Allergen immunotherapy for the prevention of allergy

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Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis

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Abstract

Background: There is a need to establish the effectiveness, cost-effectiveness and safety of allergen immunotherapy (AIT) for the prevention of allergic disease.

Methods: Two reviewers independently screened nine international biomedical databases. Studies were quantitatively synthesized using random-effects meta-analyses.

Results: 32 studies satisfied the inclusion criteria. Overall, meta-analysis found no conclusive evidence that AIT reduced the risk of developing a first allergic disease over the short-term (RR=0.30; 95%CI 0.04 to 2.09) and no randomized controlled evidence was found in relation to its longer-term effects for this outcome. There was however a reduction in the short-term risk of those with allergic rhinitis developing

asthma (RR=0.40; 95%CI 0.29 to 0.54), with this finding being robust to a pre-specified sensitivity analysis. We found inconclusive evidence that this benefit was maintained over the longer-term: RR=0.62; 95%CI 0.31 to 1.23. There was evidence that the risk of new sensitization was reduced over the short-term, but this was not confirmed in the sensitivity analysis: RR=0.72; 95%CI 0.24 to 2.18. There was no clear evidence of any longer-term reduction in the risk of sensitization: RR=0.47; 95%CI 0.08 to 2.77. AIT appeared to have an acceptable side-effect profile.

Conclusions: AIT did not result in a statistically significant reduction in the risk of developing a first allergic disease. There was however evidence of a reduced short-term risk of developing asthma in those with allergic rhinitis, but it is unclear whether this benefit was maintained over the longer-term. We are unable to comment on the cost-effectiveness of AIT.

Keywords: allergen immunotherapy, allergic diseases, allergy, atopy**,** prevention, sensitization.

BACKGROUND

Over recent decades, allergen immunotherapy (AIT) has been investigated and used for the treatment of allergic rhinitis (AR)/rhinoconjunctivitis, asthma and venom allergy. AR and asthma often co-exist and up to 50% of patients with AR have bronchial hyperreactivity(BHR)(1). Children with AR have over three times greater risk of developing asthma later on in life when compared to those without AR(2), especially those with BHR(3). Studies assessing the long-term effectiveness of AIT–especially in those with AR–suggest that AIT might reduce the risk of developing asthma(4;5). AIT may also result in a reduced risk for development of new allergic sensitization(s) suggesting a possible mechanism through which this protection is conferred(6;7;8). As a consequence, interest has broadened from a sole focus on the therapeutic effects of AIT treatment to one that also includes investigation of the potential preventive effects of AIT.

Several populations might benefit from the preventive effects of AIT. Firstly, in healthy individuals, with or without IgE-sensitization, AIT might prevent the development of allergic diseases. Secondly, in individuals with allergic manifestations at any stage, AIT may prevent the development of other allergic conditions such as the development of asthma in those with AR. Finally, AIT may prevent the development of addiitonal sensitization in patients who are already sensitized, as well as the spreading of allergic sensitization at the molecular level.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines for AIT. This systematic review is one of five inter-linked evidence syntheses conducted in order to provide a state-of-the-art synopsis of the current evidence base in relation to evaluating AIT for the treatment of AR, food allergy, venom allergy, allergic asthma and its role in allergy prevention. The focus of this review is on assessing the preventive capacity of AIT. The information derived from this systematic review will help to inform key clinical recommendations and the identification of future research needs. The potential effect of early introduction of different food allergens into the diet of infants will not be addressed in this review, since it will be covered by the planned update of the prevention part of the EAACI Food Allergy and Anaphylaxis Guidelines.

AIMS

We sought to assess the effectiveness, cost-effectiveness and safety of AIT for the prevention of allergic disease and allergic sensitization.

METHODS

Details of the methodology used for this review, including search terms and filters; databases searched; inclusion and exclusion criteria; data extraction and quality appraisal have been previously reported(9). We therefore confine ourselves here to a synopsis of the methods employed.

Inclusion criteria

Patient characteristics

We were interested in studies on subjects of any age with or without allergic sensitization(s) and subjects with or without allergic disease.

Interventions and comparators

We were interested in AIT administered through any route (e.g. subcutaneous (SCIT), sublingual (SLIT)) compared with no intervention, placebo or any active comparator using different allergens (e.g. pollens, house dust mites (HDM)), including modified allergens.

Outcomes

Primary outcomes

The primary outcomes of interest were the development of first allergic disease or of a new allergic disease, in those with a previous allergic condition, assessed over the short-term (i.e. <2 years of completion of AIT) and longer-term (i.e. ≥2 years post-completion of AIT) using well defined diagnostic criteria.

Secondary outcomes

Secondary outcomes were: the development of: new allergic sensitization(s) (or allergic immunresponse(s)); spreading of allergic sensitization(s) from one allergen to other non-related allergen(s); spreading of allergic sensitization(s) at molecular level, from one allergenic molecule to other molecules; development of new oral allergy syndrome (OAS); health economic analyses from the

perspective of the health system/payer; and safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects(10;11).

Study design

We were interested in systematic reviews, randomized controlled trials (RCTs), quasi-experimental studies, health economic analyses, and large case series with a minimum of 300 patients.

Search strategy

Our search strategy was conceptualized to incorporate the four elements shown in Figure 1 (Appendix 1). Additional unpublished work and research in progress was identified through discussion with experts in the field (Appendix 2). No language restrictions were employed.

Quality assessment

Quality assessment was conducted using established tools as detailed in the protocol(9). Assessments were independently carried out on each study by two reviewers. Any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by the third reviewer.

Data analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers, and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer.

A descriptive summary with data tables was produced to summarize the literature. Where possible and appropriate, meta-analysis was undertaken using random-effects meta-analyses using Stata (version 14).

Sensitivity and subgroup analyses, and assessment for publication bias

Sensitivity analyses were undertaken by comparing the summary estimates obtained by excluding studies judged to be at high risk of bias with those judged to be at low or moderate risk of bias.

Subgroup analyses were undertaken to compare:

- Children versus adults
- Route of administration
- Allergens used for AIT.

We were unable to assess publication bias through the creation of funnel plots due to the small number of studies, but were able to use Eggar's test(12).

Registration and reporting of this systematic review

This systematic review is registered with PROSPERO with registration number: CRD42016035380 . It is reported in accordance with the PRISMA guidelines (Appendix 3).

RESULTS

Overview of studies

We identified a total of 10,704 potentially eligible studies after removal of duplicates. Of these, 32 studies reported in 34 publications and one entry into an online trial repository fulfilled the inclusion criteria (Figure 2)(3;6-8;13-43).

In terms of study design, 17 RCTs and 15 controlled-before-after (CBA) studies were identified. The key characteristics and main findings of the RCTs can be found in Table 1 and for the CBAs in Table 2. Nineteen studies included children; eight studies enrolled adults only; and five studies included both child and adult subjects. The numbers of subjects included in these studies varied from 28-691 for the majority (N=30) of studies. However, two CBAs reported on substantially larger populations: 8,396 subjects(7), and 118,754 subjects(16), respectively.

The allergens in the AIT studied were HDM, peach, pollen from grass, birch, ragweed, Japanese cedar or *Parietaria Judaica*, *Cladosporium herbarum*, *Penicillium notatum*, *Aspergillus fumigatus*, *Alternaria alternata*, *Mucor racemosus*, *Quercus alba*, *Cynodon dactylon*, *Ambrosia elatior*, *Plantago lanceolata*, *Phleum pratense/Dactylis glomerata/Lolium perenne* (PDL) grass mix, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, either as single allergens or as multiple allergens. Peach was the only food allergen included in the identified AIT studies. The routes of administration were SCIT, oral and SLIT in the form of tablets and drops.

The overall quality of the identified RCTs varied with five RCTs judged to be at low risk of bias(8;14;19;31;42) six at medium risk(13;18;23;24;35;40) and six at high risk of bias(3;17;22;25;28;37). All CBAs were judged to be at high risk of bias (Tables 3 and 4).

Our main findings are presented according to primary and secondary outcomes of the review.

Primary outcomes: development of new allergic disease

We identified 12 studies reported in a total of 14 publications and an entry into an online trial repository on the effectiveness of AIT for the prevention of development of new allergic disease in previously healthy subjects or in subjects already suffering from one or more allergic disease(3;8;13;15-25). All except the study by Schmitt(16) were RCTs. The Preventive Allergy Treatment (PAT) study reported two updates from the same trial (i.e. three reports in total)(3;20;21).

Three RCTs investigated the preventive effects of AIT in relation to development of the first allergic disease in healthy asymptomatic individuals. They focused on the effect of SLIT on cedar pollinosis(25), eczema, wheeze and food allergy(8), and asthma(13), respectively.

The majority of studies (N=8) focused on the preventive effect of AIT in relation to the development of asthma in patients with established AR(3;14;15;17-24). SCIT was used in four of these RCTs (3;17-21) whilst SLIT through drops or tablets were used in four RCTs(14;15;22-24). In the CBA study using routine healthcare data, patients were stratified according to mode of administration (i.e. SCIT, SLIT drops, SLIT tablets, and combinations of SCIT and SLIT)(16).

Short-term preventive effects of AIT

The short-term preventive effect of AIT was investigated in two RCTs judged to be at low risk of bias(8;19), three RCTs at medium risk of bias(18;23;24), two RCTs at high risk of bias(22;25), and one CBA at high risk of bias(16).

In terms of mode of administration, SCIT was used in two RCTs(18;19), oral (drops or capsules) (8;23) and SLIT (tablets and drops) in the remaining three RCTs(8;23;24). In the CBA, SCIT, SLIT drops and SLIT tablets were administered(16).

RCTs on short-term preventive effects

Prevention of the onset of first allergic disease

The potential effects of oral AIT for the primary prevention of atopic eczema, wheeze, food allergy and sensitizations were investigated in a recent RCT at low risk of bias by Zolkipli.(8) Infants at high risk of atopy based on family history of allergic diseases were randomized to receive either oral HDM AIT (drops) or placebo twice daily for a year. Upon completion of the trial, no significant difference was seen between the active or placebo groups in the risk of developing eczema (P=0.20), wheeze (P=0.40) or food allergy (P=0.26) in these children(8).

A second RCT by Yamanaka, at high risk of bias, looked at primary prevention in asymptomatic adults sensitised to Japanese cedar pollen. They were randomized to SLIT or placebo and in the second year none of the active group had developed pollinosis compared to seven in the placebo group (P=0.0098)(25).

Meta-analysis of data from these two trials showed no overall reduction in the risk of developing a first allergic disease: RR=0.30 (95%CI 0.04 to 2.09) (Figure 3). Sensitivity analysis excluding Yamanaka did not alter this conclusion.

Prevention of onset of asthma in those with established AR

An RCT at low risk of bias by Grembiale, investigating the preventive effects of SCIT administered for a two-year period to subjects with AR, found no significant differences in asthma prevalence at the end of the trial among the AIT group compared to controls (P=0.49)(19).

The RCT at medium risk of bias by Crimi investigated the effect of SCIT for three years on the development of asthma and BHR among 30 non-asthmatic adults with seasonal AR who were mono-sensitized to Parietaria judaica(18). No significant differences in preventive effect were identified across intervention and control group. At the end of the trial, 47% of patients in the placebo group (7/15) had developed asthma compared to 14% (2/14) in the SCIT group (P=0.056)(18).

The RCT by Moller, at medium risk of bias, randomized 30 children with AR to birch pollen to AIT capsules or placebo(23). They found no cases of asthma at the end of the 10-month treatment period in the AIT group and five cases out of 16 in the control group (P-value not given).

The large RCT by Novembre, at medium risk of bias, randomized 113 children, aged 5-14 with hay fever to grass pollen to SLIT drops co-seasonally for three years or conventional pharmacotherapy(24). At the end of the three year trial, the relative risk of developing asthma was 3.8 (95%CI 1.5 to 10.0; P=0.041) in control subjects compared to the SLIT group(24).

In the RCT by Marogna, at high risk of bias, 216 children with AR and intermittent asthma were randomized to SLIT or conventional pharmacotherapy for a period of three years. They found a lower occurrence of asthma in the SLIT group (30/66, 45.4%) compared with the control group (OR=0.04; 95%CI 0.01 to 0.17)(22).

Random effects meta-analysis of these five RCTs plus the short-term effects of the first publication from the PAT trial (20) demonstrated a significant reduction in the risk of developing asthma: RR=0.40 (95%CI 0.29 to 0.54) (Figure 4). There was no evidence of publication bias (P=0.27). This result remained significant after excluding the trial by Marogna and Moller (2002), which were both judged to be at high risk of bias: RR=0.38 (95%CI 0.20 to 0.72). Subgroup analyses showed that AIT was beneficial in those:

- aged <18 (RR=0.40; 95%CI 0.26 to 0.61), but not in those aged ≥18 years (RR=0.28; 95%CI 0.07 to 1.15)
- receiving SLIT (RR=0.33; 95%CI 0.21 to 0.50) and those receiving SCIT (RR=0.49; 95%CI 0.32 to 0.77)
- receiving pollen AIT (RR=0.48; 95%CI 0.33 to 0.71), but not those receiving HDM AIT (RR=0.20; 95%CI 0.01 to 3.94).

CBAs on short-term preventive effects

Prevention of the onset of first allergic disease

We found no relevant studies.

Prevention of onset of asthma in those with established AR

Only one CBA investigated the preventive effects of AIT(16). The study by Schmitt looked at 118,754 patients with AR, but with no comorbid asthma, between 2007-12. Patients were stratified according to exposure to AIT in 2006 and followed to assess incident asthma. The authors reported a preventive effect of AIT on the progression from AR to asthma in patients exposed to AIT through any mode of administration (RR=0.60; 95%CI 0.42 to 0.84; P=0.003) compared to unexposed patients. When subdivided according to route of administration, there was a significant preventive effect of SCIT (RR=0.57; 95%CI 0.38 to 0.84; P=0.005) whereas effects of SLIT drops and combinations of SCIT and SLIT did not reach statistical significance(16).

Long-term preventive effects of AIT

There were four RCTs, one judged to be at low risk(15), one to be medium risk(13) and two assessed to be of high risk of bias(3;17) investigating the longer-term preventive effects of AIT.

RCTs on long-term preventive effects

Prevention of onset of first allergic disease

We found no relevant studies.

Prevention of onset of asthma in those with established atopic dermatitis or AR

An RCT at medium risk of bias explored the effect of 12 months of daily SLIT on prevention of asthma and new sensitizations in children with atopic dermatitis and sensitization to one or more food allergens(13). As no differences in antibody levels between the SLIT and the placebo group could be identified six months into the trial, recruitment was terminated and the trial reduced to pilot study status. After 48 months of follow-up, there were no differences in asthma prevalence between the two groups(13).

A large yet unpublished trial at low risk of bias explored the effect of SLIT tablets on the prevention of asthma in 812 children with grass pollen allergic rhinoconjuctivitis. Based on data available in EudraCT, the trial, undertaken in mono-sensitized children carried out over a five year period with three years of treatment and two years of follow-up study, failed to demonstrate the preventive effect of AIT on the development of asthma (OR=0.9; (95%CI 0.57 to 1.43)(14;15).

A third RCT by Jacobsen, at high risk of bias, explored the preventive effects of SCIT in relation to onset of asthma over a 10-year follow-up period(3;20;21). This trial enrolled 205 children with seasonal AR at baseline who were randomized to a three-year course of SCIT or no intervention. At 10-years follow-up, the adjusted treatment effect showed a significantly higher OR of not having asthma of 4.6 (95%CI 1.5 to 13.7) among subjects treated with SCIT compared to controls.

The RCT by Song, at high risk of bias, looked at patients with AR, allergic to HDM, two years after discontinuation of three years of SCIT compared to standard pharmacotherapy. They found that no (0/51) patients in the SCIT group developed asthma compared to 9/51 in the control group (P-value not given)(17).

Meta-analysis showed no overall evidence of reduction in the long term risk of developing asthma: RR=0.62; (95%CI 0.31 to 1.23) (Figure 5).

Secondary outcomes

We were planning to assess a range of six different secondary outcomes according to the protocol(9). However, we did not find studies related to spreading of allergic sensitization(s) at the molecular level, nor did we identify studies exploring development of new OAS after the end of the intervention or health economic analyses of AIT used for prevention.

In the sections below, findings related to development of new allergic sensitization(s) and safety will be described.

Development of new allergic sensitization

We found 23 studies investigating the effect of AIT on the development of new allergic sensitizations (6-8;17;22;26-43) including one trial reported in two publications(29;30). Nine studies were RCTs (8;17;22;28;31;35;36;40;42) and three of these(8;31;42) were assessed to be at low risk of bias. The remaining studies were all CBAs assessed to be at a high risk of bias. Of these, 12 (six RCTs and six CBAs) provided data on short-term effects and 11 (three RCTs and eight CBAs) provided data on long-term effects.

Short-term preventive effects

RCTs

There were six RCTs investigating this outcome. Three low risk of bias RCTs investigated the short-term effects of AIT on the risk of developing new sensitizations (8;31;42). The remaining three RCTs were moderate(40) or high risk of bias(22;36).

The Zolkipli HDM oral AIT trial among infants at high risk of developing allergic disease found a significant reduction in sensitization to any common allergen in the active group compared to the placebo group (P=0.03) at the end of the trial, but no difference in HDM sensitization between the AIT (5.7%) and control groups (7.8%): risk difference: 2.2%; 95%CI -7.5 to 11.8; P=0.61(8).

Garcia studied adult patients allergic to peach, and found no relevant new sensitizations in the placebo group (n=17) and three new sensitizations to single allergens among the 37 patients in the SLIT group after six months of treatment; the AIT was therefore judged to be ineffective(31).

The RCT by Szépfalusi looked at the preventive effect of SLIT with grass pollen or HDM extract in mono-sensitized children aged 2-5 years; they found no difference in the rate of new sensitizations to HDM between groups after 12 and 24 months of SLIT(42).

Three additional RCTs investigating the short-term effects of AIT, of medium to high risk of bias, found significantly lower incidence of new sensitizations among children and adults with AR. The first, Marogna, found that in the group treated with SLIT for three years, 4/130 developed new sensitizations compared to the controls in whom 23/66 developed new sensitisations (OR=0.06; 95%CI 0.02 to 0.17). They further concluded that the SLIT group was less likely to be polysensitized compared to the SLIT group at year 3: OR=0.33 (95%CI 0.17 to 0.61)(22). A second RCT conducted by Marogna found a significantly lower incidence of new sensitizations among the SLIT group compared to controls(36). At the end of the three-year treatment period, 16/271 (5.9%) in the SLIT group had developed new sensitizations compared to 64/170 (38%) among controls (P<0.001). The third RCT by Pifferi looked at children with asthma monosensitized to HDM treated with SCIT for three years compared to controls(40). At the end of treatment, they found no new sensitizations in the SCIT group (0/15) compared to 5/14 in the control group (P=0.01).

Meta-analysis showed an overall reduction in the risk of allergic sensitization: RR=0.33 (95%CI 0.12 to 0.93) (Figure 6). The Eggar test showed no evidence of publication bias (P=0.60). Sensitivity analyses excluding the two studies by Marogna, at high risk of bias, however failed to confirm this risk reduction: RR=0.72; 95% CI 0.24 to 2.18.

Subgroup analyses lacked precision, but suggested that AIT was:

- likely to be beneficial in those aged <18 (RR=0.32; 95% CI 0.08 to 1.28), but not in those aged ≥18 years (RR=3.32; 95%CI 0.18 to 60.85)

- more likely to be beneficial in those receiving ≥3 years therapy (RR=0.13; 95%CI 0.08 to 0.21) than in those receiving <3 years therapy (RR=0.74; 95%CI 0.13 to 4.21)
- more likely to be beneficial in those receiving SCIT (RR=0.09; 95%CI 0.01 to 1.41) than SLIT (RR=0.38; 95%CI 0.13 to 1.13)
- likely to be beneficial in those receiving HDM (RR=0.33; 95%CI 0.09 to 1.20), but not in those receiving peach (RR=3.32; 95%CI 0.18 to 60.85).

CBAs

The inconsistent evidence found in RCTs was also reflected in the included CBAs with four studies finding a lower occurrence of new sensitizations among AIT exposed subjects compared to unexposed subjects(6;34;38;41), one study reporting higher occurrence in the AIT group compared to controls(26), and three studies reporting no differences between groups (Table 2)(33;38;43).

Long term preventive effects of AIT on the development of new allergic sensitization

RCTs

Three RCTs investigated the preventive long term (i.e. post-intervention) effects of AIT on onset of new sensitizations(17;28;35).

The Limb RCT, at medium risk of bias, explored the effect of SCIT for 24 months with a mixture of up to seven aero-allergens among children with moderate-to-severe asthma recruited between 5-12 years of age and followed into adulthood(35). The mean follow-up time of the 82 subjects was 10.8 years. There was a similar development of new sensitivities among both the SCIT and placebo groups (P=0.13), and the types of new sensitivities were also found to be similar across groups(35).

The high risk of bias RCT conducted by Dominicus followed adult patients with allergic rhinoconjuncitivitis three years after cessation of SCIT for grass pollen and found that the number of subjects who did not develop new sensitizations were higher in the group exposed to SCIT (20/26; 77%) compared to the placebo group (3/13; 23%; P-value not given) (28).

In an RCT at high risk of bias, Song followed patients with AR two years after cessation of SCIT for HDMs compared to patients receiving pharmacotherapy only(17). In the SCIT group, the occurrence of new sensitizations was 2/43 (4.7%) compared to 17/41 (41.5%) among controls (P<0.01).

Meta-analyses of these studies showed no evidence of a reduction in the long-term risk of allergic sensitization: RR=0.47 (95%CI 0.08 to 2.77) (Figure 7). The Eggar test showed no evidence of publication bias (P=0.23)

CBAs

Among the seven CBAs investigating long-term preventive effects of AIT, one SLIT study by Di Rienzo found no significant differences in onset of new sensitizations among intervention and control groups during the 10 years of follow-up(27). Five studies, four SCIT and one SLIT, found reduced onset of new sensitizations among subjects exposed to AIT(7;29;34;37;39).

In contrast to these findings, a SCIT CBA by Gulen found a significantly higher occurrence of new sensitization among children with asthma who were monosensitized to HDM exposed to AIT compared to controls(32).

Cost-effectiveness

We found no studies investigating the cost-effectiveness of AIT for the prevention of allergy.

Safety

We identified a total of seven studies, six SLIT (five of these RCTs and one CBA), and one SCIT RCT, that reported on adverse events(8;15;22;36;37;40;42).

In the SLIT studies, an RCT at low risk of bias investigating effects of SLIT administered as drops to infants reported no differences in numbers or type of adverse reactions between intervention and control groups (8), and a further RCT with low risk of bias among children between 2-5 years of age also reported no relevant side effects in 21,170 single applications(42). The incidence of generalized itching was reported in three SLIT studies assessed to be at high risk of bias: one RCT finding that 4/271 (1.5%) of the children exposed to SLIT experienced one episode of generalized itching that resolved without therapy(36), another RCT reported one incidence of systemic itching after SLIT among 144 children in the SLIT group(22), and a CBA reported that 5/57 adult patients exposed to SLIT had transient oral itching(37). In an RCT, assessed to be at medium risk of bias, the safety of SCIT was assessed among children aged 6-14 years(40). It reported no major local or systemic effects of AIT during three years of treatment among the 15 patients randomized to SCIT(40).

DISCUSSION

Statement of principal findings

We found no consistent evidence from the limited body of RCT evidence that AIT can prevent the first onset of allergic disease over the short-term and no RCTs investigating the long-term preventive effects of AIT. We did however find clear evidence of a substantial reduced risk of developing asthma in those

with pre-existing AR over the short-term, although it is unclear if this benefit was maintained over the longer-term. There was some evidence to indicate that the risk of allergic sensitization can be reduced over the short-term, but this was not confirmed in the pre-specified sensitivity analysis. There was no evidence of a long-term reduction in the risk of allergic sensitization. These risks were however in many cases imprecisely estimated and so need to be interpreted with caution. Overall, the safety profile of AIT appeared acceptable, but we found no data on cost-effectiveness considerations and so are unable to comment on this outcome.

Strengths and limitations

The strengths of this study include the comprehensive literature search that was undertaken and adherence to a pre-published protocol with clearly defined objectives and a detailed pre-specified analysis plan. The main limitations relate to the possibility of not uncovering the total body of evidence on this subject and the challenges of interpreting a heterogeneous body of relatively small-scale trial evidence.

Implications for policy, practice and research

This review has highlighted the inconsistent evidence-base and the lack of robust evidence, in particular for long-term preventive effects of AIT and in terms of detailed subgroup analysis, which impedes our ability to tease out clear implications for healthcare policy and clinical practice. In terms of research, there is a need for high quality well powered RCTs with long-term follow-up and well defined diagnostic criteria to answer the above research questions. Furthermore, there is a need for studies with more robust assessment of adherence to AIT to ascertain the dose received and take into consideration the effect of non-adherence to treatment on preventive effectiveness. Future studies should also include possible effect modification caused by measures taken to alter behaviours and/or environmental triggers of allergy (e.g. exposure to passive smoking in childhood, presence of pets) as this may modify the effect of AIT on onset of allergy.

Conclusions

This systematic review found only limited evidence to support the use of AIT in a preventive capacity. Based on the current evidence, we are unable to conclude that AIT prevents the development of first allergic disease. There appears to be short-term benefit in preventing asthma in those with AR, particularly if AIT is started in childhood with this benefit being seen for SCIT and SLIT. It is however unclear if this benefit is maintained over several years post-discontinuation of AIT or indeed whether AIT is a cost-effective intervention.

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Conflicts of interest: M Kristiansen: support to undertake the systematic review, S Dhami: support to co-ordinate the undertaking of the systematic review; S Halken: in the Grazax Asthma prevention study steering committee (ALK-Abello);M A Calderon: lectures honorarium (ALK, Stallergens, Merck and Allergopharma), consultancy honorarium (ALK, Stallergenes and Hal); M Penagos: payment for presentations and travel support from Stallergenes and ALK-Abello; A Muraro: Acting in consulting capacity for ALK, Meda Pharma, Nestle, Nutricia, Novartis. Grants from: Nestlé: Co-investigator for research protocol, Nutricia: Co-investigator for research protocols; G Du Toit: Equity in the FoodMaestro Application. Grants supporting the LEAP Study paid to Kings College, London. Author of the 2015 NEJM LEAP Study manuscrips that do not primarily deal with immunotherapy; Ignacio J Ansotegui: none;J Kleine Tebbe: Consulting fees from various companies (ALK--Abelló, Allergy Therapeutics, Circassia, LETI, Merck USA); lecture fees (ALK-Abelló, Allergopharma, Bencard, Circassia, HAL, LETI, Lovafarma, Novartis, Stallergenes). Fees for participation in review activities from Biotech Tools, LETI, Lofarma, Merck USA. Financial interest in ALK-Abello; D Larenas-Linnemann: none; S Lau:

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Supporting information

Figure 1: Conceptualization of systematic review

Figure 2: PRISMA flow diagram

Figure 3: Random-effects meta-analysis of effectiveness of AIT in preventing short-term risk of developing first new allergic disease

Figure 4: Random-effects meta-analysis of effectiveness of AIT in short-term prevention of asthma in those with allergic rhinitis

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Figure 1: Conceptualization of systematic review of allergen immunotherapy for the prevention of allergic disease

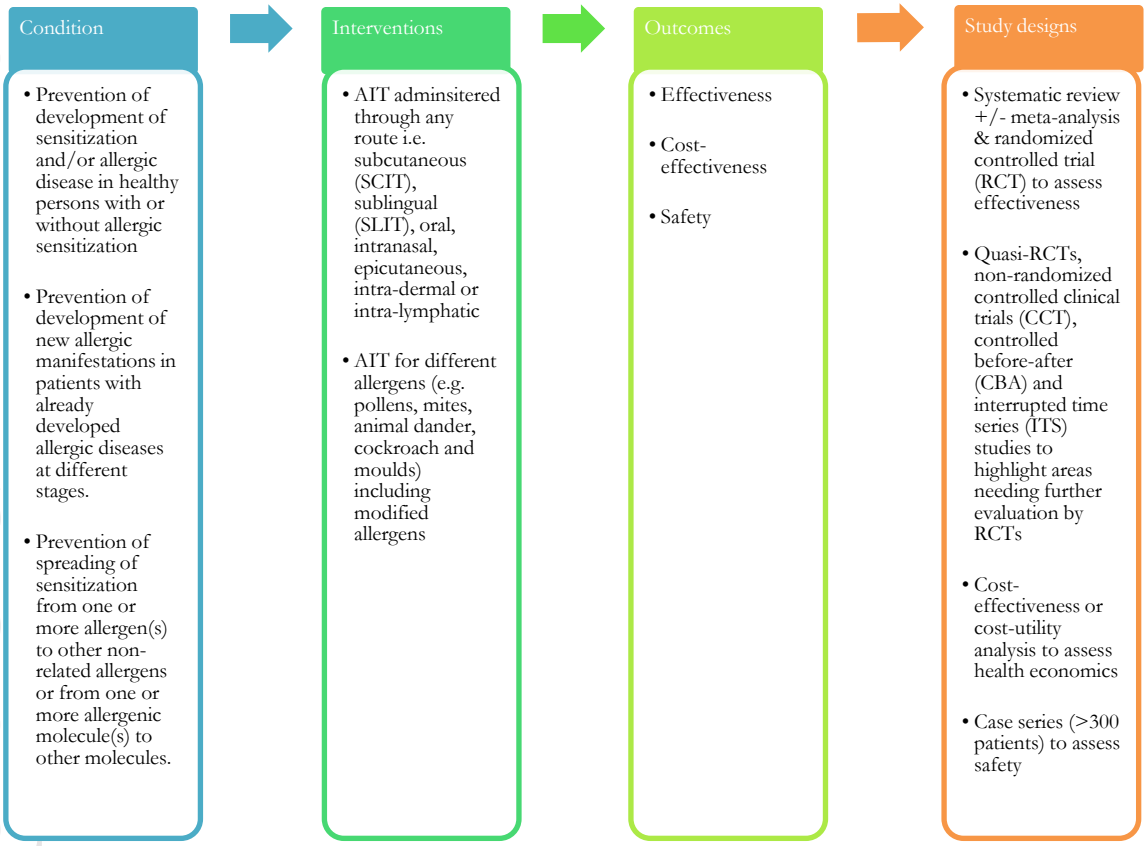


Figure 2: PRISMA flow diagram

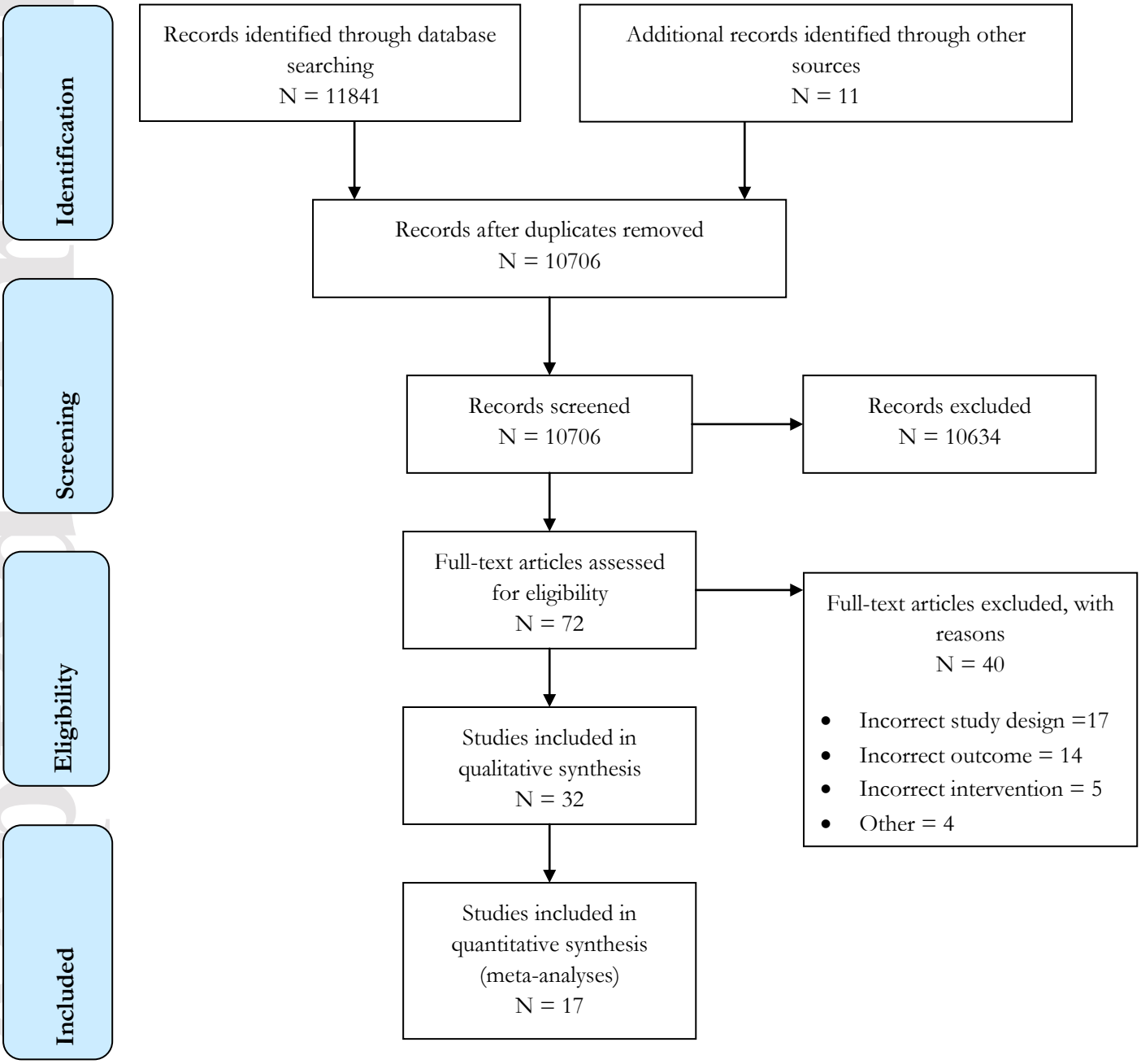
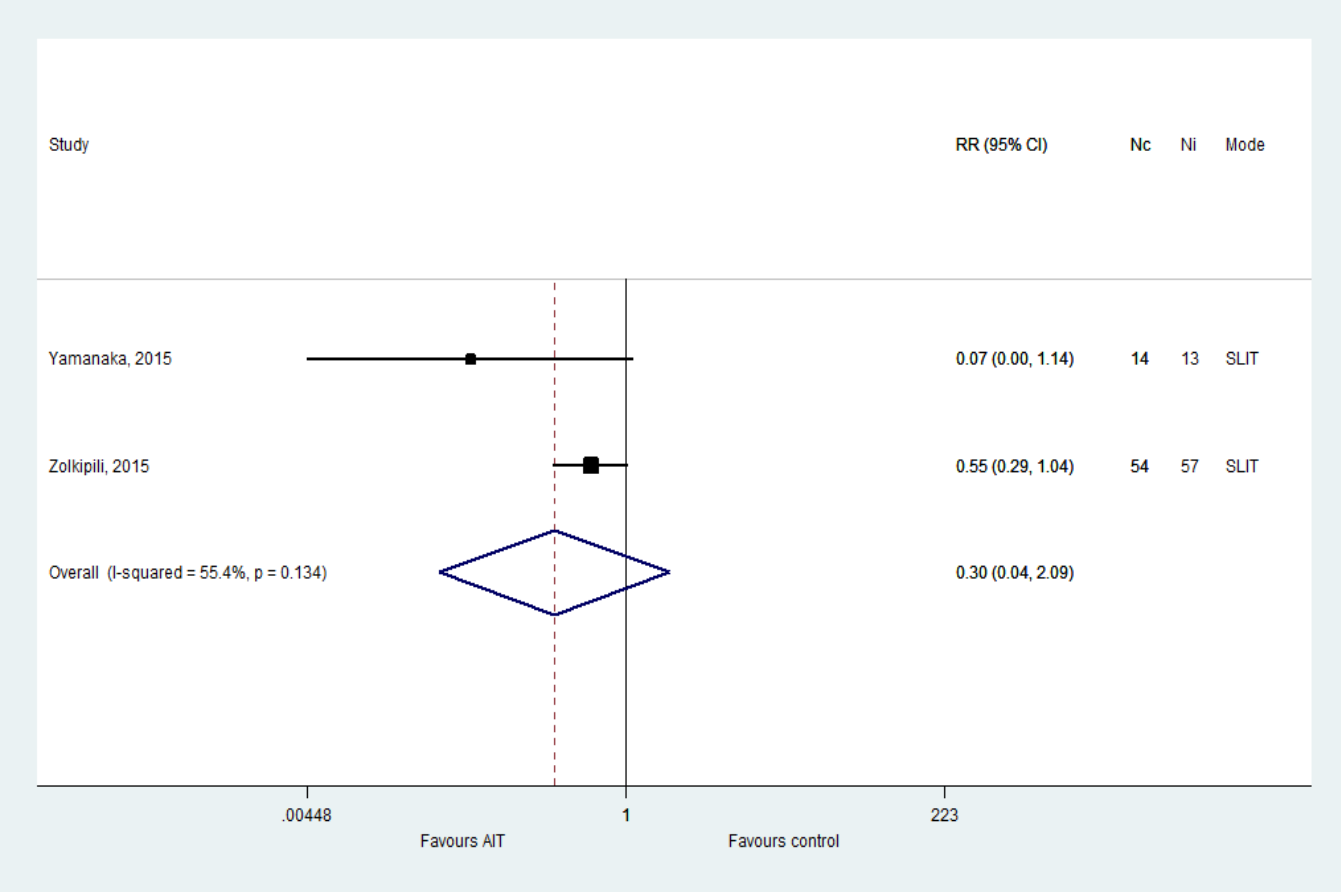
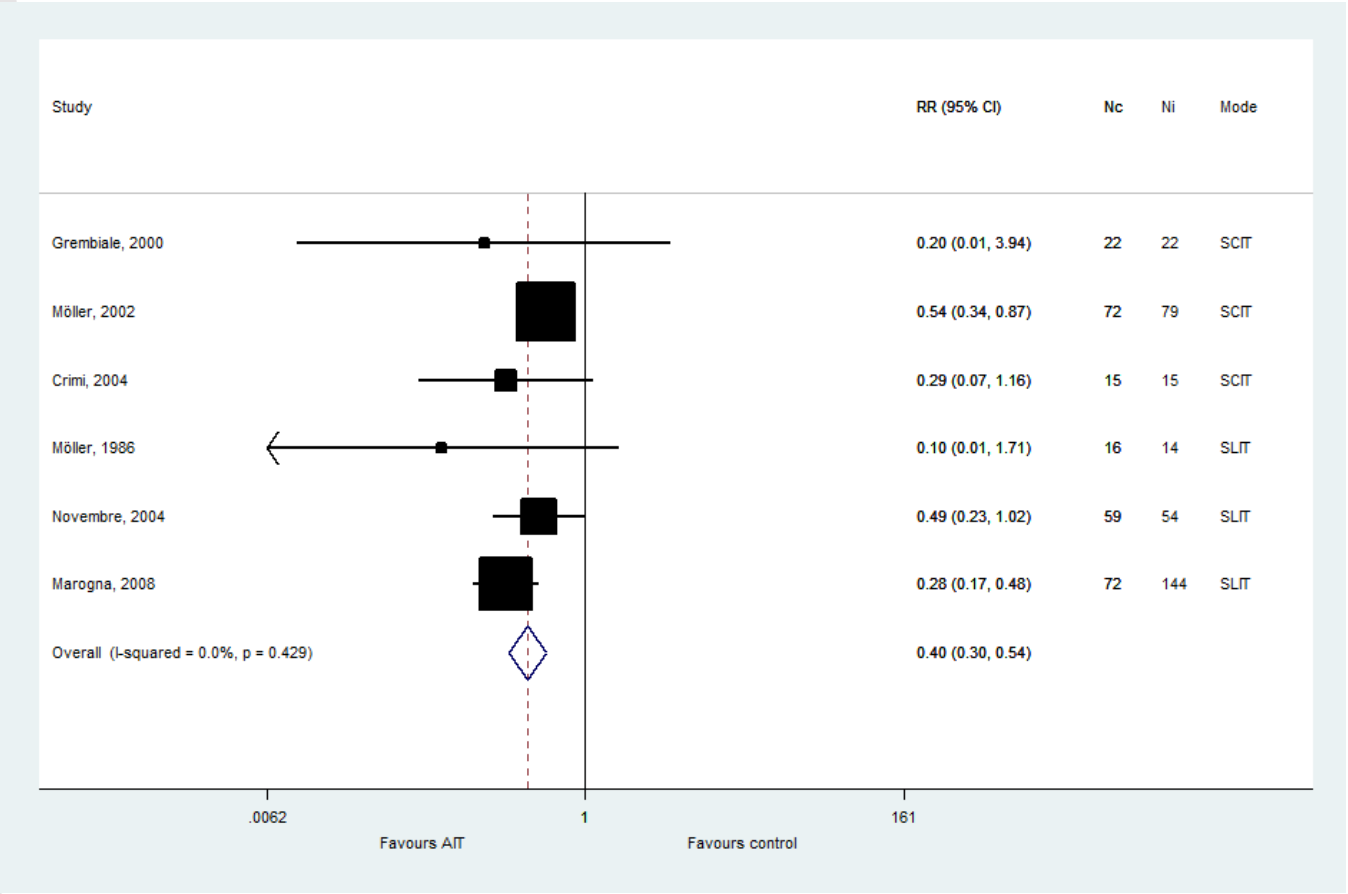


Figure 3: Random-effects meta-analysis of effectiveness of AIT in preventing short-term risk of developing first new allergic disease



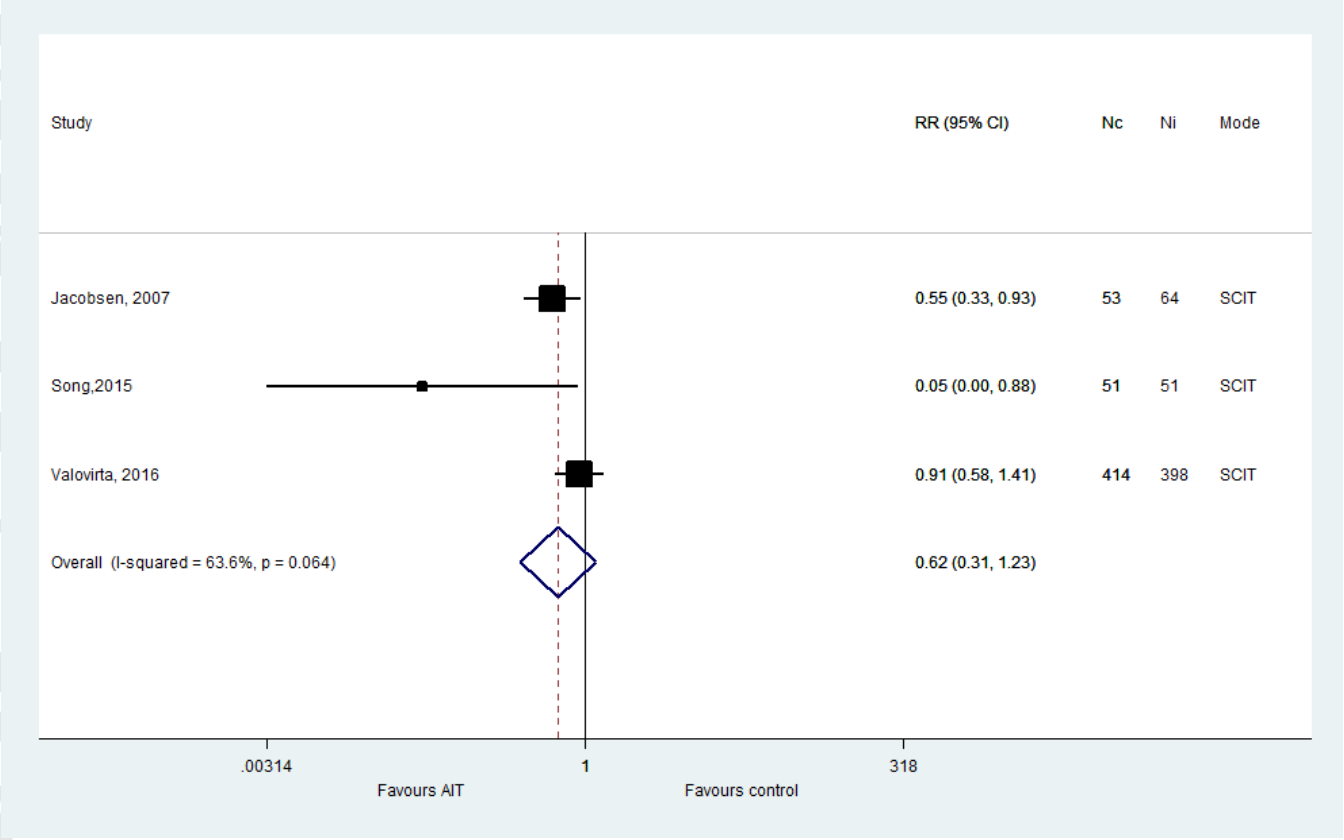
Nc=number in control group; Ni=number in intervention group; mode=route of administration of AIT

Figure 4: Random-effects meta-analysis of effectiveness of AIT in short-term prevention of asthma in those with allergic rhinitis



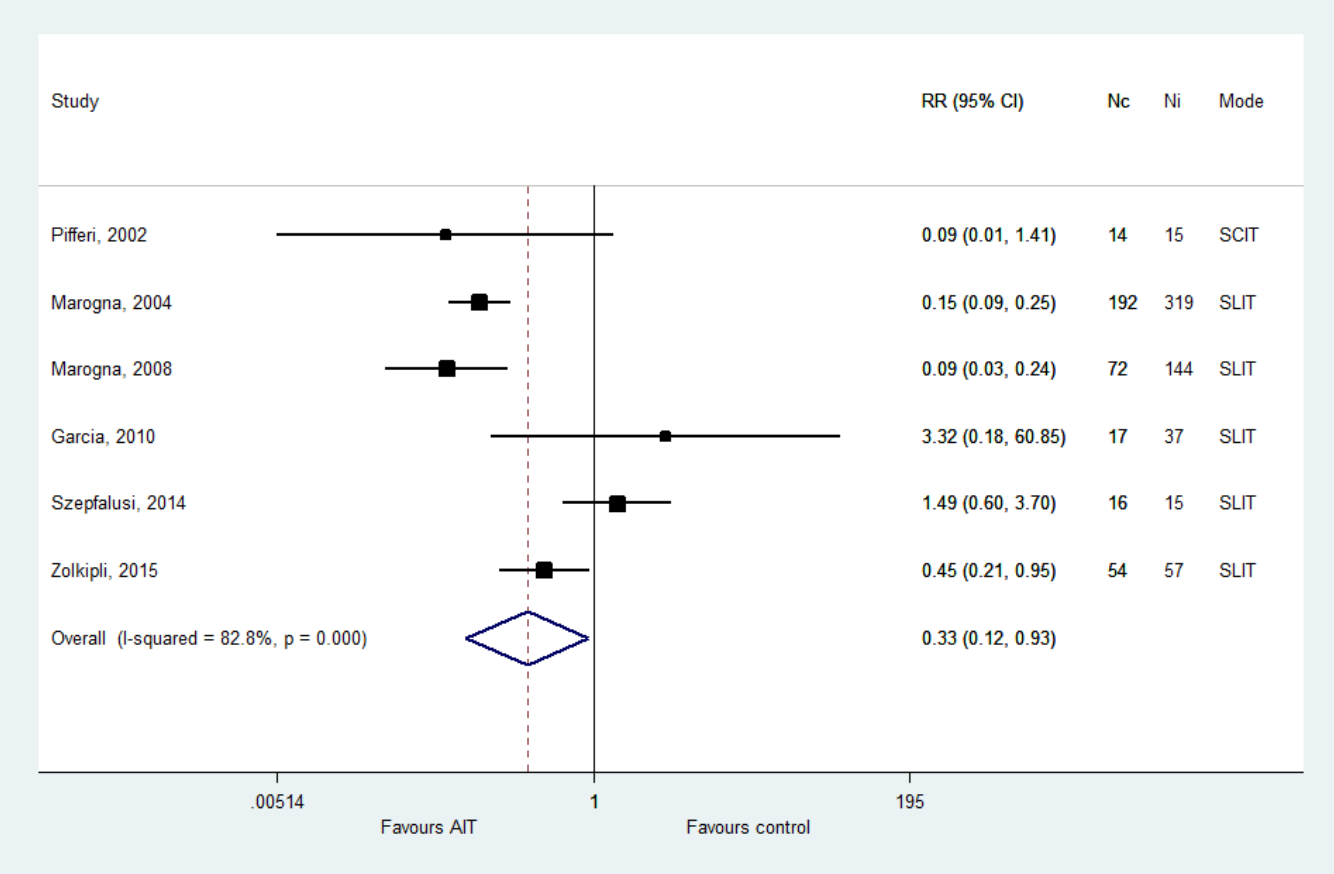
Nc=number in control group; Ni=number in intervention group; mode=route of administration of AIT

Figure 5: Random-effects meta-analysis of effectiveness of AIT in long-term prevention of asthma in those with allergic rhinitis



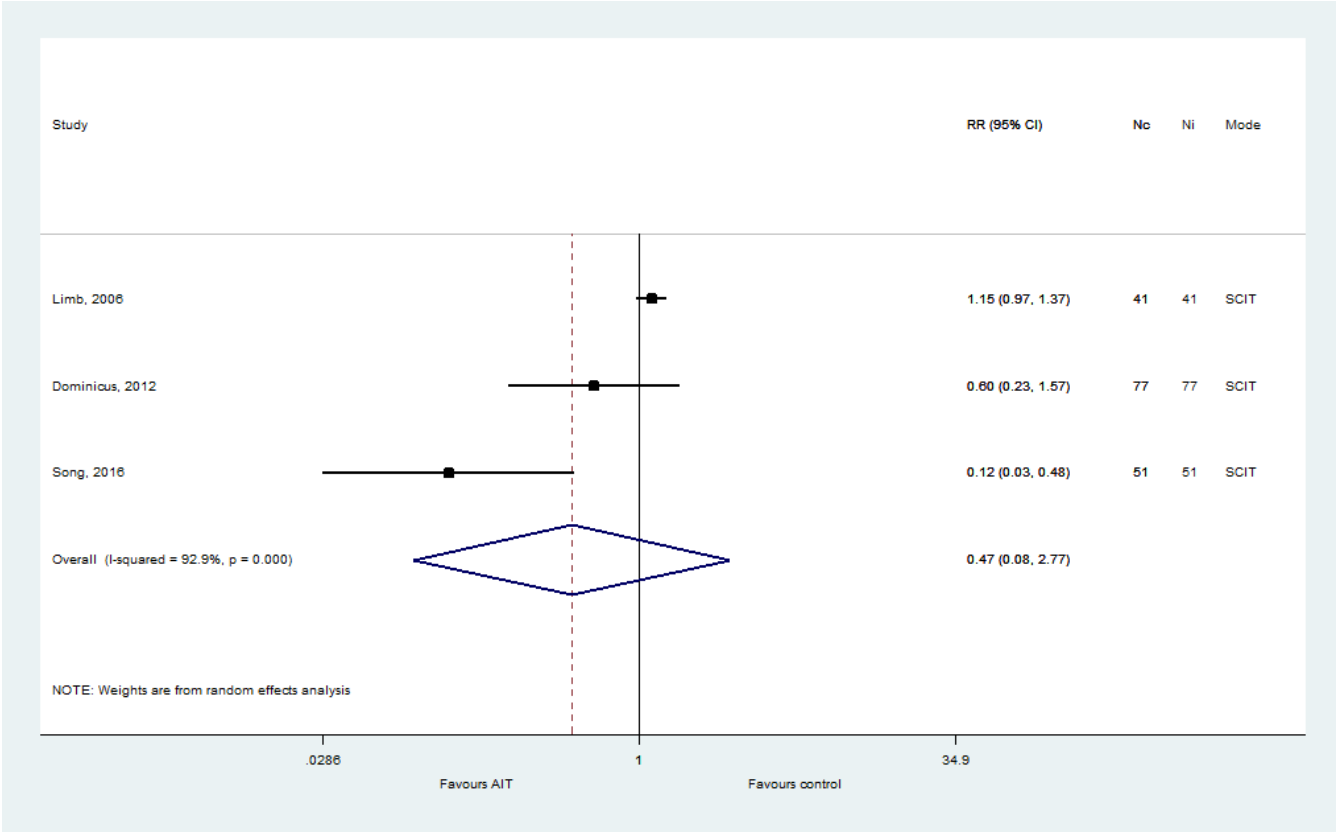
Nc=number in control group;vNi=number in intervention group;vmode=route of administration of AIT

Figure 6: Random-effects meta-analysis of effectiveness of AIT in short-term prevention of allergic sensitization



Nc=number in control group; Ni=number in intervention group; mode=route of administration of AIT

Figure 7: Random-effects meta-analysis of effectiveness of AIT in long-term prevention of allergic sesnitization



Nc=number in control group; Ni=number in intervention group; mode=route of administration of AIT

Table 1: Characteristics and main findings from RCTs

Author/ year/ country	Number of studies(N)/ subjects included(n)/age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls)/ route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Primary outcome: Development of new allergic disease in previously healthy subjects or development of a second allergic disease in subjects already suffering from another allergic disease								
Crimi, 2004, Italy	n=30 15 randomized to receive injections of Parietaria pollen vaccine, 15 received placebo injections Age range: 20-54 yrs.	Non-asthmatic subjects with seasonal rhinitis and monosensitized to Parietaria judaica.	Effect on development of asthma and bronchial hyperresponsiveness.	SCIT vs. placebo Rapid updosing cluster regimen for 7 weeks, followed by monthly injections for 34 months.	Allergic rhinitis. Parietaria pollen.	Medium	A total of 9/29 patients developed asthma symptoms at the end of the study: of these 7 (47%) were in the placebo group, 2(14%) in the SCIT group (P=0.056). No changes seen in bronchial hyper-responsiveness to methacholine or sputum	Authors conclude that Parietaria SCIT appears to prevent natural progression of allergic rhinitis to asthma suggesting that SCIT should be considered earlier in the management of AR, however the results were

							eosinophilia.	not statistically significant.
Grembiale, 2000, Italy	n=44 22 randomized to receive increasing doses of house dust mite allergen extract subcutaneously, 22 received placebo. Age range: 10-38 yrs.	Subjects with a documented history of atopic rhinitis, no reported symptoms compatible with asthma.	Effect on development of asthma and bronchial hyperresponsiveness.	SCIT vs. placebo Increasing doses of allergen extract followed by monthly maintenance treatment.	Allergic rhinitis. House dust mite.	High	None of the SCIT group developed asthma at the end of the 2-yrs treatment period compared to 9% in the placebo group (p=0.49). At end of study, methacholine $PD_{20}FEV_1$ was within normal range of 50% of treated subjects ($p<0.0001$) and it was significantly higher in intervention group compared to placebo group ($p<0.0001$). No changes in methacholine $PD_{20}FEV_1$ in	All subjects had normal lung function test at inclusion and were well matche on methacholine responsiveness at the beginning of the study. All subjects underwent Methacholine challenge after 1 yr and 2 yrs of treatment.

							placebo group throughout the study.	Positive correlation between methacholine $PD_{20}FEV_1$ before SCIT and magnitude of improvement in bronchial reactivity suggest that early intervention is likely to be of greater benefit.
Holt, 2013, USA and Australia	n=50 25 randomized to receive mixture of soluble allergens given daily for 12 months, 25 randomized to placebo.	Children with positive atopic family history; a personal history of atopic dermatitis, and sensitization to one or more food	Effect on development of asthma and sensitizations, safety.	SLIT (drops) vs. placebo. 12 months course of SLIT. Outcome assessment at 48 months.	Atopic dermatitis. House dust mite, cat, timothy grass.	Medium	No difference in asthma prevalence between the two groups (4/25 in SLIT group; 4/25 in placebo group) at 48 months. No	Since there was no differences in antibody titers between active

	Age range: 18-3 months, subsequently reduced to 12 months.	allergen.					significant differences in rates of sensitization.	and placebo group at the 6-month sampling point, recruitment was terminated and the study status changed to pilot study.
Jacobsen, 2007, multi-sited study (Europe) Niggemann, 2006 Möller, 2002	n=205 at baseline, 103 randomized to 3 yrs of subcutaneous SIT, 102 served as open control group. Age range at baseline: 6-14 yrs. Total follow up at 10 yrs: n=147 (79 from intervention group, 68 controls). Follow-up at 5 years (2 years after end of treatment): 183. Follow-up at 3 years (end of treatment): 191.	Children with history of birch and/or grass pollen induced seasonal AR.	Effect on development of asthma and bronchial hyperresponsiveness.	SCIT vs. no intervention 3-year course of SCIT after a 0-season. Up-dosing performed with depot extracts with weekly injections over 15-20 weeks or as rush immonutherapy with aqueous extracts. Maintenance injections every 6 weeks for 3 yrs.	Allergic rhinitis. Grass, birch.	Low	Longitudinal treatment effect shows OR for no-asthma 4.6 (95% CI; 1.5-13.7) in favour of SCIT group after 10 years. At 5 yrs. follow-up, SCIT-group had significantly less asthma compared to controls (OR 2.68, 95% CI; 1.3-	Treatment effect was adjusted for bronchial hyperresponsiven asthma status at baseline, and includes observations at 3, 5 and 10 yrs follow-up.

							5.7). Result after 3 years i.e. at end of treatment show significantly fewer asthma symptoms among actively treated children compared to controls (OR 2.52, P<0.05). No significant differences between SCIT and control group in bronchial responsiveness to methacholine in change from baseline of PC_{20} after 10 years.	Authors conclude that findings from 10 yrs. follow up long-lasting benef to prevention of a
Marogna, 2008, Italy	n=216 144 randomized to SLIT, 72 received drugs only. Age range: 5-17 yrs.	Children with allergic rhinitis with/without intermittent asthma.	Effect on development of asthma, new sensitizations and bronchial hyperreactivity.	SLIT vs. pharmacotherapy. Build-up phase for approx.. 50 days followed by SLIT 3 times a week in the maintenance phase. SLIT administered as	AR, asthma. Mite, grass, birch, Parietaria.	Low	Higher occurence of intermittent and persistent asthma in control group (30/66, 45.4%) compared to the SLIT group (17/130, 13.1%).	Patients were followed up for 3 yrs. Adherence to SLIT was 80% or higher in 73.8% of patients. No

			Safety.	drops. 98 for mites, 41 for grasses, 4 for birch, and 1 for Parietaria			Lower occurence of new sensitizations in SLIT group (4/130) than among controls (23/66) (OR 0.06; 95% CI, 0.02-0.17). Increased rate of polysensitizations in control group compared to SLIT group (OR SLIT vs. control at yr. 3: 0.33; 95% CI, 0.17-0.61). One patient reported systemic itching	difference in dropout frequency between groups. Reduced onset of new sensitizations and intermittent or mild persistent asthma, and decreased bronchial hyperreactivity in children 3 years after treatment.
Möller, 1986, Sweden	n=30 14 randomized to active capsules (birch pollen preparation), 16 to placebo. Age range: 8-16 yrs.	Children with rhinoconjunctivitis.	Effect on development of asthma and safety (part of aim of studying immune responses during OIT).	Oral (capsules) vs. placebo. Treatment with capsules continued for 10 months.	Rhinoconjunctivitis due to birch pollinosis. Birch.	Medium	No development of asthma in oral IT arm compared with 5 patients in the placebo arm.	Similar side effects noted (nausea, abdominal colic, diarrhea) in both

								groups. No systemic reactions seen.
Novembre, 2004, Italy	n=113 54 randomized to SLIT group, 59 randomized to standard symptomatic therapy. Age range: 5-14 yrs.	Children with hay fever limited to grass pollen.	Effect on development of asthma.	SLIT (drops) vs. pharmacotherapy. A 3-year coseasonal protocol was used consisting of build-up and maintenance phases with an extract of mixed grass pollens. SLIT was administered for 4 months a year.	Hay fever due to grass pollen. Mixed grass pollens.	Medium	After first year of treatment, 6 of the SLIT patients had asthma compared to 6 in the control group. After the second year, 7 SLIT patients and 16 controls had asthma (p=.058). After the third year, 8 SLIT patients and 18 controls had asthma (P=.0412). Relative risk of development of asthma after 3 years was 3.8 (95 CI; 1.5-10.0) in control group compared to intervention group.	At entry into the study, no subject reported seasonal asthma with more than 3 episodes per season.

Song, 2014, China	n=102 51 randomized to SCIT, 51 to pharmacotherapy/symptomatic treatment only. Age: >5 yrs.	Patients with AR allergic to house dust mites.	Effect on onset of asthma and development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT for 3 yrs. with initial updosing followed by maintenance once every 6 weeks for 3 yrs.	AR, asthma. House dust mite.	Low	In the SCIT group no patients developed asthma and few new sensitizations occurred (2/43, [4.7%]). In the control group, 9/41 (22%) developed asthma and 17/41 (41.5%) new sensitizations. Differences were statistically significant ($p<0.01$).	Follow-up 2 yrs. after discontinuation of SCIT. Authors conclude that early application of SCIT can prevent the development of asthma.
Valovirta, multinational (11 European countries)	n=812 after seven months of screening Age range: 5-12 yrs.	Patients with grass pollen-induced AR, without asthma, and no overlapping symptomatic allergies	Time to onset of asthma	SLIT vs. placebo once daily for 3 years, followed by a blinded observational period of 2 years. SQ-standardized grass	Grass.	High	In SLIT group of 398 patients 34 developed asthma and in the control group of 414, 39 developed asthma defined by strict diagnostic criteria including beta-2-	Not yet published but data available at EudraCT

				allergy immunotherapy tablet			reversibilitest, no difference demonstrated between groups P=0.67. At the end of the five year trial period the number of subjects with asthma symptoms or asthma medication usage in the SLIT group was less than in the placebo group (OR 0.66; P 0.036; 95%CI [0.45;0.97])	
Yamanaka, 2015, Japan	n=29 (27 due to withdrawal during the course of the study). 13 were randomized to SLIT group, 14 to placebo group. Age range: 18-52 yrs.	Asymptomatic subjects sensitized to Japanese cedar pollen.	Effect on development of cedar pollinosis.	SLIT vs. placebo. SLIT group received graded extracts of standardized Japanese cedar pollen followed by maintenance therapy.	Sensitized to pollen. Japanese cedar pollen.	Low	No significant difference in development of symptoms of pollionosis between groups after first year of treatment (4 in SLIT/1 in placebo group). In the second year, 7 of the placebo group and none of the SLIT group developed	Significant increase in IL-10 producing T cells and B cells in SLIT group, Significant decrease in IL-10 producing

							symptoms. Ratio of development of pollinosis in the SLIT group was significantly lower than in the placebo group in the second year of the trial (p=.0098, Fisher's exact test).	monocytes in placebo group.
Zolkipli, 2015, United Kingdom	n=111 57 assigned to house dust mite oral IT, 54 assigned to placebo. Age range: less than 1 yr.	Infants at high risk of atopy (2 or more first-degree family members with allergic diseases (asthma, AR, eczema, or food allergy) but negative skin prick test responses to common allergens at randomization.	Effect on development of eczema, wheeze, and food allergy; development of sensitizations and, and adverse events/safety.	Oral AIT (drops) vs. placebo. House dust mite extract and placebo solution were administered orally twice daily for 12 months.	High risk. House dust mite.	High	No effect on house dust mite sensitization, eczema, wheeze, and food allergy. Significant reduction (P=.03) in sensitization to any common allergen (16%; 95% CI 1.7-30.4%) in the active group (5[9.4%]) compared to the placebo group (13[25.5%]) after 12 months of	Children were assessed every 3 months. Differences in morbidity and pe ownership across groups did not influence direction or size

							treatment. Treatment was well tolerated with no differences in numbers or nature of adverse events between groups.	of estimated differences in outcomes. .
Secondary outcome: Development of new allergic sensitization(s) (or allergic immunresponse(s)) after end of intervention								
Dominicus, 2012, Germany	n=154 77 patients were randomized to receive SCIT with grass pollen, 77 were assigned to placebo group. Follow-up included 26 patients from ex-SCIT group and 13 control patients. Age range:18-60 years.	Adult patients allergic to grass pollen with rhinoconjunctivitis with or without asthma.	Effect on development of new sensitizations.	SCIT vs. placebo. Patients received weekly pre-seasonal subcutaneous immunotherapy with either grass pollen extract or placebo for 2 yrs. Both groups received active treatment in the third treatment yr.	Grass pollen allergy. Grass pollen.	Low	Number of patients who did not develop new sensitizations during the 3 year's follow-up after cessation of SCIT was higher in Ex-SCIT group (20 patients, 77%) compared to control group (3 patients, 23%).	This prospective follow-up study ended 3 yrs after cessation of SCIT Authors conclude that SCIT has long-term effects in reducing onset of new

								sensitizations.
García, 2010, Spain	n=56 37 patients were randomized to the SLIT group, 17 were in the placebo group. Age range: 18-65 yrs.	Peach-allergic patients.	Effect on development of new sensitizations.	SLIT vs. placebo. Treatment with standardized peach extract or placebo continued for 6 months.	Peach allergy. Peach.	High	A total of 3 patients in the SLIT group developed clinically irrelevant sensitizations. No new sensitizations in the placebo group.	New sensitization were to single allergens and rated as of scarce magnitude and no clinical relevance.
Limb, 2006, USA	n=82 41 were randomized to immunotherapy, 41 to placebo. Subjects were enrolled in childhood (age at inclusion 5-12 yrs) and followed up in adulthood (age at follow-up 17-31yrs).	Children with moderate-to-severe asthma.	Effect on development of new sensitizations	SCIT vs. placebo. SCIT was given with a mixture of up to seven aeroallergen extracts and maintenance injections continued every 2 weeks for 24 months, and every 3 weeks until debriefing.	Asthma. Broad-spectrum aeroallergens.	Medium	Similar acquisition of new skin test sensitivities from time of randomization into original childhood trial to debriefing (15 vs. 20%; p=0.28) and to adult follow-up (30 vs. 31%; p=0.75) among both SCIT and placebo group. 23/41 (56%) in the SCIT group vs. 31/41 (76%)	The 82 evaluated patients did not differ from the remaining 39 patients from the original trial with regard to age,ethnicity, gender, number of positive

							in the placebo group acquired one or more new sensitivity between randomization and debriefing (p=0.19). From debriefing to adult follow-up, 38/40 (95%) in the SCIT group vs. 33/39 (85%) in the placebo group acquired at least one more new sensitivity.	skin tests or treatment-designated allergens at randomization, or total serum IgE (all p-values >0.1) Long-term evaluation of broad-spectrum IT (mean follow-up 10.8 yrs). Types of new ensitivities

								were similar between treatment and placebo groups.
Marogna, 2004, Italy	n=511 319 patients were randomized to SLIT, 192 patients to control group. Mean age SLIT group = 22.8 yrs Mean age control group = 21.5 yrs.	Patients with allergic rhinitis with/without intermittent asthma.	Effect on development of new sensitizations, safety/adverse events.	SLIT vs. pharmacotherapy. Patients were evaluated in an observation period of 1 yr, followed by SLIT prescribed for relevant allergens in a build-up and maintenance phase for approximately 3 yrs.	AR, asthma. Mites, grass, birch, parietaria, mugworth.	Low	Significantly lower incidence of new sensitizations in SLIT group (16/271 [5.9%]) compared to pharmacotherapy group (64/170 [38%]) at the end of the 3-yrs. treatment period ($p < 0.0001$). Four of 271 patients (1.5%) reported one episode of generalized itching within 30 min. of taking the dose, all appeared in maintenance phase and self-resolved without therapy in <2	Adherence to SLIT measured by volume of remaining extract. During the 3yrs of study,70 patients dropped out: 48 (15%) in SLIT group, 22 (12%) in control

							hours. Five dropouts in SLIT group due to adverse events (oral itching, asthma, abdominal pain).	group. No significant overall difference between the two groups.
Pifferi, 2002, Italy	n=29 15 patients were randomized to SCIT group, 14 to control group. Age range: 6-14 yrs.	Children with asthma and monosensitizedto house dust mite.	Effect on development of new sensitizations, bronchial hyperreactivity and safety.	SCIT vs. Pharmacotherapy (?) After a 1-yr. run-in period, SCIT were administered through gradually increasing doses until maximum tolerated dose. SCIT continued for 3 yrs.	Asthma, AR. House dust mite.	Medium	SCIT group showed significant decrease in non-specific bronchial hyperreactivity. The ratio of incidence of "non-improvement" in bronchial reactivity in the SCIT group compared to controls was 0.3; 95%CI 0.11-0.87). No new sensitivity occured in SCIT group whilst	All SCIT patients reached the suggested dose for maintenance phase. Four dropouts in control group. Treatment and control groups were matched for age, asthma severity, respiratory function and bronchial

							5/10 in the control group developed new sensitizations (P=0.01). No major local or systemic side-effects reported during the study.	hyperreactivity.
Szépfalusi, 2015, Austria	n=31 15 randomized to SLIT group with either grass pollen or house dust mite extract according to the individual sensitization profile), 16 randomized to placebo group. Age range: 2-5 yrs.	Healthy persons with allergic sensitizations but no clinical disease.	Effect on development of new sensitizations. Safety.	SLIT vs. placebo. After dose-up phase, therapy continued for 2 yrs.	Sensitization to pollen and/or mites. House dust mite, grass.	High	Preventive application of SLIT in young children was safe (no relevant side effects in 21.170 single applications). No difference in rate of new sensitizations in SLIT group compared to placebo group after 12 and 24 months of treatment. Verum-treated patients had a significant up-regulation of	Children were mono/ oligoclonally sensitized, clinically asymptomatic. Rate of new Sensitizations increased significantly over time in both

							allergen-specific IgG ($p<0.05$) and IL10-dependent inhibition was observed in vitro in treatment group but not in placebo group.	groups.

Table 2: Characteristics and main findings from CBAs

Author/ year/ country	Number of studies(N)/ subjects included(n) /age	Participants: Disease status	Specified primary outcome, and secondary outcomes of interest	Comparators (intervention/controls) / route of administration	Type of allergy and allergens used for AIT	Quality	Main outcome/key findings	Comment
Primary outcome:Development of new allergic disease in previously healthy subjects or development of a second allergic disease in subjects already suffering from another allergic disease								
Schmitt, 2015, Germany	n=118,754 stratified into one group exposed to AIT in 2006 (n=2,431) or an unexposed group (n=116,323) All ages included.	Patients with AR but without comorbid asthma. AR at least two ICD-10 codes for AR.	Effect on onset of asthma.	AIT stratified as SCIT, SLIT drops, SLIT tablets, and combinations.	Asthma. All types of allergens used for AIT included.	Low	Risk of incident asthma was significantly lower in patients exposed to AIT (RR, 0.60;95% CI, 0.42-0.84) compared to patients not exposed to AIT in 2006. Sensitivity analyses found significant preventive effects of SCIT (RR, 0.57; 95% CI, 0.38-0.84) and AIT including native allergens (RR, 0.22; 95% CI, 0.02-0.68) but no statistical	Consecutive cohort of patients based on routine health care data from German National Health Insurance beneficiaries. Exposed and unexposed groups were observed for incident

							significance for SLIT drops, or combinations of SCIT and SLIT. AIT for 3 yrs. tended to have stronger preventive effects than AIT for a shorter duration (RR, 0.62; 95% CI, 0.39-0.98 vs. 0.57; 95% CI, 0.34-0.94). No effect modification by age and sex was observed.	asthma from 2007-12. Authors conclude that AIT effectively prevents asthma in patients with AR in a real-world setting.
Secondary outcome: Development of new allergic sensitization(s) (or allergic immunresponse(s)) after end of intervention								
Asero, 2004, Italy	n=691 284 patients received SCIT as part of routine outpatient care, 407 not undertaking SCIT served as controls. Age range: >12 years	Patients monosensitized to airborne allergens (grass, pellitory, ragweed, birch or house dust mite) first seen between Jan 1st 1989-Dec 31st 1998 and reevaluated no less than 2 years after the first visit/after	Effect on development of new sensitizations	SCIT/pharmacotherapy. SCIT was administered following a perennial schedule. Patients enrolled in SCIT treatment according to own choice.	Sensitization to pollen. Grass, pellitory, birch, ragweed, house dust mite.	Low	Significantly higher prevalence of new sensitizations to ragweed and/or birch pollen in subjects receiving SCIT (132/284; 46%) than among controls (95/407; 23%) ($p<0.001$).	No preventive effect against denovo sensitizations birch and ragweed polle

		the end of SCIT.		Weekly doses given during build-up phase followed by maintenance doses.			Denovo sensitizations to other airborne allergens (besides ragweed and birch pollen) were rare and did not show any difference between SCIT and control groups.	in adult monosensitize patients.
Des Roches, 1997, France	n=44 22 patients received SCIT, 22 age-matched patients served as controls. Age range: 2-6 yrs.	Children with asthma and monosensitizedto house dust mite.	Effect on development of new sensitizations	SCIT vs. pharmacotherapy. Rush immunotherapy and maintenance injections using a standardized Dermatophagoides pteronyssinus extract. Follow-up on an annual basis for 3 yrs.	Asthmatic children sensitized to house dust mites. Dermatophagoid es pteronyssinus.	Low	Ten of 22 children in SCIT group (45%) did not develop new sensitizations compared to none of the 22 children in the control group. Occurence of new sensitizations was thus significantly less in SCIT group compared to controls ($p<0.001$).	The findings suggest that SCIT in asthmatic children monosensitize to house dust mites alters th natural course preventing the

								development new sensitizations.
Di Rienzo, 2003, Italy	n=60 35 accepted treatment with SLIT, 25 received only medication. Age range: 3-17, mean age 8.5 yrs.	Children with AR and/or mild to moderate asthma due to house dust mites.	Effect on development of new sensitizations.	SLIT vs. pharmacotherapy. SLIT was administered continuously for 4-5 yrs. according to guidelines.	AR with/without asthma. 28 children were monosensitized to mites alone, the remaining patients had concomitant sensitizations. House dust mite.	Low	No significant difference in onset of new sensitizations in the two groups. Only 3/35 patients in SLIT group and 2/25 patients in control group developed new sensitizations during the 10 yrs. period.	Patients were evaluated at baseline, end SLIT and 4-5 yrs. after SLIT discontinuatio
Eng, 2006, Switzerland	n=28 included in the original study and self-assigned to receive either SCIT (n=14) or standardized pharmacotherapy (n=14) for 3 yrs.. At 6 yrs. follow-up after	Children with a history of severe grass pollen AR for at least 2 yrs. with/without asthma but with immunoglobulin (Ig)E-mediated sensitivity to seasonal allergens only (grass pollen with/without tree	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. Grass pollen SCIT was administered preseasonally for 3 years.	AR, asthma. Grass.	Low	Six yrs. after discontinuation of SCIT, a significantly lower number of SCIT patients had developed new sensitizations (8/13) compared to controls (10/10) ($p<0.02$).	The two study groups were matched for gender, age, prevalenc of seasonal asthma, and

	discontinuation of SCIT, 13 SCIT patients and 10 controls were included. At 12 yrs. of follow-up, 12 SCIT patients and 10 controls were included. Age range at inclusion: 5-16 yrs.	pollen).					There was a significantly lower occurence of new sensitizations in SCIT group compared to controls at 12-yrs follow-up (58% vs. 100%; p<0.05).	wheal size at study enrollme This prospecti follow-up stud finds a reduction in onset of new sensitizations yrs after discontinuatio of SCIT. The reduction is sustained a 12 yrs. of follow-up.
Gulen, 2007, Turkey	n=129 patients. 70 patients accepted SCIT, 59 were treated with	Children with asthma monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT was administered	Asthma. House dust mite.	Low	At the end of the 6-yrs. study period, a total of 41 (33%) of patients had developed new	The study fou no association between famil

	medication only. Age range: 6-10 yrs.			for four yrs.			sensitizations. Significantly higher prevalence of new sensitizations in SCIT group (31/68; 45.5%) compared to controls (10/55; 18.1%) (OR 3.77, 95% CI, 1.52-9.5, p=0.001).	history of atop and developm of new allergic sensitizations.
Harmanci, 2010, Turkey	n=122 patients. 62 patients accepted SCIT, remaining 60 patients were treated with medication only. Age range: 8-18 yrs.	Children with intermittent asthma with/without AR, monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT was administered for four yrs.	Asthmawith/without AR. House dust mite.	Low	No significant difference in development of new sensitizations after the 4-yrs. study period. A total of 36/53 (67.9%) patients in SCIT group had no new sensitizations compared to 38/52 (73.0%) in control group (P=0.141).	Authors concl that SCIT may not prevent onset of new sensitizations asthmatic children who monosensitize to house dust mites.

Inal, 2007, Turkey	n=147 45 patients underwent SCIT with absorbed extracts, 40 patients underwent SCIT with aqueous extracts, 62 patients were controls receiving only pharmacologic treatment. Age range: 6-16 yrs.	Children with rhinitis and/or asthma monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. SCIT treatment continued for 5 yrs. Follow-up at end of treatment. SCIT group was subdivided into absorbed extracts and aqueous extracts because the latter was used more commonly than absorbed extracts at the beginning of the study.	AR/asthma. House dust mite.	Low	At 5 year follow-up, a total of 64/85 (75.3%) in the SCIT group showed no new sensitizations compared to 29/62 children (46.7%) in the control group (P=.002).	SCIT was recommended to all patients. Those who rejected SCIT were included controls. Children developing ne sensitizations had higher ato scores compar to those who not develop n sensitizations. The same pattern was observed in th

								SCIT group but this was n statistically significant.
Marogna, 2010, Italy	n=78 57 in SLIT group subdivided into different length of SLIT (3 yrs: 19; 4 yrs: 21; 5 yrs:17) 21 patients in control group. Adult patients (mean age of 22.2 +/- 5.2 yrs. at inclusion).	Patients with allergic rhinitis with/without asthma lasting for at least 2 yrs and monosensitized to house dust mites.	Effect on development of new sensitizations and bronchial hyperreactivity. Safety.	SLIT for 3, 4 or 5 yrs. vs. pharmacotherapy. Build-up phase for approx.. 50 days followed by SLIT 3 times a week in the maintenance phase.	AR, asthma, sensitized to house dust mites. House dust mite.	Low	New sensitizations occurred in all control subjects over 15 yrs. Among the SLIT group, 3/14 (21.4%) in the SLIT3 group, 2/16 (12.5%) in the SLIT4 group, and 2/17 (11.7%) in the SLIT5 group developed new sensitizations. Difference in occurence of new sensitizations	The study-des was prospecti open, controll 4-parallel-grou partially randomized. I patients refus SLIT,they wer assigned to th control group. Assignment t groups was

							across SLIT and control group became significant at year 6 (P=.03). 5 patients had transient oral itching during build-up phase, 2 patients reported 1 episode of generalized itching on maintenance. All adverse events occurred 30 min. after dosing and spontaneously disappeared.	made yearly. Length of foll -up was 15 yrs All dropouts were due to protocol deviations. Adherence to SLIT greater than 80% measured by volume of extract in returned vials.
Ohashi[a],	n=159	Patients	Effect on	IT (unknown route)	Monosensitized to	Unclear	Four years after	Patients

2009, Japan	80 in mite immunotherapy group, 27 in house dust mite IT group, 52 in pharmacotherapy group. Age: >20 yrs.	monosensitized to house dust mites.	development of new sensitizations	for 4 yrs using a) D. farinae extracts (mite immunotherapy group) or b) house dust mite mixtures vs. pharmacotherapy.	mites. House dust mite.		enrollment, the incidence of new sensitizations to pollen was 28.0% in the pharmacotherapy group, 6.3% in the mite IT group, and 22.2% in the house dust mite IT group. Significantly lower incidence of new sensitizations in mite IT group compared to control group (p=0.0008), but no significant differences between HD IT group and controls (p=0.5999).	were divided into groups according to their own choice.
Ohashi[b], 2009, Japan	n=176, 194 in pollen immunotherapy group, 72 in pharmacotherapy group. Age: adult.	Patients monosensitized to Japanese cedar pollen.	Effect on development of new sensitizations	IT (unknown route) for 4 yrs. vs. pharmacotherapy	Monosensitized to Japanese cedar pollen. Japanese cedar pollen.	Unclear	After four years of follow-up, there were no significant differences in new sensitizations (to other types of pollen) between groups.	Patients were divided into groups according to their own choice.

								Authors conclude that new sensitizations in allergic patients can be inhibited by mite immunotherapy but not by immunotherapy using other kinds of allergen extracts.
Pajno, 2001, Italy	n=134 enrolled 75 patients in SCIT group, 63 children in control group according to own choice. Age range: 5-8 yrs.	Children with intermittent asthma with/without rhinitis monosensitized to house dust mite.	Effect on development of new sensitizations.	SCIT vs. pharmcotherapy. SCIT with mite mix was administered during the first three years in the intervention group. After induction phase, maintenance dose was administered once a month for 3 years.	AR, asthma. House dust mite.	Low	At the end of the 6-year study period, 52/69 (75.4%) patients in the SCIT group showed no new sensitizations compared to 18/54 (33.3%) in the control group ($p<0.0002$). Authors conclude that SCIT may prevent onset of new sensitizations in children with respiratory	Allocation to treatment vs. control arm dependent upon parent's willingness to accept SCIT. All patients had intermittent asthma at enrolment. All patient's

							symptoms monosensitized to house dust mite.	parents were instructed to decrease exposure to mites (e.g. by frequent vacuuming, washing sheets at least once a week, removal of plants/soft toys from bedroom). Both groups were followed for a total of 6 yrs.
Purello-D'Ambrosio, 2001, Italy	n=8396 Group A included 7182 patients given SCIT for 4 yrs. Followed by drugs for at least 3 yrs. Group B included 1214 patients treated only with drugs for at least 7 yrs.	Patients with allergic rhinitis and/or asthma monosensitized to respiratory allergens.	Effect on development of new sensitizations	SCIT vs. pharmacotherapy. Patients in group A underwent SCIT with relevant allergens for 4 yrs. with an induction phase followed by maintenance injections at 4-week	Asthma, AR, monosensitization. Parietaria, grass, olea, Compositae (mix), Corylaceae-Betulaceae (mix), mites.	Low	Significantly lower risk of new sensitizations in SCIT group (1706/7182, [23.75%]) compared to controls (826/1214, [68.03%]) after 4 yrs. of treatment.	Effect of SCIT observed retrospectively. SCIT was proposed to all patients. Those who accepted were

	Age range: >13 yrs old.			intervals.			Three yrs. later, 1936/7182 (26.95%) among SCIT group and 932/1214 (76.77%) in control group had developed new sensitizations. Both comparisons were highly significant ($p<0.0001$). Asthmatic patients, treated with SIT or not, were more prone to develop polysensitization compared to patients with rhinitis only.	allocated into group A. Both groups were divided into subgroups according to presence of asthmatic symptoms at enrolment. All patients were followed-up as outpatients in the period 1980-99. Authors conclude that specific immunotherapy reduced new sensitizations in monosensitized subjects

								suffering from respiratory allergic diseases.
Reha, 2007, Turkey	n=107 56 patients in the SCIT group, 51 patients in the control group. Age range: 7-12 yrs.	Children with intermittent asthma sensitized to house dust mite or pollen species.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy.	Asthma, AR, monosensitization to grass pollen species or house dust mites. House dust mite, grass.	Low	At 5 years follow-up, 35/43 (81.39%) of patients in house dust mite IT group and 10/13 (76.92%) patients in grass pollen IT group showed no new sensitizations. In the control group, 20/51 (53.84%) had developed new sensitizations. Difference between SIT groups and control group was statistically significant (p=0.033).	SCIT and control group were matched for age, asthma and/or AR severity, and respiratory function. Authors conclude that SCIT appears to prevent developmen t of new sensitization s.
Tella, 2003, Spain	n=100 66 were treated with SCIT, 34 received	Patients with AR and/or asthma monosensitized.	Effect on development of new sensitizations.	SCIT vs. pharmacotherapy. Duration of treatment	AR, asthma, monosensitization to grass pollen, Parietaria judaica pollen or Dermatophagoides	Low	No statistically significant differences in risk of developing new sensitizations between SCIT	Comparisons were made between

	medication only. Age range: 6-69 yrs.			was at least 3 yrs.	spp. Grass pollen, Parietaria judaica, Dermatophagoides pteronyssinus, Dermatophagoides farinae.		group and controls (RR=0.97, 95% CI, 0.72-1.3). A total of 24/66 (36.4%) patients in the SCIT group had new sensitizations compared to 13/34 (38.2%) among controls.	baseline and after 3-5 yrs. of SCIT.

Table 3: Quality assessment of RCTs

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding patients/personnel	Blinding of outcome assessors	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Crimi, 2004	RCT	Yes	Yes	Yes	Yes	No	Yes	No	Medium
Dominicus, 2012	RCT	Unclear	Yes	Yes	No	Unclear	No	No	Low
Garcia, 2010	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Grembiale, 2000	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Holt, 2013	RCT	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Medium
Jacobsen, 2007	RCT	Yes	Yes	No	No	No	Yes	No	Low
Limb, 2006	RCT	Yes	Yes	Yes	Yes	No	Yes	No	Medium
Marogna, 2004	RCT	Yes	No	No	No	Yes	Yes	No	Low
Marogna, 2008	RCT	Unclear	No	No	No	Yes	Yes	No	Low

Möller, 1986	RCT	Unclear	Yes	Yes	Yes	No	Yes	No	Medium
Novembre, 2004	RCT	Yes	No	No	No	Yes	Yes	No	Medium
Pifferi, 2002	RCT	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	Medium
Song, 2014	RCT	Yes	No	Unclear	Unclear	No	Yes	Yes	Low
Szepfalusi, 2014	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Valovirta, 2016	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Yamanaka, 2014	RCT	No	Unclear	Unclear	Unclear	Yes	Yes	Yes	Low
Zolkipli, 2015	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

Table 4: Quality assessment of CBAs

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding patients/personnel	Blinding of outcome assessors	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Asero, 2004	CBA	No	No	No	No	Yes	Yes	No	Low
Des Roches 1997	CBA	No	No	No	No	Yes	Yes	No	Low
Di Rienzo, 2003	CBA	No	No	No	No	Yes	Yes	No	Low
Eng 2006	CBA	No	No	No	No	Yes	Yes	No	Low
Gulen, 2007	CBA	No	No	No	No	Yes	Yes	No	Low
Harmanci, 2010	CBA	No	No	No	No	Yes	Yes	No	Low
Inal, 2007	CBA	No	No	No	No	Yes	Yes	No	Low
Marogna, 2010	CBA	No	No	No	No	Yes	Yes	No	Low
Ohashi, 2009	CBA	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low

Ohashi, 2009	CBA	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Pajno, 2001	CBA	No	No	No	No	Yes	Yes	No	Low
Purello D'Ambrosia, 2001	CBA	No	No	No	No	Yes	Yes	No	Low
Reha, 2007	CBA	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Low
Schmitt, 2015	CBA	No	No	No	No	Yes	Yes	No	Low
Tella, 2003	CBA	No	No	No	No	Yes	Yes	No	Low

Table 5: List of excluded studies with reasons for exclusion

Reference	Incorrect study design	Incorrect outcome	Incorrect intervention	Other
Antúnez C, Mayorga C, Corzo JL, Jurado A, Torres MJ. Two year follow-up of immunological response in mite-allergic children treated with sublingual immunotherapy. Comparison with subcutaneous administration. Pediatr Allergy Immunol 2008; 19:210-8.		X		
Bachert C. Sublingual immunotherapy. A survey on the basis of controlled studies on efficacy, tolerability, long-term effects and prevention in children and adults with ALK-Scherax preparations. [German]. Allergologie 2007;30:1-13.	X			
Baron-Bodo V, Zimmer A, Bouley J, Bonvalet M, Moussu H, Wambre E, Ricarte C, Horiot S, Kwok WW, Horak F, Beaumont O, Nony E, Mascarell L, Moingeon P. Clinical efficacy of allergen-specific sublingual immunotherapy correlates with the induction of tolerogenic dendritic cell, but not CD4+ regulatory T cell, markers. Allergy 2013; 68:20.		X		
Blumberga G, Groes L, Dahl R. SQ-standardized house dust mite immunotherapy as an immunomodulatory treatment in patients with asthma. Allergy 2011; 66:178-85.		X		
Bousquet J. Sublingual immunotherapy: from proven prevention to putative rapid relief of allergic symptoms. Allergy 2005; 60:1-3.	X			
Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 2004; 59:1272-6.		X		
Cantani A, Micera M. Significant decrease of IgE antibodies after a three-year controlled study of specific immunotherapy to pollen allergens in children with allergic asthma. Eur Rev Med Pharmacol Sci 2005; 9:103-11.		X		

Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, Sundaram V, Paige NM, Towfigh A, Hulley BJ, Shekelle PG. Diagnosing and managing common food allergies: A systematic review. JAMA 2010; 303:1848-1856.			X	
Cortegano I, Del Pozo V, Rojo M, Cardaba B, Aceituno E, Gallardo S, Minguez A, Arrieta I, Palomino P, Lahoz C. [Other forms of immunomodulation in allergic patients]. Allergol Immunopathol (Madr) 2000; 28:102-7.	X			
Daniel C, Repa A, Mercenier A, Wiedermann U, Wells J. The European LABDEL project and its relevance to the prevention and treatment of allergies. Allergy 2007; 62:1237-1242.	X			
Galli E, Chini L, Nardi S, Benincori N, Panei P, Fraioli G, Moschese V, Rossi P. Use of a specific oral hyposensitization therapy to Dermatophagoides pteronyssinus in children with atopic dermatitis. Allergol Immunopathol (Madr) 1994; 22:18-22.		X		
Gore C, Custovic A. Primary and secondary prevention of allergic airway disease. Paediatr Respir Rev 2003; 4:213-224.	X			
Greenhawt M. The Learning Early About Peanut Allergy Study The Benefits of Early Peanut Introduction, and a New Horizon in Fighting the Food Allergy Epidemic. Pediatr Clin North Am 2015; 62:1509.	X			
Halken S, Lau S, Valovirta E. New visions in specific immunotherapy in children: an iPAC summary and future trends. Pediatr Allergy Immunol 2008; 19:60-70.	X			
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Appendix 1: Search strategy

Search strategy 1

(MEDLINE, EMBASE)

1. exp Primary prevention/
2. Primary prevention.mp.
3. exp Secondary prevention/
4. Secondary prevention.mp.
5. exp Tertiary prevention/
6. Tertiary prevention.mp.
7. Prevention.mp.
8. Etiology.mp.
9. Epidemiologic*.mp.
10. ("risk of developing" or "risk for development").mp.
11. (effect* or cause* or protect* or risk*).mp.
12. or/1-11
13. exp Desensitization, Immunologic/
14. exp Immunotherapy/
15. Desensitization.mp.
16. Hyposensitisation.mp.
17. Allergy vaccination.mp.
18. (Immunotherapy or allergen immunotherapy).mp.
19. Subcutaneous immunotherapy.mp.
20. Epicutaneous immunotherapy.mp.
21. Intradermal immunotherapy.mp.
22. Sublingual immunotherapy.mp.
23. Oral Immunotherapy.mp.
24. Oral desensitization.mp.

25. Specific oral tolerance induction.mp.
26. Oral tolerance induction.mp.
27. Intranasal immunotherapy.mp.
28. Bronchial immunotherapy.mp.
29. Intralymphatic immunotherapy.mp.
30. Specific immunotherapy.mp.
31. Or/13-30
32. exp Intervention Studies/
33. Intervention studies.mp.
34. exp Clinical Trial/
35. trial.mp.
36. Clinical trial.mp.
37. exp Controlled Clinical Trial/
38. Controlled Clinical Trial.mp.
39. Randomized Controlled Trial.mp.
40. Quasi-randomized trial.mp.
41. Non-randomized trial.mp.
42. exp Placebos/
43. Placebos.mp.
44. exp Random allocation.mp.
45. Random allocation.mp.
46. exp Double-blind method/
47. Double-blind method.mp.
48. Double-blind design.mp.
49. exp single-blind method/
50. Single-blind method.mp.
51. Single-blind design.mp.
52. Triple-blind method.mp.
53. Random*.mp.

54. (Controlled before and after stud*).mp.
55. Interrupted Time Series Analysis/ or interrupted time series.mp.
56. Search:.tw.
57. Review.pt.
58. Systematic review.tw.
59. Meta analysis.mp,pt.
60. Case series.mp.
61. (Case$ and series).tw.
62. Cost:.mp.
63. Cost effective:.mp.
64. Cost utility:.mp.
65. Exp Health care Costs/
66. (Costs and Costs Analysis).mp.
67. Economic evaluation*.mp.
68. ((cost effective* adj1 analys*) or cost minimi?ation analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances).mp.
69. Or/32-68
70. 12 and 31 and 69

Search strategy 2

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

(Prevention or "primary prevention" or secondary prevention" or "tertiary prevention" or etiology or "risk of developing" or "risk for development" or effect* or cause* or protect* or risk)

AND

(Immunologic, desensiti* or hyposensitization or immunotherapy or allergen immunotherapy or specific immunotherapy or allergen specific immunotherapy or allergy vaccination or subcutaneous immunotherapy or epicutaneous immunotherapy or intradermal immunotherapy or sublingual immunotherapy or oral immunotherapy or oral desensitization or specific oral tolerance induction or oral tolerance induction or intranasal immunotherapy or bronchial immunotherapy or intralymphatic immunotherapy)

AND

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

Appendix 2: Experts consulted

1. Lars Jacobsen, Denmark
2. Eva Maria Varga, Austria
3. Erkka Valovirta, Finland
4. Peter Eng, Switzerland
5. Ojedo, Pedro, Spain

Appendix 3: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5, 8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, 61-63

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	61-63
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, 31
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-21, 37-56
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-21, 58-59
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-21, 37-56
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-14, 16-17, 19, 32-36
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-13, 16-17, 19, 32-36
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-14, 16-17, 19, 32-36
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	21-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

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