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Sublingual immunotherapy for asthma (Review)

Normansell R, Kew KM, Bridgman AL

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Sublingual immunotherapy for asthma.
Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD011293.
DOI: 10.1002/14651858.CD011293.pub2.

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[Intervention Review]

Sublingual immunotherapy for asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 8, 2015.
Review content assessed as up-to-date: 25 March 2015.

Citation: Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No.: CD011293. DOI: 10.1002/14651858.CD011293.pub2.

ABSTRACT

Background

Asthma is a common long-term respiratory disease affecting approximately 300 million people worldwide. Approximately half of people with asthma have an important allergic component to their disease, which may provide an opportunity for targeted treatment. Sublingual immunotherapy (SLIT) aims to reduce asthma symptoms by delivering increasing doses of an allergen (e.g. house dust mite, pollen extract) under the tongue to induce immune tolerance. However, it is not clear whether the sublingual delivery route is safe and effective in asthma.

Objectives

To assess the efficacy and safety of sublingual immunotherapy compared with placebo or standard care for adults and children with asthma.

Search methods

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) and reference lists of all primary studies and review articles. The search is up to date as of 25 March 2015.

Selection criteria

We included parallel randomised controlled trials (RCTs), irrespective of blinding or duration, that evaluated sublingual immunotherapy versus placebo or as an add-on to standard asthma management. We included both adults and children with asthma of any severity and with any allergen-sensitisation pattern. We included studies that recruited participants with asthma, rhinitis, or both, providing at least 80% of trial participants had a diagnosis of asthma.

Data collection and analysis

Two review authors independently screened the search results for included trials, extracted numerical data and assessed risk of bias, all of which were cross-checked for accuracy. We resolved disagreements by discussion.

We analysed dichotomous data as odds ratios (ORs) or risk differences (RDs) using study participants as the unit of analysis; we analysed continuous data as mean differences (MDs) or standardised mean differences (SMDs) using random-effects models. We rated all outcomes using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) and presented results in the 'Summary of findings' table.

Main results

Fifty-two studies met our inclusion criteria, randomly assigning 5077 participants to comparisons of interest. Most studies were double-blind and placebo-controlled, but studies varied in duration from one day to three years. Most participants had mild or intermittent asthma, often with co-morbid allergic rhinitis. Eighteen studies recruited only adults, 25 recruited only children and several recruited both or did not specify (n = 9).

With the exception of adverse events, reporting of outcomes of interest to this review was infrequent, and selective reporting may have had a serious effect on the completeness of the evidence. Allocation procedures generally were not well described, about a quarter of the studies were at high risk of bias for performance or detection bias or both and participant attrition was high or unknown in around half of the studies.

One short study reported exacerbations requiring a hospital visit and observed no adverse events. Five studies reported quality of life, but the data were not suitable for meta-analysis. Serious adverse events were infrequent, and analysis using risk differences suggests that no more than 1 in 100 are likely to suffer a serious adverse event as a result of treatment with SLIT (RD 0.0012, 95% confidence interval (CI) -0.0077 to 0.0102; participants = 2560; studies = 22; moderate-quality evidence).

Within secondary outcomes, wide but varied reporting of largely unvalidated asthma symptom and medication scores precluded meaningful meta-analysis; a general trend suggested SLIT benefit over placebo, but variation in scales meant that results were difficult to interpret.

Changes in inhaled corticosteroid use in micrograms per day (MD 35.10 mcg/d, 95% CI -50.21 to 120.42; low-quality evidence), exacerbations requiring oral steroids (studies = 2; no events) and bronchial provocation (SMD 0.69, 95% CI -0.04 to 1.43; very low-quality evidence) were not often reported. This led to many imprecise estimates with wide confidence intervals that included the possibility of both benefit and harm from SLIT.

More people taking SLIT had adverse events of any kind compared with control (OR 1.70, 95% CI 1.21 to 2.38; low-quality evidence; participants = 1755; studies = 19), but events were usually reported to be transient and mild.

Lack of data prevented most of the planned subgroup and sensitivity analyses.

Authors' conclusions

Lack of data for important outcomes such as exacerbations and quality of life and use of different unvalidated symptom and medication scores have limited our ability to draw a clinically useful conclusion. Further research using validated scales and important outcomes for patients and decision makers is needed so that SLIT can be properly assessed as clinical treatment for asthma. Very few serious adverse events have been reported, but most studies have included patients with intermittent or mild asthma, so we cannot comment on the safety of SLIT for those with moderate or severe asthma. SLIT is associated with increased risk of all adverse events.

PLAIN LANGUAGE SUMMARY

Sublingual immunotherapy for asthma

Review question

We assessed the evidence on the use of sublingual immunotherapy (SLIT) for people with asthma compared with placebo or with normal treatment for asthma. We focused on whether SLIT is a good treatment for asthma and whether it is safe.

Background

Asthma is a long-term condition that causes breathing problems and cough, which sometimes develop into asthma attacks. This may lead to the need for patients to take extra medication, visit a clinic or a hospital for treatment or even be admitted to the hospital. Approximately 300 million people worldwide have asthma, and allergies may be an important trigger of asthma symptoms in about half of these people (e.g. house dust mites, pollen). The aim of SLIT is to reduce the body's allergic response that causes asthma symptoms; this is done by giving repeated doses of what the person is allergic to in liquid or tablet form under the tongue. Currently, it is not clear whether SLIT is more helpful or safer for people with asthma, when compared with placebo or just continuation of normal asthma treatments.

Study characteristics

We included 52 studies involving 5077 people. These studies lasted between one day and three years. Most of the people included in the studies had mild asthma. Both males and females were included, and about half of the studies included only children.

Most studies involved people with house dust mites or pollen allergy. The evidence presented here is current to 25 March 2015.

Key results

Very few studies recorded the number of people who had asthma attacks leading to a hospital visit or the need for additional medication, so we do not know if SLIT reduces asthma attacks, possibly because most of the patients included in these studies had mild asthma. A few studies reported quality of life, but they used different scales, so we could not really tell if SLIT had a positive effect. Some studies reported that people taking SLIT had fewer asthma symptoms and had a reduced need for asthma medication compared with controls, but studies measured this in different ways, some of which may not be accurate.

People receiving SLIT were no more or less likely to experience serious unwanted side effects, but these were generally very rare. We are not confident that this finding would apply to people with more severe asthma. People receiving SLIT were more likely to experience any unwanted side effect, but many of these were mild.

Guidelines for asthma treatment suggest that SLIT should be used only for people with asthma that is difficult to control with standard treatments. However, many of the studies in this review included people with mild asthma, so trials looking at the effects of SLIT for people with more severe asthma are needed. It would be helpful if these studies used standard scales to report their findings, so that results can be combined in the future.

Quality of the evidence

The evidence presented in this review is generally of moderate or low quality, and very few studies have reported outcomes that are important to people with asthma, such as asthma attacks and quality of life. Most studies did not clearly explain how investigators decided which people would receive SLIT and which individuals would receive placebo or normal care, and in some studies, both participants and trial organisers knew which treatment they were getting. This may have affected the results.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Subgroup and sensitivity analyses compared with placebo for asthma

Patient or population: adults and children with asthma
Settings: outpatient
Intervention: sublingual immunotherapy
Comparison: placebo or usual care
Weight mean duration of all included studies: 54 weeks (Fadel 2010 and Rodriguez 2012 excluded, as duration not reported)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	SLIT				
Exacerbation requiring ED or hospital visit **Study duration: 4 weeks**	No events	No events	Not estimable	47 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	
Quality of life	No meta-analysis possible	Not applicable	-	(0 RCTs)	Not applicable	5 studies reported quality of life outcomes but we were not able to perform a meta-analysis
Serious adverse events **Weighted mean duration of studies: 49 weeks**	14 per 1000	12 per 1000 (0 to 24)	RD 0.0012, (-0.0077 to 0.0102)	2560 (22 RCTs)	⊕⊕⊕◯ Moderate[d,e,f]	
Exacerbation requiring OCS **Weighted mean duration of studies: 25 weeks**	No events	No events	Not estimable	77 (2 RCTs)	⊕⊕◯◯ Low[a,b,c]	

All adverse events **Weighted mean duration of studies: 60 weeks****	222 per 1000	327 per 1000 (257 to 404)	OR 1.70 (1.21 to 2.38)	1755 (19 RCTs)	⊕⊕◯◯ Low[g,h]	
Bronchial provocation	Mean bronchial provocation in control group was 1020 mcg (PD20) and 5.45 mg/mL (PC20)	Mean bronchial provocation in intervention group was 0.69 standard deviations higher (0.04 lower to 1.43 higher)	-	139 (4 RCTs)	⊕◯◯◯ Very low[i,j,k]	3 studies reported outcome as PC20 and 1 as PD20. We combined the different scales using standardised mean differences
ICS use	Mean ICS use in control group was 255 mcg[l]	Mean ICS use in intervention group was 35.1 higher (-50.21 to 120.42)	-	174 (2 RCTs)	⊕⊕◯◯ Low[m,n]	Both treatment and control groups in both studies included in this analysis showed significantly decreased ICS use at end of study compared with baseline but no intergroup difference was detected

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **ED:** emergency department; **OCS:** oral corticosteroids; **PD20:** provocative dose of methacholine required to produce a 20% fall in forced expiratory volume in 1 second; **PC20:** provocative concentration of methacholine required to produce a 20% fall in forced expiratory volume in 1 second; **ICS:** inhaled corticosteroids.
**All adverse events was not a prespecified outcome, but we have included it in the 'Summary of findings' table, as substantial data were contributed to this outcome. We have left out the asthma symptom scores outcome, as we were able to perform only a limited narrative analysis

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

[a] Only a small number of included studies reported this outcome, suggesting lack of relevance in this study population. Treatment period in Calderon 2006 was just 4 weeks and exacerbations requiring ED/hospital admission/OCS are rare events. Downgrade once.
[b] No events but could be a product of the asthma severity of the recruited population. No downgrade.
[c] Funnel plot not possible as no one outcome shows > 10 studies contributing events. Many reports are conference abstracts without associated peer-reviewed full publication. Downgrade once.

[d] 5/21 studies included in this analysis were assessed as having high risk of performance and detection bias, but none of the 5 contributing events. No other serious issues.

[e] 5/21 studies included a mixed population of participants with asthma and rhinitis (but all > 80% with asthma), but the 5 studies contributing events to this analysis recruited exclusively participants with asthma.

[f] Events rare. Participants had largely mild to moderate asthma and may have been less at risk of serious adverse events. Downgraded once for indirectness.

[g] Two studies contributing events assessed as having high risk of performance and detection bias, with 3 others at high risk but not contributing events. Study contributing greatest weight (41%) to the analysis reported only as a conference abstract with uncertainty about attrition bias. Downgrade once.

[h] Six out of 19 studies included mixed rhinitis and asthma populations, and of those contributing events made up approximately 25% of the analysis weight. Most of these events were mild and transient and did not lead to participant withdrawal. Downgrade once.

[i] Two out of four (contributing > 50% of analysis weight) studies assessed at high risk of performance and detection bias. Downgrade once.

[j] High level of heterogeneity ($I^2 = 76\%$) and combines PC20 with PD20 scores using SMDs. Downgrade once.

[k] Possibility of benefit in control group not excluded by confidence intervals. Downgrade once.

[l] Calculated as the weighted mean of control group scores of the included studies.

[m] Imprecise estimate with confidence intervals including the possibility of a clinically important harm or benefit from SLIT. Downgrade once.

[n] Many participants in included studies had mild asthma and so would be less likely to be using ICS. This was a predefined outcome, which may have less relevance to the study population.. Downgrade once.

BACKGROUND

Description of the condition

Asthma is a common long-term respiratory disease that affects both adults and children. It is characterised by reversible airflow limitation, typically leading to recurrent wheezing, chest tightness, shortness of breath and cough. Symptoms may vary over time and in intensity and can be triggered by factors including allergens, viral illnesses and exercise (CDC 2013; GINA 2014). Airflow limitation is a result of several factors including bronchoconstriction, airway oedema, bronchial hyper-responsiveness and airway remodelling, which may become irreversible over time (NAEPP 2007). Asthma therapy generally aims to reduce smooth muscle constriction through the use of inhaled agents such as long- and short-acting beta$_2$-agonists (LABA and SABA) and to reduce airway inflammation through therapies such as inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) (BTS/SIGN 2014).

Although estimates vary between populations, it is increasingly recognised that for as many as 50% of those with asthma, their condition has an important atopic component (Agache 2012; Arbes 2007; Normansell 2014; Pearce 1999), defined by a positive skin prick test to a recognised allergen, which may provide a therapeutic target for immunotherapy.

Atopy is defined as the production of specific immunoglobulin (Ig)E in response to common environmental allergens; it can be identified through skin prick testing. Total serum IgE has also been associated with asthma. Up to 95% of adults and children with asthma are skin prick test positive for one or more allergens (Craig 2008), but it should be noted that more than 50% of non-asthmatic children and adults are also skin prick test positive (Arbes 2007).

Description of the intervention

The aim of immunotherapy is to build up tolerance to an allergen through repeated exposure to the causative allergen. Subcutaneous immunotherapy (SCIT) is well established in the United States, whereas survey data from 2011 suggest that only 11.4% of US allergists prescribe sublingual immunotherapy (SLIT) (Sikora 2013). In Europe, SLIT represents approximately 45% of immunotherapy and up to 80% of new prescriptions for immunotherapy (Cox 2009; Linkov 2014). SLIT is available as tablets or as a solution and is usually taken in the morning, once daily, on alternate days, or twice weekly, according to manufacturer instructions. The drops or tablets are kept under the tongue for one to two minutes before they are swallowed. A build-up phase of gradually increasing doses is usually followed by a maintenance phase at the maximum dose. It is currently thought that a SLIT course should last for three to five years, which is consistent with evidence derived from trials of SCIT (Passalacqua 2012). Considerable inconsistency can be seen in the literature about safe and effective dosing of SLIT, and a recent World Allergy Organization position paper states that a regimen will have to be established individually for each allergen extract formulation (Canonica 2014).

How the intervention might work

Recognition of the important allergic component for many people with asthma has led to interest in the use of immunotherapy directed against specific allergens; although the efficacy of subcutaneous immunotherapy for asthma has been established, evidence for SLIT is conflicting (Incorvaia 2010; Passalacqua 2012). Allergen-specific sublingual and subcutaneous immunotherapy is thought to work primarily by inducing T-cell tolerance and promoting regulatory T-cells, which secrete the suppressive cytokines interleukin (IL)-10 and transforming growth factor (TGF)-beta. This in turn leads to production of the non-inflammatory immunoglobulins IgG4 and IgA, thus directing the immune response away from the inflammatory, atopic IgE response.(Fujita 2012). The hope is that targeting the dysregulated underlying immune response and thus desensitising the immune system to the specific allergen will permit those with allergic asthma to experience improvement in symptoms (Jutel 2014). The sublingual route of administration may offer advantages over the subcutaneous route, not only in terms of acceptability to patients. The oral cavity is a naturally 'tolerogenic environment', as it frequently encounters foreign proteins without the provocation of a local or systemic immune response and therefore may be an appropriate site for delivery of a treatment intended to produce immune tolerance (Canonica 2014). Pharmacokinetic studies suggest that the allergen extracts are retained for some time in the oral mucosa before they drain to local lymph nodes. This may account for the relative frequency of local reactions and infrequency of serious, systemic reactions (Marcucci 2007).

Why it is important to do this review

Asthma is thought to affect approximately 300 million people worldwide (Partridge 2006)-between 1% and 18% of the population in different countries (GINA 2014). The burden of the disease is considerable; in the United States alone, asthma costs approximately $56 billion a year and in 2009 led to 479,300 hospitalisations and 3388 deaths (CDC 2013); more asthma-related death is thought to occur in middle- and low-income countries (WHO). Many people with asthma remain inadequately controlled despite treatment and therefore are at high risk of exacerbation (Partridge 2006). Allergen-specific immunotherapy may represent an important addition to the more established asthma therapies and thus may help to reduce the morbidity and mortality associated with this disease. Indeed, it is the only treatment that specifically targets

underlying causes of allergen-triggered asthma, and it may lead to long-term desensitisation (Di Rienzo 2003). Moroever, SLIT may represent a more acceptable and safer route of administration than SCIT (Linkov 2014). However, the position of SLIT as a therapeutic option for asthma has yet to be established. Most national and international guidelines do not recommend its routine use for asthma because evidence of efficacy and safety is robust, or they recommend use only in those with symptoms difficult to control with standard treatments (BTS/SIGN 2014; GINA 2014; NAEPP 2007).

OBJECTIVES

To assess the efficacy and safety of sublingual immunotherapy compared with placebo or standard care for adults and children with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel randomised controlled trials (RCTs), blinded and unblinded, of any duration that evaluated sublingual immunotherapy versus placebo or as an add-on to standard medical management of asthma. We excluded cross-over trials because of the long-term effects of treatment. We included studies reported as full text, those published as abstract only and unpublished data.

Types of participants

We included both adults and children with asthma of any severity, diagnosed by a clinician or according to validated national or international guidelines (e.g. BTS/SIGN 2014; GINA 2014). Participants could have any allergen-sensitisation pattern. We included participants with a dual diagnosis of asthma and allergic rhinitis. As a pragmatic decision, and in a change to our protocol, we chose to exclude studies in which less than 80% of participants were reported to be diagnosed with asthma at baseline, as findings for patients with asthma were rarely presented separately. We excluded patients with other respiratory co-morbidities.

Types of interventions

We included trials evaluating any type or dose of SLIT (including single-allergen and multiple-allergen preparations) versus placebo or as an add-on to standard medical management of asthma.

We included trials that allowed the use of short-acting reliever medications such as salbutamol, provided these medications were not part of the randomly assigned treatment. We also included trials that allowed participants to continue their usual preventative asthma medication (e.g. LABA/ICS/LTRA), again provided this was not part of the randomly assigned treatment.

Types of outcome measures

Primary outcomes

1. Exacerbation requiring emergency department (ED) visit or hospitalisation (participants with at least one).
2. Quality of life* (measured on a validated scale, e.g. Asthma Quality of Life Questionnaire).
3. Serious adverse events (all-cause).

Secondary outcomes

1. Asthma symptom scores* (measured on a validated scale, e.g. Asthma Control Questionnaire).
2. Exacerbations requiring systemic corticosteroids (participants with at least one).
3. Response to provocation tests*.
4. Required dose of ICS.

Reporting by trial authors of one or more of the outcomes listed here was not an inclusion criterion for the review.

*If more than one validated scale measuring the same construct was reported within a study, or if different scales were used across studies, we analysed them together using standardised mean differences.

Outcomes were selected to reflect those most important to people with asthma after a check of the existing literature (Busse 2012; Sinha 2012).

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and through handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We

searched all records in the CAGR using the search strategy provided in Appendix 2. We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) for relevant studies. We conducted the most recent search on 25 March 2015.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references.

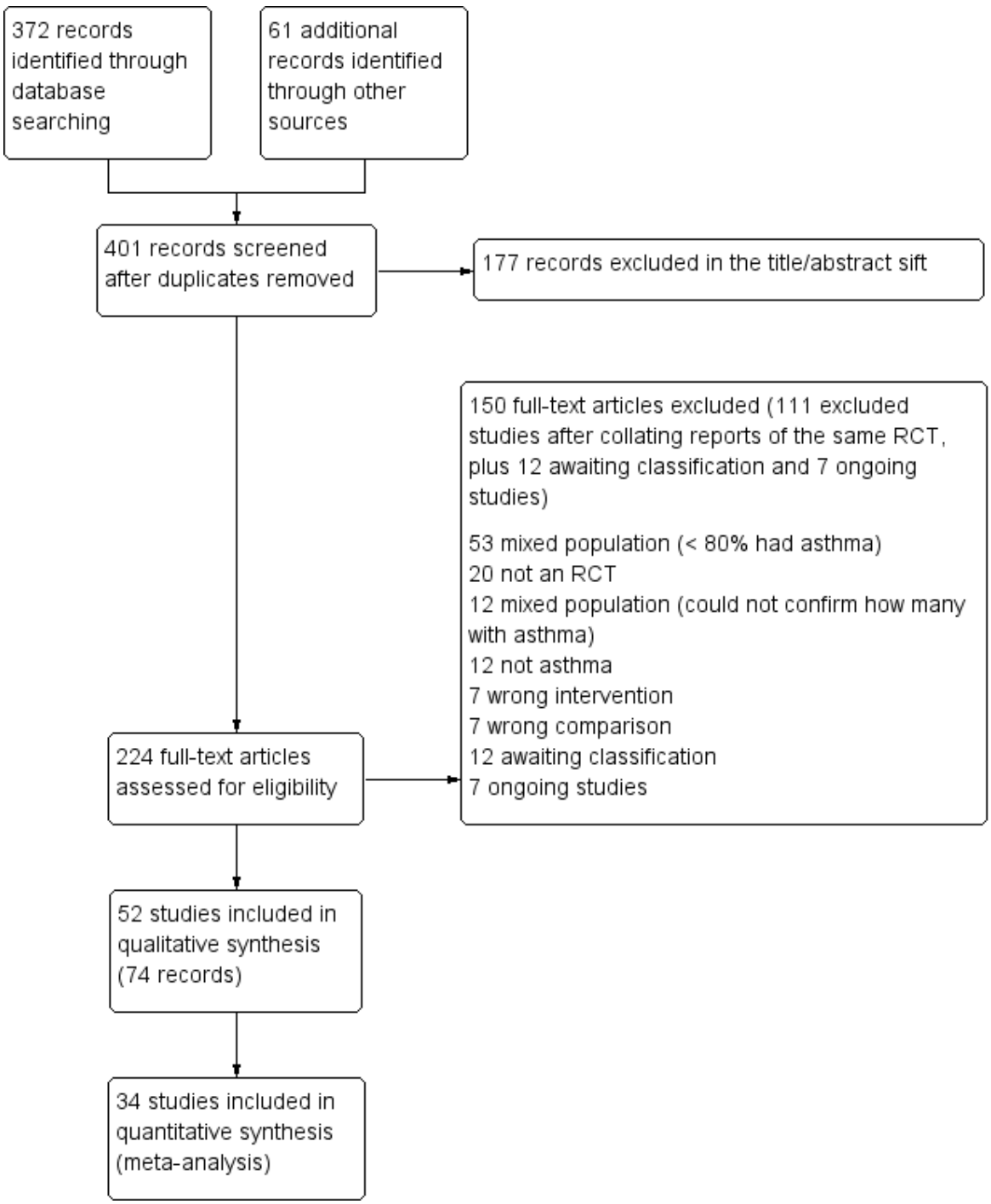
We searched on 14 March 2015 for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

Two review authors (RN and KMK) independently screened titles and abstracts to consider inclusion of all potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports and publications, and two review authors (RN and KMK) independently screened the full texts to identify studies for inclusion. We identified and recorded reasons for exclusion of ineligible studies, resolving disagreements through discussion or, if required, by consultation with a third person. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1) and a Characteristics of excluded studies table.

Figure 1. Study flow diagram.



Data extraction and management

We used a Microsoft Excel data collection form that had been piloted on at least one study in the review to document study characteristics and outcome data. Two review authors (RN, KMK or ALB) extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals, dates of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (RN, KMK or ALB) independently extracted outcome data from included studies. We resolved disagreements by reaching consensus or by involving the third review author. All three review authors transferred data into the Review Manager (RevMan 2012) file. We double-checked that data were entered correctly by comparing data presented in the systematic review with data from the study reports.

Assessment of risk of bias in included studies

Two review authors (RN, KMK or ALB) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion or by consultation with a third review author. We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' tables within the Characteristics of included studies table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported symptom scale). When considering treatment effects, we took into account risk of bias for studies that contributed data to that outcome.

Assesment of bias in conducting the systematic review

We conducted the review according to the published protocol (Normansell 2014a), and we report deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios and continuous data as mean differences (MDs) or standardised mean differences (SMDs). For rare events, we used risk differences (RDs) to account for trials with no events in either arm. We entered data presented as a scale with a consistent direction of effect. We used change from baseline scores when possible.

We undertook meta-analyses only when this was meaningful (i.e. if treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

We narratively described skewed data reported as medians and interquartile ranges and explained when meta-analysis was not considered appropriate.

When multiple trial arms were reported in a single trial, we included only the relevant arms. If two (or more) comparisons (e.g. drug A vs placebo, drug B vs placebo) were combined in the same meta-analysis, we halved (or divided by the appropriate number to reflect the number of treatment arms) the control group to avoid double-counting.

If trials reported outcomes at multiple time points, we used the end of treatment time point. As the benefits of immunotherapy are intended to persist beyond the treatment period, we also looked for primary outcomes reported at follow-up off treatment and described them, when available.

Unit of analysis issues

For dichotomous outcomes, we used participants rather than events as the unit of analysis (i.e. number of participants admitted to hospital at least once rather than number of admissions per participant).

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome

data when possible (e.g. when a study is identified as an abstract only), but owing to the large number of studies included, we attempted to contact study authors only to clarify whether a study did or did not meet our inclusion criteria.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we reported this and explored possible causes by performing prespecified subgroup analysis.

Assessment of reporting biases

We were not able to construct a funnel plot because the only primary outcome that was included in more than 10 trials was serious adverse events (SAEs), and only five studies contributed events.

Data synthesis

We used a random-effects model for all analyses, as we expected variation in effects due to differences in study populations and methods. We performed sensitivity analyses using a fixed-effect model when we encountered substantial heterogeneity.

Summary of findings table

We created Summary of findings for the main comparison using data from seven outcomes. In a change to our protocol, we did not include asthma symptoms as we did not perform a meta-analysis for this outcome and instead included all adverse events. We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to the meta-analyses for prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) with GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

When possible, we intended to carry out the following subgroup analyses for primary outcomes, using the formal test for subgroup differences in Review Manager (version 5.3) (RevMan 2012).

1. Age of participants (adults vs children).
2. Asthma severity (as defined by baseline severity reported in the trial or by review authors' assessment according to the asthma medication used).
3. Type of target allergen for sublingual immunotherapy (e.g. house dust mite (HDM), grass pollen).
4. Study duration (> or < one year).

Sensitivity analysis

We carried out sensitivity analyses while excluding the following.

1. Studies at high risk of bias for blinding.
2. Unpublished data (i.e. no peer-reviewed full paper available).

RESULTS

Description of studies

Details of methods, participants, interventions and outcomes for all included studies can be found in the Characteristics of included studies tables.

Results of the search

We identified 372 records through initial database searching and a further 61 from searches of clinicaltrials.gov and the World Health Organization (WHO) Clinical Trials Register. After removing duplicates, we screened 401 records, checking title and abstract only, and excluded 177. We assessed the remaining 224 full texts for eligibility and excluded 150 records (referring to 111 unique studies, plus seven ongoing studies and 12 studies awaiting classification) at this stage. Of those excluded, the majority included a mixed study population of participants with asthma, rhinitis or both, and results from participants with asthma were not presented separately (n = 53). As a pragmatic decision, and in a change to our protocol, we chose to exclude studies in which less than 80% of participants were reported to be diagnosed with asthma at baseline. We excluded 12 studies because we were unable to ascertain the percentage of participants with asthma at baseline.

We included 52 individual studies (74 records) in the qualitative synthesis; 34 contributed data to at least one meta-analysis, but 27 of these appeared only in the adverse or serious adverse events analyses. Three studies appeared only in the narrative synthesis of unvalidated symptom or medication scores (Cooper 1984; Lewith 2002; Reilly 1994). Fifteen studies did not report any data relevant to this review (Almarales 2012; Hanna 2013; Inal 2009; Karakoc-Aydiner 2011; Keles 2009; Marcucci 2003; Mosges 2010; Muratore 1993; Orefice 2004; Radu 2007; Rodriguez 2012; Rodriguez Santos 2004; Tian 2014; Virchow 2014; Yukselen 2013). A study flow diagram is presented in Figure 1.

Included studies

Fifty-two studies met our inclusion criteria, given the pragmatic change to the protocol described above. These studies included a total of 5256 participants, and 5077 were randomly assigned to comparisons of interest in this review. The largest included study randomly assigned 834 participants, and the smallest just 15. The median total number of participants across all 52 studies was 56. Thirty-seven were reported as full peer-reviewed articles, 14 were published as abstracts only (i.e. we did not identify a linked full-text article) and one was found only on clinicaltrials.gov.

Methods

As per our protocol, all included trials were RCTs with parallel design and compared SLIT versus placebo plus conventional therapy (n = 39) or conventional pharmacotherapy alone (n = 13). Six studies (Eifan 2009; Hanna 2013; Karakoc-Aydiner 2011; Keles 2009; Keles 2011; Mungan 1999; Yukselen 2013) included one or more arms that were not relevant to this review, for example, SCIT or SCIT plus SLIT. Trial duration varied greatly across studies, with the shortest lasting just one day and the longest 156 weeks. Several studies included a run-in period, and 10 included a period of post-treatment follow-up ranging from two weeks to two years. Outcomes data were extracted at the last time point reported, which was end of treatment in six studies and post-treatment in three studies; in one study different outcomes were reported at different time points. Trials were conducted in a variety of countries worldwide, but most were carried out in Europe (including Turkey) (n = 33) and Asia (n = 8). Only one study recruited participants in the USA.

Participants

We included studies involving both children and adults. Eighteen studies recruited only teenagers and adults and 25 studies children only; two studies included mixed populations of adults and children. In seven studies, the age range of participants was not reported. Most studies did not specify the ethnicity of participants. Most of the included studies (n = 44) recruited exclusively participants with asthma, although severity of the condition ranged from mild and intermittent to moderately severe. Eight studies stated that participants with asthma 'and/or' rhinitis were included, meaning that investigators recruited participants with a diagnosis of asthma *or* rhinitis *or* both. As has been mentioned, we included these studies *only* if we could confirm that more than 80% of participants had an asthma diagnosis at baseline. We excluded 53 studies because less than 80% of participants had asthma; we excluded12 because we were unable to confirm the percentage of participants with asthma at baseline despite attempts to contact the trial authors.

The inclusion criteria of most studies stated that participants must have had a positive skin prick test to the allergen of interest and/or serum allergen-specific IgE above a specified threshold. Usually, participants were also required to have a clinical history consistent with allergic asthma or rhinitis or both. Some studies stated that they excluded participants sensitised to other common aero-allergens and those with severe asthma or with other co-morbidities. Most studies excluded participants who had received immunotherapy in the past.

Interventions

More than half of the included studies (n = 34) targeted house dust mite (HDM) allergy, with the remainder targeting grass pollen (n = 6), birch pollen (n = 3), cockroach (n = 1), cat dander (n = 1), *Alternaria* (n = 1), *Parietaria* (n = 1), olive pollen (n = 1), *Artemisia* (n = 1) and a combination of HDM and *Parietaria* (n = 1). The remaining two studies involved homeopathic SLIT compared with placebo: One used HDM homeopathic SLIT and the other various allergens according to participant allergic response, with HDM the dominant allergen (84% of participants). As homeopathic SLIT represents a different entity from standard SLIT (with the allergen far more diluted), we intended to exclude these studies in a sensitivity analysis. However, neither study (Lewith 2002; Reilly 1994) contributed data to a meta-analysis, so this was not necessary. Dosing also varied across studies; when possible, we have extracted this information and presented it in the Characteristics of included studies tables.

Typically, SLIT interventions targeting perennial allergens, such as HDM, were administered continuously, while those targeting seasonal allergens, such as grass pollen, were administered before the start of the pollen season or during the pollen season. Most studies stated that participants were allowed to continue using specified rescue medication for asthma and rhinitis symptoms throughout the study, and in some trials the frequency of use of rescue medication was an efficacy outcome. Most studies made no changes to baseline preventer medication, such as ICS.

Outcomes

Outcomes reported were not consistent across reviews, and validated scales were rarely used. Asthma symptoms were reported by a large majority of included studies (n = 42), as were medication use scores (n = 36). Many studies also reported outcomes not specified in our protocol, including lung function such as peak expiratory flow rate (PEFR) (n = 32) and laboratory immunological outcomes such as serum allergen-specific IgE and IgG levels (n = 31). Adverse events were reported by just over half of the included studies (n = 27). Outcomes less frequently reported included skin prick tests (n = 16), bronchial provocation tests (n = 11), quality of life (n = 6) and exacerbations (n = 5). Despite the large number of outcomes reported in the included studies, meta-analysis was somewhat hampered by the wide range of unvalidated measures used; two out of our three primary outcomes of interest were rarely

reported (exacerbations and quality of life). We have presented the data extracted for symptom scores and medication use by using unvalidated or incompatible scales in Analysis 1.8 and Analysis 1.9.

Subgroup and sensitivity analyses

Studies contributing data to our primary analyses were insufficient for us to complete the planned sensitivity and subgroup analyses. In a post hoc change to the protocol, we chose to investigate the subgroups of age, target allergen and study duration for all adverse events; these results are presented in Analysis 2.1, Analysis 2.2 and Analysis 2.3. We chose to perform a sensitivity analysis by excluding studies assessed to be at high risk of performance bias for all adverse events (Analysis 2.4).

Summary characteristics of the included trials including information about potential effect modifiers (e.g. age, treatment duration, allergen) are presented in Table 1, and full details of each included study are given in Characteristics of included studies.

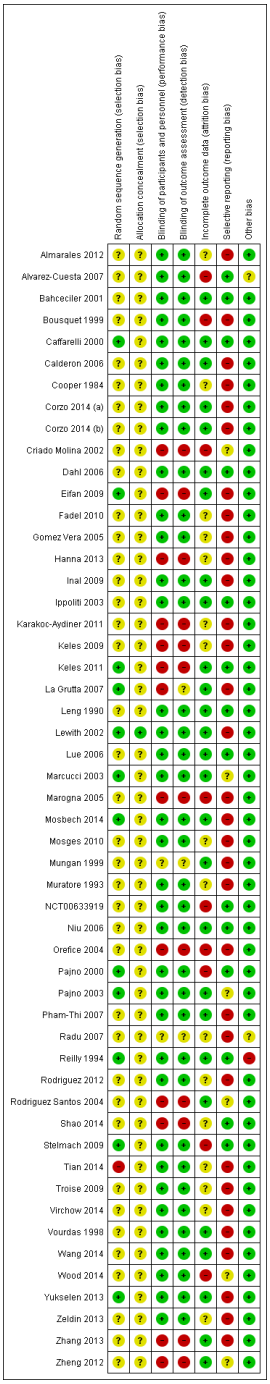
Excluded studies

We excluded studies that did not meet the criteria specified in our protocol or in which less than 80% of participants had received a diagnosis of asthma. We excluded 12 studies because we were unable to ascertain what percentage of the participants had asthma despite an attempt to contact the study authors. Reasons for exclusion of studies after the full text had been retrieved can be found in the Characteristics of excluded studies tables.

Risk of bias in included studies

For details on the risk of bias rating for each study and the reasons for each rating, see Characteristics of included studies. A summary of risk of bias judgements by study and by domain (sequence generation, allocation concealment, blinding, incomplete data and selective reporting) can be found in Figure 2.

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



Overall, a lot of uncertainty surrounded allocation procedures because of insufficient reporting, and about a quarter of the studies were at high risk of bias for blinding because they applied open-label designs. Participant attrition was high or unknown in around half of the studies, and selective reporting is likely to have had a serious effect on the completeness of this evidence base.

Allocation

We assessed one study (Lewith 2002) as having low risk of bias for both random sequence generation and allocation concealment. Investigators used sealed envelopes followed by randomisation by minimisation according to age, sex, smoking status and asthma severity.

We considered 11 further studies to be at low risk of bias for random sequence generation. Seven studies (Caffarelli 2000; Eifan 2009; La Grutta 2007; Marcucci 2003; Mosbech 2014; Stelmach 2009; Yukselen 2013) used computer-generated lists. Keles 2011 used the table randomisation method. Two studies (Pajno 2000; Pajno 2003) used a key code for random sequence generation. Reilly 1994 used a restricted technique of permuted blocks, stratified for intended allergen and daily dose of steroid. For these studies, no details were given on allocation concealment, and they were considered to be at unclear risk of bias in this domain.

Thirty-nine studies stated that they were randomised but provided no specific details about sequence generation nor allocation concealment and were assessed to be at unclear risk of bias for both domains.

One study (Tian 2014) was at high risk of bias for random sequence generation, as participants were divided into treatment group and control group in order of admission. No details were given about allocation concealment; therefore we assessed risk of bias as unclear in this domain.

Blinding

We assessed most included studies (n = 37) described as double-blind and placebo-controlled as having low risk of bias in both performance bias and detection bias domains.

Two studies were assessed as having unclear risk of bias in both domains. Although Mungan 1999 was placebo-controlled and single-blind, no details were provided about who exactly was blinded. Radu 2007 was also single-blind and did not include details on who was blinded.

La Grutta 2007 was rated as having high risk of performance bias, as the study was open-label. Assessor blinding was not described for some outcomes, so we considered detection bias to be unclear.

We assessed 12 studies as having high risk of bias for both domains. Eight studies (Criado Molina 2002; Eifan 2009; Marogna 2005; Orefice 2004; Rodriguez Santos 2004; Shao 2014; Zhang 2013; Zheng 2012) were open-label, which may have introduced bias. Hanna 2013 was a prospective study, with participants randomly assigned to three parallel groups with no mention of blinding. We made the assumption that three studies (Karakoc-Aydiner 2011; Keles 2009; Keles 2011) were open-label, as participant or assessor blinding was not mentioned.

Incomplete outcome data

Participant attrition was adequately described in 27 included studies, and we considered risk of attrition bias to be low. In 12 of these studies, no dropout was reported. In 14 other studies, withdrawal rates were low (no more than 20%), with similar rates reported in control groups. Pham-Thi 2007 performed data analysis according to the intention-to-treat principle.

Altogether, we considered 16 studies to be at unclear risk for attrition bias. Of these, 13 studies provided no information about withdrawal rates. Cooper 1984 excluded three participants from its treatment group and four from the placebo group who were not included in the analysis. However, the paper does not report whether these exclusions were part of the asthma series and did not attempt to impute results for dropouts. One study (Radu 2007) was stopped after six months and also did not report dropout rates. Shao 2014 had a balanced and low dropout below 20% but did not include these data in the efficacy analysis.

We assessed nine studies (Alvarez-Cuesta 2007; Bousquet 1999; Criado Molina 2002; Marogna 2005; NCT00633919; Orefice 2004; Pajno 2000; Stelmach 2009; Wood 2014) as having high risk of bias in this domain because of high withdrawal rates and/or unbalanced dropout between treatment and control groups and/or because only completers were analysed. Orefice 2004 also excluded individuals with more severe asthma during the trial; however, it is not clear whether this was baseline exclusion or exclusion during the study.

Selective reporting

Only 14 studies reported all stated outcomes and were assessed as having low risk of reporting bias.

We considered six studies to be at unclear risk of reporting bias. The numerical reporting of Criado Molina 2002 was inconsistent, and data could not be included in the meta-analysis. Marcucci 2003 reported outcomes well (although mainly non-clinical) but did not report a trial registration to check whether all prespecified outcomes were included in the write-up. Pajno 2003 reported several outcomes narratively or gave 'ranges' of P values. Some discrepancies between reports appear to be related to the same participant group. All stated outcomes were reported in Rodriguez Santos 2004, but numerical data were not well presented; within-group outcomes were reported rather than comparisons with con-

trol. Wood 2014 and Zheng 2012 did not clearly report adverse event outcomes.

We assessed 32 included studies as having high risk of bias for this domain. Fourteen studies were provided only as conference abstracts, with minimal information and details regarding the conduct of the study as well as data that could not be meta-analysed. Fourteen studies did not report data for all outcomes, selectively reported outcome data or lacked numerical supporting data (Bousquet 1999; Calderon 2006; Cooper 1984; Corzo 2014 (a); Corzo 2014 (b); Eifan 2009; Gomez Vera 2005; Mosbech 2014; Mosges 2010; Mungan 1999; Pham-Thi 2007; Tian 2014; Wang 2014; Yukselen 2013). Most outcomes were reported with a level of statistical significance in only three studies (La Grutta 2007; Lewith 2002; Vourdas 1998) and could not be included in the meta-analysis. Although Marogna 2005reported all stated outcomes, several were provided only in graphical form or with inexact P values that also could not be meta-analysed.

Other potential sources of bias

We considered three studies as having other potential sources of bias. Alvarez-Cuesta 2007 had an unbalanced male-to-female ratio, and Radu 2007 was stopped after six months (planned for 36 months) because of statistically significant differences in outcomes that favoured the active treatment. Reilly 1994, a study of homeopathic SLIT, stated that "both doctors (homeopathic and asthma clinic doctor) could also veto any patient they considered unsuitable", which may have introduced bias.

Effects of interventions

See: **Summary of findings for the main comparison** SLIT vs control

Primary outcomes

Exacerbations requiring ED or hospital admission

Only one short study of 43 participants, involving four different SLIT dosing arms (Calderon 2006), included this outcome and reported no events during the four-week treatment period nor during the five- to six-week follow-up period (Analysis 1.1; low-quality evidence).

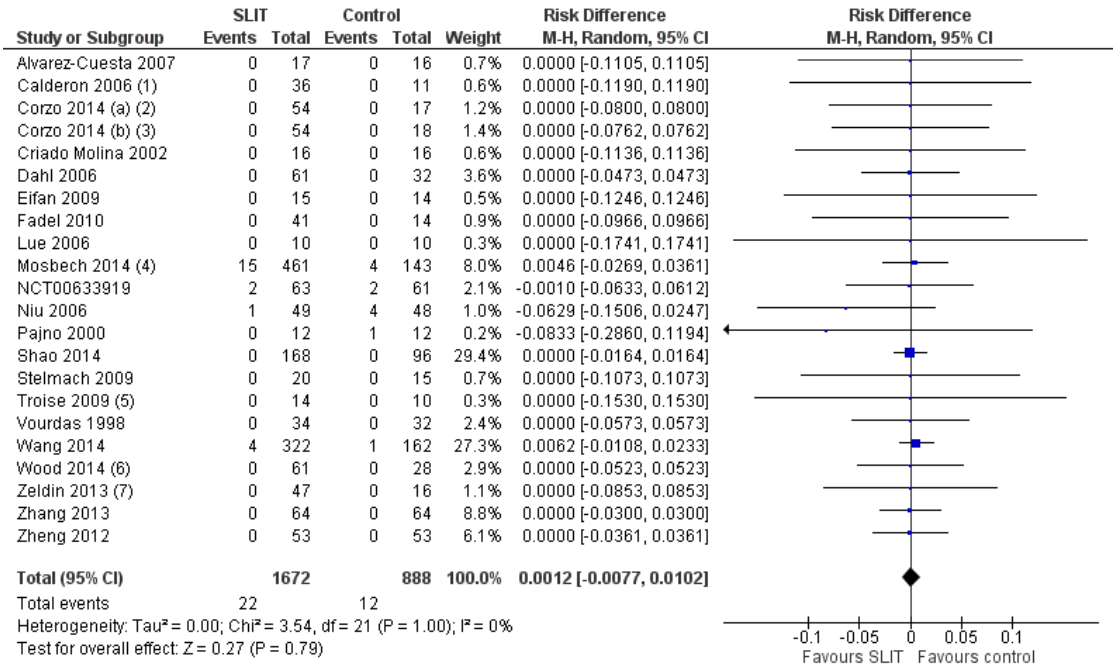
Quality of life

Quality of life (QoL) was a stated outcome in five included studies (Bousquet 1999; Inal 2009; Lewith 2002; Mosbech 2014; Pham-Thi 2007), but none presented data in a manner that allowed for meta-analysis. Bousquet 1999 reported increased QoL scores using the Short-Form Health Status Survey (not specific for asthma) in the SLIT group compared with the placebo group after 25 months of treatment, and improvements were statistically significant in several domains, including general mental health, general perception of health and physical pain. Inal 2009, a conference abstract, also reported significant improvement in QoL scores after two years of SLIT treatment when compared with placebo, but the scale used was not reported. Lewith 2002, a study of homeopathic SLIT versus placebo, reported asthma QoL using the 'asthma bother profile' and did not find a statistically significant difference between groups. Mosbech 2014 narratively and graphically reported the Asthma Quality of Life Questionnaire (AQLQ) after a year of SLIT treatment (including three different dosing arms) and did not find a statistically significant difference between active treatment and placebo. Finally, Pham-Thi 2007 assessed QoL using two forms of the Childhood Asthma Questionnaire (CAQ). The severity dimension showed statistically significant improvement in the SLIT group compared with the placebo group, but in all domains, average changes were not statistically different between groups. We have presented in Analysis 1.2 the numerical data extracted from Bousquet 1999 and Lewith 2002.

Serious adverse events

Occurrence of serious adverse events (SAEs) was a reported outcome for 22 included studies involving 2560 participants, but only five studies (Mosbech 2014; NCT00633919; Niu 2006; Pajno 2000; Wang 2014) observed any events. Although events were infrequent, analysis using risk differences (RDs) suggests that no more than one in 100 are likely to suffer an SAE as a result of treatment with SLIT (Figure 3; Analysis 1.3; RD 0.0012, 95% confidence interval (CI) -0.0077 to 0.0102; moderate-quality evidence).

Figure 3. Forest plot of comparison: 1 SLIT vs control, outcome: 1.3 Serious adverse events.



Footnotes
(1) 4 different dosing arms combined
(2) 4 different dosing arms combined
(3) 4 different dosing arms combined
(4) 3 different dosing arms combined
(5) "Severe" adverse events
(6) High dose and low dose combined
(7) 4 different dose arms combined

In total, 22 participants receiving SLIT and 12 in the control groups experienced an SAE. Mosbech 2014 reported that 15 participants receiving active treatment experienced an SAE: six in the 1 standard quality (SQ)-HDM group, three in the 3 SQ-HDM group and six in the 6 SQ-HDM group. Of these events, only two were deemed by investigators to be possibly related to SLIT and were described in detail: One was a case of migraine and the other dizziness. Four participants receiving placebo experienced an SAE. In NCT00633919, two participants receiving active treatment experienced an SAE (one road traffic accident and one femur fracture) and two in the placebo group (one perianal abscess and one a diagnosis of obsessive-compulsive disorder). Five participants experienced an SAE in Niu 2006 (one in the SLIT group and four in the control group), but these events were not further described. In Pajno 2000, a 'serious asthma attack' led to withdrawal of a participant from the control group. In Wang 2014, six SAEs occurred involving five participants (four in the SLIT group and one in the control group) and included a knee fracture, Arnold-Chiari Syndrome, contact dermatitis, ovarian cyst rupture, pneumonia and traumatic brain injury. None of these events were thought to be treatment-related, and none of the included studies reported any deaths.

Secondary outcomes

Asthma symptom scores

Most included studies (n = 42) reported asthma symptoms as an outcome, but a variety of often unvalidated scales were used and numerical data were not always presented. Details of the scoring systems used are presented in Analysis 1.8. We judged that a meta-analysis using standardised mean differences of those studies presenting numerical data would not be a sound methodological approach, and so the data extracted from the included studies are tabulated in Analysis 1.8 but were not meta-analysed. In summary, of those presenting numerical data, five studies found no

statistically significant differences in asthma symptom scores between groups (Bousquet 1999; Dahl 2006; Lewith 2002; Mungan 1999; Pham-Thi 2007). Alvarez-Cuesta 2007 reported a marked reduction in asthma symptoms during cat exposure for the SLIT group, with no significant improvement observed in the placebo group. Caffarelli 2000, Eifan 2009, Ippoliti 2003, Marogna 2005, Niu 2006, Pajno 2000, Reilly 1994, Stelmach 2009 and Zheng 2012 reported statistically significant reductions in asthma symptom scores in the SLIT group compared with the placebo group at the end of treatment. Cooper 1984 reports a 'small advantage' in favour of SLIT in number of days with asthma symptoms and in symptoms graded according to severity. Lue 2006 found improvements in both daytime and nighttime asthma symptom scores in the SLIT group, although the between-group difference for the former was not statistically significant.

Medication use scores

Similarly, 12 studies reported numerical medication use scores, which were frequently unvalidated aggregate scores including rescue medication use and use of inhaled corticosteroid (ICS) and oral corticosteroid (OCS). Details of the scoring systems used are presented in Analysis 1.9. Although medication scores were not a predefined outcome, as many of them incorporated ICS use (which was an outcome of interest), we extracted the data and have presented them, again without meta-analysis (Analysis 1.9). Seven studies did not find a statistically significant difference between medication use scores for SLIT and control groups at the end of treatment (Bousquet 1999; Dahl 2006; Lewith 2002; Lue 2006; NCT00633919; Niu 2006; Pham-Thi 2007). Four studies found a statistically significant difference favouring SLIT when compared with control in asthma medication scores at the end of treatment (Eifan 2009; Marogna 2005; Pajno 2000; Stelmach 2009). Mungan 1999 reports a statistically significant decrease from baseline in asthma medication scores in the SLIT group but no decrease in the control group.

Exacerbations requiring systemic corticosteroids

Both Calderon 2006 and Pajno 2003 included this outcome, but neither study observed any events (Analysis 1.4; low quality).

Response to provocation tests

Response to bronchial provocation using the methacholine challenge test was included as an outcome in 11 studies, and four (Keles 2011; Marogna 2005; Pajno 2003; Stelmach 2009) contributed to the meta-analysis. Marogna 2005 reported this outcome using provocative dose (PD)20 and the remaining studies provocative concentration (PC)20. Studies targeted a variety of allergens including HDM (n = 1), birch pollen (n = 1), *Parietaria* (n = 1) and grass pollen (n = 1). All four studies were at least a year in duration. Reilly 1994 reported change from baseline (rather than endpoint) $PC20_{log}$ and for this reason could not be reliably pooled with the other measures in the meta-analysis. This study reported a small benefit for homeopathic SLIT over placebo, which was not statistically significant.

Heterogeneity between the four studies that contributed to the meta-analysis was significant for response to bronchial provocation tests, and the confidence intervals were too wide to allow a clear judgement of SLIT benefit (Analysis 1.6; SMD 0.69, 95% CI -0.04 to 1.43; participants = 139; studies = 4; very low quality) with a high level of heterogeneity (I^2 = 76%). When a fixed-effect model was used to further investigate heterogeneity, the effect suggested a small benefit from SLIT (SMD 0.72, 95% CI 0.37 to 1.08). If Marogna 2005, the only study reporting PD20, was removed from the analysis, heterogeneity was somewhat lower (I^2 = 55%), but the pooled effect remained imprecise and was not statistically significant.

Required dose of ICS

Three studies (Bousquet 1999; Niu 2006; Pham-Thi 2007) reported ICS use numerically at the end of treatment: Bousquet 1999 in beclomethasone mcg/d, Pham-Thi 2007 in budesonide mcg/d (equivalent) and Niu 2006 in puffs/d. Differences between groups in puffs per day of ICS were not statistically significant (Niu 2006) at the end of treatment. We have not included these results in the meta-analysis. Although ICS use significantly decreased from baseline in both treatment and control groups in Bousquet 1999 and Pham-Thi 2007, pooling of ICS use at the end of treatment yielded an imprecise estimate with wide confidence intervals including the possibility of both benefit and harm from SLIT (Analysis 1.7; MD 35.10, 95% CI -50.21 to 120.42, low quality) with no heterogeneity (I^2 = 0%).

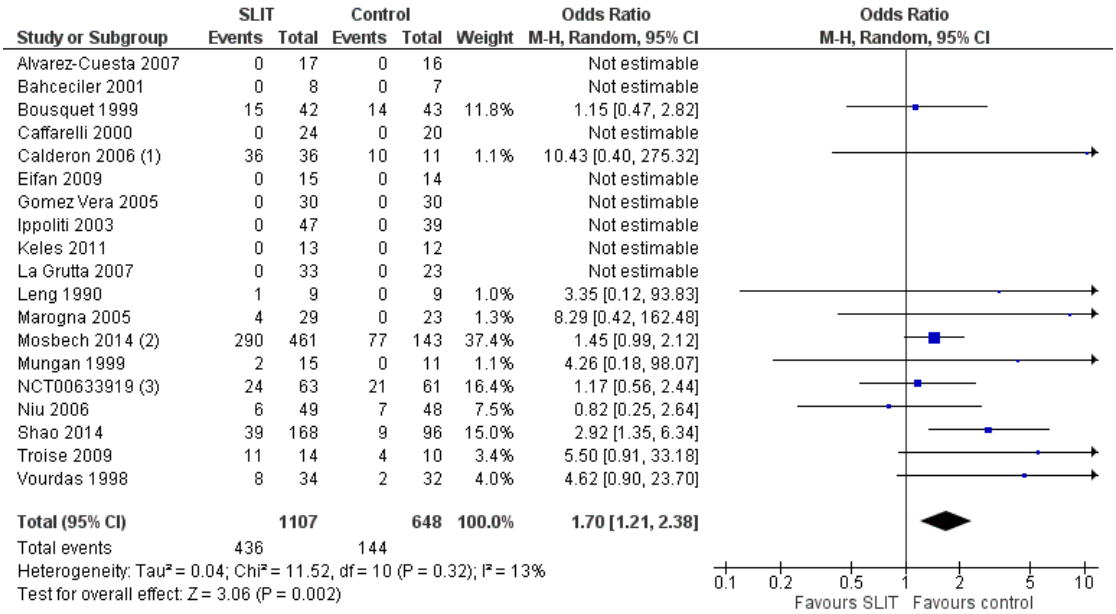
Both Mosbech 2014 and Virchow 2014 also assessed ICS reduction and reported that participants taking higher-dose SLIT treatment experienced a significant reduction in ICS use compared with those given placebo at the end of treatment, but neither study presented data in a way that allowed for meta-analysis.

All adverse events

In a change to the protocol and as a result of the infrequency of SAEs, we chose to include an analysis of all adverse events. We extracted data for *all* adverse events, not just those deemed to be treatment-related. Nineteen studies including 1755 participants reported all adverse events, and 11 contributed more than 500 events to the meta-analysis. Pooled results demonstrated increased risk of experiencing an adverse event in the SLIT group compared with the control group; this finding was statistically significant (Figure 4; Analysis 1.5; odds ratio (OR) 1.70, 95% CI 1.21 to 2.38; low quality) with a low level of heterogeneity (I^2 = 13%). This translates into an absolute increase from 222 per 1000 people in the control group to 327 per 1000 (257 to 404) and is presented

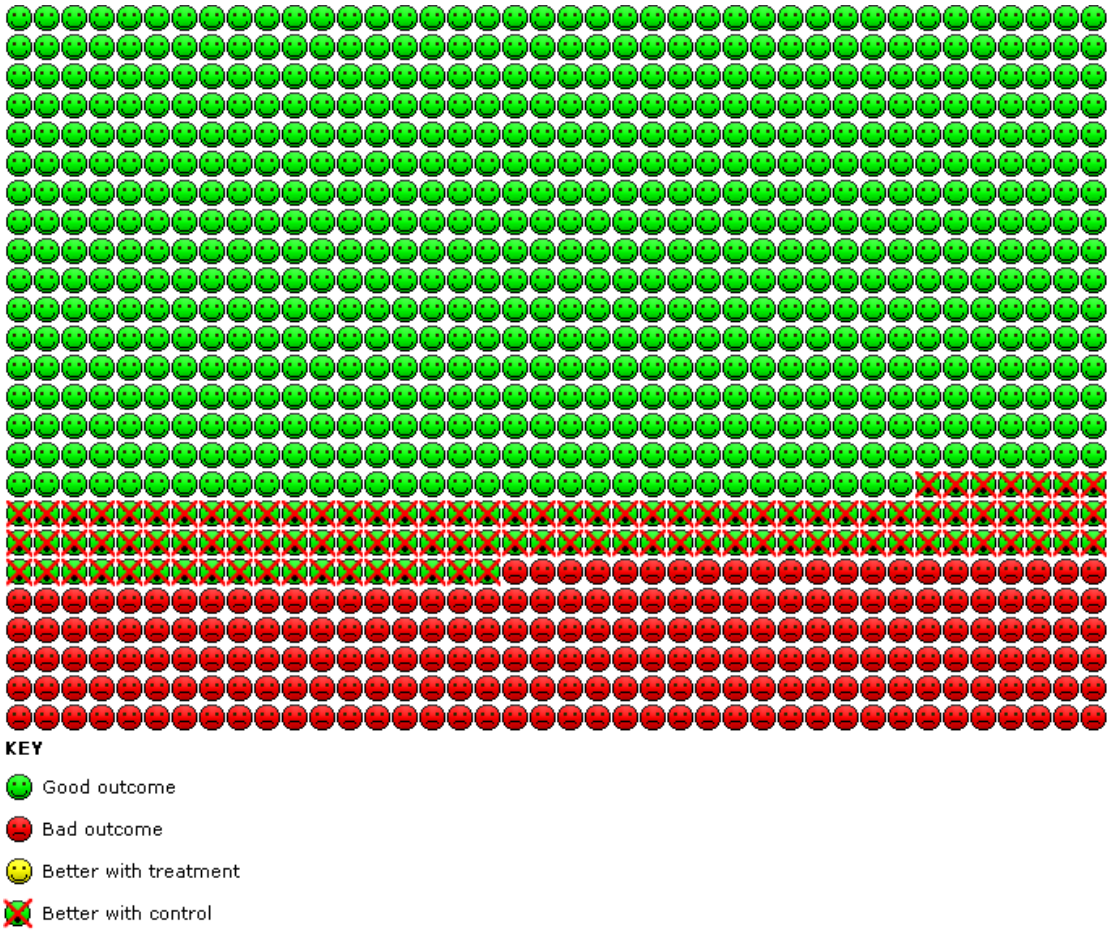
graphically in Figure 5 by way of a Cates' plot. However, most adverse events were reported to be mild and transient and rarely led to withdrawal from the trial.

Figure 4. Forest plot of comparison: 1 SLIT vs control, outcome: 1.5 All adverse events.



Footnotes
(1) 4 different dosing arms combined
(2) 3 different dosing arms combined
(3) Adverse events only reported if over 5% of participants were affected

Figure 5. Cates plot illustrating all adverse events (created at: www.nntonline.net)



Subgroup analyses

In a change to our protocol and as described above, we chose to perform subgroup analyses on adverse events, rather than serious adverse events, as so few data contributed to this primary outcome.

Participant age

We examined subgroups of children (mean participant age < 18) versus teenagers and adults (mean participant age ≥ 18) versus mixed age study populations or those for which the age range was not specified. The effect for adults and teenagers was more precise than for children because of the numbers of participants in the trials and the numbers of events observed in either group (Analysis 2.1; OR 1.48, 95% CI 1.06 to 2.06 vs OR 2.13, 95% CI 0.83 to 5.47), but results of tests for subgroup differences were not statistically significant (I^2 = 0%, P value = 0.72).

Target allergen

More than half of the included studies targeted SLIT at HDM (n = 34); the next most common target allergen was pollen (n = 13). We chose to examine the subgroups of HDM versus pollen versus other or mixed allergens; no events were observed in studies within the other or mixed allergen subgroup, so this subgroup did not contribute statistically to the analysis. Participants receiving HDM SLIT and pollen SLIT were more likely to experience adverse events than those in the control group (Analysis 2.2; OR 1.47, 95% CI 1.10 to 1.97 and OR 5.48, 95% CI 1.99 to 15.05), and results of the test for subgroup differences were statistically significant (P value = 0.01), suggesting that those receiving pollen SLIT experienced more adverse events than those receiving HDM

SLIT. However, we cannot conclude that this finding is a result of the different SLIT target allergen, as additional confounding between studies is likely.

Study duration

We chose to use a cutoff duration of less than 52 weeks versus 52 weeks or longer for this subgroup analysis. As we might expect, a smaller percentage of participants in the shorter studies experienced an adverse event during the study (Analysis 2.3; OR 1.53, 95% CI 0.38 to 6.19 vs OR 1.77, 95% CI 1.22 to 2.58), but results of tests for subgroup differences were not statistically significant (P value = 0.84), so we cannot draw any conclusions from this analysis about the interaction between study length and all adverse events.

Asthma severity

We did not perform the planned subgroup analysis according to baseline asthma severity as the majority of studies included participants with mild or intermittent symptoms, or did not describe baseline asthma severity in sufficient detail.

Sensitivity analyses

We chose to perform only two sensitivity analyses. First, we examined the effect of removing studies at high risk of performance or detection bias, or both, from the adverse events analysis. This analysis demonstrated a consistent direction of effect despite the removal of open-label and unblinded trials (Analysis 2.4; OR 1.47, 95% CI 1.10 to 1.96).

Second, we removed studies that recruited a mixed population of participants with asthma and rhinitis from the adverse event analysis. As above, this had minimal impact on the pooled effect (Analysis 2.5; OR 1.42, 95% CI 1.06 to 1.91).

DISCUSSION

Summary of main results

Fifty-two studies met our inclusion criteria, randomly assigning 5077 participants to comparisons of interest in this review. Most of the studies were double-blind and placebo-controlled, but studies varied in duration from just one day to three years. The largest study included 834 participants, and the smallest 15. Just over half were conducted in Europe (including Turkey), and half recruited children only. Participants with severe asthma were excluded from most of the included studies, resulting in a study population consisting largely of participants with intermittent or mild symptoms. With the exception of adverse events, reporting of meaningful clinical outcomes was generally poor. Only 22 studies contributed data to the primary outcome meta-analyses: 22 to the serious adverse events outcome (with only five contributing events) and one to the analysis of exacerbations requiring hospital visits (no events). Although five studies numerically reported quality of life outcomes, the data were not suitable for meta-analysis. This scarcity of evidence limits our ability to draw any conclusions about the effect of SLIT on exacerbations or quality of life. It would appear that SLIT is probably safe, at least in the population studied; although events were infrequent, analysis using risk differences suggests that no more than 1 in 100 are likely to suffer a serious adverse event as a result of treatment with SLIT.

Evidence from meta-analysis is again lacking for secondary outcomes. Although many studies reported asthma symptom scores, a variety of largely unvalidated scales were used, and a narrative synthesis of those studies presenting numerical data did not reveal a consistent effect. However, no study reported statistically significant worsening of asthma symptoms with active treatment.

Similarly, a narrative synthesis of asthma medication use scores did not reveal a consistent effect; some studies reported improvement and others no improvement. Asthma medication use scores were generally unvalidated aggregate scores including, for example, rescue medication use, ICS use and OCS use. Again, no study reported significantly increased asthma medication use in the SLIT group. We were able to pool reduction in ICS use from two studies, which reported this in micrograms per day; no difference was found between active treatment and control, with wide confidence intervals including the possibility of both benefit and harm from SLIT. Two studies reported exacerbations requiring OCS, but no events occurred.

Eleven studies reported response to bronchial provocation testing, and four contributed to the meta-analysis. The benefit of SLIT over control was not statistically significant, again with wide confidence intervals and a high level of heterogeneity.

All adverse events was not a prespecified outcome in our protocol, but we chose to extract these data because of the very infrequent occurrence of serious adverse events. Meta-analysis of 19 studies with 11 contributing more than 500 events revealed a significant increase in participants reporting an adverse event on active treatment compared with control. However, the clinical importance of these events is doubtful, as they were usually transient and mild and rarely prevented participants from continuing in the trial. In addition, inclusion of respiratory symptoms as adverse events may have masked or minimised differences between groups, as an expected benefit of SLIT would be *reduction* of these symptoms.

Subgroup analysis of all adverse events according to participant age and study duration did not reveal significant subgroup differences. Findings suggest that those receiving SLIT for pollen allergy may experience more adverse events than those receiving SLIT for HDM allergy. Similarly, sensitivity analysis excluding those studies at high risk of performance and detection bias did not significantly alter this outcome.

Overall completeness and applicability of evidence

Despite identifying 52 unique studies that met our inclusion criteria, we were able to perform a very limited meta-analysis. Fourteen of our included studies were reported as abstracts only and therefore provided minimal numerical data. Use of largely unvalidated symptom and medication scores also impeded quantitative synthesis of findings. Although a pooled analysis of composite asthma symptom and medication use scores using standardised mean differences would have been possible, we considered this approach to be not methodologically sound and believed it might result in misleading conclusions. We decided to include exacerbations, serious adverse events and quality of life as our primary outcomes, as these have been identified as important to people with asthma (Busse 2012; Sinha 2012). However, we recognise that this decision is also a limitation of this review, as most study participants had intermittent or mild persistent asthma and therefore were unlikely to be experiencing frequent exacerbations. In addition, we recognise that although treatment-related adverse events are important in immunotherapy, risk of attribution bias is present if trialists are making this judgement, and unanticipated treatment-related adverse events might not be identified. For this reason, we chose to include all-cause adverse events.

Insufficient data contributing to the meta-analysis also restricted potential subgroup analyses, resulting in difficulties in reaching any conclusions about SLIT efficacy in different age groups, for different allergens or for different treatment durations. As only a small minority of studies (n = 3) reported outcomes during post-treatment follow-up, we cannot comment in this review on the lasting benefits of SLIT for asthma.

The position of both SCIT and SLIT as potential therapeutic options for asthma has yet to be clearly established within international asthma guidelines. The Global Initiative for Asthma Guidelines (GINA 2014) state that the efficacy of allergen immunotherapy for asthma is limited, and that potential benefits of immunotherapy must be weighed against risk of adverse reactions, cost and duration of treatment. The UK guidance adopts a similar position and does not routinely recommend immunotherapy for asthma in adults or children (BTS/SIGN 2014). The organisation that advises the National Health Service (NHS) in the UK on cost-effective treatments (the National Insitiute of Clinical Excellence - NICE) currently does not provide guidance on asthma therapies. The British National Formulary states that "desensitising vaccines should generally be avoided or used with particular care in patients with asthma" because of the risk of life-threatening adverse events (BNF), and indeed both SCIT and SLIT are absolutely contraindicated in patients with severe or uncontrolled asthma (Slovick 2014). However, somewhat at odds with this, US Guidelines for the Diagnosis and Management of Asthma (NAEPP 2007) state that immunotherapy (SCIT) should be considered only in patients for whom standard pharmacological methods are insufficient (which implies that symptoms are not well controlled) and for whom a clear relationship between allergen exposure and symptoms is not evident. A more recent task force report in the USA (Cox 2011) further supports this by stating that "candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures", but does go on to specify that asthma must be controlled at the time of immunotherapy administration. Cox 2011 also highlights the investigational nature of SLIT in the USA at the time of the report and conflicting available evidence regarding its benefits. Until last year, no Food and Drug Admiistration (FDA) approval had been provided for any SLIT products in the USA; the first SLIT product ('Oralair') was approved in April 2014 for the treatment of allergic rhinitis (FDA Press Release 2014).

In the light of all information provided above, the applicability of our findings is somewhat limited, as most participants recruited to the studies included in this review had mild or intermittent symptoms, and so would not be likely candidates for immunotherapy for their asthma symptoms, at least according to current guidance (BTS/SIGN 2014; Cox 2011; GINA 2014; NAEPP 2007). Many of the included studies stated that participants must have a positive skin prick test or serum-specific IgE to the allergen in question, but investigators did not necessarily specify that asthma symptoms must be linked to allergen exposure, again raising doubts about the appropriateness of the study populations. In addition, patterns of allergen sensitisation and association with asthma may vary geographically, limiting the generalisability of the findings of this review, given that most of the included studies were conducted in Europe (ISAAC 1998).

Quality of the evidence

We assessed the quality of the evidence presented in this review using GRADEpro software and present this information in Summary of findings for the main comparison. Overall, evidence was assessed to be of moderate, low or very low quality, and evidence was downgraded for several reasons. Heterogeneity varied across individual outcomes, ranging from I^2 = 0% for decrease in ICS use and serious adverse events to I^2 = 76% for bronchial provocation.

We assessed evidence on exacerbations requiring ED visit or hospital admission and exacerbations requiring OCS to be of low quality. Neither outcome had any contributory events, and these outcomes were reported by very few studies (n = 1, Calderon 2006 for exacerbations requiring ED/hospital admission; n = 2 for exacerbations requiring OCS, Calderon 2006 and Pajno 2003). In addition, Calderon 2006 was a short study of just four weeks' duration, during which differences in rare events, such as exacerbations, might not be detected. The small number of studies reporting this outcome might also represent a publication bias.

We did not assess the quality of evidence for the quality of life outcome, as no study contributed numerical data to this outcome.

We assessed evidence for serious adverse events and all adverse events to be of moderate quality. We downgraded quality to reflect risk of performance and detection bias in contributing studies and mixed study populations including patients with asthma, rhinitis or both. Recruiting a 'mixed' population may have resulted in a population of patients with very mild and intermittent asthma symptoms, leading to concerns that adverse events might be under-represented compared with those expected in a study population including participants with a diagnosis of more severe asthma.

We also assessed evidence for reduction in use of ICS to be of low quality. Only two studies contributed to the meta-analysis (Bousquet 1999; Pham-Thi 2007). We downgraded the evidence for imprecision and possible publication bias. Both studies reported a statistically significant decrease from baseline ICS use in both treatment and control groups with no intergroup differences at the end of the treatment period.

Finally, we assessed evidence for bronchial provocation to be very low in quality. Only four studies (Keles 2011; Marogna 2005; Pajno 2003; Stelmach 2009) contributed to this analysis. We were required to use standardised mean difference (SMD) analyses to combine PD20 and PC20 data, and we found that levels of heterogeneity and imprecision were high, as was risk of performance and detection bias, in two of the contributing studies.

Potential biases in the review process

We conducted this review in accordance with established Cochrane standards. Two review authors independently screened search results and resolved discrepancies by discussion and, if necessary, consultation with a third person. We did not restrict the search by language and as a result included four studies published in languages other than English (three in Spanish and one in Chinese). We attempted to contact study authors when it was not clear whether a study met our inclusion criteria. We may have missed some unpublished data as, owing to the large number of manufacturers, we did not search individual manufacturers' trial registers for possible included studies.

At least two review authors extracted all study characteristics and numerical data and resolved discrepancies through discussion. The same was true for risk of bias ratings. In a change to our protocol, and as a result of the large number of included studies (14 of which were abstracts), we did not attempt to contact study authors to clarify methodological and outcome information, relying instead on what was presented in the report.

We adapted the protocol in two other ways that may have introduced bias. First, we had not anticipated how many studies had recruited mixed populations of patients with rhinitis 'and/or' asthma. As outcomes for participants with asthma were rarely presented separately, we had to make a pragmatic decision as to whether or not to include these studies. We decided, after consultation with a third person, to include studies in which at least 80% of participants had received a diagnosis of asthma. If this was not clear from the report, we attempted to contact study authors to confirm this. We excluded these 'mixed population' studies from the sensitivity analysis for adverse events, although this exclusion did not substantially alter the outcome.

Second, we had not planned to extract outcome data for all adverse events, instead opting to include the more clinically important serious adverse events as a primary outcome. So few serious adverse events were reported that we decided to extract all adverse events additionally. Analysis of this additional post hoc outcome was the only analysis with enough data to allow exploratory analyses with subgroups, and so these results should be interpreted with caution.

None of the review authors have reported conflicting interests.

Agreements and disagreements with other studies or reviews

Several published systematic reviews have addressed the question of whether SLIT is effective and safe in asthma (Calamita 2006; Compalati 2009; Lin 2013; Penagos 2008; Tao 2014) and have reached somewhat conflicting conclusions. Tao 2014 reported findings from 16 double-blind placebo-controlled trials that randomly assigned 794 participants with asthma. Lin 2013 is a systematic review that reported on SLIT for allergic rhinoconjunctivitis and asthma but without a formal meta-analysis. This review synthesised findings from 63 studies, including 5131 participants. Calamita 2006 included 25 studies that randomly assigned 1706 participants. Penagos 2008, a systematic review of SLIT for allergic asthma in children three to 18 years of age, included nine studies assessing 441 participants. Compalati 2009 reported the findings of nine double-blind placebo-controlled studies of SLIT for allergic asthma that assessed 452 study participants.

All four meta-analyses used SMD to meta-analyse composite asthma symptom scores. Compalati 2009, Penagos 2008 and Tao 2014 reported a statistically significant reduction in asthma symptoms favouring SLIT, but with a high level of heterogeneity ($I^2 \geq$ 90%). Calamita 2006 reported a statistically significant 'general improvement' in asthma, but this conclusion appears to have been reached from a combined analysis of asthma symptoms, need for reliever medication, lung function tests and lung hyper-reactivity. Study authors reported improvement in asthma symptoms alone when data were analysed using SMDs, but this finding did not reach statistical significance. Lin 2013 narratively reported improvement in asthma symptoms favouring SLIT in all placebo-controlled studies included in the review and rated the strength of this evidence as 'high'.

Similarly, all four meta-analyses reported composite asthma medication use scores. Compalati 2009, Penagos 2008 and Tao 2014 reported a statistically significant reduction in medication scores favouring SLIT, but again using an SMD analysis and with high heterogeneity ($I^2 \geq$ 90%). Calamita 2006 found no statistically significant differences between groups in asthma symptom scores. Lin 2013 narratively reported benefit of SLIT over control in 40

out of 41 studies that reported medication use scores but did not present findings for asthma separately from those for rhinoconjunctivitis.

Calamita 2006, Tao 2014 and Penagos 2008 reported adverse events and, consistent with our findings, observed very few serious events. Tao 2014 concluded that participants receiving SLIT experience more adverse events overall than those receiving placebo, but that most of these events were considered to be mild in severity, again in keeping with our findings. Lin 2013 concluded that adverse events were insufficiently reported to allow further comment on the safety of SLIT.

None of the four meta-analyses included quality of life or exacerbations as a prespecified primary or secondary outcome. Lin 2013 found that validated disease-specific quality of life was reported in only eight of the 63 studies included in the review; half reported a statistically significant benefit of SLIT over control, but none of these eight studies met our inclusion criteria.

In contrast to the meta-analyses described above, and as per our protocol, we chose not to combine different, unvalidated symptom and medication scores in a meta-analysis. We believe that heterogeneity across measurements would lead to a potentially misleading outcome. As in Lin 2013, we reported these findings only narratively.

In Nieto 2009, review authors evaluated five meta-analyses of SLIT for respiratory disease and recommended that as a result of discrepancies, inconsistencies and lack of robustness in the included meta-analyses, evidence at that time did not support its use. Similarly, Incorvaia 2010 presented an overview on the position of SLIT for treatment of allergic asthma and called for additional research to resolve conflicting results.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings are consistent with the current international position that SLIT should not be prescribed routinely for the treatment of asthma alone. Lack of studies reporting important outcomes such as exacerbations and quality of life and use of different, unvalidated symptom and medication scores have reduced the quality of the evidence presented in this review, thus limiting the conclusions that we can reach. However, at least in this study population (largely comprising participants with mild and moderate asthma), SLIT does appear to be relatively free from serious adverse events, although participants receiving SLIT are more likely to experience any adverse event than those in the control group. This finding supports continued use of SLIT for people with other respiratory allergies, such as allergic rhinitis, who may also have well-controlled mild to moderate asthma.

Implications for research

Further research using validated scales such as the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire would be greatly beneficial for future meta-analyses and would increase confidence in the quality of the evidence. In addition, inclusion of participants with more severe asthma might result in studies reporting less frequent, but nonetheless, important events such as exacerbations requiring oral corticosteroids or hospital visits. Larger trials with explicit reporting of serious adverse events would increase our confidence regarding the safety of SLIT in patients with asthma.

ACKNOWLEDGEMENTS

Thank you to Elizabeth Stovold for help with the search strategy and to Chris Cates and Emma Welsh for advice and support provided.

Jimmy Chong was the Contact Editor for the review and commented critically on the review. We thank Jimmy Chong for his comments.

We thank Dr Hendrik Nolte and Prof Vesna Tomic Spiric for confirming that two studies did not meet our inclusion criteria.

We are very grateful to Samantha Lowry, Zhi Hui Chang, Julia Bidonde, Miguel Maldonado Fernandez, Alejandro Chavez-Badiola and Uwe Wollina for their excellent translations of included studies.

The Background and Methods sections of this review are based on a standard template used by the Cochrane Airways Group.

The National Institute for Health Research (NIHR) is the largest single funder of the work of the Cochrane Airways Group. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the NIHR, the NHS or the Department of Health.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Almarales 2012

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 52 weeks **Setting:** Cuba
Participants	**Population:** 120 participants randomly assigned to HDM SLIT group or placebo group (n for each group not reported) **Age:** not reported **Inclusion criteria:** asthmatic symptoms and a positive predominant skin prick test to *D. pteronyssinus, D. siboney* and *Blomia tropicalis* house dust mites **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT daily for 3 weeks then twice weekly until 12 months. Maintenance dose 2000 BU **Co-interventions:** not reported
Outcomes	Symptoms/medication diary cards, PEFRs, skin sensitivity to investigated mites, adverse reactions
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled

Almarales 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals not reported
Selective reporting (reporting bias)	High risk	Conference abstract only. Data not consistently reported and could not be included in meta-analysis
Other bias	Low risk	None noted

Alvarez-Cuesta 2007

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 52 weeks **Setting:** Spain
Participants	**Population:** 50 participants randomly assigned to cat dander SLIT group (25) and placebo group (25) **Age:** 14 to 55 years; mean age 29.1 (7.4) years in SLIT group and 27.8 (7.3) years in placebo group **Inclusion criteria:** positive clinical history of respiratory allergic symptoms related to cat exposure and mono-sensitisation to cat allergens; positive skin prick test to a standardised cat dander extract (wheal $\geq$ 7 mm) and specific IgE to cat dander **Exclusion criteria:** use of immunotherapy during the past 5 years and any contraindication for the immunotherapy according to criteria of the European Allergy and Clinical Immunology Immunotherapy Subcommittee **Percentage withdrawn:** 32% withdrawal from cat dander SLIT group and 36% withdrawal from placebo group **Percentage with asthma:** 81.8% **Co-morbidities:** persistent moderate to severe rhinitis **Allowed medication:** antihistamines, local corticosteroids (nasal and bronchial budesonide), nedocromil and salbutamol **Disallowed medication:** beta-blockers
Interventions	**Control group:** placebo SLIT **SLIT group:** cat dander SLIT once daily. Total accumulated dose 17.1 mcg **Co-interventions:** not reported
Outcomes	Exposure to cat in a cat room scoring symptoms (conjunctival, nasal and bronchial symptoms), PEF values, skin reactivity, adverse events
Notes	**Type of publication:** peer reviewed **Funding:** Laboratorios LETI, S.L., Tres Cantos, Madrid, Spain

Risk of bias

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

Alvarez-Cuesta 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	'Randomised' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - "At the end of the study and when the code was opened", "the qualitative and quantitative composition of the placebo was identical to the experimental product, but without the active ingredients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind - "At the end of the study and when the code was opened"
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was high (32% and 36% in active and placebo groups, respectively), and these participants were not included in the descriptive or efficacy data
Selective reporting (reporting bias)	Low risk	All stated outcomes reported, although non-parametric tests used (appropriately), so unable to use in meta-analysis
Other bias	Unclear risk	Unbalanced male/female ratio

Bahceciler 2001

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial, 8-week run-in period **Duration:** 26 weeks **Setting:** outpatient clinics at 1 hospital, Turkey
Participants	**Population:** 15 participants randomly assigned to HDM SLIT group (8) or placebo group (7) **Age:** 7 to 18 years; median age 12.4 (range 7.8 to 18) years and 12 (range 7.3 to 15) years in placebo group **Inclusion criteria:** require ICS for control of asthma symptoms, positive skin prick test to *D. farinea* and *D. pteronyssinus* plus negative response to all other aero-allergens tested, older than 7 years, ongoing respiratory symptoms in spite of mite avoidance measures and appropriate ICS treatment, FEV_1 greater than 70% of predicted **Exclusion criteria:** not reported **Percentage withdrawn:** 0% withdrawal in both HDM SLIT group and placebo group **Percentage with asthma:** 100% **Co-morbidities:** rhinitis **Allowed medication:** SABA, ICS, intranasal steroids **Disallowed medication:** not reported

Bahceciler 2001 (*Continued*)

Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT daily for 4 weeks then twice weekly for 4 months. Average cumulative dose 7000 IR **Co-interventions:** ICS
Outcomes	Symptom scores, use of rescue beta$_2$-mimetics, compliance with ICS and intranasal steroid therapy, skin prick test, lung function test, methacholine bronchial challenge test, serum total IgE level
Notes	**Type of publication:** peer reviewed **Funding:** Say Tip and Stallergenes supplied *D. pteronyssinus* and *D. farinea* extract and placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - code not broken until after 6 months of treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind - code not broken until after 6 months of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Low risk	None noted

Bousquet 1999

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial; 4- or 8-week run-in period **Duration:** 108 weeks **Setting:** France
Participants	**Population:** 85 participants randomly assigned to HDM SLIT group (42) and placebo group (43) **Age:** 7 to 42 years; mean age 21 (10) years in SLIT group and 22 (10) years in placebo group **Inclusion criteria:** at least 1-year history of moderate or moderately severe asthma due to

Bousquet 1999 (*Continued*)

	HDM, diagnosis based on clinical history, positive skin tests using standardised extracts and the presence of specific IgE as shown by RAST (with class 2 as a cutoff), FEV_1 > 70% predicted **Exclusion criteria:** sensitisation to *Alternaria* or *Cladosporium*, sensitisation to animal danders if animals were present in the home, received immunotherapy to mite in previous 2 years; using oral or parenteral steroids (more than 15 consecutive days), intramuscular steroids, ICS (> 1000 mcg/d), inhaled $beta_2$-agonists (> 4 times/d) and/or oral $beta_2$-agonists or methylxanthines **Percentage withdrawn:** 45.24% withdrawal from HDM SLIT group and 37.21% withdrawal from placebo group **Percentage with asthma:** 100% **Co-morbidities:** rhinitis **Allowed medication:** ICS up to 1000 mcg/d, 'rescue medication' **Disallowed medication:** oral or parenteral corticosteroids for more than 15 consecutive days, depot steroids, ICS dose > 1000 mcg/d BDP, SABA use more than 4 times/d, oral beta-agonists, methylxanthines, immunotherapy for mite in the previous 2 years
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT once daily initially then decreasing to three times per week for 24 weeks. Maintenance dose 20 drops of 300 IR/mL 3 times a week **Co-interventions:** usual medication
Outcomes	Diary card, asthma severity, vital capacity, FEV_1, PEFR, methacholine bronchial challenge, QoL, assessment of mite exposure, drug consumption, blood IgE and IgG4
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	High risk	45% attrition in treatment group, 37% in placebo group (but all included in safety analysis)

Bousquet 1999 (*Continued*)

Selective reporting (reporting bias)	High risk	Selective reporting of QoL outcomes
Other bias	Low risk	None noted

Caffarelli 2000

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial **Duration:** 13 weeks and 9 weeks post-treatment follow-up **Setting:** outpatient clinic in Parma, Perugia and Brescia, Italy
Participants	**Population:** 48 participants randomly assigned to grass pollen tablet group (24) and placebo group (24) **Age:** 4 to 14 years; mean age 8.7 (3.3) years in SLIT group and 8.1 (2.7) years in placebo group **Inclusion criteria:** had rhinitis and/or conjunctivitis and/or bronchial asthma in the grass pollen season, serum grass-specific IgE antibodies, positive skin prick test with grass pollens including pollens contained in extracts for immunotherapy **Exclusion criteria:** Sensitisations to allergens other than grass pollens (mites, pellitory, cat and dog dander, birch, mugwort, *Alternaria* and *Aspergillus*) were excluded on the basis of clinical symptoms and negative skin prick test reactions; also, those with perennial asthma and/or rhinitis who had received specific immunotherapy in the 3 years before the beginning of the present study were excluded, as well as those undergoing treatment with systemic steroids and those with contraindications for immunotherapy of the European Academy of Allergy and Clinical Immunology (EAACI) **Percentage withdrawn:** 0% withdrawal from grass pollen tablet group and 16.67% withdrawal from placebo group **Percentage with asthma:** 89.6% **Co-morbidities:** rhinitis and/or conjunctivitis **Allowed medication:** ;local (both nasal sprays and eye drops) or systemic antihistamines, inhaled beta$_2$-agonists, ICS, theophylline **Disallowed medication:** not reported
Interventions	**Control group:** placebo tablet **SLIT group:** grass pollen tablet (33% *Holcus lanatus*, 33% *Phleum pratense* and 33% *Poa pratensis*) 3 times per week. Cumulative dosage 37,250 AU **Co-interventions:** usual medication
Outcomes	Symptom and medication diary cards, adverse events, nasal levels of ECP
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomly assigned by a computer generated list"

Caffarelli 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% completion in intervention group, > 80% completion in placebo group
Selective reporting (reporting bias)	Low risk	All stated outcomes reported, but non-parametric tests appropriately used, so not possible to meta-analyse
Other bias	Low risk	None noted

Calderon 2006

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial **Duration:** 4 weeks and 5 or 6 weeks post-treatment follow-up **Setting:** unclear
Participants	**Population:** 43 participants randomly assigned to grass pollen SLIT group 1 (9), grass pollen SLIT group 2 (9), grass pollen SLIT group 3 (9), grass pollen SLIT group 4 (5) and placebo group (11) **Age:** 18 to 65 years; mean age 22.1 (3.2) years in grass pollen SLIT group 1, 23.2 (2.8) years in grass pollen SLIT group 2, 28.0 (9.5) years in grass pollen SLIT group 3, 25.8 (5.5) years in grass pollen SLIT group 4 and 24.5 (5.5) years in placebo group **Inclusion criteria:** clinical history of significant grass pollen-induced allergic rhinoconjunctivitis and mild to moderate grass pollen-induced asthma of 2 years or longer; well-controlled seasonal asthma in accordance with British Thoracic Society criteria; positive skin prick test and specific IgE to *Phelum pratense* **Exclusion criteria:** significant asthma outside the grass pollen season; FEV_1 < 70% of predicted value; significant allergic rhinitis (requiring medication) caused by allergens other than grass pollen during the planned treatment period; conjunctivitis, rhinitis or asthma at screening or randomisation visits; history of anaphylaxis; immunosuppressive treatment; hypersensitivity to excipients of trial medication or of rescue medication; received immunotherapy with grass pollen allergen within the previous 10 years or any other allergen within the previous 5 years; pregnancy or lactation **Percentage withdrawn:** 0% withdrawal from all groups **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** reliever medication **Disallowed medication:** not reported

Calderon 2006 (*Continued*)

Interventions	**Control group:** placebo SLIT **SLIT group 1:** grass pollen SLIT (*Phelum pratense*) once daily. Dose 75,000 SQ-T **SLIT group 2:** grass pollen SLIT (*Phelum pratense*) once daily. Dose 150,000 SQ-T **SLIT group 3:** grass pollen SLIT (*Phelum pratense*) once daily. Dose 300,000 SQ-T **SLIT group 4:** grass pollen SLIT (*Phelum pratense*) once daily. Dose 500,000 SQ-T **Co-interventions:** not reported
Outcomes	FEV_1, PEF, adverse events, medication use
Notes	**Type of publication:** peer reviewed **Funding:** ALK-Abelló A/S, Denmark

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	High risk	No clinical data reported, just says 'No clinically significant changes were observed in FEV1 or PEF values during the trial period'
Other bias	Low risk	None noted

Cooper 1984

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration**: > 8 but < 16 weeks, 10 weeks post-treatment follow-up **Setting:** outpatient allergy/respiratory clinic, UK
Participants	**Population:** 19 participants randomly assigned to grass pollen SLIT group (11 completed) and placebo group (8 completed) **Age:** 5 to 15 years; mean age not reported **Inclusion criteria:** seasonal symptoms poorly controlled on conventional therapy, pos-

	itive allergen test to mixed grass pollen solution **Exclusion criteria:** received oral hyposensitisation within 3 years of enrolment, took oral steroids with 1 year of enrolment **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (in asthma series presented separately) **Co-morbidities:** hayfever **Allowed medication:** antihistamines, sodium cromoglycate, topical steroids, salbutamol, aminophylline, ICS **Disallowed medication:** OCS
Interventions	**Control group:** placebo SLIT **SLIT group:** grass pollen SLIT (12 grass pollens (B2 grasses, Bencard)) once daily decreasing to twice per week for maintenance. Dose not reported **Co-interventions:** usual medication
Outcomes	Adverse events, peak flow, symptom diary cards, medication usage, respiratory infection, days taken off school
Notes	**Type of publication:** peer reviewed **Funding:** Beechams Research Laboratory

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified before random allocation - no further details given
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double-blind study' with 'matched placebo'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double-blind study' with 'matched placebo'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 grass pollen SLIT patients and 4 placebo patients were excluded from the study and were not included in the analysis. Study authors do not report whether these exclusions were part of the hayfever or asthma series and did not attempt to impute results for dropouts
Selective reporting (reporting bias)	High risk	Some stated outcomes were not reported at all in the paper (e.g. school absence) or were not reported for asthma and hayfever

Cooper 1984 (*Continued*)

		separately (e.g. adverse events)
Other bias	Low risk	None noted

Corzo 2014 (a)

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 4 weeks **Setting:** UK and Denmark; phase 1 clinical trials unit
Participants	**Population:** 71 participants randomly assigned to HDM SLIT group 1 (9), HDM SLIT group 2 (9), HDM SLIT group 3 (9), HDM SLIT group 4 (9), HDM SLIT group 5 (9), HDM SLIT group 6 (9) and placebo group (17) **Age:** 18 to 65 years; mean age range 25 to 32 years across arms **Inclusion criteria:** clinical history of HDM-induced mild to moderate asthma of at least 1 year before trial entry; use of appropriate medications for control of asthma symptoms (in accordance with GINA guideline); positive specific IgE (≥ class 2) and positive skin prick test (wheal diameter ≥ 3 mm) to *D. pteronyssinus* or *D. farinae* **Exclusion criteria:** history of severe asthma within the past 2 years; history of anaphylaxis **Percentage withdrawn:** 0% withdrawal from groups 1 to 4; 11.1% withdrawal from group 5; group 6 (32 DU) discontinued before end of trial because of severe adverse event in 1 participant **Percentage with asthma:** 100% **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group 1:** HDM SLIT once daily. Dose 1 DU **SLIT group 2:** HDM SLIT once daily. Dose 2 DU **SLIT group 3:** HDM SLIT once daily. Dose 4 DU **SLIT group 4:** HDM SLIT once daily. Dose 8 DU **SLIT group 5:** HDM SLIT once daily. Dose 16 DU **SLIT group 6:** HDM SLIT once daily. Dose 32 DU (discontinued before end of trial) **Co-interventions:** not applicable
Outcomes	Adverse events (according to MedDRA, lung function (FEV_1 and PEFR), physical and oral examination, laboratory safety assessments and immunological measurements
Notes	**Type of publication:** peer reviewed **Funding:** ALK

Risk of bias

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

Corzo 2014 (a) (*Continued*)

Random sequence generation (selection bias)	Unclear risk	'Participants were allocated to 6 dosage groups and randomised 3:1 to active or placebo' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled; 'active and placebo were identical in appearance, smell, and taste'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled; 'active and placebo were identical in appearance, smell, and taste'
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 withdrawal in this trial (from the 16 DU group) due to occurrence of oedema under the tongue and itching throat, but the 32 DU group discontinued because of a severe AE
Selective reporting (reporting bias)	High risk	Lung function and laboratory results not reported numerically. Adverse events not reported in a way that allows meta-analysis (only those occurring in > 5% and numbers of events rather than participants affected reported)
Other bias	Low risk	None noted

Corzo 2014 (b)

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 4 weeks **Setting:** 4 centres, Spain; 'specialised allergy centre'
Participants	**Population:** 72 participants randomly assigned to HDM SLIT group 1 (9), HDM SLIT group 2 (9), HDM SLIT group 3 (9), HDM SLIT group 4 (9), HDM SLIT group 5 (9), HDM SLIT group 6 (9) and placebo group (18) **Age:** 5 to 14 years; mean age range 7.9 to 10.6 years across arms **Inclusion criteria:** clinical history of HDM-induced mild to moderate asthma of at least 1 year before trial entry; use of appropriate medications for control of asthma symptoms (in accordance with GINA guideline); positive specific IgE (≥ class 2) and positive skin prick test (wheal diameter ≥ 3 mm) to *D. pteronyssinus* or *D. farinae* **Exclusion criteria:** history of severe asthma within the past 2 years; history of anaphylaxis **Percentage withdrawn:** 0% withdrawal from all groups **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinoconjunctivitis

Corzo 2014 (b) (*Continued*)

	Allowed medication: not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group 1:** HDM SLIT once daily. Dose 0.5 DU **SLIT group 2:** HDM SLIT once daily. Dose 1 DU **SLIT group 3:** HDM SLIT once daily. Dose 3 DU **SLIT group 4:** HDM SLIT once daily. Dose 6 DU **SLIT group 5:** HDM SLIT once daily. Dose 9 DU **SLIT group 6:** HDM SLIT once daily. Dose 12 DU **Co-interventions:** not applicable
Outcomes	Adverse events (according to MedDRA, lung function (FEV_1 and PEFR), physical and oral examination, laboratory safety assessments and immunological measurements
Notes	**Type of publication:** conference abstract **Funding:** ALK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Participants were allocated to 6 dosage groups and randomised 3:1 to active or placebo' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled; 'active and placebo were identical in appearance, smell, and taste'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled; 'active and placebo were identical in appearance, smell, and taste'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	High risk	Lung function and laboratory results not reported numerically. Adverse events not reported in a way that allows meta-analysis (only those occurring in > 5% and numbers of events rather than participants affected reported)
Other bias	Low risk	None noted

Criado Molina 2002

Methods	**Design:** randomised, parallel, open-label, pharmacotherapy-controlled trial **Duration:** 52 weeks **Setting:** Allergy and Immunology Unit, Spain
Participants	**Population:** 44 children were randomly assigned to *Alternaria* SLIT (22) and placebo (22) **Age:** 18 to 65 years **Inclusion criteria:** clinical history compatible with asthma and/or fungus-induced rhinoconjunctivitis; *Alternaria* alternate specific sensitisation/sensitivity alone or in combination with pollen and/or epithelia shown by IgE and positive prick test; positive bronchial provocation test with *Alternaria* extract **Exclusion criteria:** systemic immunological disease; severe atopic dermatitis; severe asthma for which daily medication was needed; corticoid long-term treatment; yeast/fungus/mould extract treatment in the past 2 years **Percentage withdrawn:** 27.3% in each group **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinoconjunctivitis
Interventions	**Control group:** pharmacotherapy only **SLIT group:** *Alternaria* SLIT, 3 times per week as maintenance at 29,848 PNU/mo (mean accumulated dose was 280,000 PNU) **Co-interventions:** not reported **Allowed medication:** green zone: loratadine 5 to 10 mg/24 h or Budesonida 100 to 200 mcg/24 h (taken only if nasal symptoms persisted after loratadine was taken); yellow zone: terbutaline sulfate 0.5 to 1 mg/6 to 8 h. If not returning to green zone, add Budesonide 200 to 400 mcg/12 h; red zone: terbutaline sulfate double dose and add deflazacort ¼ mg/kg **Disallowed medication:** not reported
Outcomes	Symptom medication score, skin prick, bronchial challenge test, peak flow, total and specific IgE and IgG4
Notes	**Type of publication:** peer reviewed, original publication in Spanish (duplicate translation) **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

Criado Molina 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Apparently high dropout but not clearly reported and no participant flow diagram
Selective reporting (reporting bias)	Unclear risk	Numerical reporting inconsistent and not possible to include data in meta-analysis
Other bias	Low risk	None noted

Dahl 2006

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration**: 19.5 weeks (mean 84 days preseasonal exposure, 53 days seasonal exposure) **Setting:** Denmark and Sweden
Participants	**Population:** 114 participants were randomly assigned to Timothy grass SLIT group (74) or placebo group (40) **Age:** 18 to 65 years; mean age 36.5 (SLIT) years and 34.1 (placebo) years **Inclusion criteria:** age 18 to 65; clinical history of significant grass pollen-induced allergic rhinoconjunctivitis and mild to moderate grass pollen-induced asthma of 2 years or longer; well-controlled seasonal asthma in accordance with GINA guideline; positive skin prick test and specific immunoglobulin E to *Phleum pratense* **Exclusion criteria:** significant asthma outside the grass pollen season; FEV_1 < 70% of predicted value; significant allergic rhinitis (requiring medication) caused by allergens other than grass during the planned treatment period; conjunctivitis, rhinitis or asthma at screening or randomisation visits; history of anaphylaxis; immunosuppressive treatment; hypersensitivity to excipients of trial medication or rescue medication; received immunotherapy with grass pollen allergen within the previous 10 years or any other allergen within the previous 5 years; pregnancy **Percentage withdrawn:** SLIT 10.9%, placebo 9.9% **Percentage with asthma:** 100% **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** loratadine 10 mg once daily, levocabastine eye drops (0.5 mg/mL; 1 drop in each eye twice daily), Budesonide nasal spray (up to 32 mcg; 2 puffs per nostril twice daily), prednisolone (up to 50 mg once daily), salbutamol (200 mcg per inhalation; 1 to 2 inhalations twice daily), fluticasone (250 mcg per inhalation; 1 to 2 inhalations twice daily) **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** Timothy grass (*Phleum pratense*) GRAZAX tablet 75,000 SQ-T once daily **Co-interventions:** not reported

Dahl 2006 (*Continued*)

Outcomes	Average daily asthma medication and symptom scores before and during the grass pollen season, average daily rhinoconjunctivitis symptom and medication scores during the grass pollen season
Notes	**Type of publication:** peer reviewed **Funding:** ALK-Abello A/S, Denmark

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double-blind', placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double-blind', placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	10% dropout in both groups
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Low risk	None noted

Eifan 2009

Methods	**Design:** randomised, open-label, parallel, pharmacotherapy-controlled trial **Duration:** 52 weeks **Setting:** 1 paediatric allergy centre in Istanbul, Turkey
Participants	**Population:** 48 children were randomly assigned to house dust mite SLIT (16), usual pharmacotherapy (16) and 1 other treatment that was not relevant to this review (subcutaneous immunotherapy, 16) **Age:** 5 to 10 years; mean age 6.5 (SLIT) years and 7.6 (placebo) years **Inclusion criteria:** 5 to 10 years of age, suffering from mild persistent asthma/rhinitis according to GINA guidelines, having HDM-related asthma/rhinitis symptoms, strictly mono-sensitised to *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* as confirmed by a positive skin prick test and HDM specific IgE level greater than or equal to 0. 35 IU/mL, who were prospectively followed up and received inhaled/intranasal steroids for at least 2 years with no reduction of symptoms **Exclusion criteria:** systemic immunological disorders, severe asthma with FEV_1 < 70%,

	severe atopic dermatitis, previous use of allergen immunotherapy **Percentage withdrawn:** SLIT 6.25%, placebo 12.5% **Percentage with asthma:** 85% (41/48) **Co-morbidities:** rhinitis **Allowed medication:** rescue medications, inhaled/intranasal corticosteroids, antihistamines and oral steroids **Disallowed medication:** not reported
Interventions	**Control group:** usual pharmacotherapy only **SLIT group:** house dust mite SLIT (*D. pteronyssinus* and *D. farinae*), cumulative 1-year dose ~ 73,876.8 SU (standard units) **Co-interventions:** not reported
Outcomes	Symptom score diary for asthma and rhinitis symptoms, medication use, VAS symptom score, skin prick testing, nasal provocation tests, lung function test, methacholine challenge and immunoglobulin E levels, peripheral blood mononuclear cell isolation and detection of secreted cytokines
Notes	**Type of publication:** peer reviewed **Funding:** The Marmara University Scientific Research Committee

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Using a computer-generated randomisation method"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	'Open-label'
Blinding of outcome assessment (detection bias) All outcomes	High risk	'Open-label'
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% attrition in treatment group, 12% in control group
Selective reporting (reporting bias)	High risk	Data for several outcomes (lung function, bronchial hyper-reactivity, skin prick test, blood markers) were not reported in full (i.e. significance only), and others and other data were reported only in graphical form
Other bias	Low risk	None noted

Fadel 2010

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** not reported **Setting:** university hospital, Syria
Participants	**Population:** 55 participants randomly assigned to grass pollen SLIT group (41) and placebo group (14) **Age:** 18 to 50 years; mean age not reported **Inclusion criteria:** 18 to 50 years with allergic asthma due to grass pollens **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** grass pollen SLIT, dose progression phase then 3 times per week. Dose 2400 IR **Co-interventions:** not applicable
Outcomes	Symptoms, medication scores, global assessment of efficacy
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no specific details about sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - no specific details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind - no specific details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract only. No useable numerical data and minimal details regarding the conduct of the study

Other bias	Low risk	None noted

Gomez Vera 2005

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 26 weeks **Setting:** regional hospital allergy clinic in Mexico
Participants	**Population:** 60 participants were randomly assigned to SLIT (30) and placebo (30) **Age:** 13 to 45 years; mean age 21.4 (whole population) years **Inclusion criteria:** mild and moderate persistent asthma, according to clinical and spirometry criteria (GINA); differences in pre and post FEV_1 salbutamol spirometry equal to or greater than 14%; age between 13 and 45 years; prick test and intradermal skin tests positive to *Dermatophagoides pteronyssinus*; total IgE higher than 200 IU **Exclusion criteria:** other diseases that might alter results; diagnosed by chest, paranasal sinus and oesophageal x-rays; exacerbation of asthma that needed oral steroids **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** Salbutamol and antihistamines were used as rescue treatment. For mild persistent asthma, ICS were NOT used. For moderate asthma, ICS at doses recommended by GINA were included **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** house dust mite SLIT (*D. pteronyssinus*), cumulative dose of 10,469 UBE. 710 UBE 3 times/wk **Co-interventions:** conventional pharmacological treatment
Outcomes	Spirometry before and after salbutamol (FEV_1), secondary effects, number of asthma crises admitted to Emergency Department, rescue treatment with salbutamol, inhaled steroids or systemic steroids, asthma symptoms (requested from participants every month), lack of ability to carry out daily tasks, night symptoms
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details

Gomez Vera 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - no specific details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind - no specific details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Not all outcomes reported and few numerical data presented
Other bias	Low risk	None noted

Hanna 2013

Methods	**Design:** prospective, randomised, placebo-controlled trial **Duration:** 13 weeks **Setting:** not reported
Participants	**Population:** 60 participants were randomly assigned to house dust mite SLIT (30), placebo (15) and 1 other treatment that was not relevant to this review (subcutaneous immunotherapy, 15) **Age:** no details **Inclusion criteria:** allergic asthma to *D. farinae* **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** house dust mite SLIT (*D. farinae*), maintenance dose 5 drops of 10 BU/mL 3 times a week **Co-interventions:** not reported
Outcomes	Symptoms, medication scores and *D. farinae* specific IgE, IL-4, IL-10 and IFN-gamma
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

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

Hanna 2013 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	'No mention of blinding'; 'prospective, randomised 3 parallel groups'
Blinding of outcome assessment (detection bias) All outcomes	High risk	'No mention of blinding'; 'prospective, randomised 3 parallel groups'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract, no full paper. Minimal study characteristics and no useable data
Other bias	Low risk	None noted

Inal 2009

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 52 weeks **Setting:** Turkey
Participants	**Population:** 32 participants were randomly assigned to house dust mite SLIT and placebo (unclear how many in each group) **Age:** no details **Inclusion criteria:** mite allergic children with asthma and rhinitis **Exclusion criteria:** not reported **Percentage withdrawn:** 6.7% overall (not given per group); 93% (28/30) completed the study **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinitis **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** house dust mite SLIT (dosing not stated) **Co-interventions:** not reported
Outcomes	Symptom scores, medication scores, VAS scores, QoL
Notes	**Type of publication:** conference abstract **Funding:** not reported

Inal 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomization to treatment groups was based on disease severity assessed with symptom score for rhinitis and asthma in the baseline year, gender and age'. Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy but no specific details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy but no specific details
Incomplete outcome data (attrition bias) All outcomes	Low risk	93% (28/30) completed the study
Selective reporting (reporting bias)	High risk	Minimal study information or data presented in the abstract, and only P values provided
Other bias	Low risk	None noted

Ippoliti 2003

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 26 weeks (with 3-month run-in) **Setting:** Italy
Participants	**Population:** 86 participants were randomly assigned to house dust mite SLIT (47) and placebo (36) **Age:** 5 to 12 years; median age of 9 in both groups **Inclusion criteria:** children 5 to 12 years old, history of mild/moderate asthma, positive skin prick test with wheal diameter > 5 mm to house dust mites (HDM) (*D. pteronyssinus*) and specific IgE to HDM at least of class 3, FEV_1 greater than 70% **Exclusion criteria:** positive skin test to other inhalant allergens, clinical history of other allergies such as seasonal asthma due to pollens, history of immunotherapy in the previous year or severe asthma **Percentage withdrawn:** 0% SLIT, 0% placebo **Percentage with asthma:** 100% **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** drugs for relief of symptoms, if needed, for no more than 7

	consecutive days: inhaled steroids (200 mcg/puff, 2 to 4 puffs) and inhaled salbutamol (250 mcg/puff, 1 to 3 puffs) on demand **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** house dust mite SLIT (*D. pteronyssinus*), maintenance dose 5 drops of 10 BU/mL 3 times a week **Co-interventions:** not reported
Outcomes	Daily symptom scores on diary cards, clinical evaluation, FEV_1, CD40 count, serum ECP, IL-13, PRL and ACTH
Notes	**Type of publication:** peer reviewed **Funding:** Grant MURST, 1998

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - no specific details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind - no specific details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Low risk	None noted

Karakoc-Aydiner 2011

Methods	**Design:** parallel, pharmacotherapy-controlled trial **Duration:** 156 weeks (3 years) **Setting:** unclear
Participants	**Population:** 31 participants were randomly assigned to house dust mite SLIT (9), pharmacotherapy only (10) and one other treatment that was not relevant to this review (subcutaneous immunotherapy, 12)

	Age: children; mean age 10.0 (SLIT) years and 7.5 (pharmacotherapy) years **Inclusion criteria:** children with mild to moderate persistent asthma **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** usual pharmacotherapy only **SLIT group:** house dust mite SLIT (dosing not reported) **Co-interventions:** not reported
Outcomes	Total symptom scores, total medication scores, visual asthma score, skin reactivity and laboratory outcomes including allergen-induced IL-4, IL-5, IL-13, IFN-gamma, IL-10, LI-17 and TGF-beta
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of blinding; assume open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract, no full paper. Minimal study characteristics and no useable data
Other bias	Low risk	None noted

Keles 2009

Methods	**Design:** parallel, pharmacotherapy-controlled trial **Duration:** 17.3 weeks **Setting:** unclear
Participants	**Population:** 53 participants were randomly assigned to HDM SLIT (15), pharmacotherapy only (12) or to 2 other treatments not relevant to this review **Age:** not reported **Inclusion criteria:** children with mild to moderate asthma **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** Usual pharmacotherapy only **SLIT group:** HDM SLIT. Dosing not reported **Co-interventions:** Not reported
Outcomes	Symptom and medication scores, lung function tests, skin-prick tests, bronchial and nasal provocation tests and allergen-induced cytokine response (IL-5, IL-10, IL-13, TGF-beta and IFN-gamma)
Notes	**Type of publication:** Conference abstract **Funding:** Nor reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of blinding; assume open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop out not reported
Selective reporting (reporting bias)	High risk	Conference abstract, no full paper. Minimal study characteristics and no useable data

Keles 2009 (*Continued*)

Other bias	Low risk	None noted

Keles 2011

Methods	**Design:** parallel, pharmacotherapy-controlled trial (8-week run-in period) **Duration:** 52 weeks (26 weeks post-treatment follow-up) **Setting:** pediatric allergy and immunology outpatient clinic, Turkey
Participants	**Population:** 58 participants randomly assigned to HDM SLIT group (15), to pharmacotherapy only group (15) or to 2 other treatment arms not relevant to this group **Age:** 5 to 12 years; mean age 8.6 (2.1) years in HDM SLIT group and 7.9 (2.8) years in pharmacotherapy group **Inclusion criteria:** children (5 to 12 years) with mild persistent/moderate asthma/rhinitis according to Global Initiative for Asthma guidelines, mono-sensitised to HDM, received inhaled/intranasal steroids for at least 2 years with no reduction in symptoms **Exclusion criteria:** not reported **Percentage withdrawn:** HDM SLIT 13.3%, pharmacotherapy 20% **Percentage with asthma:** 100% (from abstract methods) **Co-morbidities:** rhinitis **Allowed medication:** rescue medications (beta$_2$-agonists and antihistamines) as needed and ICS or intranasal corticosteroids in a stepwise fashion depending on persistence and severity of symptoms **Disallowed medication:** not reported
Interventions	**Control group:** usual pharmacotherapy only **SLIT group:** HDM SLIT 1-month induction phase followed by maintenance of 5 drops 3 times a week. 1.5 mg and 52.8 mg of *D. pteronyssinus* (Der p1) and 1.5 mg and 52.8 mg of *D. farinae* (Der f1) **Co-interventions:** not reported
Outcomes	Medications, symptoms, visual analogue scale (VAS) score, number of asthma attacks, dose of ICS and side effects, total serum and allergen-specific IgE, allergen-specific IgG4, IL-5, IL-13, INF-gamma, IL-10, TGF-beta and IL-17
Notes	**Type of publication:** peer reviewed **Funding:** Marmara University Scientific Research Committee

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"By using the table randomisation method patients were randomised into one of 4 parallel groups"
Allocation concealment (selection bias)	Unclear risk	No details

Keles 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of blinding; assume open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Relatively low and balanced dropout; 13% withdrawal in treatment group, 20% in control group
Selective reporting (reporting bias)	Low risk	All stated outcomes reported numerically or narratively but not possible to include data in meta-analysis
Other bias	Low risk	None noted

La Grutta 2007

Methods	**Design:** 'randomised', open-label, parallel, pharmacotherapy-controlled trial **Duration:** 52 weeks **Setting:** Italy
Participants	**Population:** 56 participants randomly assigned to HDM/*Parietaria* SLIT group (33) and pharmacotherapy only (23) **Age:** HDM/*Parietaria* SLIT group 15.4 (mean) years, 8 to 44 (range) years, pharmacotherapy only group 21.8 (mean) years, 7 to 68 (range) years **Inclusion criteria:** mild persistent asthma with/without intermittent moderate rhinitis, sensitised to HDM **Exclusion criteria:** systemic or immunological disease, major anatomical alterations of the upper airways, renal insufficiency, coronary heart disease, neurological or psychiatric, receiving long-term corticosteroid or beta-blocking treatments, pregnant women, no bronchial hyper-reactivity, no nasal inflammation **Percentage withdrawn:** 0% from both groups **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinitis **Allowed medication:** on demand rescue medication for short periods; cetirizine 10 mg, $beta_2$-agonist 100 mcg 2 puffs, intranasal fluticasone 50 mcg 1 spray per nostril, short course of systemic steroid if severe symptoms unresponsive to standard treatment; 50 mg prednisolone for 3 days **Disallowed medication:** long-term corticosteroid and/or beta-blockers
Interventions	**Control group:** usual pharmacotherapy only **SLIT group:** HDM/*Parietaria* SLIT initiation phase then twice/wk. Dose 1000 AU **Co-interventions:** not reported

La Grutta 2007 (*Continued*)

Outcomes	Symptom scores, medication use, adverse events, bronchial provocation tests, nasal eosinophilia
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated to allergoid SLIT or pharmacotherapy according to a computer-generated list with an active-controlled ratio of 3:2
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Placebo not used, active comparison of pharmacotherapy. No mention of outcome assessor blinding for some outcomes, but nasal eosinophils were done by a blinded operator (not involved in the clinical study) who counted the various inflammatory cells
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	High risk	Several outcomes were reported only with a significance level and could not be included in the meta-analysis
Other bias	Low risk	None noted

Leng 1990

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 7.14 weeks (13 weeks post-treatment follow-up) **Setting:** unclear
Participants	**Population:** 18 participants randomly assigned to *Artemisia* pollen SLIT group (9) and placebo group (9) **Age:** 15 to 56 years; *Artemisia* pollen SLIT group mean 34.8 years, placebo group mean 36.2 years

	Inclusion criteria: Participants had to be in good health, history of asthma in the *Artemisia* pollination season, positive skin prick and bronchial provocation test to *Artemisia*, FEV_1 at least 80% predicted **Exclusion criteria:** previous immunotherapy to grass pollen extract in the preceding 5 years **Percentage withdrawn:** 0% in both groups **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** hayfever **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT (Coca's solution) **SLIT group:** *Artemisia* pollen SLIT daily up-dosing to a maximum of 16416 PNU. Cumulative dose 396,652.06 PNU **Co-interventions:** not reported
Outcomes	Bronchial provocation test, serum-specific IgE, adverse events
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, specifically mentions blinding of participants and assessors. 'The color and amounts [of SLIT and placebo] ingested of these two solutions were the same. The patients were not informed of the contents of the oral solutions'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, specifically mentions blinding of participants and assessors. 'The color and amounts [of SLIT and placebo] ingested of these two solutions were the same. The patients were not informed of the contents of the oral solutions'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Low risk	All stated outcomes reported

Leng 1990 (*Continued*)

Other bias	Low risk	None noted

Lewith 2002

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial **Duration:** 16 weeks **Setting:** 38 general practices in Hampshire and Dorset, UK
Participants	**Population:** 242 participants randomly assigned to homeopathic HDM SLIT group (122) and placebo group (120) **Age:** 18 to 55 years; homeopathic HDM SLIT group mean 38.2 (9) years, placebo group mean 37.9 (10.4) years **Inclusion criteria:** positive result to house dust mite (wheal diameter > 3 mm > negative control 15 minutes after test) that was greater than for other aero-allergen extracts tested, considered to have asthma if > 15% improvement in FEV_1 or PEF 15 minutes after 200 mcg inhalation of salbutamol before randomisation and 2 of 3 criteria of an asthma symptom diary score > 1 on at least 7 of the 14 baseline days during run-in period or diurnal variation in PEF > 15% on at least 7 of the 14 baseline days or a need for inhaled salbutamol on at least 7 of the 14 baseline days **Exclusion criteria:** recorded no impairment in quality of life in diaries during their run-in period or filled in fewer than 10 out of 14 days, took part in another drug trial in the preceding 30 days, had previously been treated with homeopathic immunotherapy, were pregnant or lactating, were unlikely to comply with trial requirements, had a respiratory infection in the preceding 3 weeks, changed their concurrent medication in the two weeks before entry **Percentage withdrawn:** homeopathic HDM SLIT group 17.2%, placebo group 15.8% **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** no changes made to background medications **Disallowed medication:** Participants requiring OCS were withdrawn from the study
Interventions	**Control group:** placebo SLIT **SLIT group:** homeopathic HDM SLIT administered on 3 occasions over 24 hours. Dose 30 dilutions of 1:100 **Co-interventions:** usual medication
Outcomes	Questionnaires on negative and positive trait mood and quality of life specific to asthma (the asthma bother profile), PEF, perceived asthma severity on a VAS, perceived mood on a bipolar scale, bronchodilator consumption
Notes	**Type of publication:** peer reviewed **Funding:** Smith's Charity, NHS Executive South and West Research and Development Directorate, Boiron, Maurice Laing Foundation

Risk of bias

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

Lewith 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	First 10 randomly allocated using sealed envelopes followed by randomisation by minimisation according to age, sex, smoking status and asthma severity
Allocation concealment (selection bias)	Low risk	First 10 randomly allocated using sealed envelopes followed by randomisation by minimisation according to age, sex, smoking status and asthma severity
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomisation codes broken only after study completed. 'The indistinguishable preparations'. 'As a check for blinding, one day after randomisation we asked participants and investigators to guess whether the treatment was homeopathic immunotherapy or placebo'. 'Neither participants nor investigators were better than chance at guessing treatment (114 (47%) participants and 116 (48%) investigators guessed correctly)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation codes broken only after study completed. 'The indistinguishable preparations'. 'As a check for blinding, one day after randomisation we asked participants and investigators to guess whether the treatment was homeopathic immunotherapy or placebo'. 'Neither participants nor investigators were better than chance at guessing treatment (114 (47%) participants and 116 (48%) investigators guessed correctly)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced dropout (17% in homeopathy group and 16% in placebo group), but all participants were followed up
Selective reporting (reporting bias)	High risk	Several outcomes were reported only with a significance level or visually in line graphs and data could not be included in the meta-analysis
Other bias	Low risk	None noted

Lue 2006

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial **Duration:** 24 weeks (2 weeks post-treatment follow-up) **Setting:** Outpatient Clinic of the Pediatric Allergy and Immunology Division of Chung-Shan Medical University Hospital, Taiwan
Participants	**Population:** 20 participants randomly assigned to HDM SLIT group (10) and placebo group (10) **Age:** 6 to 12 years; HDM SLIT group mean 7.7 (1.8) years and placebo group mean 8. 6 (1.8) years **Inclusion criteria:** at least 1-year histories of mildly persistent to moderately persistent asthma, sensitised to HDM only. Diagnosis was based on clinical history, positive skin tests and presence of specific IgE (3+, as detected by MAST CLA allergen testing). Children were enrolled only if their FEV_1 was greater than 70% of predicted value and their reversibility of PEFR exceeded 15% after administration of an inhaled b_2-agonist **Exclusion criteria:** sensitive to any other airborne allergens by standardised prick test or specific IgE; received prior immunotherapy; treated with oral or parenteral corticosteroids (> 15 consecutive days), ICS at dosage greater than 1000 mcg/d (beclomethasone dipropionate) and inhaled $beta_2$-agonists more than 4 times per day; contraindications to specific allergen immunotherapy (e.g. immunodepression, autoimmune disease, progressive nephropathy, malignancy of any organ system) **Percentage withdrawn:** 0% for both groups **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** ICS (Pulmicort Turbuhaler), inhaled $beta_2$-agonist (Bricanyl Turbuhaler) and OCS (prednisolone, 5 mg) **Disallowed medication:** oral or parenteral corticosteroids (> 15 consecutive days), ICS at dosage greater than 1000 mcg/d (beclomethasone dipropionate) and inhaled $beta_2$-agonists more than 4 times per day
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT daily with 3 week initiation phase. Maximum 20 drop dose of 300 IR/mL. Cumulative dose of 41,824 IR **Co-interventions:** not reported
Outcomes	Asthma symptom scores, medication scores, PEFR, skin prick test, lung function tests, serum total IgE, ECP, eosinophil count, mite-specific IgE and IgG4, adverse events
Notes	**Type of publication:** peer reviewed **Funding:** Stallergenes provided the Staloral used in this study. "This study did not receive any support from the pharmaceutical industry"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Enrolled and randomly assigned" - no further details
Allocation concealment (selection bias)	Unclear risk	No details

Lue 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, no specific details. Placebo was given 'in the same glycerosaline diluents'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, no specific details. Placebo was given 'in the same glycerosaline diluents'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Low risk	All stated outcome reported
Other bias	Low risk	None noted

Marcucci 2003

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 52 weeks **Setting:** Italy
Participants	**Population:** 24 children were randomly assigned to house dust mite SLIT (13) and placebo (11) **Age:** 4 to 16 years; mean age 7.7 (SLIT) years and 7.3 (placebo) years **Inclusion criteria:** eligible for the study if mono-sensitised to HDMs, with a clinical history of at least 2 years of rhinitis and/or asthma related to perennial allergens **Exclusion criteria:** no previous specific immunotherapy treatment **Percentage withdrawn:** 0 **Percentage with asthma:** 84.6% (SLIT), 81.8% (placebo) **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** oral antihistamines, nasal corticosteroids, ICS, cromolyn and salbutamol **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT (*D. pteronyssinus* and *D. farinea*) daily with 3 week initiation phase, maximum 20 drop dose of 300 IR (cumulative dose 41,824 IR) **Co-interventions:** not reported
Outcomes	ECP and tryptase in sputum, nasal and serum mite-specific IgE, nasal ECP, allergen-specific nasal challenge
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

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

Marcucci 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	'Randomised by means of a computer-generated code'. 'The randomisation key followed did not allow for a good balancing for gender between groups but we believe that this had little or no effect on the final outcomes'
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial. 'The placebo treatment had the same composition and presentation of the active treatment'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial. Placebo was given 'in the same glycerosaline diluents'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	Mainly non-clinical outcomes, but well reported. Did not report trial registration to check whether all prespecified outcomes were included in the write-up
Other bias	Low risk	None noted

Marogna 2005

Methods	**Design:** 'randomised', open-label, parallel, pharmacotherapy-controlled trial **Duration:** 156 weeks with 52 weeks post-treatment follow-up **Setting:** Outpatient Allergy Unit, Cuasso al Monte Hospital, Varese, Italy
Participants	**Population:** 79 (enrolled) participants were randomly assigned to birch pollen SLIT group (39) and pharmacotherapy only group (40) **Age:** 18 to 65 years; birch pollen SLIT group mean 27.8, pharmacotherapy only group mean 29.0 **Inclusion criteria:** clinical history of rhinitis with or without mild intermittent or persistent asthma due to birch pollen in the past 2 years; positive skin prick test response (> 5 mm) and positive CAP-RAST assay result (class III or greater) for birch pollen only; age between 18 and 65 years; FEV_1 within normal limits (> 79% of predicted value) **Exclusion criteria:** sensitised to other common inhalant allergens, moderate persistent asthma, anatomic abnormalities of the upper respiratory tract, long-term treatment with systemic steroids, malignancies, systemic immunological disorders During the study, participants with onset of nasal eosinophilia, bronchial hyperreactivity out of the pollen season or new sensitisations **Percentage withdrawn:** birch pollen SLIT group 25.6%, pharmacotherapy only group

	42.5% **Percentage with asthma:** 100% **Co-morbidities:** rhinitis **Allowed medication:** All participants received the following continuous pharmacological treatment during pollen seasons: cetirizine or loratadine (10 mg once daily) and nasal cromolyn (10 mg/d). Inhaled salbutamol (2 puffs) on demand for asthma attacks. Intranasal beclomethasone dipropionate, 2 puffs per nostril twice daily (400 mg/d) by physician prescription only if poor response to antihistamines and cromolyn **Disallowed medication:** In birch season, participants were advised to discontinue use of intranasal nasal steroids (if any) at least 10 days before the nasal scraping
Interventions	**Control group:** usual pharmacotherapy only **SLIT group:** birch pollen SLIT initiation phase of 50 days then daily for 3 years. Dose was reduced by one-third during the pollen season. Cumulative dose of 102 mcg per year **Co-interventions:** none reported
Outcomes	Symptom scores (nasal itching, sneezing, rhinorrhoea, nasal obstruction, cough, wheezing and eye itching-redness), medication use, lung function tests, methacholine challenge, nasal eosinophils
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	25% dropout from treatment group, 42% from control group; only completers were analysed
Selective reporting (reporting bias)	High risk	All stated outcomes reported but several only in graphical form or with inexact P values (i.e. not in a format that could be meta-analysed)

Other bias	Low risk	None noted

Mosbech 2014

Methods	**Design:** block randomised, parallel, double-blind, placebo-controlled trial **Duration:** 52 weeks **Setting:** 81 centres in Denmark, Germany, Italy, Spain, United Kingdom, Sweden, France and Poland
Participants	**Population:** 604 participants randomly assigned to HDM SLIT group 1 (146), HDM SLIT group 2 (159), HDM SLIT group 3 (156) and placebo group (143) **Age:** 14 years and above (mean age/age range not reported but across groups 6% were reported to be adolescents) **Inclusion criteria:** 14 years of age or older with controlled (based on ACQ score), mild to moderate (steps 2 and 3 in GINA 2002 Guideline), HDM-allergic asthma of at least 1 year duration requiring ICS use (100 to 800 mg/d) and mild to severe HDM-allergic rhinitis, positive diagnostic test results to HDM (i.e. skin prick tests with wheal size > 3 mm to *D. farinae, D. pteronyssinus* or both and specific IgE test results against *D. farinae* extract, *D. pteronyssinus* extract or both) > CAP class 2 and documented history of reversible airway obstruction **Exclusion criteria:** FEV_1 < 70% of predicted value with appropriate medication; clinical history of allergy with symptoms to a perennial allergen or a seasonal allergen causing symptoms in the pretreatment ICS adjustment and/or stable periods; clinical history of severe asthma within the past 2 years before enrolment; immunotherapy with HDM allergen within previous 5 years before randomisation; concurrent or previous (within the past 6 months before randomisation) immunotherapy with other allergens than HDM; history of anaphylactic shock or angio-oedema **Percentage withdrawn:** SLIT group 1 10%, SLIT group 2 16%, SLIT group 3 10%, placebo group 12% **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** allergic rhinitis **Allowed medication:** Before treatment initiation, use of ICS was standardised and tapered to the lowest dose providing asthma control. Symptomatic medication was provided as rescue medication to all **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group 1:** HDM SLIT 1 DU daily **SLIT group 2:** HDM SLIT 3 DU daily **SLIT group 3:** HDM SLIT 6 DU daily **Co-interventions:** ICS
Outcomes	Reduction in ICS dose, FEV_1, PEF, exacerbation frequency, asthma control questionnaire, asthma QoL questionnaire, adverse events, withdrawals
Notes	**Type of publication:** peer-reviewed **Funding:** ALK-Abello, Denmark, assumed overall responsibility for the trial and has been involved in both trial design and conduct

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomization was performed in blocks of 8 by the sponsor by using the SAS system for Windows which generates random assignment of treatment groups to randomization numbers. The randomization list was generated by a trial-independent statistician, and the list was reviewed by another trial-independent person'
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets (active and placebo) were manufactured and provided by the sponsor and were oral lyophilisates, containing standardised extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in a 1:1 ratio or a placebo that was similar in appearance, smell and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation codes were kept strictly confidential and accessible only to authorised persons until un-blinding. Only when the trial had been completed was the data file verified, and the protocol violations determined were the randomisation codes broken and made available for data analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and balanced (9.6% to 15.7% across groups). 'Imputation for prematurely discontinued subjects was done by using the last-observation-carried-forward method, and the analysis thus followed the ICH intent-to-treat principle'
Selective reporting (reporting bias)	High risk	Multiple outcomes, including AQLQ, ACQ, lung function tests, not reported numerically or only significant results reported numerically, so unable to include in meta-analysis. Reduction in ICS dose reported only for 1-dose group and for placebo group
Other bias	Low risk	None noted

Mosges 2010

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial **Duration:** 0.015 weeks (90 minutes) **Setting:** 14 centres in Germany
Participants	**Population:** 116 (54 with asthma) randomly assigned to ultra-rush birch pollen SLIT group (27) and placebo group (27) **Age:** 6 to 14 years; ultra-rush birch pollen SLIT group mean 10.2 (2.64) years, placebo group mean 10.5 (2.55) years **Inclusion criteria:** 6 to 14 years, medical history of allergic rhinitis or rhinoconjunctivitis with or without mild to moderate asthma because of tree pollens (birch and possibly alder and/or hazel), positive skin prick tests and presence of specific IgE $\geq$ 0.7 IU/L to respective tree pollens, Retrospective Rhinoconjunctivitis Total Symptom Score (RRTSS) $\geq$ 8 **Exclusion criteria:** previous immunotherapy within the past 3 years, perennial allergic rhinitis, perennial allergic asthma, absolute or relative contraindications to immunotherapy, any other condition that could compromise participant safety during the study **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinitis and/or conjunctivitis **Allowed medication:** The following symptomatic drugs were allowed for the treatment of allergic reactions during titration: local (nasal and ocular) levocabastine (step 1), oral cetirizine (step 2), nasal fluticasone (step 3) and eventually an OCS (step 4). In participants with asthma, previous medication with corticosteroids for inhalation and/or selective beta$_2$-adrenoceptor agonists for inhalation was continued at the same dose **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** ultra-rush high-dose birch pollen (*Betula alba*) SLIT titration regimen reaching maintenance dose of 300 IR within 90 minutes (30-90-150-300 IR) **Co-interventions:** not reported
Outcomes	Lung function tests, laboratory safety measures (RBC, haemoglobin, haematocrit, platelets, WBC including differential, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase (LDH) and C-reactive protein (CRP) , adverse events
Notes	**Type of publication:** peer reviewed **Funding:** Stallergenes GmbH, Kamp-Lintfort, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	No details

Mosges 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, no specific details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, no specific details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not clearly reported
Selective reporting (reporting bias)	High risk	Most outcomes reported narratively; almost no supporting data
Other bias	Low risk	None noted

Mungan 1999

Methods	**Design:** 'randomised' (unclear), single-blind, parallel, placebo-controlled trial **Duration:** 52 weeks **Setting:** Turkey
Participants	**Population:** 36 participants were randomly assigned to HDM SLIT group (15), to placebo group (11) and to 1 other treatment arm not relevant to this review **Age:** 18 to 46 years; HDM SLIT group mean 31.7 (7.28) years, placebo group mean 33.3 (8.45) years **Inclusion criteria:** hypersensitivity to inhaled HDM with history of asthma and rhinitis symptoms for at least 3 consecutive years, presence of symptoms despite optimal treatment and environmental controlling procedures, FEV_1 > 70% predicted, positive skin prick test for *D. pteronyssinus* and *D. farinae*, positive in vitro specific IgE test for *D. pteronyssinus* and *D. farinae* **Exclusion criteria:** hypersensitivty to any other air-bourne allergen on skin prick test, previous immunotherapy, active immunological or systemic disease or malignancy **Percentage withdrawn:** 0% in both groups **Percentage with asthma:** 88% **Co-morbidities:** rhinitis **Allowed medication:** salbutamol and antihistamines only for symptomatic treatment, ICS **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT initiation phase followed by twice per week. Cumulative dose 11,316 IR/y **Co-interventions:** not reported
Outcomes	Rescue medication use, symptom scores, skin prick test, bronchial challenge test, total IgE, specific IgE, IgG4

Mungan 1999 (*Continued*)

Notes	**Type of publication:** peer reviewed **Funding:** not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Separated' into 3 groups; possibly not randomly assigned? "patients with rhinitis and asthma due to mite allergy were randomly divided into three groups"
Allocation concealment (selection bias)	Unclear risk	'Separated' into 3 groups; possibly not randomly assigned?
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo controlled', "single blind", but no details about exactly who was blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Placebo-controlled but no details about exactly who was blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	High risk	Many outcomes reported only narratively and compared with baseline rather than placebo. Symptom and medication scores reported but without variance
Other bias	Low risk	None noted

Muratore 1993

Methods	**Design:** 'randomised', double-blind, parallel, placebo-controlled trial **Duration:** 52 weeks **Setting:** Italy
Participants	**Population:** 28 participants randomly assigned to HDM SLIT group and placebo group (number for each group not reported) **Age:** 4 to 9 years (mean age for each group not reported) **Inclusion criteria:** children suffering from bronchial asthma **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** all participants allowed 'bronchodilating and anti-inflammatory

Muratore 1993 (*Continued*)

	medication as required' **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM (*Dermatophagoides* antigen extract) SLIT incremental dosing schedule then 3 times/wk maintenance dose of 2.5 UB **Co-interventions:** not reported
Outcomes	Clinical symptoms on a 3-point scale and drug consumption
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomly allocated' but no specific details
Allocation concealment (selection bias)	Unclear risk	'Randomly allocated' but no specific details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, no specific details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, no specific details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract only. No useable numerical data and minimal details regarding the conduct of the study
Other bias	Low risk	None noted

NCT00633919

Methods	**Design:** 'randomised', double-blind, parallel, multi-centre, placebo-controlled trial **Duration:** 104 weeks **Setting:** Spain
Participants	**Population:** 124 participants randomly assigned to SLIT group (63) and placebo group (61) **Age:** 18 to 65 years; HDM SLIT group mean 32.0 (8.0) years, placebo group mean 30.

	0 (9.0) years **Inclusion criteria:** clinical history of house dust mite induced persistent mild to moderate asthma, with or without concurrent rhinoconjunctivitis, of at least 1 year duration, positive specific serum IgE test to *Dermatophagoides* during the year before the screening visit (CAP class 2 or higher or equivalent), positive skin prick test response (wheal diameter $\geq$ 3 mm) to *Dermatophagoides* mix; if premenopausal female of childbearing potential, participant must test negative on standard urine pregnancy test, willingness to comply with this protocol **Exlusion criteria:** FEV_1 < 70% predicted, asthma controlled at randomisation without need for inhaled corticosteroids or with dose higher than 1000 mcg/d of beclometasone or equivalent, clinical history of symptomatic perennial allergic asthma caused by other allergens, chronic sinusitis, aspirin or sulfite intolerance, COPD, severe asthma or atopic dermatitis, previous immunotherapy with HDM allergens within previous 10 years; current symptoms of, or treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infectious process, cystic fibrosis, malignancy, insulin-dependent diabetes, malabsorption or malnutrition, renal or hepatic insufficiency, chronic infection, drug dependency or alcoholism, ischaemic heart disease or angina requiring current daily medication or with any evidence of disease, making implementation of the protocol or interpretation of protocol results difficult, or jeopardising the safety of the participant **Percentage withdrawn:** HDM SLIT group 42.8%, placebo group 36.1% **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** SABA, LABA, ICS, OCS, antihistamines, nasal steroids **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT (*Dermatophagoides* mix) 200 STU daily for 2 years **Co-interventions:** during the 2 evaluation periods, participants were provided with standardised medication to use as required/according to symptom severity: desloratadine (5 mg), budesonide nasal spray (64 mcg per puff), salbutamol inhaler (200 mcg per puff), budesonide/formoterol inhaler (80/4.5 mcg per inhalation), oral prednisolone (5 mg per tablet)
Outcomes	Average daily asthma medication score, global evaluation of efficacy by participant, global evaluation of efficacy by investigator, adverse events
Notes	**Type of publication:** clinical trials website only; no peer-reviewed article identified **Funding:** ALK-Abelló A/S

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but no further details
Allocation concealment (selection bias)	Unclear risk	No details

NCT00633919 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participant, caregiver, investigator), placebo-controlled; 'SLITone placebo'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind (participant, caregiver, investigator), placebo-controlled; 'SLITone placebo'
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout in both arms; 42.8% in SLIT group and 36.0% in control group; efficacy outcomes reported only for those with available data; no imputation done for missing data
Selective reporting (reporting bias)	Low risk	All started outcomes reported numerically
Other bias	Low risk	None noted

Niu 2006

Methods	**Design:** randomised, double-blind, parallel, placebo-controlled trial **Duration:** 24 weeks (+ 2 week off-treatment follow-up) **Setting:** 5 medical centres in Taiwan
Participants	**Population:** 110 children were randomly assigned to house dust mite SLIT (56) and placebo (54) **Age:** 6 to 12 years; mean age 7.9 (SLIT) years and 8.2 (placebo) years **Inclusion criteria:** Patients with at least 1-year history of mildly persistent to moderately persistent (GINA-global initiative for asthma, steps 2 and 3) asthma were enrolled in this study. They were allergic to HDM only. Children were enrolled in this study only if their FEV_1 was > 70% of that predicted, and if reversible PEFR exceeded 15% after inhalation of $beta_2$-agonists **Exclusion criteria:** Patients were excluded if they were sensitive to cockroach, *Alternaria*, *Cladosporium*, dog/cat danders or pollens by skin prick tests (wheal $\geq$ 5 mm), or had allergen-specific IgE antibodies ($\geq$ 1 +) against above allergens. Patients who had previously been treated with immunotherapy, oral or parenteral corticosteroids for more than 15 consecutive days, depot steroids, ICS in doses > 1000 mcg/d (beclomethasone dipropionate), inhaled $beta_2$-agonists more than 4 times/d and those suffering from other respiratory diseases that were not suitable for immunotherapy, such as anatomical abnormality of upper respiratory tract and congenital cardiovascular diseases, were excluded **Percentage withdrawn:** 12.5% SLIT, 11.1% placebo **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** During the trial, participants were allowed to take the following rescue medications if needed: ICS (budesonide turbuhaler), inhaled $beta_2$-agonist (terbutaline aerosol), OCS (prednisolone 5 mg) **Disallowed medication:** not reported

Niu 2006 (*Continued*)

Interventions	**Control group:** placebo SLIT **SLIT group:** 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.*) **Co-interventions:** not reported
Outcomes	Daily asthma scores, drug consumption, PEFR, lung function tests, skin prick tests, total serum and specific IgE, global assessment by blinded physician, adverse events
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned' but no specific details
Allocation concealment (selection bias)	Unclear risk	'Randomly assigned' but no specific details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'The extract and placebo were dispensed in the same glycerosaline dilutents'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Before and after 24 weeks of therapy, participants were interviewed and physically examined by an attending physician who had no previous knowledge of participant treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout in both groups (12.5% in intervention group and 11.1% in control group)
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Low risk	None noted

Orefice 2004

Methods	**Design:** randomised, parallel, open-label, pharmacotherapy-controlled trial **Duration:** 156 weeks (3 years) **Setting:** Italy
Participants	**Population:** 47 participants were randomly assigned to HDM SLIT (23) or pharmacotherapy alone (24) **Age:** no details

	Inclusion criteria: patients with mild/moderate allergic asthma sensitive to HDM **Exclusion criteria:** patients with a symptom score less than 12 and/or needing a dose of budesonide greater than 400 mcg/d for longer than 2 weeks were excluded - not clear whether this was baseline exclusion or occurred during the study **Percentage withdrawn:** 8.7% SLIT, 20.8% pharmacotherapy alone **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** usual pharmacotherapy alone **SLIT group:** HDM SLIT (no details of dosing) **Co-interventions:** not reported
Outcomes	Bronchial provocation tests, symptom scores and morning and evening PEFR
Notes	**Type of publication:** conference abstract **Funding:** "self funded"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	'Randomised' but no details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Unbalanced dropout and concerns re: exclusion of participants with more severe asthma during trial: "Patients with a symptom score less than 12 and/or needing a dose of budesonide greater than 400 mcg/day for more than 2 weeks were excluded" - not clear whether this was baseline exclusion or occurred during the study (dropout rate 8% in treatment group, 20% in control group)

Orefice 2004 (*Continued*)

Selective reporting (reporting bias)	High risk	Conference abstract, no full paper. Minimal study characteristics and no useable data
Other bias	Low risk	None noted

Pajno 2000

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 104 weeks (2 years) **Setting:** Italy
Participants	**Population:** 24 children were randomly assigned to HDM SLIT (12) and placebo (12) **Age:** 8 to 15 years; mean age 11 (SLIT) years and 12 (placebo) years **Inclusion criteria:** history of mild to moderate asthma with methacholine PC20 (concentration of inhaled methacholine that causes a 20% decrease in FEV_1 not below 2 mg/mL, positive skin prick test (wheal diameter > 5 mm) to HDM, specific IgE to HDM of at least class 3 **Exclusion criteria:** positive skin response to at least 1 other inhalant allergen of the standard panel for southern Italy, clinical history of other allergies such as seasonal asthma due to pollens, history of immunotherapy in previous years, history of cardiovascular or other medical or immunological diseases, severe asthma **Percentage withdrawn:** 0% SLIT, 25% placebo **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** Only rescue drugs ($beta_2$-agonist and OCS or ICS) were allowed during the study **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** 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) **Co-interventions:** not reported
Outcomes	Drug consumption; asthma scores on a VAS; specific IgE, IgG and IgG4; adverse events
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned separately to active or placebo group according to a keyed code

Pajno 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"Keyed code" may imply concealed but not clear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial. Placebo was indistinguishable from active treatment in flavour and appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All data were gathered in a double-blind fashion in accordance with the clinical protocol. The co-ordinator, who was blinded as to the group each child was assigned to, was in charge of participant supervision and adjusted rescue treatment according to symptoms; was also responsible for reporting any reactions and/or side effects
Incomplete outcome data (attrition bias) All outcomes	High risk	Unbalanced dropout (0% in treatment group, 25% in control group). Not included in the analysis
Selective reporting (reporting bias)	Low risk	All started outcomes reported narratively or numerically
Other bias	Low risk	None noted

Pajno 2003

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 56 weeks (with 52 week off-treatment follow-up) **Setting:** Italy
Participants	**Population:** 30 children were randomly assigned to *Parietaria* SLIT (15) and placebo (15) **Age:** 8 to 14 years; mean age 11 years **Inclusion criteria:** history of seasonal asthma and rhinoconjunctivitis. Diagnosis of asthma was established on the basis of at least 3 doctor-diagnosed episodes separated by at least 1 week of wheezing/breath difficulty during the 2 previous *Parietaria* pollen seasons in a clinical setting in which asthma was likely and conditions other than allergy had been excluded; poor symptom control in previous years despite antiallergic treatment including antihistamines, ICS and nedocromil sodium for 3 to 4 months (i.e. almost the full pollen season); positive skin prick test result (wheal diameter > 5 mm) to *Parietaria* pollen extract (*Parietaria judaica*); specific IgE to *P. judaica* levels in sera of at least class 2 was determined by means of the RAST technique **Exclusion criteria:** appreciable clinical history of sensitisation to other inhalant allergens (confirmed by skin prick test and/or in vitro IgE analysis), history of previous immunotherapy; severe asthma (FEV_1 < 70% of predicted values); history of cardiovascular or other medical or immunological disease. Children showing at baseline a methacholine PC20 (concentration of inhaled methacholine that caused a 20% decrease in FEV_1) <

	2 mg/mL were also excluded so that only children with mild or no specific bronchial hyperreactivity outside the pollen season of *Parietaria* were included **Percentage withdrawn:** 6.7% SLIT, 13.3% placebo **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** Both SLIT groups (active and placebo) were prescribed and instructed to use rescue drugs (nedocromil sodium eye drops and nasal spray, loratadine, salbutamol) during the peak of the following pollen season of *Parietaria* (i.e. from April to June 2000). They also inhaled fluticasone propionate (50 mg per actuation) twice daily. If symptoms developed that were not controlled by regular drugs, the co-ordinator could prescribe a 5-day course of prednisone (1 mg/kg/d) **Disallowed medication:** intranasal steroids
Interventions	**Control group:** placebo SLIT **SLIT group:** *Parietaria* pollen SLIT (*Parietaria judaica*), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg) **Co-interventions:** inhaled fluticasone propionate 50 mcg twice daily April to June of first pollen season
Outcomes	Symptom and drug scores, VAS asthma scores, early and late skin prick responses, adverse events, bronchial hyperreactivity, lung function tests
Notes	**Type of publication:** peer reviewed **Funding:** University Hospital of Messina

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random assignment to active (15 children) , placebo (15 children) or control (8 children) group was obtained by means of a computer-generated key code
Allocation concealment (selection bias)	Unclear risk	"Keyed code" may imply concealed but not clear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was indistinguishable from active treatment for appearance, colour and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The co-ordinator, who was blinded as to the group to which each child was assigned, was in charge of participant supervision and adjustment of rescue medications according to symptoms; was also responsible for reporting any reaction and/or side effects certainly or possibly related to treatment

Pajno 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Relatively low dropout in both groups (6% in treatment group, 13% in control group), although dropouts not included in efficacy analysis
Selective reporting (reporting bias)	Unclear risk	Several outcomes reported only narratively or 'ranges' of P values given. Discrepancies between different reports appear to be related to same participant group
Other bias	Low risk	None noted

Pham-Thi 2007

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 78 weeks **Setting:** Department of Paediatric Pneumology and Allergy, Hopital Necker-Enfants Malades, Paris, France
Participants	**Population:** 111 children were randomly assigned to house dust mite SLIT (55) and placebo (56) **Age:** 5 to 16 years; mean age 9.6 (SLIT) years and 9.5 (placebo) years **Inclusion criteria:** asthma, with or without perennial rhinitis, for at least 2 years, receiving treatment with an ICS (> 200 and ≤ 1000 mcg/d/equivalent budesonide) daily and continuously for at least 6 months during the previous 12 months; reversible bronchial obstruction, as assessed by salbutamol inhalation test (increase in FEV_1 ≥ 15% after inhaled salbutamol) during the past 2 years; sensitised to dust mites, as proved by positive skin tests to HDM extract and HDM-specific IgE level ≥ class 2 (CAP RAST) **Exclusion criteria:** concomitant sensitisation to perennial allergens such as cockroach, *Alternaria* or *Cladosporium* mould species, cat, dog (if animal at home) and to seasonal pollen allergens, inducing allergic symptoms lasting longer than 4 months/y. Sensitisations were based on a clear-cut clinical history, positive skin tests and specific IgE (CAP RAST ≥ class 2). Previous immunotherapy with HDM extracts within 3 years from the date of inclusion; contraindications to SIT, according to international guidelines (WHO) **Percentage withdrawn:** 20% SLIT, 14.3% placebo **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinitis **Allowed medication:** Terbutaline (MDI, 250 mcg per actuation) was used as a short-acting bronchodilator. Budesonide (MDI, 100 or 200 mcg per actuation) was used as a regulatory ICS. In case of asthma exacerbation, the investigator prescribed a short course of prednisolone (20 mg per tablet). No other antiasthma drugs were allowed. Intake of antiasthma drugs was recorded as the number of puffs per day. Pharmacological treatment was adjusted every 3 months following a step-down approach **Disallowed medication:** antiasthma medication not mentioned in allowed list
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT (*D. pteronyssinus* and *D. farinae*), up-dosing for 2 weeks 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) **Co-interventions:** terbutaline, budesonide
Outcomes	Asthma symptom scores, reduction in use of ICS and inhaled beta$_2$-agonists, rhinitis symptoms, lung function tests, skin sensitivity to HDM, dust mite-specific immunoglobulin E and IgG4, QoL
Notes	**Type of publication:** peer reviewed **Funding:** Stallergenes SA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were then randomly assigned 1: 1 to receive SLIT or placebo with stratification based on ICS daily intake (sequence generation method not described)
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind, placebo-controlled trial". "Placebo tablets were identical to the active extract in appearance, presentation, taste and colour"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Among the 19 participants who withdrew, 10 in the SLIT group (all but 1) and 7 in the placebo group (all but 1) were considered evaluable for the intent-to-treat analysis (ITT), which included 54 participants in the SLIT group and 55 participants in the placebo group
Selective reporting (reporting bias)	High risk	QoL total score comparison was not properly reported, just non-significance between groups stated
Other bias	Low risk	None noted

Radu 2007

Methods	**Design:** 'randomised', single-blind, parallel, placebo-controlled trial **Duration:** 26 weeks **Setting:** Romania
Participants	**Population:** 106 participants were randomly assigned to HDM SLIT group (55) and placebo group (51) **Age:** 5 to 13 years; HDM SLIT group range 5 to 12 years, placebo group range 5 to 13 years **Inclusion criteria:** stable asthma and taking ICS **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinitis **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT, dose not reported **Co-interventions:** not reported
Outcomes	Symptom scores, rescue medication use, PEFR
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details
Allocation concealment (selection bias)	Unclear risk	Drugs and sealed codes were delivered directly to the pharmacy department of Glasgow Royal Infirmary
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blind but not clear who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single-blind but not clear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported, study stopped after 6 months

Radu 2007 (*Continued*)

Selective reporting (reporting bias)	High risk	Conference abstract only. Minimal numerical data or details regarding the conduct of the study
Other bias	Unclear risk	Planned for 36 months but stopped after 6 months because of statistically significant differences in outcome favouring active treatment

Reilly 1994

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 4 weeks (with 4 weeks 'optional' post-treatment follow-up) **Setting:** asthma outpatient clinic, Scotland
Participants	**Population:** 28 participants were randomly assigned to homeopathic SLIT group (13) and placebo group (15) **Age:** minimum age 16 years; mean age of homeopathic SLIT group 40 (16.3) years, placebo group 37 (14.3) years **Inclusion criteria:** 16 years of age and older; asthma with > 15% improvement in FEV_1 with bronchodilators; > 1 year history of asthma; atopic and reactive to inhaled allergens and positive skin tests **Exclusion criteria:** deterioration during the grass pollen season, allergen avoidance within past 6 weeks, previous homeopathic immunotherapy for asthma, respiratory infection, severe concomitant disease, pregnancy, antihistamines in the past 4 weeks, parenteral steroids in the past 6 months. Both doctors (homeopathic and asthma clinic doctor) could veto inclusion of any patient they considered unsuitable **Percentage withdrawn:** 15.39% homeopathic SLIT group, 13.33% placebo group **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** 'unaltered conventional care' **Disallowed medication:** antihistamines in past 4 weeks, parenteral steroids in past 6 months
Interventions	**Control group:** placebo SLIT **SLIT group:** 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 weeks (according to patient choice) **Co-interventions:** 77% taking ICS plus usual medication in homeopathic SLIT group, 67% taking ICS plus usual medication in placebo group
Outcomes	Lung function tests, skin testing, allergen-specific IgE, symptom scores, PEFR
Notes	**Type of publication:** peer reviewed **Funding:** RCCM Research Fellowship for Complementary Medicine, Blackie Foundation Trust, Foundation Francaise pour le Recherche en Homeopathie

Risk of bias

Reilly 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned by a restricted technique of permuted blocks, stratified for intended allergen and daily dose of steroid
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; placebo vials were prepared with globules impregnated with the same batch of dilutant, which, without the addition of antigen, had been identically diluted and vibrated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both study doctors and statisticians were blinded to participant allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced, reasonably low dropout (15% in treatment group, 13% in placebo group) . "Analysis was intention to treat". "4 patients did not attend for follow-up: 3 (2 homeopathy gave social reasons and reported no marked change in symptoms; 1 (placebo) was withdrawn by her GP…Thus, 24 of 28 patients' data were used in the principal analyses". Dropouts were not accounted for in the analyses, but dropout was balanced and was less than 20% in both groups
Selective reporting (reporting bias)	Low risk	All named outcomes were reported but were not relevant to the review and used non-parametric tests
Other bias	High risk	"Both doctors (homeopathic and asthma clinic doctor) could also veto any patient they considered unsuitable"; may represent high risk of selection bias

Rodriguez 2012

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial **Duration:** not reported **Setting:** Cuba

Rodriguez 2012 (*Continued*)

Participants	**Population:** 40 participants were randomly assigned to HDM SLIT group and placebo group (number for each group not reported) **Age:** 'adult' **Inclusion criteria:** adult patients with mild or moderate asthma and specific sensibility preponderant to this mite **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT (*D. pteronyssinus*), up-dosing to 2000 BU **Co-interventions:** not reported
Outcomes	Clinical symptoms, medication use, skin reactivity, PERF variability
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details (does not specifically state randomised but double-blind, placebo-controlled)
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled but no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled but no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract only. Minimal numerical data or details regarding the conduct of the study
Other bias	Low risk	None noted

Rodriguez Santos 2004

Methods	**Design:** 'randomised', open-label, parallel, pharmacotherapy-controlled trial **Duration:** 104 weeks **Setting:** outpatient clinic, Cuba
Participants	**Population:** 50 participants were randomly assigned to HDM SLIT group (25) and pharmacotherapy group (25) **Age:** 6 to 15 years (mean age not reported) **Inclusion criteria:** children aged 6 to 15 years with asthma and elevated IgE, personal and family history of atopy **Exclusion criteria:** not reported **Percentage withdrawn:** 0% withdrawal in both groups **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** pharmacotherapy only **SLIT group:** HDM SLIT (*D. pteronyssinus*). Daily for 24 months. Dose 500, 1000, 2000, 5000, 8000, 10,000 BU **Co-interventions:** not reported
Outcomes	PEFR, emergency department attendance, steroid consumption
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly divided according to 'severity of attacks' - not clear whether this was random stratification, or if participants were purposely allocated on the basis of 'attack severity'
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout

Rodriguez Santos 2004 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Stated outcomes reported but numerical data not well presented; appears that within-group outcomes reported rather than comparisons with control
Other bias	Low risk	None noted

Shao 2014

Methods	**Design:** 'randomised', open-label, parallel, pharmacotherapy-controlled trial **Duration:** 52 weeks **Setting:** 6 centres located in 4 provinces in China
Participants	**Population:** 264 participants were randomly assigned to HDM SLIT group (168) and pharmacotherapy group (96) **Age:** 3 to 13 years; mean age of HDM SLIT group 6.4 (2.59) years, pharmacotherapy group 5.9 (3.037) years **Inclusion criteria:** moderate to severe/persistent allergic rhinitis without severe/uncontrolled asthma according to Allergic Rhinitis and Its Impact on Asthma and the Global Initiative for Asthma, clinical history of mite allergy and sensitisation to *D. farinae* confirmed by positive skin prick test and serum-specific IgE > 0.7I U/L and $FEV_1 \geq 70\%$ predicted **Exclusion criteria:** not reported **Percentage withdrawn:** HDM SLIT group 16%, pharmacotherapy group 19.8% **Percentage with asthma:** 82% (218/264) **Co-morbidities:** rhinitis **Allowed medication:** oral antihistamines, nasal corticosteroids, ICS, antileukotrienes, $beta_2$-agonists **Disallowed medication:** not reported
Interventions	**Control group:** pharmacotherapy only **SLIT group:** HDM SLIT (*D. farinae*) daily. Dose not reported **Co-interventions:** standard pharmacotherapy
Outcomes	Symptom scores, medication consumption, adverse events, serum-specific IgE and IgG4, lung function tests
Notes	**Type of publication:** peer reviewed **Funding:** Zhejiang Wolwo Bio-Pharmaceutical Co. Ltd.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomised' but no details

Shao 2014 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Balanced dropout (16% in SLIT group, 19% in control group) but only completers were analysed
Selective reporting (reporting bias)	Low risk	All stated outcomes reported
Other bias	Low risk	None noted

Stelmach 2009

Methods	**Design:** 'randomised', double-blind, placebo-controlled trial **Duration:** 104 weeks **Setting:** specialty clinic setting, Poland
Participants	**Population:** 50 participants randomly assigned to grass pollen SLIT group (25) and placebo group (25) **Age:** 6 to 17 years; mean age of participants in grass pollen group who completed study 9.1 (2.4) years, placebo group who completed study 8.5 (2.8) years **Inclusion criteria:** children sensitive only to grass pollen (positive skin prick tests and presence of specific IgE), clinical diagnosis of asthma with duration of at least 2 years before the first study visit, with and without current symptoms of seasonal allergic rhinoconjunctivitis. Diagnosis of asthma was established by symptoms of asthma and by improvement in prebronchodilator $FEV_1 \geq 12\%$ after administration of salbutamol 200 mcg **Exclusion criteria:** participants with asthma and/or rhinitis allergic to perennial allergens or severe intermittent or persistent asthma; active upper respiratory tract infection within 1 month before the first visit and between first and second visits; known contraindications of SIT according to the EAACI; clinically significant pulmonary, haematological, hepatic, gastrointestinal, renal, endocrine, neuronal, cardiovascular and/or psychiatric disease or malignancy that put the participant at risk when participating in the study or may have influenced results of the study as judged by the investigator **Percentage withdrawn:** grass pollen SLIT group 20%, placebo group 40% **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** All children in pollen season received budesonide 200 mcg twice daily and salbutamol 100 mg/dose as quick reliever. Other permissible treatments: standard treatments for infections and exacerbations of asthma and standard treatments for allergic rhinoconjunctivitis during pollen seasons (local cromones, local and/or systemic

	antihistamines and nasal steroids) **Disallowed medication:** Excluded medications were systemic corticosteroids or immune suppressive drugs, used within 4 weeks before the study
Interventions	**Control group:** placebo SLIT **SLIT group:** grass pollen SLIT (*Dactylis glomerata*, *Anthoxanthum odoratum*, *Lolium perenne*, *Poa pratensis*, *Phleum pretense*). Ultra-rush induction: 1-3-6-12 (10-30-60-120 IR) drops separated by a 30 minute observation period (total of 240 IR). At the beginning of the next day, every morning before breakfast, received 4 puffs (120 IR) for 6 months. Cumulative dose 43,800 IR **Co-interventions:** budesonide 200 mcg twice daily and salbutamol 100 mcg/dose as required during pollen season
Outcomes	Symptom scores, lung function tests, nasal provocation tests, bronchial provocation tests, serum IgE and IgG4, adverse events
Notes	**Type of publication:** peer reviewed **Funding:** Stallergenes Pharmaceutical Company supplied verum and placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	All suitable participants were randomly assigned to the 2 treatment arms according to a computer-generated allocation schedule
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo group received identical-looking placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Immunotherapy was administered blindly by a treatment team that was also responsible for assessment and treatment of any adverse reactions
Incomplete outcome data (attrition bias) All outcomes	High risk	Unbalanced and high dropout (20% from SLIT group and 40% from placebo group by end of study)
Selective reporting (reporting bias)	Low risk	All stated outcomes reported narratively or numerically
Other bias	Low risk	None noted

Tian 2014

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 48 weeks **Setting:** asthma special outpatient centre in China
Participants	**Population:** 60 children were randomly assigned to house dust mite SLIT (30) and placebo (30) **Age:** 4 to 18 years; mean age 11.1 (SLIT) years and 10.8 (placebo) years **Inclusion criteria:** diagnosed with mild to moderate allergic asthma according to diagnostic criteria for bronchial asthma in children, and without allergic rhinitis, allergic to *D. farinae* as confirmed by skin prick test (++ or greater), serum IgE detection (> 2) with species of allergen not > 3 **Exclusion criteria:** other cardiovascular or autoimmune disease **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** SABA, ICS, antihistamines, LTRA, OCS **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** house dust mite SLIT (*D. farinae*), titrated up over the first 4 weeks to 333 mcg/mL once daily **Co-interventions:** not reported
Outcomes	Symptom scores, medication scores, ratio of Th17 and CD4+CD25+Treg cells
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'Divided into treatment group and control group in order of admission' - not clear whether truly random
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled. Appearance, smell, packaging, volume, storage conditions and modes and methods of administration were identical between placebo and drug
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind; no further details about outcome assessors

Tian 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Data for all time points were reported for the active treatment group, but not for the control group. Data not consistently reported for each arm, most graphically or just with levels of statistical significance
Other bias	Low risk	None noted

Troise 2009

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 104 weeks **Setting:** single centre
Participants	**Population:** 24 participants were randomly assigned to birch pollen SLIT (14) and placebo (10) **Age:** no information **Inclusion criteria:** severe rhinitis and mild to moderate asthma **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% **Co-morbidities:** severe rhinitis **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group:** birch pollen SLIT (*Betula alba*), no details of dosing **Co-interventions:** not reported
Outcomes	Rhinorrhoea, nasal obstruction, median days with asthma, severe adverse events
Notes	**Type of publication:** conference abstract **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but no details
Allocation concealment (selection bias)	Unclear risk	No details

Troise 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind but no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind but no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract only. Minimal numerical data or details regarding the conduct of the study
Other bias	Low risk	None noted

Virchow 2014

Methods	**Design:** randomised, double-blind, placebo-controlled trial ('MITRA' trial) **Duration:** 78 weeks **Setting:** '13 European countries' including Austria, Croatia, Denmark, France, Germany, Lithuaina, Netherlands, Poland, Serbia, Slovakia, Spain, United Kingdom
Participants	**Population:** 834 participants randomly assigned to 3 groups; HDM SLIT 6 SQ, 12 SQ and placebo SLIT (numbers randomly assigned to each arm not reported) **Age:** adults **Inclusion criteria:** clinically relevant history consistent with HDM-induced asthma of at least 1 year before trial entry; use of an appropriate amount of ICS in accordance with the GINA Guideline steps 2 to 4 for a period of at least 6 months within the past year (in a range of budesonide 400 to 1200 mcg); documented reversible airway obstruction; asthma control level $\geq$ 1.0 (asthma control questionnaire (ACQ) $\geq$ 1.0) at screening; asthma control level between 1.0 and 1.5 (1.0 $\leq$ ACQ $\leq$ 1.5) at visit 3 (randomisation) ; $FEV_1 \geq 70\%$ of predicted value; clinical history consistent with mild to severe HDM-induced allergic rhinitis for at least 1 year; positive SPT response to HDM; positive specific IgE against HDM ($\geq$ IgE class 2; $\geq$ 0.70 KU/L) **Exclusion criteria:** clinical history of persistent allergic asthma and/or rhinitis caused by an allergen to which the participant is regularly exposed and sensitised (except HDM); clinical history of intermittent allergic asthma and/or rhinitis if the seasonal allergen may cause symptoms in the ICS reduction period; previous treatment with immunotherapy with HDM allergen for longer than 1 month within the past 5 years; hospitalisation for longer than 12 hours due to asthma exacerbation within the last 3 months before the screening visit **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** allergic rhinitis **Allowed medication:** not reported **Disallowed medication:** not reported

Virchow 2014 (*Continued*)

Interventions	**Control group:** placebo SLIT daily **SLIT group 1:** HDM SLIT 6 SQ daily **SLIT group 2:** HDM SLIT 12 SQ daily **Co-interventions:** ICS 400 to 1200 budesonide or equivalent
Outcomes	First moderate or severe asthma exacerbation during the ICS reduction period (ICS was reduced in the past 6 months - 50% for 3 months and 100% for 3 months) analysed by time-to-event, immunological measures; asthma symptoms; use of symptomatic medication; lung function; AQLQ; ACQ; adverse events
Notes	**Type of publication:** conference abstract; protocol on European Trials Register (2010-018621-19) **Funding:** ALK-Abello

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled but no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled but no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract and European trials register protocol. Minimal numerical data presented
Other bias	Low risk	None noted

Vourdas 1998

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 104 weeks (2 years) **Setting:** Greece

Vourdas 1998 (*Continued*)

Participants	**Population:** 66 children were randomly assigned to olive pollen SLIT (34) and placebo (32) **Age:** 7 to 17 years; mean age 12 years **Inclusion criteria:** rhinoconjunctivitis and/or mild asthma due to olive pollen sensitisation proved by positive skin prick test and RAST class II and above **Exclusion criteria:** uncontrolled asthma or polysensitisation **Percentage withdrawn:** 2.9% SLIT, 3.1% placebo **Percentage with asthma:** 90.6% **Co-morbidities:** rhinoconjunctivitis **Allowed medication:** cetirizine, salbutamol, terbutaline, theophylline, sodium cromoglycate, budesonide, prednisolone **Disallowed medication:** beta-blockers and 'retard' corticosteroids
Interventions	**Control group:** placebo SLIT **SLIT group:** olive pollen SLIT, daily up-dosing then each morning pre- and co-seasonally from January to July for 2 years up to a maximum of 20 drops of 300 IR (total 30,000 IR/y) **Co-interventions:** not reported
Outcomes	Symptom and medication scores, physician and participant overall evaluation of treatment, PEFR, skin prick tests, allergen-specific IgE and IgG4, adverse events
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was a glycerinated phenolated saline solution with an appearance similar to that of the active agent
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind but no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant from each group dropped out and was not included in the efficacy analysis (3% of total population). "All 66 patients were included in the tolerance analysis"

Vourdas 1998 (*Continued*)

Selective reporting (reporting bias)	High risk	Most measures were reported only with level of statistical significance, or in other ways that could not be meta-analysed
Other bias	Low risk	None noted

Wang 2014

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 52 weeks (+ 12 week baseline period before randomisation) **Setting:** 14 centres in cities, China
Participants	**Population:** 484 participants were randomly assigned to house dust mite SLIT (322) and placebo (162) **Age:** 16 to 50 years; mean age 31.2 (SLIT) years and 31.3 (placebo) years **Inclusion criteria:** adult patients (aged 16 to 50) with mild or moderate, persistent, HDM-induced asthma for at least previous 12 months. Asthma was diagnosed with a bronchial reversibility test (12% after inhalation of $beta_2$-agonist) or a positive methacholine challenge within the previous year or at screening **Exclusion criteria:** Main exclusion criteria were previous AIT, severe asthma, co-sensitisation to confounding aero-allergens and smoking history of more than 10 pack-years **Percentage withdrawn:** 4.3% SLIT, 3.1% placebo **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** allergic rhinitis **Allowed medication:** budesonide dry powder 100 mcg (controller), salbutamol, prednisolone (for asthma exacerbations) and loratadine (for allergic rhinitis) **Disallowed medication:** The only authorised medications are listed under 'Allowed medication'
Interventions	**Control group:** placebo SLIT **SLIT group:** HDM SLIT (*D. pteronyssinus* and *D. farinae*), approximately 28 mcg Der P 1 and 50 mcg Der f 1 daily (300 IR) **Co-interventions:** ICS
Outcomes	Well-controlled asthma for at least 16 of the last 20 weeks of treatment, ICS use, Asthma Control Questionnaire, lung function test, skin prick test, laboratory tests, treatment-related serious adverse events
Notes	**Type of publication:** peer reviewed **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomized 2:1 to active treatment or placebo' but no further details

Wang 2014 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled but no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled but no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was low and balanced 4% from SLIT and 2% from placebo groups; 96% were included in the full analysis set (14 excluded from SLIT group and 5 from placebo group) because of lack of assessable weeks during treatment period
Selective reporting (reporting bias)	High risk	Lack of clarity with outcome reporting; reporting of participants with moderate asthma separately; numerical data not always presented. KK: some important outcomes (ACQ and ICS dose reduction) reported only for subgroups with statistically significant results
Other bias	Low risk	None noted

Wood 2014

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled trial **Duration:** 13 weeks **Setting:** multiple centres in the USA and the UK
Participants	**Population:** 89 children were randomly assigned to low dose (31) and high dose cockroach SLIT (30) and placebo (28) **Age:** 5 to 17 years; mean age 11 (low SLIT) years, 10 (high SLIT) years and 11 (placebo) years **Inclusion criteria:** history of perennial rhinitis, asthma or both and sensitivity to German cockroach (positive SPT response and cockroach-specific IgE level > 0.35 kUA/L) **Exclusion criteria:** not reported **Percentage withdrawn:** 9.7% (low SLIT), 10% (high SLIT), 25% (placebo) **Percentage with asthma:** 80% **Co-morbidities:** rhinitis **Allowed medication:** not reported **Disallowed medication:** not reported

Interventions	**Control group:** placebo SLIT **SLIT group (low):** 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) **SLIT group (high):** Greer German cockroach 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) **Co-interventions:** not reported
Outcomes	Changes in cockroach IgE, IgG and IgG4 levels and FAB activity, safety assessments and adherence
Notes	**Type of publication:** peer reviewed **Funding:** supported in whole or in part with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health and National Center for Research Resources and National Center for Advancing Translational Sciences, National Institutes of Health. Immunological extracts were donated for some studies by Greer Pharmaceuticals (Lenoir, NC)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind but no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind but no further details
Incomplete outcome data (attrition bias) All outcomes	High risk	Unbalanced dropout (10% in both treatment arms, 25% in control group)
Selective reporting (reporting bias)	Unclear risk	Adverse event outcomes not clearly reported
Other bias	Low risk	None noted

Yukselen 2013

Methods	**Design:** randomised, parallel, double-blind, double-dummy, placebo-controlled trial **Duration:** 52 weeks **Setting:** outpatient clinic in Turkey
Participants	**Population:** 32 participants were randomly assigned to house dust mite SLIT (11), placebo (10) and 1 other treatment that was not relevant to this review (subcutaneous immunotherapy, 11) **Age:** no information **Inclusion criteria:** clinical history of at least 1 year of rhinitis with asthma related to symptoms with house dust mites and no previous treatment with specific immunotherapy **Exclusion criteria:** no previous immunotherapy **Percentage withdrawn:** 9.1% (SLIT), 0% (placebo) **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** rhinitis **Allowed medication:** inhaled budesonide 100 to 800 mcg/d and inhaled salbutamol as required for control of asthma. Intranasal mometasone and antihistamines were given as needed to alleviate symptoms of rhinitis **Disallowed medication:** None of the participants were treated with OCS or LTRA
Interventions	**Control group:** placebo SLIT **SLIT group:** house dust mite SLIT (*D. pteronyssinus* and *D. farinae*), initiation phase then 3 times/wk maintenance up to 28 drops of 1000 TU/mL (cumulative 2 year dose for SLIT approx 347466 TU) **Co-interventions:** inhaled budesonide 100 to 800 mcg/d
Outcomes	Symptom and medication scores, nasal provocation tests, nasal eosinophils, sputum eosinophils; serum-specific IgE, IgG4, IL-10 and IFN-gamma; assessment of clinical efficacy
Notes	**Type of publication:** peer reviewed **Funding:** Allergopharma and Allergo provided allergen solutions

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Based on computer generated randomisation'
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy; 'All study personnel and participants were blinded to treatment assignment for the first year of the immunotherapy'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double dummy; 'All study personnel and participants were blinded to treatment assignment for the first year of

Yukselen 2013 (*Continued*)

		the immunotherapy'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Unbalanced but low dropout (< 10% in both groups). Only 2 randomly assigned participants were not included in the efficacy analyses (6.25%)
Selective reporting (reporting bias)	High risk	Many outcomes not reported at the end of the controlled portion of the study and compared with run-in/baseline rather than with placebo
Other bias	Low risk	None noted

Zeldin 2013

Methods	**Design:** randomised, parallel, double-blind, placebo-controlled dosing trial **Duration:** 10 days (1.4 weeks) **Setting:** France
Participants	**Population:** 63 participants were randomly assigned to 4 doses of house dust mite SLIT (11, 12, 12, 12) and placebo (16) **Age:** adults; no specific details of age **Inclusion criteria:** adults with > 1 year history of HDM-associated allergic asthma controlled with therapies consistent with GINA treatment step 2, 3 or 4; positive skin prick test to HDM; HDM-specific serum IgE 0.7 kU/L **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** placebo SLIT **SLIT group 1:** HDM SLIT 300 IR daily **SLIT group 2:** HDM SLIT 500 IR daily **SLIT group 3:** HDM SLIT 800 IR daily **SLIT group 4:** HDM SLIT 1000 IR daily **Co-interventions:** not reported
Outcomes	Adverse events, physical examination, vital signs, spirometry, ECG and safety laboratory tests
Notes	**Type of publication:** conference abstract **Funding:** not reported
Risk of bias	

Zeldin 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomized 3:1 within dose-regimen groups' but no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind but no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind but no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported
Selective reporting (reporting bias)	High risk	Conference abstract only. Minimal numerical data or details regarding the conduct of the study
Other bias	Low risk	None noted

Zhang 2013

Methods	**Design:** randomised, parallel, open-label, pharmacotherapy controlled trial **Duration:** 104 weeks (2 years) **Setting:** Taiwan
Participants	**Population:** 128 children were randomly assigned to house dust mite SLIT (64) and pharmacotherapy only (64) **Age:** 4 to 14 years (mean not reported) **Inclusion criteria:** mild to moderate asthma symptoms **Exclusion criteria:** not reported **Percentage withdrawn:** not reported **Percentage with asthma:** 100% **Co-morbidities:** not reported **Allowed medication:** not reported **Disallowed medication:** not reported
Interventions	**Control group:** pharmacotherapy only - patients were treated "according to the manufacturer's instructions" **SLIT group:** HDM SLIT (*D. farinae*), dosing not reported **Co-interventions:** not reported
Outcomes	Asthma symptom scores, PEFR, adverse events

Zhang 2013 (*Continued*)

Notes	**Type of publication:** English abstract of a Chinese article **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned to treatment group and control group' but no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	'Of the 128 children, 5 cases dropped out before the study completion'
Selective reporting (reporting bias)	High risk	Conference abstract only. Minimal numerical data or details regarding the conduct of the study
Other bias	Low risk	None noted

Zheng 2012

Methods	**Design:** randomised, parallel, open-label, pharmacotherapy controlled trial **Duration:** 104 weeks but outcomes reported at 25 weeks **Setting:** single-centre hospital asthma centre in China
Participants	**Population:** 106 children randomly assigned to HDM SLIT group (53) and conventional treatment group (53) **Age:** range 4 to 14 years; mean 10 (5) years **Inclusion criteria:** cough variant asthma and a positive skin prick test to *Dermatophagoides farinae*, PEFR not less than 70% predicted; no use of beta$_2$-agonists, H1 receptor blockers or corticosteroids before treatment **Exclusion criteria:** not reported **Percentage withdrawn:** 0 **Percentage with asthma:** 100% (from inclusion criteria) **Co-morbidities:** not reported **Allowed medication:** 'conventional therapy' **Disallowed medication:** No use of beta$_2$-agonists, H1 receptor blockers or corticosteroids before treatment

Zheng 2012 (*Continued*)

Interventions	**Control group:** 'conventional therapy' **SLIT group:** HDM (*D. farinae*) SLIT drops **Co-interventions:** inhaled fluticasone
Outcomes	Improvement in cough/asthma symptom score; time taken until improvement in symptoms; serum eosinophil level; peak expiratory flow
Notes	**Type of publication:** peer-reviewed; published in Chinese only **Funding:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomly divided' - no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears all randomly assigned participants were reported on in safety and efficacy outcomes
Selective reporting (reporting bias)	Unclear risk	Adverse event outcomes not clearly reported
Other bias	Low risk	None noted

ACQ: Asthma Control Questionnaire;**ACTH:** adrenocorticotrophic hormone;**AE:** adverse events;**AU:** allergy units;**BAE:** bioequivalent allergy units; **BU:** biological units; **CAP-RAST:** immunocap-radioallergosorbent test; **CD:** cluster of differentiation; **ECG:** electrocardiogram; **ECP:** eosinophil cationic protein; **DU:** developmental units; **EAACI:** European Academy of Allergy and Clinical Immunology; **FEV_1:** forced expiratory volume in 1 second; **GINA:** Global Initiative for Asthma; **GP:** general practitioner; **HDM:** house dust mite; **ICS:** inhaled corticosteroids; **IFN:** interferon; **IgE:** immunoglobulin E: **IgG:** immunoglobulin G; **IL:** interleukin; **IR:** index units of reactivity; **IU:** international units; **kU/L:** kilounits per litre;**LABA:** long-acting beta$_2$-agonist; **LTRA:** leukotriene receptor antagonist; **MDI:** metered dose inhaler; **OCS:** oral corticosteroids; **PEFR:** peak expiratory flow rate; **PD20:** provocative dose of methacholine required to produce a 20% fall in forced expiratory volume in 1 second; **PC20:** provocative concentration of methacholine required to produce a 20% fall in forced expiratory volume in 1 second; **PEFR:** peak expiratory flow rate; **PNU:** protein nitrogen units; **PRL:** prolactin; **RAST:** radioallergosorbent test; **SABA:** short-acting beta$_2$-agonist; **SLIT:** sublingual immunotherapy; **SQ-T:** standardised quality tablet; **STU:** specific treatment units; **TGF:** transforming growth factor; **Th:** T-helper

cells; **Treg:** T-regulatory cells; **TU:** therapeutic units; **UBE:** equivalent biologic units; **UK:** United Kingdom of Great Britain and Northern Ireland; **USA:** United States of America; **VAS:** visual analogue score.

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

Study	Reason for exclusion
Abdou 1993	Design - not randomised
Agostinis 2009	Population mixed - only 60% had asthma
Andre 2000	Design - not an RCT (review paper)
Andre 2003	Population did not have asthma
Ariano 1998	Design - not randomised
Ariano 2001	Population mixed - only 15% (3/20) had asthma
Ariano 2005	Design - not randomised
Bergmann 2014	Population mixed - only 30% of participants had asthma
Bernstein 2011	Population mixed - unclear how many had asthma (study author contacted, no reply)
Blaiss 2011	Population mixed - only 26% (89/344) had asthma
Bommarito 2009	Population mixed - unclear how many had asthma (study author contacted, no reply)
Buchanan 2004	Population did not have asthma - egg allergy
Bufe 2004	Population mixed - only 42% (68/161) had asthma
Bufe 2009	Population mixed - only 42% (105/243) had asthma
Bush 2011	Population mixed - only 32% (10/31) had asthma
Cadario 2008	Wrong comparator - continuous vs intermittent SLIT
Cao 2007	Population mixed - unclear how many had asthma (study author contacted, no reply)
Clavel 1998	Population mixed - only 9% (26/136) had asthma
Cortellini 2010	Population mixed - only 14% (4/27) had asthma
Cosmi 2006	Population mixed - only 45% (9/20) had asthma

(*Continued*)

Cox 2012	Population mixed - only 20% of participants had asthma
Creticos 2014	Population mixed - only 8% (36/429) had asthma
D'Ambrosio 1996	Population mixed - only 23% (7/30) of completers had asthma
D'Anneo 2008	Population mixed - unclear how many had asthma (study author contacted, no reply)
D'Anneo 2010	Population mixed - only 50% (15/30) had asthma
de Blay 2007	Population mixed - only 28% (29/104) had asthma
de Bot 2008	Population mixed - only 37% (93/251) had asthma
Deb 2012	Design - not randomised
Di Rienzo 2003	Design - not randomised
Di Rienzo 2006	Population did not have asthma
Didier 2011	Population mixed - only 14% (81/581) had asthma
Drachenberg 2001	Population mixed - only 22% had asthma
Durham 2012	Population mixed - only 24% (151/634) had asthma
Fancello 2008	Population mixed - unclear how many had asthma (study author contacted, no reply)
Feliziani 1995	Population mixed - unclear how many had asthma (study author contacted, no reply)
Ferrer 2003	Wrong intervention - subcutaneous immunotherapy
Germouty 1986	Wrong intervention
Giovane 1994	Population did not have asthma
Gozalo 1997	Design - not randomised
Hedlin 1999	Wrong intervention - subcutaneous immunotherapy
Hirsch 1997	Population mixed - only 73% (22/30) had asthma
Holt 2013	Population did not have asthma (prevention study)
Ibañez 2007	Population mixed - only 40% (24/60) had asthma

(*Continued*)

Leonardi 2009	Population did not have asthma (retrospective study)
Leonardi 2010	Population mixed - only 64% (21/33) had asthma
Lombardi 2001	Design - not randomised (alternate allocation)
Ma 2010	Wrong comparator
Maksimovic 2002	Population mixed - unclear how many had asthma (study author contacted, no reply)
Malling 2005	Population did not have asthma
Malling 2009	Population mixed - across groups, only 8.8% to 11% had asthma
Maloney 2014	Design - post hoc analysis, not an RCT
Marappan 2007	Population mixed - unclear how many had asthma (study author contacted, no reply)
Marappan 2008	Population mixed - unclear how many had asthma (study author contacted, no reply)
Maria 2004	Design - not randomised
Marogna 2004	Population mixed - only 61% (311/511) had asthma
Marogna 2010	Population mixed - rhinitis and intermittent asthma
Marogna 2012	Wrong comparator
Mauro 2004	Wrong comparator - head-to-head SLIT vs SCIT (no placebo)
Mayorga 2004	Wrong comparator - head-to-head SLIT vs SCIT (no placebo)
Melarnanci 2004	Design - not randomised
Moreno-Ancillo 2007	Population mixed - only 61% (64/105) had asthma
Murphy 2013	Population mixed - only 27% (89/329) had asthma
Mussler 2009	Design - no control group (trial extension)
NCT02014623	Methods - non-randomised, not asthma
Nelson 2011	Population mixed - only 24% (104/438) had asthma
Nettis 2007	Population mixed - only 25% (10/40) had asthma

(*Continued*)

Nolte 2014	Population mixed and did not all have asthma (study author confirmed the study was not designed to assess asthma and should not be included)
O'Hehir 2009	Population mixed - only 78% (21/27) had asthma
Oppenheimer 1994	Population did not have asthma
Osipova 2003	Population did not have asthma (latex allergy)
Ozdemir 2007	Design - not randomised
Palma-Carlos 2007	Population did not have asthma
Passalacqua 1998	Population mixed - only 30% (6/20) had asthma
Passalacqua 1999	Population mixed - only 43% (13/30) had asthma
Passalacqua 2006	Population mixed - only 23% (13/56) of completers had asthma
Peter 2009	Population mixed - unclear how many had asthma (study author contacted, no reply)
Pfaar 2008	Population mixed - only 29% (54/185) had asthma
Pozzan 2010	Population mixed - only 33% (17/52) had asthma
Pradalier 1999	Population mixed - only 34% (42/123) had asthma; the study excluded patients taking daily medications
Purello-D'Ambrosio 1999	Population mixed - only 50% (15/30) had asthma
Queiros 2012	Population mixed - only 51% (36/70) of completers had asthma
Quercia 2011	Population mixed - only 44% (14/32) had asthma
Reich 2011	Population mixed - only 41% (113/276) had asthma
Reinert 1983	Population did not have asthma
Rodriguez 2006	Wrong comparator
Rodriguez Santos 2008	Population mixed - only 70% had asthma (or asthma and rhinitis)
Romano 2006	Design - not randomised
Romo 1996	Wrong comparator
Sambugaro 2003	Design - not randomised

(*Continued*)

Sanchez 1989	Design - not randomised
Scordamaglia 1997	Population mixed - only 43% had asthma
Shore 1980	Design - not randomised
Srivastava 2007	Wrong intervention - subcutaneous immunotherapy
Stelmach 2012	Population mixed - only 33% (20/60) had asthma
Stevenson 1984	Wrong intervention
Stosovic 2011	Design - 'adequate matched controls'
Sánchez 2001	Design - not randomised
Tabar 2008	Wrong intervention - subcutaneous immunotherapy
Tari 1990	Population mixed - unclear how many had asthma (study author contacted, no reply)
Taudorf 1987	Population mixed - only 38% (15/39) had asthma
TePas 2004	Population did not have asthma
Tomic-Spiric 2010	Population mixed - only 44% had asthma (confirmed by study authors)
Urbanek 1982	Population mixed - unclear how many had asthma (confirmed by translator)
Valovirta 2006	Population mixed - only 41% (36/88) had asthma
Wahn 2009	Population mixed - only 21% (57/266) had asthma
Wahn 2012	Population mixed - only 31% (64/207) had asthma
Wang 2006	Wrong intervention - subcutaneous immunotherapy
Worm 2006	Population mixed - only 28% (52/185) had asthma
Worm 2014	Population mixed - only 24.6% of participants had asthma
Wüthrich 2003	Population mixed - only 50% (14/28) had asthma
Yuksel 1999	Population mixed - only 28% (11/39) had asthma

Characteristics of studies awaiting assessment *[ordered by study ID]*

EUCTR2008-03906-32-CZ

Methods	Randomised, double-blind, placebo-controlled, multi-national, phase 3 study
Participants	Adults aged 18 to 65 years with grass pollen-related allergic rhinoconjunctivitis for at least the last 2 grass pollen seasons. Patients with moderate or persistent asthma, or requiring doses of ICS greater than 400 mcg budesonide (or equivalent), were excluded (full inclusion and exclusion criteria at http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-003906-32-CZ)
Interventions	ORALAIR Grasses 300 IR sublingual tablets vs placebo
Outcomes	Average adjusted symptom score (AASS), average rhinoconjunctivitis total symptom score (ARTSS), average rescue medication score (ARMS), average combined score (ACS) (taking into account the RTSS and rescue medication score (RMS)), average rhinoconjunctivitis symptom score (ARSS), proportion of symptom-controlled days (PSCD) , global evaluation of the efficacy of sublingual tablets of grass pollen allergen extract by the patient, adverse events
Notes	Not clear if ongoing or completed, no results published, unable to link to a peer-reviewed full text. Unlikely to have recruited sufficient patients with asthma for inclusion

Kozhem'iaka 1979

Methods	Unknown, conducted in 1979
Participants	Children with allergies, no other information
Interventions	Peroral house dust mite vaccine
Outcomes	Unknown
Notes	Title only, unable to find additional information but no indication the children had asthma

Ma 2014

Methods	Randomised, parallel, open-label trial
Participants	120 children aged 5 to 14 years with asthma and allergic rhinitis
Interventions	HDM SLIT
Outcomes	ACQ, specific IgE, rhinitis symptoms, monthly medication use, adverse reactions
Notes	Identified in prepublication search. Abstract only available in English; full text translation will be obtained for review update

NCT00172341

Methods	Randomised, parallel, double-blind trial at the National Taiwan University Hospital
Participants	Children between 5 and 15 years of age with mild to moderate asthma for at least 1 year and with sensitisation to domestic mites (positive skin prick test to D. pt and D. f) (full inclusion and exclusion criteria at https://clinicaltrials.gov/ct2/show/NCT00172341)
Interventions	Staloral (house dust mite SLIT) vs placebo
Outcomes	"Change of asthmatic scores from baseline"
Notes	First received: September 12, 2005 Last updated: November 2, 2005 Last verified: July 2004 Li-Chieh Wang, MD 886-2-23123456 ext 5127 lcwang5@ha.mc.ntu.edu.tw Clinicaltrials.gov record: NCT00172341 No study results found

NCT00501527

Methods	Randomised, double-blind, placebo-controlled, safety/efficacy study
Participants	Ages 12 to 50 years with confirmed *Phleum pratense* allergy and clinical history of allergic rhinoconjunctivitis and/or asthma (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT00501527)
Interventions	2 different doses of *P. pratense* pollen SLIT vs placebo
Outcomes	Symptom scores, nasal provocation tests, dose-response skin prick tests, Asthma Quality of Life Questionnaire, Rhinitis Quality of Life Questionnaire, medication scores, visual scales, 'in vitro' immunological tests, adverse events
Notes	Study completed in 2010 but no results published on Clinical Trials website and unable to link to a peer-reviewed full text

NCT00623701

Methods	Randomised, double-blind, placebo-controlled, multi-centre, multi-national, efficacy/safety study
Participants	Aged 18 to 65 years with allergic rhinoconjunctivitis attributable to grass pollen (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT00623701 and https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-000823-16/DE)
Interventions	Grass pollen SLIT vs placebo
Outcomes	Primary endpoint: difference between active treatment and placebo in the change of the area under the curve of the symptom - medication - score (SMS) from the baseline season to the season after 1 year of treatment

NCT00623701 (*Continued*)

Notes	Study completed in 2011 but no results published on Clinical Trials website and unable to link to a peer-reviewed full text

NCT00803244

Methods	Randomised, double-blind, placebo-controlled, multi-national, phase 3 efficacy/safety study
Participants	Aged 12 to 65 years with grass pollen-related allergic rhinoconjunctivitis for at least the last 2 grass pollen seasons. Patients with moderate or persistent asthma, or requiring doses of ICS greater than 400 mcg budesonide (or equivalent) , were excluded (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT00803244)
Interventions	Grass pollen SLIT vs placebo
Outcomes	Average adjusted symptom score, proportion of symptom-controlled days, global patient evaluation of the efficacy of treatment, adverse events
Notes	Not clear if ongoing or completed, no results published, unable to link to a peer-reviewed full text. Unlikely to have recruited sufficient patients with asthma for inclusion

NCT01052610

Methods	Randomised, double-blind, placebo-controlled
Participants	Children aged 6 to 18 years with bronchial asthma and/or allergic rhinitis allergic to house dust mites first diagnosed at least 2 years before the study (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT01052610)
Interventions	HDM SLIT vs placebo
Outcomes	Clinical symptoms of asthma and allergic rhinitis and use of rescue medication, change in percent of regulatory lymphocytes in peripheral blood, assessment of inflammatory markers in exhaled breath condensate and FeNO, non-specific bronchial hyperreactivity
Notes	Staus of study unknown, no results published on Clinical Trials website, unable to link to a peer-reviewed full text

NCT01529437

Methods	Randomised, double-blind, placebo-controlled phase 1 safety study
Participants	Aged 5 years and older with timothy grass and *Dermatophagoides farinae* sensitivity and allergic rhinoconjunctivitis with or without asthma perennially or during grass pollen season (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT01529437)
Interventions	HDM and/or Timothy grass pollen SLIT vs placebo

NCT01529437 (*Continued*)

Outcomes	Adverse events
Notes	Study reported as completed but no study results published on Clinical Trials website and unable to link to a peer-reviewed full text

NCT01603056

Methods	Randomised, double-blind, placebo-controlled, multi-centre, efficacy/safety study
Participants	Aged 5 to 55 years with history of HDM-induced allergic rhinitis. Patients with severe asthma excluded (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT01603056)
Interventions	HDM SLIT vs placebo
Outcomes	Rhinoconjunctivitis symptoms and medication scores, asthma symptom scores, number of healthy days in the study, Asthma Quality of Life Questionnaire, Rhinitis Quality of Life Questionnaire, rescue medication use, nasal complaint scores on visual analogue scale
Notes	Large study reporting enrolment of 617 participants but no results published on Clincal Trials website and unable to link to peer-reviewed full text

Novembre 1991

Methods	"Controlled study"
Participants	Children with allergic asthma
Interventions	Sublingual immunotherapy (no other details)
Outcomes	Unknown
Notes	Title only, unable to find additional information

Potter 2003

Methods	Unknown
Participants	Unknown
Interventions	Sublingual immunotherapy (no other details)
Outcomes	Unknown
Notes	Title only, unable to find additional information

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

EUCTR2012-005678-76

Trial name or title	24-month, multi-centre, prospective, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, tolerability and cost-effectiveness of allergen-specific sublingual immunotherapy (SLIT) in combination with standard of care (SoC) in paediatric allergic asthma
Methods	Multi-centre, prospective, randomised, double-blind, placebo controlled, parallel-group study
Participants	Outpatient children aged 5 to < 18 years, clinically stable allergic asthma diagnosed by physician according to the GINA guidelines (2) at least 1 year before study entry, with/without concomitant allergic rhinoconjunctivitis; mono-sensitisation to HDM, assessed by skin prick testing (wheal diameter > 3 mm) and/or by ImmunoCAP (specific IgE > 3.5 kU/L) (full inclusion and exclusion criteria at http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2012-005678-76-IT)
Interventions	HDM SLIT vs placebo
Outcomes	Reduction from baseline of at least 50% in inhaled CS (ICS) doses or withdrawal of asthma-controller medications, Asthma Control Test-ACT and Childhood-ACT, asthma exacerbations requiring OCS, rhinoconjunctivitis symptoms and signs, adverse events, QoL, changes in skin test reactivity, SLIT adherence, cost-effectiveness
Starting date	30/08/2013
Contact information	Clinical Pharmacology & Trials Address: via G. Gaslini 3-5 16147 Genova Italy Telephone: +390105636461 Email: ornelladellacasa@ospedale-gaslini.ge.it
Notes	Ongoing study, highly likely to be relevant and including important and validated outcomes

Hassan 2010

Trial name or title	Efficacy of sublingual immunotherapy in patient with bronchial asthma with allergic rhinitis
Methods	Double-blind randomised controlled trial conducted at the National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka, Bangladesh
Participants	60 patients with bronchial asthma and allergic rhinitis
Interventions	Mite allergen SLIT

Hassan 2010 (*Continued*)

Outcomes	Not stated
Starting date	February 2009 to January 2010
Contact information	None
Notes	Conference abstract

NCT01700192

Trial name or title	Long-Term Efficacy and Safety Study of SCH 900237/MK-8237 in Children and Adults With House Dust Mite-Induced Allergic Rhinitis/Rhinoconjunctivitis (P05607)
Methods	Randomised, double-blind, placebo-controlled safety and efficacy study
Participants	Aged 12 years and over with history of AR/ARC to house dust of 1 year duration or more (with or without asthma). Patients with unstable or severe asthma or requiring high doses of ICS in the 6 months before enrolment excluded (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT01700192)
Interventions	HDM SLIT vs placebo
Outcomes	Average total combined rhinitis score (TCRS), adverse events, average rhinitis daily symptom score (Rhinitis DSS), average total combined rhinoconjunctivitis score (TCS), average rhinitis daily medication score (Rhinitis DMS), average allergic rhinitis/rhinoconjunctivitis symptoms assessed by visual analogue scale (VAS)
Starting date	01/2013
Contact information	Responsible party: Merck Sharp & Dohme Corp
Notes	Unlikely to recruit sufficient patients with asthma to meet inclusion criteria for this review

NCT01930461

Trial name or title	Dose Ranging Study of SLIT Tablets of House Dust Mite Allergen Extracts (HDM) in Adults With HDM-associated Allergic Asthma
Methods	Randomised, double-blind, placebo-controlled, dose-ranging efficacy/safety study
Participants	Aged 18 to 50 years, diagnosed asthma and rhinitis with medical history consistent with HDM-induced allergic asthma and rhinitis. Asthma must be stable at time of enrolment (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT01930461)
Interventions	3 different doses of HDM SLIT vs placebo

NCT01930461 (*Continued*)

Outcomes	Asthma control test (ACT) score, rhinoconjunctivitis symptoms and rescue medication use, Asthma Quality of Life (AQLQ), number of asthma exacerbations, adverse events
Starting date	09/2013
Contact information	Pascal Demoly, MD, Montpellier, France. Responsible party: Stallergenes
Notes	Ongoing study, highly likely to be relevant and including important and validated outcomes

NCT02005627

Trial name or title	Grass Pollen Allergen Immunotherapy Tablet (AIT) Time Course Study (Pollen+)
Methods	Randomised, double-blind, placebo-controlled, efficacy/safety study
Participants	Aged 18 to 65 years with grass pollen-induced allergic rhinoconjunctivitis for at least 2 years with peak symptoms in May-July, with or without mild seasonal asthma. Patients with perennial asthma requiring regular inhaled corticosteroids excluded (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT02005627)
Interventions	Grass pollen SLIT vs placebo
Outcomes	Early phase response (EPS) after nasal allergen challenge (NAC), the area under the curve (AUC) of the early phase response (total nasal symptom score (TNSS) 0 to 60 minutes) following grass pollen nasal allergen challenge, early phase (EP) and late phase response (LPR) to intradermal grass pollen allergen, blood basophil activation, combined symptom + medication score, change from proportion of allergen-specific T reg cells
Starting date	12/2013
Contact information	Esther H Steveling, MD Tel: +44(0)7872850275 e.steveling@imperial.ac.uk
Notes	Unlikely to recruit sufficient patients with asthma to meet inclusion criteria for this review

NCT02277483

Trial name or title	Efficacy and Safety of LAIS® Mites Sublingual Tablets in Patients Aged Over 60 Years Suffering From House Dust Mite-induced Allergic Rhino-conjunctivitis With/Without Asthma
Methods	Randomised, open-label, safety/efficacy study
Participants	Aged 60 years or older with a history of at least 2 years of house dust mite (HDM)-induced allergic rhinitis and/or allergic rhinoconjunctivitis with or without mild to moderate controlled asthma (full inclusion and exclusion criteria at https://www.clinicaltrials.gov/ct2/show/NCT02277483)

NCT02277483 (*Continued*)

Interventions	HDM SLIT vs standard pharmacotherapy
Outcomes	Total combined score (TCS) (TCS = rhinoconjunctivitis total symptom score (RTSS) and total rescue medication score (RTMS)), Total rescue medication score (RTMS)
Starting date	10/2014
Contact information	Yun-Kyoung Kim Tel: 82-31-219-4467 forsake326@gmail.com
Notes	Unlikely to recruit sufficient patients with asthma to meet inclusion criteria for this review

RPCEC00000125

Trial name or title	Therapeutic effect and security of the sublingual vaccines of house-dust mites, with different posological regimens in asthmatic children sensitive to those mites
Methods	Randomised, double-blind, placebo controlled trial
Participants	Aged 5 to 15 years with allergic asthma provoked by house dust mite (*D. pteronyssinus* or *B. tropicalis*). Only patients with mild or moderate asthma included; those with intermittent or severe asthma excluded (full inclusion and exclusion criteria at http://apps.who.int/trialsearch/Trial2.aspx?TrialID=RPCEC00000125)
Interventions	HDM SLIT vs placebo
Outcomes	Symptom score (dyspnoea, cough, expectoration, wheeze and tightness), medication scores, PEFR, skin reactivity, QOL, allergen-specific antibodies, adverse events
Starting date	16/10/2013
Contact information	R. Castro Almarales National Center of Bioproducts (BIOCEN), Allergen Department Carretera de Beltran Km 1 1/2 CP 13050, Box 6048 Bejucal, Mayabeque Cuba Tel: 53-047-066-82201 - 07, ext 2100, 2101 rcastro@biocen.cu
Notes	Likely to meet inclusion criteria for this review

DATA AND ANALYSES

Comparison 1. SLIT vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation requiring ED or hospital visit	1	47	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Quality of life			Other data	No numeric data
3 Serious adverse events	22	2560	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
4 Exacerbation requiring OCS	2	77	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 All adverse events	19	1755	Odds Ratio (M-H, Random, 95% CI)	1.70 [1.21, 2.38]
6 Bronchial provocation	4	139	Std. Mean Difference (IV, Random, 95% CI)	0.69 [-0.04, 1.43]
6.1 PD20	1	52	Std. Mean Difference (IV, Random, 95% CI)	1.46 [0.84, 2.08]
6.2 PC20	3	87	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.26, 1.05]
7 ICS use	2	174	Mean Difference (IV, Random, 95% CI)	35.10 [-50.21, 120.42]
8 Unvalidated asthma symptom scores			Other data	No numeric data
9 Unvalidated medication use scores			Other data	No numeric data

Comparison 2. Subgroup and sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events by age	19	1755	Odds Ratio (M-H, Random, 95% CI)	1.70 [1.21, 2.38]
1.1 Children (mean age < 18 years)	8	626	Odds Ratio (M-H, Random, 95% CI)	2.13 [0.83, 5.47]
1.2 Teenagers and adults (mean age > 18 years)	8	964	Odds Ratio (M-H, Random, 95% CI)	1.48 [1.06, 2.06]
1.3 Mixed age study population or age range not specified	3	165	Odds Ratio (M-H, Random, 95% CI)	2.06 [0.47, 9.05]
2 Adverse events by allergen	18	1726	Odds Ratio (M-H, Random, 95% CI)	1.70 [1.21, 2.38]
2.1 HDM SLIT	10	1386	Odds Ratio (M-H, Random, 95% CI)	1.47 [1.10, 1.97]
2.2 Pollen SLIT	6	251	Odds Ratio (M-H, Random, 95% CI)	5.48 [1.99, 15.05]
2.3 Other/mixed allergens	2	89	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events by study duration	19	1815	Odds Ratio (M-H, Random, 95% CI)	1.70 [1.21, 2.38]
3.1 Duration less than 52 weeks	7	427	Odds Ratio (M-H, Random, 95% CI)	1.53 [0.38, 6.19]
3.2 Duration 52 weeks and longer	12	1388	Odds Ratio (M-H, Random, 95% CI)	1.77 [1.22, 2.58]

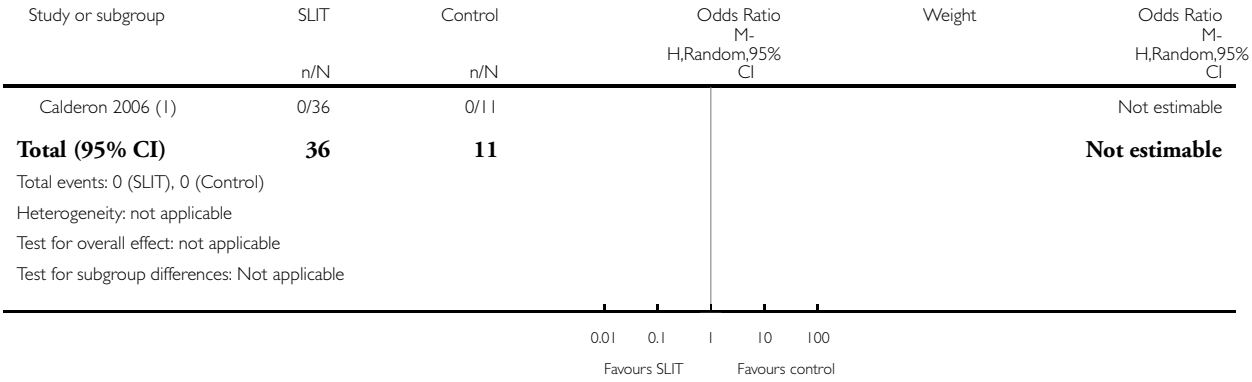
4 Adverse events (sensitivity for risk of bias: blinded studies only)	14	1329	Odds Ratio (M-H, Random, 95% CI)	1.47 [1.10, 1.96]
5 Adverse events (sensitivity analysis removing studies with mixed population of asthma and rhinitis)	13	1293	Odds Ratio (M-H, Random, 95% CI)	1.42 [1.06, 1.91]

Analysis 1.1. Comparison 1 SLIT vs control, Outcome 1 Exacerbation requiring ED or hospital visit.

Review: Sublingual immunotherapy for asthma

Comparison: 1 SLIT vs control

Outcome: 1 Exacerbation requiring ED or hospital visit



(1) 4 different dose arms combined

Analysis 1.2. Comparison 1 SLIT vs control, Outcome 2 Quality of life.

Quality of life

Study	Outcome name	Scoring	Data type	SLIT	Control
Bousquet 1999	Short-Form Health Status Survey; physical pain	22 items divided into 7 scales measuring physical functioning, limitations in role functioning due to physical health problems,social functioning, general	Means, no variance	86.2 (n=18)	68.3 (n=20)

Quality of life (*Continued*)

		mental health, general health perception, physical pain and vitality. Each scale is 0 to 100 with lower score for poorer health. Measured at 25 months.			
Bousquet 1999	Short-Form Health Status Survey; general mental health domain	22 items divided into 7 scales measuring physical functioning, limitations in role functioning due to physical health problems,social functioning, general mental health, general health perception, physical pain and vitality. Each scale is 0 to 100 with lower score for poorer health. Measured at 25 months.	Means, no variance	79.7 (n=18)	60.7 (n=20)
Bousquet 1999	Short-Form Health Status Survey; general perception of health domain	22 items divided into 7 scales measuring physical functioning, limitations in role functioning due to physical health problems,social functioning, general mental health, general health perception, physical pain and vitality. Each scale is 0 to 100 with lower score for	Means, no variance	76.5 (n=18)	56.8 (n=20)

Quality of life (*Continued*)

		poorer health. Measured at 25 months.			
Lewith 2002	Diary quality of life assessment	Proportion of days in each of the assessment periods when no problem was reported in six categories of life. Mean improvement scores at end of treatment	Means (SD)	0.090 (-0.096 to 0.150)	0.117 (-0.096 to 0.150)

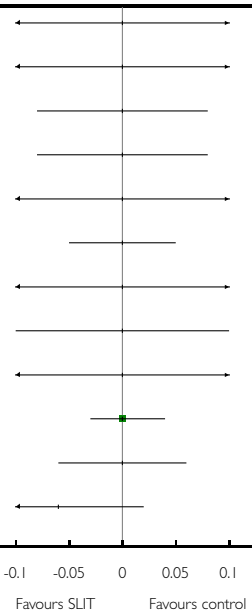
Analysis 1.3. Comparison 1 SLIT vs control, Outcome 3 Serious adverse events.

Review: Sublingual immunotherapy for asthma

Comparison: 1 SLIT vs control

Outcome: 3 Serious adverse events

Study or subgroup	SLIT n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Alvarez-Cuesta 2007	0/17	0/16		0.7 %	0.0 [-0.11, 0.11]
Calderon 2006 (1)	0/36	0/11		0.6 %	0.0 [-0.12, 0.12]
Corzo 2014 (a) (2)	0/54	0/17		1.2 %	0.0 [-0.08, 0.08]
Corzo 2014 (b) (3)	0/54	0/18		1.4 %	0.0 [-0.08, 0.08]
Criado Molina 2002	0/16	0/16		0.6 %	0.0 [-0.11, 0.11]
Dahl 2006	0/61	0/32		3.6 %	0.0 [-0.05, 0.05]
Eifan 2009	0/15	0/14		0.5 %	0.0 [-0.12, 0.12]
Fadel 2010	0/41	0/14		0.9 %	0.0 [-0.10, 0.10]
Lue 2006	0/10	0/10		0.3 %	0.0 [-0.17, 0.17]
Mosbech 2014 (4)	15/461	4/143		8.0 %	0.00 [-0.03, 0.04]
NCT00633919	2/63	2/61		2.1 %	0.00 [-0.06, 0.06]
Niu 2006	1/49	4/48		1.0 %	-0.06 [-0.15, 0.02]



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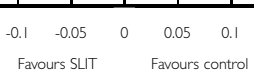
Study or subgroup	SLIT n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Pajno 2000	0/12	1/12		0.2 %	-0.08 [-0.29, 0.12]
Shao 2014	0/168	0/96		29.4 %	0.0 [-0.02, 0.02]
Stelmach 2009	0/20	0/15		0.7 %	0.0 [-0.11, 0.11]
Troise 2009 (5)	0/14	0/10		0.3 %	0.0 [-0.15, 0.15]
Vourdas 1998	0/34	0/32		2.4 %	0.0 [-0.06, 0.06]
Wang 2014	4/322	1/162		27.3 %	0.01 [-0.01, 0.02]
Wood 2014 (6)	0/61	0/28		2.9 %	0.0 [-0.05, 0.05]
Zeldin 2013 (7)	0/47	0/16		1.1 %	0.0 [-0.09, 0.09]
Zhang 2013	0/64	0/64		8.8 %	0.0 [-0.03, 0.03]
Zheng 2012	0/53	0/53		6.1 %	0.0 [-0.04, 0.04]
Total (95% CI)	**1672**	**888**		**100.0 %**	**0.00 [-0.01, 0.01]**

Total events: 22 (SLIT), 12 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.54$, df = 21 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable



(1) 4 different dosing arms combined

(2) 4 different dosing arms combined

(3) 4 different dosing arms combined

(4) 3 different dosing arms combined

(5) "Severe" adverse events

(6) High dose and low dose combined

(7) 4 different dose arms combined

Analysis 1.4. Comparison 1 SLIT vs control, Outcome 4 Exacerbation requiring OCS.

Review: Sublingual immunotherapy for asthma

Comparison: 1 SLIT vs control

Outcome: 4 Exacerbation requiring OCS

Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Calderon 2006 (1)	0/36	0/11			Not estimable
Pajno 2003	0/15	0/15			Not estimable
Total (95% CI)	**51**	**26**			**Not estimable**
Total events: 0 (SLIT), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

(1) 4 different dose arms combined

Analysis 1.5. Comparison 1 SLIT vs control, Outcome 5 All adverse events.

Review: Sublingual immunotherapy for asthma

Comparison: 1 SLIT vs control

Outcome: 5 All adverse events

Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Alvarez-Cuesta 2007	0/17	0/16			Not estimable
Bahceciler 2001	0/8	0/7			Not estimable
Bousquet 1999	15/42	14/43		11.8 %	1.15 [0.47, 2.82]
Caffarelli 2000	0/24	0/20			Not estimable
Calderon 2006 (1)	36/36	10/11		1.1 %	10.43 [0.40, 275.32]
Eifan 2009	0/15	0/14			Not estimable
Gomez Vera 2005	0/30	0/30			Not estimable

(*Continued* . . .)

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Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Ippoliti 2003	0/47	0/39			Not estimable
Keles 2011	0/13	0/12			Not estimable
La Grutta 2007	0/33	0/23			Not estimable
Leng 1990	1/9	0/9		1.0 %	3.35 [0.12, 93.83]
Marogna 2005	4/29	0/23		1.3 %	8.29 [0.42, 162.48]
Mosbech 2014 (2)	290/461	77/143		37.4 %	1.45 [0.99, 2.12]
Mungan 1999	2/15	0/11		1.1 %	4.26 [0.18, 98.07]
NCT00633919 (3)	24/63	21/61		16.4 %	1.17 [0.56, 2.44]
Niu 2006	6/49	7/48		7.5 %	0.82 [0.25, 2.64]
Shao 2014	39/168	9/96		15.0 %	2.92 [1.35, 6.34]
Troise 2009	11/14	4/10		3.4 %	5.50 [0.91, 33.18]
Vourdas 1998	8/34	2/32		4.0 %	4.62 [0.90, 23.70]
Total (95% CI)	**1107**	**648**		**100.0 %**	**1.70 [1.21, 2.38]**

Total events: 436 (SLIT), 144 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 11.52$, df = 10 (P = 0.32); $I^2 = 13\%$

Test for overall effect: Z = 3.06 (P = 0.0022)

Test for subgroup differences: Not applicable

(1) 4 different dosing arms combined

(2) 3 different dosing arms combined

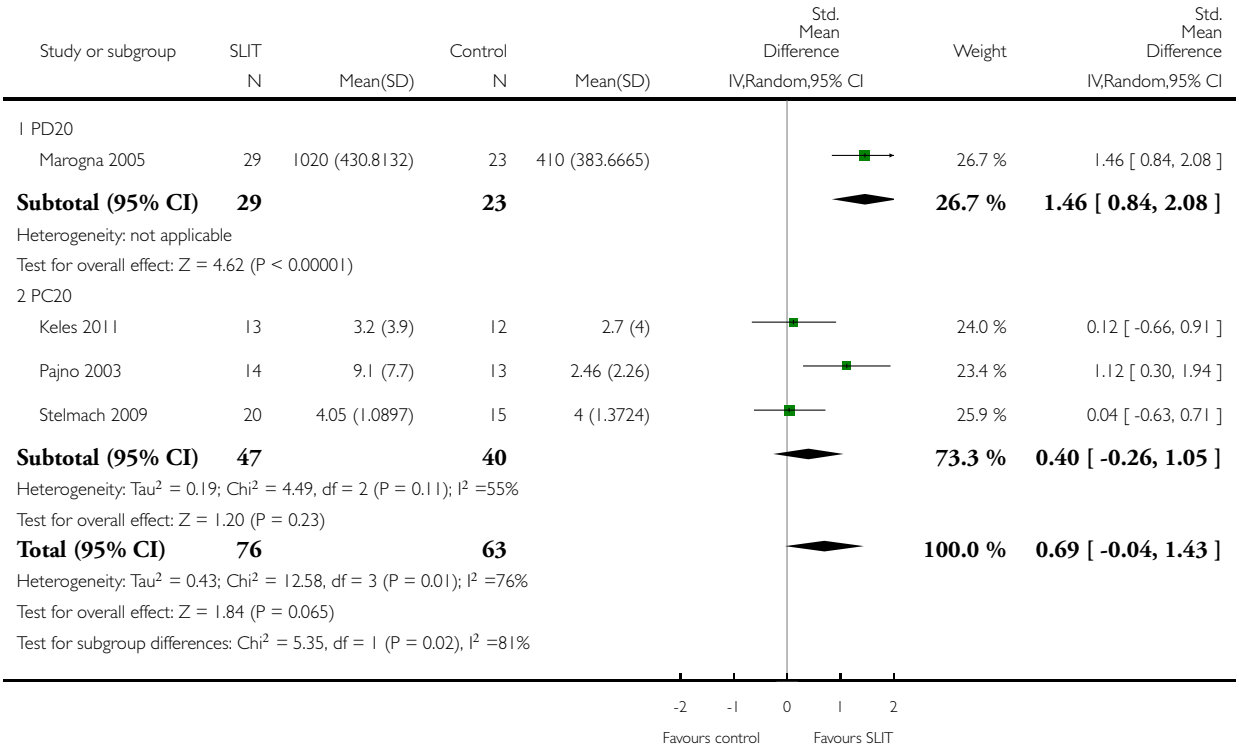
(3) Adverse events only reported if over 5% of participants were affected

Analysis 1.6. Comparison 1 SLIT vs control, Outcome 6 Bronchial provocation.

Review: Sublingual immunotherapy for asthma

Comparison: 1 SLIT vs control

Outcome: 6 Bronchial provocation

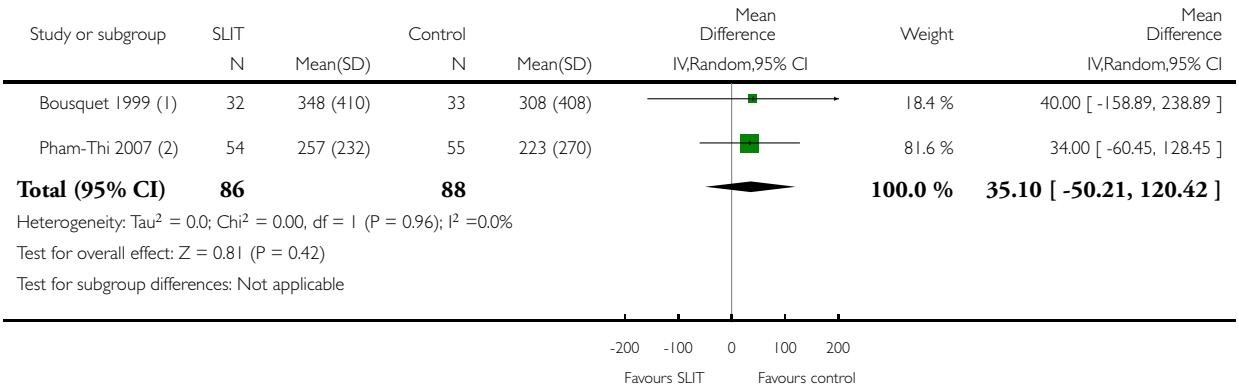


Analysis 1.7. Comparison 1 SLIT vs control, Outcome 7 ICS use.

Review: Sublingual immunotherapy for asthma

Comparison: 1 SLIT vs control

Outcome: 7 ICS use



(1) ICS use (mcg beclomethasone/day)

(2) ICS use (mcg budesonide/day)

Analysis 1.8. Comparison 1 SLIT vs control, Outcome 8 Unvalidated asthma symptom scores.

Unvalidated asthma symptom scores

Study	Outcome name	Scoring	Data type	SLIT	Control
Alvarez-Cuesta 2007	Bronchial symptom scores during cat exposure	0 (absent) to 3 (severe), multiple measurements	Mean area under the curve (CI)	45.74 (10.8 to 80. 67) n=17	143.44 (61.98 to 224.9) n=16
Bousquet 1999	Daytime asthma score	0 (no symptoms) to 3 (severe symptoms)	Mean change (SD)	0.17 (0.5) n=32	0.19 (0.44) n=33
Bousquet 1999	Nighttime asthma score	0 (no symptoms) to 3 (severe symptoms)	Mean change (SD)	0.17 (0.51) n=32	0.11 (0.35) n=33
Caffarelli 2000	Bronchial symptom score	0 (no symptoms) to 3 (severe symptoms) , weekly mean of daily ratings during pollen season	Weekly mean (SD)	2.4 (2.7) n=24	4.6 (3.5) n=20
Cooper 1984	Days with asthma symptoms	Number of days during pollen season (max 70)	Means, no variance	34.3, n=11	40.3, n=8

Unvalidated asthma symptom scores (*Continued*)

Cooper 1984	Asthma symptom severity score	0 (none) to 3 (severe)	Means, no variance	40.5, n=11	58.2, n=8
Dahl 2006	Asthma symptom score (before pollen season)	0 (no symptoms) to 3 (severe symptoms) , rated daily	Mean (SD)	0.23 (0.34) n=73	0.33 (0.33) n=40
Dahl 2006	Asthma symptom score (during pollen season)	0 (no symptoms) to 3 (severe symptoms) , rated daily	Mean (SD)	0.44 (0.68) n=68	0.74 (0.92) n=39
Dahl 2006	Percentage well days	Defined post hoc as a day during the pollen season with a symptom score 2 or less and no rescue medication required	Mean (SD)	58.9 (27.6) n=61	38.2 (32.9) n=32
Eifan 2009	Visual analogue score for asthma/rhinitis symptoms	0 cm (no symptoms) to 10 cm (highest level of symptoms)	Mean (SD)	2.7 (2.1) n=15	4.6 (1.5) n=14
Eifan 2009	Asthma symptom score	0 (no symptoms) to 3 (severe symptoms) , rated daily	Mean (SD)	0.2 (0.4) n=15	2.5 (1.6) n=14
Ippoliti 2003	Asthma symptom score	0 (no symptoms) to 3 (severe symptoms) , mean of daily ratings throughout 6 months of therapy	Means, no variance	1.28, n=47	3.15, n=39
Lewith 2002	Visual analogue scale, asthma severity	Higher scores indicate more severe asthma	Mean (SE), read from graph	2.44 (0.32) n=101	2.62 (0.31) n=101
Lewith 2002	Number of asthma symptoms	Unclear	Mean (SE), read from graph	0.99 (0.14) n=101	1.14 (0.15) n=101
Lue 2006	Daytime asthma symptom score	0 (no symptoms) to 3 (severe symptoms) , rated daily	Mean (SD)	0.13 (0.19) n=10	0.49 (0.38) n=10
Lue 2006	Nighttime asthma symptom score	0 (no symptoms) to 3 (severe symptoms) , rated daily	Mean (SD)	0.16 (0.15) n=10	0.50 (0.47) n=10

Unvalidated asthma symptom scores (*Continued*)

Marogna 2005	Composite asthma symptom score	Monthly individual symptom ratings 0 (absent) to 3 (severe) combined	Mean (SEM), read from graph	50 (15) n=29	150 (25) n=23
Mungan 1999	Asthma symptom score	0 (no symptoms) to 3 (severe symptoms) , rated daily during second 6 months of treatment	Means, no variance	0.41, n=15	0.88, n=11
Niu 2006	Daily asthma symptom score	Combined daytime and nighttime score, each rated 0 (no symptoms) to 3 (severe symptoms)	Means and p-values for within group change	-0.07 (p=0.108) n=49	0.01 (p=0.998) n=48
Pajno 2000	Nighttime asthma symptom score	Number per month during last year of treatment	Means (p<0.0001 for difference between groups)	6, n=12	13.2, n=9
Pham-Thi 2007	% asthma-free days	Number of days when day and nighttime score was 0 (no symptoms)	Mean (SD)	85.8 (23.8) n=54	91.1 (15.4) n=55
Pham-Thi 2007	Nighttime asthma score	0 (no symptoms) to 3 (severe symptoms)	Mean (SD)	0.10 (0.19) n=54	0.07 (0.16) n=55
Pham-Thi 2007	Daytime asthma score	0 (no symptoms) to 3 (severe symptoms), mean of daily scores from past 3 weeks	Mean (SD)	0.15 (0.26) n=54	0.08 (0.17) n=55
Reilly 1994	Visual analogue scale for asthma symptoms	Minimum= fine, maximum=terrible (measured in mm)	Mean change (SEM)	-7.2 (3.2) n=11	7.8 (3.0) n=13
Stelmach 2009	Asthma symptom score (second pollen season)	As for first pollen season	Mean weekly score (SD)	7.15 (5.43) n=20	11.99 (7.32) n=15
Stelmach 2009	Asthma symptom score (first pollen season)	Day, night and beta-agonist use rated 0 to 3 and combined 0 (no symptoms and no use of b-ago-	Mean weekly score (SD)	18.07 (11.58) n=20	16.13 (9.34) n=15

Unvalidated asthma symptom scores (*Continued*)

		nists use) to 9 (severe symptoms during day and night, and > 3 beta$_2$-agonists), rated daily			
Zheng 2012	Cough/asthma symptom score	0 (no symptoms) to 3 (severe symptoms) ; assessed for both night and day	Mean decrease in score after 25 weeks treatment	3.3 (2.1) n=53	1.3 (2.1) n=53

Analysis 1.9. Comparison 1 SLIT vs control, Outcome 9 Unvalidated medication use scores.

Unvalidated medication use scores

Study	**Outcome name**	**Scoring**	**Data type**	**SLIT**	**Control**
Bousquet 1999	Inhaled corticosteroid use	mcg beclomethasone/day	Mean (SD)	348 (410) n=32	308 (408) n=33
Dahl 2006	Asthma medication score (during season)	Average daily composite score of beta$_2$-agnoist, ICS use and OCS use; maximum daily score 16	Daily mean (SD)	0.71 (1.28) n=68	0.66 (1.08) n=39
Dahl 2006	Asthma medication score (before season)	Average daily composite score of beta$_2$-agnoist, ICS use and OCS use; maximum daily score 16	Daily mean (SD)	0.09 (0.23) n=73	0.09 (0.14) n=40
Eifan 2009	Total medication score	1 point: beta$_2$-agnoists and antihistamines; 2 points: inhaled/intranasal steroids 3 points: one tablet of corticosteroid	Mean (SD)	1.2 (0.9) n=15	2.8 (1.1) n=14
Lewith 2002	Short acting bronchodilator use	Puffs/week	Mean (SD), read from graph	3.35 (0.48) n=101	3.4 (0.5) n=101
Lue 2006	Medication score	Mean daily use of corticosteroids, beta$_2$-agnoist, antihistamines	Mean (SD)	1.0 (0.94) n=10	1.1 (1.15) n=10

Unvalidated medication use scores (*Continued*)

		- scoring unclear			
Marogna 2005	Salbutamol use	Puffs/month at end of treatment	Mean (SD), read from graph	2 (0.5) n=29	11.5 (1) n=23
Mungan 1999	Medication scores (second 6 months of treatment)	ICS, beta$_2$-agnoists and antihistamines scored 1 to 4 depend- ing on dose and/ or frequency (maximum score 12)	Means, no variance	1.97, n=15	5.24, n=11
NCT00633919	Average Daily Asthma Medication Score During a 2-months Evaluation Period Autumn 2008 (later time point)	1 to 2 inhalations twice daily of salbutamol (200 mcg per in- halation) = 2 scores; 1 to 2 inhalation twice daily of budesonide/formoterol 80 (4.5 mcg per inhalation) = 4 scores; 1 inhalation twice daily of budesonide/ formoterol 160 (4.5 mcg per inhalation) = 8 scores; up to 10 tablets once daily of prednisone (5 mg) = 1.6 scores. The total maximum daily scores were 40	Mean (SD)	4.4 (5.9) n=36	4.7 (5.4) (n=)39
Niu 2006	Short acting broncodilator use	Puffs/day	Mean change (SD)	-0.04 (0.32) n=49	0.02 (0.27) n=48
Niu 2006	Oral corticosteroid use	Tablets/day	Mean change (SD)	-0.08 (0.42) n=49	0 (0.27) n=48
Niu 2006	Inhaled corticosteroid use	Puffs/day	Mean change (SD)	-0.23 (0.67) n=49	-0.1 (1.08) n=48
Pajno 2000	Total medication score (end of treatment)	1: bronchodilators; 2: ICS; 4: 7-day course of OCS	Means (SD imputed from p-value)	82.68 (55) n=12	205.2 (55) n=9
Pham-Thi 2007	Inhaled corticosteroid use	mcg budesonide/day	Mean (SD)	257 (232) n=54	223 (270) n=55

Unvalidated medication use scores (*Continued*)

Pham-Thi 2007	Short acting bronchodilator use	Puffs/day	Mean (SD)	0.55 (0.6) n=54	0.47 (0.5) n=55
Stelmach 2009	Medication score (second pollen season)	Mean weekly medication score during second pollen season, adjusted for pollen concentration	Mean (SD)	6.22 (2.45) n=20	7.37 (2.7) n=15
Stelmach 2009	Medication score (first pollen season)	Mean weekly medication score during first pollen season, adjusted for pollen concentration	Mean (SD)	5.1 (1.77) n=20	7.48 (2.78) n=15

Analysis 2.1. Comparison 2 Subgroup and sensitivity analyses, Outcome 1 Adverse events by age.

Review: Sublingual immunotherapy for asthma
Comparison: 2 Subgroup and sensitivity analyses
Outcome: 1 Adverse events by age

Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Children (mean age < 18 years)					
Bahceciler 2001	0/8	0/7			Not estimable
Caffarelli 2000	0/24	0/20			Not estimable
Eifan 2009	0/15	0/14			Not estimable
Ippoliti 2003	0/47	0/39			Not estimable
Keles 2011	0/13	0/12			Not estimable
Niu 2006	6/49	7/48		7.5 %	0.82 [0.25, 2.64]
Shao 2014	39/168	9/96		15.0 %	2.92 [1.35, 6.34]
Vourdas 1998	8/34	2/32		4.0 %	4.62 [0.90, 23.70]
Subtotal (95% CI)	**358**	**268**		**26.6 %**	**2.13 [0.83, 5.47]**
Total events: 53 (SLIT), 18 (Control)					
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 4.06$, df = 2 (P = 0.13); $I^2 = 51\%$					
Test for overall effect: Z = 1.58 (P = 0.11)					

(*Continued* . . .)

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Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
2 Teenagers and adults (mean age > 18 years)					
Alvarez-Cuesta 2007	0/17	0/16			Not estimable
Calderon 2006 (1)	36/36	10/11		1.1 %	10.43 [0.40, 275.32]
Gomez Vera 2005	0/30	0/30			Not estimable
Leng 1990	1/9	0/9		1.0 %	3.35 [0.12, 93.83]
Marogna 2005	4/29	0/23		1.3 %	8.29 [0.42, 162.48]
Mosbech 2014 (2)	290/461	77/143		37.4 %	1.45 [0.99, 2.12]
Mungan 1999	2/15	0/11		1.1 %	4.26 [0.18, 98.07]
NCT00633919 (3)	24/63	21/61		16.4 %	1.17 [0.56, 2.44]
Subtotal (95% CI)	**660**	**304**		**58.2 %**	**1.48 [1.06, 2.06]**
Total events: 357 (SLIT), 108 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.74, df = 5 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 2.33 (P = 0.020)					
3 Mixed age study population or age range not specified					
Bousquet 1999	15/42	14/43		11.8 %	1.15 [0.47, 2.82]
La Grutta 2007	0/33	0/23			Not estimable
Troise 2009	11/14	4/10		3.4 %	5.50 [0.91, 33.18]
Subtotal (95% CI)	**89**	**76**		**15.2 %**	**2.06 [0.47, 9.05]**
Total events: 26 (SLIT), 18 (Control)					
Heterogeneity: Tau^2 = 0.70; Chi^2 = 2.33, df = 1 (P = 0.13); I^2 =57%					
Test for overall effect: Z = 0.95 (P = 0.34)					
Total (95% CI)	**1107**	**648**		**100.0 %**	**1.70 [1.21, 2.38]**
Total events: 436 (SLIT), 144 (Control)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 11.52, df = 10 (P = 0.32); I^2 =13%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
Test for subgroup differences: Chi^2 = 0.66, df = 2 (P = 0.72), I^2 =0.0%					

(1) 4 different dosing arms combined

(2) 3 different dosing arms combined

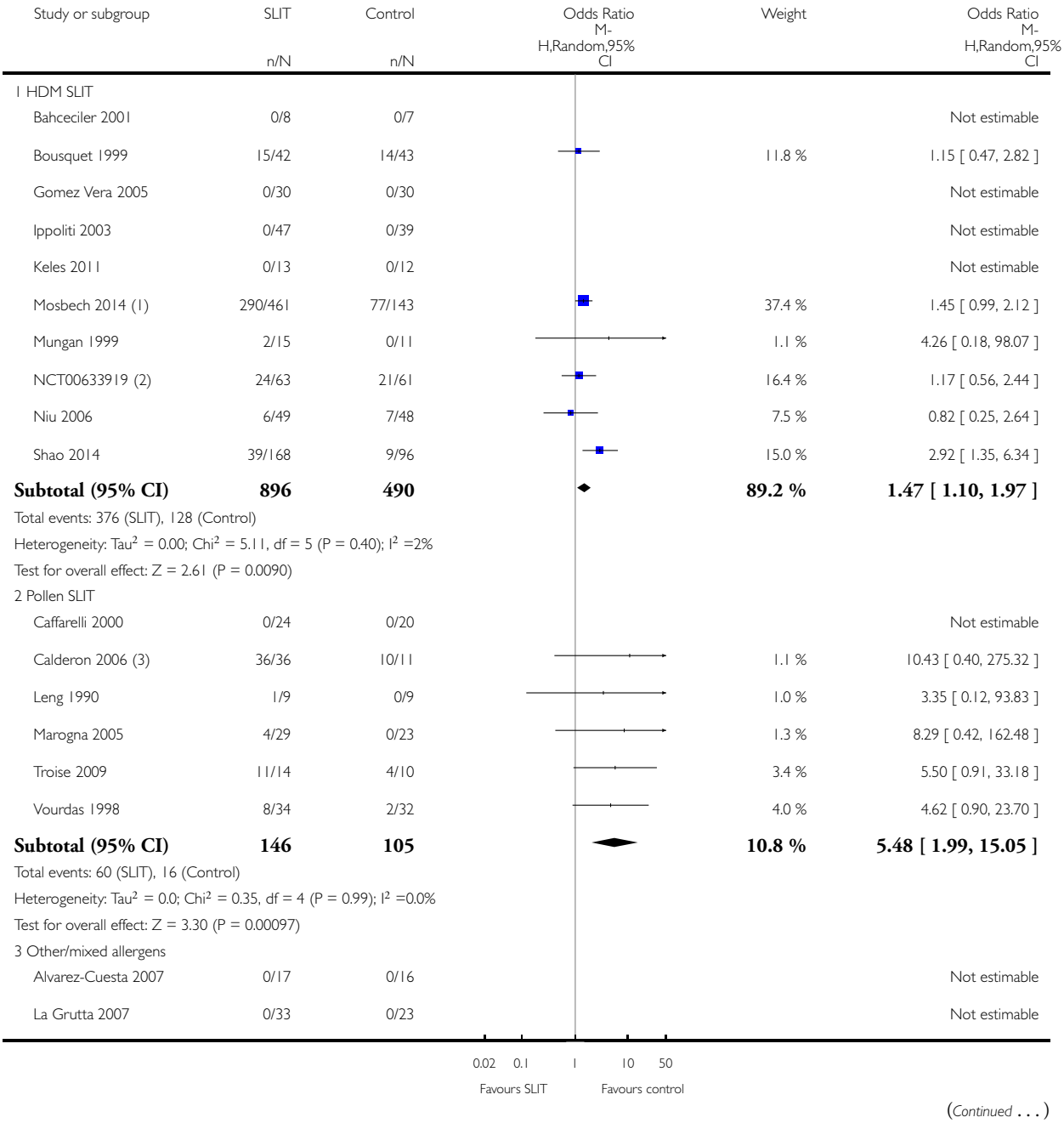
(3) Adverse events only reported if over 5% of participants were affected

Analysis 2.2. Comparison 2 Subgroup and sensitivity analyses, Outcome 2 Adverse events by allergen.

Review: Sublingual immunotherapy for asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 2 Adverse events by allergen



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Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**50**	**39**			**Not estimable**
Total events: 0 (SLIT), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1092**	**634**		**100.0 %**	**1.70 [1.21, 2.38]**
Total events: 436 (SLIT), 144 (Control)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 11.52, df = 10 (P = 0.32); I^2 =13%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
Test for subgroup differences: Chi^2 = 6.00, df = 1 (P = 0.01), I^2 =83%					

(1) 3 different dosing arms combined

(2) Adverse events only reported if over 5% of participants were affected

(3) 4 different dosing arms combined

Analysis 2.3. Comparison 2 Subgroup and sensitivity analyses, Outcome 3 Adverse events by study duration.

Review: Sublingual immunotherapy for asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 3 Adverse events by study duration

Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Duration less than 52 weeks					
Bahceciler 2001	0/8	0/7			Not estimable
Caffarelli 2000	0/24	0/20			Not estimable
Calderon 2006 (1)	36/36	10/11		1.1 %	10.43 [0.40, 275.32]
Gomez Vera 2005	0/30	0/30			Not estimable
Gomez Vera 2005	0/30	0/30			Not estimable
Ippoliti 2003	0/47	0/39			Not estimable
Leng 1990	1/9	0/9		1.0 %	3.35 [0.12, 93.83]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Niu 2006	6/49	7/48		7.5 %	0.82 [0.25, 2.64]
Subtotal (95% CI)	**233**	**194**		**9.5 %**	**1.53 [0.38, 6.19]**
Total events: 43 (SLIT), 17 (Control)					
Heterogeneity: Tau^2 = 0.39; Chi^2 = 2.46, df = 2 (P = 0.29); I^2 =19%					
Test for overall effect: Z = 0.60 (P = 0.55)					
2 Duration 52 weeks and longer					
Alvarez-Cuesta 2007	0/17	0/16			Not estimable
Bousquet 1999	15/42	14/43		11.8 %	1.15 [0.47, 2.82]
Eifan 2009	0/15	0/14			Not estimable
Keles 2011	0/13	0/12			Not estimable
La Grutta 2007	0/33	0/23			Not estimable
Marogna 2005	4/29	0/23		1.3 %	8.29 [0.42, 162.48]
Mosbech 2014 (2)	290/461	77/143		37.4 %	1.45 [0.99, 2.12]
Mungan 1999	2/15	0/11		1.1 %	4.26 [0.18, 98.07]
NCT00633919 (3)	24/63	21/61		16.4 %	1.17 [0.56, 2.44]
Shao 2014	39/168	9/96		15.0 %	2.92 [1.35, 6.34]
Troise 2009	11/14	4/10		3.4 %	5.50 [0.91, 33.18]
Vourdas 1998	8/34	2/32		4.0 %	4.62 [0.90, 23.70]
Subtotal (95% CI)	**904**	**484**		**90.5 %**	**1.77 [1.22, 2.58]**
Total events: 393 (SLIT), 127 (Control)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 8.76, df = 7 (P = 0.27); I^2 =20%					
Test for overall effect: Z = 3.01 (P = 0.0026)					
Total (95% CI)	**1137**	**678**		**100.0 %**	**1.70 [1.21, 2.38]**
Total events: 436 (SLIT), 144 (Control)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 11.52, df = 10 (P = 0.32); I^2 =13%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.84), I^2 =0.0%					

(1) 4 different dosing arms combined

(2) 3 different dosing arms combined

(3) Adverse events only reported if over 5% of participants were affected

Analysis 2.4. Comparison 2 Subgroup and sensitivity analyses, Outcome 4 Adverse events (sensitivity for risk of bias: blinded studies only).

Review: Sublingual immunotherapy for asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 4 Adverse events (sensitivity for risk of bias: blinded studies only)

Study or subgroup	SLIT n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Alvarez-Cuesta 2007	0/17	0/16			Not estimable
Bahceciler 2001	0/8	0/7			Not estimable
Bousquet 1999	15/42	14/43		10.6 %	1.15 [0.47, 2.82]
Caffarelli 2000	0/24	0/20			Not estimable
Calderon 2006 (1)	36/36	10/11		0.8 %	10.43 [0.40, 275.32]
Gomez Vera 2005	0/30	0/30			Not estimable
Ippoliti 2003	0/47	0/39			Not estimable
Leng 1990	1/9	0/9		0.8 %	3.35 [0.12, 93.83]
Mosbech 2014 (2)	290/461	77/143		59.2 %	1.45 [0.99, 2.12]
Mungan 1999	2/15	0/11		0.9 %	4.26 [0.18, 98.07]
NCT00633919 (3)	24/63	21/61		15.8 %	1.17 [0.56, 2.44]
Niu 2006	6/49	7/48		6.2 %	0.82 [0.25, 2.64]
Troise 2009	11/14	4/10		2.6 %	5.50 [0.91, 33.18]
Vourdas 1998	8/34	2/32		3.2 %	4.62 [0.90, 23.70]
Total (95% CI)	**849**	**480**		**100.0 %**	**1.47 [1.10, 1.96]**

Total events: 393 (SLIT), 135 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.63$, df = 8 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 2.57 (P = 0.010)

Test for subgroup differences: Not applicable

(1) 4 different dosing arms combined

(2) 3 different dosing arms combined

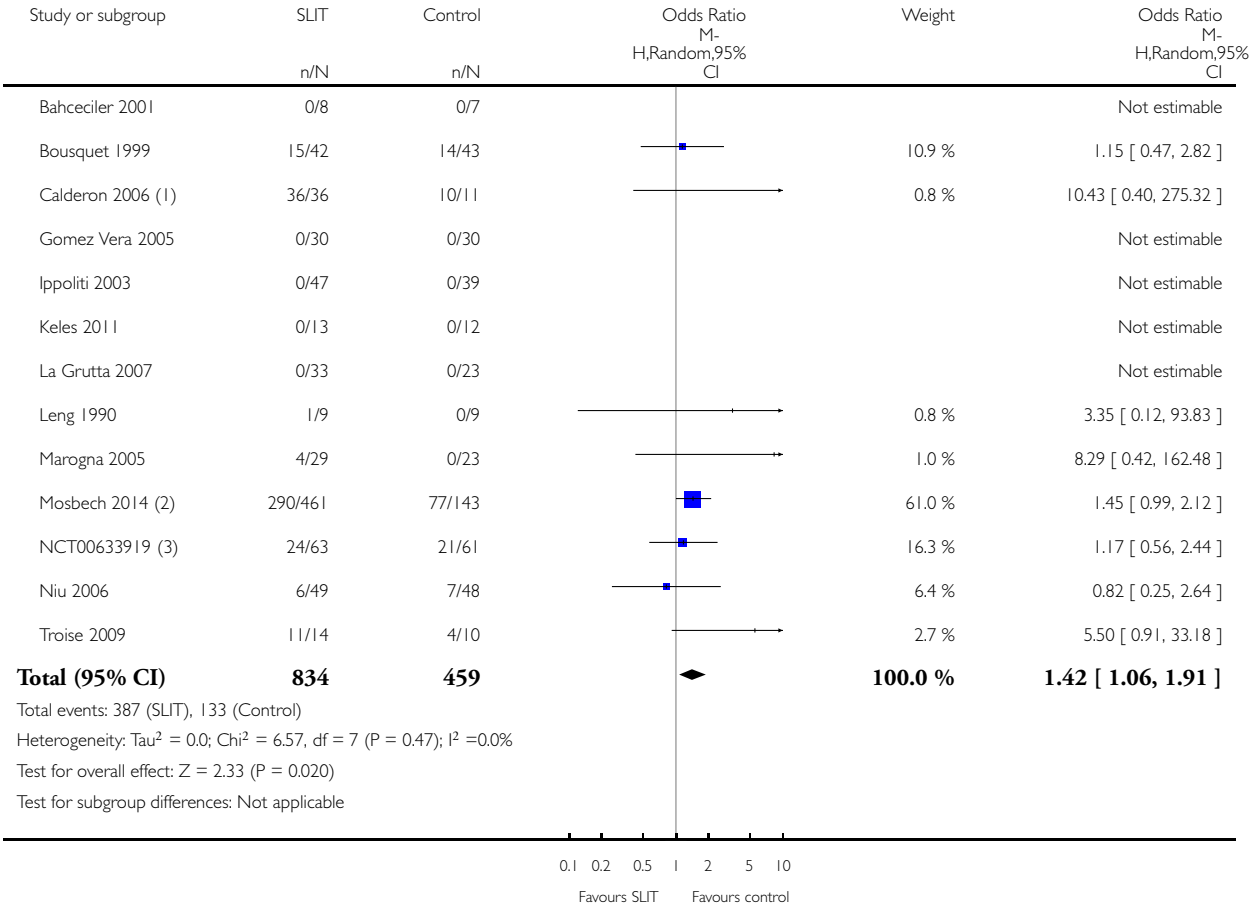
(3) Adverse events only reported if over 5% of participants were affected

Analysis 2.5. Comparison 2 Subgroup and sensitivity analyses, Outcome 5 Adverse events (sensitivity analysis removing studies with mixed population of asthma and rhinitis).

Review: Sublingual immunotherapy for asthma

Comparison: 2 Subgroup and sensitivity analyses

Outcome: 5 Adverse events (sensitivity analysis removing studies with mixed population of asthma and rhinitis)



(1) 4 different dosing arms combined

(2) 3 different dosing arms combined

(3) Adverse events only reported if over 5% of participants were affected

ADDITIONAL TABLES

Table 1. Summary of study characteristics

Study ID	Total N	Allergen	Comparator	Age range	Country	Duration	% with asthma
Almarales 2012	120	HDM	Placebo	Not reported	Cuba	52 weeks	100
Alvarez-Cuesta 2007	50	Cat dander	Placebo	14-55	Spain	52 weeks	81.8
Bahceciler 2001	15	HDM	Placebo	7-18	Turkey	26 weeks*	100
Bousquet 1999	85	HDM	Placebo	7-42	France	108 weeks*	100
Caffarelli 2000	48	Grass pollen	Placebo	4-14	Italy	13 weeks*	89.6
Calderon 2006	43	Grass pollen	Placebo	18-65	Unclear	4 weeks*	100
Corzo 2014 (a)	71	HDM	Placebo	18-65	UK and Denmark	4 weeks	100
Corzo 2014 (b)	72	HDM	Placebo	5-14	Spain	4 weeks	100
Cooper 1984	19	Grass pollen	Placebo	5-15	UK	> 8 but < 16 weeks*	100
Criado Molina 2002	44	*Alternaria*	Pharmacotherapy	18-65	Spain	52 weeks	100
Dahl 2006	114	Timothy grass	Placebo	18-65	Denmark and Sweden	19.5 weeks	100
Eifan 2009	48	HDM	Pharmacotherapy	5-10	Turkey	52 weeks	85
Fadel 2010	55	Grass pollen	Placebo	18-50	Syria	Not reported	100
Gomez Vera 2005	60	HDM	Placebo	13-45	Mexico	26 weeks	100
Hanna 2013	60	HDM	Placebo	Not reported	Not reported	13 weeks	100
Inal 2009	32	HDM	Placebo	Not reported	Turkey	52 weeks	100
Ippoliti 2003	86	HDM	Placebo	5-12	Italy	26 weeks*	100

Table 1. Summary of study characteristics (*Continued*)

Karakoc-Aydiner 2011	31	HDM	Pharmacotherapy	'Children'	Unclear	156 weeks	100
Keles 2009	53	HDM	Pharmacotherapy	Not reported	Unclear	17.3 weeks	100
Keles 2011	58	HDM	Pharmacotherapy	5-12	Turkey	52 weeks*	100
La Grutta 2007	56	HDM/ *Parietaria*	Pharmacotherapy	7-68	Italy	52 weeks	100
Leng 1990	18	*Artemisia* pollen	Placebo	15-56	Unclear	7.14 weeks*	100
Lewith 2002	242	Homeopathic HDM	Placebo	18-55	UK	16 weeks	100
Lue 2006	20	HDM	Placebo	6-12	Taiwan	24 weeks*	100
Marcucci 2003	24	HDM	Placebo	4-16	Italy	52 weeks	84.6
Marogna 2005	79	Birch pollen	Pharmacotherapy	18-65	Italy	156 weeks*	100
Mosbech 2014	604	HDM	Placebo	14+	Denmark, Germany, Italy, Spain, United Kingdom, Sweden, France, Poland	52 weeks	100
Mosges 2010	116	Ultra-rush birch pollen	Placebo	6-14	Germany	0.015 weeks	100
Mungan 1999	36	HDM	Placebo	18-46	Turkey	52 weeks	88
Muratore 1993	28	HDM	Placebo	4-9	Italy	52 weeks	100
NCT00633919	124	HDM	Placebo	18-65	Spain	104 weeks	100
Niu 2006	110	HDM	Placebo	6-12	Taiwan	24 weeks*	100
Orefice 2004	47	HDM	Pharmacotherapy	Not reported	Italy	156 weeks	100

Table 1. Summary of study characteristics (*Continued*)

Pajno 2000	24	HDM	Placebo	8-15	Italy	104 weeks	100
Pajno 2003	30	*Parietaria*	Placebo	8-14	Italy	56 weeks*	100
Pham-Thi 2007	111	HDM	Placebo	5-16	France	78 weeks	100
Radu 2007	106	HDM	Placebo	5-13	Romania	26 weeks	100
Reilly 1994	28	Homeopathic HDM/ feathers/ mixed moulds	Placebo	16+	Scotland	4 weeks*	100
Rodriguez 2012	40	HDM	Placebo	'Adults'	Cuba	Not reported	100
Rodriguez Santos 2004	50	HDM	Pharmacotherapy	6-15	Cuba	104 weeks	100
Shao 2014	264	HDM	Pharmacotherapy	3-13	China	52 weeks	82
Stelmach 2009	50	Grass pollen	Placebo	6-17	Poland	104 weeks	100
Tian 2014	60	HDM	Placebo	4-18	China	48 weeks	100
Troise 2009	24	Birch pollen	Placebo	Not reported	Unclear	104 weeks	100
Virchow 2014	834	HDM	Plaecbo	Not reported	Austria, Croatia, Denmark, France, Germany, Lithuaina, Netherlands, Poland, Serbia, Slovakia, Spain, United Kingdom	78 weeks	100
Vourdas 1998	66	Olive pollen	Placebo	7-17	Greece	104 weeks	90.6
Wang 2014	484	HDM	Placebo	16-50	China	52 weeks*	100
Wood 2014	89	Greer German cockroach	Placebo	5-17	USA and UK	13 weeks	80

Table 1. Summary of study characteristics (*Continued*)

Yukselen 2013	32	HDM	Placebo	Not reported	Turkey	52 weeks	100
Zeldin 2013	63	HDM	Placebo	'Adults'	France	1.4 weeks	100
Zhang 2013	128	HDM	Pharmacotherapy	4-14	Taiwan	104 weeks	100
Zheng 2012	106	HDM	Pharmacotherapy	4-14	China	Outcomes reported at 25 weeks	100

*Studies that included post-treatment follow-up periods.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.

7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Administration, Sublingual
#6 sublingual*
#7 tongue*
#8 oral*
#9 #5 or #6 or #7 or #8
#10 MeSH DESCRIPTOR immunotherapy Explode All
#11 immunotherap*
#12 hyposensit*
#13 desensit*
#14 #10 or #11 or #12 or #13
#15 #9 and #14
#16 SLIT:ti,ab
#17 #4 and (#15 or #16)
[Note: in search line #1, MISC1 denotes the field in which the reference has been coded for condition, in this case, asthma]

CONTRIBUTIONS OF AUTHORS

RN and KMK sifted the search results and compiled the list of included studies.

RN, KMK and ALB extracted data and entered them into the review.

RN and KMK performed and interpreted the analyses.

RN wrote the Background, Methods and Discussion sections with substantial input from KMK and ALB.

RN and ALB wrote the Results section with substantial input from KMK.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- RN, KK, UK.

St George's, University of London

External sources

- RN, KK, UK.

National Institute for Health Research. Evidence to guide care in adults and children with asthma, 13/89/14

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not anticipate identifying so many trials that included participants with asthma and/or rhinitis and did not provide disaggregated data for participants with asthma. As a pragmatic change to our protocol, we decided to include studies in which 80% or more of the participants were diagnosed with asthma. We have taken this into account in our GRADE assessments of the quality of the evidence and have performed a sensitivity analysis removing the 'mixed population' trials from the adverse events outcome. Furthermore, we specified in our protocol that studies should cite a specific guideline for the purpose of asthma diagnosis. If no guideline was cited we specified that trialists should provide sufficient information to allow us to establish the diagnosis according to an established guideline. However, we found insufficient description in most of the studies identified by our search and accepted that if participants were described as having asthma, we would consider this as meeting our inclusion criteria.

In view of the large number of included studies, we attempted to contact study authors only to clarify whether or not the study met our inclusion criteria; we did not attempt to obtain further information regarding trial methods or results. Furthermore, because of the large number of manufacturers of SLIT, we did not search individual company websites for relevant trials.

We chose to extract data for all adverse events as well as serious adverse events because of the paucity of events in the latter outcome.We included all adverse events in our summary of findings table, rather than asthma symptoms, as we were not able to perform a meta-analysis for asthma symptoms.

We decided to use risk differences (RDs) rather than odds ratios (ORs) to analyse serious adverse events to account for trials with no events in either arm.

None of our primary outcomes had sufficient data for subgroup or sensitivity analyses to be carried out; as a result, we performed these analyses on the all adverse events outcome.We were not able to perform a subgroup analysis according to baseline asthma severity as the majority of studies included participants with mild or intermittent symptoms, or did not describe baseline asthma severity in sufficient detail. We did not include any unpublished data in the review so this sensitivity analysis was not required. As described above, we included an additional sensitivity analysis excluding studies which recruited a 'mixed population' of participants with asthma and/or rhinitis.

INDEX TERMS

Medical Subject Headings (MeSH)

Asthma [*therapy]; Pollen; Pyroglyphidae; Randomized Controlled Trials as Topic; Sublingual Immunotherapy [adverse effects; *methods]

MeSH check words

Adult; Animals; Child; Humans