12 #10 OR #11 #13 TS=(SUBLINGUAL* or ORAL* or TONGUE or MUCOSA) #14 #12 AND #13 #15 SLIT #16 #14 OR #15 #17 #9 AND #16	1 IMMUNOTHERAPY/ or IMMUNOLOGICAL TOLERANCE/ or exp IMMUNOMODULATING AGENT/ or exp IMMUNOSUPPRESSIVE TREATMENT/77 2 ((ALLERGEN* or IMMUNOLOGIC) and (HYPOSENSITIZ* or HYPOSENSITIS* or DESENSITIZ* or DESENSITIS*)).tw. 3 1 or 2 4 (SUBLINGUAL* or ORAL* or TONGUE or MUCOSA).tw. 5 4 and 3 6 (SLIT or (SUBLINGUAL* and IMMUNOTHERAP*)).tw. 7 6 or 5 8 Rhinitis/ 9 Rhinit*.tw. 10 9 or 10 11 exp Hypersensitivity/ 12 allerg*.tw. 13 11 or 12 14 10 and 13 15 (perennial or persistent or nonseasonal or nose or nasal or cat* or fur or hair* or dander or dust* or mite* or pet* or dog* or cockroach*).ti. 16 (seasonal or intermittent or spring or summer or pollen or grass* or birch or ragweed or tree* or weed* or mugwort or willow or alder).ti. 17 15 or 16 18 13 AND 17 19 (hayfever or "hay fever" or pollenosis or pollinosis or SAR).tw. 20 10 or 18 OR 19 21 7 AND 20	(rhinit% OR hayfever OR allerg%) AND (sublingual% OR oral% OR tongue OR mucosa)

WHAT'S NEW

Date	Event	Description
14 December 2010	Amended	Contact details and conflict of interest statement updated.

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 2, 2003

Date	Event	Description
11 May 2010	New citation required and conclusions have changed	We included 38 new studies in the review, strengthening the conclusions. The authorship has also changed.
11 May 2010	New search has been performed	New searches run 14 August 2009.
28 February 2009	Amended	Converted to new review format.
23 February 2004	Amended	Correction submitted for Issue 2, 2004.
25 November 2003	Feedback has been incorporated	Feedback and authors' response incorporated.

CONTRIBUTIONS OF AUTHORS

SUZANA RADULOVIC: Lead review author, searching for trials, quality assessment of trials, design of data extraction form, data extraction, data analysis.

MOISES CALDERON: Review author, searching for trials, quality assessment of trials, data analysis, input at all other stages of review.

DUNCAN WILSON: Review author, protocol development, quality assessment of trials, design of data extraction form, data extraction, data analysis.

STEPHEN DURHAM: Protocol development, input at all other stages of review.

DECLARATIONS OF INTEREST

The lead review author, Dr Suzana Radulovic, has received financial support from the ITN (Immune Tolerance Network) as an employee of the Paediatric Allergy Research Department at King's College London, UK.

The Department of Upper Respiratory Medicine, National Heart & Lung Institute, London, UK, headed by Professor Durham, has received financial support from ALK Abello, Horsholm, Denmark - manufacturers of allergen extracts. Stephen Durham has received consultancy and lecture fees and research grants from Alk Abello, a manufacturer of allergy vaccines, via Imperial College.

There are no other conflicts of interest to be declared.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Evaluation of safety has been noted as a primary objective of the review.
2. The I^2 statistic has now been used to quantify heterogeneity.
3. The Cochrane 'Risk of bias' tool has now been used to assess the methodological quality of the included trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Sublingual; Allergens [*administration & dosage]; Desensitization, Immunologic [*methods]; Randomized Controlled Trials as Topic; Rhinitis, Allergic, Perennial [*therapy]; Rhinitis, Allergic, Seasonal [*therapy]

MeSH check words

Adult; Child; Humans