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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

DOI: 10.1111/all.13583

Efficacy and safety of subcutaneous immunotherapy with house dust mite for allergic rhinitis: A Meta-analysis of Randomized Controlled Trials

To the Editor,

The local sensitizing patterns for allergic rhinitis (AR) vary globally, while house dust mite (HDM) was a common aeroallergen responsible, causing perennial nasal symptoms. The efficacies of AR are evaluated by assessing changes in individual and total nasal symptom score by means of visual analogue scale, medication score, and quality of life (QoL) using rhinoconjunctivitis quality-of-life questionnaire (RQLQ), following treatment. The safety profile is usually assessed as incidence or prevalence of adverse effects (AEs).

Allergen-specific immunotherapy (AIT), including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), is the only etiological treatment available for AR,¹ while selective immunomodulator is also available for perennial allergic rhinitis (PAR).² There are relatively few AIT trials on HDM-induced AR, and although it is not clear whether SCIT or SLIT is better in this respect, while promising evidence of efficacy for SLIT has been confirmed.³ To our knowledge, no meta-analysis has been reported of SCIT for HDM-induced PAR. Thus, we performed a meta-analysis of appropriate studies studying the efficacy and safety of HDM-SCIT in patients with HDM-induced PAR.

Study methods are described in Appendix S1, and a flowchart is provided in Figure S1. A total of 186 studies were identified by the search strategy employed, of which eight were finally included (Figure S1). The risks of bias are shown in Figure S2. The specific details of the eight studies are presented in Appendix S1: Table S1.

Symptom scores from six randomized controlled trials (RCTs) (Figure 1A) were pooled and analyzed further, as the primary endpoint. The present meta-analysis indicated that SCIT led to a greater mean

reduction in nasal symptom scores compared to placebo/conventional medicine; with statistically significant between-study heterogeneity (standardized mean difference [SMD], -2.17 ; $P = 0.001$; $I^2 = 96\%$) (Figure 1A). However, SCIT was compared with SLIT in only three trials (Figure 1B), and analysis of these data indicated no significant difference for symptom scores between SCIT- and SLIT-treated groups (mean difference [MD], -0.40 ; $P = 0.21$; $I^2 = 80\%$) (Figure 1B).

Furthermore, we performed a subgroup analysis on age, including children (aged <18 years) and a group comprising adults (≥ 18 years) and the mixed group. In this regard, children showed a significantly favorable effect on medication scores compared with others (SMD, -1.18 ; $P = 0.0005$; $I^2 = 0\%$) (Figure 1C).

A pooled analysis demonstrated a significant reduction in medication scores in SCIT group compared with the placebo/conventional medicine group (SMD, -1.17 ; $P = 0.003$; $I^2 = 86\%$) (Figure 2A). Two trials^{4,5} employed different scoring methods for medications scores compared with the other three; with these two employing a score of 1 point when β_2 -agonist was taken for controlling comorbid asthma, and the others for use of an antihistamine. Thus, to perform a sensitivity analysis of the medication scores, data from these trials^{4,5} were removed and the pooled were reanalyzed for the remaining trials (Figure 2B). This demonstrated a SMD of -1.69 ($P < 0.00001$, $I^2 = 0\%$), which did not modify the statistical significance of the studies, but did influence the heterogeneity of the analysis.

A pooled analysis of systemic AEs reported in four studies during treatment (Figure S3) showed that prevalence of systemic AEs (7.32%), calculated as the percentage of patients who had at least

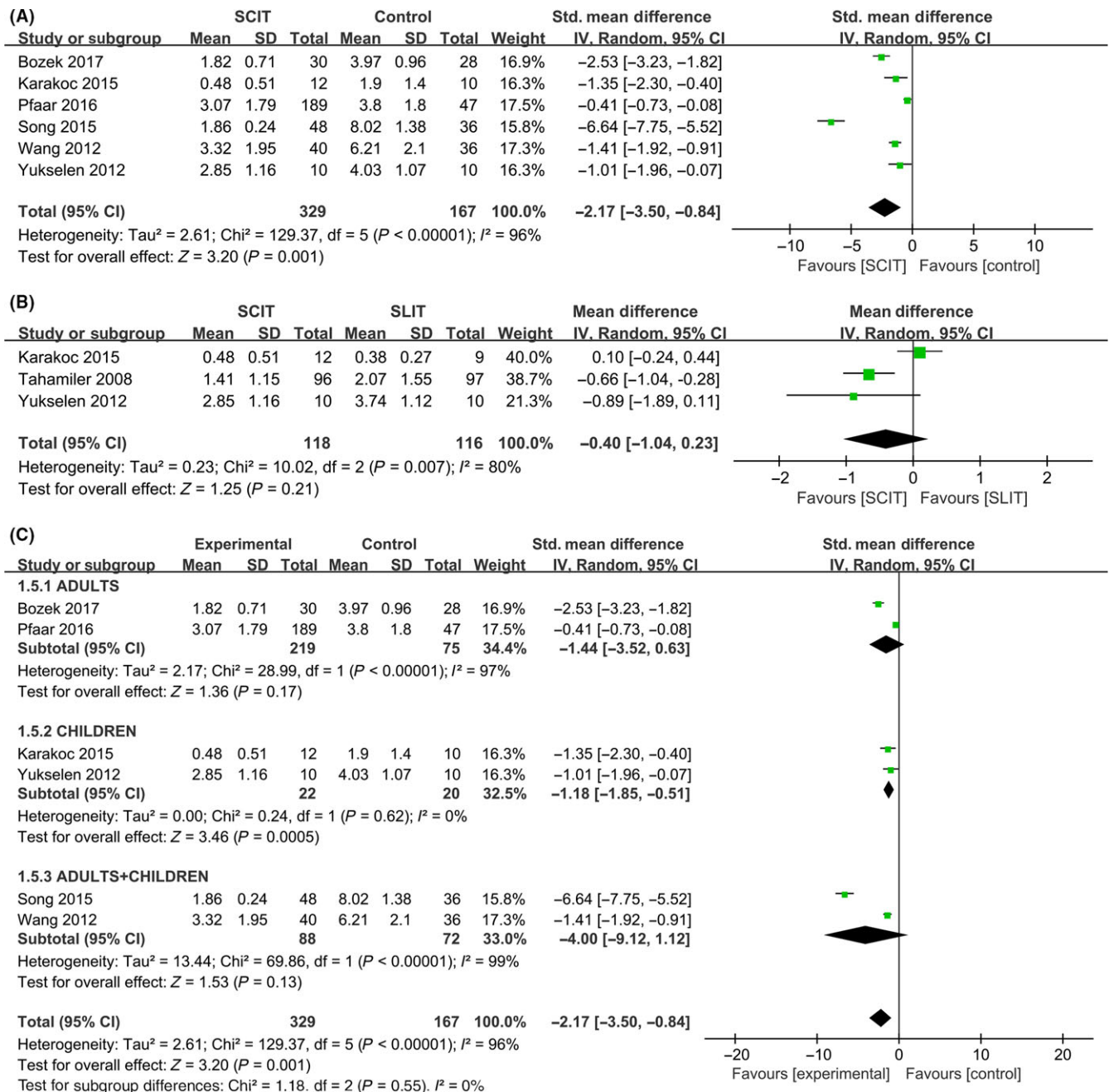


FIGURE 1 Meta-analysis of the RCTs comparing symptom scores between SCIT group and control group. Forest plots of SCIT versus control (A), SCIT versus SLIT (B) and subgroup analysis for age between SCIT group and SLIT group (C) [Colour figure can be viewed at wileyonlinelibrary.com]

one AE, was greater with SCIT than with control groups; with statistically significant between-study heterogeneity (risk ratio, 6.23; $P = 0.02$; $I^2 = 0\%$). Apart from two cases of severe systemic AEs, other systemic AEs were mild and well tolerated, and included localized urticaria, mild-to-moderate rhinitis, and asthma.

To our knowledge, this is the first meta-analysis on efficacy and safety of SCIT for patients with HDM-induced PAR. Our results show that SCIT was significantly more efficacious in the reduction of both nasal symptom and medication scores, compared with placebo and conventional medical treatment. Although no significant

difference was found between SCIT and SLIT in the reduction of symptom score, the risk of systemic AEs was increased in SCIT group compared with SLIT. There is no evidence that SCIT is superior to SLIT.⁶ To date, there is no consensus on the efficacy SCIT versus SLIT in HDM-induced AR, particularly because direct comparisons are inadequate, and indirect comparisons are inconsistent. While Nelson et al⁷ showed comparable efficacy of commercialized SCIT and SLIT products for grass pollens by performing a network meta-analysis. Di Bona et al,⁸ performing a meta-analysis-based comparison, showed that SCIT could be more effective than SLIT in grass

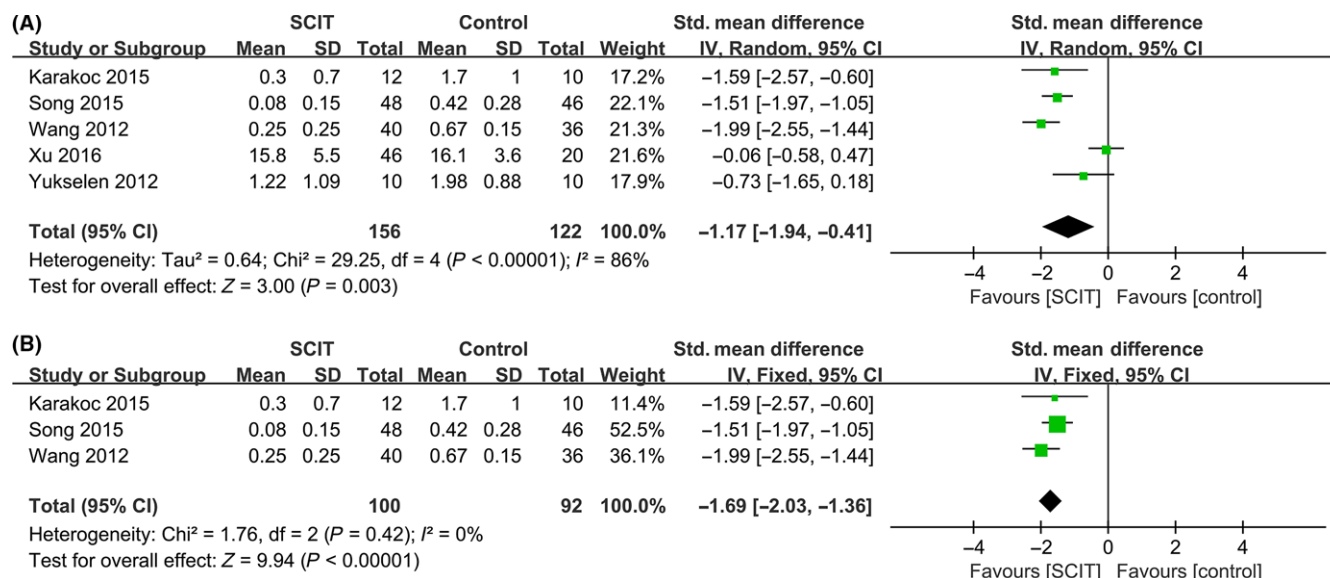


FIGURE 2 Meta-analysis of the RCTs comparing medication scores between SCIT group and control group, including forest plot (A) and sensitivity analysis (B) [Colour figure can be viewed at wileyonlinelibrary.com]

pollen-induced allergic rhinoconjunctivitis. Durham and Penagos⁹ performed a subgroup analysis of Cochrane databases for efficacy of seasonal AR, and indicated that the findings favoured the use of SCIT over SLIT in pollen-induced AR.

Findings from subgroup analysis performed in this study indicated that the efficacy of HDM-SCIT might be better in pediatric patients compared with adult subgroups. This is in partly accordance with limited evidence from a prospective observational study by Soh et al,¹⁰ who demonstrated that although there was no significant difference in improvements in nasal symptom and RQLQ noted in the two groups, the reduction of medication usage scores in children was greater than in adult group. However, as pooled data were available from only a few studies for subgroup analysis on age, the robustness of these results needs to be confirmed in further head-to-head studies. Indeed, clinical observation of patients undergoing AIT in our center indicated that children tended to achieve superior efficacy of HDM-SCIT compared to adults, at the end of 3-year AIT and 2 years after discontinuation of AIT (unpublished data).

A limitation of this meta-analysis is that the long-termed efficacy, QoL and cost-effectiveness are unknown, as relevant RCTs are scant. Secondly, differences in study protocols and cohorts, such as different populations (comorbidities, type and number of sensitization) and different extracts administered, which would lead to heterogeneity among studies, may affect clinical outcomes. Moreover, double-blind placebo-controlled studies were limited and all the studies were relatively small.

In conclusion, we confirmed that HDM-SCIT significantly reduces nasal symptoms and medication needs in patients with HDM-induced AR. However, large well-controlled rigorous head-to-head trials of SCIT versus SLIT are needed to evaluate the efficacy and safety, before either can be recommended as a commonly employed treatment strategy.

CONFLICT OF INTEREST

All authors declare no financial or commercial conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Immunomodulatory function of surfactant protein D in eosinophilic asthma

To the Editor,

Asthma is a chronic inflammatory disease in the lungs with several phenotypes.¹ Traditionally, asthma has long been considered a Th2 response mediated by multiple factors.² In particular, periostin (a secreted matricellular protein) contributes to eosinophilic inflammation.³ In addition, it has been suggested that periostin induces transforming growth factor (TGF)- β 1 production, leading to structural changes in the airways.⁴ Recently, we have demonstrated the function of surfactant protein D (SPD) in patients with aspirin-exacerbated respiratory disease (AERD), a representing phenotype of eosinophilic asthma.⁵ All these molecules are released from airway epithelium and are involved in airway inflammation; however, little is known about the relation of SPD with type 2 cytokines in the process of eosinophilic asthma.

This study enrolled 884 adult patients and 230 healthy control subjects (HCs). The patients with asthma showed significantly higher serum levels of periostin and TGF- β 1 than HCs ($P < 0.001$ and $P < 0.001$, respectively). When patients with asthma were classified according to peripheral total eosinophil count (TEC), patients with eosinophilic asthma ($\text{TEC} \geq 300 \text{ cells}/\mu\text{L}$) had a higher

prevalence of severe asthma, a higher total IgE, and a lower PC_{20} methacholine than those with noneosinophilic asthma ($P = 0.005$, $P < 0.001$, and $P = 0.026$, respectively; Table S1). In addition, the serum levels of periostin and TGF- β 1 were significantly higher in patients with eosinophilic asthma ($P < 0.001$ and $P = 0.006$, respectively; Table S1) than those with noneosinophilic asthma ($\text{TEC} < 300 \text{ cells}/\mu\text{L}$).

Furthermore, when patients with asthma were classified by the cutoff value (116.7 ng/mL) of serum periostin (high/low periostin group), an interval (mean+2SD) indicating the chance of a test value coming outside less than 5%, TEC as well as serum levels of TGF- β 1 and SPD was significantly higher in the high periostin group than in the low periostin group ($P = 0.011$, $P = 0.001$, and $P = 0.040$, respectively; Table S2). Considering that periostin is a systemic biomarker for eosinophilic airway inflammation and associated with TGF- β 1 activation, significantly positive correlations were found between serum periostin and TEC ($r = 0.207$, $P < 0.001$; Figure S1A) or TGF- β 1 levels ($r = 0.221$, $P < 0.001$; Figure S1B). These observations were weaker than expected due to the complexity that several cells including immune cells and structural cells are the potential

Identification

Records identified through
database searching
(n = 186)

Additional records identified
through other sources
(n = 0)

Screening

Records after duplicates removed
(n = 158)

Records screened (Title &
Abstract)
(n = 158)

Records excluded (n = 75),
with reasons
Reviews (n=20)
Not an RCT (n= 10)
Not SCIT (n= 10)
Not HDM (n= 2)
Not AR (n= 33)

Eligibility

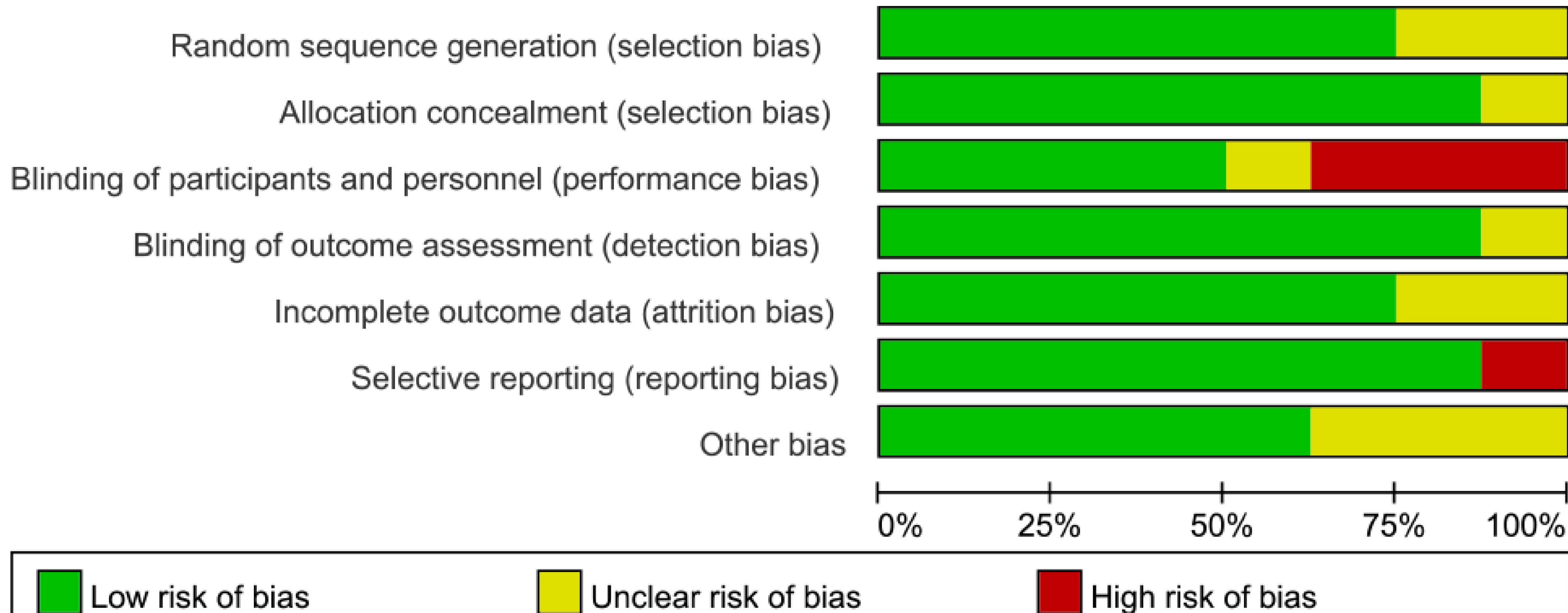
Full-text articles assessed
for eligibility
(n = 83)

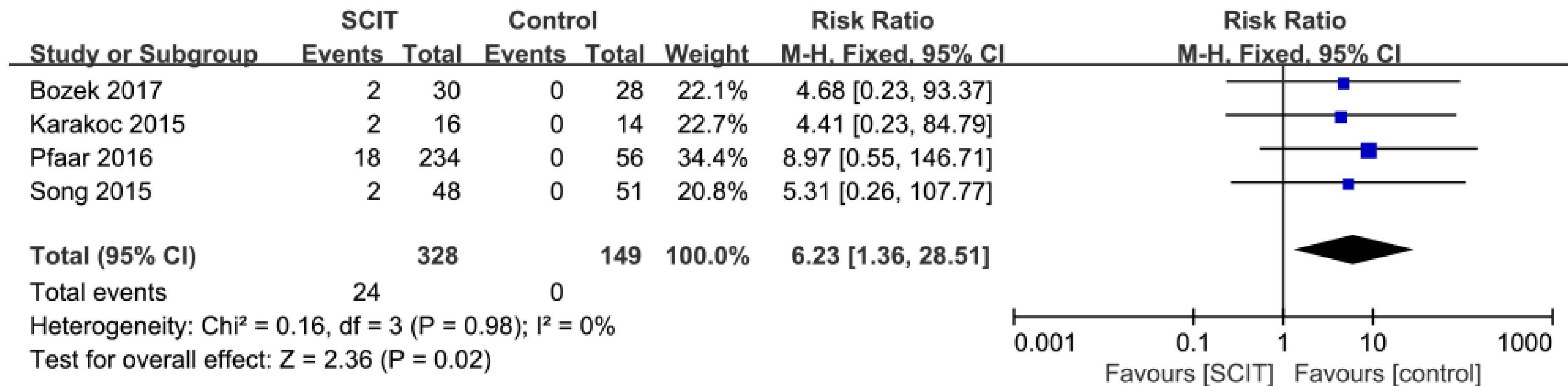
Full-text articles excluded
(n = 75),
with reasons
Not an RCT (n= 18)
Not SCIT (n= 40)
Not with relevant
outcomes (n= 17)

Included

Studies included in
qualitative synthesis
(n = 8)

Studies included in
quantitative synthesis
(meta-analysis)
(n = 8)





METHODS

Search strategy and selection criteria

This study was registered with the International Prospective Register of Systematic Reviews (CRD42018091610) and reported in full accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

The MEDLINE, EMBASE, and Cochrane library database were searched for studies investigating the efficacy and safety of HDM-SCIT for treatment of allergic rhinitis, published from 1990 to 2017. English or Chinese restrictions were applied for the search and the following MeSH terms and combined text were used: “subcutaneous immunotherapy” and “allergic rhinitis”. The complete search strategy employed for MEDLINE was combinations of the search terms (“subcutaneous” or “injections”) and (“immunotherapy” or “desensitization” or “immunologic desensitization” or “hyposensitization”) and (“hay fever” or “allergic” or “rhinitis” or “rhinoconjunctivitis” or “persistent rhinitis”) and (“house dust mites” or “pyroglyphidae” or “dermatophagoides” or “farinae” or “pteronysinus” or “euroglyphus”) and (“randomized controlled trial” or “randomized” or “placebo”).

Study selection and data extraction

Studies were regarded to be eligible for inclusion in the meta-analysis if they were i) randomized-controlled trials (RCTs) performed in patients with HDM-induced AR, ii) compared HDM-SCIT in any dose and duration to other treatment strategy (placebo, conventional medical treatment, or SLIT), and iii) reported changes in the nasal symptom scores and medication score between baseline and the end of intervention, and events of adverse effects.

Studies were excluded from this meta-analysis based on the PRISMA recommendations, as shown in Figure S1. Thus, studies which were reviews or meta-analyses, not an RCT, not SCIT, not HDM, not AR, and not with relevant outcomes (nasal symptom scores and medication score) were excluded. Furthermore, observational and retrospective studies, studies with less than 6-month duration of treatment, and studies which were not published English or Chinese were also excluded.

HDM-SCIT was compared to other treatment strategy, such as placebo, conventional medical treatment and SLIT, with no restriction on treatment history. The primary outcomes were symptom scores and medication scores before and after the treatment. Two independent investigators evaluated the titles and abstracts of all publications highlighted by the search strategy, and then further assessed the full texts of relevant studies for eligibility to be selected for meta-analysis. Data from the selected studies were extracted and analysed by the two investigators,

and any disagreement with regard to the extracted information was discussed between the two investigators and a third investigator to reach a general consensus on the information in question.

Data were extracted from the original publications, while data of one study were provided by the author (1). The extracted information from each study included detailed data of total number of participants, age, gender, intervention duration, follow-up duration, cumulative dose, outcomes assessed, change in symptom scores and medication scores (mean and standard deviation), and the prevalence of adverse effects calculated as the percentage of patients who had at least once AEs. Risk for bias was assessed by the two independent reviewers, who “ascertained the validity of eligible randomized trials by determining the adequacy of randomization and concealment of allocation, blinding of patients, health care providers, data collectors, and outcome assessors; and extent of loss to follow-up (i.e. proportion of patients in whom the investigators were not able to ascertain outcomes)”, in full accordance with the PRISMA recommendations (2), an international guideline of meta-analysis, using RevMan 5.3 provided in the Cochrane handbook.

Statistical analysis

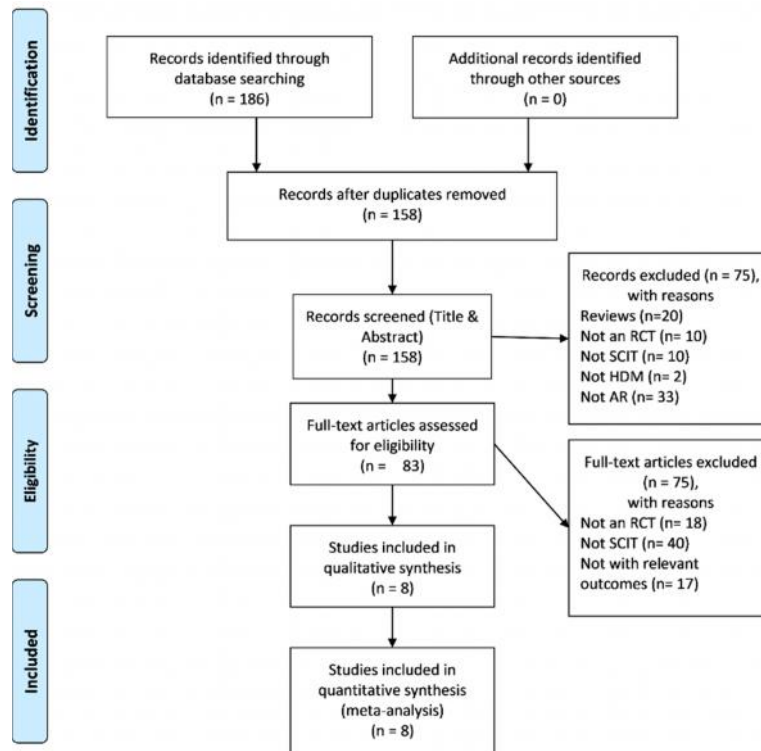
The effect of HDM-SCIT for patients with HDM-induced AR was assessed based on two outcomes; as assessed by both symptom scores and medication scores. The safety of HDM-SCIT was assessed based on incidence of any adverse effects recorded. The symptom scores and medication scores were analysed as continuous variables and reported as absolute differences of means between baseline and end of intervention. For the incidence of adverse effects, an overall relative risk (RR) was used.

Pooled estimates of the mean differences in symptom scores and medication scores between intervention groups were measured using a random-effects model. For categorical outcomes, we also calculated pooled estimate of RR using a random-effects model.

Heterogeneity between studies was assessed by I^2 testing; with a value for $I^2 > 50\%$ regarded to indicate moderate-to-high heterogeneity. For those with considerable heterogeneity, random-effects models were used instead of fixed-effects models. Further, Sensitivity analyses were also performed to analyse the heterogeneity. All statistical analyses were performed with RevMan 5.3 provided by Cochrane. $P \leq 0.05$ would be considered to be statistically significant in this study.

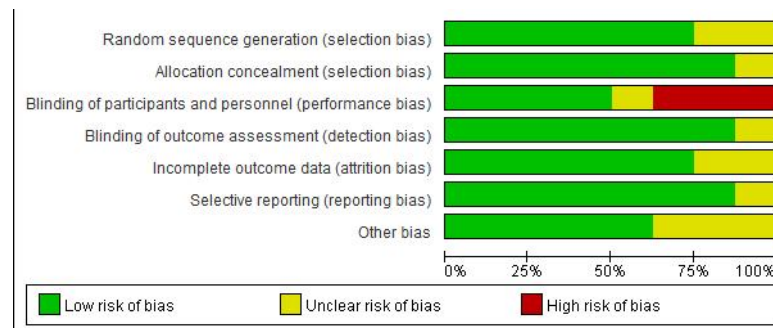
Figures and Tables

Figure S1.



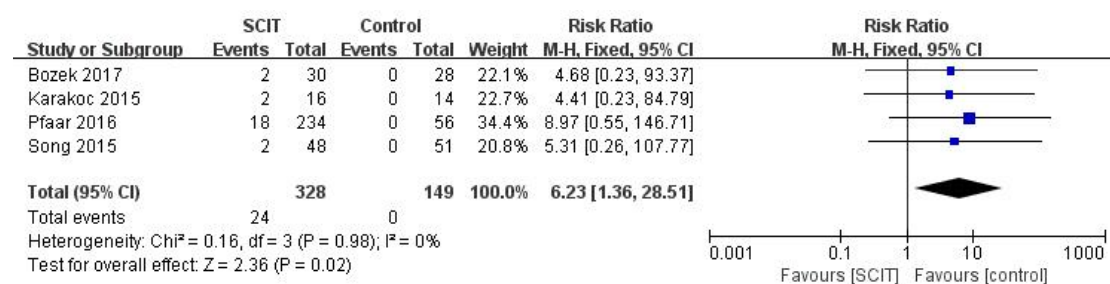
Flow diagram of study selection.

Figure S2.



Risk of bias graph for RCT studies.

Figure S3.



Meta-analysis of the RCTs comparing systemic adverse reactions between SCIT group and control group.

Table S1. Details of studies included in the meta-analysis

1 st Author Year (Ref#)	Country	Intervention (No.)	Mean Age(year)	Indication	Build-up phase (WEEK)	Cumulative dose	Final Dose	Manufacturer	Duration (months)	N(all)	Dropout (No.)	Outcomes assessed
Tahamiler 2008 (3)	Turkey	SCIT(97)	26.54±5.67	PAR	15	633300 SQ-U	100,000 SQ-U/ml	ALK-Abello	36	230	37	SS
		SLIT(96)	24.91±4.93									
Wang 2012 (1)	China	SCIT(40)	26±17.78	PAR	15	1925540	100,000 SQ-U/ml	ALK-Abello	36	92	16	SS/MS
		Medicine(36)	29±13.33			SQ-U						
Yukselen 2012 (4)	Turkey	SCIT(10)	10.9±3.2	PAR	12	43770 TU	5,000 TU/ml	NovoHelisen Depot,	12	30	0	SS/MS
		SLIT(10)	9.2±3.4					Allergopharma				
		Placebo(10)	10.1±2.7									
Karakoc 2015 (5)	Turkey	SCIT(9)	7±1.77	PAR	16	1131540	100,000 SQ-U/ml	ALK-Abello	36	79	31	SS/MS/AE
		SLIT(12)	6.5±1.6			SQ-U						
		Medicine(10)	7.67±1.98									
Song 2015 (6)	China	SCIT(48)	19.40±1.03	PAR	16	1925540	100,000 SQ-U/ml	ALK-Abello	36	102	3	SS/MS/AE
		Medicine(51)	19.60±1.02			SQ-U						
Pfaar 2016 (7)	Germany	SCIT(234)	30.89±9.72	PAR	6	NR	6667/20000/50000/100000	HAL Allergy B.V.,	12	344	54	SS/AE
		Placebo(56)	30.2±10.1				AUeq/ml	Purethal				
Xu 2016 (8)	China	SCIT(46)	25/26(median)	PAR	15	NR	100,000 U	Allergopharma Joachim	6	66	0	MS
		Placebo(20)						Ganzer KG;				
								Reinbek,Germany				
Bozek 2017 (9)	Poland	SCIT(30)	68.1±5.9/69.2±6.3	PAR	6	560500 BAU	20,000 Aueq/ml	HAL Allergy B.V., Leiden,	24	60	2	SS/AE
		Placebo(28)						Netherlands				

SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy; PAR, perennial allergic rhinitis; NR, no reported; SS, symptom scores; MS, medication score; AE, adverse effects; AU, allergic units; SQ-U, standardized quality units

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