

Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials

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Abstract

Background: Allergen-specific immunotherapy (SIT) is the only available curative choice with a disease-modifying effect against respiratory allergies. The efficacy of SIT via the sublingual route was demonstrated by a number of clinical trials. This meta-analysis was performed to investigate the clinical efficacy and safety of sublingual-specific immunotherapy (SLIT) for allergic asthma.

Methods: PubMed, EMBASE and the Cochrane Central Register of Controlled Trials were searched for randomized, double-blind and placebo-controlled (DBPC) trials evaluating the efficacy and safety of SLIT on allergic asthma. Subgroup analyses were performed according to age, type of allergen and duration of SLIT treatment.

Results: Sixteen randomized DBPC trials comprising 794 patients in total met the inclusion criteria. The results suggest that SLIT significantly reduces both symptom [standardized mean difference (SMD), -0.74 ; $P = 0.006$] and medication scores (SMD, -0.78 ; $P = 0.02$) compared with placebo. SLIT offers a better clinical response in mite sensitive asthmatics but without confirmed proof from subgroup analyses. Prolonged duration of treatment for more than 12 months brings no additive effects. Improvement in the skin prick test was also observed following immunotherapy. There was no consistent effect on forced expiratory volume in 1 s, serum levels of antigen-specific immunoglobulin G4 and immunoglobulin E in the treated group. The risk of adverse effects was relative risk 2.23 ($P = 0.01$).

Conclusions: SLIT is safe and clinically effective in reducing symptoms and medication use for allergic asthma. Our subgroup analyses failed to identify a disproportionate benefit of SLIT in any specific group of asthmatics, but some possible trends did emerge.

Please cite this paper as: Tao L, Shi B, Shi G and Wan H. Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials. *Clin Respir J* 2014; 8: 192–205.

Key words

allergic asthma – meta-analysis – safety – subgroup analysis – sublingual specific immunotherapy – treatment efficacy

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Received: 01 May 2013

Revision requested: 27 August 2013

Accepted: 22 September 2013

DOI:10.1111/crj.12058

Authorship and contributorship

Lianqin Tao and Baoyu Shi searched the database, judged study eligibility and extracted data. Lianqin Tao did the meta-analysis and drafted the article. Guochao Shi and Huanying Wan designed the study and revised this paper. All authors have read and approve this version of the article.

Conflict of interest

We have received research grant from the 2012 National Natural Science Foundation of China (81270083). And none of the authors has any potential conflict of interest related to this manuscript.

Introduction

Allergic asthma (AA) is a chronic inflammatory disorder characterized as airway inflammation and hyper-reactivity, with approximately 300 million affected individuals worldwide (1). The prevalence of AA is widely increasing, as detailed by the International Study of Asthma and Allergies in Childhood epidemiological research (2). Current medications for asthma

are relatively effective and safe at temporarily relieving symptoms but cannot cure the disease (3). However, a long-term cure for allergic diseases can be achieved through the use of allergen-specific immunotherapy (SIT), which induces specific immune tolerance and disease-modifying effects (4, 5). Since the application of subcutaneous immunotherapy (SCIT) is restricted because of its inconvenience and risk of severe adverse effects (5), interest in alternative forms

of immunotherapy has been increasing (6). After the report of sublingual administration of dust mite allergen in 1986 (7), published reports concerning the clinical effect and safety of sublingual-specific immunotherapy (SLIT) have been increasing (8–11).

SLIT is helpful in asthma through preventing the development of new sensitivities to allergens (6). However, the effectiveness of this method is still unclear, with several inconsistent results (12–14). Three meta-analyses (9, 15, 16) demonstrated the clinical benefits of SLIT for asthmatics. One meta-analysis published in 2006 suggested that SLIT was efficacious in reducing symptoms and medication use for allergy combinations (asthma together with rhinitis and conjunctivitis); however, there was no significant effect on asthma alone (10). Given that several new clinical trials have been recently published, we investigated the clinical efficacy and safety of SLIT in allergic asthma by performing meta-analysis of an increased number of adequate randomized double-blind and placebo-controlled (DBPC) trials.

Methods

Search strategy

Two reviewers (Lianqin Tao and Baoyu Shi) independently searched PubMed, EMBASE and the Cochrane Central Register of Controlled Trials up to March 2012 using MeSH headings and keywords. We searched 'asthma', 'Desensitization, Immunologic' and 'Administration, Sublingual' as subject headings, with Immunotherap*, Hyposensiti*, Desensiti*, sublingual and oromucosal as keywords. The search was limited to 'English language' and 'humans'.

Study selection

Included studies had to meet the following criteria: (i) studies were randomized DBPC trials; (ii) participants were patients with allergic asthma, with or without allergic rhinitis and/or conjunctivitis; (iii) studies reporting at least one clinical outcome, such as asthmatic symptoms, medication requirements, lung function and bronchial hyper-reactivity; and (iv) relevant clinical outcomes reported separately for asthma. Studies designed to compare SLIT efficacy according to different routes or different modalities of allergen extract were excluded. Relevant literatures were identified independently according to the stated criteria strictly, and disagreements were resolved by consensus. We used the Jadad scale (17) to assess the methodological quality of trials and selected those with no less

than 3 points. Studies with insufficient data and no replies from authors after six weeks via email were excluded.

Data extraction and risk of bias assessment

The same two reviewers independently extracted the data, and characteristics of the included studies were summarized in Table 1. The main outcome measures were asthma symptoms, medication scores, lung function, serum allergen-specific antibodies, skin prick test and safety. Discrepancies were resolved by consensus, and insufficient data were requested by contacting the authors.

Risk of bias for each included study was assessed following the guidelines of the Cochrane Collaboration (18). Publication bias was evaluated using a funnel plot. Selection bias (methods of random sequence generation and allocation concealment), performance bias and detection bias (methods of blinding) were assessed.

Statistical analysis

We used the Review Manager 5.1.6 (RevMan, Version 5.1.6. The Nordic Cochrane Centre, The Cochrane Collaboration 2012, Copenhagen, Denmark) to conduct statistical analysis. Statistical heterogeneity among trials was assessed using chi-squared (χ^2) tests and the I^2 test (19). If there was a substantial heterogeneity with an I^2 statistic value $>50\%$, a random-effects model was used to calculate the standardized mean difference (SMD), relative risk (RR) and 95% confidence intervals (95% CIs); otherwise, a fixed-effects model was chosen (20).

Sensitivity analyses were conducted to determine the impact of excluding studies with lower Jadad scores or using different statistical models (21). We chose the characteristics age (children versus adults), allergen type of SLIT (mite immunotherapy vs pollen immunotherapy) and treatment duration (treatment ≥ 12 months vs <12 months) to perform subgroup analyses. P values <0.05 were considered statistically significant and all p values were two-tailed.

Results

Characteristics of included studies

The initial literature search identified 411 published articles, of which 88 were potentially relevant trials on SLIT in allergic asthma. Sixteen randomized DBPC trials (12–14, 22–34) were eligible for our meta-analysis

Table 1. The main characteristics of included studies

Year	Study	Participants (number)#		Quality Score*		Allocation concealment	Age range (year)	Dropout rate (%)	Allergen extracts	Cumulative dose	Treatment duration
		SLIT	Placebo	R	B	D					
1990	Tari	30	28	1	2	1	B	12	Mites	365 STU	18 months
1997	Hirsch	11	10	2	2	1	A	5	Der p 1	570 µg	12 months
1998	Vourdas	33	29	1	2	1	B	NC	Ole e 1	60 000 IR (8.1 mg)	24 months
1999	Bousquet	23	27	1	1	1	B	41	50% <i>D. pteronyssinus</i> + 50% <i>D. farinae</i>	104 000 IR (4.2 mg Der p1 + 7.3 mg Der f1)	25 months
2000	Caffarelli	23	20	2	2	1	A	8	Monomeric allergoid grass pollen allergens (Holcus, <i>P. pratense</i>)	37250 AU	3 months
2000	Pajno	12	9	2	2	1	A	13	Der p1, Der p2	250 µg + 125 µg	24 months
2001	Bahcecler	8	7	1	1	1	B	0	50% <i>D. pteronyssinus</i> + 50% <i>D. farinae</i>	7000 IR (0.56 mg Der p + 0.98 mg Der f)	6 months
2003	Ippoliti	47	39	1	1	1	B	0	Der p1, Der p2	12 mg	6 months
2003	Pajno	14	13	2	2	1	A	10	Par j 1	20.3 µg	13 months
2006	Dahl	68	39	1	1	1	B	11	Grass allergen tablets SQ-T	2.7 mg	10–14 weeks
2006	Lue	10	10	1	1	1	B	0	50% <i>D. pteronyssinus</i> + 50% <i>D. farinae</i>	41 824 IR (1.7 mg Der p + 3.0 mg Der f)	6 months
2006	Niu	49	48	1	1	1	B	12	50% <i>D. pteronyssinus</i> + 50% <i>D. farinae</i>	41 824 IR (1.7 mg Der p + 3.0 mg Der f)	24 weeks
2007	Pham-Thi	54	55	2	1	1	B	17	50% <i>D. pteronyssinus</i> + 50% <i>D. farinae</i>	155 000 IR (6.9 mg Der p1 + 14.7 mg Der f1)	18 months
2009	O'Hehir	10	11	2	1	1	A	0	<i>D. pteronyssinus</i>	85 621 IR (17.1 mg Der p1 + 3.4 mg Der p2)	12 months
2009	Stelmach	20	15	2	2	1	B	3	Five grass pollen (<i>Dactylis glomerata</i> , <i>Anthoxanthum odoratum</i> , <i>Lolium perenne</i> , <i>Poa pratensis</i> , <i>Phleum pratense</i>)	43 800 IR (3.65 mg of major allergens)	24 months
2010	Voltolini	13	9	2	2	1	B	8	Birch pollen allergen extract	13 800 IR (6.900 mcg of Bet v 1)	24 months

#Subjects analyzed in previous original articles.

*Jadad score; B: blinding; D: dropouts/withdrawals; R: randomization. **Expressed in mean ± standard deviation.

AU, allergenic units; Der f, *Dermatophagoides farinae*; Der p, *Dermatophagoides pteronyssinus*; IR, index of reactivity; NC, not clear; Ole e, *Olea europaea*; Par j, *Parietaria judaica*; SLIT, sublingual immunotherapy; STU, specific treatment units.

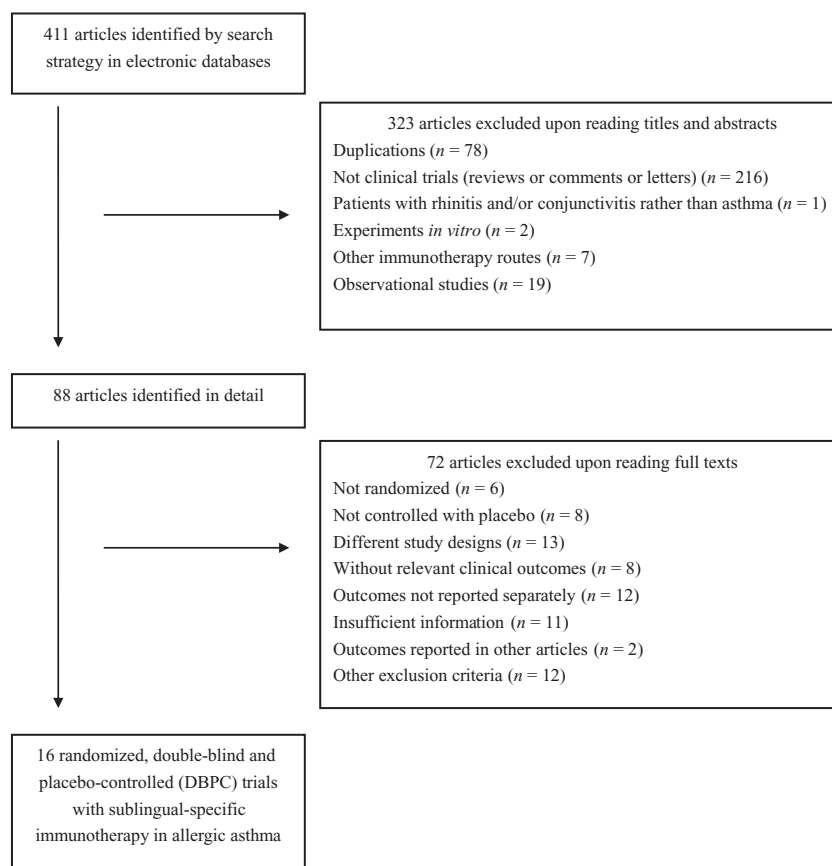


Figure 1. Flow diagram showing the trial selection process for the present meta-analysis.

upon reading the full texts in detail (Fig. 1). A total of 794 patients with generally at minimum of 1-year histories of mild to moderate asthma were involved, and the majority suffered from allergic rhinitis and/or conjunctivitis. SLIT was given to 425 patients and placebo to 369 patients. Ten trials reported immunotherapy for mite, and six for pollen allergy. The age range in these trials was 4–65 years, and sample size ranged from 15 to 109 subjects. The duration of treatment varied considerably, ranging from 10 to 108 weeks (25 months). High variability was also observed in cumulative dose of the same type of allergen.

Methodological quality of included studies

We discovered reasonable symmetry in the funnel plot (Fig. 2). According to the Jadad scale, six studies had a score of 5/5, four studies 4/5 and the rest were 3/5. The allocation concealment was clearly adequate (category A) in five studies (23, 25, 26, 29, 32), while it was not described in detail (category B) in 11 studies (Table 1). All studies reported dropouts or withdrawals. Only two trials (24, 32) followed the Consolidated Standards of Reporting Trials (CONSORT) statement for the

publication of randomized controlled trials (RCTs), and also two trials (14, 31) conducted intention-to-treat analysis to assess the influence of dropouts/withdrawals.

Asthma symptom scores

Asthmatic symptoms were analyzed separately from other allergic symptoms such as rhinitis and conjunctivitis. The pooled SMD was -0.74 with a 95% CI from -1.26 to -0.22 , indicating a significant reduction in asthmatic symptoms among subjects receiving SLIT compared with those receiving placebo. Significant inter-study heterogeneity was found ($I^2 = 91.0\%$) (Fig. 3A–C). Subgroup analysis according to age showed that SMD was -0.87 ($P = 0.01$) in children (<18 years old) and -0.40 ($P = 0.03$) in adults (Fig. 3A). However, there was no significant improvement on symptom scores compared with placebo in pollen immunotherapy, while SMD was -0.97 ($P = 0.008$) in mite immunotherapy (Fig. 3B). Subgroup analysis for efficacy in SLIT treatment ≥ 12 months failed to identify a significant difference from the placebo (Fig. 3C).

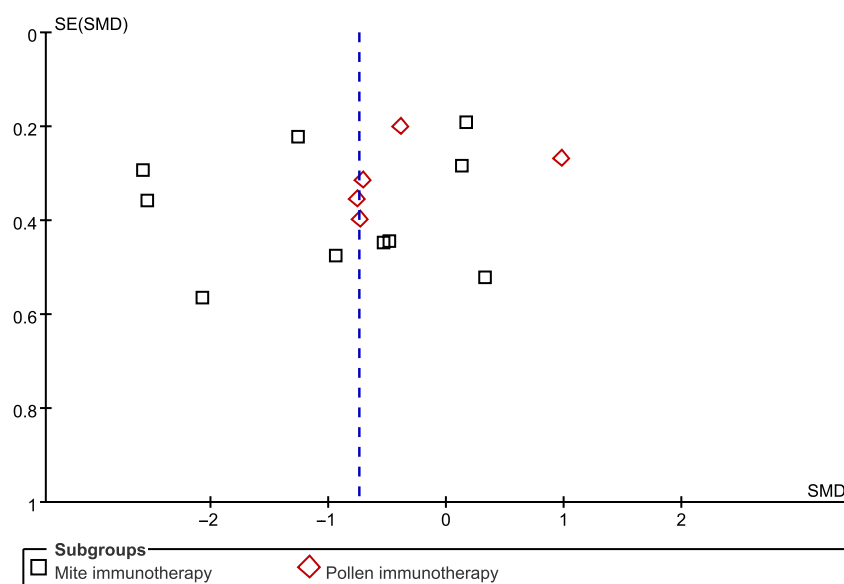


Figure 2. Funnel plot for publication bias detection for asthma symptom scores.

Asthma medication scores

The pooled SMD of medication score was -0.78 (95% CI, -1.45 to -0.11 ; $P = 0.02$), indicating that SLIT had an effect on reducing medication use for asthma (Fig. 4A–C). SLIT significantly reduced medication scores (SMD, -1.10 ; 95% CI, -2.06 to -0.14 ; $P = 0.03$) in children compared with placebos, while no statistical significance was found among adults (SMD, -0.00 ; 95% CI, -0.36 to 0.36 ; $P = 0.99$) (Fig. 4A). No significant difference was found during subgroup analysis according to age and treatment duration when medication scores were considered (Fig. 4B, C).

Lung function

Ten trials assessed several lung function parameters [forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity (FEF25/75), peak expiratory flow (PEF)], and only five studies (14, 24, 29, 30, 32) reported valid data for FEV1 were included for the meta-analysis. The results showed no significant improvement of FEV1 (SMD, 0.49 ; 95% CI, -0.36 to 1.34 ; $P = 0.26$) in the SLIT group (Fig. 5).

Serologic test and skin prick test

No significant increase was found for antigen specific sIgG4 and sIgE in the SLIT group (SMD, 1.86 ; 95% CI, -0.81 to 4.53 ; $P = 0.17$ and SMD, 0.74 ; 95% CI, -0.77 to 2.25 ; $P = 0.34$, respectively) (Fig. 6). The pooled SMD for the skin prick test was -0.45 (95% CI, -0.77

to -0.13 ; $P = 0.006$), indicating a significant reduction in skin sensitivity after immunotherapy (Fig. 7).

Global improvement

Two studies (31, 34) assessed the efficacy of SLIT by using global improvement considering symptom remission, medication use and lung function. No significant improvement was found in these two studies (RR, 3.31 ; 95% CI, 0.25 to 44.44 ; $P = 0.37$) (Fig. 8).

Safety

The main adverse reactions in our analysis were mild local reactions, such as mouth and/or throat itchiness, redness and swelling. The risk of adverse effects found in our meta-analysis was RR 2.23 (95% CI, 1.17 to 4.24 ; $P = 0.01$) (Fig. 9). However, Tari *et al.* reported that severe asthma occurred in three patients attributing to the side effects of SLIT (22).

Sensitivity analysis

Analysis using a random-effects model yielded estimates similar to those of the fixed-effects model for asthma symptom scores, medication scores and FEV1. Sensitivity analysis restricted to studies classified as 5A or 5B slightly improved effects on the pooled estimates for symptom and medication scores (SMD, -0.85 and SMD, -1.1 , respectively). When excluding studies (14, 24) with a dropout rate superior to 20%, we found an obvious reduction in medication scores (SMD, -1.01) and symptom scores (SMD, -0.89). If we removed

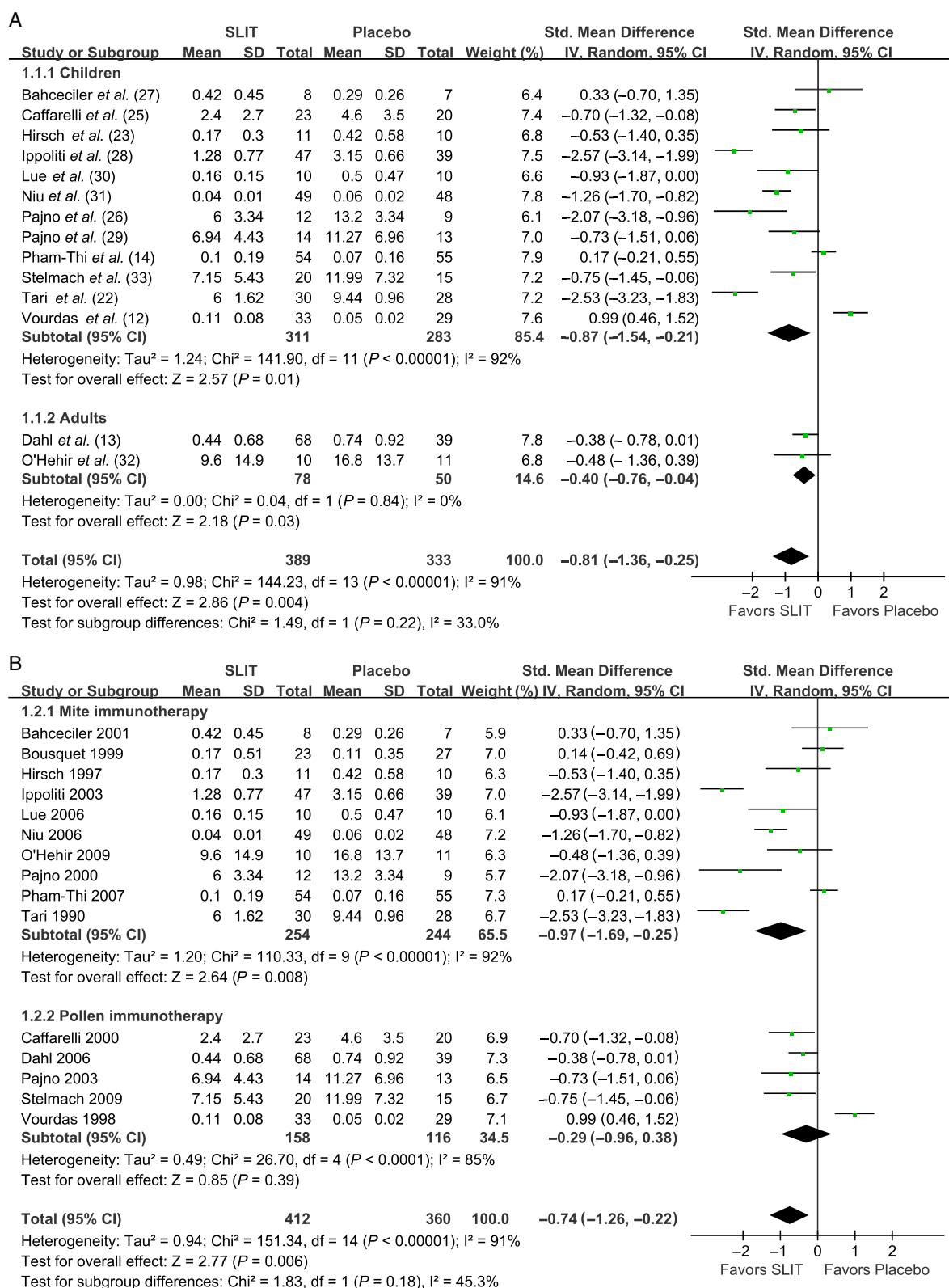


Figure 3. (A) Efficacy of sublingual-specific immunotherapy (SLIT) on asthma symptom scores with subgroup analysis according to age. (B) Efficacy of SLIT on asthma symptom scores with subgroup analysis according to allergen type. (C) Efficacy of SLIT on asthma symptom scores with subgroup analysis according to treatment duration.

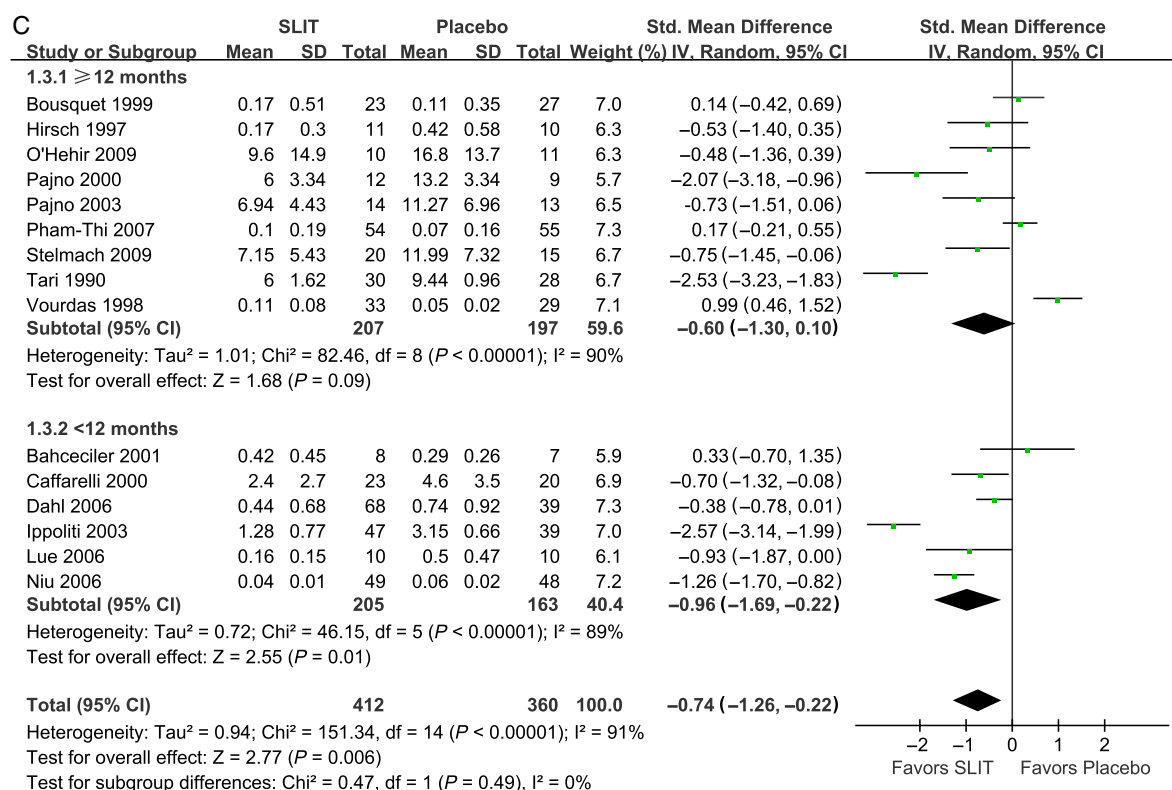


Figure 3. Continued

the outlier results (12, 22, 26, 28, 31), SMD was -0.34 for symptom scores with reduced heterogeneity ($I^2 = 45.0\%$). Similarly, when we removed outlier results (13, 26, 28), SMD was -0.20 for medication scores with reduced heterogeneity ($I^2 = 44.0\%$).

Discussion

This meta-analysis of randomized DBPC trials confirmed that SLIT could significantly reduce asthma symptoms and medication scores with a favorable safety profile, while no significant improvement of FEV1 was shown. Improvement in the skin prick test was also observed following SLIT, although there was no consistent effect on antigen-specific sIgG4 and sIgE. We performed subgroup analysis to evaluate whether the effect of SLIT was different in any specific group of asthmatics. It turned out that some possible trends emerged, but these were by no means proven.

Our subgroup analysis showed that reduction in asthmatic symptoms was evident in mite immunotherapy compared with the placebo, but not in pollen immunotherapy. When switching to the effect on medication use, we found no statistical significance for both mite and pollen immunotherapy. It may imply

that SLIT has a better clinical response in mite sensitive asthmatics, although there was no confirmed proof in the present subgroup analyses. Meta-analysis conducted by Penagos and colleagues observed a significant effect on the reduction of symptom scores and medication use in mite SLIT, while pollen SLIT did not experience a significant effect (15). These inconsistent results showed a favorable trend for pollen immunotherapy but with no statistical significance. Further studies could help to confirm this. On the other hand, further modifications might be made to pollen allergen extract, such as producing hypoallergenic and high immunogenicity allergen extract, which are hoped to improve the effect of pollen SLIT. We also conducted subgroup analysis according to seasonal and perennial immunotherapy, and inconsistent results were found. Effects in seasonal asthmatics appeared to be better than that in perennial asthmatics (data not shown).

Subgroup analysis showed that the effect of SLIT on symptom scores was higher in children than in adults when compared with placebo. And furthermore, we could not find significant reduction in medication use of SLIT in adults. Among the total 794 patients with asthma, there were only a little bit more than 128 adult asthmatics included in our study. Therefore, the

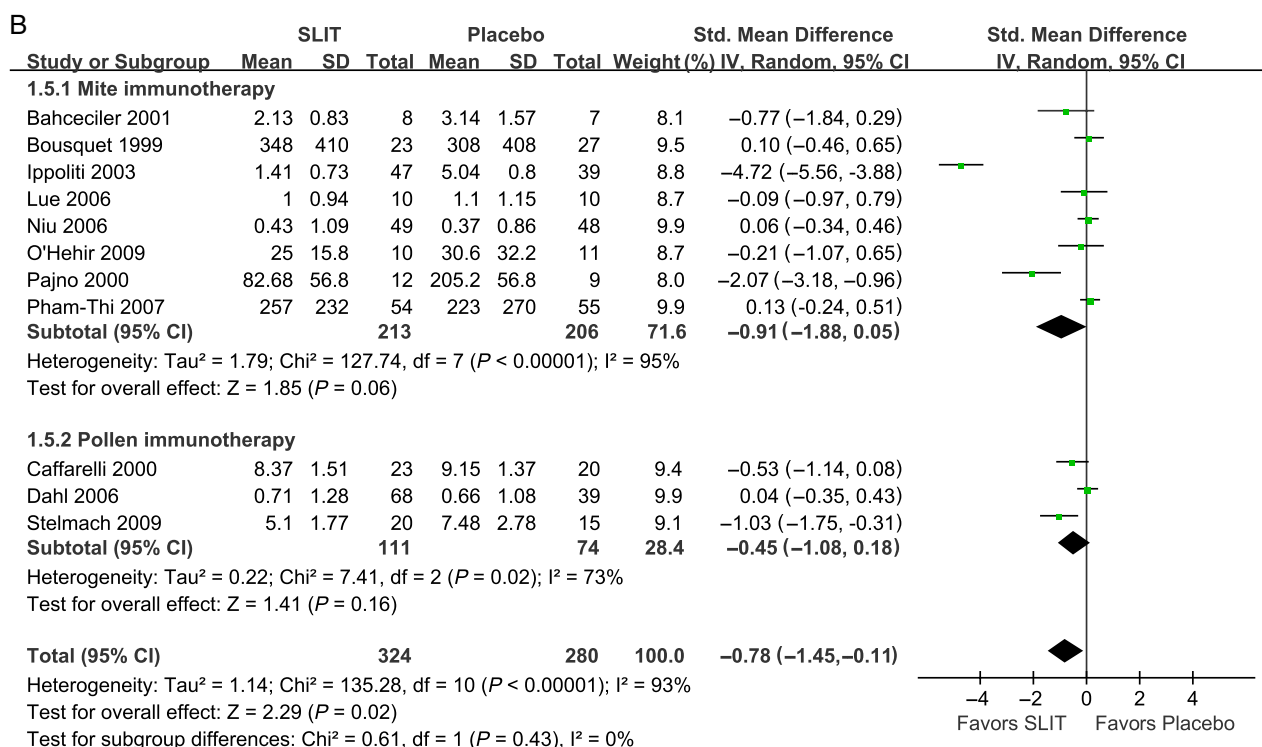
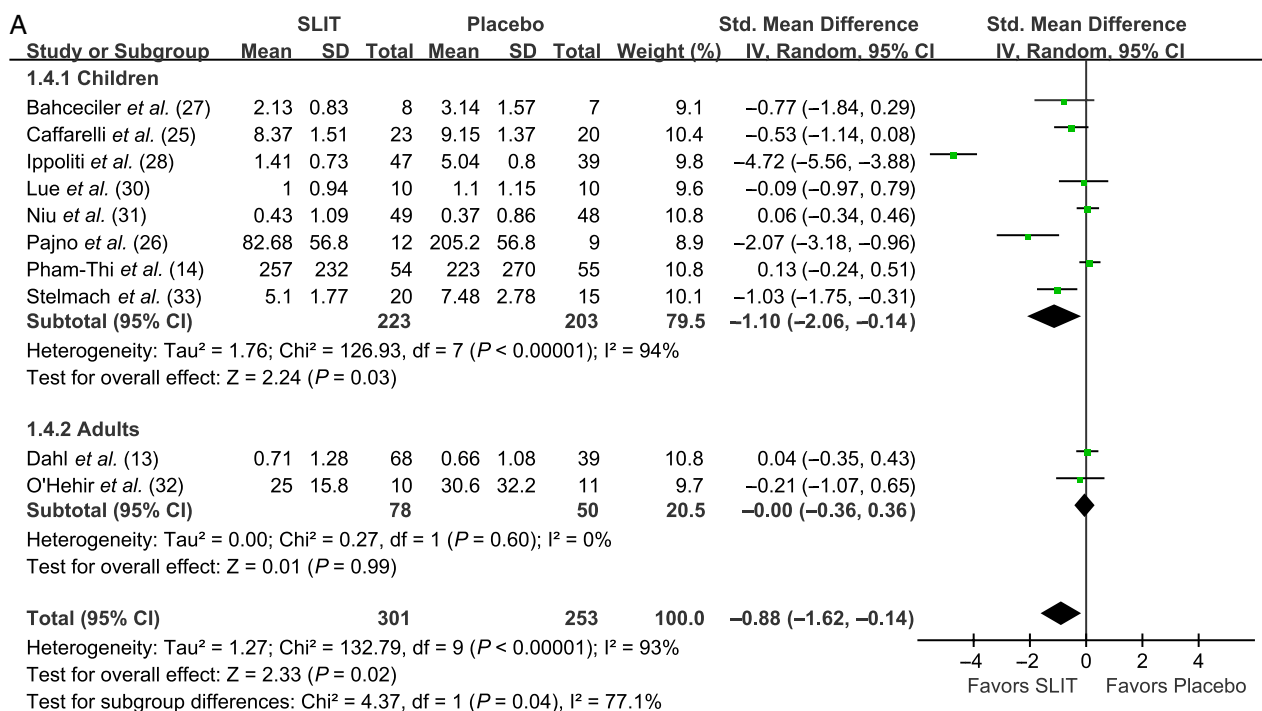


Figure 4. (A) Efficacy of sublingual-specific immunotherapy (SLIT) on asthma medication scores with subgroup analysis according to age. (B) Efficacy of SLIT on asthma medication scores with subgroup analysis according to allergen type. (C) Efficacy of SLIT on asthma medication scores with subgroup analysis according to treatment duration.

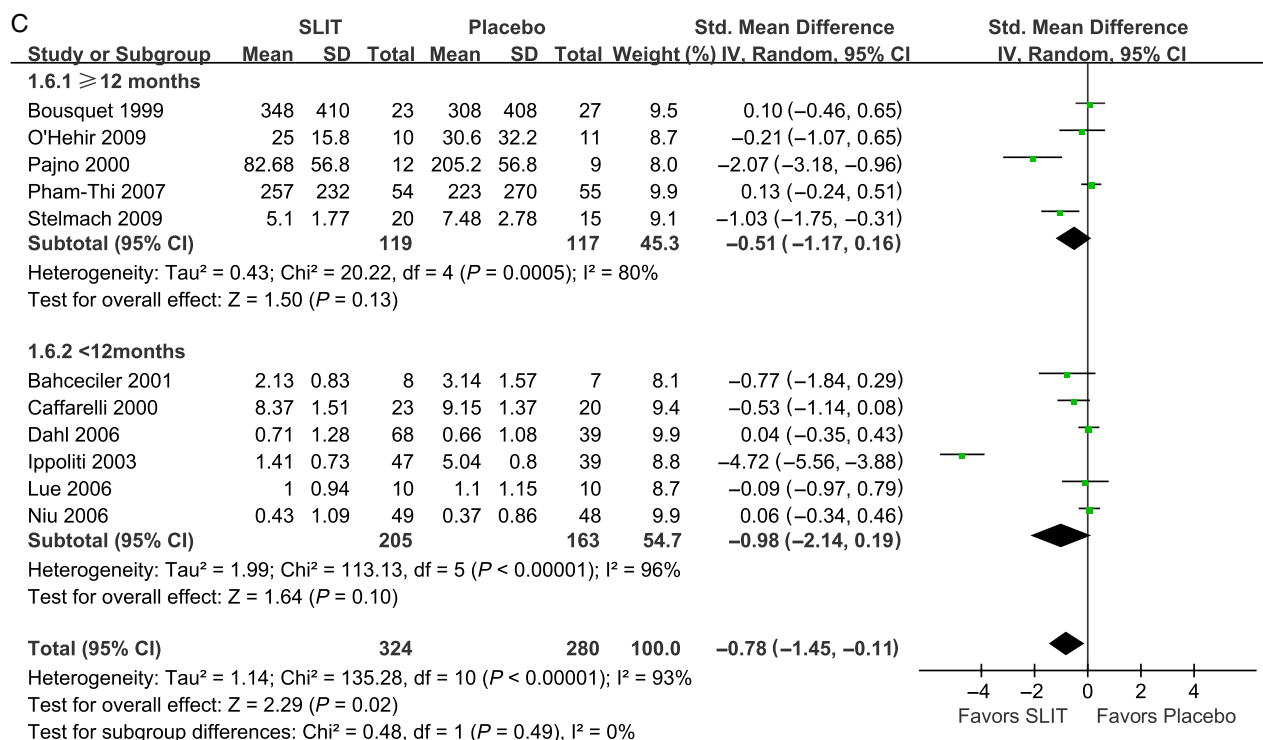


Figure 4. Continued

discrepancy could be due to the small sample size for adult asthmatics. And one previous meta-analysis on home dust mite SLIT for asthma performed by Compalati *et al.* also showed similar results. Their study found that the symptom scores and medication requirements were reduced significantly in pediatric populations but not in adults (16). So more clinical trials in adult asthmatics are needed to further confirm the treatment effect.

Interestingly, increasing the treatment duration beyond 12 months did not appear to improve asthmatic symptoms and reduce medication use in our analysis. Actually, no subgroup analysis according to

treatment duration was conducted in previous studies (9, 10, 15, 16, 35–38) on asthma immunotherapy. A meta-analysis on SLIT for allergic rhinitis showed the analogous results and drew the conclusion that increasing treatment duration does not clearly increase efficacy (8). Another meta-analysis found that a course of SLIT treatment no longer than 12 months is better than long-term treatment (>12 months) for allergic rhinitis (39). Here what we evaluated was the short-term or present treatment effects of SLIT. We think that a better effect may not always be achieved by longer treatment duration. A long-term prospective study aimed at examining optimal treatment duration for

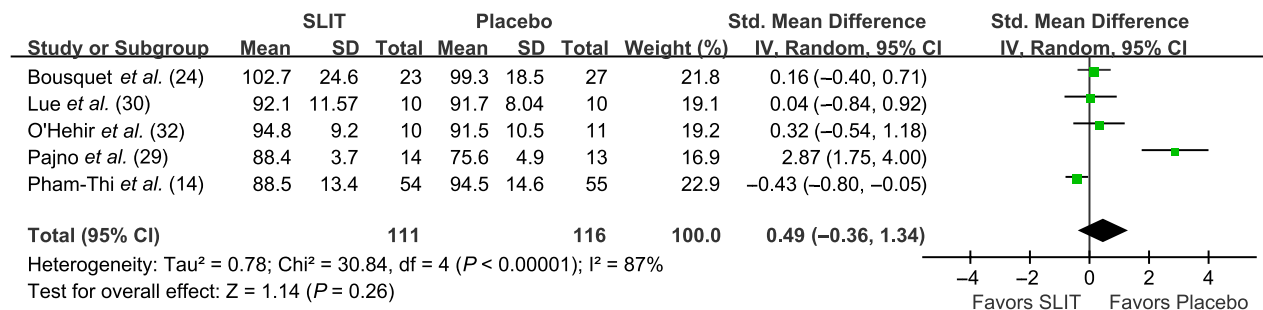


Figure 5. Efficacy of sublingual-specific immunotherapy (SLIT) on lung function [forced expiratory volume in 1 s (FEV1)].

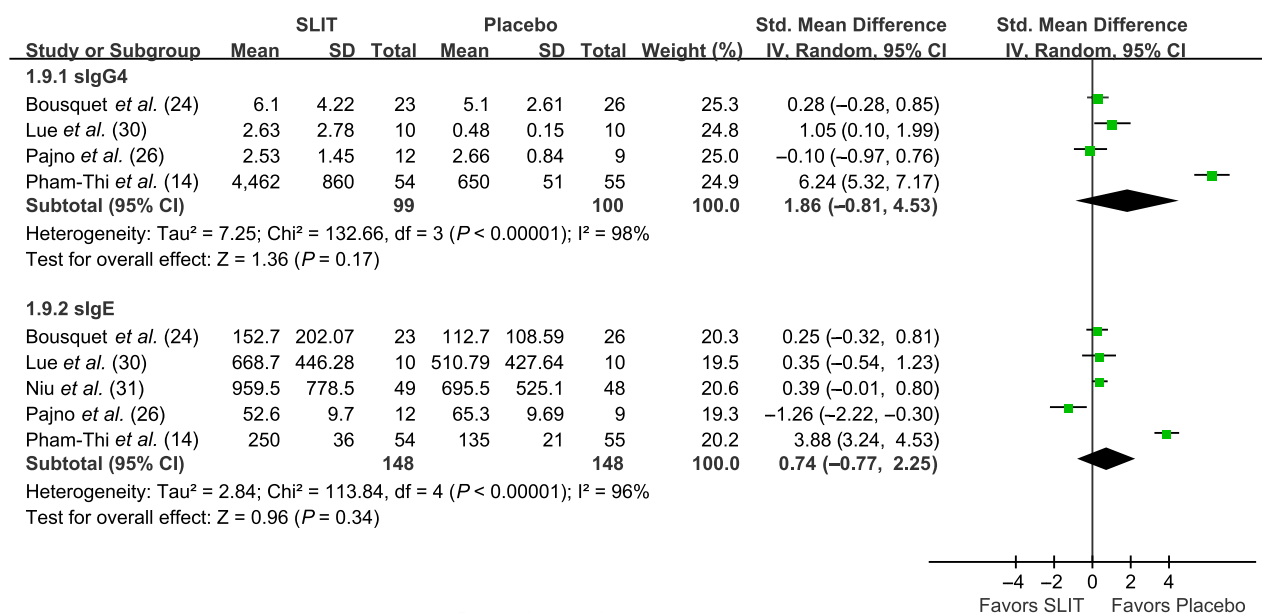


Figure 6. Efficacy of sublingual-specific immunotherapy (SLIT) on the level of serum specific serum levels of antigen-specific immunoglobulin G4 (IgG4) and immunoglobulin E (IgE).

the best long-lasting effects of respiratory allergy SLIT found that a 4-year duration of SLIT is the optimal choice because it induces a long-lasting clinical improvement similar to that seen with a 5-year course and greater than that of a 3-year vaccination (40). So the relationship between treatment duration and

short-term or long-lasting effects remain a problem to the cost-effectiveness of SLIT.

So far, the effect of SIT on lung function remains controversial. A significant improvement on FEV1 (% predicted) and FEF25/75 favored by SLIT was seen in one meta-analysis on asthma SLIT, although a

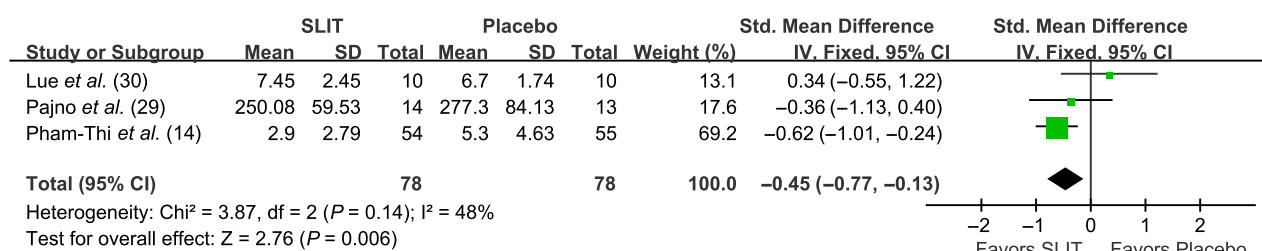


Figure 7. Efficacy of sublingual-specific immunotherapy (SLIT) on the skin prick test.

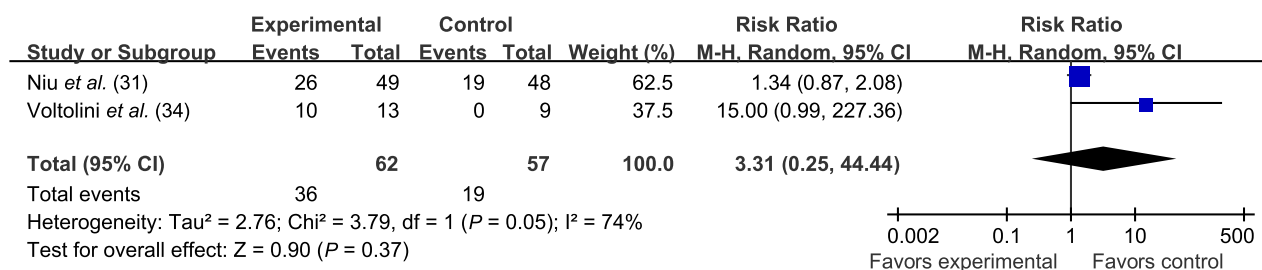


Figure 8. Efficacy of sublingual-specific immunotherapy (SLIT) on global improvement of asthma.

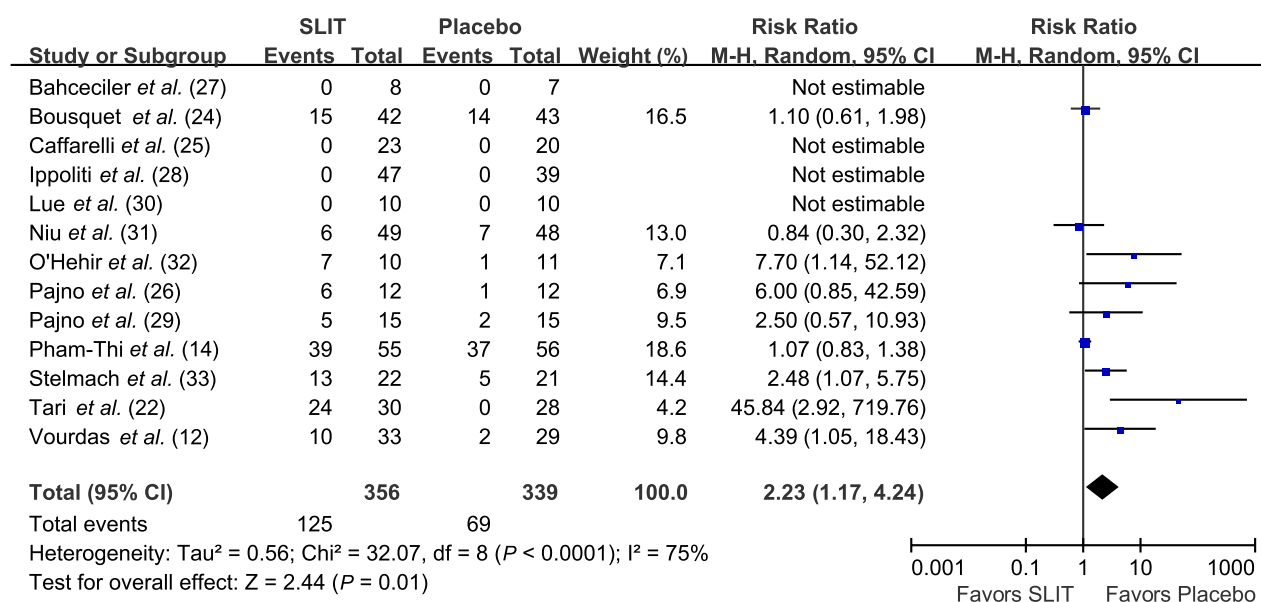


Figure 9. Adverse effects of sublingual-specific immunotherapy (SLIT).

bronchial provocation test did not show any significant improvements (10). However, Abramson *et al.* found that there was no consistent effect on lung function following SCIT (36, 37). However, they found that SCIT could significantly reduce allergen-specific bronchial hyper-reactivity, with some reduction in nonspecific bronchial hyper-reactivity (36, 37). Our analysis found a tendency toward lung function improvement following SLIT, but without statistical significance. Given that insufficient data may make the meta-analysis results impractical, the effectiveness of SLIT on lung function remains subject to discussion. Because there were insufficient valid data for the bronchial provocation test, we were unable to analyze its effect on bronchial hyper-reactivity. However, we discovered a significant reduction in skin sensitivity after immunotherapy, indicating that SLIT could induce immune tolerance.

The basic principle of SIT is to induce specific immune tolerance to allergens through multiple cellular and molecular mechanisms by administering repeated, gradually increasing doses of the causative allergen (3, 41). The immunological mechanism of SLIT has not been fully elucidated; relevant observations include changes in serum antibody levels and induction of regulatory T cells (42), reduced skin sensitivity (43) and alteration from allergic (T helper cell type 2) profile to a non-allergic (T helper cell type 1) profile (44). It was also shown that the protolerogenic oral mucosa acted as an important prerequisite for SLIT (45). We analyzed the levels of allergen-specific

IgG4 and sIgE and found nothing significant. But these effects should be considered with caution for they were based on a relatively small population. The role of serum-responding antibodies is unclear, and indeed they may merely act as a marker of allergen exposure (8).

The safety profile of SLIT compared with SCIT is one of the reasons for increased interest in the sublingual dosing route (6). Adverse reactions of SIT can be classified into two categories: local reactions appearing as redness, tingling, itching and swelling at the administrated site, and systemic reactions appearing as anaphylaxis from mild to serious life-threatening severity (46). The common adverse reactions in SLIT are mild local reactions (47), as shown in our study. However, serious systemic anaphylaxis would happen in rare cases (48, 49). Systemic reactions such as urticaria, gastrointestinal complaints, wheezing, shortness of breath, headache and tiredness were reported in our studies. Consequently, we could draw the validating conclusion that SLIT is generally safe and well tolerated. Taking caution when applying SLIT and informing patients of the signs and symptoms of anaphylaxis can help reduce the frequency of adverse reactions.

Although SLIT has been demonstrated to be efficacious and safe, identifying the optimal dosage, timing of administration and optimal length of treatment is necessary (6, 50). Di Bona *et al.* suggested that a monthly dose of 450 μ g might be the best cost-effective dose through meta-analysis on allergic rhinitis SLIT; and the majority of trials use the same allergen

(Group V allergen, Phl p 5) (39). Because the allergen extracts used in the studies herein included trials that varied much in components and manufacture procedures, we found that only five (31.3%) trials used the same standardized extract of 50% *Dermatophagoides pteronyssinus* and 50% *Dermatophagoides farinae*. Given the small number, future studies describing the correlation between the effect and dose may be of interest. Similarly, identification of optimal treatment duration also remains.

The methodological quality of these included trials was mainly moderate or appropriately good according to the Jadad scale. Publication bias is an important shortcoming of meta-analysis and its effects can never be eliminated. In the present meta-analysis, we discovered no evidence of publication bias through funnel plot analysis. So publication bias could be considered unlikely to influence our pooled estimates. There are still several limitations that should be considered when interpreting these results. First, significant heterogeneity was common in our meta-analysis, as shown in previous meta-analyses (10, 15, 16, 36, 37). Significant heterogeneity still existed but reduced to some extent after sensitivity analysis; showing trials with low methodological quality and high dropout/withdrawal rate may account for the heterogeneity. The heterogeneity remained significant after stratifying according to age, allergen type and treatment duration. We considered that widely different scoring systems may contribute to the relevant heterogeneity. In this regard, more homogeneous and high-quality large RCTs with standardized scoring systems are needed to evaluate the efficacy of SLIT for much more confidence. Although some caution is required when drawing conclusions because of this significant heterogeneity, it is reasonable to support the pooled treatment effect because of the high degree of statistical significance. Second, insufficient data and the paucity of studies evaluating certain variables such as lung function parameters, serum allergen-specific antibodies and so forth may impair and confine the results in our meta-analysis. Third, absence of conducting intention-to-treat analysis and following the CONSORT statement should not be neglected.

Conclusion

The present meta-analysis of randomized DBPC trials confirms that SLIT is clinically effective and safe in significantly reducing symptoms and medication use for allergic asthma. There was a tendency toward lung function (FEV1) improvement following SLIT, but

without statistical significance. We discovered a significant reduction in skin sensitivity after SLIT, while no significant results were shown for levels of serum allergen-specific antibodies. Additionally, we found some discrepant effect of SLIT through subgroup analyses. SLIT seems to have a better clinical response in mite-sensitive asthmatics but without confirmed proof in our subgroup analyses. Prolonging duration of treatment for more than 12 months may bring no more additive effect. The evidence-based recommendations of optimal dosage and treatment duration of SLIT need further elucidation.

Acknowledgement

This study was funded by the grant from the 2012 National Natural Science Foundation of China (81270083).

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