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REVIEW

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Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis

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Abstract

Background: The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines on Allergen Immunotherapy (AIT) for Allergic Rhinoconjunctivitis. To inform the development of clinical recommendations, we undertook a systematic review to assess the effectiveness, cost-effectiveness, and safety of AIT in the management of allergic rhinoconjunctivitis.

Methods: We searched nine international biomedical databases for published, in-progress, and unpublished evidence. Studies were independently screened by two reviewers against predefined eligibility criteria and critically appraised using established instruments. Our primary outcomes of interest were symptom, medication, and combined symptom and medication scores. Secondary outcomes of interest included cost-effectiveness and safety. Data were descriptively summarized and then quantitatively synthesized using random-effects meta-analyses.

Results: We identified 5960 studies of which 160 studies satisfied our eligibility criteria. There was a substantial body of evidence demonstrating significant reductions in standardized mean differences (SMD) of symptom (SMD −0.53, 95% CI −0.63, −0.42), medication (SMD −0.37, 95% CI −0.49, −0.26), and combined symptom and medication (SMD −0.49, 95% CI −0.69, −0.30) scores while on treatment that were robust to prespecified sensitivity analyses. There was in comparison a more modest body of evidence on effectiveness post-discontinuation of AIT, suggesting a benefit in relation to symptom scores.

Conclusions: AIT is effective in improving symptom, medication, and combined symptom and medication scores in patients with allergic rhinoconjunctivitis while on treatment, and there is some evidence suggesting that these benefits are maintained in relation to symptom scores after discontinuation of therapy.

KEYWORDS
allergen, allergen immunotherapy, allergic rhinoconjunctivitis, subcutaneous, sublingual

1 | BACKGROUND

Allergic rhinoconjunctivitis is a very common chronic condition that can result in considerable morbidity and impairment of quality of life.[1,2] The disease is triggered by exposure to seasonal and/or perennial allergens and, depending on the nature of the allergenic trigger(s) and patterns of exposure, symptoms may be persistent or intermittent.[3] Allergic rhinitis is typically characterized by symptoms of nasal obstruction, a watery nasal discharge, sneezing and itching, and there is often (but not invariably) involvement of the conjunctiva (allergic conjunctivitis), which manifests with itching, injection and tearing.[4] There may in addition be an impact on the ability to concentrate, on school and work performance,[5,6] and interference with daily activities and sleep; furthermore, allergic rhinitis is a risk factor for the development of asthma.[7]

Symptoms can, in many cases, be controlled with avoidance measures and pharmacological therapies such as oral, intranasal and topical (ophthalmic) H_1-antihistamines, intranasal corticosteroids and antileukotrienes, as monotherapy or in combination.[8,9] Allergen immunotherapy (AIT) is an additional potential treatment option, particularly for those with more troublesome disease which remains inadequately controlled despite avoidance measures and regular pharmacotherapy.[8-10] The problem of inadequately controlled allergic rhinoconjunctivitis, despite optimal medical treatment, continues to represent a therapeutic challenge in the majority of patients.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines on AIT for Allergic Rhinoconjunctivitis and this systematic review has been undertaken to inform the formulation of key clinical recommendations. Specifically, we sought to assess the effectiveness, cost-effectiveness and safety of AIT in patients with allergic rhinoconjunctivitis.[11]

2 | METHODS

As our methods have been reported in detail in our published protocol,[12] we confine ourselves to a synopsis of the methods employed.

2.1 | Search strategy

A highly sensitive search strategy was developed and validated study design filters were applied to search nine electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Appendix S1). In all cases, the databases were searched from inception to October 31, 2015. Additional references were located through searching the references cited by the identified studies, and unpublished work, while research in progress was identified through discussion with experts in the field. We invited experts from a range of disciplines and regions to add to the list of included studies by identifying additional published and unpublished papers they were aware of and research in progress. There were no language restrictions employed; where possible, relevant literature was translated into English.

2.2 | Inclusion criteria

We focused on studies conducted on patients of any age with allergic rhinoconjunctivitis investigating the effect of AIT. See Box 1 for full details.

Box 1 Inclusion and exclusion criteria

Patient characteristics	Studies conducted on patients of any age with a physician-confirmed diagnosis of allergic rhinoconjunctivitis or allergic rhinitis, plus evidence of clinically relevant allergic sensitization (eg, skin prick test or specific IgE).
Interventions of interest	Allergen immunotherapy (AIT) for different allergens (eg, pollen, house dust mites (HDM), animal dander, cockroach and molds), including modified allergens, administered through the subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), intralymphatic immunotherapy (ILIT) or any other routes.
Comparator	Placebo or any active comparator.
Study designs	*Effectiveness:* Robust double-blind RCTs. Originally, we planned to include data from any RCT, irrespective of whether there was blinding. This was changed due to the volume of RCT studies. This decision was made prior to any analyses being undertaken. *Cost-effectiveness:* health economic analysis. *Safety:* Double-blind RCTs and large case series (≥300 patients).
Study outcomes	*Primary outcomes:* effectiveness, both short-term (ie, during treatment) and long-term (ie, at least a year after discontinuation of AIT), as assessed by symptom and/or medication scores. *Secondary outcomes:* disease-specific quality of life (QoL); threshold of allergen exposure to trigger symptoms on allergen challenge or in an environmental exposure chamber; health economic analysis from the perspective of the health system/payer; and safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects.[14,15]
Exclusion criteria	Reviews, discussion papers, nonresearch letters and editorials, animal studies, and studies not employing double-blind RCT designs.

2.3 | Study selection

All references were uploaded into the systematic review software DistillerSR and underwent initial de-duplication. Study titles were independently checked by two reviewers (SD and UN) according to the above selection criteria and categorized as included, not included or unsure. For those papers in the unsure category, we retrieved the abstract and recategorized as above. Any discrepancies were resolved through discussion and, if necessary, a third reviewer (AS) was consulted. Full-text copies of potentially relevant studies were obtained and their eligibility for inclusion independently assessed by two reviewers (SD and UN). Studies that did not fulfill all of the inclusion criteria were excluded.

2.4 | Quality assessment strategy

Quality assessments were independently carried out on each study by two reviewers (UN, SA, AA, MA, or TM) using a range of instruments. RCTs were assessed for generation of allocation sequence, concealment of allocation, baseline outcome measurements, baseline characteristics, incomplete outcome data, blinding of outcome assessor, protection against contamination, selective outcome reporting and other risks of bias using the Cochrane Risk of Bias (ROB) Tool.[13] We used the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies.[14] For case series, we used the quality assessment tool produced by the National Institute for Health and Clinical Excellence (NICE).[15] Any disagreements were resolved through discussion and, if necessary, a third reviewer (SD or AS) was consulted.

2.5 | Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (UN, SA, AA, MA, SD or TM), and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (SD or AS). A descriptive summary with detailed data tables was initially produced to summarize the literature. Where clinically and statistically appropriate, meta-analyses were undertaken using random-effects modeling.[16] Data were extracted from primary studies, but where these were not available in a suitable format we first contacted authors for data and then if data were still not available we extracted data from previous Cochrane reviews. For outcomes for which it was not possible to produce a meta-analysis, we narratively synthesized data. Heterogeneity statistics are reported with each forest plot.

2.6 | Sensitivity analyses and assessment for publication bias

Sensitivity analyses were undertaken for the primary outcomes by comparing the summary estimates obtained by excluding studies considered to be at high ROB.

Publication bias was assessed for these same primary outcomes through the creation of funnel plots, and tested by Egger's regression test and Begg's rank correlation test.[17,18]

2.7 | Subgroup analyses

A number of subgroup analyses were undertaken, which are listed in the protocol.

2.8 | Registration and reporting

This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/prospero/. The registration number is CRD42016035373. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist has been used to guide the reporting of this systematic review: http://www.prisma-statement.org/ (Appendix 2, Supplementary file).

3 | RESULTS

Our search strategy yielded 5960 titles of which 160 studies (reported in 166 papers) met our overall review eligibility criteria. These eligible papers included 134 double-blind RCTs, 19 health economic analyses and seven case series (Figure 1).

3.1 | Effectiveness

3.1.1 | Description of trials

We identified 61 subcutaneous immunotherapy (SCIT) RCTs (reported in 63 papers)[19-81] including 6379 patients, 71 sublingual immunotherapy (SLIT) RCTs (reported in 75 papers)[82-119,119-121,121-156] including 13 636 patients and two intralymphatic immunotherapy (ILIT) RCTs[157,158] including 56 patients (Table 1a-c). The majority of studies only included adult participants. A range of allergens were assessed including weed, tree and grass pollens, molds, cat and dog dander, and house dust mites. A range of AIT protocols were utilized. The overwhelming majority of trials only reported on short-term effectiveness (Table S1a-c). A full description of the trials is given in the Data S1.

3.1.2 | Quality assessment

Subcutaneous immunotherapy

Overall, the quality of included studies was high. Thirty-seven studies were found to be at low ROB, eight studies at high ROB, and 16 were judged at unclear ROB (Table S1d).

Sublingual immunotherapy

The quality of studies was assessed to be low ROB in 26 studies, high ROB in 16 studies and unclear ROB in 28 studies (Table S1e). In one study, ROB could not reliably be assessed from the translation.

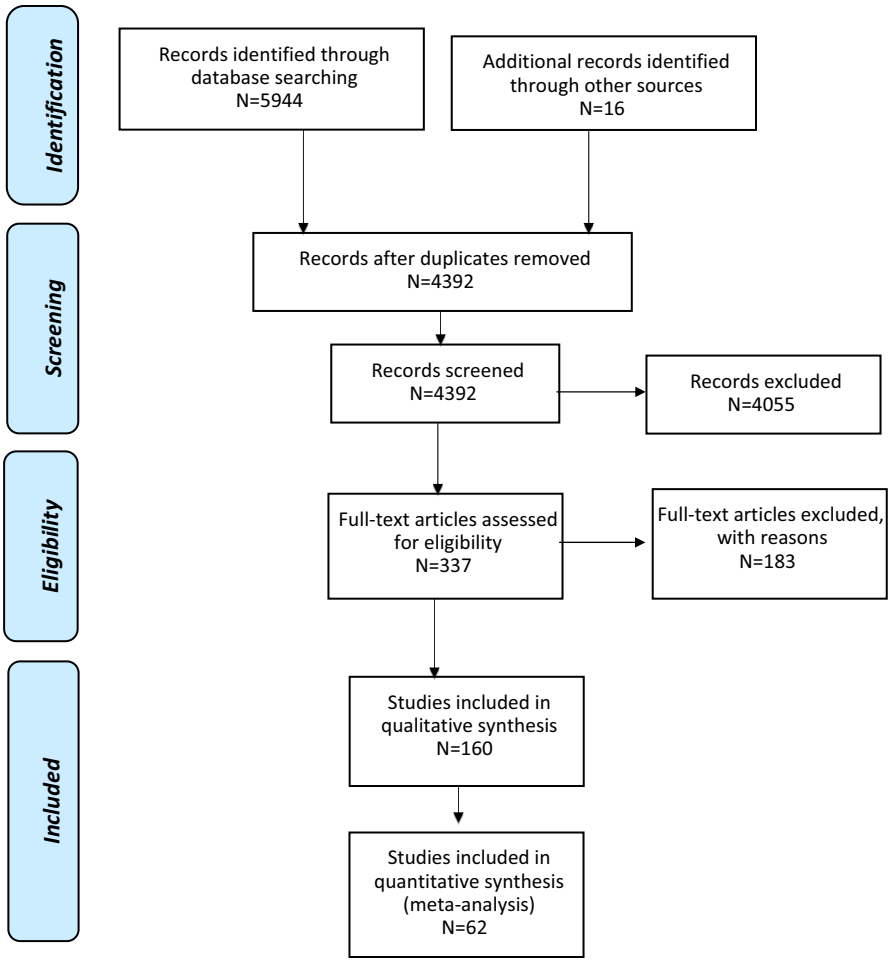


FIGURE 1 PRISMA Diagram

Intralymphatic immunotherapy

Both studies had a low ROB (Table S1f).

3.2 | Primary outcomes

Data on primary outcomes are summarized in Tables S1g-i.

3.2.1 | Symptom scores

Short-term

105 studies reported on the short-term effectiveness of AIT administered by the SCIT (n=51), SLIT (n=52) and ILIT (n=2) routes assessed by symptom scores.

We were able to pool data from 58 SCIT and SLIT studies assessing the effectiveness of AIT by symptom scores. This showed a standardized mean difference (SMD) of −0.53 (95% CI −0.63, −0.42) this suggesting a moderate effect in favor of AIT (Figure 2).

Sensitivity analysis Sensitivity analysis was performed excluding all studies at high ROB, which demonstrated a SMD of −0.57 (95% CI −0.68, −0.46) (Figure S1).

Assessment for publication bias There was evidence of potential publication bias (Figure S2) which was also suggested by the Begg (P=0.003) and Egger (P=0.003) tests.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- SCIT vs SLIT: SMD −0.65 (95% CI −0.86, −0.43) for SCIT and SMD −0.48 (95% CI −0.61, −0.36) for SLIT (Figures 3A and B), these both showing evidence of benefit; data from the two ILIT trials could not be pooled, but these studies also demonstrated an improvement in short-term symptom scores.
- Children vs adults for AIT (SCIT and SLIT): SMD −0.25 (95% CI −0.46, −0.05) for children and SMD −0.56 (95% CI −0.70, −0.42) for adults (Figures 4A and B), these analyses showing evidence of benefit in both adults and children.
- Children vs adults for SLIT only: SMD −0.42 (95% CI −0.63, −0.21) for children and SMD −0.47 (95% CI −0.64, −0.29) for adults (Figures S3A and B), these analyses showing benefit in both adults and children.
- Seasonal vs perennial allergens: SMD −0.37 (95% CI −0.45, −0.28) for seasonal and SMD −0.91 (95% CI −1.47, −0.36) for perennial (Figures S4A and B), these demonstrating evidence of benefit from both approaches.

TABLE 1 (a) Characteristics of SCIT studies (n=61 studies, reported in 63 papers). (b) Characteristics of SLIT studies (n=71 studies, reported in 75 papers). (c) Characteristics of ILIT studies (n=2)

	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness				
(a) Study (first author, y, country)	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Product type/Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Alvarez-Cuesta, 2005, Spain	X	X								X	X					X	X					1 yr	Glutaraldehyde-polymerized extracts/NR (Laboratorios LETI, S.L.)	X	X					X	X
Ariano, 1999, Italy			X						X		X					X	X					1 yr	Glutaraldehyde-modified allergoid extract of *Parietaria judaica (50%) & Parietaria officinalis* (50%)/PURETHAL®			X				X	
Arvidsson, 2002, Sweden		X							X		X						X	X				2 yr	Birch depot extract adsorbed onto aluminum hydroxide/ Alutard SQ®	X	X					X	
Balda, 1998, Germany		X							X		X			X			X					7 wk	Purified and standardized extracts composed of equal parts of *Corylus avellana, Alnus glutinosa, and Betula verrucosa*/ALK7 Frűhbltihermischúng®	X	X					X	
Bodtger, 2002, Denmark		X							X		X			X	X			X				1 yr	*Betula verrucosa* extract/Soluprick SQ® (ALK-Abelló)	X	X					X	
Bousquet, 1987, France	X								X		X		X	X	X					X		10 mo	Six-mixed grass pollen allergoid and standardized orchard grass pollen extract/Alyostal ST® (Stallergenes)	X	X					X	
Bousquet, 1989, France	X								X				X	X	X					X		8 mo	SCIT with a high molecular weight formalinized allergoid (HMW-GOID) vs SCIT with unfractionated allergoid (GOID) vs SCIT with standardized extract vs placebo/ NR	X	X					X	
Bousquet, 1990, France	X								X		X		X	X	X					X		NR	High molecular weight mixed grass pollen allergoids/NR	X	X					X	
Bousquet, 1991, France	X	X	X							X	X			X						X		1 yr	Standardized extracts from orchard grass (*Dactylis glomerata*), olive (*Olea europaea*), plane tree (*Platanus occidentalis*), mugwort (*Artemisia vulgaris*), and *Parietaria ofiicinalis* pollens/NR (manufactured by Stallergenes)			X				X	
Bozek, 2016, Poland	X								X		X			X			X					3 yr	Pollen mixture extract solution of grass pollens (*Agrostis stolonifera, A odoratum, Arrhenatherum elatius, D glomerata, Festuca rubra, Holcus lanatus, Lolium perenne, P. pratense, P. pratensis, Secale cereal, and Loe edasi*)/ PURETHAL grasses (HAL-Allergy BV)	X	X	X				X	X
Brunet, 1992, Canada			X						X		X			X			X					3 mo	Alum-precipitated aqueous ragweed extracts/NR	X	X					X	
Ceuppens, 2009, Belgium & the Netherlands		X							X		X					X	X					18 mo	Glutaraldehyde-modified birch pollen extract adsorbed onto aluminum hydroxide/PURETHAL® Birch			X				X	

(Continues)

TABLE 1 (Continued)

(a) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Chakraborty, 2006, India		X							X		X					X	X					2 yr	*Phoenix sylvestris Roxb* or sugar palm allergoid extract/NR			X				X	
Charpin, 2007, France		X							X		X					X	X					15 mo	Standardized, aluminum hydroxide-adsorbed *Juniperus ashei* extract/Alustal® (Stallergenes)	X	X					X	X
Colas, 2006, Spain			X						X		X					X		X				1 yr	Depigmented and glutaraldehyde-polymerized extract of *Salsola kali* absorbed onto aluminum hydroxide/NR (supplied by Laboratorios LETI, SL.)	X	X					X	X
Corrigan, 2005, UK	X								X		X			X			X					2 yr	Aluminum-adsorbed six-grass pollen allergoid/Allergovit®	X	X					X	X
Crimi, 2004, Italy			X						X		X					X		X				3 yr	Intact *Parietaria judaica* extract adsorbed onto aluminum hydroxide/Alutard SQ®	X	X					X	
Dokic, 2005, Macedonia					X				X		X						X					3 yr	Aluminum hydroxide-adsorbed *D. pt.* allergoid/NR (Allergopharma)	X	X					X	
Dolz, 1996, Spain	X								X		X					X				X		3 yr	Grass pollen allergen extract (*Phleum*, *Dactylis*, *Lolium*) adsorbed onto aluminum hydroxide/Alutard SQ® (ALK-Abelló)	X	X					X	
Drachenberg, 2001, Germany and Austria	X								X		X			X			X					4-7 wk	Tyrosine-adsorbed glutaraldehyde-modified grass pollen extract containing monophosphoryl lipid A as adjuvant/Pollinex Quattro®	X	X	X				X	
Drachenberg, 2002, Germany		X							X		X			X			X					4-7 wk	L-tyrosine-adsorbed birch, alder, hazel pollen allergoids treated with glutaraldehyde plus monophosphoryl lipid A (MPL)/Pollinex Quattro®			X				X	
DuBuske, 2011, USA, Canada, UK, Austria	X								X		X			X			X					4-8 wk	Modified Allergen Tyrosine Adsorbate (MATA) consisting of a mixture of modified pollen allergens from 13 grass species adsorbed onto tyrosine/Pollinex Quattro, Pollinex Complete; Allergy Therapeutics, UK.			X				X	
Durham, 1999, UK Primary study Varney, 1991	X								X		X		X			X	X					3 yr	Standardized, aluminum hydroxide-adsorbed, depot grass pollen vaccine/Alutard SQ® (ALK-Abelló)				X	X		X	
Ewan, 1988, UK					X				X		X								X			3 mo	Partially purified extract of *D. pteronyssinus*/Pharmalgen®	X						X	
Fell, 1988, UK	X								X		X			X							X	1 injection	Enzyme (glucuronidase) potentiated grass pollen allergens/(Pharmacia)	X	X						

(Continues)

TABLE 1 (Continued)

(a) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Ferrer, 2005, Spain			X						X		X					X	X					20 mo	Biologically standardized extract of *Parietaria judaica* adsorbed onto aluminum hydroxide gel/Pangramin® Depot, ALK-Abelló	X	X	X				X	X
Frew, 2006, UK	X								X		X		X	X	X		X					1 yr	Standardized depot preparations of grass pollen extract/ Alutard SQ grass pollen® (ALK-Abelló)	X	X					X	X
Grammer, 1982, USA			X						X		X	X		X			X					15 wk	Polymerized ragweed extract (PRW)/NR	X						X	
Grammer, 1983, USA	X								X		X			X			X					4 mo	Six-grass pollen allergoid prepared by polymerization with glutaraldehyde/NR	X	X					X	
Grammer, 1984, USA			X						X		X	X		X			X					>30 mo (UR)	Polymerized ragweed extract/NR			X			X	X	
Grammer, 1987, USA	X								X		X			X			X					4 mo	Polymerized ragweed extract/NR			X				X	
Höiby, 2010, Sweden & Germany		X							X		X					X	X					18 mo	Depigmented polymerized birch pollen (Betula alba) extract adsorbed onto aluminum hydroxide/Depigoid® (Laboratorios LETI Sl)			X				X	
Horst, 1989, France				X					X		X					X				X		1 yr	Lyophilized and standardized Alt extract Stallergenes Laboratories			X				X	
Iliopoulos, 1991, USA			X						X		X			X	X		X					~8 mo	Short ragweed extract/NR (Greer Laboratories, Lenoir, N.C.)			X				X	
James, 2011, UK	X								X		X					X	X					2/4 yr	*Phleum pratense* extract adsorbed with aluminum hydroxide/Alutard SQ®				X		X		
Juniper, 1990, Canada			X						X			X		X	X		X					6 wk	Modified ragweed tyrosine adsorbate/Pollinex® (Bencard Allergy Service)	X	X					X	
Jutel, 2005, Poland	X								X		X			X	X		X					8-9 mo	Five recombinant grass pollen allergens/NR (Allergopharma)			X				X	X
Kleine-Tebbe, 2014, Spain, Germany & Austria	X								X		X		X			X	X					1 yr	Aluminum hydroxide-adsorbed Phleum pratense extract/ AVANZ® Phleum pratense (ALK)	X	X					X	
Klimek, 2014, Germany	X								X		X			X	X			X				1 yr	Glutaraldehyde-modified high polymerized allergen extract containing 6 grasses (60%) and rye pollen adsorbed onto aluminum hydroxide/CLUSTOID® (ROXALL Medizin)	X	X	X				X	

(Continues)

TABLE 1 (Continued)

(a) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Kuna, 2011, Poland				X					X		X					X	X					3 yr	*Alternaria alternata* extract in a depot formulation with aluminum hydroxide/Novo-Helisen Depot® A alternata 100% (Allergopharma)	X	X	X				X	X
Leynadier, 2001, France	X								X		X					X	X					1 yr	Standardized five-grass pollen (equal parts of: orchard, meadow, rye, sweet vernal and timothy) depot extract adsorbed onto calcium phosphate/Phostal® (Stallergenes)	X	X	X				X	
Metzger, 1981, England			X						X		X			X			X					5 wk	Glutaraldehyde-modified, tyrosine-adsorbed short ragweed extract/NR (Beecham Laboratories)	X						X	
Mirone, 2004, Italy			X						X		X					X	X					1yr (DBRCT)	*Ambrosia artemisiifolia* absorbed onto aluminum hydroxide and suspended in phenolated (0.4% w/v) saline solution/NR (ALK-Abelló)	X	X					X	
Olsen, 1995, Denmark	X	X	X							X			X			X	X					2 yr	Aluminum hydroxide-adsorbed extracts of standardized extracts of *Betula, Phleum and Artemisia*/Alutard® SQ (ALK)	X						X	
Ortolani, 1994, Italy			X						X		X					X	X					1 yr	Partially purified alginate-conjugated extract of *Parietaria judaica*/Conjuvac Parietaria® (Dome Hollister-Stier)			X				X	
Pastorello, 1992, Italy	X								X		X			X	X		X					5-12 mo	Formalinized depot 6 grass allergoid absorbed onto aluminum hydroxide/NR (Allergopharma)			X				X	
Patel, 2012, Canada						X			X		X		X					X				3 mo	Fel d 1-derived peptide antigen (Cat-PAD)/NR (Bachem and Patheon)	X[a]			X[a]			X	
Pauli, 2008, Austria, Denmark, France, Italy & Sweden		X							X		X		X			X	X					2 yr	Aluminum hydroxide-adsorbed vaccines of birch pollen extract, *rBet v 1*, and *nBet v 1*/NR (Stallergenes SA)	X	X					X	
Pfaar, 2010, Lithuania, Poland & Germany		X							X		X					X	X					19 mo	Standardized depigmented and glutaraldehyde-polymerized tree pollen extract (33% *Corylus avellana*, 33% *Alnus glutinosa*, 34% *Betula alba*) adsorbed onto aluminum hydroxide/Depigoid (Laboratorios LETI SL, Tres Cantos, Spain),	X		X				X	
Pfaar, 2012, Germany	X								X		X			X						X		2 yr	Depigmented and glutaraldehyde-polymerized grass pollen mix adsorbed onto aluminum hydroxide/ Depiquick® (Laboratorios LETI)	X	X	X				X	X

(Continues)

TABLE 1 (Continued)

(a) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Powell, 2007, UK Primary study Frew, 2006	X								X		X		X			X	X					14 mo	Standardized depot preparations of grass pollen extract/ Alutard® SQ grass pollen (ALK-Abelló)								X
Radcliffe, 2003, UK	X	X	X	X	X	X	X	X		X	X			X								2-3 mo	Enzyme potentiated mixed inhaled allergen extract (pollen mixes for trees, grasses, and weeds; allergenic fungal spores; cat and dog danders; dust and storage mites)/NR	X						X	X
Rak, 2001, Sweden		X							X			X		X				X				1 yr	Birch pollen extract adsorbed onto aluminum/Alutard® (ALK-Abelló)	X	X						
Riechelmann, 2010, Germany & Austria					X				X		X					X	X					1 yr	Single-strength glutaraldehyde-modified aluminum hydroxide-adsorbed extract/HDM PURETHAL Mites® (HAL-Allergy)	X	X					X	X
Tabar, 2005, Spain					X				X				X				X	X				1 yr	Biologically standardized HDM depot extract adsorbed onto aluminum hydroxide/Pangramin Depot UM D pteronyssinus® (ALK-Abelló)	X	X					X	
Tabar, 2008, Spain				X					X		X					X	X					18 mo	Metabolic extract of *Alternaria alternata*/Allergovac® depot	X	X					X	X
Tari, 1997, Italy			X						X		X					X	X					2 yr	Alum-adsorbed *Parietaria judaica* pollen allergoid/ Allergovit® (Allergopharma)	X	X					X	
Tworek, 2013, Poland	X		X							X			X	X		X	X					3 yr	Allergoid preparation consisting of 80% grass pollen and 20% rye pollen extracts/Allergovit® (Allergopharma)	X	X	X				X	
Varney, 1991, UK		X							X		X			X	X		X					8 mo	Partially purified and standardized extract of *Phleum pratense* adsorbed onto aluminum/Alutard SQ® (ALK-Abelló)	X	X					X	
Varney, 2003, UK					X				X							X	X					1 yr	Intact HDM extract vaccine adsorbed onto aluminum hydroxide/Alutard SQ® (ALK-Abelló)	X	X					X	
Walker, 2001, UK	X								X		X					X		X				2 yr	Alutard SQ (ALK-Abelló, Hørsholm, Denmark), a standardized extract of Phleum pratense (timothy grass pollen), 7 aluminum adsorbed for slow release	X	X					X	X
Weyer, 1981, France	X								X		X			X			X					8 mo	Crude 4-grass pollen extract/NR	X	X	X				X	
Zenner, 1997, Germany	X		X						X		X				X		X					4 mo	Partially purified and standardized extracts of 6 grasses (50%, *Dactylis glomerata, Lolium perenne, Arena elatior, Phleum pratense, Poa pratensis, and Fetuca pratensis*) and rye (50%, *Secale cereale*) adsorbed onto aluminum hydroxide/NR (manufactured by ALK A/S)	X	X					X	

(Continues)

TABLE 1 (Continued)

(b) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Ahmadiafshar, 2012, Iran	X								X		X			X	X						X	6 mo	10, 100, and 300 IR rye grass spray (Staloral 638)	X	X					X	
Alvarez-Cuesta, 2007, Spain						X			X		X											12 mo	Aqueous solution of cat dander extract with NaCl 0.9%, phenol 0.4% and glycerol 50% (protocol supplied by Laboratorios LETI, S.L.	X						X	
Amar, 2009, USA	X									X	X		X			X						10 mo	Monotherapy group: timothy extract Multiple allergen group: same amount of timothy plus 1 mL each of an additional 9 unstandardized extracts 1:20 wt/vol in 50% glycerin: maple, ash, juniper, American elm, cottonwood, Kochia, ragweed, sagebrush, and Russian thistle (ALK-Abelló).	X	X					X	
André, 2003, France			X						X		X				X							6.5 mo	Standardized ragweed extract (Stallergenes SA, Antony, France)	X	X					X	
Ariano, 2001, Italy & France		X							X		X					X						12 mo	Aqueous solution of an allergic fraction of *Cupressus arizonica* partially purified through dialysis in a physiological solution with 15% glycerin	X	X					X	
Aydogan, 2013, Turkey, UK & Cyprus.					X				X		X											12 mo	1:1 mixture of *D. pteronyssinus and D. farinae* (STALORAL, Stallergenes SA, Antony, France)	X	X						
Bahçeciler, 2007, Turkey					X				X		X											6 mo	*D. pteronyssinus and D. farinae* 50/50 extract.	X							
Bergmann, 2013, Germany, France, the Netherlands & Spain					X				X		X											2 yr	Oral tablets of 1:1 mixture of *D pteronyssinus and D farinae* (28 mg and 120 mg respectively for the 500 IR tablet, 16 mg and 68 mg respectively for the 300 IR tablet)	X			X			X	
Blaiss, 2010, USA & Canada	X								X		X											18 mo	f 2800 bioequivalent allergen units of grass AIT treatment (oral lyophilisate, *Phleum pratense*, 75 000 standardized quality tablet, containing approximately 15 mg of Phl p 5; Schering-Plough Corp, a division of Merck & Co, Kenilworth, NJ)	X	X	X				X	X
Bowen, 2004, Canada			X						X		X			X								4 mo	Ragweed allergen extract	X	X					X	
Bozek, 2012, Poland					X				X		X											3 yr	Oral Staloral 300 SR Der p and Der f (1:1)	X	X					X	

(Continues)

TABLE 1 (Continued)

(b) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Bozek, 2014, Poland	X								X		X											3 yr	Oral Staloral 300 SR 5-grass pollen solution *of P. pratense, D. glomerata, A. odoratum, L. perenne, and P. pratensis* (Stallergenes)	X	X					X	
Bufe, 2004, Germany	X								X		X				X							3 yr	Grass pollen extracts (Sublivac B.E.S.T.TM, HAL-Allergy, Haarlem, the Netherlands)								
Bufe, 2009, Germany	X								X		X			X	X							8-23 wk	Orodispersible, fast-dissolving, SQ-standardized grass allergen tablet (Grazax; ALK, Hørsholm, Denmark; 75 000 SQ-T/2800 bioequivalent allergen units, approximately 15 mg Phl p 5, Phleum pratense major allergen 5)	X	X					X	
Caffarelli, 2000, Italy	X								X		X			X								3 mo	Mixture of monomeric grass pollen allergens (33% *Holcus lanatus*, 33% *Phleum pratense*, and 33% *Poa pratensis*) in tablets (LAIS, Lofarma S.p.A., Milan, Italy)	X	X					X	
Clavel, 1998, France	X								X		X											7 mo	Mixture of five major grass pollens (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass	X	X					X	
Cortellini, 2010, Italy				X					X		X											10 mo	Glycerinated *Alternaria alternata* extract in droplets (Anallergo, Firenze, Italy)	X	X					X	
Cox, 2012, USA	X								X		X											6 mo	300IR SLIT tablets containing a standardized 5-grass pollen allergen obtained by means of extraction of a mixture of 5 grass pollens in equal amounts (orchard grass, *Dactylis glomerata*; Kentucky bluegrass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, *Phleum pratense*)	X	X	X				X	X
Creticos, 2013, USA			X						X		X			X	X							20 mo	Short ragweed tablets (1.5, 6, or 12 units of *Ambrosia artemisiifolia* major allergen 1 [Amb a 1-U])	X	X	X				X	
Creticos, 2013, Canada			X						X		X				X							12 wk	Ragweed SAIL (RW-SAIL) Standardized glycerinated short ragweed	X		X				X	
Dahl, 2006, Denmark, Germany, Italy, the Netherlands, Sweden, Austria, Spain & UK	X								X		X			X	X							1 yr	Grass pollen allergen tablet (Grazax) (75 000 SQ-T; 15 mg major allergen *Phleum p* 5)	X	X					X	

(Continues)

TABLE 1 (Continued)

(b) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Dahl, 2006, Denmark & Sweden	X								X		X			X	X								Orodispersible grass allergen tablet (Grazax; approximately 15 mg major allergen *Phleum pratense* (75 000 SQ-T)	X	X					X	
de Blay, 2007, France	X								X		X			X	X							12 mo	3-grass pollen extract (33.3% *Dactylis glomerata* [orchard grass], 33.3% *Phleum pratense* timothy grass], and 33.3% *Lolium perenne* [rye grass]) Allerbio, Varennes-en-Argonne, France) in 50% glycerin	X	X					X	X
De Bot, 2011, the Netherlands					X				X		X											2 yr	Aqueous extract of house dust mites (*D. pter*) in a glycerinated isotonic phosphate-buffered solution (Oralgen Mijten)/placebo treatment consisting of the glycerol-containing solvent	X	X					X	X
Demoly, 2015, Europe					X				X		X											1 yr	1:1 mixture of two species of house dust mite allergens (*D. pteronyssinus and D. farinae*) (1:1:1:1 ratio of the major allergens *Der p 1*, *Der f 1*, *Der p 2*, and *Der f 2*)	X	X					X	X
Didier, 2007, Europe	X								X		X			X	X							6 mo	Mixture of 5 grass pollens (orchard, meadow, perennial rye, sweet vernal, and timothy grasses)	X						X	X
Didler, 2009, France, Germany & Spain	X								X		X		X	X	X							6 mo	Lyophilized vaccines of five grass pollens (orchard or cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), perennial rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*), and timothy (*Phleum pratense*))	X						X	
Didier, 2013, Denmark, Austria, France, Canada & Germany	X								X		X			X	X							4 yr	300IR tablets containing mixture of 5 grasses [cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*) and timothy (*Phleum pratense*)	X						X	X
Durham, 2005, Canada, Denmark & Sweden	X								X		X			X	X							2 yr	Fast-dissolving grass allergen tablet (ALK-Abelló A/S) containing timothy grass extract (*Phleum pratense*)	X	X					X	X
Durham, 2007, UK Primary study: Dahl, 2006	X								X		X											16 wk	Grass allergen tablet (Grazax)								

(Continues)

TABLE 1 (Continued)

(b) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Durham, 2009, UK Results after 1-y follow-up of the Dahl (2006) study	X								X		X			X	X							3 yr	Grass allergen tablet with *Phleum pratense* 75 000 SQ-T/2800 BAU (ALK-Abelló, Hørsholm, Denmark) (Grazax)								
Durham, 2011, UK Results of 2-y follow-up of the Dahl (2006) trial	X								X		X										X	2 yr	SQ-standardized grass allergy tablet (*Phleum pratense* 75 000 SQ-T/2800 BAU, ALK, Denmark) (Grazax)						X		
Durham., 2012, UK, Austria, Germany, the Netherlands, Sweden & Denmark Results of 2-y follow-up of the Dahl (2006) trial	X								X		X			X	X							3 yr	SQ-standardized grass allergy tablet (Grazax)				X			X	
Drachenberg, 2002, Germany	X	X								X	X						X						Grass, rye or birch pollens	X	X	X					
Feliziani, 1995, Italy	X								X		X			X	X					X			Grass pollen extracts (5 x 1 drop of 0.04 BU/mL, up until 5 x 1 drop of 100 BU/mL)	X	X					X	
Frølund, 2010, Austria, Denmark & UK	X								X		X			X	X							4 yr	SQ-standardized grass allergy immunotherapy tablet (AIT), Grazax (*Phleum pratense* 75 000 SQ-T/2800 BAU; ALK, Denmark).								X
Guez, 2000, France					X				X		X											24 mo	*D. pteronyssinus and D. farinae* 50/50 extract	X	X					X	
Halken, 2010, Germany, Denmark, Poland, France & Spain	X								X		X			X	X							10 mo	Five-grass pollen 300IR tablets (Stallergenes SA, France)	X						X	
Hirsch, 1997, Germany					X				X		X											12 mo	Purified *D. pteronyssinus* extract in 50% aqueous glycerol (cumulative dose 570 jag) (Allergopharma J. Ganzer KG, Reinhek, FRG)	X	X						
Horak, 1998, Austria		X							X		X											4 mo	Biologically standardized *Betula Alba* Alergia e Immunologia Abello SA	X						X	
Horak, 2009, Austria	X								X		X											4 mo	300-IR 5-grass pollen tablet (orchard, meadow, perennial rye, sweet vernal, timothy)	X						X	

(Continues)

TABLE 1 (Continued)

	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness				
(b) Study (first author, y, country)	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Product type/Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Hordijk, 1998, the Netherlands	X								X		X				X							10 mo	Glycerinated (50% w/v) five-grass pollen extract (*Anthoxanthum odoratum* (Sweet vernal grass), *Cynodon dactylon* (Bermuda grass), *Dactylis glomerata* (Orchard grass), *Holcus lanatus* (Velvet grass) and *Phleum pratense* (Timothy grass)) (9500 BU/mL) (Oralgen) (ARTU Biologicals Europe B.V., Lelystad, the Netherlands)	X						X	
Ibanez, 2007, Spain & Germany	X								X													28 d	Orodispersible grass allergen tablet (75 000 SQ-T; 15 Ig *P. pratense* major allergen (Phl p 5)) (Grazax) ALK-Abelló A/S, Hørsholm, Denmark)							X	
Ippoliti, 2003, Italy					X				X		X											6 mo	*D. pteronyssinus* extract	X							
Kaluzinska-Parzyzek, 2011, Poland (Polish, translated)	X								X		X			X	X			X				2 yr	Staloral 300 IR (Stallergenes)								
La Rosa, 1999, Italy & France			X						X		X											2 yr	*P judaica* extract (Stallergenes, Antony, France) in drops	X	X					X	
Marcucci, 2003, Italy					X				X		X											1 yr	House dust mite allergens (1 mL of the top-dose vial 1000 STU/mL/4 Ig of the major mite allergen Group 1 and 2 Ig of the major mite allergen Group 2)								
Moreno-Ancillo, 2007, Spain	X									X	X			X	X							10 mo	2 μg of grass Group 5 and 3 μg of Olive europaea Ole e 1 (daily)	X	X	X				X	X
Mosbech., 2014, Denmark, Italy, Germany & France					X				X		X											1 yr	Oral lyophilisates containing *D. pteronyssinus* and *D. farinae* in a 1:1 ratio. Three active strengths were investigated: 1, 3, and 6 SQ-HDM.			X				X	X
Mosges, 2007, Germany	X									X	X											9 mo	Grass and rye pollen extract mixture solution (Staloral(r) (Stallergenes, Antony, France)) and a tablet (freeze-dried pollen extract)		X	X				X	
Okubo, 2008, Japan		X							X		X			X	X		X					7 mo	Diluted cedar antigen extract (2 to 2000 JAU/mL)		X					X	X

(Continues)

TABLE 1 (Continued)

(b) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness				
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life
Ott, 2009, Germany	X								X		X				X						X	3 yr	Pollen extract mixture of five grasses (cocksfoot or orchard, meadow, perennial rye, sweet vernal and timothy grasses; Staloral, Stallergenes SA, France) (300 IR/mL, equivalent to 21 lg/mL of Phleum pratense major allergen)	X	X	X	X	X	X	X	
Nelson, 1993, USA						X			X		X											105 d	Cat dander extract (total dose: 4.5 AU)	X						X	
Pajno, 2003, Italy			X						X		X	X	X	X	X							14 mo	*P. judaica*, fluticasone	X	X						
Palma-Carlos, 2006, Italy	X								X		X		X	X								2 yr	Mixture of carbamylated grass pollens (*Holcus lanatus* 33%, *Phleum pratense* 33%, and *Poa pratensis* 33%) in tablets	X						X	
Panzner, 2008, Czech Republic	X								X		X			X								1 yr	Mixture of six grass pollen species extracts (oat grass (*Arrhenatherum elatius*), orchard grass (*Dactylis glomerata*), fescue (*Festuca sp.*), rye grass (*Lolium sp.*), timothy grass (*Phleum pratense*), and rye (*Secale cereale*)) (H-Al per os) (Sevapharma A.S., Prague, Czech Republic)	X	X					X	
Passalacqua, 1996, Italy					X				X		X											2 yr	Monomeric allergoid tablets with *Dermatophagoides pteronyssinus and D farina*	X						X	
Passalacqua, 1999, Italy	X								X		X			X						X		7 mo	ALK-Abelló (major allergen Par j) (0.016, 0.08, 0.4, 2, and 10 BU/mL)	X	X					X	
Passalacqua, 2006, Italy					X				X		X					X						2 yr	Monomeric carbamylated grass pollen allergen (Lais)	X	X					X	X
Pfaar, 2008, Germany, Poland & Macedonia	X								X		X											2 yr	Six-grass pollen mixture (high-dose)	X	X	X				X	
Pradalier, 1999, France	X								X		X											4.5 mo	Five-grass pollen extracts (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass) (Stallergenes SA, Antony, France)	X	X					X	
Purello-D'Ambrosio, 1999, Italy			X						X		X			X						X		6 mo	*P. judaica* extract (five 3-ml vials: 0.016 BU/ml (vial 0), 0.08 (#1), 0.04 (#2), 2.00 (#3), and 10.00 (#4) in physiological saline with 50% v/v of glycerol & 0.4% w/v of phenol) (maximum concentration of major allergen Par j 1: 0.6 mg/mL)	X	X					X	

(Continues)

TABLE 1 (Continued)

(b) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Qeuiros, 2013, Brazil & USA					X				X		X		X									18 mo	SLIT 1: *D. pteronyssinus* extract (FDA Allergenic Ltda, Rio de Janeiro, Brazil) SLIT 2: *Dpt plus* mixed respiratory bacterial (MRB) (FDA Allergenic Ltda)			X				X	
Rak, 2006, UK	X								X		X											174 d	Grass pollen allergen tablets (2500, 25 000, and 75 000 SQ-T)								X
Roder, 2007, the Netherlands	X								X		X					X						2 yr	Aqueous extracts of 5 grass pollens (*Lollium perenne, Phleu*m pratense, Dactylis glomeratein, Anthoxanthum odoratum, Holcus lanatus), Oralgen grass pollen, Artu Biologicals	X	X					X	X
Rolinck-Werninghaus, 2004, Germany	X								X		X					XX						32 mo	Pangramin (0.5 lg major allergens) (ALK-SCHERAX) three times weekly	X	X					X	
Sabbah, 1994, France	X								X		X											4 mo	Five-grass pollen extracts in glycerol-saline diluent (from 1 drop of 1 IR/mL up to 20 drops of 100 IR/mL)	X	X					X	
Stelmach, 2011, Poland	X								X		X			X	X							2 yr	Staloral 300 IR with five grass pollens (*Dactylis glomerata, Anthoxanthum odoratum, Lolium perenne, Poa pratensis and Phleum pratense*)	X	X					X	
Tari, 1990, Italy					X				X		X											18 mo	Graded courses of aqueous mite extract with 0.4% phenol	X						X	
Valovirta, 2006, Finland		X							X		X		X									19 mo	Intervention arm #1: *Betula verrucosa, Corylus avellana and Alnus glutinosa* (weekly dose: 24 000 SQ-U); intervention arm #2: *Betula verrucosa, Corylus avellana and Alnus glutinosa* (weekly dose: 200 000 SQ-U)	X	X					X	
Van Niekerk, 1987, South Africa	X								X		X											24 mo	Mixture of aqueous extracts of twelve grass pollens (B2 grasses) (Bencard, UK), plus Bermuda grass pollen and maize pollen in phosphate-buffered physiological saline with 0 5% w/v phenol identical to Bencard SDV® vaccine (Beechams, UK)	X						X	
Vourdas, 1998, Greece & France		X							X		X											2 yr	Olive pollen extract (major allergen Ole e 1 13.5 jig/mL (100 IR/mL)) (four concentrations: 1, 10, 100, and 300 IR/mL) (Stallergenes SA)	X	X					X	

(Continues)

TABLE 1 (Continued)

(b) Study (first author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Wang, 2013, China					X				X		X											6 mo	Mixture of *D. pteronyssinus and D. farinae* in 50% glycerol solution (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China) (five treatment dosages with different concentrations: 0.75 lg/ml, 7.5 lg/ml, 75 lg/mL, 250 lg/ml, and 750 lg/mL)	X	X					X	
Wahn, 2012, Germany & Poland	X								X		X			X	X							8 mo	Aqueous grass pollen preparation containing 6 species (*Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense, and Poa pratensis*) in a water/glycerol solution with phosphate-buffered saline (40 μg per maintenance dose) Allergopharma Joachim Ganzer KG, Reinbek, Germany			X				x	
Wahn, 2009, Denmark & France	X								X		X			X	X							Approx 5-6 mo	SLIT tablets of 5-grass pollen extracts (orchard, meadow, perennial rye, sweet vernal, and timothy; Stallergenes SA, Antony, France) (300 IR)	X	X					X	

(c) Study (first author, year, country)	Allergen(s) type								Allergen number		Route AIT			Comparator			AIT Protocol									Product type/Name (manufacturer)	Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weeds	Molds	House dust mite	Cat	Dog	Other(s)	Single	Multiple	SCIT	SLIT	ILIT	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush type	Ultrarush	Duration of Rx		Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Hylander et al., 2016, Spain	X	X							X				X	X			X				X				2 mo	Aluminum hydroxide-adsorbed, depot birch or grass pollen vaccine/Alutard (ALK-Abelló)	X	X					X	
Senti et al., 2012, Switzerland						X			X				X	X					X		X				2 mo	Recombinant major cat dander allergen Fel d 1 fused to a modular antigen transporter (MAT) vaccine (MAT-Fel d 1)/NR (extract purchased from Stallergenes)	X[b]						X	X

AIT, allergen-specific immunotherapy; ILIT, intralymphatic immunotherapy; mo, month; NBS, not better specified; NR, not reported; Rx, treatment; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; UR, unclear reporting wk, week; yr, year.

[a]Environmental exposure chamber.

[b]Assessment after 300 days of discontinuation of ILIT.

Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Amar 2009	.030	−.625	.684	19	17	1.39
Andre 2003	−.449	−.848	−.050	48	51	2.13
Ariano 2001	−2.274	−3.398	−1.149	10	10	.67
Bahceciler 2001	.333	−.689	1.354	8	7	.77
Bowen 2004	−.433	−.888	.022	37	39	1.94
Bufe 2004	−.058	−.399	.284	68	64	2.32
Bufe 2009	−.221	−.476	.034	117	121	2.62
Caffarelli 2000	−.453	−1.134	.228	17	17	1.33
Cortellini 2010	−1.457	−2.310	−.604	15	12	1.00
Creticos 2014	−.297	−.487	−.107	218	211	2.81
Dahl 2006a	−.637	−1.074	−.199	61	32	2.00
Dahl 2006b	−.519	−.687	−.352	282	286	2.88
de Blay 2003	−.167	−.624	.289	33	42	1.94
de Bot 2011	.069	−.192	.330	110	116	2.60
Didier 2007	−.434	−.670	−.198	136	148	2.68
Drachenbergh 2001	−.268	−.921	.386	37	12	1.39
Durham 2006	−.229	−.473	.015	131	129	2.65
Feliziani 1995	−1.028	−1.744	−.312	18	16	1.25
Guez 2000	−.416	−.883	.051	36	36	1.90
Halken 2010	−.437	−.680	−.193	131	135	2.65
Hirsch 1997	.525	−.329	1.378	12	10	1.00
Horak 2009	−.778	−1.208	−.347	45	44	2.02
Hordijk 1998	−.575	−1.050	−.100	35	36	1.88
La Rosa 1999	−.249	−.934	.437	16	17	1.32
Marcucci 2003	−.235	−1.041	.571	13	11	1.08
Nelson 1993	−.570	−1.194	.055	20	21	1.46
Ott 2009	−.515	−.829	−.202	123	60	2.42
Paino 2003	−.850	−1.638	−.061	14	13	1.11
Palma Carlos 2006	−.585	−1.283	.112	17	16	1.29
Panzner 2008	−1.291	−2.025	−.556	20	15	1.21
Passalacqua 1998	−1.327	−2.321	−.332	10	9	.80
Passalacqua 1999	−.018	−.734	.698	15	15	1.25
Passalacqua 2006	−1.624	−2.228	−1.020	28	28	1.51
Pfaar 2008	−.699	−1.125	−.272	42	48	2.03
Pradalier 1999	−.177	−.527	.173	63	63	2.29
Rolinck-Werninghaus 2004	.047	−.400	.494	39	38	1.97
Stelmach 2012	−1.165	−1.862	−.468	19	18	1.29
Tari 1990	−2.274	−2.935	−1.613	30	28	1.37
Valovirta 2006	−.500	−1.032	.032	27	29	1.71
Vourdas 1998	−.170	−.654	.314	34	32	1.85
Wahn 2009	−.435	−.678	−.192	131	135	2.65
Balda 1998*	−.270	−.655	.115	49	56	2.17
Bodtger 2002*	−.900	−1.616	−.183	16	17	1.25
Bousquet 1990*	−1.371	−2.078	−.663	20	18	1.27
Charpin 2007*	−.694	−1.409	.021	17	15	1.25
Corrigan 2005*	−.410	−.729	−.091	77	77	2.40
Drachenberg 2001*	−.467	−.831	−.104	74	50	2.25
Ferrer 2005*	−.821	−1.451	−.191	22	20	1.44
Frew 2006*	−.493	−.749	−.238	187	89	2.61
Jutel 2005*	−.563	−1.092	−.033	29	28	1.71
Klimek 2014*	−.599	−.963	−.234	61	60	2.24
Ortolani 1994*	−2.457	−3.335	−1.579	18	17	.96
Tabar 2008*	.313	−.432	1.058	14	14	1.19
Varney 1991*	−.466	−1.140	.208	19	16	1.34
Varney 2003*	−1.588	−2.439	−.737	15	13	1.00
Walker 2001*	−.515	−1.249	.219	17	13	1.21
Weyer 1981*	−.554	−1.250	.141	17	16	1.29
Zenner 1997*	−.453	−.894	−.012	41	40	1.99
	−.527	−.631	−.424	2978	2746	

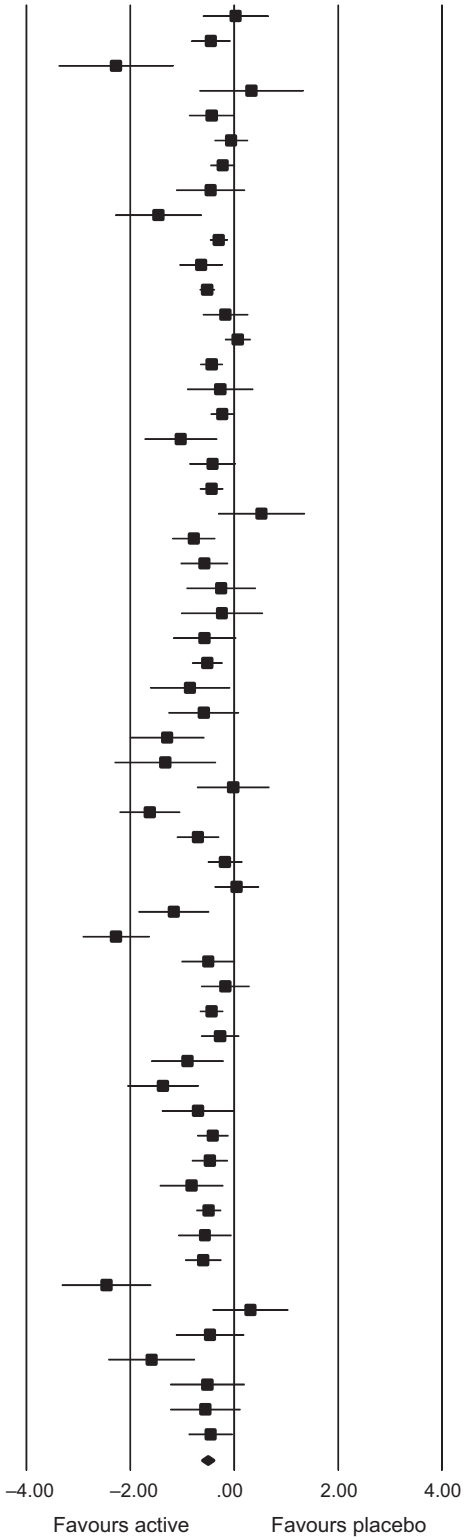
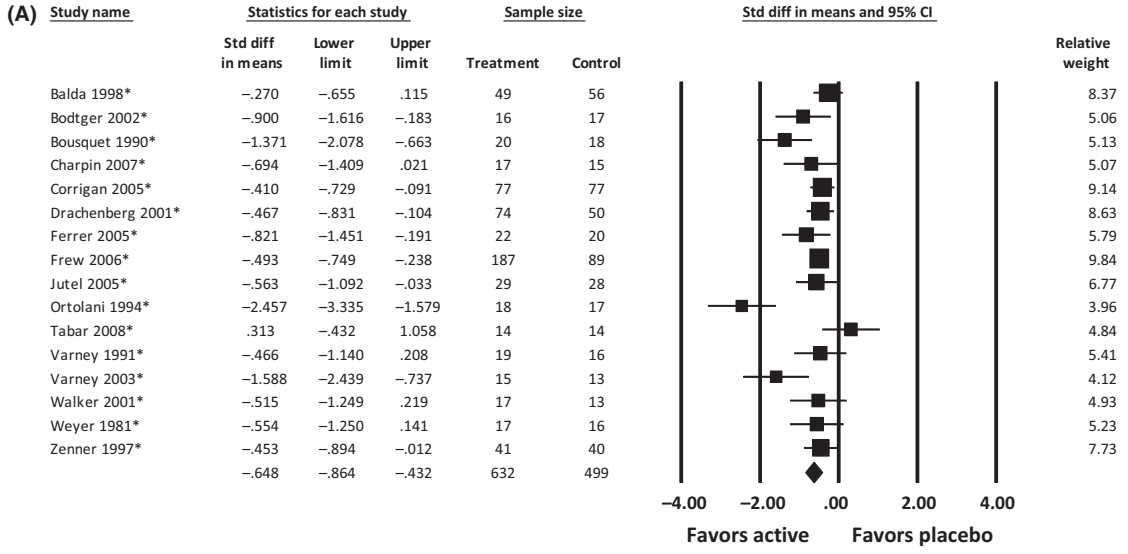


FIGURE 2 Meta-analysis of double-blind RCTs comparing symptom scores between allergen immunotherapy (AIT) (subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT)) and placebo groups (random-effects model). Heterogeneity: τ^2=.090; χ^2=173.586, *df*=57 (*P*<.0001); I^2=67%. Test for overall effect: *Z*=−9.992 (*P*<.0001). *denotes SCIT studies



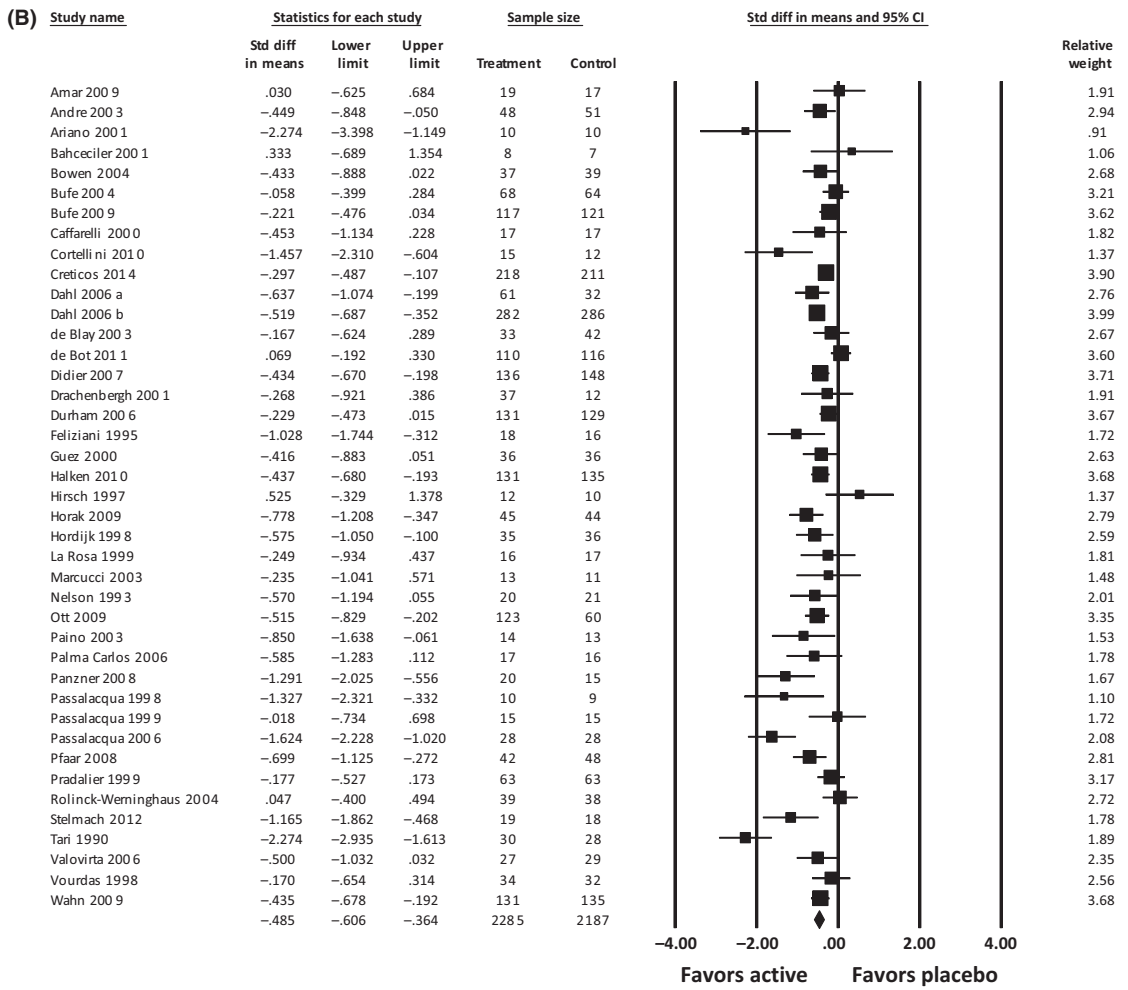


FIGURE 3 Meta-analysis of double-blind RCTs comparing symptom scores between (A) subcutaneous immunotherapy (SCIT) and placebo groups and (B) sublingual immunotherapy (SLIT) and placebo group (random-effects models). (A) Heterogeneity: τ^2=.106; χ^2=39.357, *df*=15 (*P*<.001); I^2=62%. Test for overall effect: *Z*=−5.875 (*P*<.0001). *denotes SCIT studies. (B) Heterogeneity: τ^2=.088; χ^2=129.171, *df*=40 (*P*<.0001); I^2=69%. Test for overall effect: *Z*=−7.855 (*P*<.0001).

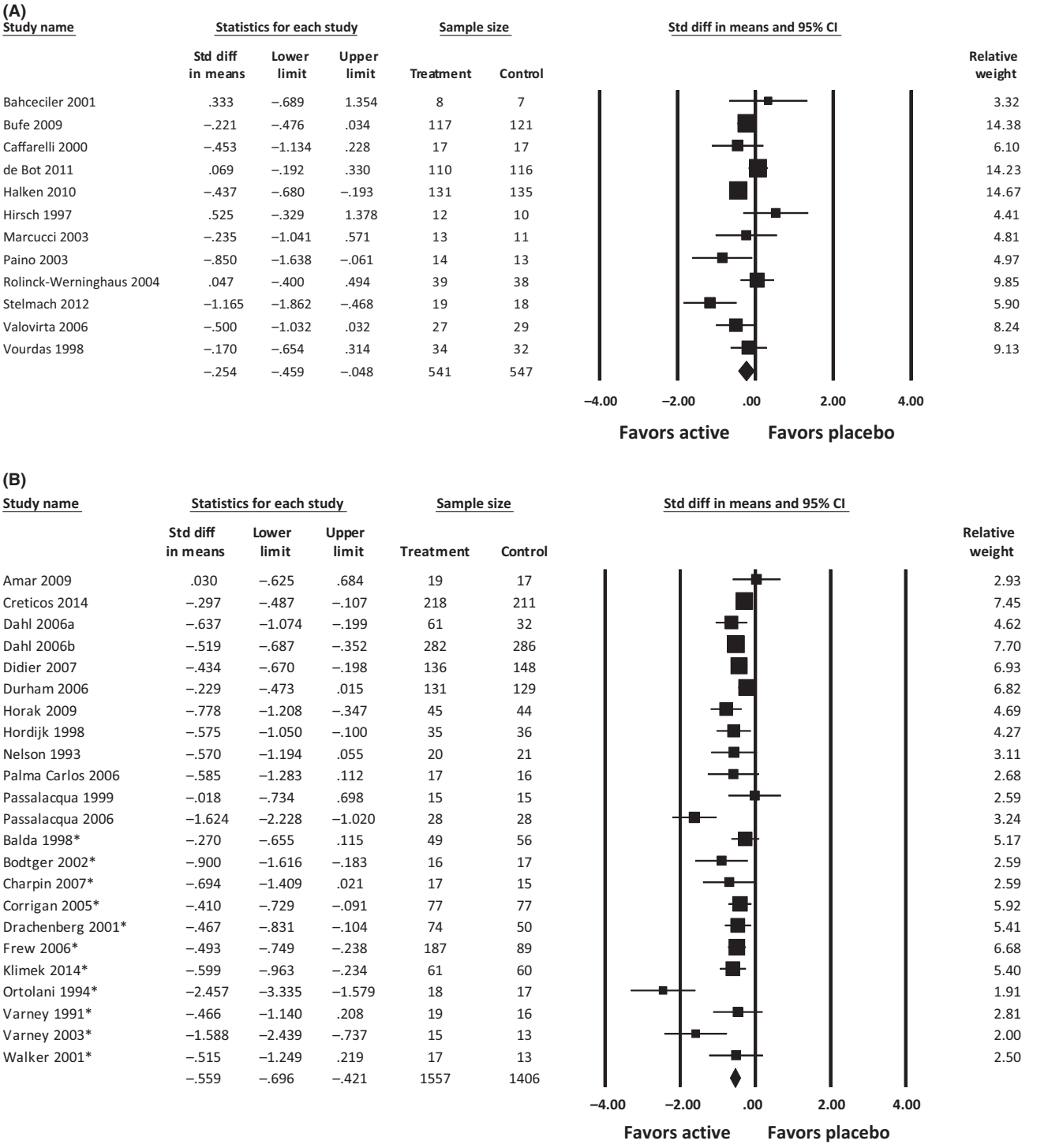


FIGURE 4 Meta-analysis of double-blind RCTs comparing symptom scores between allergen immunotherapy (AIT) (subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT)) and placebo group in (A) those <18 years old and (B) those ≥ 18 years old (random-effects models). (A) Heterogeneity: τ^2=.059; χ^2=24.209, *df*=11 (*P*<.012); I^2=54%. Test for overall effect: *Z*=−2.423 (*P*<.015). (B) Heterogeneity: τ^2=.057; χ^2=57.748, *df*=22 (*P*<.0001); I^2=62%. Test for overall effect: *Z*=−7.969 (*P*<.0001). *denotes SCIT studies

- Seasonal vs perennial allergens for SCIT: SMD −0.49 (95% CI −0.72, −0.27) for seasonal and SMD −1.59 (95% CI −2.44, −0.74) for perennial (results from only one study) (Figures S5A and B), these demonstrating evidence of benefit from both approaches.
- Seasonal vs perennial allergens for SLIT: SMD −0.35 (95% CI −0.45, −0.26) for seasonal and SMD −0.81 (95% CI −1.41, −0.20) for perennial allergens (Figure S6A,B)
- Pre-/coseasonal vs continuous treatment in SCIT for pollen: SMD −0.51 (95% CI −0.63, −0.38) in pre-/coseasonal and SMD −0.69

(95% CI −1.09, −0.29) (Figures S7A and B), these analyses demonstrating evidence of benefit from both approaches.

- Pre-/coseasonal vs continuous treatment in SLIT for pollens: SMD −0.40 (95% CI −0.48, −0.32) in pre-/coseasonal and SMD −0.55 (95% CI −0.98, −0.11) in continuous (Figures S8A and B), these analyses demonstrating a clear benefit associated with both approaches.
- Modified allergen extracts (allergoids) vs unmodified allergen extracts in SCIT: SMD −0.60 (95% CI −0.89, −0.31) vs SMD −0.65 (95% CI −0.93, −0.36) (Figures S9A and B), these analyses demonstrating evidence of benefit from both modalities
- Aqueous solutions vs tablets in SLIT: SMD −0.42 (95% CI −0.68, −0.15) in aqueous and SMD −0.53 (95% CI −0.73, −0.34) with tablets (Figures S10A and B), these analyses confirming benefit with both preparations.
- Different allergens for AIT (SCIT and SLIT): HDM: SMD −0.73 (95% CI −1.37, −0.10); grass: SMD −0.45 (95% CI −0.54, −0.36); tree: SMD −0.57 (95% CI −0.92, −0.21); molds: SMD −0.56 (95% CI −2.29, 1.18); weeds: SMD −0.68 (95% CI −1.06, −0.30), these showing that AIT was clearly effective for all allergens except molds for which there was evidence suggestive of benefit but this was imprecisely estimated (Figure S11A-E),

Long-term

To investigate long-term effectiveness, a number of investigators studied a discontinuation period following trials that involved randomization to AIT or placebo in which the superiority of AIT was confirmed. In this longer-term phase, patients were followed up and outcomes were then again assessed at least one year post-discontinuation of AIT.

There were four trials that studied this outcome, one SCIT[42] and three SLIT,[89,114,133] all of which were judged to be at low ROB. Meta-analysis of data was not possible. A full descriptive summary of the main findings are provided in the supplement. In summary, all four trials at low ROB found a beneficial effect on the long-term effectiveness of AIT on symptom scores.

3.2.2 | Medication scores

Short-term

Eighty nine studies reported on the short-term effectiveness of AIT administered by the SCIT (n=46), SLIT (n=42) and ILIT (n=1) routes on medication scores.

We were able to pool data from 45 SCIT and SLIT trials. This showed an overall SMD of −0.38 (95% CI −0.49, −0.26), this suggesting a small-to-medium effect in favor of AIT in improving medication scores (Figure 5).

Sensitivity analyses Sensitivity analysis, performed by excluding all studies at high ROB, gave an SMD of −0.35 (95% CI −0.46, −0.24) (Figure S12).

Assessment of publication bias The Funnel plot revealed evidence of potential publication bias (Figure S13) which was also suggested by the Begg (P=0.004) and Egger (P=0.03) tests.

Subgroup analyses Subgroup analyses were undertaken to compare:

- SCIT vs SLIT: SMD −0.52 (95% CI −0.75, −0.29) for SCIT and −0.31 (95% CI −0.44, −0.18) for SLIT (Figures 6A and B), these analyses demonstrating that both routes were effective.
- Children vs adults: SMD −0.21 (95% CI −0.42, 0.01) for children and SMD −0.43 (95% CI −0.56, −0.30) for adults (Figures S14A and B), these showing a clear benefit in adults and the suggestion of benefit in children (but this was not confirmed)
- Children vs adults for SLIT only: SMD −0.60 (95% CI −1.12, −0.07) for children and SMD −0.45 (95% CI −0.69, −0.22) for adults showing a benefit in both (Figures S15A and B).
- Seasonal vs perennial allergens for AIT (SCIT and SLIT): SMD −0.30 (95% CI −0.43, −0.16) for seasonal and SMD −0.63 (95% CI −1.12, −0.15) for perennial allergens (Figures S16A and B), these indicating that both were effective.
- Seasonal vs perennial allergens for SCIT: SMD −0.77 (95% CI−1.28, −0.25) for seasonal and SMD −0.27 (95% CI −1.01, 0.48) for perennial (results from only one study) (Figures S17A and B)
- Seasonal vs perennial allergens for SLIT: SMD −0.24 (95% CI −0.38, −0.10) for seasonal, SMD −0.72 (95% CI −1.30, −0.13) (Figures S18A and B), indicating that both were effective.
- Pre-/coseasonal vs continuous treatment in SCIT for pollens: SMD −0.40 (95% CI −0.56, −0.25) in preseasonal and SMD −1.23 (95% CI −2.34, −0.12) in continuous (Figures S19A and B), these indicating that both were effective.
- Pre-/coseasonal vs continuous treatment in SLIT for pollens: SMD −0.30 (95% CI −0.42, −0.18) in pre-/coseasonal and SMD 0.00 (95% CI −0.32, 0.33) for continuous (Figures S20A and B), these analyses suggesting that pre-/coseasonal was effective and that continuous treatment was ineffective.
- Modified allergen extracts (allergoids) vs unmodified allergen extracts in SCIT SMD −0.94 (95% CI −1.73, −0.16) vs SMD −0.44 (95% CI −0.64, −0.24) (Figures S21A and B),
- Aqueous solutions vs tablets in SLIT: SMD −0.42 (95% CI −0.68, −0.15) for those receiving aqueous and SMD −0.53 (95% CI −0.73, −0.34) for tablets (Figures S22A and B), these analyses showing that both preparations were effective.
- Different allergens for AIT (SCIT and SLIT): HDM: SMD−0.63 (95% CI −1.12, −0.15) vs Grass: SMD −0.32 (95% CI −0.46, −0.18) vs Tree: SMD −0.40 (95% CI −0.59, −0.20) vs Molds: SMD 0.34 (95% CI −0.41, 1.09)(results from only one study) vs Weeds: SMD −0.44 (95% CI −0.80, −0.09) (Figures S23A-E), these showing evidence of benefit for all allergens except molds.

Long-term

There were three low ROB trials that assessed this outcome: one SCIT[42] and two SLIT.[114,133] These three trials are described in detail

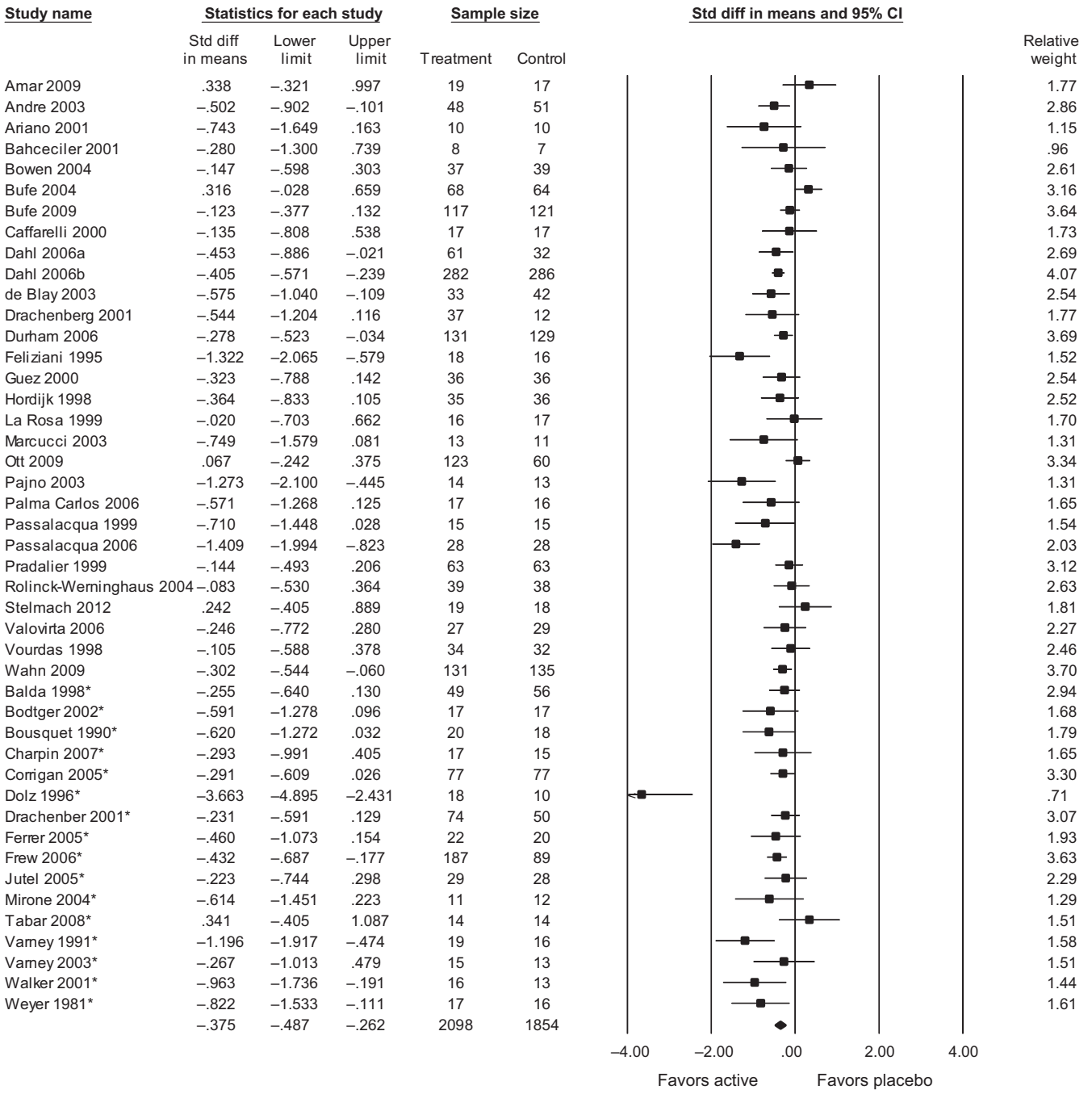


FIGURE 5 Meta-analysis of double-blind RCTs studies comparing medication scores between allergen immunotherapy (AIT) (subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT)) and placebo groups (random-effects model). Heterogeneity: τ^2=.074; χ^2=110.337, *df*=44 (*P*<.0001); I^2=60%. Test for overall effect: *Z*=−6.502 (*P*<.0001). *denotes SCIT studies

in the supplement. Overall, one trial found a benefit of AIT (SCIT) on long-term medication scores; the two other SLIT trials did not show a sustained effect.

3.2.3 | Combined symptom and medication scores

Twenty-nine studies reported on the short-term effectiveness of AIT administered by the SCIT (n=20) and SLIT (n=9) routes on combined symptom and medication scores. Two studies (one SCIT and one SLIT) reported on long-term effectiveness in relation to this outcome.

Short-term

We were able to pool data from 15 studies. Meta-analysis found a SMD of −0.49 (95% CI −0.69, −0.30), this suggesting a small-to-moderate effect in favor of AIT (Figure 7).

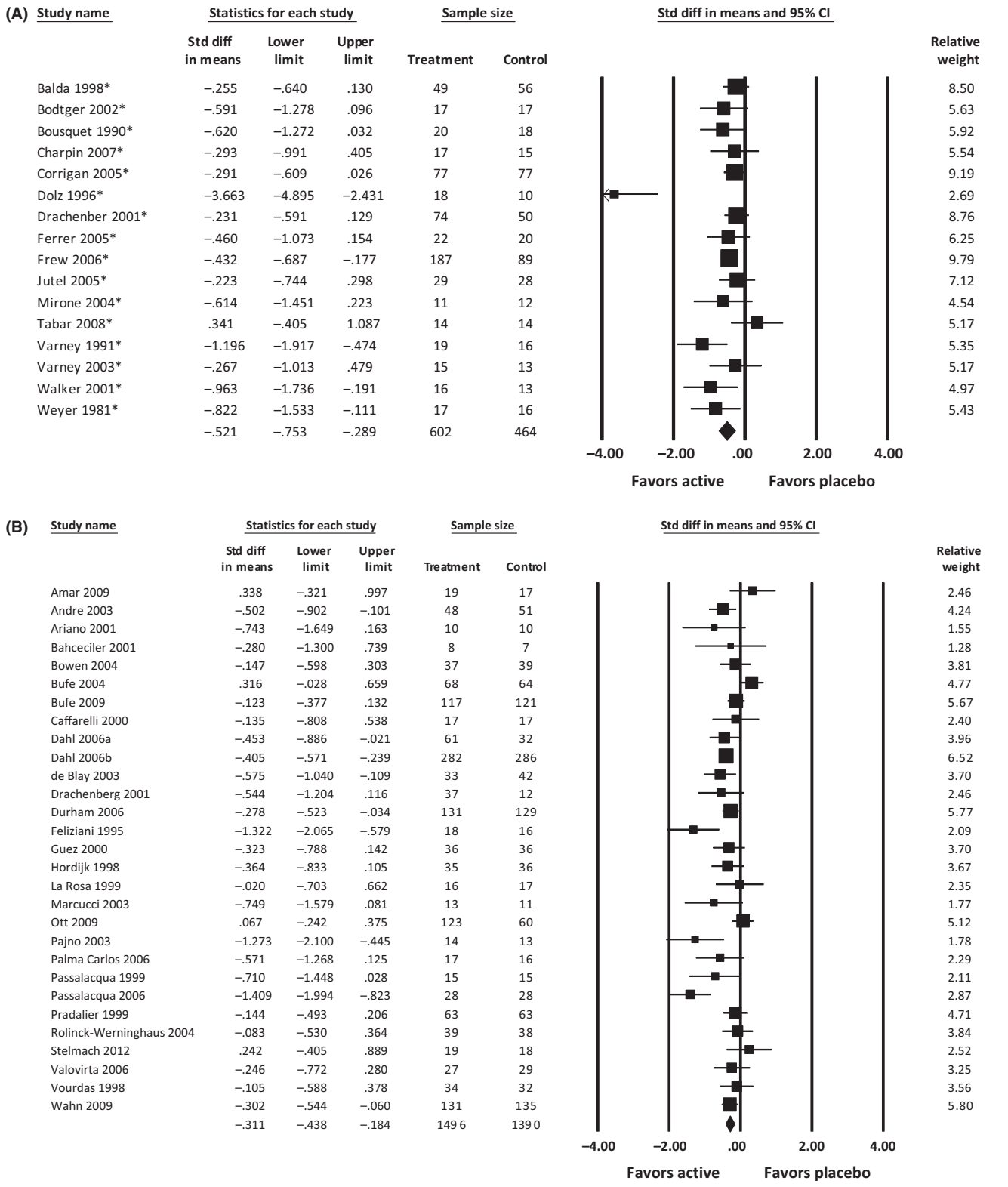


FIGURE 6 Meta-analysis of double-blind RCTs comparing medication scores between (A) subcutaneous immunotherapy (SCIT) and placebo groups and (B) sublingual immunotherapy (SLIT) and placebo groups (random-effects models). (A) Heterogeneity: τ^2=.126; χ^2=42.241, *df*=15 (*P*<.0001); I^2=64%. Test for overall effect: *Z*=−4.399 (*P*<.0001). *denotes SCIT studies. (B) Heterogeneity: τ^2=.057; χ^2=64.535, *df*=28 (*P*<.0001); I^2=57%. Test for overall effect: *Z*=−4.805 (*P*<.0001)

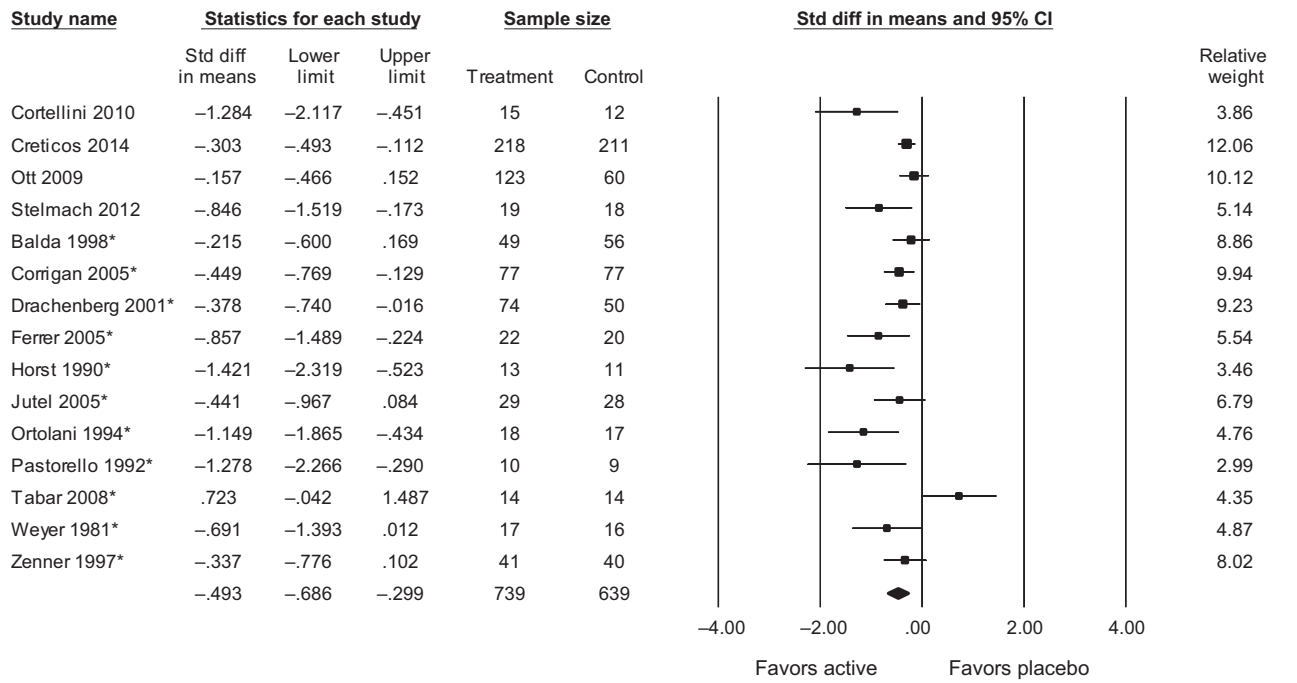


FIGURE 7 Meta-analysis of double-blind RCTs studies comparing combined symptom and medication scores between allergen immunotherapy (AIT) (subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT)) and placebo groups (random-effects model). Heterogeneity: τ^2=.071; χ^2=33.631, *df*=14 (*P*<.002); I^2=58%. Test for overall effect: *Z*=−4.997 (*P*<.001). *denotes SCIT studies

Sensitivity analysis No sensitivity analysis was possible as no studies were judged to be at high ROB.

Publication bias The funnel plot showed evidence of potential publication bias, (Figure S24) which was also suggested by the Begg (*P*=0.005) and Egger (*P*=0.03) tests.

Subgroup analyses Subgroup analyses were undertaken to compare:

- SCIT vs SLIT: SMD −0.51 (95% CI −0.77, −0.26) for SCIT and SMD −0.47 (95% CI −0.81, −0.12) (Figures 8A and B), these analyses showing a benefit from both SCIT and SLIT.
- Children (<18) vs adults (≥18 years) for AIT (SCIT and SLIT): SMD −0.85 (95% CI −1.52, −0.17) (results from one study only) for children and SMD −0.44 (95% CI −0.65, −0.22) for adults (Figures S25A and B), these analyses showing a benefit in both children and adults
- Pre-/coseasonal (short-term treatment) vs continuous treatment in SCIT for pollen: SMD −0.41 (95% CI −0.58, −0.24) for preseasonal and SMD −0.86 (95% CI −1.49, −0.22) for continuous (results from one study only) (Figures S26A and B), these analyses showing a clear benefit from pre-/coseasonal treatment and the suggestion (but not confirming) benefit from continuous treatment
- Modified allergen extracts (allergoids) vs unmodified allergen extracts in SCIT: SMD −0.49 (95% CI −0.79, −0.19) for allergoids and SMD −0.36 (95% CI −0.73, 0.03) (Figures S27A and B), these finding a clear benefit from allergoids and suggesting (but not confirming) a benefit from unmodified preparations.
- Different allergens for AIT (SCIT and SLIT): Grass: SMD −0.41 (95% CI −0.58, −0.24) vs Tree (one study only): SMD −0.26 (95% CI −0.64, 0.13) vs Molds: SMD −0.65 (95% CI −2.06, 0.76) vs Weeds: SMD −0.69 (95% CI −1.24, −0.13) (Figure S28A-D), this showing clear evidence of benefit for grass and tree pollens, and suggesting (but not confirming) evidence of benefit for molds and weeds.

Long-term

We found one SCIT trial[53] and two SLIT trials[109,133]that reported on this outcome. These are described in detail in the supplement. Overall, one of the three trials found evidence of a sustained beneficial effect on combined symptom and medication scores. The one trial at an unclear ROB demonstrated a two-year carryover effect of AIT in the active SLIT group that received AIT four months preseasonally for three consecutive seasons but not for the group which received AIT two months preseasonally.[109,159]

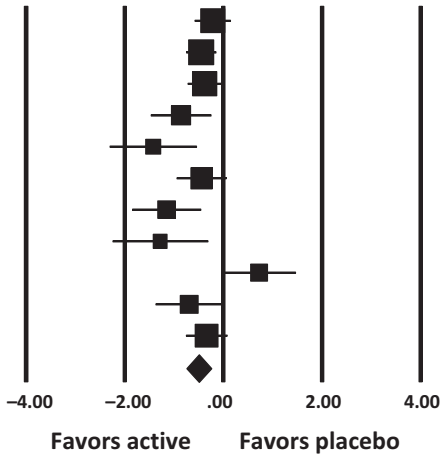
3.3 | Secondary outcomes

3.3.1 | Disease-specific quality of life

Thirty studies reported data on quality of life (QoL): these comprised SCIT (n=17)[19,20,23,28,33-35,45,46,55,58,68-70,72,74,79] and SLIT (n=13)[90,99,104,106,108,110,117,129,130,132,140,145,149] trials (Table S1j and k). The majority of trials (n=29) used one of the disease-specific, validated Rhinitis Quality of Life Questionnaire (RQLQ) instruments. However, one SLIT study (eligible because it reported on other outcomes) used a generic, non-disease-specific tool, the SF-

(A)

Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Balda 1998*	−.215	−.600	.169	49	56	12.39
Corrigan 2005*	−.449	−.769	−.129	77	77	13.59
Drachenberg 2001*	−.378	−.740	−.016	74	50	12.81
Ferrer 2005*	−.857	−1.489	−.224	22	20	8.32
Horst 1990*	−1.421	−2.319	−.523	13	11	5.44
Jutel 2005*	−.441	−.967	.084	29	28	9.92
Ortolani 1994*	−1.149	−1.865	−.434	18	17	7.26
Pastorello 1992*	−1.278	−2.266	−.290	10	9	4.75
Tabar 2008*	.723	−.042	1.487	14	14	6.71
Weyer 1981*	−.691	−1.393	.012	17	16	7.41
Zenner 1997*	−.337	−.776	.102	41	40	11.40
	−.514	−.766	−.261	364	338	



(B)

Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Cortellini 2010	−1.284	−2.117	−.451	15	12	12.33
Creticos 2014	−.303	−.493	−.112	218	211	38.76
Ott 2009	−.157	−.466	.152	123	60	32.48
Stelmach 2012	−.846	−1.519	−.173	19	18	16.43
	−.466	−.810	−.121	375	301	

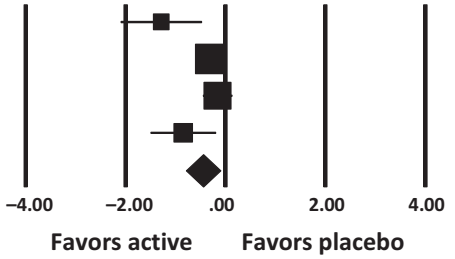


FIGURE 8 Meta-analysis of double-blind RCTs comparing combined symptom and medication scores between (A) subcutaneous immunotherapy (SCIT) and placebo groups and (B) sublingual immunotherapy (SLIT) and placebo groups (random-effects models). (A) Heterogeneity: τ^2=.096; χ^2=23.777, *df*=10 (*P*<.008); I^2=58%. Test for overall effect: *Z*=−3.984 (*P*<.0001). *denotes SCIT studies. (B) Heterogeneity: τ^2=.070; χ^2=8.584, *df*=3 (*P*<.035); I^2=65%. Test for overall effect: *Z*=−2.648 (*P*<.008)

36, and this was therefore not considered further.[140] Due to inconsistencies of reporting data, it was not possible to pool results from all of the studies and no SLIT studies were suitable for inclusion in meta-analysis. Pooling data from the six SCIT studies with suitably reported data derived from the original and standardized RQLQ instruments found a SMD of −0.35 (95% CI −0.74, 0.04), this corresponding to a likely small-to-medium improvement in the AIT group when compared to placebo (Figure 9).

3.3.2 | Allergen challenge models in AIT

A detailed description of environmental exposure chamber, nasal and conjunctival challenge studies is described in the supplement. One SCIT and three SLIT[83,120,121] chamber studies demonstrated the effectiveness of AIT. Results of nasal challenge studies for 15 SCIT[23,24,27,29,30,33,37,43,52,57-59,63,64,75] and 11 SLIT[84,86,87,92,93,122,128,136,139,146,150] (Table S1l) were conflicting making it difficult to make clear conclusions. There was no clear evidence of effectiveness in 12 SCIT[21,23,35,38,42,45,55,62-64,70,72] and four SLIT conjunctival challenges studies[120,127,138,146] (Table S1m).

3.3.3 | Cost-effectiveness

Characteristics of studies

We identified 19 eligible studies that reported on health economic evaluations of SCIT and SLIT in both children and adults (Table S1n).[160-178] Studies were based in a range of countries. Seven of the studies reported results against disease-specific outcome measures while the remaining 12 reported results based on quality-adjusted life years (QALYs). Thirteen of the studies were based on RCT data or meta-analyses of RCT data.[160-169,176-178] Full details are in the supplement.

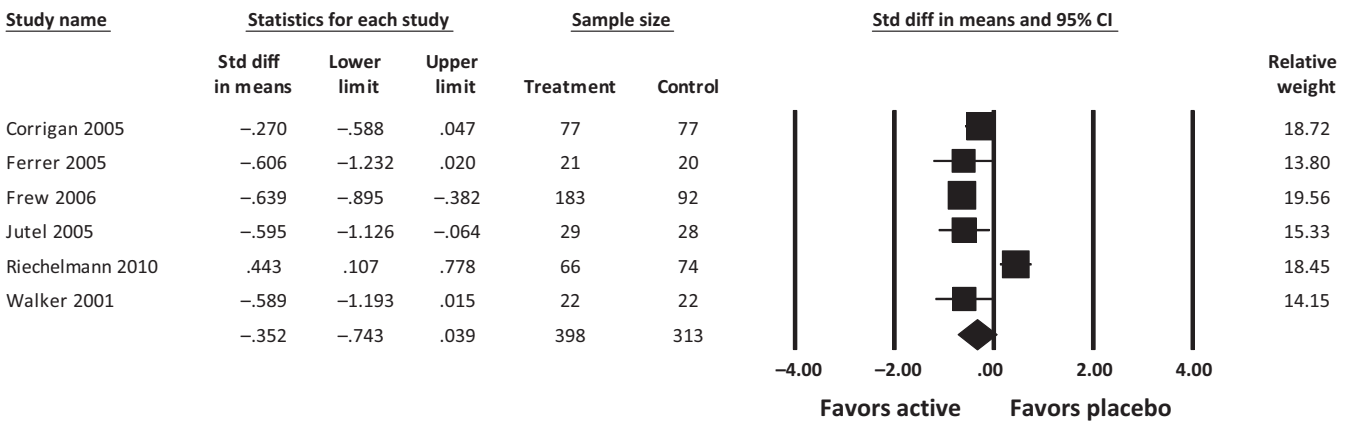


FIGURE 9 Meta-analysis of double-blind RCTs comparing quality of life scores between subcutaneous immunotherapy (SCIT) and placebo groups (random-effects models). Heterogeneity: τ^2=.186; χ^2=28.432, *df*=5 (*P*<.0001); I^2=82%. Test for overall effect: *Z*=−1.764 (*P*<.078)

Quality appraisal

The quality appraisal of the included studies is detailed in Table S1o.

Main findings

In general, the studies found that AIT, and where defined both SLIT and SCIT, were more effective than standard care including pharmacotherapy, but also more expensive. The studies that compared SLIT with SCIT gave very mixed results not allowing a clear conclusion to be drawn that either treatment was necessarily more effective or more costly than the other from a health system perspective. The studies comparing Grazax (SLIT) and Oralair (SLIT) suggested that Oralair is both more effective and cheaper than Grazax.[165,167]

For those studies based on RCT data conducted from a health system perspective and using QALYs as their outcome measure (n=7), we found that:

- Nasser 2008: In patients with both rhinitis and asthma in England the incremental cost-effectiveness ratio (ICER) for SLIT vs standard care was £8816 (€10 851) per QALY at 2005 prices inflated using national health service (NHS) inflation indices (ie, Personal Social Services Research Unit (PSSRU)) to £10 726 (€13 202) per QALY at 2014/15 prices.[177]
- Poulsen 2008: In adult patients with rhinoconjunctivitis in Denmark the ICER for SLIT vs standard care was 134 105 DKK per QALY (no price year was given so we assumed study year of 2008) updating to current prices and £ at 0.1 £ per DKK gave an ICER of £15 294 (€18 824) per QALY at 2014/15 prices.[164]
- Keiding 2007: In a study in adult patients with rhino-conjunctivitis performed in the U.K. ICERs of SCIT were calculated using health care data from Austria, Denmark, Finland, Germany, Netherlands, Sweden. The ICERs of SCIT compared to standard care in 2005 Euro per QALY were 9716, 2586, 13683, 10300, 24519 and 22675, respectively. Updating to current prices and £ at 0.75 GBP per Euro gives ICERs of £8866, £2360, £12486, £9399, £22374 and £20691 per QALY respectively at 2014/15 prices.[162]
- Ronaldson 2014: In 5- to 16-year-olds with rhinoconjunctivitis with or without asthma in the UK, the ICER for SLIT vs standard care was £12 168 (€14 976) per QALY at 2008 prices. Updating to current prices gives an ICER of £13 357 (€16 440) per QALY at 2014/15 prices.[166]
- Westerhout 2012: In patients with rhinoconjunctivitis without asthma in Germany the ICER for SLIT (Oralair) vs standard care was 14 728 euros per QALY at 2011 prices. Converting to current prices and GBP at 0.75 £ per Euro gives an ICER of £11 460 per QALY.[167]
- Verheggen 2015: In patients with rhinoconjunctivitis without asthma in Germany the ICER for SLIT (Oralair) vs SCIT is 12 593 euros per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro gives an ICER of £9627 per QALY[168]
- Reinhold 2016: In patients with rhinoconjunctivitis without asthma in Germany SCIT (Allergovit) is cheaper and more effective than SLIT (Oralair). The ICER for SCIT (Allergovit) standard care is 11 000 euros per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro gives an ICER of £8334 per QALY.[169]

When assessing these results, it was unclear how comparable the patient populations were between the studies; a key factor that impacts the costs and quality of life observed is the proportion of patients who have asthma as well as rhinitis—these proportions were not reported in the studies. Also noteworthy was that the ICERs for AIT seemed to vary substantially between different health systems as demonstrated in Keiding et al.[162] 2007 where ICERs range from £2360 per QALY in Denmark to £22 374 per QALY in the Netherlands suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries.[162]

Overall interpretation

The seven key studies identified, disregarding the caveats about generalizability, suggested that SLIT and SCIT treatment would be considered cost-effective in this patient population in England at the standard NICE cost-effectiveness threshold of £20 000 (€24 616) per QALY. However, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data need to be taken into account when interpreting these results.[162,164,166-169,177]

3.3.4 | Safety

RCTs and case series were eligible for inclusion to consider the safety of AIT.

Randomized controlled trials

Safety data for SCIT and SLIT RCTs are summarized in Table S1p-v. There was a great variation in reporting of adverse events (AEs) and a number of grading scales including WAO and EAACI were used. As detailed in the tables some studies reported limited or unclear data on number of AEs, some studies reported no data on AEs and others reported that no AEs occurred at all through the duration of the trial period. Conversely some studies reported all treatment emergent AEs.

Total AEs We were able to pool data for this outcome for total number of AEs. Safety data for 51 SCIT and SLIT RCTs were pooled to give an overall risk ratio (RR) of experiencing an AE of 1.64 (95% CI 1.43, 1.89) (Figure S3A).

For SCIT studies (n=19), we found an RR of 1.58 (95% CI 1.13, 2.20) of experiencing an AE and for SLIT studies (n=32) an RR of 1.68 (95% CI 1.44, 1.98), (Figure S3B,C) suggesting a comparable safety profile for both modes of AIT.

Systemic AEs We were able to pool data for number of systemic AEs for 39 SCIT and SLIT RCTs to give an overall RR of experiencing a systemic AE of 1.26 (95% CI 1.03, 1.55) (Figure S3D). For SCIT studies (n=15), we found a RR of 1.15 (95% CI 0.67, 2.00) of experiencing a systemic AE and for SLIT studies (n=24) a RR of 1.31 (95% CI 1.05, 1.63) (Figure S3E,F).

We were able to pool data for the number of patients experiencing a systemic AE for SCIT and SLIT RCTs (n=18) to give a RR of 2.37 (95% CI 1.09, 5.16) (Figure S3G).

Local AEs We were able to pool data for local AEs for 39 SCIT and SLIT RCTs to give an overall RR of experiencing a local AE of 1.78 (95% CI 1.51, 2.11) (Figure S3H). For SCIT studies (n=9), we found an RR of 2.21 (95% CI 1.43, 3.41) of experiencing a local AE and for SLIT studies (n=30) an RR of 1.71(95% CI 1.43, 2.05) (Figure S3I,J).

We were able to pool data for the number of patients experiencing a local AE for SCIT and SLIT RCTs (n=17) to give a RR of 1.72 (95% CI 1.32, 2.23) (Figure S3K).

Case series

Seven large case series were identified.[179-185] (Table S1w-y) Local (LR) and systemic (SR) AEs were recorded in a range of treatment protocols, including conventional, rush, ultrarush and cluster. In total 4045 patients were included in these case series however only 3541 were patients with allergic rhinoconjunctivitis; we therefore focused on data for these patients.

The case series were conducted in a number of countries including Spain, Colombia, the USA, Germany and Portugal.

The case series highlighted that where modified allergen extracts were used to deliver AIT this was safer in terms of number of AEs reported compared to unmodified extracts.[180-183]

Safety data from the rush[180] and ultrarush[181,182] protocols were evaluated and are presented in Table S1 w and x. The studies concluded that the frequency of SRs were similar to conventional buildup schedules, but importantly rush and ultrarush protocols were associated with improved patient adherence to treatment by reducing the number of injections required and the cost associated with treatment. Comparable benefits of cluster treatment protocol were also reported in one study.[184] Finally, one case series looked at investigating the number of AEs where patients received either conventional or cluster IT via the SLIT route. AEs were reported in 0.15% of all administered doses in which 9.3% of patients experienced a SR. The study concluded that SLIT was safe in the treatment of allergic rhinoconjunctivitis.[179]

No fatalities were reported in any of these studies.

4 | DISCUSSION

4.1 | Statement of principal findings

This review of a very substantial body of international trial evidence, many of which were judged to be at low ROB, has found clear evidence that AIT improved all three of our primary outcomes—that is, symptom, medication, and combined symptom and medication scores over the short term. These findings were robust to prespecified sensitivity analyses but evidence of potential publication bias was identified for all three primary outcomes. Although the long-term studies are fewer in number, there was a modest evidence-base in support of the effectiveness of AIT in improving symptom scores after treatment discontinuation for both SCIT and SLIT. The evidence was less clear in relation to the impact on medication and combined symptom and medication scores. SCIT improved disease-specific quality of life. We could draw no clear conclusions on the effectiveness of AIT on nasal and conjunctival challenges and on cost-effectiveness which may be cost-effective in an English NHS setting, but due to the poor quality of the studies this needs to be interpreted with caution. AIT increased the risk of AEs for both SCIT and SLIT, but no fatalities occurred.

4.2 | Strengths and limitations

To our knowledge, this is the most comprehensive assessment of AIT in allergic rhinoconjunctivitis ever undertaken. We employed internationally accepted techniques to systematically identify, assess, and synthesize a substantial body of evidence. This involved taking

advantage of and building on other recent systematic reviews focusing on distinct modes of delivering AIT.

The limitations of this review need to be considered. First, despite our extensive searches we may not have uncovered all relevant evidence on this subject. Second, we were limited by the heterogeneity in approaches used to assess outcomes, which meant we were unable to pool data from all trials or undertake all the planned subgroup analyses. Furthermore studies for which data was pooled also showed heterogeneity which may be related to the diverse populations studied, protocols followed, products used and duration of trial period. For the subgroup analyses that were undertaken, there was in some cases imprecision which impacted on our ability to draw clear conclusions. These subgroup analyses were indirect comparisons between SCIT and SLIT and the findings should therefore be cautiously interpreted. Third, because of the heterogeneity in scoring systems used, we undertook meta-analyses using random-effects modeling and pooled data using SMDs, which can be difficult to interpret. The absolute size of the SMD was used to guide assessment of the likely effect size demonstrated.[186] Finally, it needs to be borne in mind that there may have been important differences in effectiveness between specific AIT products. Investigating this issue was however beyond the scope of this review. In terms of safety there was heterogeneity in reporting of AEs with many differing scoring systems used due to this we were unable to report this outcome as originally planned using only the WAO grading system.

4.3 | Implications for policy, practice, and research

Our findings clearly show that AIT is effective in improving the three patient-reported outcomes that represented our primary outcomes, at least over the short term, and that AIT should therefore be considered in the management of patients with allergic rhinoconjunctivitis.

Greater standardization of trial designs and reporting techniques—in particular, in relation to choice of outcomes and their reporting so as to facilitate evidence syntheses and key subgroup analyses, would greatly help to advance the research base underpinning AIT. We therefore appreciate initiatives of the EAACI in, for example, harmonizing and standardizing clinical endpoints in AIT[187] or determining threshold level of relevant pollen seasons for assessing clinical effect sizes.[188] We also wish to highlight the need for additional studies focusing on long-term outcomes and on studies of ILIT and other novel modes of delivery. We hope that future researchers will build on the findings from this systematic review and aim to fill key evidence gaps and areas of continuing uncertainty.

The findings from this review will be used to inform the development of recommendations for EAACI's Guidelines on AIT for Allergic Rhinoconjunctivitis.

5 | CONCLUSIONS

AIT is effective in achieving clinically important short-term improvements in symptom, medication, and combined symptom and medication scores. There is a limited body of evidence on the longer-term effectiveness of AIT in improving symptom scores.

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CONFLICT OF INTERESTS

S. Dhami reports grants from EAACI to carry out the review, during the conduct of the study. U. Nurmatov, S. Arasi, and M. Asaria report payment from Evidence-Based Health Care Ltd during the conduct of the study. G. Roberts has a patent issued: "Use of sublingual immunotherapy to prevent the development of allergy in at risk infants"; and his university has received payments for the activities he has undertaken: giving expert advice to ALK, and presenting at company symposia for ALK, Allergen Therapeutics, and Meda, and serving as a member of an Independent Data Monitoring Committee for Merck. O. Pfaar reports grants and personal fees from ALK-Abelló, Allergopharma, Stallergenes Greer, HAL-Allergy Holding B.V./HAL-Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, Biotech Tools S.A., Laboratorios LETI/LETI Pharma, and Anergis S.A.; grants from Biomay, Nuvo, and Circassia; and personal fees from MEDA Pharma, Sanofi US Services, Mobile Chamber Experts (a GA^{2}LEN Partner), Novartis Pharma and Pohl-Boskamp, outside the submitted work. A. Muraro reports personal fees from Novartis, Meda, and Mylan, outside the submitted work. IJ. Ansotegui reports personal fees from SANOFI, Bayer, Pfizer, FAES FARMA, MIT FARMA, HIKMA, Menarini, and Bial Aristegui, outside the submitted work. M. Calderon has received honorarium in advisory boards for ALK and Hal-Allergy and served as a speaker for ALK, Merck, and Stallergenes Greer. S. Durham reports grants from Regeneron (USA), Biotech Tools, ALK (Denmark), Food Standards Agency (UK), and National Institute of Health Research (UK) and personal fees from Anergis (Switzerland), Circassia (UK), Biomay (Austria), Merck, Allergy Therapeutics (UK), ALK (Hørsholm, Denmark), med update GmbH (Germany), and Allergy Therapeutics, outside the submitted work. R. Gerth van Wijk reports personal fees from ALK-Abelló, Circassia, and Allergopharma, during the conduct of the study. S. Halken reports personal fees from ALK-Abelló and from different companies, for example, Meda, Stallergenes, Allergopharma, and ALK-Abelló, outside the submitted work. E. Hamelmann is giving lectures in industry symposia and takes part in advisory board meetings for the following companies: Boehringer Ingelheim, Novartis, ALK, HAL-Allergy, Bencard, Stallergenes, Leti Pharma, and SymbioPharm. L. Jacobsen reports personal fees from EAMG, outside the submitted work. D. Larenas-Linnemann has no influence in the presented paper. R. Mosges reports personal fees from ALK, Allergopharma, Allergy Therapeutics, Friulchem, Hexal, Servier, Klosterfrau, Bayer, FAES, GSK, MSD, Johnson&Johnson,

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AUTHOR CONTRIBUTIONS

This review was drafted by S. Dhami, U. Nurmatov, and A. Sheikh. It was initially revised following critical review by G. Roberts and O. Pfaar and then by all co-authors. This paper is part of the EAACI AIT guidelines project, chaired by Antonella Muraro and coordinated by Graham Roberts.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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