

Efficacy and safety of sublingual immunotherapy for allergic rhinitis in pediatric patients: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Allergic rhinitis (AR) has become a global health problem that constantly affects a large part of the general population, especially children.

Objective: Sublingual allergen immunotherapy (SLIT) has been used extensively for pediatric AR, although its efficacy and safety are often questioned. In this meta-analysis of randomized controlled trials (RCT), we evaluated the use of SLIT for pediatric AR.

Methods: A number of medical literature data bases were searched through January 2016 to identify RCTs that examined the use of SLIT for pediatric AR and that assessed clinical outcomes related to efficacy. Descriptive and quantitative information was abstracted. Standardized mean differences (SMD) were calculated by using fixed- and random-effects models. Subgroup analyses were performed. Heterogeneity was assessed by using the I^2 metric. A network meta-analysis was used to estimate SMDs between two SLIT protocols for pediatric seasonal AR. All data were extracted from publications or received from the authors.

Results: Twenty-six studies were eligible for inclusion in the meta-analysis of rhinitis or rhinoconjunctivitis symptom scores, and 19 studies were eligible for the meta-analysis of medication scores. Descriptive and quantitative data were extracted. SLIT differed significantly from placebo in terms of symptom scores (SMD -0.55 [95% confidence interval (CI), -0.86 to -0.25]; $p = 0.0003$, $I^2 = 90\%$) and medication scores (SMD -0.67 [95% CI, -0.96 to -0.38]; $p < 0.00001$, $I^2 = 83\%$). Oral pruritus was the adverse effect, which occurred most commonly in children who were receiving SLIT. Network meta-analysis revealed no significant difference between the pre-seasonal and continuous SLIT protocols for seasonal AR in symptom scores (SMD -6.55 [95% CI, -25.38 to 12.29]; $p = 0.496$) and medication scores (SMD -8.83 [95% CI, -22.10 to 4.43]; $p = 0.192$).

Conclusions: Our meta-analysis results indicated that SLIT provided significant symptom relief and reduced the need for medication in pediatric patients. Moreover, the safety of SLIT needs to be confirmed in RCTs with larger samples.

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Allergic rhinitis (AR) has become a global health problem that affects 10% to 30% of adults and at least 40% of children.^{1–4} Poorly controlled AR may influence work efficiency, affect sleep quality, and have major impacts on quality of life.^{5–7} Symptomatic treatment with new-generation oral H_1 antihistamines and intranasal glucocorticosteroids remains the first treatment choice for patients with AR.^{8,9} However, these methods are costly and impose a significant economic burden on individuals and nations. The estimated direct annual cost in the United States alone is 3.4 billion dollars.¹⁰ Allergen immunotherapy is a guideline-recommended treatment for AR.^{11–13} Unlike symptomatic drugs, specific immunotherapy provides unique and appropriate management that transforms the process of AR. Remarkably, early treatment of AR with specific immunotherapy may prevent AR from evolving to asthma.¹⁴

Subcutaneous immunotherapy (SCIT) has been the criterion standard for the management of AR, whereas sublingual allergen immunotherapy (SLIT) has emerged as a novel, effective, and safe alternative.^{15–17} Regulatory authorities in many countries have approved the use of different SLIT modalities (e.g., drop and tablet administration) for adults and children. Analysis of the results obtained in many trials indicated that the appropriate pre-seasonal treatment period showed great improvement in the clinical effect^{18–20}; however, some studies with pollen SLIT were given continuously, in which considerable benefits in rhinitis and asthma were gained.²¹ A World Allergy Or-

ganization position paper established the use of SLIT for the management of pediatric allergic respiratory diseases with appropriate diagnostic workup.²² Recently, the European Academy of Allergy and Clinical Immunology provided evidence-based insight on the treatment of pediatric AR and confirmed that SLIT was effective for AR caused by house-dust mites and grass pollens.²³

Previous Cochrane systematic reviews and meta-analyses^{24–28} confirmed that SLIT and SCIT are effective for the management of AR, but efficacy evidence for the use of SLIT in pediatric patients with AR has been less convincing. Moreover, evidence for the safety of SLIT in the treatment of pediatric AR has been conflicting. In addition, the efficacy and safety of pre-seasonal and continuous SLIT protocols for pediatric seasonal AR (SAR) have not been examined by direct head-to-head comparison. To address these questions, we conducted a systematic review and meta-analysis of published randomized controlled trials (RCT) that examined the efficacy and safety of SLIT for pediatric AR.

METHODS

We searched for well-powered RCTs published within the past 26 years (1990 to 2016) that examined the treatment of perennial AR (PAR) and SAR in children. Studies that assessed outcomes of AR-related symptoms and/or medication scores in children were enrolled. The Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ), MEDLINE, and Embase data bases (Elsevier Science, Inc., Amsterdam, Netherlands) were searched by using logical combinations of the following terms: (“sublingual” or “swallow”) and (“immunotherapy” or “desensitization” or “immunologic”) and (“allergic” or “hay fever” or “rhinitis” or “rhinoconjunctivitis”). When reports pertained to the same patient at different follow-up intervals, the report with the longer follow-up period was used to avoid duplication. Alternatively, in cases of multiple reports on different outcomes from the same RCT, we included all pertinent studies without overlapping information. Also, for RCTs that involved multiple intervention and control arms, we considered the placebo arm to be the control group and used data

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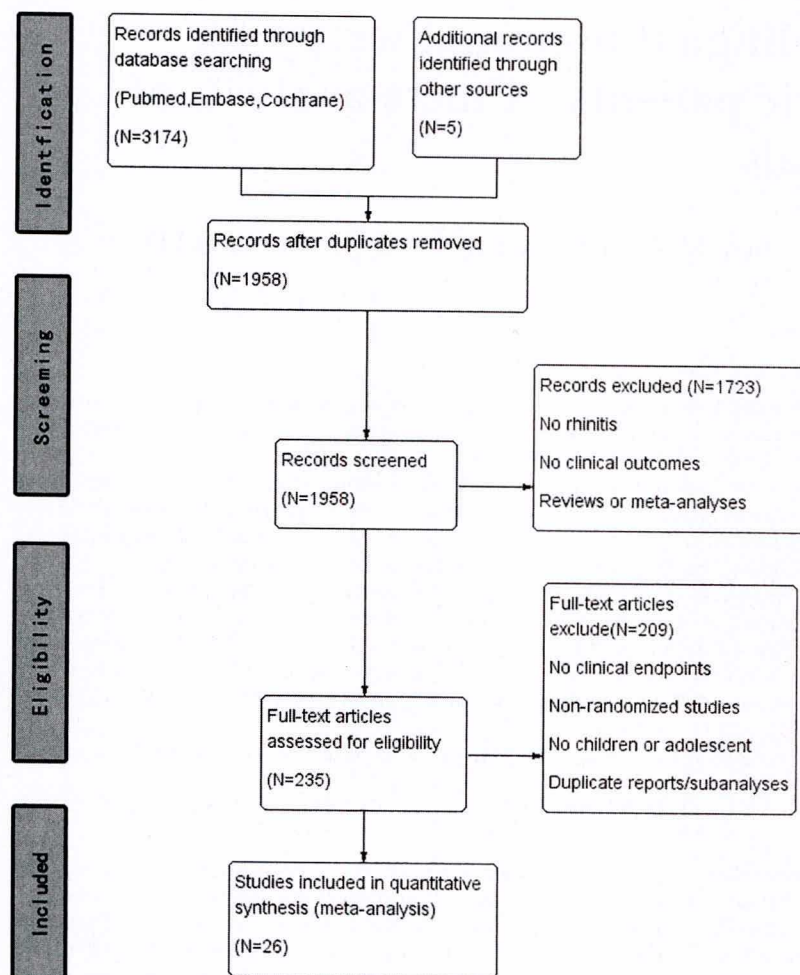


Figure 1. Classification of material reviewed for this meta-analysis.

from the SLIT arm closest to the U.S. Food and Drug Administration ratified dosage scheme as the active comparator. Additional data were requested from authors and study sponsors when data reported in the published articles were insufficient or unsuitable for inclusion in the meta-analysis. Multiple available scores related to rhinitis symptoms (those for rhinitis symptoms only, rhinoconjunctivitis symptoms, and rhinoconjunctivitis and asthma symptoms) were included in the analysis. Rhinoconjunctivitis symptom scores were preferred, followed by rhinitis-only scores. Regardless of the type and number of outcomes examined, studies that assessed SLIT were enrolled in the meta-analysis to estimate the safety and efficacy of this treatment.

Data Extraction

We extracted information on the following study and demographic characteristics: investigators, publication year, journal title, total and per-arm sample sizes, population characteristics, treatment indication, dose and modality, study duration, and rhinitis-related outcomes and definitions thereof. Continuous outcomes, including nasal symptom and medication scores, were assessed by using mean differences and standardized mean differences (SMD), with corresponding standard deviations. Independent investigators extracted data, and discrepancies were resolved by consensus. All the data were extracted from publications or received from the authors.

Quality Assessment

The evaluation of potential biases in the selected studies is an essential component of systematic literature reviews and meta-analysis. Risk of

bias of the selected RCTs was assessed by using the Cochrane Collaboration's Risk of Bias tool in RevMan 5.3.

Statistical Analysis

Outcomes assessed in the meta-analyses were symptom scores and medication scores. Outcomes were compared directly between each protocol and placebo, and indirectly between pre-coseasonal and continuous SLIT. The degree of heterogeneity in the estimates was measured, and the sources of heterogeneity were explored by removing possible study outliers in subgroup and sensitivity analyses. Random- and fixed-effects models were applied. Direct pairwise comparison of each modality with placebo was performed with RevMan 5.3 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Two main clinical outcomes that indicate improvement in AR are the reduction of symptoms and medication use, as reflected in composite summary scores. We quantified the extent of heterogeneity by using the I^2 metric (range, 0–100%), with values of >75% considered to indicate considerable heterogeneity. The sources of observed between-study heterogeneity were explored in analyses, including subgroups defined in the RCTs. Subgroup-specific differences in the effects of the intervention were also examined. Publication bias was examined by constructing funnel plots for all outcomes assessed, and asymmetry was evaluated by using funnel plots and the Egger regression, which enables the identification of significant relationships between effect sizes and their precision. Multivariate meta-analysis was conducted in a Bayesian framework by using STATA 12.0 software (StataCorp LP, College Station, TX). An indirect comparison between the pre-coseasonal and continuous SLIT protocols

Table 1 Characteristics of the included studies

Study, y	Country	Mean age (range), y	Allergen	Indication	Modality	Cumulative dose	Follow-up, mo	N(all)	Not Located	Outcomes Assessed
Tari <i>et al.</i> , ⁵² 1990	Italy	(5–12)	Mites	PAR	Drops	363 STU	18	66	8	SS
Hirsch <i>et al.</i> , ³² 1997	Germany	10.6 (6–16)	Mites	PAR	Drops	570 µg	12	30	12	SS
Vourdas <i>et al.</i> , ⁴⁵ 1998*	Greece	12 (7–17)	Olive	SAR	Drops	30,000 IR	5	66	2	SSMS
La Rosa <i>et al.</i> , ³⁷ 1999	Italy	10 (6–14)	<i>Parietaria</i>	SAR	Drops	75,000 IR	24	41	8	SSMS
Caffarelli <i>et al.</i> , ⁴⁹ 2000*	Italy	8.4 (4–14)	Grass mix	SAR	Tablets	37,250 AU	3	278	12	SSMS
Bahçeciler <i>et al.</i> , ³⁰ 2001	Turkey	11.7 (7–18)	Mites	PAR	Drops	7000 IR	6	15	1	SSMS
Ippoliti <i>et al.</i> , ³¹ 2003	Italy	9 (5–12)	Mites	PAR and asthma	Drops	12 mg	6	86	0	SSMS
Marcucci <i>et al.</i> , ⁵⁴ 2003	Italy	8.5 (4–16)	Mites	PAR	Drops	110 µg	12	24	0	SS
Wüthrich <i>et al.</i> , ³⁴ 2003	Switzerland	7.85 (4–11)	Grass mix	SAR	Drops	139.88 µg	18	28	6	SSMS
Rolinck-Werninghaus, <i>et al.</i> , ⁴⁸ 2004	German	(3–14)	Grass mix	SAR	Drops	188 µg	32	97	20	SSMS
Bufe <i>et al.</i> , ⁵⁰ 2003	German	9.25	Grass mix	SAR	Drops	2,625,000 AU	36	161	29	SS
Valovirta <i>et al.</i> , ⁴⁶ 2006	Finland	(5–15)	Grass mix	SAR	Drops	200,000 SQ-U	3	98	14	SSMS
Röder, <i>et al.</i> , ³⁶ 2007	Netherlands	(6–18)	Grass mix	SAR	Drops	1,976,000 BU	24	204	50	SS
Tseng <i>et al.</i> , ⁴³ 2008	Taiwan	9.7 (6–18)	Mites	PAR	Drops	37,312 IR	6	63	4	SS
Wahn <i>et al.</i> , ³⁵ 2009*	Multicenter	10.9 (5–17)	Grass mix	SAR	Tablets	NA	4	278	12	SSMS
Bufe <i>et al.</i> , ³⁸ 2009*	German	10.2 (5–16)	Grass mix	SAR	Tablets	75,000 SQ-T	6	253	19	SSMS
Stelmach <i>et al.</i> , ⁴² 2009*	Poland	8.9 (6–17)	Grass mix	SAR	Drops	43,800 IR	24	50	15	SSMS
Eifan <i>et al.</i> , ⁵³ 2010#	Turkey	7 (5–10)	Mites	PAR	Drops	73,876.8 STU	12	48	5	SSMS
Yonekura <i>et al.</i> , ⁵¹ 2010	Japan	9.5 (7–15)	Mites	PAR	Drops	200 µg	40wk	31	3	SSMS
Blaiss <i>et al.</i> , ³⁹ 2011*	USA	12.3 (5–17)	Grass mix	SAR	Tablets	75,000 SQ-T	6	345	63	SSMS
Stelmach <i>et al.</i> , ⁴⁷ 2011§	Poland	8.9 (6–18)	Grass mix	SAR	Drops	7300 µg 3600 µg	24	60	6	SSMS
Yukselen <i>et al.</i> , ⁴¹ 2012	Turkey	10.1	Mites	PAR and asthma	Drops	173,733 TU	12	32	2	SSMS
Ahmadiafshar <i>et al.</i> , ⁴⁰ 2012	Iran	(5–18)	Grass mix	SAR	Drops	NA	6	24	4	SSMS
de Bot <i>et al.</i> , ³³ 2012	Netherlands	11.7 (6–18)	Mites	PAR	Drops	435 µg	24	257	31	SS
Aydogan <i>et al.</i> , ²⁹ 2013	Turkey	(5–10)	Mites	PAR	Drops	44,500 IR	12	18	2	SSMS
Shao <i>et al.</i> , ⁴⁴ 2014#	China	6.2 (3–13)	Mites	PAR	Drops	2638.7 µg	12	264	46	SSMS

PAR = Perennial allergic rhinitis; STU = specific treatment unit; SS = symptom score; SAR = seasonal allergic rhinitis; IR = index of reactivity; MS = medication score; AU = allergic unit; SQ-U = standardized quality unit; SQ-T = standardized quality tablet; BU = biologic unit; NA = not afforded; N(all) = the number of total sample; Not Located = the study subjects dropped out; TU = treatment unit.

*The study used a pre-cosensational schedule.

#An open-label randomized controlled trial.

§The study used both pre-cosensational and continuous schedules.

for SAR was performed by examining symptom and medication scores.

RESULTS

Study Selection

Briefly, of the 3179 citations retrieved initially through the search algorithm, we ultimately included in our study 26 eligible clinical trials^{29–54} that assessed 2917 randomized children. Duplicate publications and those with unsuitable data were excluded from the meta-analysis (Fig. 1).

Population and Study Characteristics

The characteristics of the included studies are summarized in Table 1. Trials were published from 1990 to 2016. The majority (17 studies, 2077 participants) of the trials assessed patients of primarily European background. Other patient backgrounds included North America (1 study, 345 participants), East Asia (3 studies, 358 participants), and Western Asia (5 studies, 137 participants). The largest trial included 345 participants. Of 2917 participants, 1409 and 1244 were randomized to receive SLIT and to serve as controls, respectively. The ages ranged from 3 to 18 years. The SLIT used in the studies in different units was standardized. The allergens used in the studies were house-dust mites ($n = 12$), grass pollen mixes ($n = 12$), *Parietaria* ($n = 1$), and olive ($n = 1$). Twenty-two^{29–34,36,37,40–48,50–54} trials provided the allergens in drops, four trials^{35,38,39,49} provided them in tablets. The period of study drug or placebo administration ranged from 3 to 36 months. The protocols used in the SAR studies^{34–40,42,45–50} were pre-seasonal ($n = 6$) and continuous ($n = 7$). One study³⁷ included both protocols. The prevalence of AR-related comorbidities differed among included studies. Two studies^{46,47} compared the effectiveness of SLIT protocols that used different doses. The cumulative dose was variable and measured in different units. Most studies were of high quality and double blinded, and intention-to-treat analyses were conducted in four such studies.^{33,36,38,43} The risk of bias of all studies is shown in Fig. 2A and summarized in Fig. 2B.

Patient Adherence

In the overall population, 374 patients (12.8%), of whom 191 received SLIT, discontinued treatment. Treatment discontinuation was due to AEs in 65 patients (2.5%), lack of compliance in 95 patients (3.6%), loss to follow up in 35 patients (1.0%), poor efficacy in 13 patients (0.5%), and incomplete data in 38 patients (1.4%). One trial did not provide data regarding discontinuation.

Outcomes and Synthesis of Evidence

Symptom Scores. Twenty-six studies,^{29–54} including 2261 randomized patients, provided sufficient data for quantitative synthesis of the evidence based on symptom scores. Overall, SLIT significantly reduced the daily nasal severity symptom score (SMD -0.55 [95% CI, -0.86 to -0.25 ; $p = 0.0003$, $I^2 = 90\%$) (Fig. 3), which indicated a 0.55 reduction in the standard deviation for symptom scores. Significant heterogeneity among studies was observed. Visual inspection of the funnel plot indicated asymmetry.

Medication Scores. The type of rescue medication varied among studies and included systemic antihistamines (available in all the studies), naphazoline nitrate as the decongestant, topical antihistamines, topical nasal corticosteroids, and systemic corticosteroids. Information on the use of rescue medication was available for 19 studies.^{29–31,34,35,37–42,44–49,51,53} However, the tools used to assess the use of rescue medication differed substantially among the studies. Overall, SLIT reduced the use of rescue medication (SMD -0.67 [95% CI, -0.96 to -0.38]; $p < 0.00001$, $I^2 = 83\%$) (Fig. 4), which corresponded to a 0.67 reduction in the standard deviation for the assessed scores.

A

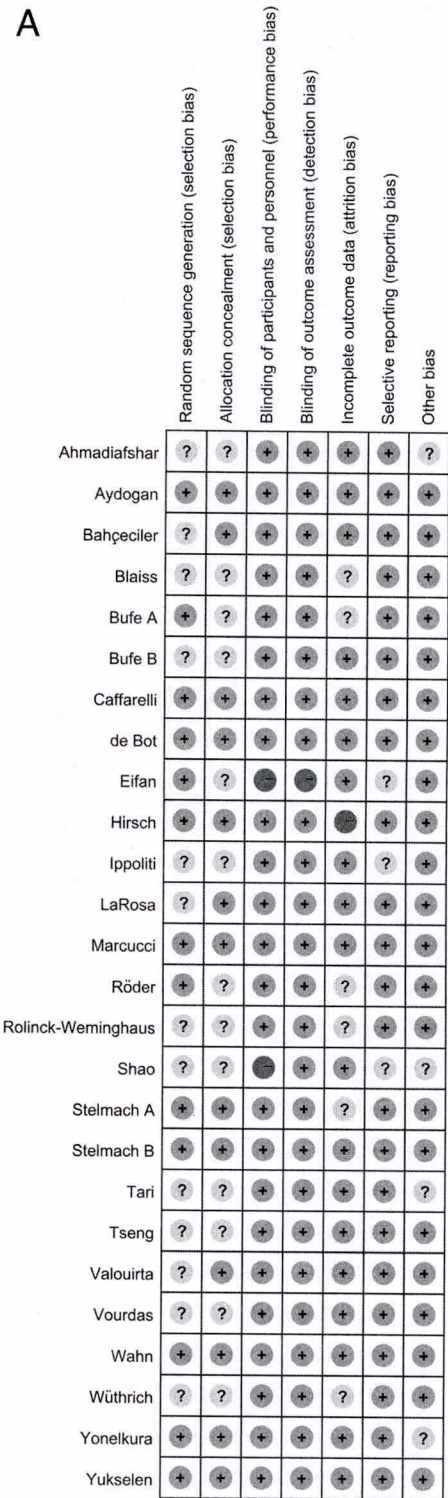


Figure 2. (A) Risk of bias summary.

As for symptom scores, significant heterogeneity among studies was observed. Visual inspection of the funnel plot indicated asymmetry.

AEs. Overall, 19 studies^{29,30,33–39,42–47,49,51–53} reported the number of AEs. The most frequently reported AEs in SLIT-treated and the placebo groups are listed in Table 2 according to anatomic classification. Oral pruritus was the AE that occurred most commonly in patients who were receiving SLIT.

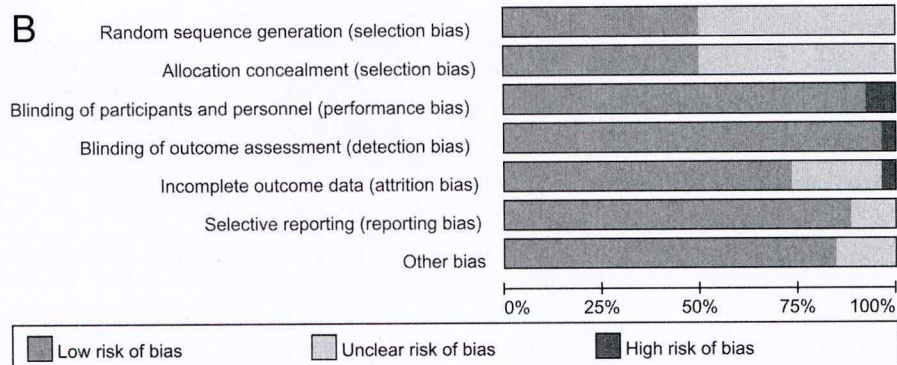


Figure 2. (B) Risk of bias graph.

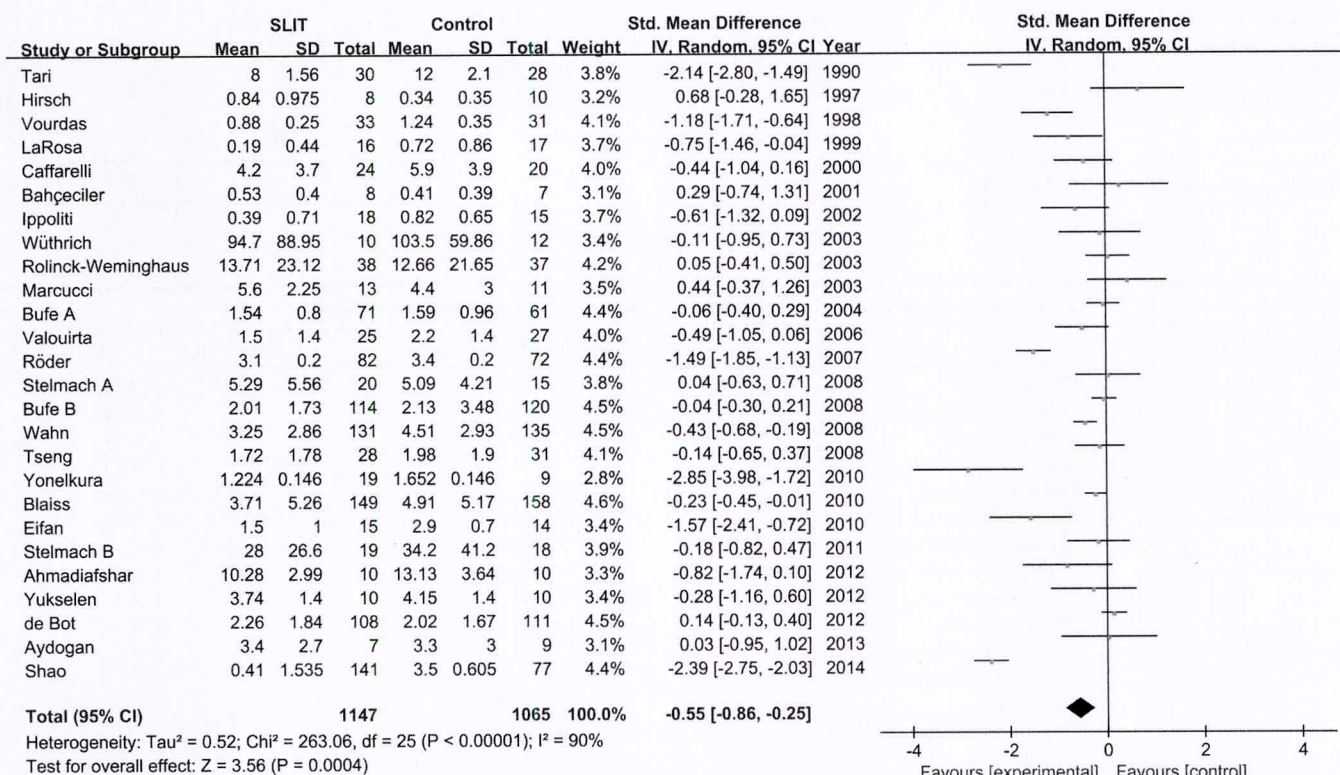


Figure 3. Nasal symptom scores.

Network Meta-Analysis. Network meta-analysis revealed no significant difference between the pre-coseasonal and continuous SLIT protocols for SAR in symptom scores (SMD -6.55 [95% CI, -25.38 to 12.29]; $p = 0.496$) and medication scores (SMD -8.83 [95% CI, -22.10 to 4.43]; $p = 0.192$).

Subgroup and Sensitivity Analysis. We performed a subgroup analysis that evaluated the trials that used SLIT for the type of allergen, different modality, and treatment duration (Table 3). Interestingly, in the subgroup analysis, we detected that SLIT produced significant reductions in symptom scores of pediatric patients with SAR (SMD -0.43 [95% CI, -0.69 to -0.17]; $p = 0.001$) but not in PAR (SMD -0.70 [95% CI, -1.43 to 0.03]; $p = 0.06$). *Post hoc* sensitivity analyses by using the fixed-effects model did not substantially change the overall significance for AR symptoms or medication scores. When a sensitivity analysis was conducted in which small studies ($n < 30$) were excluded, we did not find significant changes in any primary outcome of AR. Analogous results were obtained when excluding open-label trials for AR symptoms and medication scores. Excluding those studies with dropout rates of $>20\%$, the reduction was statistically significant for AR symptoms and rhinitis medication (Table 4).

Publication Bias. Visual inspection of funnel plots revealed some asymmetry in symptom score (Fig. 5A) and medication score (Fig. 5B) data from patients who received SLIT. The Egger regression analysis produced p values for these outcomes of 0.466 and 0.008, symptom score and medication score, respectively. These values provide no evidence of publication bias for studies that investigated symptom scores but evidence of potential publication bias or asymmetry for those who investigated medication scores. The numbers of studies included in the latter analysis (medication score studies, $n = 19$) may also have limited the power of an Egger regression.

DISCUSSION

The present systematic review and meta-analysis was based on 26 RCTs that examined the efficacy of SLIT for pediatric AR and included 2922 children. Our meta-analysis illuminated that SLIT is associated significantly with symptom relief and with reducing the need for medication in pediatric patients. The results of multiple systematic reviews led to recommendations for the use of SLIT in the management of pediatric AR. Moreover, more RCTs with larger

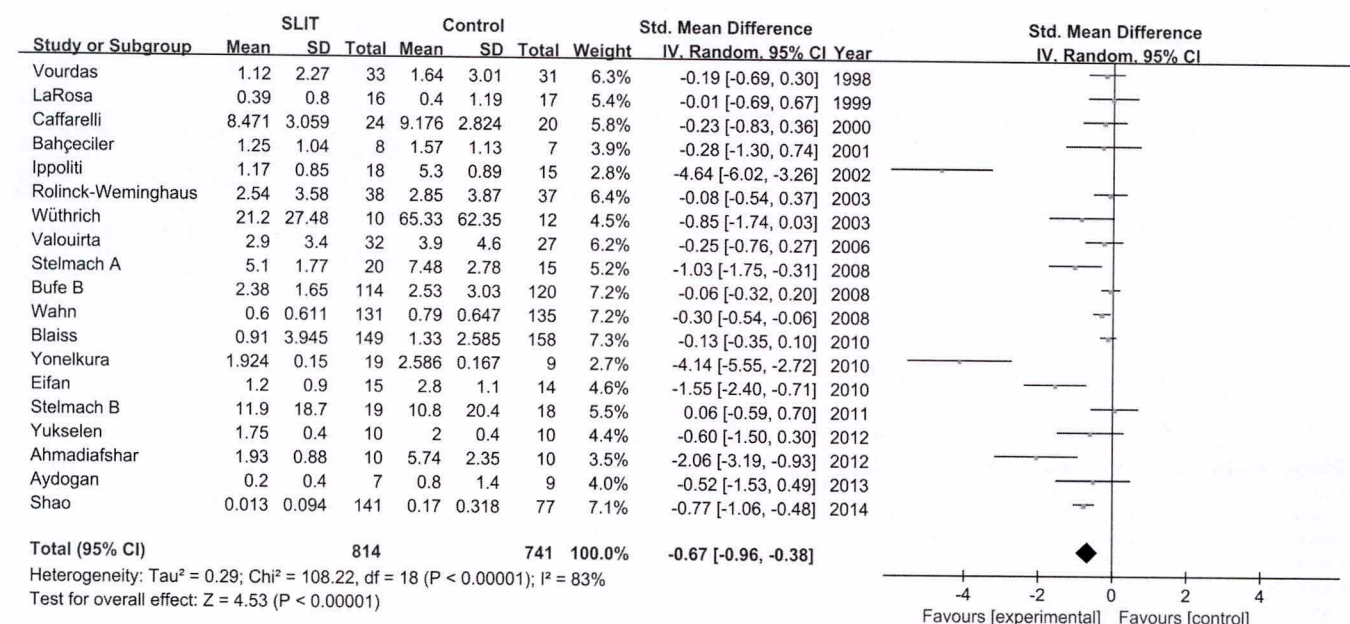


Figure 4. Nasal medication scores.

Table 2 Reported AEs in the patients in the active and placebo groups included in the safety evaluation

Organ Class	AEs	SLIT, no. (%) (n = 1167)	Placebo, no. (%) (n = 1025)
Oral	Oral pruritus	273 (23.4)	47 (4.6)
	Labial swelling	25 (2.1)	3 (0.3)
	Edema mouth	36 (2.8)	1 (0.1)
Nose	Aggravating rhinitis	164 (14.1)	124 (12.1)
	Nasal symptoms	123 (10.5)	122 (11.9)
Gastrointestinal	Gastrointestinal symptoms	199 (17.1)	155 (15.1)
	Stomach symptoms	30 (2.3)	4 (0.4)
Pharyngeal	Pharyngeal edema	16 (1.4)	3 (0.3)
	Pharyngolaryngeal pain	14 (1.2)	4 (0.4)
	Throat irritation	102 (8.1)	32 (3.1)
Others	Aggravating asthma	23 (1.8)	2 (0.2)
	Conjunctivitis symptoms	168 (14.4)	169 (16.5)
	Ear pruritus	20 (1.7)	2 (0.2)
	Local skin allergic reaction	183 (15.7)	174 (17.0)
	Headaches	10 (0.9)	7 (0.7)
	Upper respiratory tract infection	197 (16.9)	184 (18.0)

AE = Adverse event.

Table 3 Subgroup analysis of efficacy according to treatment characteristics

Subanalysis	Symptom Score				Medication Score			
	No. Studies	No. Patients	SMD (95% CI)	p Value	No. Studies	No. Patients	SMD (95% CI)	p Value
Pollen	14	1475	-0.43 (-0.69 to -0.17)	0.001	12	1196	-0.26 (-0.44 to -0.08)	0.005
House dust mites	12	737	-0.70 (-1.43 to 0.03)	0.06	7	359	-1.66 (-2.60 to -0.71)	0.0006
Tablets	4	851	-0.26 (-0.44 to -0.07)	0.007	4	851	-0.94 (-1.38 to -0.50)	<0.0001
Drops	22	1361	-0.61 (-1.02 to -0.20)	0.004	15	704	-0.17 (-0.30 to -0.03)	0.01

SMD = Standardized mean difference; CI = confidence interval.

samples are needed to confirm the safety of SLIT. In 2006, Penagos *et al.*,²⁶ to our knowledge, published the first meta-analysis of RCTs that examined SLIT for AR in children and recommended the standardized application of this therapy. In two recent reviews, Kim *et al.*⁵⁵ and Larenas-Linnemann *et al.*⁵⁶ also highlighted evidence that supported the efficacy and safety of SLIT for the management of allergic respiratory diseases.

This analysis mostly focused on the use of commercially available allergen immunotherapy products in children. Compared with controls, SLIT significantly reduced AR symptoms and medication use. SLIT administration in drop ($p = 0.004$) and tablet ($p = 0.007$) forms resulted in significant differences in symptom scores. SLIT produced significant reductions in symptom scores of pediatric patients with SAR but not of those with PAR ($p = 0.06$). Moreover, the observed

Table 4 Sensitivity analysis of efficacy

Sensitivity Analysis	Symptom Score			Medication Score		
	No. Studies	SMD (95% CI)	p Value	No. Studies	SMD (95% CI)	p Value
Fixed-effects model	26	-0.47 (-0.56 to -0.38)	<0.00001	19	-0.36 (-0.46 to -0.25)	<0.00001
Excluded small studies ($N < 30$)	17	-0.60 (-0.96 to -0.24)	0.001	12	-0.40 (-0.68 to -0.12)	0.005
Excluded open label trials	24	-0.42 (-0.67 to -0.18)	0.0007	17	-0.61 (-0.92 to -0.31)	<0.0001
Excluded high dropout rate ($>20\%$)	21	-0.63 (-0.97 to -0.29)	0.0002	16	-0.69 (-1.02 to -0.37)	<0.0001

SMD = Standardized mean difference; CI = confidence interval.

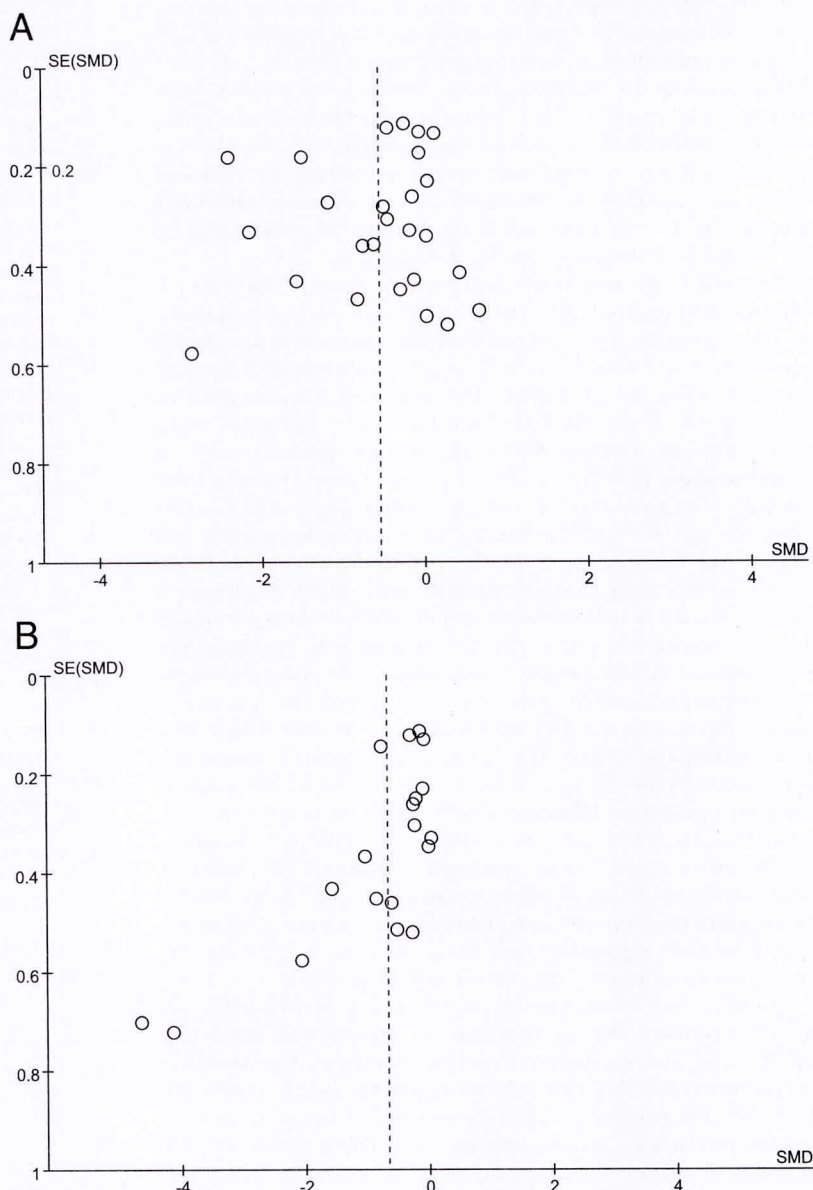


Figure 5. Funnel plot for nasal symptom scores (A) and nasal medication scores (B).

SLIT effect was mild in some included PAR studies. This phenomenon may be related to the following reasons, stated in publications included in the present analysis: lack of effectiveness due to low dosage,⁵² use of a twice-weekly regimen during the maintenance phase,³⁰ and the inclusion of small numbers of patients.³³ Larenas-Linnemann *et al.*⁵⁶ indicated that the severity of disease in patients included in some reviews was insufficient to enable the detection of treatment effects. These investigators concluded that SLIT was effective for pediatric AR caused by grass

pollen but that its efficacy for pediatric AR caused by house-dust mites remained controversial. Thus, more trials are needed for the development of recommendations regarding the use of SLIT for pediatric AR caused by house-dust mites.

This analysis provided indirect evidence that commercially available pre-coseasonal and continuous SLIT protocols for SAR have similar efficacy. Both protocols resulted in significant reductions in symptom scores compared with placebo, with little difference be-

tween these protocols.⁴⁷ Network meta-analysis revealed no significant difference between the pre-coseasonal and continuous SLIT protocols for pediatric SAR in symptom scores ($p = 0.496$) and medication scores ($p = 0.192$). These results were robust because studies that contributed large amounts of heterogeneity were removed, and only those that involved the use of commercially available products were included, which may have provided a more valid clinical comparison. Gaps and limitations remain because outcome assessment differed among studies and data on key covariates, which could affect AR symptoms more or less, including ambient temperature,⁵⁷ air pollution,⁵⁸ environmental tobacco smoking,⁵⁹ were often not captured or reported. Direct head-to-head comparisons with control for other variables would be useful, but the performance of such studies is challenging because large samples are required. Such trials are also expensive, and they remain dependent on uncontrollable factors, such as pollen counts. With the lack of head-to-head trials, indirect methodology can provide useful evidence of differences in treatment effects. A movement toward examining common end points and capturing key covariates for ease of interpretation and comparison of study results would aid clinicians' identification of the most suitable treatment options for their patients.

Reported treatment-related AEs occurred at comparable rates in patients who received SLIT and placebo. Oral pruritus and throat irritation were the most common treatment-related AEs. Cox *et al.*⁶⁰ showed that SLIT is safer than SCIT, with no death reported during 23 years of testing and clinical use. The number of AEs seemed to be dose dependent, as with SCIT. Two serious AEs (not anaphylactic shock) were reported in patients who had previously experienced severe reactions to SCIT⁶¹; thus, SLIT tolerance should be considered carefully in patients who experienced previous serious AEs. Furthermore, Rienzo *et al.*⁶² and Fiocchi *et al.*⁶³ concluded in their surveys that SLIT is safe for children. In the included studies, five serious AEs were reported³⁵; two AEs occurred in the active group (exacerbation of asthma and Burkitt lymphoma, neither of which were considered to be treatment related), and three AEs occurred in the placebo group. Data from all included studies showed that discontinuation due to local treatment-related AEs generally occurred within the first several weeks of treatment, that they are transient and their occurrence may differ among applications, and that their occurrence decreases over time. A considerable amount of RCTs on SLIT used for pediatric AR have been published. However, a large part of them are short term, small samples, and single center, which is restricted to the evidence for the safety of SLIT in the treatment of pediatric AR. Although anaphylactic reactions fall within the range of rare, life-threatening events, very large samples, long-term, and multicenter trials are required for their appropriate assessment, and their quantification requires the use of passive and active surveillance systems.

Our study had certain limitations. Differences in the baseline severity of pediatric AR, the prevalence of patients with respiratory allergic complications, the scores used for assessment, pharmaceutical preparations, and SLIT protocols among studies compromised comparability and may have limited the accuracy of this meta-analysis. For this reason, we used a robust measure (SMD) to control outcome diversity. To reduce the bias due to interstudy heterogeneity, we used a random-effects model. Moreover, language and publication biases should also be considered in analyses of efficacy trials. In our study, publication bias may have been attributable to preferential publication of positive results, bias toward publication of negative results, and analysis of small samples in RCTs. Caution should be practiced in interpreting the results, because the sensitivity analysis erased the statistical significance. Also, although the majority of eligible trials were double blind and placebo controlled, the reporting of measures taken to safeguard the blinding process was far from adequate in the analyzed trials, which resulted in considerable uncertainty regarding important methodologic aspects of these studies.

CONCLUSION

This meta-analysis demonstrated that SLIT was significantly associated with symptom relief and decreased rescue medication use in pediatric patients. Also, according to the limitation of published RCTs, we stressed the concept that SLIT for pediatric AR would be more effective with an experienced diagnostic pathway as well as appropriate planned follow-up. Large clinical trials are needed to address the rare occurrence of serious AEs.

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