Allergen immunotherapy for asthma

[Review]

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Date of Most Recent Update: 6-January-2004

Date of Most Recent Substantive Update: 19-August-2003

Cochrane Airways Group.
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Abstract

Background: Allergen specific immunotherapy has long been a controversial treatment for asthma. Although beneficial effects upon clinically relevant outcomes have been demonstrated in randomised controlled trials, there remains a risk of severe and sometimes fatal anaphylaxis. The recommendations of professional bodies have ranged from cautious acceptance to outright dismissal. With increasing interest in new allergen preparations and new methods of delivery, it was time to conduct another systematic review of allergen specific immunotherapy for asthma.

Objectives: The objective of this review was to assess the effects of allergen specific immunotherapy for asthma.

Search strategy: We searched the Cochrane Airways Group trials register up to June 2001, MEDLINE, Dissertation Abstracts, Current Contents and reference lists of articles.
Selection criteria: Randomised controlled trials using various forms of allergen specific immunotherapy to treat asthma and reporting at least one clinical outcome.

Data collection and analysis: Three reviewers independently assessed eligibility of studies for inclusion. Two reviewers independently performed quality assessment of studies.

Main results: Seventy-five trials were included (52 of 54 previously included trials and 23 new trials). A total of 3,506 participants (3,188 with asthma) were involved. There were 36 trials of immunotherapy for house mite allergy; 20 pollen allergy trials; ten animal dander allergy trials; two Cladosporium mould allergy, one latex and six trials looking at multiple allergens. Concealment of allocation was assessed as clearly adequate in only 15 of these trials. Significant heterogeneity was present in a number of comparisons. Overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyper-reactivity following immunotherapy. There was a significant improvement in asthma symptom scores (standardised mean difference -0.72, 95% confidence interval -0.99 to -0.33) and it would have been necessary to treat 4 (95%CI 3 to 5) patients with immunotherapy to avoid one deterioration in asthma symptoms. Overall it would have been necessary to treat 5 (95%CI 4 to 6) patients with immunotherapy to avoid one requiring increased medication. Allergen immunotherapy significantly reduced allergen specific bronchial hyper-reactivity, with some reduction in non-specific bronchial hyper-reactivity as well. There was no consistent effect on lung function.

Conclusions: Immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity. One trial found that the size of the benefit is possibly comparable to inhaled steroids. The possibility of adverse effects (such as anaphylaxis) must be considered.
We have previously conducted a meta-analysis of 20 double blind randomised controlled trials of allergen immunotherapy for asthma published between 1954 and 1990 (Abramson 1995). Subsequently we updated the systematic review to include 62 trials published between 1954 and 1998 (Abramson 1999). Allergen immunotherapy significantly reduced asthma symptoms and treated patients were significantly less likely to report symptomatic deterioration. Allergen immunotherapy also significantly reduced medication requirements and treated patients were significantly less likely to require increased medication. There was no consistent effect on lung function. There was an overall reduction in nonspecific bronchial hyper-reactivity (BHR) following immunotherapy and treated patients were significantly less likely to develop increased BHR. There was an even greater homogeneous reduction in allergen specific BHR and treated patients were significantly less likely to develop increased allergen specific BHR.

During the last 12 years, there has been increasing interest in new allergen preparations, such as allergen-antibody complexes and new methods of delivery including oral, sublingual and inhaled immunotherapy. Recombinant peptides containing the relevant epitopes, but lacking the ability to crosslink IgE bound to mast cells have been evaluated in clinical trials. Finally the Cochrane Collaboration has continued to improve the statistical software for performing meta-analysis. Thus it was again time to update our systematic review of allergen specific immunotherapy for asthma.

Objectives
* To identify published randomised controlled trials of allergen specific immunotherapy ('hyposensitisation' or 'desensitisation') in allergic asthma.
* To assess the methodological quality of these randomised controlled trials.
* To estimate the overall efficacy of allergen specific immunotherapy upon asthmatic symptoms, medication requirements, lung function, nonspecific BHR and allergen specific BHR.
* To compare the efficacy in asthma of mite, pollen, animal dander and immunotherapy with extracts of other allergens.

Criteria for considering studies for this review

Types of participants
We only included studies that focussed upon asthma. Studies of immunotherapy for hay fever were considered only if the results for participants with asthma were separately identified.

Types of intervention
For the purposes of this review, allergen specific immunotherapy included the administration of extracts of house dust mites, pollens, animal danders or moulds, chemically modified allergoids or antigen-antibody complexes. We only considered the subcutaneous route of administration. Oral, sublingual, intranasal and inhaled immunotherapy may be the topics of future reviews.

Types of outcome measures
At least one of the following clinical outcomes had to be reported:

* asthmatic symptoms (including symptom scores)
* asthma medication requirements
* lung function (including peak expiratory flow, forced expiratory volume in one second ($FEV_1$) and thoracic gas volume)
* nonspecific bronchial hyper reactivity (to histamine or methacholine)
* allergen specific bronchial hyper reactivity

We excluded studies which only reported nonclinical outcomes such as allergen specific IgE (by RAST (radioallergosorbent test) or skin prick test) or other in vitro results.

Types of studies
We restricted this review to randomised controlled trials (RCT), which provided the strongest evidence for the efficacy of any medical treatment. Placebo controlled trials are methodologically stronger, although we also considered studies which have administered house dust or other relatively antigenically inactive preparations to the control group. Double blinded trials were preferred, but we also reviewed single blind and open studies for possible inclusion.

Search strategy for identification of studies
We searched the Cochrane Airways Group trials register (June 2001), MEDLINE (January 1966 to December 2001), Current Contents and dissertation abstracts to identify more recently published and unpublished studies of immunotherapy and asthma. Review articles identified in this process were surveyed for additional and earlier citations.

In the Cochrane Airways Group trials register, we identified all studies with the keywords Asthma or Wheez* from the MEDLINE, EMBASE and CINAHL databases, together with other studies identified by hand searching. We identified a total of over 1,000 non unique citations with the keywords Immunotherap* or Hyposensiti* or Desensiti* and we examined these for possible inclusion.

We considered studies published in languages other than English if the translated abstract indicated that the study was an RCT of allergen immunotherapy for asthma and we sought a translator (see acknowledgments).

Methods of the review
All three reviewers independently decided by a simple majority which studies would be included in the review. They did this by reading the methods sections of papers identified by the search strategy and applying the stated criteria. Two reviewers (RMP and JMW) independently performed quality assessment by assessing the concealment of allocation following the guidelines of the Cochrane Collaboration and applied the scoring system of Jadad 1996.

Statistical Considerations
The planned comparisons were:

* Allergen immunotherapy versus placebo
* Allergen immunotherapy versus antigenically inactive control
* House dust versus placebo
* Allergen immunotherapy versus untreated control
* Allergen immunotherapy versus inhaled steroid

We performed these comparisons separately for each outcome, namely asthma symptoms, medication, lung function, non-specific BHR and allergen specific BHR, whenever the results were reported.
Two reviewers independently extracted data (MJA and RMP).

We extracted outcome data and entered into RevMan 4.2.2 for statistical analysis. We analysed categorical outcomes as relative risks (RR) and calculated 95% confidence intervals (95%CI) for individual studies. The relative risk is simply the ratio between the immunotherapy and control groups for the risk of participants being the same or worse after treatment. The convention of the Cochrane Collaboration is to consider a RR > 1 as indicating clinically undesirable outcomes (in this review, worse symptoms, increased medication, deteriorating lung function and increased nonspecific and allergen specific BHR). We then used the combined relative risks to estimate the number of patients who would need to be treated (NNT) to avoid these undesirable outcomes. Visual Rx 2003 computer programme was used to calculate NNT.

We also extracted continuous outcomes (symptom and medication scores, lung function parameters and indices of nonspecific and allergen specific BHR) from tables of results. Where the results were only presented in graphs, these were digitised and then converted to numbers with Un-Scan-It 1996 software. We analysed continuous outcomes as standardised mean differences (SMD). The SMD is a statistic which expresses the difference in means between immunotherapy and control groups in units of the pooled standard deviation. Although the Cochrane Collaboration currently favours the Weighted Mean Difference, we chose the SMD because many studies measured the same outcomes on different scales.

We generally used fixed effect models to obtain summary statistics for the overall efficacy of allergen immunotherapy upon both categorical and continuous outcomes and we performed chi squared (\(\chi^2\)) tests to assess heterogeneity between studies. In this context, a p value < 0.05 indicated significant differences between studies and raised questions whether the results could be meaningfully combined. When significant heterogeneity was found, we calculated the overall efficacy using random effects models, which provided more realistic estimates of the confidence intervals under these circumstances (Lau 1997).

Description of the studies

We identified seventy five randomised controlled trials published in 80 papers between 1954 and 2001 which satisfied the inclusion criteria (52 of 54 previously included trials and 23 new trials). The methods, participants, interventions and outcomes of included studies are listed in Table 1. A total of 3,506 participants (3,188 with asthma) were involved. There were 33 studies reporting immunotherapy for mite allergy, generally Dermatophagoides pteronyssinus or D. farinae, although Armentia 1995 used extracts of the storage mite Lepidoglyphus destructor. Three early studies (B.T.A. 1968; Vooren 1969; Aas 1971) used extracts of house dust, which has since often been considered antigenically inactive. There were 20 studies of immunotherapy for pollen allergy, utilising extracts of Bermuda grass, orchard grass/cockspfoot, Timothy grass, velvet grass, sweet vernal grass, perennial rye grass, birch or ragweed pollen. Ten studies reported immunotherapy for animal dander allergy, particularly to cats and dogs. Two studies utilised extracts of the mould Cladosporium, one used latex extracts and six attempted simultaneous immunotherapy for multiple aeroallergens. Four studies from one group of investigators (Machiels 1990a; Machiels 1990b; Machiels 1991; Machiels 1993) used allergen-antibody complexes for immunotherapy.

A further 166 studies were excluded (91 previously excluded, two previously included and 73 new studies). The most common reasons were that the studies were: not randomised (49), not controlled (35), involved participants with rhinitis rather than asthma (33), did not report clinically relevant outcomes (15) or were not analysed by intention to treat (1). We identified a number of clinical trials of oral immunotherapy (13), inhaled or intranasal immunotherapy (6) and sublingual immunotherapy (17), which may be the subject of other reviews. Finally
there were seven abstracts, which contained insufficient information for any further assessment.

**Methodological qualities of included studies**

Concealment of allocation was assessed as clearly adequate (category A) in only 15 studies (Johnstone 1961; Aas 1971; Ohman 1984; Valovirta 1984; Bousquet I 1985; Reid 1986; Bousquet II 1988; Bousquet III 1989; Mosbech 1989; Bousquet IV 1990; Varney 1991; Cantani 1996; Creticos 1996; Olsen 1997; Walker 2000). The adequacy or otherwise of 49 studies could not be determined from the details published in the papers (category B) and further information was sought from the authors, but rarely forthcoming. Only two studies (Machiels 1991; Haugaard 1992) used a clearly inadequate method for concealment of allocation (category C). Concealment was not reported in nine open studies (category D). There was almost perfect agreement between reviewers.

The overall methodological quality of the included trials was moderate. Only four trials (Johnstone 1961; Johnstone 1968; Varney 1991; Olsen 1997) received the maximum score of five out of five. Thirteen trials scored four points, twenty seven trials three points, nineteen trials two points and eleven trials one point. The other trial could not be classified on the published information and further methodological details were not forthcoming from authors. Blinding of participants and/or evaluators is a design feature that reduces bias in randomised controlled trials. Fifty six of the 74 studies were double blind, five single blind, one mixed, 11 open and the remaining two unclear.

Sixty five studies were placebo controlled trials of allergen specific immunotherapy, two compared immunotherapy with an antigenically inactive control (Maunsell 1971; Choovoravech 1974), three compared house dust with placebo (B.T.A. 1968; Vooren 1969; Aas 1971) and four utilised untreated controls (Bousquet II 1988; Bertelsen 1989; Garcia-Ortega 1993; Kohno 1998). Shaikh 1997 compared allergen immunotherapy with inhaled steroid.

**Results**

**Symptoms**

Symptom scores were reported by 28 studies, although Dreborg 1986 and Mungan 1999 did not publish standard deviations (SD) thus preventing the calculation of the standardised mean differences (SMD) for these studies. The combined SMD for symptom scores following mite immunotherapy was -0.78 with a 95% confidence interval from -1.27 to -0.29 that excluded 0, thus indicating a significant reduction in asthma symptoms. The combined SMD following pollen immunotherapy was -0.66 (95%CI -0.99 to -0.33) also indicating significant symptomatic improvement. However there was no significant improvement following immunotherapy with cat, dog or multiple allergen extracts. For all allergens combined, the SMD was -0.72 (95%CI -0.99 to -0.44), but there was significant heterogeneity between studies ($\chi^2 = 96.4, p < 0.00001$).

Symptoms were simply reported as worse, the same or improved in 22 studies. Overall it would have been necessary to treat four (95%CI 3 to 5) patients with immunotherapy to avoid one deterioration in asthma symptoms (see Figure). Symptoms were significantly more likely to improve following immunotherapy with extracts of pollen (NNT 3; 95%CI 2 to 16), animal dander (NNT 3; 95%CI 2 to 24) and other allergens (NNT 3; 95%CI 3 to 4). A smaller improvement was seen following mite immunotherapy where six (95%CI 4 to 16) patients would have to be treated to avoid one deteriorating. There was significant heterogeneity between the results of all studies ($\chi^2 = 44, p = 0.002$), with the B.T.A. 1979 and Buchanan 1981 actually finding symptoms to be more likely in treated patients.
Figure. Of every 100 asthma patients treated with immunotherapy, 30 patients will be prevented from having an attack (worse symptoms), 40 would not have had an attack anyway and 30 will still have an attack. In other words, about 4 patients have to be treated to prevent one attack of asthma.

Medication

Asthma medication scores were reported by 15 studies, with Mungan 1999 failing to publish the SD. The combined SMD was -0.80 (95%CI -1.13 to -0.48) indicating a significant reduction in medication following immunotherapy. Medication requirements were simply reported as increased, unchanged or decreased in 16 studies. Overall it would have been necessary to treat five (95%CI 4 to 6) patients with immunotherapy to avoid one requiring increased medication. Although there was significant heterogeneity between the studies reporting medication scores (\[\chi^2 = 37.7, p < 0.0003\]), there was substantial homogeneity between the latter group. Together, these findings suggest that at some of the heterogeneity in medication scores may have been due to the different methods of collecting this data.

Lung Function

Lung function results were reported by 16 studies, with many studies failing to provide SDs for FEV₁ (Gaddie 1976; Machiels 1993), Thoracic Gas Volume (Warner 1978; Price 1984) or Peak Expiratory Flow (Dreborg 1986). Data for FEV₁ and PEF could be aggregated in meta-analyses. There was no overall difference between treatment groups, but there was significant heterogeneity between studies (\[\chi^2 = 27.7, p < 0.0001\]). In seven studies, lung function was simply reported as worse, the same or improved. Although there was homogeneity between these studies and an overall trend suggesting an improvement in lung function following
immunotherapy, this did not achieve statistical significance.

**Bronchial Hyperreactivity**

Indices of nonspecific bronchial hyperreactivity were reported by 15 studies. The combined results varied significantly with the challenge agent (heterogeneity $\chi^2 = 28.2$, $p = 0.013$). There was a marginal improvement in PD$_{20}$ FEV$_1$ (provocative dose of methacholine required to produce a 20% fall in FEV$_1$) and Machiels 1990a reported an improvement in PC$_{35}$SGaw (concentration of acetylcholine required to produce a 35% fall in specific airways conductance) following immunotherapy with allergen-antibody complexes. However, there were no significant changes in PC$_{20}$FEV$_1$ (concentration of histamine required to induce a 20% fall in FEV$_1$) to histamine challenge or Delta FEV$_1$ to cold air. Nonetheless, there was an overall modest reduction in nonspecific BHR following immunotherapy (SMD -0.43; 95%CI -0.71 to -0.14) corresponding to a 3.1 (95%CI 1.6 to 5.9) fold increase in PD$_{20}$.

Nonspecific BHR was simply reported as increased, unchanged or reduced in five small studies. There was homogeneity between these studies and patients randomised to immunotherapy were significantly less likely to develop increased nonspecific BHR than those randomised to placebo. Overall, it would have been necessary to treat three (95%CI 3 to 6) patients with immunotherapy to avoid worsening BHR in one.

Indices of allergen specific BHR (such as PD$_{20}$ FEV$_1$ to allergen challenge) were reported by 15 studies. There was homogeneity between these studies with an overall SMD of -0.66 (95%CI -0.87 to -0.45) indicating a significant reduction in allergen specific BHR following immunotherapy. This corresponded to a 4.6 fold (95%CI 2.8 to 7.4) fold increase in PD$_{20}$. The effect was most marked for mite immunotherapy (SMD -1.14, 95%CI -1.62 to -0.65), similar for pollen (SMD -0.69, 95%CI -1.09 to -0.3) and animal dander (SMD -0.61, 95%CI -0.95 to -0.27), but not significant for other allergens. There was however, no significant difference between the results in the different subgroups ($\chi^2 = 6.65$, df 3, $p = 0.08$).

Allergen specific BHR was simply reported as increased, unchanged or reduced in 16 studies. There was homogeneity between studies and patients randomised to immunotherapy were significantly less likely to develop increased allergen specific BHR. Overall, it would have been necessary to treat four (95%CI 3 to 5) patients to avoid worsening allergen specific BHR in one.

**Other Comparisons**

Because of the small number and disparate outcomes reported by the non placebo controlled randomised trials, only limited meta-analysis could be performed. Choovoravech 1974 did not find a significant reduction in asthma symptoms comparing house dust mite (HDM) immunotherapy with house dust. However, the results of Maunsell 1971 indicated that three (95%CI 2 to 18) patients would have to be treated with HDM immunotherapy to avoid one reporting worse asthma symptoms. Choovoravech 1974 did not find any significant reduction in asthma medications following immunotherapy.

The three studies (B.T.A. 1968; Vooren 1969; Aas 1971) that compared house dust extracts with placebo found negative results for most outcomes. Participants randomised to house dust were less likely to report worse asthma symptoms, but the combined effect did not achieve statistical significance. In the B.T.A. 1968 study, those randomised to house dust had minimal reduction in asthma medication and no real change in lung function. However, Aas 1971 found that asthmatic children randomised to house dust had significantly reduced allergen specific BHR, four (95%CI 3 to 9) children would have to be treated to avoid one deteriorating.
On the other hand, studies with untreated controls reported strongly positive results of allergen immunotherapy. Bousquet II 1988, Garcia-Ortega 1993 and Kohno 1998 found that patients randomised to immunotherapy demonstrated significant reductions in asthma symptoms (combined SMD -1.84; 95%CI -3.21 to -0.47) and medication (SMD -2.53; 95%CI -3.05 to -2.01) and even a significant improvement in lung function (combined SMD -0.80; 95%CI -1.21 to -0.39). Kohno 1998 also reported a significant reduction in non-specific BHR (SMD -2.15; 95%CI -3.56 to -0.73). Bertelsen 1989 also found that patients randomised to immunotherapy were marginally less likely to develop increased allergen specific BHR. Although Garcia-Ortega 1993 found a significant improvement in allergen specific BHR following immunotherapy, Kohno 1998 did not, so that the combined effect was not significant.

The only trial to directly compare allergen immunotherapy with inhaled steroids (Shaikh 1997) found that symptom scores and FEV1 rose more rapidly in the group randomised to budesonide. However as no standard deviations were reported, it was not possible to calculate standardised mean differences. In any case, there were no other trials with which these results could be meaningfully combined.

**Discussion**

This updated systematic review of allergen immunotherapy for asthma has identified an additional 23 randomised controlled trials, which were not covered by our previous Cochrane review of studies published up to 1997. The most common reason for these studies not being included previously was that they were published after 1997. However in some cases, we were awaiting confirmation that allocation of treatment was randomised or other methodological details. Most of the non English language publications on allergen immunotherapy were not randomised controlled trials. A total of 166 studies were excluded from this review, predominantly because they were not randomised, not controlled, did not report clinically relevant outcomes or only involved subjects with rhinitis. Two studies previously included (Tuchinda & Chai 1973; Murray 1985) were excluded, because on re-examination it became apparent that they were not truly randomised.

Given the well-recognised bias favouring the publication of positive studies, it is quite possible that some additional negative studies have been conducted, but that their results have not been published in the medical literature. This problem could be avoided in the future by prospective registration of all clinical trials of allergen immunotherapy, as has been attempted in other clinical disciplines. Unfortunately the methodological quality of most studies, particularly the concealment of allocation following randomisation could not be clearly determined from the information presented in the papers. We would encourage authors of future papers to follow the CONSORT guidelines and fully report such details.

This meta-analysis has confirmed that allergen specific immunotherapy can significantly reduce asthma symptoms and medication requirements. The heterogeneity of symptom and medication scores may have arisen, in part, from the different scoring schemes used in different studies, since changes in lung function or bronchial hyper-reactivity reported as dichotomous outcomes did not show heterogeneity. The heterogeneity in medication and symptom scores remained significant after stratifying for the allergen administered. Standardisation of asthma symptom and medication scores is required for easier interpretation of future studies. However we do not believe that the heterogeneity of the results means that the studies could not be meaningfully combined or invalidates the conclusions.

Medication requirements which were reported as categories, in contrast to the analysis using medication scores, showed significant homogeneity. We believe that this finding can translate into a clinically useful outcome, as one of the principal aims of attempting allergen
immunotherapy is to decrease medication requirements. Whilst inhaled corticosteroid therapy remains the mainstay of asthma management, any reduction in this type of treatment while maintaining good asthma control would be welcome.

There was no consistent effect of immunotherapy upon lung function and there was significant heterogeneity in the trials that reported PEF measurements. Unlike the previous review, we did not infer SDs from studies of normal participants, because they were more likely to have more reproducible measurements than asthmatic patients. In the current analysis, the point estimates of PEF from the different studies are distributed around the line of no difference, two studies falling to one side and five to the other.

As in the previous Cochrane review, nonspecific and allergen specific BHR were analysed separately. Patients randomised to immunotherapy were significantly less likely to develop increased nonspecific BHR, and there were modest improvements in indices of nonspecific BHR. Since indices of BHR are generally considered to follow a log normal distribution, the means and standard deviations of Log PD20 were entered into RevMan to calculate the SMD.

Allergen immunotherapy significantly reduced allergen specific BHR. Stratifying the meta-analysis for the allergen administered and expressing the results as Log PD20 achieved homogeneity. It would be desirable for future studies to use a standardised protocol for bronchial allergen challenges and to report the results in a more consistent fashion. Not surprisingly it would appear that allergen immunotherapy has a greater effect upon allergen specific BHR than upon nonspecific BHR.

The finding that allergen immunotherapy significantly and homogeneously improves allergen specific bronchial BHR is clinically important. Patients with brittle extrinsic (allergic) asthma are at risk of sudden deterioration when exposed to increased levels of an aeroallergen to which they are sensitive. An intervention that reduces the risk of an acute episode of asthma under these circumstances may be clinically useful. Currently, the measurement of allergen specific BHR is the only accurate method of assessing such a risk.

Less importance should be attached to the results of the relatively small number of non-placebo controlled trials. There is some evidence that house dust mite extracts may reduce asthma symptoms and allergen specific BHR compared to house dust extracts. One study even suggested that house dust extracts alone could reduce allergen specific BHR, challenging the view that such extracts are antigenically inactive. However taken together, these results are consistent with the greater efficacy of house dust mite extracts compared with placebo. Studies with untreated controls are particularly susceptible to bias and may overestimate the true benefit of treatment. The effects of immunotherapy upon symptoms, medication and lung function found in one such study are beyond the upper confidence limits for placebo controlled studies.

Although not consistently reported in the randomised controlled trials, there are well recognised adverse effects of immunotherapy. Three recent studies (one prospective [Businco 1995] and two retrospective [Karaayva 1999, Ragusa 1997] reported the incidence of non-fatal systemic reactions to inhalant allergen immunotherapy. The total number of participants was 4768 and the studies recorded events over 7 to 12 years. The incidence of systemic reactions was one per 1250 to one per 2206 injections. Most reactions were mild. Deaths due to allergen immunotherapy were extremely rare, with estimates ranging from one per one million to one per two million injections.

The results of this systematic review are consistent with our previous Cochrane review and our original conclusions have not been overturned by the inclusion of 23 additional
randomised controlled trials of allergen immunotherapy. In the initial meta-analysis (Abramson 1995), we intuitively calculated the combined odds ratios for symptomatic improvement, reduction in medication and BHR. These odds ratios can be converted to the Cochrane convention of clinically unfavourable outcomes being greater than one by taking their reciprocals. When the reciprocals are compared with the odds ratios from the present review, the results are strikingly similar and in all cases lie within the 95% confidence intervals. For the first time, we have expressed the effect on dichotomous outcomes as NNT. The numbers needed to treat for one person to benefit are small, and compare favourably with other preventive treatments for asthma. Furthermore the overall effects of immunotherapy upon continuous outcomes (Effect size or SMD) are also comparable between reviews.

Conclusions

Implications for practice

The evidence assembled in this review confirms the efficacy of immunotherapy in terms of a reduction in asthma symptoms and use of asthma medication, but it gives limited guidance concerning the size of benefit compared to other therapies. For example, it is not confidently known whether the effect is the same in patients receiving inhaled corticosteroids as those who are not. The data show that immunotherapy can be considered when asthma is extrinsic and an unavoidable clinically relevant allergen can be identified. A specific effective extract should be used and there should be flexibility in the dosage schedule. The question of side effects must be fully discussed with the patients. They must be observed long enough to deal with any major systemic reactions (typically 45 minutes) and adequate resuscitation measures must be available because of the well-known possibility of anaphylaxis. There must be access to expert advice at all times.

Implications for research

(1) Specific to immunotherapy:

* What are the most important determinants of the clinical relevance of an allergen?
* Which patients respond best?
* Is the result better when there is a narrow range of positive skin tests or is it just as effective in pan-reactors?
* Is mono-component immunotherapy better than the use of a cocktail of allergens to which the patient reacted?
* What is the optimal length of treatment and the best duration of effect?

(2) Immunotherapy in relation to other asthma therapies:

* What is the size of effect compared to other therapies?
* What is the effect of concurrent steroid therapy?
* What is the risk benefit profile?

Internal sources of support to the review

External sources of support to the review

* Garfield Weston Foundation UK

Potential conflict of interest

None declared

Acknowledgements
We wish to thank Daniel Czarny, Rosa Dias Santilhiano, Andrei Saramovich, Fiona Savio, Georg Schappi, Noortje Hamse, Brechje Gosens, Paul Angel and Alicia Stein-Oakley for their assistance in translating studies published in languages other than English. The German Assistant (Microtac software) was used to translate papers published in German. David Hill kindly gave us access to the original data from his RCT of grass pollen immunotherapy in children with asthma. Betul Sin provided individual patient data from his RCT of immunotherapy with grass pollen and mite extracts. Jean Bousquet and Alicia Armentia provided methodological details of studies conducted by their groups. Steve Milan, Anna Bara and Karen Blackhall searched the Cochrane Airways Group database. David Badger and Vivienne Moore from the Australasian Cochrane Centre and Anna Bara provided helpful advice on the use of RevMan. Paul Montgomery read and approved the consumer synopsis.

**Contribution of Reviewer(s)**

Michael Abramson participated in the selection of studies, obtained papers reporting trials, wrote to authors, extracted data and entered it into RevMan for meta-analysis and wrote the first draft of the results.

Robert Puy performed literature searches, participated in the selection of studies, performed quality assessments and checked some of the extracted data.

John Weiner participated in the selection of studies, performed quality assessments and wrote the first draft of the discussion.

All reviewers contributed to the protocol and approved the final version of the review.

**Most recent changes**

Overall an additional 21 randomised controlled trials of allergen immunotherapy published up to 2001 have been included in this version. These include a trial of a new class of allergen (latex) and another trial comparing immunotherapy with inhaled corticosteroid. Categorical outcomes have been summarised as numbers needed to treat rather than odds ratios. However the overall effects of immunotherapy are very similar to those published in previous systematic reviews.

**Synopsis**

Injecting allergens under the skin (allergen specific immunotherapy) can reduce asthma and use of medication, but with a risk of severe reactions.

Asthma attacks can be caused by allergies, pollens, cigarette smoke or air pollution and can be fatal. An allergen is a substance that causes an allergic reaction in a person sensitive to it. Allergen specific immunotherapy involves having injections of increasing amounts of the allergen under the skin. It is also called hyposensitisation or desensitisation, and there is a risk of severe allergic reactions. The review of trials found that immunotherapy can reduce asthma symptoms, the need for medications, improve the sensitivity of the lungs and reduce the risk of severe asthma attacks after future exposure to the allergen.

**Table of comparisons**

Fig 01 Allergen immunotherapy versus placebo
### Asthma symptom scores

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**Subtotal (99.9) 3.05 with 117 degrees of freedom**

Test for heterogeneity: chi-square = 22.40 with 117 degrees of freedom.

Test for overall effect: 0.14 with 117 degrees of freedom.

### Additional Immunotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy</th>
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<th>N</th>
<th>Placebo</th>
<th>Mean (SD)</th>
<th>N</th>
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**Subtotal (99.9) 3.05 with 117 degrees of freedom**

Test for heterogeneity: chi-square = 22.40 with 117 degrees of freedom.

Test for overall effect: 0.14 with 117 degrees of freedom.
### Symptomatic deterioration

#### Table: Allergen immunotherapy for asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy n/N</th>
<th>Placebo n/N</th>
<th>Relative Risk (Random) 65% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Random) 65% CI</th>
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<tr>
<td>Amaral-Marcos 1978</td>
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<td>7/12</td>
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<td>3.0</td>
<td>0.32 [0.10, 0.99]</td>
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<tr>
<td>B.T.A. 1979</td>
<td>18/37</td>
<td>8/19</td>
<td></td>
<td>6.0</td>
<td>1.37 [0.64, 2.92]</td>
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<tr>
<td>Buchanan 1981</td>
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<td>1/10</td>
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<td>1.2</td>
<td>4.96 [6.66, 31.96]</td>
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<tr>
<td>Cantani 1986</td>
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<td>7/10</td>
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<td>2.4</td>
<td>0.29 [0.08, 1.05]</td>
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<td>D'Souza 1973</td>
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<td>29/43</td>
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<td>0.56 [0.35, 0.97]</td>
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<td>Merheb 1980</td>
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<td>11/16</td>
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<td>Paul 1984</td>
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<td>4/12</td>
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<td>Sabbath 1991</td>
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<td>8/20</td>
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<td>Smith 1987</td>
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<td>Wiener 1976</td>
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<td><strong>Subtotal (0%)</strong></td>
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<td>Frankland 1954</td>
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<td>MacNeele 1961</td>
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<td><strong>Subtotal (0%)</strong></td>
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<tr>
<td><strong>Subtotal (0%)</strong></td>
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<td>22/46</td>
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### Asthma medication scores

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<th>Immunotherapy N</th>
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<th>Standardised Mean Difference (Randomised) 65% CI</th>
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<td>1999a</td>
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<td>19</td>
<td>0.80 (0.93)</td>
<td>1.11 (0.18)</td>
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<td>Tannith 1997</td>
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<td>7</td>
<td>1.09 (0.15)</td>
<td>2.40 (1.40)</td>
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<td>51</td>
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<td>0.46 (0.52)</td>
<td>1.0</td>
<td>-0.22 [-0.78, 0.34]</td>
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<tr>
<td>July 1999</td>
<td>10</td>
<td>10</td>
<td>0.91 (0.30)</td>
<td>0.61 (0.20)</td>
<td>1.0</td>
<td>-0.22 [-0.78, 0.34]</td>
</tr>
<tr>
<td>1998</td>
<td>11</td>
<td>9</td>
<td>0.06 (0.20)</td>
<td>1.34 (0.10)</td>
<td>1.0</td>
<td>-0.22 [-0.78, 0.34]</td>
</tr>
<tr>
<td>1998</td>
<td>9</td>
<td>7</td>
<td>1.27 (0.23)</td>
<td>7.40 (2.20)</td>
<td>1.0</td>
<td>-0.22 [-0.78, 0.34]</td>
</tr>
<tr>
<td>Walker 2006</td>
<td>22</td>
<td>22</td>
<td>0.07 (0.56)</td>
<td>0.98 (0.20)</td>
<td>1.0</td>
<td>-0.22 [-0.78, 0.34]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>102</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td>Other immunotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adlard 1997</td>
<td>81</td>
<td>80</td>
<td>3.80 (0.51)</td>
<td>3.80 (0.52)</td>
<td>1.0</td>
<td>-0.22 [-0.78, 0.34]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>102</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>306</td>
<td>304</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Test for heterogeneity chi-square:** 13.00 df = 5 p = 0.0244

**Test for overall effect:** 2.95 p = 0.003

### Increased asthma medication

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy n/N</th>
<th>Placebo n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amaral-Moura 1978</td>
<td>6/14</td>
<td>12/12</td>
<td>0.90 [0.40, 2.23]</td>
<td>8.9</td>
<td>0.40 [0.22, 0.78]</td>
</tr>
<tr>
<td>B.T.A. 1979</td>
<td>20/27</td>
<td>17/17</td>
<td>1.11 [0.74, 1.59]</td>
<td>11.1</td>
<td>0.74 [0.59, 0.93]</td>
</tr>
<tr>
<td>Buchanan 1981</td>
<td>15/37</td>
<td>9/10</td>
<td>6.70 [1.40, 17.40]</td>
<td>4.7</td>
<td>1.40 [1.74, 17.40]</td>
</tr>
<tr>
<td>D'Souza 1973</td>
<td>23/40</td>
<td>35/43</td>
<td>11.9 [0.71, 1.62]</td>
<td>0.71 [1.62, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Marshalo 1961</td>
<td>2/10</td>
<td>4/12</td>
<td>4.00 [0.15, 0.75]</td>
<td>0.15 [0.75, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Marshalo 1963</td>
<td>2/11</td>
<td>3/11</td>
<td>4.00 [0.15, 0.75]</td>
<td>0.15 [0.75, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Marding 1968</td>
<td>6/11</td>
<td>19/11</td>
<td>6.00 [1.34, 1.06]</td>
<td>1.34 [1.06, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Middey 1969</td>
<td>17/31</td>
<td>11/15</td>
<td>7.90 [0.60, 1.10]</td>
<td>0.60 [1.10, 0.79]</td>
<td></td>
</tr>
<tr>
<td>Nepon 1976</td>
<td>5/7</td>
<td>5/7</td>
<td>2.70 [0.52, 1.94]</td>
<td>0.52 [1.94, 1.96]</td>
<td></td>
</tr>
<tr>
<td>Paul 1964</td>
<td>4/9</td>
<td>4/8</td>
<td>2.30 [0.65, 2.43]</td>
<td>0.65 [2.43, 1.96]</td>
<td></td>
</tr>
<tr>
<td>Pickler 1967</td>
<td>9/15</td>
<td>8/14</td>
<td>1.40 [1.26, 1.50]</td>
<td>1.26 [1.50, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Prince 1966</td>
<td>10/10</td>
<td>9/10</td>
<td>1.50 [1.26, 1.50]</td>
<td>1.26 [1.50, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Sabbath 1961</td>
<td>17/23</td>
<td>19/20</td>
<td>10.00 [0.76, 1.10]</td>
<td>0.76 [1.10, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Smith 1971</td>
<td>1/9</td>
<td>7/6</td>
<td>4.00 [0.15, 0.75]</td>
<td>0.15 [0.75, 1.20]</td>
<td></td>
</tr>
<tr>
<td>van de Ven 1962</td>
<td>4/9</td>
<td>8/6</td>
<td>3.20 [0.67, 1.60]</td>
<td>0.67 [1.60, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Woman 1970</td>
<td>8/21</td>
<td>15/21</td>
<td>4.00 [0.19, 0.82]</td>
<td>0.19 [0.82, 0.40]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>140/227</td>
<td>127/237</td>
<td>100.00 [0.65, 0.78]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for heterogeneity chi-square:** 17.74 df = 16 p = 0.2278

**Test for overall effect:** 6.06 p < 0.0001
### Lung function parameters

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Relative Risk (Random)</th>
<th>Weight (k)</th>
<th>Relative Risk (Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.T.A. 1979</td>
<td>17 / 37</td>
<td>12 / 19</td>
<td>12.2</td>
<td>0.70</td>
<td>1.19</td>
</tr>
<tr>
<td>Chooever 1974</td>
<td>9 / 32</td>
<td>9 / 25</td>
<td>4.4</td>
<td>0.56</td>
<td>1.47</td>
</tr>
<tr>
<td>Moolch 1979</td>
<td>30 / 31</td>
<td>14 / 15</td>
<td>30.5</td>
<td>0.97</td>
<td>1.10</td>
</tr>
<tr>
<td>Newton 1978</td>
<td>7 / 7</td>
<td>7 / 7</td>
<td>4.0</td>
<td>0.86</td>
<td>1.69</td>
</tr>
<tr>
<td>Peel 1974</td>
<td>7 / 9</td>
<td>7 / 7</td>
<td>7.0</td>
<td>0.90</td>
<td>1.60</td>
</tr>
<tr>
<td>Smith 1971</td>
<td>7 / 11</td>
<td>11 / 11</td>
<td>12.4</td>
<td>0.76</td>
<td>1.14</td>
</tr>
<tr>
<td>Taylor 1974</td>
<td>20 / 21</td>
<td>11 / 21</td>
<td>28.8</td>
<td>1.11</td>
<td>1.38</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>87 / 148</td>
<td>72 / 105</td>
<td>100.0</td>
<td>0.99</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi²=19.80 df=8 p=0.0117
Test for overall effect=1.27 p<0.01

Deterioration in lung function
Nonspecific BHR indices

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
</tr>
<tr>
<td>Franco 1985</td>
<td>8/18</td>
<td>11/18</td>
<td>0.75 [0.59, 1.00]</td>
</tr>
<tr>
<td>Machels 1983</td>
<td>7/14</td>
<td>7/17</td>
<td>0.65 [0.41, 1.02]</td>
</tr>
<tr>
<td>Mochel 1989</td>
<td>4/32</td>
<td>4/32</td>
<td>0.92 [0.23, 3.73]</td>
</tr>
<tr>
<td>Nearey 1976</td>
<td>1/15</td>
<td>4/4</td>
<td>0.25 [0.01, 5.06]</td>
</tr>
<tr>
<td>Taylor 1979</td>
<td>0/15</td>
<td>4/4</td>
<td>0.00 [0.00, 0.37]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20/74</strong></td>
<td><strong>39/47</strong></td>
<td><strong>0.67 [0.31, 1.49]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: chi-square = 2.09 df = 4 p = 0.40
Test for overall effect: d = 0.00 p = 0.0001

Increased nonspecific BHR
Allergen specific BHR indices

### Table 1: Allergen-specific BHR indices

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy</th>
<th>Placebo</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight (k)</th>
<th>Standardised Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>65% CI</td>
</tr>
<tr>
<td>Allergen 1990</td>
<td>30</td>
<td>-4.8 (0.68)</td>
<td>10</td>
<td>-7.8 (0.60)</td>
<td>-5.1 to -7.5</td>
</tr>
<tr>
<td>Bosquejo 1986</td>
<td>30</td>
<td>-2.8 (0.41)</td>
<td>10</td>
<td>-3.2 (0.39)</td>
<td>-3.0 to -3.4</td>
</tr>
<tr>
<td>Merckel 1980</td>
<td>11</td>
<td>-2.6 (0.77)</td>
<td>9</td>
<td>-3.2 (0.82)</td>
<td>-1.8 to -4.6</td>
</tr>
<tr>
<td>Van Bever 1992</td>
<td>9</td>
<td>-2.8 (0.24)</td>
<td>6</td>
<td>-3.8 (0.18)</td>
<td>-2.8 to -3.8</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>81</td>
<td>-2.8 (0.24)</td>
<td>50</td>
<td>-3.8 (0.18)</td>
<td>-2.8 to -3.8</td>
</tr>
</tbody>
</table>

#### Test for heterogeneity:
- Chi-square: 63.39, df = 60, p = 0.45
- I² = 0%

### Figure 1: Relative Risk

- Favoring Immunotherapy
- Favoring Placebo

#### Relative Risk (Fixed)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen 1990</td>
<td>1.0</td>
<td>1.0 to 1.0</td>
</tr>
<tr>
<td>Bosquejo 1986</td>
<td>0.8</td>
<td>0.6 to 1.0</td>
</tr>
<tr>
<td>Merckel 1980</td>
<td>0.5</td>
<td>0.3 to 0.8</td>
</tr>
<tr>
<td>Van Bever 1992</td>
<td>0.5</td>
<td>0.3 to 0.8</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.0</td>
<td>1.0 to 1.0</td>
</tr>
</tbody>
</table>

#### Test for heterogeneity:
- Chi-square: 1.39, df = 60, p = 0.24
- I² = 0%

---

Increased allergen specific BHR

**Table of comparisons**

Fig 02 Allergen immunotherapy versus antigenically inactive control

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy N</th>
<th>Control N</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choovoravech 1974</td>
<td>32 (1.8)</td>
<td>25 (1.16)</td>
<td>-10.0 (-0.39; 3.11)</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Asthma symptom scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy N</th>
<th>Control N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsnell 1971</td>
<td>41/18</td>
<td>13/10</td>
<td>0.86 [0.14; 0.91]</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Symptomatic deterioration

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy N</th>
<th>Control N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choovoravech 1974</td>
<td>5/32</td>
<td>5/25</td>
<td>0.59 [0.23; 1.47]</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Increased asthma medication

**Table of comparisons**

Fig 03 House dust versus placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Dust N</th>
<th>Placebo N</th>
<th>Relative Risk (Fixed) 95 % CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aus 1971</td>
<td>4/52</td>
<td>9/20</td>
<td>7.60 [1.11; 4.17]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>B.T.A 1959</td>
<td>1/32</td>
<td>2/27</td>
<td>0.56 [0.05; 5.00]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Woburn 1969</td>
<td>1/6</td>
<td>3/6</td>
<td>4.00 [0.16; 6.14]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Total (95 % CI)</td>
<td>5/81</td>
<td>8/71</td>
<td>1.00 [0.21; 4.35]</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Symptomatic deterioration
Revue: Allergen immunotherapy for asthma
Comparison: 02 Dust versus placebo
Outcome: 02 Increased asthma medication

<table>
<thead>
<tr>
<th>Study</th>
<th>Dust n/N</th>
<th>Placebo n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.T.A. 1995</td>
<td>9/33</td>
<td>11/27</td>
<td>1.12 [0.37, 1.78]</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Favours dust / Favours placebo

Increased asthma medication

Revue: Allergen immunotherapy for asthma
Comparison: 02 Dust versus placebo
Outcome: 02 Deterioration in lung function

<table>
<thead>
<tr>
<th>Study</th>
<th>Dust n/N</th>
<th>Placebo n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.T.A. 1995</td>
<td>12/39</td>
<td>15/25</td>
<td>1.06 [0.50, 1.54]</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Favours dust / Favours placebo

Deterioration in lung function

Revue: Allergen immunotherapy for asthma
Comparison: 02 Dust versus placebo
Outcome: 04 Increased allergen specific BHR

<table>
<thead>
<tr>
<th>Study</th>
<th>Dust n/N</th>
<th>Placebo n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ass 1971</td>
<td>6/52</td>
<td>11/28</td>
<td>1.32 [0.12, 0.71]</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Favours dust / Favours placebo

Increased allergen specific BHR

Table of comparisons

Fig 04 Allergen immunotherapy versus untreated control

Revue: Allergen immunotherapy for asthma
Comparison: 04 Allergen immunotherapy versus untreated control
Outcome: 01 Asthma symptom scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunotherapy</th>
<th>Mean (SD)</th>
<th>Control</th>
<th>Mean (SD)</th>
<th>Standardised Mean Difference (Random) 95% CI</th>
<th>Weight</th>
<th>Standardised Mean Difference (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bousquet II 1986</td>
<td>125</td>
<td>1.10 (0.95)</td>
<td>125</td>
<td>1.30 (0.99)</td>
<td>-0.20 (9.20)</td>
<td>31.3</td>
<td>-2.51 [-3.30, -1.73]</td>
</tr>
<tr>
<td>Santa-Maria 1993</td>
<td>18</td>
<td>1.00 (1.00)</td>
<td>18</td>
<td>2.00 (1.00)</td>
<td>1.00 (1.54)</td>
<td>35.0</td>
<td>-0.80 [-1.37, -0.20]</td>
</tr>
<tr>
<td>Gohier 1989</td>
<td>9</td>
<td>1.05 (1.10)</td>
<td>9</td>
<td>1.10 (0.24)</td>
<td>-0.05 (9.24)</td>
<td>26.7</td>
<td>-2.26 [-3.86, -0.65]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>151</td>
<td>-</td>
<td>151</td>
<td>-</td>
<td>1.00 (0.24)</td>
<td>104.0</td>
<td>1.00 [-2.25, 0.00]</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square 10.17, p&lt;0.001</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect 2.33 p=0.308</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Asthma symptom scores
Asthma medication scores

Lung function parameters

Nonspecific BHR indices

Allergen specific BHR indices

Increased allergen specific BHR

Table of comparisons
Fig 05 Allergen immunotherapy versus Inhaled steroid

Asthma symptom scores

Deterioration in FEV1

Characteristics of included studies

Study: Aas 1971

Methods: RCT, coloured sugar phenol placebo, Double blind

Participants: 80 asthmatic children aged 2-14 yrs

Interventions: Subcutaneous house dust immunotherapy

Outcomes: Clinical state (subjective parental impression)

Specific bronchial hyperreactivity to house dust

Notes: Quality Score 4

Allocation concealment: A

Study: Adkinson 1997

Methods: Double blind placebo controlled parallel group RCT

Placebo caramelised saline + histamine

Participants: 121 allergic children with perennial asthma

Mean age 9.2 (range 5.4-14) years, 79% boys

Allergies: 80% dust mite, 77% ragweed, 69% rye grass

Interventions: Subcutaneous multiple allergen immunotherapy
Median 6 (range 2-7) ALK extracts

Major allergens: Der p1, Der f1, Amb a1, Lol p1, Alt a1

**Outcomes:** Symptom scores

Medication scores

Peak Expiratory Flow Rates

Nonspecific BHR (PC20 methacholine FEV1)

Nonspecific BHR (Methacholine)

**Notes:** Concluded that immunotherapy not useful in moderate to severe perennial allergic asthma

Quality Score 4

**Allocation concealment:** B

**Study:** Altintas 1999

**Methods:** Open placebo controlled RCT multiple groups

**Participants:** 34 poorly controlled mild to moderate asthmatics aged 4-18 years

**Interventions:** Subcutaneous immunotherapy with adsorbed or aqueous extracts D.pteronyssinus

**Outcomes:** Symptom medication scores, Allergen specific BHR

**Notes:** Quality score 2

**Allocation concealment:** B

**Study:** Alvarez 1994

**Methods:** RCT, Histamine placebo, Double blind

**Participants:** 28 patients with rhinoconjunctivitis and asthma aged 15-28 yrs

**Interventions:** Subcutaneous Fel d1 immunotherapy

**Outcomes:** Symptom medication scores

Nonspecific BHR (PC20 methacholine FEV1)

Allergen specific bronchial hyperreactivity (PC20 FEV1 cat)

**Notes:** Quality Score 3

**Allocation concealment:** B
Study: Amaral-Marques 1978

Methods: RCT, unstated placebo, Double blind

Participants: 28 asthmatics aged 12-55 years with positive skin tests to house dust mite

Interventions: Tyrosine adsorbed D.pteronyssinus subcutaneous immunotherapy

Outcomes: Symptoms, Medication

Notes: Quality Score 2

Allocation concealment: B

Study: Armentia 1989

Methods: RCT, placebo, Double blind

Participants: 30 (21 asthmatic) patients with Bermuda Grass Pollen allergy

Age 12-50 yrs

Interventions: Subcutaneous Bermuda Grass Pollen immunotherapy

Outcomes: Nonspecific BHR (methacholine score 0-4)

Allergen (PD20 FEV1 Bermuda Grass Pollen) specific BHR

Notes: Quality Score 1

Allocation concealment: B

Study: Armentia 1995

Methods: RCT, Double blind

Participants: 35 (25 asthmatic) patients sensitised to storage mite (Lepidoglyphus destructor)

Age 13-63 yrs

Interventions: Subcutaneous immunotherapy with L.destructor extract

Outcomes: Subjective clinical assessment based upon symptoms and drug intake

Nonspecific (PD20 methacholine FEV1) BHR

Notes: Quality Score 4

Allocation concealment: B

Study: B.T.A. 1968
**Methods:** RCT, carbol saline placebo, Double blind

**Participants:** 96 asthmatic patients, mean age 24

**Interventions:** House dust subcutaneous immunotherapy

**Outcomes:** Symptoms, Medication, Peak expiratory flow

**Notes:** Quality Score 4

**Allocation concealment:** A

**Study:** B.T.A. 1979

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**Methods:** RCT, glycerated extraction medium placebo, Double blind

**Participants:** 70 asthmatic patients

66% > 30 yrs

**Interventions:** House dust mite subcutaneous immunotherapy

**Outcomes:** Symptoms, Medications, FEV1

**Notes:** Quality Score 3

**Allocation concealment:** B

**Study:** Baur 1989

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**Methods:** RCT, cross-over design, placebo control, single blind

**Participants:** 39 asthmatics aged 18-45 years

**Interventions:** Pollen, House dust mite & fungal subcutaneous immunotherapy

**Outcomes:** Allergen Specific BHR (PC100 SRaw)

**Notes:** Quality Score 1

**Allocation concealment:** B

**Study:** Bertelsen 1989

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**Methods:** RCT, Untreated controls, open study

**Participants:** 27 asthmatic children allergic to dog or cat

Age 7-15 yrs

**Interventions:** Dog & cat subcutaneous immunotherapy

**Outcomes:** Allergen specific BHR
Notes: Quality Score 2

Allocation concealment: D

Study: Bousquet 1985

Methods: Open RCT, unstated placebo

Participants: 48 (39 asthmatic) patients with grass pollen allergy aged 10-51 years

Interventions: Subcutaneous immunotherapy with D.glomerata extracts. Rush immunotherapy with standardised lyophilized extract was compared to classical immunotherapy with alum precipitated pyridine extracted material.

Outcomes: Symptom medication scores

Notes: Quality score 1

Allocation concealment: D

Study: Bousquet I 1985

Methods: RCT, unstated placebo, Double blind

Participants: 30 patients with perennial asthma, aged 18-42 years

Interventions: D.pteronyssinus subcutaneous immunotherapy

Outcomes: Allergen Specific BHR (PD20 FEV1 mite)

Notes: Quality Score 2

Allocation concealment: A

Study: Bousquet II 1988

Methods: RCT, untreated controls, open study

Participants: 215 patients with perennial asthma, aged 3-72 years

Interventions: House dust mite subcutaneous immunotherapy

Outcomes: Symptoms, Medication, FEV1

Notes: Quality Score 1

Allocation concealment: D

Study: Bousquet III 1989

Methods: RCT, placebo phenol histamine in normal saline

Mixed design - 3 groups double blindered, 1 open
**Participants:** 60 (38 asthmatic) patients with grass pollen allergy

Age 12-46 yrs

**Interventions:** Subcutaneous immunotherapy with high molecular weight formalinised allergoid, unfractionated allergoid and standardised orchard grass pollen extract

**Outcomes:** Symptoms, Medication

**Notes:** Quality Score 2

**Allocation concealment:** A

**Study:** Bousquet IV 1990

**Methods:** RCT, phenol saline placebo, Double blind

**Participants:** 57 (30 asthmatic) patients with orchard grass pollen allergy, aged 11-45 years

**Interventions:** Subcutaneous immunotherapy with high molecular weight formalinised allergoid in high and low dose schedules

**Outcomes:** Symptoms

**Notes:** Quality Score 3

**Allocation concealment:** A

**Study:** Bruce 1977

**Methods:** RCT, coloured histamine placebo, stratified allocation, blinding not specified

**Participants:** 39 ragweed allergic seasonal asthmatics

**Interventions:** Subcutaneous immunotherapy with aqueous ragweed extract

**Outcomes:** Symptoms

Allergen specific BHR

**Notes:** Quality Score 3

**Allocation concealment:** B

**Study:** Buchanan 1981

**Methods:** RCT, saline placebo, Double blind

**Participants:** 55 adult asthmatic patients

**Interventions:** House dust mite subcutaneous immunotherapy
**Outcomes:** Symptoms (self assessed)
Medication & asthma attacks (physician assessment)

**Notes:** Quality Score 2

**Allocation concealment:** B

**Study:** Cantani 1996

**Methods:** Randomised placebo controlled double blind parallel group design

**Participants:** 20 asthmatic children (14 boys)
Median age 6 (range 4 - 13) years

**Interventions:** Intradermal immunotherapy with multiple allergens (including glucuronidase)
2 injections 1 NU, 8 weeks apart

**Outcomes:** Symptoms (days with asthma)
Medication (days with drug consumption)
Global clinical evaluation

**Notes:** Salbutamol, theophylline or oral betamethasone permitted for rescue
Quality Score 2

**Allocation concealment:** A

**Study:** Choovoravech 1974

**Methods:** RCT, House dust control, Single blind

**Participants:** 57 adult asthmatics
Mean age 30.4 yrs

**Interventions:** D.pteronyssinus & D.farinae subcutaneous immunotherapy

**Outcomes:** Symptom scores
Physician evaluation based upon examination, PEF & medication requirements

**Notes:** Quality Score 1

**Allocation concealment:** B

**Study:** Creticos 1996
Methods: RCT, unstated placebo, Double blind

Participants: 77 adult asthmatics
Mean age 35.5 yrs

Interventions: Ragweed pollen subcutaneous immunotherapy

Outcomes: Symptom scores
Medication scores
Peak expiratory flow
Allergen specific BHR (PD20 FEV1 Ragweed pollen)

Notes: Quality Score 4

Allocation concealment: A

Study: D'Souza 1973

Methods: RCT, carbol saline placebo, Double blind

Participants: 91 (83 asthmatic) patients with house dust mite allergy, aged over 10 years

Interventions: House dust mite subcutaneous immunotherapy

Outcomes: Symptoms, Medication

Notes: Quality Score 4

Allocation concealment: B

Study: Dolz 1996

Methods: Double blind placebo controlled parallel group RCT
Placebo 0.01mg histamine + 0.4mg human serum albumin

Participants: 28 patients with grass pollen allergy (6 asthmatics)
Mean age 19.4 (15-35) years

Interventions: Subcutaneous immunotherapy mostly with alum adsorbed grass pollen extracts
Initial rush protocol with aqueous extracts over 4 days
Followup 3 years

Outcomes: Symptom scores
Medication scores

Allergen specific BHR

Notes: Medication scores included antihistamines

No SD reported for PD20 FEV1

Quality Score 3

Allocation concealment: B

Study: Dreborg 1986

Methods: RCT, freeze dried caramelised histamine placebo, Double blind

Participants: 30 children with Cladosporium allergy, aged 5-17 years

Interventions: Cladosporium subcutaneous immunotherapy

Outcomes: Symptoms, Medication, Peak Expiratory Flow (no SD reported)

Allergen specific BHR

Notes: Quality score 2

Allocation concealment: B

Study: Franco 1995

Methods: Double blind placebo controlled probably randomised trial

Histamine placebo

Participants: 49 patients with mite allergic asthma

Mean (SD) age 24.5 (11.2) yrs

Interventions: Subcutaneous immunotherapy with depot D.pteronyssinus extract

Duration 15 months

Outcomes: Symptoms (Visual analogue scale)

Medication score

Lung function (PEF)

Nonspecific BHR (PD20 FEV1 methacholine)

Notes: Median change in PD20 reported, but not SD

Wrote to authors to clarify randomisation
Allocation concealment: B

Study: Frankland 1954

Methods: RCT, coloured phenol saline and ultrafiltrate controls, observers blinded

Participants: 200 (57 asthmatic) patients with pollen allergy, aged over 10 years

Interventions: Subcutaneous immunotherapy with mixed Timothy & cocksfoot grass pollen extract, purified pollen protein

Outcomes: Symptoms

Notes: Quality Score 3

Allocation concealment: B

Study: Gaddie 1976

Methods: RCT, placebo controlled, double blind

Participants: 55 patients with perennial asthma

Age 13-68 yrs

Interventions: Subcutaneous immunotherapy with tyrosine adsorbed depot Dermatophagoides pteronyssinus preparation

Outcomes: Symptoms, Medication, FEV1 (no SD reported)

Notes: Quality score 2

Allocation concealment: B

Study: Garcia-Ortega 1993

Methods: RCT, untreated controls

Participants: 36 patients with mite allergic asthma. Age 13-45 years

Interventions: Subcutaneous intensive immunotherapy with aqueous D.pteronyssinus extracts

Outcomes: Clinical score (symptoms + medications), Nonspecific BHR, Allergen specific BHR (methacholine),

Notes: Quality score 1

Allocation concealment: D

Study: Gruber 1999

Methods: Open RCT
Participants: 31 patients with mite allergic asthma, Mean age 11.7 years

Interventions: Subcutaneous immunotherapy with alum depot mite extract

Outcomes: Lung function, Nonspecific BHR (cold air challenge)

Notes: Quality score 2

Allocation concealment: B

Study: Haugaard 1992

Methods: RCT, histamine control with burnt glucose, double blind

Participants: 24 asthmatics allergic to cat &/ dog dander

Age 13-48 yrs

Interventions: Subcutaneous immunotherapy with cat epithelium and dog dander extracts

Outcomes: Symptoms

Nonspecific (PC20 histamine PEF) BHR

Allergen specific BHR (PD20 PEF cat/dog)

Notes: No SD estimable for PD20

Quality score 3

Allocation concealment: C

Study: Hedlin 1999

Methods: Partially blinded RCT with parallel group design

Participants: 29 children with allergic asthma, aged 7-16 years

Interventions: Subcutaneous immunotherapy with cat/dust mite and pollen extracts

Outcomes: Symptoms

Medications

Nonspecific BHR

Allergen specific BHR

Notes: Control group received pollen immunotherapy

Quality score 3

Allocation concealment: B
Study: Hill 1982

Methods: RCT, 1PNU rye grass pollen placebo

Participants: 20 asthmatic children, aged 9-14 years, with rye grass pollen allergy

Interventions: Subcutaneous immunotherapy with aqueous rye grass pollen extract

Outcomes: Symptoms, Medications (medians only reported, no SD)

Notes: SD calculated from original data provided by Dr D. Hill

Quality score 3

Allocation concealment: D

Study: Hakansson 1998

Methods: Double blind controlled trial

Participants: 24 birch pollen allergic patients aged 21-42 years

Interventions: Subcutaneous immunotherapy with depot birch pollen extract

Outcomes: Symptoms, Medications, PEF, Nonspecific BHR(PC20 MCh)

Notes: Quality score 1

Wrote to authors requesting details of randomisation and concealment

Allocation concealment: B

Study: Johnstone 1957

Methods: RCT, buffered saline control, double blind

Participants: 112 (72 asthmatic) children with pollenosis

Interventions: Subcutaneous immunotherapy with ragweed pollen extract, administered by 3 regimens

Outcomes: Asthma symptoms reported by mother

Notes: Quality score 1

Allocation concealment: C

Study: Johnstone 1961

Methods: RCT, buffered saline control, double blind, 4 year followup

Participants: 173 children with perennial asthma
**Interventions:** Subcutaneous immunotherapy with relevant allergen extracts, administered by 3 regimens

**Outcomes:** Asthma symptoms reported by mother

**Notes:** Quality score 5

**Allocation concealment:** B

**Study:** Johnstone 1968

**Methods:** RCT, buffered saline control, double blind

**Participants:** 130 children with perennial asthma followed to age 16 years

**Interventions:** Subcutaneous immunotherapy with relevant allergens administered by 3 regimens

**Outcomes:** Asthma symptoms reported by mother

**Notes:** Quality score 5

**Allocation concealment:** B

**Study:** Kohno 1998

**Methods:** Placebo controlled parallel group design RCT

Untreated controls viz open

**Participants:** 16 patients with mite allergic asthma

Mean age 26 (19-41) years

**Interventions:** Subcutaneous rush immunotherapy with aqueous D.farinae extract

6 month duration

**Outcomes:** Asthma symptoms (Scored 0-9 in diaries)

Lung function (PEF)

Nonspecific BHR (PC20 histamine)

Allergen specific BHR (PC20 FEV1 D.farinae extract)

**Notes:** Quality Score 2

**Allocation concealment:** D

**Study:** Kuna 1989

**Methods:** RCT, saline placebo, double blind
**Participants:** 24 patients with seasonal asthma

Mean age 27.2 yrs

**Interventions:** Subcutaneous immunotherapy with glutaraldehyde modified tyrosine adsorbed grass pollen extracts

**Outcomes:** Symptoms

FEV1 (only baseline results reported)

Nonspecific (PC20 histamine FEV1) BHR

**Notes:** Quality score 3

**Allocation concealment:** A

**Study:** Leynadier 2000

**Methods:** Double blind placebo controlled RCT

**Participants:** 17 patients with latex allergy, 9 had asthma, Mean age 30.5 (range 22-41) yrs

**Interventions:** Subcutaneous immunotherapy with latex extract

**Outcomes:** Symptom scores (asthma reported separately), Medication scores

**Notes:** Quality score 3

**Allocation concealment:** B

**Study:** Machiels 1990a

**Methods:** RCT, albumin buffer placebo controlled, double blind, 2 year followup

**Participants:** 39 asthmatic patients with Dermatophagoides pteronyssinus allergy, aged 16-57 years

**Interventions:** Subcutaneous immunotherapy with D.pteronyssinus allergen antibody complexes by 2 regimens

**Outcomes:** Symptoms, Medication, Peak Expiratory Flow

Nonspecific (PC35 acetylcholine SGaw) BHR

Allergen specific BHR (PD20 FEV1 mite)

**Notes:** Quality score 3

**Allocation concealment:** B

**Study:** Machiels 1990b
Methods: RCT, albumin phenol buffer control, double blind

Participants: 30 (18 asthmatic) patients with grass pollen allergy, aged 14-57 years

Interventions: Intradermal immunotherapy with grass pollen antibody complexes

Outcomes: Asthma symptoms

Medication (vasconstrictors, antihistamines, oral steroids)

Notes: Quality score 3

Allocation concealment: B

Study: Machiels 1991

Methods: RCT, albumin phenol saline buffer placebo control, double blind

Participants: 51 grass pollen hypersensitive patients, aged 12-51 years

Including 12 previously treated patients

Interventions: Subcutaneous immunotherapy with grass pollen allergen antibody complexes by 2 regimens

Outcomes: Symptoms, Medications

Notes: Quality score 3

Allocation concealment: B

Study: Machiels 1993

Methods: RCT, albumin buffer placebo controlled, double blind, 4 year followup

Participants: 39 asthmatic patients with Dermatophagoides pteronyssinus allergy, aged 16-57 years

Interventions: Subcutaneous immunotherapy with D.pteronyssinus allergen antibody complexes by 2 regimens

Outcomes: Symptoms, Medication

Lung function (FEV1%, TLV, sGaw)

Nonspecific (PC35 acetylcholine SGaw) BHR

Allergen specific BHR

Notes: Quality score 3

Allocation concealment: B
Study: Malling 1986

Methods: RCT, caramellised histamine placebo control, double blind

Participants: 22 adult asthmatics with Cladosporium allergy, aged 16-60 years

Interventions: Subcutaneous immunotherapy with lyophilised partially purified Cladosporium herbarum extract

Outcomes: Symptoms, Medication

Allergen specific BHR (PC20 FEV1 Cladosporium)

Notes: Quality score 4

Allocation concealment: B

Study: Maunsell 1971

Methods: RCT, house dust control, double blind

Participants: 34 asthmatic patients with house dust allergy, aged 16-56 years

Interventions: Subcutaneous immunotherapy with Dermatophagoides farinae extracts

Outcomes: Symptoms (clinical improvement)

Notes: Quality score 2

Allocation concealment: B

Study: Mosbech 1989

Methods: RCT, placebo control, double blind

Participants: 46 house dust mite allergic asthmatics, aged 18-56 years

Interventions: Subcutaneous immunotherapy with Dermatophagoides pteronyssinus & monomethoxypolyethylene glycol modified extracts

Outcomes: Symptoms, Medications

Peak Expiratory Flow

Nonspecific BHR to histamine

Allergen specific BHR

Notes: Quality score 4

Randomisation (minimisation) by computer

Allocation concealment: A
Study: Mungan 1999

Methods: Placebo controlled RCT, multiple groups

Participants: 36 patients with mite sensitive asthma and rhinitis, mean age 31 years

Interventions: Subcutaneous and sublingual D.pteronyssinus and D.farinae extracts

Outcomes: Symptoms, Medications, Nonspecific BHR

Notes: Quality score 2

Allocation concealment: B

Study: Newton 1978

Methods: RCT, normal saline placebo control, double blind

Stratified randomisation

Participants: 14 patients with perennial asthma and house dust mite allergy, aged 18-44 years

Interventions: Subcutaneous immunotherapy with alum precipitated D.farinae extracts

Outcomes: Symptoms, Medication

Peak Expiratory Flow

Allergen specific BHR (PD25 PEF mite)

Notes: Quality Score 3

Allocation concealment: B

Study: Ohman 1984

Methods: RCT, histamine placebo control, double blind

Participants: 17 asthmatic patients with cat allergy, aged 22-48 years

Interventions: Subcutaneous immunotherapy with cat pelt extract

Outcomes: Symptoms & Peak Expiratory Flow on cat exposure

Nonspecific (methacholine) BHR

Allergen specific BHR (PD20 FEV1 cat)

Notes: Quality Score 3

Allocation concealment: A
Study: Olsen 1997

Methods: Randomised placebo controlled double blind parallel group design

Computer generated randomisation stratified by age, gender and severity

Placebo contained histamine & aluminium hydroxide in vials of identical appearance

Participants: 31 asthmatic adults (aged 18 - 64 years)

Positive skin & RAST to house dust mite

Positive allergen specific BHR

Interventions: Subcutaneous immunotherapy with D.pteronyssinus or D.farinae extracts

Outcomes: Symptoms (Patient global assessment, scores)

Medication (Inhaled beta agonist, steroid)

Lung function (FEV1, PEF)

Allergen specific BHR (PC20 Der p/Der f FEV1)

Notes: Randomised to D.pteronyssinus or D.farinae

Wrote to authors seeking SDs

Quality Score 5

Allocation concealment: A

Study: Ortolani 1984

Methods: RCT, riboflavin coloured coca solution placebo control, double blind

Participants: 15 grass pollen allergic asthmatic patients, aged 15-45 years

Interventions: Cutaneous immunotherapy with aqueous velvet, sweet vernal & Timothy grass pollen extracts

Outcomes: Symptoms

Allergen specific BHR (medians only presented)

Notes: Quality Score 2

Allocation concealment: B

Study: Paranos 1997

Methods: Placebo controlled single blind parallel group RCT
Saline placebo

Participants: 14 patients with mite allergic asthma, age 20-40 yrs

Interventions: Subcutaneous rush immunotherapy with aqueous D.pteronyssinus extract

6 months duration

Outcomes: Medication score

Lung function (PEF, FEV1)

Notes: Baseline lung function poorly matched

Quality Score 1

Allocation concealment: B

Study: Pauli 1984

Methods: RCT, tyrosine phenol placebo control, double blind

Participants: 18 patients with perennial asthma, aged 19-40 years

Interventions: Subcutaneous immunotherapy with tyrosine adsorbed Dermatophagoides pteronyssinus extract

Outcomes: Symptoms, Medication

Peak Expiratory Flow

Notes: Quality Score 4

Allocation concealment: B

Study: Pene 1998

Methods: Double blind placebo controlled RCT

Participants: 31 patients with cat allergy, Mean age 27.7 years

Interventions: Subcutaneous immunotherapy with Fel d 1 peptides

Outcomes: Allergen specific BHR

Notes: Quality Score 2

Allocation concealment: B

Study: Pichler 1997

Methods: Randomised double blind placebo controlled parallel group design
**Participants:** 30 mite allergic patients with perennial rhinitis or bronchial asthma

Median Age 33 (20 - 46) years

20 men, 10 women, 3 lost to follow-up

**Interventions:** Subcutaneous immunotherapy with depot house mite mixture (Alutard)

12 month duration double blind followup

**Outcomes:** Symptom score (Visual analogue scale)

Medication score

Nonspecific BHR (PD20 FEV1 MCh)

**Notes:** Quality Score 2

**Allocation concealment:** B

**Study:** Price 1984

**Methods:** RCT, saline placebo control, double blind

**Participants:** 25 children with perennial asthma, aged 5-15 years

**Interventions:** Subcutaneous immunotherapy with Dermatophagoides pteronyssinus extracts

**Outcomes:** Symptoms

Medication

Lung function (TGV)

**Notes:** Continuation of study by Warner et al (1978) for second year with placebo group crossed over to active immunotherapy

Quality Score 3

**Allocation concealment:** B

**Study:** Reid 1986

**Methods:** RCT, nongrass extract placebo control, double blind

**Participants:** 18 patients with seasonal asthma and grass pollen allergy

Mean age 27.7 (range 20-39) yrs

**Interventions:** Subcutaneous allergen immunotherapy with rye grass pollen extract

**Outcomes:** Symptom Medication Scores
Notes: Quality Score 4

Allocation concealment: A

Study: Sabbah 1991

Methods: RCT, placebo control, double blind

Participants: 52 perennial asthmatics with house dust mite allergy, mean age 28.7 years

Interventions: Subcutaneous immunotherapy with alpha fraction slow release Dermatophagoides pteronyssinus extract

Outcomes: Symptoms (patient self evaluation)

Medication (physician's opinion)

Notes: Quality Score 2

Allocation concealment: B

Study: Shaikh 1997

Methods: Open parallel group randomised controlled trial

12 month duration

Participants: 51 perennial bronchial asthma patients with D.farinae sensitisation

29 males, 22 females

Mean age 26 (22 - 36) years

Interventions: Subcutaneous immunotherapy with standardised D.farinae extract

Budesonide 600 ug/d

Outcomes: Symptoms (VAS, Global evaluation)

Medication (Salbutamol)

Lung function (FEV1)

Notes: Salbutamol requirements not reported

Symptoms improved more rapidly on inhaled steroid than immunotherapy

Quality Score 3

Allocation concealment: D

Study: Sin 1996
**Methods:** Single blind placebo controlled parallel group RCT

**Participants:** 31 patients with allergic rhinitis and asthma sensitised to mixed grass pollen or D. pteronyssinus

**Interventions:** Subcutaneous immunotherapy with grass pollen or mite extracts

**Outcomes:** Symptoms

Medication

Lung function (FEV1)

BHR (MCh)

**Notes:** Quality score 1

Individual patient data provided by authors

**Allocation concealment:** B

**Study:** Smith 1971

**Methods:** RCT, human skin scale control, double blind

**Participants:** 22 asthmatic patients with house dust mite allergy, aged 11-48 years

**Interventions:** Subcutaneous immunotherapy with Dermatophagoides pteronyssinus

**Outcomes:** Symptoms

Medication

Peak Expiratory Flow

**Notes:** Quality Score 3

**Allocation concealment:** B

**Study:** Sundin 1986

**Methods:** RCT, histamine albumin aluminium hydroxide control, double blind

Stratified randomisation

**Participants:** 39 asthmatic patients with cat or dog allergy, aged 8-47 years

**Interventions:** Subcutaneous immunotherapy with cat or dog dander extracts

**Outcomes:** Symptoms (patient subjective assessment)

Nonspecific (histamine) BHR
Allergen specific BHR (PC20 PEF cat/dog)

Notes: Quality Score 3

Allocation concealment: B

Study: Tabar 1999

Methods: Open RCT with untreated controls

Participants: 63 patients with rhinoconjunctivitis and/or asthma, aged 5-50 years

Interventions: Subcutaneous immunotherapy with mite extracts by cluster or conventional schedule

Outcomes: Clinical severity, Bronchial symptoms and medications, Peak expiratory flow

Notes: Quality Score 2

Allocation concealment: D

Study: Taylor 1974

Methods: RCT, phenol saline placebo control, double blind

Participants: 42 asthmatic children with house dust mite allergy, aged 6-15 years

Interventions: Subcutaneous immunotherapy with mite fortified house dust extract

Outcomes: Height & weight
Lung function (PEF, FEV0.75, VC, Raw, FRC, TGV)
Chest examination

Notes: Quality Score 2

Allocation concealment: B

Study: Taylor 1978

Methods: RCT, histamine placebo control, double blind

Participants: 10 patients with cat induced asthma
Age 20-43 yrs

Interventions: Subcutaneous immunotherapy with cat pelt extract

Outcomes: Nonspecific BHR (PD20 histamine FEV1)

Allergen specific BHR
Notes: Blinding well described
Quality Score 4

Allocation concealment: B

Study: Torres Costa 1996

Methods: Open parallel group randomised controlled trial
27 month duration

Participants: 22 patients with asthma and D. pteronyssinus sensitisation
11 males, 11 females
Mean age 20 (12 - 38) years

Interventions: Subcutaneous immunotherapy with standardised D. pteronyssinus extract
Beclomethasone 600 - 800 ug/d withdrawn after 18 months

Outcomes: Symptoms (Score)
Medication (Salbutamol)
Lung function (PEFR, FEV1)
Nonspecific BHR (PC20 MCh)

Notes: Quality Score 3

Allocation concealment: D

Study: Valovirta 1984

Methods: RCT, caramel histamine placebo control, double blind

Participants: 27 asthmatic children allergic to dog dander, aged 5-18 years

Interventions: Subcutaneous immunotherapy with aluminium hydroxide bound dog dander extract

Outcomes: Symptoms
Allergen specific BHR

Notes: Quality Score 3

Allocation concealment: A

Study: Van Bever 1992
Methods: RCT, histamine placebo, double blind

Participants: 18 young asthmatics, with late reactions to Dermatophagoides pteronyssinus on bronchial challenge

Age 7-22 yrs

Interventions: Subcutaneous immunotherapy with standardised aqueous D.pteronyssinus extracts

Outcomes: Nonspecific (PD20 histamine FEV1) BHR

Allergic specific BHR (PD20 FEV1 mite)

Notes: Quality Score 3

Allocation concealment: B

Study: Van Metre 1988

Methods: RCT, histamine placebo control, double blind

Participants: 22 asthmatic patients allergic to cats, aged 21-52 years

Interventions: Subcutaneous immunotherapy with cat hair & dander extract

Outcomes: Nonspecific (PD20 methacholine FEV1) BHR

Allergen specific BHR (PD20 FEV1 cat)

Notes: Blinding well described

Quality Score 3

Allocation concealment: B

Study: Varney 1991

Methods: Randomised double blind placebo controlled trial

Participants: 40 adults (mean age 35 years) with severe grass pollen allergy

Interventions: Subcutaneous immunotherapy with grass pollen (P. pratense) extract

Outcomes: Chest symptoms reported separately

Notes: Quality Score 5

Allocation concealment: A

Study: Varney 1997

Methods: Randomised double blind placebo controlled parallel group design
Stratified by skin test and symptomatic response to cat challenge

Histamine placebo

**Participants:** 28 cat allergic patients with rhinoconjunctivitis and asthma

Mean age 32 (range 19 - 50) years

10 men, 18 women

**Interventions:** Subcutaneous immunotherapy with standardised cat dander extract

**Outcomes:** Cat challenge symptom score (Diary cards)

Cat challenge lung function (PEF)

**Notes:** Quality Score 3

**Allocation concealment:** B

**Study:** Vooren 1969

**Methods:** Double blind placebo controlled parallel group RCT

Carbachol + phenol red placebo

**Participants:** 12 asthmatic patients attending outpatient clinic at Leiden Hospital

**Interventions:** Subcutaneous house dust immunotherapy

**Outcomes:** Symptoms

Medications

Lung function (FEV1)

Allergen specific BHR

**Notes:** No SD reported

Quality Score 3

**Allocation concealment:** B

**Study:** Walker 2000

**Methods:** Double blind placebo controlled RCT

**Participants:** 44 patients with hayfever (36 had asthma), Mean age 22 (Range 22-64) years

**Interventions:** Subcutaneous immunotherapy with depot grass pollen extract
**Outcomes:** Chest symptoms

Medication score

Nonspecific BHR

Quality of life

**Notes:** Quality score 4

**Allocation concealment:** A

**Study:** Warner 1978

**Methods:** RCT, tyrosine placebo control, double blind

**Participants:** 51 asthmatic children, aged 5-14 years, with positive Dermatophagoides pteronyssinus challenge

**Interventions:** Subcutaneous immunotherapy with tyrosine adsorbed D. pteronyssinus extracts

**Outcomes:** Symptoms, Medication

Lung function (PEF, FEV0.75, TGV)

Allergen specific BHR

**Notes:** Quality Score 4

**Allocation concealment:** B

**Study:** Zenner 1999

**Methods:** Double blind placebo controlled RCT

**Participants:** 87 patients with grass pollen allergy, aged 16-53 years

**Interventions:** Subcutaneous immunotherapy with depot grass pollen extract

**Outcomes:** Bronchial symptoms and medications reported separately

**Notes:** Quality Score 3

**Allocation concealment:** B

Alt a1: Alternaria alternata (mould) allergen; Amb a 1: Ambrosia artemisiifolia (short ragweed) allergen; Der p 1: Dermatophagoides pteronyssinus (house dust mite) allergen; Der f 1: Dermatophagoides farinae (house dust mite) allergen; BHR: Bronchial Hyperresponsiveness; Fel d 1: Felis domesticus (cat) allergen; FEV1: Forced expiratory volume in one second; FEV0.75: Forced expiratory volume in 0.75 seconds; FRC: Functional residual capacity of the lung; Lol p 1: Lolium perenne (rye grass) allergen; MCh: methacholine; PC100 SRaw: Provocative concentration to produce a 100% increase in
specific airways resistance; PD20: Provocative dose required to induce a 20% fall in FEV1; PNU: Protein nitrogen unit; Raw: Resistance of the airways; VAS: Visual analogue scale (symptom scale); PEF: Peak expiratory flow; SD: standard deviation; SGaw: Specific conductance of the airways; TGV: Thoracic gas volume; VC: Vital capacity

**Characteristics of excluded studies**

**Study:** Adamek-Guzik 1979  
**Reason for exclusion:** Relevant outcomes not reported separately for patients with asthma  

**Study:** Akmanlar 2000  
**Reason for exclusion:** Both groups received immunotherapy  

**Study:** Almagro 1995  
**Reason for exclusion:** Sublingual immunotherapy  

**Study:** Andre 2000  
**Reason for exclusion:** Sublingual immunotherapy  

**Study:** Andri 1995  
**Reason for exclusion:** Local nasal immunotherapy for seasonal allergic rhinitis  

**Study:** Ariano 1993  
**Reason for exclusion:** Local nasal immunotherapy for seasonal allergic rhinitis  

**Study:** Ariano 1999  
**Reason for exclusion:** Asthma not reported separately  

**Study:** Armentia 1990  
**Reason for exclusion:** Probably not randomised - unclear following communication with author  

**Study:** Armentia 1992  
**Reason for exclusion:** Controlled trial of wheat flour immunotherapy - only an in vitro outcome (circulating immune complexes) reported in this paper  

**Study:** Armentia 1997  
**Reason for exclusion:** Review of previous studies - no original data presented  

**Study:** Asaoku 2000  
**Reason for exclusion:** Not controlled
Study: Astarita 1996

**Reason for exclusion:** RCT of EPD in allergic rhinitis due to Parietaria

Study: Bahceciler 2001

**Reason for exclusion:** Sublingual immunotherapy

Study: Bessot 1980

**Reason for exclusion:** Abstract - insufficient detail reported

Study: Botey 1981

**Reason for exclusion:** Probably not randomised, Inadequate reporting of outcomes

Study: Bousquet 1991

**Reason for exclusion:** No asthma outcomes reported

Study: Bousquet 1999

**Reason for exclusion:** Sublingual immunotherapy

Study: Bruun 1949

**Reason for exclusion:** Not randomised controlled trial - Alternate allocation

Study: Bucur 1989

**Reason for exclusion:** Not controlled

Study: Caffarelli 2000

**Reason for exclusion:** Oral immunotherapy

Study: Cantani 1984

**Reason for exclusion:** Not randomised

Study: Caramia 1996

**Reason for exclusion:** Not randomised

Study: Choovoravech 1976

**Reason for exclusion:** Uncontrolled study

Study: Choovoravech 1980

**Reason for exclusion:** Uncontrolled study

Study: Chowdhury Chatterjee
**Reason for exclusion:** Symptom medication score combined nasal and chest symptoms with medication requirements. Asthma not reported separately

**Study:** Chu 1981

**Reason for exclusion:** Uncontrolled study

**Study:** Clavel 1998

**Reason for exclusion:** Sublingual immunotherapy for allergic rhinitis

**Study:** ClevelandMetzger1992

**Reason for exclusion:** Not randomised, untreated controls

**Study:** Cools 2000

**Reason for exclusion:** Not a randomised controlled trial

**Study:** Cooper 1984

**Reason for exclusion:** Oral immunotherapy

**Study:** Corbetta 1992

**Reason for exclusion:** Not randomised controlled trial

**Study:** Corrado 1989

**Reason for exclusion:** Immunotherapy for perennial rhinitis

**Study:** Crimi 1991

**Reason for exclusion:** Local (inhaled) immunotherapy

**Study:** D'Amato 1995

**Reason for exclusion:** Only 12/36 patients had asthma - results not presented separately

**Study:** D'Ambrosio 1996

**Reason for exclusion:** Sublingual immunotherapy

**Study:** Des Roches 1996

**Reason for exclusion:** No untreated control group

**Study:** Des Roches 1997

**Reason for exclusion:** Not randomised

**Study:** Durham 1999
Reason for exclusion: Excluded patients with chronic asthma, although chest symptoms reported separately. Control group not allocated at random.

Study: Ebner 1989

Reason for exclusion: Comparison of two mite immunotherapy extracts

Study: Echechipia 1995

Reason for exclusion: Not obviously randomised, comparison of glutaraldehyde modified versus unmodified D.pteronyssinus immunotherapy

Study: Engstrom 1957

Reason for exclusion: Retrospective uncontrolled case series

Study: Eriksson 1979

Reason for exclusion: Subjects had hayfever not asthma

Study: Fanti 1988

Reason for exclusion: All patients received allergen immunotherapy

Study: Feliziani 1995

Reason for exclusion: Sublingual immunotherapy

Study: Ferreira 1993

Reason for exclusion: Nonrandomised trial

Study: Formgren 1984

Reason for exclusion: Abstract only - insufficient results reported

Study: Frostad 1983

Reason for exclusion: Control group not randomised. Focus on allergic rhinitis.

Study: Garcia 1997

Reason for exclusion: Not truly randomised - divided into 2 groups matched for age and sex

Study: Garcia-Villal 1999

Reason for exclusion: Open uncontrolled trial

Study: Garde Garde 1999

Reason for exclusion: Not a randomised controlled trial
Study: Gerrard 1989

Reason for exclusion: Not obviously randomised. Asthma not reported separately.

Study: Giovane 1994

Reason for exclusion: Oral immunotherapy

Study: Goldstein Chai 1981

Reason for exclusion: Uncontrolled study

Study: Goor Wuthrich 1971

Reason for exclusion: Not randomised, not all subjects asthmatic

Study: Gordon 1972

Reason for exclusion: Results for asthma symptoms not reported separately

Study: Gozalo 1997

Reason for exclusion: Sublingual immunotherapy for seasonal rhinoconjunctivitis +/- asthma

Study: Grammer 1982

Reason for exclusion: Hayfever subjects only

Study: Grammer 1983

Reason for exclusion: Asthmatic subjects not clearly identified

Study: Grembiale 2000

Reason for exclusion: Allergic rhinitis

Study: Haartela 1984

Reason for exclusion: Subjects only had hayfever

Study: Haugaard 1993

Reason for exclusion: Nonrandom allocation

Study: Hedlin 1991

Reason for exclusion: Uncontrolled followup

Study: Hedlin 1995

Reason for exclusion: Patients randomised to placebo in previous study (Sundin et al 1986) subsequently treated with allergen immunotherapy in an open fashion
Study: Henocq 1973
Reason for exclusion: Nonrandomised trial

Study: Hirokawa 1996
Reason for exclusion: Uncontrolled - all patients received rush immunotherapy

Study: Hirsch 1982
Reason for exclusion: Participants only had hayfever

Study: Horst 1990
Reason for exclusion: s only had hayfever

Study: Iikura 1997
Reason for exclusion: Not randomised

Study: Jacobsen 1996
Reason for exclusion: Abstract only, patients had allergic rhinitis

Study: Jacobsen 1997
Reason for exclusion: Effectively uncontrolled - followup of patients treated with immunotherapy

Study: Jarisch 1979
Reason for exclusion: Not a randomised controlled trial

Study: Kalla 1979
Reason for exclusion: Uncontrolled trial

Study: Kang 1988
Reason for exclusion: Alternate allocation to cockroach immunotherapy or immunotherapy with other relevant allergens. Most controls lost to followup.

Study: Kozhemiaka 1979
Reason for exclusion: Not a randomised controlled trial

Study: Laetsch 1973
Reason for exclusion: Oral immunotherapy

Study: Leng 1990
Reason for exclusion: Oral immunotherapy
Study: Levin 1959

Reason for exclusion: Not randomised controlled trial

Study: Lichtenstein 1971

Reason for exclusion: Hayfever subjects only

Study: Lilja 1989

Reason for exclusion: Second year of study reported by Sundin et al (1986) - placebo treated patients crossed over to active immunotherapy, thus uncontrolled study

Study: Lu 1998

Reason for exclusion: Uncontrolled study only reporting in vitro outcomes

Study: Majori 1998

Reason for exclusion: Not randomised

Study: Majori 2000

Reason for exclusion: Uncontrolled study focusing on in vitro outcomes

Study: Mallet 1994

Reason for exclusion: Not randomised controlled trial, asthmatics not clearly identified

Study: Martin Munoz 1996

Reason for exclusion: Not randomised

Study: Martorell Aragones

Reason for exclusion: Not randomised controlled trial, comparison of 2 groups treated for different durations

Study: Maruo 1990

Reason for exclusion: Not a randomised controlled trial

Study: Matoga 1989

Reason for exclusion: Not randomised controlled trial

Study: Matsumoto 1998

Reason for exclusion: Not randomised

Study: Matsuoka 1998

Reason for exclusion: Uncontrolled study only reporting in vitro outcomes
Study: McAllen 1967
Reason for exclusion: Not randomised trial

Study: Metzger 1983
Reason for exclusion: Abstract only - insufficient results reported

Study: Miguel Lozano 1992
Reason for exclusion: Uncontrolled study

Study: Miller 1971
Reason for exclusion: Uncontrolled study

Study: Mischler 1981
Reason for exclusion: Rhinitis subjects only

Study: Moller 1986
Reason for exclusion: Oral immunotherapy for rhinoconjunctivitis

Study: Mosbech 1985
Reason for exclusion: Abstract only - probably preliminary report of Mosbech et al 1989

Study: Mosbech 1990
Reason for exclusion: All subjects desensitised with different extracts, not randomised

Study: Moscato 1991
Reason for exclusion: Comparison of inhaled with parenteral immunotherapy

Study: Moshkevich 1985
Reason for exclusion: Inhaled immunotherapy

Study: Moverare 1998
Reason for exclusion: Pilot RCT of birch pollen immunotherapy - insufficient clinical data reported in paper

Study: Munoz-Lejarazu 1993
Reason for exclusion: Not randomised

Study: Munoz-Lopez 1981
Reason for exclusion: Not a randomised controlled trial
Study: Munoz-Lopez 1994

Reason for exclusion: Topical intranasal immunotherapy

Study: Munro-Ashman 1976

Reason for exclusion: Uncontrolled trial

Study: Murray 1985

Reason for exclusion: Untreated controls not allocated randomly. 'Placebo' control group contaminated by concurrent administration of pollen immunotherapy.

Study: Nagata 1989

Reason for exclusion: Uncontrolled trial of rush immunotherapy

Study: Nagata 1993a

Reason for exclusion: Uncontrolled study

Study: Nagata 1993b

Reason for exclusion: Not randomised

Study: Nagata 1998

Reason for exclusion: Only in vitro outcomes reported

Study: Negro 1999

Reason for exclusion: Comparison of two alternative regimes for Parietaria immunotherapy

Study: Norman 1978

Reason for exclusion: Only hayfever subjects

Study: Novembre 1991

Reason for exclusion: Sublingual immunotherapy

Study: NuchelPetersen 1988

Reason for exclusion: Not placebo controlled - all patients received immunotherapy

Study: Oda 1998

Reason for exclusion: Uncontrolled study only reporting in vitro outcomes

Study: Olaguibel 1997

Reason for exclusion: Not randomised or controlled
Study: Olive Perez 2000

Reason for exclusion: Not randomised - control group comprised children whose parents had refused immunotherapy

Study: Oppenheimer 1994

Reason for exclusion: Oral immunotherapy

Study: Osterballe 1982

Reason for exclusion: Not randomised, comparison of immunotherapy regimens

Study: PAT

Reason for exclusion: Prevention of asthma in children with allergic rhinoconjunctivitis

Study: Pajno 2000

Reason for exclusion: Sublingual immunotherapy

Study: Park 2001

Reason for exclusion: Not controlled

Study: Passalacqua 1998

Reason for exclusion: Sublingual/oral immunotherapy for allergic conjunctivitis

Study: Passalacqua 1999

Reason for exclusion: Sublingual immunotherapy for seasonal allergic rhinoconjunctivitis

Study: Paul 1998

Reason for exclusion: Not randomised - groups matched according to dust mite concentration, age and therapy

Study: Pence 1976

Reason for exclusion: Asthma symptom score not reported separately

Study: Peroni 1995

Reason for exclusion: Not randomised. Conducted at high altitude (low allergen environment)

Study: Petersen 1988

Reason for exclusion: 26/54 participants had asthma, but only global symptoms reported and results not reported separately

Study: Pichler 2001
**Reason for exclusion:** Continuation of Pichler et al 1997 - placebo group crossed over to immunotherapy

**Study:** Pradalier 1999

**Reason for exclusion:** Sublingual immunotherapy for rhinitis

**Study:** Purello-D'Ambrosio

**Reason for exclusion:** Sublingual immunotherapy

**Study:** Quirino 1996

**Reason for exclusion:** Comparison of sublingual versus subcutaneous immunotherapy

**Study:** Rak 1988-90

**Reason for exclusion:** Controlled clinical trial of birch pollen immunotherapy - not randomised

**Study:** Rak 1993a

**Reason for exclusion:** No clinical outcomes reported

**Study:** Rak 1993b

**Reason for exclusion:** Not a randomised controlled trial, no relevant outcomes reported

**Study:** Reiben 1980

**Reason for exclusion:** Oral immunotherapy

**Study:** Reilly 1993

**Reason for exclusion:** Trial of sublingual homeopathic immunotherapy reported only in abstract form

**Study:** Reinert 1983

**Reason for exclusion:** Oral immunotherapy

**Study:** Reinert Biro 1981

**Reason for exclusion:** Uncontrolled study

**Study:** Rocha 1986

**Reason for exclusion:** 30 controls received immunotherapy, but not analysed by intention to treat

**Study:** Rohatgi 1988

**Reason for exclusion:** Uncontrolled study
Study: Rose 1996

Reason for exclusion: No clinical outcomes reported

Study: Sadan 1969

Reason for exclusion: Hayfever subjects only

Study: Sanchez Palacios 1989

Reason for exclusion: Comparison of oral with parenteral immunotherapy

Study: Sanchez Palacios 2001

Reason for exclusion: Sublingual immunotherapy

Study: Sanders 1966

Reason for exclusion: Matched pairs, but not clearly randomised; Global symptom score, asthmatics not clearly identified

Study: Saraclar 1998

Reason for exclusion: Not randomised - 13/18 patients volunteered for immunotherapy

Study: Shen 1998

Reason for exclusion: Abstract only

Study: Simons 1996

Reason for exclusion: Only in vitro results presented in paper

Study: Swineford 1955

Reason for exclusion: Not a randomised controlled trial

Study: Sychlowy 1979

Reason for exclusion: Uncontrolled study

Study: Tari 1990

Reason for exclusion: Sublingual immunotherapy

Study: Tari 1992

Reason for exclusion: Inhaled immunotherapy

Study: Tari 1997

Reason for exclusion: Asthma not reported separately
Study: Taskapan 1998
Reason for exclusion: Controlled trial of single v multiple allergen immunotherapy

Study: Taub 1969
Reason for exclusion: Editorial with personal experience - not a randomised controlled trial

Study: Taudorf 1985
Reason for exclusion: Oral immunotherapy

Study: Taudorf 1987
Reason for exclusion: Oral immunotherapy

Study: Taudorf Weeke 1983
Reason for exclusion: Oral immunotherapy

Study: Tuchinda & Chai 1973
Reason for exclusion: All subjects received immunotherapy. Allocation to high or low dose not randomised.

Study: Turner 1984
Reason for exclusion: No clinical outcomes reported

Study: Urbanek 1982
Reason for exclusion: Oral immunotherapy

Study: Van Bever 1988
Reason for exclusion: Not a randomised controlled trial

Study: Van Bever 1989
Reason for exclusion: Not randomised

Study: Van Bever 1990
Reason for exclusion: All patients received immunotherapy during first year

Study: Van Bever 1998
Reason for exclusion: Only in vitro outcomes reported

Study: Vidal 1999
Reason for exclusion: Not controlled
Study: Vourdas 1998

Reason for exclusion: Sublingual immunotherapy

Study: Wahn 1988

Reason for exclusion: All children received D.pteronyssinus immunotherapy - RCT of extracts prepared from whole mite culture and mite bodies

Study: Wahn Siraganian

Reason for exclusion: Not a randomised controlled trial

Study: Wang 1999

Reason for exclusion: Only in vitro outcomes reported

Study: Weyer 1981

Reason for exclusion: No clinical outcomes reported

Study: Wuthrich Hafner 1980

Reason for exclusion: Uncontrolled study

Study: Yuksel 1999

Reason for exclusion: Sublingual immunotherapy

Study: Zietkowski 1999

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Medical Subject Headings (MeSH): Human; Allergens/ad (administration & dosage); Allergens/im (immunology); Asthma/im (immunology); *Asthma/tp (therapy); *Desensitization, Immunologic; Injections, Subcutaneous; Randomized Controlled Trials

Accession Number: 00075320-100000000-01195

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