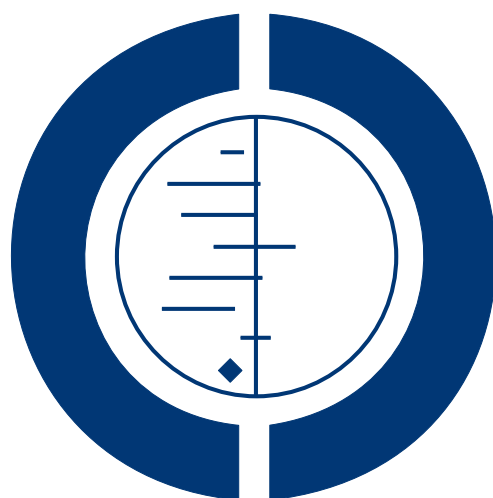


Injection allergen immunotherapy for asthma (Review)

Abramson MJ, Puy RM, Weiner JM



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Injection allergen immunotherapy for asthma (Review)

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[Intervention Review]

Injection allergen immunotherapy for asthma

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Editorial group: Cochrane Airways Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 8, 2010.

Review content assessed as up-to-date: 11 April 2009.

Citation: Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD001186. DOI: 10.1002/14651858.CD001186.pub2.

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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 methods of delivery, we updated the 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 2005, Dissertation Abstracts and Current Contents.

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 authors independently assessed eligibility of studies for inclusion. Two authors independently performed quality assessment of studies.

Main results

Eighty-eight trials were included (13 new trials). There were 42 trials of immunotherapy for house mite allergy; 27 pollen allergy trials; 10 animal dander allergy trials; two *Cladosporium* mould allergy, two latex and six trials looking at multiple allergens. Concealment of allocation was assessed as clearly adequate in only 16 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 -0.59, 95% confidence interval -0.83 to -0.35) and it would have been necessary to treat three patients (95% CI 3 to 5) with immunotherapy to avoid one deterioration in asthma symptoms. Overall it would have been necessary to treat four patients (95% CI 3 to 6) 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. If 16 patients were treated with immunotherapy, one would be expected to develop a local adverse reaction. If nine patients were treated with immunotherapy, one would be expected to develop a systemic reaction (of any severity).

Authors' 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 local or systemic adverse effects (such as anaphylaxis) must be considered.

PLAIN LANGUAGE SUMMARY

Allergen immunotherapy for the treatment of chronic asthma

Injecting allergens under the skin (allergen specific immunotherapy) can reduce asthma and use of medication and improve the sensitivity of the lungs, 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 and the risk of severe asthma attacks after future exposure to the allergen. It is possibly as effective as inhaled steroids. However, there is an increased risk of a lump at the injection site, rash, wheezing, breathlessness and very rarely a fatal allergic reaction.

BACKGROUND

Allergen specific immunotherapy ('hyposensitisation' or 'desensitisation') 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 (TSANZ/ASCI 1997; Weeke 1991) to outright dismissal (Henry 1990).

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 75 trials published between 1954 and 2001 (Abramson 2003). 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 non-specific 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. However, we did not extract data on adverse effects of immunotherapy.

Adverse effects of allergen immunotherapy are classified as local and systemic. There is no agreement in the literature as to what defines a local adverse reaction (LR), apart from the proviso that it occurs in the immediate vicinity of the site of the injection. Systemic reactions are further reported as systemic reactions not further classified (usually wheezing and urticaria) (SR), near-fatal reactions (severe hypotension and/or severe dyspnoea) (NFR) and fatal reactions (FR). While this classification does not use the term anaphylaxis, it is clear that near-fatal reactions as described do constitute anaphylaxis. The problem lies in the recognition of mild anaphylaxis as a term sometimes applied to significant wheezing and/or urticaria without hypotension, severe dyspnoea or collapse.

In recent 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

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

METHODS

Criteria for considering studies for this review

Types of studies

This review was restricted to randomised controlled trials (RCTs), which provide the strongest evidence for the efficacy of any medical treatment. Placebo controlled trials are methodologically stronger, although studies which have administered house dust or relatively antigenically inactive preparations to the control group were also considered. Double blinded trials were preferred, but single blind and open studies were also reviewed for possible inclusion. We considered studies published in languages other than English if the translated abstract indicated that the study was a RCT of allergen immunotherapy for asthma and a translator was sought (see [Acknowledgements](#)).

Types of participants

We only included studies that focused upon asthma. We considered studies of immunotherapy for hayfever only if the results for subjects with asthma were separately identified.

Types of interventions

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. Only the subcutaneous route of administration was considered. Sublingual immunotherapy for rhinitis ([Wilson 2003](#)) and asthma ([Calamita 2006](#)) has been reviewed elsewhere. Oral, intranasal and inhaled immunotherapy may be the topics of separate reviews.

Types of outcome measures

At least one of the following primary 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 (FEV₁) and thoracic gas volume);
- nonspecific bronchial hyper-reactivity (to histamine or methacholine);
- allergen specific bronchial hyper-reactivity.

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

Secondary outcomes included the following adverse events:

- local reactions (large or delayed wheals at injection site);
- systemic reactions (anaphylaxis, asthma, rhinitis or urticaria).

Search methods for identification of studies

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the [Airways Group Module](#) for further details). All records in the Specialised Register coded as 'asthma' were searched using the following terms: immunotherap* or hyposensit* or desensit*

We also undertook MEDLINE searches from 1950 to 2005 for studies of immunotherapy and asthma. We surveyed review articles identified in this process for additional and earlier citations. We also searched dissertation abstracts and Current Contents to identify more recently published and unpublished studies. The searches in this review are current to August 2005. Searches covering the period 2005 to 2008 are currently being assessed.

Data collection and analysis

Inclusion of studies in the review was decided by a simple majority of all three authors, who independently read the methods sections of papers identified by the search strategy and applied the stated criteria. Two authors performed quality assessment (RMP and JMW), independently assessed the concealment of allocation following the guidelines of the Cochrane Collaboration and applied the scoring system of [Jadad 1996](#).

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.

These comparisons were performed separately for each primary outcome, namely asthma symptoms, medication, lung function, non-specific BHR and allergen specific BHR, whenever the results were reported. Comparisons were also performed for adverse events when these were reported.

Outcome data were extracted and entered into RevMan 5.0 ([RevMan 2008](#)) for statistical analysis. We analysed categorical outcomes as relative risks (RR) and 95% confidence intervals (95% CI) calculated for individual studies. The relative risk is the ratio between the immunotherapy and control groups for the risk of subjects 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). The combined relative risks were then used to estimate the number of patients who would need to be treated (NNT(B)) to avoid these undesirable outcomes. The combined relative risks of adverse events were used to estimate the number of treated patients who would be harmed (NNT(H)) by immunotherapy. We used visual Rx 3.0 ([Visual Rx 2008](#)) to calculate NNT(B) and NNT(H).

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 v4.0 (Silk Scientific Corporation 1996, [Un-Scan-It 1996](#)). 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. 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 performed χ^2 tests to assess heterogeneity between studies. In this context, a P value < 0.05 indicated significant differences between studies and raised questions as to whether the results could be meaningfully combined.

We also expressed heterogeneity as the I^2 statistic which measures the proportion of inconsistency between studies that could not be explained by chance ([Higgins 2003](#)). When significant heterogeneity was found, we recalculated the overall efficacy using random-effects models, which provided more realistic estimates of the confidence intervals under these circumstances ([Lau et al 1997](#)).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Eighty-eight randomised controlled trials published in 98 papers between 1954 and 2005 were identified which satisfied the inclusion criteria (2009 update: 13 new trials). The methods, participants, interventions and outcomes of included studies are listed in the '[Characteristics of included studies](#)' table. A total of 3792 patients (3459 with asthma) were involved. There were 42 studies reporting immunotherapy for mite allergy, generally *Dermatophagoides pteronyssinus* or *D. farinae*, although [Armentia Medina 1995](#) used extracts of the storage mite *Lepidoglyphus destructor*. Three early studies ([Aas 1971](#); [BTA 1968](#); [Vooren 1969](#)) used extracts of house dust. There were 27 studies of immunotherapy for pollen allergy, utilising extracts of Bermuda grass, orchard grass/cocksfoot, Timothy grass, velvet grass, sweet vernal grass, perennial rye grass, birch, olive or ragweed pollen. One study ([Sin 1996](#)) included separate groups of patients with mite and pollen allergy. Ten studies reported immunotherapy for animal dander allergy, particularly to cats and dogs. Two studies utilised extracts of the mould *Cladosporium*, two 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.

We excluded a further 222 studies (2009 update: 56 new studies). The most common reasons were that the studies were: not controlled (64), not randomised (41), involved subjects with rhinitis rather than asthma (30), did not report clinically relevant outcomes (11) or were not analysed by intention-to-treat (one). There were two Phase I studies, a trial of withdrawing immunotherapy and two of homeopathy. We identified many new clinical trials of oral immunotherapy (13), inhaled or intranasal immunotherapy (eight) and particularly sublingual immunotherapy (49), some of which have been reviewed elsewhere ([Calamita 2006](#)). Finally, there were 12 abstracts which contained insufficient information for any further assessment.

Risk of bias in included studies

We assessed concealment of allocation as clearly adequate (category A) in only 16 studies (Aas 1971; Bødtger 2002; Bousquet 1985b; Bousquet 1989; Bousquet 1990; Cantani 1996; Creticos 1996; Maestrelli 2004; Mosbech 1989; Ohman 1984; Olsen 1997; Reid 1986; Valovirta 1984; Varney 1991; Varney 2003; Walker 2001). The adequacy or otherwise of 57 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 (Haugaard 1992, Machiels 1991) used a clearly inadequate method for concealment of allocation (category C). Concealment was not reported in 13 open studies (category D). There was almost perfect agreement between authors.

The overall methodological quality of the included trials was moderate. Only six trials (Bødtger 2002; Johnstone 1961; Johnstone 1968; Olsen 1997; Sastre 2003; Varney 1991) received the maximum score of five out of five. Sixteen trials scored four points, 32 trials three points, 23 trials two points and 11 trials one point. Blinding of subjects and/or evaluators is a design feature that reduces bias in randomised controlled trials. Sixty-three of the 88 studies were double blind, nine single blind, two mixed, 13 open and the remaining one unclear.

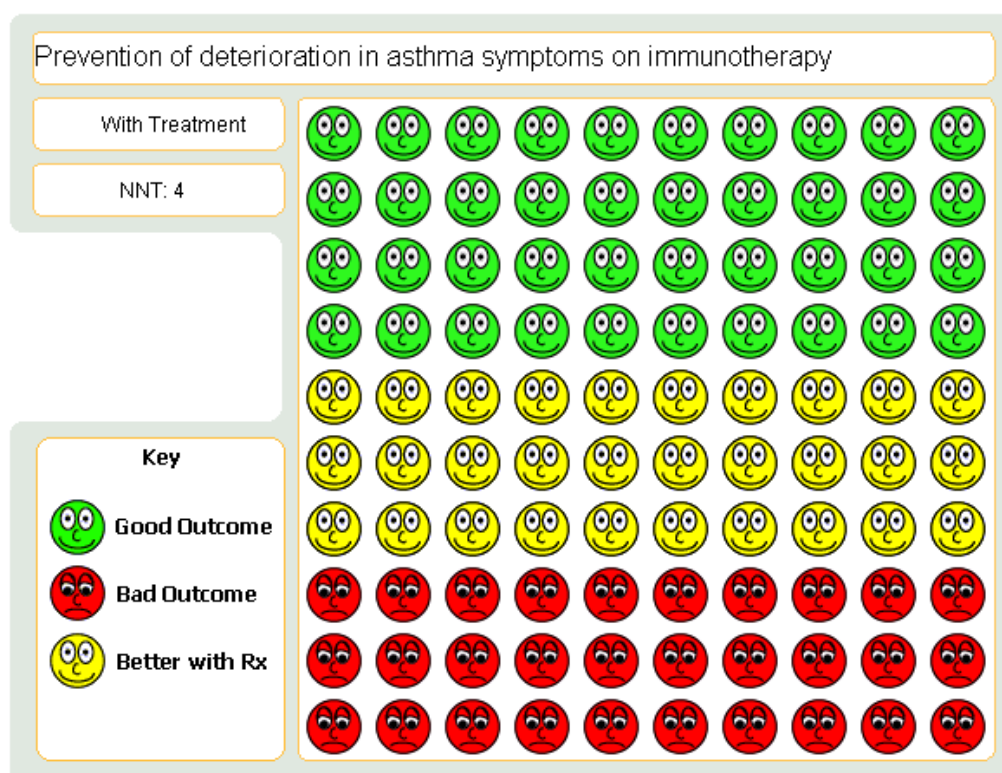
Seventy studies were placebo controlled trials of allergen specific immunotherapy, two compared immunotherapy with an antigenically less active control (Choovoravech 1974; Maunsell 1971), three compared house dust with placebo (Aas 1971; BTA 1968; Vooren 1969) and eleven utilised untreated controls (Bousquet 1988; Bertelsen 1989; Ferrer Garcia-Selles 2003; Garcia-Ortega 1993; Gonzalez 2002; Gruber 1999; Guerra 2003; Kohno 1998; Pifferi 2002; Tabar 1999; Torres Costa 1996). Shaikh 1997 compared allergen immunotherapy with inhaled steroid.

Effects of interventions

Symptoms

Symptom scores were reported by 35 studies, although Dreborg 1986, Mungan 1999 and Leynadier 2000 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 -0.48 with a 95% confidence interval from -0.96 to 0.0 thus indicating a borderline reduction in asthma symptoms. The combined SMD following pollen immunotherapy was -0.61 (95% CI -0.87 to -0.35) 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 -0.59 (95% CI -0.83 to -0.35), but there was high heterogeneity between studies ($\text{Chi}^2 = 119$, $P < 0.00001$, $I^2 = 90\%$). In part this may have been due to studies by Franco 1995, Varney 2003, Basomba 2002, Hill 1982, Bruce 1977 and Adkinson 1997 not finding any reduction in symptoms. Symptoms were simply reported as worse, the same or improved in 26 studies. Overall it would have been necessary to treat four patients (95% CI 3 to 5) with immunotherapy to avoid one deterioration in asthma symptoms (see Figure 1). 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 18) and other allergens (NNT 3; 95% CI 3 to 4). A smaller improvement was seen following mite immunotherapy where six patients (95% CI 4 to 16) would have to be treated to avoid one deteriorating. There was moderate heterogeneity between the results of all studies ($\text{Chi}^2 = 44$, $Lp = 0.003$, $I^2 = 51.8\%$), with BTA 1979 and Buchanan 1981 actually finding symptoms to be more likely in treated patients.

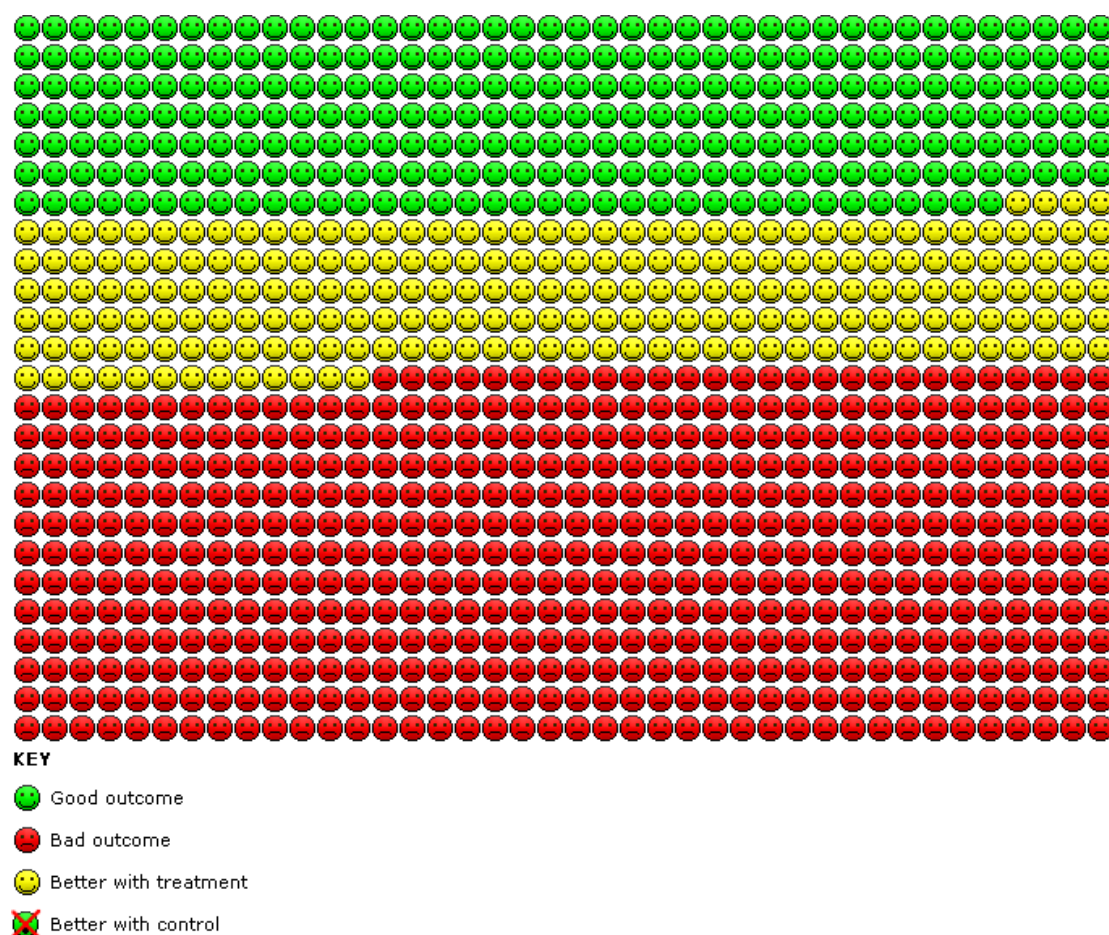
Figure 1. Of every 100 asthma patients treated with immunotherapy, 30 patients will be prevented from having an attack (worse symptoms), 40 would not have had an attack anyway and 30 will still have an attack. In other words, about four patients have to be treated to prevent one attack of asthma.



Medication

Asthma medication scores were reported by 21 studies, with [Mungan 1999](#) failing to publish the SD. The combined SMD was -0.53 (95% CI -0.80 to -0.27) indicating a significant reduction in medication following immunotherapy. Medication requirements were simply reported as increased, unchanged or decreased in 17 studies. Overall it would have been necessary to treat five patients (95% CI 4 to 7) with immunotherapy to avoid one requiring increased medication (see [Figure 2](#)). Although there was moderate heterogeneity between the studies reporting medication scores ($\text{Chi}^2 = 57.3$, $P < 0.0001$, $I^2 = 66.9\%$), there was substantial homogeneity within the latter group. Together, these findings suggest that some of the heterogeneity in medication scores may have been due to the different methods of collecting these data.

Figure 2. In the control group 724 patients out of 1000 required increased asthma medication, compared to 507 (95% CI 449 to 572) out of 1000 for the immunotherapy group



Lung function

Lung function results were reported by 20 studies, with many studies failing to provide SDs for FEV₁ (Gaddie 1976; Machiels 1993), Thoracic Gas Volume (Price 1984; Warner 1978) or Peak Expiratory Flow (Dreborg 1986; Rak 2001). Data for FEV₁ and PEF could be aggregated in meta-analyses. There was no overall difference between treatment groups, but there was substantial heterogeneity between studies ($\text{Chi}^2 = 41.4$, $P < 0.0001$, $I^2 = 80.7\%$). 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.

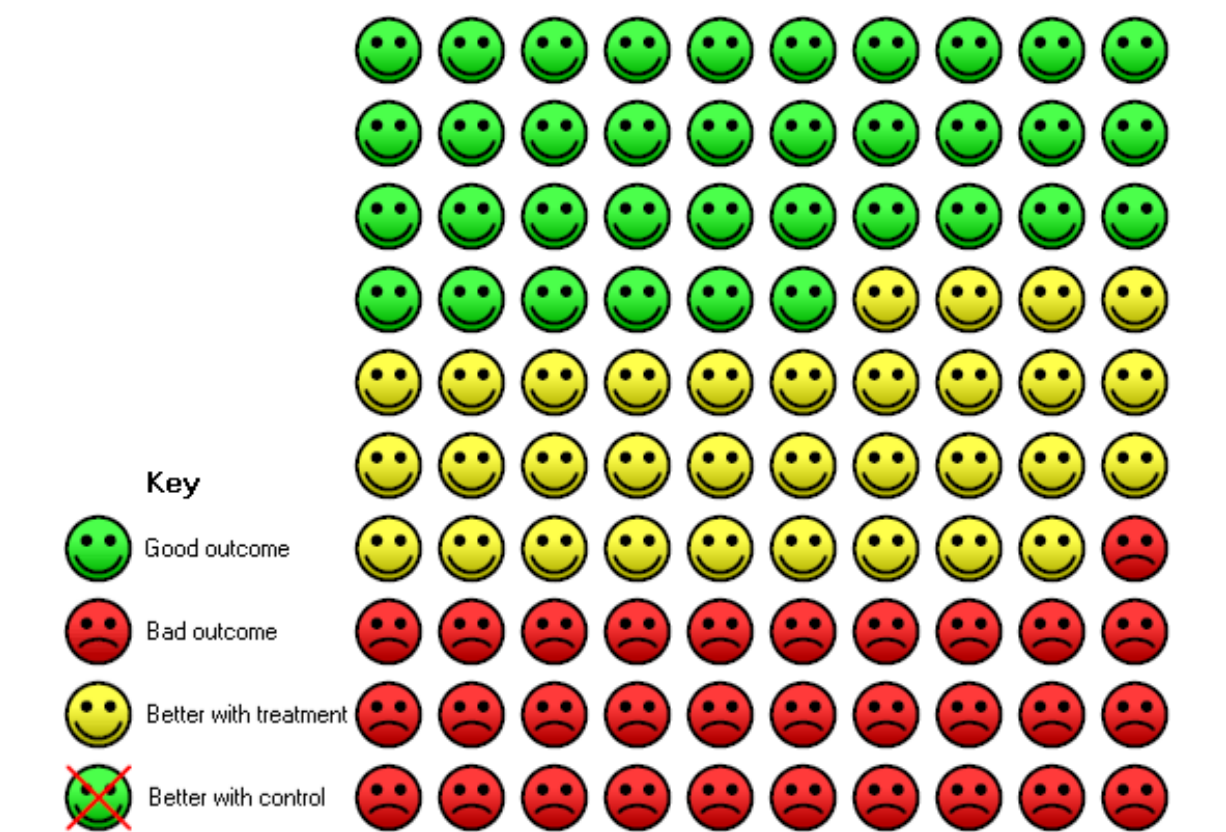
Bronchial hyper-reactivity

Indices of nonspecific bronchial hyper-reactivity were reported by 18 studies. The combined results varied significantly with the challenge agent (heterogeneity $\text{Chi}^2 = 30.4$, $P = 0.02$, $I^2 = 44.1\%$). There was a marginal improvement in PD₂₀ FEV₁ to methacholine and Machiels 1990a reported an improvement in PC₃₅SGaw to acetylcholine following immunotherapy with allergen-antibody complexes. However, there were no significant changes in PC₂₀FEV₁ to histamine challenge or the change in FEV₁ to cold air. Nonetheless there was an overall modest reduction in nonspecific BHR following immunotherapy (SMD -0.35, 95% CI -0.59 to -0.11) corresponding to a 2.2 fold (95% CI 1.3 to 3.9) increase in PD₂₀.

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 four patients (95% CI 3 to 6) with immunotherapy to avoid worsening BHR in one (see [Figure 3](#)).

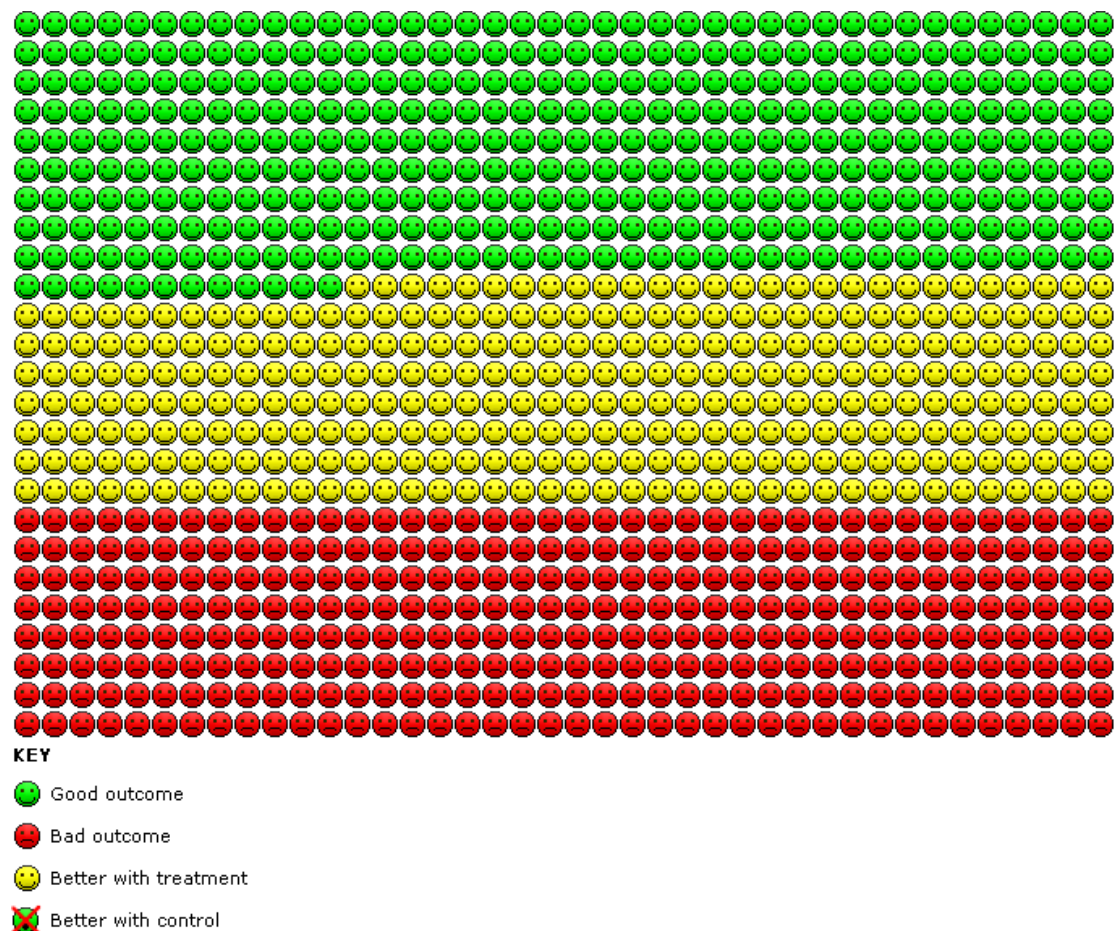
Figure 3. In the control group 64 patients out of 100 had increased nonspecific BHR, compared to 31 (95% CI 21 to 46) out of 100 for the immunotherapy group



Indices of allergen specific BHR (such as PD₂₀ FEV₁ to allergen challenge) were reported by 19 studies. There was homogeneity between these studies with an overall SMD of -0.61 (95% CI -0.79 to -0.43) indicating a significant reduction in allergen specific BHR following immunotherapy. This corresponded to a 4.1 fold (95% CI 2.7 to 6.2) increase in PD₂₀. The effect was most marked for mite immunotherapy (SMD -0.98, 95% CI -1.39 to -0.58), similar for pollen (SMD -0.55, 95% CI -0.84 to -0.27) and animal dander (SMD -0.61, 95% CI -0.95 to -0.27), but not significant

for other allergens. 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 patients (95% CI 3 to 5) to avoid worsening allergen specific BHR in one (see [Figure 4](#)).

Figure 4. In the control group 628 patients out of 1000 had increased allergen specific BHR, compared to 320 (95% CI 257 to 396) out of 1000 for the immunotherapy group

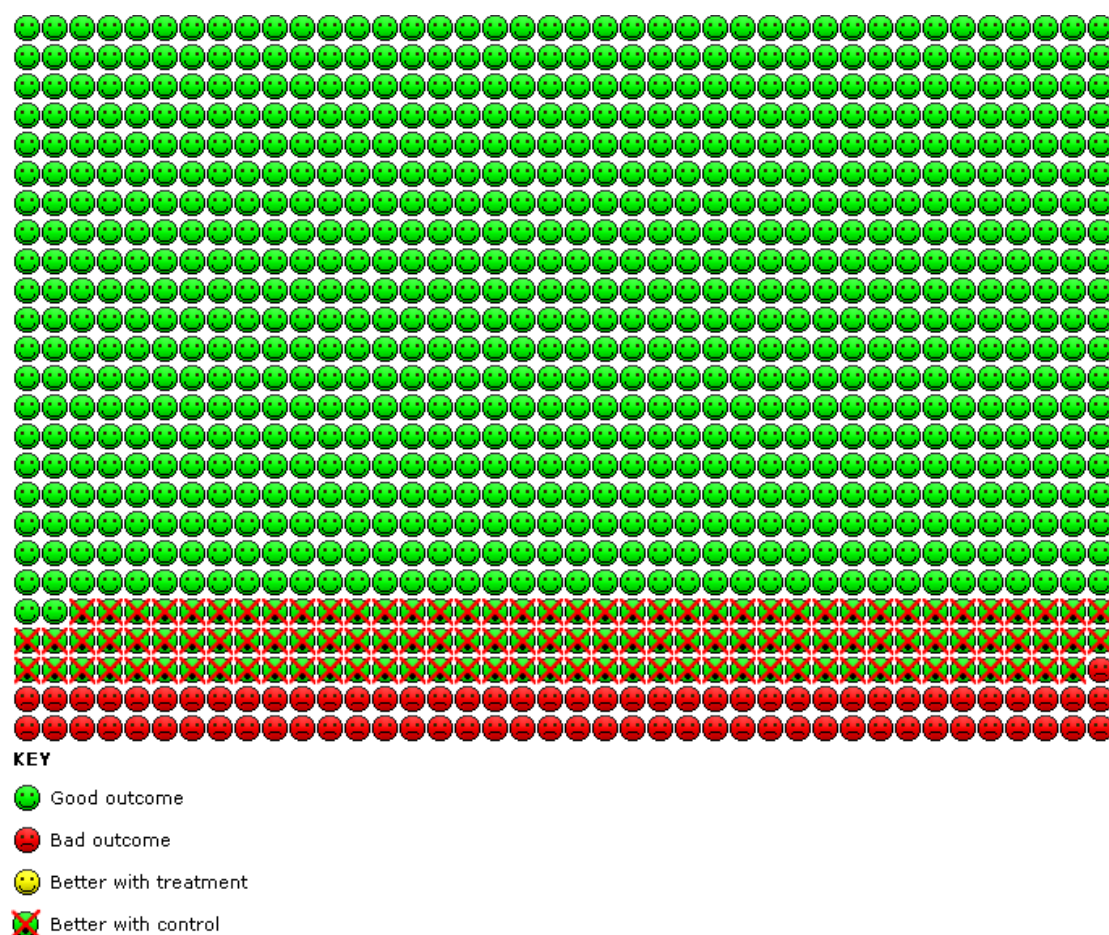


Adverse reactions

Large local adverse reactions were reported by 16 studies comparing immunotherapy with placebo. The pooled relative risk was 1.4 (95% CI 0.97 to 2.02) and homogeneous in the 10 studies that reported reactions per patient. Thus if 16 patients were treated with immunotherapy, one would be expected to develop a local reaction.

Systemic adverse reactions were reported by 32 studies. Systemic reactions were defined as any of anaphylaxis, asthma, rhinitis or urticaria, or any combination of these. The pooled relative risk was 2.45 (95% CI 1.91 to 3.13) in the 26 reporting reactions per patient and this was relatively homogeneous ($I^2 = 27\%$). Thus if nine patients (95% CI 6 to 14) were treated with immunotherapy, one would be expected to develop a systemic reaction (see [Figure 5](#)).

Figure 5. In the control group 81 patients out of 1000 had systemic adverse reactions (of any severity), compared to 198 (95% CI 155 to 254) out of 1000 for the immunotherapy group



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 patients (95% CI 2 to 18) 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 ([Aas 1971](#); [BTA 1968](#); [Vooren 1969](#)) that compared house dust extracts with placebo found negative results for most outcomes. Subjects randomised to house dust were less likely to report worse asthma symptoms, but the combined effect did

not achieve statistical significance. In the [BTA 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, so four children (95% CI 3 to 9) 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 1988](#), [Garcia-Ortega 1993](#) and [Kohno 1998](#) found that patients randomised to immunotherapy demonstrated significant reductions in asthma symptoms (combined SMD -1.8, 95% CI -3.2 to -0.5) and medication (SMD -2.5, 95% CI -3.1 to -2.0) and even a significant improvement in lung function (combined SMD = -0.8, 95% CI -0.4 to -1.2). [Kohno 1998](#) also reported a significant reduction in non-specific BHR (SMD -2.2, 95% CI -3.6 to -0.7). [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 13 randomised controlled trials, which were not covered by our previous Cochrane Review of studies published up to 2001 ([Abramson 2003](#)). The most common reason for these studies not being included previously was that they were published after 2001. 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 222 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.

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 revised [CONSORT 2001](#) 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 peak expiratory flow (PEF) measurements. Unlike the previous review, we did not infer standard deviations (SDs) from studies of normal subjects, 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.

Adverse effects

While adverse effects of allergen immunotherapy have been well-described over the previous half-century, such reports have usually been case reports, prospective or retrospective reviews of case series, or structured databases set up by specialist allergy societies to which practising allergists report adverse effects on a voluntary basis. As expected, the incidence of reported adverse effects thus varies according to the reporting method, but a representative estimate of this problem is summarised in the table below (Amin 2006; Tankersley 2000; Tinkleman 1995).

	Local reaction (LR)	Systemic reaction (SR)	Near-fatal reaction (NFR)	Fatal reaction (FR)
Per patient	26% to 82%	5% to 7%	-	-
Per injection	0.7% to 4%	0.06% to 1.01%	1 per million	1 per 2.5 million

The incidence of local reactions (LR) per patient is comparable to that in the literature, although we suspect that they may have been under-reported in those studies that did not report any. The incidence of systemic reactions (SR) per patient is far greater than that reported in the literature (19.9% compared to 5% to 7%) and this estimate was relatively homogeneous. However without information on grading of these reactions, we cannot analyse further, except to say that we consider that mild systemic reactions may have previously been under-reported.

The systemic reaction rates reported among patients receiving placebo (8.1% of patients and 3.7% of injections) are intriguing. Most placebo preparations contained an ingredient to cause itch (such as histamine) so as to mimic an active dose. This may have caused an over-reaction, such as hyper-ventilation, in susceptible subjects, and such subjects may have reported dyspnoea or wheezing, or skin symptoms.

We conclude that allergen immunotherapy by injection is not without risk of significant systemic adverse effects and clinicians should weigh up carefully the pros and cons of this intervention. We also conclude that systemic adverse effects may be under-reported in the literature. We await similar analysis for sublingual immunotherapy (SLIT) as that intervention has promises of reduced serious adverse effects while maintaining efficacy.

Authors' conclusions

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 13 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. We have expressed the effect on dichotomous outcomes as NNT. These numbers 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.

AUTHORS' 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 in 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. Patients should be informed that subcutaneous allergen immunotherapy is not without risk of significant adverse effects. 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. Finally, patients should be informed that other types of allergen immunotherapy, such as sublingual immunotherapy, are available, and patients should be allowed an informed choice as to which intervention they would prefer.

Implications for research

A. Specific to immunotherapy:

1. What are the most important determinants of the clinical relevance of an allergen?
2. Which patients respond best?
3. Is the result better when there is a narrow range of positive skin tests or is it just as effective in pan-reactors?
4. Is mono-component immunotherapy better than the use of a cocktail of allergens to which the patient reacted?
5. What is the optimal length of treatment and the best duration of effect?
6. Can the risk of systemic reactions be further reduced?
7. A proper evaluation of dose-efficacy for injection allergen immunotherapy for asthma

B. Immunotherapy in relation to other asthma therapies:

1. What is the size of effect compared to other therapies?
2. What is the effect of concurrent steroid therapy?
3. What is the risk benefit profile?

ACKNOWLEDGEMENTS

We wish to thank Paul Angel, Daniel Czarny, Barbora de Courten, Rosa Dias Santilhiano, Brechje Gosens, Noortje Hamse, Alex Loszynsky, Alessandra Sandrini, Andrei Saramovich, Fiona Savio, Georg Schäppi 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. Uffe Bødtger provided individual patient data from her RCT of birch pollen immunotherapy. Jean Bousquet and Alicia Armentia provided methodological details of studies conducted by their groups. Steve Milan, Anna Bara, Karen Blackhall and Elizabeth Arnold searched the Cochrane Airways Group database. David Badger and Vivienne Moore from the Australasian Cochrane Centre, Anna Bara and Toby Lasserson from the Cochrane Airways Group provided helpful advice on the use of RevMan. Paul Montgomery read and approved the consumer synopsis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aas 1971

Methods	RCT, double blind Coloured sugar phenol placebo	
Participants	80 asthmatic children aged 2 to 14 years	
Interventions	Subcutaneous house dust immunotherapy	
Outcomes	Clinical state (subjective parental impression) Specific bronchial hyper-reactivity to house dust	
Notes	Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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 to 14) years, 79% boys Allergies: 80% dust mite, 77% ragweed, 69% rye grass
Interventions	Subcutaneous multiple allergen immunotherapy Median 6 (range 2 to 7) ALK extracts Major allergens: Der p1, Der f1, Amb a1, Lol p1, Alt a1
Outcomes	Symptom scores Medication scores Peak Expiratory Flow (PEF) rates Nonspecific BHR (PC ₂₀ methacholine FEV ₁) Nonspecific BHR (methacholine)
Notes	Concluded that immunotherapy not useful in moderate to severe perennial allergic asthma Quality score 4
Risk of bias	

Adkinson 1997 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Altintas 1999

Methods	Open placebo controlled RCT multiple groups	
Participants	34 poorly controlled mild to moderate asthmatics aged 4 to 18 years	
Interventions	Subcutaneous immunotherapy with adsorbed or aqueous <i>D. pteronyssinus</i> extracts	
Outcomes	Symptom medication scores Allergen specific BHR	
Notes	Quality score 2	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Alvarez Cuesta 1994

Methods	RCT, double blind Histamine placebo	
Participants	28 patients with rhinoconjunctivitis and asthma aged 15 to 28 years	
Interventions	Subcutaneous Fel d1 immunotherapy	
Outcomes	Symptom medication scores Nonspecific BHR (PC ₂₀ methacholine FEV ₁) Allergen specific bronchial hyper-reactivity (PC ₂₀ FEV ₁ cat)	
Notes	Quality score 3	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Amaral-Marques 1978

Methods	RCT, double blind Unstated placebo
Participants	28 asthmatics aged 12 to 55 years with positive skin tests to house dust mite
Interventions	Tyrosine adsorbed <i>D. pteronyssinus</i> subcutaneous immunotherapy
Outcomes	Symptoms Medication
Notes	Quality score 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Armentia Medina 1989

Methods	RCT, placebo, double blind
Participants	30 (21 asthmatic) patients with Bermuda grass pollen allergy Age 12 to 50 years
Interventions	Subcutaneous Bermuda grass pollen immunotherapy
Outcomes	Nonspecific BHR (methacholine score 0 to 4) Allergen specific BHR (PD ₂₀ FEV ₁ Bermuda grass pollen)
Notes	Quality score 1

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Armentia Medina 1995

Methods	RCT, double blind
Participants	35 (25 asthmatic) patients sensitised to storage mite (<i>Lepidoglyphus destructor</i>) Age 13 to 63 years
Interventions	Subcutaneous immunotherapy with <i>L. destructor</i> extract

Armentia Medina 1995 (Continued)

Outcomes	Subjective clinical assessment based upon symptoms and drug intake Nonspecific BHR (PD ₂₀ methacholine FEV ₁)	
Notes	Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Arvidsson 2004

Methods	RCT, double blind Placebo diluent with histamine	
Participants	19 birch pollen allergic patients Age 31 (19 to 44)	
Interventions	Subcutaneous immunotherapy with depot Betula preparation	
Outcomes	Nonspecific BHR (methacholine) Allergen specific BHR (max FEV ₁ fall)	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Basomba 2002

Methods	RCT, double blind Placebo liposomes including solvent	
Participants	55 asthmatic patients with positive skin tests to HDM Age 21 (14 to 50)	
Interventions	Subcutaneous immunotherapy with liposome encapsulated <i>D. pteronyssinus</i>	
Outcomes	Symptoms (diary cards) Medication score PEF variability Visual analogue scale	

Basomba 2002 (Continued)

Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Baur 1989

Methods	RCT, cross-over design, placebo control, single blind	
Participants	39 asthmatics aged 18 to 45 years	
Interventions	Pollen, house dust mite and fungal subcutaneous immunotherapy	
Outcomes	Allergen specific BHR (PC ₁₀₀ SRaw)	
Notes	Quality score 1	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bertelsen 1989

Bernheim 1987

Methods	RCT, open study Untreated controls	
Participants	27 asthmatic children allergic to dog or cat Age 7 to 15 years	
Interventions	Dog and cat subcutaneous immunotherapy	
Outcomes	Allergen specific BHR	
Notes	Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Bousquet 1985a

Methods	Open RCT, unstated placebo	
Participants	48 (39 asthmatic) patients with grass pollen allergy aged 10 to 51 years	
Interventions	Subcutaneous immunotherapy with <i>D. glomerata</i> extracts. Rush immunotherapy with standardised lyophilised extract was compared to classical immunotherapy with alum precipitated pyridine extracted material.	
Outcomes	Symptom medication scores	
Notes	Quality score 1	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Bousquet 1985b

Methods	RCT, double blind Unstated placebo	
Participants	30 patients with perennial asthma, aged 18 to 42 years	
Interventions	<i>D. pteronyssinus</i> subcutaneous immunotherapy	
Outcomes	Allergen specific BHR (PD ₂₀ FEV ₁ mite)	
Notes	Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Bousquet 1988

Methods	RCT, untreated controls, open study	
Participants	215 patients with perennial asthma, aged 3 to 72 years	
Interventions	House dust mite subcutaneous immunotherapy	

Bousquet 1988 (Continued)

Outcomes	Symptoms Medication FEV ₁	
Notes	Quality score 1	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Bousquet 1989

Methods	RCT, mixed design - 3 groups double blinded, 1 open Placebo phenol histamine in normal saline	
Participants	60 (38 asthmatic) patients with grass pollen allergy Age 12 to 46 years	
Interventions	Subcutaneous immunotherapy with high molecular weight formalinised allergoid, unfractionated allergoid and standardised orchard grass pollen extract	
Outcomes	Symptoms Medication	
Notes	Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Bousquet 1990

Methods	RCT, double blind Phenol saline placebo	
Participants	57 (30 asthmatic) patients with orchard grass pollen allergy, aged 11 to 45 years	
Interventions	Subcutaneous immunotherapy with high molecular weight formalinised allergoid in high and low-dose schedules	
Outcomes	Symptoms	

Bousquet 1990 (Continued)

Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Bruce 1977

Methods	RCT, stratified allocation, blinding not specified Coloured histamine placebo	
Participants	39 ragweed allergic seasonal asthmatics	
Interventions	Subcutaneous immunotherapy with aqueous ragweed extract	
Outcomes	Symptoms Allergen specific BHR	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

BTA 1968

Methods	RCT, double blind Carbol saline placebo	
Participants	96 asthmatic patients, mean age 24	
Interventions	House dust subcutaneous immunotherapy	
Outcomes	Symptoms Medication Peak expiratory flow	
Notes	Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description

BTA 1968 (Continued)

Allocation concealment?	Unclear	B - unclear
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BTA 1979

Methods	RCT, double blind Glycerated extraction medium placebo
Participants	70 asthmatic patients 66% > 30 years
Interventions	House dust mite subcutaneous immunotherapy
Outcomes	Symptoms Medications FEV ₁
Notes	Quality score 3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Buchanan 1981

Methods	RCT, double blind Saline placebo
Participants	55 adult asthmatic patients
Interventions	House dust mite subcutaneous immunotherapy
Outcomes	Symptoms (self assessed) Medication and asthma attacks (physician assessment)
Notes	Quality score 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bødtger 2002

Methods	RCT, double blind Placebo histamine buffered	
Participants	35 (14 asthma) birch allergic patients Age 27 (19 to 46)	
Interventions	Subcutaneous cluster immunotherapy with depot Betula preparation	
Outcomes	Symptom scores (nasal, lung) Medication score	
Notes	Quality score 5	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Cantani 1996

Methods	Randomised, placebo controlled, double blind, parallel group design	
Participants	20 asthmatic children (14 boys) Median age 6 (range 4 to 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	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Choovoravech 1974

Methods	RCT, single blind House dust control	
Participants	57 adult asthmatics Mean age 30.4 years	
Interventions	<i>D. pteronyssinus</i> and <i>D. farinae</i> subcutaneous immunotherapy	
Outcomes	Symptom scores Physician evaluation based upon examination PEF and medication requirements	
Notes	Quality score 1	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Creticos 1996

Methods	RCT, double blind Unstated placebo	
Participants	77 adult asthmatics Mean age 35.5 years	
Interventions	Ragweed pollen subcutaneous immunotherapy	
Outcomes	Symptom scores Medication scores Peak expiratory flow Allergen specific BHR (PD ₂₀ FEV ₁ ragweed pollen)	
Notes	Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

D'Souza 1973

Methods	RCT, double blind Carbol saline placebo	
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	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Dolz 1996

Methods	Double blind, placebo controlled, parallel group RCT Placebo 0.01 mg histamine + 0.4 mg human serum albumin	
Participants	28 patients with grass pollen allergy (6 asthmatics) Mean age 19.4 (15 to 35) years	
Interventions	Subcutaneous immunotherapy mostly with alum adsorbed grass pollen extracts Initial rush protocol with aqueous extracts over 4 days Follow up 3 years	
Outcomes	Symptom scores Medication scores Allergen specific BHR	
Notes	Medication scores included antihistamines No SD reported for PD ₂₀ FEV ₁ Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Dreborg 1986

Methods	RCT, double blind Freeze dried caramelised histamine placebo
Participants	30 children with <i>Cladosporium</i> allergy, aged 5 to 17 years
Interventions	<i>Cladosporium</i> subcutaneous immunotherapy
Outcomes	Symptoms Medication Peak Expiratory Flow (no SD reported) Allergen specific BHR
Notes	Quality score 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ferrer Garcia-Selles 2003

Methods	Pragmatic RCT Untreated controls
Participants	33 asthmatic patients with HDM allergy Mean age 27
Interventions	Subcutaneous immunotherapy with depigmented <i>D. pteronyssinus</i> or <i>D. farinae</i> extracts
Outcomes	Symptom scores Medication scores Ag specific BHR
Notes	Quality score 1

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

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) years
Interventions	Subcutaneous immunotherapy with depot <i>D. pteronyssinus</i> extract Duration 15 months
Outcomes	Symptoms (Visual analogue scale) Medication score Lung function (PEF) Nonspecific BHR (PD ₂₀ FEV ₁ methacholine)
Notes	Median change in PD ₂₀ reported, but not SD Wrote to authors to clarify randomisation Quality score 3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Frankland 1954

Methods	RCT, observers blinded Coloured phenol saline and ultrafiltrate controls
Participants	200 (57 asthmatic) patients with pollen allergy, aged over 10 years
Interventions	Subcutaneous immunotherapy with mixed Timothy and cocksfoot grass pollen extract, purified pollen protein
Outcomes	Symptoms
Notes	Quality score 3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gaddie 1976

Methods	RCT, placebo controlled, double blind	
Participants	55 patients with perennial asthma Age 13 to 68 years	
Interventions	Subcutaneous immunotherapy with tyrosine adsorbed depot <i>Dermatophagoides pteronyssinus</i> preparation	
Outcomes	Symptoms Medication FEV ₁ (no SD reported)	
Notes	Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Garcia-Ortega 1993

Methods	RCT, untreated controls	
Participants	36 patients with mite allergic asthma Age 13 to 45 years	
Interventions	Subcutaneous intensive immunotherapy with aqueous <i>D. pteronyssinus</i> extracts	
Outcomes	Clinical score (symptoms + medications) Nonspecific BHR Allergen specific BHR (methacholine)	
Notes	Quality score 1	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Gonzalez 2002

Methods	Open RCT, controls received symptomatic therapy	
Participants	46 (39 asthmatic) patients with olive allergy	
Interventions	Subcutaneous immunotherapy <i>Olea europaeae</i> extracts	

Gonzalez 2002 (Continued)

Outcomes	Symptom scores (nasal, bronchial, conjunctival) Medications	
Notes	Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Gruber 1999

Methods	Open RCT, untreated controls	
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	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Guerra 2003

Methods	RCT with untreated controls
Participants	45 asthmatic patients with olive pollen allergy
Interventions	Subcutaneous immunotherapy with depigmented glutaraldehyde modified olive pollen extract
Outcomes	Symptoms Medication score Allergen specific BHR
Notes	Quality score 2
<i>Risk of bias</i>	

Guerra 2003 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Haugaard 1992

Methods	RCT, double blind Histamine control with burnt glucose
Participants	24 asthmatics allergic to cat and/or dog dander Age 13 to 48 years
Interventions	Subcutaneous immunotherapy with cat epithelium and dog dander extracts
Outcomes	Symptoms Nonspecific (PC20 histamine PEF) BHR Allergen specific BHR (PD ₂₀ PEF cat/dog)
Notes	No SD estimable for PD ₂₀ Quality score 3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Hedlin 1999

Methods	Mixed, double blinded, placebo controlled and open RCT with parallel group design
Participants	29 children with allergic asthma, aged 7 to 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

Risk of bias

Item	Authors' judgement	Description
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Hedlin 1999 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Hill 1982

Methods	Single blind RCT, 1PNU rye grass pollen placebo
Participants	20 asthmatic children, aged 9 to 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Håkansson 1998

Methods	Double blind controlled trial Control group received topical nasal steroid
Participants	24 birch pollen allergic patients (11 asthmatic) aged 21 to 42 years
Interventions	Subcutaneous immunotherapy with depot birch pollen extract
Outcomes	Symptoms Medications PEF Nonspecific BHR (PC ₂₀ MCh)
Notes	Wrote to authors requesting details of randomisation and concealment Quality score 1

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Johnstone 1957

Methods	RCT, double blind Buffered saline control	
Participants	112 (72 asthmatic) children with pollinosis	
Interventions	Subcutaneous immunotherapy with ragweed pollen extract, administered by 3 regimens	
Outcomes	Asthma symptoms reported by mother	
Notes	Quality score 1	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Johnstone 1961

Methods	RCT, double blind, 4-year follow up Buffered saline control	
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	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Johnstone 1968

Methods	RCT, double blind Buffered saline control	
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	

Johnstone 1968 (Continued)

Notes	Quality score 5	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kohno 1998

Methods	Placebo controlled, parallel group design RCT Untreated controls viz open	
Participants	16 patients with mite allergic asthma Mean age 26 (19 to 41) years	
Interventions	Subcutaneous rush immunotherapy with aqueous <i>D. farinae</i> extract 6-month duration	
Outcomes	Asthma symptoms (scored 0 to 9 in diaries) Lung function (PEF) Nonspecific BHR (PC ₂₀ histamine) Allergen specific BHR (PC ₂₀ FEV ₁ <i>D. farinae</i> extract)	
Notes	Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Kuna 1989

Methods	RCT, double blind Saline placebo	
Participants	24 patients with seasonal asthma Mean age 27.2 years	
Interventions	Subcutaneous immunotherapy with glutaraldehyde modified tyrosine adsorbed grass pollen extracts	
Outcomes	Symptoms FEV ₁ (only baseline results reported) Nonspecific BHR (PC ₂₀ histamine FEV ₁)	

Kuna 1989 (Continued)

Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - unclear

Leynadier 2000

Methods	Double blind, placebo controlled RCT	
Participants	17 patients with latex allergy, 9 had asthma Mean age 30.5 (range 22 to 41) years	
Interventions	Subcutaneous immunotherapy with latex extract	
Outcomes	Symptom scores (asthma reported separately) Medication scores	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Machiels 1990a

Methods	RCT, albumin buffer placebo controlled, double blind, 2-year follow up
Participants	39 asthmatic patients with <i>Dermatophagoides pteronyssinus</i> allergy, aged 16 to 57 years
Interventions	Subcutaneous immunotherapy with <i>D. pteronyssinus</i> allergen antibody complexes by 2 regimens
Outcomes	Symptoms Medication Peak Expiratory Flow Nonspecific BHR (PC ₃₅ acetylcholine SGaw) Allergen specific BHR (PD ₂₀ FEV ₁ mite)
Notes	Quality score 3
<i>Risk of bias</i>	

Machiels 1990a (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Machiels 1990b

Methods	RCT, double blind Albumin phenol buffer control
Participants	30 (18 asthmatic) patients with grass pollen allergy, aged 14 to 57 years
Interventions	Intradermal immunotherapy with grass pollen antibody complexes
Outcomes	Asthma symptoms Medication (vasoconstrictors, antihistamines, oral steroids)
Notes	Quality score 3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Machiels 1991

Methods	RCT, double blind Albumin phenol saline buffer placebo control
Participants	51 grass pollen hypersensitive patients, aged 12 to 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Machiels 1993

Methods	RCT, double blind, 4-year follow up Albumin buffer placebo controlled	
Participants	39 asthmatic patients with <i>Dermatophagoides pteronyssinus</i> allergy, aged 16 to 57 years	
Interventions	Subcutaneous immunotherapy with <i>D. pteronyssinus</i> allergen antibody complexes by 2 regimens	
Outcomes	Symptoms Medication Lung function (FEV ₁ %, TLV, sGaw) Nonspecific BHR (PC ₃₅ acetylcholine sGaw) Allergen specific BHR	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Maestrelli 2004

Methods	Double blind, placebo controlled RCT Histamine placebo	
Participants	72 asthmatic patients with HDM allergy	
Interventions	Subcutaneous immunotherapy with mixture of <i>D. pteronyssinus</i> or <i>D. farinae</i> extracts for 3 years	
Outcomes	Symptoms Medication Lung function (PEF, FEV ₁) Nonspecific BHR (methacholine)	
Notes	Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Malling 1986

Methods	RCT, double blind Caramelised histamine placebo control
Participants	22 adult asthmatics with <i>Cladosporium</i> allergy, aged 16 to 60 years
Interventions	Subcutaneous immunotherapy with lyophilised partially purified <i>Cladosporium herbarum</i> extract
Outcomes	Symptoms Medication Allergen specific BHR (PC ₂₀ FEV ₁ <i>Cladosporium</i>)
Notes	Quality score 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Maunsell 1971

Methods	RCT, house dust control, double blind
Participants	34 asthmatic patients with house dust allergy, aged 16 to 56 years
Interventions	Subcutaneous immunotherapy with <i>Dermatophagoides farinae</i> extracts
Outcomes	Symptoms (clinical improvement)
Notes	Quality score 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mirone 2004

Methods	Double blind, placebo controlled RCT
Participants	32 patients allergic to ragweed (13 asthmatic), age 23 to 60 years
Interventions	Subcutaneous immunotherapy with <i>Ambrosia artemisiifolia</i> depot preparation
Outcomes	Symptoms Medication score

Mirone 2004 (Continued)

Notes	Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mosbech 1989

Methods	RCT, placebo control, double blind	
Participants	46 house dust mite allergic asthmatics, aged 18 to 56 years	
Interventions	Subcutaneous immunotherapy with <i>Dermatophagoides pteronyssinus</i> and monomethoxypolyethylene glycol modified extracts	
Outcomes	Symptoms Medications Peak Expiratory Flow Nonspecific BHR to histamine Allergen specific BHR	
Notes	Randomisation (minimisation) by computer Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mungan 1999

Methods	Placebo controlled, single blind RCT, multiple groups	
Participants	36 patients with mite sensitive asthma and rhinitis, mean age 31 years	
Interventions	Subcutaneous and sublingual <i>D. pteronyssinus</i> and <i>D. farinae</i> extracts	
Outcomes	Symptoms Medications Nonspecific BHR	
Notes	Quality score 2	

Mungan 1999 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Newton 1978

Methods	RCT, double blind, stratified randomisation Normal saline placebo control	
Participants	14 patients with perennial asthma and house dust mite allergy, aged 18 to 44 years	
Interventions	Subcutaneous immunotherapy with alum precipitated <i>D. farinae</i> extracts	
Outcomes	Symptoms Medication Peak Expiratory Flow Allergen specific BHR (PD ₂₅ PEF mite)	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ohman 1984

Methods	RCT, double blind Histamine placebo control	
Participants	17 asthmatic patients with cat allergy, aged 22 to 48 years	
Interventions	Subcutaneous immunotherapy with cat pelt extract	
Outcomes	Symptoms and Peak Expiratory Flow on cat exposure Nonspecific (methacholine) BHR Allergen specific BHR (PD ₂₀ FEV ₁ cat)	
Notes	Quality score 3	
Risk of bias		
Item	Authors' judgement	Description

Ohman 1984 (Continued)

Allocation concealment?	Yes	A - Adequate
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Olsen 1997

Methods	Randomised, placebo controlled, double blind, parallel group design Computer generated randomisation stratified by age, gender and severity Placebo contained histamine and aluminium hydroxide in vials of identical appearance
Participants	31 asthmatic adults (aged 18 to 64 years) Positive skin and RAST to house dust mite Positive allergen specific BHR
Interventions	Subcutaneous immunotherapy with <i>D. pteronyssinus</i> or <i>D. farinae</i> extracts
Outcomes	Symptoms (patient global assessment, scores) Medication (inhaled beta agonist, steroid) Lung function (FEV ₁ , PEF) Allergen specific BHR (PC ₂₀ FEV ₁ Der p/Der f)
Notes	Randomised to <i>D. pteronyssinus</i> or <i>D. farinae</i> Wrote to authors seeking SDs Quality score 5

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ortolani 1984

Methods	RCT, double blind Riboflavin coloured coca solution placebo control
Participants	15 grass pollen allergic asthmatic patients, aged 15 to 45 years
Interventions	Cutaneous immunotherapy with aqueous velvet, sweet vernal and Timothy grass pollen extracts
Outcomes	Symptoms Allergen specific BHR (medians only presented)
Notes	Quality score 2

Risk of bias

Item	Authors' judgement	Description
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Ortolani 1984 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Paranos 1997

Methods	Placebo controlled, single blind, parallel group RCT Saline placebo
Participants	14 patients with mite allergic asthma, age 20 to 40 years
Interventions	Subcutaneous rush immunotherapy with aqueous <i>D. pteronyssinus</i> extract 6 months duration
Outcomes	Medication score Lung function (PEF, FEV ₁)
Notes	Baseline lung function poorly matched Quality score 1

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pauli 1984

Methods	RCT, tyrosine phenol placebo control, double blind
Participants	18 patients with perennial asthma, aged 19 to 40 years
Interventions	Subcutaneous immunotherapy with tyrosine adsorbed <i>Dermatophagoides pteronyssinus</i> extract
Outcomes	Symptoms Medication Peak Expiratory Flow
Notes	Quality score 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pene 1998

Methods	Double blind, placebo controlled RCT
Participants	31 patients with cat allergy Mean age 27.7 years
Interventions	Subcutaneous immunotherapy with Fel d1 peptides
Outcomes	Allergen specific BHR
Notes	Quality score 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 to 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 follow up
Outcomes	Symptom score (visual analogue scale) Medication score Nonspecific BHR (PD ₂₀ FEV ₁ MCh)
Notes	Quality score 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pifferi 2002

Methods	Single blind RCT
Participants	29 asthmatic children with HDM allergy Age 10.6 (6 to 14)

Pifferi 2002 (Continued)

Interventions	Subcutaneous immunotherapy with extracts of <i>D. pteronyssinus</i>	
Outcomes	Symptoms (diary) Lung function Nonspecific BHR	
Notes	Variation in salbutamol & FEV ₁ not clear from figures Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Price 1984

Methods	RCT, double blind Saline placebo control	
Participants	25 children with perennial asthma, aged 5 to 15 years	
Interventions	Subcutaneous immunotherapy with <i>Dermatophagoides pteronyssinus</i> extracts	
Outcomes	Symptoms Medication Lung function (TGV)	
Notes	Continuation of study by Warner 1978 for second year with placebo group crossed over to active immunotherapy Quality score 3	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rak 2001

Methods	RCT, double blind Placebo diluent + histamine	
Participants	41 birch pollen allergic patients (21 asthmatic) Age 29 (19 to 42)	

Rak 2001 (Continued)

Interventions	Subcutaneous depot birch pollen extract	
Outcomes	Symptoms Medication Nonspecific BHR (methacholine)	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Reid 1986

Methods	RCT, non-grass extract placebo control, double blind	
Participants	18 patients with seasonal asthma and grass pollen allergy Mean age 27.7 (range 20 to 39) years	
Interventions	Subcutaneous allergen immunotherapy with rye grass pollen extract	
Outcomes	Symptom/medication scores	
Notes	Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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 <i>Dermatophagoides pteronyssinus</i> extract	
Outcomes	Symptoms (patient self evaluation) Medication (physician's opinion)	
Notes	Quality score 2	

Sabbah 1991 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sastre 2003

Methods	RCT, double blind Placebo alum buffer with histamine
Participants	24 patients with latex allergy (15 asthmatic)
Interventions	Subcutaneous immunotherapy with depot natural rubber latex extract
Outcomes	Symptoms Medication Nonspecific BHR (methacholine) Ag specific (latex glove challenge) Adverse reaction
Notes	Quality score 5

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Shaikh 1997

Methods	Open parallel group, randomised controlled trial 12-month duration
Participants	51 perennial bronchial asthma patients with <i>D. farinae</i> sensitisation 29 males, 22 females Mean age 26 (22 to 36) years
Interventions	Subcutaneous immunotherapy with standardised <i>D. farinae</i> extract Budesonide 600 ug/d
Outcomes	Symptoms (VAS, global evaluation) Medication (Salbutamol) Lung function (FEV ₁)

Shaikh 1997 (Continued)

Notes	Salbutamol requirements not reported Symptoms improved more rapidly on inhaled steroid than immunotherapy Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Sin 1996

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Methods	Single blind, placebo controlled, parallel group RCT	
Participants	31 patients with allergic rhinitis and asthma sensitised to mixed grass pollen or <i>D. pteronyssinus</i>	
Interventions	Subcutaneous immunotherapy with grass pollen or mite extracts	
Outcomes	Symptoms Medication Lung function (FEV ₁) Nonspecific BHR (MCh)	
Notes	Individual patient data provided by authors Quality score 1	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Smith 1971

Methods	RCT, double blind Human skin scale control	
Participants	22 asthmatic patients with house dust mite allergy, aged 11 to 48 years	
Interventions	Subcutaneous immunotherapy with <i>Dermatophagoides pteronyssinus</i>	
Outcomes	Symptoms Medication Peak Expiratory Flow	
Notes	Quality score 3	

Smith 1971 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sundin 1986

Methods	RCT, double blind, stratified randomisation Histamine albumin aluminium hydroxide control	
Participants	39 asthmatic patients with cat or dog allergy, aged 8 to 47 years	
Interventions	Subcutaneous immunotherapy with cat or dog dander extracts	
Outcomes	Symptoms (patient subjective assessment) Nonspecific BHR (histamine) Allergen specific BHR (PC ₂₀ PEF cat/dog)	
Notes	Quality score 3	

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sykora 2004

Methods	Single blind, placebo controlled RCT	
Participants	34 patients with allergic rhinoconjunctivitis (14 asthmatics), mean age 29.4 years	
Interventions	Subcutaneous immunotherapy with standardised depot grass pollen mix	
Outcomes	Symptom scores Rescue medication (including antihistamines)	
Notes	Quality score 2	

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Tabar 1999

Methods	Open RCT with untreated controls	
Participants	63 patients with rhinoconjunctivitis and/or asthma, aged 5 to 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	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Taylor 1974

Methods	RCT, double blind Phenol saline placebo control	
Participants	42 asthmatic children with house dust mite allergy, aged 6 to 15 years	
Interventions	Subcutaneous immunotherapy with mite fortified house dust extract	
Outcomes	Height and weight Lung function (PEF, FEV _{0.75} , VC, Raw, FRC, TGV) Chest examination	
Notes	Quality score 2	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Taylor 1978

Methods	RCT, double blind Histamine placebo control	
Participants	10 patients with cat induced asthma Age 20 to 43 years	

Taylor 1978 (Continued)

Interventions	Subcutaneous immunotherapy with cat pelt extract	
Outcomes	Nonspecific BHR (PD ₂₀ histamine FEV ₁) Allergen specific BHR	
Notes	Blinding well-described Quality score 4	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Torres Costa 1996

Methods	Open parallel group randomised controlled trial 27 month duration	
Participants	22 patients with asthma and <i>D. pteronyssinus</i> sensitisation 11 males, 11 females Mean age 20 (12 to 38) years	
Interventions	Subcutaneous immunotherapy with standardised <i>D. pteronyssinus</i> extract Beclomethasone 600 to 800 ug/d withdrawn after 18 months	
Outcomes	Symptoms (score) Medication (Salbutamol) Lung function (PEFR, FEV ₁) Nonspecific BHR (PC ₂₀ MCh)	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

Valovirta 1984

Methods	RCT, double blind Carmel histamine placebo control	
Participants	27 asthmatic children allergic to dog dander, aged 5 to 18 years	

Valovirta 1984 (Continued)

Interventions	Subcutaneous immunotherapy with aluminium hydroxide bound dog dander extract	
Outcomes	Symptoms Allergen specific BHR	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Van Bever 1992

Methods	RCT, double blind Histamine placebo	
Participants	18 young asthmatics, with late reactions to <i>Dermatophagoides pteronyssinus</i> on bronchial challenge Age 7 to 22 years	
Interventions	Subcutaneous immunotherapy with standardised aqueous <i>D. pteronyssinus</i> extracts	
Outcomes	Nonspecific (PD ₂₀ histamine FEV ₁) BHR Allergic specific BHR (PD ₂₀ FEV ₁ mite)	
Notes	Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Van Metre 1988

Methods	RCT, double blind Histamine placebo control	
Participants	22 asthmatic patients allergic to cats, aged 21 to 52 years	
Interventions	Subcutaneous immunotherapy with cat hair and dander extract	
Outcomes	Nonspecific (PD ₂₀ methacholine FEV ₁) BHR Allergen specific BHR (PD ₂₀ FEV ₁ cat)	

Van Metre 1988 (Continued)

Notes	Blinding well-described Quality score 3	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Varney 1991

Methods	Randomised, double blind, placebo controlled trial	
Participants	40 adults (mean age 35 years) with severe grass pollen allergy (18 asthmatic)	
Interventions	Subcutaneous immunotherapy with grass pollen (<i>P. pratense</i>) extract	
Outcomes	Chest symptoms reported separately	
Notes	Quality score 5	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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 to 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
Risk of bias	

Varney 1997 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Varney 2003

Methods	Double blind RCT Placebo diluent + histamine
Participants	36 (28 asthmatic) patients with HDM allergy
Interventions	Subcutaneous immunotherapy with depot <i>D. pteronyssinus</i> extract
Outcomes	Symptoms (nasal, chest) Medication PEF
Notes	Quality score 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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 (FEV ₁) Allergen specific BHR
Notes	No SD reported Quality score 3

Risk of bias

Item	Authors' judgement	Description
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Vooren 1969 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Walker 2001

Methods	Double blind, placebo controlled RCT
Participants	44 patients with hayfever (36 had asthma) Mean age 22 (range 22 to 64) years
Interventions	Subcutaneous immunotherapy with depot grass pollen extract
Outcomes	Chest symptoms Medication score Nonspecific BHR Quality of life
Notes	Quality score 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Warner 1978

Methods	RCT, double blind Tyrosine placebo control
Participants	51 asthmatic children, aged 5 to 14 years, with positive <i>Dermatophagoides pteronyssinus</i> challenge
Interventions	Subcutaneous immunotherapy with tyrosine adsorbed <i>D. pteronyssinus</i> extracts
Outcomes	Symptoms Medication Lung function (PEF, FEV _{0.75} , TGV) Allergen specific BHR
Notes	Quality score 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Zenner 1997

Methods	Double blind, placebo controlled RCT
Participants	87 patients with grass pollen allergy, aged 16 to 53 years (32 asthmatic)
Interventions	Subcutaneous immunotherapy with depot grass pollen extract
Outcomes	Bronchial symptoms and medications reported separately
Notes	Quality score 3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ag: allergen; 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 hyper-responsiveness; Fel d1: *Felis domesticus* (cat) allergen; FEV₁: forced expiratory volume in one second; FEV_{0.75}: forced expiratory volume in 0.75 seconds; FRC: functional residual capacity of the lung; HDM: house dust mite; 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; RAST: radioallergosorbent test; Raw: resistance of the airways; RCT: randomised controlled trial; VAS: visual analogue scale (symptom scale); PEF: peak expiratory flow; SD: standard deviation; SGaw: specific conductance of the airways; TGV: thoracic gas volume; VAS: visual Analogue Scale; VC: vital capacity

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adamek-Guzik 1979	Relevant outcomes not reported separately for patients with asthma
Akmanlar 2000	Both groups received immunotherapy
Almagro 1995	Sublingual immunotherapy
Andre 2000	Sublingual immunotherapy
Andri 1995	Local nasal immunotherapy for seasonal allergic rhinitis
Arbesman 1964	Results not reported separately for asthma
Arbesman 1965	No clearly identified asthmatic subjects, no clinical outcomes

(Continued)

Ariano 1993	Local nasal immunotherapy for seasonal allergic rhinitis
Ariano 1997	Asthma not reported separately
Ariano 1999	Asthma not reported separately
Ariano 2005	Sublingual immunotherapy
Armentia 1990	Probably not randomised - unclear following communication with author
Armentia 1992	Controlled trial of wheat flour immunotherapy - only an in vitro outcome (circulating immune complexes) reported in this paper
Armentia 1997	Review of previous studies - no original data presented
Arvidsson 2002	Bronchial symptoms and respiratory medications not reported separately
Asaoku 2000	Not controlled
Astarita 1996	RCT of EPD in allergic rhinitis due to <i>Parietaria</i>
Bahceciler 2001	Sublingual immunotherapy
Bahceciler 2005	Sublingual immunotherapy
Bessot 1980	Abstract - insufficient detail reported
Botey 1981	Probably not randomised, inadequate reporting of outcomes
Bousquet 1991	No asthma outcomes reported
Bousquet 1999	Sublingual immunotherapy
Breton 1961	Not controlled
Bruun 1949	Not randomised controlled trial - alternate allocation
Bruun 1957	Not controlled
Bucur 1989	Not controlled
Bufe 2004	Sublingual immunotherapy
Caffarelli 2000	Oral immunotherapy
Cantani 1984	Not randomised

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Cantani 2005	Not randomised
Caramia 1996	Not randomised
Carbone 2005	Not randomised
Casanovas 2004	Sublingual immunotherapy
Casanovas 2005	Phase I trial, safety data only
Choovoravech 1976	Uncontrolled study
Choovoravech 1980	Uncontrolled study
Chowdhury 1999	Symptom medication score combined nasal and chest symptoms with medication requirements. Asthma not reported separately
Chu 1981	Uncontrolled study
Clavel 1998	Sublingual immunotherapy for allergic rhinitis
Cleveland 1992	Not randomised, untreated controls
Cools 2000	Not a randomised controlled trial
Cooper 1984	Oral immunotherapy
Corbetta 1992	Not randomised controlled trial
Corrado 1989	Immunotherapy for perennial rhinitis
Cosmi 2006	Sublingual immunotherapy, mostly in vitro outcomes
Creticos 2003	Abstract only, no clinical data reported
Crimi 1991	Local (inhaled) immunotherapy
Crimi 2004	Preventive immunotherapy - patients had allergic rhinitis
D'Amato1995	Only 12/36 patients had asthma - results not presented separately
D'Ambrosio 1996	Sublingual immunotherapy
Dahl 2006	Oral immunotherapy
Des Roches 1996	No untreated control group

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Des Roches 1997	Not randomised
Durham 1999	Excluded patients with chronic asthma, although chest symptoms reported separately. Control group not allocated at random.
Durieu 1961	Not controlled
Ebner 1989	Comparison of 2 mite immunotherapy extracts
Echechipia 1995	Not obviously randomised, comparison of glutaraldehyde modified versus unmodified <i>D. pteronyssinus</i> immunotherapy
Engstrom 1957	Retrospective uncontrolled case series
Eriksson 1979	Subjects had hayfever not asthma
Fanti 1988	All patients received allergen immunotherapy
Feliziani 1995	Sublingual immunotherapy
Ferreira 1993	Not a randomised trial
Formgren 1984	Abstract only - insufficient results reported
Frostad 1983	Control group not randomised. Focus on allergic rhinitis.
Galli 1994	Oral immunotherapy for atopic dermatitis
Garcia 1997	Not truly randomised - divided into 2 groups matched for age and sex
Garcia 1999	Open uncontrolled trial
Garde 1999	Not a randomised controlled trial
Gerrard 1989	Not obviously randomised. Asthma not reported separately.
Giovane 1994	Oral immunotherapy
Goldstein 1981	Uncontrolled study
Goor 1971	Not randomised, not all subjects asthmatic
Gordon 1972	Results for asthma symptoms not reported separately
Gozalo 1997	Sublingual immunotherapy for seasonal rhinoconjunctivitis +/- asthma
Grammer 1982	Hayfever subjects only

(Continued)

Grammer 1983	Asthmatic subjects not clearly identified
Grembiale 2000	Allergic rhinitis
Guardia 2004	Not randomised
Haahtela 1984	Subjects only had hayfever
Hanneuse 1982	Not randomised, in vitro outcomes
Haugaard 1993	Non-random allocation
Hedlin 1991	Uncontrolled follow up
Hedlin 1995	Patients randomised to placebo in previous study (Sundin 1986) subsequently treated with allergen immunotherapy in an open fashion
Henocq 1973	Non-randomised trial
Herxheimer 1950	Not randomised
Herxheimer 1952	Not a randomised controlled trial
Hirokawa 1996	Uncontrolled - all patients received rush immunotherapy
Hirsch 1982	Participants only had hayfever
Horst 1990	Participants only had hayfever
Hurley 2003	Abstract only
Iikura 1997	Not randomised
Jacobsen 1996	Abstract only, patients had allergic rhinitis
Jacobsen 1997	Effectively uncontrolled - follow up of patients treated with immunotherapy
Jarisch 1979	Not a randomised controlled trial
Jyo 1989	Not controlled
Kalla 1979	Uncontrolled trial
Kang 1988	Alternate allocation to cockroach immunotherapy or immunotherapy with other relevant allergens. Most controls lost to follow up.
Kerr 1963	Subjects had hayfever, not asthma. Not randomised allocation.

(Continued)

Kozhem'iaka 1979	Not a randomised controlled trial
Kraepelien 1963	Not controlled
Laetsch 1973	Oral immunotherapy
Leng 1990	Oral immunotherapy
Levin 1959	Not randomised controlled trial
Lewith 2002	Homeopathic immunotherapy
Lichtenstein 1971	Hayfever subjects only
Lilja 1989	Second year of study reported by Sundin 1986 - placebo treated patients crossed over to active immunotherapy, thus uncontrolled study
Lizaso 2003	Phase I trial
Lombardi 2005	Sublingual immunotherapy
Lu 1998	Uncontrolled study only reporting in vitro outcomes
Majori 1998	Not randomised
Majori 2000	Uncontrolled study focusing on in vitro outcomes
Mallet 1994	Not randomised controlled trial, asthmatics not clearly identified
Marcucci 2005	Sublingual immunotherapy
Marogna 2004	Sublingual immunotherapy
Marogna 2005	Sublingual immunotherapy
Martin Munoz 1996	Not randomised
Martorell 1980	Not randomised controlled trial, comparison of 2 groups treated for different durations
Maruo 1990	Not a randomised controlled trial
Matoga 1989	Not randomised controlled trial
Matsumoto 1998	Not randomised
Matsuoka 1998	Uncontrolled study only reporting in vitro outcomes

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McAllen 1967	Not randomised trial
Metzger 1983	Abstract only - insufficient results reported
Miguel Lozano 1992	Uncontrolled study
Miller 1964	Not all patients had asthma
Miller 1971	Uncontrolled study
Mischler 1981	Rhinitis subjects only
Moller 1986	Oral immunotherapy for rhinoconjunctivitis
Mosbech 1985	Abstract only - probably preliminary report of Mosbech 1989
Mosbech 1990	All subjects desensitised with different extracts, not randomised
Moscato 1991	Comparison of inhaled with parenteral immunotherapy
Moshkevich 1985	Inhaled immunotherapy
Moverare 1998	Pilot RCT of birch pollen immunotherapy - insufficient clinical data reported in paper
Munoz-Lejarazu 1993	Not randomised
Munoz-Lopez 1981	Not a randomised controlled trial
Munoz-Lopez 1994	Topical intranasal immunotherapy
Munro-Ashman 1976	Uncontrolled trial
Murray 1985	Untreated controls not allocated randomly. 'Placebo' control group contaminated by concurrent administration of pollen immunotherapy.
Nagata 1989	Uncontrolled trial of rush immunotherapy
Nagata 1993a	Uncontrolled study
Nagata 1993b	Not randomised
Nagata 1998	Only in vitro outcomes reported
Negro 1999	Comparison of 2 alternative regimes for <i>Parietaria</i> immunotherapy
Norman 1978	Only hayfever subjects

(Continued)

Novembre 1991	Sublingual immunotherapy
Nüchel Petersen 1988	Not placebo controlled - all patients received immunotherapy
Oda 1998	Uncontrolled study only reporting in vitro outcomes
Olaguibel 1997	Not randomised or controlled
Olive Perez 2000	Not randomised - control group comprised children whose parents had refused immunotherapy
Oppenheimer 1994	Oral immunotherapy
Osterballe 1982	Not randomised, comparison of immunotherapy regimens
Osvath 1976	Not controlled
Pajno 2000	Sublingual immunotherapy
Pajno 2002	Sublingual immunotherapy
Park 2001	Not controlled
Passalacqua 1998	Sublingual/oral immunotherapy for allergic conjunctivitis
Passalacqua 1999	Sublingual immunotherapy for seasonal allergic rhinoconjunctivitis
PAT	Prevention of asthma in children with allergic rhinoconjunctivitis
Paul 1998	Not randomised - groups matched according to dust mite concentration, age and therapy
Pence 1976	Asthma symptom score not reported separately
Peroni 1995	Not randomised. Conducted at high altitude (low allergen environment)
Pichler 2001	Continuation of Pichler 1997 - placebo group crossed over to immunotherapy
Pradalier 1999	Sublingual immunotherapy for rhinitis
Purello-D'Ambrosio 1999	Sublingual immunotherapy
Quirino 1996	Comparison of sublingual versus subcutaneous immunotherapy
Rak 1988	Controlled clinical trial of birch pollen immunotherapy - not randomised
Rak 1991	Not randomised
Rak 1993a	No clinical outcomes reported

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Rak 1993b	Not a randomised controlled trial, no relevant outcomes reported
Rebien 1980	Oral immunotherapy
Reilly 1993	Trial of sublingual homeopathic immunotherapy reported only in abstract form
Reinert 1981	Uncontrolled study
Reinert 1983	Oral immunotherapy
Rocha 1986	30 controls received immunotherapy, but not analysed by intention-to-treat
Rodriguez 2005	Sublingual immunotherapy
Rodriguez Santos 2004	Sublingual immunotherapy
Rohatgi 1988	Uncontrolled study
Rose 1996	No clinical outcomes reported
Sadan 1969	Hayfever subjects only
Sanchez 1989	Comparison of oral with parenteral immunotherapy
Sanchez 2001	Sublingual immunotherapy
Sanders 1966	Matched pairs, but not clearly randomised; global symptom score, asthmatics not clearly identified
Saraclar 1998	Not randomised - 13/18 patients volunteered for immunotherapy
Scordamaglia 1997	Sublingual immunotherapy
Shen 1998	Abstract only
Shore 1980	Abstract only
Simons 1996	Only in vitro results presented in paper
Smith 2004	Only in vitro results presented in paper
Smits 2003	Not controlled
Swineford 1955	Not a randomised controlled trial
Sychlowy 1979	Uncontrolled study
Tabar 2005	RCT of two alternative immunotherapy regimens

(Continued)

Tari 1990	Sublingual immunotherapy
Tari 1992	Inhaled immunotherapy
Tari 1997	Asthma not reported separately
Taskapan 1998	Controlled trial of single versus multiple allergen immunotherapy
Taub 1969	Editorial with personal experience - not a randomised controlled trial
Taudorf 1983	Oral immunotherapy
Taudorf 1985	Oral immunotherapy
Taudorf 1987	Oral immunotherapy
Tsai 2005	In vitro outcomes only
Tuchinda 1973	All subjects received immunotherapy. Allocation to high or low dose not randomised.
Turner 1984	No clinical outcomes reported
Urbanek 1982	Oral immunotherapy
Van Bever 1988	Not a randomised controlled trial
Van Bever 1989	Not randomised
Van Bever 1990	All patients received immunotherapy during first year
Van Bever 1998	Only in vitro outcomes reported
Vidal 1999	Not controlled
Voltolini 2001	Sublingual immunotherapy
Vourdas 1998	Sublingual immunotherapy
Wahn 1980	Not a randomised controlled trial
Wahn 1988	All children received <i>D. pteronyssinus</i> immunotherapy - RCT of extracts prepared from whole mite culture and mite bodies
Walker 2003	Trial of withdrawal of immunotherapy
Wang 1999	Only in vitro outcomes reported

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Wang 2004	Abstract only
Weyer 1981	No clinical outcomes reported
Wüthrich 1980	Uncontrolled study
Yuksel 1999	Sublingual immunotherapy
Zietkowski 1999	Local (intrabronchial) immunotherapy

EPD = enzyme potentiated desensitisation

RCT = randomised controlled trial

DATA AND ANALYSES

Comparison 1. Allergen immunotherapy versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma symptom scores	34	1284	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.83, -0.35]
1.1 Mite immunotherapy	12	408	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.96, -0.00]
1.2 Pollen immunotherapy	18	663	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-0.87, -0.35]
1.3 Other immunotherapy	5	213	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.92, 0.26]
2 Symptomatic deterioration	22	1112	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.41, 0.65]
2.1 Mite immunotherapy	12	460	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.87]
2.2 Pollen immunotherapy	3	220	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.07, 0.90]
2.3 Animal dander immunotherapy	4	107	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.24, 0.92]
2.4 Other immunotherapy	3	325	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.33, 0.65]
3 Asthma medication scores	20	869	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.80, -0.27]
3.1 Mite immunotherapy	12	424	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.04, -0.18]
3.2 Pollen immunotherapy	8	324	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.91, -0.13]
3.3 Other immunotherapy	1	121	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.62, 0.10]
4 Increased asthma medication	17	636	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.62, 0.79]
5 Lung function parameters	20		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Peak Expiratory Flow	11	524	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.33, 0.61]
5.2 FEV1	7	199	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.96, 0.31]
5.3 Thoracic Gas Volume	2	81	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
6 Deterioration in lung function	7	253	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.10]
7 Nonspecific BHR indices	18	576	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.59, -0.11]
7.1 LogPD20 Methacholine	12	453	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
7.2 LogPC20 Histamine	4	76	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-1.37, 0.28]
7.3 LogPC35 Acetylcholine	1	21	Std. Mean Difference (IV, Random, 95% CI)	-1.29 [-2.28, -0.31]
7.4 DeltaFEV1% Cold air	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.31, 0.26]
8 Increased nonspecific BHR	5	121	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.33, 0.72]
9 Allergen specific BHR indices	19	564	Std. Mean Difference (IV, Fixed, 95% CI)	-0.61 [-0.79, -0.43]
9.1 LogPD20 Mite	6	148	Std. Mean Difference (IV, Fixed, 95% CI)	-0.98 [-1.39, -0.58]
9.2 LogPD20 Pollen	5	202	Std. Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.84, -0.27]
9.3 LogPD20 Animal dander	6	153	Std. Mean Difference (IV, Fixed, 95% CI)	-0.61 [-0.95, -0.27]
9.4 LogPD20/PC100 Other allergens	2	61	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.70, 0.33]
10 Increased allergen specific BHR	16	430	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.41, 0.63]
11 Local reactions	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Per patient	14	396	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.86, 1.70]
12 Systemic reactions	37		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Per patient	37	1784	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [1.91, 3.13]
13 Asthma symptom scores (adequate allocation concealment)	9	362	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.08, -0.26]
13.1 Mite immunotherapy	1	22	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-0.53, 1.22]
13.2 Pollen immunotherapy	7	313	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-1.29, -0.40]
13.3 Other immunotherapy	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-1.01, 0.52]

14 Systemic reactions (adequate allocation concealment)	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Per patient	13	445	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.07, 3.02]

Comparison 2. Allergen immunotherapy versus antigenically inactive control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma symptom scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Symptomatic deterioration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Increased asthma medication	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Systemic reactions	1	57	Odds Ratio (M-H, Fixed, 95% CI)	4.44 [0.48, 40.77]

Comparison 3. House dust versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic deterioration	3	162	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.21, 1.35]
2 Increased asthma medication	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Deterioration in lung function	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Increased allergen specific BHR	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Systemic reactions	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.31, 2.96]

Comparison 4. Allergen immunotherapy versus untreated control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma symptom scores	3	200	Std. Mean Difference (IV, Random, 95% CI)	-1.84 [-3.21, -0.47]
2 Asthma medication scores	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Lung function parameters	2	164	Std. Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.21, -0.39]
4 Nonspecific BHR indices	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Allergen specific BHR indices	2	50	Std. Mean Difference (IV, Fixed, 95% CI)	-0.62 [-1.22, -0.01]
6 Increased allergen specific BHR	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Systemic reactions	3	124	Odds Ratio (M-H, Fixed, 95% CI)	6.04 [0.75, 48.86]

Comparison 5. Allergen immunotherapy versus inhaled steroid

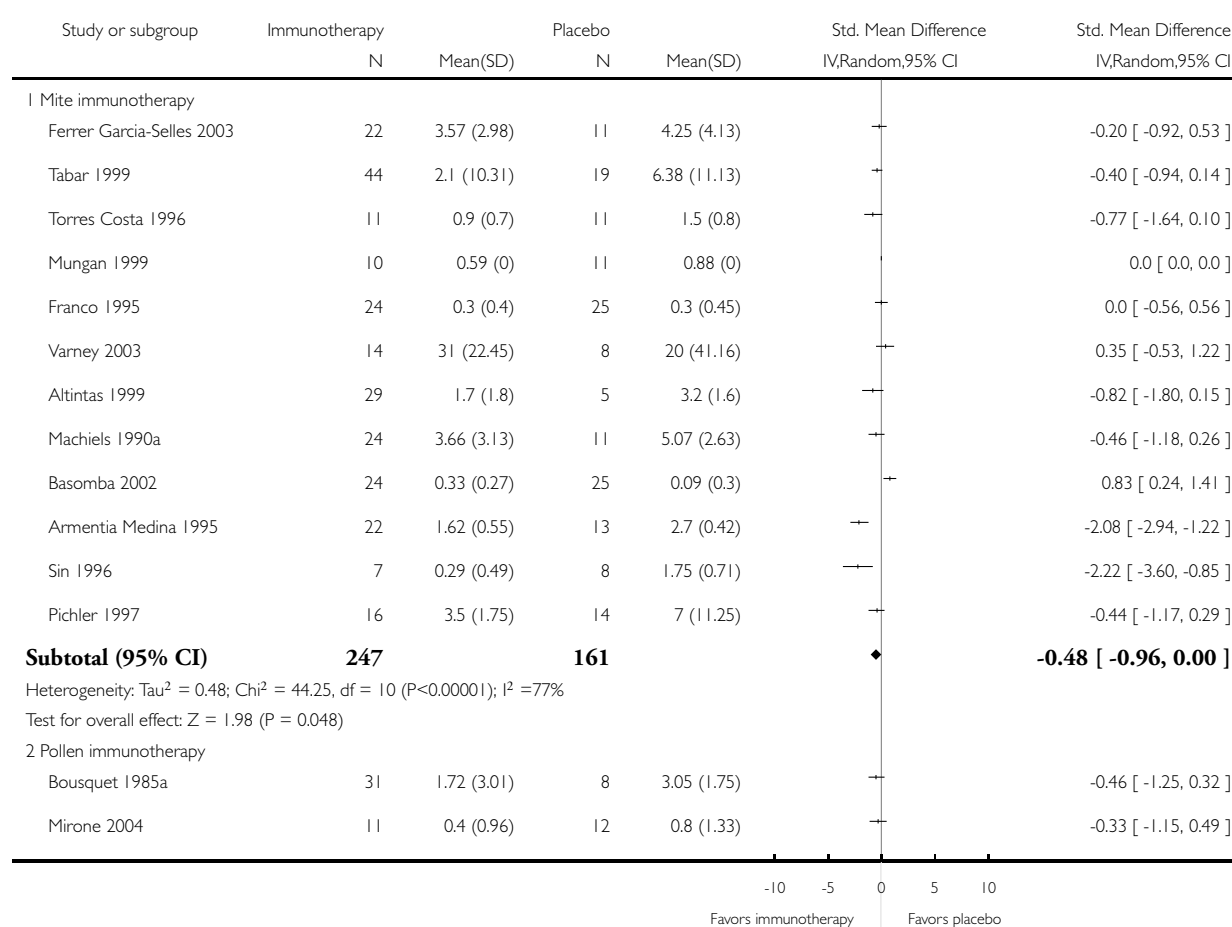
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma symptom scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Deterioration in FEV1	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Systemic reactions	1	51	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Allergen immunotherapy versus placebo, Outcome 1 Asthma symptom scores.

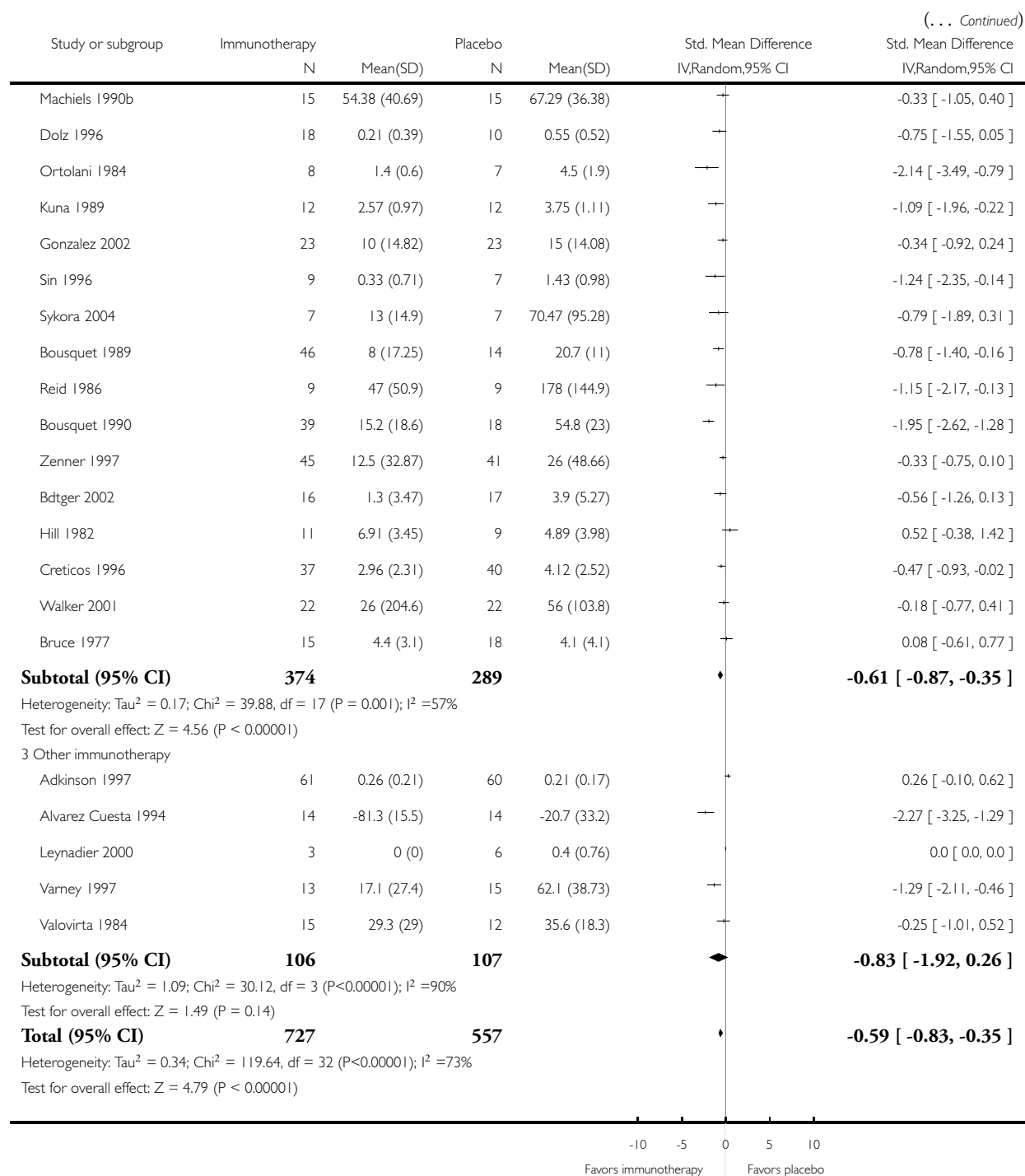
Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 1 Asthma symptom scores



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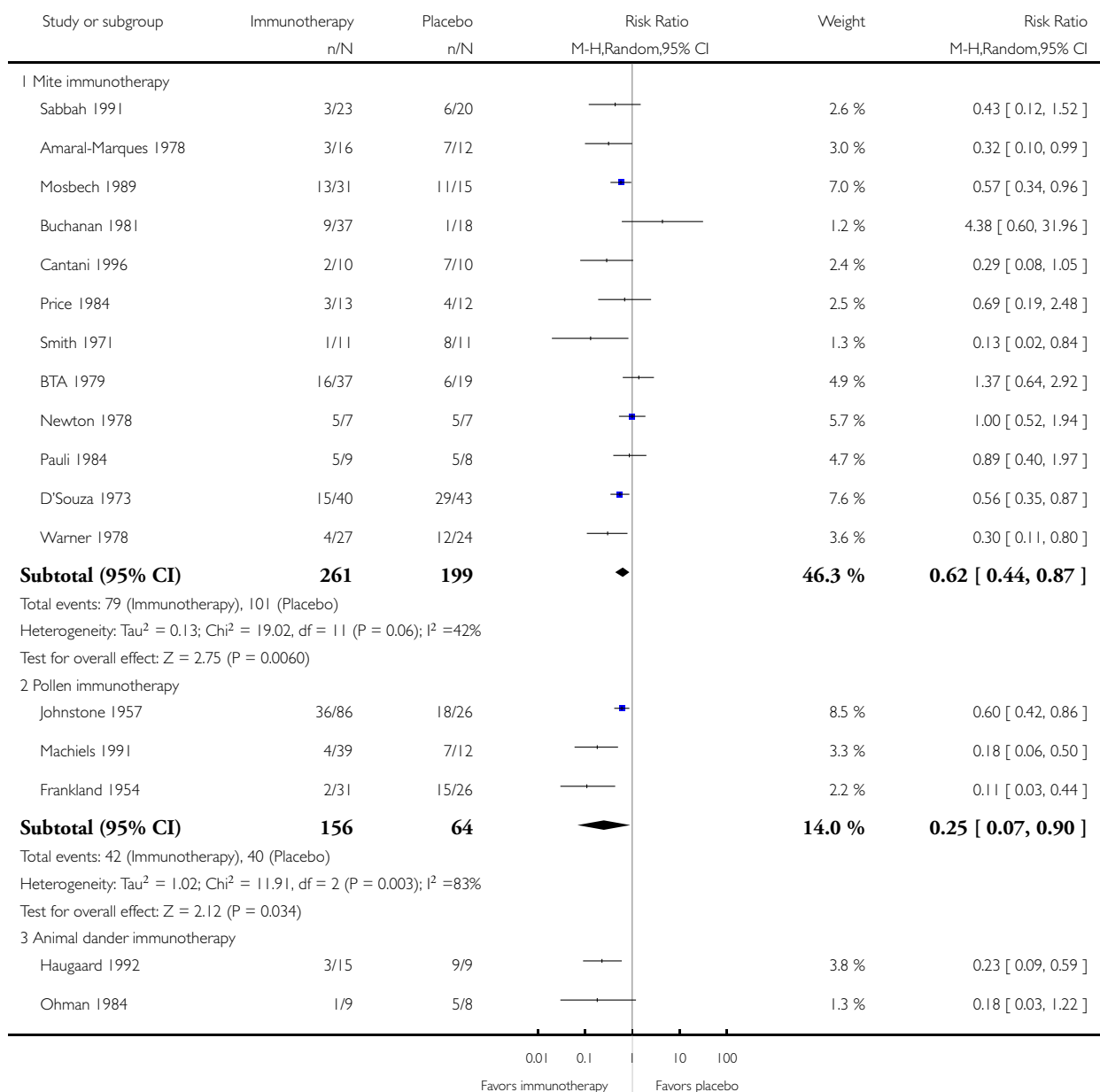


Analysis 1.2. Comparison 1 Allergen immunotherapy versus placebo, Outcome 2 Symptomatic deterioration.

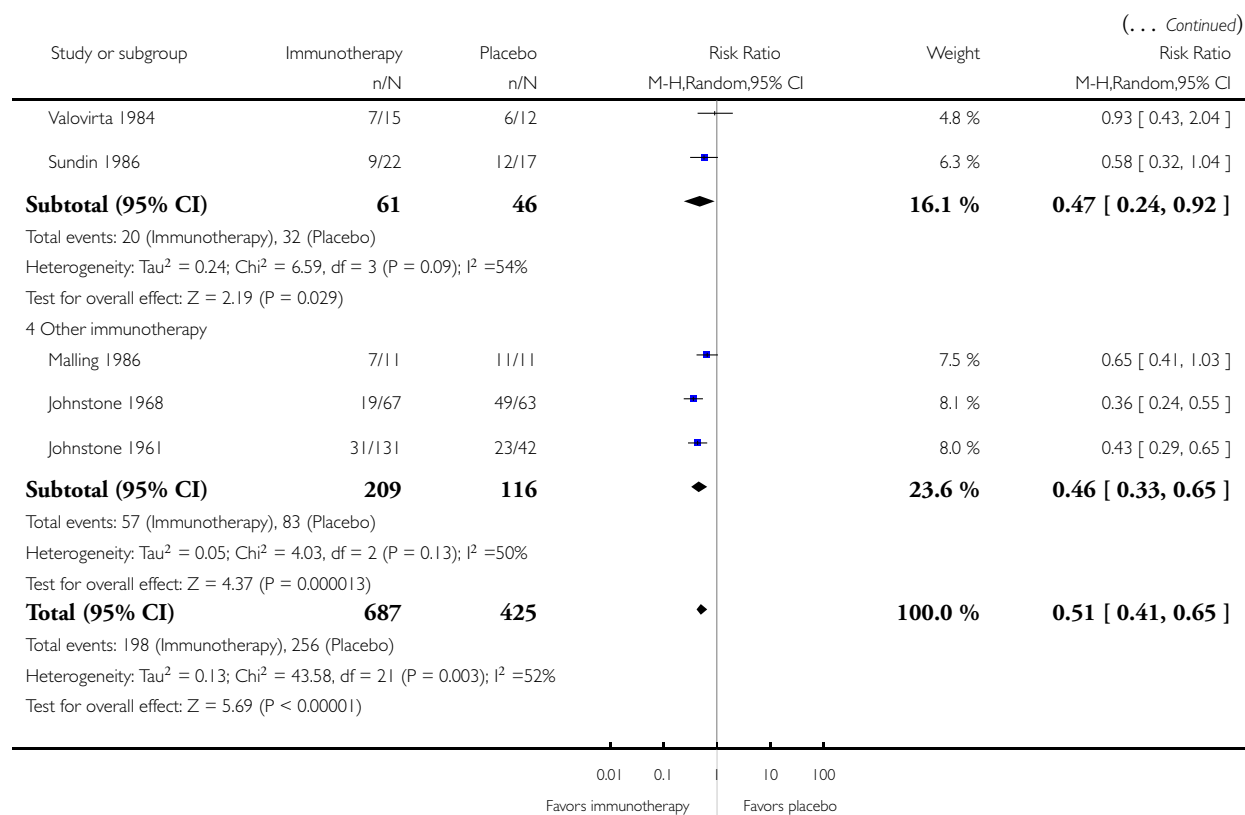
Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 2 Symptomatic deterioration



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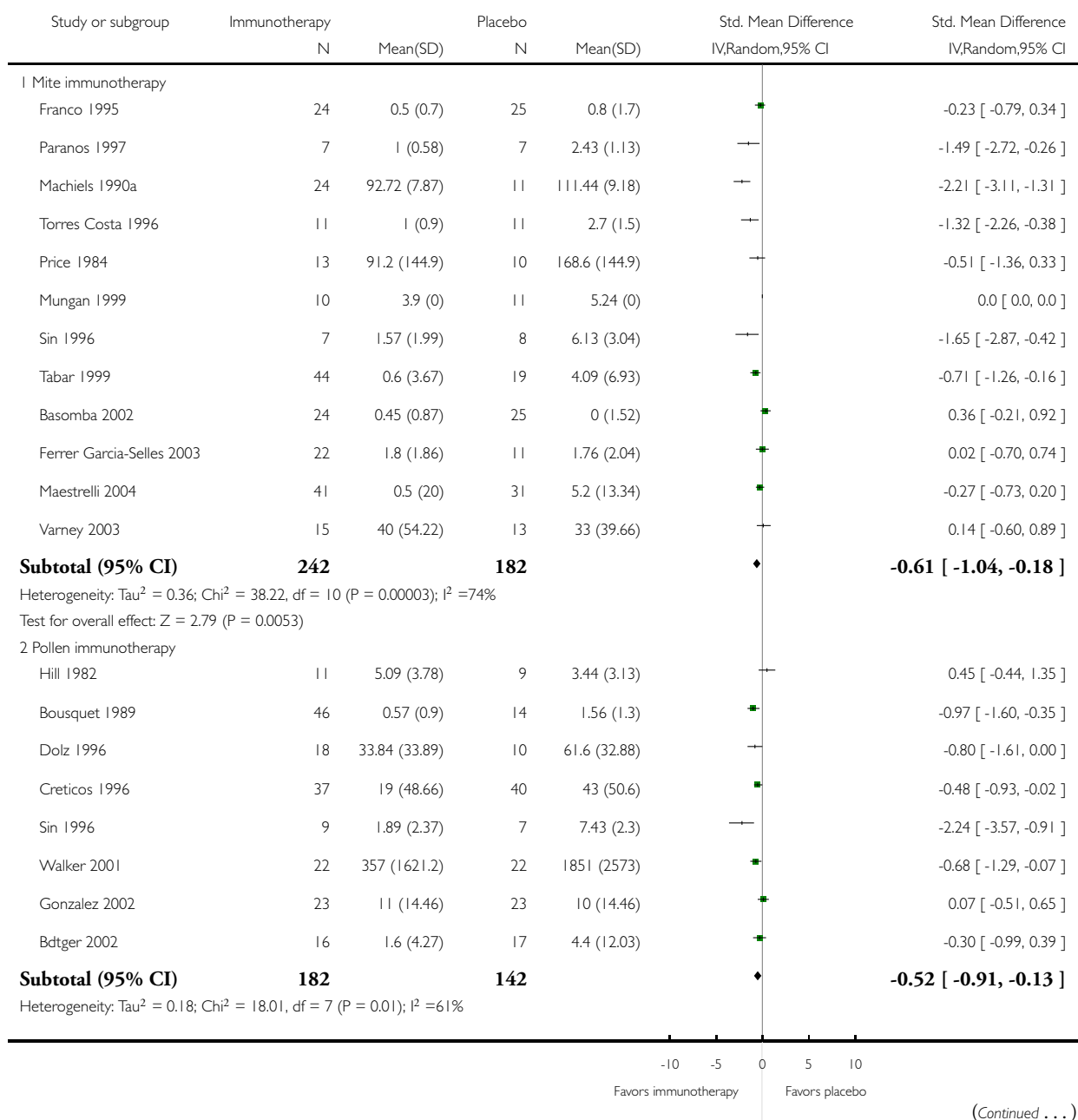


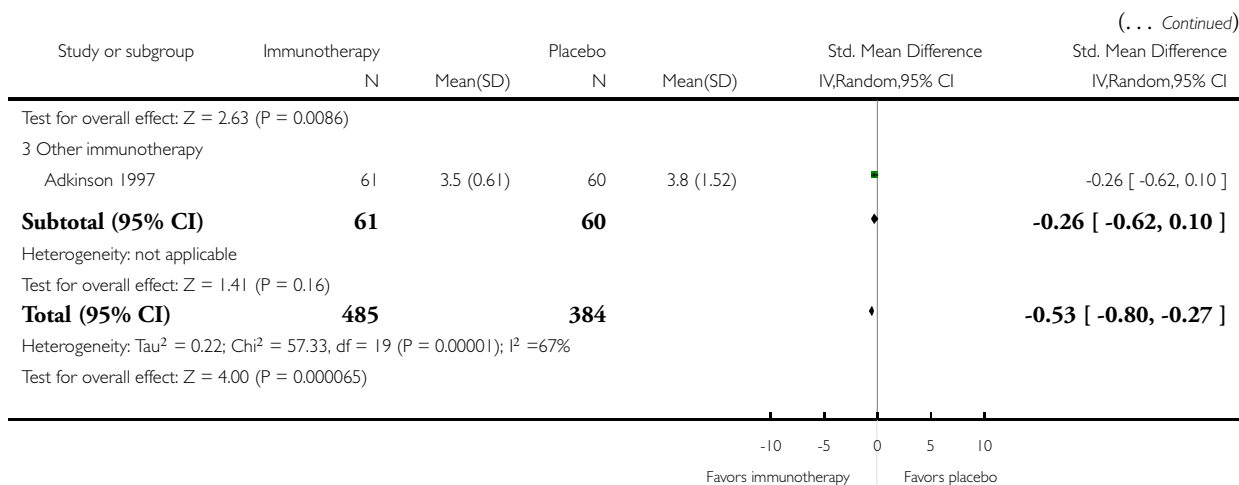
Analysis 1.3. Comparison 1 Allergen immunotherapy versus placebo, Outcome 3 Asthma medication scores.

Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 3 Asthma medication scores



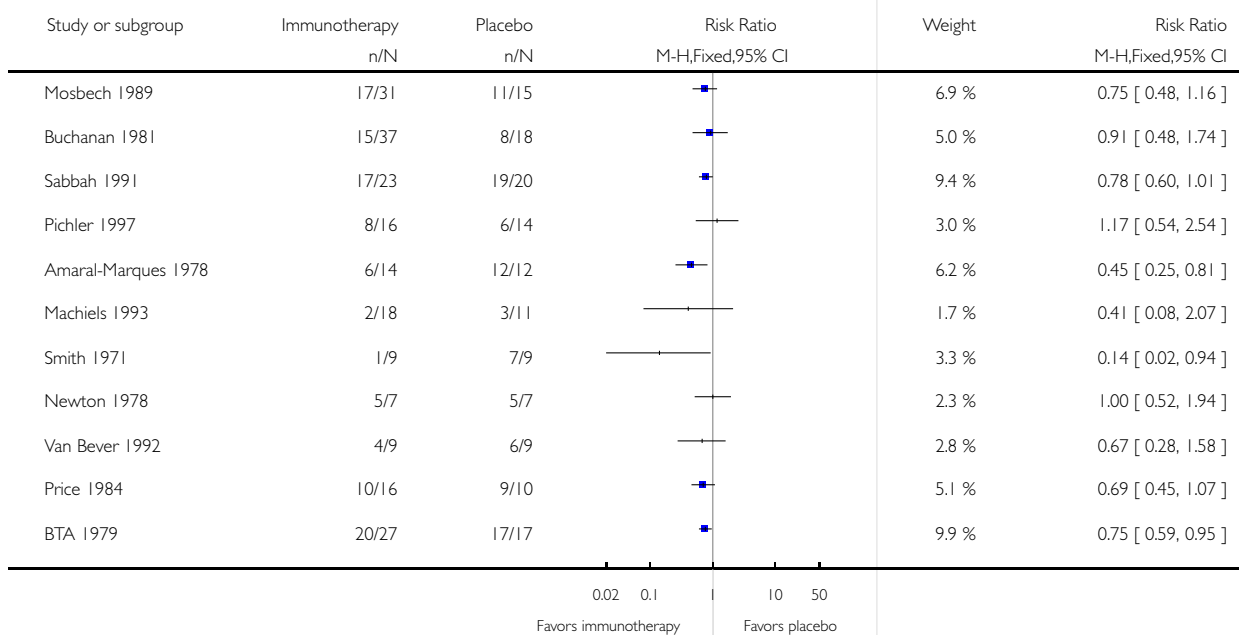


Analysis 1.4. Comparison 1 Allergen immunotherapy versus placebo, Outcome 4 Increased asthma medication.

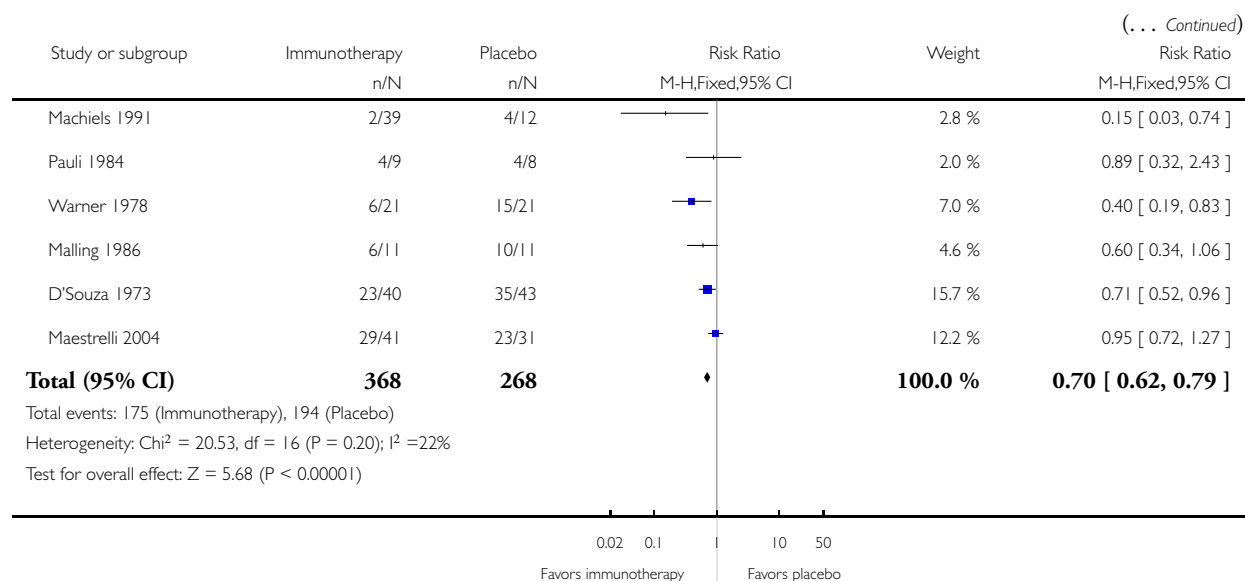
Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 4 Increased asthma medication



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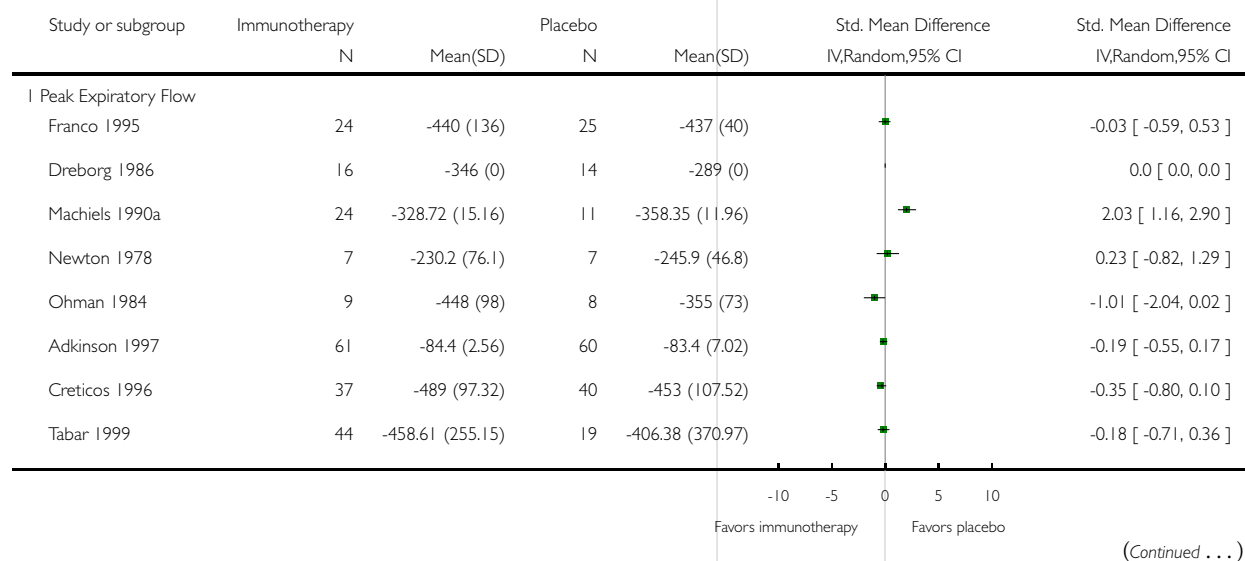


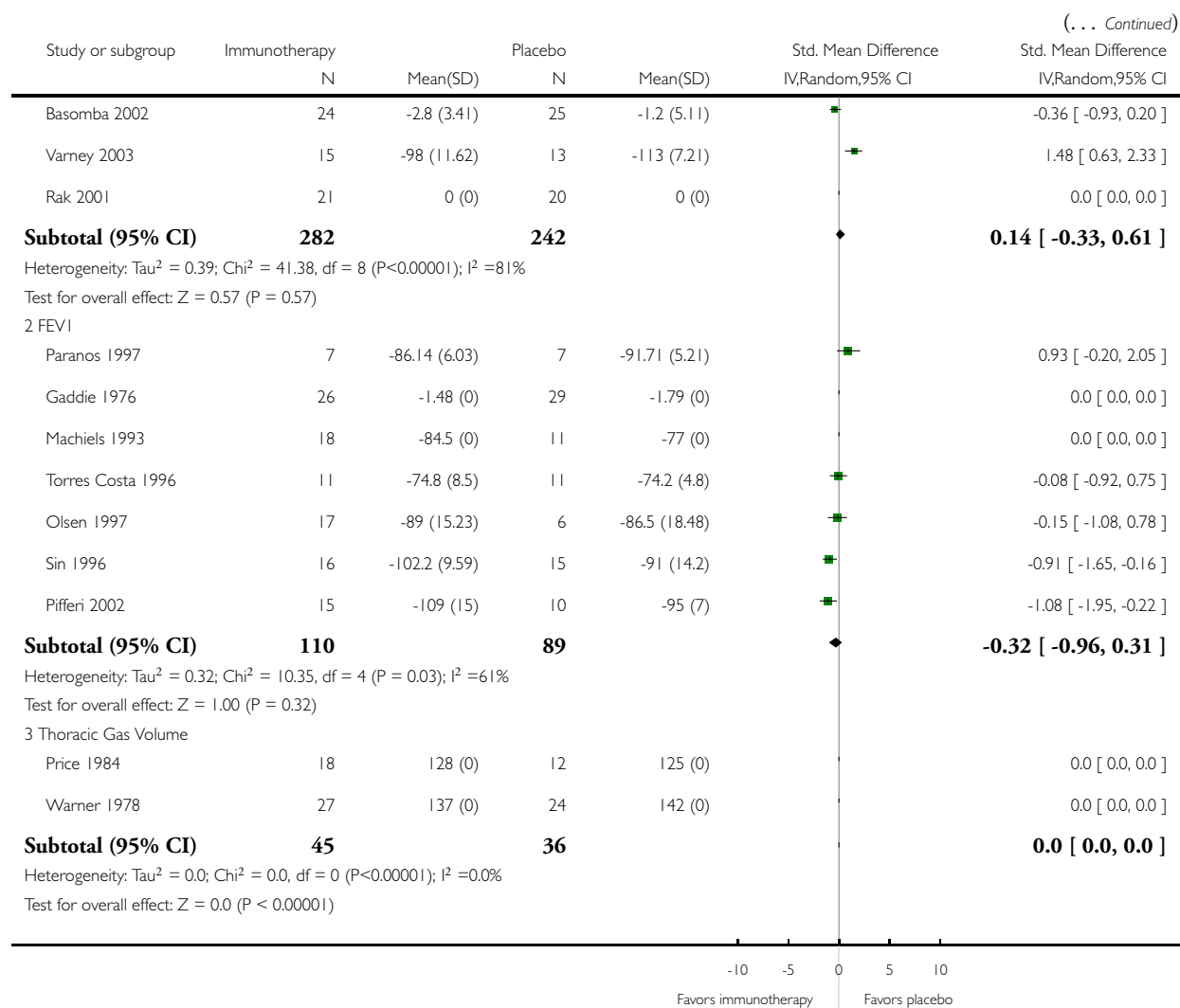
Analysis 1.5. Comparison 1 Allergen immunotherapy versus placebo, Outcome 5 Lung function parameters.

Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 5 Lung function parameters



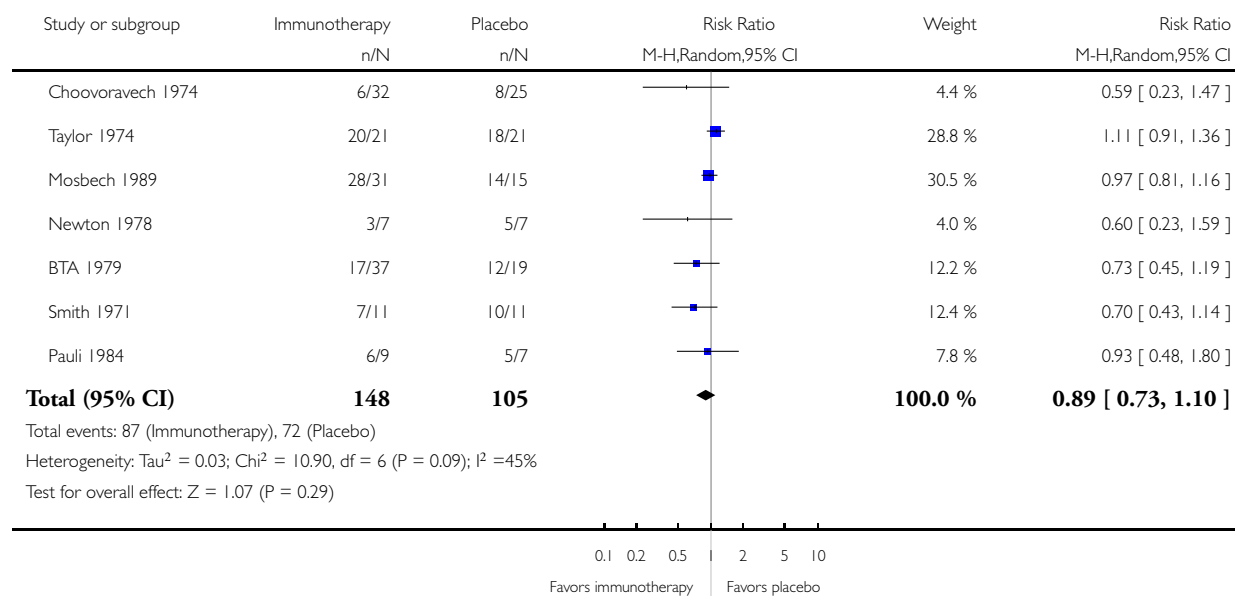


Analysis 1.6. Comparison 1 Allergen immunotherapy versus placebo, Outcome 6 Deterioration in lung function.

Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 6 Deterioration in lung function

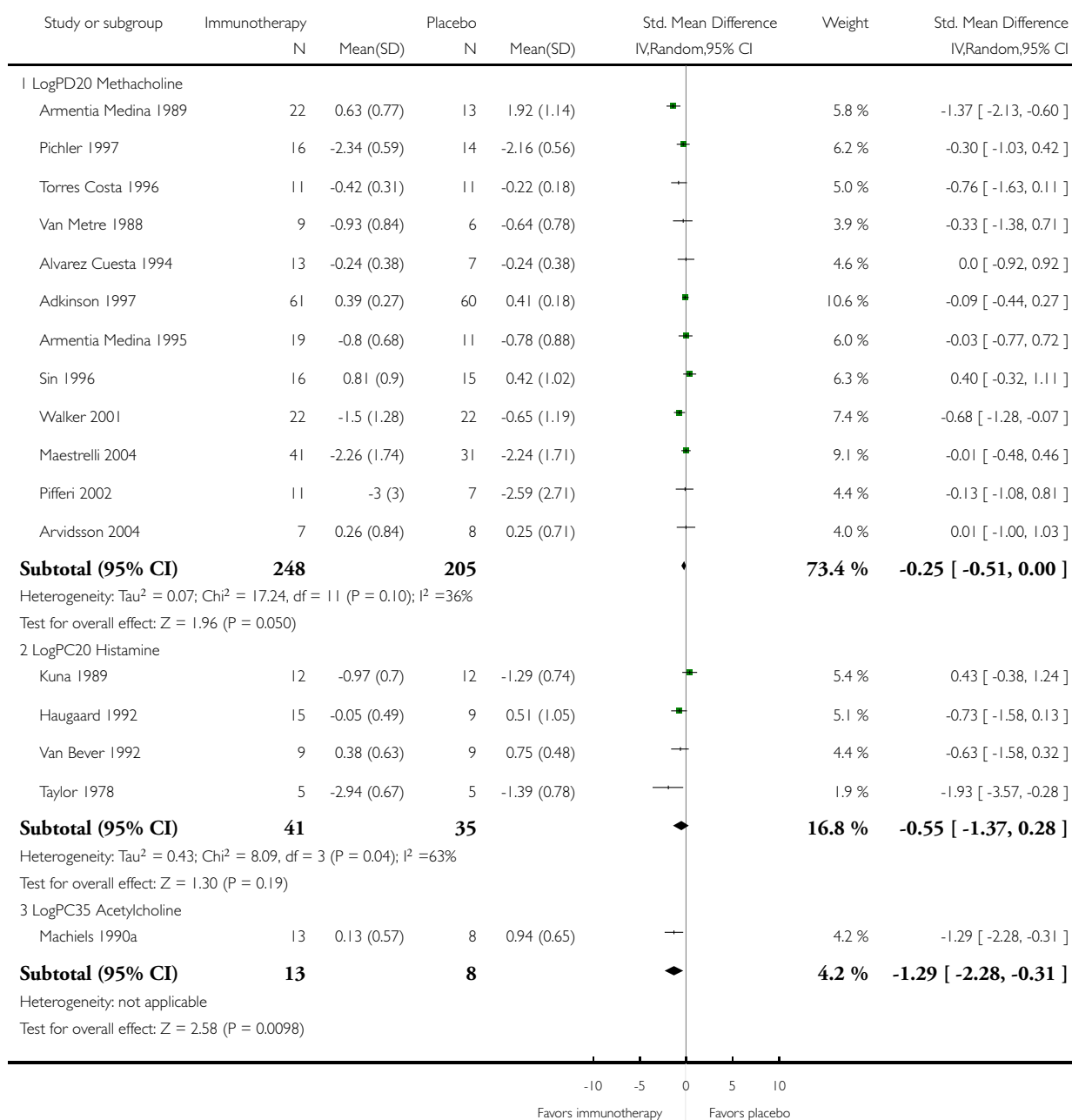


Analysis 1.7. Comparison 1 Allergen immunotherapy versus placebo, Outcome 7 Nonspecific BHR indices.

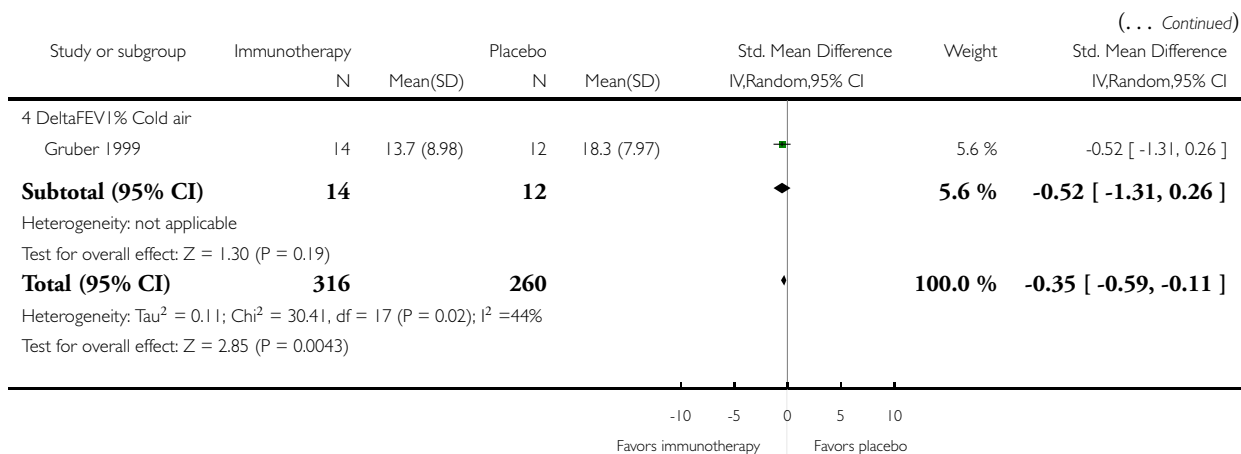
Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 7 Nonspecific BHR indices



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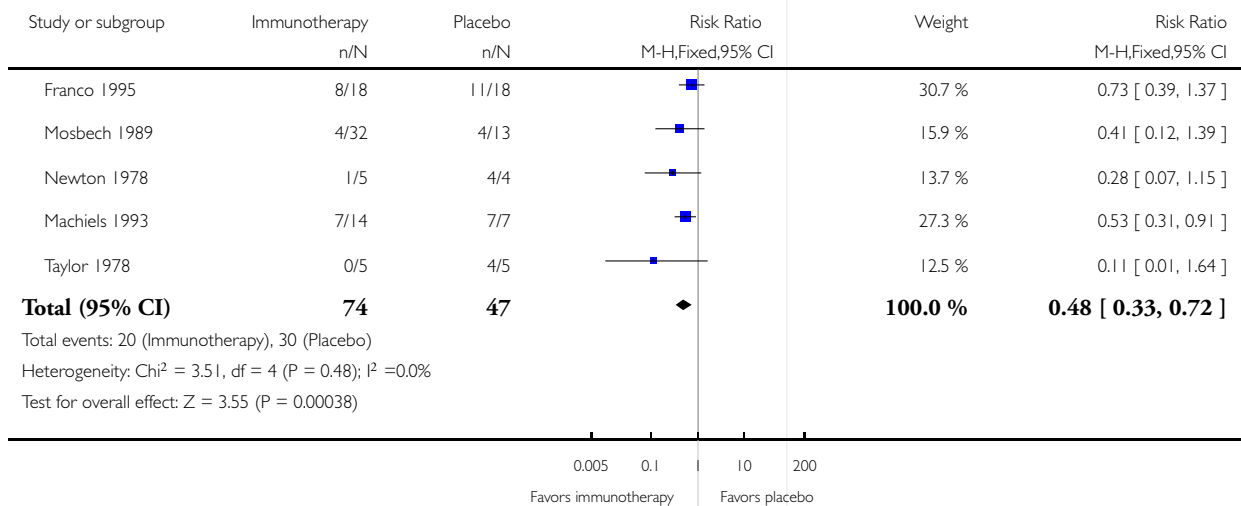


Analysis 1.8. Comparison 1 Allergen immunotherapy versus placebo, Outcome 8 Increased nonspecific BHR.

Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 8 Increased nonspecific BHR

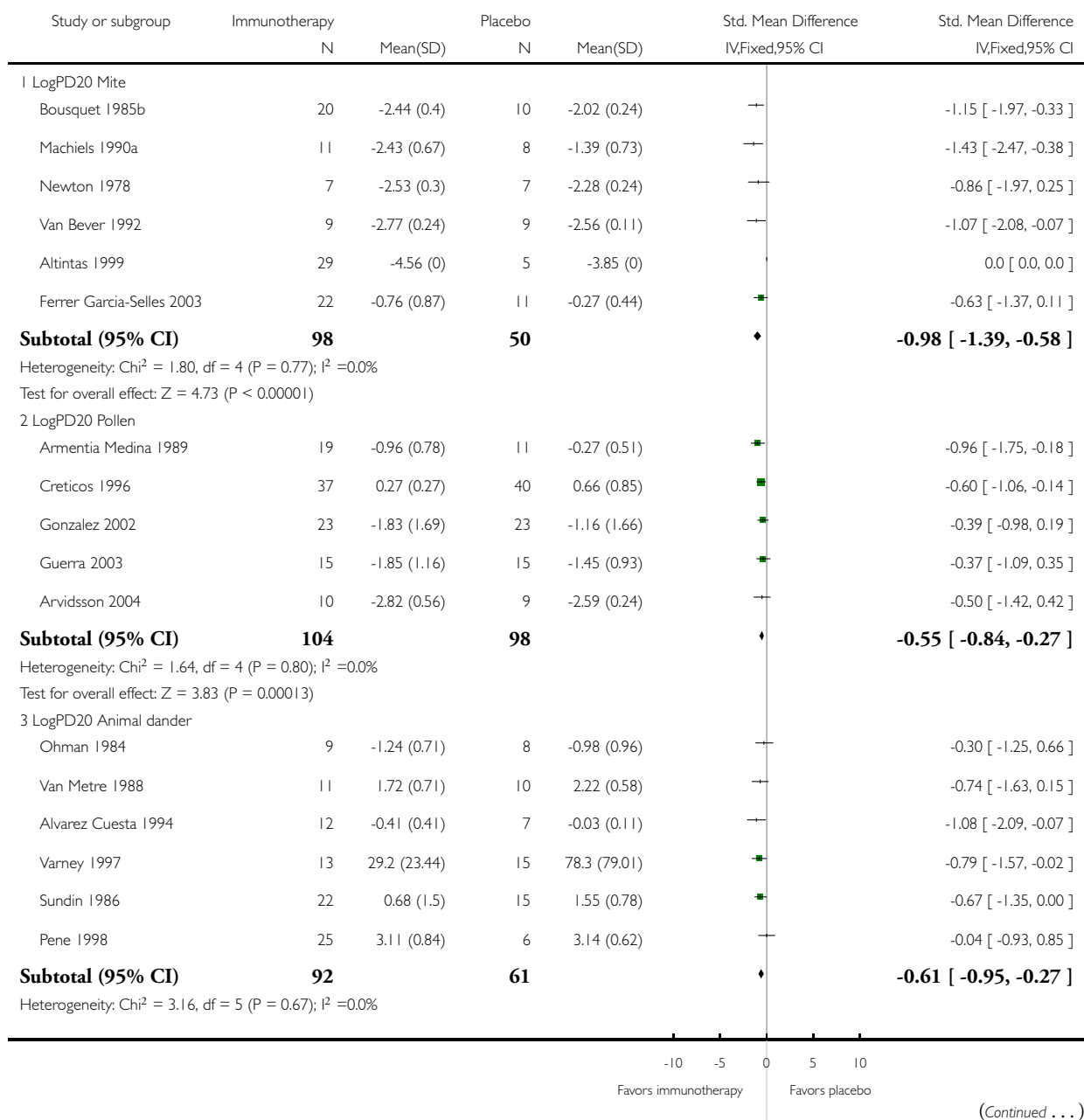


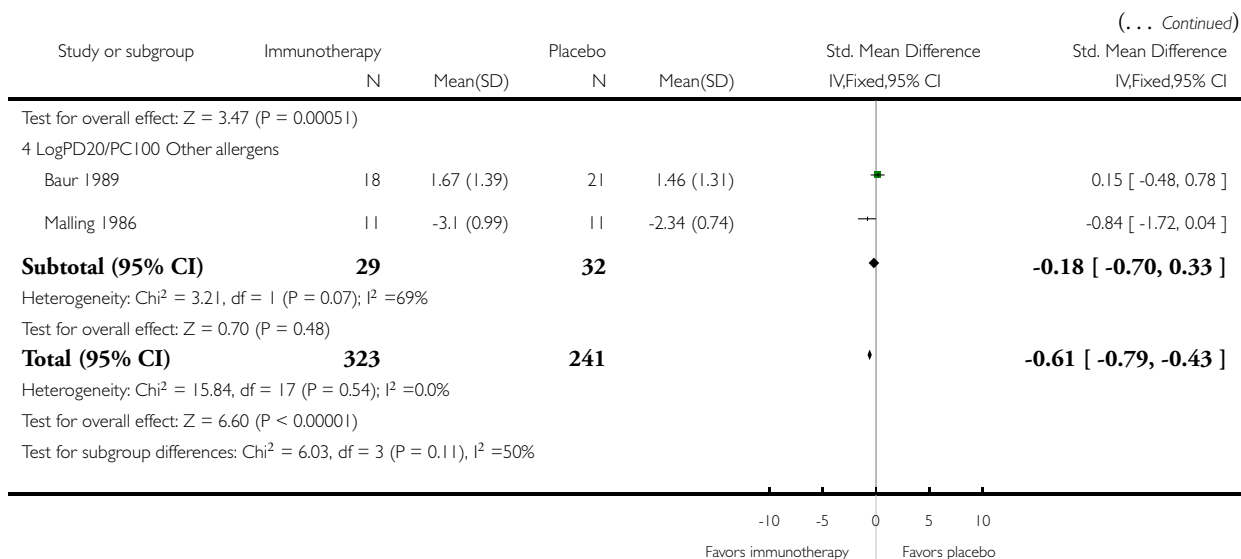
Analysis 1.9. Comparison 1 Allergen immunotherapy versus placebo, Outcome 9 Allergen specific BHR indices.

Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 9 Allergen specific BHR indices



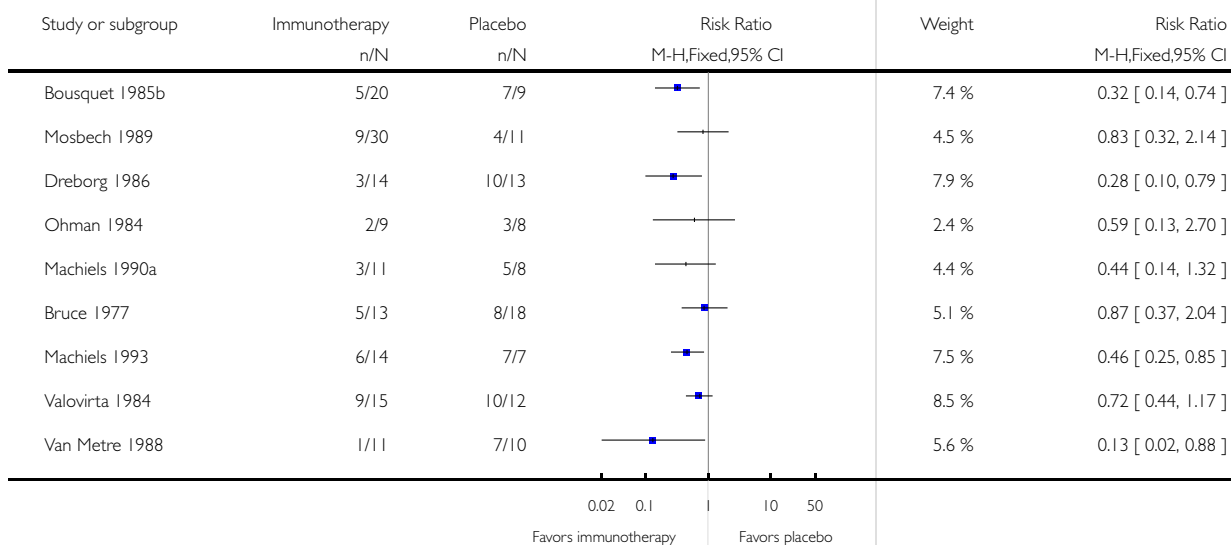


Analysis 1.10. Comparison 1 Allergen immunotherapy versus placebo, Outcome 10 Increased allergen specific BHR.

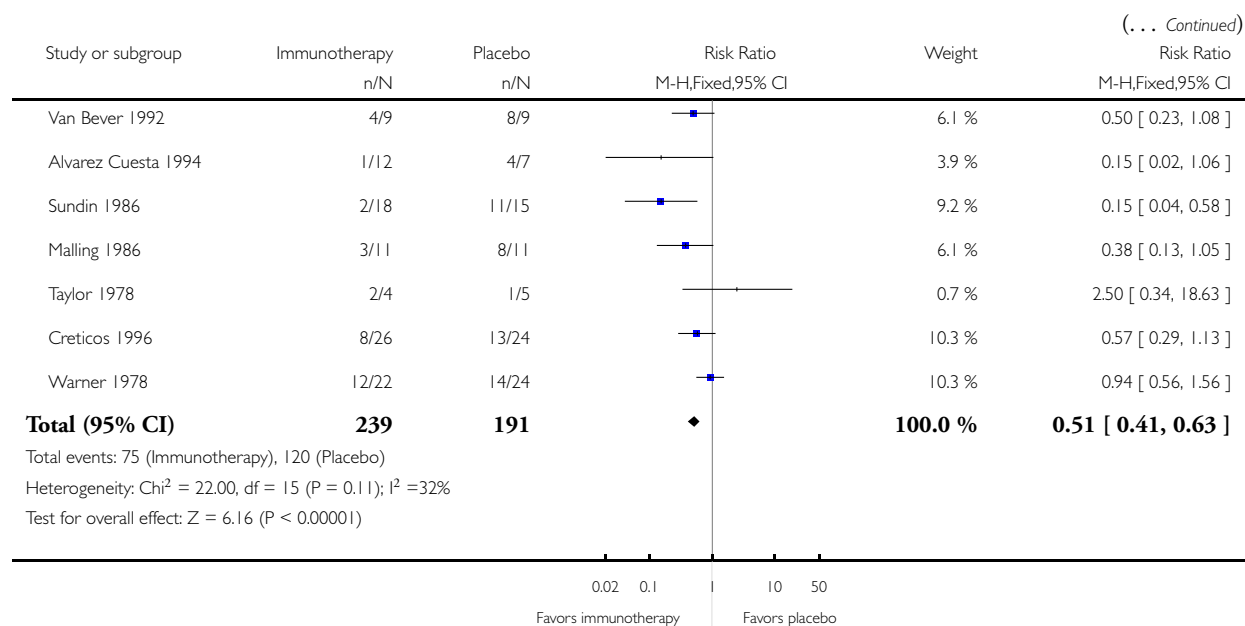
Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 10 Increased allergen specific BHR



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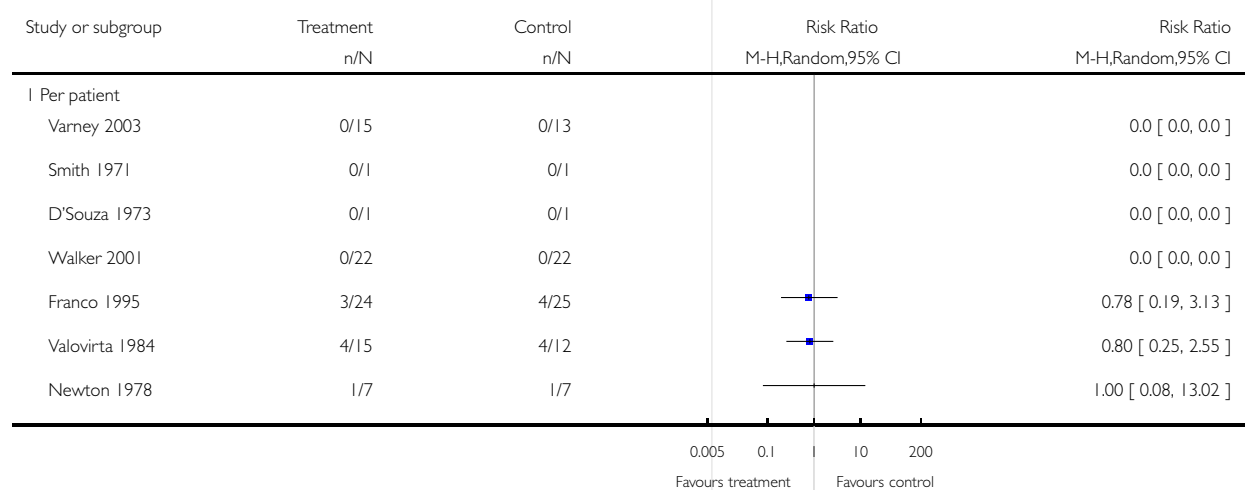


Analysis 1.11. Comparison 1 Allergen immunotherapy versus placebo, Outcome 11 Local reactions.

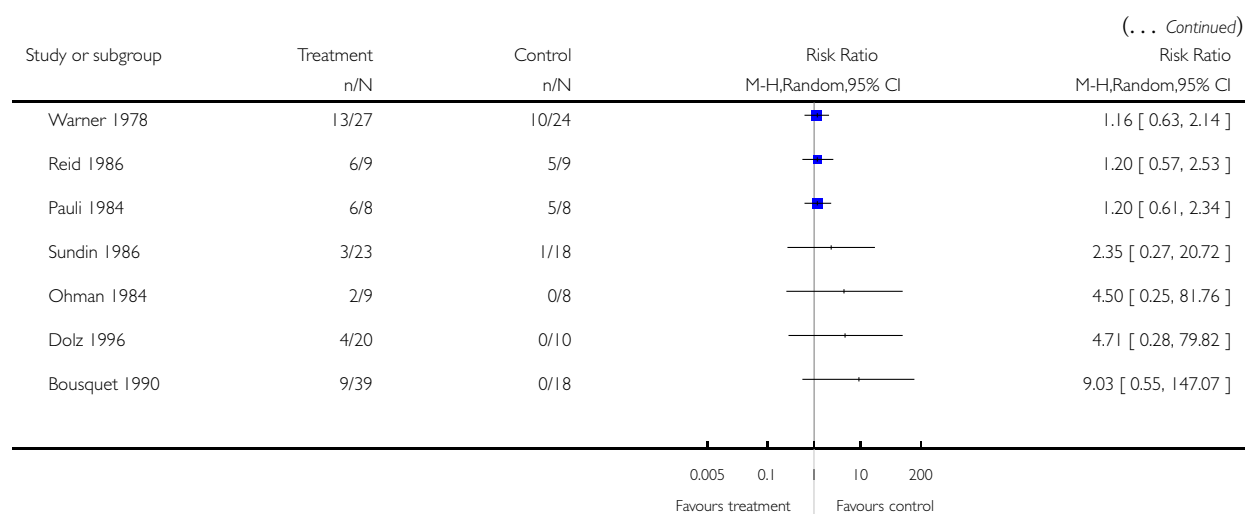
Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 11 Local reactions



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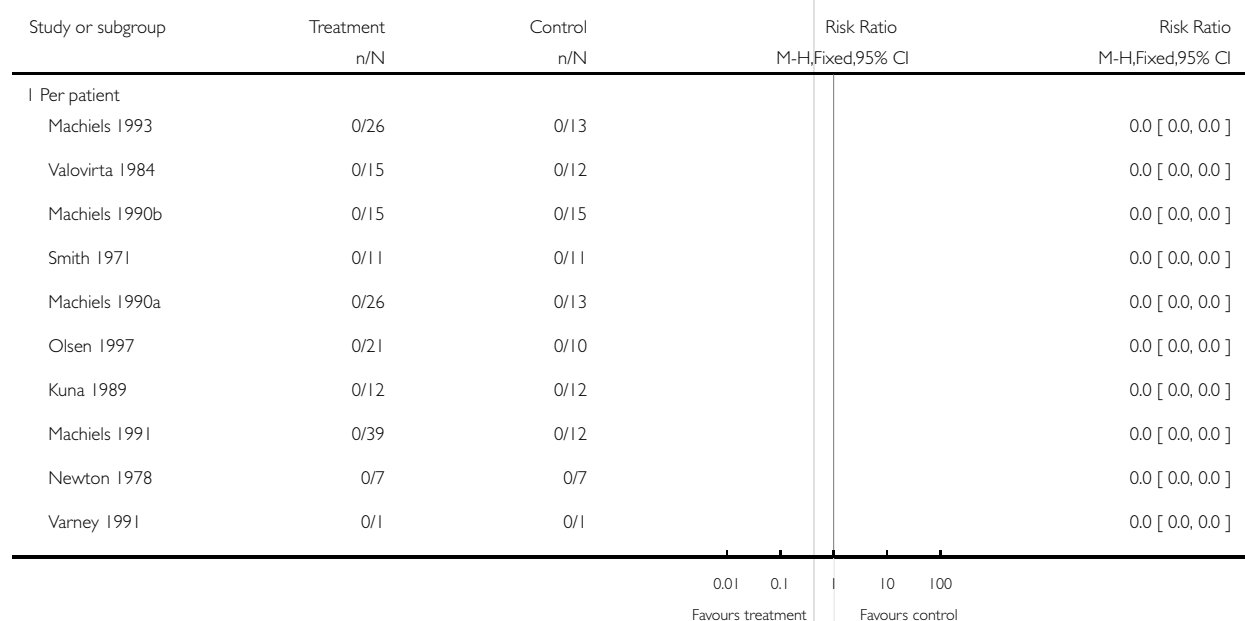


Analysis 1.12. Comparison 1 Allergen immunotherapy versus placebo, Outcome 12 Systemic reactions.

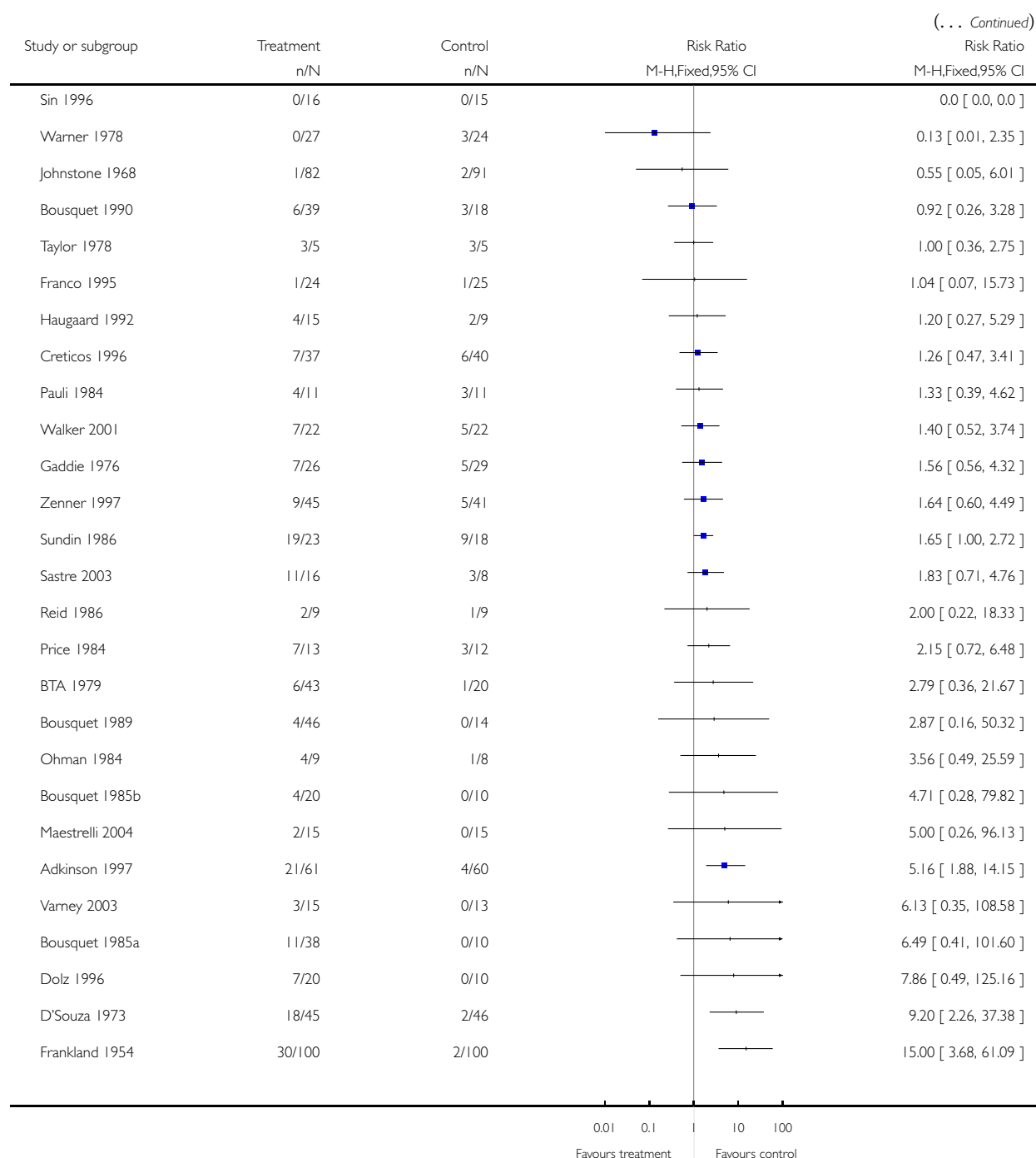
Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 12 Systemic reactions



(Continued . . .)

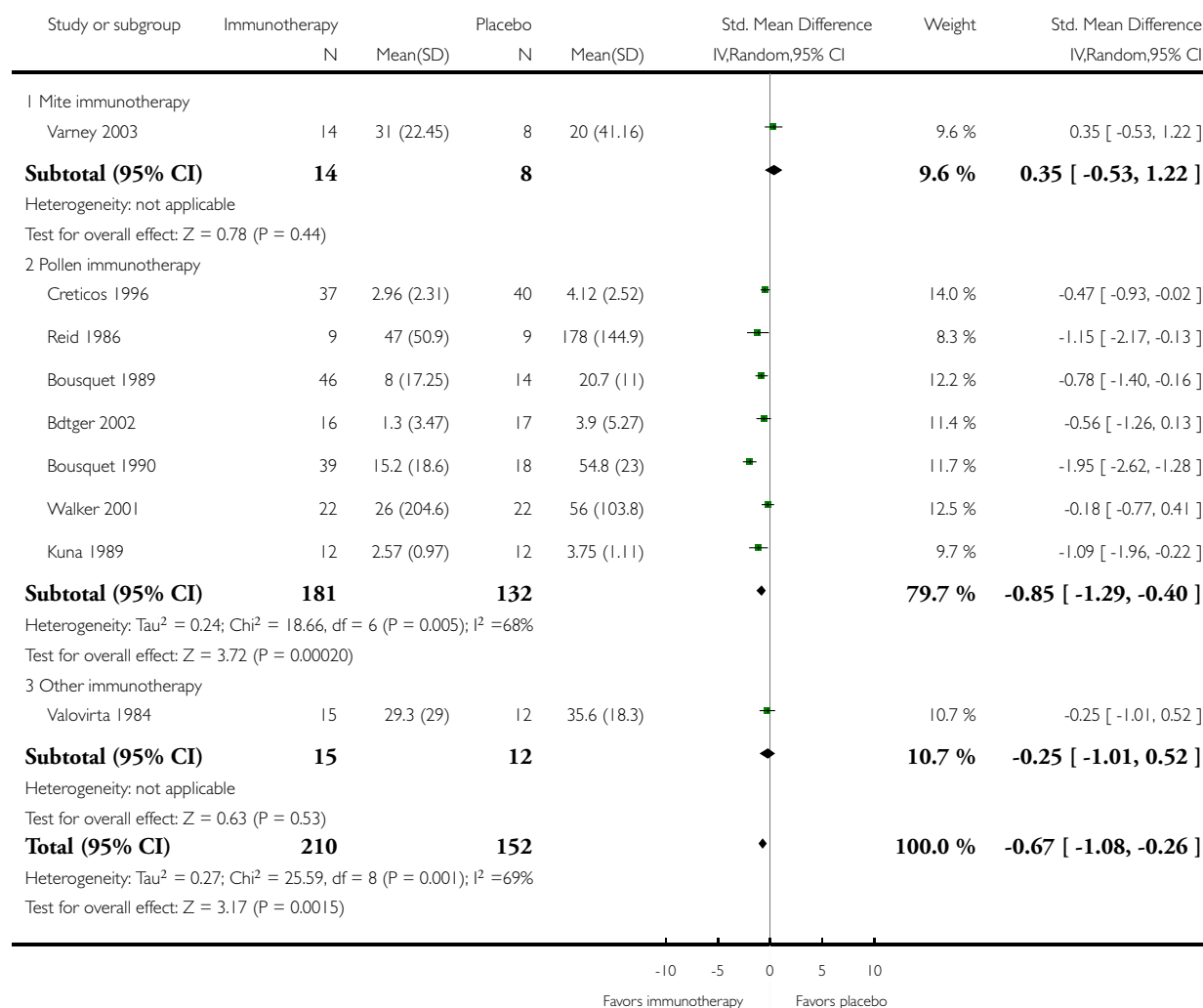


Analysis 1.13. Comparison 1 Allergen immunotherapy versus placebo, Outcome 13 Asthma symptom scores (adequate allocation concealment).

Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 13 Asthma symptom scores (adequate allocation concealment)

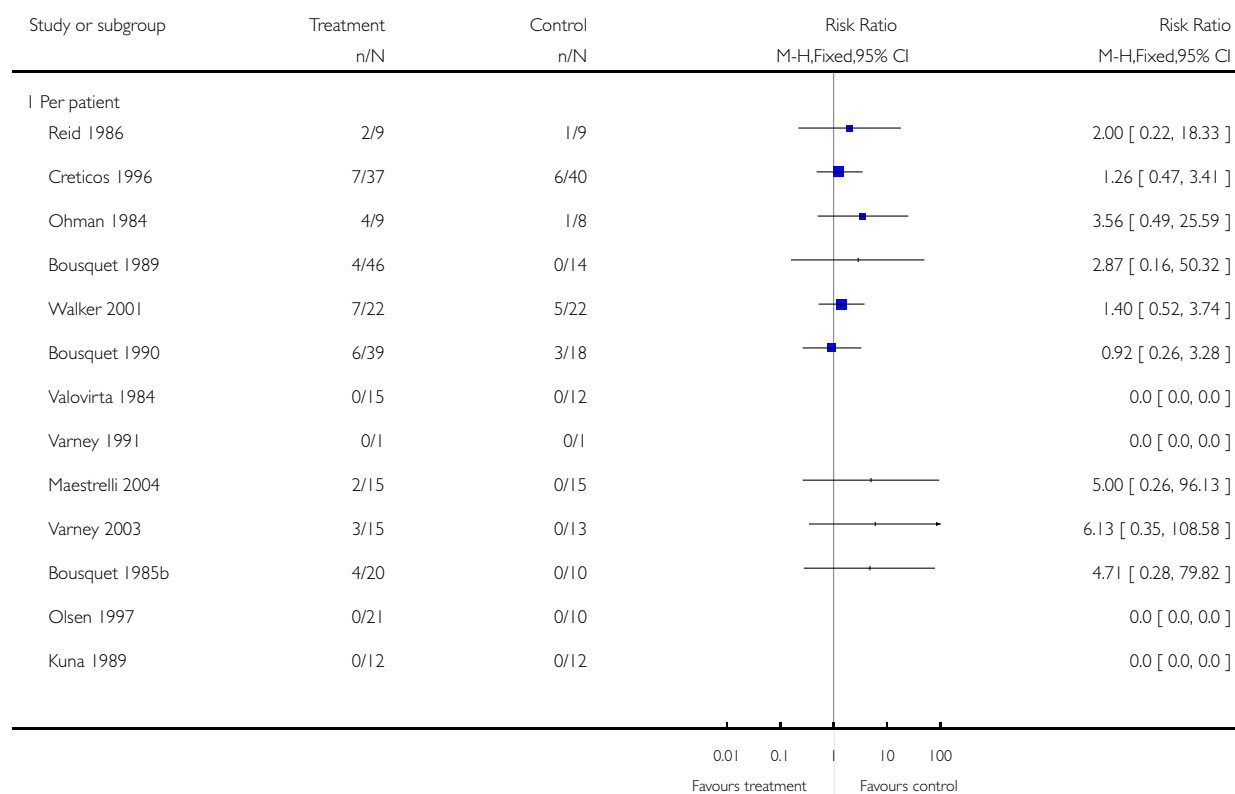


Analysis 1.14. Comparison 1 Allergen immunotherapy versus placebo, Outcome 14 Systemic reactions (adequate allocation concealment).

Review: Injection allergen immunotherapy for asthma

Comparison: 1 Allergen immunotherapy versus placebo

Outcome: 14 Systemic reactions (adequate allocation concealment)

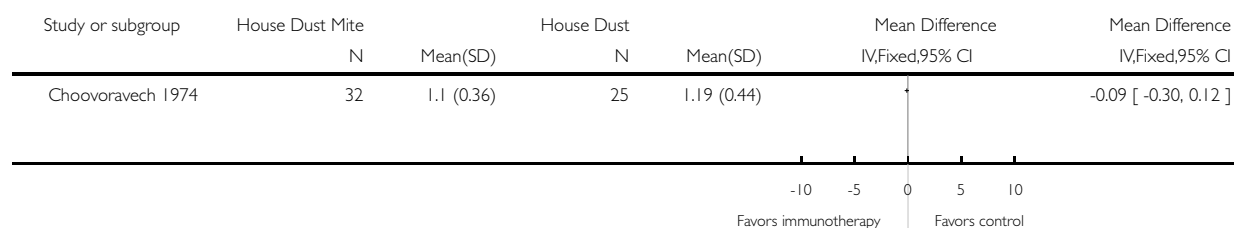


Analysis 2.1. Comparison 2 Allergen immunotherapy versus antigenically inactive control, Outcome 1 Asthma symptom scores.

Review: Injection allergen immunotherapy for asthma

Comparison: 2 Allergen immunotherapy versus antigenically inactive control

Outcome: 1 Asthma symptom scores

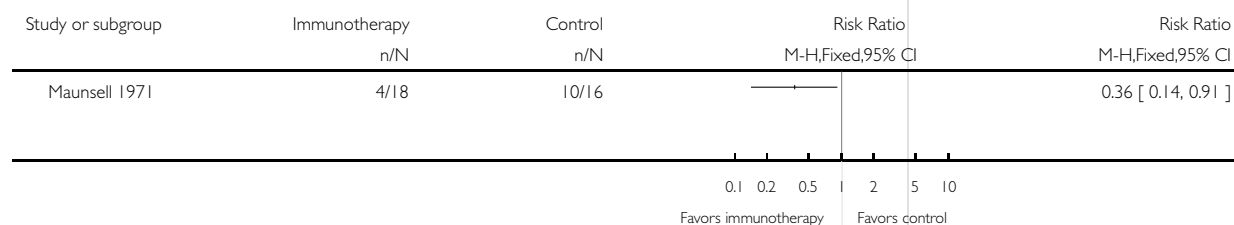


Analysis 2.2. Comparison 2 Allergen immunotherapy versus antigenically inactive control, Outcome 2 Symptomatic deterioration.

Review: Injection allergen immunotherapy for asthma

Comparison: 2 Allergen immunotherapy versus antigenically inactive control

Outcome: 2 Symptomatic deterioration

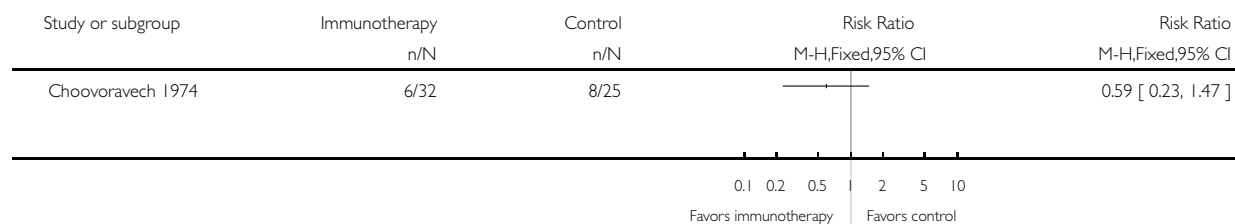


Analysis 2.3. Comparison 2 Allergen immunotherapy versus antigenically inactive control, Outcome 3 Increased asthma medication.

Review: Injection allergen immunotherapy for asthma

Comparison: 2 Allergen immunotherapy versus antigenically inactive control

Outcome: 3 Increased asthma medication

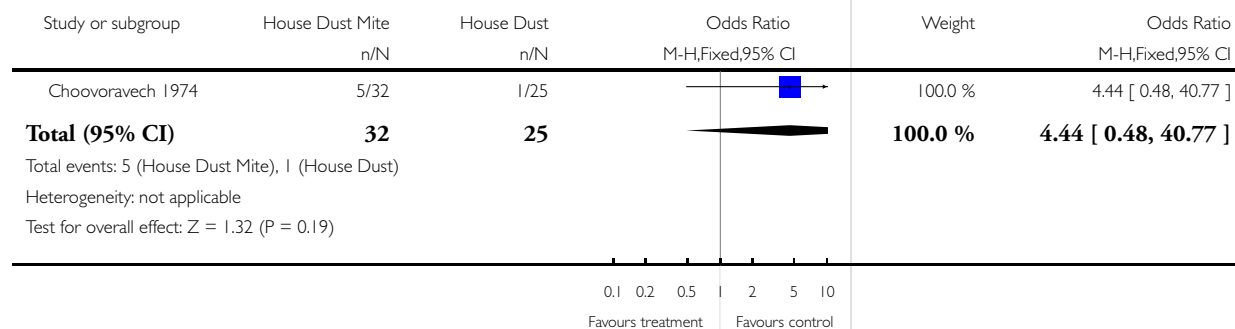


Analysis 2.4. Comparison 2 Allergen immunotherapy versus antigenically inactive control, Outcome 4 Systemic reactions.

Review: Injection allergen immunotherapy for asthma

Comparison: 2 Allergen immunotherapy versus antigenically inactive control

Outcome: 4 Systemic reactions

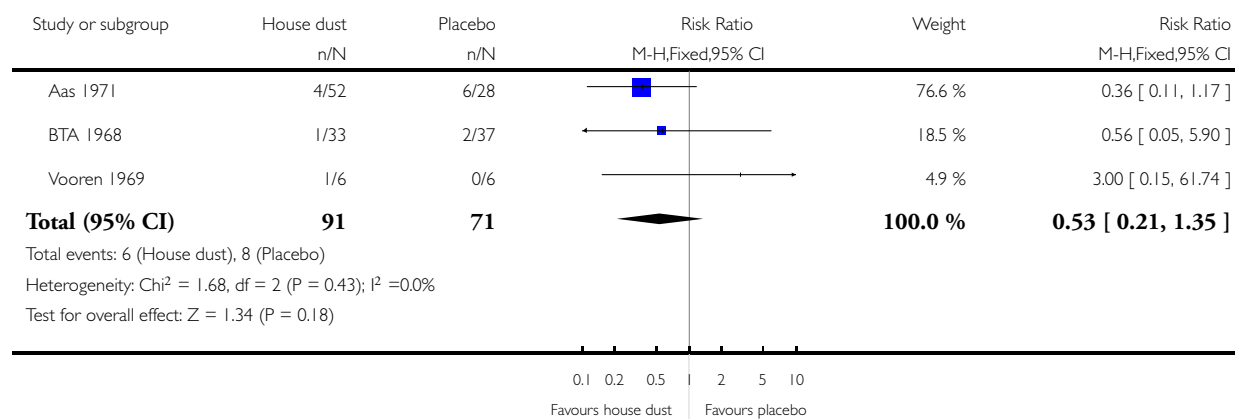


Analysis 3.1. Comparison 3 House dust versus placebo, Outcome 1 Symptomatic deterioration.

Review: Injection allergen immunotherapy for asthma

Comparison: 3 House dust versus placebo

Outcome: 1 Symptomatic deterioration

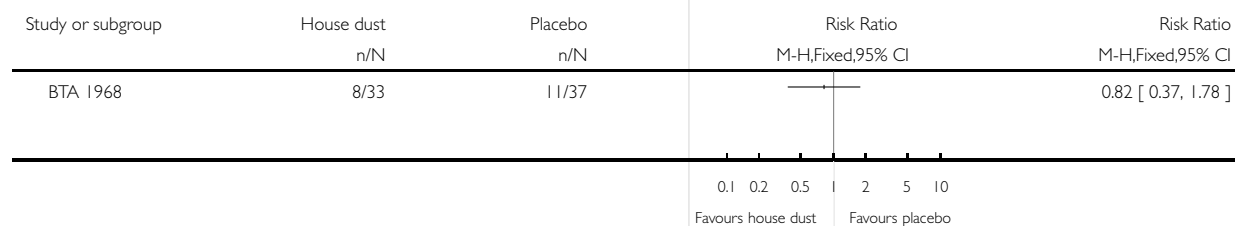


Analysis 3.2. Comparison 3 House dust versus placebo, Outcome 2 Increased asthma medication.

Review: Injection allergen immunotherapy for asthma

Comparison: 3 House dust versus placebo

Outcome: 2 Increased asthma medication

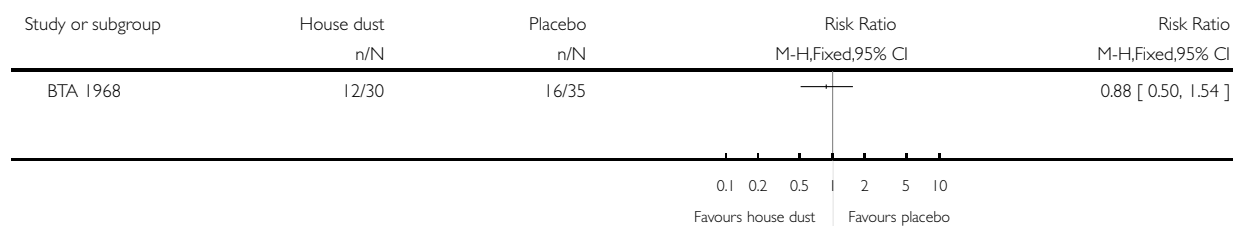


Analysis 3.3. Comparison 3 House dust versus placebo, Outcome 3 Deterioration in lung function.

Review: Injection allergen immunotherapy for asthma

Comparison: 3 House dust versus placebo

Outcome: 3 Deterioration in lung function

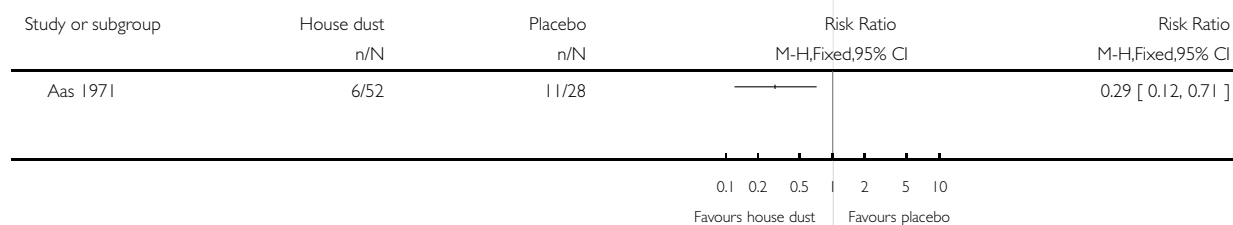


Analysis 3.4. Comparison 3 House dust versus placebo, Outcome 4 Increased allergen specific BHR.

Review: Injection allergen immunotherapy for asthma

Comparison: 3 House dust versus placebo

Outcome: 4 Increased allergen specific BHR

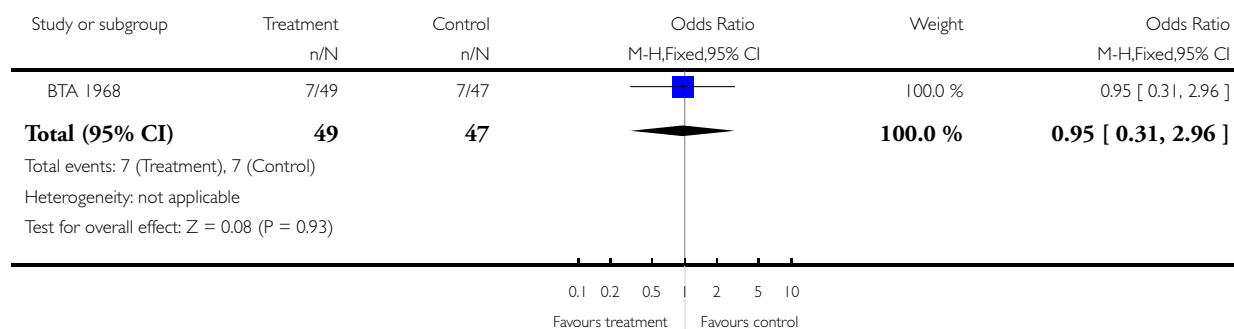


Analysis 3.5. Comparison 3 House dust versus placebo, Outcome 5 Systemic reactions.

Review: Injection allergen immunotherapy for asthma

Comparison: 3 House dust versus placebo

Outcome: 5 Systemic reactions

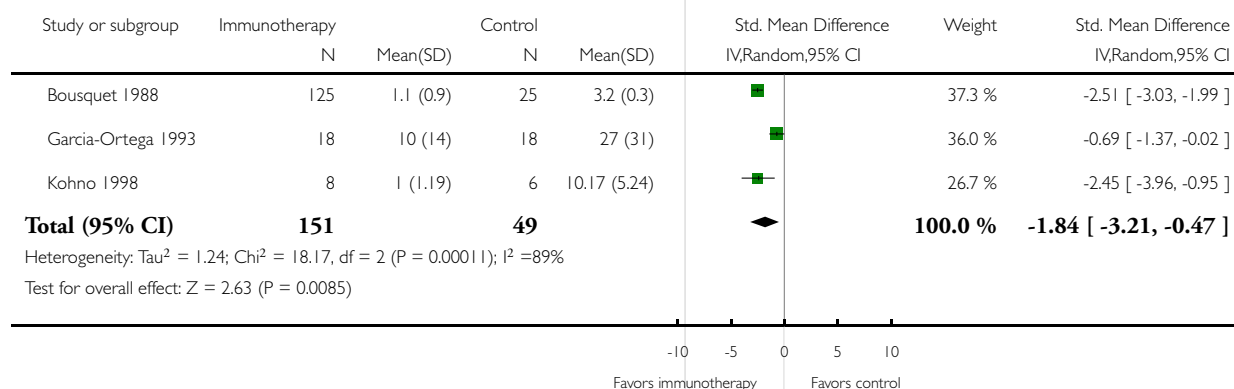


Analysis 4.1. Comparison 4 Allergen immunotherapy versus untreated control, Outcome 1 Asthma symptom scores.

Review: Injection allergen immunotherapy for asthma

Comparison: 4 Allergen immunotherapy versus untreated control

Outcome: 1 Asthma symptom scores

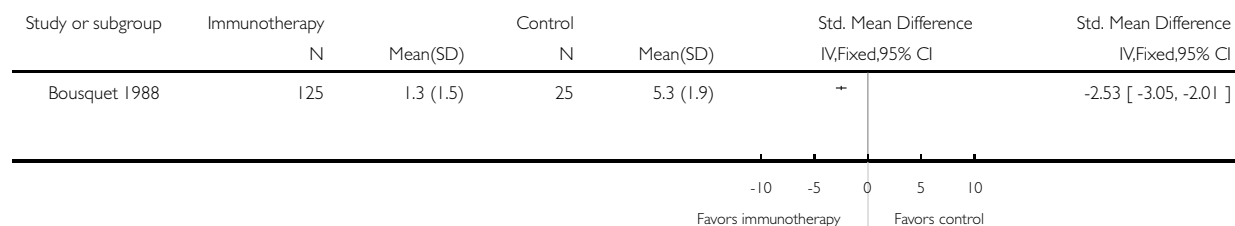


Analysis 4.2. Comparison 4 Allergen immunotherapy versus untreated control, Outcome 2 Asthma medication scores.

Review: Injection allergen immunotherapy for asthma

Comparison: 4 Allergen immunotherapy versus untreated control

Outcome: 2 Asthma medication scores

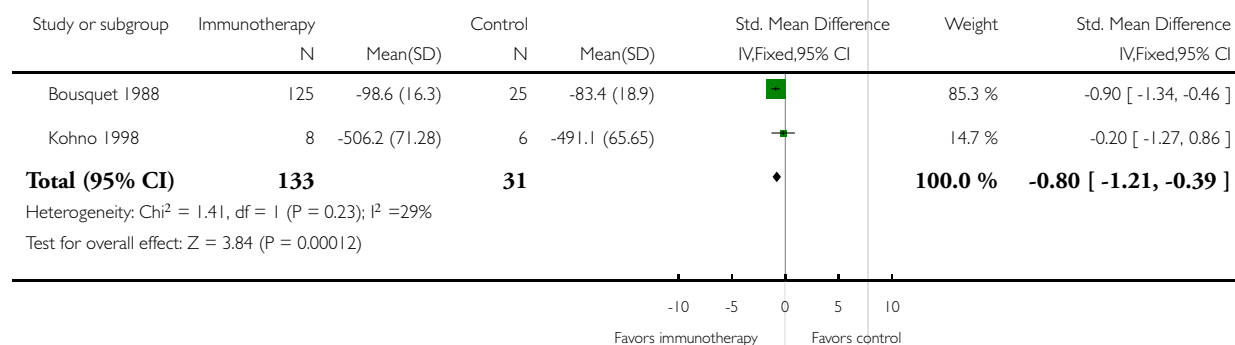


Analysis 4.3. Comparison 4 Allergen immunotherapy versus untreated control, Outcome 3 Lung function parameters.

Review: Injection allergen immunotherapy for asthma

Comparison: 4 Allergen immunotherapy versus untreated control

Outcome: 3 Lung function parameters

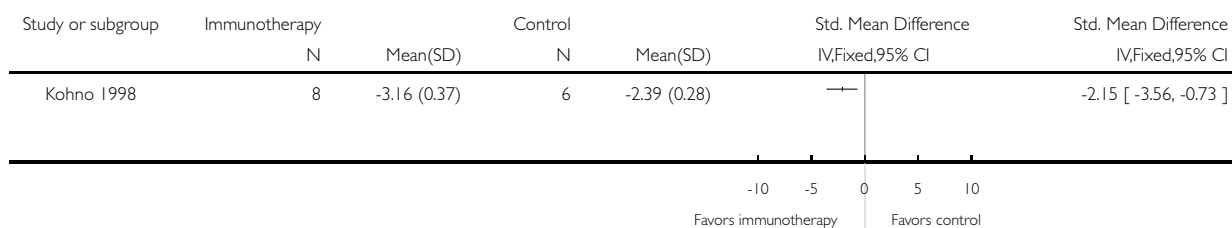


Analysis 4.4. Comparison 4 Allergen immunotherapy versus untreated control, Outcome 4 Nonspecific BHR indices.

Review: Injection allergen immunotherapy for asthma

Comparison: 4 Allergen immunotherapy versus untreated control

Outcome: 4 Nonspecific BHR indices

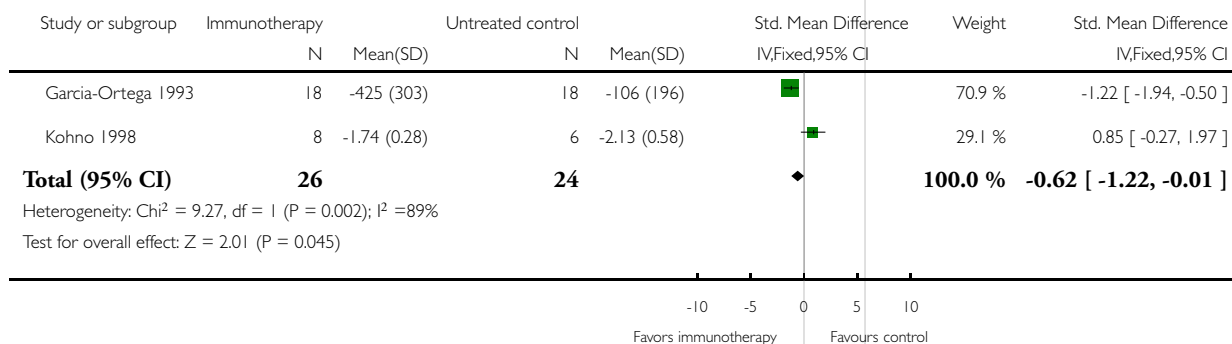


Analysis 4.5. Comparison 4 Allergen immunotherapy versus untreated control, Outcome 5 Allergen specific BHR indices.

Review: Injection allergen immunotherapy for asthma

Comparison: 4 Allergen immunotherapy versus untreated control

Outcome: 5 Allergen specific BHR indices

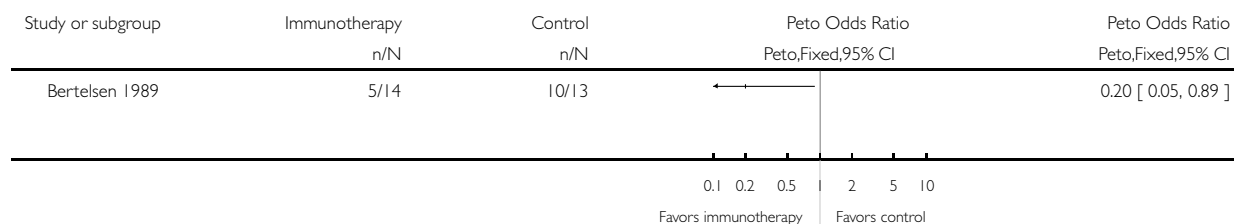


Analysis 4.6. Comparison 4 Allergen immunotherapy versus untreated control, Outcome 6 Increased allergen specific BHR.

Review: Injection allergen immunotherapy for asthma

Comparison: 4 Allergen immunotherapy versus untreated control

Outcome: 6 Increased allergen specific BHR

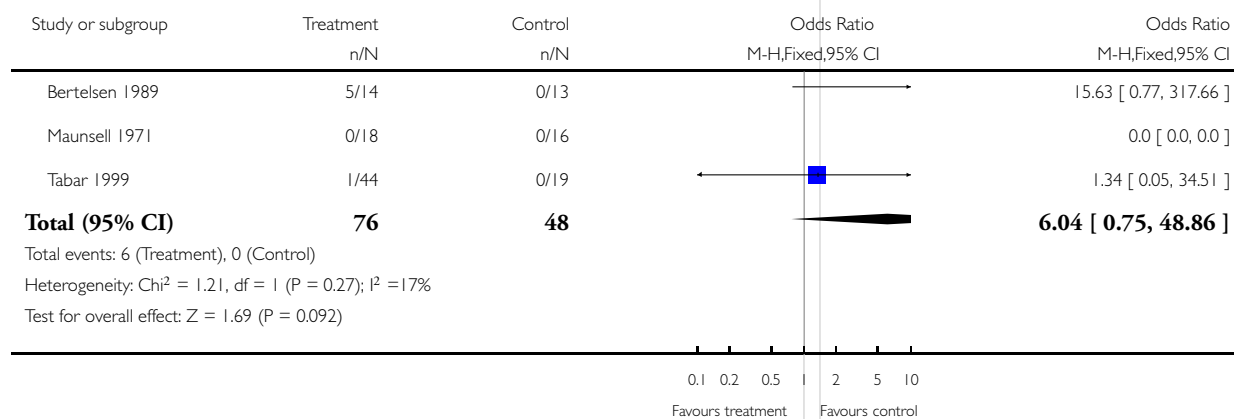


Analysis 4.7. Comparison 4 Allergen immunotherapy versus untreated control, Outcome 7 Systemic reactions.

Review: Injection allergen immunotherapy for asthma

Comparison: 4 Allergen immunotherapy versus untreated control

Outcome: 7 Systemic reactions

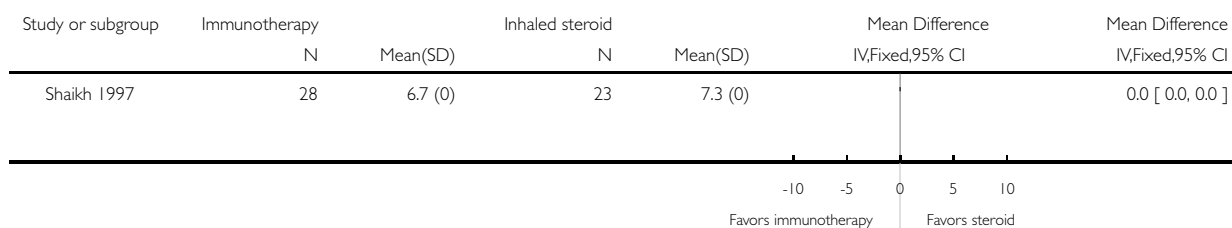


Analysis 5.1. Comparison 5 Allergen immunotherapy versus inhaled steroid, Outcome 1 Asthma symptom scores.

Review: Injection allergen immunotherapy for asthma

Comparison: 5 Allergen immunotherapy versus inhaled steroid

Outcome: 1 Asthma symptom scores

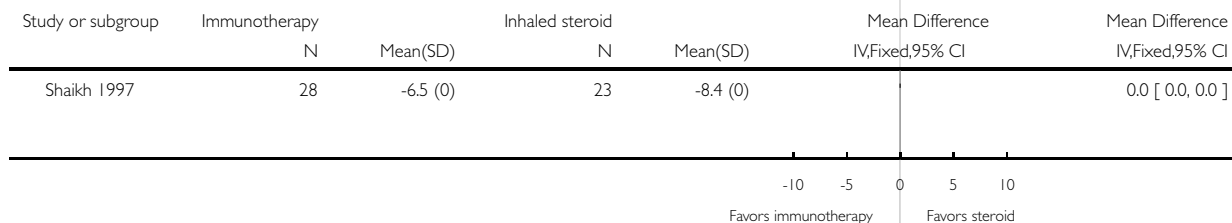


Analysis 5.2. Comparison 5 Allergen immunotherapy versus inhaled steroid, Outcome 2 Deterioration in FEV1.

Review: Injection allergen immunotherapy for asthma

Comparison: 5 Allergen immunotherapy versus inhaled steroid

Outcome: 2 Deterioration in FEV1



Analysis 5.3. Comparison 5 Allergen immunotherapy versus inhaled steroid, Outcome 3 Systemic reactions.

Review: Injection allergen immunotherapy for asthma

Comparison: 5 Allergen immunotherapy versus inhaled steroid

Outcome: 3 Systemic reactions

Study or subgroup	Immunotherapy n/N	Inhaled steroid n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Shaikh 1997	0/28	0/23		0.0 [0.0, 0.0]
Total (95% CI)	28	23		0.0 [0.0, 0.0]
Total events: 0 (Immunotherapy), 0 (Inhaled steroid)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
			0.1 0.2 0.5 2 5 10	
			Favours treatment	Favours control

WHAT'S NEW

Last assessed as up-to-date: 11 April 2009.

Date	Event	Description
18 June 2010	New citation required and conclusions have changed	This review also examined adverse effects of injection immunotherapy. If 16 patients were treated with immunotherapy, one would be expected to develop a local adverse reaction. If nine patients were treated with immunotherapy, one would be expected to develop a systemic reaction (of any severity).
22 October 2008	New search has been performed	Thirteen additional trials included. Data extracted on local and systemic adverse reactions. Meta-analysis undertaken per patient.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 3, 1998

Date	Event	Description
22 August 2008	Amended	Converted to new review format.
29 August 2006	New citation required and conclusions have changed	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.
19 August 2003	New search has been performed	New literature search run.

CONTRIBUTIONS OF AUTHORS

Michael Abramson participated in the selection of studies, obtained papers reporting trials, wrote to authors, extracted data and entered data 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 authors contributed to the protocol and approved the final version of the review.

DECLARATIONS OF INTEREST

RMP and JMW None declared.

MJA received an honorarium from Boehringer Ingelheim for speaking at the Airways 2006 meeting. he was awarded a grant from Reckitt Benckiser for a study of NSAID induced asthma.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Allergens [immunology; *therapeutic use]; Anti-Asthmatic Agents [administration & dosage]; Asthma [immunology; *therapy]; Desensitization, Immunologic [adverse effects; *methods]; Injections, Subcutaneous; Randomized Controlled Trials as Topic

MeSH check words

Humans