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GRADE systematic review of immunotherapy in childhood asthma: evidence from previous systematic reviews no longer applicable in current clinical practice

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3 1 **GRADE systematic review of immunotherapy in childhood asthma: evidence from**
4 2 **previous systematic reviews no longer applicable in current clinical practice**
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9 4 **Authors**

- 10
11 5 1. Erik-Jonas **van de Griendt*** MD, paediatric pulmonologist,
12 6 DeKinderkliniek Almere and Academic Medical Centre Amsterdam,
13 7 Hospitaaldreef 29, 1315 RC Almere, The Netherlands
14 8 e.j.vandegriendt@amc.uva.nl *and*
15 9
16 10 Mariska K **Tuut***, MSc, epidemiologist,
17 11 PROVA, Spoorstraat 31, 7051 CG Varsseveld, The Netherlands,
18 12 m.tuut@provaweb.nl
19 13
20 14 2. Hans de Groot MD, PhD, allergologist,
21 15 Department of Paediatric Allergology, Reinier de Graaf Group, Reinier de Graafweg
22 16 5, 2625 AD Delft, The Netherlands, h.degroot@rdgg.nl
23 17
24 18 3. Paul L.P. Brand MD, PhD, paediatrician, Princess Amalia Children's Center, Isala
25 19 Hospital, P.O. Box 10400, 8000 GK Zwolle, the Netherlands; UMCG Postgraduate
26 20 School of Medicine, University Medical Center and University of Groningen, The
27 21 Netherlands, p.l.p.brand@isala.nl
28 22
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21 **both authors contributed equally*

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25 **Correspondence:**

26 Erik-Jonas van de Griendt, dept of paediatrics, DeKinderkliniek
27 Hospitaaldreef 29
28 1315 RC Almere
29 The Netherlands
30 telephone: +31 36 7630030
31 e-mail: e.j.vandegriendt@amc.uva.nl

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22 43 **Conflict of interest**
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45 55 **Contributorship statement**
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47 56 EJJ designed the study, chaired the guideline working group, provided clinical input (e.g.
48 57 defined clinical relevant outcome measures, judged the literature review from a clinical point
49 58 of view), wrote and revised the manuscript, and approved the final version.
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52 59 MKT designed the study, was methodologist of the guideline working group, provided
53 60 methodological input (e.g. provided literature search, selection, critical appraisal, GRADE
54 61 evidence profiles), wrote and revised the manuscript, and approved the final version.
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3 62 HdG was member of the guideline working group, designed the study, revised the
4 63 manuscript and approved the final version.

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7 64 PB provided clinical input, revised the manuscript and approved the final version.

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9 65 All authors meet full criteria for authorship, i.e. all contributed substantially, revised, approved
10 66 the final version of the manuscript and agreed to be accountable for all aspects of the work.

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15 68 **Data sharing statement**

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17 69 Extra data can be accessed in the online repository. Apart from this, no additional data are
18 70 available.

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23 72 **Transparency declaration**

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26 73 The corresponding author affirms that this manuscript is an honest, accurate, and
27 74 transparent account of the study being reported; that no important aspects of the study have
28 75 been omitted; and that any discrepancies from the study as planned (and, if relevant,
29 76 registered) have been explained.
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3 77 **Abbreviations**
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- 5 78 • 95%CI: 95% confidence interval
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7 79 • AMSTAR: A Measurement Tool to Assess Systematic Reviews
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9 80 • FEV₁: forced expiratory volume in 1 second
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11 81 • GRADE: Grading of Recommendations, Assessment, Development and Evaluation
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13 82 • ICS: inhaled corticosteroids
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15 83 • RCT: randomized controlled trial
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17 84 • SCIT: subcutaneous immunotherapy
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19 85 • SR: systematic review
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21 86 • SLIT: sublingual immunotherapy
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24 88 **Key words:** allergy, asthma, children, adolescents, immunotherapy, efficacy, GRADE,
25 89 systematic review

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3 91 **Abstract**
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5 92 **Background.** Allergy plays a major role in both asthma and its common comorbidity allergic
6 rhinitis. Immunotherapy is effective in the treatment of allergic rhinitis. Previous systematic
7 reviews indicated its effectiveness in children with asthma. Because most children with
8 persistent asthma now use ICS, the added benefit of immunotherapy in asthmatic children
9 needs to be examined.
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13 97 **Objective.** We re-assessed the effectiveness of subcutaneous (SCIT) and sublingual
14 immunotherapy (SLIT) in childhood asthma treatment focusing on studies with patient
15 relevant outcome measures and children using ICS.
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19 100 **Methods.** We used the GRADE approach to systematically search and appraise the
20 evidence using predefined critical patient relevant outcomes (asthma symptoms, asthma
21 control and exacerbations). We searched to retrieve systematic reviews and randomized
22 controlled trials on immunotherapy for asthma in children (1960 - 2015). We assessed the
23 quality of the body of evidence with GRADE criteria.
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27 105 **Results.** The quality of the evidence for SCIT was very low due to a large risk of bias and
28 indirectness (dated studies in children not using ICS). No effect of SCIT was found for
29 asthma symptoms; no studies reported on asthma control. For asthma exacerbations,
30 studies favoured SCIT. We have little confidence in this effect estimate, due to the very low
31 quality of evidence. For SLIT, quality of the evidence was very low due to a large risk of bias,
32 indirectness and imprecision. The outcome "asthma symptoms" could not be calculated due
33 to lack of standardization and large clinical heterogeneity. Other predefined outcomes were
34 not reported.
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40 113 **Conclusion.** The beneficial effects of immunotherapy in childhood asthma found in earlier
41 reviews are no longer considered applicable, because of indirectness (studies performed in
42 children not being treated according to current asthma guidelines with inhaled
43 corticosteroids). There was absence of evidence to properly determine the effectiveness or
44 lack thereof of immunotherapy in childhood asthma treatment.
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118 **Article Summary**

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

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3 131 **Introduction**
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5 132 Asthma affects 10-15% of school-aged children. For children with persistent asthma, all
6 133 international guidelines recommend daily controller treatment with inhaled corticosteroids
7 134 (ICS), and reliever medication (short-acting β -2-agonists) as needed.^{1,2} Although many
8 135 children achieve complete asthma control using this effective and safe treatment,¹ some
9 136 need additional treatment to obtain disease control.^{3,4} Identification and treatment of
10 137 comorbidities in children with problematic severe asthma is part of the stepwise approach to
11 138 improve asthma control in these children.^{5,6}

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17 139 The most common of these comorbidities in children with asthma is allergic rhinitis,⁵
18 140 symptoms of which occur in 60-80% of asthmatic children.^{7,8} Allergic rhinitis shares a
19 141 common pathophysiological pathway with asthma, which has been described as the united
20 142 airway concept.⁹ Allergic rhinitis is associated with worse asthma control in children, and
21 143 accumulating evidence suggests that treatment of allergic rhinitis with intranasal steroids
22 144 improves not only rhinitis, but also asthma symptoms in these patients.^{7,10,11}

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27 145 When symptoms of allergic rhinitis cannot be sufficiently controlled with nasal corticosteroids
28 146 and oral antihistamines,^{9,12} immunotherapy can be considered as additional treatment.¹³
29 147 Subcutaneous immunotherapy (SCIT) requires repeated injections with an allergen extract
30 148 and is available for allergens such as grass and tree pollen and house dust mite. After
31 149 disappointing results of low-dose preparations in drops, effective high-dose sublingual
32 150 immunotherapy (SLIT) has now become available with grass pollen allergen extract in a daily
33 151 sublingual tablet.^{14,15} A Cochrane systematic review, first published in 2000, and last updated
34 152 in 2010, reported beneficial effects of immunotherapy in children with asthma.¹⁶ Most studies
35 153 in this review, however, were performed in the 1980s, when most children with asthma were
36 154 not using ICS.

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43 155 As part of the update of the Dutch pediatric guideline on childhood asthma, we evaluated the
44 156 literature on the added value of SCIT and SLIT in childhood asthma.¹⁷ Our structured clinical
45 157 question was to assess whether immunotherapy (subcutaneous or sublingual), as an add-on
46 158 to usual care with daily ICS, improves asthma outcomes in children (6-12 years) and
47 159 adolescents (>12 years) with persistent asthma and sensitization to relevant aeroallergens
48 160 (grass or tree pollen, house dust mite, or combinations), with or without symptoms of allergic
49 161 rhinitis.

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163 Methods

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

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

186 **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

187 * or comparable differences on other valid scales representing this outcome

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

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

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3 195 reviews. Literature searches were performed in March 2012 for the guideline (from 1960
4 196 onwards), and updated in April 2015 for the purpose of this review (*see table E1 in the*
5 *Online Repository*). Two reviewers (EJvdG, MKT) independently screened the abstracts
6 197 using predefined inclusion criteria: methodology (SRs and RCTs), patients (children with
7 198 allergic asthma), and SCIT and/or SLIT as an intervention. Animal studies, conference
8 199 abstracts, and studies published in languages other than English, Dutch and German were
9 200 excluded. Differences between reviewers were resolved by consensus. Selected abstracts
10 201 were critically appraised with respect to study population and methodological aspects
11 202 (systematic search and selection, randomization of patients), which led to a further selection.
12 203 An expert in the field (HdG) judged the selection for completeness.
13 204

14
15 205 All included studies were summarized in evidence tables by two reviewers (EJvdG, MKT).
16 206 SRs were critically appraised using the AMSTAR checklist (A Measurement Tool to Assess
17 207 Systematic Reviews).²⁵ AMSTAR scores range from 0-11, a higher score indicating better
18 208 quality (less bias). The Jadad scale was used to assess the methodological quality of each
19 209 RCT.²⁶ This score ranges from 0-5, a higher score denoting a better quality. All eligible
20 210 studies together defined the body of evidence, of which the quality was determined (per
21 211 relevant outcome and overall quality) and GRADE Profiles were created. Results from SRs
22 212 and RCTs were pooled, if possible, in meta-analyses using RevMan 5. We calculated
23 213 standardized mean differences for continuous outcomes, because of the usage of different
24 214 symptom scales in the underlying studies. We calculated risk ratios for dichotomous
25 215 outcomes, to compare the probability of these outcomes between the intervention and
26 216 control groups. In the meta-analyses we used random effects models, because of the
27 217 possibility of generalization of the outcomes for different allergens, and tested the difference
28 218 between intervention and control with the inverse variance method, since this method is
29 219 typically used in meta-analyses to combine the results of independent studies. We reported
30 220 95% confidence intervals (pre-defined significance level: 0.05). Conclusions were drawn,
31 221 based on quality and content, per outcome and discussed in the expert group until
32 222 consensus was reached.

33 223 **Patient involvement**

34 224 The guideline development group included patient representatives who helped defining our
35 225 clinical question, approved outcome measures and assessed its clinical relevancy. The
36 226 burden of interventions and patient considerations were assessed as part of the GRADE
37 227 evaluation. Patients were not directly involved in this systematic review since we reviewed
38 228 published literature.

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3 229 **Results**

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5 230 ***Literature search and selection***

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7 231 Screening of titles and abstracts yielded 83 eligible studies, 10 of which fulfilled the inclusion
8 criteria.^{16,27-35} After examining these 10 papers in full, 5 more studies were excluded (*figure*
9 232 1).
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12 234 Experts in the guideline working group confirmed that no relevant publications were missed.
13 235 The updated search (April 2015) revealed 43 additional studies, of which 2 fulfilled the
14 236 inclusion criteria.^{36,37} Full text examination resulted in exclusion of these 2 studies.

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18 238 < *figure 1* >

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22 240 ***Results of SCIT***

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24 241 *Description of studies*

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26 242 We retrieved one Cochrane SR on the effectiveness of SCIT in patients with asthma ,
27 243 including 90 RCTs with a total of 3,792 patients.¹⁶ This was a high-quality review (AMSTAR
28 244 score 10/11). Fourteen of the included RCTs were performed in children exclusively; another
29 245 24 included children and adults. In a few studies the age inclusion criteria were not clear. The
30 246 characteristics of this review are summarized in an evidence table (*see table E2 in the Online*
31 247 *Repository*). Only nine RCTs included in this review reported on our predefined outcomes in
32 248 children. In these nine studies different allergens or combinations were studied (house dust
33 249 mite (3), dog dander (1), grass pollen (1), mold (1), grass pollen/house dust mite (1), tailored
34 250 combinations (2)). Two RCTs published after the 2010 Cochrane review were retrieved. In
35 251 the first, the clinical efficacy of house dust mite-specific SCIT in 20 asthmatic children was
36 252 compared to no intervention in 20 others; patients were followed up for six months.³⁴ In the
37 253 other, the effects of allergen-specific SCIT on corticosteroid dose in asthmatic children was
38 254 evaluated.³⁵ Details of all included RCTs are summarized in the evidence table (*see table E3*
39 255 *in the Online Repository*).

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41 256 *Quality of the evidence*

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43 257 Little information was given about the included studies in the Cochrane review; e.g. follow-up
44 258 was not stated. There were also other concerns about the quality of the literature, e.g. not all
45 259 studies were double-blind and placebo-controlled, and randomization procedures were poor.
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260 Therefore we re-analyzed the individual paediatric studies in the Cochrane review, plus the
261 added studies.^{34,35} Jadad scores of the single studies are presented in *table 2*.

262 **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

263 * 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1
264 point if the method of randomization is inappropriate

265 ** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the
266 method of blinding is inappropriate

267 [#] 1 point if the number and the reasons for withdrawal in each group are stated

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

273 **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)	⊕○○○ 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)	⊕○○○ VERY LOW	CRITICAL

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

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

275 immunotherapy

276 a. Studies in Cochrane review Abramson + Tsai

277 b. The underlying studies had a quite large risk of bias, due to lack of allocation concealment, problems with

278 blinding, and lack of information on follow-up (and loss-to-follow-up)

279 c. We downgraded for indirectness, because the included studies are quite old and maintenance medication may

280 have changed probably; thus, study populations may alter from nowadays patients with moderate to severe

281 asthma

282 d. We downgraded for risk of bias, because of problems with blinding and loss-to-follow-up

283 e. We assessed very serious indirectness, because most included studies for this outcome are very old, and

284 carried out before the ICS-era; thus, patients nowadays differ from study populations

285 Critical outcomes

286 Asthma symptoms. Four small studies carried out in children only reported this outcome in

287 the Cochrane review.¹⁶ We extracted these results from the Cochrane review and updated

288 these with the results from Tsai et al.³⁴ Results are presented in *figure 2*.

289

290 <figure 2 >

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

293 Asthma exacerbations. Five studies (published 1961-1984) in the Cochrane review, carried

294 out in children only, reported this outcome.¹⁶ No relevant studies of sufficient quality were

295 published afterwards. Our meta-analysis included 253 patients on immunotherapy and 153

296 on placebo. The pooled risk ratio was 0.47 (95%CI: 0.31 – 0.72), favouring immunotherapy

297 (see *figure 3*). The absolute risk reduction was 35%, giving a number needed to treat of 3.

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299 < figure 3 >

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301 No studies reported results on the critical outcome asthma control.

302 Important outcomes

303 No studies reported results on quality of life and lung function (FEV₁).

304 **Results of SLIT**

305 Description of studies and quality of the evidence

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

320 **Table 4. Summary of quality and outcome measures of selected RCT's in reviews**
 321 **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	+	-	-	-	-
	Yuksele 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

322 Abbreviations: FEV₁: forced expiratory volume in 1 second; RCT: randomized controlled trial

323 * 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1
324 point if the method of randomization is inappropriate

325 ** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the
326 method of blinding is inappropriate

327 # 1 point if the number and the reasons for withdrawal in each group are stated

328 § Same patients as Pajno 2003⁶⁰

329 Critical outcomes

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

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

339 Important outcomes

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

341 Lung function. Three studies reported results on lung function (FEV₁). One of the studies
342 reported no numeric data on lung function.⁵⁷ One study reported no variance (standard
343 deviation), and no comparison of the baseline data.⁵⁶ The only remaining study reported on
344 FEV₁ percentage predicted,⁵¹ and reported no significant differences between treatment
345 groups, neither at baseline nor at follow-up.

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3 347 **Discussion**

4
5 348 Summary of main results

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7 349 Our GRADE systematic review showed no evidence of a significant difference in asthma
8 350 symptoms between SCIT and placebo in children with allergic asthma, but some evidence for
9 351 a significant and clinically relevant reduction in asthma exacerbations was found in SCIT-
10 352 treated children. We have little confidence in the effect estimate, however, due to a large risk
11 353 of bias and indirectness. Thus, the true effect of SCIT on exacerbations and asthma
12 354 symptoms in the target population of interest is likely to be substantially different from the
13 355 estimate of effect. There was absence of evidence on the effects of SCIT on lung function,
14 356 asthma control, and quality of life in children with allergic asthma. There was no evidence for
15 357 a beneficial effect of SLIT in reducing asthma symptoms and exacerbations, quality of life
16 358 and lung function in children with allergic asthma. Our review does not address the efficacy
17 359 of immunotherapy in children regarding complaints of allergic rhinitis and/or conjunctivitis,
18 360 without having asthma.

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21 361 Quality of the evidence / GRADE methodology

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24 362 The overall quality of the evidence about the effectiveness of SCIT and SLIT was very low.
25 363 This implicates that our confidence in the effect estimates is very limited. The true effect of
26 364 SCIT and SLIT on patient relevant asthma outcomes in children with asthma may be
27 365 substantially different from our estimates of the effect. We cannot conclude that the possible
28 366 desirable effects of SCIT and SLIT outweigh the undesirable effects (e.g. influence on quality
29 367 of life, adverse events, or increased resource expenditure), nor can we reject that
30 368 hypothesis. Our concerns about the quality of evidence are based on (very) serious risk of
31 369 bias and indirectness in the underlying primary studies. Firstly, the quality of many studies
32 370 had to be downgraded because of risk of bias due to lack of allocation concealment, lack of
33 371 information on follow-up, and loss to follow-up. Secondly, included studies were
34 372 heterogeneous in the patients included and allergen extracts used, with different dosing
35 373 regimens and duration being studied, targeting different inhaled allergens. We have concerns
36 374 about the potential different responses and the generalizability of the evidence. Thirdly, and
37 375 most importantly, for SCIT, the quality of the body of evidence was downgraded because of
38 376 indirectness, since patients in the original studies long ago are likely to differ considerably
39 377 from patients nowadays.

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42 378 Thirdly, different studies used variable definitions of asthma exacerbations. We had to use
43 379 'worsening of asthma', which may not represent real-life patient relevant exacerbations. This
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3 380 may decrease the applicability of the evidence. In addition, there were no studies using the
4 381 predefined important outcomes quality of life and asthma control.

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6 382 Finally, and most importantly, several included studies dated from the 1980s or earlier, when
7 383 allergic rhinitis treatment with selective antihistamines and nasal corticosteroids was not
8 384 available. As a result, the allergic rhinitis patients in these studies cannot be compared to
9 385 patients in clinical practice today. Similarly, widespread use of ICS was not introduced in
10 386 childhood asthma treatment until the 1990s.⁶¹ Most studies on SCIT in children with asthma
11 387 were published decades ago, during the pre-ICS era. The patients in the described studies
12 388 represent an incomparable group compared to the child with asthma in contemporary clinical
13 389 practice. Specifically, it is unclear whether the beneficial effects found in the systematic
14 390 review of earlier studies is applicable to children with asthma treated according to
15 391 contemporary guidelines with daily ICS controller therapy.¹⁶

16
17 392 In our opinion and that of others, the GRADE approach is superior to former methods of SRs,
18 393 because it focuses on predefined patient relevant outcomes, predefined minimally clinical
19 394 important differences and because it judges the complete body of evidence. One RCT
20 395 among paediatricians studied the influence of different guideline grading systems on
21 396 clinician's decisions.⁶² GRADE showed the largest change in direction on the clinical
22 397 decision. However, the added value of GRADE on guideline implementation or patient care,
23 398 has not been formally evaluated, the GRADE approach is still rather complex for non-
24 399 methodologists.

25
26 400 To formulate recommendations for clinical practice, not only the body of evidence concerning
27 401 effectiveness of an intervention is important. Recommendations should balance the benefits
28 402 and harms of the intervention of interest, and take patient preferences and resource use into
29 403 account. Since (after critical evaluation) no benefits of SCIT and SLIT for children with
30 404 asthma were determined, we consider it unlikely that the benefits will exceed the harms.
31 405 Patient preferences were included in the formulation of our guideline recommendations.

32 406 Agreements and disagreements with other studies or reviews

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34 407 Using GRADE and re-analyzing data from children with allergic asthma only, we came to
35 408 different conclusions on the effectiveness of SCIT and SLIT in children with asthma than the
36 409 authors of the original SRs. We believe this highlights the importance of using GRADE
37 410 methodology to systematically review evidence for patient relevant outcomes, not focusing
38 411 on levels of evidence, but on underlying study validity, precision, directness, and applicability
39 412 in current clinical practice. A recent The 2009 position paper on SLIT describes history, use
40 413 and applicability of this treatment for allergic rhinitis.⁶³ It positions SLIT in children as a safe

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3 414 and useful therapy above and after more regular treatment for allergic rhinitis. Potential
4 415 positive treatment outcome for allergic asthma is however mainly based on literature in
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6 416 adults. We show the lack of evidence and lack of applicability of treatment of immunotherapy
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8 417 for asthma in children. Since we have worries on the applicability of evidence in adults on
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10 418 children (who are still developing their immune system), we think further studies that
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12 419 compare immunotherapy for the contemporary treatment of asthma in children are urgently
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14 420 needed to fill in this gap.

15 421 Recently, a Cochrane SR on SLIT for asthma found a similar lack of data for important
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17 422 outcomes (e.g. exacerbations, symptom scores, quality of life) as we did.⁶⁴ Contrary to our
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19 423 study, the authors did no separate analysis for adults and children, and patients with asthma
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21 424 were not separately analyzed from patients without asthma.

22 425 **Conclusions**

23
24 426 Focusing on predefined patient relevant outcomes, and critically appraising the body of
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26 427 evidence using original studies and GRADE methodology, our systematic review on the
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28 428 effects of immunotherapy in children with asthma came to different conclusions than previous
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30 429 systematic reviews . We believe that this underscores the importance of using GRADE
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32 430 methodology in systematically reviewing evidence.

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34 431 We found absence of valid applicable evidence on improvement of clinically relevant asthma
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36 432 outcomes in children with allergic asthma using SCIT or SLIT. This absence of evidence is
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38 433 due to serious risk of bias, large clinical heterogeneity between studies, and most importantly
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40 434 due to lack of applicability because studies were performed in the pre-ICS era.

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42 435 Since the effect of immunotherapy added to contemporary asthma treatment with daily
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44 436 controller therapy is not clear, the drawbacks of immunotherapy should be considered
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46 437 carefully. SCIT is a complex and intensive form of treatment, associated with a (very) long
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48 438 duration of treatment, and considerable burden to the patient with (monthly) injections under
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50 439 adequate medical supervision due to potential (however rare) dangerous side effects, and
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52 440 may have relatively high costs and resource use. In SLIT the risk of serious side-effects is
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54 441 considerably smaller, but the other drawbacks of immunotherapy apply equally to this
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56 442 treatment. In our opinion therefore, when balancing the absence of evidence on a clear
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58 443 beneficial effect of SCIT or SLIT on clinically relevant patient outcomes in children with
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60 444 asthma with the considerable burden and costs of SCIT and SLIT, we do not recommend this
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446 treatment to children with asthma until further high-quality evidence from well-designed RCTs
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448 in children comparing SCIT or SLIT to contemporary asthma treatment becomes available.

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4

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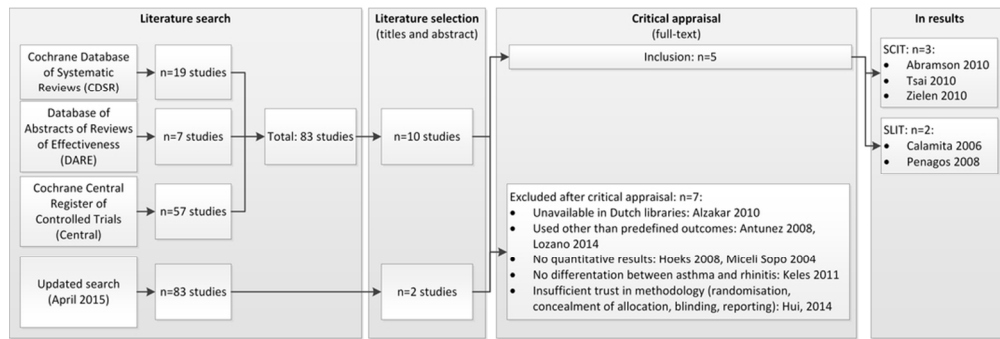
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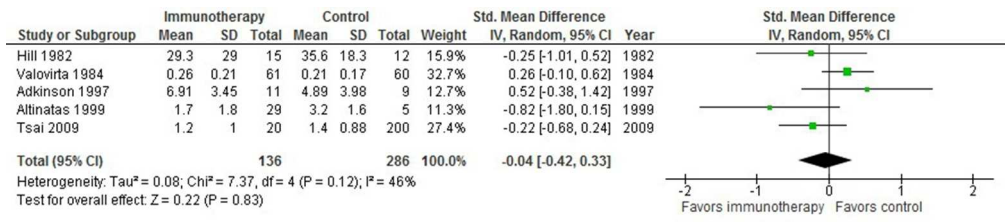


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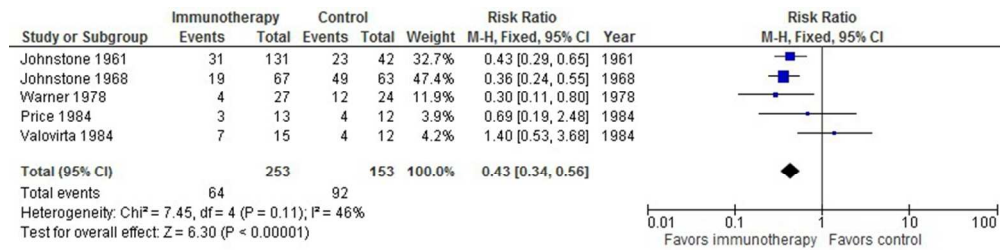
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Table E1. Literature search

Search Cochrane Databases of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Central; Literature search 2015, April 25th	
1.	"asthmazoeacties 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: <i>O europaea</i> , <i>Holcus</i> , <i>P pretense</i> <i>Dermatophagoides pteronyssinus</i> , 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	-

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	conducted new suitable meta-analyses.		
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Abbreviations: FEF25-75: maximum mid expiratory flow; FEV₁: forced expiratory volume in 1 second; PEFR: peak expiratory flow rate; RCT: randomized controlled trial; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

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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 authorst	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 <i>Dermatophagoides pteronyssinus</i>	Subcutaneous immunotherapy with adsorbed or aqueous <i>Dermatophagoides pteronyssinus</i> 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 <i>Cladosporium</i> allergy, aged 5 to 17 years	Clinical history suggesting mold-induced asthma and/or rhinoconjunctivitis ICS not stated	<i>Cladosporium</i> allergy	10 months <i>Cladosporium</i> 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 <i>Cladosporium</i>

												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 beclomethas on 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 <i>Dermatophagoides pteronyssinus</i>	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	
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	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 <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farina</i> (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 differences 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	
37 38 39 40 41 42 43 44 45 46 47 48 49	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 <i>Dermatophagoides pteronyssinus</i> challenge	ICS n=12, cromoglycate n=24 SABA n=14	House dust mite, SPT and bronchoprovocation positive	Subcutaneous immunotherapy with tyrosine adsorbed <i>Dermatophagoides pteronyssinus</i> 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 <i>Dermatophagoides pteronyssinus</i> 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-bronchodilator y 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	
Bahceci et al 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 aeroallergens	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 towards 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 patients, 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	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

												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		
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	Pajno 2003 ⁵⁰	double-blind placebo-controlled SLIT drops <i>Parietaria</i>	Mono-center, Italy	Inclusion: seasonal asthma and rhinoconjunctivitis, DDA, poor symptom control despite antihistamine, ICS and nedocromil use during pollen season, positive skin prick test <i>Parietaria</i> , Specific IgE to <i>Parietaria</i> . Exclusion: sensitization 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 sensitization to <i>Parietaria</i> , SPT and RAST positive	Drops SLIT <i>Parietaria</i> , 4 weeks run-in, maintenance every other day, total 12 months, co-medication with fluticasone	Placebo drops + fluticasone 2 nd control group: no protocolled medication	12 months	Symptom scores, VAS score during pollen season, compliance, SPT 6 months, serum IgE	No difference in 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

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			asthma (FEV ₁ <70%), other diseases										
Pajno 2004 ^{# 51}	double-blind placebo - controlled SLIT drops <i>Parietaria</i>	Mono-center, Italy	seasonal asthma during spring and allergic rhinitis	30 (8-14 years)	DDA	Mono sensitization to <i>Parietaria</i> , SPT and RAST positive	Drops SLIT <i>Parietaria</i> , 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 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	2 nd 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 <i>Dermatophagoides pteronyssinus</i> 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 <i>Dermatophagoides pteronyssinus</i> + <i>Dermatophagoides farinae</i> , 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 <i>Dermatophagoides pteronyssinus</i> 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; FEV₁: 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 FEV₁; 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?

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† 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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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016326.R1
Article Type:	Research
Date Submitted by the Author:	10-Aug-2017
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Respiratory medicine, Paediatrics, Immunology (including allergy)
Keywords:	Allergy < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, Paediatric thoracic medicine < PAEDIATRICS, GRADE systematic review, Children, Immunotherapy

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3 1 **A GRADE (Grading of Recommendations Assessment, Development and Evaluation)**
4 2 **systematic review of immunotherapy in childhood asthma: evidence from previous**
5 3 **systematic reviews no longer applicable in current clinical practice**
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10
11 5 **Authors**

- 12
13 6 1. Erik-Jonas **van de Griendt*** MD, paediatric pulmonologist,
14 7 DeKinderkliniek Almere and Academic Medical Centre Amsterdam,
15 8 Hospitaaldreef 29, 1315 RC Almere, The Netherlands
16 9 e.j.vandegriendt@amc.uva.nl *and*
17
18
19
20
21 11 Mariska K **Tuut***, MSc, epidemiologist,
22 12 PROVA, Spoorstraat 31, 7051 CG Varsseveld, The Netherlands,
23 13 m.tuut@provaweb.nl
24
25
26 14 2. Hans de Groot MD, PhD, allergologist,
27 15 Department of Paediatric Allergology, Reinier de Graaf Group, Reinier de Graafweg
28 16 5, 2625 AD Delft, The Netherlands, h.degroot@rdgg.nl
29
30
31
32
33 18 3. Paul L.P. Brand MD, PhD, paediatrician, Princess Amalia Children's Center, Isala
34 19 Hospital, P.O. Box 10400, 8000 GK Zwolle, the Netherlands; UMCG Postgraduate
35 20 School of Medicine, University Medical Center and University of Groningen, The
36 21 Netherlands, p.l.p.brand@isala.nl
37
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39

40 22 **both authors contributed equally*
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46
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49 26 **Correspondence:**

50
51 27 Erik-Jonas van de Griendt, dept of paediatrics, DeKinderkliniek
52 28 Hospitaaldreef 29
53 29 1315 RC Almere
54 30 The Netherlands
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31 telephone: +31 36 7630030

32 e-mail: e.j.vandegriendt@amc.uva.nl

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45 All authors have completed the ICMJE uniform disclosure form at
46 http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the
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56 **Contributorship statement**

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

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

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3 63 HdG was member of the guideline working group, designed the study, revised the
4 64 manuscript and approved the final version.

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7 65 PB provided clinical input, revised the manuscript and approved the final version.

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9 66 All authors meet full criteria for authorship, i.e. all contributed substantially, revised, approved
10 67 the final version of the manuscript and agreed to be accountable for all aspects of the work.

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15 69 **Data sharing statement**

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17 70 Extra data can be accessed in the online repository. Apart from this, no additional data are
18 71 available.

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24 73 **Transparency declaration**

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26 74 The corresponding author affirms that this manuscript is an honest, accurate, and
27 75 transparent account of the study being reported; that no important aspects of the study have
28 76 been omitted; and that any discrepancies from the study as planned (and, if relevant,
29 77 registered) have been explained.
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78 **Abbreviations**

- 79 • 95%CI: 95% confidence interval
- 80 • AMSTAR: A Measurement Tool to Assess Systematic Reviews
- 81 • FEV₁: forced expiratory volume in 1 second
- 82 • GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- 83 • ICS: inhaled corticosteroids
- 84 • RCT: randomized controlled trial
- 85 • SCIT: subcutaneous immunotherapy
- 86 • SR: systematic review
- 87 • SLIT: sublingual immunotherapy

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

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1
2
3 92 **Abstract**
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5 93 **Objective.** Because most children with asthma now use inhaled corticosteroids (ICS), the
6 added benefit of immunotherapy in asthmatic children needs to be examined. We re-
7 94 assessed the effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) in
8 95 childhood asthma treatment focusing on studies with patient relevant outcome measures and
9 96 children using ICS.
10 97

11 98 **Methods.** We used the GRADE approach to systematically search and appraise the
12 99 evidence using predefined critical patient relevant outcomes (asthma symptoms, asthma
13 100 control and exacerbations). We searched to retrieve systematic reviews and randomized
14 101 controlled trials on immunotherapy for asthma in children (1960 - 2017). We assessed the
15 102 quality of the body of evidence with GRADE criteria.
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22 103 **Results.** The quality of the evidence for SCIT was very low due to a large risk of bias and
23 104 indirectness (dated studies in children not using ICS). No effect of SCIT was found for
24 105 asthma symptoms; no studies reported on asthma control. For asthma exacerbations,
25 106 studies favoured SCIT. We have little confidence in this effect estimate, due to the very low
26 107 quality of evidence. For SLIT, quality of the evidence was very low due to a large risk of bias,
27 108 indirectness and imprecision. The outcome "asthma symptoms" could not be calculated due
28 109 to lack of standardization and large clinical heterogeneity. Other predefined outcomes were
29 110 not reported.
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35 111 **Conclusion.** The beneficial effects of immunotherapy in childhood asthma found in earlier
36 112 reviews are no longer considered applicable, because of indirectness (studies performed in
37 113 children not being treated according to current asthma guidelines with inhaled
38 114 corticosteroids). There was absence of evidence to properly determine the effectiveness or
39 115 lack thereof of immunotherapy in childhood asthma treatment.
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3 116 **Strengths and limitations**
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- 5 117 • This study is the first review evaluating immunotherapy in asthmatic children using
6 118 the GRADE approach, focusing more on clinically relevant than on statistically
7 119 significant differences in patient relevant outcomes.
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10 120 • Contrary to earlier reviews our study concluded that there is no evidence for
11 121 beneficial effects of immunotherapy for asthma in children.
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14 122 • A limitation of the study was the lack of evidence, especially the lack of recent studies
15 123 in current pediatric asthma populations, and lack of reported outcomes in the included
16 124 studies.
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19 125 • This study has focused on critically appraising ancient evidence for nowadays
20 126 practice, rather than endeavoring to be complete.
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127 Introduction

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

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

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

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

158

159 **Methods**

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

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

181 **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

182 * or comparable differences on other valid scales representing this outcome

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

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

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3 191 Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the
4 192 Cochrane Central Trial Register. . In the 2017 update we also searched for systematic
5 193 reviews in the Medline and Embase databases (again from 1960 onwards). Two reviewers
6 194 (EJvdG, MKT) independently screened the abstracts using predefined inclusion criteria:
7 195 methodology (SRs), patients (children with allergic asthma), and SCIT and/or SLIT as an
8 196 intervention. Animal studies, conference abstracts, and studies published in languages other
9 197 than English, Dutch and German were excluded. Differences between reviewers were
10 198 resolved by consensus. Selected abstracts were critically appraised with respect to study
11 199 population, intervention and methodological aspects (e.g. systematic search and selection,
12 200 inclusion of randomized controlled trials (RCTs)), which led to a further selection. An expert
13 201 in the field (HdG) judged the selection for completeness.

14
15 202 All included studies were summarized in evidence tables by two reviewers (EJvdG, MKT).
16 203 SRs were critically appraised using the AMSTAR checklist (A Measurement Tool to Assess
17 204 Systematic Reviews).²⁵ AMSTAR scores range from 0-11, a higher score indicating better
18 205 quality (less bias). The Jadad scale was used to assess the methodological quality of each
19 206 included RCT.²⁶ This score ranges from 0-5, a higher score denoting a better quality. All
20 207 eligible studies together defined the body of evidence, of which the quality was determined
21 208 (per relevant outcome and overall quality) and GRADE Profiles were created. Results from
22 209 SRs and RCTs were pooled, if possible, in meta-analyses using RevMan 5. We calculated
23 210 standardized mean differences for continuous outcomes, because of the usage of different
24 211 symptom scales in the underlying studies. We calculated risk ratios for dichotomous
25 212 outcomes, to compare the probability of these outcomes between the intervention and
26 213 control groups. In the meta-analyses we used random effects models, because of the
27 214 possibility of generalization of the outcomes for different allergens, and tested the difference
28 215 between intervention and control with the inverse variance method, since this method is
29 216 typically used in meta-analyses to combine the results of independent studies. We reported
30 217 95% confidence intervals (pre-defined significance level: 0.05). Conclusions were drawn,
31 218 based on quality and content, per outcome and discussed in the expert group until
32 219 consensus was reached.

33 220 **Patient involvement**

34 221 The guideline development group included patient representatives who helped defining our
35 222 clinical question, approved outcome measures and assessed its clinical relevancy. The
36 223 burden of interventions and patient considerations were assessed as part of the GRADE
37 224 evaluation. Patients were not directly involved in this systematic review since we reviewed
38 225 published literature.

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3 226 **Results**

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5 227 ***Literature search and selection***

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7 228 Screening of titles and abstracts yielded 83 eligible studies, 10 of which fulfilled the inclusion
8 criteria.^{16,27-35} After examining these 10 papers in full, 5 more studies were excluded (*figure*
9 229 1).

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12 231 Experts in the guideline working group confirmed that no relevant publications were missed.
13 232 The updated search (April 2015) revealed 43 additional studies, of which 2 fulfilled the
14 233 inclusion criteria.^{36,37} Full text examination resulted in exclusion of these 2 studies. The
15 234 extended and updated search in June 2017 resulted in 177 hits, of which 6 were selected to
16 235 full paper study³⁸⁻⁴³. These studies were systematic reviews in the field of SCIT and/or SLIT
17 236 in children with asthma. Most of the included RCT's in these reviews had already been
18 237 included in the 2015 search. We only added RCT's of those reviews to our meta-analyses
19 238 that have not been included earlier. As a result, we added one study⁴⁴.

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22 240 < *figure 1* > *Literature selection*

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26 242 ***Results of SCIT***

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28 243 *Description of studies*

29
30 244 We retrieved one Cochrane SR on the effectiveness of SCIT in patients with asthma ,
31 245 including 90 RCTs with a total of 3,792 patients.¹⁶ This was a high-quality review (AMSTAR
32 246 score 10/11). Fourteen of the included RCTs were performed in children exclusively; another
33 247 24 included children and adults. In a few studies the age inclusion criteria were not clear. The
34 248 characteristics of this review are summarized in an evidence table (*see table E2 in the Online*
35 249 *Repository*). Only nine RCTs included in this review reported on our predefined outcomes in
36 250 children. In these nine studies different allergens or combinations were studied (house dust
37 251 mite (3), dog dander (1), grass pollen (1), mold (1), grass pollen/house dust mite (1), tailored
38 252 combinations (2)). Two RCTs published after the 2010 Cochrane review were retrieved. In
39 253 the first, the clinical efficacy of house dust mite-specific SCIT in 20 asthmatic children was
40 254 compared to no intervention in 20 others; patients were followed up for six months.³⁴ In the
41 255 other, the effects of allergen-specific SCIT on corticosteroid dose in asthmatic children was
42 256 evaluated.³⁵ Details of all included RCTs are summarized in the evidence table (*see table E3*
43 257 *in the Online Repository*).

258 Quality of the evidence

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

264 **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

265 * 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1
 266 point if the method of randomization is inappropriate

267 ** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the
 268 method of blinding is inappropriate

269 [#] 1 point if the number and the reasons for withdrawal in each group are stated

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

275 **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)	⊕○○○ 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 -)	⊕○○○ VERY LOW	CRITICAL
Asthma control – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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

278 a. Studies in Cochrane review Abramson + Tsai

279 b. The underlying studies had a quite large risk of bias, due to lack of allocation concealment, problems with
280 blinding, and lack of information on follow-up (and loss-to-follow-up)

281 c. We downgraded for indirectness, because the included studies are quite old and maintenance medication may
282 have changed probably; thus, study populations may alter from nowadays patients with moderate to severe
283 asthma

284 d. We downgraded for risk of bias, because of problems with blinding and loss-to-follow-up

285 e. We assessed very serious indirectness, because most included studies for this outcome are very old, and
286 carried out before the ICS-era; thus, patients nowadays differ from study populations

287 Critical outcomes

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

291

292 <figure 2 >

293

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

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

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301 < figure 3 >

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303 No studies reported results on the critical outcome asthma control.

304 Important outcomes305 No studies reported results on quality of life or lung function (FEV₁).306 **Results of SLIT**307 Description of studies and quality of the evidence

308 We retrieved two SRs on SLIT in patients with asthma.^{29,32} The updated search in 2017
 309 resulted in the addition of one RCT⁴⁴. The characteristics of the SRs are summarized in
 310 evidence table E2 (*Online Repository*). The quality of the reviews was moderate; both had an
 311 AMSTAR score of 7/11. Weaknesses included the absence of an 'a priori design', exclusion
 312 of grey literature, not assessing the likelihood of publication bias and not mentioning conflicts
 313 of interest in one review,²⁹ and the absence of an 'a priori design', no information about
 314 excluded studies, too firm conclusions compared to the weak evidence, and not assessing
 315 the likelihood of publication bias in the other.³² One review included both children and adults,
 316 and patients with asthma and/or rhinitis.²⁹ Because of the quality concerns of both existing
 317 SRs, we set out to perform a meta-analysis of the original studies that fulfilled our selection
 318 criteria. Jadad scores of selected studies, as well as an overview of the outcomes of those
 319 studies, are presented in *table 4*. Study characteristics are summarized in the evidence table
 320 (*see table E4 in the Online Repository*). We rated the quality of evidence to be very low, due
 321 to a large risk of bias, imprecision and indirect evidence.

322 **Table 4. Summary of quality and outcome measures of selected RCT's in reviews**
 323 **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 ^{5,58}	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	

324 Abbreviations: FEV₁: forced expiratory volume in 1 second; RCT: randomized controlled trial

325 * 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1
326 point if the method of randomization is inappropriate

327 ** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the
328 method of blinding is inappropriate

329 # 1 point if the number and the reasons for withdrawal in each group are stated

330 § Same patients as Pajno 2003⁶⁷

331 Critical outcomes

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

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

341 Important outcomes

342 Quality of life. Pham-Thi et al. published results on quality of life using Childhood Asthma
343 Questionnaires⁴⁴. The authors reported a difference in severity between SLIT and placebo in
344 the younger population (age 6-11 years), but not in older children (age 12-16 years). It is not
345 stated whether this difference is clinically relevant.

346 Lung function. Four studies reported results on lung function (FEV₁). One of the studies
347 reported no numeric data on lung function.⁶⁴ One study reported no variance (standard
348 deviation), and no comparison of the baseline data.⁶³ The two remaining studies reported on
349 FEV₁ percentage predicted,⁵⁸ and reported no significant differences between treatment
350 groups, neither at baseline nor at follow-up.

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For peer review only

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3 352 **Discussion**

4
5 353 Summary of main results

6
7 354 Our GRADE systematic review showed no evidence of a significant difference in asthma
8 355 symptoms between SCIT and placebo in children with allergic asthma, but some evidence for
9 356 a significant and clinically relevant reduction in asthma exacerbations was found in SCIT-
10 357 treated children. We have little confidence in the effect estimate, however, due to a large risk
11 358 of bias and indirectness. Thus, the true effect of SCIT on exacerbations and asthma
12 359 symptoms in the target population of interest is likely to be substantially different from the
13 360 estimate of effect. There was absence of evidence on the effects of SCIT on lung function,
14 361 asthma control, and quality of life in children with allergic asthma. There was no evidence for
15 362 a beneficial effect of SLIT in reducing asthma symptoms and exacerbations, quality of life
16 363 and lung function in children with allergic asthma. Our review does not address the efficacy
17 364 of immunotherapy in children regarding complaints of allergic rhinitis and/or conjunctivitis,
18 365 without having asthma.

19
20
21 366 Quality of the evidence / GRADE methodology

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23
24 367 The overall quality of the evidence about the effectiveness of SCIT and SLIT was very low.
25 368 This implicates that our confidence in the effect estimates is very limited. The true effect of
26 369 SCIT and SLIT on patient relevant asthma outcomes in children with asthma may be
27 370 substantially different from our estimates of the effect. We cannot conclude that the possible
28 371 desirable effects of SCIT and SLIT outweigh the undesirable effects (e.g. influence on quality
29 372 of life, adverse events, or increased resource expenditure), nor can we reject that
30 373 hypothesis. Our concerns about the quality of evidence are based on (very) serious risk of
31 374 bias and indirectness in the underlying primary studies. Firstly, the quality of many studies
32 375 had to be downgraded because of risk of bias due to lack of allocation concealment, lack of
33 376 information on follow-up, and loss to follow-up. Secondly, included studies were
34 377 heterogeneous in the patients included and allergen extracts used, with different dosing
35 378 regimens and duration being studied, targeting different inhaled allergens. We have concerns
36 379 about the potential different responses and the generalizability of the evidence. Thirdly, and
37 380 most importantly, for SCIT, the quality of the body of evidence was downgraded because of
38 381 indirectness, since patients in the original studies long ago are likely to differ considerably
39 382 from patients nowadays.

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42 383 Fourth, different studies used variable definitions of asthma exacerbations. We had to use
43 384 'worsening of asthma', which may not represent real-life patient relevant exacerbations. This

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3 385 may decrease the applicability of the evidence. In addition, there were no studies using the
4 386 predefined important outcomes quality of life and asthma control.

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7 387 Finally, and most importantly, we have concerns on comparability of patients. Several
8 388 included studies dated from the 1980s or earlier, when allergic rhinitis treatment with
9
10 389 selective antihistamines and nasal corticosteroids was not available. Against the background
11 390 of the united airway concept, the comorbidity allergic rhinitis in patients in these studies
12 391 cannot be compared to patients in clinical practice today.⁹ Similarly, widespread use of ICS
13 392 was not introduced in childhood asthma treatment until the 1990s.⁶⁸ Most studies on SCIT in
14 393 children with asthma were published decades ago, during the pre-ICS era. The patients in
15 394 the described studies represent an incomparable group compared to the child with asthma in
16 395 contemporary clinical practice. Specifically, it is unclear whether the beneficial effects found
17 396 in the systematic review of earlier studies is applicable to children with asthma treated
18 397 according to contemporary guidelines with daily ICS controller therapy.¹⁶

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24 398 In our opinion and that of others, the GRADE approach is superior to former methods of SRs,
25 399 because it focuses on predefined patient relevant outcomes, predefined minimally clinical
26 400 important differences and because it judges the complete body of evidence. One RCT
27 401 among paediatricians studied the influence of different guideline grading systems on
28 402 clinician's decisions.⁶⁹ GRADE showed the largest change in direction on the clinical
29 403 decision. However, the added value of GRADE on guideline implementation or patient care,
30 404 has not been formally evaluated, the GRADE approach is still rather complex for non-
31 405 methodologists.

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37 406 To formulate recommendations for clinical practice, not only the body of evidence concerning
38 407 effectiveness of an intervention is important. Recommendations should balance the benefits
39 408 and harms of the intervention of interest, and take patient preferences and resource use into
40 409 account. Since (after critical evaluation) no benefits of SCIT and SLIT for children with
41 410 asthma were determined, we consider it unlikely that the benefits will exceed the harms.
42 411 Patient preferences were included in the formulation of our guideline recommendations.

43 44 45 46 47 412 Agreements and disagreements with other studies or reviews

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49 413 Using GRADE and re-analyzing data from children with allergic asthma only, we came to
50 414 different conclusions on the effectiveness of SCIT and SLIT in children with asthma than the
51 415 authors of the original SRs. We believe this highlights the importance of using GRADE
52 416 methodology to systematically review evidence for patient relevant outcomes, not focusing
53 417 on levels of evidence, but on underlying study validity, precision, directness, and applicability
54 418 in current clinical practice. The 2009 position paper on SLIT describes history, use and
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3 419 applicability of this treatment for allergic rhinitis.⁷⁰ It positions SLIT in children as a safe and
4 420 useful therapy above and after more regular treatment for allergic rhinitis. Potential positive
5 421 treatment outcome for allergic asthma is however mainly based on literature in adults. We
6 422 show the lack of evidence and lack of applicability of treatment of immunotherapy for asthma
7 423 in children. Since we have worries on the applicability of evidence in adults on children (who
8 424 are still developing their immune system), we think further studies that compare
9 425 immunotherapy for the contemporary treatment of asthma in children are urgently needed to
10 426 fill in this gap.

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12 427 Recently, a Cochrane SR on SLIT for asthma found a similar lack of data for important
13 428 outcomes (e.g. exacerbations, symptom scores, quality of life) as we did.⁷¹ Contrary to our
14 429 study, the authors did no separate analysis for adults and children, and patients with asthma
15 430 were not separately analyzed from patients without asthma.

16 431 **Conclusions**

17 432 Focusing on predefined patient relevant outcomes, and critically appraising the body of
18 433 evidence using original studies and GRADE methodology, our systematic review on the
19 434 effects of immunotherapy in children with asthma came to different conclusions than previous
20 435 systematic reviews. We believe that this underscores the importance of using GRADE
21 436 methodology in systematically reviewing evidence.

22 437 We found absence of valid applicable evidence on improvement of clinically relevant asthma
23 438 outcomes in children with allergic asthma using SCIT or SLIT. This absence of evidence is
24 439 due to serious risk of bias, large clinical heterogeneity between studies, and most importantly
25 440 due to lack of applicability because studies were performed in the pre-ICS era.

26 441 Since the effect of immunotherapy added to contemporary asthma treatment with daily
27 442 controller therapy is not clear, the drawbacks of immunotherapy should be considered
28 443 carefully. SCIT is a complex and intensive form of treatment, associated with a (very) long
29 444 duration of treatment, and considerable burden to the patient with (monthly) injections under
30 445 adequate medical supervision due to potential (however rare) dangerous side effects, and
31 446 may have relatively high costs and resource use. In SLIT the risk of serious side-effects is
32 447 considerably smaller, but the other drawbacks of immunotherapy apply equally to this
33 448 treatment. In our opinion therefore, when balancing the absence of evidence on a clear
34 449 beneficial effect of SCIT or SLIT on clinically relevant patient outcomes in children with
35 450 asthma with the considerable burden and costs of SCIT and SLIT, we do not recommend this
36 451 treatment to children with asthma until further high-quality evidence from well-designed RCTs
37 452 in children comparing SCIT or SLIT to contemporary asthma treatment becomes available.

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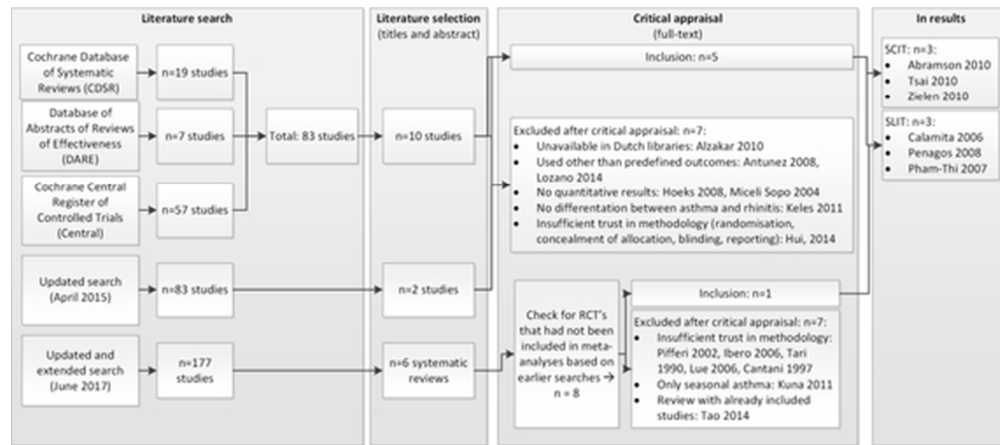
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3 664 **Figure legends**
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5 665 Figure 1. Literature search and selection
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7 666 Figure 2. Meta-analysis of SCIT vs. placebo, outcome asthma symptoms. *Abbreviations: SD:*
8 667 *Standard deviation; Std: Standardized; IV: inverse variance; random: random effect model; 95%CI: 95%*
9 668 *Confidence Interval*
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11 669 Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. *Abbreviations:*
12 670 *95%CI: 95% Confidence Interval; Fixed: Fixed effect model; M-H: Mantel-Haenszel*
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Literature search and selection

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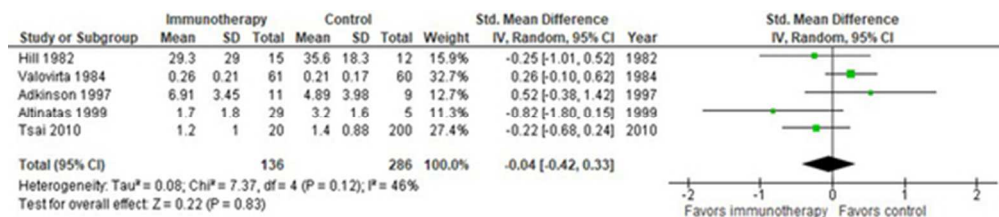


Figure 2. Meta-analysis of SCIT vs. placebo, outcome asthma symptoms. Abbreviations: SD: Standard deviation; Std: Standardized; IV: inverse variance; random: random effect model; 95%CI: 95% Confidence Interval

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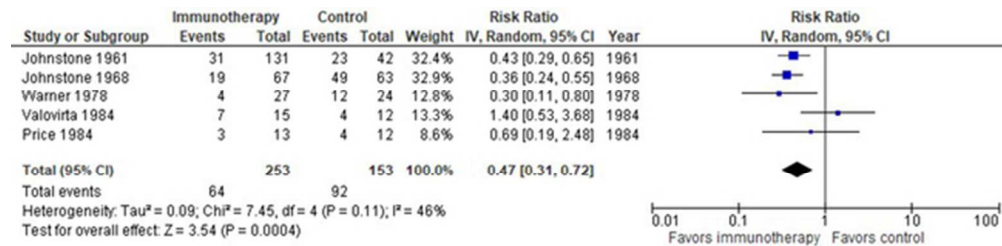


Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. Abbreviations: 95%CI: 95% Confidence Interval; Fixed: Fixed effect model; M-H: Mantel-Haenszel

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.	"asthmazoeacties 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)

1	
2	
3	
4	35 "Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to
5	Parietaria pollen treated with ".fc_titl. (1)
6	36 "Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract
7	".fc_titl. (1)
8	37 "Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-
9	controlled study. ".fc_titl. (1)
10	38 or/18-20 (3)
11	39 or/21-37 (19)
12	40 38 or 39 (22)
13	41 "controle refs slit scit".ti. (0)
14	42 "filter systematic reviews & meta-analyses Embase".ti. (0)
15	43 meta analysis/ (127495)
16	44 "systematic review"/ (139284)
17	45 (meta-analy\$ or metaanaly\$).tw. (145912)
18	46 (systematic\$ adj4 (review\$ or overview\$)).tw. (139834)
19	47 (quantitativ\$ adj5 (review? or overview?)).tw. (3786)
20	48 (methodologic adj5 (overview? or review?)).tw. (325)
21	49 (review\$ adj3 (database? or medline or embase or cinahl)).tw. (19428)
22	50 (pooled adj3 analy\$).tw. (20108)
23	51 (extensive adj3 review\$ adj3 literature).tw. (2903)
24	52 (meta or synthesis or (literature adj8 database?) or extraction).tw. (1197812)
25	53 review.pt. (2259303)
26	54 52 and 53 (112526)
27	55 (systematic\$ adj4 (review\$ or overview\$)).kw. (16750)
28	56 (quantitativ\$ adj5 (review? or overview?)).kw. (48)
29	57 (pooled adj3 analy\$).kw. (354)
30	58 or/43-51,54-57 (381419)
31	59 "filter rct embase".ti. (0)
32	60 controlled clinical trial/ or randomized controlled trial/ (614267)
33	61 randomization/ (73811)
34	62 Major Clinical Study/ (2803898)
35	63 random\$.tw. (1196822)
36	64 Double Blind Procedure/ (139034)
37	65 or/60-64 (3916117)
38	66 "einde filter rct embase".ti. (0)
39	67 (child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or
40	girl? or kid? or schoolage* or juvenil* or adolescen* or toddler?).tw. (2468214)
41	68 child/ (1526632)
42	69 infant/ (566151)
43	70 adolescent/ (1414197)
44	71 or/67-70 (3656088)
45	72 17 and 58 and 71 (85) systrev
46	73 (17 and 65 and 71) not 58 (370) rct
47	74 17 and 58 (208)
48	75 74 not 72 (123)
49	76 75 (123)
50	77 limit 76 to yr="2016 -Current" (14)
51	78 76 (123)
52	79 limit 78 to yr="2015 -Current" (31) extra systrev
53	Search Cochrane 2017, June, 2nd
54	
55	
56	#1 asthma*:ti,ab,kw 26843
57	#2 MeSH descriptor: [Asthma] this term only 9761
58	#3 MeSH descriptor: [Bronchial Spasm] explode all trees 360
59	#4 wheez*:ti,ab,kw 1642
60	#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 <i>Dermatophagoides pteronyssinus</i> , 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	-
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Abbreviations: FEF25-75: maximum mid expiratory flow; FEV₁: forced expiratory volume in 1 second; PEFr: peak expiratory flow rate; RCT: randomized controlled trial; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

For peer review only

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 author†	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 <i>Dermatophagoides pteronyssinus</i>	Subcutaneous immunotherapy with adsorbed or aqueous <i>Dermatophagoides pteronyssinus</i> 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 <i>Cladosporium</i> allergy, aged 5 to 17 years	Clinical history suggesting mold-induced asthma and/or rhinoconjunctivitis ICS not stated	<i>Cladosporium</i> allergy	10 months <i>Cladosporium</i> 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 <i>Cladospori</i>

												um season)	
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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 beclomethasone 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
16 17 18 19 20 21 22 23 24 25 26 27 28	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
29 30 31 32 33 34 35 36 37 38 39	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
40 41 42 43 44 45 46 47	Price, 1984 ⁵¹	RCT, double blind		25 children with perennial asthma, aged 5 to 15 years	Asthma severity not specified asthma		Subcutaneous immunotherapy with <i>Dermatophag</i>	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

1		Saline placebo control			medication not specified		<i>oides pteronyssinus</i> extracts				children with severe asthma improved	surrogate outcome;	year with placebo group crossed over to active immunotherapy
2													
3													
4													
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7													
8	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 <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farina</i> (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 differences 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	
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37													
38	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
39													
40													
41													
42													
43													
44													
45													
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47													

						dander extract				statistically not significant		to pharmaceutical company	
1 2 3 4 5 6 7 8 9 10 11 12 13	Warner, 1978 ⁵³	RCT, double blind Tyrosine placebo control	University, United Kingdom	51 asthmatic children, aged 5 to 14 years, with positive <i>Dermatophagoides pteronyssinus</i> challenge	ICS n=12, cromoglycate n=24 SABA n=14	House dust mite, SPT and bronchoprovocation positive	Subcutaneous immunotherapy with tyrosine adsorbed <i>Dermatophagoides pteronyssinus</i> 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
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38	Zielen, 2010 ⁵⁵	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 <i>Dermatophagoides pteronyssinus</i> 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-bronchodilator y 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

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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
Bahceciler 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 aeroallergens	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 towards 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 patients, 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 <i>Parietaria</i>	Mono-center, Italy	Inclusion: seasonal asthma and rhinoconjunctivitis, DDA, poor symptom control despite antihistamine, ICS and nedocromil use during pollen season, positive skin prick test <i>Parietaria</i> , 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 <i>Parietaria</i> , SPT and RAST positive	Drops SLIT <i>Parietaria</i> , 4 weeks run-in, maintenance every other day, total 12 months, co-medication with fluticasone	Placebo drops + fluticasone 2 nd control group: no protocol medication	12 months	Symptom scores, VAS score during pollen season, compliance, SPT 6 months, serum IgE	No difference in 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

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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	Result†	Critical appraisal‡	Comments	
			<i>Parietaria</i> . Exclusion: sensitization to other allergens, previous immunotherapy, severe asthma (FEV ₁ <70%), other diseases										
Pajno 2004 ^{# 58}	double-blind placebo-controlled SLIT drops <i>Parietaria</i>	Mono-center, Italy	seasonal asthma during spring and allergic rhinitis	30 (8-14 years)	DDA	Mono sensitization to <i>Parietaria</i> , SPT and RAST positive	Drops SLIT <i>Parietaria</i> , 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	
Rolnick-Werninghaus 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 inconclusive	2 nd author affiliated to pharmaceutical industry	"this is not my patient" (perennial asthma excluded); 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 <i>Dermatophagoides pteronyssinus</i> 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 <i>Dermatophagoides</i>	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	Result†	Critical appraisal‡	Comments
	- controlled SLIT drops HDM		allergy HDM, FEV ₁ > 70%. Exclusion: other allergies, severe asthma	up (39 female)		<i>pteronysinus</i> + <i>Dermatophagoides farinae</i> , 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 <i>Dermatophagoides pteronyssinus</i> 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 <i>Dermatophagoides pteronyssinus</i> + <i>Dermatophagoides farinae</i> , 2 weeks up dosing, 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	Result†	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; FEV₁: 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 FEV₁; 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

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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. http://bmjopen.bmj.com/site/about/guidelines.xhtml)	10



PRISMA 2009 Checklist

Page 1 of 2

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, E4
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



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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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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Respiratory medicine, Paediatrics, Immunology (including allergy)
Keywords:	Allergy < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, Paediatric thoracic medicine < PAEDIATRICS, GRADE systematic review, Children, Immunotherapy

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3 1 **Applicability of evidence from previous systematic reviews on immunotherapy in**
4 **current practice of childhood asthma treatment: A GRADE (Grading of**
5 **Recommendations Assessment, Development and Evaluation) systematic review**
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8 **Authors**
9

- 10 1. Erik-Jonas **van de Griendt*** MD, paediatric pulmonologist,
11 DeKinderkliniek Almere and Academic Medical Centre Amsterdam,
12 Hospitaaldreef 29, 1315 RC Almere, The Netherlands
13 e.j.vandegriendt@amc.uva.nl *and*
14
15
16
17
18 Mariska K **Tuut***, MSc, epidemiologist,
19 PROVA, Spoorstraat 31, 7051 CG Varsseveld, The Netherlands,
20 m.tuut@provaweb.nl
21
22
23 2. Hans de Groot MD, PhD, allergologist,
24 Department of Paediatric Allergology, Reinier de Graaf Group, Reinier de Graafweg
25 5, 2625 AD Delft, The Netherlands, h.degroot@rdgg.nl
26
27
28
29
30 3. Paul L.P. Brand MD, PhD, paediatrician, Princess Amalia Children's Center, Isala
31 Hospital, P.O. Box 10400, 8000 GK Zwolle, the Netherlands; UMCG Postgraduate
32 School of Medicine, University Medical Center and University of Groningen, The
33 Netherlands, p.l.p.brand@isala.nl
34
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37 **both authors contributed equally*
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46 **Correspondence:**
47

48 Erik-Jonas van de Griendt, dept of paediatrics, DeKinderkliniek
49 Hospitaaldreef 29
50 1315 RC Almere
51 The Netherlands
52 telephone: +31 36 7630030
53 e-mail: e.j.vandegriendt@amc.uva.nl
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22 43 **Conflict of interest**
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24 44 All authors have completed the ICMJE uniform disclosure form at
25 45 http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the
26 46 submitted work, no financial relationships with any organisations that might have an interest
27 47 in the submitted work in the previous three years, no other relationships or activities that
28 48 could appear to have influenced the submitted work.
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44 55 **Contributorship statement**
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46 56 EJJ designed the study, chaired the guideline working group, provided clinical input (e.g.
47 57 defined clinical relevant outcome measures, judged the literature review from a clinical point
48 58 of view), wrote and revised the manuscript, and approved the final version.
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52 59 MKT designed the study, was methodologist of the guideline working group, provided
53 60 methodological input (e.g. provided literature search, selection, critical appraisal, GRADE
54 61 evidence profiles), wrote and revised the manuscript, and approved the final version.
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3 62 HdG was member of the guideline working group, designed the study, revised the
4 63 manuscript and approved the final version.

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7 64 PB provided clinical input, revised the manuscript and approved the final version.

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9 65 All authors meet full criteria for authorship, i.e. all contributed substantially, revised, approved
10 66 the final version of the manuscript and agreed to be accountable for all aspects of the work.

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15 68 **Data sharing statement**

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17 69 Extra data can be accessed in the online repository. Apart from this, no additional data are
18 70 available.

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23 72 **Transparency declaration**

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26 73 The corresponding author affirms that this manuscript is an honest, accurate, and
27 74 transparent account of the study being reported; that no important aspects of the study have
28 75 been omitted; and that any discrepancies from the study as planned (and, if relevant,
29 76 registered) have been explained.
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77 **Abbreviations**

- 78 • 95%CI: 95% confidence interval
- 79 • AMSTAR: A Measurement Tool to Assess Systematic Reviews
- 80 • FEV₁: forced expiratory volume in 1 second
- 81 • GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- 82 • ICS: inhaled corticosteroids
- 83 • RCT: randomized controlled trial
- 84 • SCIT: subcutaneous immunotherapy
- 85 • SR: systematic review
- 86 • SLIT: sublingual immunotherapy

87

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

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1
2
3 91 **Abstract**
4

5 92 **Objective.** Because most children with asthma now use inhaled corticosteroids (ICS), the
6 added benefit of immunotherapy in asthmatic children needs to be examined. We re-
7 93 assessed the effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) in
8 94 childhood asthma treatment focusing on studies with patient relevant outcome measures and
9 95 children using ICS.
10 96

11 97 **Methods.** We used the GRADE approach to systematically search and appraise the
12 98 evidence using predefined critical patient relevant outcomes (asthma symptoms, asthma
13 99 control and exacerbations). We searched to retrieve systematic reviews and randomized
14 100 controlled trials on immunotherapy for asthma in children (1960 - 2017). We assessed the
15 101 quality of the body of evidence with GRADE criteria.
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18 102 **Results.** The quality of the evidence for SCIT was very low due to a large risk of bias and
19 103 indirectness (dated studies in children not using ICS). No effect of SCIT was found for
20 104 asthma symptoms; no studies reported on asthma control. For asthma exacerbations,
21 105 studies favoured SCIT. We have little confidence in this effect estimate, due to the very low
22 106 quality of evidence. For SLIT, quality of the evidence was very low due to a large risk of bias,
23 107 indirectness and imprecision. The outcome "asthma symptoms" could not be calculated due
24 108 to lack of standardization and large clinical heterogeneity. Other predefined outcomes were
25 109 not reported.
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28 110 **Conclusion.** The beneficial effects of immunotherapy in childhood asthma found in earlier
29 111 reviews are no longer considered applicable, because of indirectness (studies performed in
30 112 children not being treated according to current asthma guidelines with inhaled
31 113 corticosteroids). There was absence of evidence to properly determine the effectiveness or
32 114 lack thereof of immunotherapy in asthma treatment in children with inhaled corticosteroids.
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3 115 **Strengths and limitations of this study**
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- 5 116 • This study is the first review evaluating immunotherapy in asthmatic children using
6 117 the GRADE approach, focusing more on clinically relevant than on statistically
7 118 significant differences in patient relevant outcomes.
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10 119 • By using GRADE we identified indirectness in previous systematic reviews in this
11 120 field, which highlight a lack of applicable evidence
12
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14 121 • A strength of the study is the use of predefined clinically relevant patient outcomes,
15 122 rather than statistically significant differences.
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18 123 • A general limitation of a systematic review is the use of aggregated data, that, in
19 124 theory might mask potential specific results.
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22 125 • This study has focused on critically appraising earlier evidence for nowadays practice,
23 126 rather than endeavoring to be complete.
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127 Introduction

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

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

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

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

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3 159 **Methods**
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5 160 We used the GRADE approach (Grading of Recommendations Assessment, Development
6 and Evaluation) to appraise and summarize the body of evidence. GRADE is an
7 161 internationally approved standard for managing complex evidence reviews.¹⁸ In contrast to
8 162 former grading systems, GRADE focuses on the quality of the total body of evidence, instead
9 163 of judging single studies. Another important characteristic of GRADE is that predefined
10 164 outcomes with thresholds for clinical relevance are being used.¹⁹ In earlier grading systems,
11 165 the evidence was summarized using outcomes reported in studies, not necessarily being
12 166 outcomes a guideline development group would be interested in.²⁰ GRADE avoids the use of
13 167 surrogate or intermediate outcomes, and uses outcomes and differences that are more
14 168 clinically relevant to patients instead. Starting from a systematic review, for each outcome the
15 169 quality of evidence can be downgraded or upgraded, for instance based on risk of bias,
16 170 inconsistency, indirectness, possible publication bias, and dose-response relation.
17 171

18 172 The guideline development group included an epidemiologist, paediatric respiratory
19 173 physicians, paediatricians, an allergist, an ear-nose-throat specialist, a family physician, a
20 174 lung function technician, a youth public health care physician, and patient representatives.
21 175 The guideline development group predefined clinically relevant outcomes and divided these
22 176 into critical (contributing to the overall quality of evidence), important (also relevant to the
23 177 content of the guideline) and not important outcomes. For each outcome, a minimal clinically
24 178 important difference was defined *a priori*. The outcomes taken into account in our literature
25 179 review are summarized in *table 1*, with corresponding minimal clinically important
26 180 differences.²¹⁻²⁴

27 181 **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

28 182 * or comparable differences on other valid scales representing this outcome

29 183 Abbreviations: ACT: asthma control test; c-ACT: child ACT; NNT: number needed to treat (to prevent one
30 184 exacerbation); PAQLQ: Pediatric Asthma Quality of Life Questionnaire

31 185 We applied a sensitive search strategy to retrieve all available evidence addressing the
32 186 clinical question, focusing on systematic reviews (SRs) about asthma and immunotherapy in
33 187 children. Literature searches were performed in March 2012 for the guideline (from 1960
34 188 onwards), and updated in April 2015 for the purpose of this review. A second update,
35 189 including an expansion of the searching scope, was performed in June 2017. (see *table E1 in*
36 190 *the Online Repository*). In the original search, we searched in the Cochrane Database of

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3 191 Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the
4 192 Cochrane Central Trial Register. In the 2017 update we also searched for systematic reviews
5 193 in the Medline and Embase databases (again from 1960 onwards). Two reviewers (EJvdG,
6 194 MKT) independently screened the abstracts using predefined inclusion criteria: methodology
7 195 (SRs), patients (children with allergic asthma), and SCIT and/or SLIT as an intervention.
8 196 Animal studies, conference abstracts, and studies published in languages other than English,
9 197 Dutch and German were excluded. Differences between reviewers were resolved by
10 198 consensus. Selected abstracts were critically appraised with respect to study population,
11 199 intervention and methodological aspects (e.g. systematic search and selection, inclusion of
12 200 randomized controlled trials (RCTs)), which led to a further selection. An expert in the field
13 201 (HdG) judged the selection for completeness.

14
15 202 All included studies were summarized in evidence tables by two reviewers (EJvdG, MKT).
16 203 SRs were critically appraised using the AMSTAR checklist (A Measurement Tool to Assess
17 204 Systematic Reviews).²⁵ AMSTAR scores range from 0-11, a higher score indicating better
18 205 quality (less bias). The Jadad scale was used to assess the methodological quality of each
19 206 included RCT.²⁶ This score ranges from 0-5, a higher score denoting a better quality. All
20 207 eligible studies together defined the body of evidence, of which the quality was determined
21 208 (per relevant outcome and overall quality) and GRADE Profiles were created. Results from
22 209 SRs and RCTs were pooled, if possible, in meta-analyses using RevMan 5. We calculated
23 210 standardized mean differences for continuous outcomes, because of the usage of different
24 211 symptom scales in the underlying studies. We calculated risk ratios for dichotomous
25 212 outcomes, to compare the probability of these outcomes between the intervention and
26 213 control groups. In the meta-analyses we used random effects models, because of the
27 214 possibility of generalization of the outcomes for different allergens, and tested the difference
28 215 between intervention and control with the inverse variance method, since this method is
29 216 typically used in meta-analyses to combine the results of independent studies. We reported
30 217 95% confidence intervals (pre-defined significance level: 0.05). Conclusions were drawn,
31 218 based on quality and content, per outcome and discussed in the expert group until
32 219 consensus was reached.

33 220 **Patient involvement**

34 221 The guideline development group included patient representatives who helped defining our
35 222 clinical question, approved outcome measures and assessed its clinical relevancy. The
36 223 burden of interventions and patient considerations were assessed as part of the GRADE
37 224 evaluation. Patients were not directly involved in this systematic review since we reviewed
38 225 published literature.

226 Results

227 *Literature search and selection*

228 Screening of titles and abstracts yielded 83 eligible studies, 10 of which fulfilled the inclusion
229 criteria.^{16,27-35} After examining these 10 papers in full, 5 more studies were excluded (*figure*
230 1).

231 Experts in the guideline working group confirmed that no relevant publications were missed.
232 The updated search (April 2015) revealed 43 additional studies, of which 2 fulfilled the
233 inclusion criteria.^{36,37} Full text examination resulted in exclusion of these 2 studies. The
234 extended and updated search in June 2017 resulted in 177 hits, of which 6 were selected to
235 full paper study³⁸⁻⁴³. These studies were systematic reviews in the field of SCIT and/or SLIT
236 in children with asthma. Most of the included RCT's in these reviews had already been
237 included in the 2015 search. We only added RCT's of those reviews to our meta-analyses
238 that have not been included earlier. As a result, we added one study⁴⁴.

239

240 < *figure 1* > *Literature selection*

241

242 **Results of SCIT**

243 Description of studies

244 We retrieved one Cochrane SR on the effectiveness of SCIT in patients with asthma ,
245 including 90 RCTs with a total of 3,792 patients.¹⁶ This was a high-quality review (AMSTAR
246 score 10/11). Fourteen of the included RCTs were performed in children exclusively; another
247 24 included children and adults. In a few studies the age inclusion criteria were not clear. The
248 characteristics of these review are summarized in an evidence table (*see table E2 in the*
249 *Online Repository*).^{16,29,32} Only nine RCTs included in these reviews reported on our
250 predefined outcomes in children.⁴⁵⁻⁵³ In these nine studies different allergens or
251 combinations were studied (house dust mite (3), dog dander (1), grass pollen (1), mold (1),
252 grass pollen/house dust mite (1), tailored combinations (2)). Two RCTs published after the
253 2010 Cochrane review were retrieved.^{34,35} In the first, the clinical efficacy of house dust mite-
254 specific SCIT in 20 asthmatic children was compared to no intervention in 20 others; patients
255 were followed up for six months.³⁴ In the other, the effects of allergen-specific SCIT on
256 corticosteroid dose in asthmatic children was evaluated.³⁵ Details of all included RCTs are
257 summarized in the evidence table (*see table E3 in the Online Repository*).^{34,35,45-53}

258 Quality of the evidence

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

264 **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

265 * 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1
 266 point if the method of randomization is inappropriate

267 ** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the
 268 method of blinding is inappropriate

269 [#] 1 point if the number and the reasons for withdrawal in each group are stated

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

275 **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)	⊕○○○ 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)	⊕○○○ VERY LOW	CRITICAL
Asthma control – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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

278 a. Studies in Cochrane review Abramson + Tsai

279 b. The underlying studies had a quite large risk of bias, due to lack of allocation concealment, problems with
280 blinding, and lack of information on follow-up (and loss-to-follow-up)

281 c. We downgraded for indirectness, because the included studies are quite old and maintenance medication may
282 have changed probably; thus, study populations may alter from nowadays patients with moderate to severe
283 asthma

284 d. We downgraded for risk of bias, because of problems with blinding and loss-to-follow-up

285 e. We assessed very serious indirectness, because most included studies for this outcome are very old, and
286 carried out before the ICS-era; thus, patients nowadays differ from study populations

287 Critical outcomes

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

291

292 <figure 2 >

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

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

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301 < figure 3 >

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303 No studies reported results on the critical outcome asthma control.

304 Important outcomes305 No studies reported results on quality of life or lung function (FEV₁).306 **Results of SLIT**307 Description of studies and quality of the evidence

308 We retrieved two SRs on SLIT in patients with asthma.^{29,32} The updated search in 2017
 309 resulted in the addition of one RCT⁴⁴. The characteristics of the SRs are summarized in
 310 evidence table E2 (*Online Repository*). The quality of the reviews was moderate; both had an
 311 AMSTAR score of 7/11. Weaknesses included the absence of an 'a priori design', exclusion
 312 of grey literature, not assessing the likelihood of publication bias and not mentioning conflicts
 313 of interest in one review,²⁹ and the absence of an 'a priori design', no information about
 314 excluded studies, too firm conclusions compared to the weak evidence, and not assessing
 315 the likelihood of publication bias in the other.³² One review included both children and adults,
 316 and patients with asthma and/or rhinitis.²⁹ Because of the quality concerns of both existing
 317 SRs, we set out to perform a meta-analysis of the original studies that fulfilled our selection
 318 criteria. Jadad scores of selected studies, as well as an overview of the outcomes of those
 319 studies, are presented in *table 4*.^{24,29,32,44,54-67} Study characteristics are summarized in the
 320 evidence table (*see table E4 in the Online Repository*).^{44,54,55,57,58,60,63-65} We rated the quality
 321 of evidence to be very low, due to a large risk of bias, imprecision and indirect evidence.

322 **Table 4. Summary of quality and outcome measures of selected RCT's in reviews**
 323 **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 ^{5,58}	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	

324 Abbreviations: FEV₁: forced expiratory volume in 1 second; RCT: randomized controlled trial

325 * 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1
326 point if the method of randomization is inappropriate

327 ** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the
328 method of blinding is inappropriate

329 # 1 point if the number and the reasons for withdrawal in each group are stated

330 § Same patients as Pajno 2003⁶⁷

331 Critical outcomes

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

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

341 Important outcomes

342 Quality of life. Pham-Thi et al. published results on quality of life using Childhood Asthma
343 Questionnaires⁴⁴. The authors reported a difference in severity between SLIT and placebo in
344 the younger population (age 6-11 years), but not in older children (age 12-16 years). It is not
345 stated whether this difference is clinically relevant.

346 Lung function. Four studies reported results on lung function (FEV₁). One of the studies
347 reported no numeric data on lung function.⁶⁴ One study reported no variance (standard
348 deviation), and no comparison of the baseline data.⁶³ The two remaining studies reported on
349 FEV₁ percentage predicted,⁵⁸ and reported no significant differences between treatment
350 groups, neither at baseline nor at follow-up.

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For peer review only

1
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3 352 **Discussion**
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5 353 Summary of main results
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7 354 Our GRADE systematic review showed no evidence of a significant difference in asthma
8 355 symptoms between SCIT and placebo in children with allergic asthma, but some evidence for
9 356 a significant and clinically relevant reduction in asthma exacerbations was found in SCIT-
10 357 treated children. We have little confidence in the effect estimate, however, due to a large risk
11 358 of bias and indirectness. Thus, the true effect of SCIT on exacerbations and asthma
12 359 symptoms in the target population of interest is likely to be substantially different from the
13 360 estimate of effect. There was absence of evidence on the effects of SCIT on lung function,
14 361 asthma control, and quality of life in children with allergic asthma. There was no evidence for
15 362 a beneficial effect of SLIT in reducing asthma symptoms and exacerbations, quality of life
16 363 and lung function in children with allergic asthma. Our review does not address the efficacy
17 364 of immunotherapy in children regarding complaints of allergic rhinitis and/or conjunctivitis,
18 365 without having asthma.
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26 366 Quality of the evidence / GRADE methodology
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29 367 The overall quality of the evidence about the effectiveness of SCIT and SLIT was very low.
30 368 This implicates that our confidence in the effect estimates is very limited. The true effect of
31 369 SCIT and SLIT on patient relevant asthma outcomes in children with asthma may be
32 370 substantially different from our estimates of the effect. We cannot conclude that the possible
33 371 desirable effects of SCIT and SLIT outweigh the undesirable effects (e.g. influence on quality
34 372 of life, adverse events, or increased resource expenditure), nor can we reject that
35 373 hypothesis. Our concerns about the quality of evidence are based on (very) serious risk of
36 374 bias and indirectness in the underlying primary studies. Firstly, the quality of many studies
37 375 had to be downgraded because of risk of bias due to lack of allocation concealment, lack of
38 376 information on follow-up, and loss to follow-up. Secondly, included studies were
39 377 heterogeneous in the patients included and allergen extracts used, with different dosing
40 378 regimens and duration being studied, targeting different inhaled allergens. We have concerns
41 379 about the potential different responses and the generalizability of the evidence. Thirdly, and
42 380 most importantly, for SCIT, the quality of the body of evidence was downgraded because of
43 381 indirectness, since patients in the original studies long ago are likely to differ considerably
44 382 from patients nowadays.
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54 383 Fourth, different studies used variable definitions of asthma exacerbations. We had to use
55 384 'worsening of asthma', which may not represent real-life patient relevant exacerbations. This
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3 385 may decrease the applicability of the evidence. In addition, there were no studies using the
4 386 predefined important outcomes quality of life and asthma control.

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6 387 Finally, and most importantly, we have concerns on comparability of patients. Several
7 388 included studies dated from the 1980s or earlier, when allergic rhinitis treatment with
8 389 selective antihistamines and nasal corticosteroids was not available. Against the background
9 390 of the united airway concept, the comorbidity allergic rhinitis in patients in these studies
10 391 cannot be compared to patients in clinical practice today.⁹ Similarly, widespread use of ICS
11 392 was not introduced in childhood asthma treatment until the 1990s.⁶⁸ Most studies on SCIT in
12 393 children with asthma were published decades ago, during the pre-ICS era. Although SCIT
13 394 appeared to be effective in some of the included studies,^{49, 50} we cannot draw conclusions
14 395 from these findings, because the patients in the described studies represent an incomparable
15 396 group when compared to the child with asthma in contemporary clinical practice. Specifically,
16 397 it is unclear whether the beneficial effects found in the systematic review of earlier studies is
17 398 applicable to children with asthma treated according to contemporary guidelines with daily
18 399 ICS controller therapy.¹⁶

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27 400 In our opinion and that of others, the GRADE approach is superior to former methods of SRs,
28 401 because it focuses on predefined patient relevant outcomes, predefined minimally clinical
29 402 important differences and because it judges the complete body of evidence. One RCT
30 403 among paediatricians studied the influence of different guideline grading systems on
31 404 clinician's decisions.⁶⁹ GRADE showed the largest change in direction on the clinical
32 405 decision. However, the added value of GRADE on guideline implementation or patient care,
33 406 has not been formally evaluated, the GRADE approach is still rather complex for non-
34 407 methodologists.

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40 408 To formulate recommendations for clinical practice, not only the body of evidence concerning
41 409 effectiveness of an intervention is important. Recommendations should balance the benefits
42 410 and harms of the intervention of interest, and take patient preferences and resource use into
43 411 account. Since (after critical evaluation) no benefits of SCIT and SLIT for children with
44 412 asthma were determined, we consider it unlikely that the benefits will exceed the harms.
45 413 Patient preferences were included in the formulation of our guideline recommendations.

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50 414 Agreements and disagreements with other studies or reviews

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53 415 Using GRADE and re-analyzing data from children with allergic asthma only, we came to
54 416 different conclusions on the effectiveness of SCIT and SLIT in children with asthma than the
55 417 authors of the original SRs. We believe this highlights the importance of using GRADE
56 418 methodology to systematically review evidence for patient relevant outcomes, not focusing
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3 419 on levels of evidence, but on underlying study validity, precision, directness, and applicability
4 420 in current clinical practice. The 2009 position paper on SLIT describes history, use and
5 421 applicability of this treatment for allergic rhinitis.⁷⁰ It positions SLIT in children as a safe and
6 422 useful therapy above and after more regular treatment for allergic rhinitis. Potential positive
7 423 treatment outcome for allergic asthma is however mainly based on literature in adults. We
8 424 show the lack of evidence and lack of applicability of treatment of immunotherapy for asthma
9 425 in children. Since we have worries on the applicability of evidence in adults on children (who
10 426 are still developing their immune system), we think further studies that compare
11 427 immunotherapy for the contemporary treatment of asthma in children are urgently needed to
12 428 fill in this gap.

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15 429 Recently, a Cochrane SR on SLIT for asthma found a similar lack of data for important
16 430 outcomes (e.g. exacerbations, symptom scores, quality of life) as we did.⁷¹ Contrary to our
17 431 study, the authors did no separate analysis for adults and children, and patients with asthma
18 432 were not separately analyzed from patients without asthma.

25 433 **Conclusions**

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28 434 Focusing on predefined patient relevant outcomes, and critically appraising the body of
29 435 evidence using original studies and GRADE methodology, our systematic review on the
30 436 effects of immunotherapy in children with asthma came to different conclusions than previous
31 437 systematic reviews. We believe that this underscores the importance of using GRADE
32 438 methodology in systematically reviewing evidence.

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37 439 We found absence of valid applicable evidence on improvement of clinically relevant asthma
38 440 outcomes in children with allergic asthma using SCIT or SLIT. This absence of evidence is
39 441 due to serious risk of bias, large clinical heterogeneity between studies, and most importantly
40 442 due to lack of applicability because studies were performed in the pre-ICS era.

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43 443 Since the effect of immunotherapy added to contemporary asthma treatment with daily
44 444 controller therapy is not clear, the drawbacks of immunotherapy should be considered
45 445 carefully. SCIT is a complex and intensive form of treatment, associated with a (very) long
46 446 duration of treatment, and considerable burden to the patient with (monthly) injections under
47 447 adequate medical supervision due to potential (however rare) dangerous side effects, and
48 448 may have relatively high costs and resource use. In SLIT the risk of serious side-effects is
49 449 considerably smaller, but the other drawbacks of immunotherapy apply equally to this
50 450 treatment. In our opinion therefore, when balancing the absence of evidence on a clear
51 451 beneficial effect of SCIT or SLIT on clinically relevant patient outcomes in children with
52 452 asthma with the considerable burden and costs of SCIT and SLIT, we do not recommend this

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453 treatment to children with asthma until further high-quality evidence from well-designed RCTs
454 in children comparing SCIT or SLIT to contemporary asthma treatment becomes available.
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3 456 **Acknowledgments**
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5 457 We like to thank Nicole Boluyt MD, PhD, Diemen, The Netherlands, for her help in the study
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7 458 design and revision of an earlier version of the manuscript.
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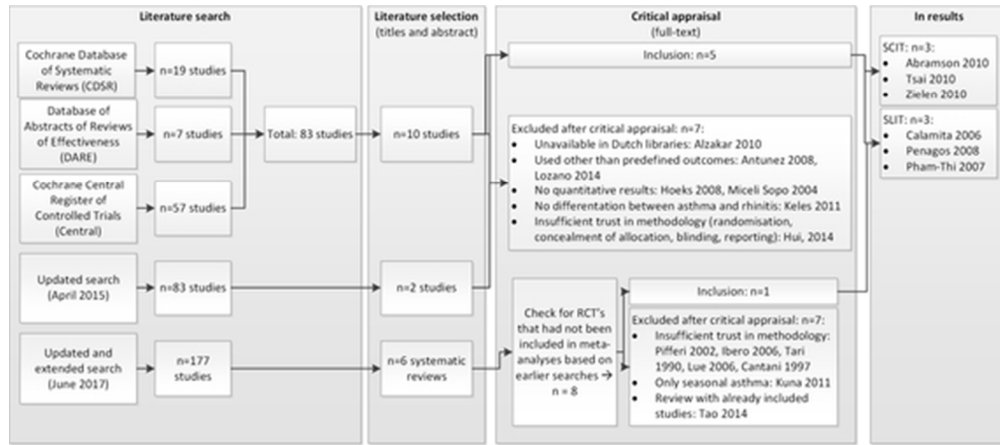
666 **Figure legends**

667 Figure 1. Literature search and selection

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

671 Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. *Abbreviations:*
672 *95%CI: 95% Confidence Interval; IV: Inverse Variance*

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Literature search and selection

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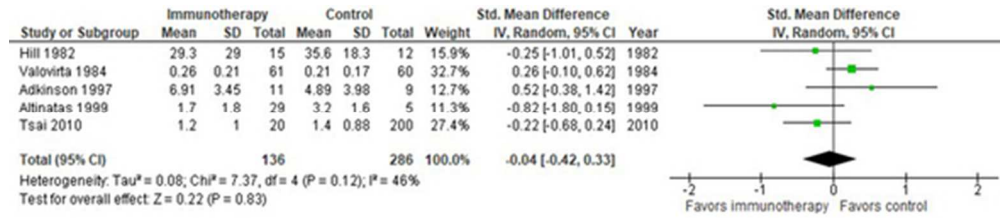


Figure 2. Meta-analysis of SCIT vs. placebo, outcome asthma symptoms. Abbreviations: SD: Standard deviation; Std: Standardized; IV: Inverse Variance; random: random effect model; 95%CI: 95% Confidence Interval

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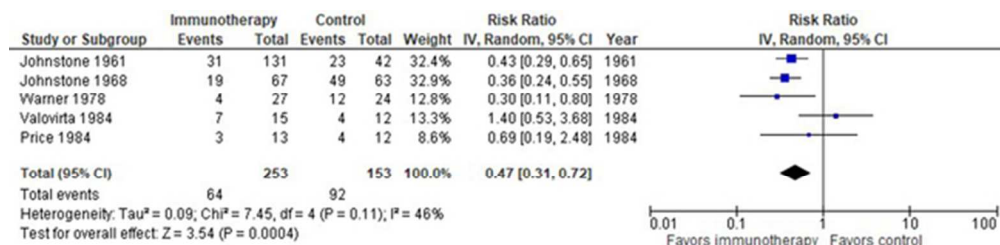


Figure 3. Meta-analysis of SCIT vs. placebo, outcome asthma exacerbations. Abbreviations: 95%CI: 95% Confidence Interval; IV: Inverse Variance

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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.	"asthmazoeacties 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)

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4	35 "Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with ".fc_titl. (1)
5	36 "Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract ".fc_titl. (1)
6	37 "Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. ".fc_titl. (1)
7	38 or/18-20 (3)
8	39 or/21-37 (19)
9	40 38 or 39 (22)
10	41 "controle refs slit scit".ti. (0)
11	42 "filter systematic reviews & meta-analyses Embase".ti. (0)
12	43 meta analysis/ (127495)
13	44 "systematic review"/ (139284)
14	45 (meta-analy\$ or metaanaly\$).tw. (145912)
15	46 (systematic\$ adj4 (review\$ or overview\$)).tw. (139834)
16	47 (quantitativ\$ adj5 (review? or overview?)).tw. (3786)
17	48 (methodologic adj5 (overview? or review?)).tw. (325)
18	49 (review\$ adj3 (database? or medline or embase or cinahl)).tw. (19428)
19	50 (pooled adj3 analy\$).tw. (20108)
20	51 (extensive adj3 review\$ adj3 literature).tw. (2903)
21	52 (meta or synthesis or (literature adj8 database?) or extraction).tw. (1197812)
22	53 review.pt. (2259303)
23	54 52 and 53 (112526)
24	55 (systematic\$ adj4 (review\$ or overview\$)).kw. (16750)
25	56 (quantitativ\$ adj5 (review? or overview?)).kw. (48)
26	57 (pooled adj3 analy\$).kw. (354)
27	58 or/43-51,54-57 (381419)
28	59 "filter rct embase".ti. (0)
29	60 controlled clinical trial/ or randomized controlled trial/ (614267)
30	61 randomization/ (73811)
31	62 Major Clinical Study/ (2803898)
32	63 random\$.tw. (1196822)
33	64 Double Blind Procedure/ (139034)
34	65 or/60-64 (3916117)
35	66 "einde filter rct embase".ti. (0)
36	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)
37	68 child/ (1526632)
38	69 infant/ (566151)
39	70 adolescent/ (1414197)
40	71 or/67-70 (3656088)
41	72 17 and 58 and 71 (85) systrev
42	73 (17 and 65 and 71) not 58 (370) rct
43	74 17 and 58 (208)
44	75 74 not 72 (123)
45	76 75 (123)
46	77 limit 76 to yr="2016 -Current" (14)
47	78 76 (123)
48	79 limit 78 to yr="2015 -Current" (31) extra systrev
49	Search Cochrane 2017, June, 2nd
50	#1 asthma*:ti,ab,kw 26843
51	#2 MeSH descriptor: [Asthma] this term only 9761
52	#3 MeSH descriptor: [Bronchial Spasm] explode all trees 360
53	#4 wheez*:ti,ab,kw 1642
54	#5 bronchospas*:ti,ab,kw 1594
55	#6 (bronch* near/8 spas*):ti,ab,kw 460
56	#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 <i>Dermatophagoides pteronyssinus</i> , 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	-
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Abbreviations: FEF25-75: maximum mid expiratory flow; FEV₁: forced expiratory volume in 1 second; PEFr: peak expiratory flow rate; RCT: randomized controlled trial; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

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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 author†	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 34% ICS, 13% 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, 5 placebo	ICS use not specified, no medical details on asthma	Mono-sensitization <i>Dermatophagoides pteronyssinus</i>	Subcutaneous immunotherapy with adsorbed or aqueous <i>Dermatophagoides pteronyssinus</i> 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 <i>Cladosporium</i> allergy, aged 5 to 17 years	Clinical history suggesting mold-induced asthma and/or rhinoconjunctivitis ICS not stated	<i>Cladosporium</i> allergy	10 months <i>Cladosporium</i> 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 <i>Cladospori</i>

												um season)	
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	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 beclomethas on 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
16 17 18 19 20 21 22 23 24 25 26 27 28	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
29 30 31 32 33 34 35 36 37 38 39	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
40 41 42 43 44	Price, 1984 ⁵¹	RCT, double blind		25 children with perennial asthma, aged 5 to 15 years	Asthma severity not specified asthma		Subcutaneous immunotherapy with <i>Dermatophag</i>	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		<i>oides pteronyssinus</i> 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 <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farina</i> (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 differences 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

						danger extract				statistically not significant		to pharmaceutical company	
1 2 3 4 5 6 7 8 9 10 11 12 13	Warner, 1978 ⁵³	RCT, double blind Tyrosine placebo control	University, United Kingdom	51 asthmatic children, aged 5 to 14 years, with positive <i>Dermatophagoides pteronyssinus</i> challenge	ICS n=12, cromoglycate n=24 SABA n=14	House dust mite, SPT and bronchoprovocation positive	Subcutaneous immunotherapy with tyrosine adsorbed <i>Dermatophagoides pteronyssinus</i> 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
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38	Zielen, 2010 ⁵⁵	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 <i>Dermatophagoides pteronyssinus</i> 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-bronchodilator y 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	
Bahceciler 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 aeroallergens	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 towards 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 patients, 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 <i>Parietaria</i>	Mono-center, Italy	Inclusion: seasonal asthma and rhinoconjunctivitis, DDA, poor symptom control despite antihistamine, ICS and nedocromil use during pollen season, positive skin prick test <i>Parietaria</i> , 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 <i>Parietaria</i> , SPT and RAST positive	Placebo drops + fluticasone 2 nd control group: no protocol medication	12 months	Symptom scores, VAS score during pollen season, compliance, SPT 6 months, serum IgE	No difference in 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	Result†	Critical appraisal‡	Comments	
			<i>Parietaria</i> . Exclusion: sensitization to other allergens, previous immunotherapy, severe asthma (FEV ₁ <70%), other diseases										
Pajno 2004 ^{# 58}	double-blind placebo-controlled SLIT drops <i>Parietaria</i>	Mono-center, Italy	seasonal asthma during spring and allergic rhinitis	30 (8-14 years)	DDA	Mono sensitization to <i>Parietaria</i> , SPT and RAST positive	Drops SLIT <i>Parietaria</i> , 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	
Rolnick-Werninghaus 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 inconclusive	2 nd author affiliated to pharmaceutical industry	"this is not my patient" (perennial asthma excluded); 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 <i>Dermatophagoides pteronyssinus</i> 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 <i>Dermatophagoides</i>	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	Result†	Critical appraisal‡	Comments
	- controlled SLIT drops HDM		allergy HDM, FEV ₁ > 70%. Exclusion: other allergies, severe asthma	up (39 female)		<i>pteronysinus</i> + <i>Dermatophagoides farinae</i> , 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 <i>Dermatophagoides pteronyssinus</i> 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 <i>Dermatophagoides pteronyssinus</i> + <i>Dermatophagoides farinae</i> , 2 weeks up dosing, 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	Result†	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; FEV₁: 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 FEV₁; 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. http://bmjopen.bmj.com/site/about/guidelines.xhtml)	10



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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, E4
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



PRISMA 2009 Checklist

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