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Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis

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Abstract

Background: To inform the development of the European Academy of Allergy and Clinical Immunology's (EAACI) Guidelines on Allergen Immunotherapy (AIT) for allergic asthma, we assessed the evidence on the effectiveness, cost-effectiveness and safety of AIT.

Methods: We performed a systematic review, which involved searching nine databases. Studies were screened against pre-defined eligibility criteria and critically appraised using established instruments. Data were synthesized using random-effects meta-analyses.

Results: 98 studies satisfied the inclusion criteria. Short-term symptom scores were reduced with a standardized mean difference (SMD) of -1.11 (95%CI -1.66, -0.56). This was robust to a pre-specified sensitivity analyses, but there was evidence suggestive of publication bias. Short-term medication scores were reduced SMD -1.21 (95%CI -1.87, -0.54), again with evidence of potential publication bias. There was no reduction in short-term combined medication and symptom scores SMD 0.17 (95%CI -0.23, 0.58), but one study showed a beneficial long-term effect.

For secondary outcomes subcutaneous immunotherapy (SCIT) improved quality of life and decreased allergen specific airways hyperreactivity (AHR) but this was not the case for sub-lingual immunotherapy (SLIT). There were no consistent effects on asthma control, exacerbations, lung function, and non-specific AHR.

AIT resulted in a modest increased risk of adverse events (AEs). Although relatively uncommon, systemic AEs were more frequent with SCIT; however no fatalities were reported.

The limited evidence on cost-effectiveness was mainly available for sublingual immunotherapy (SLIT) and this suggested that SLIT is likely to be cost-effective.

Conclusions: AIT can achieve substantial reductions in short-term symptom and medication scores in allergic asthma. It was however associated with a modest increased risk of systemic and local AEs. More data are needed in relation to secondary outcomes, longer-term effectiveness and cost-effectiveness.

Keywords: allergy, allergen immunotherapy, asthma, cost-effectiveness, desensitization, effectiveness, exacerbations, lung function, quality of life, safety.

BACKGROUND

Asthma is a major public health problem affecting over 300 million people worldwide.(1) Its prevalence and impact are particularly on the rise and it is estimated that by 2025 an additional 100 million people may develop asthma.(2) Asthma is therefore set to become one of the world's most prevalent chronic diseases.

Based on the clinical history, examination and investigative procedures, different asthma phenotypes have been described.(3) The pathogenesis of asthma is extremely complex and several disease endotypes have been suggested.(3,4) Allergic asthma is one of best described asthma phenotypes of primary studies. Allergic sensitization is a strong risk factor for asthma inception and severity in children and in adults.(5) Current asthma therapies can effectively control symptoms and the ongoing inflammatory process but do not affect the underlying, dysregulated immune response. Thus, they are very limited in controlling the progression of the disease. Allergen immunotherapy (AIT) is the only etiology-based treatment for allergic diseases capable of disease modification, as demonstrated by prevention of both the onset of new allergic sensitizations and disease progression.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing *Guidelines on Allergen Immunotherapy (AIT) for Allergic Asthma*. We undertook a systematic review of primary studies on the effectiveness, cost-effectiveness and safety of AIT for allergic asthma in order to inform the formulation of key clinical recommendations.

METHODS

A detailed outline of the methods have previously been published in the protocol of this review.⁽⁶⁾ We therefore confine ourselves to a synopsis of the methods employed.

A highly sensitive search strategy was developed, and validated study design filters were applied to retrieve articles pertaining to the use of AIT for allergic asthma from electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Appendix 1, Supplementary file). In all cases, the databases were searched from inception to October 31, 2015. Additional papers were located through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field.

There were no language restrictions employed.

Inclusion and exclusion criteria are detailed in Box 1

Patient characteristics	Studies conducted on patients of any age with a physician confirmed diagnosis of asthma, plus evidence of clinically relevant allergic sensitization as assessed by an objective biomarker (e.g., skin prick test or specific-IgE), in combination with a history of asthma symptoms due to allergen exposure
Interventions of interest	AIT for different allergens (e.g. pollens, house dust mites (HDM), animal dander, cockroach and molds), administered through either subcutaneous (SCIT) or sublingual (SLIT) routes.
Comparator	Placebo or any active comparator.
Study designs	<i>Effectiveness:</i> Double-blind randomized controlled trials (RCTs). Originally, we planned to include data from any RCT, irrespective of whether there was blinding. This was changed due to the large volume of RCT studies. This decision was made prior to any analyses being undertaken. <i>Cost-effectiveness:</i> Health economic analysis. <i>Safety:</i> Double-blind RCTs and large case series (≥ 300 patients).
Outcomes	<i>Primary outcomes:</i> Effectiveness, both short-term (i.e. during treatment) and long-term (i.e. at least a year after discontinuation of AIT) as assessed by symptom and/or medication scores. <i>Secondary outcomes:</i> Asthma control; asthma specific quality of life (QoL); exacerbations; lung function; response to environmental exposure chamber or bronchial allergen challenge; health economic analysis from the perspective of the health system/payer; and safety as assessed by local and systemic reactions. ^(7,8)
Exclusion criteria	Reviews, discussion papers, non-research letters and editorials, animal studies and studies not employing double-blind RCT designs.

Box 1. Inclusion and exclusion criteria

Study selection

All references were uploaded into the systematic review software DistillerSR and underwent de-duplication. Studies were independently checked by two reviewers (SD, FA or AK) against the above inclusion criteria. Any discrepancies were resolved through discussion and, when necessary, a third reviewer was consulted (AS).

Quality assessment

Quality assessments were independently carried out on each study by two reviewers (FA, AK, DD, SD or MK). We used the Cochrane Risk of Bias (ROB) tool to assess RCTs,(9) the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies,(10) and the National Institute for Health and Clinical Excellence (NICE) quality assessment tool to critically appraise case series.(11) Any discrepancies were resolved by discussion or arbitration by a third reviewer (AS).

Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (FA, AK, HZ, DD or SD) and any discrepancies were resolved by discussion or arbitration by a third reviewer (AS). A descriptive report with summary data tables was produced to summarize the literature. Where clinically and statistically appropriate, meta-analyses were undertaken using random-effects modeling.(12) Where standardized mean difference (SMD) has been used the scale used is 0.2 represents a small effect size, 0.5 a medium effect size and 0.8 a large effect size. (105)

Sensitivity and assessment for publication bias

Sensitivity analyses were, where possible, undertaken by comparing the summary estimates obtained by excluding studies judged to be at high ROB with those judged to be at low or moderate ROB.

Where possible, publication bias was assessed through the creation of funnel plots, and tested by Begg's rank correlation test and Egger's regression test.(13,14)

Subgroup analyses

A number of sub-group analyses were undertaken, details of which are in the protocol.

Registration and reporting

This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42016035372. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review (Appendix 2, Supplementary file).

RESULTS

Our search strategy yielded 7,490 papers of which 98 studies were eligible; these comprised of 89 double-blind RCTs (reported in 94 papers), three cost-effectiveness studies and six case series (see Figure 1).

Effectiveness

Description of studies

The RCTs enrolled a total of 7,413 patients. The route of administration of AIT was SCIT (n=54), SLIT (n=34), and SCIT versus SLIT (n=1). The majority of trials reported on the short-term effectiveness of AIT with only one SLIT trial reporting on long-term effectiveness. The 54 SCIT trials (reported in 57 papers) included 2,305 patients (15–70) and the 34 SLIT trials (71–104) (reported in 36 papers) included 5,108 patients. SCIT studies included adults (n=24), both children and adults (n=17), and children (n=13). SLIT studies included children (n=20), both children and adults (n=10), and adults (n=4).

Allergen extracts administered included HDM, grass, cat, dog, trees, molds, latex and weeds. Various AIT protocols were utilized. The severity of asthma tended to be mild-to-moderate. Further details are included in Tables 1a, 1b, 1c and S1a, S1b, S1c (Supplementary file).

Quality assessment

The majority of SCIT trials (n=32) were judged as unclear ROB, seven low ROB and 15 studies as at high ROB (Table S1d, Supplementary file). Twenty SLIT studies were assessed to be at high ROB; 13 studies were at unclear ROB; and one study at low ROB (Table S1e, Supplementary file). The one SCIT vs SLIT study was judged to be at a low ROB (Table S1f, Supplementary file).

Primary outcomes

Symptom scores

Short-term

Fifty-eight (36 SCIT and 22 SLIT) trials reported on the effect of symptoms at the end of the AIT treatment period. We were able to pool data from 15 SCIT and SLIT trials with placebo as comparator. The metaanalysis showed that AIT improved symptom scores with a standardized mean difference (SMD) of -1.11 (95%CI -1.66, -0.56) (Figure 2), these suggesting a large effect of AIT. (105)

Sensitivity analysis

By excluding studies at high ROB sensitivity analysis confirmed the effect of AIT on asthma symptom scores: SMD -1.44 (95%CI -2.14, -0.74) (Figure S2a, Supplementary file).

Publication bias

The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Figures S2b, Supplementary file). Publication bias was also suggested by the Egger test ($P=0.024$). There were insufficient studies to undertake the Begg test

Subgroup analyses

- Children (<18 years) versus adults (≥ 18 years): SMD -0.58 (95%CI -1.17, -0.01) in children and SMD -1.95 (95%CI -3.28, -0.62) in adults (Figure 3), supporting AIT effectiveness in both children and adults.
- SCIT versus SLIT: the analyses found that SCIT is effective with SMD -1.64 (95%CI -2.51, -0.78) and suggested (but did not confirm) that SLIT was effective SMD -0.35 (95%CI -0.75, 0.05) (Figure 4); this indirect comparison suggested that SCIT was more effective than SLIT.
- Treatment duration: SMD -1.15 (95%CI -1.77, -0.53) in those treated for <3 years and SMD -0.79 (95%CI -1.10, -0.49) in those treated for ≥ 3 years (Figure S2c, Supplementary file), these analyses finding that both treatment durations were effective.
- Mild/moderate versus moderate/severe disease: this subgroup analyses found that AIT is effective for mild/moderate asthma SMD -1.00 (95%CI -1.81, -0.19) and suggested (but did not confirm) a possible benefit in those with moderate/severe disease SMD -0.23 (95%CI -0.89, 0.43) (Figure S2d, Supplementary file)
- Individual allergens: this subgroup analyses found evidence of benefit for AIT with HDM SMD -1.41 (95%CI -2.27, -0.55), grass pollen SMD -1.18 (95%CI -2.17, -0.20) and cat/dog dander (SMD -0.77 (95%CI -1.48, -0.06)), suggested (but did not confirm) benefit for tree pollen SMD -0.24 (95%CI -0.91, 0.42), and found no benefit for mold SMD 0.36 (95%CI -0.39, 1.11). (Figure S2e, Supplementary file)
- Monosensitized/mono-allergic versus polysensitized: there is evidence of AIT benefit in monosensitized/mono-allergic patients SMD -4.23 (95%CI -5.53, -2.94) and a suggested benefit

(but not confirmed) for polysensitized patients SMD -0.31 (95%CI -0.65, 0.04) (Figure S2f, Supplementary file),

Long-term

No studies reported on the long-term effectiveness of AIT on symptom score.

Medication scores

Short-term

Forty-two (28 SCIT and 14 SLIT) studies reported on medication scores.. Pooling of data with placebo as the comparator was possible for 10 studies. Meta-analysis found evidence that AIT improved medication scores (i.e. reduced medication use) with a SMD of -1.21 (95%CI -1.87, -0.54) (Figure 5), this corresponding to a large effect.

Sensitivity analysis

Sensitivity analysis for this outcome was not possible as no studies were found to be at high ROB.

Publication bias

The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Figures S2g, Supplementary file), but this was not confirmed by the Egger test (P=0.09). There were insufficient studies to undertake the Begg test.

Subgroup analyses

- Children (<18 years) versus adults (≥ 18 years): there is evidence for benefit in children SMD -0.49 (95%CI -0.98, 0.00) and a suggested benefit (but not confirmed) in adults SMD -4.45 (95%CI -11.23, 2.32) (Figure 6)
- SCIT versus SLIT: SMD -1.65 (95%CI -2.52, -0.79) for SCIT and SMD -0.29 (95%CI -0.82, 0.24) for SLIT (Figure 7), these analyses showing benefit of SCIT and suggesting (but not confirming) benefit from SLIT.
- Mild/moderate versus moderate/severe disease: SMD -1.59 (95%CI -2.48, -0.70) for mild/moderate disease and SMD -0.36 (95%CI -1.03, 0.31) (Figure S2h, Supplementary file),

these analyses showing a benefit in those with mild/moderate disease and suggesting (but not confirming) benefit in those with moderate/severe disease.

- Treatment duration: SMD -1.21 (95%CI -1.94, -0.49) for those treated for <3 years and SMD -1.29 (95%CI -2.00, -0.59) for those receiving ≥ 3 years of treatment (Figure S2i, Supplementary file), these analyses showing evidence of benefit in both groups.
- Individual allergens: this subgroup analysis demonstrated a benefit of AIT with HDM (SMD -2.10 (95%CI -3.29, -0.91) and tree pollen (one study) (SMD -1.08 (95%CI -1.79, -0.37)) and suggested (but not confirmed) a benefit for, grass pollen (SMD -0.06 (95%CI -0.41, 0.28)) and molds (SMD -0.65 (95%CI -1.92, 0.62) (Figure S2j, Supplementary file).
- Monosensitized and mono-allergic versus polysensitized: SMD -1.18 (95%CI -1.16, 0.13) in mono-sensitized and mono-allergic and the polysensitized group (SMD -0.36 (95%CI -2.11, 0.25)) in the polysensitized group (Figure S2k) these analyses suggesting (but not confirming) benefit in both groups.

Long-term

No studies reported on the long-term effectiveness of AIT on medication score.

Combined symptom and medication scores

Short-term

Six studies (two SCIT, three SLIT studies and one SCIT vs. SLIT) reported a combined assessment of the effectiveness of AIT on symptoms and medication usage. Pooling of data was possible for two studies, this showing a SMD of 0.17 (95%CI -0.23, 0.58) (Figure 8).

Sensitivity analysis, assessment of publication bias and subgroup analyses

These analyses were not possible for this outcome.

Long-term

One SLIT study at low ROB reported on this outcome. A five-year double blind placebo RCT by Durham (2012) had a three year SLIT tablets or placebo treatment period in grass pollen allergic patients followed by a two-year blinded observation period when no active treatment was administered. At the

end of the five years the group who had received SLIT were found to have a significant improvement in combined asthma symptom and medication scores when compared to placebo for the whole five-year period ($p=0.049$).

Secondary outcomes

Asthma control

Seven SLIT studies reported on a measure of asthma control (see Table S1g for details). (77,78,85,88,93,98,100). We were unable to pool data due to the differences in reporting of results. The one study at low ROB found that AIT did not improve asthma control(98) . We found no evidence to assess whether SCIT is effective in improving asthma control in allergic asthma patients.

Quality of life

Eleven AIT trials reported on a measure of disease-specific QoL (Table S1h).

Three SCIT studies (19,35,106), all judged to be at low ROB, reported significant improvements in disease-specific QoL. Pooled data from two of these trials (19,35), showed a large treatment effect with an SMD of -0.83 (95%CI -1.19, -0.47) in favor of SCIT (Figure 9).

Seven SLIT trials reported on disease-specific QoL (77,78,83,88,93,98,100). We were unable to pool data from these studies for meta-analysis due to the variable reporting of results (Table 2). The one low ROB trial of SLIT(98) showed no significant improvement in disease-specific QoL.

Exacerbations

Six trials (69,78,80,88,91,98) reported on asthma exacerbations, which were defined in a number of ways (Table S1i). The one SCIT trial at low ROB (69) reported on exacerbations defined by the number of courses of oral corticosteroids required to restore asthma control found no significant difference between the SCIT and placebo groups (P-value not given). Five SLIT studies reported on exacerbations, which we were unable to pool due to variations in the ways in which trial results were reported.

In summary, focusing on the trials at low ROB, the Wang (2006) SCIT trial failed to demonstrate evidence of a reduction in exacerbations in those treated with AIT compared with those treated with placebo. Two SLIT trials reported a positive effect of AIT on asthma exacerbations, one in the context of reducing the dose of ICS.

Lung function

Twenty-five studies, of variable quality, reported on measures of lung function: peak expiratory flow rate (PEF), forced expiratory volume in 1 second (FEV1) and forced expiratory flow at 25–75% of forced vital capacity (FEF 25-75%). Data on these outcomes were recorded in a number of ways and at varying times throughout the study.

Peak expiratory flow rate (PEF)

Fourteen studies reported on this outcome. (16,29,38,43,48,50,61,69,72,73,93,96,107,108) (Table S1j).

Pooled data from six studies suggested no clear benefit of AIT with a SMD of 0.48 (95%CI -0.21, 1.18) (Figure S4a)

Forced expiratory volume (FEV1)

Nine studies reported on FEV1. Reporting of data was varied (18,28,43,57,73,93,96,108,109) (Table S1k).

Data pooled from two studies indicated no clear evidence of benefit associated with AIT with a SMD of 0.41 (95%CI -0.46, 1.27) (Figure S4a)

Forced expiratory flow at 25–75% of forced vital capacity (FEF25-75)

We were able to pool data on FEF 25-75 from three trials (72,96,109) and found an SMD of 0.83 (95%CI 0.31, 1.35), this suggesting a large beneficial effect of AIT (Figure S4a).

In summary, the evidence identified from meta-analysis evaluating the effect of AIT on lung function in allergic asthma supports the effectiveness of AIT on small airways (FEF 25-75%), but with no clear evidence of benefit on improving PEF or FEV1.

Bronchial provocation tests

Thirty-one trials reported on bronchial provocation tests. Twenty-one trials looked at allergen specific provocation tests and 18 studies evaluated non-specific measures of bronchial hyperreactivity. There was a wide variation in reporting of outcome data (Tables S1l and S1m).

Allergen specific airway hyperreactivity

Twenty-one trials performed allergen specific bronchial provocation tests (15,17–20,25,30,31,35,44,48,53,60,62,64,67,70,82,107,108,110). They were of variable quality and were mainly SCIT trials (n=20), SLIT being evaluated in only one trial (82). (Table S1l).

Pooled data from three SCIT studies, demonstrated a large effect of AIT with a SMD of 0.93 (95%CI 0.08, 1.79) (Figure S4b). Furthermore, there was evidence from eight high quality RCTs that SCIT was effective in reducing allergen specific bronchial reactivity in patients with allergic asthma

One SLIT study reported on allergen specific bronchial responsiveness to Artemisia pollen (Leng 1990). This study, at moderate ROB, found no significant difference between the SLIT and placebo groups.

Non- specific airway hyperreactivity

Eighteen studies reported on this outcome (16–18,20,33,36,48,55,62,67,69,72,73,94,96,106,109,110) (Table S1m).

Pooling of data was possible for metacholine PC20 for three studies which showed an SMD of 0.74 (95%CI -0.17, 1.66) , showing no clear evidence of benefit for AIT; Histamine PC20 for two studies with an SMD of 0.33 (95% CI 0.03, 0.64) favouring AIT and for metacholine PD20 for two studies showing an SMD of 0.03 (95%CI -0.32, 0.39) showing no clear evidence in favour of AIT (Figure S4c). We were able to combine data from seven of these studies which showed an overall SMD of 0.33 (95%CI 0.01, 0.64) in favour of AIT (Figure S4d)

Cost-effectiveness

One SCIT and two SLIT studies satisfied the eligibility criteria. (111–113) These included children and adults with or without allergic rhinitis (Tables S1m and S1n). The quality appraisal is detailed in Tables S1o and S1p.

Of the three studies included only one focused on patients with allergic asthma who did not also have allergic rhinitis.(111) This study was carried out in Germany and compared SCIT with standard care based on a small scale RCT (N=65) with three years of follow-up data. The study used a disease specific outcome measure (i.e. mean morning peak flow) with no attempt to convert it to a general quality of life measure such as quality adjusted life years (QALYs) making it impossible to assess the cost-effectiveness of the treatment. The study found that, over the three years, SCIT was more expensive than standard care and performed better than standard care on the disease specific outcome measure.

The remaining two studies looked at patients with both asthma and allergic rhinitis. SLIT was compared with standard care in an RCT (N=151) with one year of follow-up conducted in Austria, Denmark, Germany, Holland, Italy, Spain, Sweden and the UK, and with results evaluated from an English National Health Service (NHS) perspective.(112) This study used one year of treatment data and assumed a constant treatment effect over the three year treatment period and the six years following the end of the treatment. EQ5D was used to evaluate the treatment outcome. The incremental cost-effectiveness ratio (ICER) of SLIT, as compared to standard care at 2005 prices, was calculated at £8816 (€10850) per QALY over the nine year period. The study did not attempt to characterize the uncertainty around this estimate. Updating this to 2014/15 prices using Personal Social Services Resource Unit (PSSRU) NHS inflation indices gave an ICER of £10726 (€13202) per QALY. Another RCT (N=70) with five years of follow-up conducted in Italy comparing SLIT with standard care in patients with asthma and rhinitis and found that patients on SLIT cost less and experienced less symptoms than those on standard care.(113) Methods for calculating the costs were not presented in enough detail to understand the analysis that had been performed and there was no attempt to convert the symptom score to a general quality of life scale making it impossible to assess the cost-effectiveness of SLIT.

Safety

Data from randomized controlled trials (RCTs) and case series were included to assess the safety of AIT.

RCTs

Fifty-two RCTs (36 SCIT studies and 16 SLIT) reported safety data (Tables S3a-f). We were able to pool data from 38 of these studies (SCIT=29;SLIT=9) including both local and systemic adverse events (AEs)

Risk of patients experiencing one or more AE

AIT delivered by any route (SCIT or SLIT) increased the risk of patients experiencing one or more AE (i.e. local and systemic) with a rate ratio (RR) of 1.74 (95%CI 1.38, 2.2) (Figure S3a). Subgroup analysis found that the increased risk was higher for SCIT RR=2.22 (95% CI 1.48, 3.33) than SLIT RR=1.49 (95%CI 1.13, 1.98), although this is an indirect comparison.(Figures S3b and S3c)

Total number of AEs reported

AIT delivered by any route (SCIT or SLIT) increased the risk of total AEs (i.e. local and/or systemic) with a RR=1.50 (95%CI 1.12, 2.02) (Figure S3d). Subgroup analysis found increased risk both for SCIT(RR=1.32 (95%CI 1.01, 1.74) and SLIT (RR=1.93 (95%CI 0.95, 3.95) . (Figures S3e and S3f).

Risk of systemic AEs

AIT delivered by any route (SCIT or SLIT) increased the risk of systemic AEs with a RR of 1.85 (95%CI 1.20, 2.84) (Figure S3g). Subgroup analysis found that there was clearly an increased risk of systemic AEs with SCIT RR=1.92 (95%CI 1.19, 3.09), but not for SLIT RR=1.39 (95%CI 0.67, 2.92) (Figures S3h and S3i)

Risk of local AEs

AIT delivered by any route was not found to increase the risk of local AEs: RR=1.18 (95%CI 0.83, 1.67) (Figure S3j). The available data suggested that the risk of local AEs was however substantially greater in those receiving SLIT when compared to those receiving SCIT (Figure S3j).

Case-series

We identified six eligible case-series studies in our searches; SCIT (n=5) and SLIT (n=1). The main characteristics of these studies and quality appraisal are presented in Tables S3g and S3h. The reported incidence of local AEs varied from 0.66 per patient and 0.33 per injection to 1.8%. The reported incidence of systemic AEs varied from 0.0074% to 0.06%.

No deaths from AIT were reported in any of these studies.

DISCUSSION

Statement of principal findings

This review has found a substantial body of evidence showing that administration of AIT in patients with allergic asthma can result in reductions in short-term symptom and medication scores. These findings do however need to be interpreted with caution given that the majority of trials were found to be at high or unclear ROB and the possibility of publication bias in relation to both these outcomes. Further subgroup analysis confirmed the beneficial effect for SCIT but was questionable for SLIT. There was a more modest body of evidence for the combined symptom and medication scores, which meta-analysis suggested was ineffective but this was not conclusively demonstrated on account of the wide confidence intervals. We found only one trial, judged to be at low ROB, evaluating long-term outcomes, which found a significant improvement in combined symptom and medication scores.

There is evidence for SCIT in improving asthma specific quality-of-life and reducing allergen specific airway hyperreactivity. In terms of lung function we were unable to demonstrate any significant beneficial effect on PEF and FEV1 however SCIT does have a beneficial effect on FEV25-75. No beneficial effect of AIT could be demonstrated on asthma control. As for asthma exacerbations, no beneficial effect could be demonstrated for SCIT, but there was limited evidence in favour of SLIT.

AIT was associated with a moderate increased risk of AEs, both for SCIT and SLIT. Severe systemic AEs were observed, but these were uncommon and mainly occurred with SCIT. No fatalities were reported in the studies included in this review.

Strengths and limitations

To our knowledge, this is the most comprehensive assessment of AIT in asthma ever undertaken. We employed internationally accepted techniques to systematically identify, assess and synthesize a substantial body of evidence, which included a number of pre-specified sensitivity and subgroup analyses.

The limitations of this review need to be considered. First, despite our extensive searches we may not have uncovered all relevant evidence on this subject. Second, we were limited by the heterogeneity in approaches used to assess outcomes, which meant we were unable to pool data from all trials or undertake all the planned subgroup analyses. The results of this review, particularly for primary outcomes, are based on the trials which we were able to meta-analyse which may not be representative of all trials. For example, data for combined scores was only available for six studies of which only two could be pooled for meta-analysis the results of which had a wide confidence interval allowing no clear conclusion to be drawn. For the subgroup analyses that were undertaken, there was in some cases imprecision which impacted on our ability to draw clear conclusions. Third, because of the heterogeneity in scoring systems used, we undertook meta-analyses using random-effects modeling and pooled data using SMDs, which can be difficult to interpret. The absolute size of the SMD was used to guide assessment of the likely effect size demonstrated. Finally, it needs to be borne in mind that there may have been important differences between specific AIT products. Investigating this issue was however beyond the scope of this review.

Interpretation in the light of the previous literature

The findings from this review are in keeping with earlier evidence syntheses on this subject (see companion paper), which found that SCIT improved short-term symptom and medication scores and measures of bronchial reactivity, but the evidence for SLIT was less consistent. There was no clear improvement of lung function for either SCIT or SLIT. This present study has built on this body of

work by adding a broader range of subgroup analyses, including additional studies at low ROB, and achieving greater precision in summary results.

Implications for policy, practice and research

Our findings provide evidence that AIT may be effective in improving two of our three patient-reported primary outcomes over the short-term. Interpretation of these results is however complicated by considerations about the quality of the substantial number of studies and possible publication bias. The subgroup analyses suggest that SCIT is likely to be more effective than SLIT, and that AIT may be more effective in children than in adults.

Greater standardization of trial designs, looking at the compliance of patients to AIT for the differing routes of administration, reporting and choice of outcomes and their reporting so as to facilitate evidence syntheses and key subgroup analyses would greatly help to advance the body of evidence underpinning AIT in allergic asthma. Future well conducted studies looking at the combined symptom and medication score are needed to determine whether AIT is beneficial for this outcome. We hope that future researchers will build on the findings from this systematic review and aim to fill key evidence gaps and areas of continuing uncertainty.

The findings from this review will be used to inform the development of recommendations for EAACPs Guidelines on AIT. We anticipate that this review will report mid 2017.

Conclusions

There is evidence that AIT in allergic asthma can achieve substantial reductions in short-term symptom and medication scores, with subgroup analyses confirming a benefit from SCIT and a questionable benefit from SLIT. These findings however need to be interpreted with caution given concerns about study quality and potential publication bias. Further there is evidence showing that SCIT decreases allergen-specific airway hyperactivity and improves asthma specific quality-of-life. The effect of AIT on asthma control and exacerbations is not conclusive, neither its long-term efficacy after stopping AIT, which requires further investigation. More research is needed to establish the cost-effectiveness of AIT but evidence suggest that SLIT is cost-effective in a UK NHS environment.

AIT is associated with a modest increase in the risk of AEs, both for SCIT and SLIT. Severe systemic AEs can occur, but are uncommon and mainly associated with SCIT. No fatalities were reported in the studies included in this review.

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Additional material:

Figures and tables for main paper

Appendix 1: Search strategy

Appendix 2: PRISMA Checklist

S1: Supplementary tables

S2: Supplementary figures for primary outcomes

S3: Safety tables and figures

S4: Supplementary figures for secondary outcomes

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Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis

Figures and tables for main paper

Table 1a: Overview of SCIT trials (n=54 studies in 57 papers)

Study Author, year, country	Allergen(s) type							Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial tests		
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other (s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score							Combined score	
Aas, 1971, Norway					X				X		X						X					3 y	Two house dust extracts from Nyegaard et Co., Oslo (house dust group A), and from Allergologisk Laboratorium, Copenhagen (House dust B), respectively.												X	X
Adkinson, 1997, US	X	X		X	X			X		X	X						X					2 y	SCIT mixture of seven aeroallergens(HDM ragweed, grass mix, Bemuda grass, white oak, Alternaria, cladosporium, aspergillus) prepared by ALK Laboratories, Copenhagen, Denmark, vs placebo	X	X						X		X	X		X
Alvarez-Cuesta, 1994, Spain						X			X		X						X					1 y	The allergen extract was obtained from Alergia e Inmunologia (Abell6, S.A., Madrid, Spain) and prepared by extracting the raw material (cat dander supplied by Allergon AB Engdholm, Valinge, Sweden)	X	X						X				X	X
Alvarez, 2002, Spain					X				X		X											1y	D. pteronyssinus D. pteronyssinus extract at 10													

																					biological units /mL contained 4µg/mL of Der p1 and 2 µg/mL of Der p2, entrapped in liposomes vs placebo											X				X
Ameal, 2005, Spain					X				X		X				X						1 y	The active group received a modified allergen extract of D. pteronyssinus. The modified extract was adsorbed onto aluminium hydroxide.	X	X						X	X			X	X	
Armentia-Medina, 1995, Spain								X	X		X				X						1 y	Standardised extract of storage mite Lepidoglyphus destructor with an activity of 100BU/ml. Concentration 18%	X											X	X	
Arvidsson, 2004, Sweden		X							X		X										1 y	Standardized birch pollen extract (Alutard SQ Betula verrucosa; ALK-Abello) vs dilute histamine dihydrochloride.										X		X	X	
Basomba, 2002, Spain					X				X		X				X						1 y	D pteronyssinus encapsulated in liposomes containing 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, and 3.2 µg of Der p 1.	X	X					X				X	X		
Blumberga, 2006, Denmark					X				X		X				X						3 y	Subcutaneous SIT with Alutard SQ D.								X			X			
Bødter, 2002, Denmark		X							X		X					X					1 y	High dose birch pollen extract, commercially available and produced by ALK-Abello, Hørsholm, Denmark. The content of the major birch pollen allergen Bet v 1 was 12 mg/100 000 SQ-U.	x	x						x						
Bousquet, 1985, France					X				X		X							X			7 w	Standardized Dermatophagoides pteronyssinus extract								x		X		X	X	
Bousquet, 1990, France	X								X		X		X					X			1 y	High and low dose grass extract.	X							X						

[illegible]

Haugaard, 1992, Denmark						X	X			X	X									5 m	Extracts used for diagnosis and treatment were Pharmed® cat epithelium extract and dog dander extract (Pharmacia AB, Uppsala, Sweden. AEK, Hersholt, Denmark).								X		X		X	X
Hedlin, 1999, Denmark	X	X			X	X			X	X		X				X				3 y	Partly purified and standardized extracts of cat dander, Dermatophagoides pteronyssinus, timothy pollen, and birch pollen were provided by ALK (Hørsholm, Denmark).								X		X			X
Hui, 2014, China					X					X	X				X				3 y	The SCIT treatment was initiated at a dosage of 20 U/ml, and was continued weekly with an increase in the dosage each week	X								X		X	X		
Kuna, 1989, Poland	X								X		X				X				1 y	Glutaraldehyde-modified, tyrosine-adsorbed grass pollen (Pollinex, Bencard Allergy Service, Brentford, Middlesex, England).	X								X					
Kuna, 2011, Poland				X						X		X							3 y	Standardized A alternata extract (Novo-Helisen Depot, A alternata 100%; Allergopharma Joachim Ganzer KG, Reinbek, Germany) in a depot formulation with aluminium hydroxide	X	X							X	X				
Lewis, 1971 UK					X					X			X	X					6-9 months	HDM D. farinae 0.002% to 0.1% w/v	X											X		
Leynadier, 2000, Germany								X	X		X						X		1 y	Standardized latex extract (Stallergenes)	X													

[illegible]

[illegible]

Rak, 2001, Sweden		X							X		X		X				X				Standardized depot preparations of birch pollen allergen extract (Alutard SQ, ALKAbelló) containing water-soluble allergen extract and aluminium hydroxide	X	X									X	X
Reid, 1986, US	X								X			X					X			8 m	Seven grass mix in serum, plus other allergens specific to individuals	X	X						X				
Roberts, 2006, UK	X								X		X						X			2 y	Alutard SQ P pratense (ALK-Abello) was used. This is an alum-adsorbed preparation of pollen from P pratense with a recommended dose of 100,000 SQ-U.	X	X						X		X	X	
Sabbah, 1991, France					X				X		X						X			180 d	Alpha-Fraction-Retard-D. pteronyssinus	X	X						X				
Smith, 1971, UK					X				X			X					X				HDM extract	X	X						X				
Sundlin, 1986, Sweden						X	X			X	X						X			18 m	Partially purified, standardized allergenic extracts of cat or dog dander								X			X	X
Tabar, 2008, Spain				X					X		X						X			1 y	Metabolic extract of A. alternata that had been biologically standardised	X	X						X		X		
Taylor, 1978, US						X			X		X						X			4 m	1.6 mg/ml cat allergen								X		X		

Taylor, 1978, UK					X				X		X					X					10 w	HDM fortified house dust vaccine								X		X				
Valovirta, 1984, Finland							X		X		X					X					1 y	Commercial standardised aluminium hydroxide bound dog dander extract (Alutard SQ)												X		X
Valovirta, 1986, Finland 2nd paper original study 1984							X		X		X					X					1 y	Commercial standardised aluminium hydroxide bound dog dander extract (Alutard SQ)	X							X						
Van Bever, 1992, Belgium					X				X		X						X				1 y	Aqueous extract of Dermatophagoides pteronyssinus (10 BU·ml ⁻¹)	X									X				X
Van Metre, 1988, US						X			X		X					X					2 y	Cat allergenic extract ALK 1209/229452 was supplied by Allergologisk Laboratories, Copenhagen, Denmark								X		X		X		X
Vidal, 2011, Spain					X				X		X										4 m	D. pteronyssinus extract with the major allergens Der p 1 and 2		X						X			X			
Wang 2006 China					X				X		X										52w	Dermatophagoides pteronyssinus extract	X	X							X		X	X		X
Warner, 1978 UK					X				X		X										1 year	D. pteronyssinus absorbed into tyrosine ('Migen', Bencard).	X	X						X			X			X

AIT, allergen specific immunotherapy; *d*, day; *HDM*, house dust mite; *m*, month; *NR*, not reported; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy; *w*, week; *y*, year

Table 1b: Overview of SLIT trials (n=34 studies in 36 papers)

Study Author, year, country	Allergen(s) type							Allergen number		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score							Combined score			
Alvarez-Cuesta, 2007, Spain						X			X		X						X					1 y	Aqueous solution of standardized semi-purified cat dander extract	X	X	X												
Bachelier, 2001, Turkey					X				X		X						X					26 w	Dermatophagoide(D.pteronyssinus)+Dermatophagoide(sfarinea (D. farinea) 50/50 extract	X	X						X			X		X		X
Bousquet, 1999, France					X				X		X						X					108 w.	HDM SLIT	X	X	X					X	X	X	X		X		
Caffarelli, 2000, Italy	X								X		X						X					13 w and 9 week follow up post treatment	Grass pollen tablet (33% Holcus lanatus, 33% Phleum pratense and 33% Poa pratensis)	X	X	X					X							
Cao, 2007, China					X				X		X						X					3 m	Dermatophagoides Farinae Drops		X						X			X		X		

Dahl, 2006, Denmark & Sweden	X								X		X			X	X		X			19.5 w	Timothy grass (Phleumpratense) GRAZAX tablet 75,000 SQ-T once daily	X	X											
de Blay, 2014, Denmark, Germany, Italy, Spain, UK, Sweden, France & Poland					X				X		X		X		X					1 y	Oral lyophilisates containing standardized extracts of D pteronyssinus and D farinae in a 1:1 ratio. One development unit corresponds to 1 SQ-HDM				X			X	X	X	X			
Devillier, 2015, China					X				X		X				X					"52 w (+ 12 week baseline period before randomisation)"	HDM SLIT (D. pteronyssinus and D. farinae), approximately 28 mcg Der P 1 and 50mcg Der f 1 daily (300 IR)							X	X	X		X		
Drachenberg, 2001, Germany	X								X		X				X					6 m	Standardized allergen extract (ORALVAC birch n = 21 resp. grass/rye = 28)				X				X					
Durham, 2012	X								X		X		X	X		X				5y(3 Rx, 2 follow up)	Timothy grass (Phleumpratense) GRAZAX tablet 75,000 SQ-T once daily							x						
Gomez Vera et al, 2005, Mexico					X				X		X				X					6 m	Dermatophagoides pteronyssinus 1 standardized allergens (IPI-ASAC, Mexico) at a total dose of 10,469 UBE				X				X			X		
Ippoliti, 2003, Italy						X			X		X				X					26 w (with 3-month run-in)	HDM SLIT (D. pteronyssinus), maintenance dose 5 drops of 10 BU/mL 3 times a week	X									X			

Leng, 1990, unclear country				X					X	X		X						x																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
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[illegible]

Pham-Thi, 2007, France					X				X		X									78 w.	HDM SLIT' (D. Pteronyssinus and D.farinae), up-dosing for 2 w up to 300 IR concentration once daily (average cumulative dose was 155,000 IR, corresponding to 6.9 mg Der P 1 and 14.7 mg Der f 1)	X	X						X	X	X	X							
Reilly, 1994, UK					X	X			X	X		X								4 w (with 4 w 'optional' post-treatment follow-up)	Homeopathic SLIT' (allergen varied, decided on case-by-case basis; HDM (84.6% of participants); feathers (7.7%); mixed moulds (7.7%)). 3 doses in 24 hours then optionally repeated at 4 w (according to patient choice)				X							X				X			
Reinert, 1983, Germany	X								X		X								X	2 y	Troponholistersteir				X														
Stelmach, 2009, Poland	X									X		X							X	104 w.	Grass pollen SLIT' (Dactylisglomerata, Anthoxanthumodoratum, Loliumperenne, Poapratensis, Phleumpretense). Ultra-rush period (total of 24 0IR). At the beginning of the next day, every morning before breakfast, received 4 puffs (120 IR) for 6 m. Cumulative dose 43,800 IR	X			X					X				X					X
Tian, 2014, China					X					X		X							X	48 w.	HDM SLIT' (D. farinae), titrated up over the first 4 w to 333 mcg/mL once daily	X																	

Virchow, 2016, Germany					X				X		X								20 m (11 August 2011 to 24 April 2013)	HDM SLIT [®] tablet contains extract from 2 species of cultivated HDM (<i>D pteronyssinus</i> and <i>D farinae</i>), produced in a standardized process with a 1:1:1:1 ratio of the major allergens (Group1 allergens of <i>D farinae</i> and <i>D pteronyssinus</i> and Group2 allergens of <i>D farinae</i> and <i>D pteronyssinus</i>), and formulated as rapidly dissolving oral lyophilisate for sublingual administration (ALK).	X							X			X		
Vourdas, 1998, Greece		X							X		X								104 w (2 y)	Olive pollen SLIT [®] , daily up-dosing then each morning pre- and co-seasonally from January to July for 2 y up to a maximum of 20 drops of 300 IR (total 30,000 IR/y)	X	X						X		X			
Wang, 2014, China		X							X		X								52 w (+12 w baseline period before randomisation)	HDM SLIT [®] (<i>D.pteronyssinus</i> and <i>D. farinae</i>), approximately 28 mcg Der P 1 and 50 mcg Der f 1 daily (300 IR)	X	X						X	X	X	X		
Wood, 201, US & UK								X	X		X		X	X					13 w.	Greer German cockroach extract								X					

[illegible]

Table 1c: Overview of SCIT vs SLIT trials (n=1)

Study Author, year, country	Allergen(s) type							Allergen no.	Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial tests			
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog		Other (s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/Name (manufacture)	Symptom score	Medication score	Combined score							Symptom score	Medication score	Combined score
Yukselen,2012, Turkey					X				X		X		X				X						HDM (D. pteronyssinus and D. farinae) (50/50) for sublingual and subcutaneous administration.	X	X						X		X			

Figure 1: PRISMA diagram

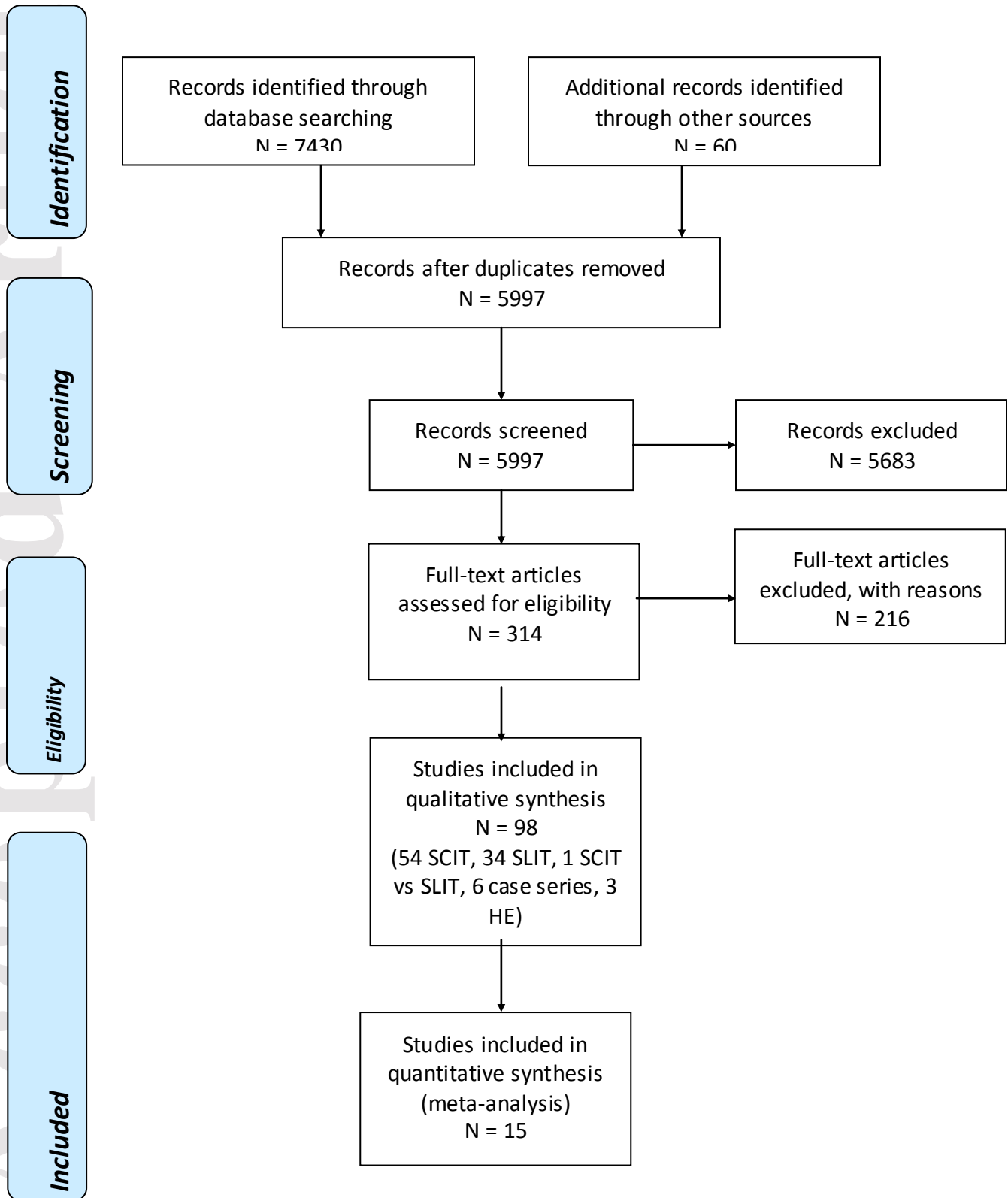
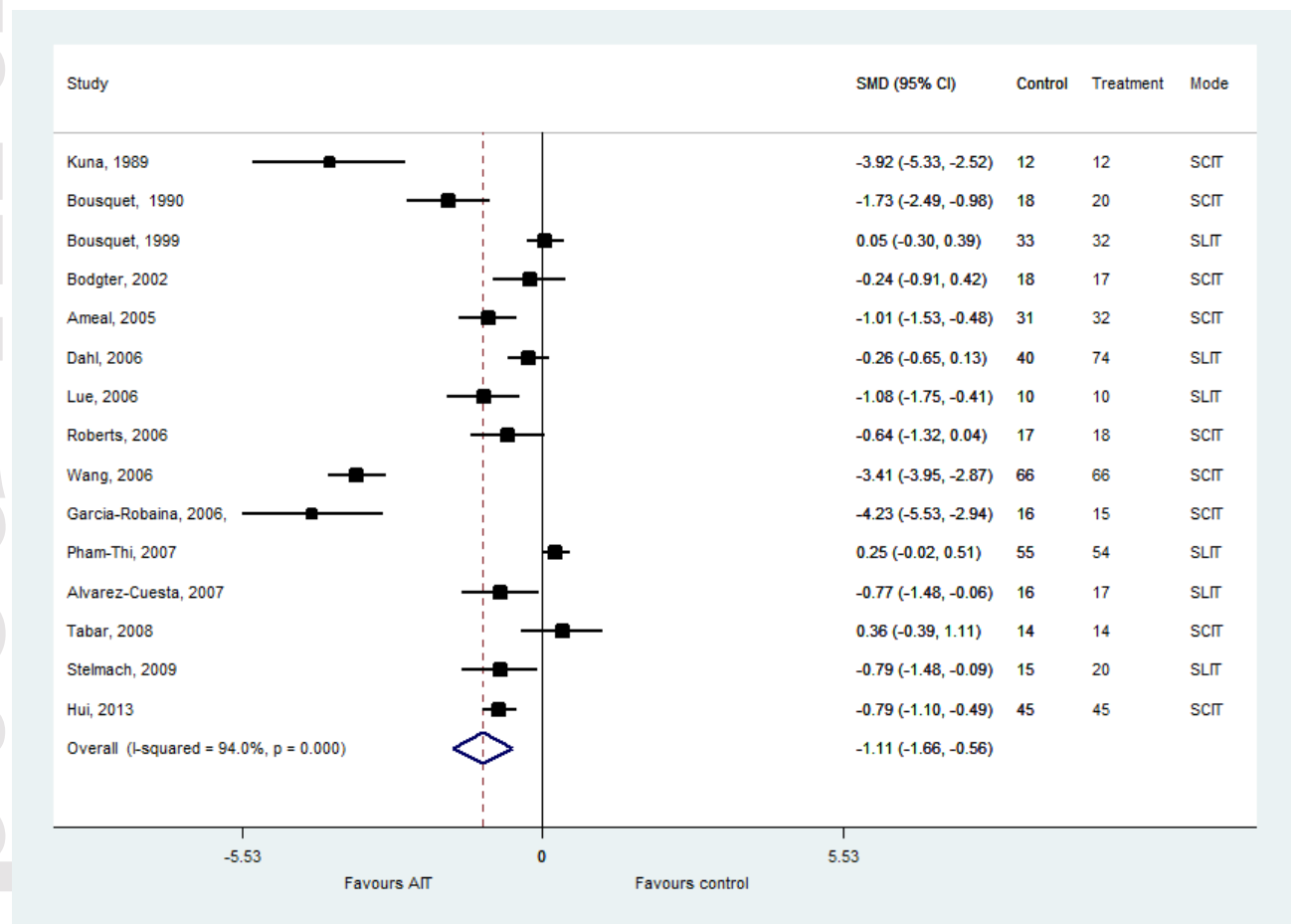
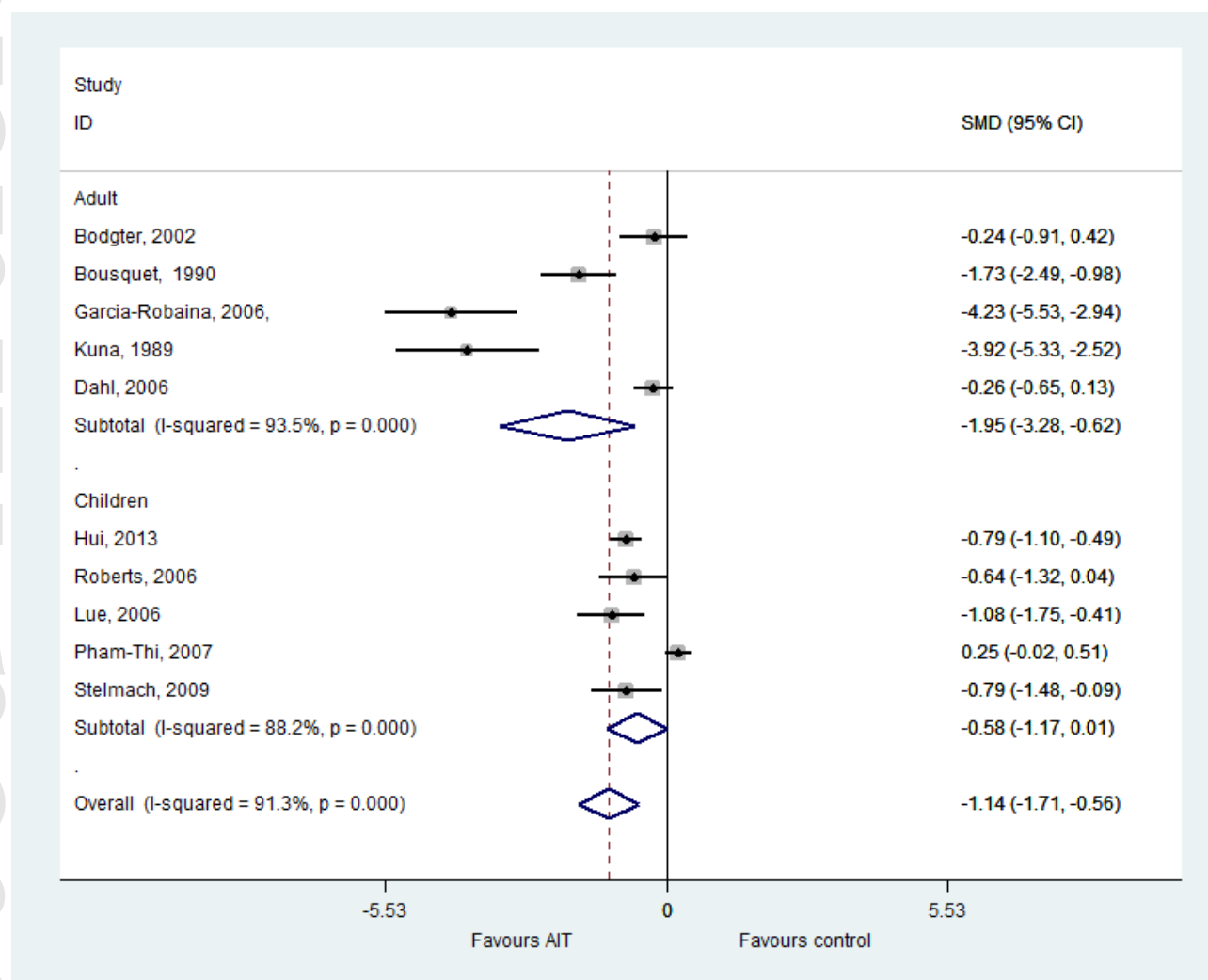


Figure 2: Meta-analysis of double-blind RCTs for symptom scores comparing AIT (SLIT and SCIT) and placebo groups (random effects model)



Test of ES=0: $\chi^2 = 3.96$ $p = 0.000$
Heterogeneity $di-squared = 234.28$ ($df = 14$) $p = 0.000$
I-squared (variation in ES attributable to heterogeneity) = 94.0%
Estimate of between-study variance $Tau-squared = 1.0488$

Figure 3: Meta-analysis of double-blind RCTs, comparing symptom scores between AIT (SLIT and SCIT) and placebo groups in children <18 versus adults ≥18 years (random effects model)



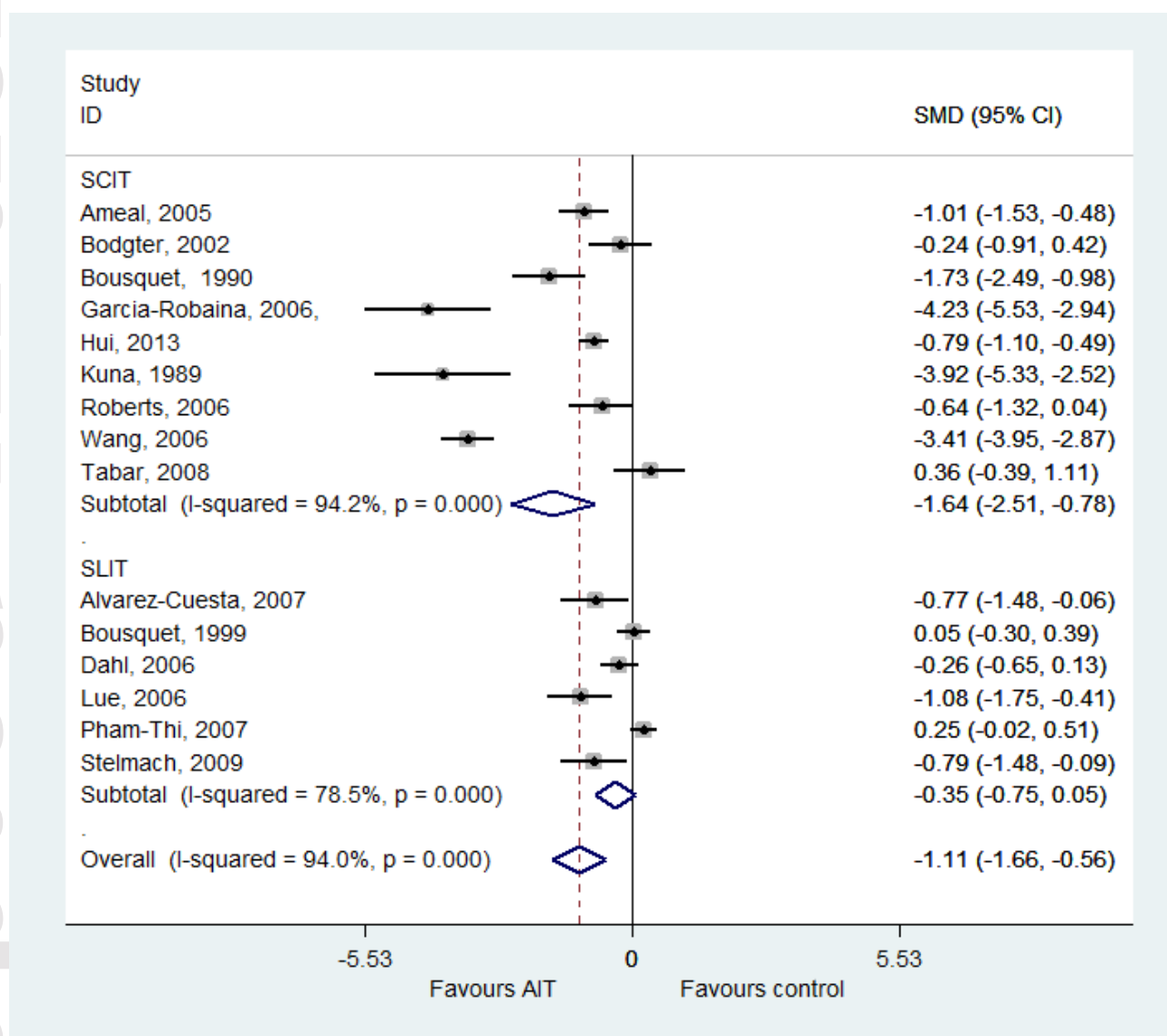
Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	P	Isquared**	Tau-squared
Adult	61.83	4	0.000	93.5%	2.0670
Children	34.02	4	0.000	88.2%	0.3750
Overall	104.04	9	0.000	91.3%	0.7215

Significance test(s) of ES=0

Adult	z= 2.87	p = 0.004
Children	z= 1.93	p = 0.054
Overall	z= 3.87	p = 0.000

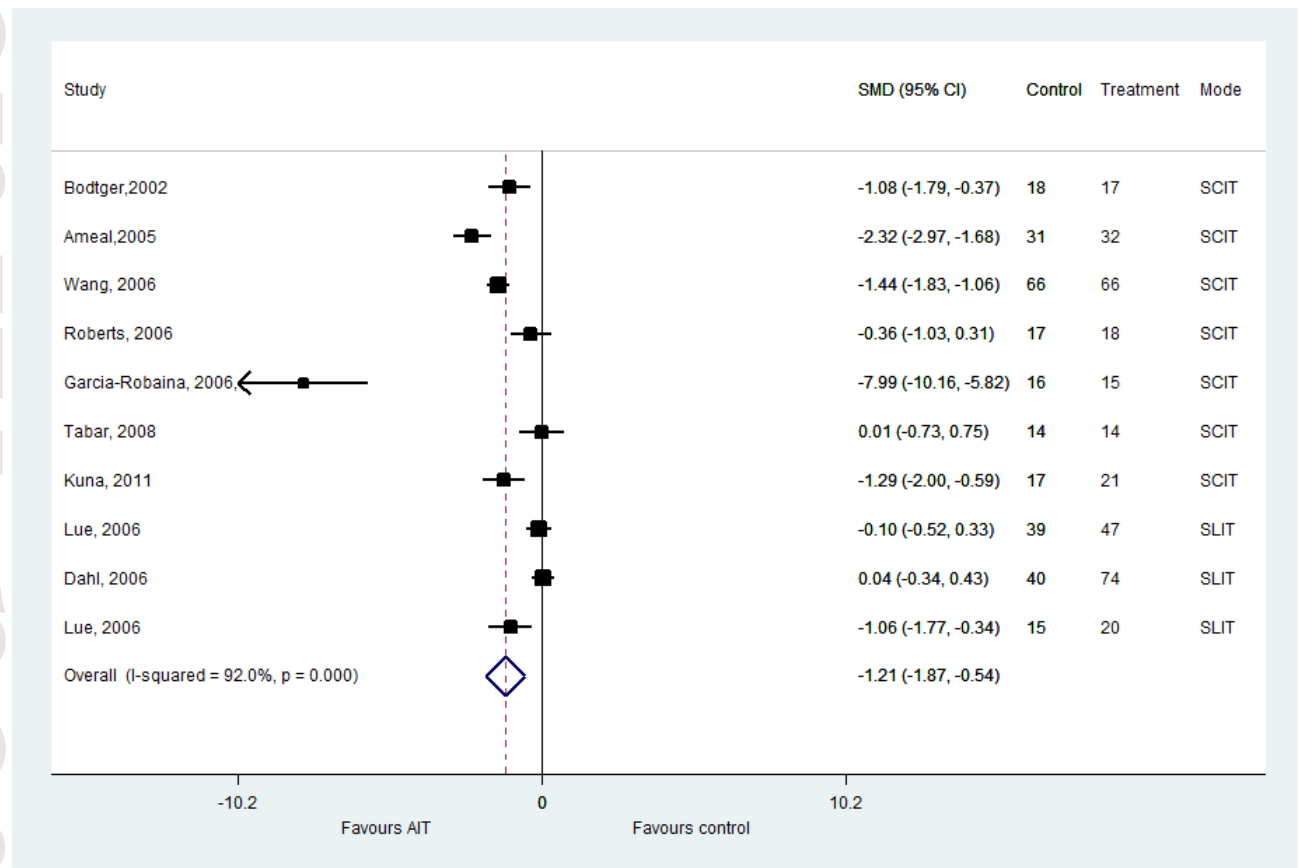
Figure 4: Meta-analysis of double-blind RCTs, comparing symptom scores between SCIT versus SLIT (random effects model)



	Heterogeneity Statistic	degrees of freedom	P	Isquared**	Tau-squared
SCIT	137.11	8	0.000	94.2%	1.5937
SLIT	23.26	5	0.000	78.5%	0.1810
Overall	234.28	14	0.000	94.0%	1.0488

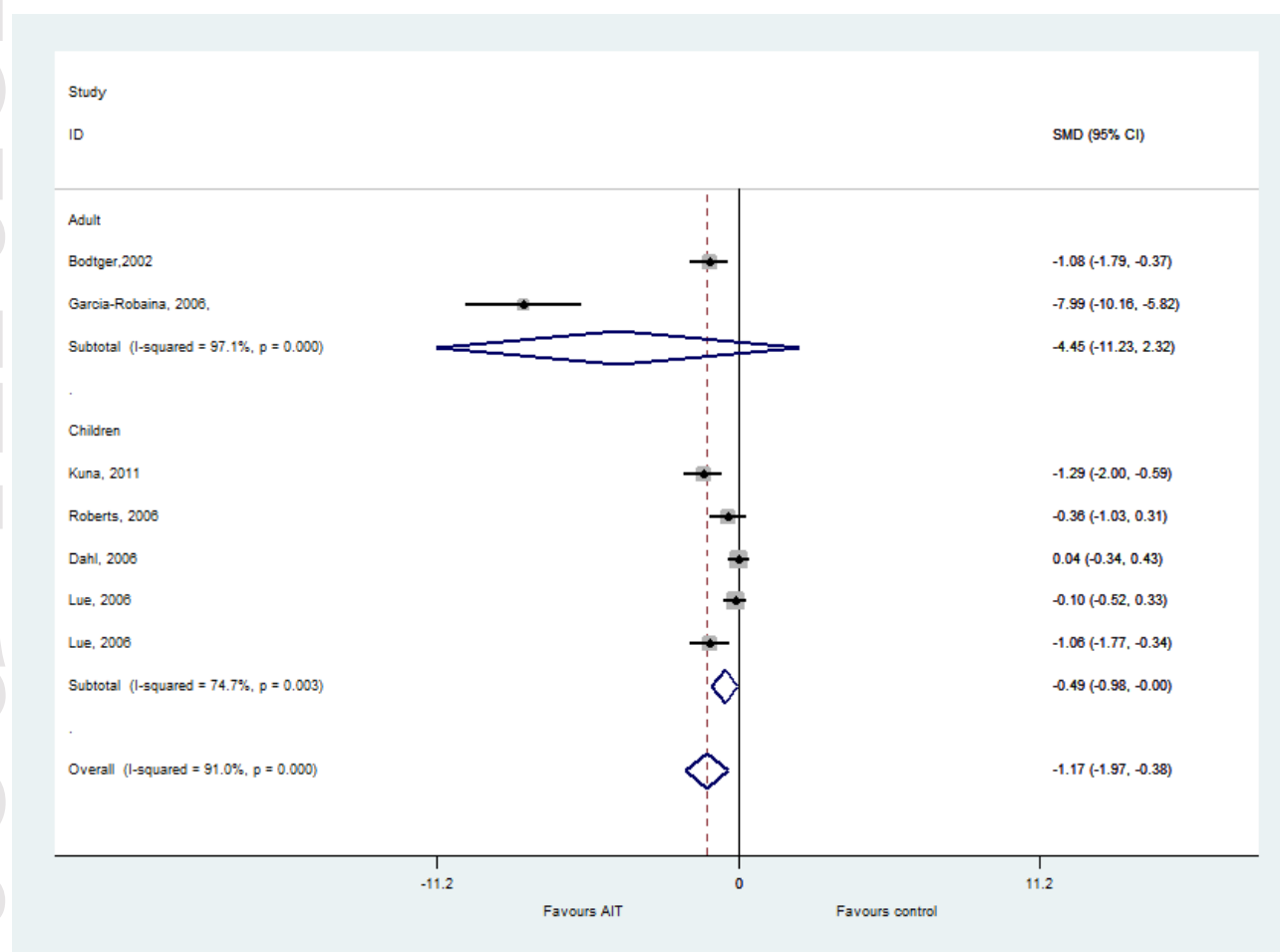
SCIT	z= 3.71	p = 0.000
SLIT	z= 1.71	p = 0.087
Overall	z= 3.96	p = 0.000

Figure 5: Meta-analysis of double-blind RCTs, comparing medication scores between AIT (SLIT and SCIT) and placebo groups (random effects model)



Test of ES=0 : $z = 3.56$ $p = 0.000$
Heterogeneity chi-squared = 112.48 (d.f. = 9) $p = 0.000$
I-squared (variation in ES attributable to heterogeneity) = 92.0%
Estimate of between-study variance Tau-squared = 0.9967

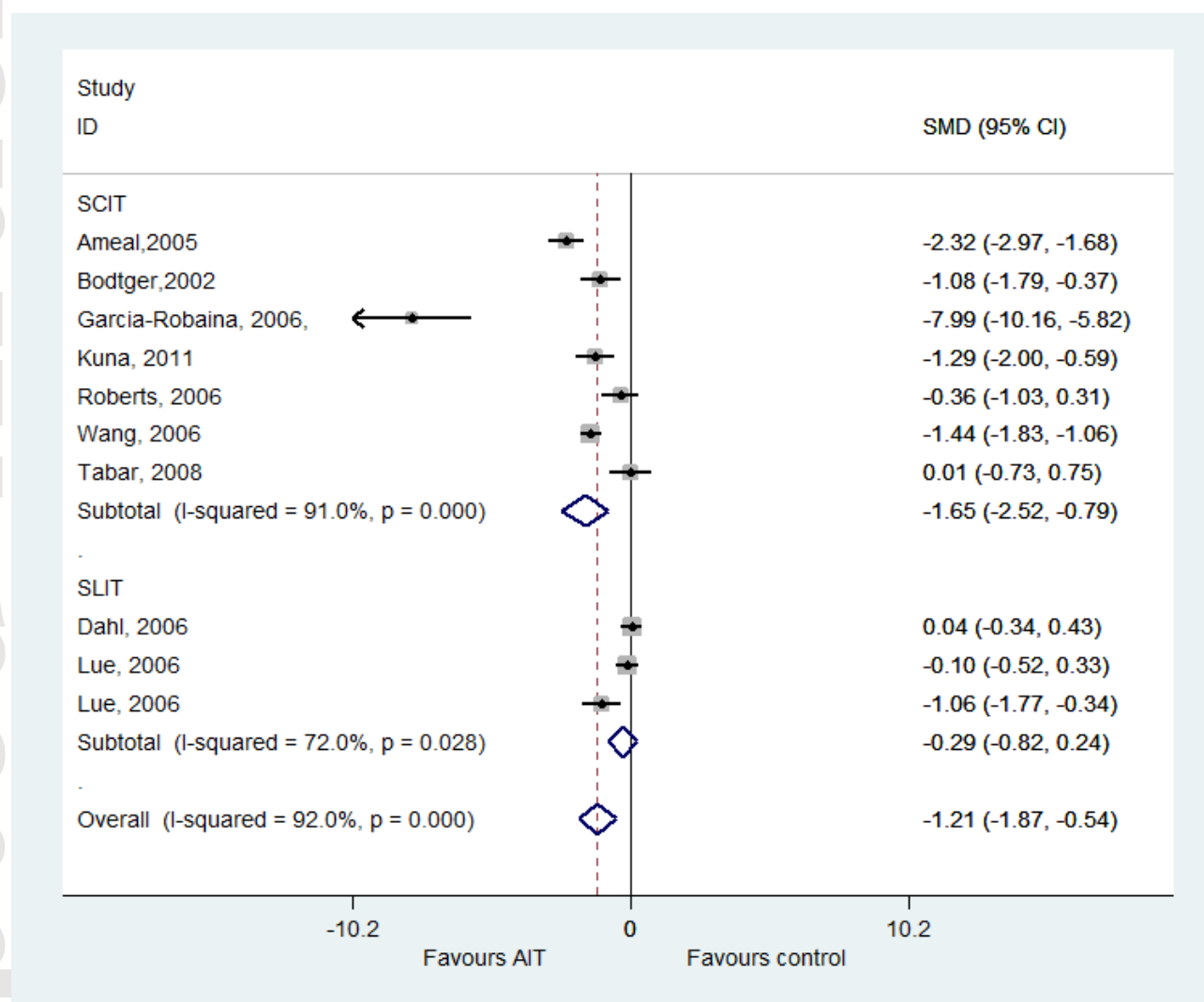
Figure 6: Meta-analysis of double-blind RCTs, comparing medication scores between AIT (SLIT and SCIT) and placebo groups in children <18 versus adults ≥18 years (random effects model)



	Het.stat.	df	P	I-squared**	Tau-squared
Adult	35.08	1	0.000	97.1%	23.2029
Children	15.79	4	0.003	74.7%	0.2244
Overall	66.41	6	0.000	91.0%	0.9722

Adult	z= 1.29	p = 0.197
Children	z= 1.96	p = 0.050
Overall	z= 2.89	p = 0.004

Figure 7: Meta-analysis of double-blind RCTs, comparing medication scores between SLIT and SCIT (random effects model)



	Het. statistic	df	P	I-squared**	Tau-squared
SCIT	66.59	6	0.000	91.0%	1.1642
SLIT	7.14	2	0.028	72.0%	0.1553
Overall	112.48	9	0.000	92.0%	0.9967
Significance test(s) of ES=0					
SCIT	z= 3.74	p = 0.000			
SLIT	z= 1.06	p = 0.287			
Overall	z= 3.56	p = 0.000			

Figure 8: Meta-analysis of double-blind RCTs, comparing combined symptom medication scores between AIT (SLIT and SCIT) and placebo groups (random effects model)

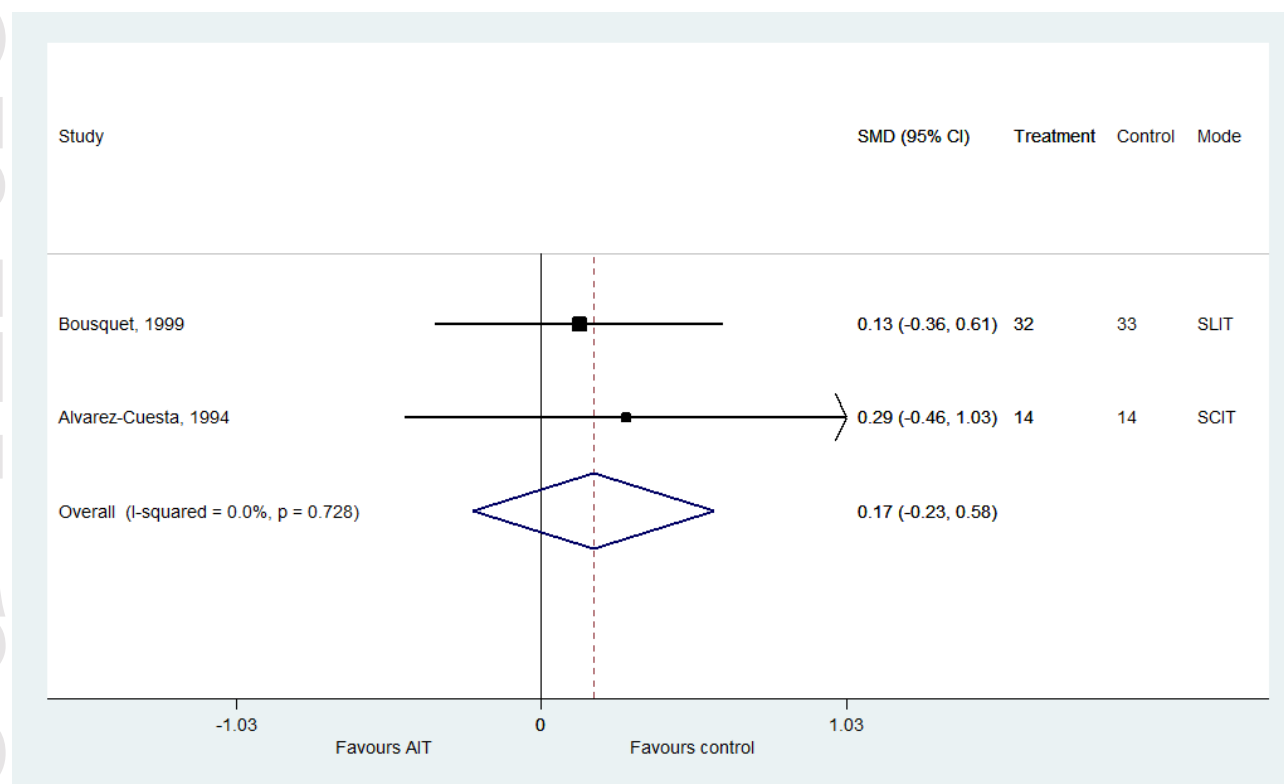
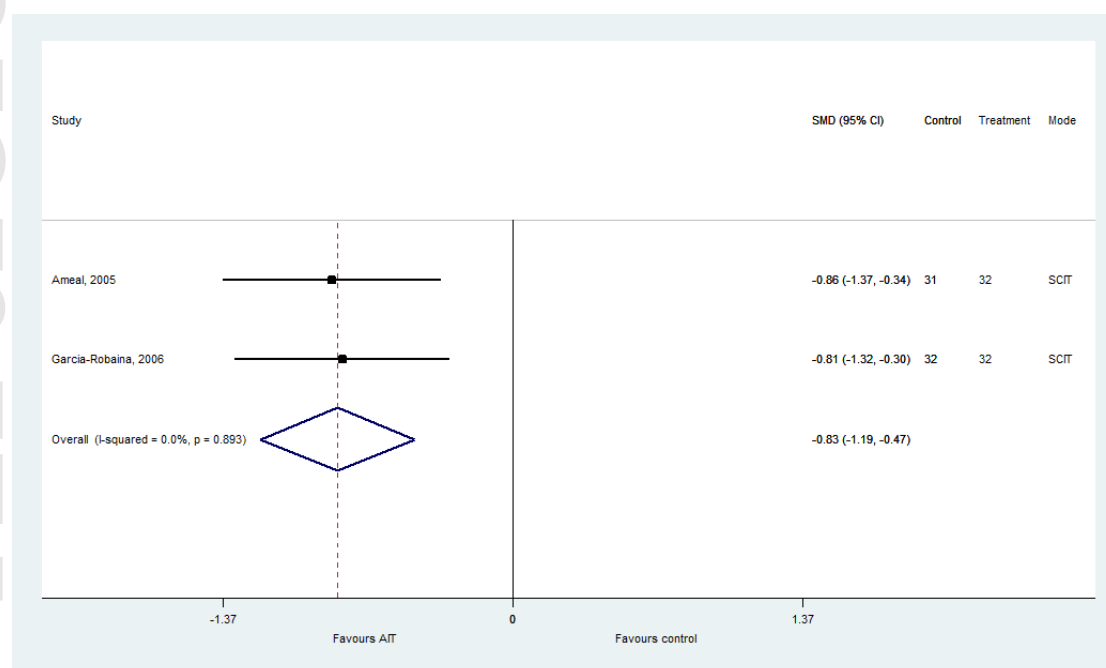


Figure 9: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for asthma specific quality of life (random effects model)



Test of SMD=0 : $z = 4.48$ $p = 0.000$

Heterogeneity chi-squared = 0.02 (d.f. = 1) $p = 0.893$

I-squared (variation in SMD attributable to heterogeneity) = 0.0%

Estimate of between-study variance Tau-squared = 0.0000

Supplementary material:
Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis
S1: Tables

Table S1a: Detailed characteristics of SCIT trials (n=54 reported in 57 papers)

Study Author, year, country	Age/sex	Number of patients (N)/No randomized	Mono/polyse nsitized	Stud y duration (trea tme nt dura tion)	Disea se severi ty (mild , mode rate, sever e)	Type of Immunothera py (intervention vs comparator) Type of allergen	Natural allergen or allergoid	Primary outcomes <i>Short-term effectiveness</i> <i>Long-term effectiveness</i>	Secondary outcomes <i>QoL</i> <i>Safety</i> <i>Lung function</i> <i>Corticosteroid use</i> <i>Exacerbations</i> <i>Environmental exposure chamber/bronchial allergen challenge</i>
Aas,1971, Norway	2-14 y	93/SCIT 36 HDM A and 24 HDM B,33 to placebo	NR	3 y	Sever e	HDM using two different extracts (A and B) vs 0.9% Saline containing 0.5% phenol HDM SCIT vs placebo	Natural	NR	<u>Environmental exposure chamber or bronchial allergen challenge</u> Evaluated by repeated bronchial provocative tests with estimation of the specific bronchial sensitivity threshold to the HDM extracts. Complete bronchial tolerance to the HDM provocations had been achieved in 21(Group A) and 14 (Group B) patients, respectively, compared with only 7 patients in the placebo group. Results showed that HDM extracts were significantly superior to the placebo (p < 0.01).
Adkinson,1997, US	Male (95) and Female (26) children aged 5-12 y old. Mean age of 8.2 y	121/SCIT =61, Placebo=60	All polysen sitised	2 y	88 severe , 31 mode rate, 2 mild	Up to seven allergens allocated per child. Allergens used were dermatophagoides mites, short ragweed, and	Natural	<u>Short term effectiveness:</u> The principal outcome measure was the amount of medication required to control symptoms and maintain peak flows within acceptable limits. Both groups had significant reductions in symptom scores. Change from baseline for treatment: 0.08(0.34), control: -0.16(0.39). The median medication score declined from 5.4 to 4.9 in the immunotherapy group (P 0.001) and from 5.2 to 5.0 in the placebo group (P	<u>Lung function:</u> Difference in the peak expiratory flow rate between the two groups approached significance, the estimated treatment effect was quite small (a mean difference of 3.8 percentage points in the predicted value in favour of immunotherapy, P = 0.05). <u>Corticosteroid use:</u> Reduction in corticosteroid use in both the intervention arm 1.9 (12.4) and placebo 1.7 (12.1) at baseline. <u>Safety:</u> 21 out of 61 children (34%) reported a systemic adverse event in

	old					grass mix. SCIT Various allergens vs placebo		0.001), but there was no significant difference between the groups (P = 0.6).	the intervention arm compared to 4 out of 60 children (7%) in the comparator arm. <u>Environmental exposure chamber or bronchial allergen challenge:</u> The median PC 20 increased significantly in both groups, but again with no difference between the two groups.
Alvarez-Cuesta, 1994, Spain	Females (22) and males (6) between 15-65 yrs. Mean 26 y old.	28/ SCIT= 14, placebo= 14	All monose nsitised	1 y	NR	Cat dander extract, Fel-D1 vs histamine phosphate solution Cat dander extract SCIT vs placebo	Natural	<u>Short term effectiveness:</u> Symptom and medication scores, reported as mean daily score and self-assessed percentage efficacy. Symptom medication score 0.14% -/+ 0.36% treated group, 1.42% +/- 0.51% placebo group; p < 0.001. Improvement was observed in the SCIT group in comparison to placebo in the medication-symptom score (p<0.001).	<u>Safety:</u> 14 adverse events reported in the intervention arm (1.9 reactions for every 100 injections administered) and 3 systemic reactions 0.41% of all injections administered, treated with epinephrine. Zero adverse events reported in comparator arm. 7 patients reported local adverse events equating 1.5% of all injections administered. <u>Environmental exposure chamber or bronchial allergen challenge</u> an improvement in the allergen Broncho provocation test (p < 0.05) results in the SCIT group, and in nonspecific bronchial hyper reactivity measured with methacholine, which was not statistically significant.
Alvarez, 2002, Spain	Median age of 20 y old; 18-29	26/ SCIT=14, placebo=12	All monose nsitised	1 y	Mild	D. pteronyssinus extract entrapped in liposomes vs Empty liposomes prepared at the same lipid concentrations as the active liposomes as comparator. D. pteronyssinus SCIT vs placebo	Natural + adjuvant	NR	<u>Lung function:</u> FEV 1 before intervention for active and placebo groups; median 100%, IQR 88-101 vs 93.5%, IQR 84-107. After intervention, significant difference in SCIT group; median active group 106.5%, IQR 98-110 vs 96.5%, IQR 87.5-101 in placebo group, p = 0.034 Allergen and methacholine bronchial challenge are reported

Ameal,2005, Spain	Mean age of whole sample is 23 y old, range 14- 48. Female 29 and Male 26.	63/ SCIT=32, placebo=3 1	NR	1 y	Mild/ mode rate	D. pteronysinus extract vs comparator (placebo contained all the components of the vaccine with the exception of the extract). D. pteronysinus SCIT vs placebo	Allergoid	Short term effectiveness: Asthma symptom score SCIT group before treatment median 1.5, IQR 0.5- 2.35, after treatment median 0.14, IQR 0-1.93; placebo before treatment median 1.43, IQR 0.33- 2.4, after treatment median 2.93, IQR 1.11-4.19. Asthma medication scores SCIT group before treatment median 3.57, IQR 2.58-5.29, after treatment median 1, IQR 0.29-1.50; placebo before treatment median 4, IQR 2.54-5.36, after treatment median 3.13, IQR 2.47-3.63.	QoL: Asthma quality of life reported using the AQLQ (Marks et al). Significant difference at end of treatment for SCIT group compared to placebo P=0.0025 Safety: 7 patients in the intervention arm reported adverse events compared to 6 in the placebo arm. 5 systemic reactions reported in the intervention arm compared to 3 in the comparator. 2 local adverse events reported in the intervention group and 3 in comparator group. Environmental exposure chamber or bronchial allergen challenge the primary outcome was bronchial provocation test. At baseline, the active group needed a median of 2.56 HEP (IQR: 0.54–5.61), and placebo 2.77 (IQR: 1.69–4.02) (P ¼ 0.9173). At the end of the study, these values were 7.14 (IQR: 4.29–14.38) and 2.76 HEP (IQR: 1.50– 10.81), respectively (P ¼ 0.0029). The differences of the values between those obtained after 12 m with those at baseline in the active group had a median value of 4.27 HEP (IQR: 1.74– 8.45), and of)0.05 HEP (95% IQR:)1.17 to 5.19) in the placebo (P ¼ 0.0004). The results of the Hodges– Lehmann estimator were)0.21 (95% CL:)2, 0.95) at baseline and 3.11 (95% CL: 0.4–5.88) at the end; and 4.41 (95% CL: 1.78–8.44) for the differences between baseline and at the end. The active group showed a significant difference from baseline (P < 0.0001), whereas the placebo group did not (P ¼ 0.9292). After 12 m, the active group needed a median of 2.8 times more allergen to achieve the value. In contrast, in the placebo group this value was 1, indicating no changes.
Armentia- Medina,1995, Spain	Age 15-50, gender data NR	35/SCIT= 22, Placebo= 13 Asthma=2 5	NR	1 y	Mild to mode rate	Standardised mite extract (Lepidoglyphus destructor0) placebo was 0.9% saline solution SCIT storage mite vs comparator	Natural	Short term effectiveness: Subjective assessment of symptoms showed a significant improvement in the SCIT group compared to the control group, P<0.01	Environmental exposure chamber or bronchial allergen challenge Significant decrease in NBR, P<0.001

Arvidsson,2004 , Sweden	Mean 31 y old, range 19-45 y old. 12 Females and 7 males	19/ SCIT=10, placebo=9	12 patient' s poly sensitis ed and 7 patients monose nstised	1 y	NR	standardized birch pollen extract vs dilute histamine dihydrochloride . SCIT depot Betula preparation extract vs placebo	Natural	NR	<u>Lung function:</u> Late phase reaction: Time point of maximal fall in FEV1 was similar in both treatment groups and before and after treatment approximately 6 h following PD20 time point. Percentage of maximal fall in FEV1 in SIT-group, before and after treatment, was 24% (21–34) and 19% (5–21), respectively and in placebo-group 25% (13–38) and 27% (14–43), respectively. The decrease was statistically significant in the SIT-group ($P < 0.02$), but not for placebo. <u>Environmental exposure chamber or bronchial allergen challenge</u> Early and late phase asthmatic responses after treatment using allergen bronchial provocation test. Measures at one y. Reported as change in PD20 values. Early phase reaction: After the treatment, a significant increase in PD20 values was seen within the SIT-group ($P < 0.01$), but not in the placebo group. There was also a statistically significant difference in PD20 values between the groups after 1 y of treatment ($P < 0.01$).
Basomba, 2002, Spain	Median 22, range 14– 50 y old. 27 Female and 28 males;	55/SCIT= 29, placebo=2 6	Polysen sitised	1 y	Mild and mode rate	D pteronyssinus mite bodies encapsulated in liposomes vs placebo liposomes D pteronyssinus mite bodies SCIT vs comparator	Natural+ adjuvant	<u>Short term effectiveness:</u> Changes in symptom and medication consumption scores reported using medians and IQR. The percentage of healthy d (i.e., d without medication and with absent or mild symptoms) was calculated and measured over 1 y. Asthma scores difference intervention group median change 0.21 (IQR -0.03-0.44), $p < 0.01$. Placebo change 0.06 (-16-0.25), $p > 0.05$. Asthma medication score differences after intervention group median change 0.8 (IQR 0-1.6), $p < 0.01$. Placebo 0.1 (-1.4-0.7), $p > 0.05$. 45.8% of patients in active group reduced their symptom and medication scores by 60%, placebo group reduced by 12%, $P=0.038$	<u>Safety:</u> patients had systemic reactions in the intervention group, the frequency was 1.66% (95% CI, 0.6%-2.7%) per dose for the intervention group and 1 patient in the comparator group had a systemic reaction. 8 local adverse events were reported in the intervention group and 0 in the comparator group. <u>Environmental exposure chamber or bronchial allergen challenge</u> Reduced sensitivity to bronchial challenge test in active group, $P=0.02$ compared to no change in the placebo group $P=0.372$. No across group comparison
Blumberga,200 6, Denmark	Mean age 29, 22 females and 32 males	54/SCIT= 26, Placebo=2 8	Polysen sitised	3 y	Mode rate to severe asthma	HDM vs histamine dihydrochloride HDM SCIT vs placebo	Natural	<u>Short term effectiveness:</u> Median % reduction in inhaled corticosteroids with up to 3 y of treatment	<u>Corticosteroid use:</u> Corticosteroid use before intervention median dose 1000µ FP daily and for comparator median dose 750µ FP daily. After intervention, median dose 250µ FP daily and for comparator median dose 500µ FP daily. 82% reduction in baseline for intervention group compared to 42% in comparator group. <u>Safety:</u> 10 Patients had systemic reactions to the intervention compared to 8 patients in the comparator group

Bødter, 2002, Denmark	Median age 27 range 19-46. Females 21 and males 14	35/SCIT=17, Placebo=18 Asthma=14 and rhinoconjunctivitis=35;	Polysensitised	1 y	NR	Birch pollen extract vs histamine dihydrochloride SCIT Birch pollen extract vs placebo	Natural	Short term effectiveness: Change in total symptom score and medication score, expressed as means, measured over 1 y. Active asthma symptom score 0 (0-13), placebo 1 (0-15).	Corticosteroid use: Three patients (SCIT=1, placebo=2) needed a one-week course of oral prednisolone 12.5 mg late in the season. Safety: 7 adverse events were reported in the intervention group and 16 in the comparator. Exact numbers of systemic and/or local reactions were not reported.
Bousquet, 1985, France	Age range 18-42. Mean age 28.1. Females 10 and males 20.	30/SCIT=20, Placebo=10	NR	7 w	NR	Standardized HDM extract vs placebo HDM SCIT vs placebo	Natural	NR	Safety: 4 patients reported systemic reactions in the intervention group and 3 patients needed adrenaline. Lung function: In placebo group 2 had improved PD20 in FEV1, 5 had no change and 2 had worsened comparing before and after. In the immunotherapy group, 15 had improved, 5 were equal and 0 worsened. Placebo group was not significant; immunotherapy group was significant p<0.01. Environmental exposure chamber or bronchial allergen challenge Bronchial provocation tests performed in a standardized manner demonstrated that a provocative dose causing a 20% fall in FEV1, a 25% fall in maximum mild expiratory flow rate, a 25% fall in maximum flow when 5070 of the forced vital capacity has been expired, and a 35% fall in specific airway conductance were significantly (p < 0.005 to p < 0.01, Wilcoxon W test) improved in the treated group and remained unchanged in the placebo group
Bousquet, 1990, France	Mean age 24.8, gender NR	57/SCIT=20 high dose, 19 low dose, Placebo=18	Sensitisation NR	1 y	NR	Mixed grass extract vs placebo (0.9% saline containing 0.4% phenol as a preservative and increasing concentrations of histamine dihydrochloride) SCIT mixed grass extract	Natural + Allergoid	Short term effectiveness: Symptom scores and safety over 1 y period, measured using mean scores and number of reactions. Mean asthma symptom score 15.1 (18.5) in the intervention group compared to 54.8 (23) in comparator group.	Safety: 5 systemic reactions reported in the intervention group compared to 3 in comparator group. 5 local adverse events reported in the intervention group and 0 reported in comparator group. Lung function: In asthma, only patients pulmonary function tests there was comparatively better performance for asthmatics in the SIT group than in the control group after completion of the 2-y schedule. FEV1 also improved significantly between the baseline pollen season and after the SIT schedule. Exact numbers are not reported

						high dose vs low dose vs placebo			
Cantani, 1996, Italy	Median age 6.5, range 4 to 13. Males 14 and 6 females	20/SCIT= 10, Placebo=1 0	Monose nsitised	3 m	NR	Mixture of grass, other pollen, mould, house dust mite and cat and dog dander vs comparator (buffer solution) Intradermal injection of grass, other pollen, mould, house dust mite and cat and dog dander vs placebo	Natural	Short term effectiveness: Effectiveness measured using mean symptom score and medication use. Total days with asthma drug medication consumption was 52 for intervention group and 180 for placebo, p = 0.00000. Number of days with asthma was 36 in intervention group and 93 for placebo, p = 0.0000.	Safety: Zero systemic reactions reported.no local reactions reported in the active group and 1 in the placebo group.
Chakraborty, 2006, India	Whole sample mean 32.4, range 20- 59, 24 males and 11 females	35/SCIT= 18, Placebo=1 7 Asthma n= 14; allergic rhinitis n=35; rhinoconju nctivitis n=35	Monose nsitised	2 y	NR	P sylvestris pollen extract vs placebo P sylvestris pollen extract	Natural	Short term effectiveness: Effectiveness measured through medication and symptom score. The SIT group showed decreases of 33.5% and 57% from the baseline symptom medication scores during the first and second treatment season, respectively. This group showed significant increases in FEV1.	Safety: The rate of local adverse reactions was 0.024%. Lung function: In asthma, only patients pulmonary function tests there was comparatively better performance for asthmatics in the SIT' group than in the control group after completion of the 2-y schedule. FEV1 also improved significantly between the baseline pollen season and after the SIT schedule. Exact numbers are not reported

Creticos, 1996, US	Mean age=36, SCIT group, 35.1 placebo; age range 16-70.19 males and 20 females	77/SCIT=37, Placebo=40	Sensitisation NR	2 y of treatment	NR	Extract of short ragweed pollen vs placebo SCIT short ragweed pollen vs placebo	Natural	Short term effectiveness: Effectiveness measured using mean symptom score and medication use. Seasonal symptom scores for the SCIT group improved throughout the two seasons of treatment, whereas those for the placebo group showed less improvement. Comparing the two groups, the difference in symptoms was not significant ($P = 0.08$ in y 1 and $P = 0.3$ in y 2). Medication score was lower for the first treatment year (19 ± 8 vs. 43 ± 8 , $P = 0.01$). SCIT group had a reduction in the inhaled steroids and inhaled bronchodilators (data not shown). There was no significant difference between the groups in medication use during the second treatment year (29 ± 8 vs. 33 ± 8 , $P = 0.7$). Combined chi-square test of peak flow measurements, medication use, and asthma symptoms was significant in the first year ($P = 0.003$; with a Bonferroni correction for multiple evaluations, $P = 0.009$), indicating a significant difference between the two study groups; results for the second year were not significant ($P = 0.1$).	Safety: Seven patients receiving ragweed extract reported systemic allergic symptoms in the intervention group compared to four in the comparator group.
Dreborg, 1986, Sweden and Finland	Whole mean age 11, range 5-17, females = 16 and males = 14	30/SCIT=16, Placebo=14	Polysensitised	10 m	NR	Cladosporium herbarum vs caramelised histamine HCl (placebo) SCIT Cladosporium herbarum vs placebo	Natural	Short term effectiveness: Effectiveness measured using symptom and medication scores. There was no difference in total medication or symptom scores.	Safety: 4 large local adverse events reported in the intervention group compared to zero in comparator group. Environmental exposure chamber or bronchial allergen challenge: Patients in the intervention group showed significantly improved bronchial tolerance $p < 0.01$ compared to placebo.

Dolz,1996, Spain	Whole sample mean 19.9, gender NR	30/28, asthma n=6, allergic rhinitis n=28, rhinoconjunctivitis n=28	Monosensitised	3 y	NR	Grass-pollen extract vs comparator (placebo extract composed of histamine hydrochloride). SCIT grass pollen vs comparator	Natural	Short term effectiveness: symptom and medication scores measured over 3 years. A significant difference existing between the initial and final time of the intervention group, and there were significant differences between the two groups for all the parameters considered. Bronchial symptoms significantly improved ($P < 0.001$) in the active group.	Safety: Total of 11 adverse events reported in the intervention group and zero in comparator group. 7 systemic reactions reported in intervention group requiring epinephrine and zero in comparator group. 4 local adverse events were reported in the whole sample Environmental exposure chamber or bronchial allergen challenge: Bronchial provocation test positive in active group and show a significant difference, ($P < 0.001$), this is not the case for the control group.
D'Souza, 1973, UK	Whole sample: 23 aged 10-20, 30 aged 21-30, 19 aged 31-40 and 19 aged 41+. Females =37 and males = 54.	91/SCIT=48, Placebo=48. Asthma n= 83, allergic rhinitis n=84	Polysensitised	3 m	NR	D. pteronyssinus extract vs comparator (placebo contained 0.5% carbol saline solution). SCIT D. pteronyssinus vs placebo	Natural	Short term effectiveness: Effectiveness measured using proportion of patients with improved asthma. The mean improvement in asthma scores for the treated group was 36% with a range of 14-100%, whereas for the controls it was 25% with a range of 5-100%. Significant improvement in asthma, drug use and dust tolerance recorded in the treated group as compared with controls at 3 m after treatment, but not at 1 month after treatment. The overall self-assessment at 1 and 3 m after treatment showed differences in those recording themselves as "Very much improved". 31% (14/45) of the SCIT as opposed to 13% (6/46) of the controls recording themselves as very much improved at 1 month and 35% (14/40) compared with 19% (8/43) at 3 m after the end of the treatment. The D. pteronyssinus group recorded less asthma, less use of drugs and an increased clinical tolerance of household dust.	Safety: 34 patients had local reactions to injections.
Franco, 1995, Italy	Mean age 24.5, females = 24 and males 25.	49/SCIT=24, Placebo=25	Monosensitised	15 m	NR	D pteronyssinus extract vs comparator (placebo aluminium hydroxide suspension) SCIT D pteronyssinus	Natural	Short term effectiveness: Visual analogue symptom score showed improvement in both groups but greater in the active treatment group which was statistically significant at both 9 and 15 m of treatment. No statistically significant difference was recorded in medication score.	Safety: 17% of patients in the intervention group reported adverse events compared to 20% of patients in the comparator group. One systemic adverse event reported in each of the intervention and comparator group. Environmental exposure chamber or bronchial allergen challenge: After 15 m 6 patients in the SCIT group showed a decrease in their sensitivity to methacholine compared to only 4 in the placebo group. The difference between the groups was not statistically significant

						vs placebo			
Gaddie,1976, UK	Mean age 33.5 range 13 to 68, males 24 and females 31	55/SCIT=26, Placebo=29; asthma n=55, allergic rhinitis n=28	Monosensitised	1 y	NR	D pteronyssinus extract vs comparator placebo (histamine) SCIT D pteronyssinus vs placebo	Natural	Short term effectiveness: Effectiveness measured using mean change in symptom scores. There was no significant difference between the two groups at any time for any of the symptoms recorded.	Safety: Seven systemic adverse events reported in intervention group and 5 systemic adverse events reported in comparator group. 27% patients in the intervention group reported local adverse events compared to 38% in the comparator group.
Garcia-Robaina, 2006, Spain	Mean age 23.65, 27 males and 37 females.	64/SCIT=32, Placebo=32, asthma n=64, allergic rhinitis n=64	Monosensitised	54 w	NR	D pteronyssinus and D farinae extracts (50:50) vs placebo (NR) SCIT D pteronyssinus and D farinae extracts vs placebo	Allergoid	Short term effectiveness: The median improvement in the intervention group over placebo was 53.76% in total symptom and 58.09% in medication scores.	QoL: AQLQ (Marks et al): Significant improvement in SCIT group compared to placebo (P=0.043) Safety: Zero systemic adverse events reported for intervention and comparator groups. Four local adverse events reported for both intervention and comparator groups. Before intervention median PD20 FEV1 10.05, IQR 5.48 to 81.00; comparator median 43.5, IQR 6.1 to 511 after intervention median 111.06, IQR 41.05 to 686 comparator median 41, IQR 3.35 to 311, p = 0.029. Environmental exposure chamber or bronchial allergen challenge: Effectiveness measured through bronchial provocation test, reported as change from baseline. The intervention group experienced a significant improvement in BPT (P < .001), whereas the placebo group did not (P = .648). At the end of the study, 20 patients in the intervention group versus 9 in the placebo group (P = .013; odds ratio, 5.71 [1.76, 18.51]) needed more than twice the amount of allergen to obtain a positive BPT.

Haugaard,1992, Denmark	Mean age C24:P2428 , range 13 to 48 y. Females = 15 and males = 12.	27/SCIT= 15, Placebo=1 6	Polysen sitised	5 m dou ble blind follo wed by open 12 m	NR	Cat epithelium extract and dog dander extract vs comparator placebo preparation containing histamine chloride SCIT cat epithelium extract and dog dander extract vs placebo	Natural	NR	Safety: After 8-12 hours, local swelling of 5-10 cm in diameter was reported after 19% of the injections, and a swelling > 10 cm after 6%, of the injections. Environmental exposure chamber or bronchial allergen challenge: A comparison of the change in PD20 between the placebo group and the group of patients treated with cat extract showed no significant difference after 5 m of IT (P = 0.13). For the patients treated for 12 m, the decrease in PD20 to cat was more pronounced (P = 0.003). Patients treated with dog allergen demonstrated no significant decrease in PD20 to dog extracts after 5 and 12 m, and neither did the placebo group. No significant difference between placebo and dog extract-treated patients was found. Bronchial sensitivity to histamine did not change significantly in any of the groups. More prolonged IT, 19 patients allergic to cats (17) and/or dogs (9) were treated for 12 m. Bronchial sensitivity to cat decreased further (P = 0.003), while no significant change was found in dog extracted patients. In cat extract-treated patients a significant decrease in bronchial histamine sensitivity developed (P = 0.02).
Hedlin,1999, Denmark	7 to 16 y old	29/SCIT= 17, Placebo=1 5	Polysen sitised	3 y	Mild to mode rate	Cat dander, Dermatophagoi des pteronysinus, timothy pollen, and birch pollen extracts vs placebo containing histamine chlorideSCIT cat dander, Dermatophagoi des pteronysinus, timothy pollen, and birch pollen extracts vs placebo	Natural	NR	Safety: Five systemic adverse events reported in the intervention group compared to zero in comparator group. Environmental exposure chamber or bronchial allergen challenge Before the study, median PC20 allergen was comparable (1900 and 1400 SQU/mL) in intervention group vs placebo groups. PC20 allergen increased significantly in both the intervention immunotherapy group (P < .001) and in the placebo-pollen group (P < .05). PC20 histamine increased continuously in the intervention immunotherapy group (P < .05 and P = .002 after 1 and 3 y, respectively) and had also increased after 3 y in the placebo-pollen group (P < .05). The difference between the 2 groups was significant for PC20 allergen (P = .001) but not for PC20 histamine.

Hui, 2013, China	Mean age 9.9. Males =46 and females 44	90/SCIT=45, Comparato r=45	Sensitisation NR	3 y	Mild to moderate	HDM vs control group receiving glucocorticoid management SCIT HDM vs comparator	Natural	Short term effectiveness: Effectiveness measured by reduced dose of inhaled corticosteroids. Asthma symptom score before intervention day mean 2.8 (0.7) and for comparator day mean 2.8(0.5). After intervention 0.7(0.5) and for comparator 1.0(0.5).	Safety: Total adverse events reported in intervention group were 203 out of 1735 injections administered; adverse events for the comparator group were NR. Of these 1 out of 203 was systemic adverse reaction and 202 were local adverse events. Treatment NR. Lung function: PEF before intervention 63.3(5.4) and for comparator 62.3(5.1) after intervention 91.3(5.8) and for comparator 81.6(4.5). Corticosteroid use before intervention was 196.7 and for comparator 206.7, after intervention it was 175 and for comparator 193.2. The ICS discontinuation rate in the treatment group (28.9%) was significantly higher than that in the control group (20.0%) (Z=-2.327, P=0.020). The median dose of ICS was reduced in the treatment group after two and three y of treatment compared with that of the control group. After three y of treatment, the discontinuation percentage of ICS in the treatment group was higher than that in the control group.
Johnstone,1968 , US	Children < 16. Males = 88 and females = 42	210 children initially recruited at the completion of the study, 130 children who had reached their sixteenth birthday were still under observatio n. SCIT=67, Placebo=64	Polysensitised	14 y	NR	Pollen, animal dander, mould allergens and HDM vs placebo buffered saline SCIT Pollen, animal dander, mould allergens and HDM vs placebo	Natural	Long term effectiveness: Effectiveness measured whether asthma persisted at age 16 (treatment was ongoing). Of the 130 children, still under observation at the time of their sixteenth birthday, 22% of the placebo treated children were free of asthma compared to 72% of the treated children.	NR

Kuna,1989, Poland	Mean age 27.2. Females = 7 and males = 17	24/SCIT= 12, Placebo=1 2	Sensitisation NR	2 y, 1 y blind , 1 y open	NR	Grass pollen extract vs placebo saline SCIT Grass pollen extract vs placebo	Allergoid	Short term effectiveness: Effectiveness measured through mean symptom scores (measured daily). Daily symptom score was lower in the grass pollen treated group compared to the placebo-treated group (2.57 + or - 0.28 versus 3.75 + or - 0.32; p = 0.015).	Safety: Zero adverse events were reported in the intervention and comparator groups. Lung function: The change in the provocative concentration of histamine that causes 20% fall in FEV1 during the pollen season highly correlated with the change in HRF production
Kuna,2011, Poland	Mean age 11.5, range 5.6-18. Females = 25 and males = 25	50, asthma n= 38, SCIT=21, Placebo=1 7; allergic rhinitis n=46, rhinoconjunctivitis n= 34.	Monosensitised	3 y	Mild to moderate	Alternaria alternata extract vs comparator placebo using histamine dihydrochloride . SCIT Alternaria alternata vs placebo	Natural	Short term effectiveness: Effectiveness measured based on symptom and medication scores, with up to three y of treatment. The reductions in combined symptom-medication score after therapy, compared with placebo, were 10.8%, 38.7%, and 63.5% after the first, second, and third y of SIT, respectively (P 5 .73, .102, <.001, and <.001 for baseline, 1, 2, and 3 y of SIT, respectively, active therapy vs placebo, 1-way ANOVA test). Asthma medication score before intervention was 13.8 and for comparator 11.2 after intervention 9.1, 7.2, and 2.3 after the first, second, and third y of SIT (P < .001 for baseline vs consecutive y, respectively). Increase in use of rescue medication in the placebo group, from 11.2 at baseline, to 16.0, 18.0, and 21.4 after the first, second, and third y of SIT (P 5 .9, .0015, and .001 for baseline vs consecutive y, respectively).	Safety: Total adverse events reported in intervention group were 5 (30) and comparator group 2 (20). 12 local adverse events reported in the intervention group.

Lewis,	34 patients (19 females and 15 males aged 16-56 y)	34/18Mite extract, 16 HDM	NR	6-9 m	NR	HDM D. farinae 0.002% to 0-1% w/v weekly subdermal injections followed by fortnightly maintenance vs HD HDM D farinae SCIT vs HD vaccine (0-118% to 7-5% w/v	Natural	Short term effectiveness: 14 (78%) of the 18 patients receiving D. farinae improved but only 6 (38%) of the 16 patients getting house-dust. The difference was significant $P < 0.05$.	Corticosteroid: In the active group the corticosteroid dose could be reduced in 7 out of 9 patients	
Maestrelli, 2004, Italy	Mean age 21.8. Females =25 and males =47.	95/SCIT=49, Placebo=46	Polysensitised	4 y	Mild to moderate	D pteronyssinus and Dermatophagoides farinae vs comparator placebo aluminium hydroxide solution SCIT D pteronyssinus and Dermatophagoides farinae vs placebo	Natural	Short term effectiveness: Median asthma symptom scores in both the placebo and immunotherapy groups tended to decrease during the study, but the changes were not statistically significant. A difference in asthma symptom scores between the 2 groups in the second y of treatment was not confirmed at the end of the study. The proportion of subjects who did not use bronchodilators during the autumn increased significantly from the observational y to the third y of treatment in the immunotherapy group but not in the placebo group. No significant change in the average use of inhaled steroids and bronchodilators was observed in the 2 groups after randomization.	Lung function: Morning and evening PEF values improved significantly in the immunotherapy group but did not change in the placebo group. The average increase in the immunotherapy group was between 1.6% and 4.7% in the predicted value of morning PEF and between 2.5% and 5.5% in the predicted value of evening PEF during the autumn m of the last y of the study. No significant differences in FEV1 or in degree of bronchial responsiveness between groups. Exact data NR	

Malling, 1986, Sweden	Mean age 28, range 16-54. Females= 6 and males= 16	22/SCIT= 11, Placebo=11	Polysensitised	1 y	Severe	Cladosporium herbarum vs comparator placebo Caramelized histamine HCl	Natural	Short term effectiveness: Clinical efficacy by comparing symptom score (asthma + peak flow score), medication score and the combined (total) score obtained in the two seasons. A statistically significant difference was not found in either symptom or medication score, but the combined (total) evaluation with respect to clinical efficacy showed a significant (P = 0.03) difference in favour of Cladosporium immunotherapy. "Improvement" of asthma was found in 45 % of the Cladosporium group versus 9 % in the placebo treated. "Unchanged" clinical symptoms were found in 36 % (Cladosporium) and 18% (placebo) and "deterioration" in 18% versus 73%, respectively.	Safety: Systemic adverse events in intervention group mean 0.74 system reactions per cluster (range 0.4-1.0), mean 0.21 systemic reactions per injection (range 0.13-0.25) and in the comparator group mean 0.04 systemic reactions per cluster (range 0-0.4), mean 0.01 systemic reactions per injection (range 0-0.1). Local adverse events mean 0.58 delayed local reactions per cluster (range 0-1.0), mean 0.15 delayed local reactions per injection (range 0-0.35). Environmental exposure chamber or bronchial allergen challenge the bronchial sensitivity (PC20) decreased > 0.5 log step in 8/11 (73%) Cladosporium- versus 3/11 (27%) in the placebo group
Marques, 1978, Italy	Whole sample mean 27, range 13 to 49. Females= 16 and males= 12.	28/SCIT= 16, Placebo=12	Polysensitised	14 m	NR	D. pteronyssinus extract vs comparator (placebo tyrosine) SCIT D. pteronyssinus vs placebo	Natural	Short term effectiveness: Effectiveness measured by symptom scores. Number who achieved various results (e.g. good response, same, worse) reported but no overall average difference or p value reported.	Safety: Systemic adverse events one in each group, local Aes, 11 in SCIT group and 4 in placebo group.
Mosbech, 1989, Denmark	Mean age 34.33, range 18-56. Females= 20 and males= 26	46/SCIT Dp-mod= 16, Dp=15, Placebo=15	Polysensitised	2 y	NR	D. pteronyssinus modified extract vs Dp non-modified extract, and a third group acted as controls receiving no injections. SCIT D. pteronyssinus monomethoxy polyethylene glycol modified (mPEG) vs SCIT D.	Natural+ adjuvant	Short term effectiveness: Effectiveness measured using symptom and medication scores. After 6 m, there was an improvement in symptoms and medication scores in 11/14 of Dp-treated, 6/17 of the mPEG-Dp 'group (P> 0.05) and 3/15 of openly treated controls. Few patients had changes in PEF. During the second y, several Dp-treated relapsed and some controls improved. At the end of the study the same improvement rate was seen in all groups.	NR

						pteronysinus vs placebo			
Mosbech, 1990, Denmark -2nd paper primary study Mosbech 1989	Mean age 34.33, range 18- 56.	55/SCIT Dp group=18, SCIT Dp m=PEG= 19, Placebo=1 8	Sensitiz ation NR	3 y - 2 y blind ed, 1 y further treat ment	NR	D. pteronysinus extract plus aluminium hydroxide vs D. pteronysinus extract binding to monomethoxy polyethylene glycol (mPEG) vs placebo SCIT D. pteronysinus extracts vs placebo	Allergoid	NR	Safety: Systemic reactions were reported in 27 patients ($P > 0.05$); 14.1% of total injections caused systemic adverse events Local adverse events were reported in 19.6% of injections administered in the intervention group. In the unmodified Dp-extract group two patients experienced anaphylaxis with collapse responding adequately to adrenalin. The frequency of injections giving systemic reactions was reduced in the mPEG-Dp-group: 5,1 % compared to 9,0% in the Dp-group ($P < 0,01$)
Ohman,1984, US	Mean age 28, range 22-48. Females= 15 and males= 2	17/SCIT= 9, Placebo=8	Sensitiz ation NR	3 m	Mild	Cat allergen vs placebo containing histamine phosphate. SCIT cat allergen vs placebo	Natural	NR	Safety: Three local adverse events reported in the intervention group compared to zero in the comparator group. <u>Environmental exposure chamber or bronchial allergen challenge</u> Intervention treatment resulted in a significant decrease in bronchial sensitivity to cat allergen. The PD20 FEV1 for allergen increased significantly in the intervention treatment group ($p < 0.05$), but no significant change occurred in the placebo treatment group. A direct comparison of change scores from baseline revealed no significant difference between the intervention treatment and placebo treatment groups.

Newton,1979, UK	Mean age 29.5 range 18 to 44. Females= 7 and males =7.	16/SCIT= 8, Placebo=8 Asthma n=16, allergic rhinitis n= 8.	Monosensitised	15 m	NR	D. farinae extract vs comparator saline SCIT D. farinae vs placebo	Natural	Short term effectiveness: Effectiveness measured through mean peak flow values.	Lung function: PEF before intervention 273 and for comparator 292. After intervention 260 and for comparator 292. The individual mean peak flow values for each group was analysed, for the first and last month only. Fisher's exact test for independence shows that the proportion improved could have occurred by chance.
Olsen, 1997, Denmark	Mean age 36.35, range 18-64. Gender NR. Demographics are reported only for 23 of the follow up patients.	31/SCIT= 21, Placebo=10. Follow up was of 23 patients.	Monosensitised	1 y	NR	Extracts of either Dermatophagoides pterotryssinus (Dpt) or D. farinae (Dfa) vs placebo group receiving histamine dihydrochloride. SCIT Dermatophagoides pterotryssinus (Dpt) or D. farinae (Dfa) vs placebo	Natural	Short term effectiveness: Effectiveness measured using mean symptom score and medication use. Symptom scores before and after treatment showed a significant decrease for the intervention treated group (P<0.001), where all patients had a reduction in symptoms. Of the placebo treated group, two thirds of the patients had either increased or unchanged symptoms. In the treatment group, a decrease in the use of inhaled B-agonists (46%) and inhaled steroids (38%) was observed after SIT, and these findings were statistically significant (P<0.05), No statistically significant changes before and after placebo were observed.	Safety: Zero adverse (including local) and systemic events were reported in the intervention and comparator groups. Lung function: FEV1 before intervention mean 84.98, range 54.8-109.8 and for comparator mean 83.6, range 47.8-100.5. FEV1 after intervention mean 88, range 85.1-109.9 and for comparator mean 86.5, range 58.8-98.1. Spirometry lung-function measurements showed a significant increase in forced expiratory volume in 1 s (FEV ₁) from 85% before to 89% of predicted values after treatment for the intervention treated group. Peak-flow measurements at home showed no significant changes during the study. Environmental exposure chamber or bronchial allergen challenge Bronchial sensitivity decreased significantly to Dpt and Dfa (P=0.022 and 0.039, respectively) in the SCIT group. No significant change was seen in the placebo group Dpt (P=0.60) or Dfa (P=0.75)
Ortolani, 1984, Italy	Mean age 20, range 15 to 45. Females= 9 and males=6	15/SCIT= 8, Placebo=7	Monosensitised	6 m	NR	Timothy grass pollen extract vs riboflavin placebo SCIT Timothy grass pollen vs placebo	Natural	Short term effectiveness: Effectiveness measured by symptom scores. In the intervention group of patients significantly lower mean score values than controls were noted during similar natural allergen exposure (p < 0.001). Also, when only the score values of the three symptoms most related to lower respiratory allergy (shortness of breath, wheezing, and cough) were considered, the intervention group of patients had lower mean score values than the controls had who were treated with placebo (p < 0.01).	NR

Pauli,1984, (not stated. Authors are from France and UK)	Age range 19-40. Females= 4 and males= 14.	22/SCIT= 11, Placebo=11	Monosensitised	1 y	NR	D. pteronyssinus extract vs tyrosine placebo. SCIT D. pteronyssinus vs placebo	Natural	Short term effectiveness: Effectiveness measured using symptom and medication scores. There were no significant differences between the PEFR scores and global scores of patients treated with intervention and those of placebo treated patients; however, the symptom score is significantly higher for the intervention patients over the whole period. Numbers NR. There was a diminution in medication score in the intervention group: however, after the first 6 m an increase in intake of medication was observed. The mean medication score of the intervention group is significantly lower than that of the placebo treated group, considering the whole period from 6 w to 1 y and more, especially in the first 6 m of treatment. $p < 0.05$. Exact numbers not reported	NR
Pene, 1998, France	20 to 37 y (mean $\pm$ SD: 27.7 + 5.1 y) Females=12, Males=19	31/ SCIT:8 received 15 to 45 I.tg, "low dose" group, 6= received 150 to 450 pg, "medium dose" group, 11 =received 1500 to 4500 p.g, "high dose" group. 6 =placebo,	Not clearly reported	6 w treatment and follow up 6 w later	Mild	Fel d 1 peptides or placebo were administrated by subcutaneous injection once a week for 6 w Fel d1 vs placebo	Natural	NR	Environmental exposure chamber or bronchial allergen challenge Assessment at 6 weeks' post treatment showed no significant difference in PD20FEV 1 between placebo groups and all 3 doses. The medium and high doses of FelD1 did show a significant difference between baseline and post=treatment, $P,0.05$ and $P,0.04$ respectively.

Price,1984, UK	Age range 5-15; gender of children NR.	56/SCIT=28, Placebo=28	Sensitisation NR.	2 y	Mild to moderate	D. pteronyssinus extract vs placebo (tyrosine suspension). SCIT D. pteronyssinus vs placebo	Allergoid	Short term effectiveness: Effectiveness measured by fall in medication use. Asthma medication score: 17 in the intervention group and 7 in placebo group had a fall in drug score in y 1, $p = 0.0278$.	NR
Rak,2001, Sweden	Mean age 29.5, range 18-41. Females=19 and males=22.	41/SCIT=21, Nasal steroids=20, control=9; asthma =21, rhinoconjunctivitis n=41	Polysensitised	6 w	NR	Birch pollen extract vs budesonide 400 µg daily vs placebo containing histamine dihydrochloride. SCIT Birch pollen extract vs nasal steroids vs placebo	Natural	Short term effectiveness: No significant differences were found between the groups with respect to medication for Rhino conjunctivitis and asthma. No difference in the use of β_2 -agonists was noted in the asthma group. Exact numbers NR. Mean morning and evening PEF values were added, and weekly means were calculated. No significant difference between the groups was observed before the season. The SIT-treated group remained stable throughout the season. In the NS-treated group, PEF was lower during week 2, though the difference did not reach significance in comparison with pre-season values ($P = .07$), and values were significantly lower during w 3 and 4 ($P = .01$ and $P = .02$, respectively). No differences were recorded during w 5 and 6	Environmental exposure chamber or bronchial allergen challenge methacholine sensitivity increased significantly ($P = .0007$) only in rhinitics, from $PC_{20} >16$ mg/mL before the season to a median of 3.0 mg/mL (range, 1.075-16) during the season. Methacholine sensitivity did not increase in asthmatics (median PC_{20} [range]: before the season, 1.25 [0.28-2.45]; during the season, 0.4 [0.19-1.6]) When PC_{20} values of rhinitis patients and asthmatic patients were calculated with respect to the given treatment, all except those of the SIT-treated asthmatics showed significant seasonal increases
Reid,1986, US	Mean age 27.31, range 20-39. Females=9 and males=9.	18/SCIT=9, comparator=9	Polysensitised	8 m	NR	Grass pollen extracts (7 different types) vs active comparator without grass pollen. SCIT grass pollen vs comparator	Natural	Short term effectiveness: Symptom medication scores. The grass treated intervention group reported lower asthma and symptom medication scores daily and in total, $p < 0.05$.	Safety: Four systemic adverse events reported in the intervention group and 1 reported in the comparator group. They were 287 local adverse events reported in the intervention group and 214 in the comparator group.

Roberts,2006, UK	Mean age 9.9. Females= 10 and males= 25	35/SCIT= 18, Placebo=1 7	Polysen sitised	2 y	NR	Grass pollen extract vs placebo containing histamine dihydrochloride . SCIT Grass pollen vs placebo	Natural	Short term effectiveness: The primary end was the asthma symptom medication score during the second pollen season. Asthma symptom score before intervention: median first season 0.9 (IQR 0.4-1.8); median season 2 0.5 (IQR 0.1-0.8) and for comparator: median 1.5 (IQR 0.5-2.3); median 0.8 (IQR 0.4-2.1). There was a substantial reduction in the asthma symptom medication score (P5.04) in the intervention treated group compared with the placebo group. The median daily asthma symptom medication scores were 1.0 (interquartile range [IQR], 0.4-2.0) in the placebo group and 0.5 (IQR, 0.1-0.9) in the intervention group. Asthma medication score before intervention: median season 1, 0.6 (IQR 0.0-1.5); median season 2, 0.5 (IQR 0.0-1.7) and for comparator: median season 2, 1.4 (IQR 0.5-1.9); median 2, 2.2 (IQR 0.0-3.2).	Safety: Total of 20 adverse events reported by 7 patients. Systemic adverse events reported in the intervention group was 21 and in the comparator group 9. They were 13 local adverse events reported in the intervention group compared to 11 in the comparator group. Lung function: FEV1 in both the active and placebo groups was less than 85% of predicted value a third of the time Corticosteroids: There was a trend toward a reduction in the total corticosteroid score in the second pollen season in the intervention immunotherapy group (median score of 0.7 vs 1.6 in the placebo group, (P =0.16).
Sabbah,1991, France	Mean age: interventio n-26.26; comparato r-31.19. Females=1 7, males=35	52/SCIT= 26, Placebo=2 6	Monose nsitised	180 d	NR	Alpha-Fraction- Retard-D. pteronysinus vs placebo SCIT HDM vs placebo	Modified	Short term effectiveness: increased asthma medication: 9% in the treated group vs 25% in the placebo group- decreased asthma medication: 24% in the treated group decreased or stopped their asthma medication vs 5% in the placebo group Symptomatic deterioration: VAS for patient : 87% efficacy with intervention versus 70% with comparator	Safety: local reactions 1 in 10 for active and 2 in 14 for the comparator no difference for systemic reactions
Smith,1971, UK	Age range 11-48. Females= 8 and males= 14.	22/SCIT= 11, Human skin cells (comparat or)=11. Asthma n=22, allergic rhinitis n= 18.	Monose nsitised	NR	NR	House dust mite extract (D. pteronysinus) vs human skin scales SCIT HDM vs comparator	Natural	Short term effectiveness: Effectiveness measured by number not needing additional therapy. Patients in the two groups significantly more in the intervention treated group were less breathless during the daytime (P<0.005), had fewer attacks of nocturnal breathlessness (P<0005), and used their inhalers less at night (P<0-01). More patients in the intervention treated group were classified as better in respect of the number of attacks of wheezing and the daytime inhaler score, but not enough to exclude the possibility of the findings being due to chance. PEFr was greatly improved in 4 of the SCIT group, which was not significant(P>0.1)	Safety: Eight local adverse events reported in the intervention group and zero in the comparator group.

Sundin, 1986, Sweden	Mean age 21.5. Females= 23 and males= 18.	41/SCIT= 23, Placebo=1 8. Asthma=4 1, rhinoconjunctivitis= 31.	Polysensitised	18 m	Mild to moderate	Extracts of cat or dog dander vs placebo extracts composed of histamine hydrochloride. SCIT cat or dog dander vs placebo	Natural	NR	Safety: 22 patients (12 children and 10 adults) in the intervention group and 18 patients (8 children and 10 adults) in the comparator group reported local adverse events. Systemic adverse events were reported in 12 children and 10 adults. Environmental exposure chamber or bronchial allergen challenge in the cat allergen- treated group, the bronchial sensitivity toward cat and histamine decreased ($p < 0.001$ and $p < 0.05$, respectively). Measured by bronchial challenge. the cat allergen-treated patients could tolerate 11 times more allergen at the end than at the start of the study, and they also demonstrated a tendency toward less pronounced symptoms after exposure to cat and dog allergens. No significant changes were observed in the dog allergen treated- or placebo-treated groups.
Tabar, 2008, Spain	Whole sample mean 13.88. Females=8 and males= 20	28/SCIT= 14, Placebo=1 4 Asthma=2 5, allergic rhinitis= 28.	Monosensitised	1 y	NR	Alternaria alternata extract vs placebo consisting of excipients used to prepare the allergenic extract suspension. SCIT Alternaria alternata vs placebo	Natural	Short term effectiveness: Effectiveness measured through symptoms and medication diary. Asthma symptoms before intervention: mean 0.5(0.39); comparator: mean 0.43(0.35) after intervention: mean 0.55(0.49); comparator: mean 0.41(0.4). Asthma medication scores before intervention: mean 0.37(0.57); comparator: mean 1.77(2.43) after intervention: mean 0.51(1.19); comparator: mean 0.21(0.36).	Safety: Two adverse reactions were recorded in the intervention group in two different patients (0.28% of all doses, 7.14% of all patients). Lung function: PEF before intervention: 362.67(106.79); comparator: 351.97(116.99) after intervention: 403.90(128.72); comparator: 349.14(99.78).
Taylor, 1978a, US	Age range 20-43. Females= 9 and males=1.	10/SCIT= 5, Placebo=5 . Asthma=1 0, allergic rhinitis=3.	Monosensitised	3-4 m	NR	Cat allergen extract vs placebo solution containing histamine phosphate SCIT cat extract vs placebo	Natural	NR	Safety: Three systemic adverse events reported in both intervention and comparator groups. Environmental exposure chamber or bronchial allergen challenge Effectiveness measured using mean BHR to cat allergen. At baseline mean PD20-FEV₁ were similar in the SCIT group and placebo group. Following treatment there was a significant increase in mean PD20-FEV₁ (from 51 to 2,354 units, $p < 0.01$). there was no significant change in the placebo group. No changes were seen in bronchial responsiveness to histamine in active and placebo groups.

Taylor, 1978b, UK	Age 6 to 15	42/SCIT=21, Placebo=21	Sensitisation NR	10 w of treatment	Severe	HDM (D. pteronyssinus and D. farinae) vs placebo containing saline and phenol. SCIT HDM vs placebo	Natural	NR	Safety: Total adverse events reported in intervention and comparator were 4 in each group Lung function tests did not show an improvement. No exact data are given
Valovirta, 1984, Finland	Total sample age range was 5 to 18. Gender NR. - Females=11 and males= 16.	27/SCIT=15, Placebo=12	Monosensitised	1 y	NR	Dog dander extract vs placebo injections containing histamine SCIT Dog dander extract vs placebo	Natural	NR	Environmental exposure chamber or bronchial allergen challenge There was a non-significant decrease in bronchial sensitivity, reduction in 6/15 in the active group(P<0.1) compared to 2/12 in the placebo. group
Valovirta,1986, Finland - 2nd paper from primary study Valovirta 1984	Mean age 11, range 5-18. Females=11 and males= 16.	27/SCIT=15, Placebo=12	Polysensitised	1 y	NR	Dog dander extract vs placebo injections containing histamine SCIT Dog dander extract vs placebo	Natural	Short term effectiveness: After one y of therapy the intervention group had no symptoms on short exposure to dogs. Number of d with asthma was 29.3 + or - 29 in the intervention group and 35.6 + or - 18.3 in the placebo group was not significant.	Safety: Zero systemic adverse events reported. They were 309 local adverse events reported in the intervention group and 251 reported in the comparator group.

Van Bever, 1992, Belgium	Mean age 10.5, range 7-22. Gender NR.	18/SCIT=9, Placebo=9	Sensitisation NR.	1 y	NR	Dermatophagoides pteronyssinus extract vs histamine buffer solution. SCIT Dermatophagoides pteronyssinus vs placebo	Natural	NR	<u>Environmental exposure chamber or bronchial allergen challenge</u> in the intervention group a small but significant increase of the median PD20 HDM was observed (p=0.04) while the PD20 HDM was not influenced by placebo injections (p=0.11).
Van Metre, 1988, US	21-30 y=8, 31-40 y=8, 41-50 y=4, 51-55 y=2. Females=12 and males=10.	22/22	Sensitisation NR.	2 y	NR	Cat allergenic extract vs placebo solution containing histamine phosphate. SCIT Cat allergenic extract vs comparator	Natural	NR	<u>Safety:</u> Two systemic adverse events reported in the intervention group (0.6 reactions per 100 injections) and zero in the comparator group. Twenty-six large local reactions occurred in 11 patients, a reaction rate of 7.7 per 100 injections. Twelve of these reactions (46% of the total) were observed in one patient. Zero local adverse events reported in the comparator group. <u>Environmental exposure chamber or bronchial allergen challenge</u> After 1 y of immunotherapy patients had decreased sensitivity to the effects of broncho provocation with cat extract. The ratio between the value of cat extract PD, now to the value before treatment was larger in patients in the treatment group (median ratio, 2.8) than in patients in the control group (median ratio, 0.8). This difference in ratios was highly significant (p < 0.01), albeit relatively small.
Vidal, 2011, Spain	Mean age 27.1, range 14-52. Females=19 and males=26.	48/SCIT=23, Placebo=25	Monosensitised	4 m	Mild to moderate rate	D. pteronyssinus extract vs placebo (same as active treatment but without active substance). SCIT D. pteronyssinus vs placebo	Natural	<u>Short term effectiveness:</u> 4 m of treatment assessed by difference between groups in proportion requiring lower medication dose (% with lower budesonide dose). Unable to detect significant differences between the intervention and placebo groups with regard to concomitant medication, which was the principal variable.	<u>Safety:</u> Eight systemic adverse events reported in the intervention group and six reported in placebo group. Ten local adverse events reported in the intervention group compared to four in the placebo group. <u>Corticosteroids:</u> 42.9% in the treatment group required lower dose afterwards. 7.1% difference between groups in proportion requiring lower dose of inhaled corticosteroid at the end of the study compared to baseline. 50% in placebo group required lower dose afterwards. Not significance p = 0.638.

Wang, 2006, China	6-45 y, male/female ratio 76/53	132 randomized, 66 to HDM SCIT, 66 to placebo	79 subjects (38 in SCIT group) were monosensitized, 50 subjects (26 in SCIT group) were polysensitized	52 w	Mild to moderate	Dermatophagoides pteronyssinus extract vs placebo. HDM SCIT vs placebo	allergoid	Short term effectiveness: Symptom scores diverged at week 29 at which point the SCIT group began having significantly lower scores ($P=0.018$) lasting until week 48. During the 2. half of the treatment period, SCIT group had a significant decline in symptom ($P=0.002$) and medication ($P=0.007$) scores.	Safety: A total of seven (0.4% of all injections) had a grade 1 reaction; 71 (4.8%) had a grade 2 reaction and seven had a grade 3 reaction in the SCIT group. In the placebo group two (0.1%) had a grade 1 reaction and 25 (1.7%) had a grade 2 reaction ($P<0.001$). No hospitalizations occurred. Lung function: Significant improvement in peak flow rate morning (active: $P=1/4$ 0.02, placebo: $P=1/4$ 0.01) and evening (active: $P=0.02$, placebo: $P=0.015$) Corticosteroids: No significant difference in courses of oral prednisolone given for acute exacerbations between the two groups SCIT group, 48 courses of oral prednisolone, total dose of 4710 mg, to 24 patients over 206 d for acute exacerbations. Placebo group, 46 courses, total dose of 4560 mg, to 19 subjects over a total of 223 d. Environmental exposure chamber or bronchial allergen challenge PC20 Histamine challenge at the end of the trial showed no significant difference between active and control groups, $P=0.765$
Warner 1978, UK	5-14 y	52/SCIT=27, placebo=24	majority polysensitized	1 y	Moderate to severe	D. pteronyssinus absorbed into tyrosine ('Migen', Bencard).vs placebo HDM SCIT vs placebo	Natural	Short term effectiveness: there was a significant reduction in wheeze and nocturnal cough scores in the SCIT group at end of treatment ($P<0.05$). 15 of the 21 in the SCIT group could stop all regular medication compared to 6/21 in placebo group	Safety: 2 patients on placebo had SRs and left the trial. LRS in 13 on SCIT and 10 on placebo Corticosteroids: 2 SCIT patients and 1 placebo could stop inhaled steroid therapy, Environmental exposure chamber or bronchial allergen challenge SCIT group, 27/27 had an immediate reaction to BPT pre-treatment and 23 after treatment, 22 had a reaction pre-treatment compared to 12 after. Placebo 24/24 had an immediate reaction to BPT and 22 post treatment, 15 had a late reaction pre-and 14 post treatment.

Table S1b: Detailed characteristics of SLIT trials (n=34 studies in 36 papers)

Study (First author, y, country)	Age/sex	Number of patients (N)/No randomized	Mono / polysensitized	Study duration (treatment duration)	Disease severity (mild, moderate, severe)	Type of Immunotherapy (intervention vs comparator) Type of allergen	Natural allergen or allergoid	Effectiveness: short term (during treatment)	Asthma quality of life Safety Lung function parameters Corticosteroid use Asthma exacerbations Environmental exposure chamber or bronchial allergen challenge
Alvarez-Cuesta et al, 2007, Spain	14 to 55 y; mean age 29.1 (7.4) y in SLIT group and 27.8 (7.3) y in placebo group / 8 male and 25 females	50 (25 in cat dander SLIT group and 25 in placebo SLIT group)	monosensitized	52 w	NR	Cat dander SLIT vs Placebo SLIT once daily. Total accumulated dose 17.1 mc	natural	Short term effectiveness: Cat dander SLIT (95% lower and upper CI): bronchial symptom score baseline: 174.41 (118.10, 237.03) bronchial symptom score end: 45.74 (10.80, 80.67) P=0.003% of improvement: 73.77 Placebo SLIT (95% lower and upper CI): bronchial symptom score baseline: 160.00 (81.60, 238.40) bronchial symptom score end: 143.44 (61.98, 224.90) P=0.263 % of improvement of active vs placebo at the end: 68.11; P=0.118 not a significant improvement	Safety: No local or systemic reactions were reported. None of the 17 withdrawals caused by an AE.
Bachelier et al, 2001, Turkey	7 to 18 y; median age 12.4 (range 7.8 to 18) y and 12 (range 7.3 to 15) y in placebo group / 8 male and 7	15 participants (8 in HDM SLIT group and 7 in placebo group)	NR	26 w	disease severity NR	HDM SLIT vs placebo SLIT HDM SLIT daily for 4 w then twice weekly for 4 m. Average cumulative dose 7000 IR	natural	Short term effectiveness: Median Asthma score (range): Placebo run-in-period: 0.33 (0-1.16), Placebo last 4 m: 0.26 (0-0.7) SLIT run-in-period: 0.64 (0.1-2), SLIT last 4 m: 0.3 (0.01-1.44) Median β 2-mimetic use (range): Placebo run-in-period: 0.17 (0-1), Placebo last 4 m: 0.08 (0-0.29). SLIT run-in-period: 0.17 (0-0.77), SLIT last 4 m: 0.03 (0-0.48)	Safety: None of the patients reported local or systemic side effects during the treatment Lung function: Median FVC % (range): Placebo baseline: 110 (97±122), Placebo last visit: 108 (84±111) SLIT baseline: 102 (88±122), SLIT last visit: 109 (85±124) Median FEV1/FVC % (range): Placebo baseline: 88 (73±94), Placebo last visit: 82 (72±85) SLIT baseline: 86 (78±95), SLIT last visit: 85 (76±95) Median FEV1 % (range): Placebo baseline: 101 (75±115),

	females								Placebo last visit: 93 (61±104) SLIT baseline: 95 (75±113), SLIT last visit: 100 (78±119) <u>Median FEF25±75 % (range):</u>Placebo baseline:93 (46±114), Placebo last visit: 70 (31±97) SLIT baseline: 85 (53±121), SLIT last visit: 80 (64±149) <u>Median PEF % (range):</u>Placebo baseline: 99 (82±128), Placebo last visit: 76 (62±106) SLIT baseline: 97 (77±117), SLIT last visit: 99 (75±116) Corticosteroids: <u>Median ICS dose (range):</u> Placebo baseline: 3 (2±5), Placebo last visit: 3 (0±5) SLIT baseline: 3.5 (2±4), SLIT last visit: 2 (1±3) <u>Median Intranasal budesonide dose (range):</u> Placebo baseline: 2 (0±3), Placebo last visit: 2 (0±3) SLIT baseline: 3 (0±3), SLIT last visit: 1 (0±3) Environmental exposure chamber or bronchial allergen challenge <u>Median PC20 in mg/dl (range):</u> Placebo baseline:0.78 (0.04-1.8), Placebo last visit: 0.98 (0.18-3.9) SLIT baseline: 0.28 (0.03-3.8), SLIT last visit: 0.85 (0.17-2.2)
Bousquet et al, 1999, France	7 to 42 y; mean age 21 (10) y in SLIT group and 22 (10) y in placebo group / 48 male and 37 female	85 (42 in HDM SLIT group and 43 in placebo SLIT group)	monosensitized	108 w	moderate or moderately severe allergic asthma	HDM SLIT vs placebo SLIT HDM SLIT once daily initially then decreasing to three times per week for 24 w. Maintenance dose 20 drops of 300 IR/mL 3 times a week	natural	Short term effectiveness: <u>Nighttime asthma:</u> SLIT baseline: 0.20±0.47, SLIT last diary card:0.17±0.52. Placebo baseline:0.26±0.51, Placebo last diary card:0.11±0.35 <u>Daytime asthma:</u> SLIT baseline: 0.32±0.53, SLIT last diary card: 0.17±0.50. Placebo baseline:0.37±0.40, Placebo last diary card:0.19±0.44 <u>Use of inhaled b2-agonists (µg salbutamol/day):</u> SLIT baseline: 181±192, SLIT last diary card:122±235. Placebo baseline:168±172, Placebo last diary card:79±136 <u>Cumulative score(symptoms+drugs):</u> SLIT baseline:8.10±5.87, SLIT last diary card: 5.21±5.88	QoL: Non-disease specific QoL analysis; 18 in the SLIT group and 20 in the placebo group. After 25 m, all QoL scores higher in SLIT group than placebo group, differences being most marked for general mental health (79.7 and 60.7, respectively –P=0.07), general perception of health (76.5 and 56.8, respectively –P=0.01), and physical pain (86.2 and 68.3, respectively –P=0.02). The changes from baseline to end showed significant differences in favor of the SLIT group compared with the placebo for social functioning (+12.2 and –2.1, respectively –

							Placebo baseline:7.64±5.22, Placebo last diary card:4.52±4.89	P=0.04) and bodily pain (+20.0 and −4.2, respectively −P=0.01) <u>Safety:</u> An AE occurred at least once in 15 of the 42 patients in the SLIT group (35.7%) and in 14 of the 43 patients (32.6%) in the placebo group (P=0.84). The overall incidence was similar in both treatment groups. <u>Lung function:</u> Morning PEF(l/min): SLIT baseline: 401.4±134.1, SLIT last diary card:426.3±136.7 Placebo baseline:415.7±100.6, Placebo last diary card:424.3±114.5 <u>Evening PEF(l/min):</u> SLIT baseline: 414.1±137.3, SLIT last diary card:433.2±139.1 Placebo baseline:429.6±100.5, Placebo last diary card:437.7±117.4 VC: SLIT baseline: 3.291.45, SLIT last diary card: 3.52±1.38 Placebo baseline:3.56±1.42, Placebo last diary card:3.89±1.56 <u>FEV1:</u> SLIT baseline:2.76±1.13, SLIT last diary card: 2.88±1.05 Placebo baseline:2.91±0.99, Placebo last diary card:2.97±0.92 <u>FEV1(% predicted):</u> SLIT baseline: 95.9±18.4, SLIT last diary card: 102.7±24.6 Placebo baseline:95.2±13.4, Placebo last diary card:99.3±18.5 <u>Corticosteroids</u> (µg beclomethasone/day): SLIT baseline: 555±455, SLIT last diary card:348±410 Placebo baseline:495±430, Placebo last diary card:308±408 <u>Environmental exposure chamber or bronchial allergen challenge:</u> no statistically significant between-group difference in post-treatment
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									PD20, in the SLIT group, PD20 after 11 and 25 m was 1.98 and 1.75 times higher than at baseline, respectively.
Caffarelli et al, 2000, Italy	4 to 14 y; mean age 8.7 (3.3) y in SLIT group and 8.1 (2.7) y in placebo group/ 25 male and 19 females	48 (14 in grass pollen tablet group and 14 in placebo group)	monosensitized	13 w and 9 w post-treatment follow-up	NR	Grass pollen tablet vs placebo tablet Grass pollen tablet (33% Holcus lanatus, 33% Phleum pratense and 33% Poa pratensis) 3 times per week. Cumulative dosage 37,250 AU	allergoid	Short term effectiveness: Total symptom scores during the pollen season (as weekly mean) were lower in the treated group than with placebo, the difference being statistically significant (mean [SD] 9.5 [7.2] vs 14.5 [8.3]; P<0.05). The difference was statistically significant only for bronchial symptoms (2.4 [2.7] vs 4.6 [3.5]; P<0.05). The symptom-medication score in the immunotherapy group was lower than in the placebo group during the pollen season in all w. This difference was statistically significant at week 3 (P<0.05), week 7 (P<0.05), and week 8 (P<0.03). The symptom medication score for elevated pollen concentration was significantly lower in the SLIT group than in the placebo group (10.1 [3.3] vs 16.84 [4.3]; P<0.03). There was no significant difference between actively treated and placebo patients for the symptom medication score under moderate pollen exposure (8.75 [4.6] vs 11.5 [6.2]; P>0.05).	Safety: Neither systemic nor local adverse reactions were observed during treatment
Cao et al, 2007, China	4-18 y/174 male and 104 female	278 (139 in SLIT group and 139 in placebo group)	NR	3 m	mild to moderate allergic asthma	HDM SLIT vs placebo SLIT SLIT with 'Dermatophagoides Farinae Drops	NR	Short term effectiveness: the mean variability of medicine score of asthma was -0.08 for SLIT group and 0.52 for the placebo (P < 0.05)	Safety: No severe AEs in the trial and the most-likely AEs were mild asthma and local rash. Lung function: After 25 w of treatment, the median variability of PEFr was -1.38 for SLIT group and -0.90 for the placebo (P < 0.05) Corticosteroids: The rescue medicine use of SLIT reduced but did not show significant differences between SLIT and placebo

Dahl et al, 2006, Denmark and Sweden	18 to 65 y; mean age 36.5 (SLIT) y and 34.1 (placebo) y/ 77 male and 37 females	114 (74 in Timothy grass SLIT group and 40 in placebo group)	Majority polysensitized	19.5 w (mean 84 d preseasonal exposure, 53 d seasonal exposure)	mild to moderate grass pollen-induced asthma of 2 y or longer	Timothy grass SLIT vs placebo SLIT: Timothy grass (Phleum pratense) GRAZAX tablet 75,000 SQ-T once daily	natural	Short term effectiveness: <u>Asthma symptom score during grass pollen season:</u> Placebo: mean (SD)=0.74 (0.92)/median=0.36/min-max=0.00-3.60 75,000 SQ-T: mean (SD)=0.44 (0.68)/median=0.18/min-max=0.00-3.67 <u>Asthma medication score preseason:</u> Placebo: mean (SD)=0.09 (0.14)/median=0.00/min-max=0.00-0.49 75,000: SQ-T: mean (SD)=0.09 (0.23)/median=0.00/min-max=0.00-1.35 <u>Asthma medication score during grass pollen season:</u> Placebo: mean (SD)=0.66 (1.08)/median=0.07/min-max=0.00-4.00 75,000 SQ-T: mean (SD)=0.71 (1.28)/median=0.00/min-max=0.00-5.33 <u>Asthma symptom score preseason:</u> Placebo: mean (SD)=0.33 (0.33)/median=0.23/min-max=0.00-1.05 75,000 SQ-T: mean (SD)=0.23 (0.34)/median=0.10/min-max=0.00-2.00	Safety: equal proportion of subjects in both groups reported AEs; majority were mild. Most frequent AEs were: oral pruritus (reported by 53% active, 5% placebo), nasopharyngitis (36% active, 25% placebo) and throat irritation (32% active, 25% placebo). No serious AEs were. The number of AEs linked to asthma (chest discomfort, chest pain, asthma, cough, dry throat, dyspnea, increased bronchial secretion, respiratory disorder, wheezing) was similar between groups and there was no indication of asthma aggravation.
de Blay et al, 2014, Denmark, Germany, Italy, Spain, United Kingdom, Sweden, France, and Poland	14 y and above (mean age/age range NR but across groups 6% were reported to be adolescents)/ 50% were male and 50% were female	108	83% were polysensitized	52 w (1 y treatment duration)	mild to moderate HDM Allergic Asthma requiring ICS use	HDM SLIT 1 DU daily vs HDM SLIT 3 DU daily vs HDM SLIT 6 DU daily vs Placebo SLIT oral lyophilisates containing standardized extracts of D Pteronyssinus and D farina in a 1:1 ratio. Three active strengths were investigated: 1, 3, and 6 SQ-HDM. The units were designated in development units. One development unit corresponds to 1 SQ-HDM	natural	Short term effectiveness the difference from baseline in overall ACQ score at the end of trial ICS stable period was statistically significantly lower in the 6 SQ-HDM group than in the placebo group (difference: -0.41, p=0.0002), implying better asthma control after treatment in the 6 SQ-HDM group. In the 1 SQ-HDM and 3 SQ-HDM groups, differences were not statistically significant	QoL: statistically significant difference in asthma quality of life between placebo and 6 SQ-HDM in overall AQLQ(S) scores of 0.52, p=0.010. The differences to placebo were lower in the 1 SQ-HDM and 3 SQ-HDM groups (0.30 and 0.32) and not statistically significant. The difference to placebo in the subgroup was significantly higher than for the rest of the population (p=0.044). The increased AQLQ(S) score in the 6 SQ-HDM group was primarily related to the symptoms domain (difference to placebo 0.61, p=0.006) and to the activity limitation domain (difference to placebo 0.52, p=0.011) Safety: dose-dependent increase in SLIT-related AEs, from 0.1 IMP (investigational medical product)-related AEs/subject in the placebo group to 1.1 IMP-related AEs/subject in the 6 SQ-HDM group, majority of AEs mild or moderate only 5 severe AEs (bacterial

								infection in the 1 SQ-HDM group, phlebitis, alopecia areata, nasopharyngitis and foot fracture in the 3 SQ-HDM group) were reported. most frequent AEs: oral pruritus, nasopharyngitis, asthma, and ear pruritus, with nasopharyngitis being reported with similar frequency in active and placebo groups while oral pruritus, asthma, and ear pruritus were more frequent in the active groups than in placebo. There was a higher incidence of reporting of asthma as an AE in the subgroup (11 subjects, 10%) as compared with the full analysis set (18 subjects, 3%). No IMP-related serious (as per ICH E2A definitions) AEs were reported. <u>Lung function</u> (in terms of mean FEV1) was around 85% of predicted value in all treatment groups at all visits during the trial (mean changes from randomization were within $\pm$ 4%; data not shown) There was a statistically significant difference in the ICS reduction between 6 SQ-HDM and placebo (81 μg/day, [CI 95% :27-136 μg/day], p=0.004). In the subgroup, the difference in adjusted mean to placebo in the 6 SQ-HDM group during the end of trial ICS stable period was 327 μg/day, [CI 95%: 182-471 μg/day], p<0.0001. The ICS reduction in the 1 SQ-HDM and 3 SQ-HDM groups was less pronounced and not significantly different from placebo. 6 SQ-HDM group, 17 subjects (59%) could reduce ICS use by 75%-100% without impairment in asthma control, and 13 subjects (45%) withdrew ICS use completely. In placebo group 1 subject (4%) could withdraw ICS. No subjects on 6 SQ-HDM
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									increased their ICS use during the 1-y trial, while 5 (19%) in the placebo group
Dewillie r at al, 2015, China	16-50 y/ 209 male and 256 female	484(322 in HDM SLIT group and 162 in placebo group)	monos ensitiz ed	52 w (+ 12-week baseline period before randomi zation)	mild (n=237) or moderat e (n=175) allergic asthma	HDM SLIT vs placebo SLIT HDM SLIT (D. pteronysinus and D. farinae), approximately 28 mcg Der P 1 and 50 mcg Der f 1 daily (300 IR)	natural	NR	QoL: There were no statistically significant differences between the active and placebo groups in terms of the change in the overall AQI.Q score from baseline to V12 Safety: More patients in the SLIT group experienced at least one AE (87.0% SLIT vs 75.9% placebo, P = 0.0029), and, respectively, 78.9% and 48.1% (P < 0.0001) experienced at least one ADR). There were 751 ADRs in 254 patients in the active treatment group and 184 ADRs in 78 patients in the placebo group. AEs led to TRW in 8 (2.5%) patients in the SLIT group and 1 (0.6%) patient in placebo group. Most AEs were mild (affecting 80.4% of the participants in the SLIT group and 62.3% of the placebo group; P < 0.0001) or moderate (affecting 46.3% of the active treatment group and 38.9% of the placebo group; P = n.s.). Similarly, most ADRs (i.e. AEs that were possibly, probably or certainly related to the investigational product) were mild or moderate. 5 patients (four in the SLIT group and one placebo) reported treatment-emergent SAEs. None of these AEs were classified as ADRs and all resolved during the study. Hence, there were no life-threatening ADRs, serious allergic reactions or deaths in either treatment group. Lung function: Overall, the mean FEV1 (% predicted, calculated for the FAS) remained above 75% during the treatment period in both the active treatment and placebo groups

									(data not shown). Exacerbations: The incidence of asthma exacerbation during the study was similar in the active treatment group (3.7% in the SAS) and the placebo group (4.3% in the SAS) – incidences of exacerbations requiring oral corticosteroids with antibiotics were similar in SLIT group (1.6%) and placebo (2.5%). In the FAS, the mean SD [95% confidence interval] number of asthma exacerbations standardized over a y in the active treatment group (0.06 ± 0.38 [0.02; 0.11]) did not differ significantly from that recorded in the placebo group (0.04 ± 0.24) [0.01; 0.08]. Corticosteroids: patients with moderate (but not mild) asthma had a greater mean absolute decrease in budesonide dose than those in the placebo group (218.5 lg and 126.2 lg, respectively, in the FAS; P = 0.004
Drachenberg et al, 2001, Germany	Age >6 y / 31 female and 37 males	68 participants (49 in Pollen SLIT group and 19 in Placebo SLIT group)	monosensitized	6 m	mild asthma	Pollen SLIT vs placebo SLIT standardized allergen extract (ORALVAC birch n = 21 resp. grass/rye = 28)	Natural	Short term effectiveness: There was a significant advantage in favor of SLIT for the combined symptom/medication score (p = 0.035).	Safety: Local AEs (e.g. stomatitis, pharyngitis) were more common in the active group (p = 0.05). There were no reports of serious or severe AEs
Durham, 2012 UK, Austria, Germany, the	Age range=18-65; Mean age: SLIT=33.8	634 [SLIT (n = 316); placebo (n = 318)] Asthma: SLIT=79,	Majority polysensitized	3 y (September 2004 - September	Moderate to severe grass pollen-induced	SLIT vs. placebo SQ-standardized grass allergy tablet (Grazax) (preseason)	Natural	Long term effectiveness: After 3 years of AIT, patients followed for 2 years When combining all 5 years the combined asthma symptom score was reduced significantly by 39% compared to placebo (P=0.049)	NR

Netherlands, Sweden & Denmark Results of 2 y follow up of Dahl, 2006 trial	Placebo: =34.5	placebo=72		2009), 2 y follow-up	ARC seasonal inadequately controlled with conventional pharmacotherapy Pollen: grass				
Gomez Vera et al, 2005, Mexico	Mean age in HDM SLIT group: 22.8; mean age in placebo group: 20.6/ 26 male and 24 females	60 participants (30 in HDM SLIT group and 30 in Placebo SLIT group)	NR	6 m	mild or moderate allergic asthma	HDM SLIT vs placebo SLIT Dermatophagoides pteronyssinus 1 standardized allergens (IPI-ASAC, Mexico) at a total dose of 10,469 UBE	NR	Short term effectiveness: beta-2 use: SLIT 50% reduction, Placebo 21% reduction. (z=1.44 p<0.03)	Safety: No AEs reported Lung function: FEV1 pre-BD: 25% rise in SLIT vs. 9% in placebo (z=0.66<0.03) FVC improvement in both SLIT (15%) and placebo (14.7%) (NS) SLIT: 1st month 32, 6th month 6. Placebo: 34 and 24. Total 6month 61 vs. 123 T 2.6 (p<0.001), z value for that difference 1.56 (p>0.01; CI 1.54-1.57)
Ippoliti et al, 2003, Italy	5 to 12 y; median age of 9 in both groups/ 50 male and 36 females	86 (47 in HDM SLIT group and 39 in placebo SLIT group)	monosensitized	26 w (with 3-month run-in)	mild or moderate allergic asthma	HDM SLIT vs placebo SLIT House dust mite SLIT (D. pteronyssinus), maintenance dose 5 drops of 10 BU/mL 3 times a week	NR	Short term effectiveness: <u>Mean symptom score: before treatment:</u> SLIT group: 3.28, Placebo group: 3.08 <u>6 m after treatment:</u> SLIT group: 1.28, Placebo group: 3.15	Safety: no side-effects and no patient withdrew from treatment Lung function: FEV1 values: <u>before treatment:</u> SLIT group: 83.4, Placebo group: 80.7 <u>6 m after treatment:</u> SLIT group: 92.6, Placebo group: 81.2

Leng et al, 1990, China	15 to 56 y; Artemisia pollen SLIT group mean 34.8y, placebo group mean 36.2y / 9 male and 9 females	18 (9 in Artemisia pollen SLIT group and 9 in placebo group)	NR	7.14 w (13 w post-treatment follow-up)	NR	Artemisia pollen SLIT vs placebo SLIT: Artemisia pollen SLIT daily up-dosing to a maximum of 16416 PNU. Cumulative dose 396,652.06 PNU	natural	NR	Safety: 1/9 in SLIT group and 0/9 in placebo group experienced an AE Environmental exposure chamber or bronchial allergen challenge SLIT group: mean PD20-FEV1 was 25.28 and 10.81 PNU before and after treatment respectively Placebo group: mean PD20-FEV1 was 10.48 and 10.81 PNU before and after treatment respectively
Lewith et al, 2002, UK	18 to 55y; homeopathic HDM SLIT group mean 38.2 (9) y, placebo group mean 37.9 (10.4) y / 89 male and 153 females	242 (122 in homeopathic HDM SLIT group and 120 in placebo SLIT group)	NR	16 w	84 with mild asthma, 119 with moderate and 40 severe asthma	Homeopathic HDM SLIT vs placebo SLIT: Homeopathic HDM SLIT administered on 3 occasions over 24 hours. Dose 30 dilutions of 1:100	Homeopathic HDM SLIT	NR	QoL: mean improvement for diary quality of life was 0.117 for placebo and 0.090 for active treatment (−0.096 to 0.150) Safety: No AEs reported due to homeopathic immunotherapy Lung function: Mean improvement in FEV1 from baseline was 0.414 l/sec for placebo and 0.136 l/sec for active treatment (95% confidence interval for difference 0.136 to 0.693)
Lue et al, 2006, Taiwan	6 to 12 y; HDM SLIT group mean 7.7 (1.8) y and placebo group mean 8.6	20 participants (10 in HDM SLIT group and 10 in placebo group)	monosensitized	24 w (2 w post-treatment follow-up)	mildly persistent to moderately persistent	HDM SLIT vs placebo SLIT HDM SLIT daily with 3-week initiation phase. Maximum 20 drop dose of 300 IR/mL. Cumulative dose of 41,824 IR	natural	Short term effectiveness: <u>Daytime symptom scores (mean±SD):</u> SLIT baseline:0.42±0.23 SLIT week 24: 0.113±0.19 Placebo baseline: 0.42±0.34. Placebo week 24:0.49±0.38 <u>Nighttime symptom score(mean±SD):</u> SLIT baseline:0.51±0.24 SLIT week 24:0.16±0.15 Placebo baseline:0.50±0.38 Placebo week 24:0.50±0.47 <u>Medication score(mean±SD):</u> SLIT baseline:1.7±1.08 SLIT week 24:1.0±0.94 Placebo baseline:1.25±0.72 Placebo week 24:1.1±1.15	Safety: No severe AEs reported Lung function: Compared with baseline, PEFR in the SLIT group increased in the morning and evening (196.8 ± 26.3 and 215.5 ± 47.6 l/min, respectively); only the difference in Lung function: evening PEFR reached statistical significance (p=0.008). No statistically significant difference between the

	(1.8) y / 8 male and 12 female				asthma				two groups. Endpoint FEV1 increased in the SLIT group (p=0.01). no statistically significant difference in the placebo group. FEV1 did not differ between the two groups
Ma et al, 2010, China	8±2.9 yrs. in SLIT+ICS group and 7.2±2.5 yrs. in ICS alone group/23 male and 9 females	32 (18 in SLIT+ICS group and 14 in ICS alone group)	NR	1 y	mild and moderate dust mite allergic asthma	SLIT+ICS vs ICS alone SLIT immunotherapy with Der F drops	NR	Short term effectiveness: Compared with the ICS alone group, the day and night symptom scores decreased in the SLIT group.	Safety: No severe AEs occurred in both groups during the follow-up period Lung function: Compared with the ICS alone group, the day and night symptom scores decreased, FEF25-75% increased significantly. There were no statistical differences in FEV1. Corticosteroids: By the end of one y the SLIT + ICS group had significantly decreased amount of ICS administration than the ICS alone group
Ma et al, 2014, China	5-14 y old	120 (60 in SLIT group and 60 in placebo group)	NR	1 y	mild to moderate allergic asthma	HDM SLIT vs placebo SLIT SLIT immunotherapy with Der F drops	NR	Short term effectiveness: After treatment for one y, the scores of ACQ, rhinitis symptom, and monthly asthmatic medicine and the SIgE value of serum dermatophagoides farinae of the SLIT treatment group and conventional treatment group were decreased. The decrease in the SLITt group was significantly more than that of the conventional treatment group. (P<0.01).	Safety: The incidence of side effects (including skin rash, nasopharyngeal itch, and asthma attack) relevant to immunotherapy was 13.3% and no serious AEs.
Moreno-Ancillo et al, 2007, Spain	14 to 55 y / 58 males and 47 females	105 (53 in Grass mix plus olive pollen SLIT group and 52 in placebo group)-only 61% (64/105) had	polyse nsitize d	248 d	23 with low intermittent asthma, 15 with low persistent asthma, 26 with moderate	Grass mix plus olive pollen SLIT vs Placebo biologically standardized by major allergens and quantified in micrograms, without up dosing	natural	Short term effectiveness: <u>Pulmonary symptoms:</u> Active 2004: 0.30 (0.43), Active 2006: 0.16 (0.21) Placebo 2004: 0.28 (0.35), Placebo 2006: 0.14 (0.22) <u>Medication pulmonary:</u> Active 2004: 1.10 (2.72), Active 2006: 0.73 (1.63) Placebo 2004: 1.20 (1.89), Placebo 2006: 0.64 (1.41) <u>Symptom and medication pulmonary:</u> Active 2004: 0.85 (1.61), Active 2006: 0.52 (0.92) Placebo 2004: 0.88 (1.27), Placebo 2006: 0.46 (0.85)	NR

		asthma			persiste nt and 41 with absent asthma				
Mosbec h et al, 2014, Denmar k, German y, Italy, Spain, United Kingdo m, Sweden, France, and Poland	14 y and above (mean age/age range NR but across groups 6% were reported to be adolescent s)/ 50% were male and 50% were female	604 (1SQ- HDM=14 6; 3SQ- HDM=15 9; 6SQ- HDM=15 6;Placebo =143)	83% were polyse nsitize d	1y	mild to moderat e HDM Allergic Asthma requirin g ICS use	HDM SLIT 1 DU daily vs HDM SLIT 3 DU daily vs HDM SLIT 6 DU daily vs Placebo SLIT oral lyophilisates containing standardized extracts of D pteronysinus and D farina in a 1:1 ratio. Three active strengths were investigated: 1, 3, and 6 SQ-HDM. The units were designated in development units. One development unit corresponds to 1 SQ- HDM	natural	Short term effectiveness: no statistically significant differences between the active and placebo groups for any of the assessed asthma parameters (ACQ score, peak expiratory flow, FEV1, asthma exacerbations, and AQLQ score). activity limitations, shortness of breath, and wheeze.	QoL: For the AQLQ (asthma quality of life) score, the mean change from baseline was numerically greater for all 4 domains for 6 SQ- HDM than for the other groups (by 0.1-0.2 on average), but this difference was not statistically significant Safety: <u>Total AEs:</u> 290/461 (63%) in the SLIT groups and 77/143 (54%) in the placebo group <u>Mild AEs:</u> 232/461 (50%) in the SLIT groups and 65/143 (45%) in the placebo group <u>Moderate AEs:</u> 119/143 (30%) in the SLIT groups and 35/107 (24%) in the placebo group <u>Severe AEs:</u> 18/461 (4%) in the SLIT groups and 5/143 (3%) in the placebo group <u>Serious</u> <u>AEs:</u> 14/461 (4%) in the SLIT groups and 15/143 (17%) in the placebo group. Corticosteroids: For all 3 actively treated groups the distribution of ICS doses after 1 y of treatment was shifted toward lower doses compared with placebo. The primary analysis revealed a statistically significant difference between 6 SQ-HDM and placebo. The daily ICS dose was reduced from baseline by 208 µg (adjusted mean) for 6 SQ-HDM and 126 µg for placebo, leading to the mean ICS reduction being larger by 81 µg/d for 6 SQ-HDM than for placebo (95% CI, 27-136 µg/d; P= .004). The difference from placebo was not statistically significant for 1 and 3 SQ-HDM. 34% of the subjects in the 6 SQ-HDM group could completely discontinue ICS use after 1 y

									of treatment compared with 21% of the subjects in the placebo group and fewer subjects in the 6 SQ-HDM group (8%) versus the placebo group (15%) experienced an increase in the ICS dose needed to maintain asthma control. Mean and median values for the relative reduction from baseline in ICS dose were 42% and 50% for 6 SQ-HDM compared with 15% and 25% for placebo. No statistically significant difference from placebo was observed for 1 and 3 SQ-HDM
Mosges et al, 2010, Germany	6-14 y/ 28 male and 26 female	54 participants (27 in SLIT group and 27 in no SLIT group)	monosensitized	9 m	mild to moderate allergic asthma	Pollen SLIT vs placebo SLIT Standardized birch pollen (Betula alba) allergen extract. Ultra-rush high-dose SLIT titration regimen reaching the maintenance dose of 300 IR within 90 min (30–90–150–300 IR)	natural	NR	Safety: most frequent AEs were application site itching and paresthesia. No anaphylaxis or other serious AEs occurred. Lung function: Mean PFR slightly increased in both groups. The difference in mean PFR changes between SLIT and placebo was not significant (p = 0.056).
Niu et al, 2006, Taiwan	6 to 12 y; mean age 7.9 (SLIT) y and 8.2 (placebo) y/ 58 males and 39 females	110 (56 in HDM SLIT group and 54 in placebo group)	monosensitized	24 w (+ 2 week off-treatment follow-up)	mild to moderate allergic asthma	HDM SLIT vs placebo SLIT HDM SLIT (D. pteronyssinus and D. farinae), incremental dosing up to maintenance dose (cumulative dose ~ 41824 IR, which was equivalent to 1.7 mg D.p. and 3.0 mg D.f.)	natural	Short term effectiveness: Significant difference between the two groups in daily (P=0:011), nighttime (P=0:028), and daytime (P=0:009) asthmatic scores after 24 w of treatment. Improvement of asthma symptoms took place gradually in the SLIT group. Placebo group had almost the same asthma score at the endpoint as they had at baseline. The use of oral corticosteroids was reduced with SLIT (0.087±0.42), though the reduction was not statistically significant (P=0:183).	Safety: No serious AEs reported. Between-group differences in all adverse events (6 in SLIT vs. 7 in placebo, P = 0:861), drug-related adverse events (5 in SLIT vs. 3 in placebo, P= 0:487), and serious events (1 in SLIT vs. 4 in placebo, P = 0:129) were not significant different. Lung function: From baseline, SLIT group had increased morning and night PEF (10.9+40.0 and 11.1+41.6 L/min, respectively), but not significant (P=0:072 in morning PEF and P= 0:070 in night PEF). Endpoint FVC, FEV1, and PEF was found to be significantly increased in the SLIT group (P

									= 0.042, 0.048, and 0.001, respectively). But no statistically significant between-group difference.
Pajno et al, 2000, Italy	8 to 15 y; mean age 11 (SLIT) y and 12 (placebo) y / 11 male and 13 females	24 (12 in HDM SLIT group and 12 in placebo SLIT group)	monosensitized	104 w(2 y)	mild to moderate allergic asthma	HDM SLIT vs placebo SLIT House dust mite SLIT (D. pteronyssinus), incremental dosing schedule followed by maintenance 2.4 mg Der P 1 and 1.2 mg Der P 2 per week (in 3 doses/wk.)	natural	Short term effectiveness: After 2 y SLIT 68.16% reduction in comparison to the observation period, was seen In the SLIT group (P=0.0066, in comparison to the first y of treatment), but not in the placebo group (P=0.6875). Nighttime symptoms, non-significant (P=0.439) decrease in the placebo group, and a significant decrease in the SLIT group (P=0.001). Significant difference in 2nd y of treatment, in favor of SLIT (P<0.0001). The mean score for nighttime symptoms decreased by 11.7% in the placebo group and by 57.14% in the active treatment group. Medication use in SLIT group was significantly lower than in the placebo group after the second y of treatment (P=0.0001).	Safety: Tiredness in 4 SLIT patients and 1 in placebo group. 2 local delayed reactions in 2 SLIT patients: one case of swelling of the mouth, lips, and face (at 2 h) and one case of itching of the mouth (at 3 h). These AEs resolved spontaneously, and were during the induction phase with the first administrations of the most diluted vial Exacerbations: Baseline (1993), both groups had more than 1.5 asthma episodes/month, with a significantly higher (P=0.02) number of episodes in the group to be treated with active SLIT. Both the placebo and the active treatment groups showed significant improvement during the second y of treatment in comparison to the observation period (P=0.0039 for placebo, P=0.0005 for active treatment). However, the improvement in the active group (60.7%) was significantly greater than the improvement in the placebo group (18.75%, P=0.0001)
Pajno et al, 2002, Italy	8 to 14 y; mean age 11 y / 13 male and 17 females	30 children (15 in Parietaria SLIT group and 15 in placebo group)	monosensitized	56 w (with 52 week off-treatment follow-up)	mild or moderate allergic asthma	Parietaria pollen SLIT plus fluticasone vs placebo plus fluticasone SLIT: Parietaria pollen SLIT (Parietaria judaica), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg)	natural	Short term effectiveness: Considering the overall season, chest symptoms, nose symptoms, drugs scores, and the VASs were significantly better in SLIT groups compared to placebo (P ranging from 0.001 and 0.043). A significant difference could be shown in favour of the SLIT group as compared to the P1F group for the VAS (P=0.037) but not for chest symptoms, drug scores, eye symptoms, and nose symptoms. The difference between the control group and the others two groups began to be significant from the fifth week of the pollen season (for chest symptoms from fourth week).	Safety: Tiredness reported by three patients belonging to the SLIT+F group and 2 patients in the P+F group. In all cases, no adjustment of the dose was necessary and all five patients completed the study with no further problems.

Pajno et al, 2004, Italy 2nd paper from 2002 study	8 to 14 y; mean age 11 y/ 13 male and 17 females	30 (15 in Parietaria pollen SLIT group and 15 Placebo SLIT group)	monosensitized		mild or moderate allergic asthma	Parietaria pollen SLIT vs placebo SLIT: Parietaria pollen SLIT (Parietaria judaica), incremental dosing schedule followed by maintenance twice/wk. (cumulative Par j ~ 20.3 mcg)	natural	NR	Lung function: FEV1 (% pred): Winter 1999: SLIT group: 88.2 (4.1) Placebo group: 92.6 (5.0) Spring 1999: SLIT group: 82.0 (5.4) Placebo group: 78.9 (5.9) Spring 2000: SLIT group: 86.1 (6.3) Placebo group: 78.4 (4.6) Spring 2001: SLIT group: 88.4 (3.7) Placebo group: 75.6 (4.9) FEF25-75 (% pred): Winter 1999: SLIT group: 82.1 (5.3) Placebo group: 80.0 (4.5) Spring 1999: SLIT group: 70.6 (4.2) Placebo group: 73.5 (5.4) Spring 2000: SLIT group: 74.0 (6.6) Placebo group: 67.6 (6.0) Spring 2001: SLIT group: 73.4 (6.1) Placebo group: 65.5 (5.8) Environmental exposure chamber or bronchial allergen challenge: MCh PC20 in winter 1999 (baseline): SLIT group: 9.78 ± 5.95 mg/ml Placebo group: 8.70 ± 6.25 mg/ml p-value: 0.01 MCh PC20 in spring 1999: SLIT group: 3.37 ± 2.99 mg/ml Placebo group: 2.44 ± 2.25 mg/ml p-value: 0.005 MCh PC20 in spring 2001: SLIT group: 9.10 ± 7.7 mg/ml Placebo group: 2.46 ± 2.2 p-value: 0.001
Pham-Thi et al, 2007, France	5 to 16 y; mean age 9.6 (SLIT) y and 9.5 (placebo) y / 78 male and 31 females	111 (55 in HDM SLIT group and 56 in placebo group)	monosensitized	78 w	mild to moderate allergic asthma	HDM SLIT vs placebo SLIT HDM SLIT (D. pteronyssinus and D. farinae), up-dosing for 2 w up to 300 IR concentration once daily (average cumulative dose was 155,000 IR, corresponding to 6.9 mg Der P 1 and 14.7 mg Der f 1)	natural	Short term effectiveness: Mean diurnal asthma (SD): SLIT baseline: 0.19 ± 0.30 ,SLIT endpoint: 0.15 ± 0.26 Placebo baseline: 0.17 ± 0.24 ,Placebo endpoint: 0.08 ± 0.17 Mean nocturnal asthma(SD): SLIT baseline: 0.17 ± 0.30 ,SLIT endpoint: 0.10 ± 0.19 Placebo baseline: 0.11 ± 0.18 ,Placebo endpoint: 0.07 ± 0.16 Mean % asthma free d(SD): SLIT baseline: 78.5 ± 27.4,SLIT endpoint: 85.8 ± 23.8 Placebo baseline: 80.8 ± 23.8,Placebo endpoint: 91.1 ± 15.4 Mean use of β_2-agonists (terbutaline puffs/day):SLIT baseline: 0.87 ± 0.5,SLIT endpoint: 0.55 ± 0.6 Placebo baseline: 0.90 ± 0.8,Placebo endpoint: 0.47 ± 0.5	QoL: CAC-B population (age 6–11 yr.), the severity dimension showed a significant improvement in the SLIT group compared with the placebo group (p = 0.04). In the CAC-C population (age 12–16 yr.), 14% of the patients had a maximum QoL score for reactivity dimension. In both SLIT and placebo groups, the average changes in all dimensions were comparable and no statistically significant differences were observed. Safety: AEs related to SLIT occurred at least once in 39 of 55 (71%) patients treated with

								SLIT and 37 of 56 (66%) placebo-treated patients. Local oral and gastro-intestinal reactions occurred more frequently in SLIT-treated group. Some adverse events were effectively treated by either dose reduction or/and antihistamines. Gastrointestinal complaints led to one patient's withdrawal in each group. One patient in the placebo group withdrew after a severe acute exacerbation of asthma. No anaphylaxis. <u>Lung function:</u> Mean PEF variability % (SD): SLIT baseline: 8.03 ± 7.21, SLIT endpoint: 6.06 ± 5.45 Placebo baseline: 7.48 ± 6.14, Placebo endpoint: 6.36 ± 5.65 <u>Mean % FEV1 predicted value (SD):</u> SLIT baseline: 91.9 ± 13.4, SLIT endpoint: 88.5 ± 13.4 Placebo baseline: 95.1 ± 15.1, Placebo endpoint: 94.5 ± 14.6 <u>Mean use of inhaled steroids (μg budesonide/day):</u> SLIT baseline: 548 ± 220, SLIT endpoint: 257 ± 232 Placebo baseline: 534 ± 237, Placebo endpoint: 223 ± 270
Reilly et al, 1994, UK	minimum age 16 y; mean age of homeopathic SLIT group 40 (16.3) y, placebo group 37 (14.3) y / 15 male and 13	28 (13 in and 15 in placebo SLIT group)	poly-sensitized	4 w (with 4 w 'optional' post-treatment follow-up)	NR	homeopathic SLIT vs placebo SLIT homeopathic SLIT (allergen varied, decided on case-by-case basis; HDM (84.6% of participants); feathers (7.7%); mixed moulds (7.7%)). 3 doses in 24 hours then optionally repeated at 4 w (according to patient choice)	natural	<u>Short term effectiveness:</u> mean (SEM) reduction of 7.2 (3.2) mm for homeopathy versus an increase of 7.8 (3.0) for placebo ($p=0.003$, 95% CI of -24.1 to -5.9 mm) <u>Lung function:</u> FVC(L) median(quarters): Homeopathy: 0.07 (-0.2 to 0.4) Placebo: -0.33 (-0.4 to 0.0) FEV1% of predicted median (quarters): Homeopathy: 3.0 (-3.0 to 8.3) Placebo: -7.0 (-11 to 5.0) <u>Environmental exposure chamber or bronchial allergen challenge</u> Log10 PC20 mean(SEM): Homeopathy: 0.09 (0-12) Placebo: -0.02 (0-11)

	females								
Reinert et al, 1983, Germany	4-11 y / sex not reported	20 participants (10 in pollen SLIT group and 10 in placebo group)	NR	2 y	NR	Pollen SLIT vs placebo SLIT Tropon holister stier	NR	Short term effectiveness: "No effect of treatment. Placebo was as good as active treatment. Authors state a slight improvement in both groups"	NR
Stelmach et al, 2009, Poland	6 to 17 y; mean age of participants in grass pollen group who completed study 9.1 (2.4) y, placebo group who completed study 8.5 (2.8) y / 22 male and 13 females	50 (25 in grass pollen SLIT group and 25 in placebo group)	monosensitized	104 w	mild or moderate allergic asthma	Grass pollen SLIT vs placebo SLIT grass pollen SLIT (Dactylis glomerata, Anthoxanthum odoratum, Lolium perenne, Poa pratensis, Phleum pratense). Ultra-rush induction: 1-3-6-12 (10-30-60-120 IR) drops separated by a 30-minute observation period (total of 24 0IR). At the beginning of the next day, every morning before breakfast, received 4 puffs (120 IR) for 6 m. Cumulative dose 43,800 IR	natural	Short term effectiveness: Treatment with SLIT significantly improved asthma symptoms score and reduced nasal symptoms over 2 y of therapy, compared with placebo treatment, although there was no significant changes in ocular score. Comparing with previous season, scores were reduced by 61.6% (41% vs. placebo) in the SLIT group and 20.16% in the placebo group for asthma symptoms score, 55.7 (25% vs. placebo) and 30.5%, respectively, and 1.8% for medication.	Safety: AEs possibly related to SLIT in 13 of 22 (59.1%) subjects with SLIT and 5 of 21 (23.8%) placebo-treated subjects in the first y of SLIT, and in 7 of 20 (35%) subjects with SLIT and 5 of 15 (33.3%) placebo-treated in the second y of immunotherapy. Mainly local reactions, sublingual itching (50% vs. 14.3%, in the first y of immunotherapy and 35% vs. 20%, in the second y of immunotherapy), were reported. Other adverse events with possible association to treatment were headache in the first y of immunotherapy (4.5% vs. 4.8%), 0 vs. 6.6% in the second y of immunotherapy, and stomachache in the first y of immunotherapy (4.5% vs. 4.8%), 5% vs. 6.6% in the second y of immunotherapy. There was no termination of the study due to adverse events in any group. The global assessment of tolerability by subjects and doctors was better in the second y of treatment. Lung function: 1st pollen season FEV1 (mean % pred, Upper CI-lower CI):SLIT: 92.9 (87.7-98.1) Placebo: 87.9 (82.8-92.9) 2nd pollen season FEV1 (mean % pred, Upper CI-lower CI): SLIT: 100.4 (95.6-105.1) Placebo:

								88.2 (81.7-94.7) 1st pollen season FEF25/75 (mean % pred, Upper CI-lower CI): SLIT: 84.9 (76.9-92.9) Placebo: 77.1 (68.5-85.6) 2nd pollen season FEF25/75 (mean % pred, Upper CI-lower CI): SLIT:88.7 (81.8-95.7) Placebo: 81.2 (70.4-92.0) 1st pollen season PEF (mean % pred, Upper CI-lower CI): SLIT: 81.4 (72.9-89.8) Placebo: 78.7 (71.0-86.5) 2nd pollen season PEF (mean % pred, Upper CI-lower CI): SLIT: 92.9 (84.4-101.4) Placebo: 84.0 (75.4-92.6) <u>Environmental exposure chamber or bronchial allergen challenge</u> Mean MchPC20 Active: 4.05 (95% CI 3.54-4.55) Mean MchPC20 Placebo: 4 (95% CI 3.24-4.77)	
Tian et al, 2014, China	4-18 y/30 male and 30 female	60	monosensitized	48 w	mild to moderate allergic asthma	HDM SLIT vs placebo SLIT house dust mite SLIT (D. farinae), titrated up over the first 4 w to 333 mcg/mL once daily	natural	<u>Short term effectiveness</u> : Mean daily symptom scores in the treatment group were 1.52 ± 0.29, 1.03 ± 0.22, 0.56 ± 0.19, 0.35 ± 0.17, and 0.16±0.08, before treatment, and 12 w, 24 week, 36 w, and 48 w after treatment, respectively. These scores significantly decreased over the study period (F=226.305, p=0.001). Although mean daily symptom scores appeared to decrease in the control group, the changes were not statistically different (F=2.120, p=0.083). Intergroup comparison demonstrated that the magnitude of change in the treatment group was significantly higher than in the control group (F=299.879, p=0.001). The difference of mean daily symptom scores between the 2 groups became statistically significant from 12 w after treatment (p<0.05)	NR

Virchow et al, 2016, German y	Adults/ 431 male and 403 female	834 participants (275 in 6SQ-HDM group, 282 in 12SQ-HDM group and 277 in placebo group)	Polysensitized (only 283/834 were sensitized only to HDM)	20 months (11 August 2011 to 24 April 2013)	mild or moderate allergic asthma	HDM SLIT vs placebo SLIT: The HDM SLIT tablet contains extract from 2 species of cultivated HDM (D pteronyssinus and D farinae), produced in a standardized process with a 1:1:1:1 ratio of the major allergens (Group 1 allergens of D farinae and D pteronyssinus and Group 2 allergens of D farinae and D pteronyssinus), and formulated as rapidly dissolving oral lyophilisate for sublingual administration (ALK).	natural	Short term effectiveness: The analyses of the odds for improvement in ACQ score without an increased dose of ICS showed no statistically significant differences between active treatment and placebo (ACQ score odds ratio [OR]: 1.12 [95% CI, 0.73-1.70] for the 6SQ-HDM group vs placebo group and 1.31 [95% CI, 0.85-2.01] for the 12 SQ-HDM group vs placebo group; QoL: The odds for improvement in AQLQ(S) score without an increased dose of ICS showed no statistically significant differences between active treatment and placebo; AQLQ(S) score OR: 1.01 [95% CI, 0.63-1.62] for the 6SQ-HDM group vs placebo group and 0.97 [95% CI, 0.61-1.53] for the 12SQ-HDM group vs placebo group Safety: 599 participants (72%) reported AEs in a dose-dependent manner, most were mild. Dose dependent change in the numbers of participants with TRAEs (39% from the 6SQ-HDM group, 46% from the 12SQ-HDM group, and 17% from the placebo group). Most frequently: oral pruritus, mouth edema, and throat irritation. No safety findings of clinical concern in the subgroup with asthma classified as uncontrolled according to GINA. No deaths occurred during the trial and there were no anaphylactic reactions, severe systemic allergic reactions, adverse events requiring epinephrine, or local allergic reactions compromising the airways. Exacerbations: The 6SQ-HDM and 12SQ-HDM doses both significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (hazard ratio [HR]: 0.72 [95% CI, 0.52-0.99] for the 6SQ-HDM group, P = .045, and 0.69 [95% CI, 0.50-0.96] for the 12 SQ-HDM group, P = .03). The absolute risk differences based on the observed data (full analysis set) in the active groups vs the placebo group were 0.09 (95% CI, 0.01-0.15) for the 6SQ-HDM group and 0.10 (95% CI, 0.02-0.16) for the 12SQ-HDM group. There was no significant difference between the 2 active
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									groups. Compared with placebo, there was a reduced risk of an exacerbation with deterioration in asthma symptoms (HR,0.72 [95%CI,0.49-1.02] for the 6SQ-HDM group, P = .11, and0.64 [95%CI,0.42-0.96] for the 12SQ-HDMgroup, P = .03).
Vourdas et al, 1998, Greece	7 to 17 y; mean age 12 y/ 17 male and 49 females	66 (34 in olive pollen SLIT group and 32 in placebo SLIT group)	30/34 in the active group were polysensitized and 26/32 in the placebo group.	104 w (2 y)	mild allergic asthma	Olive pollen SLIT vs placebo SLIT Olive pollen SLIT, daily up-dosing then each morning pre- and co-seasonally from January to July for 2 y up to a maximum of 20 drops of 300 IR (total 30,000 IR/y)	natural	Short term effectiveness: SLIT patients had a significantly (p<0.04) lower score of dyspnea (49% less than placebo) during the first pollen peak, this continued (p<0.03) during the second season. The medication score did not differ significantly between the groups. Oral steroids were the only variables with a P value near the significance level (p=0.06) in favor of the actively treated group.	Safety: No major AEs. A few minor AEs during the progression phase for eight patients in the SLIT group (eight occurrences of buccal itching or oropharyngeal pruritus, one labial swelling, and conjunctivitis symptoms) and two patients in the placebo group (buccal itching, labial swelling). One tablet of cetirizine (10 mg) was administered in only one patient. In all but one patient with side effects, the dosage was reduced temporarily, and reached the final dose with a delay. In one patient, the optimum maintenance dose was lower than the one suggested by the manufacturer. Lung function: No difference in peak expiratory flow rate (PFR) between groups was noted. average PFR level was better after the pollination season than before in both groups.
Wang et al, 2014, China	16-50 y/ 209 male and 256 female	484(322 in HDM SLIT group and 162 in placebo group)	monosensitized	52 w (+12-week baseline period before randomization)	mild (n=237) or moderate (n=175) allergic asthma	HDM SLIT vs placebo SLIT HDM SLIT (D. pteronyssinus and D. farinae), approximately 28 mcg Der P 1 and 50 mcg Der f 1 daily (300 IR)	natural	Short term effectiveness: The proportions of patients achieving WCA (well controlled asthma) or TCA (total controlled asthma) by the study end were not significantly greater in the SLIT group than placebo. For patients with moderate asthma (n=175), the WCA success rate was greater in the active treatment group than in the placebo group (80.5% and 66.1%, respectively; P=0.021). There was no significant difference for patients with mild asthma (n=237). subgroup of patients with moderate asthma, the percentage of patients achieving TCA was higher (P=0.008) in the active treatment group when compared with the	QoL: AQLQ scores in both groups improved from baseline a mean value of 4.5 (1.08) at screening to 5.9 (0.91) to randomization but no end of study scores given. Safety: TEAEs (recorded in 5% of the patients) more frequent in the SLIT group than placebo group, with (generally mild) abdominal pain, swollen tongue, oral pruritus, glossitis, chelates and mouth edema. The active and placebo groups did not differ greatly in terms of the incidence of rhinitis, upper

								placebo group (54.0% and 33.9%, respectively).	respiratory tract infections, nasopharyngitis and asthma events. Serious AEs not related to treatment. No deaths or anaphylactic reactions were reported Lung function: mean FEV 1% predicted remained above 80% during the treatment period in both the SLIT and placebo groups. The study end vs baseline changes were non-significant in both groups Corticosteroids: In patients with moderate (but not mild) asthma, mean absolute decrease in budesonide dose was significantly greater in the active treatment group than in the placebo group (218.5 µg and 126.2 µg, respectively; P=0.004) Asthma control: The ACQ score improved markedly during the baseline period, and over 80% of patients had an ACQ score<1.5 at randomization. In moderate (but not mild) asthma, the percentage of individuals with ACQ <0.75 was higher in the active treatment group than in the placebo group (56.6% and 40.0%, respectively; P=0.039).
Wood et al, 2014, USA and UK	5 to17 y; mean age 11 (low SLIT) y,10 (high SLIT) and 11 (placebo) y / 63 male and 26 females	89 (31 in low dose cockroach SLIT group, 30 in high dose cockroach SLIT group and28 in placebo	NR	13 w	NR	cockroach SLIT (low) vs cockroach SLIT (high) vs placebo SLIT <u>SLIT group (low):</u> Greer German cockroach extract SLIT, 1 day escalation up to 3685 BAU (approx. 4.2 mcg Bla g 2 and 50 mcg Bla g 1 daily) <u>SLIT group (high):</u> Greer German cockroach	natural	NR	Safety: 343 non-serious AEs in 78 of the 89 participants; 12.5% definitely/probably related to treatment, no differences among any of the treatment groups, and no AEs required dose adjustments or study discontinuation. Eight participants experienced oral pruritis, tongue pruritus, or both during the study: 6 receiving the low active extract dose, 1 receiving the high dose, and 1 receiving placebo.

		SLIT group)				extract SLIT,1-day escalation then 4-week escalation to 14740 BAU (approx 16.8 mcg Bla g 2 and 202 mcg Bla g 1 daily)			
Zhang et al, 2013, China	4-14 y/ sex not reported	128 participants (64 in SLIT group and 64 in no SLIT group)	NR	2 y	mild to moderate allergic asthma	HDM SLIT vs no SLIT Dermatophagoides farinae drops First week to third week: 1,10 and 100mg/L concentration of dust mite drop, once a day; 1,2,3,4,6,8 and 10 drops indifferent day in every week. From forth week: 333 mg/L dust mite drops, 3 drops /time/day	NR	Short term effectiveness: After 6 m, 1 y and 2 y of treatment, the allergic asthma symptom scores of the patients in treatment group were significantly decreased compared with control group (P<0.05).	Safety: There were no severe adverse events during the course of immunotherapy, except for mild reactions. Lung function: After 6 months, 1 year and 2 years of treatment, the PEF% of the patients in SLIT group were significantly increased compared with control group (P<0.05).
Zhang et al, 2015, China	6-14 y / 45 male and 57 female	102 participants (51 in SLIT group and 51 in no SLIT group)	NR	36 m	NR	HDM SLIT vs no SLIT Dermatophagoides farina drop (1drop/time and 1 time/day)	NR	Short term effectiveness sublingual dermatophagoides farina drop could effectively improve the lung function and alleviate the symptoms of acarid allergic asthma in children	NR
Zheng et al, 2012, China	10±5 y / 56 male and 50 female	106 participants (53 in SLIT group and 53 in no SLIT group)	NR	36 m	NR	HDM SLIT vs no SLIT Standard dermatophagoides farinae drops (1~4) usage:1~3 were for increasing period of treatment for 3 w, 1 times a day.	NR	Short term effectiveness Specific sublingual immunotherapy with dermatophagoides farina drops is an effective and highly safe treatment for cough variant asthma in children	NR

Table S1c: Detailed characteristics of SCIT vs SLIT studies (n=1)

Study Author, year, country	Age/sex	Number of patients (N)/No randomized	Mono / polysensitized	Study duration (treatment duration)	Disease severity (mild, moderate, severe)	Type of Immunotherapy (intervention vs comparator) Type of allergen	Natural allergen or allergoid	Primary outcomes <i>Short-term effectiveness</i> <i>Long-term effectiveness</i>	Secondary outcomes <i>QoL</i> <i>Safety</i> <i>Lung function</i> <i>Corticosteroid use</i> <i>Exacerbations</i> <i>Environmental exposure chamber/bronchial allergen challenge</i>
Yukselen, 2012, Turkey	Mean age 10.06. Females= 13 males= 17	30/, SCIT=10, SLIT=11 Placebo=10 allergic Asthma=30, rhinitis=30.	Mono sensitized	2 years	mild	HDM (D. pteronyssinus and D. farinae) (50/50) for sublingual and subcutaneous administration. Natural	SCIT/SLIT HDM (D. pteronyssinus and D. farinae) vs placebo	Effectiveness measured using symptom and medication scores. Statistically significant difference in symptoms for asthma with both SCIT (p = 0.005) and SLIT (p = 0.012) in comparison to the baseline year. Regarding asthma symptoms, SCIT significantly reduced complaints (p = 0.01), while SLIT yielded no statistically significant effect (p = 0.48) in comparison to the placebo group. The medication scores significantly decreased in SCIT patients (p = 0.05) when compared with placebo. There was a tendency to a decrease (p = 0.18) in medication scores regarding asthma with SLIT in comparison to the baseline year.	Safety: Zero systemic AEs reported. Five patients in the intervention group reported local adverse events and 2 patients in the placebo group. Lung function: After 12-months immunotherapy FEV 1 values showed an average increase of 6.3% with SCIT, 5.5% with SLIT and 0.7% in the placebo group. When compared with the baseline year, FEV 1 values increased significantly with SCIT and SLIT (p = 0.04 for both), but did not change significantly in the placebo group (p = 0.88). The FEV 1 values of the SCIT and SLIT groups did not show a significant increase in comparison to the placebo group.

Table S1d: Quality appraisal of SCIT trials (n=55)

[illegible]

Denmark							
Bødter,2002, Denmark	Low	Low	Low	Low	Low	Low	Low
Bousquet,1985, France	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Bousquet,1990, France	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Cantani,1996, Italy	Low	Low	Low	Unclear	Low	Low	Low
Chakraborty, 2006, India	Low	Unclear	Unclear	Low	Unclear	Low	Unclear
Creticos,1996, US	Low	Low	Unclear	Unclear	Low	High	Unclear
Dreborg, 1986, Sweden and Finland	Low	Low	Low	Low	Unclear	Low	Unclear
Dolz,1996, Spain	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
D'Souza,1973, UK	Low	Low	Low	Unclear	Low	Low	Unclear
Franco,1995, Italy	Low	Unclear	Low	Unclear	Low	Low	Unclear

Gaddie,1976, UK	Low	Low	Low	Unclear	Unclear	Low	Unclear
Garcia-Robaina, 2006, Spain	Low	Low	Unclear	Unclear	Low	Low	Unclear
Haugaard,1992, Denmark	Low	High	Unclear	Unclear	Unclear	High	High
Hedlin,1999, Denmark	Low	High	High	Unclear	Low	Low	High
Hui, 2014, China	Low	Low	Unclear	Unclear	Low	Low	Unclear
Kuna,1989, Poland	Low	Low	Unclear	Unclear	Low	Low	Unclear
Kuna,2011, Poland	Low	Low	Low	Unclear	Unclear	Low	Unclear
Leynadier,2000, Germany	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Lewis, 1971,UK	Low	Low	Low	Unclear	Low	Unclear	Unclear
Maestrelli,2004, Italy	Low	Low	Low	High	High	Low	High
Malling,1986, Sweden	Unclear	Unclear	Low	Unclear	Low	Low	Unclear

Marques,1978, Italy	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Mosbech,1989, Denmark	Low	High	High	Low	High	Low	High
Ohman,1984, US	Low	Low	Low	Low	Low	High	Low
Newton,1979, UK	Low	Low	Unclear	Unclear	Unclear	High	High
Olsen,1997, Denmark	Low	Low	Low	Low	Low	Unclear	Low
Ortolani,1984, Italy	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Pauli,1984, France	Low	Low	Unclear	Unclear	High	High	High
Pene, 1998, France	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Price,1984,UK	Low	Low	Low	High	Low	Low	High
Rak,2001, Sweden	Unclear	Low	Unclear	Low	High	High	High
Reid,1986, US	Unclear	Unclear	Low	Low	Low	High	Unclear
Roberts,2006,	Unclear	Unclear	Low	Low	Low	Low	Unclear

UK							
Sabbah,1991, France	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear
Smith,1971, UK	Unclear	Unclear	Unclear	Low	Low	High	High
Sundlin/1986/Sw eeden	Low	Low	Unclear	Unclear	Low	Low	Unclear
Tabar,2008, Spain	Low	Low	Unclear	Low	Low	Low	Unclear
Taylor,1978a,US	Low	Low	Low	Low	Low	High	Low
Taylor,1978b,UK	Low	Low	Low	Unclear	High	High	High
Valovirta,1984, Finland	Low	Low	Low	Unclear	High	High	High
Van Bever, 1992, Belgium	Unclear	Unclear	Unclear	Low	High	Low	High
Van Metre, 1988, US	High	Unclear	Low	Low	Low	Unclear	High
Vidal,2011, Spain	Unclear	Unclear	Unclear	Low	Low	High	High
Wang, 2006, China	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Warner, 1978, UK	Low	Unclear	Unclear	Low	Low	Low	Unclear

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Table S1e: Quality appraisal of SLIT trials (n=34)

Study (author, year, country)	Adequate sequence generation	Allocation concealment	Blinding/ patient- related outcomes	Incomplete outcome data addressed?	Free of selecting reporting	Free of other bias*	Overall risk of bias
Alvarez- Cuesta et al, 2007, Spain	Unclear	Unclear	Low	High	Low	Unclear	High
Bachelier et al, 2001, Turkey	Unclear	Unclear	Low	Low	Low	Low	Unclear
Bousquet et al, 1999, France	Unclear	Unclear	Low	High	High	Low	High
Caffarelli et al,	Low	Unclear	Low	Low	Low	Low	Unclear

2000, Italy							
Cao et al, 2007, China	Unclear	Unclear	Low	Unclear	Low	Low	High
Dahl et al, 2006, Denmark and Sweden	Unclear	Unclear	Low	Low	Low	Low	Unclear
de Blay et al, 2014, Denmark, Germany, Italy, Spain, United Kingdom, Sweden, France, and Poland	Low	Unclear	Low	Low	High	Low	High
Devillier at al, 2015, China	Unclear	Unclear	Low	Low	Low	Low	Unclear
Drachenberg et al, 2001, Germany	Unclear	Unclear	Unclear	High	High	Unclear	High
Gomez Vera et al, 2005, Mexico	Unclear	Unclear	Low	Unclear	High	Unclear	High

Ippoliti et al, 2003, Italy	Unclear	Unclear	Low	Low	Low	Low	Unclear
Leng et al, 1990, unclear country	Unclear	Unclear	Low	Low	Low	Low	Unclear
Lewith et al, 2002, UK	Low	Low	Low	Low	High	Low	High
Lue et al, 2006, Taiwan	Unclear	Unclear	Low	Low	Low	Low	Unclear
Ma et al, 2010, China	Unclear	High	High	High	Unclear	Unclear	High
Ma et al, 2014, China	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Moreno-Ancillo et al, 2007, Spain	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
Mosbech et al, 2014, Denmark, Germany, Italy, Spain, United Kingdom, Sweden, France, and	Low	Unclear	Low	Low	Mosges et al, 2010, Germany	Unclear	Unclear

Poland							
Niu et al, 2006, Taiwan	Unclear	Low	Low	Low	Low	Low	Unclear
Pajno et al, 2000, Italy	Low	Unclear	Low	High	Low	Low	High
Pajno et al, 2002, Italy	Low	Unclear	Low	Low	Unclear	Low	Unclear
Pham-Thi et al, 2007, France	Unclear	Unclear	Low	Low	High	Low	High
Reilly et al, 1994, UK	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Reinert et al, 1983, Germany	Unclear	High	Low	High	High	High	High
Stelmach et al, 2009, Poland	Low	Unclear	Low	High	Low	Low	High
Tian et al, 2014, China	High	Unclear	Low	Unclear	High	Low	High
Virchow et al, 2016	Low	Low	Low	Low	Low	Low	Low
Vourdas et al,	Unclear	Unclear	Low	Low	High	Low	High

1998, Greece							
Wang et al, 2014, China	Unclear	Unclear	Low	Low	High	Low	High
Wood et al, 2014, USA and UK	Unclear	Unclear	Low	High	Unclear	Low	High
Zhang et al, 2013, China	Unclear	High	Unclear	Low	Low	High	High
Zhang et al, 2015, China	Low	Unclear	High	Low	Low	Low	High
Zheng et al, 2012, China	Unclear	Unclear	Low	Unclear	Unclear	High	High

Table S1f: Quality appraisal of SCIT vs SLIT trials (n=1)

Author, year	Adequate sequence generation	Allocation concealment	Blinding/ patient-related outcomes	Incomplete outcome data addressed	Free of selective reporting	Free of other bias*	Overall quality assessment

Yukselen,2012, Turkey	Low	Low	Low	Low	Low	Unclear	Low

Table S1g: Studies investigating the impact of AIT on asthma control in patients with asthma

Author, year	Instrument, data type and main findings				Summary
	Outcome name	Data type	Active n, summary data	Placebo n, summary data	
SLIT					
de Blay 2014	Asthma Control Questionnaire score	Mean difference (MD) between 6-SQ-HDM and placebo in overall	n=29 0.41	n=27 0.41	Statistically significant improvement in 6-SQ-HDM SLIT group compared to placebo (P=0.0002) at end of treatment
Devillier at al, 2016, China	Asthma Control Questionnaire score	Mean (SD)	n=322 0.68 (0.53)	n=162 0.75 (0.58)	No significant improvement in SLIT group compared to placebo (statistical significance not reported)
Ma et al, 2014, China	Asthma Control Questionnaire score	NR	n=60 NR	n=60 NR	Statistically significant improvement in SLIT group compared to placebo (P<0.1) at end of treatment
Mosbec h 2014	Asthma Control Questionnaire score	Mean difference between 6-SQ-HDM and placebo in overall Asthma Control Questionnaire score	n=101 0.1	n=92 0.1	Statistically significant improvement in 6-SQ-HDM SLIT group compared to placebo (P=0.0334) at end of treatment

Pham-Thi 2007	Asthma Free days (%)	Mean (SD)	n=55 85.8 (23.8)	n=56 91.1 (15.4)	No significant improvement in SLIT group compared to placebo (statistical significance not reported)
Virchow 2016,	Odds for improvement in Asthma Control Questionnaire score between 6SQ-HDM and placebo	OR (95% CI)	n=275 1.12 (0.73-1.07)	n=277 1.12 (0.73-1.07)	Not statistically significant improvement in 6-SQ-HDM SLIT group compared to placebo at end of treatment
Virchow 2016	Odds for improvement in Asthma Control Questionnaire score between 12SQ-HDM and placebo	OR (95% CI)	n=282 1,31 (0.85-2.01)	n=277 1,31 (0.85-2.01)	No statistically significant improvement in 12-SQ-HDM SLIT group compared to placebo at end of treatment
Wang 2014	Asthma Control Questionnaire score	Mean (SD)	n=308 0.68 (0.52)	n=157 0.74 (0.58)	Improvement in SLIT group compared to placebo, P=0.039
	Totally controlled asthma Success	N (%)	n=308 188 (61.0)	n=157 83 (52.9)	Improvement in SLIT group compared to placebo but statistical significance not reported
	Totally controlled asthma success	OR (95% CI)	n=308 1.41 (0.95-2.09)	n=157 1.41 (0.95-2.09)	No statistically significant improvement in SLIT group compared to placebo

					(p=0.085) at end of treatment
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Table S1h: Studies investigating the impact of AIT on generic and disease-specific QoL in patients with asthma

Author, year	Instrument, data type and main findings				Summary
	Outcome name	Data type	Active n, summary data	Placebo n, summary data	
SCIT					
Ameal, 2005	AQLQ, Marks	Median (IQR)	n=32 4 (1.0-8.0)	n=31 10.5 (5.0-17.0)	Significant improvement in SCIT group compared to placebo (P=0.0025) at end of treatment
Garcia-Robaina, 2006	AQLQ, Marks	Mean (95%CI)	n=32 7.44 (5.78-9.11)	n=32 11.44 (9.67-13.22)	Significant improvement in SCIT group compared to placebo (P=0.043)
Kuna, 2011	AQLQ, Juniper	Mean given for ≤12 and 12-18 years	n=30 ≤12= 5.8 12-18=6.5	n=20 ≤12= 3.9 12-18=4.2	Significant improvement in SCIT group compared to placebo: ≤12: P=0.04 12-18: P=0.018
SLIT					

Bousquet, 1999	Short-Form Health Status Survey; physical pain Short-Form Health Status Survey; general mental health domain Short-Form Health Status Survey; general perception of health domain	Mean	n=18 86.2 n=18 79.7 n=18 76.5	n=20 68.3 n=20 60.7 n=20 56.8	Not disease specific
de Blay, 2014	AQLQ-S, Juniper	Graphic and narrative description	n=29 (6SQHDM) n=27 (3SQHDM) n=26 (1SQ)	n=27	Significant difference in higher dose SLIT group, 6SQ-HDM and placebo P=0.01. Not significance in the 1SQ and 3SQ groups (P=0.30 and 0.32)
Devillier, 2015	AQLQ, Juniper	Narrative description	n=322 No summary data	n=162 No summary data	No statistically significant difference between active and placebo groups
Lewith, 2002	Diary quality of life assessment (Hyland et al)	Means (95% CIs)	n=122 0.090 (-0.096 to 0.150)	n=120 0.117 (-0.096 to 0.150)	No statistically significant difference between active and placebo groups

Mosbech, 2014 SLIT	AQLQ, Juniper	Graphic and narrative description	n=337 No summary data	n=96 No summary data	No statistically significant difference between active and placebo groups
Pham-Thi 2007	Childhood Asthma Questionnaire (CAQ): form CAC-B (6-11 years)	Narrative description	No summary data	No summary data	Significant improvement in active compared to placebo (P=0.04)
Pham-Thi 2007	Childhood Asthma Questionnaire (CAQ): form CAC-C (12-16)	Narrative description	No summary data	No summary data	No statistically significant difference between active and placebo groups
Virchow, 2016	AQLQ-S, Juniper	Odds ratio for 6SQ-HDM (95% CI) Odds ratio for 12SQ-HDM (95% CI)	1.01 (95% CI 0.63-1.62) 0.97 (95% CI 0.61-1.53)		No statistically significant difference between active and placebo groups for both 6SQ-HDM and 12SQ-HDM
Wang, 2014	AQLQ, Juniper		n=308	n=157	No end of treatment scores reported

Table S1i: Studies investigating the impact of AIT on asthma exacerbations

Author, year	Instrument, data type and main findings				Summary
	Definition of exacerbation	Data type	Active n, summary data	Placebo n, summary data	
SCIT					
Wang, 2006	Symptoms requiring a course of oral prednisolone	Number of courses of oral prednisolone needed	n=66 48 courses to 4 patients	n=66 46 courses to 19 patients	No significant difference between active and placebo groups
SLIT					
Devillier, 2015	Symptoms requiring a course of oral prednisolone	Mean (SD), for number of events standardized over a year	n=322 0.06 (0.38) 95%CI: 0.02-0.11	n=162 0.04 (0.24) 95%CI: 0.01-0.08	No significant difference between active and placebo groups
Gomez Vera, 2005	Symptoms requiring a course of oral prednisolone	No of events	n=30 61	n=30 123	No significant difference between active and placebo groups
Mosbech, 2014	Need for oral corticosteroids, visit to the trial centre due to asthma or hospitalization.	Narrative description only	NR	NR	No significant difference between active and placebo groups

Pajno, 2003	Symptoms requiring a course of oral prednisone	Number of events	n=15 0	n=15 0	No events in either group, so no significant difference between active and placebo groups
Virchow, 2016	Time to exacerbation during inhaled corticosteroid reduction, with exacerbation defined by the American Thoracic Society and European Respiratory Society	HRs for 6SQ-HDM compared to placebo HRs for 12SQ-HDM compared to placebo	0.72, 95%CI 0.52-0.99 p=0.045 0.64, 95%CI 0.42-0.96 p=0.03		Significant reduction in exacerbations in SLIT group compared with placebo Significant reduction in exacerbations in SLIT group compared with placebo

Table S1j: Studies investigating the impact of AIT on PEF in patients with asthma

Author, year	Instrument, data type and main findings				Summary
	PEF reporting	Data type	Active n, summary data	Placebo n, summary data	
SCIT					
Adkinson, 1997	PEF (% predicted value)	Mean and SD	n=61 Baseline 81.9 Change from baseline 2.5 ±10.8 ±11.1	n=60 Baseline 84.8 Change from baseline - 1.4 ±8.6 ±11.1	Difference between groups not significant P=0.05
Basomba, 2002	PEF variability, recorded morning and evening	Median and IQR	n=25 Baseline 9 Change from baseline 2.8 (6.3 to 12.1) (1.2 to 5.8)	n=25 Baseline 8.1 Change from baseline 1.2 (5.4 to 12.9) (-1.7 to 5.2)	No significant difference between SCIT and placebo P=0.2007
Creticos 1996	PEF throughout treatment period	Mean and SE of mean	n=37 480 ±12	n=40 461 ±13	Significant difference between SCIT and placebo P= 0.03
Hui, 2014	PEF recorded over treatment period at 10 time points	Mean and SD	n=45Baseline 63.3 Post intervention 91.3 ±5.4 ±5.8	n=45 Baseline 62.3 Post intervention 81.6 ±5.1 ±4.5	Significant difference P=0.007
Maestrelli,2004	PEF morning and evening	Average % increase from baseline within group	n=49 Average increase in the mornings 1.6-4.7% Average increase in the evenings 2,5-5.5%	n=46 no change	Improvement in active group not in placebo

Newton,1978,	Mean PEF values	Mean pre and post	n=8 Pre=273 Post=260	n=8 Pre=292 Post=292	No significant difference between SCIT and placebo
Ohman 1984	PEF taken post - treatment	Mean and SD	n=9 448 ±98	n=8 355 ±73	No P value given
Olsen, 1997	PEF %predicted pre and post treatment	Mean and range	n=21 Baseline 86.6 Post intervention 87.4 62.8-126.4, 61. 5-127.9	n=10 Baseline 85.4 Post intervention 86.6 69,5-113,0 59,6-115,2	No significant difference between SCIT and placebo
Tabar,2008,	PEF morning and evening	Figure and narrative mean and variability	n=14	n=14	Improvement in mean in active group not in variability, no improvement in placebo. No comparison of groups P value given
Wang, 2006	PEF daily throughout treatment period	Mean and SD	n=66 Baseline 304.6 (±9.25) Post intervention 309.5 (±9.29)	n=66 Baseline 322.6 (±10.73) Post intervention 330.1 (±10.42)	No significant difference between SCIT and placebo Morning P=0.144; evening P=0.109
SLIT					
Bachelier, 2001	PEF % (at last visit)	Median and range	n=8 Baseline 97 Post intervention 99 (77±117) (75±116)	n=7 Baseline 99 Post intervention 76 (82±128) (62±106)	Significant improvement in SLIT group compared to placebo P= 0.049

Bousquet, 1999	Morning PEF _R (l/min) at last diary card	Mean and SD	n=32 426.3 136.7	n=33 424.3 114.5	Both daytime and night-time PEF _R differences not significant (P=NS)
Pham-Thi 2007	Peak Expiratory Flow Rate (variability %)- at endpoint	Mean and SD	n=54 6.06 5.45	n=55 6.38 5.65	No significant difference between groups
Stelmach,2009	PEF (% predicted value)	Mean and 95% CI for mean	n=20 92.9 (84.4-101.4)	n=15 84 (75.4-92.6)	No significant difference demonstrated P=0.777

Table S1k: Studies investigating the impact of AIT on FEV1 in patients with asthma

Author, year	Instrument, data type and main findings				Summary
	FEV1 reporting	Data type	Active n, summary data	Placebo n, summary data	
SCIT					
Alvarez, 2002	FEV1 comparison at end of treatment	Median and IQR	n=14 Baseline 100% Post intervention 106.5% 88-101 98-110	n=14 Baseline 93.5% Post intervention 96.5% 84-107 87.5-101	Significant difference between SCIT and placebo P=0.034
Chakroborty, 2006	FEV1	Narrative and figure	n=8	n=6	SCIT group improved from baseline
Olsen, 1997	FEV1 at baseline and post treatment, % of predicted value	Mean and range	n=21 Baseline 84.98 (54.8-109,8) Post intervention 89 (65,1-109,9)	n=10 Baseline 83.6 (47,8-100,5) Post intervention 86.5 (58.8-98,1)	Small increase seen significant in active group but not in placebo
Maestrelli,2004	FEV1	Narrative	n=41	n=31	No significant difference in FEV1, no data given
Roberts, 2006	FEV1 predicted	Narrative	n=18	n=17	FEV1 of less than 85% a third of the time in both groups

SLIT					
Bousquet , 1999	FEV1 diary card entry at start and end of treatment FEV1 (% predicted)	Mean and SD Mean and SD	n=32 Baseline 2.76 (1.13) Post intervention 2.91 (1.05) Baseline 95.9 (18.4) Post intervention 102.7 (24.6)	n=33 Baseline 2.91 (0.99) Post intervention 2.97(0.92) Baseline 95.2 (13.4) Post intervention 99.3 (18.5)	Improvement in SLIT group but no comparative results with placebo given
Pajno , 2004	FEV1 (% predicted)	Mean and SD	n=15 Baseline 88.2 (4.1) Post intervention 88.4 (3.7)	n=15 Baseline 92.6 (95) Post intervention 75.6 (4.9)	No significant difference between SLIT and placebo
Pham-Thi, 2007	FEV1 (% predicted)	Mean and SD	n=54 Baseline 91.9 (13.4) Post intervention 88.5 (13.4)	n=55 Baseline 95.1 (15.1) Post intervention 95.5 (14.6)	No significant difference between SLIT and placebo P=NS
Stelmach, 2009	FEV1 (% predicted)	Mean and 95%CI	n= 25 100.4 (95.6-105.1)	n=25 88.2 (81.7-94.7)	No significant difference between SLIT and placebo P=0.649

Table S11: Studies investigating the impact of AIT on allergen specific bronchial provocation tests in patients with asthma

Author, year	Instrument, data type and main findings				Summary
	Bronchial provocation test	Data type	Active n, summary data	Placebo n, summary data	
SCIT					
Aas, 1971	Bronchial provocation test to HDM recording % increase from baseline	No of patients achieving 100% bronchial tolerance	Group A, n=31 21 patients achieved total bronchial tolerance Group B, n=21 14 patients achieved total bronchial tolerance	n=28 7 patients achieved total bronchial tolerance	More patients in the SCIT groups achieved bronchial tolerance than the placebo group
Alvarez Cuesta, 1984	Bronchial provocation test PC20 to Fel d1	No of patients improving at end of treatment	n=14 11 patients improved and 1 got worse	n=14 3 improved and 4 got worse	Significant improvement in SCIT group compared to placebo P<0.05
Alvarez, 2002	Dpt-PD20	Increase in tolerated dose from baseline	n=14 increased by 4 DSC	n=12 no change	Increased tolerance in the SCIT group and no change in placebo
Ameal 2005	PD20FEV1	Difference between allergen tolerated at baseline and end of SCIT. No of patients needing double the allergen load to have a positive	n=29 Active group needed a median of 2.8 times more allergen 19 patients needed double the allergen dose	n=26 Placebo needed the same amount as baseline 10 patients needed double the allergen	Significant improvement P=0.029 Significant improvement P=0.0137

		BPT No of patients needing half the dose to have a positive BPT	1 patient	dose 7 patients	
Armentia- Medina, 1995	PD20Ld		n=22	n=13	No results given after treatment
Arvidsson 2004	PD20-FEV1 Birch pollen. Area under the curve based on FEV1	Graphical description and P value	n=10	n=9	Statistically significant improvement P < 0.01
Basomba 2002	PD20-DerP1	Narrative, median and IQR for active group only, intra-group P values	n=11 7 patients showed a 4 fold increase of allergen concentration 52ng (168)DerP1 pre and 290 ng (594)post	n=11 2 patients showed a 4 fold increase of allergen concentration	
Bousquet 1985	PD20-FEV1-DP	Numbers improved and P value	n=20 15 improved, 5 same, 0 worse	n=10 2 improved, 5 same, 2 worse	Statistically significant improvement P<0.01
Dreborg, 1986	Positive reaction if asthma symptoms and reduction of PEF by 15% following exposure to Cladosporium herbarum	Narrative, graphical and P value	n=16	n=14	Statistically significant improvement P<0.05

Dolz, 1996	20% reduction of FEV1 to grass pollen extract	Narrative and intra group P value	n=18	n=10	No change in placebo, increased allergen tolerance in active group (1000 UB)
Garcia-Robaina, 2006	PD20-FEV1-Der P1	Median and IQR	n=32 10.05 (IQR, 5.48, 81.00) 111.06 (IQR, 41.05, 686.00) a	n=32 43.50 (IQR, 6.10, 511.00) 41.00 (IQR, 3.35, 311.00)	Statistically significant improvement P=0.029
Malling 1987	LogPC20-FEV1 Cladosporium herbarum	% of patients with reduced/increased sensitivity and P value	n=11 Reduced sensitivity in 73%; increased sensitivity in 0%	n=11 Reduced sensitivity in 27%; increased sensitivity in 27%	Significant improvement in reducing sensitivity in active group compared to placebo P < 0.02
Ohman 1984	PD20-FEV1 Cat	Narrative and figure	n=9	n=8	No significant difference between active and placebo groups
Olsen 1997	PC20-FEV1 HDM(Dpt and Dfa)	Narrative and graphical description plus P value	n=21	n=10	Significant improvement in active group compared to placebo P=0.037 and 0.041 for Dpt and Dfa, respectively
Pene 1998	PD20-fev1-Fel d1	Narrative and graphical	n=25	n=6	No significant difference between active and placebo groups
Sundin 1986	LogPC20-FEV1- Cat or dog	P value	n=15 cat n= 7 dog	n=17	Significant improvement in active group compared to placebo P<0.05
Taylor 1978	PD20-FEV1-Cat allergen	Narrative	n=5	n=5	All 5 SCIT patients showed a decrease in

					bronchial sensitivity
Valovirta 1984	Bronchial sensitivity to dog	Narrative and figure	n=15	n=12	Non-significant change
Van Metre 1988	PD-20 Cat extract	Median, range and P value	n=11 median 0.83; range 0.55 to 3.8	n=11	Significant improvement in active group compared to placebo P<0.01
Warner 1978	Bronchial provocation test to DerP	Numbers with an early or late reaction pre and post treatment	n=27 27 23 22 12	n=24 24 22 15 14	
SLIT					
Leng 1990	PD20-FEV1 Artemisia	Narrative and graphical	n=9	n=9	No significant difference between active and placebo groups

Table S1m: Studies investigating the impact of AIT on non-specific bronchial provocation tests in patients with asthma

Author, year	Instrument, data type and main findings				Summary
	Bronchial provocation test - outcome	Data type	Active n, summary data	Placebo n, summary data	
SCIT					

Adkinson 1997	MChPC20	Mean and SD	n=61 0.41+/-1.87	n=60 0.39+/-1.51	No significant difference between SCIT and placebo P>0.99
Alvarez Cuesta, 1984	PC20-MCh	Mean and SD of each group pre and post treatment	n=14 Pre 0.56 _+ 0.47 mg/ml Post 0.57 _+ 0.42 mg/ml	n=14 Pre 0.81 _+ 0.54 mg/ml Post 0.58 _+ 0.42 mg/ml	Active group no difference, placebo group got worse. No comparison of active and placebo group reported.
Alvarez, 2002	PD20-MCh	Median and SD	n=14 0.8 +/- 9.56	n=12 0.21 +/- 9.32	Significant improvement in SCIT compared to placebo P=0.034
Armentia-Medina, 1995	Metacholine provocation tests to storage mite, Lepidoglyphus destructor in asthmatic patients	Graphic and narrative description only	n=14	n=11	Significant decrease in non-specific reactivity P<0.001
Arvidsson 2004	PD20-FEV1 MCh	Narrative and graphical description	n=10	n=9	No statistically significant difference between active and placebo groups
Franco 1995	PD20-MCh	Number of patients with decreased sensitivity to MCh	n=9 6 had a decreased sensitivity to MCh	n=10 4 had a decreased sensitivity to MCh	No significant difference
Haugaard, 1992	PC20-Histamine	Narrative, graphical and P value	n= 14 cat n=8 dog	n=8 n=4	No significant difference between active and placebo groups for Cat (P=0.13) or Dog

Kuna 1989	PC20-Histamine correlation to histamine releasing factor measured	No of patients benefiting from SCIT	n=12 5 patients showed a benefit	n=12	
Ohman 1984	PD20-FEV1 MCh	Geometric means and ranges pre and post treatment	n=9 3.0 (0.27 to 30.3) 4.7 (0.21 to 75.7) BU	n=8 1.7 (0.34 to 54.9) 3.8 (0.24 to 17.7) BU	No significant difference between active and placebo groups
Rak 2001	PC20-FEV1-MCh	Median, range and P value	n=21 1.25 [0.28- 2.45], 0.4 [0.19-1.6])	n=20 nasal steroids n=9 placebo	No significant change in SCIT asthmatic patients p=0.08
Taylor 1978	PD20-FEV1-Histamine	Narrative and graphical	n=5	n=5	No significant change in active or placebo group
Van metre 1988	PD20-MCh	Narrative and graphical, median ratio and range	n=11 0.76 (range, 0.28 to 1.3)	n=11 1.32 (range, 0.33 to 125.9)	No significant difference in active compared to placebo group P=0.18
Wang 2006	PC20-Histamine	Mean and SD	n=66 3.58 +/-0.393	n=66 3.42 +/- 0.385	No significant difference in active compared to placebo group P=0.765
SLIT					
Bachelier 2001	PC20MCh	Median and range	n=8 0.85 (0.17-2.2)	n=7 0.98 (0.18-3.9)	No significant change
Bousquet 1999	PD20-MCh	Narrative	n=31	n=31	No significant difference in active compared to

					placebo group
Pajno 2004	PC20-MCh	Mean and SD	n=15 9.1 (7.7)	n=15 2.46 (2.26)	Significant difference between active and placebo groups (P =0.001)
Reilly, 1994	Log10PC20- Histamine	mean (SEM)- change from baseline	n=13 0.09 (0-12)	n=15 -0.02 (0-11)	No significant difference in active compared to placebo group P=0.48
Stelmach 2009	PC20-MCh	Mean and 95%CI	n=20 4.05 (3.54-4.55)	n=15 4 (3.24-4.77)	No significant difference in active compared to placebo group

Author, year, country	Sam ple size	Type of econom ic analysis	Persp ective	Study populati on	Interventi on/ comparat or	Time horizo n	Effectivene ss data	Outco me measur e	Outcom e discoun t rate	Cost discou nt rate	Cost data	Cost year/c urren cy	Results	Sensitivity analysis	General comments
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Table S1n: Studies investigating cost-effectiveness: Characteristics of included studies: Allergic asthma

Reinhold, 2013	65	CEA	Health system	Children and adolescents	SCIT / Standard Care	3 years horizon	RCT 3 year follow up	Mean morning peak flow (L/min)	0%	0%	RCT	2009/	ICER: 11 Euros per L/min morning peak flow	Bootstrapping performed but not used in cost effectiveness results	No hospital costs included 5 SCIT and 1 non-SCIT patients excluded because of "outlier" levels of costs
Author, year, country	Sample size	Type of economic analysis	Health system	Study population	Intervention and comparator	Time horizon	Effectiveness data	Outcome measure	Outcome discount rate	Cost discount rate	Cost data	Cost year/currency	Results	Sensitivity analysis	Generalisability
Nasser, 2008 UK	151	CUA	Health system	Patients with grass pollen induced rhino-conjunctivitis co-existing with asthma	SLIT (Grazax) / Standard Care	9 years	RCT 1 year follow up	EQ-5D QALY	3.5%	3.5%	RCT patient diary linked to unit costs	2005/GBP	ICER £89 per QALY	One way sensitivity analysis to explore impact of changing time horizon	Results based on patients from Germany, the Netherlands, Denmark, Sweden, Spain, Austria and Italy. Treatment effect

Table S1n: Studies investigating cost-effectiveness: Characteristics of included studies: Allergic asthma and allergic rhino-conjunctivitis

															assumed to persist through 3 years of treatment and 6 years following treatment discontinuation
Ariano, 2009 Italy	70	CEA	Health system	Patients with dust mite induced allergic asthma and rhinitis	SLIT / Standard Care	5 years	RCT 5 year follow up	VAS symptom score	0%	0%	RCT patient diary and unit costs	?/Euros	Overall costs lower in SLIT patients and lower symptom score	N/A	Very little detail provided of the analysis performed No real economic analysis or interpretation of the results provided

Key: CEA: cost-economic analysis; CUA: cost-utility analysis.

Table S1o: Studies investigating cost-effectiveness: CASP Economic Evaluation Checklist for Risk of Bias

Allergic asthma only

Author/year	1. Well defined question posed	2. Comprehensive description of competing alternatives	3. Provides evidence of effectiveness	4. Effects identified measured and valued appropriately	5. Resource use identified measured and valued appropriately	6. Discounting to adjust for timing of costs and consequences	7. What were the results	8. Incremental analysis performed	9. Sensitivity analysis performed	10. Effectiveness generalisable	11. Costs generalisable	Overall quality L/M/H
Reinhold 2013	Y	Y	Y	N	N	N	ICER 11 euro per l/min morning peak flow	Y	N	N	N	L

Table S1p: Studies investigating cost-effectiveness: CASP Economic Evaluation Checklist for Risk of Bias

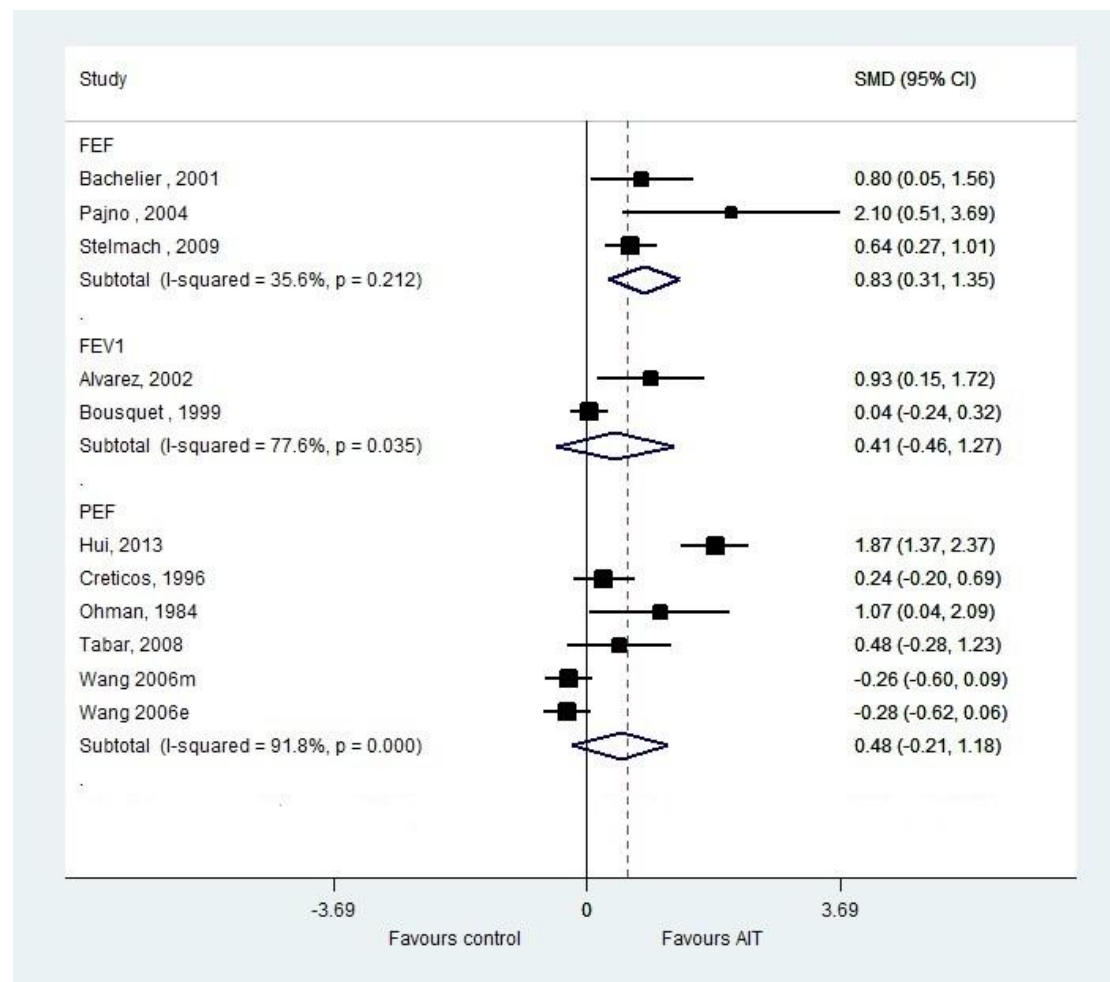
Allergic asthma and allergic rhino-conjunctivitis

Author/year	1. Well defined question posed	2. Comprehensive description of competing alternatives	3. Provides evidence of effectiveness	4. Effects identified measured and valued appropriately	5. Resource use identified measured and valued appropriately	6. Discounting to adjust for timing of costs and consequences	7. What were the results	8. Incremental analysis performed	9. Sensitivity analysis performed	10. Effectiveness generalisable	11. Costs generalisable	Overall quality L/M/H
Nasser 2008	Y	Y	Y	Y	Y	Y	SLIT ICER £8816 (2005) per QALY	Y	N	Y	Y	H
Ariano 2009	Y	Y	N	N	N	N	Lower cost and symptom score with SLIT	N	N	N	N	L

Supplementary material: S4

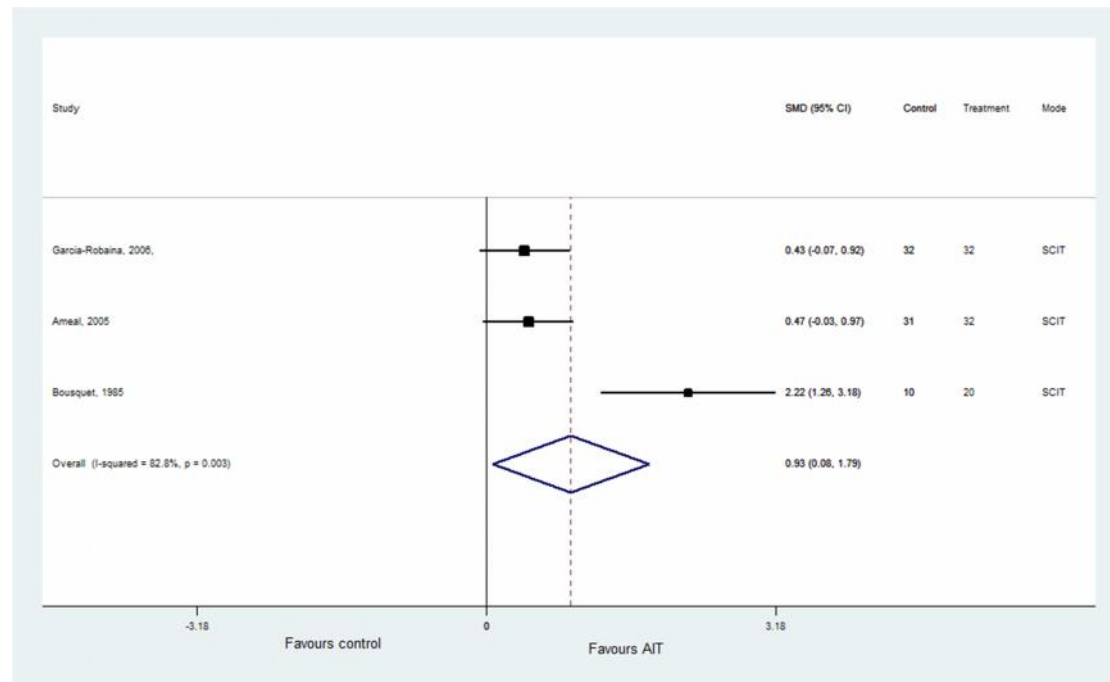
Asthma: secondary outcomes

Figure S4a: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for lung function tests (random effects model)



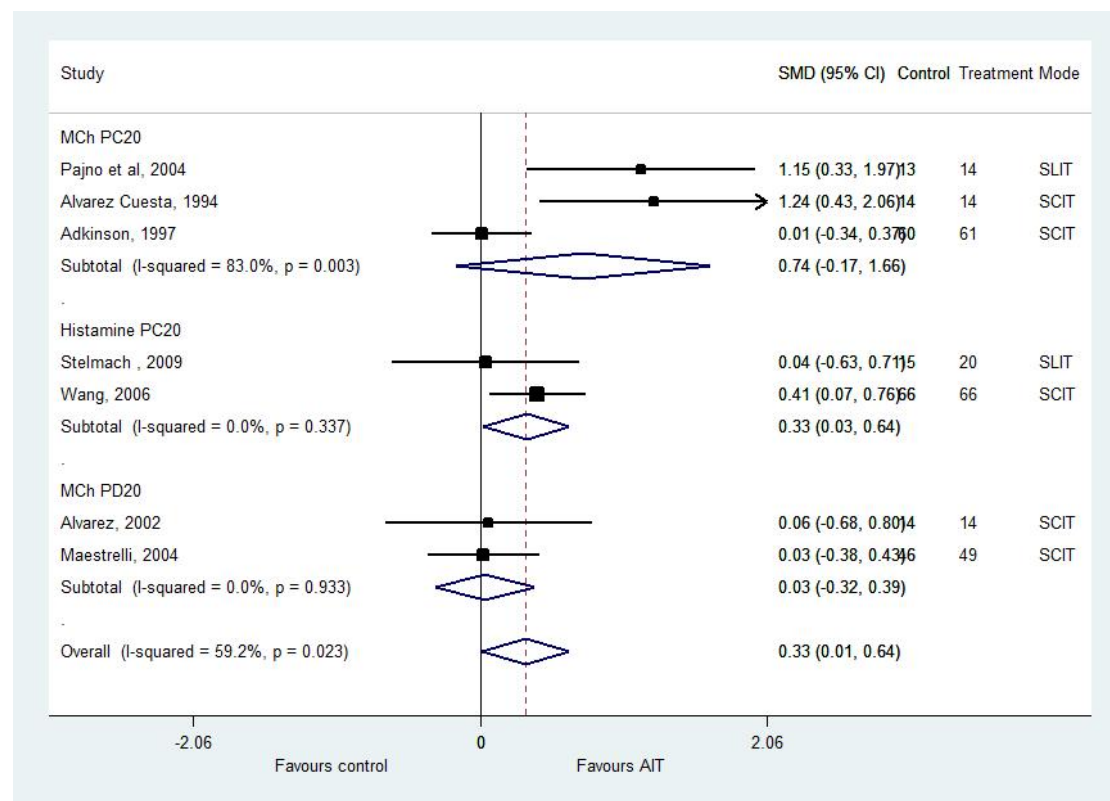
	Heterogeneity	degrees of			
	statistic	freedom	P	I-squared**	Tau-squared
FEF	3.05	2	0.218	34.4%	0.0921
FEV1	48.88	5	0.000	89.8%	0.7037
PEF	160.11	8	0.000	95.0%	1.4759
FEF	z= 2.55	p = 0.011			
FEV1	z= 1.70	p = 0.089			
PEF	z= 0.78	p = 0.436			

Figure S4b: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for allergen specific bronchial provocation tests (random effects model)



Test of SMD=0 : $z = 1.05$ $p = 0.294$
Heterogeneity chi-squared = 23.66 (d.f. = 3) $p = 0.000$
I-squared (variation in SMD attributable to heterogeneity) = 87.3%
Estimate of between-study variance Tau-squared = 0.8973

Figure S4c: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for non-specific bronchial provocation tests, separate results (random effects model)



	Het	degrees of			
	statistic	freedom	P	I-squared**	Tau-squared
MCh PC20	12.03	2	0.002	83.4%	0.5511
Histamine PC20	0.92	1	0.337	0.0%	0.0000
MCh PD20	0.01	1	0.933	0.0%	0.0000

** I-squared: the variation in SMD attributable to heterogeneity)

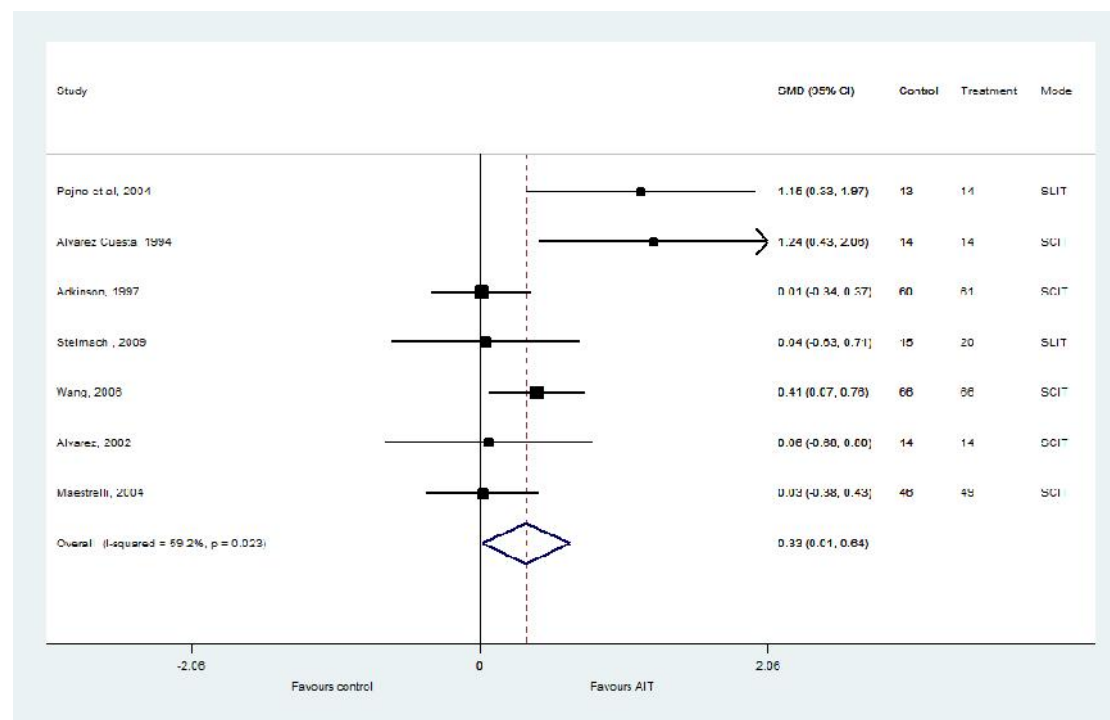
Significance test(s) of SMD=0

MCh PC20 z= 1.59 p = 0.111

Histamine PC20 z= 2.13 p = 0.033

MCh PD20 z= 0.19 p = 0.849

Figure S4d: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for non-specific bronchial provocation tests, combined results (random effects model)



Test of SMD=0: $z = -2.05$ $p = 0.040$

Heterogeneity chi-squared = 15.02 (d.f. = 6) $p = 0.020$

I-squared (variation in SMD attributable to heterogeneity) = 60.1%

Estimate of between-study variance Tau-squared = 0.1009

Appendix 1:

Search strategy 1 (MEDLINE, EMBASE)

1. exp asthma/
2. asthma.mp.
3. asthmatic children.mp.
4. acute asthmatic attack.mp.
5. asthma control.mp.
6. asthma exacerbations.mp.
7. wheez*.mp.
8. respiratory hypersensitivity/
9. bronchial disorder.mp.
10. hyper-responsiveness wheez*.mp.
11. lung function.mp.
12. ventilatory function.mp.
13. FEV.mp.
14. FEF.mp.
15. FVC.mp.
16. PEF.mp.
17. bronchial hyperreactivity.mp.
18. airway hyperreactivity.mp.
19. bronchial responsiveness.mp.
20. airway responsiveness.mp.
21. or/1-20
22. exp Desensitization, Immunologic/
23. exp Immunotherapy/
24. desensiti?ation.mp.
25. (immunotherapy or allergen immunotherapy or oral immunotherapy).mp.
26. subcutaneous immunotherapy.mp.
27. sublingual immunotherapy.mp.
28. specific immunotherapy.mp.
29. hyposensiti?ation
30. Or/22-29
31. exp Intervention Studies/
32. intervention studies.mp.
33. exp Clinical Trial/
34. (trial or clinical trial).mp.
35. Exp Randomized Controlled Trial/
36. randomi?ed controlled trial.mp.
37. exp Placebos/
38. placebos.mp.
39. exp Random allocation/
40. random allocation.mp.
41. random*.mp.
42. exp Double-blind method/
43. double-blind method.mp.
44. double-blind design.mp.
45. exp Single-blind method/
46. single-blind method.mp.

47. single-blind design.mp.
48. triple-blind method.mp.
49. search:.tw.
50. review.pt.
51. systematic review.tw.
52. meta analysis.mp,pt.
53. case series.mp.
54. (case\$ and series).tw.
55. cost:.mp.
56. cost effective:.mp.
57. cost utility:.mp.
58. exp Health Care Costs/
59. (costs and costs analysis).mp.
60. economic evaluation*.mp.
61. ((cost effective* adj1 analys*) or cost minimi?ation analys* or cost benefit
analys* or cost utility analys* or cost consequence analys* or finances).mp.
62. Or/31-61
63. 21 and 30 and 62

Search strategy 2

(Cochrane library, HTA, EED, CINAHL, ISI Web of Science, TRIP)

(Asthma or acute asthmatic attack or wheez* or respiratory hypersensitivity or bronchial disorder or hyper-responsiveness wheez* or lung function or ventilatory function or bronchial hyperreactivity or airway hyperreactivity or bronchial responsiveness or airway responsiveness)

AND

(Immunologic, desensiti* or immunotherapy or oral immunotherapy or allergen immunotherapy or specific immunotherapy or subcutaneous immunotherapy or sublingual immunotherapy or hyposensiti*)

AND

(Intervention stud* or experimental stud* or trial or clinical trial* or randomi* controlled trial or random allocation or single blind method or double blind method or triple blind method or random* or systematic review or meta-analysis or case series or economic evaluation* or cost effective* analys* or cost minimi?ation analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances)

Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis

Appendix 2: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4,9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-14
DISCUSSION			

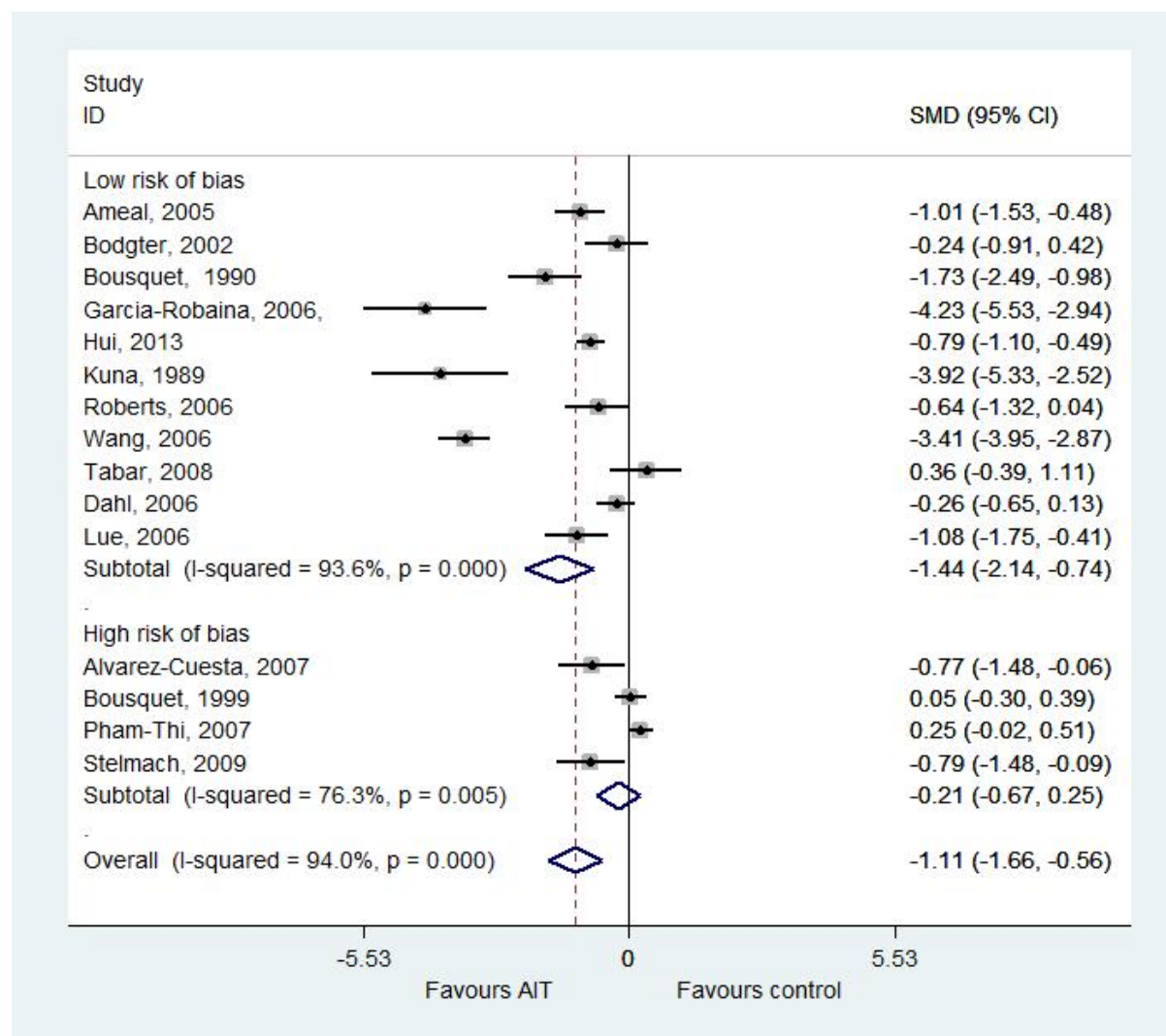
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplementary material: S2
Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis
Figures: primary outcomes

Figure S2a: Sensitivity meta-analysis of double-blind RCTs, excluding high ROB trials, comparing symptom scores between AIT (SLIT and SCIT) and placebo groups (random effects model)



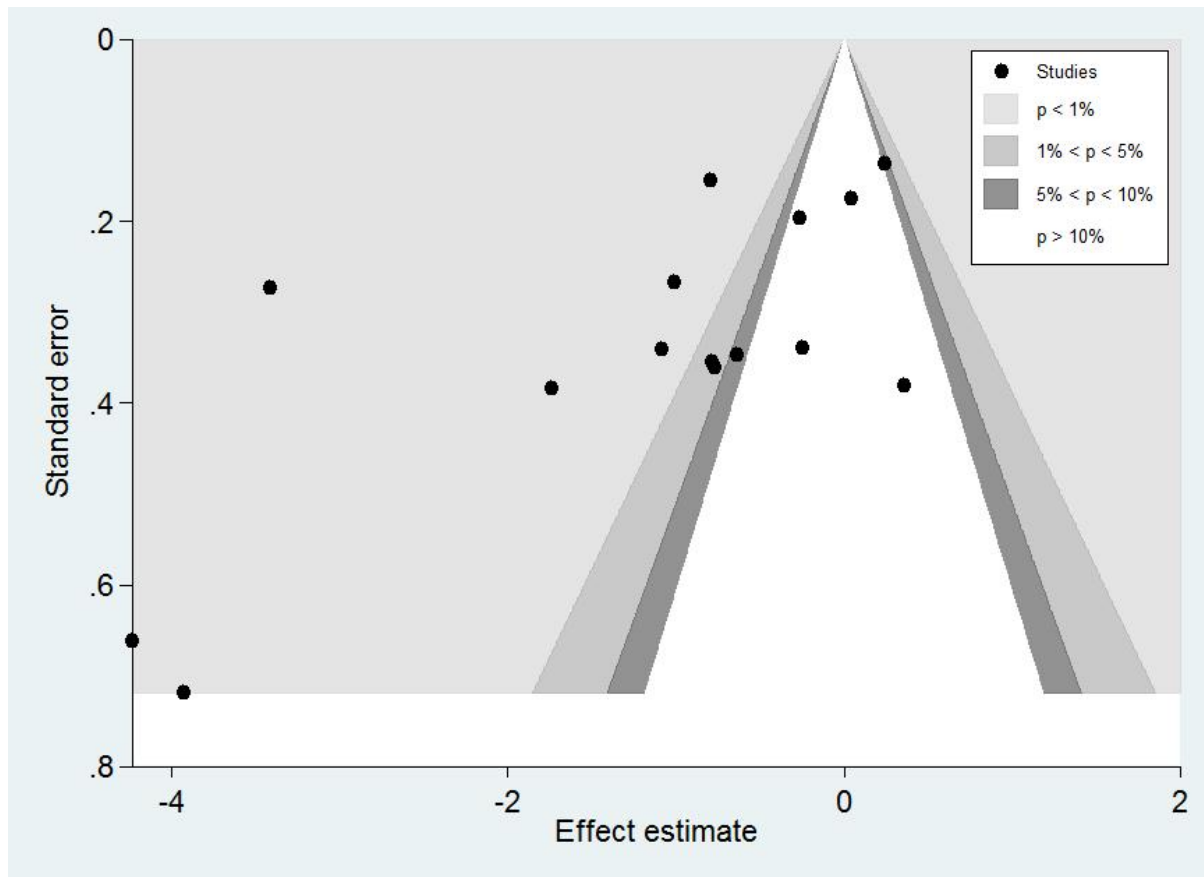
Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	P	I squared	Tau-squared
Low risk of bias	155.99	10	0.000	93.6%	1.2630
High risk of bias	12.67	3	0.005	76.3%	0.1563
Overall	234.28	14	0.000	94.0%	1.0488

Significance test(s) of ES=0

Low risk of bias	z= 4.02	p = 0.000
High risk of bias	z= 0.90	p = 0.370
Overall	z= 3.96	p = 0.000

Figure S2b: Funnel plot showing publication bias for symptom scores after AIT (SCIT or SLIT)

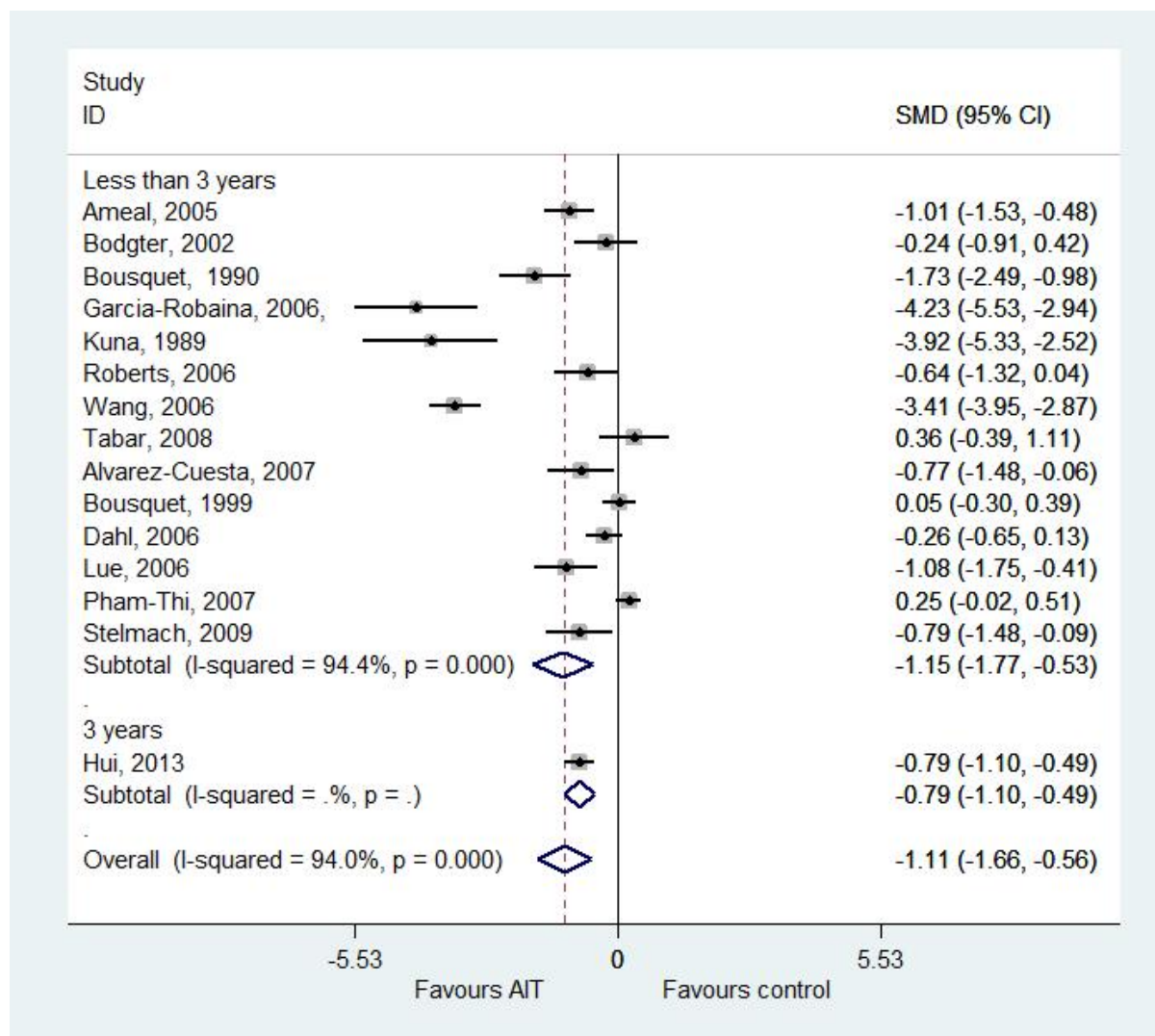


	Std_Eff	Coef.	Std. Err.	t	P>t	[95% Conf.Interval]
slope	.6444951	.5316526	1.21	0.247	-.5040705	1.793061
bias	-5.40782	2.126182	-2.54	0.024	-10.00116	-.8144826

p-value is two-sided

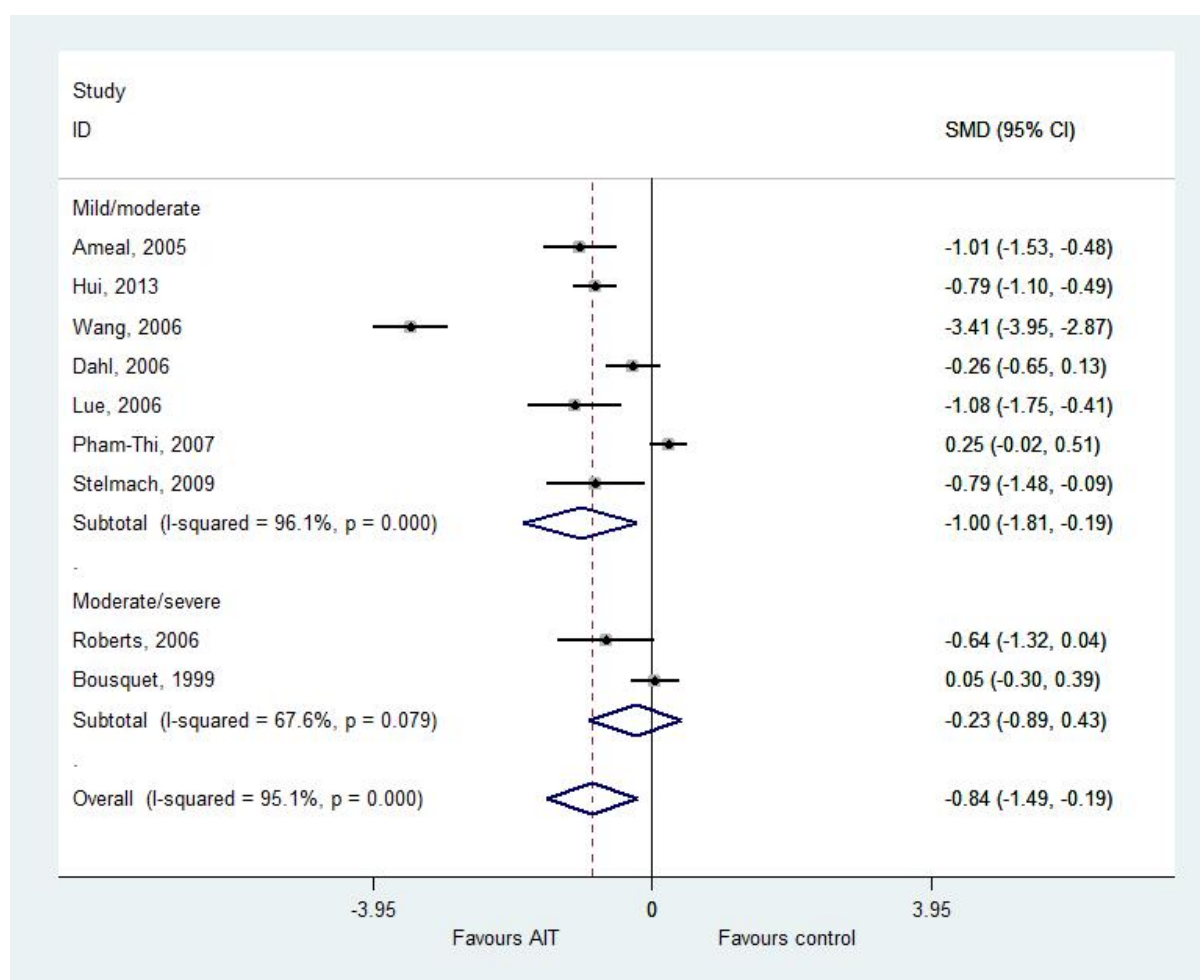
There is significant bias which can be both due to small study effects as well as the heterogeneity in the sample of studies. The small study effects are seen more clearly in the contour-enhanced funnel plot, where a cluster of small studies (they are nearer to 0 in the y-axis) lie in the region for $p < 0.01$ i.e. small studies get published with large effects only.

Figure S2c: Meta-analysis of double-blind RCTs studies comparing symptom scores between AIT (SCIT or SLIT) and placebo groups for treatment duration <3 years or ≥3 years (random effects model)



	Heterogeneity Statistic	degrees of freedom	P	Isquared**	Tau-squared
<3 years	232.07	13	0.000	94.4%	1.2810
3 years	0.00	0	.	.%	0.0000
Overall	234.28	14	0.000	94.0%	1.0488

Figure S2d: Meta-analysis of double-blind RCTs studies comparing symptom scores between AIT (SCIT or SLIT) and placebo groups for disease severity, mild/moderate versus moderate/severe (random effects model)

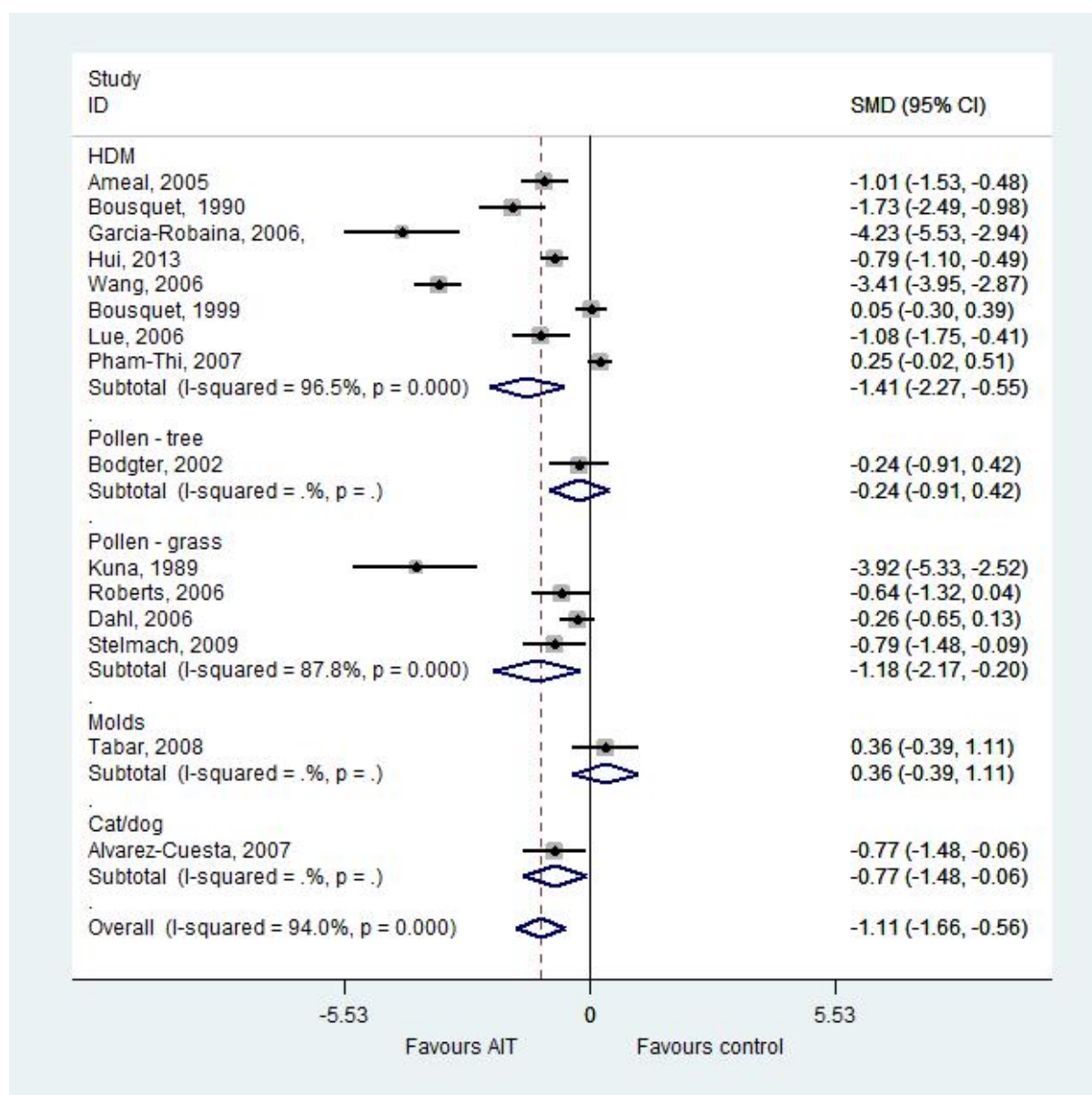


	Heterogeneity	degrees of			
	Statistic	freedom	P	Isquared**	Tau-squared
Moderate/severe	3.09	1	0.079	67.6%	0.1582
Mild/moderate	152.83	6	0.000	96.1%	1.1312
Overall	164.78	8	0.000	95.1%	0.9115

Significance test(s) of ES=0

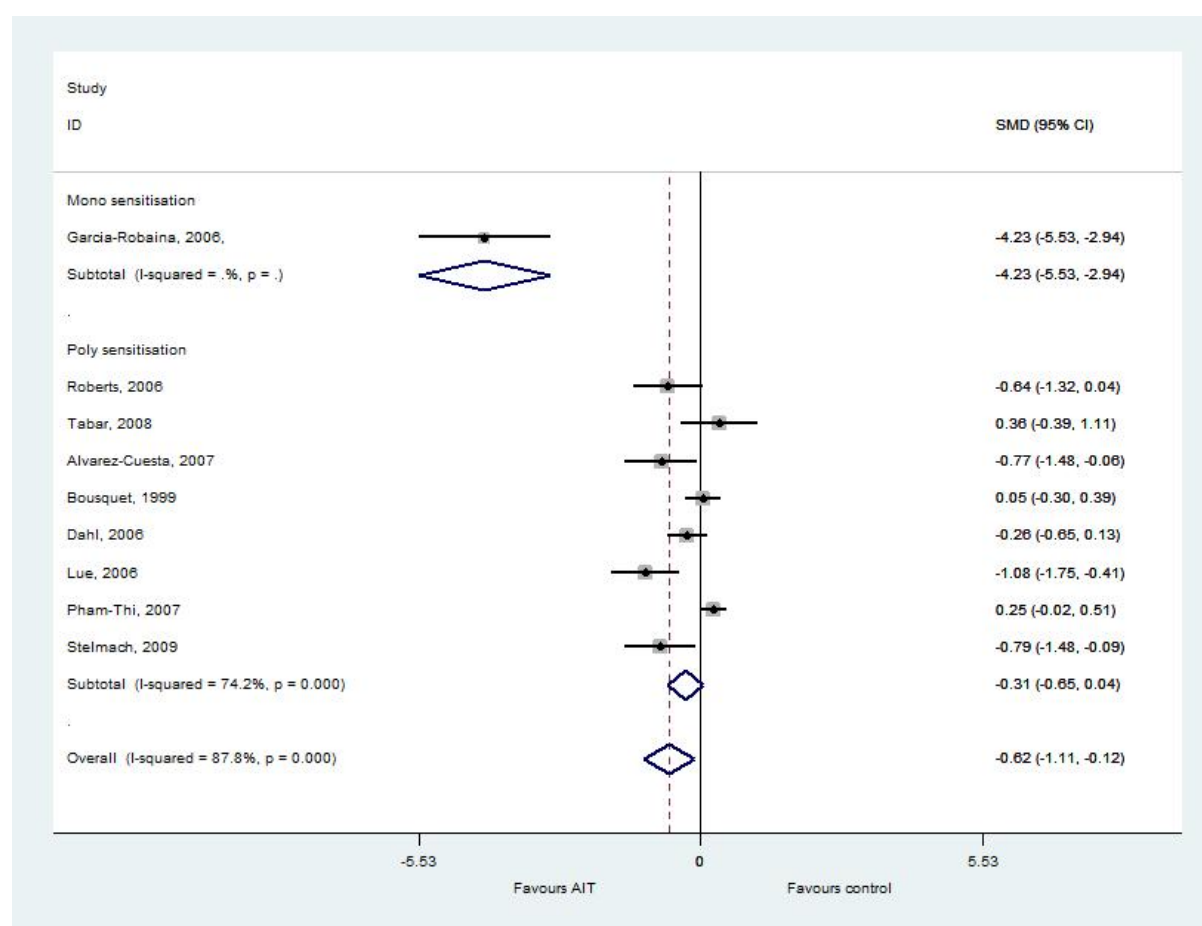
Moderate/severe z= 0.68 p = 0.494
Mild/moderate z= 2.42 p = 0.015
Overall z= 2.55 p = 0.011

Figure S2e: Meta-analysis of double-blind RCTs studies comparing symptom scores between AIT (SCIT or SLIT) and placebo groups for HDM vs tree pollen vs grass pollen vs mold vs cat/dog (random effects model)



		Het. Stati.	Df	P	Isquared**	Tau-squared
Pollen -	grass	24.61	3	0.000	87.8%	0.8399
HDM		201.94	7	0.000	96.5%	1.4229
Pollen -	tree	0.00	0	.	.%	0.0000
Cat/dog		0.00	0	.	.%	0.0000
Molds		0.00	0	.	.%	0.0000
Overall		234.28	14	0.000	94.0%	1.0488

Figure S2f: Meta-analysis of double-blind RCTs studies comparing symptom scores between AIT (SCIT or SLIT) and placebo groups for mono-sensitized versus poly-sensitized

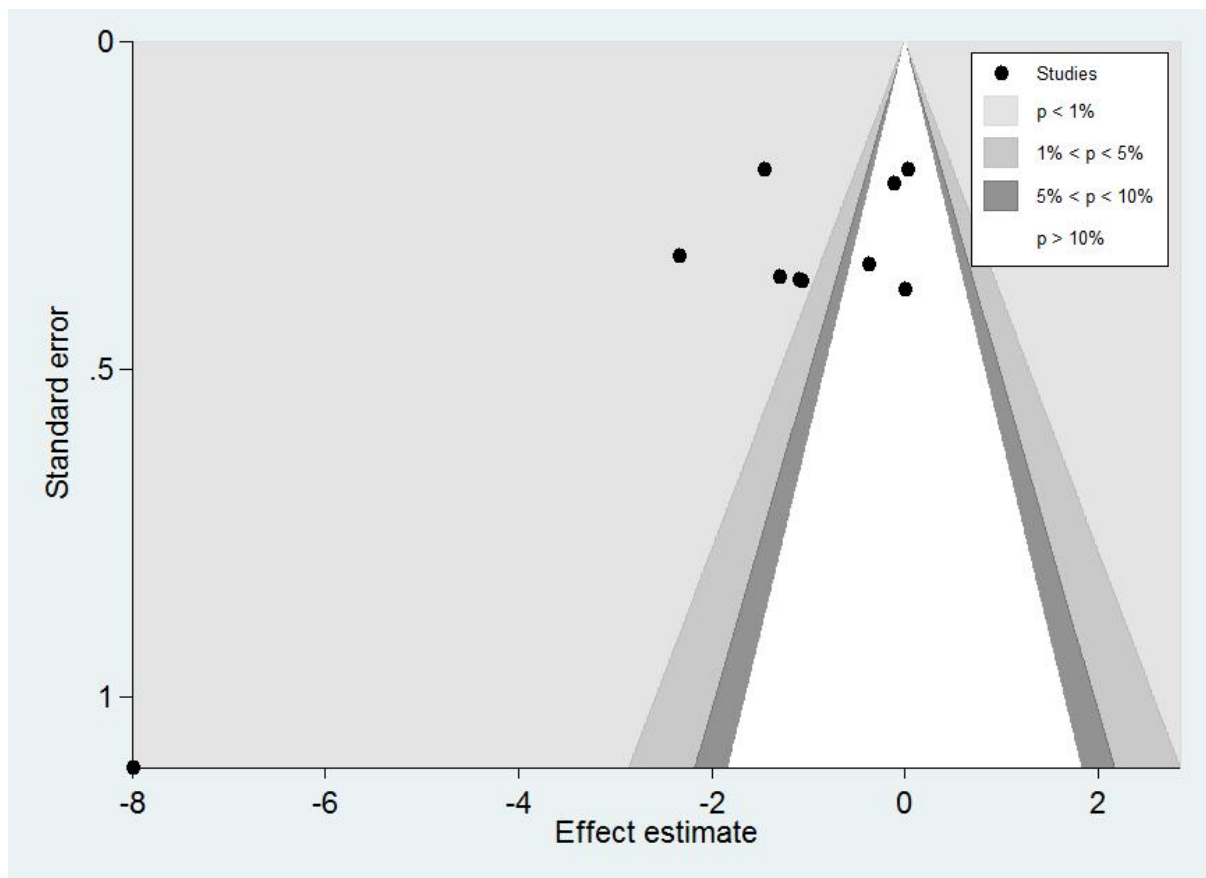


	Heterogeneity Statistic	degrees of freedom	P	I-squared	Tau-squared
Mono sensitisation	64.25	5	0.000	92.2%	1.1422
Poly sensitisation	0.00	0	.	0.0%	0.0000
Overall	64.25	6	0.000	90.7	0.9466

Significance test(s) of ES=0

Mono sensitisation z= 2.49 p = 0.013
Poly sensitisation z= 1.06 p = 0.291
Overall z= 2.51 p = 0.012

Figure S2g: Funnel plot showing publication bias for medication scores after AIT (SCIT or SLIT)



Testing Publication Bias

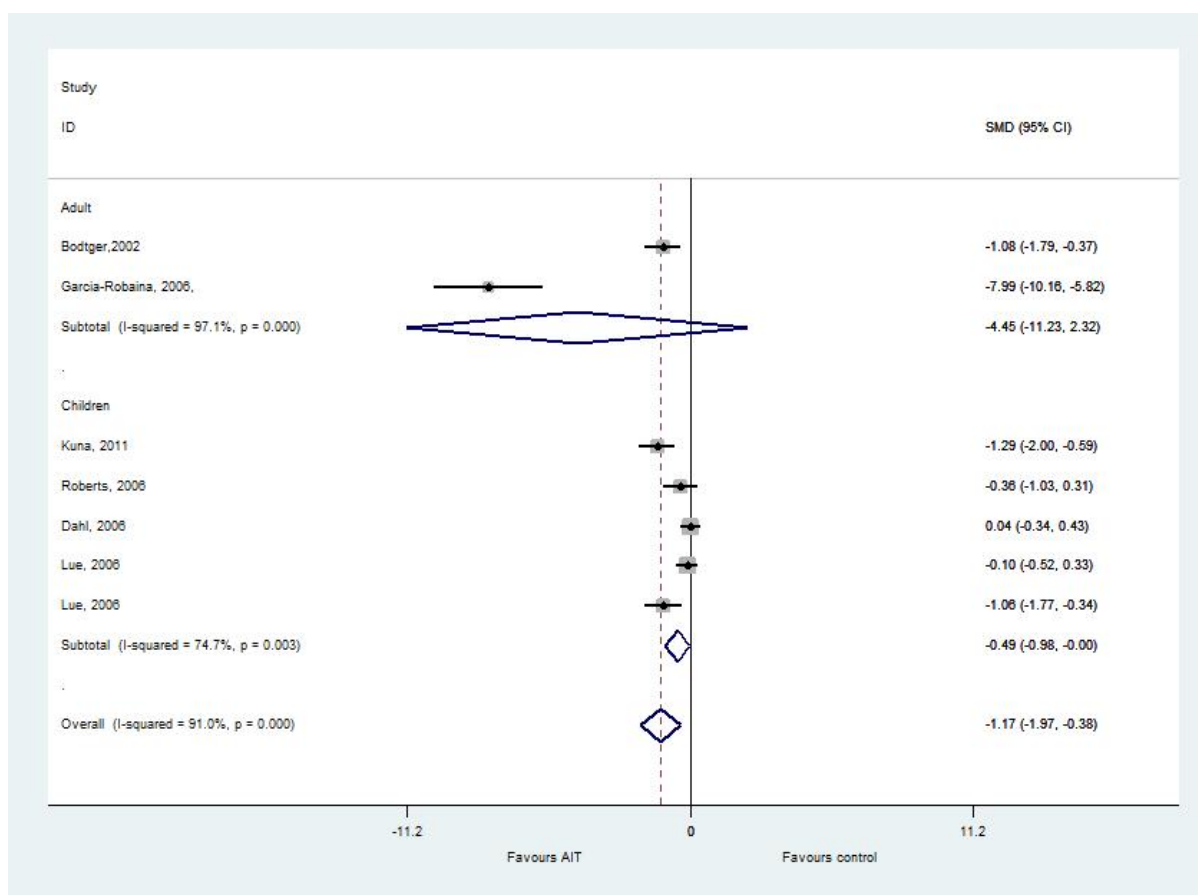
Number of studies too small for Begg's

Egger's test

	Std_Eff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
slope	.6314303	.7879293	0.80	0.446	-1.185538	2.448399
bias	-5.296661	2.749919	-1.93	0.090	-11.63799	1.044663

Although the bias is not significant, the graph suggests it. Non-significance could be the result of low power.

Figure S2h: Meta-analysis of double-blind RCTs, comparing medication scores between AIT (SLIT and SCIT) and placebo groups in children <18 versus adults ≥18 years (random effects model)

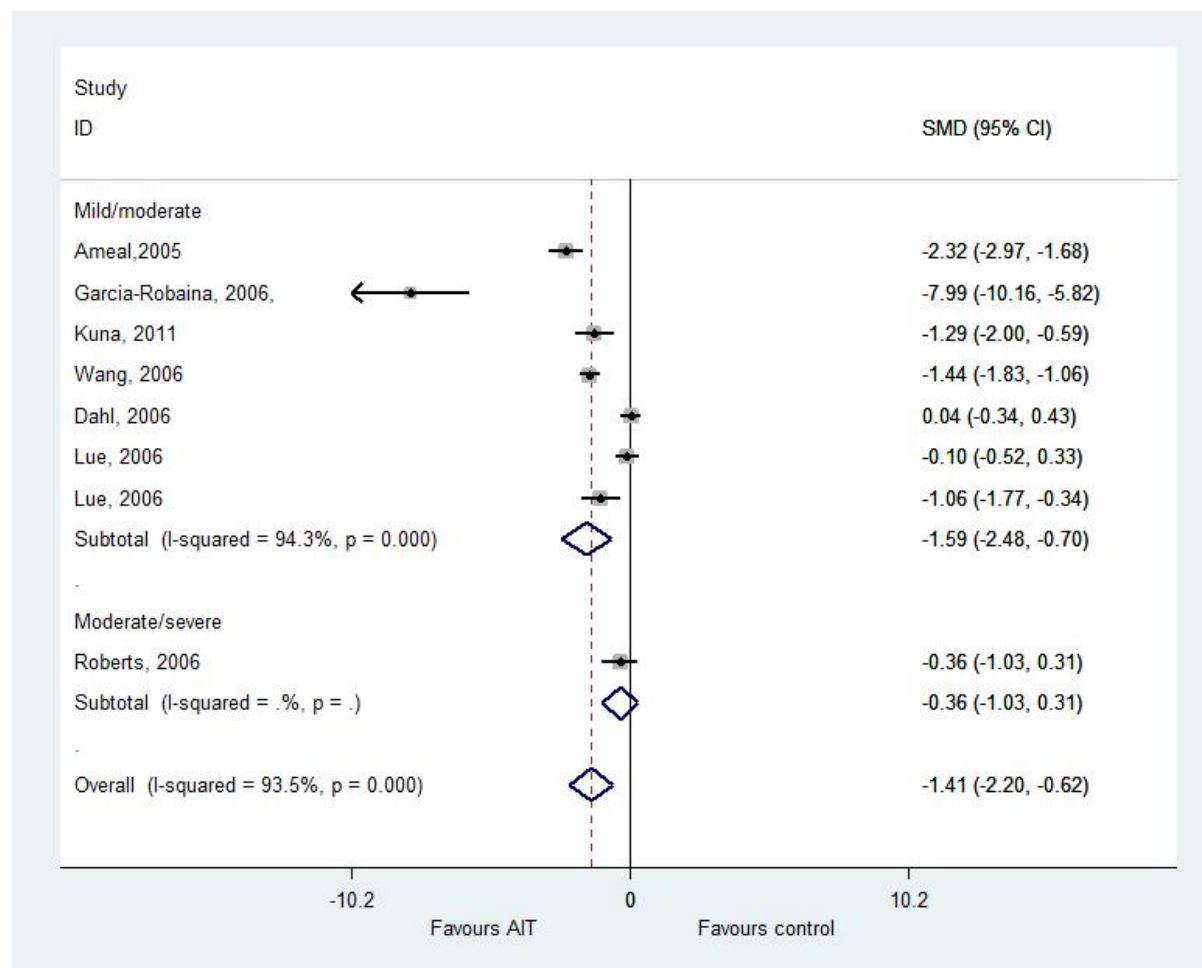


Het.stat.	df	P	I-squared**	Tau-squared			
Adult		35.08	1	0.000	97.1%	23.2029	
Children	15.79		4	0.003	74.7%	0.2244	
Overall	66.41	6	0.000		91.0%	0.9722	

Adult	z= 1.29	p = 0.197
Children	z= 1.96	p = 0.050

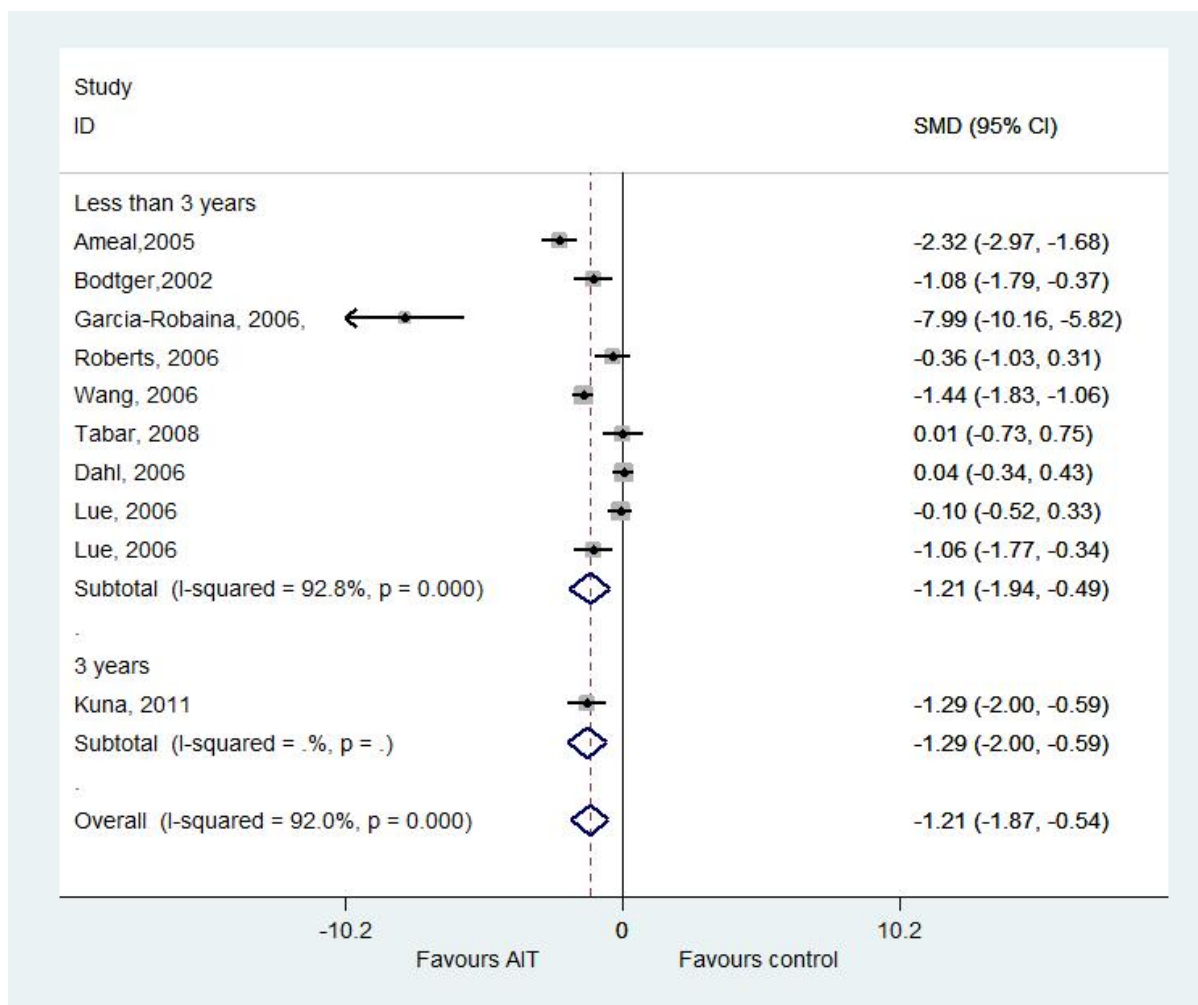
Overall $z = 2.89$ $p = 0.004$

Figure S2i: Meta-analysis of double-blind RCTs studies comparing medication scores between AIT (SCIT or SLIT) and placebo groups for disease severity, mild/moderate versus moderate/severe (random effects model)



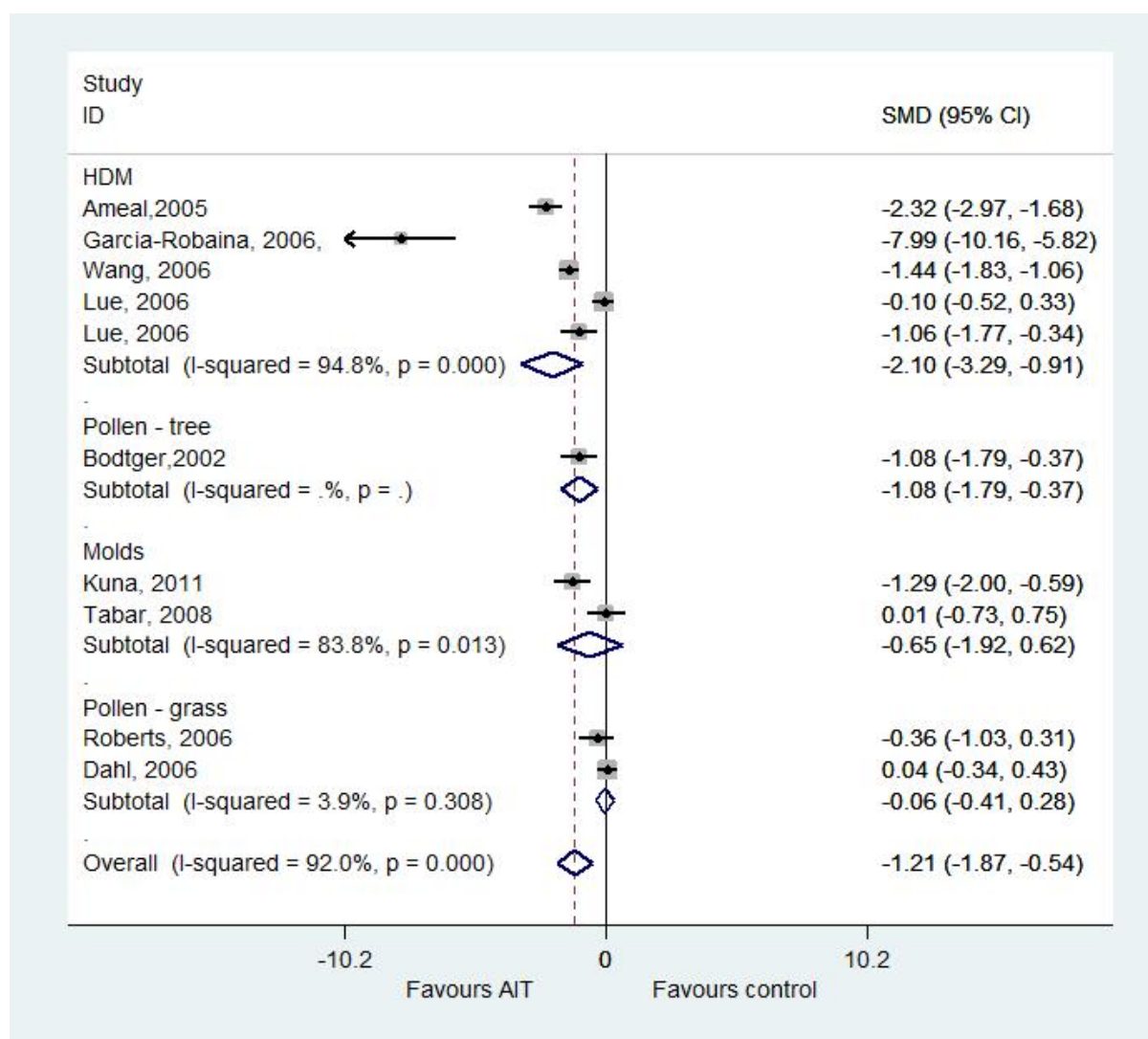
	Het. Statistic	df	P	Isquared*	Tau-squared
Mild/moderate	105.37	6	0.000	94.3%	1.2698
Moderate/severe	0.00	0	.	.%	0.0000
Overall	107.32	7	0.000	93.5%	1.1427

Figure S2j: Meta-analysis of double-blind RCTs studies comparing symptom scores between AIT (SCIT or SLIT) and placebo groups for treatment duration <3 years or ≥3 years (random effects model)



	Het. stats	df	P	I-squared**	Tau-squared	
<3 years	110.39	8	0.000	92.8%	1.0731	
3 years	0.00	0		.	0.0000	0.0000
Overall	112.48	9	0.000	92.0%	0.9967	

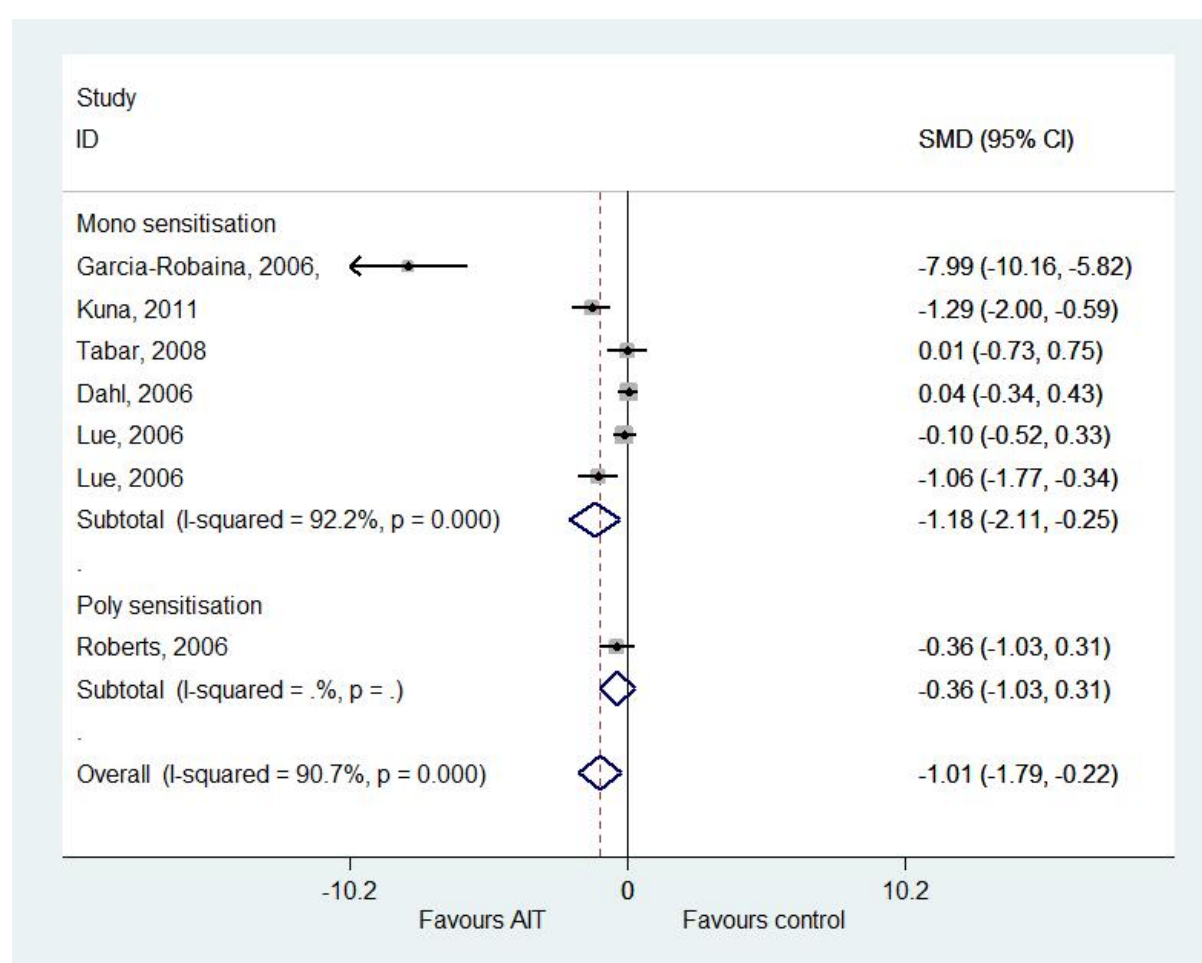
Figure S2k: Meta-analysis of double-blind RCTs studies comparing medication scores between AIT (SCIT or SLIT) and placebo groups for HDM vs tree pollen vs grass pollen vs mold (random effects model)



Significance test(s) of ES=0

Pollen - tree	z= 2.97	p=0.003
HDM	z= 3.46	p=0.001
Pollen - grass	z= 0.36	p=0.722
Molds	z= 1	p=0.319
Overall	z= 3.56	p=0.000

Figure S2I: Meta-analysis of double-blind RCTs studies comparing medication scores between AIT (SCIT or SLIT) and placebo groups for mono-sensitized versus poly-sensitized (random effects model)

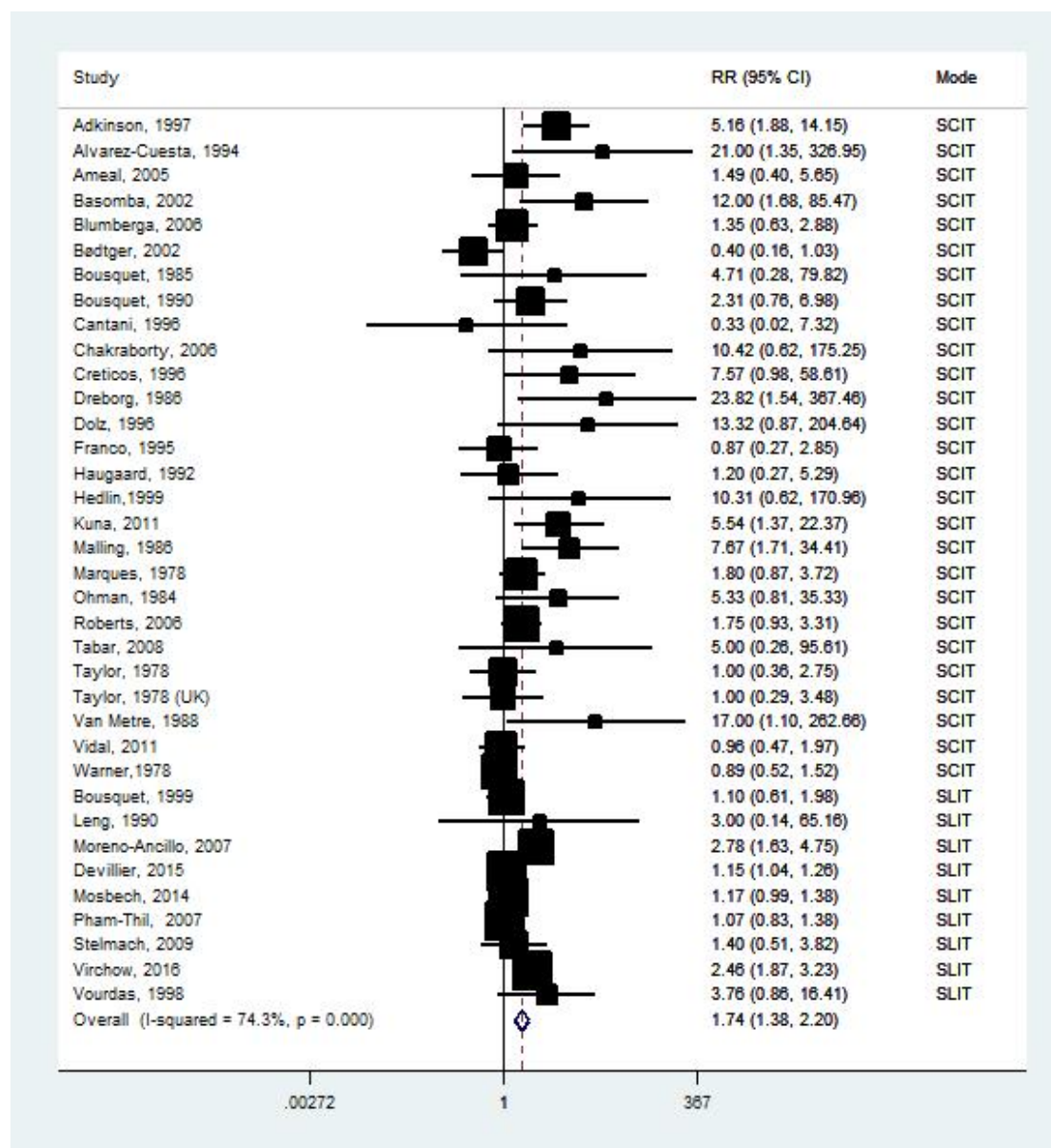


Significance test(s)	of ES=0	
Poly sensitisation	z= 1.06	p=0.291
Mono sensitisation	z= 2.49	p=0.013
Overall	z= 2.51	p=0.012

Supplementary material:
Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis
S3: Safety Figures and tables

Allergen Immunotherapy for Asthma: Safety Outcomes

Figure S3a: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) for safety data – patients experiencing one or more adverse event(s) rate ratio (RR) (random-effects model)



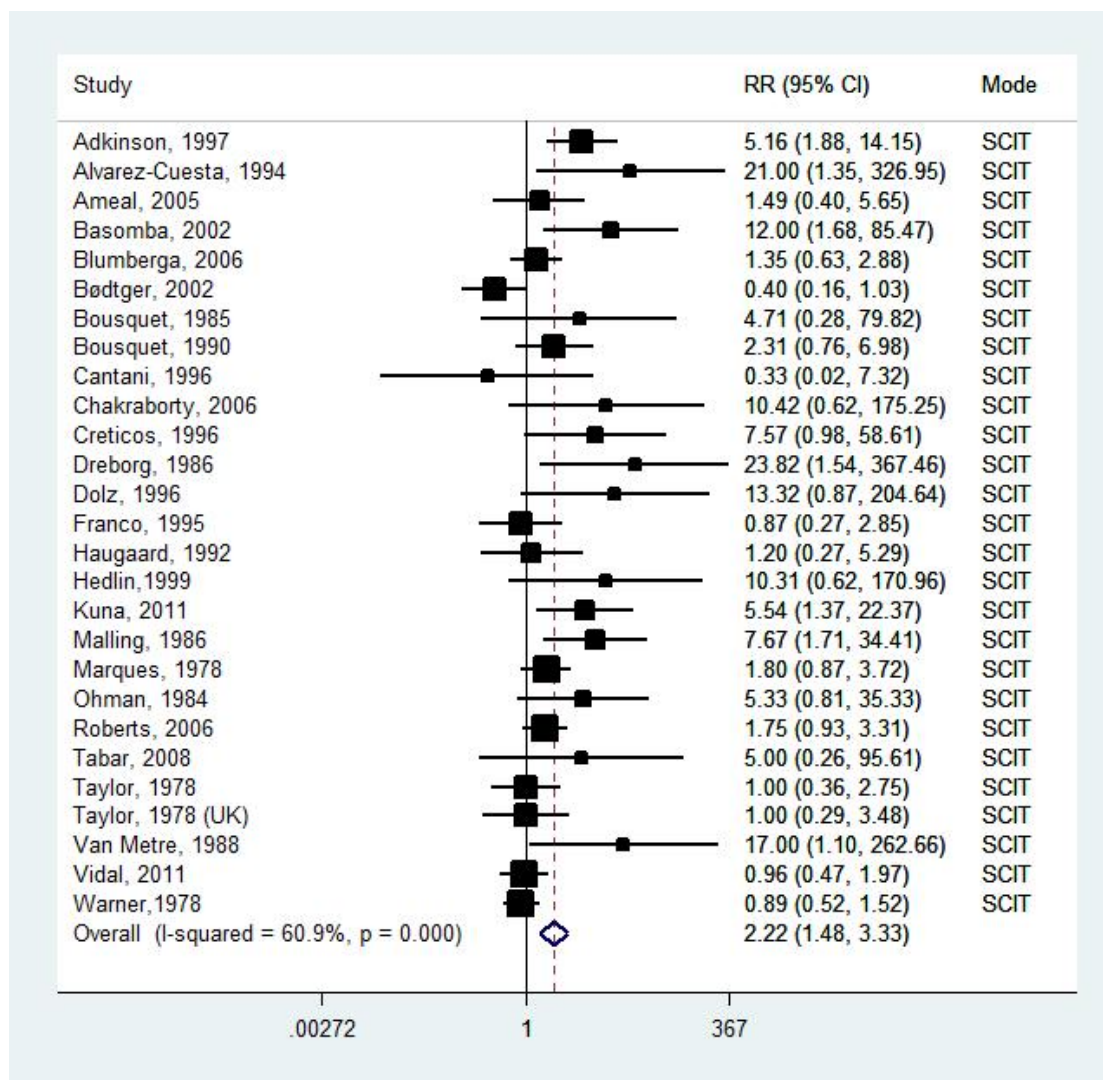
Test of RR=1 : $z = -4.66$ $p = 0.000$

Heterogeneity chi-squared = 135.99 (d.f. = 35) $p = 0.000$

I-squared (variation in RR attributable to heterogeneity) = 74.3%

Estimate of between-study variance Tau-squared = 0.1956

Figure S3b: Meta-analysis of double blind RCTs of SCIT for safety data – patients experiencing one or more adverse event(s) rate ratio (RR) (random-effects model)



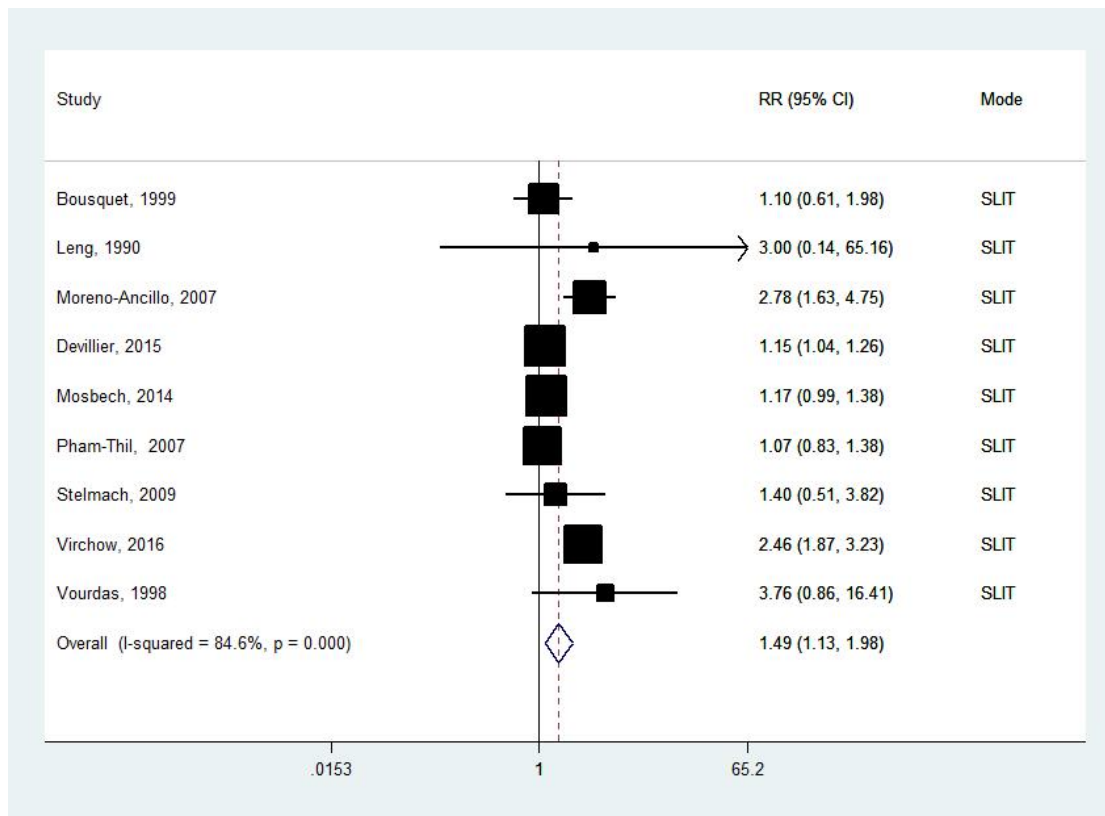
Heterogeneity chi-squared = 66.55 (d.f. = 26) p = 0.000

I-squared (variation in RR attributable to heterogeneity) = 60.9%

Estimate of between-study variance Tau-squared = 0.5563

Test of RR=1 : z= 3.85 p = 0.000

Figure S3c: Meta-analysis of double blind RCTs of SLIT for safety data – patients experiencing one or more adverse event(s) rate ratio (RR) (random-effects model)



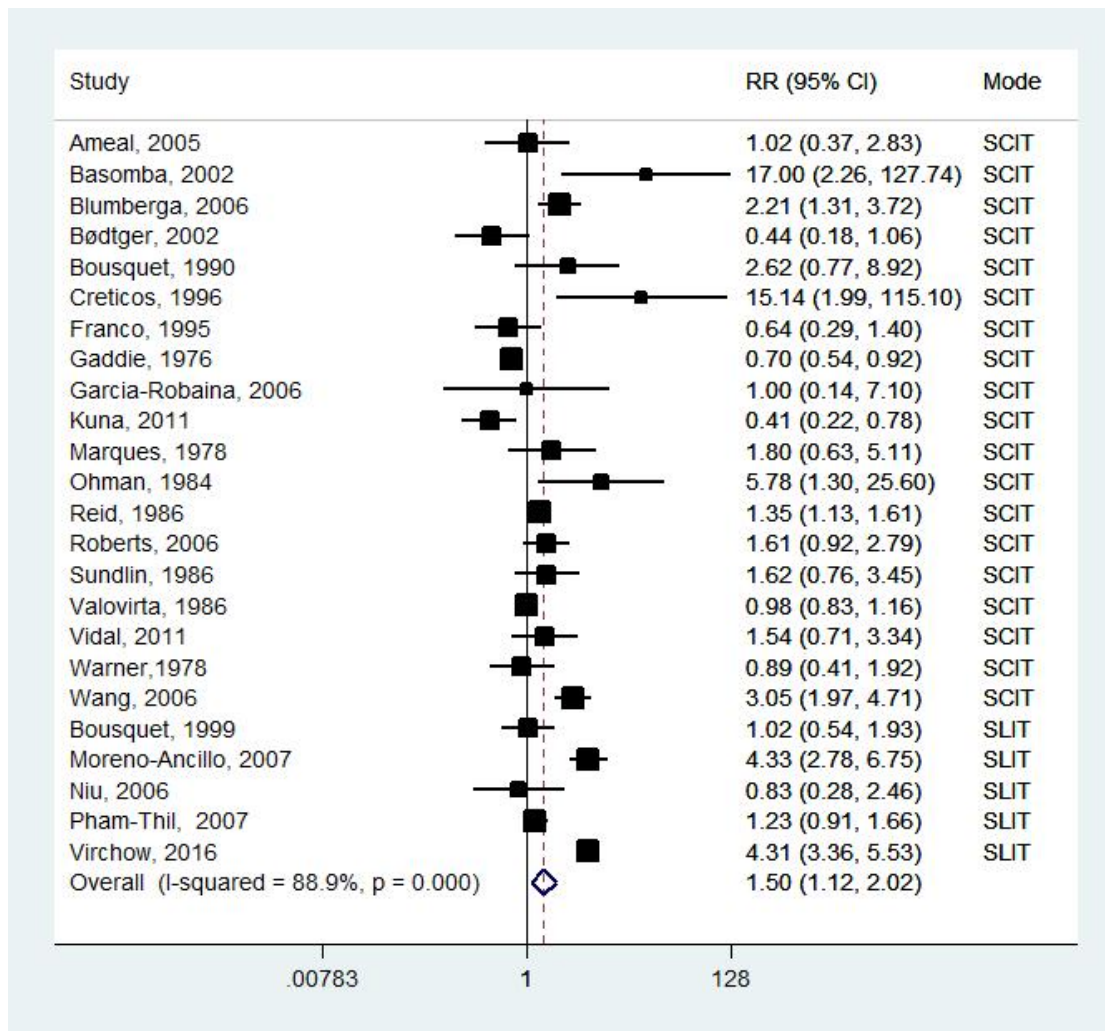
Test of $RR=1$: $z= -2.81$ $p = 0.005$

Heterogeneity chi-squared = 51.91 (d.f. = 8) $p = 0.000$

I-squared (variation in RR attributable to heterogeneity) = 84.6%

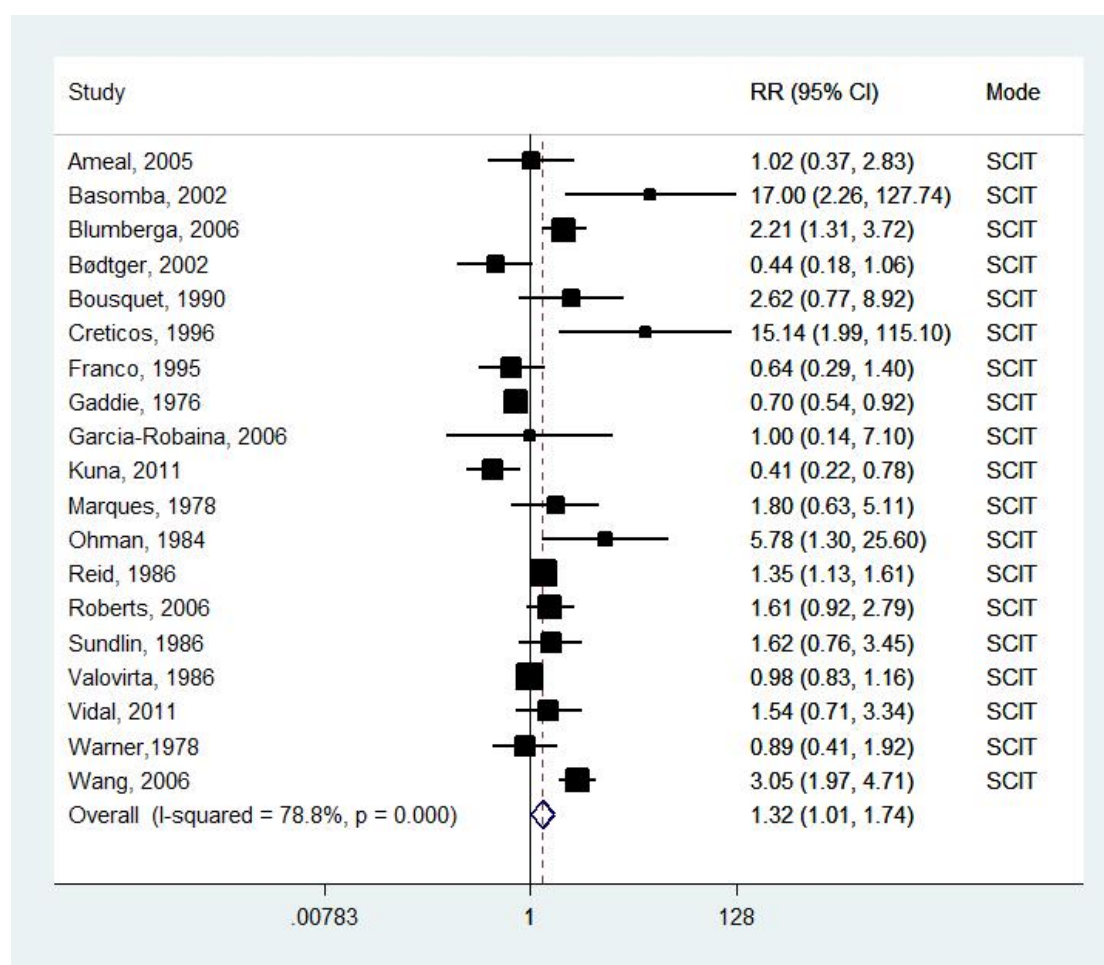
Estimate of between-study variance Tau-squared = 0.1075

Figure S3d: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for safety data – presence of total adverse events rate ratio (RR) (random-effects model)



Heterogeneity chi-squared = 206.73 (d.f. = 23) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 88.9%
Estimate of between-study variance Tau-squared = 0.3874
Test of ES=1 : z= 2.68 p = 0.007

Figure S3c: Meta-analysis of double blind RCTs of SCIT versus placebo for safety data – presence of total adverse events rate ratio (RR) (random-effects model)



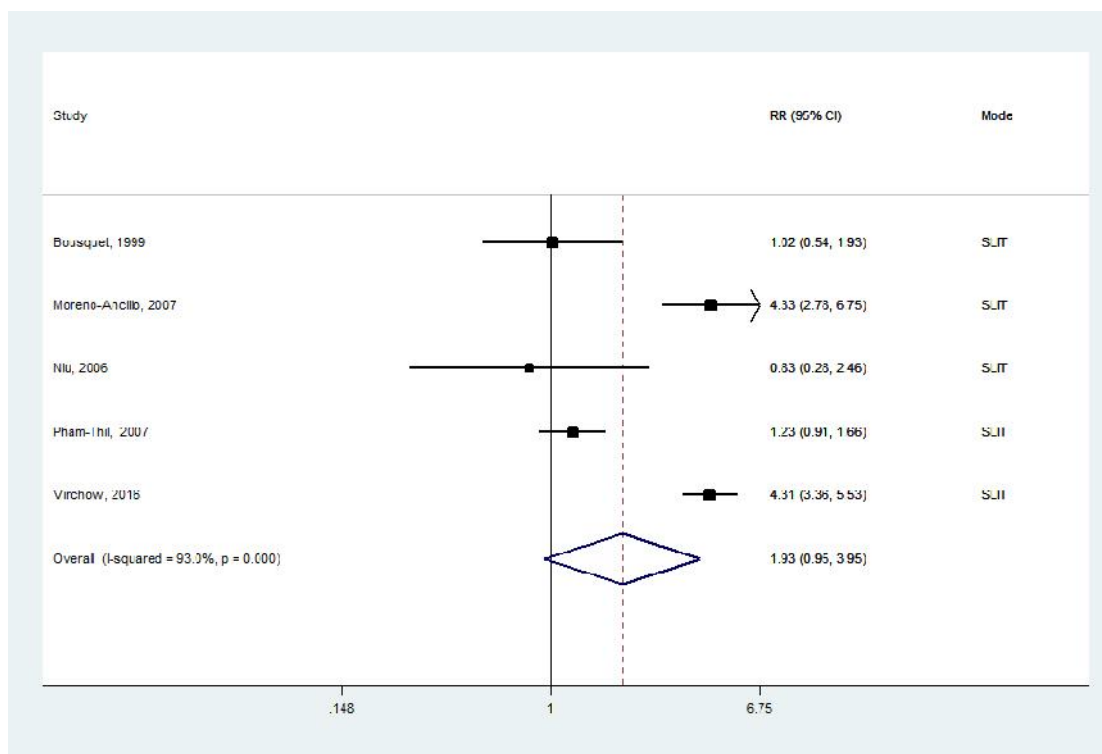
Test of ES=1 : $z = -2.00$ $p = 0.046$

Heterogeneity chi-squared = 84.91 (d.f. = 18) $p = 0.000$

I-squared (variation in ES attributable to heterogeneity) = 78.8%

Estimate of between-study variance Tau-squared = 0.2050

Figure S3f: Meta-analysis of double blind RCTs of SLIT versus placebo for safety data – presence of total adverse reactions rate ratio (RR) (random-effects model)



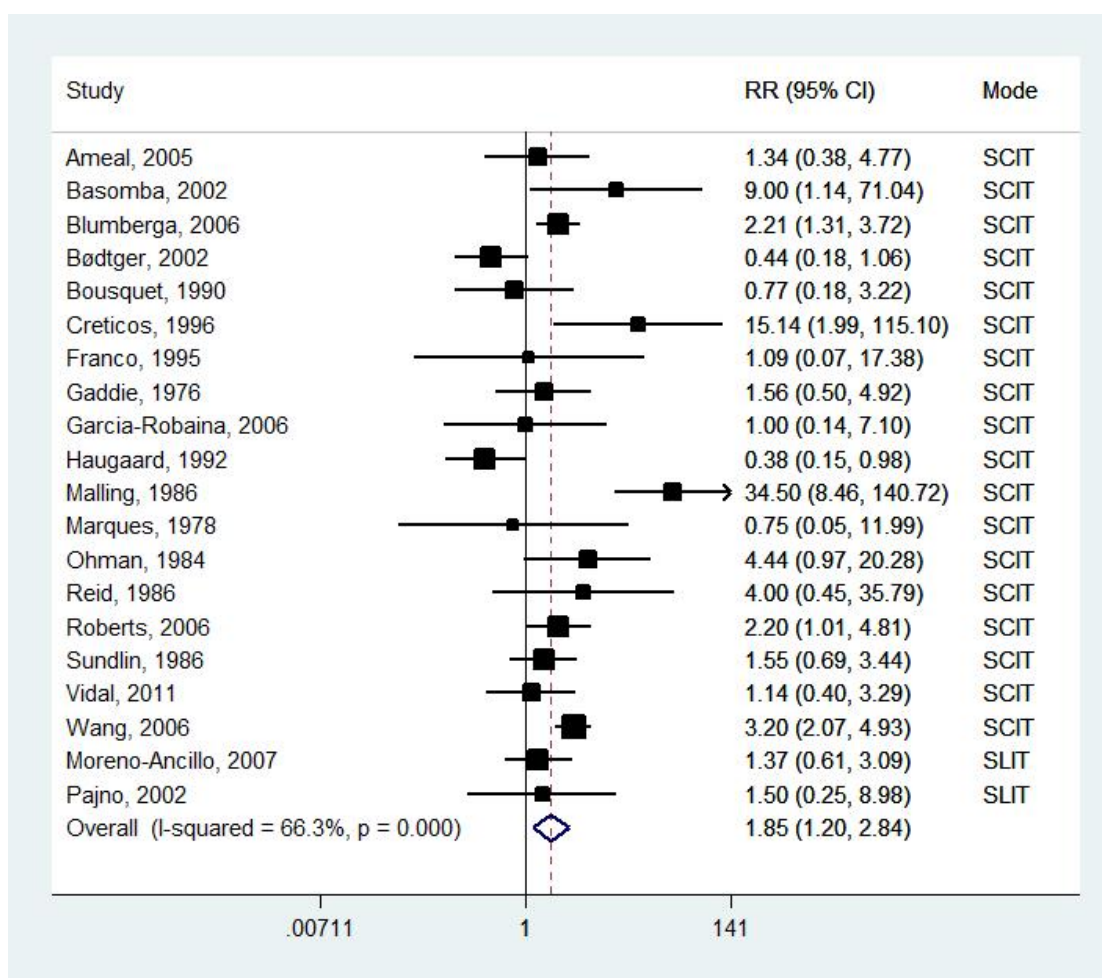
Test of ES=1 : $z = 1.81$ $p = 0.071$

Heterogeneity chi-squared = 56.96 (d.f. = 4) $p = 0.000$

I-squared (variation in ES attributable to heterogeneity) = 93.0%

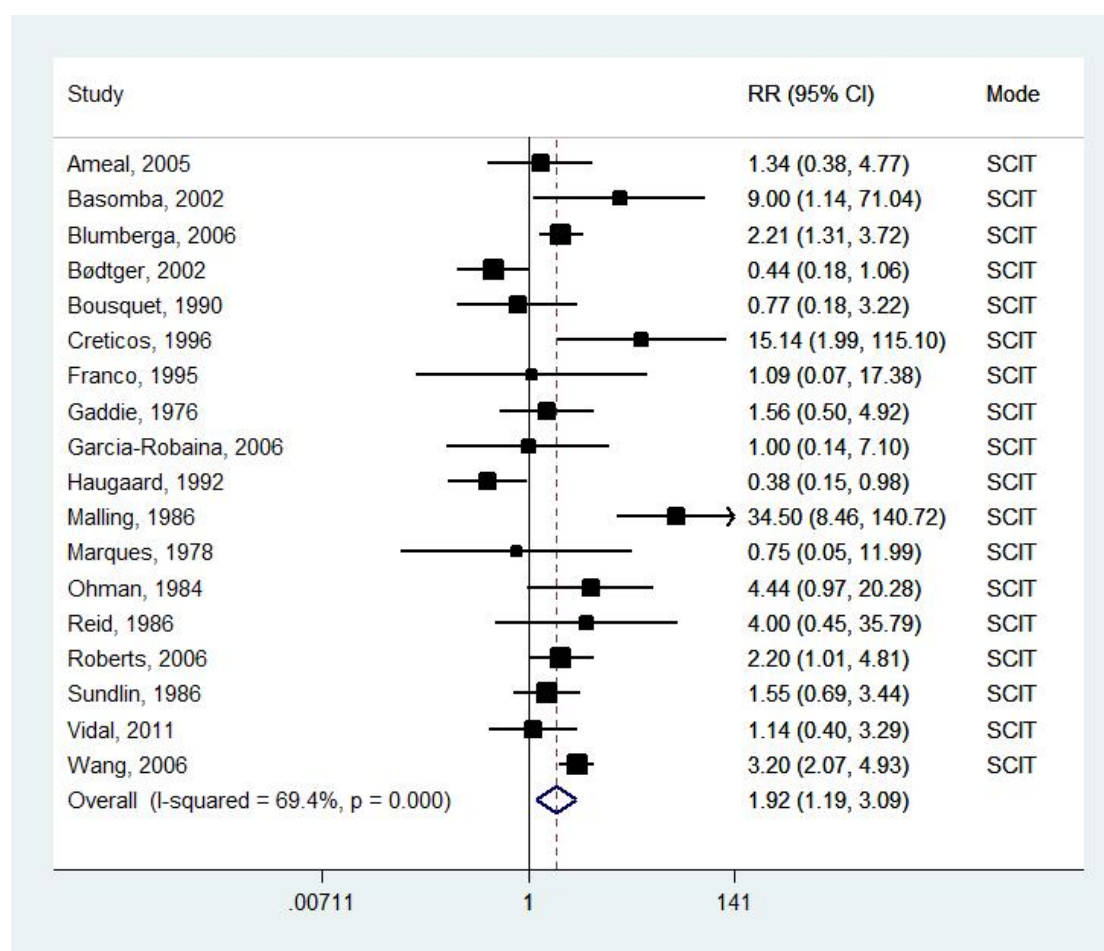
Estimate of between-study variance Tau-squared = 0.5779

Figure S3g: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for safety data – presence of systemic adverse events rate ratio (RR) (random-effects model)



Heterogeneity chi-squared = 56.44 (d.f. = 19) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 66.3%
Estimate of between-study variance Tau-squared = 0.5197
Test of ES=1 : z= 2.80 p = 0.005

Figure S3h: Meta-analysis of double blind RCTs of SCIT versus placebo for safety data – presence of systemic adverse events rate ratio (RR) (random-effects model)



Heterogeneity chi-squared = 55.64 (d.f. = 17) p = 0.000

I-squared (variation in ES attributable to heterogeneity) = 69.4%

Estimate of between-study variance Tau-squared = 0.5986

Figure S3i: Meta-analysis of double blind RCTs of SLIT versus placebo for safety data – presence of systemic adverse events rate ratio (RR) (random-effects model)

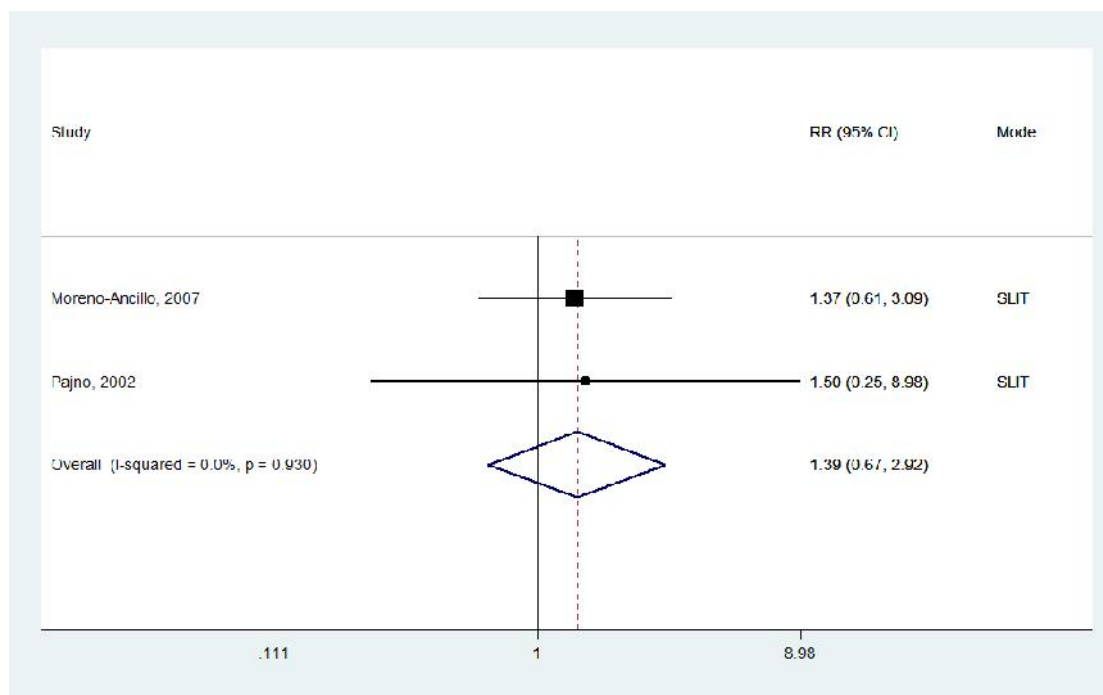
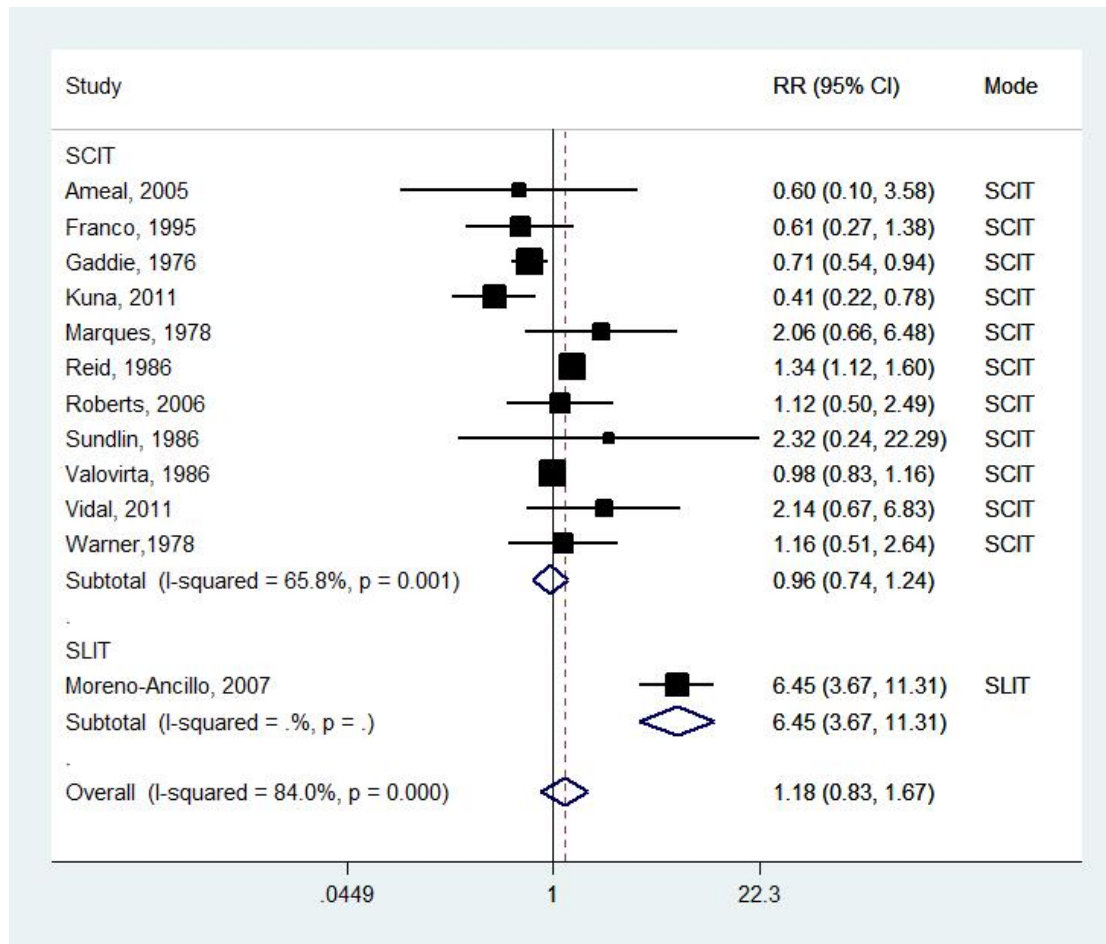


Figure S3j: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for safety data – presence of local adverse events rate ratio (RR) (random-effects model)



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
SCIT	29.23	10	0.001	65.8%	0.0804
SLIT	0.00	0	.	.%	0.0000
Overall	68.60	11	0.000	84.0%	0.2264

** I-squared: the variation in ES attributable to heterogeneity)

Significance test(s) of ES=1

SCIT	z= 0.33	p = 0.743
SLIT	z= 6.50	p = 0.000
Overall	z= 0.93	p = 0.352

Study Author, year	No. of potentially life- threatening/fatal AEs	No. of participants randomized	Any AEs: No. of patients experiencing ≥ 1 AE and total no. of any AEs	No. of local AEs	No. of systemic AEs	No. of drop- outs
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Table S3a: SCIT RCTs in asthma reporting adverse events (AEs)

	Adrenaline Rx	Anaphylaxis	Fatalities	SCIT	Placebo	SCIT: no. of patients	SCIT: no. of events	Placebo: no. of patients	Placebo: no. of events	SCIT	Placebo	SCIT	Placebo		Placebo
Adkinson, 1997	0	0	0	61	60	21	NR	4	NR	NR	NR	NR	NR	0	0
Alvarez-Cuesta, 1994	3	0	0	14	14	10	14	0	0	11	0	3	0	0	0
Ameal, 2005	0	0	0	29	26	5	8	3	7	2	3	6 (Grade 1: 4; Grade 2: 1; Grade 3: 1)	4 (Grade 1: 2; Grade 2: 2)	0	0
Basomba, 2002	0	0	0	25	25	12	17	1	1	8	0	2 (immediate)(Grade 2: 1; Grade 3: 1). 7 delayed SR	1 (delayed)	0	0
Blumberga, 2006	0	0	0	26	28	10	43	8	21	NR	NR	43 (grade 2:41, grade 3:2)	21 (Grade 1: 9; Grade 2: 12)	6	5
Bødter, 2002	0	0	0	17	17	4	7	10	16	NR	NR	7 (grade 1-2)	16 (Grade 1-2)	0	1
Bousquet, 1985	3	0	0	20	10	4	4	0	0	NR	NR	4	0	0	0
Bousquet, 1990	0	0	0	39	18	15	17	3	3	9	0	5	3	0	0
Cantani, 1996	0	0	0	10	10	0	0	1	4	0	1	0	0	0	0
Chakraborty, 2006	0	0	0	18	17	5	5	0	0	5	0	0	0	0	0
Creticos, 1996	N o t c l e a r	0	0	37	40	7	14	1	1	0	0	14	1	2	0
Dreborg, 1986	0	0	0	16	14	13	49	0	0	4	0	0	0	0	0
Dolz, 1996	7	0	0	18	10	11	12	0	0	4	0	8	0	0	0
Franco, 1995	NR	NR	NR	23	25	4	10	5	17	9	16	1	1	3	2
Gaddie, 1976	NR	NR	NR	26	29	NR	89	NR	141	82	129	7	5	6	4
Garcia-Robaina, 2006	0	0	0	32	32	NR	2	NR	2	0	0	2	2	5	5
Haugaard, 1992	NR	1	NR	15	9	4	U	2	U	U	U	7	11	5	0
Hedlin,1999	0	0	0	15	14	5	5	0	0	0	0	5	0	2	1
Kuna, 2011	NR	NR	NR	25	19	7	12	2	46	12	46	0	0	9	7

Malling, 1986	0	3	0	11	11	11	U	1	U	U	0	69 (mild: 32; severe: 27; delayed: 5; anaphylactic: 3, other: 2)	2	0	0
Marques, 1978	0	0	0	16	12	12	12	5	5	11	4	1	1	4	1
Mosbech, 1990	2	2	0	37	18	27	U	NR	NR	7	NR	37	NR	1	0
Ohman, 1984	U	U	NR	9	8	6	13	1	2	3	0	10	2	0	0
Olsen et al., 1997	0	0	0	21	10	0	0	0	0	0	0	0	0	4	4
Reid, 1986	5	0	0	9	9	9	291	9	215	287	214	4	1	U	U
Roberts, 2006	0	0	0	18	17	13	34	7	20	13	11	21	9	0	0
Smith, 1971	0	0	0	11	11	8	NR	NR	NR	NR	NR	NR	NR	U	U
Sundin, 1986	NR	NR	NR	22	17	17	21	NR	10	3	1	18	9	U	U
Tabar, 2008	NR	NR	NR	14	14	2	2	0	0	1	0	1	0	1	4
Taylor, 1978	U	NR	0	5	5	3	NR	3	NR	NR	NR	NR	NR	0	0
Taylor, 1974 (UK)	NR	NR	NR	21	21	4	NR	4	NR	NR	NR	NR	NR	NR	NR
Valovirta, 1984	0	0	0	15	12	NR	309	NR	251	309	251	0	0	NR	NR
Van Metre, 1988	0	0	0	11	11	8	28	0	0	26	0	2	0	U	U
Vidal, 2011	NR	NR	NR	21	18	9	18	8	10	10	4	8	6	2	1
Warner, 1978	0	0	0	27	24	13	13	13	13	13	10	0	3	NR	NR
Wang, 2006	U	U	0	64	65	NR	81	NR	27	NR	NR	85 (Grade 1: 7; Grade 2: 71; Grade 3: 7)	27 (Grade 1: 2; Grade 2: 25)	NR	NR

NR, not reported; **U**, unclear

Table S3b: SCIT AIT RCTs in asthma not reporting any safety data

Author, year
Aas, 1971

Alvarez, 2002
Armentia-Medina, 1995
Arvidsson, 2004
Håkansson, 1998
Johnstone, 1968
Leynadier, 2000
Maestrelli, 2004
Mosbech, 1989
Newton, 1979
Ortolani, 1984
Pauli, 1984
Price, 1984
Rak, 2001
Valovirta, 1984
Van Bever, 1992

Table S3c: SLIT AIT RCTs in asthma reporting adverse events (AEs)

Study	No. of potentially life-threatening/fatal AEs			No. of participants randomized		Any AEs: No. of patients experiencing ≥ 1 AE and total no. of any AEs				No. of local AEs		No. of systemic AEs		TEAEs no of events		TRAEs no of events		7
Author, year	Adrenaline	Anaphylaxis	Fatalities	SLIT	Placebo	SCIT: no. of patients	SCIT: no. of events	Placebo: no. of patients	Placebo: no. of events	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	8
Bousquet, 1999	0	0	0	42	43	15/42 (35.7%)	19	14/43 (32.6%)	19	NR	NR	NR	NR	NR	NR	NR	NR	5
Leng, 1990	0	0	0	9	9	1/9	1	0/9	0	1	0	0	0	1	0	1	0	1
Mosges, 2010	0	0	0	27	27	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1
Dahl, 2006	0	0	0	74	40	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1
Moreno-Ancillo, 2007	0	0	0	53	52	34/51 (66.7%)	106	12/49 (24.5%)	24	92	14	14	10	106	24	106	24	6
Pajno, 2002	0	0	0	15	15	NR	NR	NR	NR	1	0	3	2	NR	NR	NR	NR	1
de Blay, 2014	0	0	0	81	27	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2
Devillier, 2015	0	0	0	322	162	280/322 (87%)	NR	123/162 (75.9%)	NR	NR	NR	NR	NR	751	184	751	184	8
Mosbech, 2014	0	0	0	461	143	290/461 (63%)	NR	77/143 (54%)	NR	NR	NR	NR	NR	NR	NR	254	14	1
Niu, 2006	0	0	0	56	54	NR	6	NR	7	NR	NR	NR	NR	NR	NR	5	3	1
Pajno, 2000	0	0	0	12	12	NR	NR	NR	NR	2	0	NR	NR	NR	NR	NR	NR	0
Pham-Thil, 2007	0	0	0	55	56	39 / 55 (71%)	93	37 / 56 (66%)	77	NR	NR	NR	NR	NR	NR	NR	NR	0
Stelmach, 2009	0	0	0	25	25	7 / 20 (35%)	NR	5 / 15 (33.3%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	0

Virchow, 2016	0	0	0	557	277	237/557 (43%)	598	48/277 (17%)	69	NR	NR	NR	NR	NR	NR	NR	NR	NR
Vourdas, 1998	0	0	0	34	32	8/34	NR	2/32	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wang, 2014	0	0	0	322	162	NR	NR	NR	NR	NR	NR	NR	NR	0	0	0	0	NR

Table S3d: SLIT AIT RCTs in asthma that reported no AEs occurred during the study period

Author, year
Alvarez-Cuesta, 2007
Bachelier, 2001
Caffarelli, 2000
Gomez Vera, 2005
Ippoliti, 2003
Lewith, 2002

Table S3e: SLIT AIT RCTs in asthma with limited safety data reported

Author, year	Reason
Cao, 2007	"No severe adverse events happened in the trial and the most-likely adverse events were mild asthma and local rash." (Paper in Chinese, used translated version from Prof. Zhang)
Drachenberg, 2001	"Local adverse events (e.g. stomatitis, pharyngitis) were more common in the active group (p = 0.05). There were no reports of serious or severe adverse events" (Paper in German. Used translated version sent by Susanne./No separate results for asthma)
Lue, 2006	"All patients completed the study. No severe drug related adverse event was reported during the trial period."
Ma, 2010	"No severe adverse events occurred in both groups during the follow-up period" (used translated version from Prof. Zhang)
Ma, 2014	"The incidence of side effects (including skin rash, nasopharyngeal itch, and asthma attack) relevant to immunotherapy was 13.3% and no serious side effects happened." (used translated version from Prof. Zhang)
Pajno, 2003	only graphic depiction of results
Reinert, 1983	No information on safety. Paper in German. Used translated version sent by Susanne Lau
Wood, 2014	Only narrative description of results
Yin, 2011	Need full text and translation (paper in Chinese)
Zheng, 2012	No information on safety. (Used translated version sent by Prof Zhang)
Zhang, 2013	"There were no severe adverse events during the course of immunotherapy, except for mild reactions." (Used translated version sent by Prof Zhang)
Zhang, 2015	(Used translated version sent by Prof Zhang)

Table S3f: SLIT AIT RCTs in asthma that did not report on AEs

Author, year
Pajno, 2004
Reilly, 1994
Tian, 2014

Table S3g: Case-series studies in asthma that reported on safety

Study (First author, year, country)	Age/sex	Number of patients (N)/No randomised	Mono/ polysensitized	Study duration (treatment duration)	Disease severity (mild, moderate, severe)	Type of Immunotherapy (intervention vs comparator)	Type of allergen	Natural allergen or allergoid	Safety	Comments
Casanovas,2006, Spain and Portugal	Females = 519, males = 549, mean 26.2, 95% CI 25.3- 27.1.	1068. Asthma n= 528, allergic rhinitis n= 878	Polysensitised	Not reported	Mild/moderate	Modified allergen extract of mites, D. pteronyssinus, D. farinae, grass, woods, weeds and trees vs no comparator	SCIT Mites, D. pteronyssinus, D. farinae, grass, woods, weeds and trees	Allergoids	Safety - adverse reactions, defined as immediate if within 30 minutes, or delayed (timeframe not stated). Local reactions measured by cm diameter Seven clinically relevant local reactions were recorded from a total of 85 (40 immediate and 45 delayed) (0.66 per patient and 0.33 per injection). There were 8 systemic reactions: 2 immediate grade- 1 reactions and 6 delayed (3 of grade 1 and 3 of grade 2) reactions. No systemic grade 3 or 4 reactions	Prospective open label case series conducted in 66 allergy units in Spain

									were recorded.	
Copenhaver,2011,US	Whole sample mean 38.1 (16.7), range 6 to 81, females = 264, males = 177	441. Asthma n= 127	Sensitisation not reported	2.5 years	Not reported	Dust mite, grass pollen, tree pollen, weed pollen, cat, dog, mould, and cockroach vs no placebo	SCIT Dust mite, grass pollen, tree pollen, weed pollen, cat, dog, mould, and cockroach		Safety measured through number of systemic reactions. 27 patients had a systemic reaction but no fatalities	

Drachenberg,2003, Germany	Whole sample mean and median 30, SD 14, range 6-67, whole sample females= 55% and males = 45%	1808, specific asthma patients not reported. Patients with allergic rhinitis and/or allergic conjunctivitis were selected but specific figures are not reported	Polysensitised	3 months	Not reported	Pollen extract only no placebo	SCIT pollen extract (Mixed grasses, birch, mugwort, rye, alder, hazel)	Allergoid	All adverse events were recorded. During Initial treatment there were 7748 injections administered of these: 1.85% caused local reactions, 0.76% caused mild systemic reactions and 0.05% caused severe systemic reactions. During maintenance phase (5040 injections): Local reactions 1.2%; Mild systemic reactions 0.44% and Severe systemic reactions 0.06%. Severe systemic reactions were reported from 6 patients corresponding to a percentage of 0.05% (initial course) and 0.06% (maintenance course). Three local adverse events were reported in the intervention group.	
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Giovanni, 2003,Italy	Not reported	354, asthma n=354	Some polysensitized but only monosensitised reported	at least 37 moths	Not reported	Grass, olive, parietaria, dust mites, cat and alternaria alternata vs comparator group which received SLIT using spit method	Sublingual swallow method grass, olive, parietaria, dust mites, cat and alternaria alternata vs comparator sublingual spit method	Natural	Safety measured through % patients suffering adverse events No adverse events were observed in 90.4% of the children only 0.155 mild to moderate reactions per 1000 administrations. No anaphylactic reactions or multiple-organ life-threatening events occurred.	Prospective open label case series. SLIT is quite a safe therapy for the treatment of allergic children with asthma; however, careful evaluation of the single patient is necessary since SLIT is self- administered and a cumulative monthly dose higher than that normally administered as an injection is usually attainable.
Smits,2007,US	Mean age 38, range 1.5-77. Females=507 and males=386	893. Asthma = 505, allergic rhinitis= 857.	Sensitisation not reported	1 year	Not reported	Combination of aeroallergens including mould, trees, grass, weed, mites, cats and dogs vs no comparator group.	SCIT combination of allergens vs no comparator	Natural	Safety after rush treatment. Eighteen adverse events reported by patients receiving treatment. Systemic adverse events reported were 18.	Retrospective chart review of 893 patients. Rapid allergen vaccination using a modified 2.5- hour protocol with premedication is a safe and effective procedure for allergic rhinitis and allergic asthma. Patients

										undergoing this procedure are able to reach a maintenance dosage in a shorter time than with conventional allergen vaccination.
Schiappoli I, 2009, Italy	age range 5-71, females=891 and males=847	1738 patients	NR	36 months	intermittent to moderate	Combination of allergens including grass, mite, parietaria, trees, ragweed and others (cat, alternaria and cypress)	SCIT combination of allergens vs no comparator	Natural	95 SRs were recorded in 57 patients (3.28%). Out of the 57 patients, 32 experienced one single adverse event, whereas the remaining 25 patients accounted for 63 reactions. There were 34 grade 2, 60 grade 3 and one grade 4 reaction and no fatality.	

Table S3h: Quality appraisal of case-series studies in asthma that reported on safety

Study (First author, year, country)	Case series collected in more than one centre	hypothesis/aim/objective of the study clearly described	inclusion and exclusion criteria (case definition) clearly reported	clear definition of the outcomes reported	data collected prospectively	explicit statement that patients were recruited consecutively	main findings of the study clearly described	outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics)	Overall quality rating
Casanovas/2006/Spain and Portugal	yes	yes	no	yes	yes	no	yes	no	5/8
Copenhaver/2011/US	No	Yes	No	Yes	No	No	Yes	Yes	4/8
Drachenberg/2003/Germany	yes	yes	no	yes	yes	no	yes	no	5/8
Giovanni/2003 /Italy	not reported	yes	no	yes	yes	no	yes	no	4/8
Schiappoli / 2009 / Italy	yes	yes	no	yes	yes	no	yes	no	5/8
Smits/2007/US	no	yes	no	yes	no	no	yes	no	3/8