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REVIEW ARTICLE

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

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Abstract

Background: To inform the development of the European Academy of Allergy and Clinical Immunology's (EAACI) Guidelines on Allergen Immunotherapy (AIT) for allergic asthma, we assessed the evidence on the effectiveness, cost-effectiveness and safety of AIT.

Methods: We performed a systematic review, which involved searching nine databases. Studies were screened against predefined eligibility criteria and critically appraised using established instruments. Data were synthesized using random-effects meta-analyses.

Results: 98 studies satisfied the inclusion criteria. Short-term symptom scores were reduced with a standardized mean difference (SMD) of −1.11 (95% CI −1.66, −0.56). This was robust to a prespecified sensitivity analyses, but there was evidence suggestive of publication bias. Short-term medication scores were reduced SMD −1.21 (95% CI −1.87, −0.54), again with evidence of potential publication bias. There was no reduction in short-term combined medication and symptom scores SMD 0.17 (95% CI −0.23, 0.58), but one study showed a beneficial long-term effect.

For secondary outcomes, subcutaneous immunotherapy (SCIT) improved quality of life and decreased allergen-specific airway hyperreactivity (AHR), but this was not the case for sublingual immunotherapy (SLIT). There were no consistent effects on asthma control, exacerbations, lung function, and nonspecific AHR.

AIT resulted in a modest increased risk of adverse events (AEs). Although relatively uncommon, systemic AEs were more frequent with SCIT; however no fatalities were reported.

The limited evidence on cost-effectiveness was mainly available for sublingual immunotherapy (SLIT) and this suggested that SLIT is likely to be cost-effective.

Conclusions: AIT can achieve substantial reductions in short-term symptom and medication scores in allergic asthma. It was however associated with a modest increased risk of systemic and local AEs. More data are needed in relation to secondary outcomes, longer-term effectiveness and cost-effectiveness.

KEYWORDS
allergen immunotherapy, allergic asthma, cost-effectiveness, effectiveness, safety

1 | BACKGROUND

Asthma is a major public health problem affecting over 300 million people worldwide.[1] Its prevalence and impact are particularly on the rise and it is estimated that by 2025 an additional 100 million people may develop asthma.[2] Asthma is therefore set to become one of the world's most prevalent chronic diseases.

Based on the clinical history, examination and investigative procedures, different asthma phenotypes have been described.[3] The pathogenesis of asthma is extremely complex and several disease endotypes have been suggested.[3,4] Allergic asthma is one of best described asthma phenotypes of primary studies. Allergic sensitization is a strong risk factor for asthma inception and severity in children and in adults.[5]

Current asthma therapies can effectively control symptoms and the ongoing inflammatory process but do not affect the underlying, dysregulated immune response. Thus, they are very limited in controlling the progression of the disease. Allergen immunotherapy (AIT) is the only aetiology-based treatment for allergic diseases capable of disease modification, as demonstrated by prevention of both the onset of new allergic sensitizations and disease progression.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing *Guidelines on Allergen Immunotherapy (AIT) for Allergic Asthma*. We undertook a systematic review of primary studies on the effectiveness, cost-effectiveness and safety of AIT for allergic asthma to inform the formulation of key clinical recommendations.

2 | METHODS

A detailed outline of the methods have previously been published in the protocol of this review.[6] We therefore confine ourselves to a synopsis of the methods employed.

A highly sensitive search strategy was developed, and validated study design filters were applied to retrieve articles pertaining to the use of AIT for allergic asthma from electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Appendix 1). In all cases, the databases were searched from inception to 31 October 2015. Additional papers were located through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field. There were no language restrictions employed.

Inclusion and exclusion criteria are detailed in Box 1.

2.1 | Study selection

All references were uploaded into the systematic review software DistillerSR and underwent de-duplication. Studies were independently checked by two reviewers (SD, FA or AK) against the above inclusion criteria. Any discrepancies were resolved through discussion and, when necessary, a third reviewer was consulted (AS).

2.2 | Quality assessment

Quality assessments were independently carried out on each study by two reviewers (FA, AK, DD, SD or MK). We used the Cochrane Risk of Bias (ROB) tool to assess RCTs,[9] the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies,[10] and the National Institute for Health and Clinical Excellence (NICE) quality assessment tool to critically appraise case series.[11] Any discrepancies were resolved by discussion or arbitration by a third reviewer (AS).

2.3 | Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (FA, AK, HZ, DD or SD) and any discrepancies were resolved by discussion or arbitration by a third reviewer (AS). A descriptive report with summary data tables was produced to summarize the literature. Where clinically and statistically appropriate, meta-analyses were undertaken using random-effects modelling.[12] Where standardized mean difference (SMD) has been used the scale used is 0.2 represents a small effect size, 0.5 a medium effect size and 0.8 a large effect size.[105]

2.4 | Sensitivity and assessment for publication bias

Sensitivity analyses were, where possible, undertaken by comparing the summary estimates obtained by excluding studies judged to be at high ROB with those judged to be at low or moderate ROB.

BOX 1 Inclusion and exclusion criteria

Patient characteristics	Studies conducted on patients of any age with a physician confirmed diagnosis of asthma, plus evidence of clinically relevant allergic sensitization as assessed by an objective biomarker (eg skin prick test or specific IgE), in combination with a history of asthma symptoms due to allergen exposure
Interventions of interest	AIT for different allergens (eg pollens, house dust mites (HDM), animal dander, cockroach and moulds), administered through either subcutaneous (SCIT) or sublingual (SLIT) routes.
Comparator	Placebo or any active comparator.
Study designs	*Effectiveness:* Double-blind randomized controlled trials (RCTs). Originally, we planned to include data from any RCT, irrespective of whether there was blinding. This was changed due to the large 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).
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:* Asthma control; asthma-specific quality of life (QoL); exacerbations; lung function; response to environmental exposure chamber or bronchial allergen challenge; health economic analysis from the perspective of the health system/payer; and safety as assessed by local and systemic reactions.[7,8]
Exclusion criteria	Reviews, discussion papers, nonresearch letters and editorials, animal studies and studies not employing double-blind RCT designs.

Where possible, publication bias was assessed through the creation of funnel plots, and tested by Begg's rank correlation test and Egger's regression test.[13,14]

2.5 | Subgroup analyses

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

2.6 | Registration and reporting

This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42016035372. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review (Appendix 2).

3 | RESULTS

Our search strategy yielded 7490 papers of which 98 studies were eligible; these comprised 89 double-blind RCTs (reported in 94 papers), three cost-effectiveness studies and six case series (see Figure 1).

3.1 | Effectiveness

3.1.1 | Description of studies

The RCTs enrolled a total of 7413 patients. The route of administration of AIT was SCIT (n=54), SLIT (n=34), and SCIT vs SLIT (n=1). The majority of trials reported on the short-term effectiveness of AIT with only one SLIT trial reporting on long-term effectiveness. The 54 SCIT trials (reported in 57 papers) included 2305 patients.[15-70] and the 34 SLIT trials[71-104] (reported in 36 papers) included 5108 patients. SCIT studies included adults (n=24), both children and adults (n=17), and children (n=13). SLIT studies included children (n=20), both children and adults (n=10), and adults (n=4). Allergen extracts administered included HDM, grass, cat, dog, trees, moulds, latex and weeds. Various AIT protocols were utilized. The severity of asthma tended to be mild to moderate. Further details are included in Tables 1-3 and S1a-c.

3.1.2 | Quality assessment

The majority of SCIT trials (n=32) were judged as unclear ROB, seven low ROB and 15 studies as at high ROB (Table S1d). Twenty SLIT studies were assessed to be at high ROB; 13 studies were at

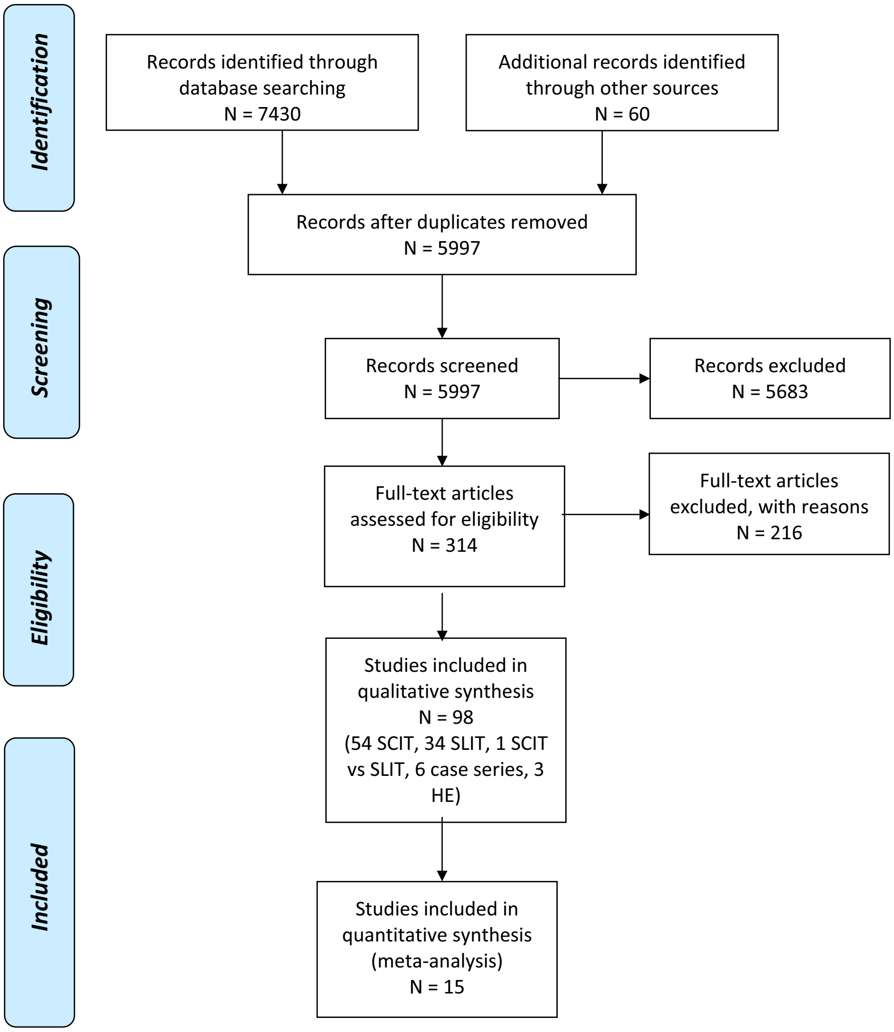

FIGURE 1 PRISMA diagram

TABLE 1 Overview of SCIT trials (n=54 studies in 57 papers)

	Allergen(s) type								Allergen no.		Comparator			AIT protocol										Short-term effectiveness			Long-term effectiveness								
Study author, year, country	Grass pollen(s)	Tree pollen(s)	Weed (s)	Mould (s)	HDM	Cat	Dog	Other (s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Producttype/name(manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Corticosteroid use	Bronchial tests
Aas, 1971, Norway					X				X		X						X					3 y	Two house dust extracts from Nyegaard et Co., Oslo (house dust group A), and from Allergologisk Laboratorium, Copenhagen (House dust B), respectively											X	X
Adkinson, 1997, USA	X	X		X	X			X		X	X						X					2 y	SCIT mixture of seven aeroallergens (HDM ragweed, grass mix, Bermuda grass, white oak, Alternaria, cladosporium, aspergillus) prepared by ALK Laboratories, Copenhagen, Denmark, vs placebo	X	X					X		X	X		X
Alvarez-Cuesta, 1994, Spain						X			X		X						X					1 y	The allergen extract was obtained from Alergia e Inmunologia (Abelló, S.A., Madrid, Spain) and prepared by extracting the raw material (cat dander supplied by Allergon AB Engelholm, Valinge, Sweden)	X	X					X				X	X
Alvarez, 2002, Spain					X				X		X											1 y	*D. pteronyssinus* extract at 10 biological units/mL contained 4 μg/mL of Der p 1 and 2 μg/mL of Der p 2, entrapped in liposomes vs placebo									X			X
Ameal, 2005, Spain					X				X		X						X					1 y	The active group received a modified allergen extract of *D. pteronyssinus*. The modified extract was adsorbed onto aluminium hydroxide	X	X					X	X			X	X
Armentia-Medina, 1995, Spain								X	X		X						X					1 y	Standardized extract of storage mite *Lepidoglyphus destructor* with an activity of 100 BU/mL. Concentration 18%	X										X	X
Arvidsson, 2004, Sweden		X							X		X											1 y	Standardized birch pollen extract (Alutard SQ Betula verrucosa; ALK-Abelló) vs dilute histamine dihydrochloride.									X		X	X
Basomba, 2002, Spain					X				X		X						X					1 y	D pteronyssinus encapsulated in liposomes containing 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, and 3.2 μg of Der p 1	X	X					X				X	X
Blumberga, 2006, Denmark					X				X		X						X					3 y	Subcutaneous SIT with Alutard SQ D							X			X		
Bødtger, 2002, Denmark		X							X		X							X				1 y	High-dose birch pollen extract, commercially available and produced by ALK-Abelló, Hørsholm, Denmark. The content of the major birch pollen allergen Bet v 1 was 12 mg/100 000 SQ-U.	x	x					x					
Bousquet, 1985, France					X				X		X									X		7 wk	Standardized *Dermatophagoides pteronyssinus* extract							x		X		X	X
Bousquet, 1990, France	X								X		X		X							X		1 y	High- and low-dose grass extract.	X						X					
Cantani, 1996 Italy	X			X	X	X	X			X	X											3 mo	Mixture of grass, other pollen, mould, house dust mite and cat and dog dander	X	X										X
Chakraborty, 2006, India		X							X		X						X					2 y	*P. sylvestris* pollen extract standardized with one of its principal allergenic fraction	X	X					X		X			
Creticos, 1996, USA			X						X		X						X					2 y	Lyophilized extract of short ragweed pollen (Greer Laboratories, Lenoir, N.C.)	X	X					X					

(Continues)

TABLE 1 (Continued)

Study author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT protocol										Producttype/name(manufacture)	Short-term effectiveness			Long-term effectiveness			Safety	Quality of life	Lung function	Corticosteroid use	Corticosteroid use	Bronchial tests
	Grass pollen(s)	Tree pollen(s)	Weed (s)	Mould (s)	HDM	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						
Dolz, 1996, Spain	X								X		X									X		3 y	The grass pollen allergen extract Alutard SQ. aluminium hydroxide-adsorbed allergens PDL (Phleum, Dactylis, Lolium), was used.												X
Dreborg, 1986, Sweden and Finland				X					X		X							X				10 mo	Purified and standardized *Cladosporium herbarum* allergen preparation.	X	X					X					X
D'Souza, 1973, UK					X				X		X						X					3 mo	The *D. pteronyssinus* extract was prepared by Beecham Research Laboratories.	X	X					X					
Franco, 1995, Italy					X				X		X						X					15 mo	Alum absorbed Alpare *D. pteronyssinus* extract	X	X					X				X	X
Gaddie, 1976, UK					X				X		X						X					1 y	Tyrosine-adsorbed depot form of *D. pteronyssinus* vaccine (Migen, Bencard)	X	X					X		X			
Garcia-Robaina, 2006, Spain					X				X		X						X					54 wk	The active group received a mixture of modified allergen extracts containing 50% *D. pteronyssinus* and 50% *D. farinae*	X	X					X		X		X	X
Haugaard, 1992, Denmark						X	X			X	X						X					5 mo	Extracts used for diagnosis and treatment were Pharmalgen® cat epithelium extract and dog dander extract (Pharmacia AB, Uppsala, Sweden. AEK, Hørsholm, Denmark).							X		X		X	X
Hedlin, 1999, Denmark	X	X			X	X				X	X		X				X					3 y	Partly purified and standardized extracts of cat dander, Dermatophagoides pteronyssinus, timothy pollen, and birch pollen were provided by ALK (Hørsholm, Denmark).							X		X			X
Hui, 2014, China					X						X	X					X					3 y	The SCIT treatment was initiated at a dosage of 20 U/mL, and was continued weekly with an increase in the dosage each week	X						X		X	X		
Kuna, 1989, Poland	X								X		X						X					1 y	Glutaraldehyde-modified, tyrosine-adsorbed grass pollen (Pollinex, Bencard Allergy Service, Brentford, Middlesex, England)	X						X					
Kuna, 2011, Poland				X					X		X											3 y	Standardized A. alternata extract (Novo-Helisen Depot, A. alternata 100%; Allergopharma Joachim Ganzer KG, Reinbek, Germany) in a depot formulation with aluminium hydroxide	X	X					X	X				
Lewis, 1971 UK					X				X				X		X							6-9 mo	HDM *D. farinae* 0.002% to 0-1% w/v	X									X		
Leynadier, 2000, Germany								X	X		X									X		1 y	Standardized latex extract (Stallergenes)	X											
Maestrelli, 2004, Italy					X				X		X						X					4 y	A 1:1 mixture of *D. pteronyssinus* and *D. farinae* extracts adsorbed to aluminium hydroxide in normal saline solution (ALK-Abelló, Madrid, Spain)	X	X							X			
Malling, 1986, Sweden				X					X		X							X				1 y	Lyophilized, partially purified and biologically standardized preparation of Cladosporium herbarum (Pharmalgen®, Pharmacia, Uppsala, Sweden)												X

(Continues)

TABLE 1 (Continued)

Study author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT protocol										Short-term effectiveness			Long-term effectiveness								
	Grass pollen(s)	Tree pollen(s)	Weed (s)	Mould (s)	HDM	Cat	Dog	Other (s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Producttype/name(manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Corticosteroid use	Bronchial tests
Malling, 1987, Sweden2nd paper original study 1986				X					X		X							X				1 y	Lyophilized, partially purified and biologically standardized preparation of Cladosporium herbarum (Pharmalgen, Pharmacia, Uppsala, Sweden) was used.												
Marques, 1978, Italy					X				X		X						X					14 mo	Six syringes numbered in order of dose, each containing 0.5 mL of *D. pteronyssinus* extract absorbed into tyrosine	X						X					
Mosbech, 1989, Denmark					X				X				X				X					2 y	Biologically standardized and purified unmodified Dp extract (Pharmalgen). The mPEG-modified Dp extract was produced by coupling activated mPEG-succinate to the unmodified Dp extract. A buffered solution of isotonic saline containing 0.3 mg/mL albumin, 0.4% phenol, and phosphate 0.95 mg/mL was used for mPEG-modified extract.	X	X										
Mosbech, 1990, Denmark					X				X				X									2 y	Single batch of unmodified, purified Dp extract (Pharmalgen) biologically standardized was used. By RAST inhibition, 10-11 000 BU of this extract equated 100 000 SQ-U of a similar mite allergen extract (Aquagen, ALK, Hørsholm, Denmark). Part of this batch was modified with mPEG (3000 Da). The unmodified extract was reconstituted in a diluent containing aluminium hydroxide, whereas no such additive was present in the buffered saline used for the mPEG-modified extract.							X					
Newton, 1979, UK					X				X		X											15 mo	Alum-precipitated *D. farinae*									X			
Ohman, 1984, USA						X			X		X						X					3 mo	Active-treatment vials reconstituted in 50% glycerine to a concentration of 13 units of cat allergen 1 per millilitre							X		X		X	X
Olsen, 1997, Denmark					X				X		X						X					1 y	Active treatment with extracts of either Dermatophagoides pteronyssinus (Dpt) or *D. farinae* (Dfa) (Alutard® SQ, ALK, Denmark)	X	X					X		X			X
Ortolani, 1984, Italy	X								X		X						X					6 mo	Aqueous lyophilized extract (Hollister-Stier, Spokane, Washington) of 89 velvet, 1/3 sweet vernal, and 89 timothy grass pollen	X											
Pauli, 1984 (not stated. Authors from France and UK)					X				X		X						X					1 y	Dpt tyrosine-adsorbed extract	X	X										
Pene, 1998 France						X			X		X											6 wk	Fel d 1 peptides												X
Price, 1984, UK					X				X		X						X					2 y	Tyrosine glutaraldehyde-modified *D. pteronyssinus* antigen, "Migen," Bencard.		X										
Rak, 2001, Sweden		X							X		X		X				X						Standardized depot preparations of birch pollen allergen extract (Alutard SQ, ALK-Abelló) containing water-soluble allergen extract and aluminium hydroxide	X	X									X	X
Reid, 1986, USA	X								X				X				X					8 mo	Seven grass mix in serum, plus other allergens specific to individuals	X	X					X					

(Continues)

TABLE 1 (Continued)

Study author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT protocol										Short-term effectiveness			Long-term effectiveness								
	Grass pollen(s)	Tree pollen(s)	Weed (s)	Mould (s)	HDM	Cat	Dog	Other (s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Producttype/name(manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Corticosteroid use	Bronchial tests
Roberts, 2006, UK	X								X		X							X				2 y	Alutard SQ P. pratense (ALK-Abelló) was used. This is an alum-adsorbed preparation of pollen from P. pratense with a recommended dose of 100 000 SQ-U.	X	X					X		X	X		
Sabbah, 1991, France					X				X		X						X					180 d	Alpha-Fraction-Retard-*D. pteronyssinus*	X	X					X					
Smith, 1971, UK					X				X				X				X						HDM extract	X	X					X					
Sundlin, 1986, Sweden						X	X			X	X						X					18 mo	Partially purified, standardized allergenic extracts of cat or dog dander							X				X	X
Tabar, 2008, Spain				X					X		X						X					1 y	Metabolic extract of A. alternata that had been biologically standardized	X	X					X		X			
Taylor, 1978, USA						X			X		X						X					4 mo	1.6 mg/mL cat allergen							X		X			
Taylor, 1978, UK					X				X		X						X					10 wk	HDM fortified house dust vaccine							X		X			
Valovirta, 1984, Finland							X		X		X						X					1 y	Commercial standardized aluminium hydroxide bound dog dander extract (Alutard SQ)											X	X
Valovirta, 1986, Finland 2nd paper original study 1984							X		X		X						X					1 y	Commercial standardized aluminium hydroxide bound dog dander extract (Alutard SQ)	X						X					
Van Bever, 1992, Belgium					X				X		X								X			1 y	Aqueous extract of *Dermatophagoides pteronyssinus* (10 BU/mL)	X								X			X
Van Metre, 1988, USA						X			X		X						X					2 y	Cat allergenic extract ALK 1209/229452 was supplied by Allergologisk Laboratories, Copenhagen, Denmark							X		X		X	X
Vidal, 2011, Spain					X				X		X											4 mo	*D. pteronyssinus* extract with the major allergens Der p 1 and 2		X					X			X		
Wang 2006 China					X				X		X											52 wk	Dermatophagoides pteronyssinus extract	X	X					X		X	X		X
Warner, 1978 UK					X				X		X											1 y	*D. pteronyssinus* absorbed into tyrosine ("Migen," Bencard).	X	X					X			X		X

AIT, allergen-specific immunotherapy; d, day; HDM, house dust mite; mo, month; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; wk, week; y, year.

TABLE 2 Overview of SLIT trials (n=34 studies in 36 papers)

	Allergen(s) type								Allergen number		Comparator			AIT protocol										Short-term effectiveness			Long-term effectiveness								
Study author, year, country	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Product type/Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial tests
Alvarez-Cuesta, 2007, Spain						X			X		X						X					1 y	Aqueous solution of standardized semipurified cat dander extract	X	X	X									
Bachelier, 2001, Turkey					X				X		X						X					26 wk	*Dermatophagoides* (*D. pteronyssinus*)+*Dermatophagoides farinae* (*D. farinae*) 50/50 extract	X	X					X		X	X		X
Bousquet, 1999, France					X				X		X						X					108 wk	HDM SLIT	X	X	X				X	X	X	X		X
Caffarelli, 2000, Italy	X								X		X						X					13-wk and 9-wk follow-up post-treatment	Grass pollen tablet (33% Holcus lanatus, 33% Phleum pratense and 33% Poa pratensis)	X	X	X				X					
Cao, 2007, China					X				X		X						X					3 mo	*Dermatophagoides farinae* drops		X					X		X	X		
Dahl, 2006, Denmark and Sweden	X								X		X			X	X		X					19.5 wk	Timothy grass (Phleum pratense) GRAZAX tablet 75000 SQ-T once daily	X	X										
De Blay, 2014, Denmark, Germany, Italy, Spain, UK, Sweden, France and Poland					X				X		X		X				X					1 y	Oral lyophilisates containing standardized extracts of *D. pteronyssinus* and *D. farinae* in a 1:1 ratio. One development unit corresponds to 1 SQ-HDM			X				X	X	X	X		
Devillier, 2015, China					X				X		X						X					"52 wk (+12 wk baseline period before randomisation)"	HDM SLIT (*D. pteronyssinus* and *D. farinae*), approximately 28 mcg Der p 1 and 50mcg Der f 1 daily (300 IR)							X	X	X		X	
Drachenberg, 2001, Germany	X								X		X						X					6 mo	Standardized allergen extract (ORALVAC birch n = 21 resp. grass/rye = 28)			X					X				
Durham, 2012	X								X		X			X	X		X					5 y (3 Rx, 2 follow-up)	Timothy grass (Phleum pratense) GRAZAX tablet 75000 SQ-T once daily						x						
Gomez Vera et al., 2005, Mexico					X				X		X						X					6 mo	Dermatophagoides pteronyssinus 1 standardized allergens (IPI-ASAC, Mexico) at a total dose of 10 469 UBE		X					X		X		X	
Ippoliti, 2003, Italy						X			X		X						X					26 wk (with 3-mo run-in)	HDM SLIT (*D. pteronyssinus*), maintenance dose 5 drops of 10 BU/mL 3 times a week	X								X			
Leng, 1990, unclear country			X					X	X		X						x					7.14 wk (13 wk post-treatment follow-up)	Artemisia pollen SLIT daily updosing to a maximum of 16 416 PNU. Cumulative dose 396 652.06 PNU							X					X
Lewith, 2002, UK					X				X		X										X	16 wk	Homoeopathic HDM SLIT administered on 3 occasions over 24 hours. Dose 30 dilutions of 1:100								X	X			
Lue, 2006, Taiwan					X				X		X						X					24 wk (2-wk post-treatment follow-up)	HDM SLIT daily with 3 wk initiation phase. Maximum 20 drop dose of 300 IR/mL. Cumulative dose of 41 824 IR	X	X							X			
Ma, 2010, China					X				X			X	X				X					1 y	SLIT immunotherapy with Der F drops	X						X		X	X		
Ma, 2014, China					X				X		X						X					1 y	SLIT immunotherapy with Der F drops		X					X					
Moreno-Ancillo, 2007, Spain	X							X		X	X						X					248 d	Biologically standardized by major allergens and quantified in micrograms, without updosing	X	X	X									

(Continues)

TABLE 2 (Continued)

Study author, year, country	Allergen(s) type								Allergen number		Comparator			AIT protocol										Product type/Name (manufacture)	Short-term effectiveness			Long-term effectiveness								
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	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	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial tests
Mosbech, 2014, Denmark, Germany, Italy, Spain, UK, Sweden, France and Poland					X				X		X		X				X					52 wk (1 y treatment duration)	Oral lyophilisates containing standardized extracts of *D. pteronyssinus* and *D. farinae* in a 1:1 ratio. Three active strengths were investigated: 1, 3, and 6 SQ-HDM. The units were designated in development units. One development unit corresponds to 1 SQ-HDM.	X						X	X	X	X	X	
Mosges et al., 2010, Germany	X								X		X										X	9 mo	Standardized birch pollen (Betula alba) allergen extract. Ultrarush high-dose SLIT titration regimen reaching the maintenance dose of 300 IR within 90 min (30-90-150-300 IR)							X		X			
Niu, 2006, Taiwan					X				X		X		X									24 wk (+2-wk off-treatment follow-up)	HDM SLIT (*D. pteronyssinus* and *D. farinae*), incremental dosing up to maintenance dose (cumulative dose ~ 41 824 IR, which was equivalent to 1.7 mg D.p. and 3.0 mg D.f.)	X	X					X		X			
Pajno, 2000, Italy					X				X		X		X									104 wk	HDM SLIT (*D. pteronyssinus*), incremental dosing schedule followed by maintenance 2.4 mg Der p 1 and 1.2 mg Der p 2 per week (in 3 doses/wk)		X	X				X				X	
Pajno, 2002, Italy									X		X		X									56 wk (with 52 wk off-treatment follow-up)	Parietaria pollen SLIT (Parietaria judaica), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg)	X	X										
Pajno, 2004, Italy			X					X	X		X						X					56 wk (with 52 wk off-treatment follow-up)	Parietaria pollen SLIT (Parietaria judaica), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg)									X			X
Pham-Thi, 2007, France					X				X		X						X					78 wk	HDM SLIT (*D. pteronyssinus* and *D. farinae*), updosing for 2 wk up to 300 IR concentration once daily (average cumulative dose was 155 000 IR, corresponding to 6.9 mg Der p 1 and 14.7 mg Der f 1)	X	X					X	X	X	X		
Reilly, 1994, UK				X	X			X	X		X						X					4 wk (with 4-w "optional" post-treatment follow-up)	Homoeopathic SLIT (allergen varied, decided on case-by-case basis; HDM (84.6% of participants); feathers (7.7%); mixed moulds (7.7%)). Three doses in 24 hours, then optionally repeated at 4 wk (according to patient choice)			X						X			X
Reinert, 1983, Germany	X								X		X						X					2 y	Troponholistersteir			X									

(Continues)

TABLE 2 (Continued)

	Allergen(s) type								Allergen number		Comparator			AIT protocol												Short-term effectiveness			Long-term effectiveness								
Study author, year, country	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Product type/Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial tests
Stelmach, 2009, Poland	X								X		X										X	104 wk	Grass pollen SLIT (*Dactylis glomerata*, Anthoxanthum odoratum, Lolium perenne, Poa pratensis, Phleum pratense). Ultrarush period (total of 240 IR). At the beginning of the next day, every morning before breakfast, received 4 puffs (120 IR) for 6 mo. Cumulative dose 43 800 IR	X	X					X		X			X
Tian, 2014, China					X				X		X						X					48 wk	HDM SLIT (*D. farinae*), titrated up over the first 4 wk to 333 mcg/mL once daily	X											
Virchow, 2016, Germany					X				X		X											20 mo (11 August 2011 to 24 April 2013)	HDM SLIT tablet contains extract from two species of cultivated HDM (*D. pteronyssinus* and *D. farinae*), produced in a standardized process with a 1:1:1:1 ratio of the major allergens (Group 1 allergens of *D. farinae* and *D. pteronyssinus* and Group 2 allergens of *D. farinae* and *D. pteronyssinus*), and formulated as rapidly dissolving oral lyophilisate for sublingual administration (ALK).	X						X				X	
Vourdas, 1998, Greece		X							X		X											104 wk (2 y)	Olive pollen SLIT, daily updosing then each morning pre- and coseasonally from January to July for 2 y up to a maximum of 20 drops of 300 IR (total 30 000 IR/y)	X	X					X		X			
Wang, 2014, China		X							X		X											52 wk (+12 wk baseline period before randomisation)	HDM SLIT (*D. pteronyssinus* and *D. farinae*), approximately 28 mcg Der p 1 and 50 mcg Der f 1 daily (300 IR)	X	X					X	X	X	X		
Wood, 201, USA and UK								X	X		X			X		X						13 wk	Greer German cockroach extract							X					
Zhang, 2013, China					X				X			X										36 mo	Standard *Dermatophagoides farinae* drops (1~4) usage: 1~3 were for increasing period of treatment for 3 wk, 1 times a day.												
Zhang, 2015, China					X				X			X										36 mo	Dermatophagoides farinae drop (1 drop/time and 1 time/ day)												
Zheng et al., 2012, China					X				X			X										36 mo	Standard *Dermatophagoides farinae* drops												

AIT, allergen-specific immunotherapy; d, day; HDM, house dust mite; mo, month; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; wk, week; y, year.

TABLE 3 Overview of SCIT vs SLIT trials (n=1)

Study author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT protocol										Short-term effectiveness			Long-term effectiveness								
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other (s)	Single	Multiple	Placebo	Routine care	Active	Preseasonal	Coseasonal	Continuous	Conventional	Cluster	Semirush	Rush	Ultrarush	Rx duration	Product type/Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score	Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations EX	Bronchial tests
Yukselen, 2012, Turkey					X				X		X		X				X						HDM (*D. pteronyssinus* and *D. farinae*) (50/50) for sublingual and subcutaneous administration	X	X					X		X			

unclear ROB; and one study at low ROB (Table S1e). The one SCIT vs SLIT study was judged to be at a low ROB (Table S1f).

3.2 | Primary outcomes

3.2.1 | Symptom scores

Short-term

Fifty-eight (36 SCIT and 22 SLIT) trials reported on the effect of symptoms at the end of the AIT treatment period. We were able to pool data from 15 SCIT and SLIT trials with placebo as comparator. The metaanalysis showed that AIT improved symptom scores with a standardized mean difference (SMD) of −1.11 (95% CI −1.66, −0.56; Figure 2), these suggesting a large effect of AIT.[105]

Sensitivity analysis By excluding studies at high ROB sensitivity analysis confirmed the effect of AIT on asthma symptom scores: SMD −1.44 (95% CI −2.14, −0.74; Fig. S2a).

Publication bias The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Fig. S2b) Publication bias was also suggested by the Egger test (*P*=0.024). There were insufficient studies to undertake the Begg test.

Subgroup analyses

- Children (<18 years) vs adults (≥18 years): SMD −0.58 (95% CI −1.17, −0.01) in children and SMD −1.95 (95% CI −3.28, −0.62) in adults (Figure 3), supporting AIT effectiveness in both children and adults.
- SCIT vs SLIT: the analyses found that SCIT is effective with SMD −1.64 (95% CI −2.51, −0.78) and suggested (but did not confirm) that SLIT was effective SMD −0.35 (95% CI −0.75, 0.05; Figure 4); this indirect comparison suggested that SCIT was more effective than SLIT.
- Treatment duration: SMD −1.15 (95% CI −1.77, −0.53) in those treated for <3 years and SMD −0.79 (95% CI −1.10, −0.49) in those treated for ≥3 years (Fig. S2c), these analyses finding that both treatment durations were effective.
- Mild/moderate vs moderate/severe disease: this subgroup analyses found that AIT is effective for mild/moderate asthma SMD −1.00 (95% CI −1.81, −0.19) and suggested (but did not confirm) a possible benefit in those with moderate/severe disease SMD −0.23 (95% CI −0.89, 0.43; Fig. S2d)
- Individual allergens: this subgroup analyses found evidence of benefit for AIT with HDM SMD −1.41 (95% CI −2.27, −0.55), grass pollen SMD −1.18 (95% CI −2.17, −0.20) and cat/dog dander (SMD −0.77 (95% CI −1.48, −0.06), suggested (but did not confirm) benefit for tree pollen SMD −0.24 (95% CI −0.91, 0.42), and found no benefit for mould SMD 0.36 (95% CI −0.39, 1.11; Fig. S2e)
- Monosensitized/mono-allergic vs polysensitized: there is evidence of AIT benefit in monosensitized/mono-allergic patients SMD

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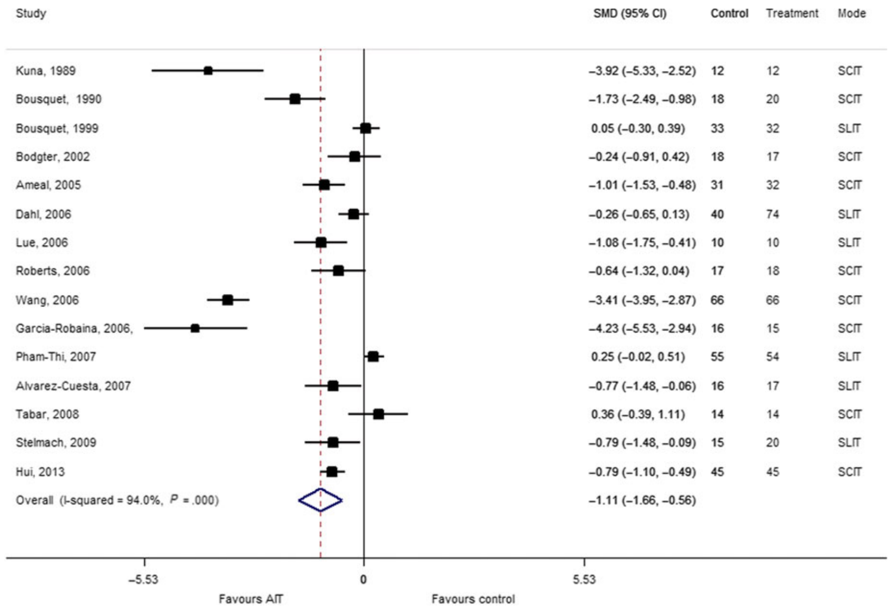
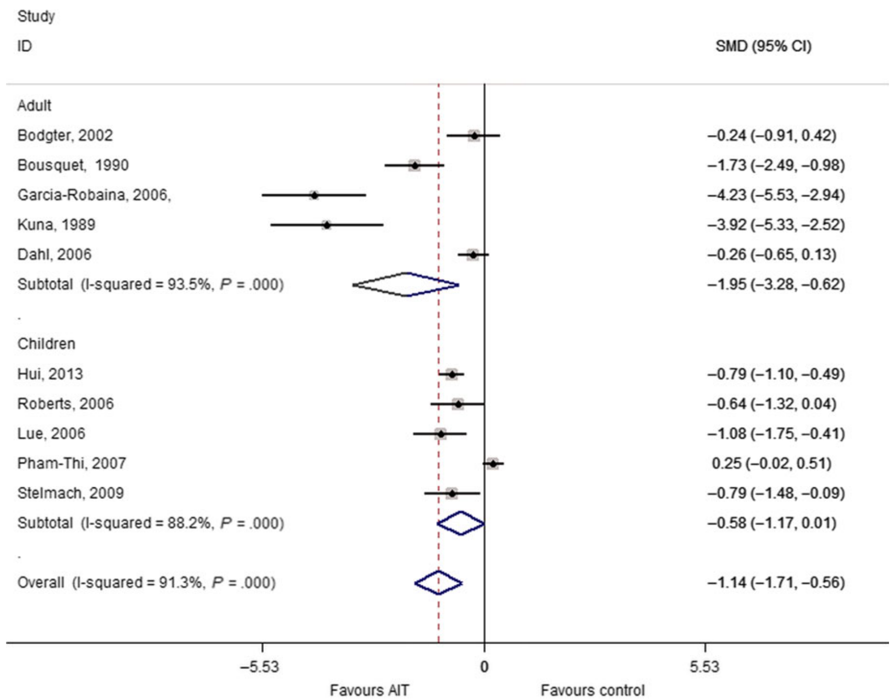


Test of ES = 0: z = 3.96 P = .000
Heterogeneity chi-squared = 234.28 (d.f. = 14) P = .000
I-squared (variation in ES attributable to heterogeneity) = 94.0%
Estimate of between-study variance Tau-squared = 1.0488

FIGURE 2 Meta-analysis of double-blind RCTs for symptom scores comparing AIT (SLIT and SCIT) and placebo groups (random-effects model)



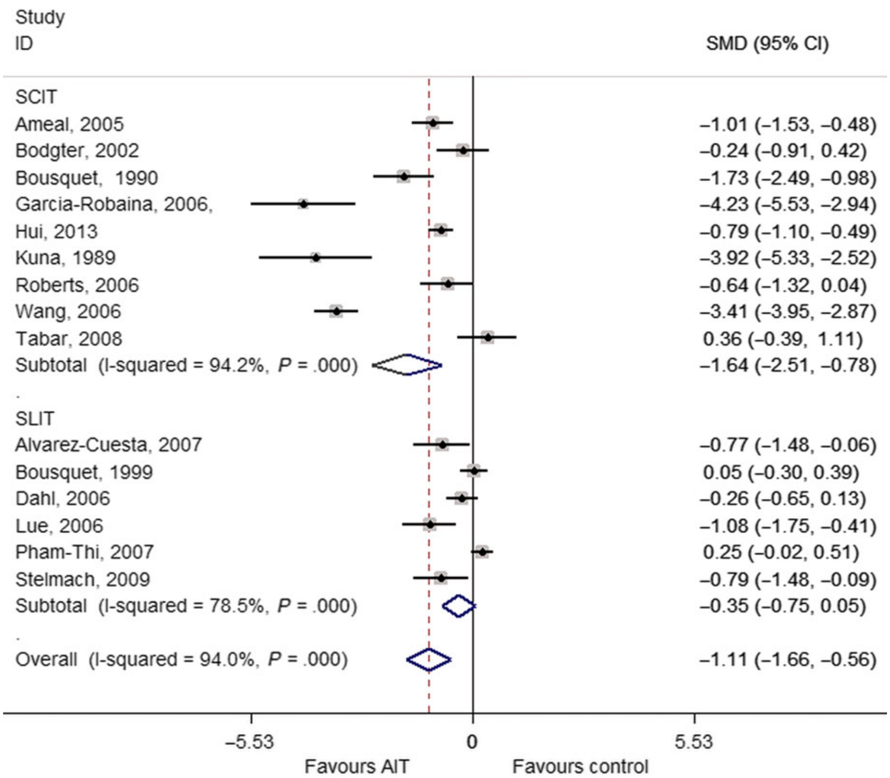
Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	*P*	Isquared**	Tau-squared
Adult	61.83	4	.000	93.5%	2.0670
Children	34.02	4	.000	88.2%	0.3750
Overall	104.04	9	.000	91.3%	0.7215

Significance test(s) of ES = 0

Adult	z = 2.87	*P* = .004
Children	z = 1.93	*P* = .054
Overall	z = 3.87	*P* = .000

FIGURE 3 Meta-analysis of double-blind RCTs, comparing symptom scores between AIT (SLIT and SCIT) and placebo groups in children <18 vs adults ≥18 y (random-effects model)



	Heterogeneity Statistic	degrees of freedom	*P*	Isquared**	Tau-squared
SCIT	137.11	8	.000	94.2%	1.5937
SLIT	23.26	5	.000	78.5%	0.1810
Overall	234.28	14	.000	94.0%	1.0488

SCIT	z = 3.71	*P* = .000
SLIT	z = 1.71	*P* = .087
Overall	z = 3.96	*P* = .000

FIGURE 4 Meta-analysis of double-blind RCTs, comparing symptom scores between SCIT vs SLIT (random-effects model)

−4.23 (95% CI −5.53, −2.94) and a suggested benefit (but not confirmed) for polysensitized patients SMD −0.31 (95% CI −0.65, 0.04; Fig. S2f)

Long-term

No studies reported on the long-term effectiveness of AIT on symptom score.

3.2.2 | Medication scores

Short-term

Forty-two (28 SCIT and 14 SLIT) studies reported on medication scores. Pooling of data with placebo as the comparator was possible for 10 studies. Meta-analysis found evidence that AIT improved medication scores (ie reduced medication use) with an SMD of −1.21 (95% CI −1.87, −0.54; Figure 5), this corresponding to a large effect.

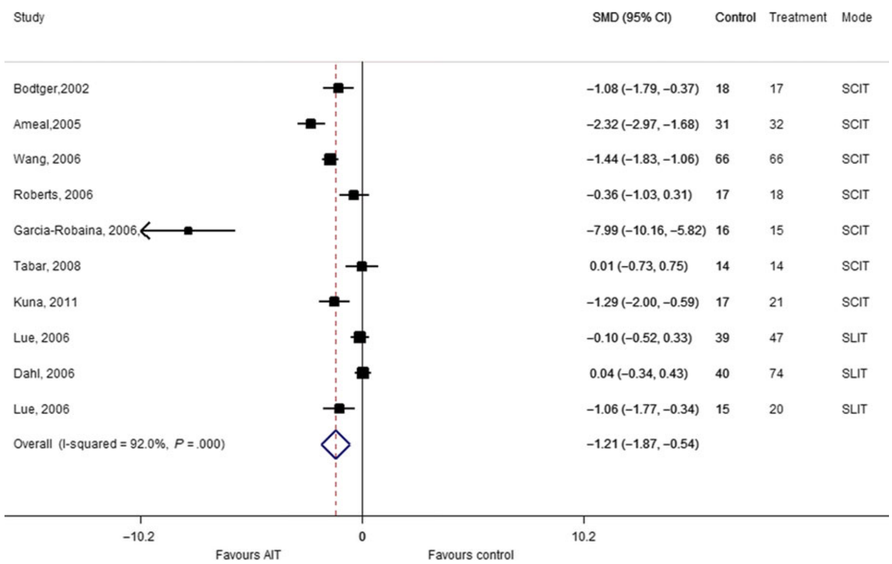
Sensitivity analysis Sensitivity analysis for this outcome was not possible as no studies were found to be at high ROB.

Publication bias The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Fig. S2g), but this was not confirmed by the Egger test (*P*=.09). There were insufficient studies to undertake the Begg test.

Subgroup analyses

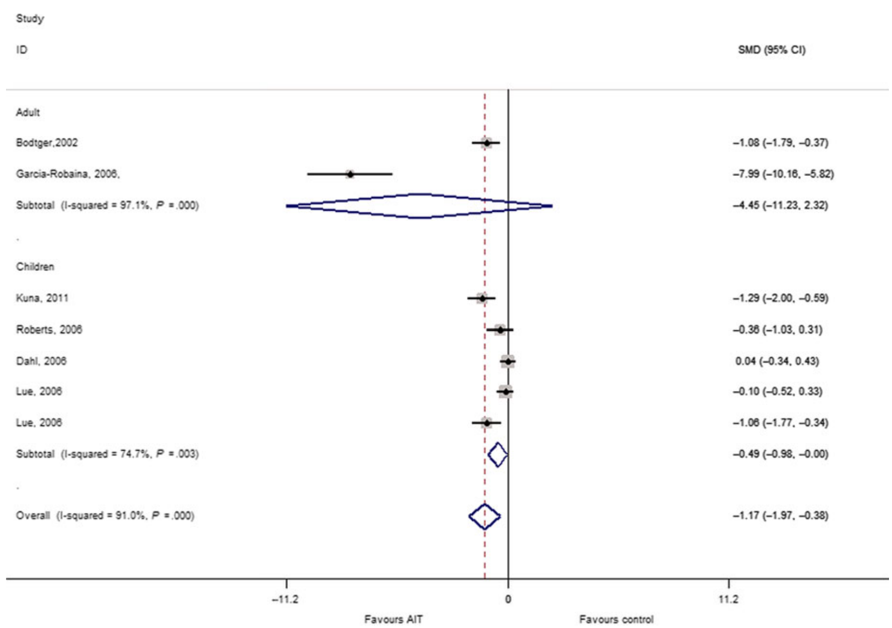
- Children (<18 years) vs adults (≥18 years): there is evidence for benefit in children SMD −0.49 (95% CI −0.98, 0.00) and a suggested benefit (but not confirmed) in adults SMD −4.45 (95% CI −11.23, 2.32; Figure 6)
- SCIT vs SLIT: SMD −1.65 (95% CI −2.52, −0.79) for SCIT and SMD −0.29 (95% CI −0.82, 0.24) for SLIT (Figure 7), these analyses showing benefit of SCIT and suggesting (but not confirming) benefit from SLIT.
- Mild/moderate vs moderate/severe disease: SMD −1.59 (95% CI −2.48, −0.70) for mild/moderate disease and SMD −0.36 (95% CI −1.03, 0.31; Fig. S2h), these analyses showing a benefit in those with mild/moderate disease and suggesting (but not confirming) benefit in those with moderate/severe disease.
- Treatment duration: SMD −1.21 (95% CI −1.94, −0.49) for those treated for <3 years and SMD −1.29 (95% CI −2.00, −0.59) for those receiving ≥3 years of treatment (Fig. S2i), these analyses showing evidence of benefit in both groups.

- Individual allergens: this subgroup analysis demonstrated a benefit of AIT with HDM (SMD −2.10 (95% CI −3.29, −0.91) and tree pollen (one study) (SMD −1.08 [95% CI −1.79, −0.37]) and suggested (but not confirmed) a benefit for, grass pollen (SMD −0.06 [95% CI −0.41, 0.28]) and moulds (SMD −0.65 [95% CI −1.92, 0.62; (Fig. S2j]
- Monosensitized and mono-allergic vs polysensitized: SMD −1.18 (95% CI −1.16, 0.13) in monosensitized and mono-allergic and the polysensitized group (SMD −0.36 (95% CI −2.11, 0.25)) in the polysensitized group (Fig. S2k) these analyses suggesting (but not confirming) benefit in both groups.



Test of ES = 0 : z = 3.56 P = .000
Heterogeneity chi-squared = 112.48 (d.f. = 9) P = .000
I-squared (variation in ES attributable to heterogeneity) = 92.0%
Estimate of between-study variance Tau-squared = 0.9967

FIGURE 5 Meta-analysis of double-blind RCTs, comparing medication scores between AIT (SLIT and SCIT) and placebo groups (random-effects model)



	Het.stat.	df	P	I-squared**	Tau-squared
Adult	35.08	1	.000	97.1%	23.2029
Children	15.79	4	.003	74.7%	0.2244
Overall	66.41	6	.000	91.0%	0.9722

Adult	z = 1.29	P = .197
Children	z = 1.96	P = .050
Overall	z = 2.89	P = .004

FIGURE 6 Meta-analysis of double-blind RCTs, comparing medication scores between AIT (SLIT and SCIT) and placebo groups in children <18 vs adults ≥18 y (random-effects model)

Long-term

No studies reported on the long-term effectiveness of AIT on medication score.

3.2.3 | Combined symptom and medication scores

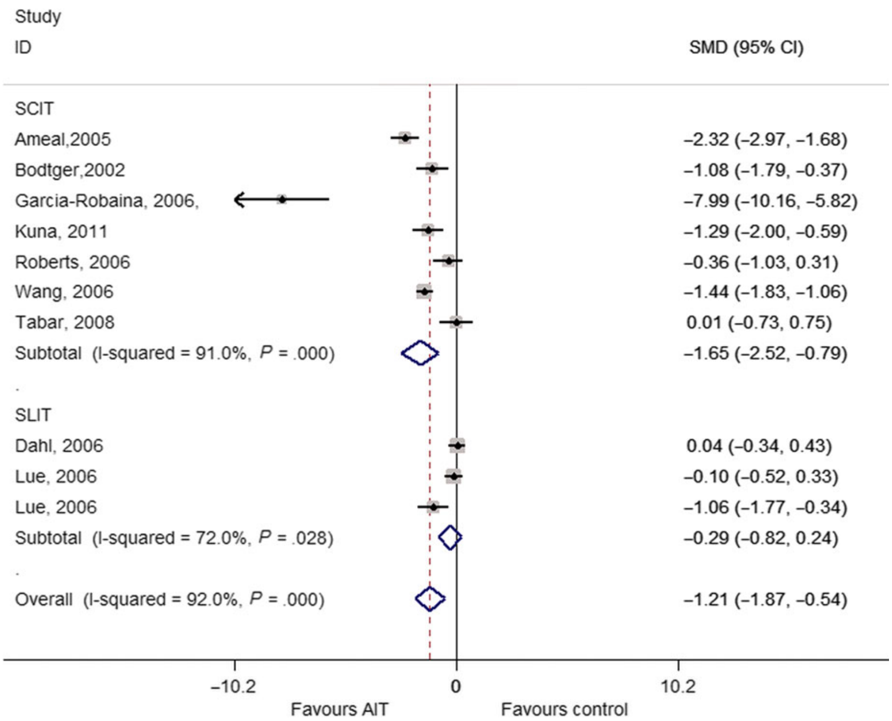
Short-term

Six studies (two SCIT, three SLIT studies and one SCIT vs. SLIT) reported a combined assessment of the effectiveness of AIT on symptoms and medication usage. Pooling of data was possible for two studies, this showing an SMD of 0.17 (95% CI −0.23, 0.58; Figure 8).

Sensitivity analysis, assessment of publication bias and subgroup analyses These analyses were not possible for this outcome.

Long-term

One SLIT study at low ROB reported on this outcome. A five-year double-blind placebo RCT by Durham (2012) had a three year SLIT

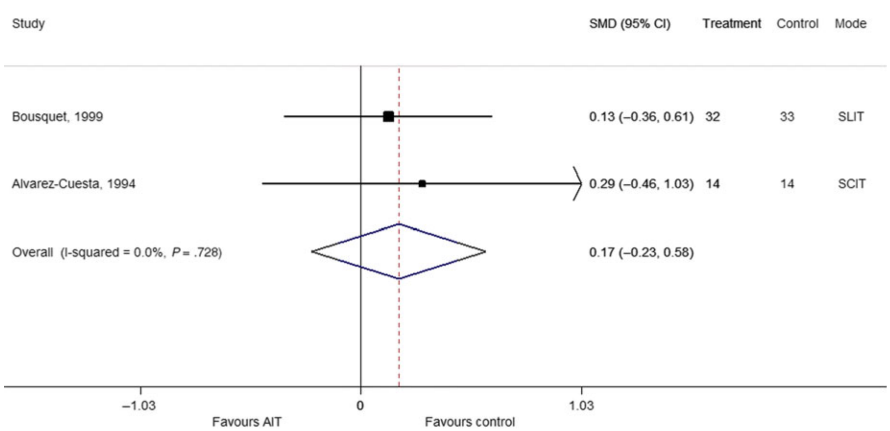


	Het. statistic	df	P	I-squared**	Tau-squared
SCIT	66.59	6	.000	91.0%	1.1642
SLIT	7.14	2	.028	72.0%	0.1553
Overall	112.48	9	.000	92.0%	0.9967

Significance test(s) of ES = 0

SCIT	z = 3.74	P = .000
SLIT	z = 1.06	P = .287
Overall	z = 3.56	P = .000

FIGURE 7 Meta-analysis of double-blind RCTs, comparing medication scores between SLIT and SCIT (random-effects model)



Test of SMD = 0 : z = 0.84 P = .400
Heterogeneity chi-squared = 0.12 (d.f. = 1) P = .728
I-squared (variation in SMD attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

FIGURE 8 Meta-analysis of double-blind RCTs, comparing combined symptom medication scores between AIT (SLIT and SCIT) and placebo groups (random-effects model)

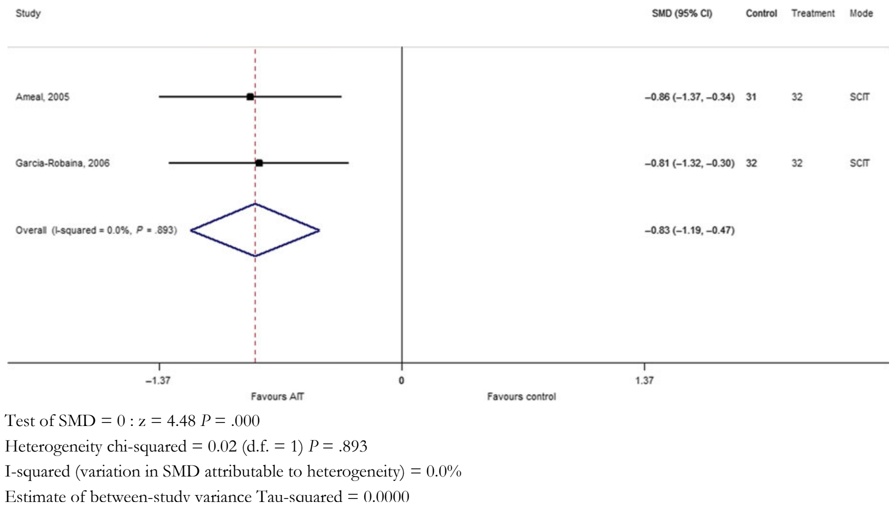


FIGURE 9 Meta-analysis of double-blind RCTs of AIT (SCIT and SLIT) vs placebo for asthma-specific quality of life (random-effects model)

tablets or placebo treatment period in grass pollen allergic patients followed by a two-year blinded observation period when no active treatment was administered. At the end of the five years the group who had received SLIT were found to have a significant improvement in combined asthma symptom and medication scores when compared to placebo for the whole five-year period (P=.049).

3.3 | Secondary outcomes

3.3.1 | Asthma control

Seven SLIT studies reported on a measure of asthma control (see Table S1g for details).[77,78,85,88,93,98,100] We were unable to pool data due to the differences in reporting of results. The one study at low ROB found that AIT did not improve asthma control.[98] We found no evidence to assess whether SCIT is effective in improving asthma control in allergic asthma patients.

3.3.2 | Quality of life

Eleven AIT trials reported on a measure of disease-specific QoL (Table S1h).

Three SCIT studies,[19,35,40] all judged to be at low ROB, reported significant improvements in disease-specific QoL. Pooled data from two of these trials[19,35] showed a large treatment effect with an SMD of −0.83 (95% CI −1.19, −0.47) in favour of SCIT (Figure 9).

Seven SLIT trials reported on disease-specific QoL.[77,78,83,88,93,98,100] We were unable to pool data from these studies for meta-analysis due to the variable reporting of results (Table 4). The one low ROB trial of SLIT[98] showed no significant improvement in disease-specific QoL.

3.3.3 | Exacerbations

Six trials[69,78,80,88,91,98] reported on asthma exacerbations, which were defined in a number of ways (Table S1i). The one SCIT trial at low ROB[69] reported on exacerbations defined by the number of courses of oral corticosteroids required to restore asthma control found no significant difference between the SCIT and placebo groups (P-value not given). Five SLIT studies reported on exacerbations, which we were unable to pool due to variations in the ways in which trial results were reported.

In summary, focusing on the trials at low ROB, the Wang (2006) SCIT trial failed to demonstrate evidence of a reduction in exacerbations in those treated with AIT compared with those treated with placebo. Two SLIT trials reported a positive effect of AIT on asthma exacerbations, one in the context of reducing the dose of ICS.

3.3.4 | Lung function

Twenty-five studies, of variable quality, reported on measures of lung function: peak expiratory flow rate (PEFR), forced expiratory volume in 1 second (FEV1) and forced expiratory flow at 25%-75% of forced vital capacity (FEF 25%-75%). Data on these outcomes were recorded in a number of ways and at varying times throughout the study.

Peak expiratory flow rate (PEFR)

Fourteen studies reported on this outcome.[16,22,29,38,43,48,50,61,69,72,73,93,96,106] (Table S1j) Pooled data from six studies suggested no clear benefit of AIT with an SMD of 0.48 (95% CI −0.21, 1.18; Fig. S4a).

Forced expiratory volume (FEV1)

Nine studies reported on FEV1. Reporting of data was varied.[18,28,43,57,73,93,96,106,107] (Table S1k) Data pooled from two studies indicated no clear evidence of benefit associated with AIT with an SMD of 0.41 (95% CI −0.46, 1.27; Fig. S4a).

Forced expiratory flow at 25%-75% of forced vital capacity (FEF25-75)

We were able to pool data on FEF25-75 from three trials[72,96,107] and found an SMD of 0.83 (95% CI 0.31, 1.35), this suggesting a large beneficial effect of AIT (Fig. S4a).

In summary, the evidence identified from meta-analysis evaluating the effect of AIT on lung function in allergic asthma supports the effectiveness of AIT on small airways (FEF 25%-75%), but with no clear evidence of benefit on improving PEFR or FEV1.

3.3.5 | Bronchial provocation tests

Thirty-one trials reported on bronchial provocation tests. Twenty-one trials looked at allergen-specific provocation tests and 18 studies evaluated nonspecific measures of bronchial hyperreactivity. There was a wide variation in reporting of outcome data (Tables S1l,m).

Allergen-specific airway hyperreactivity

Twenty-one trials performed allergen-specific bronchial provocation tests.[15,17-22,25,30,31,35,44,48,53,60,62,64,67,70,82,106] They were of variable quality and were mainly SCIT trials (n=20), SLIT being evaluated in only one trial.[82] (Table S1l).

Pooled data from three SCIT studies demonstrated a large effect of AIT with an SMD of 0.93 (95% CI 0.08, 1.79; Fig. S4b) Furthermore, there was evidence from eight high-quality RCTs that SCIT was effective in reducing allergen-specific bronchial reactivity in patients with allergic asthma.

One SLIT study reported on allergen-specific bronchial responsiveness to Artemisia pollen (Leng 1990). This study, at moderate ROB, found no significant difference between the SLIT and placebo groups.

Nonspecific airway hyperreactivity

Eighteen studies reported on this outcome.[16-18,20,21,33,36,40,48,55,62,67,69,72,73,94,96,107] (Table S1m).

Pooling of data was possible for methacholine PC20 for three studies which showed an SMD of 0.74 (95% CI −0.17, 1.66), showing no clear evidence of benefit for AIT; Histamine PC20 for two studies with an SMD of 0.33 (95% CI 0.03, 0.64) favouring AIT and for methacholine PD20 for two studies showing an SMD of 0.03 (95% CI −0.32, 0.39) showing no clear evidence in favour of AIT (Fig. S4c) We were able to combine data from seven of these studies which showed an overall SMD of 0.33 (95% CI 0.01, 0.64) in favour of AIT (Fig. S4d).

3.3.6 | Cost-effectiveness

One SCIT and two SLIT studies satisfied the eligibility criteria.[108-110] These included children and adults with or without allergic rhinitis (Tables S1m,n). The quality appraisal is detailed in Tables S1o,p.

Of the three studies included only one focused on patients with allergic asthma who did not also have allergic rhinitis.[108] This study was carried out in Germany and compared SCIT with standard care based on a small scale RCT (N=65) with three years of follow-up data. The study used a disease-specific outcome measure (ie, mean morning peak flow) with no attempt to convert it to a general quality of life measure such as quality-adjusted life years (QALYs) making it impossible to assess the cost-effectiveness of the treatment. The study found that, over the three years, SCIT was more expensive than standard care and performed better than standard care on the disease-specific outcome measure.

The remaining two studies looked at patients with both asthma and allergic rhinitis. SLIT was compared with standard care in an RCT (N=151) with one year of follow-up conducted in Austria, Denmark, Germany, the Netherlands, Italy, Spain, Sweden and the UK, and with results evaluated from an English National Health Service (NHS) perspective.[109] This study used one year of treatment data and assumed a constant treatment effect over the three year treatment period and the six years following the end of the treatment. EQ5D was used to evaluate the treatment outcome. The incremental cost-effectiveness ratio (ICER) of SLIT, as compared to standard care at 2005 prices, was calculated at £8816 (€10850) per QALY over the nine year period. The study did not attempt to characterize the uncertainty around this estimate. Updating this to 2014/15 prices using Personal Social Services Resource Unit (PSSRU) NHS inflation indices gave an ICER of £10726 (€13202) per QALY. Another RCT (N=70) with five years of follow-up conducted in Italy comparing SLIT with standard care in patients with asthma and rhinitis and found that patients on SLIT cost less and experienced less symptoms than those on standard care.[110] Methods for calculating the costs were not presented in enough detail to understand the analysis that had been performed and there was no attempt to convert the symptom score to a general quality of life scale making it impossible to assess the cost-effectiveness of SLIT.

3.3.7 | Safety

Data from randomized controlled trials (RCTs) and case series were included to assess the safety of AIT.

3.3.8 | RCTs

Fifty-two RCTs (36 SCIT studies and 16 SLIT) reported safety data (Tables S3a-f). We were able to pool data from 38 of these studies (SCIT=29; SLIT=9) including both local and systemic adverse events (AEs).

Risk of patients experiencing one or more AE

AIT delivered by any route (SCIT or SLIT) increased the risk of patients experiencing one or more AE (ie local and systemic) with a rate ratio (RR) of 1.74 (95% CI 1.38, 2.2; Fig. S3a). Subgroup analysis found that the increased risk was higher for SCIT RR=2.22 (95% CI 1.48, 3.33) than SLIT RR=1.49 (95% CI 1.13, 1.98), although this is an indirect comparison (Fig. S3b,c).

Total number of AEs reported

AIT delivered by any route (SCIT or SLIT) increased the risk of total AEs (ie local and/or systemic) with a RR=1.50 (95% CI 1.12, 2.02;

Fig. S3d). Subgroup analysis found increased risk both for SCIT (RR=1.32 (95% CI 1.01, 1.74) and SLIT (RR=1.93 [95% CI 0.95, 3.95; Fig. S3e,f]).

Risk of systemic AEs

AIT delivered by any route (SCIT or SLIT) increased the risk of systemic AEs with a RR of 1.85 (95% CI 1.20, 2.84; Fig. S3g) Subgroup analysis found that there was clearly an increased risk of systemic AEs with SCIT RR=1.92 (95% CI 1.19, 3.09), but not for SLIT RR=1.39 (95% CI 0.67, 2.92; Fig. S3h,i).

Risk of local AEs

AIT delivered by any route was not found to increase the risk of local AEs: RR=1.18 (95% CI 0.83, 1.67; Fig. S3j) The available data suggested that the risk of local AEs was however substantially greater in those receiving SLIT when compared to those receiving SCIT (Fig. S3j).

Case series

We identified six eligible case series studies in our searches; SCIT (n=5) and SLIT (n=1). The main characteristics of these studies and quality appraisal are presented in Tables S3g,h. The reported incidence of local AEs varied from 0.66 per patient and 0.33 per injection to 1.8%. The reported incidence of systemic AEs varied from 0.0074% to 0.06%.

No deaths from AIT were reported in any of these studies.

4 | DISCUSSION

4.1 | Statement of principal findings

This review has found a substantial body of evidence showing that administration of AIT in patients with allergic asthma can result in reductions in short-term symptom and medication scores. These findings do however need to be interpreted with caution given that the majority of trials were found to be at high or unclear ROB and the possibility of publication bias in relation to both these outcomes. Further subgroup analysis confirmed the beneficial effect for SCIT but was questionable for SLIT. There was a more modest body of evidence for the combined symptom and medication scores, which meta-analysis suggested was ineffective but this was not conclusively demonstrated on account of the wide confidence intervals. We found only one trial, judged to be at low ROB, evaluating long-term outcomes, which found a significant improvement in combined symptom and medication scores.

There is evidence for SCIT in improving asthma-specific quality of life and reducing allergen-specific airway hyperreactivity. In terms of lung function we were unable to demonstrate any significant beneficial effect on PEFR and FEV1 however SCIT does have a beneficial effect on FEV25-75. No beneficial effect of AIT could be demonstrated on asthma control. As for asthma exacerbations, no beneficial effect could be demonstrated for SCIT, but there was limited evidence in favour of SLIT.

AIT was associated with a moderate increased risk of AEs, both for SCIT and SLIT. Severe systemic AEs were observed, but these were uncommon and mainly occurred with SCIT. No fatalities were reported in the studies included in this review.

4.2 | Strengths and limitations

To our knowledge, this is the most comprehensive assessment of AIT in asthma ever undertaken. We employed internationally accepted techniques to systematically identify, assess and synthesize a substantial body of evidence, which included a number of prespecified sensitivity and subgroup analyses.

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. The results of this review, particularly for primary outcomes, are based on the trials which we were able to meta-analyse which may not be representative of all trials. For example, data for combined scores were only available for six studies of which only two could be pooled for meta-analysis the results of which had a wide confidence interval allowing no clear conclusion to be drawn. For the subgroup analyses that were undertaken, there was in some cases imprecision which impacted on our ability to draw clear conclusions. Third, because of the heterogeneity in scoring systems used, we undertook meta-analyses using random-effects modelling 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. Finally, it needs to be borne in mind that there may have been important differences between specific AIT products. Investigating this issue was however beyond the scope of this review.

4.3 | Interpretation in the light of the previous literature

The findings from this review are in keeping with earlier evidence syntheses on this subject (see companion paper), which found that SCIT improved short-term symptom and medication scores and measures of bronchial reactivity, but the evidence for SLIT was less consistent. There was no clear improvement of lung function for either SCIT or SLIT. This present study has built on this body of work by adding a broader range of subgroup analyses, including additional studies at low ROB, and achieving greater precision in summary results.

4.4 | Implications for policy, practice and research

Our findings provide evidence that AIT may be effective in improving two of our three patient-reported primary outcomes over the short term. Interpretation of these results is however complicated by considerations about the quality of the substantial number of studies and possible publication bias. The subgroup analyses suggest that SCIT is likely to be more effective than SLIT, and that AIT may be more effective in children than in adults.

Greater standardization of trial designs, looking at the compliance of patients to AIT for the differing routes of administration, reporting and choice of outcomes and their reporting so as to facilitate evidence syntheses and key subgroup analyses would greatly help to advance the body of evidence underpinning AIT in allergic asthma. Future well-conducted studies looking at the combined symptom and medication score are needed to determine whether AIT is beneficial for this outcome. 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. We anticipate that this review will report mid 2017.

5 | CONCLUSIONS

There is evidence that AIT in allergic asthma can achieve substantial reductions in short-term symptom and medication scores, with subgroup analyses confirming a benefit from SCIT and a questionable benefit from SLIT. These findings however need to be interpreted with caution given concerns about study quality and potential publication bias. Further, there is evidence showing that SCIT decreases allergen-specific airway hyperreactivity and improves asthma-specific quality of life. The effect of AIT on asthma control and exacerbations is not conclusive, neither its long-term efficacy after stopping AIT, which requires further investigation. More research is needed to establish the cost-effectiveness of AIT, but evidence suggests that SLIT is cost-effective in a UK NHS environment.

AIT is associated with a modest increase in the risk of AEs, both for SCIT and SLIT. Severe systemic AEs can occur, but are uncommon and mainly associated with SCIT. No fatalities were reported in the studies included in this review.

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CONFLICT OF INTEREST

S Dhami reports grants from EAACI to carry out the review, during the conduct of the study. F Asamoah reports payment from Evidence-Based Health Care Ltd during the conduct of the study. I Agache reports consulting fee from ALK and Allergopharma. S Lau reports grant from Allergopharma and grants and research support from Merck and Allergopharma and is a member of drug monitoring committee for immunotherapy for Merck. M Jutel reports consulting fee from Anergis and Allergopharma, scientific/governmental grant from NCN, Poland, and fee for review activities from Biomag. A Muraro reports consulting fee from Meda, Nestlé, Nutricia, Novartis and ALK and is a co-investigator for research protocol for Nestlé and Nutricia. G Roberts receives materials for research programme from ALK-Abelló, reports research grant from ALK-Abelló, is a member of the advisory board for ALK-Abelló and is a speaker for Allergy Therapeutics and ALK-Abelló. C Akdis reports consulting fee from Novartis and Boehringer Ingelheim and research grant from Novartis and Allergopharma and holds stocks in Davos Diagnostics and Alimentary Health Pharma Davos. K Izuhara reports grants and personal fees from Chugai Pharmaceutical Co. Ltd and grants from Shino-Test Co. Ltd, outside the submitted work. Ralph Mosges reports personal fees from ALK, Allergopharma, Allergy Therapeutics, Friulchem, Hexal, Servier, Klosterfrau, Bayer, FAES, GSK, MSD, Johnson&Johnson, Meda, Stada, UCB and Nuvo; grants from ASIT biotech, Leti, Optima, bitop AG, Hulka and Ursapharm; grants and personal fees from Bencard and Stallergenes; grants, personal fees and nonfinancial support from Lofarma; nonfinancial support from Roxall, Atmos, Bionorica, Otonomy and Ferrero; and personal fees and nonfinancial support from Novartis, outside the submitted work. O Palomares received research grants from Inmunotek S.L. under public collaborative projects from Spanish Ministry (MINECO)/CDTI: IPT-2012-0639-090000, IDI-20110410 and IDI-20141131; has received fees for giving scientific lectures from Allergic Therapeutics, Amgen, Inmunotek S.L., Stallergenes and Novartis; and has participated in advisory boards from Novartis. 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, 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. M Sokolowska reports research fellowships and grants from European Academy of Allergy and Clinical Immunology (EAACI) and European Respiratory Society (ERS). M Asaria reports payment from Evidence-Based Health Care Ltd during the conduct of the study. H Zaman reports payment from Evidence-Based Health Care Ltd during the conduct of the study. A Sheikh reports grants from EAACI during the conduct of the study. A Kakourou, M Bonini, O Cavkaytar, B Flood, P Gajdanowicz, Ö Kalayci, S Smolinska, G Netuveli and A Akhlaq have nothing to disclose.

AUTHOR CONTRIBUTIONS

This review was drafted by Sangeeta Dhami. It was revised following critical review initially by Aziz Sheikh, Ioana Agache, Marek Jutel and Susanne Lau and then by all the co-authors.

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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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