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SYSTEMATIC REVIEW AND META-ANALYSIS

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Sublingual Immunotherapy for Asthmatic Children Sensitized to House Dust Mite

A Meta-Analysis

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Abstract: The house dust mite is one of the most common allergens worldwide. There is good evidence that house dust mite subcutaneous immunotherapy is efficacious and has long-term benefit in children. However, the evidence of the benefit of house dust mite sublingual immunotherapy (SLIT) is less convincing. The purpose of this meta-analysis was to evaluate that efficacy and safety of dust mite SLIT in children with asthma.

Medical Literature Analysis and Retrieval System Online, ISI Web of Knowledge, and Cochrane Central Register of Controlled Trials databases until February 2014 were searched. The primary outcome was mean change in asthma symptom score. Secondary outcomes included mean change in serum immunoglobulin G4 (sIgG4), specific *Dermatophagoides pteronyssinus*, immunoglobulin E (IgE) levels, and medication score. Safety was also assessed.

We found that SLIT significantly decreased asthma symptom score ($P = 0.007$) and increased sIgG4 levels ($P = 0.011$) greater than control in children (<18 years of age) with asthma. There was no difference between SLIT and control groups in specific *D pteronyssinus* IgE levels ($P = 0.076$) and medication score ($P = 0.408$). The safety profile was similar between groups.

Our study indicates that dust mite SLIT therapy was effective in reducing asthma symptoms and in increasing sIgG4 but did not significantly reduce medication scores or specific *D pteronyssinus* IgE levels. Our findings are not enough to support the use of dust mite SLIT in children with asthma.

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Abbreviations: SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy.

INTRODUCTION

Allergen-specific immunotherapy along with allergy avoidance and patient education are mainstay approaches for treating allergic disease.[1–4] Specific allergen immunotherapy is the sole treatment for changing the natural course of allergic disease and minimizing the risk of an exacerbation.[4] Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are often used in clinical practice, but the frequency of their use differs worldwide with SCIT being commonly used in the United States, whereas in Europe SLIT and SCIT are about equally prescribed.[5–7]

There has been an increase in the prevalence of asthma and allergies over the past few decades, and it is thought that it may, in part, be due to an increase in indoor environmental exposure.[8] Allergens and irritants such as house dust mite, domestic pets, mold, cockroaches, mice, tobacco smoke, endotoxin, and air pollution are important indoor allergens.[9] The house dust mite is one of the most common allergens worldwide, and the major strains are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

SCIT and SLIT show efficacy in treating allergies in children.[10] SCIT has been validated for the treatment of asthma and rhinitis, using standardized house dust mite extracts.[11–14] However, in the pediatric age group, SCIT has some limitations due to the discomfort of repeated injections and side effects.[15,16] Prior meta-analyses in children indicate that SLIT is an effective and safe alternative to SCIT in treating allergic respiratory symptoms.[10,17] There is growing evidence that SLIT therapy is associated with a lower incidence of systemic reactions compared with control and that it reduces the durations and dose of inhaled corticosteroids used and improves lung function in children with asthma.[5,16,18,19]

A number of studies focused on house dust mite SCIT and house dust mite SLIT in treating asthma or rhinitis in general but not for a particular antigen. However, many of these studies were small and used variable doses of antigen. There is good evidence that house dust mite SCIT is efficacious and has long-term benefit in children.[3] However, the evidence of the benefit of house dust mite SLIT is less convincing.[3] The studies that have evaluated the efficacy and safety of house dust mite SLIT in treating asthma show high clinical and methodological heterogeneity, which make it difficult to determine the benefit of house dust mite SLIT as allergen immunotherapy.[3] Many studies were underpowered to be able to make firm conclusions, and the efficacy findings across studies have been variable.[3] The objective of this current meta-analysis was to further evaluate that efficacy and safety of dust mite SLIT in children with asthma.

METHODS

Search Strategy

Medical Literature Analysis and Retrieval System Online, ISI Web of Knowledge, and Cochrane Central Register of

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Controlled Trials databases until February 2014 were searched for randomized controlled trials that investigated the efficacy of SLIT in children with asthma. Search terms included asthma, sublingual, immunotherapy, mite allergen, and house dust mite. Included studies were randomized, controlled, and prospective in design and published in English. The studies had to have evaluated children (<18 years of age) with asthma who were treated with SLIT or control and must have reported clinical efficacy outcome, *D pteronyssinus* immunoglobulin E (IgE) levels, serum IgG4 levels, and safety. Studies that included only children with rhinitis or in which subjects received SCIT were excluded. Letters, comments, editorials, and case reports were also excluded. The approval by an institutional review board is not required for this study because human subjects were not studied.

Data Extraction

The following data was extracted from the different studies: name of the first author, type of patients studied, treatments, number of patients, duration of treatment, cumulative dose, sex, and mean age. Other information extracted included treatment outcomes (ie, specific *D pteronyssinus* IgE, serum immunoglobulin G4 [sIgG4], asthma symptom score, medication score) and adverse events. Two independent reviewers extracted the data from the eligible studies, and a third reviewer was consulted to resolve any disagreement(s).

Quality Assessment

The included studies were assessed for risk bias using the "Risk of Bias" assessment tool, Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, and recommendations for judging risk of bias provided in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[20]

Statistical Analysis

The primary outcome was mean change in asthma symptom score. Secondary outcomes included mean change in medication score, specific *D pteronyssinus* IgE levels, and sIgG4 levels. Safety was also assessed. The mean ± standard deviation [SD] for the measurements of asthma symptom score and *D pteronyssinus* IgE levels were used for the meta-analysis because across the studies the data were reported in multiple ways (ie, mean ± SD or median [range: minimum, maximum]).[21] Because the scale or unit across the studies for the efficacy outcomes (asthma symptom score, medication score, specific *D pteronyssinus* IgE level, and sIgG4) differed, the standardized differences in mean changes with 95% confidence intervals (CIs) were calculated.[22] The values for the different outcomes when changed to the same unit (international units per milliliter) were diverse, making it not meaningful to change the standardized difference in means to the clinical values. The odds ratio (OR) with 95% CI between SLIT and control groups was calculated for the occurrence of adverse event among children treated with SLIT compared with the control group. Heterogeneity among the studies was assessed by calculating Cochran Q and the I^2 statistic. For the Q statistic, $P < 0.10$ indicated statistically significant heterogeneity. I^2 statistics indicate the percentage of the observed between-study variability caused by heterogeneity. Heterogeneity was determined using I^2 statistics and was defined as follows: 0% to 24% = no heterogeneity, 25% to 49% = moderate heterogeneity, 50% to 74% = large heterogeneity, and 75% to 100% = extreme heterogeneity. The random effects model (DerSimonian–Laird method)[23] was adopted for the current study because it assumes that different studies may have different underlying effects, and it also takes into consideration both within and between-study variation. Combined standardized differences in mean change or ORs were calculated, and a 2-sided P value < 0.05 was considered to indicate statistical significance.

Sensitivity analysis was performed for efficacy outcomes based on the leave-one-out approach. When at least 5 studies had sufficient data for the outcome, funnel plot analysis with 1-sided Egger tests were performed to evaluate the publication bias for the meta-analyses.[24] All statistical analyses were performed using the Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

The database search identified 91 potential studies of which 57 were eliminated as not being relevant (Figure 1). The text of the remaining 34 studies were assessed in detail, and 23 were excluded due to the study being a duplication of an included study (n = 3), the full text or study design was not available (n = 5), the outcomes of interest were not reported (n = 2), the subjects evaluated were adults (n = 3), the patients were children without asthma (n = 4), SLIT was not compared with control (n = 3), and SLIT was not specified as the treatment (n = 3). The 11 remaining studies were included in the review.[25–35]

Study Characteristics

The 11 studies include a total of 454 children with asthma/rhinitis who were sensitized to house dust mites and were treated with SLIT or control for between 4 months to 3 years (Table 1). The total number of patients in each of the studies ranged from 15 to 109 patients. The proportion of patients who were boys ranged from 40% to 71%, and the mean age ranged from 6.5 to 15 years. In most of the studies, some additional therapies were allowed including a minimum dose of inhaled corticosteroids,[26] rescue medication,[25,28,29,32,35] and oral antihistamines.[34] In the studies by Marcucci et al[30] and Bahceciler et al,[31] SLIT patients were also on pharmacotherapy. Across the entire population, 230 patients underwent SLIT treatment, and 224 were treated with placebo/pharmacotherapy.

The types of asthma regimens and symptom and medications scores varied across studies (Table 2). The regimens

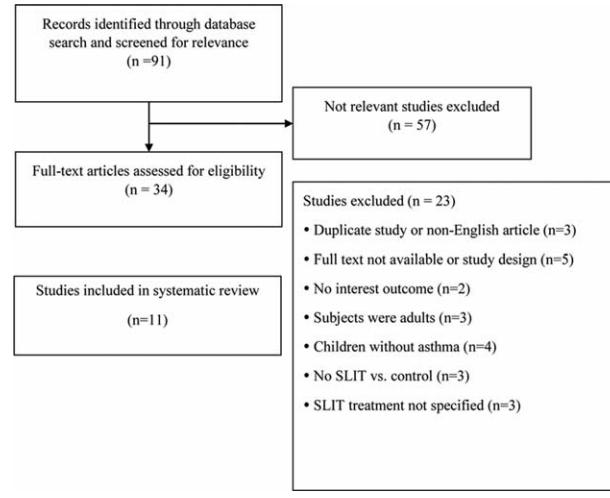


FIGURE 1. Flow diagram of study selection.

TABLE 1. Summary of Basic Characteristics of Included Studies

Study	Type of Patients	Comparison	Number of Patient	Treatment Duration	Cumulative Dose	Males	Age, y (mean ± SD)
Yukselen (2012)	Rhinitis with asthma related to HDM symptoms	SLIT	10	1 y	86866.5 TU Der p1	50%	9.2 (3.4)
		Placebo	10		86866.5 TU Der f1	60%	10.1 (2.7)
Keles (2011)	Mild persistent/moderate asthma/ rhinitis according to GINA guidelines, monosensitized to HDM	SLIT	13	1 y	54.3 g Der p1	46%	8.55 (2.1)
		Pharmacotherapy	12		54.3 g Der f1	58%	7.9 (2.8)
Eifan (2010)	Mild persistent asthma/rhinitis according to GINA guidelines, having HDM-related asthma/ rhinitis symptoms	SLIT	16	1 y	295.5 g Der p1	44%	6.5 (1.6)
		Pharmacotherapy	16		295.5 g Der f1	44%	7.57 (1.98)
Pham-Thi (2007)	HDM-induced allergic asthma	SLIT	54	18 mo	6.9 mg Der p1	72%	9.6 (5, 14)†
		Placebo	55		14.7 mg Der f1	71%	9.5 (5, 16)†
Lue (2006)	Mild-to-moderate asthma, with single sensitization to HDM	SLIT	10	24 wk	1.7 mg Der p1	40%	7.7 (1.8)
		Placebo	10		3.0 mg Der f1	40%	8.6 (1.80
Niu (2006)	Mild-to-moderate asthma with a single sensitization to HDM	SLIT	49	24 wk	1.7 mg Der p1	62%	7.9 (1.6)
		Placebo	48		3.0 mg Der f1	58%	8.2 (1.7)
Marcucci (2005)	Rhinitis with/without asthma related symptoms to HDM	SLIT	13	3 y	110 or 55 g of mite allergen	NR	8.5 (4–15)
		Placebo	11			NR	
Bahçeciler (2001)	Asthma and rhinitis allergic to HDM	SLIT	8	4 mo	0.56 mg Der p1	50%	12.4 (7.8, 18)*
		Placebo	7		0.98 mg Der f1	57%	12 (7.3, 15)*
Pajno (2000)	Mild-to-moderate asthma, with single sensitization to HDM	SLIT	12	2 y	NR	58%	11 (8, 14)†
		Placebo	12			50%	12 (8,15)†
Hirsch (1997)	Mild-to-moderate asthma, allergic rhinitis or both	SLIT	15	12 mo	570 μg Der p1	66.7%	6–15
		Placebo	15			66.7%	6–14
Tari (1990)	Asthma and rhinitis allergic to HDM	SLIT	30	18 mo	NA	NA	NA
		Placebo	28			NA	NA

GINA = Global Initiative for Asthma, HMD = house mite dust, NA = not available, SLIT = sublingual immunotherapy.
* Median (range).
† Mean (range).

TABLE 2. Summary of Treatment and Evaluation Tools of Included Studies

Study	Immunotherapy Regimen	Tools for Evaluating Symptom Score	Tools for Evaluating Medication Score
Yukselen (2012)	12-week build-up phase: 1 drop of 10 TU/mL daily increasing to 28 drops on day 28, 1–28 drops of 100 TU/mL on days 29–56 and 1–28 drops of 1,000 TU/mL on days 57–84 Maintenance phase: 3 times per week as 28 drops of 1,000 TU/mL	Self-assessment diary: 0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms; asthma symptoms (wheezing, breathlessness, dyspnoea, and cough)	1 point: β2-agonist rescue drug was taken on that day, and 0 if not. Inhaled budesonide (μg/day): 0:0; 1:0–200; 2:200–400; 3:400–800; 4:800–1,000. Intranasal mometasone (μg/day): 0:0; 1:50; 2:100; 3:200
Keles (2011)	1-mo build-up phase followed by maintenance of 5 drops 3 times a week. The dose of Der p 1 that was given in the build-up and maintenance phases was 1.5 and 52.8 mg of Der p 1 and 1.5 and 52.8 mg of Der f 1	NA	NA
Eifan (2010)	1-mo build-up phase followed by a maintenance phase of 5 drops 3 times a week	A daily evaluation of symptoms according to a 4-point scoring system: 0 (no symptoms) to 3 (severe symptoms); asthma symptoms (wheezing, breathlessness, dyspnoea, and cough)	Diary card recorded medications use: 1 point: for β2-agonists and antihistamines, 2 points: inhaled/intranasal steroids, 3 points: one tablet of corticosteroid
Pham-Thi (2007)	A tablet at a concentration of 100 IR contained 9 μg Der p1 and 19 μg Der f 1, which is the major *Dermatophagoides farinae* allergen. Four concentrations were used: 10, 30, 100, and 300 IR	Daytime and nighttime asthma symptoms were recorded using a 4-point scale (0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms)	NA
Lue (2006)	Build-up phase: 1 drop from the 10 IR/mL vial and increasing to 10 drops on day 7, and then stepped up to the 100 IR/mL vial, with 1 drop on day 8 and increasing to 20 drops on day 14. On day 15, 7 drops from the 300 IR/mL vial and increasing doses to 20 drops on day 19 Maintenance phase: Once the 20-drop dose of 300 IR/mL was reached; maintained the same dose for the following 21 weeks.	Daytime and nighttime asthma symptoms were recorded using a 4-point scale (0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms)	Patients were allowed to take the following medications if needed: inhaled corticosteroids [Pulmicort Turbuhaler (AstraZeneca AB, Södertälje, Sweden)], inhaled β2-agonist [Bricanyl Turbuhaler (AstraZeneca AB, Södertälje, Sweden)], and oral corticosteroids (prednisolone, 5 mg). The numbers of puffs and/or tables were also recorded
Niu (2006)	3-week build-up phase: one drop from the 10 IR/mL and increasing to 10 drops on day 7, then one drop from 100 IR/mL vial on day 8 and the dose was increased to 20 drops on day 14. On day 15, 7 drops from the 300 IR/mL vial and increasing to 20 drops on day 19. Maintenance phase: once the 20-drop 300 IR/mL was reached, maintained the same dose for the following 21 weeks	Daytime and nighttime asthma symptoms were recorded using a 4-point scale (0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms)	Patients were allowed to take the following rescue medications if needed: inhaled corticosteroids (budesonide turbuhaler), inhaled β2-agonist (terbutaline aerosol), and oral corticosteroids (pre dnisolone 5 mg). The number of puffs and/or tablets was recorded

Study	Immunotherapy Regimen	Tools for Evaluating Symptom Score	Tools for Evaluating Medication Score
Marcucci (2005)	30-day build-up phase Maintenance phase: 5 drops of the top-dose vial) corresponded to 0.8 and 0.4 μg of mite allergen groups 1 and 2, respectively, and were administered daily for 3 y	Yearly cumulative asthma symptom scores: 0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms; asthma symptoms (breathlessness and cough)	Diary card recorded medications use: 1 point for each application of nasal and/or ocular cromoglycate drops in both nostrils or eyes; 2 points for every inhalation of β2-agonist; 3 points for every antihistamine taken
Bahçeciler (2001)	Build-up phase: 1 drop from the 0.1 IR/mL vial and increasing to 10 drops on day 7. This process was repeated with the 1 IR/mL (for days 8 ± 14) and 10 IR/mL (for days 15 ± 21) vials. On days 22 ± 28, 1 ± 20 drops were given from the fourth vial (100 IR/mL) Maintenance phase: once the 20-drop 100 IR/mL was reached, maintained the same dose daily for 4 wk and then 2 times a week for the following 4 mo	0 no symptom, 1 mild, 2 moderate, and 3 severe symptoms; asthma symptoms (wheezing, dyspnoea, and cough)	NA
Pajno (2000)	Build-up phase: 1 drop from the first vial daily and increasing by 1 drop every day up to 5 drops. The procedure was then repeated with each of the following vials until the maximum dose (5 drops from vial 4, 10 BU/mL) was reached. Maintenance phase: 5 drops from vial 4, 10 BU/mL, corresponding to 2.4 mg Der p 1 and 1.2 mg Der p 2/wk for 3 times a week until the end of the trial	NA	Each drug was scored as follows: score 1: bronchodilators; score 2: inhaled corticosteroids (cromoglycate only during 1993); score 4: oral steroids (7-day course)
Hirsch (1997)	3-week build-up phase: daily increasing doses from 1–7 drops of a 1:100 dilution of the final preparation in the first week, 1–7 drops of a 1:10 dilution in the second week, and 1–7 drops of the final preparation in the third week Maintenance phase: 7 drops on 3 days/wk	0–3 points separately for different organs and symptom types (eyes: itching, secretion, reddening; nose: sneezing, secretion, nasal blockage; lower airways: cough, wheeze, shortness of breath)	NA
Tari (1990)	Build-up phase: 1 drop from the first vial daily and increasing by 1 drop every day up to 15 drops. The procedure was then repeated with each of the following vials until the maximum dose (15 drops from 500 STU/mL vial) was reached Maintenance phase: 15 drops from 500 STU/mL vial 3 times a week for 18 mo	0–3 points of such symptoms as sneezing, nasal discharge, nasal congestion and pruritus, itching and running eyes, and difficulty in breathing	Daily medication was recorded for each day

NA = not available.

TABLE 3. Summary of Primary and Secondary Outcomes and Adverse Event

		SLIT Group			Control Group		
			Baseline	Post-Treatment		Baseline	Post-Treatment
Outcome	Study	Sample Size	Mean (SD)	Mean (SD)	Sample Size	Mean (SD)	Mean (SD)
Asthma symptom score	Bahçeciler (2001)	8	0.64 (0.475)	0.3 (0.358)	7	0.33 (0.29)	0.26 (0.175)
	Eifan (2010)	16	1.4 (1.5)	0.2 (0.4)	16	0.95 (0.62)	2.5 (1.6)
	Lue (2006)	10	0.42 (0.23)	0.13 (0.19)	10	0.42 (0.34)	0.49 (0.38)
	Marcucci (2005)	13	0.121 (0.189)	0.022 (0.059)	11	0.096 (0.185)	0.022 (0.059)
	Niu (2006)	49	0.14 (0.05)	0.07 (0.03)	48	0.04 (0.01)	0.05 (0.02)
	Pham-Thi (2007)	54	0.19 (0.3)	0.15 (0.26)	55	0.17 (0.24)	0.08 (0.17)
	Hirsch (1997)	11	0.36 (0.04–1.3)*	0.07 (0–1.00)*	15	0.07 (0–1.4)*	0.28 (0–1.9)*
	Tari (1990)	30	9.69 (1.59)†	5.71 (1.71)†	28	9.83 (1.57)†	9.33 (1.01)†
Medication score	Eifan (2010)	16	2.8 (1.2)	1.2 (0.9)	16	2.5 (1.5)	2.8 (1.1)
	Lue (2006)	10	1.7 (1.08)	1 (0.94)	10	1.25 (0.72)	1.1 (1.15)
	Marcucci (2005)	13	14 (17.037)	0 (13.333)	11	35 (49.259)	4 (25.185)
Specific IgE *Dermatophagoides pteronyssinus* (IU/mL)	Eifan (2010)	16	98.6 (1.4)	77.4 (24.3)	16	94.3 (5.7)	77.1 (22.9)
	Keles (2011)	13	62 (52)	61 (53)	12	73 (37)	75 (41)
	Lue (2006)	10	3.93 (0.09)	3.95 (0.06)	10	3.86 (0.12)	3.84 (0.14)
	Niu (2006)	49	3.9 (0.37)	3.92 (0.28)	48	3.92 (0.35)	3.75 (0.81)
	Pajno (2000)	12	45.4 (12.6)‡	42 (10.4)‡	12	52.2 (11.2)‡	48 (7.2)‡
	Pham-Thi (2007)	54	208 (279.242)	250 (264.545)	55	197 (222.486)	135 (155.74)
	Hirsch (1997)	15	39.1 (3.5 to >100)	78.9 (20.4 to >100)	15	33.3 (2.7 to >100)	47.4 (1.8 to >100)
	Tari (1990)	30	9.59 (3.13)§	10.58 (3.68)§	28	8.61 (3.25)§	15.71 (2.84)§
sIgG4 (IU/mL)	Keles (2011)	13	0.21 (0.37)	0.22 (0.41)	12	0.11 (0.11)	0.09 (0.08)
	Lue (2006)	10	0.7 (0.1)	2.7 (0.8)	10	0.7 (0.1)	0.6 (0.1)
	Pham-Thi (2007)	54	489.72 (580.235)‖	1874.04 (2654.27)‖	55	319.62 (227.381)‖	273 (158.855)‖
	Yukselen (2012)	10	210 (217.778)‖	273 (497.778)‖	10	42 (77.778)‖	42 (62.222)‖
	Tari (1990)	30	2.49 (1.10)¶	10.71 (3.81)¶	28	2.04 (1.03)¶	2.78 (2.02)¶

Outcome	Study	SLIT Group			Control Group		
			Baseline	Post-Treatment		Baseline	Post-Treatment
		Sample Size	Mean (SD)	Mean (SD)	Sample Size	Mean (SD)	Mean (SD)
			Number of Adverse Events			Number of Adverse Event	
Adverse event	Yukselen (2012)	10	1		10	4	
	Eifan (2010)	16	0		16	0	
	Pham-Thi (2007)	54	39		55	37	
	Niu (2006)	49	6		48	7	
	Bahçeciler (2001)	8	0		7	0	
	Pajno (2000)	12	6		12	1	
	Tari (1990)	30	15		28	0	

IgE = immunoglobulin E, sIgG4 = serum immunoglobulin G4, SLIT = sublingual immunotherapy.
* Median (minimum–maximum).
† Weekly score.
‡ SU/mL.
§ PRU/mL.
‖ μg/L.
¶ μg/mL.

differed in length of the build-up phase and the dose of Index of Reactivity (IR) during the build-up and maintenance phase. Most of the studies assessed asthma symptoms using a 4-point scale that in general was 0 for no symptoms to 3 for severe asthma symptoms. The symptoms were either reported as daily scores or yearly scores. Medication scores were reported using diaries, number of rescue medication puffs or tablets used, or use of a specific rescue medication.

Asthma symptom score and medication score decreased from baseline in the SLIT treatment group in the studies that reported these outcomes. The changes of specific *D pteronyssinus* IgE varied, and sIgG4 levels increased from baseline to post-SLIT treatment across all of the 11 studies (Table 3). Overall, the frequency of adverse events was low (<15%) in most of the studies. Of the studies, 3 reported higher frequencies of adverse event. The study by Pham-Thi et al[27] reported a frequency of approximately 72% and 67% for SLIT and control groups, respectively. The studies by Pajno et al[32] and Tari et al[34] reported a frequency of approximately 50% in the SLIT group.

Four of the included studies also evaluated visual analogue score (VAS) for asthma symptoms.[25,26,32,35] Three of the studies[26,32,35] saw an improvement in VAS treatment group compared with control, whereas one study found no difference between the groups.[25] The markers used across studies to assess inflammation were diverse making this information difficult to compare.

Asthma Symptom Score

Eight of the included studies provided sufficient information regarding asthma symptom score before and after the treatment for analysis.[27–31,33–35] Evaluation of the pooled data indicated there was extreme heterogeneity among the studies ($Q = 91.19$, $df = 7$, $P < 0.001$; $I^2 = 92.32\%$). The findings of the meta-analysis indicated that the asthma symptom score significantly decreased more among children treated with SLIT compared with those treated with control (standardized differences in mean change = −1.202, 95% CI −2.071 to −0.333, $P = 0.007$, Figure 2).

Medication Score

Among the 11 included studies, only 3 provided sufficient information regarding medication score before and after treatment.[28,30,35] For these 3 studies, extreme heterogeneity among the studies was found after pooling of data ($Q = 13.16$, $df = 2$, $P = 0.001$; $I^2 = 84.8\%$). The results indicated that there was no difference in children treated with SLIT compared with those treated with control treatment (standardized differences in mean change = −0.52, 95% CI −1.753 to 0.713, $P = 0.408$, Figure 3A).

Specific *D pteronyssinus* IgE Levels

Of the 11 included studies, 7 provided sufficient information regarding specific *D pteronyssinus* IgE levels before and after treatment.[26–29,32,34,35] Analysis of the pooled data from the 7 studies indicated there was an extreme degree of heterogeneity ($Q = 26.32$, $df = 6$, $P < = 0.001$; $I^2 = 77.21\%$). The results found that there was no difference in the mean change in specific *D pteronyssinus* IgE levels between children treated with SLIT and those treated with control treatment (standardized differences in mean change = 0.430, 95% CI −0.045 to 0.905, $P = 0.076$, Figure 3B).

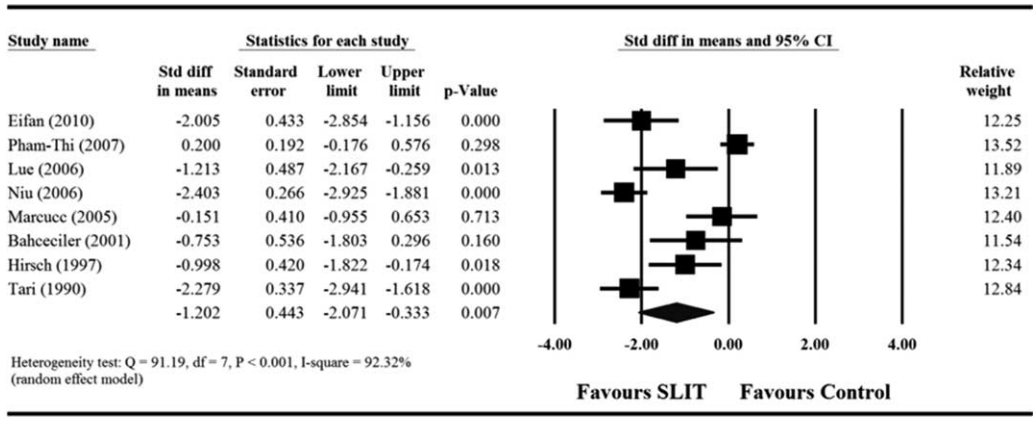


FIGURE 2. Meta-analyses for the comparisons of asthma symptom score between 2 treatment groups. CI = confidence interval.

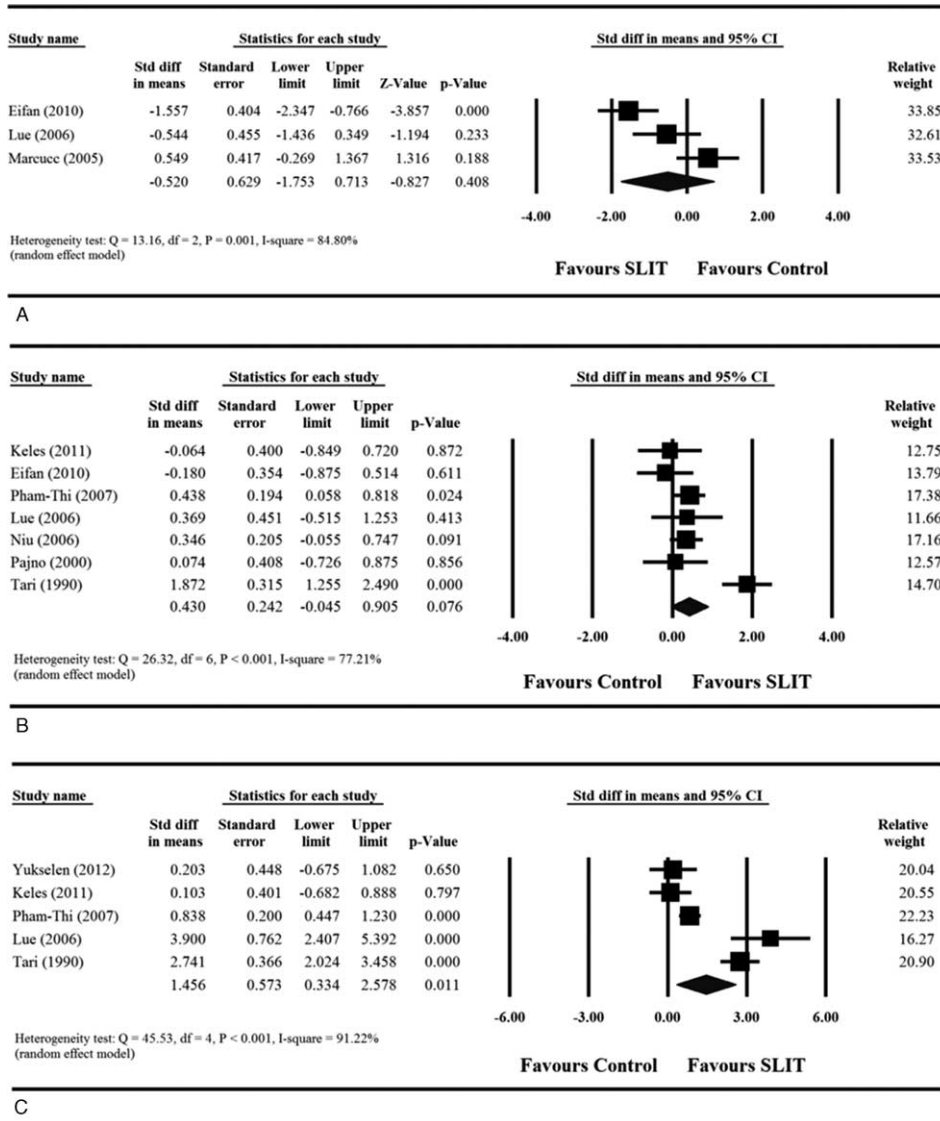


FIGURE 3. Meta-analyses for the comparisons of (A) medication score, (B) specific *Dermatophagoides pteronyssinus* IgE levels, and (C) sIgG4 levels between 2 treatment groups. CI = confidence interval, IgE = immunoglobulin E, sIgG4 = serum immunoglobulin G4.

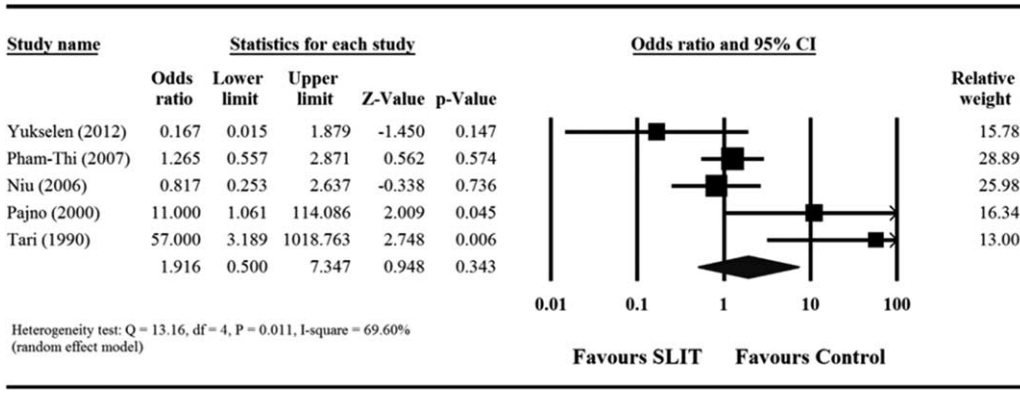


FIGURE 4. Meta-analyses for comparison of the safety outcome (adverse event) between 2 treatment groups. CI = confidence interval.

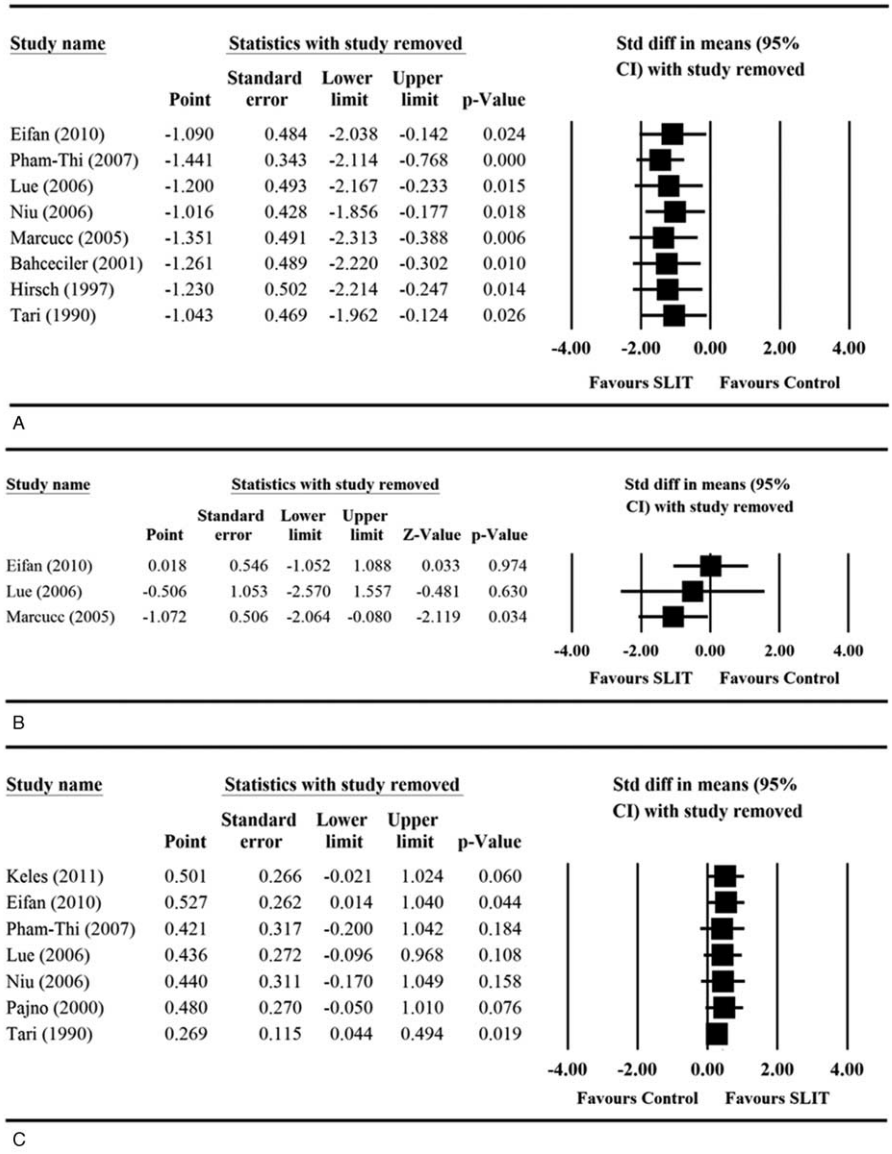
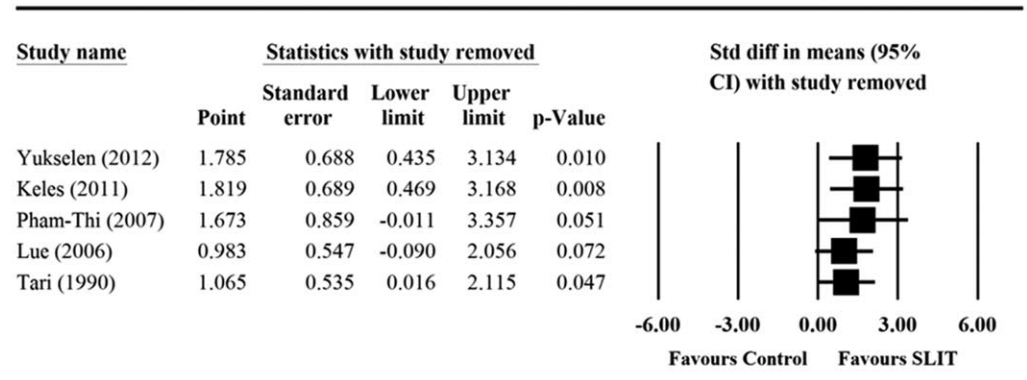
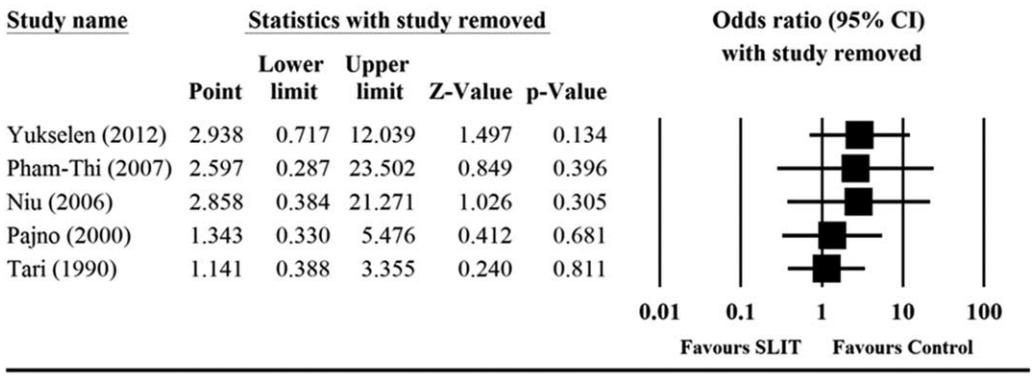


FIGURE 5. Sensitivity analyses of the comparisons of (A) asthma symptom score, (B) medication score, (C) specific *Dermatophagoides pteronyssinus* IgE levels, (D) sIgG4 levels, and (E) adverse event between two treatment groups. CI = confidence interval, IgE = immunoglobulin E, sIgG4 = serum immunoglobulin G4.



D



E

FIGURE 5. (Continued)

sIgG4 Levels

Five of the 11 studies provided sufficient information regarding sIgG4 before and after treatment.[25–28,34] Analysis of the pooled data showed there was extreme heterogeneity among the studies ($Q = 45.53$, $df = 4$, $P < 0.001$; $I^2 = 91.22\%$). The results indicate that the mean change in sIgG4 level was significantly greater among children treated with SLIT than those treated with control treatment (standardized differences in mean change = 1.456, 95% CI 0.334–2.578, $P = 0.011$, Figure 3C).

Safety

Seven of the 11 studies reported overall adverse event for both treatment and control groups.[25,27,29,32,34] However, 2 studies of them were excluded in the meta-analysis because they reported that no adverse events occurred. Analysis of the pooled data from these studies found the presence of moderate heterogeneity ($Q = 13.16$, $df = 4$, $P = 0.011$; $I^2 = 69.60\%$). The results indicated that the occurrence of adverse events was not significantly different between children treated with SLIT and those treated with control treatment (combined OR 1.916, 95% CI 0.500–7.347, $P = 0.343$, Figure 4).

Sensitivity Analysis and Quality Assessment

We performed sensitivity analysis where the results were analyzed when 1 study was removed in turn for asthma symptom score, medication score, *D pteronyssinus* IgE, sIgG4, and adverse events. The direction and magnitude of pooled estimates did not vary considerably for asthma symptom score (Figure 5A) and adverse event (Figure 5E), indicating that the meta-analysis had good reliability for these outcomes. However, the removal of some studies caused the pooled difference in means to become significant. Removal of Marcucci et al altered the medication score analysis (pooled standardized difference in means = −1.072, 95% CI −2.064 to −0.080, $P = 0.034$; Figure 5B); removal of either Eifan et al[35] or Tari et al[34] affected the results with regard to specific *D pteronyssinus* IgE levels; (pooled standardized difference in means = −1.072, 95% CI −2.064 to −0.080, $P = 0.034$ and 0.269, 95% CI 0.044–0.494, $P = 0.019$, respectively; Figure 5C); and removal of Pham-Thi et al[27] or Lue et al[28] changed the findings for sIgG4 levels (pooled standardized difference in means = 1.673, 95% CI −0.011 to 3.357, $P = 0.051$, and 0.983, 95% CI −0.090 to 2.056, $P = 0.072$, respectively; Figure 5D). These results suggest that the meta-analysis had poor reliability in the findings for medication score, specific *D pteronyssinus* IgE level, and sIgG4 level.

We evaluated the risk of bias of the included studies using the ''Risk of Bias'' assessment tool of Review Manager 5.1. Overall, there was low risk of bias across the studies (Table 4); all the studies were positive for all criteria except for that of Eifan et al[35] in which participants or personnel were not blinded, and the assessment of outcomes was also not blinded.

TABLE 4. Quality Assessment of Included Studies

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Did the Analysis Include an Intention-to-Treat Analysis?
Yukselen (2012)	Y	Y	Y	Y	Y	Y	NA
Keles (2011)	Y	Y	NA	Y	Y	Y	NA
Eifan (2010)	Y	Y	N	N	Y	Y	NA
Pham-Thi (2007)	Y	Y	Y	Y	Y	Y	Y
Lue (2006)	Y	Y	Y	Y	Y	Y	NA
Niu (2006)	Y	Y	Y	Y	Y	Y	Y
Marcucci (2005)	Y	Y	Y	Y	Y	Y	NA
Bahçeciler (2001)	Y	Y	Y	Y	Y	Y	NA
Pajno (2000)	Y	Y	Y	Y	Y	Y	NA
Hirsch (1997)	Y	Y	Y	Y	Y	Y	NA
Tari (1990)	Y	NA	Y	Y	Y	Y	NA

N = high risk of bias, NA = not available, Y = low risk of bias.

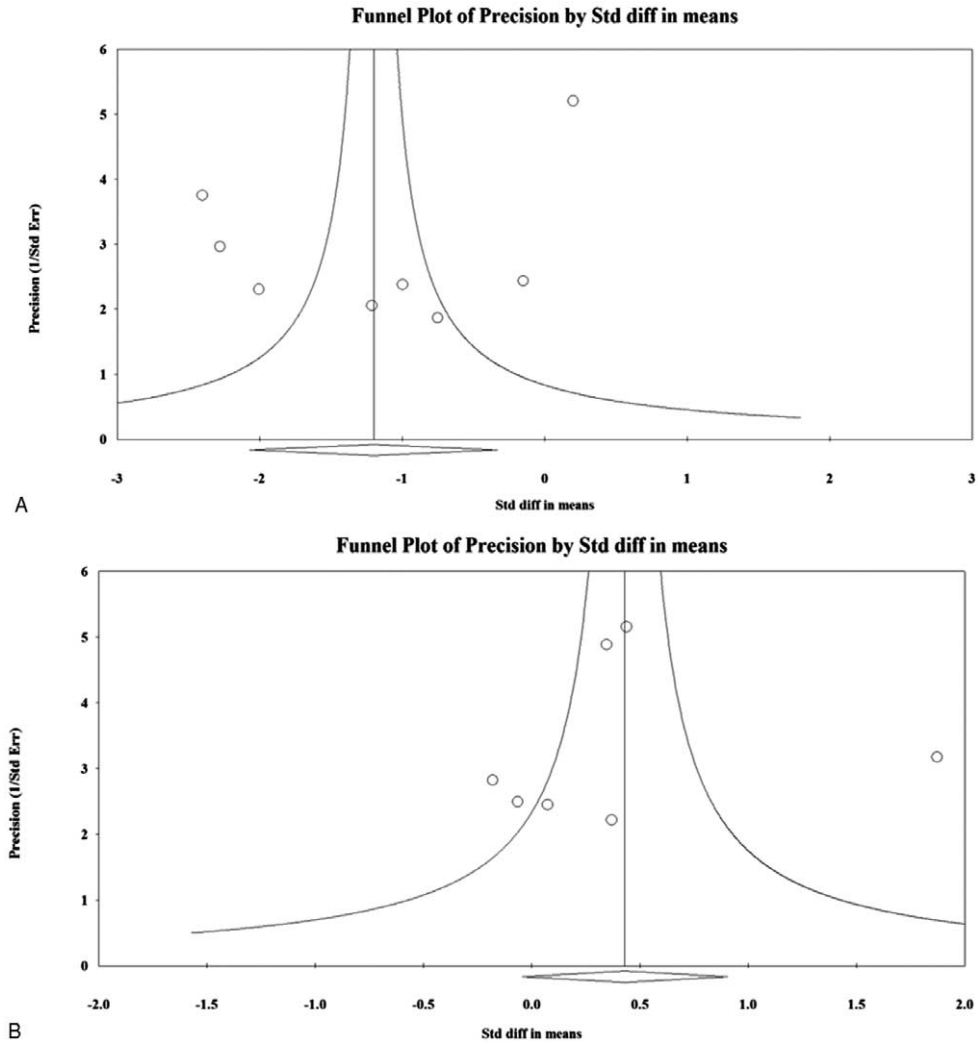


FIGURE 6. Funnel plots of evaluation of publication bias. (A) asthma symptom score and (B) specific *Dermatophagoides pteronyssinus* IgE levels. IgE = immunoglobulin E.

Publication Bias

For asthma symptom score, the Egger test for the intercept in the funnel plot showed no significant publication bias among the 8 studies (intercept = −3.66 with 1-tailed P value = 0.184, Figure 6A). For specific *D pteronyssinus* IgE levels, the Egger test for the intercept in the funnel plot also showed no significant publication bias among the 7 studies (intercept = −0.550 with 1-tailed P value = 0.423, Figure 6B).

DISCUSSION

We evaluated the efficacy and safety of dust mite SLIT in asthmatic children. We found that the reduction in asthma symptom score and the increase in sIgG4 levels were significantly greater in children treated with dust mite SLIT than in children treated with control. Dust mite SLIT did not significantly decrease medication score or specific *D pteronyssinus* IgE compared with control. Dust mite SLIT was well tolerated by children, and in most studies the frequency of adverse events also did not differ between dust mite SLIT and control. Sensitivity analysis indicated that generally the finding for the primary analysis of asthma symptom score was not dependent on any 1 study, and there was no publication bias.

The prevalence of asthma and allergic diseases has increased in different parts of the world, including China. Allergen sensitization is closely related to the development of asthma, and house dust mites are the most common allergens worldwide and are the most prevalent allergen in Chinese children with asthma and/or rhinitis.[3,36,37] It is thought that sensitization to house dust mites plays an important role in the development of asthma or allergic rhinitis.[37] In support of this idea, sensitization to house dust mites is one of the key risk factors associated with increase in wheeze in secondary school children in Guangzhou, China.[36]

Several prior meta-analyses have assessed the use of SLIT in treating children with asthma or allergic rhinitis.[10,38–41] Penagos et al evaluated the efficacy of SLIT in children with asthma (3–18 years of age) using randomized double-blind, placebo-controlled studies.[38] Their meta-analysis included 9 studies that comprised 441 children; 232 of whom received SLIT and 209 of whom received placebo. They evaluated symptom score and use of rescue medicine. Although, the included studies used a wide range of scoring systems, they found, similar to our results, SLIT with standardized extracts was associated with an overall reduction in symptom score ($P = 0.02$) and use of rescue medication ($P = 0.007$).

Olaguibel and Alvarez Puebla[10] performed a meta-analysis that assessed the efficacy of SLIT in children ≤14 years of age with either allergic rhinitis or asthma in randomized, double blind, and placebo-controlled trials. Seven studies were evaluated that included 256 children (129 treated with SLIT and 127 treated with placebo). They saw a decrease in symptoms scores for allergic rhinitis and asthma, but this did not reach statistical significance. There was a significant decrease in asthma allergy symptoms ($P = 0.01$) and medication scores ($P = 0.026$). No severe nor systemic reactions or oral and gastrointestinal complaints were seen.

The above-mentioned meta-analyses did not separately evaluate the effect of pollen or dust mite allergen. Only 1 prior meta-analysis assessed the efficacy of SLIT using dust mite extract compared with placebo.[40] Compalati et al identified 12 randomized, placebo-controlled studies that assessed dust mite SLIT in patients with allergic rhinitis or asthma (382 patients with allergic rhinitis and 476 with allergic asthma).[39] They found significant benefit in using dust mite SLIT compared with placebo for nasal symptom scores, bronchial symptom scores of allergic asthma, and decrease in rescue drug use for allergic rhinitis and asthma. Subgroup analysis also found a significant reduction in symptom scores for asthma and medication use in children with asthma.

In contrast to the previous meta-analyses, we did not find a significant decrease in medication score. Only the study by Olaguibel and Alvarez Puebla[10] evaluated medication score, and they did find a significant benefit to SLIT for this outcome. The lack of significance in our analysis may reflect the fact that the methods for evaluating medication score differed across the included studies possibly confounding the findings. In contrast to our analysis, Olaguibel and Alvarez Puebla used allergic rhinitis as part of the search term and likely had a higher proportion of patients with allergic rhinitis compared with our study, which could have influenced the findings. In addition, both the study by Olaguibel et al[10] and our study included only a small number of studies, which may have influenced the results.

Our study did not evaluate the efficacy of SCIT for asthma. Two prior systematic reviews evaluated the efficacy of SCIT in patients with rhinitis or asthma. Erekosima et al[40] identified 61 studies that evaluated SCIT in children or adults, which included 3577 subjects. The included studies compared SCIT with placebo, pharmacotherapy, or SLIT. The majority of the studies (66%) assessed a single-allergen immunotherapy regimen. They found high-grade evidence that SCIT reduces asthma symptoms, asthma medication use, allergic rhinitis symptoms, and rhinitis disease-specific quality of life compared with placebo or usual care. They found that respiratory reactions were the most common systemic adverse event.

The systematic review of Chelladurai et al (2013)[41] used only studies that performed head-to-head comparisons between SCIT and SLIT. They included 8 studies with 555 subjects. They found low-grade evidence that SCIT is more efficacious than SLIT for asthma symptom reduction, and in reducing symptoms and medication use of rhinitis symptoms. Moderate-grade evidence supported SCIT as being more effective than SLIT in reducing nasal and/or eye symptoms.

The studies included in our meta-analysis were heterogeneous. Some included children with allergic rhinitis, and the studies differed with regard to dose, dose frequency, and duration of treatment. To compensate for this, we used standardized mean difference and random effect model for combining the different type of data. We did not evaluate VAS or inflammatory markers due to insufficient data. We also did not assess change in symptoms of allergic rhinitis. Also, most of the included studies had small study populations with some having <20 people in the active treatment group. There was publication bias for the specific *D pteronyssinus* IgE levels.

In conclusion, our study indicates that dust mite SLIT therapy was effective in reducing asthma symptom score and increasing sIgG4, but did not significantly reduce medicine scores and specific *D pteronyssinus* IgE. Our findings are not enough to support the use of dust mite SLIT in children with asthma. However, the data in our meta-analysis, as well as others, suffers from the small number of clinical studies included and the small sample size of these studies. Larger well-designed studies that use similar scoring systems and monitor dust mite SLIT are necessary to further explore this question.

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