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GRADE systematic review of immunotherapy in childhood asthma: evidence from previous systematic reviews no longer applicable in current clinical practice

Authors

1. Erik-Jonas **van de Griendt*** MD, paediatric pulmonologist, DeKinderkliniek Almere and Academic Medical Centre Amsterdam, Hospitaaldreef 29, 1315 RC Almere, The Netherlands e.j.vandegriendt@amc.uva.nl *and*

   Mariska K **Tuut***, MSc, epidemiologist, PROVA, Spoorstraat 31, 7051 CG Varsseveld, The Netherlands, m.tuut@provaweb.nl

2. Hans de Groot MD, PhD, allergologist, Department of Paediatric Allergology, Reinier de Graaf Group, Reinier de Graafweg 5, 2625 AD Delft, The Netherlands, h.degroot@rdgg.nl

3. Paul L.P. Brand MD, PhD, paediatrician, Princess Amalia Children's Center, Isala Hospital, P.O. Box 10400, 8000 GK Zwolle, the Netherlands; UMCG Postgraduate School of Medicine, University Medical Center and University of Groningen, The Netherlands, p.l.p.brand@isala.nl

**both authors contributed equally*

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Correspondence:

Erik-Jonas van de Griendt, dept of paediatrics, DeKinderkliniek
Hospitaaldreef 29
1315 RC Almere
The Netherlands
telephone: +31 36 7630030
e-mail: e.j.vandegriendt@amc.uva.nl

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

EJG designed the study, chaired the guideline working group, provided clinical input (e.g. defined clinical relevant outcome measures, judged the literature review from a clinical point of view), wrote and revised the manuscript, and approved the final version.

MKT designed the study, was methodologist of the guideline working group, provided methodological input (e.g. provided literature search, selection, critical appraisal, GRADE evidence profiles), wrote and revised the manuscript, and approved the final version.

HdG was member of the guideline working group, designed the study, revised the manuscript and approved the final version.

PB provided clinical input, revised the manuscript and approved the final version.

All authors meet full criteria for authorship, i.e. all contributed substantially, revised, approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data sharing statement

Extra data can be accessed in the online repository. Apart from this, no additional data are available.

Transparency declaration

The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Abbreviations

- 95%CI: 95% confidence interval
- AMSTAR: A Measurement Tool to Assess Systematic Reviews
- FEV_1: forced expiratory volume in 1 second
- GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- ICS: inhaled corticosteroids
- RCT: randomized controlled trial
- SCIT: subcutaneous immunotherapy
- SR: systematic review
- SLIT: sublingual immunotherapy

Key words: allergy, asthma, children, adolescents, immunotherapy, efficacy, GRADE, systematic review

Abstract

Background. Allergy plays a major role in both asthma and its common comorbidity allergic rhinitis. Immunotherapy is effective in the treatment of allergic rhinitis. Previous systematic reviews indicated its effectiveness in children with asthma. Because most children with persistent asthma now use ICS, the added benefit of immunotherapy in asthmatic children needs to be examined.

Objective. We re-assessed the effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) in childhood asthma treatment focusing on studies with patient relevant outcome measures and children using ICS.

Methods. We used the GRADE approach to systematically search and appraise the evidence using predefined critical patient relevant outcomes (asthma symptoms, asthma control and exacerbations). We searched to retrieve systematic reviews and randomized controlled trials on immunotherapy for asthma in children (1960 - 2015). We assessed the quality of the body of evidence with GRADE criteria.

Results. The quality of the evidence for SCIT was very low due to a large risk of bias and indirectness (dated studies in children not using ICS). No effect of SCIT was found for asthma symptoms; no studies reported on asthma control. For asthma exacerbations, studies favoured SCIT. We have little confidence in this effect estimate, due to the very low quality of evidence. For SLIT, quality of the evidence was very low due to a large risk of bias, indirectness and imprecision. The outcome “asthma symptoms” could not be calculated due to lack of standardization and large clinical heterogeneity. Other predefined outcomes were not reported.

Conclusion. The beneficial effects of immunotherapy in childhood asthma found in earlier reviews are no longer considered applicable, because of indirectness (studies performed in children not being treated according to current asthma guidelines with inhaled corticosteroids). There was absence of evidence to properly determine the effectiveness or lack thereof of immunotherapy in childhood asthma treatment.

Article Summary

- This study is the first review evaluating immunotherapy in asthmatic children using the GRADE approach, focusing more on clinically relevant than on statistically significant differences in patient relevant outcomes.
- Contrary to earlier reviews our study concluded that there is no evidence for beneficial effects of immunotherapy for asthma in children.
- Positive conclusions from earlier reviews were mainly based on populations using treatment incomparable to current practice.
- A limitation of the study was the lack of evidence, especially the lack of recent studies in current pediatric asthma populations.
- Due to the lack of standardization in study design and large clinical heterogeneity the clinical relevant outcome measure asthma symptoms could not be calculated in our study.

Introduction

Asthma affects 10-15% of school-aged children. For children with persistent asthma, all international guidelines recommend daily controller treatment with inhaled corticosteroids (ICS), and reliever medication (short-acting β-2-agonists) as needed.[1,2] Although many children achieve complete asthma control using this effective and safe treatment,[1] some need additional treatment to obtain disease control.[3,4] Identification and treatment of comorbidities in children with problematic severe asthma is part of the stepwise approach to improve asthma control in these children.[5,6]

The most common of these comorbidities in children with asthma is allergic rhinitis,[5] symptoms of which occur in 60-80% of asthmatic children.[7,8] Allergic rhinitis shares a common pathophysiological pathway with asthma, which has been described as the united airway concept.[9] Allergic rhinitis is associated with worse asthma control in children, and accumulating evidence suggests that treatment of allergic rhinitis with intranasal steroids improves not only rhinitis, but also asthma symptoms in these patients.[7,10,11]

When symptoms of allergic rhinitis cannot be sufficiently controlled with nasal corticosteroids and oral antihistamines,[9,12] immunotherapy can be considered as additional treatment.[13] Subcutaneous immunotherapy (SCIT) requires repeated injections with an allergen extract and is available for allergens such as grass and tree pollen and house dust mite. After disappointing results of low-dose preparations in drops, effective high-dose sublingual immunotherapy (SLIT) has now become available with grass pollen allergen extract in a daily sublingual tablet.[14,15] A Cochrane systematic review, first published in 2000, and last updated in 2010, reported beneficial effects of immunotherapy in children with asthma.[16] Most studies in this review, however, were performed in the 1980s, when most children with asthma were not using ICS.

As part of the update of the Dutch pediatric guideline on childhood asthma, we evaluated the literature on the added value of SCIT and SLIT in childhood asthma.[17] Our structured clinical question was to assess whether immunotherapy (subcutaneous or sublingual), as an add-on to usual care with daily ICS, improves asthma outcomes in children (6-12 years) and adolescents (>12 years) with persistent asthma and sensitization to relevant aeroallergens (grass or tree pollen, house dust mite, or combinations), with or without symptoms of allergic rhinitis.

Methods

We used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to appraise and summarize the body of evidence. GRADE is an internationally approved standard for managing complex evidence reviews.[18] In contrast to former grading systems, GRADE focuses on the quality of the total body of evidence, instead of judging single studies. Another important characteristic of GRADE is that predefined outcomes with thresholds for clinical relevance are being used.[19] In earlier grading systems, the evidence was summarized using outcomes reported in studies, not necessarily being outcomes a guideline development group would be interested in.[20] GRADE avoids the use of surrogate or intermediate outcomes, and uses outcomes and differences that are more clinically relevant to patients instead. Starting from (several) randomized controlled trials or observational studies, for each outcome the quality of evidence can be downgraded or upgraded, for instance based on risk of bias, inconsistency, indirectness, possible publication bias, and dose-response relation.

The guideline development group included an epidemiologist, paediatric respiratory physicians, paediatricians, an allergist, an ear-nose-throat specialist, a family physician, a lung function technician, a youth public health care physician, and patient representatives. The guideline development group predefined clinically relevant outcomes and divided these into critical (contributing to the overall quality of evidence), important (also relevant to the content of the guideline) and not important outcomes. For each outcome, a minimal clinically important difference was defined *a priori*. The outcomes taken into account in our literature review are summarized in *table 1*, with corresponding minimal clinically important differences.[21-24]

Table 1. Patient relevant outcomes and clinical relevance

Outcome	Importance	Minimal clinically important difference
Asthma symptoms	Critical	ACT: 3 c-ACT: (2-)3*
(Severe) exacerbations	Critical	NNT n=10
Asthma control	Critical	ACT: 3 c-ACT: (2-)3*
(Disease-specific) quality of life	Important	PAQLQ: 0.5 (scale 0-7)*
Change in FEV_1	Important	>5%predicted

* or comparable differences on other valid scales representing this outcome

Abbreviations: ACT: asthma control test; c-ACT: child ACT; PAQLQ: Pediatric Asthma Quality of Life Questionnaire

We applied a sensitive search strategy to retrieve all available evidence addressing the clinical question, focusing on systematic reviews (SRs) and randomized controlled trials (RCTs) about asthma and immunotherapy in children. We searched for systematic reviews in the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness, and we searched The Cochrane Central Trial Register to update existing

reviews. Literature searches were performed in March 2012 for the guideline (from 1960 onwards), and updated in April 2015 for the purpose of this review *(see table E1 in the Online Repository)*. Two reviewers (EJvdG, MKT) independently screened the abstracts using predefined inclusion criteria: methodology (SRs and RCTs), patients (children with allergic asthma), and SCIT and/or SLIT as an intervention. Animal studies, conference abstracts, and studies published in languages other than English, Dutch and German were excluded. Differences between reviewers were resolved by consensus. Selected abstracts were critically appraised with respect to study population and methodological aspects (systematic search and selection, randomization of patients), which led to a further selection. An expert in the field (HdG) judged the selection for completeness.

All included studies were summarized in evidence tables by two reviewers (EJvdG, MKT). SRs were critically appraised using the AMSTAR checklist (A Measurement Tool to Assess Systematic Reviews).[25] AMSTAR scores range from 0-11, a higher score indicating better quality (less bias). The Jadad scale was used to assess the methodological quality of each RCT.[26] This score ranges from 0-5, a higher score denoting a better quality. All eligible studies together defined the body of evidence, of which the quality was determined (per relevant outcome and overall quality) and GRADE Profiles were created. Results from SRs and RCTs were pooled, if possible, in meta-analyses using RevMan 5. We calculated standardized mean differences for continuous outcomes, because of the usage of different symptom scales in the underlying studies. We calculated risk ratios for dichotomous outcomes, to compare the probability of these outcomes between the intervention and control groups. In the meta-analyses we used random effects models, because of the possibility of generalization of the outcomes for different allergens, and tested the difference between intervention and control with the inverse variance method, since this method is typically used in meta-analyses to combine the results of independent studies. We reported 95% confidence intervals (pre-defined significance level: 0.05). Conclusions were drawn, based on quality and content, per outcome and discussed in the expert group until consensus was reached.

Patient involvement

The guideline development group included patient representatives who helped defining our clinical question, approved outcome measures and assessed its clinical relevancy. The burden of interventions and patient considerations were assessed as part of the GRADE evaluation. Patients were not directly involved in this systematic review since we reviewed published literature.

Results

Literature search and selection

Screening of titles and abstracts yielded 83 eligible studies, 10 of which fulfilled the inclusion criteria.[16,27-35] After examining these 10 papers in full, 5 more studies were excluded *(figure 1)*.

Experts in the guideline working group confirmed that no relevant publications were missed. The updated search (April 2015) revealed 43 additional studies, of which 2 fulfilled the inclusion criteria.[36,37] Full text examination resulted in exclusion of these 2 studies.

< *figure 1* >

Results of SCIT

Description of studies

We retrieved one Cochrane SR on the effectiveness of SCIT in patients with asthma , including 90 RCTs with a total of 3,792 patients.[16] This was a high-quality review (AMSTAR score 10/11). Fourteen of the included RCTs were performed in children exclusively; another 24 included children and adults. In a few studies the age inclusion criteria were not clear. The characteristics of this review are summarized in an evidence table (*see table E2 in the Online Repository*). Only nine RCTs included in this review reported on our predefined outcomes in children. In these nine studies different allergens or combinations were studied (house dust mite (3), dog dander (1), grass pollen (1), mold (1), grass pollen/house dust mite (1), tailored combinations (2)). Two RCTs published after the 2010 Cochrane review were retrieved. In the first, the clinical efficacy of house dust mite-specific SCIT in 20 asthmatic children was compared to no intervention in 20 others; patients were followed up for six months.[34] In the other, the effects of allergen-specific SCIT on corticosteroid dose in asthmatic children was evaluated.[35] Details of all included RCTs are summarized in the evidence table (*see table E3 in the Online Repository*).

Quality of the evidence

Little information was given about the included studies in the Cochrane review; e.g. follow-up was not stated. There were also other concerns about the quality of the literature, e.g. not all studies were double-blind and placebo-controlled, and randomization procedures were poor.

Therefore we re-analyzed the individual paediatric studies in the Cochrane review, plus the added studies.[34,35] Jadad scores of the single studies are presented in *table 2*.

Table 2. Jadad scores of RCTs on SCIT

	Randomization*	Blinding**	Withdrawals#	Total
Adkinson 1997[38]	1	1	1	3
Altintas 1999[39]	1	1	1	3
Dreborg 1986[40]	1	-	-	1
Hill 1982[41]	1	-	-	1
Johnstone 1961[42]	2	1	-	3
Johnstone 1968[43]	2	1	1	4
Price 1984[44]	1	1	-	3
Tsai 2010[34]	1	-	1	2
Valovirta 1984[45]	1	-	1	2
Warner 1978[46]	1	1	1	3
Zielen 2010[35]	1	1	1	3

** 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate*

*** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate*

 # 1 point if the number and the reasons for withdrawal in each group are stated

The quality of the body of evidence for all critical and important outcomes was very low *(table 3)*, mainly due to large risk of bias and indirectness. The large risk of bias was caused by a lack of allocation concealment, lack of information on follow-up, and loss to follow-up. The reason for downgrading for indirectness was the publication year of the underlying studies; populations and interventions were considered inapplicable to current clinical practice.

Table 3. GRADE Evidence Profile SCIT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SCIT	No intervention	Relative (95%CI)	Absolute (95%CI)		
Asthma symptoms (assessed with: Asthma symptom scores)												
5[a]	RCT	Very serious[b]	Not serious	Serious[c]	Not serious	None	136	286	-	Standardized Mean Difference 0.04 lower (0.42 lower to 0.33 higher)	⊕OOO VERY LOW	CRITICAL
Exacerbations (assessed with: Symptomatic deterioration)												
5[a]	RCT	Serious[d]	Not serious	Very serious[e]	Not serious	None	64/253 (25.3%)	92/153 (60.1%)	Risk ratio 0.43 (0.34 to 0.56)	343 fewer per 1000 (from 265 fewer to 397 fewer)	⊕OOO VERY LOW	CRITICAL

Asthma control – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Abbreviations: 95%CI: 95% confidence interval; RCT: randomized controlled trials; SCIT: subcutaneous immunotherapy

a. *Studies in Cochrane review Abramson + Tsai*
b. *The underlying studies had a quite large risk of bias, due to lack of allocation concealment, problems with blinding, and lack of information on follow-up (and loss-to-follow-up)*
c. *We downgraded for indirectness, because the included studies are quite old and maintenance medication may have changed probably; thus, study populations may alter from nowadays patients with moderate to severe asthma*
d. *We downgraded for risk of bias, because of problems with blinding and loss-to-follow-up*
e. *We assessed very serious indirectness, because most included studies for this outcome are very old, and carried out before the ICS-era; thus, patients nowadays differ from study populations*

Critical outcomes

Asthma symptoms. Four small studies carried out in children only reported this outcome in the Cochrane review.[16] We extracted these results from the Cochrane review and updated these with the results from Tsai et al.[34] Results are presented in *figure 2*.

<figure 2 >

The meta-analysis showed no significant effect of SCIT on asthma symptoms.

Asthma exacerbations. Five studies (published 1961-1984) in the Cochrane review, carried out in children only, reported this outcome.[16] No relevant studies of sufficient quality were published afterwards. Our meta-analysis included 253 patients on immunotherapy and 153 on placebo. The pooled risk ratio was 0.47 (95%CI: 0.31 – 0.72), favouring immunotherapy (see *figure 3*). The absolute risk reduction was 35%, giving a number needed to treat of 3.

< figure 3 >

No studies reported results on the critical outcome asthma control.

Important outcomes

No studies reported results on quality of life and lung function (FEV_1).

Results of SLIT

Description of studies and quality of the evidence

We retrieved two SRs on SLIT in patients with asthma.[29,32] The characteristics of these SRs are summarized in evidence table *E2 (Online Repository*). The quality of the reviews was moderate; both had an AMSTAR score of 7/11. Weaknesses included the absence of an 'a priori design', exclusion of grey literature, not assessing the likelihood of publication bias and not mentioning conflicts of interest in one review,[29] and the absence of an 'a priori design', no information about excluded studies, too firm conclusions compared to the weak evidence, and not assessing the likelihood of publication bias in the other.[32] One review included both children and adults, and patients with asthma and/or rhinitis.[29] Because of the quality concerns of both existing SRs, we set out to perform a meta-analysis of the original studies that fulfilled our selection criteria. Jadad scores of selected studies, as well as an overview of the outcomes of those studies, are presented in *table 4*. Study characteristics are summarized in the evidence table (*see table E4 in the Online Repository*). We rated the quality of evidence to be very low, due to a large risk of bias, imprecision and indirect evidence.

Table 4. Summary of quality and outcome measures of selected RCT's in reviews Calamita et al and Penagos et al.[29,32]

Review	RCT	Eligible	Jadad-score				Reported on asthma symptoms	Reported on exacerbations	Reported on asthma control	Reported on disease specific quality of life	Reported on lung function (FEV_1)
			Randomization*	Blinding**	Withdrawals#	Total					
Calamita[29]	Bahceciler 2001[47]	Yes	1	1	1	3	+	-	-	-	-
	Hirsch 1997[48]	Yes	2	1	1	4	+	-	-	-	-
	Niu 2004[24]	No, conference abstract									
	Novembre 1991[49]	No, Italian language									
	Pajno 2003[50]	Yes	2	1	1	4	+	-	-	-	-
	Pajno 2004$ [51]	Yes	2	1	1	4	-	-	-	-	+
	Rodriguez Santos 2004[52]	No, Spanish language									
	Rolinck-Werninghaus 2004[53]	Yes	1	2	0	3	+	-	-	-	-
	Yuksel 1999[54]	No, Spanish language									
Penagos[32]	Bahceciler 2001[47]	Overlap with Calamita									
	Caffarelli 2000[55]	No, children with asthma not separately analyzed									
	Hirsch 1997[48]	Overlap with Calamita									
	Ippoliti 2003[56]	Yes	1	1	0	2	+	-	-	-	+

	Niu 2006[57]	Yes	1	1	1	3	+	-	-	-	+
	Pajno 2000[58]	Yes	2	1	0	3	+	-	-	-	-
	Rolinck-Werninghaus 2004[53]	Overlap with Calamita									
	Tari 1990[59]	No, Spanish language									
	Vourdas 1998[60]	No, children with asthma not separately analyzed									
Total							7	0	0	0	3

Abbreviations: FEV_1: forced expiratory volume in 1 second; RCT: randomized controlled trial

** 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate*

*** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate*

 # 1 point if the number and the reasons for withdrawal in each group are stated

$ Same patients as Pajno 2003[50]

Critical outcomes

Asthma symptoms. Seven of the included studies reported on asthma symptoms. Different symptom scores were used, none of them standardized or validated. Clinical differences in asthma scores were not defined and most studies reported improvement in the treatment group as well in the control group. Due to this large clinical heterogeneity we were not able to compile a meta-analysis of the results of the individual studies. Since studies did not report results in a clearly comparable way, reporting the results of the individual studies was considered unreliable.

Other critical outcomes. No studies reported results on the critical outcomes exacerbations and asthma control.

Important outcomes

Quality of life. No studies reported results on the outcome disease specific quality of life.

Lung function. Three studies reported results on lung function (FEV_1). One of the studies reported no numeric data on lung function.[57] One study reported no variance (standard deviation), and no comparison of the baseline data.[56] The only remaining study reported on FEV_1 percentage predicted,[51] and reported no significant differences between treatment groups, neither at baseline nor at follow-up.

Discussion

Summary of main results

Our GRADE systematic review showed no evidence of a significant difference in asthma symptoms between SCIT and placebo in children with allergic asthma, but some evidence for a significant and clinically relevant reduction in asthma exacerbations was found in SCIT-treated children. We have little confidence in the effect estimate, however, due to a large risk of bias and indirectness. Thus, the true effect of SCIT on exacerbations and asthma symptoms in the target population of interest is likely to be substantially different from the estimate of effect. There was absence of evidence on the effects of SCIT on lung function, asthma control, and quality of life in children with allergic asthma. There was no evidence for a beneficial effect of SLIT in reducing asthma symptoms and exacerbations, quality of life and lung function in children with allergic asthma. Our review does not address the efficacy of immunotherapy in children regarding complaints of allergic rhinitis and/or conjunctivitis, without having asthma.

Quality of the evidence / GRADE methodology

The overall quality of the evidence about the effectiveness of SCIT and SLIT was very low. This implicates that our confidence in the effect estimates is very limited. The true effect of SCIT and SLIT on patient relevant asthma outcomes in children with asthma may be substantially different from our estimates of the effect. We cannot conclude that the possible desirable effects of SCIT and SLIT outweigh the undesirable effects (e.g. influence on quality of life, adverse events, or increased resource expenditure), nor can we reject that hypothesis. Our concerns about the quality of evidence are based on (very) serious risk of bias and indirectness in the underlying primary studies. Firstly, the quality of many studies had to be downgraded because of risk of bias due to lack of allocation concealment, lack of information on follow-up, and loss to follow-up. Secondly, included studies were heterogeneous in the patients included and allergen extracts used, with different dosing regimens and duration being studied, targeting different inhaled allergens. We have concerns about the potential different responses and the generalizability of the evidence. Thirdly, and most importantly, for SCIT, the quality of the body of evidence was downgraded because of indirectness, since patients in the original studies long ago are likely to differ considerably from patients nowadays.

Thirdly, different studies used variable definitions of asthma exacerbations. We had to use ‘worsening of asthma’, which may not represent real-life patient relevant exacerbations. This

may decrease the applicability of the evidence. In addition, there were no studies using the predefined important outcomes quality of life and asthma control.

Finally, and most importantly, several included studies dated from the 1980s or earlier, when allergic rhinitis treatment with selective antihistamines and nasal corticosteroids was not available. As a result, the allergic rhinitis patients in these studies cannot be compared to patients in clinical practice today. Similarly, widespread use of ICS was not introduced in childhood asthma treatment until the 1990s.[61] Most studies on SCIT in children with asthma were published decades ago, during the pre-ICS era. The patients in the described studies represent an incomparable group compared to the child with asthma in contemporary clinical practice. Specifically, it is unclear whether the beneficial effects found in the systematic review of earlier studies is applicable to children with asthma treated according to contemporary guidelines with daily ICS controller therapy.[16]

In our opinion and that of others, the GRADE approach is superior to former methods of SRs, because it focuses on predefined patient relevant outcomes, predefined minimally clinical important differences and because it judges the complete body of evidence. One RCT among paediatricians studied the influence of different guideline grading systems on clinician's decisions.[62] GRADE showed the largest change in direction on the clinical decision. However, the added value of GRADE on guideline implementation or patient care, has not been formally evaluated, the GRADE approach is still rather complex for non-methodologists.

To formulate recommendations for clinical practice, not only the body of evidence concerning effectiveness of an intervention is important. Recommendations should balance the benefits and harms of the intervention of interest, and take patient preferences and resource use into account. Since (after critical evaluation) no benefits of SCIT and SLIT for children with asthma were determined, we consider it unlikely that the benefits will exceed the harms. Patient preferences were included in the formulation of our guideline recommendations.

Agreements and disagreements with other studies or reviews

Using GRADE and re-analyzing data from children with allergic asthma only, we came to different conclusions on the effectiveness of SCIT and SLIT in children with asthma than the authors of the original SRs. We believe this highlights the importance of using GRADE methodology to systematically review evidence for patient relevant outcomes, not focusing on levels of evidence, but on underlying study validity, precision, directness, and applicability in current clinical practice. A recent The 2009 position paper on SLIT describes history, use and applicability of this treatment for allergic rhinitis.[63] It positions SLIT in children as a safe

and useful therapy above and after more regular treatment for allergic rhinitis. Potential positive treatment outcome for allergic asthma is however mainly based on literature in adults. We show the lack of evidence and lack of applicability of treatment of immunotherapy for asthma in children. Since we have worries on the applicability of evidence in adults on children (who are still developing their immune system), we think further studies that compare immunotherapy for the contemporary treatment of asthma in children are urgently needed to fill in this gap.

Recently, a Cochrane SR on SLIT for asthma found a similar lack of data for important outcomes (e.g. exacerbations, symptom scores, quality of life) as we did.[64] Contrary to our study, the authors did no separate analysis for adults and children, and patients with asthma were not separately analyzed from patients without asthma.

Conclusions

Focusing on predefined patient relevant outcomes, and critically appraising the body of evidence using original studies and GRADE methodology, our systematic review on the effects of immunotherapy in children with asthma came to different conclusions than previous systematic reviews . We believe that this underscores the importance of using GRADE methodology in systematically reviewing evidence.

We found absence of valid applicable evidence on improvement of clinically relevant asthma outcomes in children with allergic asthma using SCIT or SLIT. This absence of evidence is due to serious risk of bias, large clinical heterogeneity between studies, and most importantly due to lack of applicability because studies were performed in the pre-ICS era.

Since the effect of immunotherapy added to contemporary asthma treatment with daily controller therapy is not clear, the drawbacks of immunotherapy should be considered carefully. SCIT is a complex and intensive form of treatment, associated with a (very) long duration of treatment, and considerable burden to the patient with (monthly) injections under adequate medical supervision due to potential (however rare) dangerous side effects, and may have relatively high costs and resource use. In SLIT the risk of serious side-effects is considerably smaller, but the other drawbacks of immunotherapy apply equally to this treatment. In our opinion therefore, when balancing the absence of evidence on a clear beneficial effect of SCIT or SLIT on clinically relevant patient outcomes in children with asthma with the considerable burden and costs of SCIT and SLIT, we do not recommend this treatment to children with asthma until further high-quality evidence from well-designed RCTs in children comparing SCIT or SLIT to contemporary asthma treatment becomes available.

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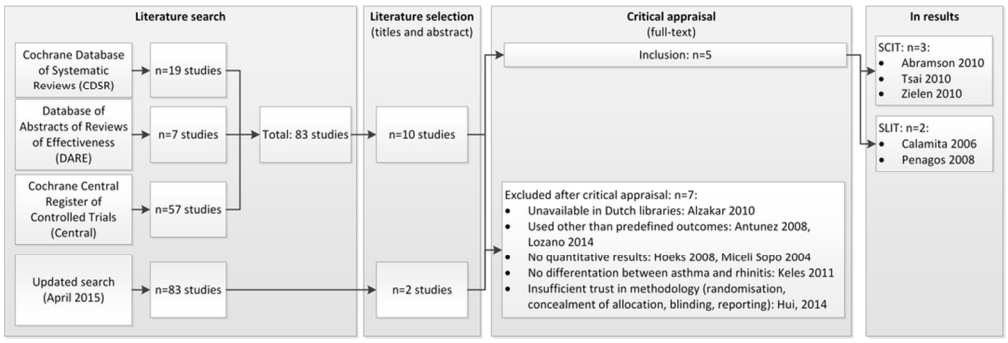

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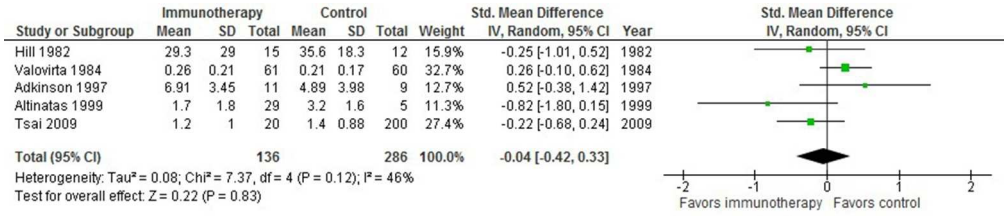

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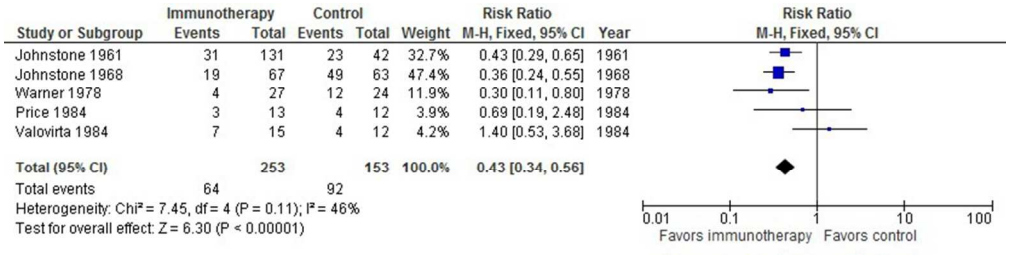

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Table E1. Literature search

Search Cochrane Databases of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Central; Literature search 2015, April 25th	
1. "asthmazoekacties jan 2012".ti. (0) 2. asthma.tw. (14671) 3. Bronchial Spasm.tw. (15) 4. asthma*.tw. (17541) 5. wheez*.tw. (869) 6. bronchospas*.tw. (777) 7. (bronch* adj8 spas*).tw. (52) 8. bronchoconstrict*.tw. (1663) 9. (bronch* adj8 constrict*).tw. (71) 10. airway* inflammation*.tw. (704) 11. or/2-10 (18894) 12. immunotherap*.kw,tw. (2803) 13. 11 and 12 (473) 14. subcutaneou*.kw,tw. (8020) 15. 12 and 14 (259) 16. 15 (259) **17.** limit 16 to yr="2008 -Current" (57)	
Results	
Cochrane Databases of Systematic Reviews	19
Database of Abstracts of Reviews of Effectiveness	7
Cochrane Central Trials Register	57

Table E2. Evidence table systematic reviews (SCIT + SLIT)

	Abramson, 2010[26]	Calamita, 2006[29]	Penagos, 2008[32]
Study design	Cochrane systematic review, consisting of 90 RCT's. 14 RCT's were carried out in children only; 24 were done in children and adults. The total study population (children and adults) consisted of 3.792 patients (of whom 3.459 had asthma)	Systematic review, consisting of 25 RCT's. Only 9 RCT's were carried out in children only. The total study population consisted of 1.706 patients (adults and children, with asthma and/or rhinitis)	Systematic review, consisting of 9 RCT's, all carried out in children. The total study population comprised 441 patients with asthma (seasonal, mild, moderate, and persistent)
Age (mean)	Not specified, variation between included studies	Not specified, there is a limited description of the characteristics of the included studies	Range specified per study, total range: 4-17 years
Setting (in RCT's)	-	-	-
Diagnosis (asthma/rhinitis)	Asthma	Asthma and rhinitis	Asthma
Eligibility criteria	RCT's, patients with asthma, allergen specific subcutaneous immunotherapy (administration of extracts of house dust mites, pollens, animal danders or molds, chemically modified allergoids or antigen-antibody complexes)	RCT's, double blinded, and open studies, patients with asthma and/or rhinitis, sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all lengths of treatment)	RCT's, double blinded, placebo controlled, patients ≤ 18 years, with a history of allergic asthma, with identified causal allergen, and proven IgE sensitization. Sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all durations of treatment)
Type of immunotherapy	Subcutaneous immunotherapy (variation of allergen abstracts in different included studies)	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy, mainly mites
Intervention	Subcutaneous immunotherapy	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy (mainly mites, further: O europaea, Holcus, P pretense *Dermatophagoides pteronyssinus*, grass mix), great variation in duration, range: 3-32 months
Control	Placebo	Placebo	Placebo
Primary outcomes	Asthmatic symptoms Asthma medication requirements Lung function Nonspecific bronchial hyper-reactivity Allergen specific bronchial hyper-reactivity	Asthmatic symptoms (symptom score) Asthmatic medication requirement Respiratory function tests (PEFR, FEV_1, FEF25-75%) Nonspecific bronchial provocation Adverse effects	Asthma symptoms Medication scores
Secondary outcomes	Local reactions Systemic reactions	-	
Comment	The results have not been presented separately for children in the review. We	The authors mentioned they used the Cochrane Collaboration method	-

	conducted new suitable meta-analyses.		

Abbreviations: FEF25-75: maximum mid expiratory flow; FEV_1: forced expiratory volume in 1 second; PEFR: peak expiratory flow rate; RCT: randomized controlled trial; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

Table E3. Evidence table SCIT studies

Author, date	Study design	Setting	Eligibility	Participants (number, gender, age, and descriptive	Asthma type,* severity (e.g. on ICS?)	Allergy type (mono/multi, allergens,	Intervention (type, dose, duration)	Control	Follow-up (from start	Outcomes	Results reported by authors†	Critical appraisal‡	Comments
Adkinson, 1997[38]	Double blind, placebo controlled, parallel group RCT Placebo caramelized saline + histamine	?		121 allergic children with perennial asthma Mean age 9.2 (range 5.4 to 14) years, 79% boys	Perennial asthma 41% ICS, 2% systemic	80% dust mite, 77% ragweed, 69% rye grass	Subcutaneous multiple allergen immunotherapy Median 6 (range 2 to 7) allergen extracts	Placebo	?	Symptom scores Medication scores PEF rates Nonspecific BHR (methacholin FEV_1)	SCIT not useful in moderate to severe perennial allergic asthma	Study useful, however low rate of ICS	Allocation concealment unclear
Altintas, 1999[39]	Open placebo controlled RCT multiple groups	university		34 poorly controlled mild to moderate asthmatics aged 4 to 18 years; 30 patients in 3 groups, 4 placebo	ICS use not specified, no medical details on asthma	Mono-sensitization *Dermatophagoides pteronyssinus*	Subcutaneous immunotherapy with adsorbed or aqueous *Dermatophagoides pteronyssinus* extracts (in different dilutions)	Placebo		Symptom medication score IgE and IgG4 level Bronchial provocation tests	SCIT is useful and safe; no conclusion on asthma	Study not useful No data on ICS,	Allocation concealment unclear Study designed to compare 3 different abstracts of immunotherapy
Dreborg, 1986[40]	RCT, double blind Freeze dried caramelized histamine placebo	European		30 children with *Cladosporium* allergy, aged 5 to 17 years	Clinical history suggesting mold-induced asthma and/or rhinoconjunctivitis ICS not stated	*Cladosporium* allergy	*10 months Cladosporium* subcutaneous immunotherapy Or placebo	Placebo		Symptoms Medication PEF (no SD reported) Allergen specific BHR	Decrease in medication score, but not in symptom score Lower medication score in verum group	Study not useful No information on asthma medication No fixed study medication scheme	Allocation concealment unclear Asthma diagnosis not specified, (worsening of asthma in the *Cladosporium*

													season)
Hill, 1982[41]	Single blind RCT, rye grass pollen placebo	University Australia		20 asthmatic children, aged 9 to 14 years, with rye grass pollen allergy, positive at bronchoprovocation	ICS N=1 beclomethason N=8 cromoglycate		Subcutaneous immunotherapy with aqueous rye grass pollen extract	Placebo		Symptoms Medications (medians only reported, no SD)	no evidence that limited hyposensitization with a pollen extract is of any clinical benefit in seasonal asthma despite evidence of an immunological response.	Study not useful Primary outcome = IgE and IgG levels	No allocation concealment
Johnstone, 1961[42]	RCT, double blind, 4-year follow up Buffered saline control	United States general hospital		173 children with perennial asthma Severity = number of days of wheeze/year Placebo: n=41	No medication mentioned at all, no medication scores		Subcutaneous immunotherapy with relevant allergen extracts, administered by 3 regimens	Placebo		Asthma symptoms reported by mother Number of new allergies developing	Less new allergies developing Less symptoms and asthma attacks in the last year in the group 4	Study not useful No asthma medication scores	Allocation concealment unclear 4 different groups, 1 placebo (n=41) Group 2-4 different strength SCIT Last year single blind
Johnstone, 1968[43]	RCT, double blind Buffered saline control			130 children with perennial asthma; Severity = number of days of wheeze/year RCT, double blind Buffered saline control	No medication mentioned, no medication scores		Subcutaneous immunotherapy with relevant allergens administered by 3 regimens	Placebo		Asthma symptoms reported by mother	More children in SCIT group high dose overgrowing asthma at the age of 16 than placebo	Study not useful No asthma medication scores	Allocation concealment unclear 14-years follow up of Johnstone 1961
Price, 1984[44]	RCT, double blind Saline placebo control			25 children with perennial asthma, aged 5 to 15 years	Asthma severity not specified asthma medication not specified		Subcutaneous immunotherapy with *Dermatophagoides pteronyssinus*	Placebo		Symptoms Medication Lung function Bronchoprovocation	Loss of late reaction on bronchoprovocation Only one out of 6 children with	Study not useful Bronchoprovocation is surrogate outcome;	Continuation of study by Warner 1978 for second year with

							extracts				severe asthma improved		placebo group crossed over to active immunotherapy
Tsai, 2010[34]	RCT, no blinding, no intervention in control group	University hospital, Taiwan		40 children (21 boys), aged 5-14 years (average 8,5) >1 year moderate persistent to severe asthma, all monosensitized to house dust mite	Moderate persistent to severe asthma, using daily medication, most patient at least on ICS	House dust mite, diagnosed by SPT or specific antibody test	Subcutaneous injections of extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* (10000 AU/ml), initial dose 0,5AU/ml once a week. Dosage was increased weekly by 25-100% to reach optimal maintenance dose, with respect to local or systemic reaction. Maintenance therapy every 2 weeks during at least 3 months	No intervention	6 months (last follow-up)	Primary: Medication score (5 point scale, modified GINA) Secondary: PEF, asthma symptom score, number of contacts with health care providers	Mean medication score declined after 6 months in both groups; no significant between group differences. Both groups had reduction of asthma symptoms after 6 months, but no between group differences. There was no difference in PEF. Patients in the intervention group had more clinical visits than the control group, but no difference in emergency room or hospitalization	Very few patients, no blinding, randomization procedure not clear	
Valovirta, 1984[45]	RCT, double blind Caramel histamine placebo control	?		27 asthmatic children allergic to dog dander, aged 5 to 18 years	Asthma severity not specified asthma medication not specified		Subcutaneous immunotherapy with aluminium hydroxide bound dog dander extract	Placebo		Symptoms Allergen specific BHR	The decrease in bronchial sensitivity was less marked than that in conjunctival sensitivity and statistically not	Study not useful No asthma medication scores	Primary outcome dog dander sensitivity, not asthma 2 authors connected to

											significant		pharmaceutical company
Warner, 1978[46]	RCT, double blind Tyrosine placebo control	University, United Kingdom		51 asthmatic children, aged 5 to 14 years, with positive *Dermatophagoides pteronyssinus* challenge	ICS n=12, cromoglycate n=24 SABA n=14	House dust mite, SPT and bronchoprovocation positive	Subcutaneous immunotherapy with tyrosine adsorbed *Dermatophagoides pteronyssinus* extracts	Placebo	1 year	Symptoms Medication Lung function (PEF, FEV 0.75) Allergen specific BHR	Less asthma medication in active group, but no difference in control or immediate response on bronchoprovocation	Useful; however incomparable low level of ICS	Allocation concealment unclear No fixed medication scheme
Zielen, 2010[35]	RCT, single blind, no control intervention	Multinational, multicenter		56 children with asthma GINA treatment II-III, on ICS, house dust mite (positive SPT), positive conjunctival provocation, significant RAST response	All on ICS, GINA II-III treatment	House dust mite SPT, provocative	SCIT with allergens extracted from *Dermatophagoides pteronyssinus* in 2 strengths: A: 1000 TU/ml; B: 10000 TU/ml. Initial therapy: weekly increasing doses strength A, followed by B. After reaching max individually tolerated dose, dosage intervals were increased to 6 weeks	No immunotherapy, only maintenance therapy with ICS	2 years	Primary: change in ICS dose steps to achieve asthma control Secondary: change in pre-bronchodilatory PEF, immunologic changes, nonspecific bronchial hyperreactivity	Less asthma medication in SCIT group as compared to control group, no change in asthma control, higher increase in PEF in intervention group. Adverse events in 97% in both groups	Block randomization. Multicenter, multinational is possible bicenter, binational. Conflict of interest in authors	

Abbreviations: AU: dosing units; BHR: bronchohyperreactivity; FEV1: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; ml: millilitres; n: number; PEF: peak expiratory flow; RAST: radioallergent sorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonist; SCIT: subcutaneous immunotherapy; SD: standard deviation; SPT: skin prick test; TU: dosing units

** Doctors diagnosed asthma? Stable/seasonal asthma? Mild/severe asthma?*

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, adverse reactions and/or complications

‡ e.g. randomization procedure, blinding, risk of bias

Table E4. Evidence table selected RCT's in children included in systematic reviews Calamita et al. and Penagos et al. (SLIT)

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
Bahcecil er 2001[47]	double-blind placebo-controlled SLIT drops HDM	Mono-center Turkey University hospital	Asthma with need for ICS, HDM allergic, ongoing respiratory symptoms despite mite avoidance and appropriate ICS treatment, > 7 years, FEV_1	15, 8 male, 11,7 years	Moderate asthma, need for ICS, respectively symptoms despite mite avoidance, FEV_1> 70%	Mono-allergy HDM but negative for all other aeroaller-gens	Drops SLIT, dose 100 IR/day, 4 weeks run-in, 4 weeks once daily, thereafter 2/week; total 6 months	Place bo drops	6 mont hs	Symptom scores, compliance, SPT 6 months, Lung function, metacholin e, serum IgE	Improvem ent asthma score. Less use of SABA, trend to-wards less ICS (not significant), no change in PD20, no serious side effects	Randomizati on and blinding not clear, possible industrial influence, disclosures not stated, small number of pa-tients, no follow-up after stop of intervention	Season not stated; decrease PEF in placebo group – stable in intervention group
Hirsch 1997[48]	double-blind placebo-controlled SLIT drops HDM	Mono-center, university hospital Germany	Not strictly specified	30, female n=10, 10,5 years (6-15 years)	'mild to moderate asthma': n=8; allergic rhinitis: n=8; asthma and rhinitis: n=14 Not further specified	Allergy SPT positive HDM, part also sensitized cat, dog, grasses	Drops SLIT HDM, 3 weeks run-in, maintenance 7 drops 3 days/week; total 12 months	Place bo drops (vehicl e only)	12 mont hs	Symptom scores, compliance, SPT 6 months, Lung function, metacholin e, serum IgE , collection of dust samples (exposure)	Less pulmonary symptoms No difference use of SABA No change in PD20 No serious side effects	Small number of patients, especially when specified per group. Enrollment of patients (possible selection bias) is not clear. Serious differences in patients	Season not stated; Asthma group not well-described, exacerbatio ns not described, 8 patients allergic rhinitis only

												groups, otherwise than intervention (type and duration of disease), no follow-up after intervention. 20% drop-out in intervention group, no intention-to-treat analysis	
Pajno 2003[50]	double-blind placebo-controlled SLIT drops *Parietaria*	Mono-center, Italy	Inclusion: seasonal asthma and rhinoconjunctivitis, DDA, poor symptom control despite antihistamine, ICS and nedocromil use du-ring pollen sea-son, positive skin prick test *Parietaria*, Specific IgE to *Parietaria*. Exclusion: sensiti-zation to other allergens, previous immunotherapy, severe	38, 20 female, 11 years,	DDA, seasonal asthma, poor control despite medication, including ICS, patients with PD20<2.0mg excluded	Mono sensibilization to *Parietaria*, SPT and RAST positive	Drops SLIT *Parietaria*, 4 weeks run-in, maintenance every other day, total 12 months, co-medication with fluticasone	Placebo drops + flutica-sone 2nd control group: no pro-tocolled medica-tion	12 months	Symptom scores, VAS score during pollen season, compliance, SPT 6 months, serum IgE	No diff symptom scores Better VAS in SLIT group	Patient selection not clear: 30/38 children were randomized; 8 were control (not willing to participate in trial?), possible selection bias	Unclear whether fluticasone was given intranasally or orally No lung function or PD20

			asthma (FEV_1<70%), other diseases										
Pajno 2004# [51]	double-blind placebo-controlled SLIT drops *Parietaria*	Mono-center, Italy	seasonal asthma during spring and allergic rhinitis	30 (8-14 years)	DDA	Mono sensibilization to *Parietaria*, SPT and RAST positive	Drops SLIT *Parietaria*, 4 weeks run-in, maintenance every other day, total 12 months	Placebo drops	24 months	Lung function and PD20	No change in lung function, improvement in BHR (PD20) after 2 years	1 author affiliated to pharmaceutical industry	
Rolinck-Werninghaus 2004[53]	double-blind placebo-controlled SLIT drops grass-pollen	Multi-center, university clinics, Germany	Allergic rhinitis with or without seasonal asthma Exclusion criteria: perennial asthma, ICS use	Total 97 (32 female), 3-14 years Asthma: n=39	DDA, seasonal asthma, no ICS use	Grasspollen IgE and SPT positive Others not mentioned	Drops SLIT 5-grass mixture, 4 week run-in, 3 doses/week, total 32 months 1000 STU were equivalent to 25 BU and contained 2.5 µg of major grass pollen allergens. The monthly dose during maintenance treatment was 6 µg (0.5 µg/dose,3 times/week). The median for the total duration of treatment was 32 months (January 1999 to November 2001) with a median cumulated dose	Placebo drops	32 months	Primary end-point: multiple symptom-medication score, lung function, FeNO (part of the participants), complications	Less use of combined medication (asthma medication not analyzed separately). Lung function inconclusive; No change in FeNO 1 patient asthma exacerbation related to SLIT	2nd author affiliated to pharmaceutical industry	"this is not my patient" (perennial asthma excluded); lung function only analyzed as absolute values (not % predicted)

							of 188 µg allergen						
Ippoliti 2003[56]	double-blind placebo-controlled SLIT drops HDM	Monocenter, Italy	Mild/moderate asthma with or without rhinoconjunctivitis, FEV_1 > 70% predicted, mono-allergy HDM Exclusion: other allergies, severe asthma	86 (5-12 years); 35 female	Mild/moderate asthma, no seasonal asthma	Mono HDM	Drops SLIT *Dermatophagoides pteronyssinus* 1 + 2, 3 doses/week, 6 months	Placebo drops	6 months	Symptoms (unexplained scale), FEV_1, serum parameters, tolerance	Symptom scale not explained FEV_1; SLIT: 83,4% → 92,6%; placebo: 80,7% → 81,2% (no test)	Poor description of methods (randomization, blinding, drop-out, outcome assessment, and results), selected population?	
Niu 2006[57]	double-blind placebo-controlled SLIT drops HDM	Multicenter, Taiwan	6-12 years, mild/moderate asthma, mono-allergy HDM, FEV_1 > 70%. Exclusion: other allergies, severe asthma	110; 97 in follow-up (39 female)	Mild/moderate asthma	Mono HDM	Drops SLIT *Dermatophagoides pteronyssinus* + *Dermatophagoides farinae*, 4 weeks pretreatment, 3 weeks inductions, 21 weeks treatment, 2 weeks evaluation follow-up	Placebo drops	30 weeks	Symptom scores, medication scores, lung function, skin prick test, serum IgE, global assessment, safety	Symptoms FEV_1: no numeric data described	Poor description of randomization and blinding procedure, poor outcome reports	
Pajno 2000[58]	double-blind placebo-controlled SLIT drops HDM	Monocenter Italy	Mild/moderate asthma, mono-allergy HDM Exclusion: other allergies, severe asthma	24 (8-15 years); 11 female	Mild/moderate asthma	Mono HDM	Drops SLIT *Dermatophagoides pteronyssinus* 1 + 2, maintenance 3 doses/week, 3 years	Placebo	3 years	Symptoms, medication use, asthma episodes, laboratory tests, side effects	Only nighttime symptoms reported	Few children, methodological failure on drop-outs, selective outcome report	

Abbreviations: µg: micrograms; BHR: bronchial hyperreactivity; BU: biological units; DDA: doctor diagnosed asthma; FeNO: fraction nitric oxide in exhaled air; FEV_1: forced expiratory volume in 1 second; HDM: house dust mite; ICS: inhaled corticosteroids; IR: index units of reactivity; n: number; PD20: concentration (metacholin/histamine) that causes a 20% fall in FEV_1; PEF: peak expiratory flow; RAST: radioallergent sorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonists; SLIT: sublingual immunotherapy; SPT: skin prick test; STU: specific treatment units; VAS: visual analogue scale

** Doctors diagnosed asthma? Stable/seasonal asthma? Mild/severe asthma?*

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, adverse reactions and/or complications
‡ e.g. randomization procedure, blinding, risk of bias
*** defined as an abrupt and/or progressive worsening of symptoms of shortness of breath, chest tightness, or some combination of these symptoms, which did not respond to regular use of beta-2-agonists for a duration of 24 hours*
 # is long term follow-up of Pajno 2003

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A GRADE (Grading of Recommendations Assessment, Development and Evaluation) systematic review of immunotherapy in childhood asthma: evidence from previous systematic reviews no longer applicable in current clinical practice

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A GRADE (Grading of Recommendations Assessment, Development and Evaluation) systematic review of immunotherapy in childhood asthma: evidence from previous systematic reviews no longer applicable in current clinical practice

Authors

1. Erik-Jonas **van de Griendt*** MD, paediatric pulmonologist, DeKinderkliniek Almere and Academic Medical Centre Amsterdam, Hospitaaldreef 29, 1315 RC Almere, The Netherlands e.j.vandegriendt@amc.uva.nl *and*

   Mariska K **Tuut***, MSc, epidemiologist, PROVA, Spoorstraat 31, 7051 CG Varsseveld, The Netherlands, m.tuut@provaweb.nl

2. Hans de Groot MD, PhD, allergologist, Department of Paediatric Allergology, Reinier de Graaf Group, Reinier de Graafweg 5, 2625 AD Delft, The Netherlands, h.degroot@rdgg.nl

3. Paul L.P. Brand MD, PhD, paediatrician, Princess Amalia Children's Center, Isala Hospital, P.O. Box 10400, 8000 GK Zwolle, the Netherlands; UMCG Postgraduate School of Medicine, University Medical Center and University of Groningen, The Netherlands, p.l.p.brand@isala.nl

**both authors contributed equally*

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Correspondence:

Erik-Jonas van de Griendt, dept of paediatrics, DeKinderkliniek
Hospitaaldreef 29
1315 RC Almere
The Netherlands

telephone: +31 36 7630030
e-mail: e.j.vandegriendt@amc.uva.nl

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

EJG designed the study, chaired the guideline working group, provided clinical input (e.g. defined clinical relevant outcome measures, judged the literature review from a clinical point of view), wrote and revised the manuscript, and approved the final version.

MKT designed the study, was methodologist of the guideline working group, provided methodological input (e.g. provided literature search, selection, critical appraisal, GRADE evidence profiles), wrote and revised the manuscript, and approved the final version.

HdG was member of the guideline working group, designed the study, revised the manuscript and approved the final version.

PB provided clinical input, revised the manuscript and approved the final version.

All authors meet full criteria for authorship, i.e. all contributed substantially, revised, approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data sharing statement

Extra data can be accessed in the online repository. Apart from this, no additional data are available.

Transparency declaration

The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Abbreviations

- 95%CI: 95% confidence interval
- AMSTAR: A Measurement Tool to Assess Systematic Reviews
- FEV_1: forced expiratory volume in 1 second
- GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- ICS: inhaled corticosteroids
- RCT: randomized controlled trial
- SCIT: subcutaneous immunotherapy
- SR: systematic review
- SLIT: sublingual immunotherapy

Key words: allergy, asthma, children, adolescents, immunotherapy, efficacy, GRADE, systematic review

Abstract

Objective. Because most children with asthma now use inhaled corticosteroids (ICS), the added benefit of immunotherapy in asthmatic children needs to be examined. We re-assessed the effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) in childhood asthma treatment focusing on studies with patient relevant outcome measures and children using ICS.

Methods. We used the GRADE approach to systematically search and appraise the evidence using predefined critical patient relevant outcomes (asthma symptoms, asthma control and exacerbations). We searched to retrieve systematic reviews and randomized controlled trials on immunotherapy for asthma in children (1960 - 2017). We assessed the quality of the body of evidence with GRADE criteria.

Results. The quality of the evidence for SCIT was very low due to a large risk of bias and indirectness (dated studies in children not using ICS). No effect of SCIT was found for asthma symptoms; no studies reported on asthma control. For asthma exacerbations, studies favoured SCIT. We have little confidence in this effect estimate, due to the very low quality of evidence. For SLIT, quality of the evidence was very low due to a large risk of bias, indirectness and imprecision. The outcome “asthma symptoms” could not be calculated due to lack of standardization and large clinical heterogeneity. Other predefined outcomes were not reported.

Conclusion. The beneficial effects of immunotherapy in childhood asthma found in earlier reviews are no longer considered applicable, because of indirectness (studies performed in children not being treated according to current asthma guidelines with inhaled corticosteroids). There was absence of evidence to properly determine the effectiveness or lack thereof of immunotherapy in childhood asthma treatment.

Strengths and limitations

- This study is the first review evaluating immunotherapy in asthmatic children using the GRADE approach, focusing more on clinically relevant than on statistically significant differences in patient relevant outcomes.
- Contrary to earlier reviews our study concluded that there is no evidence for beneficial effects of immunotherapy for asthma in children.
- A limitation of the study was the lack of evidence, especially the lack of recent studies in current pediatric asthma populations, and lack of reported outcomes in the included studies.
- This study has focused on critically appraising ancient evidence for nowadays practice, rather than endeavoring to be complete.

Introduction

Asthma affects 10-15% of school-aged children. For children with persistent asthma, all international guidelines recommend daily controller treatment with inhaled corticosteroids (ICS), and reliever medication (short-acting β-2-agonists) as needed.[1,2] Although many children achieve complete asthma control using this effective and safe treatment,[1] some need additional treatment to obtain disease control.[3,4] Identification and treatment of comorbidities in children with problematic severe asthma is part of the stepwise approach to improve asthma control in these children.[5,6]

The most common of these comorbidities in children with asthma is allergic rhinitis,[5] symptoms of which occur in 60-80% of asthmatic children.[7,8] Allergic rhinitis shares a common pathophysiological pathway with asthma, which has been described as the united airway concept.[9] Allergic rhinitis is associated with worse asthma control in children, and accumulating evidence suggests that treatment of allergic rhinitis with intranasal steroids improves not only rhinitis, but also asthma symptoms in these patients.[7,10,11]

When symptoms of allergic rhinitis cannot be sufficiently controlled with nasal corticosteroids and oral antihistamines,[9,12] immunotherapy can be considered as additional treatment.[13] Subcutaneous immunotherapy (SCIT) requires repeated injections with an allergen extract and is available for allergens such as grass and tree pollen and house dust mite. After disappointing results of low-dose preparations in drops, effective high-dose sublingual immunotherapy (SLIT) has now become available with grass pollen allergen extract in a daily sublingual tablet.[14,15] A Cochrane systematic review, first published in 2000, and last updated in 2010, reported beneficial effects of immunotherapy in children with asthma.[16] Multiple studies in this latter review, however, were performed before or in the 1980s, when most children with asthma were not using ICS.

As part of the update of the Dutch pediatric guideline on childhood asthma, we evaluated the literature on the added value of SCIT and SLIT in childhood asthma.[17] Our structured clinical question was to assess whether immunotherapy (subcutaneous or sublingual), as an add-on to usual care with daily ICS, improves asthma outcomes in children (6-12 years) and adolescents (>12 years) with persistent asthma and sensitization to relevant aeroallergens (grass or tree pollen, house dust mite, or combinations), with or without symptoms of allergic rhinitis.

Methods

We used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to appraise and summarize the body of evidence. GRADE is an internationally approved standard for managing complex evidence reviews.[18] In contrast to former grading systems, GRADE focuses on the quality of the total body of evidence, instead of judging single studies. Another important characteristic of GRADE is that predefined outcomes with thresholds for clinical relevance are being used.[19] In earlier grading systems, the evidence was summarized using outcomes reported in studies, not necessarily being outcomes a guideline development group would be interested in.[20] GRADE avoids the use of surrogate or intermediate outcomes, and uses outcomes and differences that are more clinically relevant to patients instead. Starting from a systematic review, for each outcome the quality of evidence can be downgraded or upgraded, for instance based on risk of bias, inconsistency, indirectness, possible publication bias, and dose-response relation.

The guideline development group included an epidemiologist, paediatric respiratory physicians, paediatricians, an allergist, an ear-nose-throat specialist, a family physician, a lung function technician, a youth public health care physician, and patient representatives. The guideline development group predefined clinically relevant outcomes and divided these into critical (contributing to the overall quality of evidence), important (also relevant to the content of the guideline) and not important outcomes. For each outcome, a minimal clinically important difference was defined *a priori*. The outcomes taken into account in our literature review are summarized in *table 1*, with corresponding minimal clinically important differences.[21-24]

Table 1. Patient relevant outcomes and clinical relevance

Outcome	Importance	Minimal clinically important difference
Asthma symptoms	Critical	ACT: 3 c-ACT: (2-)3*
(Severe) exacerbations	Critical	NNT n=10
Asthma control	Critical	ACT: 3 c-ACT: (2-)3*
(Disease-specific) quality of life	Important	PAQLQ: 0.5 (scale 0-7)*
Change in FEV_1	Important	>5%predicted

* or comparable differences on other valid scales representing this outcome

Abbreviations: ACT: asthma control test; c-ACT: child ACT; NNT: number needed to treat (to prevent one exacerbation); PAQLQ: Pediatric Asthma Quality of Life Questionnaire

We applied a sensitive search strategy to retrieve all available evidence addressing the clinical question, focusing on systematic reviews (SRs) about asthma and immunotherapy in children. Literature searches were performed in March 2012 for the guideline (from 1960 onwards), and updated in April 2015 for the purpose of this review. A second update, including an expansion of the searching scope, was performed in June 2017. *(see table E1 in the Online Repository)*. In the original search, we searched in the Cochrane Database of

Systematic Reviews, the Database of Abstracts of Reviews of Effectivenessand the Cochrane Central Trial Register. . In the 2017 update we also searched for systematic reviews in the Medline and Embase databases (again from 1960 onwards). Two reviewers (EJvdG, MKT) independently screened the abstracts using predefined inclusion criteria: methodology (SRs), patients (children with allergic asthma), and SCIT and/or SLIT as an intervention. Animal studies, conference abstracts, and studies published in languages other than English, Dutch and German were excluded. Differences between reviewers were resolved by consensus. Selected abstracts were critically appraised with respect to study population, intervention and methodological aspects (e.g. systematic search and selection, inclusion of randomized controlled trials (RCTs)), which led to a further selection. An expert in the field (HdG) judged the selection for completeness.

All included studies were summarized in evidence tables by two reviewers (EJvdG, MKT). SRs were critically appraised using the AMSTAR checklist (A Measurement Tool to Assess Systematic Reviews).[25] AMSTAR scores range from 0-11, a higher score indicating better quality (less bias). The Jadad scale was used to assess the methodological quality of each included RCT.[26] This score ranges from 0-5, a higher score denoting a better quality. All eligible studies together defined the body of evidence, of which the quality was determined (per relevant outcome and overall quality) and GRADE Profiles were created. Results from SRs and RCTs were pooled, if possible, in meta-analyses using RevMan 5. We calculated standardized mean differences for continuous outcomes, because of the usage of different symptom scales in the underlying studies. We calculated risk ratios for dichotomous outcomes, to compare the probability of these outcomes between the intervention and control groups. In the meta-analyses we used random effects models, because of the possibility of generalization of the outcomes for different allergens, and tested the difference between intervention and control with the inverse variance method, since this method is typically used in meta-analyses to combine the results of independent studies. We reported 95% confidence intervals (pre-defined significance level: 0.05). Conclusions were drawn, based on quality and content, per outcome and discussed in the expert group until consensus was reached.

Patient involvement

The guideline development group included patient representatives who helped defining our clinical question, approved outcome measures and assessed its clinical relevancy. The burden of interventions and patient considerations were assessed as part of the GRADE evaluation. Patients were not directly involved in this systematic review since we reviewed published literature.

Results

Literature search and selection

Screening of titles and abstracts yielded 83 eligible studies, 10 of which fulfilled the inclusion criteria.[16,27-35] After examining these 10 papers in full, 5 more studies were excluded *(figure 1)*.

Experts in the guideline working group confirmed that no relevant publications were missed. The updated search (April 2015) revealed 43 additional studies, of which 2 fulfilled the inclusion criteria.[36,37] Full text examination resulted in exclusion of these 2 studies. The extended and updated search in June 2017 resulted in 177 hits, of which 6 were selected to full paper study [38-43]. These studies were systematic reviews in the field of SCIT and/or SLIT in children with asthma. Most of the included RCT's in these reviews had already been included in the 2015 search. We only added RCT's of those reviews to our meta-analyses that have not been included earlier. As a result, we added one study[44].

< figure 1> Literature selection

Results of SCIT

Description of studies

We retrieved one Cochrane SR on the effectiveness of SCIT in patients with asthma , including 90 RCTs with a total of 3,792 patients.[16] This was a high-quality review (AMSTAR score 10/11). Fourteen of the included RCTs were performed in children exclusively; another 24 included children and adults. In a few studies the age inclusion criteria were not clear. The characteristics of this review are summarized in an evidence table (*see table E2 in the Online Repository*). Only nine RCTs included in this review reported on our predefined outcomes in children. In these nine studies different allergens or combinations were studied (house dust mite (3), dog dander (1), grass pollen (1), mold (1), grass pollen/house dust mite (1), tailored combinations (2)). Two RCTs published after the 2010 Cochrane review were retrieved. In the first, the clinical efficacy of house dust mite-specific SCIT in 20 asthmatic children was compared to no intervention in 20 others; patients were followed up for six months.[34] In the other, the effects of allergen-specific SCIT on corticosteroid dose in asthmatic children was evaluated.[35] Details of all included RCTs are summarized in the evidence table (*see table E3 in the Online Repository*).

Quality of the evidence

Little information was given about the included studies in the Cochrane review; e.g. follow-up was not stated. There were also other concerns about the quality of the literature, e.g. not all studies were double-blind and placebo-controlled, and randomization procedures were poor. Therefore we re-analyzed the individual paediatric studies in the Cochrane review, plus the added studies.[34,35] Jadad scores of the single studies are presented in *table 2*.

Table 2. Jadad scores of RCTs on SCIT

	Randomization*	Blinding**	Withdrawals#	Total
Adkinson 1997[45]	1	1	1	3
Altintas 1999[46]	1	1	1	3
Dreborg 1986[47]	1	-	-	1
Hill 1982[48]	1	-	-	1
Johnstone 1961[49]	2	1	-	3
Johnstone 1968[50]	2	1	1	4
Price 1984[51]	1	1	-	3
Tsai 2010[34]	1	-	1	2
Valovirta 1984[52]	1	-	1	2
Warner 1978[53]	1	1	1	3
Zielen 2010[35]	1	1	1	3

** 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate*

*** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate*

 # 1 point if the number and the reasons for withdrawal in each group are stated

The quality of the body of evidence for all critical and important outcomes was very low *(table 3)*, mainly due to large risk of bias and indirectness. The large risk of bias was caused by a lack of allocation concealment, lack of information on follow-up, and loss to follow-up. The reason for downgrading for indirectness was the publication year of the underlying studies; populations and interventions were considered inapplicable to current clinical practice.

Table 3. GRADE Evidence Profile SCIT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SCIT	No intervention	Relative (95%CI)	Absolute (95%CI)		
Asthma symptoms (assessed with: Asthma symptom scores)												
5[a]	RCT	Very serious[b]	Not serious	Serious[c]	Not serious	None	136	286	-	Standardized Mean Difference 0.04 lower (95%CI: -0.42 to 0.33)	⊕OOO VERY LOW	CRITICAL

Exacerbations (assessed with: Symptomatic deterioration)												
5[a]	RCT	Serious[d]	Not serious	Very serious[e]	Not serious	None	64/253 (25.3%)	92/153 (60.1%)	Risk ratio 0.43 (0.34 to 0.56)	343 fewer per 1000 (95%CI: -397 to -)	⊕OOO VERY LOW	CRITICAL
Asthma control – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Abbreviations: 95%CI: 95% confidence interval; RCT: randomized controlled trials; SCIT: subcutaneous immunotherapy

a. *Studies in Cochrane review Abramson + Tsai*
b. *The underlying studies had a quite large risk of bias, due to lack of allocation concealment, problems with blinding, and lack of information on follow-up (and loss-to-follow-up)*
c. *We downgraded for indirectness, because the included studies are quite old and maintenance medication may have changed probably; thus, study populations may alter from nowadays patients with moderate to severe asthma*
d. *We downgraded for risk of bias, because of problems with blinding and loss-to-follow-up*
e. *We assessed very serious indirectness, because most included studies for this outcome are very old, and carried out before the ICS-era; thus, patients nowadays differ from study populations*

Critical outcomes

Asthma symptoms. Four small studies carried out in children only reported this outcome in the Cochrane review.[16] We extracted these results from the Cochrane review and updated these with the results from Tsai et al.[34] Results are presented in *figure 2*.

<figure 2 >

The meta-analysis showed no significant effect of SCIT on asthma symptoms.

Asthma exacerbations. Five studies (published 1961-1984) in the Cochrane review, carried out in children only, reported this outcome.[16] No relevant studies of sufficient quality were published afterwards. Our meta-analysis included 253 patients on immunotherapy and 153 on placebo. The pooled risk ratio was 0.47 (95%CI: 0.31 – 0.72), favouring immunotherapy (see *figure 3*). The absolute risk reduction was 35%, giving a number needed to treat of 3.

< figure 3 >

No studies reported results on the critical outcome asthma control.

Important outcomes

No studies reported results on quality of life or lung function (FEV_1).

Results of SLIT

Description of studies and quality of the evidence

We retrieved two SRs on SLIT in patients with asthma.[29,32] The updated search in 2017 resulted in the addition of one RCT[44]. The characteristics of the SRs are summarized in evidence table *E2 (Online Repository*). The quality of the reviews was moderate; both had an AMSTAR score of 7/11. Weaknesses included the absence of an 'a priori design', exclusion of grey literature, not assessing the likelihood of publication bias and not mentioning conflicts of interest in one review,[29] and the absence of an 'a priori design', no information about excluded studies, too firm conclusions compared to the weak evidence, and not assessing the likelihood of publication bias in the other.[32] One review included both children and adults, and patients with asthma and/or rhinitis.[29] Because of the quality concerns of both existing SRs, we set out to perform a meta-analysis of the original studies that fulfilled our selection criteria. Jadad scores of selected studies, as well as an overview of the outcomes of those studies, are presented in *table 4*. Study characteristics are summarized in the evidence table (*see table E4 in the Online Repository*). We rated the quality of evidence to be very low, due to a large risk of bias, imprecision and indirect evidence.

Table 4. Summary of quality and outcome measures of selected RCT's in reviews Calamita et al, Penagos et al and added Pham-Thi et al.[29,32, 44]

Review	RCT	Eligible	Jadad-score				Reported on asthma symptoms	Reported on exacerbations	Reported on asthma control	Reported on disease specific quality of life	Reported on lung function (FEV_1)
			Randomization*	Blinding**	Withdrawals#	Total					
Calamita[29]	Bahceciler 2001[54]	Yes	1	1	1	3	+	-	-	-	-
	Hirsch 1997[55]	Yes	2	1	1	4	+	-	-	-	-
	Niu 2004[24]	No, conference abstract									
	Novembre 1991[56]	No, Italian language									
	Pajno 2003[57]	Yes	2	1	1	4	+	-	-	-	-
	Pajno 2004$ [58]	Yes	2	1	1	4	-	-	-	-	+

	Rodriguez Santos 2004[59]	No, Spanish language									
	Rolinck-Werninghaus 2004[60]	Yes	1	2	0	3	+	-	-	-	-
	Yuksel 1999[61]	No, Spanish language									
Penagos[32]	Bahceciler 2001[54]	Overlap with Calamita									
	Caffarelli 2000[62]	No, children with asthma not separately analyzed									
	Hirsch 1997[55]	Overlap with Calamita									
	Ippoliti 2003[63]	Yes	1	1	0	2	+	-	-	-	+
	Niu 2006[64]	Yes	1	1	1	3	+	-	-	-	+
	Pajno 2000[65]	Yes	2	1	0	3	+	-	-	-	-
	Rolinck-Werninghaus 2004[60]	Overlap with Calamita									
	Tari 1990[66]	No, Spanish language									
	Vourdas 1998[67]	No, children with asthma not separately analyzed									
Pham-Thi[44]		Yes	2	1	1	4	+			+	+
Total							8	0	0	1	4

Abbreviations: FEV_1: forced expiratory volume in 1 second; RCT: randomized controlled trial

** 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate*

*** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate*

 # 1 point if the number and the reasons for withdrawal in each group are stated

$ Same patients as Pajno 2003[57]

Critical outcomes

Asthma symptoms. Eight of the included studies reported on asthma symptoms. Different symptom scores were used, none of them standardized or validated. Clinical differences in asthma scores were not defined and most studies reported improvement in the treatment group as well in the control group. We were not able to compile a meta-analysis of the results of the individual studies, because of the use of various symptom scales in the included studies. Since studies did not report results in a clearly comparable way, reporting the results of the individual studies was considered unreliable.

Other critical outcomes. No studies reported results on the critical outcomes exacerbations and asthma control.

Important outcomes

Quality of life. Pham-Thi et al. published results on quality of life using Childhood Asthma Questionnaires[44]. The authors reported a difference in severity between SLIT and placebo in the younger population (age 6-11 years), but not in older children (age 12-16 years). It is not stated whether this difference is clinically relevant.

Lung function. Four studies reported results on lung function (FEV_1). One of the studies reported no numeric data on lung function.[64] One study reported no variance (standard deviation), and no comparison of the baseline data.[63] The two remaining studies reported on FEV_1 percentage predicted,[58] and reported no significant differences between treatment groups, neither at baseline nor at follow-up.

351

Discussion

Summary of main results

Our GRADE systematic review showed no evidence of a significant difference in asthma symptoms between SCIT and placebo in children with allergic asthma, but some evidence for a significant and clinically relevant reduction in asthma exacerbations was found in SCIT-treated children. We have little confidence in the effect estimate, however, due to a large risk of bias and indirectness. Thus, the true effect of SCIT on exacerbations and asthma symptoms in the target population of interest is likely to be substantially different from the estimate of effect. There was absence of evidence on the effects of SCIT on lung function, asthma control, and quality of life in children with allergic asthma. There was no evidence for a beneficial effect of SLIT in reducing asthma symptoms and exacerbations, quality of life and lung function in children with allergic asthma. Our review does not address the efficacy of immunotherapy in children regarding complaints of allergic rhinitis and/or conjunctivitis, without having asthma.

Quality of the evidence / GRADE methodology

The overall quality of the evidence about the effectiveness of SCIT and SLIT was very low. This implicates that our confidence in the effect estimates is very limited. The true effect of SCIT and SLIT on patient relevant asthma outcomes in children with asthma may be substantially different from our estimates of the effect. We cannot conclude that the possible desirable effects of SCIT and SLIT outweigh the undesirable effects (e.g. influence on quality of life, adverse events, or increased resource expenditure), nor can we reject that hypothesis. Our concerns about the quality of evidence are based on (very) serious risk of bias and indirectness in the underlying primary studies. Firstly, the quality of many studies had to be downgraded because of risk of bias due to lack of allocation concealment, lack of information on follow-up, and loss to follow-up. Secondly, included studies were heterogeneous in the patients included and allergen extracts used, with different dosing regimens and duration being studied, targeting different inhaled allergens. We have concerns about the potential different responses and the generalizability of the evidence. Thirdly, and most importantly, for SCIT, the quality of the body of evidence was downgraded because of indirectness, since patients in the original studies long ago are likely to differ considerably from patients nowadays.

Fourth, different studies used variable definitions of asthma exacerbations. We had to use ‘worsening of asthma’, which may not represent real-life patient relevant exacerbations. This

may decrease the applicability of the evidence. In addition, there were no studies using the predefined important outcomes quality of life and asthma control.

Finally, and most importantly, we have concerns on comparability of patients. Several included studies dated from the 1980s or earlier, when allergic rhinitis treatment with selective antihistamines and nasal corticosteroids was not available. Against the background of the united airway concept, the comorbidity allergic rhinitis in patients in these studies cannot be compared to patients in clinical practice today.[9] Similarly, widespread use of ICS was not introduced in childhood asthma treatment until the 1990s.[68] Most studies on SCIT in children with asthma were published decades ago, during the pre-ICS era. The patients in the described studies represent an incomparable group compared to the child with asthma in contemporary clinical practice. Specifically, it is unclear whether the beneficial effects found in the systematic review of earlier studies is applicable to children with asthma treated according to contemporary guidelines with daily ICS controller therapy.[16]

In our opinion and that of others, the GRADE approach is superior to former methods of SRs, because it focuses on predefined patient relevant outcomes, predefined minimally clinical important differences and because it judges the complete body of evidence. One RCT among paediatricians studied the influence of different guideline grading systems on clinician's decisions.[69] GRADE showed the largest change in direction on the clinical decision. However, the added value of GRADE on guideline implementation or patient care, has not been formally evaluated, the GRADE approach is still rather complex for non-methodologists.

To formulate recommendations for clinical practice, not only the body of evidence concerning effectiveness of an intervention is important. Recommendations should balance the benefits and harms of the intervention of interest, and take patient preferences and resource use into account. Since (after critical evaluation) no benefits of SCIT and SLIT for children with asthma were determined, we consider it unlikely that the benefits will exceed the harms. Patient preferences were included in the formulation of our guideline recommendations.

Agreements and disagreements with other studies or reviews

Using GRADE and re-analyzing data from children with allergic asthma only, we came to different conclusions on the effectiveness of SCIT and SLIT in children with asthma than the authors of the original SRs. We believe this highlights the importance of using GRADE methodology to systematically review evidence for patient relevant outcomes, not focusing on levels of evidence, but on underlying study validity, precision, directness, and applicability in current clinical practice. The 2009 position paper on SLIT describes history, use and

applicability of this treatment for allergic rhinitis.[70] It positions SLIT in children as a safe and useful therapy above and after more regular treatment for allergic rhinitis. Potential positive treatment outcome for allergic asthma is however mainly based on literature in adults. We show the lack of evidence and lack of applicability of treatment of immunotherapy for asthma in children. Since we have worries on the applicability of evidence in adults on children (who are still developing their immune system), we think further studies that compare immunotherapy for the contemporary treatment of asthma in children are urgently needed to fill in this gap.

Recently, a Cochrane SR on SLIT for asthma found a similar lack of data for important outcomes (e.g. exacerbations, symptom scores, quality of life) as we did.[71] Contrary to our study, the authors did no separate analysis for adults and children, and patients with asthma were not separately analyzed from patients without asthma.

Conclusions

Focusing on predefined patient relevant outcomes, and critically appraising the body of evidence using original studies and GRADE methodology, our systematic review on the effects of immunotherapy in children with asthma came to different conclusions than previous systematic reviews. We believe that this underscores the importance of using GRADE methodology in systematically reviewing evidence.

We found absence of valid applicable evidence on improvement of clinically relevant asthma outcomes in children with allergic asthma using SCIT or SLIT. This absence of evidence is due to serious risk of bias, large clinical heterogeneity between studies, and most importantly due to lack of applicability because studies were performed in the pre-ICS era.

Since the effect of immunotherapy added to contemporary asthma treatment with daily controller therapy is not clear, the drawbacks of immunotherapy should be considered carefully. SCIT is a complex and intensive form of treatment, associated with a (very) long duration of treatment, and considerable burden to the patient with (monthly) injections under adequate medical supervision due to potential (however rare) dangerous side effects, and may have relatively high costs and resource use. In SLIT the risk of serious side-effects is considerably smaller, but the other drawbacks of immunotherapy apply equally to this treatment. In our opinion therefore, when balancing the absence of evidence on a clear beneficial effect of SCIT or SLIT on clinically relevant patient outcomes in children with asthma with the considerable burden and costs of SCIT and SLIT, we do not recommend this treatment to children with asthma until further high-quality evidence from well-designed RCTs in children comparing SCIT or SLIT to contemporary asthma treatment becomes available.

453

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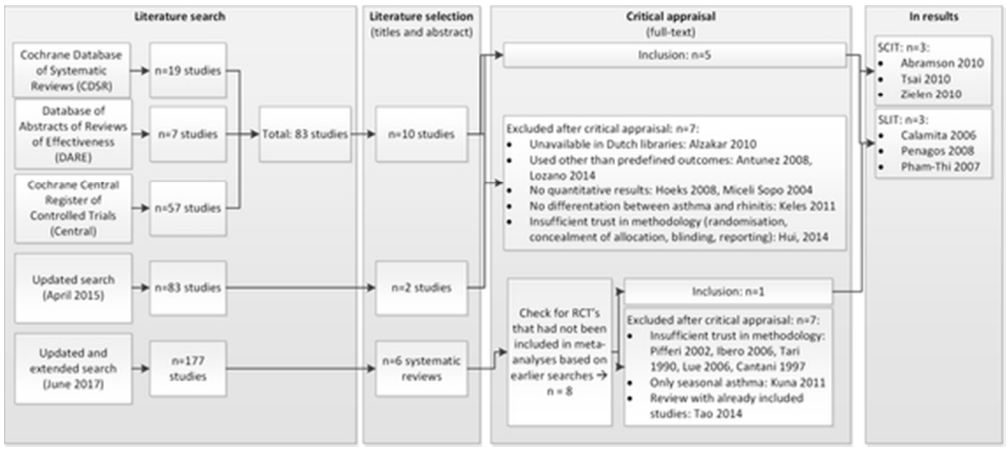
Figure legends

Figure 1. Literature search and selection

Figure 2. Meta-analysis of SCIT vs. placebo, outcome asthma symptoms. *Abbreviations: SD: Standard deviation; Std: Standardized; IV: inverse variance; random: random effect model; 95%CI: 95% Confidence Interval*

Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. *Abbreviations: 95%CI: 95% Confidence Interval; Fixed: Fixed effect model; M-H: Mantel-Haenszel*



Literature search and selection

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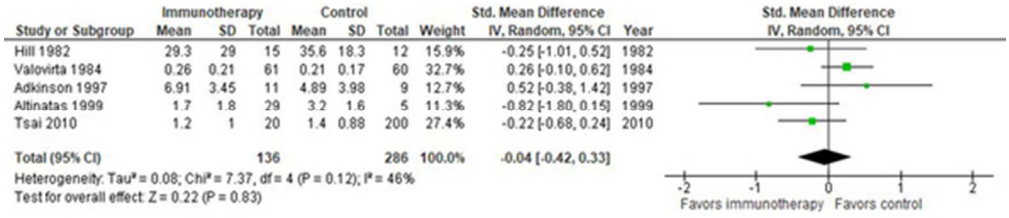

Figure 2. Meta-analysis of SCIT vs. placebo, outcome asthma symptoms. Abbreviations: SD: Standard deviation; Std: Standardized; IV: inverse variance; random: random effect model; 95%CI: 95% Confidence Interval

50x10mm (300 x 300 DPI)

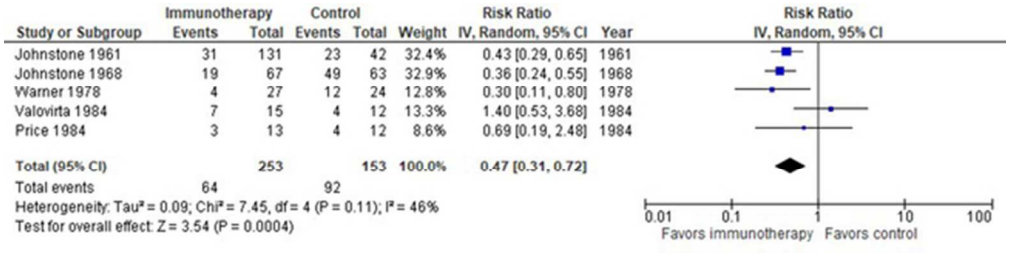

Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. Abbreviations: 95%CI: 95% Confidence Interval; Fixed: Fixed effect model; M-H: Mantel-Haenszel

54x13mm (300 x 300 DPI)

Table E1. Literature search

Search Cochrane Databases of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Central; Literature search 2015, April 25th
1. "asthmazoekacties jan 2012".ti. (0)
2. asthma.tw. (14671)
3. Bronchial Spasm.tw. (15)
4. asthma*.tw. (17541)
5. wheez*.tw. (869)
6. bronchospas*.tw. (777)
7. (bronch* adj8 spas*).tw. (52)
8. bronchoconstrict*.tw. (1663)
9. (bronch* adj8 constrict*).tw. (71)
10. airway* inflammation*.tw. (704)
11. or/2-10 (18894)
12. immunotherap*.kw,tw. (2803)
13. 11 and 12 (473)
14. subcutaneou*.kw,tw. (8020)
15. 12 and 14 (259)
16. 15 (259)
17. limit 16 to yr="2008 -Current" (57)
Search Medline 2017, June, 2nd
1 "Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study".fc_titl. (1)
2 "A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients".fc_titl. (1)
3 "Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite".fc_titl. (1)
4 "abramson$".fc_auts. and "Injection allergen immunotherapy for asthma".fc_titl. (1)
5 "Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method".fc_titl. (1)
6 "Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients".fc_titl. (1)
7 "Normansell$".fc_auts. and "Sublingual immunotherapy for asthma".fc_titl. (1)
8 "Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study".fc_titl. (1)
9 "Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric ".fc_titl. (1)
10 "Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled ".fc_titl. (1)
11 "Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan".fc_titl. (1)
12 "Immunomodulation during sublingual therapy in allergic children".fc_titl. (1)
13 "Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial".fc_titl. (1)
14 "Sublingual immunotherapy and influence on urinary leukotrienes in seasonal pediatric allergy".fc_titl. (1)
15 "A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen".fc_titl. (1)
16 "Sublingual immunotherapy with allergenic extract of Dermatophagoides pteronyssinus in asthmatic children".fc_titl. (1)
17 "Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial. ".fc_titl. (1)
18 "Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with ".fc_titl. (1)

19 "Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract ".fc_titl. (1)
20 "Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. ".fc_titl. (1)
21 or/1-3 (3)
22 or/4-20 (17)
23 21 or 22 (20)
24 "controle refs slit scit".ti. (0)
25 asthma/ or bronchial spasm/ (118686)
26 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).tw. (155964)
27 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).kf. (15593)
28 or/25-27 (176447)
29 23 and 28 (19)
30 23 not 29 (1)
31 rhinitis, allergic, perennial/ or rhinitis, allergic, seasonal/ (18469)
32 28 or 31 (188701)=P
33 Immunotherapy/ (36085)
34 Sublingual Immunotherapy/ (231)
35 Desensitization, Immunologic/ (9795)
36 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).tw. (16817)
37 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).kf. (442)
38 or/33-37 (61196)
39 "Injections, Subcutaneous"/ (31338)
40 33 and 39 (294)
41 34 or 35 or 36 or 37 or 40 (26000)=I
42 28 and 41 (3043)
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44 meta analysis.pt. (81124)
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53 (pooled adj3 analy*).tw. (14081)
54 (pooled adj3 analy*).kf. (128)
55 "cochrane$".fc_jour. (13410)
56 or/44-55 (258042)
57 randomized-controlled-trial.pt. (465042)
58 controlled-clinical-trial.pt. (94188)
59 randomized controlled trial/ (465042)
60 randomi?ed controlled trial?.tw. (131360)
61 random-allocation.tw,kf. (1445)
62 double-blind-method.tw,kf. (456)
63 single-blind-method.tw,kf. (81)
64 (random adj8 (selection? or sample?)).tw. (40888)
65 random$.tw. (952984)
66 or/57-65 (1156986)
67 "rct filter sprec".ti. (0)
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70 exp infant/ (1058929)
71 "Adolescent"/ (1847650)
72 or/68-71 (3858822)

73 "filter child".ti. (0)
74 23 and 72 (19)
75 23 not 74 (1)
76 32 and 41 and 56 (184)
77 32 and 41 and 72 and 56 (90) systrev

Search Embase 2017, June, 2nd

1 asthma/ (202909)
2 bronchospasm/ (25054)
3 bronchoconstriction/ (1300)
4 respiratory tract inflammation/ or allergic airway inflammation/ (11606)
5 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).tw. (215497)
6 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).kw. (51383)
7 perennial rhinitis/ (3627)
8 or/1-7 (279683)=P
9 sublingual immunotherapy/ (1695)
10 immunotherapy/ (67533)
11 subcutaneous drug administration/ (97428)
12 10 and 11 (1148)
13 subcutaneous immunotherapy/ (1226)
14 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).tw. (19513)
15 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).kw. (1765)
16 9 or 12 or 13 or 14 or 15 (21563)=I
17 8 and 16 (2229)
18 "Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study".fc_titl. (1)
19 "A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients".fc_titl. (1)
20 "Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite".fc_titl. (1)
21 "abramson$".fc_auts. and "Injection allergen immunotherapy for asthma".fc_titl. (1)
22 "Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method".fc_titl. (1)
23 "Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients".fc_titl. (1)
24 "Normansell$".fc_auts. and "Sublingual immunotherapy for asthma".fc_titl. (1)
25 "Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study".fc_titl. (1)
26 "Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric ".fc_titl. (1)
27 "Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled ".fc_titl. (1)
28 "Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan".fc_titl. (1)
29 "Immunomodulation during sublingual therapy in allergic children".fc_titl. (1)
30 "Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial".fc_titl. (1)
31 "Sublingual immunotherapy and influence on urinary leukotrienes in seasonal pediatric allergy".fc_titl. (1)
32 "A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen".fc_titl. (2)
33 "Sublingual immunotherapy with allergenic extract of Dermatophagoides pteronyssinus in asthmatic children".fc_titl. (2)
34 "Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial. ".fc_titl. (1)

35 "Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with ".fc_titl. (1)
36 "Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract ".fc_titl. (1)
37 "Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. ".fc_titl. (1)
38 or/18-20 (3)
39 or/21-37 (19)
40 38 or 39 (22)
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42 "filter systematic reviews & meta-analyses Embase".ti. (0)
43 meta analysis/ (127495)
44 "systematic review"/ (139284)
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47 (quantitativ$ adj5 (review? or overview?)).tw. (3786)
48 (methodologic adj5 (overview? or review?)).tw. (325)
49 (review$ adj3 (database? or medline or embase or cinahl)).tw. (19428)
50 (pooled adj3 analy$).tw. (20108)
51 (extensive adj3 review$ adj3 literature).tw. (2903)
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53 review.pt. (2259303)
54 52 and 53 (112526)
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56 (quantitativ$ adj5 (review? or overview?)).kw. (48)
57 (pooled adj3 analy$).kw. (354)
58 or/43-51,54-57 (381419)
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60 controlled clinical trial/ or randomized controlled trial/ (614267)
61 randomization/ (73811)
62 Major Clinical Study/ (2803898)
63 random$.tw. (1196822)
64 Double Blind Procedure/ (139034)
65 or/60-64 (3916117)
66 "einde filter rct embase".ti. (0)
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68 child/ (1526632)
69 infant/ (566151)
70 adolescent/ (1414197)
71 or/67-70 (3656088)
72 17 and 58 and 71 (85) systrev
73 (17 and 65 and 71) not 58 (370) rct
74 17 and 58 (208)
75 74 not 72 (123)
76 75 (123)
77 limit 76 to yr="2016 -Current" (14)
78 76 (123)
79 limit 78 to yr="2015 -Current" (31) extra systrev

Search Cochrane 2017, June, 2nd

#1 asthma*:ti,ab,kw 26843
#2 MeSH descriptor: [Asthma] this term only 9761
#3 MeSH descriptor: [Bronchial Spasm] explode all trees 360
#4 wheez*:ti,ab,kw 1642
#5 bronchospas*:ti,ab,kw 1594
#6 (bronch* near/8 spas*):ti,ab,kw 460
#7 bronchoconstrict*:ti,ab,kw 2204

#8	(bronch* near/8 constrict*):ti,ab,kw 121
#9	(airway* near/1 inflammation*):ti,ab,kw 1236
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 28980
#11	(perennial or seasonal or allergen* or hyposensiti*):ti,ab,kw 10214
#12	immunotherap*:ti,ab,kw 6399
#13	MeSH descriptor: [Immunotherapy] this term only 1140
#14	(SCIT or SLIT or (sublingual near/1 immunotherap*) or (subcutaneous near/1 immunotherap*)):ti,ab,kw 2033
#15	#11 or #12 or #13 or #14 15912
#16	#10 and #15 3351
#17	(child* or childhood or infant* or pediatr* or paediatric* or perinat* or neonat* or newborn* or infan* or boy* or girl* or kid* or schoolage* or juvenil* or adolescen* or toddler*):ti,ab,kw 239918
#18	#16 and #17 1570
#19	immunotherap*:ti,kw 5661
#20	subcutaneou*:ti,kw 12350
#21	(SCIT or SLIT or (sublingual near/1 immunotherap*) or (subcutaneous near/1 immunotherap*)):ti,kw 1257
#22	#13 or #19 or #20 or #21 17830
#23	#18 and #22 516
#24	(perennial or seasonal or allergen* or hypo-sensiti*):ti 5205
#25	#22 or #24 22321
#26	#25 and #18 927
#27	#16 and #22 1071
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#29	(#12 or #13) and (#20 or #28) 646
#30	#29 or #21 or #24 6616
#31	MeSH descriptor: [Desensitization, Immunologic] 2 tree(s) exploded 872
#32	(#31 or #30) and #10 1961
#33	MeSH descriptor: [Child] explode all trees 227
#34	MeSH descriptor: [Adolescent] explode all trees 90499
#35	MeSH descriptor: [Infant] explode all trees 15066
#36	#17 or #33 or #34 or #35 239918
#37	#32 and #36 816

Results	
Cochrane Databases of Systematic Reviews	19
Database of Abstracts of Reviews of Effectiveness	7
Cochrane Central Trials Register	57
emb20170602 scit slit systrev.	53
emb20170602 scit slit extra vanaf2015systrev	26
med20170602 scit slit systrev.	89
coc sr20170601 extra astma scit slit.	4
coc dare20170602	5

Table E2. Evidence table systematic reviews (SCIT + SLIT)

	Abramson, 2010[16]	Calamita, 2006[29]	Penagos, 2008[32]
Study design	Cochrane systematic review, consisting of 90 RCT's. 14 RCT's were carried out in children only; 24 were done in children and adults. The total study population (children and adults) consisted of 3.792 patients (of whom 3.459 had asthma)	Systematic review, consisting of 25 RCT's. Only 9 RCT's were carried out in children only. The total study population consisted of 1.706 patients (adults and children, with asthma and/or rhinitis)	Systematic review, consisting of 9 RCT's, all carried out in children. The total study population comprised 441 patients with asthma (seasonal, mild, moderate, and persistent)
Age (mean)	Not specified, variation between included studies	Not specified, there is a limited description of the characteristics of the included studies	Range specified per study, total range: 4-17 years
Setting (in RCT's)	-	-	-
Diagnosis (asthma/rhinitis)	Asthma	Asthma and rhinitis	Asthma
Eligibility criteria	RCT's, patients with asthma, allergen specific subcutaneous immunotherapy (administration of extracts of house dust mites, pollens, animal danders or molds, chemically modified allergoids or antigen-antibody complexes)	RCT's, double blinded, and open studies, patients with asthma and/or rhinitis, sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all lengths of treatment)	RCT's, double blinded, placebo controlled, patients ≤ 18 years, with a history of allergic asthma, with identified causal allergen, and proven IgE sensitization. Sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all durations of treatment)
Type of immunotherapy	Subcutaneous immunotherapy (variation of allergen abstracts in different included studies)	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy, mainly mites
Intervention	Subcutaneous immunotherapy	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy (mainly mites, further: O europaea, Holcus, P pretense *Dermatophagoides pteronyssinus*, grass mix), great variation in duration, range: 3-32 months
Control	Placebo	Placebo	Placebo
Primary outcomes	Asthmatic symptoms Asthma medication requirements Lung function Nonspecific bronchial hyper-reactivity Allergen specific bronchial hyper-reactivity	Asthmatic symptoms (symptom score) Asthmatic medication requirement Respiratory function tests (PEFR, FEV_1, FEF25-75%) Nonspecific bronchial provocation Adverse effects	Asthma symptoms Medication scores
Secondary outcomes	Local reactions Systemic reactions	-	

Comment	The results have not been presented separately for children in the review. We conducted new suitable meta-analyses.	The authors mentioned they used the Cochrane Collaboration method	-

Abbreviations: FEF25-75: maximum mid expiratory flow; FEV_1: forced expiratory volume in 1 second; PEFR: peak expiratory flow rate; RCT: randomized controlled trial; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

Table E3. Evidence table SCIT studies

Author, date	Study design	Setting	Eligibility	Participants (number, gender, age, and descriptive	Asthma type,* severity (e.g. on ICS?)	Allergy type (mono/multi, allergens,	Intervention (type, dose, duration)	Control	Follow-up (from start	Outcomes	Results reported by authors†	Critical appraisal‡	Comments
Adkinson, 1997[45]	Double blind, placebo controlled, parallel group RCT Placebo caramelized saline + histamine	?		121 allergic children with perennial asthma Mean age 9.2 (range 5.4 to 14) years, 79% boys	Perennial asthma 41% ICS, 2% systemic	80% dust mite, 77% ragweed, 69% rye grass	Subcutaneous multiple allergen immunotherapy Median 6 (range 2 to 7) allergen extracts	Placebo	?	Symptom scores Medication scores PEF rates Nonspecific BHR (methacholin FEV_1)	SCIT not useful in moderate to severe perennial allergic asthma	Study useful, however low rate of ICS	Allocation concealment unclear
Altintas, 1999[46]	Open placebo controlled RCT multiple groups	university		34 poorly controlled mild to moderate asthmatics aged 4 to 18 years; 30 patients in 3 groups, 4 placebo	ICS use not specified, no medical details on asthma	Mono-sensitization *Dermatophagoides pteronyssinus*	Subcutaneous immunotherapy with adsorbed or aqueous *Dermatophagoides pteronyssinus* extracts (in different dilutions)	Placebo		Symptom medication score IgE and IgG4 level Bronchial provocation tests	SCIT is useful and safe; no conclusion on asthma	Study not useful No data on ICS,	Allocation concealment unclear Study designed to compare 3 different abstracts of immunotherapy
Dreborg, 1986[47]	RCT, double blind Freeze dried caramelized histamine placebo	European		30 children with *Cladosporium* allergy, aged 5 to 17 years	Clinical history suggesting mold-induced asthma and/or rhinoconjunctivitis ICS not stated	*Cladosporium* allergy	*10 months Cladosporium* subcutaneous immunotherapy Or placebo	Placebo		Symptoms Medication PEF (no SD reported) Allergen specific BHR	Decrease in medication score, but not in symptom score Lower medication score in verum group	Study not useful No information on asthma medication No fixed study medication scheme	Allocation concealment unclear Asthma diagnosis not specified, (worsening of asthma in the *Cladospori*

													um season)
Hill, 1982[48]	Single blind RCT, rye grass pollen placebo	University Australia		20 asthmatic children, aged 9 to 14 years, with rye grass pollen allergy, positive at bronchoprovocation	ICS N=1 beclomethason N=8 cromoglycate		Subcutaneous immunotherapy with aqueous rye grass pollen extract	Placebo		Symptoms Medications (medians only reported, no SD)	no evidence that limited hyposensitization with a pollen extract is of any clinical benefit in seasonal asthma despite evidence of an immunological response.	Study not useful Primary outcome = IgE and IgG levels	No allocation concealment
Johnstone, 1961[49]	RCT, double blind, 4-year follow up Buffered saline control	United States general hospital		173 children with perennial asthma Severity = number of days of wheeze/year Placebo: n=41	No medication mentioned at all, no medication scores		Subcutaneous immunotherapy with relevant allergen extracts, administered by 3 regimens	Placebo		Asthma symptoms reported by mother Number of new allergies developing	Less new allergies developing Less symptoms and asthma attacks in the last year in the group 4	Study not useful No asthma medication scores	Allocation concealment unclear 4 different groups, 1 placebo (n=41) Group 2-4 different strength SCIT Last year single blind
Johnstone, 1968[50]	RCT, double blind Buffered saline control			130 children with perennial asthma; Severity = number of days of wheeze/year RCT, double blind Buffered saline control	No medication mentioned, no medication scores		Subcutaneous immunotherapy with relevant allergens administered by 3 regimens	Placebo		Asthma symptoms reported by mother	More children in SCIT group high dose overgrowing asthma at the age of 16 than placebo	Study not useful No asthma medication scores	Allocation concealment unclear 14-years follow up of Johnstone 1961
Price, 1984[51]	RCT, double blind			25 children with perennial asthma, aged 5 to 15 years	Asthma severity not specified asthma		Subcutaneous immunotherapy with *Dermatophag*	Placebo		Symptoms Medication Lung function Bronchoprovocation	Loss of late reaction on bronchoprovocation Only one out of 6	Study not useful Bronchoprovocation is	Continuation of study by Warner 1978 for second

	Saline placebo control				medication not specified		*oides pteronyssinus* extracts				children with severe asthma improved	surrogate outcome;	year with placebo group crossed over to active immunotherapy
Tsai, 2010[34]	RCT, no blinding, no intervention in control group	University hospital, Taiwan		40 children (21 boys), aged 5-14 years (average 8,5) >1 year moderate persistent to severe asthma, all monosensitized to house dust mite	Moderate persistent to severe asthma, using daily medication, most patient at least on ICS	House dust mite, diagnosed by SPT or specific antibody test	Subcutaneous injections of extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* (10000 AU/ml), initial dose 0,5AU/ml once a week. Dosage was increased weekly by 25-100% to reach optimal maintenance dose, with respect to local or systemic reaction. Maintenance therapy every 2 weeks during at least 3 months	No intervention	6 months (last follow-up)	Primary: Medication score (5 point scale, modified GINA) Secondary: PEF, asthma symptom score, number of contacts with health care providers	Mean medication score declined after 6 months in both groups; no significant between group differences. Both groups had reduction of asthma symptoms after 6 months, but no between group differences. There was no difference in PEF. Patients in the intervention group had more clinical visits than the control group, but no difference in emergency room or hospitalization	Very few patients, no blinding, randomization procedure not clear	
Valovirta, 1984[52]	RCT, double blind Caramel histamine placebo control	?		27 asthmatic children allergic to dog dander, aged 5 to 18 years	Asthma severity not specified asthma medication not specified		Subcutaneous immunotherapy with aluminium hydroxide bound dog	Placebo		Symptoms Allergen specific BHR	The decrease in bronchial sensitivity was less marked than that in conjunctival sensitivity and	Study not useful No asthma medication scores	Primary outcome dog dander sensitivity, not asthma 2 authors connected

							dander extract				statistically not significant		to pharmaceutical company
Warner, 1978[53]	RCT, double blind Tyrosine placebo control	University, United Kingdom		51 asthmatic children, aged 5 to 14 years, with positive *Dermatophagoides pteronyssinus* challenge	ICS n=12, cromoglycate n=24 SABA n=14	House dust mite, SPT and bronchoprovocation positive	Subcutaneous immunotherapy with tyrosine adsorbed *Dermatophagoides pteronyssinus* extracts	Placebo	1 year	Symptoms Medication Lung function (PEF, FEV 0.75) Allergen specific BHR	Less asthma medication in active group, but no difference in control or immediate response on bronchoprovocation	Useful; however incomparable low level of ICS	Allocation concealment unclear No fixed medication scheme
Zielen, 2010[35]	RCT, single blind, no control intervention	Multinational, multicenter		56 children with asthma GINA treatment II-III, on ICS, house dust mite (positive SPT), positive conjunctival provocation, significant RAST response	All on ICS, GINA II-III treatment	House dust mite SPT, provocative	SCIT with allergens extracted from *Dermatophagoides pteronyssinus* in 2 strengths: A: 1000 TU/ml; B: 10000 TU/ml. Initial therapy: weekly increasing doses strength A, followed by B. After reaching max individually tolerated dose, dosage intervals were increased to 6 weeks	No immunotherapy, only maintenance therapy with ICS	2 years	Primary: change in ICS dose steps to achieve asthma control Secondary: change in pre-bronchodilatory PEF, immunologic changes, nonspecific bronchial hyperreactivity	Less asthma medication in SCIT group as compared to control group, no change in asthma control, higher increase in PEF in intervention group. Adverse events in 97% in both groups	Block randomization. Multicenter, multinational is possible bicenter, binational. Conflict of interest in authors	

Abbreviations: AU: dosing units; BHR: bronchohyperreactivity; FEV1: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; ml: millilitres; n: number; PEF: peak expiratory flow; RAST: radioallergent sorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonist; SCIT: subcutaneous immunotherapy; SD: standard deviation; SPT: skin prick test; TU: dosing units

** Doctors diagnosed asthma? Stable/seasonal asthma? Mild/severe asthma?*

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, adverse reactions and/or complications

‡ e.g. randomization procedure, blinding, risk of bias

Table E4. Evidence table selected RCT's in children included in systematic reviews Calamita et al., Penagos et al. and Pham-Thi et al. (SLIT)

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
Bahcecile r 2001[54]	double-blind placebo-controlled SLIT drops HDM	Mono-center Turkey University hospital	Asthma with need for ICS, HDM allergic, ongoing respiratory symptoms despite mite avoidance and appropriate ICS treatment, > 7 years, FEV_1	15, 8 male, 11,7 years	Moderate asthma, need for ICS, respectively symptoms despite mite avoidance, FEV_1> 70%	Mono-allergy HDM but negative for all other aeroaller-gens	Drops SLIT, dose 100 IR/day, 4 weeks run-in, 4 weeks once daily, thereafter 2/week; total 6 months	Placebo drops	6 months	Symptom scores, compliance, SPT 6 months, Lung function, metacholine, serum IgE	Improvement asthma score. Less use of SABA, trend to-wards less ICS (not significant), no change in PD20, no serious side effects	Randomization and blinding not clear, possible industrial influence, disclosures not stated, small number of pa-tients, no follow-up after stop of intervention	Season not stated; decrease PEF in placebo group – stable in interventio n group
Hirsch 1997[55]	double-blind placebo-controlled SLIT drops HDM	Mono-center, university hospital Germany	Not strictly specified	30, female n=10, 10,5 years (6-15 years)	'mild to moderate asthma': n=8; allergic rhinitis: n=8; asthma and rhinitis: n=14 Not further specified	Allergy SPT positive HDM, part also sensitized cat, dog, grasses	Drops SLIT HDM, 3 weeks run-in, maintenance 7 drops 3 days/week; total 12 months	Placebo drops (vehicle only)	12 months	Symptom scores, compliance, SPT 6 months, Lung function, metacholine, serum IgE , collection of dust samples (exposure)	Less pulmonary symptoms No difference use of SABA No change in PD20 No serious side effects	Small number of patients, especially when specified per group. Enrollment of patients (possible selection bias) is not clear. Serious differences in patients	Season not stated; Asthma group not well-described, exacerbati ons not described, 8 patients allergic rhinitis only

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
												groups, otherwise than intervention (type and duration of disease), no follow-up after intervention. 20% drop-out in intervention group, no intention-to-treat analysis	
Pajno 2003[57]	double-blind placebo-controlled SLIT drops *Parietaria*	Mono-center, Italy	Inclusion: seasonal asthma and rhinoconjunctivitis, DDA, poor symptom control despite antihistamine, ICS and nedocromil use du-ring pollen sea-son, positive skin prick test *Parietaria*, Specific IgE to	38, 20 female, 11 years,	DDA, seasonal asthma, poor control despite medication, including ICS, patients with PD20<2.0 mg excluded	Mono sensibilization to *Parietaria*, SPT and RAST positive	Drops SLIT *Parietaria*, 4 weeks run-in, maintenance every other day, total 12 months, co-medication with fluticasone	Placebo drops + fluticasone 2nd control group: no pro-tocolled medica-tion	12 months	Symptom scores, VAS score during pollen season, compliance, SPT 6 months, serum IgE	No diff symptom scores Better VAS in SLIT group	Patient selection not clear: 30/38 children were randomized; 8 were control (not willing to participate in trial?), possible selection bias	Unclear whether fluticasone was given intranasally or orally No lung function or PD20

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
			Parietaria. Exclusion: sensiti-zation to other allergens, previous immunotherapy, severe asthma (FEV_1<70%), other diseases										
Pajno 2004[# 58]	double-blind placebo-controlled SLIT drops *Parie-taria*	Mono-center, Italy	seasonal asthma during spring and allergic rhinitis	30 (8-14 years)	DDA	Mono sensibilization to *Parietaria*, SPT and RAST positive	Drops SLIT *Parietaria*, 4 weeks run-in, maintenance every other day, total 12 months	Placebo drops	24 months	Lung function and PD20	No change in lung function, improvement in BHR (PD20) after 2 years	1 author affiliated to pharmaceutical industry	
Rolinck-Werning-haus 2004[60]	double-blind placebo-controlled SLIT drops grass-pollen	Multi-center, university clinics, Germany	Allergic rhinitis with or without seasonal asthma Exclusion criteria: perennial asthma, ICS use	Total 97 (32 female), 3-14 years Asthma: n=39	DDA, seasonal asthma, no ICS use	Grasspollen IgE and SPT positive Others not mentioned	Drops SLIT 5-grass mixture, 4 week run-in, 3 doses/week, total 32 months 1000 STU were equivalent to 25 BU and contained 2.5 µg of major grass pollen allergens. The	Placebo drops	32 months	Primary end-point: multiple symptom-medication score, lung function, FeNO (part of the participants),	Less use of combined medication (asthma medication not analyzed separately). Lung function inconclusi	2nd author affiliated to pharmaceutical industry	"this is not my patient" (perennial asthma ex-cluded); lung function only analyzed as absolute values (not

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
							monthly dose during maintenance treatment was 6 µg (0.5 µg/dose,3 times/week). The median for the total duration of treatment was 32 months (January 1999 to November 2001) with a median cumulated dose of 188 µg allergen			complications	ve; No change in FeNO 1 patient asthma exacerbation related to SLIT		% predicted)
Ippoliti 2003[63]	double-blind placebo-controlled SLIT drops HDM	Monocenter, Italy	Mild/moderate asthma with or without rhinoconjunctivitis, FEV_1 > 70% predicted, mono-allergy HDM Exclusion: other allergies, severe asthma	86 (5-12 years); 35 female	Mild/moderate asthma, no seasonal asthma	Mono HDM	Drops SLIT *Dermatophagoides pteronyssinus* 1 + 2, 3 doses/week, 6 months	Placebo drops	6 months	Symptoms (unexplained scale), FEV_1, serum parameters, tolerance	Symptom scale not explained FEV_1; SLIT: 83,4% → 92,6%; placebo: 80,7% → 81,2% (no test)	Poor description of methods (randomization, blinding, drop-out, outcome assessment, and results), selected population?	
Niu 2006[64]	double-blind placebo	Multicenter, Taiwan	6-12 years, mild/moderate asthma, mono-	110; 97 in follow-	Mild/moderate asthma	Mono HDM	Drops SLIT *Dermatophagoides*	Placebo drops	30 weeks	Symptom scores, medication	Symptoms FEV_1: no numeric	Poor description of	

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
	- controlled SLIT drops HDM		allergy HDM, FEV_1 > 70%. Exclusion: other allergies, severe asthma	up (39 female)			*pteronyssinus* + *Dermatophagoides farinae*, 4 weeks pretreatment, 3 weeks inductions, 21 weeks treatment, 2 weeks evaluation follow-up			scores, lung function, skin prick test, serum IgE, global assessment, safety	data described	randomization and blinding procedure, poor outcome reports	
Pajno 2000[65]	double-blind placebo-controlled SLIT drops HDM	Monocenter Italy	Mild/moderate asthma, mono-allergy HDM Exclusion: other allergies, severe asthma	24 (8-15 years); 11 female	Mild/moderate asthma	Mono HDM	Drops SLIT *Dermatophagoides pteronyssinus* 1 + 2, maintenance 3 doses/week, 3 years	Placebo	3 years	Symptoms, medication use, asthma episodes, laboratory tests, side effects	Only nighttime symptoms reported	Few children, methodological failure on drop-outs, selective outcome report	
Pham-Thi[44]	Double-blind placebo-controlled SLIT tablets HDM	Monocenter, France	Asthma, treated with inhaled corticosteroids, reversible bronchial obstruction, sensitized to HDM Exclusion: sensitization to perennial and	109 (5-16 years); 31 female	Mild asthma: 73 Moderate asthma: 36 All using ICS	Mono HDM	Tablets *Dermatophagoides pteronyssinus* + *Dermatophagoides farinae, 2 weeks updosing, then maintenance 17,5 months*	Placebo tablets	18 months	Asthma symptom score, asthma-free days, asthma medication score, lung function, quality of life, rhinitis scores,	No significant differences between SLIT and placebo in symptoms and FEV_1. Quality of life: in children 6-11	Poor description of blinding	

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
			seasonal allergens, previous immunotherapy							skin-prick tests, antibodies	significant difference on severity domain, clinical relevance not stated. Other domains, and older children: no significant difference between SLIT and placebo		

Abbreviations: µg: micrograms; BHR: bronchial hyperreactivity; BU: biological units; DDA: doctor diagnosed asthma; FeNO: fraction nitric oxide in exhaled air; FEV_1: forced expiratory volume in 1 second; HDM: house dust mite; ICS: inhaled corticosteroids; IR: index units of reactivity; n: number; PD20: concentration (metacholin/histamine) that causes a 20% fall in FEV_1; PEF: peak expiratory flow; RAST: radioallergent sorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonists; SLIT: sublingual immunotherapy; SPT: skin prick test; STU: specific treatment units; VAS: visual analogue scale

** Doctors diagnosed asthma? Stable/seasonal asthma? Mild/severe asthma?*

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, adverse reactions and/or complications

‡ e.g. randomization procedure, blinding, risk of bias

*** defined as an abrupt and/or progressive worsening of symptoms of shortness of breath, chest tightness, or some combination of these symptoms, which did not respond to regular use of beta-2-agonists for a duration of 24 hours*

 # is long term follow-up of Pajno 2003

PRISMA 2009 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.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
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.	n.a.
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.	9
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.	19
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table E1
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).	10; table E2
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.	10 (fig 1)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
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.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 1
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.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
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.	12 + fig 1
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.	Table E2, E3, E4
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).	Table 2, , table E2, E3, E4
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.	Fig 2, 3; Table E2, E3, E 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12 -15; Fig 2, 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.
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).	16
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).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

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(6): e1000097.

PRISMA 2009 Checklist

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BMJ Open

Applicability of evidence from previous systematic reviews on immunotherapy in current practice of childhood asthma treatment: A GRADE (Grading of Recommendations Assessment, Development and Evaluation) systematic review

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Applicability of evidence from previous systematic reviews on immunotherapy in current practice of childhood asthma treatment: A GRADE (Grading of Recommendations Assessment, Development and Evaluation) systematic review

Authors

1. Erik-Jonas **van de Griendt*** MD, paediatric pulmonologist, DeKinderkliniek Almere and Academic Medical Centre Amsterdam, Hospitaaldreef 29, 1315 RC Almere, The Netherlands e.j.vandegriendt@amc.uva.nl *and*

   Mariska K **Tuut***, MSc, epidemiologist, PROVA, Spoorstraat 31, 7051 CG Varsseveld, The Netherlands, m.tuut@provaweb.nl

2. Hans de Groot MD, PhD, allergologist, Department of Paediatric Allergology, Reinier de Graaf Group, Reinier de Graafweg 5, 2625 AD Delft, The Netherlands, h.degroot@rdgg.nl

3. Paul L.P. Brand MD, PhD, paediatrician, Princess Amalia Children's Center, Isala Hospital, P.O. Box 10400, 8000 GK Zwolle, the Netherlands; UMCG Postgraduate School of Medicine, University Medical Center and University of Groningen, The Netherlands, p.l.p.brand@isala.nl

**both authors contributed equally*

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Correspondence:

Erik-Jonas van de Griendt, dept of paediatrics, DeKinderkliniek
Hospitaaldreef 29
1315 RC Almere
The Netherlands
telephone: +31 36 7630030
e-mail: e.j.vandegriendt@amc.uva.nl

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

EJG designed the study, chaired the guideline working group, provided clinical input (e.g. defined clinical relevant outcome measures, judged the literature review from a clinical point of view), wrote and revised the manuscript, and approved the final version.

MKT designed the study, was methodologist of the guideline working group, provided methodological input (e.g. provided literature search, selection, critical appraisal, GRADE evidence profiles), wrote and revised the manuscript, and approved the final version.

HdG was member of the guideline working group, designed the study, revised the manuscript and approved the final version.

PB provided clinical input, revised the manuscript and approved the final version.

All authors meet full criteria for authorship, i.e. all contributed substantially, revised, approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data sharing statement

Extra data can be accessed in the online repository. Apart from this, no additional data are available.

Transparency declaration

The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Abbreviations

- 95%CI: 95% confidence interval
- AMSTAR: A Measurement Tool to Assess Systematic Reviews
- FEV_1: forced expiratory volume in 1 second
- GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- ICS: inhaled corticosteroids
- RCT: randomized controlled trial
- SCIT: subcutaneous immunotherapy
- SR: systematic review
- SLIT: sublingual immunotherapy

Key words: allergy, asthma, children, adolescents, immunotherapy, efficacy, GRADE, systematic review

Abstract

Objective. Because most children with asthma now use inhaled corticosteroids (ICS), the added benefit of immunotherapy in asthmatic children needs to be examined. We re-assessed the effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) in childhood asthma treatment focusing on studies with patient relevant outcome measures and children using ICS.

Methods. We used the GRADE approach to systematically search and appraise the evidence using predefined critical patient relevant outcomes (asthma symptoms, asthma control and exacerbations). We searched to retrieve systematic reviews and randomized controlled trials on immunotherapy for asthma in children (1960 - 2017). We assessed the quality of the body of evidence with GRADE criteria.

Results. The quality of the evidence for SCIT was very low due to a large risk of bias and indirectness (dated studies in children not using ICS). No effect of SCIT was found for asthma symptoms; no studies reported on asthma control. For asthma exacerbations, studies favoured SCIT. We have little confidence in this effect estimate, due to the very low quality of evidence. For SLIT, quality of the evidence was very low due to a large risk of bias, indirectness and imprecision. The outcome “asthma symptoms” could not be calculated due to lack of standardization and large clinical heterogeneity. Other predefined outcomes were not reported.

Conclusion. The beneficial effects of immunotherapy in childhood asthma found in earlier reviews are no longer considered applicable, because of indirectness (studies performed in children not being treated according to current asthma guidelines with inhaled corticosteroids). There was absence of evidence to properly determine the effectiveness or lack thereof of immunotherapy in asthma treatment in children with inhaled corticosteroids.

Strengths and limitations of this study

- This study is the first review evaluating immunotherapy in asthmatic children using the GRADE approach, focusing more on clinically relevant than on statistically significant differences in patient relevant outcomes.
- By using GRADE we identified indirectness in previous systematic reviews in this field, which highlight a lack of applicable evidence
- A strength of the study is the use of predefined clinically relevant patient outcomes, rather than statistically significant differences.
- A general limitation of a systematic review is the use of aggregated data, that, in theory might mask potential specific results.
- This study has focused on critically appraising earlier evidence for nowadays practice, rather than endeavoring to be complete.

Introduction

Asthma affects 10-15% of school-aged children. For children with persistent asthma, all international guidelines recommend daily controller treatment with inhaled corticosteroids (ICS), and reliever medication (short-acting β-2-agonists) as needed.[1,2] Although many children achieve complete asthma control using this effective and safe treatment,[1] some need additional treatment to obtain disease control.[3,4] Identification and treatment of comorbidities in children with problematic severe asthma is part of the stepwise approach to improve asthma control in these children.[5,6]

The most common of these comorbidities in children with asthma is allergic rhinitis,[5] symptoms of which occur in 60-80% of asthmatic children.[7,8] Allergic rhinitis shares a common pathophysiological pathway with asthma, which has been described as the united airway concept.[9] Allergic rhinitis is associated with worse asthma control in children, and accumulating evidence suggests that treatment of allergic rhinitis with intranasal steroids improves not only rhinitis, but also asthma symptoms in these patients.[7,10,11]

When symptoms of allergic rhinitis cannot be sufficiently controlled with nasal corticosteroids and oral antihistamines,[9,12] immunotherapy can be considered as additional treatment.[13] Subcutaneous immunotherapy (SCIT) requires repeated injections with an allergen extract and is available for allergens such as grass and tree pollen and house dust mite. After disappointing results of low-dose preparations in drops, effective high-dose sublingual immunotherapy (SLIT) has now become available with grass pollen allergen extract in a daily sublingual tablet.[14,15] A Cochrane systematic review, first published in 2000, and last updated in 2010, reported beneficial effects of immunotherapy in children with asthma.[16] Multiple studies in this latter review, however, were performed before or in the 1980s, when most children with asthma were not using ICS.

As part of the update of the Dutch pediatric guideline on childhood asthma, we evaluated the literature on the added value of SCIT and SLIT in childhood asthma.[17] Our structured clinical question was to assess whether immunotherapy (subcutaneous or sublingual), as an add-on to usual care with daily ICS, improves asthma outcomes in children (6-12 years) and adolescents (>12 years) with persistent asthma and sensitization to relevant aeroallergens (grass or tree pollen, house dust mite, or combinations), with or without symptoms of allergic rhinitis.

Methods

We used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to appraise and summarize the body of evidence. GRADE is an internationally approved standard for managing complex evidence reviews.[18] In contrast to former grading systems, GRADE focuses on the quality of the total body of evidence, instead of judging single studies. Another important characteristic of GRADE is that predefined outcomes with thresholds for clinical relevance are being used.[19] In earlier grading systems, the evidence was summarized using outcomes reported in studies, not necessarily being outcomes a guideline development group would be interested in.[20] GRADE avoids the use of surrogate or intermediate outcomes, and uses outcomes and differences that are more clinically relevant to patients instead. Starting from a systematic review, for each outcome the quality of evidence can be downgraded or upgraded, for instance based on risk of bias, inconsistency, indirectness, possible publication bias, and dose-response relation.

The guideline development group included an epidemiologist, paediatric respiratory physicians, paediatricians, an allergist, an ear-nose-throat specialist, a family physician, a lung function technician, a youth public health care physician, and patient representatives. The guideline development group predefined clinically relevant outcomes and divided these into critical (contributing to the overall quality of evidence), important (also relevant to the content of the guideline) and not important outcomes. For each outcome, a minimal clinically important difference was defined *a priori*. The outcomes taken into account in our literature review are summarized in *table 1*, with corresponding minimal clinically important differences.[21-24]

Table 1. Patient relevant outcomes and clinical relevance

Outcome	Importance	Minimal clinically important difference
Asthma symptoms	Critical	ACT: 3 c-ACT: (2-)3*
(Severe) exacerbations	Critical	NNT n=10
Asthma control	Critical	ACT: 3 c-ACT: (2-)3*
(Disease-specific) quality of life	Important	PAQLQ: 0.5 (scale 0-7)*
Change in FEV_1	Important	>5%predicted

* or comparable differences on other valid scales representing this outcome

Abbreviations: ACT: asthma control test; c-ACT: child ACT; NNT: number needed to treat (to prevent one exacerbation); PAQLQ: Pediatric Asthma Quality of Life Questionnaire

We applied a sensitive search strategy to retrieve all available evidence addressing the clinical question, focusing on systematic reviews (SRs) about asthma and immunotherapy in children. Literature searches were performed in March 2012 for the guideline (from 1960 onwards), and updated in April 2015 for the purpose of this review. A second update, including an expansion of the searching scope, was performed in June 2017. *(see table E1 in the Online Repository)*. In the original search, we searched in the Cochrane Database of

Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the Cochrane Central Trial Register. In the 2017 update we also searched for systematic reviews in the Medline and Embase databases (again from 1960 onwards). Two reviewers (EJvdG, MKT) independently screened the abstracts using predefined inclusion criteria: methodology (SRs), patients (children with allergic asthma), and SCIT and/or SLIT as an intervention. Animal studies, conference abstracts, and studies published in languages other than English, Dutch and German were excluded. Differences between reviewers were resolved by consensus. Selected abstracts were critically appraised with respect to study population, intervention and methodological aspects (e.g. systematic search and selection, inclusion of randomized controlled trials (RCTs)), which led to a further selection. An expert in the field (HdG) judged the selection for completeness.

All included studies were summarized in evidence tables by two reviewers (EJvdG, MKT). SRs were critically appraised using the AMSTAR checklist (A Measurement Tool to Assess Systematic Reviews).[25] AMSTAR scores range from 0-11, a higher score indicating better quality (less bias). The Jadad scale was used to assess the methodological quality of each included RCT.[26] This score ranges from 0-5, a higher score denoting a better quality. All eligible studies together defined the body of evidence, of which the quality was determined (per relevant outcome and overall quality) and GRADE Profiles were created. Results from SRs and RCTs were pooled, if possible, in meta-analyses using RevMan 5. We calculated standardized mean differences for continuous outcomes, because of the usage of different symptom scales in the underlying studies. We calculated risk ratios for dichotomous outcomes, to compare the probability of these outcomes between the intervention and control groups. In the meta-analyses we used random effects models, because of the possibility of generalization of the outcomes for different allergens, and tested the difference between intervention and control with the inverse variance method, since this method is typically used in meta-analyses to combine the results of independent studies. We reported 95% confidence intervals (pre-defined significance level: 0.05). Conclusions were drawn, based on quality and content, per outcome and discussed in the expert group until consensus was reached.

Patient involvement

The guideline development group included patient representatives who helped defining our clinical question, approved outcome measures and assessed its clinical relevancy. The burden of interventions and patient considerations were assessed as part of the GRADE evaluation. Patients were not directly involved in this systematic review since we reviewed published literature.

Results

Literature search and selection

Screening of titles and abstracts yielded 83 eligible studies, 10 of which fulfilled the inclusion criteria.[16,27-35] After examining these 10 papers in full, 5 more studies were excluded *(figure 1)*.

Experts in the guideline working group confirmed that no relevant publications were missed. The updated search (April 2015) revealed 43 additional studies, of which 2 fulfilled the inclusion criteria.[36,37] Full text examination resulted in exclusion of these 2 studies. The extended and updated search in June 2017 resulted in 177 hits, of which 6 were selected to full paper study [38-43]. These studies were systematic reviews in the field of SCIT and/or SLIT in children with asthma. Most of the included RCT's in these reviews had already been included in the 2015 search. We only added RCT's of those reviews to our meta-analyses that have not been included earlier. As a result, we added one study[44].

< figure 1> Literature selection

Results of SCIT

Description of studies

We retrieved one Cochrane SR on the effectiveness of SCIT in patients with asthma , including 90 RCTs with a total of 3,792 patients.[16] This was a high-quality review (AMSTAR score 10/11). Fourteen of the included RCTs were performed in children exclusively; another 24 included children and adults. In a few studies the age inclusion criteria were not clear. The characteristics of these review are summarized in an evidence table (*see table E2 in the Online Repository*). [16,29,32] Only nine RCTs included in these reviews reported on our predefined outcomes in children. [45-53] In these nine studies different allergens or combinations were studied (house dust mite (3), dog dander (1), grass pollen (1), mold (1), grass pollen/house dust mite (1), tailored combinations (2)). Two RCTs published after the 2010 Cochrane review were retrieved.[34,35] In the first, the clinical efficacy of house dust mite-specific SCIT in 20 asthmatic children was compared to no intervention in 20 others; patients were followed up for six months.[34] In the other, the effects of allergen-specific SCIT on corticosteroid dose in asthmatic children was evaluated.[35] Details of all included RCTs are summarized in the evidence table (*see table E3 in the Online Repository*). [34,35,45-53]

Quality of the evidence

Little information was given about the included studies in the Cochrane review; e.g. follow-up was not stated. There were also other concerns about the quality of the literature, e.g. not all studies were double-blind and placebo-controlled, and randomization procedures were poor. Therefore we re-analyzed the individual paediatric studies in the Cochrane review, plus the added studies.[34,35] Jadad scores of the single studies are presented in *table 2*.

Table 2. Jadad scores of RCTs on SCIT

	Randomization*	Blinding**	Withdrawals#	Total
Adkinson 1997[45]	1	1	1	3
Altintas 1999[46]	1	1	1	3
Dreborg 1986[47]	1	-	-	1
Hill 1982[48]	1	-	-	1
Johnstone 1961[49]	2	1	-	3
Johnstone 1968[50]	2	1	1	4
Price 1984[51]	1	1	-	3
Tsai 2010[34]	1	-	1	2
Valovirta 1984[52]	1	-	1	2
Warner 1978[53]	1	1	1	3
Zielen 2010[35]	1	1	1	3

** 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate*

*** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate*

 # 1 point if the number and the reasons for withdrawal in each group are stated

The quality of the body of evidence for all critical and important outcomes was very low *(table 3)*, mainly due to large risk of bias and indirectness. The large risk of bias was caused by a lack of allocation concealment, lack of information on follow-up, and loss to follow-up. The reason for downgrading for indirectness was the publication year of the underlying studies; populations and interventions were considered inapplicable to current clinical practice.

Table 3. GRADE Evidence Profile SCIT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SCIT	No intervention	Relative (95%CI)	Absolute (95%CI)		
Asthma symptoms (assessed with: Asthma symptom scores)												
5[a]	RCT	Very serious[b]	Not serious	Serious[c]	Not serious	None	136	286	-	Standardized Mean Difference -0.04 (95%CI: -0.42 to 0.33)	⊕OOO VERY LOW	CRITICAL

Exacerbations (assessed with: Symptomatic deterioration)												
5[a]	RCT	Serious[d]	Not serious	Very serious[e]	Not serious	None	64/253 (25.3%)	92/153 (60.1%)	Risk ratio 0.7 (0.31 to 0.72)	343 fewer per 1000 (95%CI: -397 to -265)	⊕OOO VERY LOW	CRITICAL
Asthma control – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Abbreviations: 95%CI: 95% confidence interval; RCT: randomized controlled trials; SCIT: subcutaneous immunotherapy

a. *Studies in Cochrane review Abramson + Tsai*
b. *The underlying studies had a quite large risk of bias, due to lack of allocation concealment, problems with blinding, and lack of information on follow-up (and loss-to-follow-up)*
c. *We downgraded for indirectness, because the included studies are quite old and maintenance medication may have changed probably; thus, study populations may alter from nowadays patients with moderate to severe asthma*
d. *We downgraded for risk of bias, because of problems with blinding and loss-to-follow-up*
e. *We assessed very serious indirectness, because most included studies for this outcome are very old, and carried out before the ICS-era; thus, patients nowadays differ from study populations*

Critical outcomes

Asthma symptoms. Four small studies carried out in children only reported this outcome in the Cochrane review.[16] We extracted these results from the Cochrane review and updated these with the results from Tsai et al.[34] Results are presented in *figure 2*.

<figure 2 >

The meta-analysis showed no significant effect of SCIT on asthma symptoms.

Asthma exacerbations. Five studies (published 1961-1984) in the Cochrane review, carried out in children only, reported this outcome.[16] No relevant studies of sufficient quality were published afterwards. Our meta-analysis included 253 patients on immunotherapy and 153 on placebo. The pooled risk ratio was 0.47 (95%CI: 0.31 – 0.72), favouring immunotherapy (see *figure 3*). The absolute risk reduction was 35%, giving a number needed to treat of 3.

< figure 3 >

No studies reported results on the critical outcome asthma control.

Important outcomes

No studies reported results on quality of life or lung function (FEV_1).

Results of SLIT

Description of studies and quality of the evidence

We retrieved two SRs on SLIT in patients with asthma.[29,32] The updated search in 2017 resulted in the addition of one RCT[44]. The characteristics of the SRs are summarized in evidence table *E2 (Online Repository*). The quality of the reviews was moderate; both had an AMSTAR score of 7/11. Weaknesses included the absence of an 'a priori design', exclusion of grey literature, not assessing the likelihood of publication bias and not mentioning conflicts of interest in one review,[29] and the absence of an 'a priori design', no information about excluded studies, too firm conclusions compared to the weak evidence, and not assessing the likelihood of publication bias in the other.[32] One review included both children and adults, and patients with asthma and/or rhinitis.[29] Because of the quality concerns of both existing SRs, we set out to perform a meta-analysis of the original studies that fulfilled our selection criteria. Jadad scores of selected studies, as well as an overview of the outcomes of those studies, are presented in *table 4*. [24,29,32,44,54-67] Study characteristics are summarized in the evidence table (*see table E4 in the Online Repository*). [44,54,55,57,58,60,63-65] We rated the quality of evidence to be very low, due to a large risk of bias, imprecision and indirect evidence.

Table 4. Summary of quality and outcome measures of selected RCT's in reviews Calamita et al, Penagos et al and added Pham-Thi et al. [29,32, 44]

Review	RCT	Eligible	Jadad-score				Reported on asthma symptoms	Reported on exacerbations	Reported on asthma control	Reported on disease specific quality of life	Reported on lung function (FEV_1)
			Randomization*	Blinding**	Withdrawals#	Total					
Calamita[29]	Bahceciler 2001[54]	Yes	1	1	1	3	+	-	-	-	-
	Hirsch 1997[55]	Yes	2	1	1	4	+	-	-	-	-
	Niu 2004[24]	No, conference abstract									
	Novembre 1991[56]	No, Italian language									
	Pajno 2003[57]	Yes	2	1	1	4	+	-	-	-	-
	Pajno 2004$ [58]	Yes	2	1	1	4	-	-	-	-	+

	Rodriguez Santos 2004[59]	No, Spanish language									
	Rolinck-Werninghaus 2004[60]	Yes	1	2	0	3	+	-	-	-	-
	Yuksel 1999[61]	No, Spanish language									
Penagos[32]	Bahceciler 2001[54]	Overlap with Calamita									
	Caffarelli 2000[62]	No, children with asthma not separately analyzed									
	Hirsch 1997[55]	Overlap with Calamita									
	Ippoliti 2003[63]	Yes	1	1	0	2	+	-	-	-	+
	Niu 2006[64]	Yes	1	1	1	3	+	-	-	-	+
	Pajno 2000[65]	Yes	2	1	0	3	+	-	-	-	-
	Rolinck-Werninghaus 2004[60]	Overlap with Calamita									
	Tari 1990[66]	No, Spanish language									
	Vourdas 1998[67]	No, children with asthma not separately analyzed									
Pham-Thi[44]		Yes	2	1	1	4	+			+	+
Total							8	0	0	1	4

Abbreviations: FEV_1: forced expiratory volume in 1 second; RCT: randomized controlled trial

** 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate*

*** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate*

 # 1 point if the number and the reasons for withdrawal in each group are stated

$ Same patients as Pajno 2003[57]

Critical outcomes

Asthma symptoms. Eight of the included studies reported on asthma symptoms. Different symptom scores were used, none of them standardized or validated. Clinical differences in asthma scores were not defined and most studies reported improvement in the treatment group as well in the control group. We were not able to compile a meta-analysis of the results of the individual studies, because of the use of various symptom scales in the included studies. Since studies did not report results in a clearly comparable way, reporting the results of the individual studies was considered unreliable.

Other critical outcomes. No studies reported results on the critical outcomes exacerbations and asthma control.

Important outcomes

Quality of life. Pham-Thi et al. published results on quality of life using Childhood Asthma Questionnaires[44]. The authors reported a difference in severity between SLIT and placebo in the younger population (age 6-11 years), but not in older children (age 12-16 years). It is not stated whether this difference is clinically relevant.

Lung function. Four studies reported results on lung function (FEV_1). One of the studies reported no numeric data on lung function.[64] One study reported no variance (standard deviation), and no comparison of the baseline data.[63] The two remaining studies reported on FEV_1 percentage predicted,[58] and reported no significant differences between treatment groups, neither at baseline nor at follow-up.

351

Discussion

Summary of main results

Our GRADE systematic review showed no evidence of a significant difference in asthma symptoms between SCIT and placebo in children with allergic asthma, but some evidence for a significant and clinically relevant reduction in asthma exacerbations was found in SCIT-treated children. We have little confidence in the effect estimate, however, due to a large risk of bias and indirectness. Thus, the true effect of SCIT on exacerbations and asthma symptoms in the target population of interest is likely to be substantially different from the estimate of effect. There was absence of evidence on the effects of SCIT on lung function, asthma control, and quality of life in children with allergic asthma. There was no evidence for a beneficial effect of SLIT in reducing asthma symptoms and exacerbations, quality of life and lung function in children with allergic asthma. Our review does not address the efficacy of immunotherapy in children regarding complaints of allergic rhinitis and/or conjunctivitis, without having asthma.

Quality of the evidence / GRADE methodology

The overall quality of the evidence about the effectiveness of SCIT and SLIT was very low. This implicates that our confidence in the effect estimates is very limited. The true effect of SCIT and SLIT on patient relevant asthma outcomes in children with asthma may be substantially different from our estimates of the effect. We cannot conclude that the possible desirable effects of SCIT and SLIT outweigh the undesirable effects (e.g. influence on quality of life, adverse events, or increased resource expenditure), nor can we reject that hypothesis. Our concerns about the quality of evidence are based on (very) serious risk of bias and indirectness in the underlying primary studies. Firstly, the quality of many studies had to be downgraded because of risk of bias due to lack of allocation concealment, lack of information on follow-up, and loss to follow-up. Secondly, included studies were heterogeneous in the patients included and allergen extracts used, with different dosing regimens and duration being studied, targeting different inhaled allergens. We have concerns about the potential different responses and the generalizability of the evidence. Thirdly, and most importantly, for SCIT, the quality of the body of evidence was downgraded because of indirectness, since patients in the original studies long ago are likely to differ considerably from patients nowadays.

Fourth, different studies used variable definitions of asthma exacerbations. We had to use ‘worsening of asthma’, which may not represent real-life patient relevant exacerbations. This

may decrease the applicability of the evidence. In addition, there were no studies using the predefined important outcomes quality of life and asthma control.

Finally, and most importantly, we have concerns on comparability of patients. Several included studies dated from the 1980s or earlier, when allergic rhinitis treatment with selective antihistamines and nasal corticosteroids was not available. Against the background of the united airway concept, the comorbidity allergic rhinitis in patients in these studies cannot be compared to patients in clinical practice today.[9] Similarly, widespread use of ICS was not introduced in childhood asthma treatment until the 1990s.[68] Most studies on SCIT in children with asthma were published decades ago, during the pre-ICS era. Although SCIT appeared to be effective in some of the included studies,[49, 50] we cannot draw conclusions from these findings, because the patients in the described studies represent an incomparable group when compared to the child with asthma in contemporary clinical practice. Specifically, it is unclear whether the beneficial effects found in the systematic review of earlier studies is applicable to children with asthma treated according to contemporary guidelines with daily ICS controller therapy.[16]

In our opinion and that of others, the GRADE approach is superior to former methods of SRs, because it focuses on predefined patient relevant outcomes, predefined minimally clinical important differences and because it judges the complete body of evidence. One RCT among paediatricians studied the influence of different guideline grading systems on clinician's decisions.[69] GRADE showed the largest change in direction on the clinical decision. However, the added value of GRADE on guideline implementation or patient care, has not been formally evaluated, the GRADE approach is still rather complex for non-methodologists.

To formulate recommendations for clinical practice, not only the body of evidence concerning effectiveness of an intervention is important. Recommendations should balance the benefits and harms of the intervention of interest, and take patient preferences and resource use into account. Since (after critical evaluation) no benefits of SCIT and SLIT for children with asthma were determined, we consider it unlikely that the benefits will exceed the harms. Patient preferences were included in the formulation of our guideline recommendations.

Agreements and disagreements with other studies or reviews

Using GRADE and re-analyzing data from children with allergic asthma only, we came to different conclusions on the effectiveness of SCIT and SLIT in children with asthma than the authors of the original SRs. We believe this highlights the importance of using GRADE methodology to systematically review evidence for patient relevant outcomes, not focusing

on levels of evidence, but on underlying study validity, precision, directness, and applicability in current clinical practice. The 2009 position paper on SLIT describes history, use and applicability of this treatment for allergic rhinitis.[70] It positions SLIT in children as a safe and useful therapy above and after more regular treatment for allergic rhinitis. Potential positive treatment outcome for allergic asthma is however mainly based on literature in adults. We show the lack of evidence and lack of applicability of treatment of immunotherapy for asthma in children. Since we have worries on the applicability of evidence in adults on children (who are still developing their immune system), we think further studies that compare immunotherapy for the contemporary treatment of asthma in children are urgently needed to fill in this gap.

Recently, a Cochrane SR on SLIT for asthma found a similar lack of data for important outcomes (e.g. exacerbations, symptom scores, quality of life) as we did.[71] Contrary to our study, the authors did no separate analysis for adults and children, and patients with asthma were not separately analyzed from patients without asthma.

Conclusions

Focusing on predefined patient relevant outcomes, and critically appraising the body of evidence using original studies and GRADE methodology, our systematic review on the effects of immunotherapy in children with asthma came to different conclusions than previous systematic reviews. We believe that this underscores the importance of using GRADE methodology in systematically reviewing evidence.

We found absence of valid applicable evidence on improvement of clinically relevant asthma outcomes in children with allergic asthma using SCIT or SLIT. This absence of evidence is due to serious risk of bias, large clinical heterogeneity between studies, and most importantly due to lack of applicability because studies were performed in the pre-ICS era.

Since the effect of immunotherapy added to contemporary asthma treatment with daily controller therapy is not clear, the drawbacks of immunotherapy should be considered carefully. SCIT is a complex and intensive form of treatment, associated with a (very) long duration of treatment, and considerable burden to the patient with (monthly) injections under adequate medical supervision due to potential (however rare) dangerous side effects, and may have relatively high costs and resource use. In SLIT the risk of serious side-effects is considerably smaller, but the other drawbacks of immunotherapy apply equally to this treatment. In our opinion therefore, when balancing the absence of evidence on a clear beneficial effect of SCIT or SLIT on clinically relevant patient outcomes in children with asthma with the considerable burden and costs of SCIT and SLIT, we do not recommend this

treatment to children with asthma until further high-quality evidence from well-designed RCTs in children comparing SCIT or SLIT to contemporary asthma treatment becomes available.

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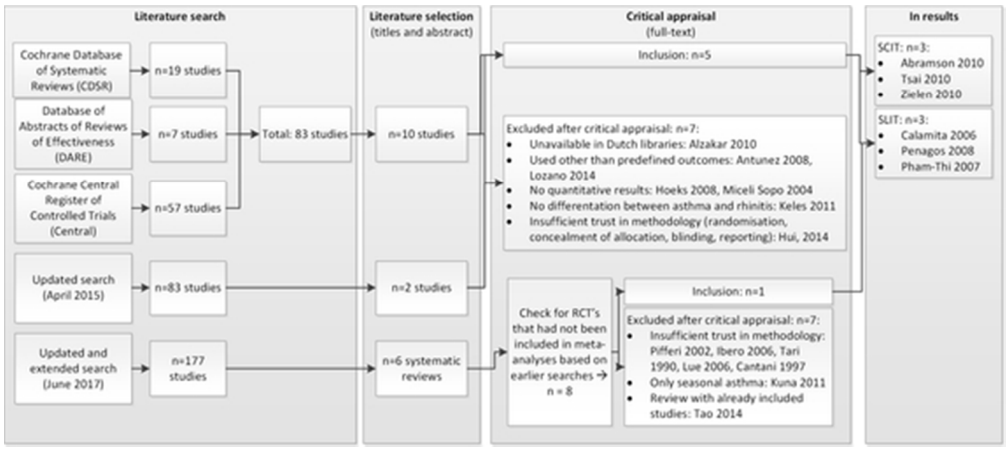
Figure legends

Figure 1. Literature search and selection

Figure 2. Meta-analysis of SCIT vs. placebo, outcome asthma symptoms. *Abbreviations: SD: Standard deviation; Std: Standardized; IV: Inverse Variance; random: random effect model; 95%CI: 95% Confidence Interval*

Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. *Abbreviations: 95%CI: 95% Confidence Interval; IV: Inverse Variance*



Literature search and selection

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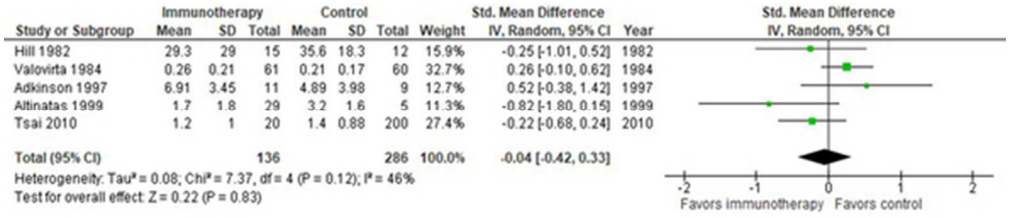

Figure 2. Meta-analysis of SCIT vs. placebo, outcome asthma symptoms. Abbreviations: SD: Standard deviation; Std: Standardized; IV: Inverse Variance; random: random effect model; 95%CI: 95% Confidence Interval

50x10mm (300 x 300 DPI)

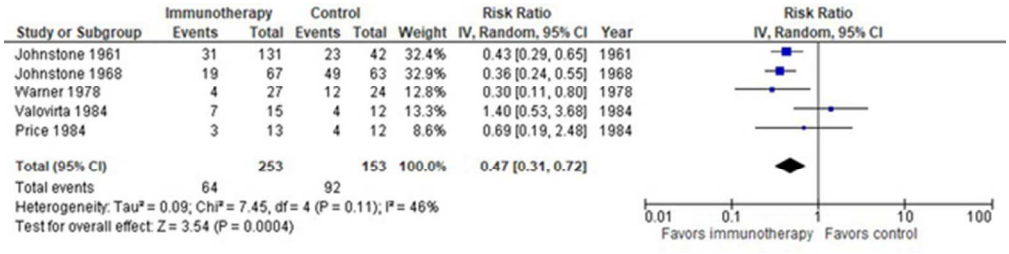

Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. Abbreviations: 95%CI: 95% Confidence Interval; IV: Inverse Variance

54x13mm (300 x 300 DPI)

Table E1. Literature search

Search Cochrane Databases of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Central; Literature search 2015, April 25th
1. "asthmazoekacties jan 2012".ti. (0)
2. asthma.tw. (14671)
3. Bronchial Spasm.tw. (15)
4. asthma*.tw. (17541)
5. wheez*.tw. (869)
6. bronchospas*.tw. (777)
7. (bronch* adj8 spas*).tw. (52)
8. bronchoconstrict*.tw. (1663)
9. (bronch* adj8 constrict*).tw. (71)
10. airway* inflammation*.tw. (704)
11. or/2-10 (18894)
12. immunotherap*.kw,tw. (2803)
13. 11 and 12 (473)
14. subcutaneou*.kw,tw. (8020)
15. 12 and 14 (259)
16. 15 (259)
17. limit 16 to yr="2008 -Current" (57)
Search Medline 2017, June, 2nd
1 "Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study".fc_titl. (1)
2 "A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients".fc_titl. (1)
3 "Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite".fc_titl. (1)
4 "abramson$".fc_auts. and "Injection allergen immunotherapy for asthma".fc_titl. (1)
5 "Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method".fc_titl. (1)
6 "Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients".fc_titl. (1)
7 "Normansell$".fc_auts. and "Sublingual immunotherapy for asthma".fc_titl. (1)
8 "Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study".fc_titl. (1)
9 "Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric ".fc_titl. (1)
10 "Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled ".fc_titl. (1)
11 "Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan".fc_titl. (1)
12 "Immunomodulation during sublingual therapy in allergic children".fc_titl. (1)
13 "Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial".fc_titl. (1)
14 "Sublingual immunotherapy and influence on urinary leukotrienes in seasonal pediatric allergy".fc_titl. (1)
15 "A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen".fc_titl. (1)
16 "Sublingual immunotherapy with allergenic extract of Dermatophagoides pteronyssinus in asthmatic children".fc_titl. (1)
17 "Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial. ".fc_titl. (1)
18 "Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with ".fc_titl. (1)

19 "Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract ".fc_titl. (1)
20 "Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. ".fc_titl. (1)
21 or/1-3 (3)
22 or/4-20 (17)
23 21 or 22 (20)
24 "controle refs slit scit".ti. (0)
25 asthma/ or bronchial spasm/ (118686)
26 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).tw. (155964)
27 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).kf. (15593)
28 or/25-27 (176447)
29 23 and 28 (19)
30 23 not 29 (1)
31 rhinitis, allergic, perennial/ or rhinitis, allergic, seasonal/ (18469)
32 28 or 31 (188701)=P
33 Immunotherapy/ (36085)
34 Sublingual Immunotherapy/ (231)
35 Desensitization, Immunologic/ (9795)
36 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).tw. (16817)
37 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).kf. (442)
38 or/33-37 (61196)
39 "Injections, Subcutaneous"/ (31338)
40 33 and 39 (294)
41 34 or 35 or 36 or 37 or 40 (26000)=I
42 28 and 41 (3043)
43 "filter systematic reviews".ti. (0)
44 meta analysis.pt. (81124)
45 (meta-anal$ or metaanal$).af. (144025)
46 (quantitativ$ adj10 (review$ or overview$)).tw. (6863)
47 (systematic$ adj10 (review$ or overview$)).tw. (119262)
48 (methodologic$ adj10 (review$ or overview$)).tw. (9132)
49 (quantitativ$ adj10 (review$ or overview$)).kf. (32)
50 (systematic$ adj10 (review$ or overview$)).kf. (8208)
51 (methodologic$ adj10 (review$ or overview$)).kf. (36)
52 medline.tw. and review.pt. (64452)
53 (pooled adj3 analy*).tw. (14081)
54 (pooled adj3 analy*).kf. (128)
55 "cochrane$".fc_jour. (13410)
56 or/44-55 (258042)
57 randomized-controlled-trial.pt. (465042)
58 controlled-clinical-trial.pt. (94188)
59 randomized controlled trial/ (465042)
60 randomi?ed controlled trial?.tw. (131360)
61 random-allocation.tw,kf. (1445)
62 double-blind-method.tw,kf. (456)
63 single-blind-method.tw,kf. (81)
64 (random adj8 (selection? or sample?)).tw. (40888)
65 random$.tw. (952984)
66 or/57-65 (1156986)
67 "rct filter sprec".ti. (0)
68 (child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or girl? or kid? or schoolage* or juvenil* or adolescen* or toddler?).tw. (2058217)
69 exp Child/ (1759435)
70 exp infant/ (1058929)
71 "Adolescent"/ (1847650)
72 or/68-71 (3858822)

73 "filter child".ti. (0)
74 23 and 72 (19)
75 23 not 74 (1)
76 32 and 41 and 56 (184)
77 32 and 41 and 72 and 56 (90) systrev

Search Embase 2017, June, 2nd

1 asthma/ (202909)
2 bronchospasm/ (25054)
3 bronchoconstriction/ (1300)
4 respiratory tract inflammation/ or allergic airway inflammation/ (11606)
5 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).tw. (215497)
6 (asthma* or wheez* or bronchospas* or bronchoconstrict* or (airway* adj inflammat*)).kw. (51383)
7 perennial rhinitis/ (3627)
8 or/1-7 (279683)=P
9 sublingual immunotherapy/ (1695)
10 immunotherapy/ (67533)
11 subcutaneous drug administration/ (97428)
12 10 and 11 (1148)
13 subcutaneous immunotherapy/ (1226)
14 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).tw. (19513)
15 (SCIT or SLIT or (sublingual adj1 immunotherap*) or (subcutaneous adj1 immunotherap*)).kw. (1765)
16 9 or 12 or 13 or 14 or 15 (21563)=I
17 8 and 16 (2229)
18 "Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study".fc_titl. (1)
19 "A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients".fc_titl. (1)
20 "Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite".fc_titl. (1)
21 "abramson$".fc_auts. and "Injection allergen immunotherapy for asthma".fc_titl. (1)
22 "Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method".fc_titl. (1)
23 "Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients".fc_titl. (1)
24 "Normansell$".fc_auts. and "Sublingual immunotherapy for asthma".fc_titl. (1)
25 "Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study".fc_titl. (1)
26 "Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric ".fc_titl. (1)
27 "Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled ".fc_titl. (1)
28 "Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan".fc_titl. (1)
29 "Immunomodulation during sublingual therapy in allergic children".fc_titl. (1)
30 "Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial".fc_titl. (1)
31 "Sublingual immunotherapy and influence on urinary leukotrienes in seasonal pediatric allergy".fc_titl. (1)
32 "A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen".fc_titl. (2)
33 "Sublingual immunotherapy with allergenic extract of Dermatophagoides pteronyssinus in asthmatic children".fc_titl. (2)
34 "Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with Parietaria-induced respiratory allergy: a randomized controlled trial. ".fc_titl. (1)

35 "Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with ".fc_titl. (1)
36 "Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract ".fc_titl. (1)
37 "Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. ".fc_titl. (1)
38 or/18-20 (3)
39 or/21-37 (19)
40 38 or 39 (22)
41 "controle refs slit scit".ti. (0)
42 "filter systematic reviews & meta-analyses Embase".ti. (0)
43 meta analysis/ (127495)
44 "systematic review"/ (139284)
45 (meta-analy$ or metaanaly$).tw. (145912)
46 (systematic$ adj4 (review$ or overview$)).tw. (139834)
47 (quantitativ$ adj5 (review? or overview?)).tw. (3786)
48 (methodologic adj5 (overview? or review?)).tw. (325)
49 (review$ adj3 (database? or medline or embase or cinahl)).tw. (19428)
50 (pooled adj3 analy$).tw. (20108)
51 (extensive adj3 review$ adj3 literature).tw. (2903)
52 (meta or synthesis or (literature adj8 database?) or extraction).tw. (1197812)
53 review.pt. (2259303)
54 52 and 53 (112526)
55 (systematic$ adj4 (review$ or overview$)).kw. (16750)
56 (quantitativ$ adj5 (review? or overview?)).kw. (48)
57 (pooled adj3 analy$).kw. (354)
58 or/43-51,54-57 (381419)
59 "filter rct embase".ti. (0)
60 controlled clinical trial/ or randomized controlled trial/ (614267)
61 randomization/ (73811)
62 Major Clinical Study/ (2803898)
63 random$.tw. (1196822)
64 Double Blind Procedure/ (139034)
65 or/60-64 (3916117)
66 "einde filter rct embase".ti. (0)
67 (child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or girl? or kid? or schoolage* or juvenil* or adolescen* or toddler?).tw. (2468214)
68 child/ (1526632)
69 infant/ (566151)
70 adolescent/ (1414197)
71 or/67-70 (3656088)
72 17 and 58 and 71 (85) systrev
73 (17 and 65 and 71) not 58 (370) rct
74 17 and 58 (208)
75 74 not 72 (123)
76 75 (123)
77 limit 76 to yr="2016 -Current" (14)
78 76 (123)
79 limit 78 to yr="2015 -Current" (31) extra systrev

Search Cochrane 2017, June, 2nd

#1 asthma*:ti,ab,kw 26843
#2 MeSH descriptor: [Asthma] this term only 9761
#3 MeSH descriptor: [Bronchial Spasm] explode all trees 360
#4 wheez*:ti,ab,kw 1642
#5 bronchospas*:ti,ab,kw 1594
#6 (bronch* near/8 spas*):ti,ab,kw 460
#7 bronchoconstrict*:ti,ab,kw 2204

#8	(bronch* near/8 constrict*):ti,ab,kw 121
#9	(airway* near/1 inflammation*):ti,ab,kw 1236
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 28980
#11	(perennial or seasonal or allergen* or hyposensiti*):ti,ab,kw 10214
#12	immunotherap*:ti,ab,kw 6399
#13	MeSH descriptor: [Immunotherapy] this term only 1140
#14	(SCIT or SLIT or (sublingual near/1 immunotherap*) or (subcutaneous near/1 immunotherap*)):ti,ab,kw 2033
#15	#11 or #12 or #13 or #14 15912
#16	#10 and #15 3351
#17	(child* or childhood or infant* or pediatr* or paediatric* or perinat* or neonat* or newborn* or infan* or boy* or girl* or kid* or schoolage* or juvenil* or adolescen* or toddler*):ti,ab,kw 239918
#18	#16 and #17 1570
#19	immunotherap*:ti,kw 5661
#20	subcutaneou*:ti,kw 12350
#21	(SCIT or SLIT or (sublingual near/1 immunotherap*) or (subcutaneous near/1 immunotherap*)):ti,kw 1257
#22	#13 or #19 or #20 or #21 17830
#23	#18 and #22 516
#24	(perennial or seasonal or allergen* or hypo-sensiti*):ti 5205
#25	#22 or #24 22321
#26	#25 and #18 927
#27	#16 and #22 1071
#28	MeSH descriptor: [Injections, Subcutaneous] explode all trees 4017
#29	(#12 or #13) and (#20 or #28) 646
#30	#29 or #21 or #24 6616
#31	MeSH descriptor: [Desensitization, Immunologic] 2 tree(s) exploded 872
#32	(#31 or #30) and #10 1961
#33	MeSH descriptor: [Child] explode all trees 227
#34	MeSH descriptor: [Adolescent] explode all trees 90499
#35	MeSH descriptor: [Infant] explode all trees 15066
#36	#17 or #33 or #34 or #35 239918
#37	#32 and #36 816

Results	
Cochrane Databases of Systematic Reviews	19
Database of Abstracts of Reviews of Effectiveness	7
Cochrane Central Trials Register	57
emb20170602 scit slit systrev.	53
emb20170602 scit slit extra vanaf2015systrev	26
med20170602 scit slit systrev.	89
coc sr20170601 extra astma scit slit.	4
coc dare20170602	5

Table E2. Evidence table systematic reviews (SCIT + SLIT)

	Abramson, 2010[16]	**Calamita, 2006[29]**	**Penagos, 2008[32]**
Study design	Cochrane systematic review, consisting of 90 RCT's. 14 RCT's were carried out in children only; 24 were done in children and adults. The total study population (children and adults) consisted of 3.792 patients (of whom 3.459 had asthma)	Systematic review, consisting of 25 RCT's. Only 9 RCT's were carried out in children only. The total study population consisted of 1.706 patients (adults and children, with asthma and/or rhinitis)	Systematic review, consisting of 9 RCT's, all carried out in children. The total study population comprised 441 patients with asthma (seasonal, mild, moderate, and persistent)
Age (mean)	Not specified, variation between included studies	Not specified, there is a limited description of the characteristics of the included studies	Range specified per study, total range: 4-17 years
Setting (in RCT's)	-	-	-
Diagnosis (asthma/rhinitis)	Asthma	Asthma and rhinitis	Asthma
Eligibility criteria	RCT's, patients with asthma, allergen specific subcutaneous immunotherapy (administration of extracts of house dust mites, pollens, animal danders or molds, chemically modified allergoids or antigen-antibody complexes)	RCT's, double blinded, and open studies, patients with asthma and/or rhinitis, sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all lengths of treatment)	RCT's, double blinded, placebo controlled, patients ≤ 18 years, with a history of allergic asthma, with identified causal allergen, and proven IgE sensitization. Sublingual immunotherapy (with or without swallowing, all types of allergen, all doses, all durations of treatment)
Type of immunotherapy	Subcutaneous immunotherapy (variation of allergen abstracts in different included studies)	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy, mainly mites
Intervention	Subcutaneous immunotherapy	Sublingual immunotherapy, mainly pollen and mite	Sublingual immunotherapy (mainly mites, further: O europaea, Holcus, P pretense *Dermatophagoides pteronyssinus*, grass mix), great variation in duration, range: 3-32 months
Control	Placebo	Placebo	Placebo
Primary outcomes	Asthmatic symptoms Asthma medication requirements Lung function Nonspecific bronchial hyper-reactivity Allergen specific bronchial hyper-reactivity	Asthmatic symptoms (symptom score) Asthmatic medication requirement Respiratory function tests (PEFR, FEV_1, FEF25-75%) Nonspecific bronchial provocation Adverse effects	Asthma symptoms Medication scores
Secondary outcomes	Local reactions Systemic reactions	-	

Comment	The results have not been presented separately for children in the review. We conducted new suitable meta-analyses.	The authors mentioned they used the Cochrane Collaboration method	-

Abbreviations: FEF25-75: maximum mid expiratory flow; FEV_1: forced expiratory volume in 1 second; PEFR: peak expiratory flow rate; RCT: randomized controlled trial; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

Table E3. Evidence table SCIT studies

Author, date	Study design	Setting	Eligibility	Participants (number, gender, age, and descriptive	Asthma type,* severity (e.g. on ICS?)	Allergy type (mono/multi, allergens,	Intervention (type, dose, duration)	Control	Follow-up (from start	Outcomes	Results reported by authors†	Critical appraisal‡	Comments
Adkinson, 1997[45]	Double blind, placebo controlled, parallel group RCT Placebo carameli zed saline + histamin e	?		121 allergic children with perennial asthma Mean age 9.2 (range 5.4 to 14) years, 79% boys	Perennial asthma 34% ICS, 13% systemic	80% dust mite, 77% ragweed, 69% rye grass	Subcutaneo us multiple allergen immunother apy Median 6 (range 2 to 7) allergen extracts	Placebo	?	Symptom scores Medication scores PEF rates Nonspecific BHR (methacholin FEV_1)	SCIT not useful in moderate to severe perennial allergic asthma	Study useful, however low rate of ICS	Allocation concealm ent unclear
Altintas, 1999[46]	Open placebo controlled RCT multiple groups	university		34 poorly controlled mild to moderate asthmatics aged 4 to 18 years; 30 patients in 3 groups, 5 placebo	ICS use not specified, no medical details on asthma	Mono-sensitization *Dermatophago ides pteronyssinus*	Subcutaneou s immunothera py with adsorbed or aqueous *Dermatophag oides pteronyssinus* extracts (in different dilutions)	Placebo		Symptom medication score IgE and IgG4 level Bronchial provocation tests	SCIT is useful and safe; no conclusion on asthma	Study not useful No data on ICS,	Allocation concealme nt unclear Study designed to compare 3 different abstracts of immunothe rapy
Dreborg, 1986[47]	RCT, double blind Freeze dried caramelized histamine placebo	European		30 children with *Cladosporium* allergy, aged 5 to 17 years	Clinical history suggesting mold-induced asthma and/or rhinoconjunct ivitis ICS not stated	*Cladosporium* allergy	*10 months Cladosporium* subcutaneous immunothera py Or placebo	Placebo		Symptoms Medication PEF (no SD reported) Allergen specific BHR	Decrease in medication score, but not in symptom score Lower medication score in verum group	Study not useful No information on asthma medication No fixed study medication scheme	Allocation concealme nt unclear Asthma diagnosis not specified, (worsening of asthma in the *Cladospori*

													um season)
Hill, 1982[48]	Single blind RCT, rye grass pollen placebo	University Australia		20 asthmatic children, aged 9 to 14 years, with rye grass pollen allergy, positive at bronchoprovocation	ICS N=1 beclomethason N=8 cromoglycate		Subcutaneous immunotherapy with aqueous rye grass pollen extract	Placebo		Symptoms Medications (medians only reported, no SD)	no evidence that limited hyposensitization with a pollen extract is of any clinical benefit in seasonal asthma despite evidence of an immunological response.	Study not useful Primary outcome = IgE and IgG levels	No allocation concealment
Johnstone, 1961[49]	RCT, double blind, 4-year follow up Buffered saline control	United States general hospital		173 children with perennial asthma Severity = number of days of wheeze/year Placebo: n=41	No medication mentioned at all, no medication scores		Subcutaneous immunotherapy with relevant allergen extracts, administered by 3 regimens	Placebo		Asthma symptoms reported by mother Number of new allergies developing	Less new allergies developing Less symptoms and asthma attacks in the last year in the group 4	Study not useful No asthma medication scores	Allocation concealment unclear 4 different groups, 1 placebo (n=41) Group 2-4 different strength SCIT Last year single blind
Johnstone, 1968[50]	RCT, double blind Buffered saline control			130 children with perennial asthma; Severity = number of days of wheeze/year RCT, double blind Buffered saline control	No medication mentioned, no medication scores		Subcutaneous immunotherapy with relevant allergens administered by 3 regimens	Placebo		Asthma symptoms reported by mother	More children in SCIT group high dose overgrowing asthma at the age of 16 than placebo	Study not useful No asthma medication scores	Allocation concealment unclear 14-years follow up of Johnstone 1961
Price, 1984[51]	RCT, double blind			25 children with perennial asthma, aged 5 to 15 years	Asthma severity not specified asthma		Subcutaneous immunotherapy with *Dermatophag*	Placebo		Symptoms Medication Lung function Bronchoprovocation	Loss of late reaction on bronchoprovocation Only one out of 6	Study not useful Bronchoprovocation is	Continuation of study by Warner 1978 for second

	Saline placebo control				medication not specified		*oides pteronyssinus* extracts				children with severe asthma improved	surrogate outcome;	year with placebo group crossed over to active immunotherapy
Tsai, 2010[34]	RCT, no blinding, no intervention in control group	University hospital, Taiwan		40 children (21 boys), aged 5-14 years (average 8,5) >1 year moderate persistent to severe asthma, all monosensitized to house dust mite	Moderate persistent to severe asthma, using daily medication, most patient at least on ICS	House dust mite, diagnosed by SPT or specific antibody test	Subcutaneous injections of extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* (10000 AU/ml), initial dose 0,5AU/ml once a week. Dosage was increased weekly by 25-100% to reach optimal maintenance dose, with respect to local or systemic reaction. Maintenance therapy every 2 weeks during at least 3 months	No intervention	6 months (last follow-up)	Primary: Medication score (5 point scale, modified GINA) Secondary: PEF, asthma symptom score, number of contacts with health care providers	Mean medication score declined after 6 months in both groups; no significant between group differences. Both groups had reduction of asthma symptoms after 6 months, but no between group differences. There was no difference in PEF. Patients in the intervention group had more clinical visits than the control group, but no difference in emergency room or hospitalization	Very few patients, no blinding, randomization procedure not clear	
Valovirta, 1984[52]	RCT, double blind Caramel histamine placebo control	?		27 asthmatic children allergic to dog dander, aged 5 to 18 years	Asthma severity not specified asthma medication not specified		Subcutaneous immunotherapy with aluminium hydroxide bound dog	Placebo		Symptoms Allergen specific BHR	The decrease in bronchial sensitivity was less marked than that in conjunctival sensitivity and	Study not useful No asthma medication scores	Primary outcome dog dander sensitivity, not asthma 2 authors connected

							dander extract				statistically not significant		to pharmaceutical company
Warner, 1978[53]	RCT, double blind Tyrosine placebo control	University, United Kingdom		51 asthmatic children, aged 5 to 14 years, with positive *Dermatophagoides pteronyssinus* challenge	ICS n=12, cromoglycate n=24 SABA n=14	House dust mite, SPT and bronchoprovocation positive	Subcutaneous immunotherapy with tyrosine adsorbed *Dermatophagoides pteronyssinus* extracts	Placebo	1 year	Symptoms Medication Lung function (PEF, FEV 0.75) Allergen specific BHR	Less asthma medication in active group, but no difference in control or immediate response on bronchoprovocation	Useful; however incomparable low level of ICS	Allocation concealment unclear No fixed medication scheme
Zielen, 2010[35]	RCT, single blind, no control intervention	Multinational, multicenter		56 children with asthma GINA treatment II-III, on ICS, house dust mite (positive SPT), positive conjunctival provocation, significant RAST response	All on ICS, GINA II-III treatment	House dust mite SPT, provocative	SCIT with allergens extracted from *Dermatophagoides pteronyssinus* in 2 strengths: A: 1000 TU/ml; B: 10000 TU/ml. Initial therapy: weekly increasing doses strength A, followed by B. After reaching max individually tolerated dose, dosage intervals were increased to 6 weeks	No immunotherapy, only maintenance therapy with ICS	2 years	Primary: change in ICS dose steps to achieve asthma control Secondary: change in pre-bronchodilatory PEF, immunologic changes, nonspecific bronchial hyperreactivity	Less asthma medication in SCIT group as compared to control group, no change in asthma control, higher increase in PEF in intervention group. Adverse events in 97% in both groups	Block randomization. Multicenter, multinational is possible bicenter, binational. Conflict of interest in authors	

Abbreviations: AU: dosing units; BHR: bronchohyperreactivity; FEV1: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; ml: millilitres; n: number; PEF: peak expiratory flow; RAST: radioallergent sorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonist; SCIT: subcutaneous immunotherapy; SD: standard deviation; SPT: skin prick test; TU: dosing units

** Doctors diagnosed asthma? Stable/seasonal asthma? Mild/severe asthma?*

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, adverse reactions and/or complications

‡ e.g. randomization procedure, blinding, risk of bias

Table E4. Evidence table selected RCT's in children included in systematic reviews Calamita et al., Penagos et al. and Pham-Thi et al. (SLIT)

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
Bahcecile r 2001[54]	double-blind placebo-controlled SLIT drops HDM	Mono-center Turkey University hospital	Asthma with need for ICS, HDM allergic, ongoing respiratory symptoms despite mite avoidance and appropriate ICS treatment, > 7 years, FEV_1	15, 8 male, 11,7 years	Moderate asthma, need for ICS, respectively symptoms despite mite avoidance, FEV_1> 70%	Mono-allergy HDM but negative for all other aeroaller-gens	Drops SLIT, dose 100 IR/day, 4 weeks run-in, 4 weeks once daily, thereafter 2/week; total 6 months	Placebo drops	6 months	Symptom scores, compliance, SPT 6 months, Lung function, metacholine, serum IgE	Improvement asthma score. Less use of SABA, trend to-wards less ICS (not significant), no change in PD20, no serious side effects	Randomization and blinding not clear, possible industrial influence, disclosures not stated, small number of pa-tients, no follow-up after stop of intervention	Season not stated; decrease PEF in placebo group – stable in intervention group
Hirsch 1997[55]	double-blind placebo-controlled SLIT drops HDM	Mono-center, university hospital Germany	Not strictly specified	30, female n=10, 10,5 years (6-15 years)	'mild to moderate asthma': n=8; allergic rhinitis: n=8; asthma and rhinitis: n=14 Not further specified	Allergy SPT positive HDM, part also sensitized cat, dog, grasses	Drops SLIT HDM, 3 weeks run-in, maintenance 7 drops 3 days/week; total 12 months	Placebo drops (vehicle only)	12 months	Symptom scores, compliance, SPT 6 months, Lung function, metacholine, serum IgE , collection of dust samples (exposure)	Less pulmonary symptoms No difference use of SABA No change in PD20 No serious side effects	Small number of patients, especially when specified per group. Enrollment of patients (possible selection bias) is not clear. Serious differences in patients	Season not stated; Asthma group not well-described, exacerbations not described, 8 patients allergic rhinitis only

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
												groups, otherwise than intervention (type and duration of disease), no follow-up after intervention. 20% drop-out in intervention group, no intention-to-treat analysis	
Pajno 2003[57]	double-blind placebo-controlled SLIT drops *Parietaria*	Mono-center, Italy	Inclusion: seasonal asthma and rhinoconjunctivitis, DDA, poor symptom control despite antihistamine, ICS and nedocromil use du-ring pollen sea-son, positive skin prick test *Parietaria*, Specific IgE to	38, 20 female, 11 years,	DDA, seasonal asthma, poor control despite medication, including ICS, patients with PD20<2.0 mg excluded	Mono sensitization to *Parietaria*, SPT and RAST positive	Drops SLIT *Parietaria*, 4 weeks run-in, maintenance every other day, total 12 months, co-medication with fluticasone	Placebo drops + fluticasone 2nd control group: no pro-tocolled medica-tion	12 months	Symptom scores, VAS score during pollen season, compliance, SPT 6 months, serum IgE	No diff symptom scores Better VAS in SLIT group	Patient selection not clear: 30/38 children were randomized; 8 were control (not willing to participate in trial?), possible selection bias	Unclear whether fluticasone was given intranasally or orally No lung function or PD20

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
			Parietaria. Exclusion: sensiti-zation to other allergens, previous immunotherapy, severe asthma (FEV_1<70%), other diseases										
Pajno 2004[# 58]	double-blind placebo-controlled SLIT drops *Parie-taria*	Mono-center, Italy	seasonal asthma during spring and allergic rhinitis	30 (8-14 years)	DDA	Mono sensitization to *Parietaria*, SPT and RAST positive	Drops SLIT *Parietaria*, 4 weeks run-in, maintenance every other day, total 12 months	Placebo drops	24 months	Lung function and PD20	No change in lung function, improvement in BHR (PD20) after 2 years	1 author affiliated to pharmaceutical industry	
Rolinck-Werning-haus 2004[60]	double-blind placebo-controlled SLIT drops grass-pollen	Multi-center, university clinics, Germany	Allergic rhinitis with or without seasonal asthma Exclusion criteria: perennial asthma, ICS use	Total 97 (32 female), 3-14 years Asthma: n=39	DDA, seasonal asthma, no ICS use	Grasspollen IgE and SPT positive Others not mentioned	Drops SLIT 5-grass mixture, 4 week run-in, 3 doses/week, total 32 months 1000 STU were equivalent to 25 BU and contained 2.5 µg of major grass pollen allergens. The	Placebo drops	32 months	Primary end-point: multiple symptom-medication score, lung function, FeNO (part of the participants),	Less use of combined medication (asthma medication not analyzed separately). Lung function inconclusi	2nd author affiliated to pharmaceutical industry	"this is not my patient" (perennial asthma ex-cluded); lung function only analyzed as absolute values (not

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
							monthly dose during maintenance treatment was 6 µg (0.5 µg/dose,3 times/week). The median for the total duration of treatment was 32 months (January 1999 to November 2001) with a median cumulated dose of 188 µg allergen			complications	ve; No change in FeNO 1 patient asthma exacerbation related to SLIT		% predicted)
Ippoliti 2003[63]	double-blind placebo-controlled SLIT drops HDM	Monocenter, Italy	Mild/moderate asthma with or without rhinoconjunctivitis, FEV_1 > 70% predicted, mono-allergy HDM Exclusion: other allergies, severe asthma	86 (5-12 years); 35 female	Mild/moderate asthma, no seasonal asthma	Mono HDM	Drops SLIT *Dermatophagoides pteronyssinus* 1 + 2, 3 doses/week, 6 months	Placebo drops	6 months	Symptoms (unexplained scale), FEV_1, serum parameters, tolerance	Symptom scale not explained FEV_1; SLIT: 83,4% → 92,6%; placebo: 80,7% → 81,2% (no test)	Poor description of methods (randomization, blinding, drop-out, outcome assessment, and results), selected population?	
Niu 2006[64]	double-blind placebo	Multicenter, Taiwan	6-12 years, mild/moderate asthma, mono-	110; 97 in follow-	Mild/moderate asthma	Mono HDM	Drops SLIT *Dermatophagoides*	Placebo drops	30 weeks	Symptom scores, medication	Symptoms FEV_1: no numeric	Poor description of	

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
	- controlled SLIT drops HDM		allergy HDM, FEV_1 > 70%. Exclusion: other allergies, severe asthma	up (39 female)			*pteronyssinus* + *Dermatophagoides farinae*, 4 weeks pretreatment, 3 weeks inductions, 21 weeks treatment, 2 weeks evaluation follow-up			scores, lung function, skin prick test, serum IgE, global assessment, safety	data described	randomization and blinding procedure, poor outcome reports	
Pajno 2000[65]	double-blind placebo-controlled SLIT drops HDM	Monocenter Italy	Mild/moderate asthma, mono-allergy HDM Exclusion: other allergies, severe asthma	24 (8-15 years); 11 female	Mild/moderate asthma	Mono HDM	Drops SLIT *Dermatophagoides pteronyssinus* 1 + 2, maintenance 3 doses/week, 3 years	Placebo	3 years	Symptoms, medication use, asthma episodes, laboratory tests, side effects	Only nighttime symptoms reported	Few children, methodological failure on drop-outs, selective outcome report	
Pham-Thi[44]	Double-blind placebo-controlled SLIT tablets HDM	Monocenter, France	Asthma, treated with inhaled corticosteroids, reversible bronchial obstruction, sensitized to HDM Exclusion: sensitization to perennial and	109 (5-16 years); 31 female	Mild asthma: 73 Moderate asthma: 36 All using ICS	Mono HDM	Tablets *Dermatophagoides pteronyssinus* + *Dermatophagoides farinae, 2 weeks updosing, then maintenance 17,5 months*	Placebo tablets	18 months	Asthma symptom score, asthma-free days, asthma medication score, lung function, quality of life, rhinitis scores,	No significant differences between SLIT and placebo in symptoms and FEV_1. Quality of life: in children 6-11	Poor description of blinding	

Author, date	Study design	Setting	Eligibility criteria	Participants (number, gender, age, and	Asthma type*, severity (e.g. on ICS?)	Allergy type (mono/multi, allergens, proven)	Intervention (type, dose, duration)	Control	Follow-up (from start trial)	Outcomes	Results†	Critical appraisal‡	Comments
			seasonal allergens, previous immunotherapy							skin-prick tests, antibodies	significant difference on severity domain, clinical relevance not stated. Other domains, and older children: no significant difference between SLIT and placebo		

Abbreviations: µg: micrograms; BHR: bronchial hyperreactivity; BU: biological units; DDA: doctor diagnosed asthma; FeNO: fraction nitric oxide in exhaled air; FEV_1: forced expiratory volume in 1 second; HDM: house dust mite; ICS: inhaled corticosteroids; IR: index units of reactivity; n: number; PD20: concentration (metacholin/histamine) that causes a 20% fall in FEV_1; PEF: peak expiratory flow; RAST: radioallergent sorbent test; RCT: randomized controlled trial; SABA: short-acting beta agonists; SLIT: sublingual immunotherapy; SPT: skin prick test; STU: specific treatment units; VAS: visual analogue scale

** Doctors diagnosed asthma? Stable/seasonal asthma? Mild/severe asthma?*

† Asthma symptoms, allergy/rhinitis symptoms, asthma control, (disease specific) quality of life, exacerbations, lung function, adverse reactions and/or complications

‡ e.g. randomization procedure, blinding, risk of bias

*** defined as an abrupt and/or progressive worsening of symptoms of shortness of breath, chest tightness, or some combination of these symptoms, which did not respond to regular use of beta-2-agonists for a duration of 24 hours*

 # is long term follow-up of Pajno 2003

PRISMA 2009 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.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
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.	n.a.
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.	9
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.	19
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table E1
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).	10; table E2
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.	10 (fig 1)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
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.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 1
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.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
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.	12 + fig 1
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.	Table E2, E3, E4
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).	Table 2, , table E2, E3, E4
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.	Fig 2, 3; Table E2, E3, E 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12 -15; Fig 2, 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.
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).	16
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).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

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(6): e1000097.

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