Supplemental Information

Appendix Figure 1

Search strategy used to identify studies for review.

PubMed (6498)
(allergen-specific immunotherapy[tiab] OR allergen immunotherapy[tiab] OR immunotherapy[tiab] OR immunotherapy[mesh] OR immunotherap*[tiab]) AND ((rhinitis[mh] OR rhinitis[tiab] OR hay fever[mh] OR hay fever[tiab] OR rhinoconjunctivitis[tiab] OR conjunctivitis[mh] OR "allergic conjunctivitis"[tiab] OR pollinosis[mh] OR pollinosis[tiab] OR pollenosis[tiab] OR asthma[mh] OR asthma[tiab]) NOT ("occupational diseases"[mh] OR "trachoma"[mh])) NOT (animals[mh] NOT humans[mh])

1	allergen-specific immunotherapy[tiab] OR allergen immunotherapy[tiab] OR immunotherapy[tiab] OR immunotherapy[mesh] OR immunotherap*[tiab]
2	rhinitis[mh] OR rhinitis[tiab] OR hay fever[mh] OR hay fever[tiab] OR rhinoconjunctivitis[tiab] OR conjunctivitis[mh] OR "allergic conjunctivitis"[tiab] OR pollinosis[mh] OR pollinosis[tiab] OR pollenosis[tiab] OR asthma[mh] OR asthma [tiab]
3	"occupational diseases"[mh] OR "trachoma"[mh]
4	2 NOT 3
5	(animals[mh] NOT humans[mh])
6	1 AND 4
7	6 NOT 5

EMBASE (9327)
('immunotherapy'/exp OR desensiti*ation) AND ('rhinitis'/exp OR 'allergic rhinitis'/exp OR 'hay'/exp AND 'fever'/exp OR 'rhinoconjunctivitis'/exp OR 'conjunctivitis'/exp OR 'allergic conjunctivitis'/exp OR ‘asthma'/exp) AND [humans]/lim AND [embase]/lim

1	'immunotherapy'/exp OR desensiti*ation
2	'rhinitis'/exp OR 'allergic rhinitis'/exp OR 'hay'/exp AND 'fever'/exp OR 'rhinoconjunctivitis'/exp OR 'conjunctivitis'/exp OR 'allergic conjunctivitis'/exp OR ‘asthma'/exp
3	[humans]/lim
4	embase]/lim
5	3 AND 4
6	1 AND 2 AND 5

COCHRANE (840)
Immunotherapy AND (rhinitis OR allergic rhinitis OR rhinoconjunctivitis OR conjunctivitis OR allergic conjunctivitis OR asthma)

LILACS (99)
Immunotherapy AND (rhinitis OR allergic rhinitis OR rhinoconjunctivitis OR conjunctivitis OR allergic conjunctivitis OR asthma

APPENDIX FIGURE 1
Search strategy used to identify studies for review.

Appendix Figure 2

PRISMA 2009 Checklist – Kim, et al. Allergen-Specific Immunotherapy for Pediatric Asthma and Rhinoconjunctivitis: A Systematic Review

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.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
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.	6, Appendix Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Fig 1
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).	6, Figure 1
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.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix Table 1
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.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7, Appendix Table 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8

APPENDIX FIGURE 2
PRISMA checklist.

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, 11, 16 Appendix Tables 4, 5, 6
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).	Appendix Tables 4, 5, 6
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.	Appendix Tables 4, 5, 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 1, 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10, 12-14, 16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
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).	17-18
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).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
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.	1

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

APPENDIX FIGURE 2
Continued.

APPENDIX TABLE 1 Study Inclusion and Exclusion Criteria

PICO Criteria	Inclusion and Exclusion Criteria
Population and condition of interest	Studies enrolled patients with allergic rhinoconjunctivitis and/or allergic asthma due to airborne allergies
	Allergic rhinoconjunctivitis must have been confirmed by using skin tests or RAST and asthma must confirmed by using pulmonary lung function tests (FEV; methacholine challenge).
	Studies included adults, the elderly, pregnant women, individuals with severe asthma, monosensitized individuals, minorities, inner-city residents, and rural residents
Interventions	The intervention was SIT alone or with usual care
	SIT preparation must be available for use in the United States
	No study of SIT was excluded because of timing or duration of treatment
	We excluded studies in which dosage units were not specified
Comparisons of interest	We included studies that compared SIT (SCIT or SLIT) versus any of the following:
	1. Placebo
	2. Any other SIT (any form available in the United States)
	3. Pharmacotherapy (positive control)
	4. Environmental control
	5. Usual care (eg, environmental control, pharmacotherapy)
	We included studies in which SIT was used alone or in combination with any other treatment and compared with the listed comparators or any other treatment

APPENDIX TABLE 1 Continued

PICO Criteria	Inclusion and Exclusion Criteria
Outcomes	We included studies that reported the following outcomes: Primary outcomes 1. Symptom scores (for rhinitis, conjunctivitis, or asthma) 2. Medication scores 3. Combined symptom and medication scores 4. QoL 5. Safety or harms Secondary outcomes 1. Functional test results (PFT, FEV) 2. Provocational test results (for nasal, conjunctival, or bronchial challenges) 3. Adherence and convenience 4. Long-term effects of SIT (disease modification/prevention of sequelae or new sensitivities)
Timing and setting	We did not impose any limitation on timing or setting
Study design	We included only RCTs

FEV, forced expiratory volume; PFT, pulmonary function testing; RAST, radioallergosorbent test.

APPENDIX TABLE 2 Definitions for Classifications of Magnitude of Effect

Classification of Magnitude of Effect	Definition
Weak	<15% difference in percent change between the SIT group and comparator arm
Moderate	15%–40% difference in percent change between the SIT group and comparator arm
Strong	>40% difference in percent change between the SIT group and comparator arm

APPENDIX TABLE 3 Criteria and Definitions for Grading the Strength of Evidence

Evidence Grade	Criteria	Definition
High	• At least 2 trials having low risk of bias, at least 1 of which has a strong magnitude of effect; and • Overall body of evidence is largely consistent	High confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect
Moderate	• 1 trial having a low risk of bias with a strong magnitude of effect; or • ≥2 trials with medium risk of bias having strong magnitudes of effect; or • 1 trial having low risk of bias with moderate magnitude of effect plus 1 trial having medium risk of bias with strong magnitude of effect; and • Overall body of evidence that is largely consistent	Moderate confidence that the evidence reflects the true effect, and future research may change our confidence in the estimate of the effect and may change the estimate
Low	• There was evidence, but it did not meet the criteria for the above categories	Low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate
Insufficient	• There were no relevant trials.	Evidence is unavailable

APPENDIX TABLE 4 SCIT Affecting Asthma Symptom Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pifferi et al, 2002[1]	Dust mite	SCIT pharmacotherapy	800 U	3 y	29	Medium	+	Direct	Strong
Dreborg et al, 1986[2]	*Cladosporium*	SCIT placebo	100 000 BU (reached after 18 wk)	10 mo	30	Low	+	Direct	Moderate
Kuna et al, 2011[3]	*Alternaria*	SCIT placebo	1.0 mL (5000 TU/mL) or the highest tolerated dose	3 y	50	Medium	+	Direct	Moderate
Hill et al, 1982[4]	Rye	SCIT placebo	75–1000 PNU = 1 PNU of rye pollen	8 mo	20	High	+	Direct	Strong
Adkinson et al, 1997[5]	Multiple	SCIT placebo	0.7 mL of concentrate	27 mo	121	Low	–	Direct	Moderate
Cantani et al, 1997[6]	Multiple (dust mite, *Parietaria*, rye)	SCIT pharmacotherapy	500 BU/month	3 y	300	High	+	Direct	Could not determine[a]

PNU, protein nitrogen unit. BU, biologic units; mL, milliliters; TU, treatment units; U label units.

[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 5 SCIT Affecting Asthma Medication Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pifferi et al, 2002[1]	Dust mite	SCIT pharmacotherapy	800 U	3 y	29	Medium	+	Direct	Strong
Hill et al, 1982[4]	Rye	SCIT placebo	75–10 00 PNU = 1 PNU of rye pollen	8 mo	20	High	+	Direct	Moderate
Adkinson et al, 1997[5]	Multiple	SCIT placebo	0.7 mL of concentrate	27 mo	121	Low	–	Direct	Weak
Cantani et al, 1997[6]	Multiple (dust mite, *Parietaria*, rye)	SCIT pharmacotherapy	500 BU/month	3 y	300	High	+	Direct	Could not determine[a]

BU, biologic units; mL, milliliters; PNU, protein nitrogen unit; U, label units.

[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 6 SCIT Affecting Asthma Plus Rhinitis/Rhinoconjunctivitis Medication Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Dreborg et al, 1986[2]	*Cladosporium*	SCIT placebo	100 000 BU (reached after 18 wk)	10 mo	30	Low	+	Direct	Weak
Kuna et al, 2011[3]	*Alternaria*	SCIT placebo	1.0 mL (5000 TU/mL) or the highest tolerated dose	3 y	50	Medium	+	Direct	Strong

BU, biologic units; mL, milliliters; TU: Treatment units.

APPENDIX TABLE 7 SCIT Affecting Combined Asthma or Asthma Plus Rhinoconjunctivitis Symptom-Medication Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Altintaş et al, 1999[7]	Dust mite	SCIT-adsorbed AI; SCIT-adsorbed Ca; SCIT-aqueous; placebo	50 000–100 000 SQ (targeted) 60 000–100 000 SQ (actual) 6–10 IR (10 IR = 1/1000 w/v)	2 y	35	High	+	Direct	Strong
Kuna et al, 2011[3]	Alternaria	SCIT Placebo	1.0 mL (5000 TU/mL) or the highest tolerated dose	3 y	50	Medium	+	Direct	Strong

IR, index of reactivity; mL, milliliters; SQU, standardized quality units; TU, treatment units; w/v, weight to volume.

APPENDIX TABLE 8 SCIT Affecting Rhinitis/Rhinoconjunctivitis Symptom Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Dreborg et al, 1986[2]	*Cladosporium*	SCIT placebo	100 000 BU (reached after 18 wk)	10 mo	30	Low	+	Direct	Weak
Kuna et al, 2011[3]	*Alternaria*	SCIT placebo	1.0 mL (5000 TU/mL) or the highest tolerated dose	3 y	50	Medium	+	Direct	Moderate
Möller et al, 2002[8]; Niggeman et al, 2006[9]	Grass/birch	SCIT placebo	100 000 SQ U/mL (Alutard SQ® [ALK, Hørsholm,] Denmark)	3 y	205	Medium	+	Direct	Strong

BU, biologic units; mL, milliliters; SQU, standardized quality units; TU, treatment units.

APPENDIX TABLE 9 SCIT Affecting Conjunctivitis Symptom Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Dreborg et al, 1986[2]	*Cladosporium*	SCIT placebo	100 000 BU (reached after 18 wk)	10 mo	30	Low	+	Direct	Weak
Möller et al, 2002[8]; Niggeman et al, 2006[9]	Grass/birch	SCIT placebo	100 000 SQ U/mL (Alutard SQ)	3 y	205	Medium	+	Direct	Could not determine[a]
Kuna et al, 2011[3]	*Alternaria*	SCIT placebo	1.0 mL (5000 TU/mL) or the highest tolerated dose	3 y	50	Medium	+	Direct	Strong

BU, biologic units; mL, milliliters; SQU, standardized quality units; TU, treatment units.
[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 10 SCIT Affecting Rhinitis QoL in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Cantani et al, 1997[6]	Dust mites, grass, weeds	SCIT pharmacotherapy	500 BU per month	3 y	300	High	+	Direct	Could not determine[a]
Kuna et al, 2011[3]	*Alternaria*	SCIT placebo	1.0 mL (5000 TU/mL) or the highest tolerated dose	3 y	50	Medium	+	Direct	Strong

BU, biologic units; mL, milliliters; TU, treatment units.
[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 11 SLIT Affecting Asthma Symptoms in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pajno et al, 2000[10]	Dust mite	SLIT placebo	5 drops of 10 BU/mL	2 y	24	Low	Night: + VAS: +	Direct	Night: strong VAS: strong
Lue et al, 2006[11]	Dust mite	SLIT placebo	20 drops of 300 IR/mL	6 mo	20	Medium	+	Direct	Strong
Niu et al, 2006[12]	Dust mite	SLIT placebo	20 drops of 300 IR/mL	24 wk	110	Medium	+	Direct	Strong
Hirsch et al, 1997[13]	Dust mite	SLIT placebo	7 drops of 11.9 μg /mL = 3.75 μg	1 y	30	Low	+	Direct	Strong
Bahçeciler et al, 2001[14]	Dust mite	SLIT placebo	20 drops of 100 IR/mL	6 mo	15	Medium	+	Direct	Moderate
Ippoliti et al, 2003[15]	Dust mite	SLIT placebo	5 drops of 10 BU/mL	6 mo	86	Medium	+	Direct	Strong
Tari et al, 1990[16]	Dust mite	SLIT placebo	15 drops of 500 STU/mL or 5BU/mL	18 mo	58	Low	+	Direct	Moderate
Pajno et al, 2003[17]	Parietaria	SLIT placebo	5 drops of 10 BU/mL	13 mo	30	Medium	Sx: + VAS: +	Direct	Sx: Could not determine VAS: could not determine[a]
Valovirta et al, 2006[18]; Savolainen et al, 2006[19]	Tree mix	High dose Low dose Placebo	100 000 SQ-U/mL (per week) 12 000 SQ-U/mL per week)	5 wk build-up up to 18 mo maintenance	98	Medium	High dose: + Low dose: +	Direct	High dose: strong; Low dose: moderate

BU, biologic units; IR: index of reactivity; Night, nightime symptom score; SQU: standardized quality units; STU: standard treatment units; Sx: asthma symptom score; VAS: visual analogue scale score.
[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 12 SLIT Affecting Asthma Plus Rhinitis or Rhinoconjunctivitis Symptoms in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Valovirta et al, 2006[18] Savolainen et al, 2006[19]	Tree mix	High dose Low dose Placebo	100 000 SQ-U/mL (per week) 12 000 SQ-U/mL (per week)	5 wk build-up up to 18 mo 18 mo maintenance	98	Medium	High dose: + Low dose: +	Direct	High dose: strong Low dose: moderate

SQ-U, standardized quality units.

APPENDIX TABLE 13 SLIT Affecting Rhinitis or Rhinoconjunctivitis Symptoms in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Röder et al, 2007[20]	Grass mix	SLIT placebo	9500 BU	2 y	204	Low	+	Direct	Weak
Novembre et al, 2004[21]	Grass mix	SLIT control	5 drops of 25 BU/mL	3 y	113	High	+	Direct	Could not determine[a]
Tseng et al, 2008[22]	Dust mite	SLIT placebo	20 drops 300 IR/mL	3 wk induction therapy, 21 wk maintenance	63	Medium	−	Direct	Weak
Hirsch et al, 1997[13]	Dust mite	SLIT placebo	7 drops of 11.9 μg /mL = 3.75 μg	1 y	30	Low	+	Direct	Weak
Bahçeciler et al, 2001[14]	Dust mite	SLIT placebo	20 drops of 100 IR/mL	6 mo	15	Medium	+	Direct	Moderate
Ippoliti et al, 2003[15]	Dust mite	SLIT placebo	5 drops of 10 BU/mL	6 mo	86	Medium	+	Direct	Strong
Tari et al, 1990[16]	Dust mite	SLIT placebo	15 drops of 500 STU/mL or 5 BU/mL	18 mo	58	Low	+	Direct	Moderate
de Bot et al, 2012[23]	Dust mite	SLIT placebo	20 drops = 700 BU	2 y	257	High	+	Direct	Weak
La Rosa et al, 1999[24]	*Parietaria*	SLIT placebo	20 drops of 300 IR/mL	2 y	41	Low	+	Direct	Could not determine[a]
Pajno et al, 2003[17]	*Parietaria*	SLIT placebo	5 drops of 10 BU/mL	13 mo	30	Medium	+	Direct	Could not determine[a]
Vourdas et al, 1998[25]	Olive	SLIT placebo	20 drops of 300 IR/mL	Seasonal (6 mo each year) for 2 y	70	Medium	+	Direct	Strong
Valovirta et al, 2006[18]; Savolainen et al, 2006[19]	Tree mix	High dose Low dose Placebo	100 000 SQ-U/mL (per week) 12 000 SQ-U/mL (per week)	5 wk build-up up to 18 mo 18 mo maintenance	98	Medium	High dose: + Low dose: +	Direct	High dose: strong Low dose: moderate

BU, biologic units; IR, index of reactivity; SQU, standardized quality units; STU, standard treatment units.

[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 14 SLIT Affecting Conjunctivitis Symptoms in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Tari et al, 1990[16]	Dust mite	SLIT placebo	15 drops of 500 STU/mL or 5BU/mL	18 mo	58	Low	+	Direct	Weak
de Bot et al, 2012[23]	Dust mite	SLIT placebo	20 drops = 700 BU	2 y	257	High	+	Direct	Could not determine[a]
Vourdas et al, 1998[25]	Olive	SLIT Placebo	20 drops of 300 IR/mL	Seasonal (6 mo each year) for 2 y	70	Medium	+	Direct	Strong
Valovirta et al, 2006[18] Savolainen et al, 2006[19]	Tree mix	High dose Low dose Placebo	100 000 SQ-U/mL (per week) 12 000 SQ-U/mL (per week)	5-wk build-up up to 18- mo maintenance	98	Medium	High dose: + Low dose: +	Direct	High dose: Strong Low dose: Moderate
Pajno et al, 2003[17]	*Parietaria*	SLIT placebo	5 drops of 10 BU/mL	13 mo	30	Low	NR	Direct	Could not determine[a]

BU, biologic units; IR, Index of Reactivity; NR, not reported; SQ-U, standardized quality units; STU, standard treatment units.
[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 15 SLIT Affecting Medication Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Pajno et al, 2000[10]	Dust mite	SLIT placebo	5 drops of 10 BU/mL	2 y	27	Low	+	Direct	Strong
Lue et al, 2006[11]	Dust mite	SLIT placebo	20 drops of 300 IR/mL	6 mo	20	Medium	+	Direct	Moderate
Niu et al, 2006[12]	Dust mite	SLIT placebo	20 drops of 300 IR/mL	24 wk	110	High	AH: + BA: + ICS: + OC: +	Direct	AH: strong BA: strong ICS: weak OC: strong
Tseng et al, 2008[22]	Dust mite	SLIT placebo	20 drops 300 IR/mL	3-wk induction therapy, 21-wk maintenance	63	Medium	AH: + BA: –	Direct	AH: moderate BA: moderate
Hirsch et al, 1997[13]	Dust mite	SLIT placebo	7 drops of 11.9 μg /mL = 3.75 μg	1 y	30	Low	AH/INS: – BA/Th: +	Direct	Could not determine[a]
de Bot et al, 2012[23]	Dust mite	SLIT placebo	20 drops = 700 BU	2 y	257	High	+	Direct	Could not determine[a]
Röder et al, 2007[20]	Grass mix	SLIT placebo	9500 BU	2 y	204	Low	–	Direct	Could not determine[a]
Novembre et al, 2004[21]	Grass mix	SLIT control	20 drops 100 IR/mL	6 mo	113	High	+	Direct	Could not determine[a]
La Rosa et al, 1999[24] Leonardi et al, 2009[26]	*Parietaria*	SLIT placebo	20 drops of 300 IR/mL	2 y	41	Low	Could not determine[a]	Direct	Could not determine[a]
Pajno et al, 2003[17]	*Parietaria*	SLIT placebo	5 drops of 10 BU/mL	13 mo	30	Low	+	Direct	Could not determine[a]
Vourdas et al, 1998[25]	Olive	SLIT placebo	20 drops of 300 IR/mL	Seasonal (6 mo each year) for 2 y	70	Medium	OC: + NR for other medications	Direct	Could not determine[a]
Valovirta et al, 2006[18] Savolainen et al, 2006[19]	Tree mix	High-dose Low-dose Placebo	100 000 SQ-U/mL (per week) 12 000 SQ-U/mL (per week)	5-wk build-up up to 18-mo maintenance	98	Medium	High dose: + Low dose: +	Direct	High dose: Moderate Low dose: Weak
Bahçeciler et al, 2001[14]	Grass mix and olive	SLIT placebo	20 drops of 100 IR/mL	6 mo	15	Medium	BA: + ICS: + INS: +	Direct	BA: Moderate ICS: Strong INS: Strong

AH, antihistamine; BA, beta agonist; BU, biologic units; ICS, inhaled corticosteroid; INS, intranasal steroid; IR, index of reactivity; NR, not reported; OC, oral corticosteroids; SQ-U: standardized quality units; Th, theophylline.
[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 16 SLIT Affecting Combined Symptom Plus Medication Scores in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
Marogna et al, 2008[27]	Dust mite, birch, grass mix, *Parietaria*	SLIT control	5 drops 10,000 RU/mL	3 y	216	Medium	+	Direct	Strong
Novembre et al, 2004[21]	Grass mix	SLIT control	20 drops 100 IR/mL	6 mo	113	High	+	Direct	Could not determine[a]

IR, index of reactivity; RU, radioallergosorbent test units.
[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 17 SLIT Affecting QoL in Children and Adolescents

Study	Measurement Tool	Allergen/Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Direction of Change	Directness	Magnitude of Effect
de Bot et al, 2012[23]	Pediatric RQLQ[1]	Dust mite/SLIT placebo	20 drops = 700 BU	2 y	257	High	−	Direct	Could not determine[a]
	Adolescent RQLQ[1]						−		Could not determine[a]
Röder et al, 2007[20]	Pediatric RQLQ[1]	Grass mix/SLIT placebo	9500 BU	2 y	204	Low	−	Direct	Could not determine[a]
	Adolescent RQLQ[1]						+		Could not determine[a]

BU, biologic units; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
[a] Could not determine, because there was not enough data provided in the article to calculate the magnitude of effect.

APPENDIX TABLE 18 SLIT Versus SCIT Affecting Asthma Symptoms in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Treatment favored	Directness	Magnitude of Effect
Yukselen et al, 2012[28]	Dust mite	SLIT + placebo injections	0.2–0.8 mL of 5000 TU/mL	1 y	31	Medium	SCIT	Direct	Moderate
		SCIT + placebo drops	28 drops of 1000 TU/mL						
		Placebo injections + drops							
Eifan et al, 2010[29]	Dust mite	SLIT	5 drops STU (1000 STU/mL)	1 y	48	Medium	SLIT	Direct	Moderate
		SCIT							
		Pharmacotherapy	100 000 SQ U/mL, 1 cm^3						
Keles et al, 2011[30]	Dust mite	SLIT	44.12 μg of Der p1 + 62.1 μg of Df1	1 y	56	Medium	SCIT	Direct	Weak
		SCIT	52.8 μg of Der p1 + 52.8 μg of Df1						
		SLIT + SCIT	43.2 μg of Der p1 + 43.2 μg of Df1						
		Pharmacotherapy							

SQU, standardized quality units; STU, standard treatment units; TU, treatment units.

APPENDIX TABLE 19 SLIT Versus SCIT Affecting Rhinitis/Rhinoconjunctivitis Symptoms in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Treatment Favored	Directness	Magnitude of Effect
Yukselen et al, 2012[28]	Dust mite	SLIT + placebo injections SCIT + placebo drops Placebo injections + drops	0.2–0.8 mL of 5000 TU/mL 28 drops of 1000 TU/mL	1 y	31	Medium	SCIT	Direct	Moderate
Eifan et al, 2010[29]	Dust mite	SLIT SCIT Pharmacotherapy	5 drops STU (1000 STU/mL) 100 000 SQ U/mL, 1cm^3	1 y	48	Medium	SLIT	Direct	Strong
Keles et al, 2011[30]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	44.12 μg of Der p1+62.1 μg of Df1 52.8 μg of Der p1+52.8 μg of Df1 43.2 μg of Der p1+43.2 μg of Df1	1 y	56	Medium	SCIT	Direct	Weak

SQU, standardized quality units; STU, standard treatment units; TU, treatment units.

APPENDIX TABLE 20 SLIT Versus SCIT Affecting Medication Use in Children and Adolescents

Study	Allergen	Comparator	Maintenance Dose	Duration of Treatment	No. of Participants	Risk of Bias	Treatment favored	Directness	Magnitude of Effect
Yukselen et al, 2012[28]	Dust mite	SLIT + placebo injections SCIT + placebo drops Placebo injections + drops	0.2–0.8 mL of 5000 TU/mL 28 drops of 1000 TU/mL	1 y	31	Medium	SCIT	Direct	Moderate
Eifan et al, 2010[29]	Dust mite	SLIT SCIT Pharmacotherapy	5 drops STU (1000 STU/mL) 100 000 SQ U/mL, 1cm^3	1 y	48	Medium	SLIT	Direct	Moderate
Keles et al, 2011[30]	Dust mite	SLIT SCIT SLIT + SCIT Pharmacotherapy	44.12 μg of Der p1+62.1 μg of Df1 52.8 μg of Der p1+52.8 μg of Df1 43.2 μg of Der p1+43.2 μg of Df1	1 y	56	Medium	SCIT	Direct	Strong

SQU, standardized quality units; STU, standard treatment units; TU, treatment units.

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