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Efficacy of Sublingual Immunotherapy for House Dust Mite-Induced Allergic Rhinitis: A Meta-Analysis of Randomized Controlled Trials

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Purpose: Allergic rhinitis (AR) has become a global issue for a large part of the general population. Sublingual immunotherapy (SLIT) has been used extensively to treat persistent allergic rhinitis (PAR). Although systematic reviews have confirmed the effectiveness of SLIT for the treatment of AR, a considerable number of studies using extracts of house dust mites (HDMs) for immunotherapy found no consensus on basic treatment parameters and questioned the efficacy of SLIT. **Methods:** In this study, we evaluated SLIT for PAR by a meta-analysis of randomized controlled trials (RCTs). Medline, Embase, and Cochrane Library database searches were performed for RCTs on the treatment of PAR by SLIT that assessed clinical outcomes related to efficacy through May 2016. Descriptive and quantitative information was abstracted. An analysis was performed with standardized mean differences (SMDs) under a fixed or random effects model. Subgroup analyses were performed. Heterogeneity was assessed using the I^2 metric. **Results:** In total, 25 studies were eligible for inclusion in the meta-analysis for symptom scores and 15 studies for medication scores. SLIT was significantly different from the controls for symptom scores (SMD=1.23; 95% confidence interval [CI]=1.74 to 0.73; $P<0.001$). For medication scores, significant differences for SLIT were also observed versus the controls (SMD=-1.39; 95% CI=-1.90 to -0.88; $P<0.001$). **Conclusions:** Our meta-analysis indicates that SLIT provided significant symptom relief and reduced the need for medications in PAR. In this study, significant evidence was obtained despite heterogeneity with regard to the use of mite extract. Specifically, the mite extract used was provided by the patients with PAR. Furthermore, to confirm both the objective outcomes and the effective doses of HDM allergen extracts, experimental data should be obtained from large high-quality population-based studies.

Key Words: Allergic rhinitis; immunotherapy; sublingual; house dust mite; meta-analysis

INTRODUCTION

Allergic rhinitis (AR) has become a global health problem that affects a large part of the general population.[1] According to previous reports, the house dust mite (HDM) is regarded as the most probable inhalant allergen.[2] HDM-induced AR is also related to an increased risk of asthma.[3] Additionally, compared with other kinds of aeroallergens, if people are exposed to HDM allergens for a long time, the symptoms seem to be more chronic and severe.[4] In fact, the prototypic perennial allergen (i.e., HDMs) have not been confirmed, although more and less mite allergens can be found in the early autumn and winter, respectively.[5] Symptomatic treatment remains the first treatment choice for patients with AR. However, these methods are costly and impose significant economic burdens on individuals and nations.[6,7] Allergen immunotherapy is the guideline-recommended treatment for AR.[8-10] 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 even prevent it from evolving into asthma.[11,12]

Sublingual immunotherapy (SLIT) is regarded as an effective therapy, and is recommended by the World Allergy Organization (WAO) on the basis of relevant research.[13] However, a later study on AR using extracts of HDMs demonstrated that there was no consensus on fundamental therapy parameters.[14]

In evidence-based medicine (EBM), data obtained from meta-analyses and randomized controlled trials (RCTs) are the most convincing regarding the efficacy of an intervention.[15,16]

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Both Cochrane's studies and reported meta-analyses[17-19] confirmed the effectiveness of AR-related immunotherapy. In 2009, to our knowledge, the first meta-analysis of RCTs examining SLIT for HDM-induced AR and allergic asthma[20] showed that there was no apparent difference in the sub-analyses on children and adults, indicating that more persuasive data are required. The needed data may now be available because of the large number of reported trials since then. In this study, we investigated the efficacy of SLIT with HDM extracts for AR to resolve the controversy related to the efficacy of desensitisation to this kind of allergen.

MATERIALS AND METHODS

We searched for well-powered RCTs within the last 26 years (1990-2016) on the treatment of PAR. RCTs assessing outcomes of AR-related symptom and/or medication scores were enrolled. The Cochrane Library, Medline, and Embase were searched using Boolean combinations of the following: ("sublingual" or "swallow") and ("immunotherapy" or "desensitization" or "immunologic") and ("allergic" or "hay fever" or "rhinitis" or "rhinoconjunctivitis"). When reports pertained to the same patients at different follow-up periods, the one with the longest follow-up was enrolled to avoid duplication. Alternatively, we included all pertinent studies as long as there was no overlap in the information provided whenever multiple reports related to the same trial with different outcomes. Finally, whenever RCTs with multiple intervention and control arms were assessed, for the analysis we retained the placebo arm as the control group and the SLIT arm closest to the US Food and Drug Administration-ratified dosage scheme as the active comparator. Data were requested from authors and study sponsors in cases where data were not reported in published articles or were unsuitable for inclusion in the meta-analysis. Multiple available scores related to rhinitis symptoms were included (i.e., rhinitis symptoms only, rhinoconjunctivitis symptoms, or rhinoconjunctivitis and asthma symptoms) between rhinitis-only scores, which were preferred, followed by rhinoconjunctivitis symptom scores. Regardless of the type and number of outcomes, studies assessing SLIT were enrolled to estimate efficacy in the meta-analysis.

Data extraction

We extracted information on study characteristics and demographics, including investigators, publication year, and journal title, total and per-arm sample sizes, population characteristics, treatment indications, dose and modalities, study duration, rhinitis-related outcomes, and definitions thereof. Continuous outcomes were assessed by the mean difference and standard deviation, which included nasal symptom score and medication score. Data extraction was conducted by 2 investigators (B.F., H.X.) independently with differences resolved by consensus.

Quality assessment

It is essential to evaluate potential biases in the studies selected for a systematic literature review or meta-analysis. Risk of bias in the selected RCTs was assessed according to the Cochrane Collaboration's Risk of Bias tool in Review Manager (RevMan) 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Statistical analysis

The meta-analyses included outcomes of symptom scores and medication scores. The degree of heterogeneity in the estimates was measured, and sources of heterogeneity were explored by removing possible study outliers, and conducting subgroup and sensitivity analyses. Both random effects and fixed effects models were used. Direct pair-wise comparisons of each modality compared with a placebo were undertaken in RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration). Two main clinical outcomes for improvement in AR are decreases in symptoms and medication use, as reflected in composite summary scores. We quantified the extent of heterogeneity with the I^2 metric (range, 0%-100%), with values of >75% indicating considerable heterogeneity. The observed between-study heterogeneity was explained by performing analyses in prior defined subgroups of trials, and subgroup-specific differences in the effect of the intervention were also defined. Publication bias was examined by funnel plots per assessed outcome and we further assessed asymmetry using Egger regression, which assesses whether there is a significant relationship between the effect sizes and their precision as well as through funnel plots.

RESULTS

Study selection

Briefly, of the 4,390 citations retrieved initially through the search algorithm, we finally included 25 eligible clinical trials[21-45] assessing 3,674 randomized patients. The trials that we excluded from the meta-analysis were not RCTs; moreover, reports that were duplicates and studies with unsuitable data were excluded (Fig. 1).

Population and study characteristics

The characteristics of the included studies are summarised in Table 1. The trials were published from 1990 to 2016. The majority of the trials assessed patients of primarily European backgrounds (13 studies, 2,845 participants). Other patient backgrounds included Eastern Asia (5 studies, 590 participants), Western Asia (5 studies, 149 participants), Oceania (1 study, 30 participants), and Africa (1 study, 60 participants). The largest trial included 992 participants. The SLIT used in the studies in different units was standardized; 19 trials provided the allergens in drops, and 6 provided them in tablets. The period of

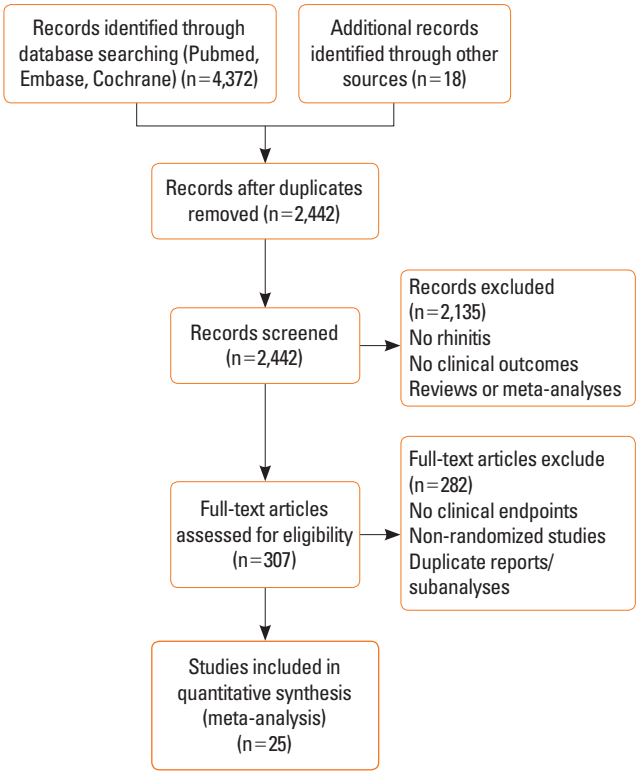

Fig. 1. Classification of material reviewed for this meta-analysis.

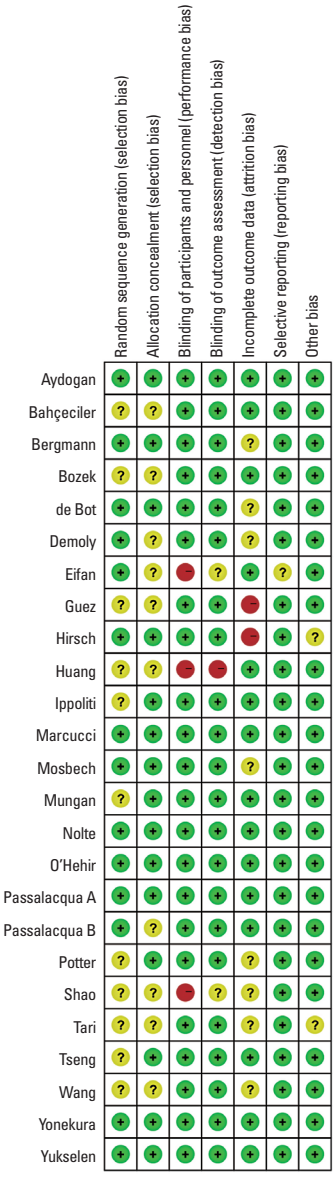

Fig. 2. Risk of bias summary.

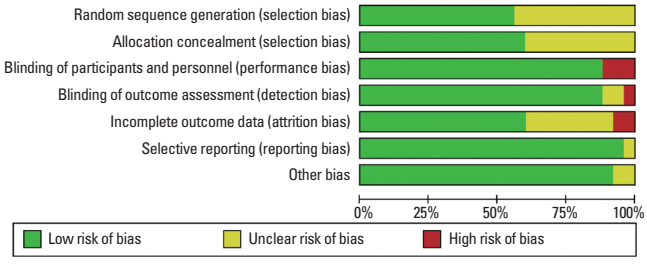

Fig. 3. Risk of bias graph.

study drug or placebo administration ranged from 6 to 36 months. The remaining 12 trials only included pediatric patients, with ages ranging from 3 to 18 years. Regarding the studies, patients were sensitised to house dust mites (*Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*), cats, or dogs. The prevalence of AR-related comorbidities differed among the included studies. The cumulative doses were 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. The risk of bias for all studies is shown in Fig. 2 and summarised in Fig. 3.

Patient adherence

In the overall population, 539 (14.6%) patients discontinued treatment. Treatment discontinuation was due to adverse events (AEs) in 109 (3.0%) patients, lack of compliance in 70 (1.9%), loss to follow-up in 75 (2.0%), and poor efficacy in 33 (0.9%). Two trials did not provide data regarding discontinuation.[39,41]

Assessed outcomes and evidence synthesis

Symptom scores

The 25 studies provided enough data to allow a quantitative evidence synthesis based on the symptom scores. Overall, SLIT statistically significantly reduced the daily nasal severity symptom score (SMD=1.23; 95% CI=1.74 to 0.73; $P<0.001$; Fig. 4), indicating a 1.24 decrease in symptom scores. Significant heterogeneity was found among the studies. Visual inspection of the funnel plot indicated asymmetry (Fig. 5).

Table 1. Characteristics of the included studies

Study (year)	Country	Mean age (year)	Indication	Modality	Cumulative dose	Follow-up (month)	N (all)	Not located	Outcomes assessd
Tari 1990[‡]	Italy	(5-12)	PAR	Drops	363STU	18	66	8	SS
Hirsch 1997[‡]	Germany	10.6 (6-16)	PAR	Drops	570 μg	12	30	12	SS
Passalacqua 1998[c]	Italy	26.1 (15-46)	PAR	Tablets	47,225 AU	24	20	1	SS
Mungan 1999[c]	Turkey	31.3 (18-46)	PAR and asthma	Drops	NA	12	36	0	SS MS
Guez 2000[§]	France	26.4 (6-51)	PAR	Drops	90,000 IR	24	72	33	SS MS
Bahçeciler 2001[‡]	Turkey	11.7 (7-18)	PAR	Drops	7,000 IR	6	15	0	SS MS
Ippoliti 2002[‡]	Italy	9 (5-12)	PAR and asthma	Drops	12 mg	6	86	0	SS
Marcucci 2003[‡]	Italy	8.5 (4-16)	PAR	Drops	110 μg	12	24	0	SS
Passalacqua 2006[c]	Italy	31.28 (18-49)	PAR	Tables	208,000 AU	24	68	12	SS MS
Tseng 2008[‡]	Taiwan	9.7 (6-18)	PAR	Drops	37,312 IR	6	63	4	SS
O'Hehir 2009[c]	Australia	33.2 (18-56)	PAR	Drops	NA	24	30	3	SS
Eifan 2010[‡φ]	Turkey	7 (5-10)	PAR	Drops	73,876.8 STU	12	48	5	SS MS
Yonekura 2010[‡]	Japan	9.5 (7-15)	PAR	Drops	200 μg	10	31	3	SS MS
de Bot 2012[‡]	Netherlands	11.7 (6-18)	PAR	Drops	435 μg	24	257	38	SS
Yukselen 2012[‡]	Turkey	10.1	PAR and asthma	Drops	173,733 TU	12	32	2	SS MS
Aydogan 2013[‡]	Turkey	(5-10)	PAR	Drops	44,500 IR	12	18	2	SS MS
Bozek 2013[c]	Poland	66.3 (60-75)	PAR	Drops	421,200 IR	36	108	13	SS MS
Wang 2013[§]	China	(4-60)	PAR	Drops	NA	6	120	35	SS
Bergmann 2014[c]	Germany	(18-50)	PAR	Tables	109,200 IR 180,500 IR	12	509	112	SS MS
Shao 2014[‡φ]	China	6.2 (3-13)	PAR	Drops	2,638.7 μg	12	264	46	SS MS
Huang 2015[cφ]	China	23.7 (16-52)	PAR	Drops	NA	24	112	9	SS MS
Mosbech 2015[§]	Multi-center	30.1 (14-75)	PAR and asthma	Tables	2,190SQ-HDM 1,095SQ-HDM 365SQ-HDM	12	489	56	SS MS
Nolte 2015[c]	Austria	27.3 (18-58)	PAR	Tables	NA	6	124	18	SS
Potter 2015[c]	South Africa	32.9 (18-60)	PAR	Drops	93,600 IR	24	60	12	SS
Demoly 2016[c]	Germany	(18-65)	PAR	Tables	NA	12	992	115	SS MS

[‡]Study only included pediatric patients; [c]Study only included adults; [§]Study included both children and adults; [φ]Open-label randomized controlled trial.
PAR, perennial allergic rhinitis; AU, allergic units; IR, index of reactivity; STU,specific treatment units; SQ-HDM, standardized quality HDM; TU, treatment units; mg, milligram; ug, micrograms; N, sample size; SS, symptom score; MS, medication score.

Medication scores

The type of rescue medication varied across the included studies: systemic antihistamines (available in all studies), naphazoline nitrate as a decongestant, topical antihistamines, topical nasal corticosteroids, and systemic corticosteroids. Information on the use of rescue medication was available in 18 studies. Nevertheless, the tools used to assess the use of rescue medication differed substantially among studies. Overall, SLIT reduced the use of rescue medication (SMD=-1.39; 95% CI= -1.90 to -0.88; $P<0.001$; Fig. 6), corresponding to a 1.12 reduction in the SD for the assessed scores. Significant heterogeneity was found among the studies. Visual inspection of the funnel plot indicated asymmetry (Fig. 7).

Subgroup and sensitivity analysis

We performed a subgroup analysis, evaluating the trials that used SLIT with different modalities. The reduction in symptom scores was significant with tablets compared with drops. Analyses of children who received SLIT did not show a significant effect on symptom scores (Table 2).

Post hoc sensitivity analyses 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 higher than 20%, the reduction was

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Tari	8	1.56	30	12	2.1	28	4.1%	-2.14 [-2.80, -1.49]	1990
Hirsch	0.84	0.975	8	0.34	0.35	10	3.8%	0.68 [-0.28, 1.65]	1997
Passalacqua A	54.89	11.28	10	108.27	25.19	9	3.4%	-2.67 [-3.98, -1.36]	1998
Mungan	0.5	0.37	15	0.67	0.2	11	4.0%	-0.53 [-1.32, 0.26]	1999
Guez	2.3	1.9	25	3.2	2.4	14	4.1%	-0.42 [-1.08, 0.24]	2000
Bahçeciler	0.53	0.4	8	0.41	0.39	7	3.7%	0.29 [-0.74, 1.31]	2001
Ippoliti	0.39	0.71	18	0.82	0.65	15	4.0%	-0.61 [-1.32, 0.09]	2002
Marcucci	5.6	2.25	13	4.4	3	11	3.9%	0.44 [-0.37, 1.26]	2003
Passalacqua B	1.737	0.135	28	2.281	0.175	28	3.9%	-3.43 [-4.27, -2.59]	2006
Tseng	1.72	1.78	28	1.98	1.9	31	4.2%	-0.14 [-0.65, 0.37]	2008
O'Hehir	36.59	22	13	36.6	29.5	14	4.0%	-0.00 [-0.76, 0.75]	2009
Eifan	1.5	1	15	2.9	0.7	14	3.9%	-1.57 [-2.41, -0.72]	2010
Yonekura	1.224	0.146	19	1.652	0.146	9	3.6%	-2.85 [-3.98, -1.72]	2010
Yukselen	3.74	1.4	10	4.15	1.4	10	3.9%	-0.28 [-1.16, 0.60]	2012
de Bot	2.26	1.84	108	2.02	1.67	111	4.3%	0.14 [-0.13, 0.40]	2012
Aydogan	3.4	2.7	7	3.3	3	9	3.8%	0.03 [-0.95, 1.02]	2013
Wang	3.293	0.267	48	6.086	0.414	37	3.4%	-8.17 [-9.50, -6.84]	2013
Bozek	2.656	0.634	47	3.977	0.501	48	4.2%	-2.30 [-2.82, -1.77]	2013
Shao	0.41	1.535	141	3.5	0.605	77	4.3%	-2.39 [-2.75, -2.03]	2014
Bergmann	2.6	2.25	133	3.13	2.317	141	4.3%	-0.23 [-0.47, 0.01]	2014
Nolte	5.47	2.69	36	7.45	2.69	34	4.2%	-0.73 [-1.21, -0.24]	2015
Mosbech	0.41	0.061	120	0.745	0.107	96	4.2%	-3.95 [-4.41, -3.49]	2015
Potter	5.25	1.22	32	6	1.22	16	4.1%	-0.60 [-1.22, 0.01]	2015
Huang	3.89	2.01	51	5.2	2.43	52	4.3%	-0.58 [-0.98, -0.19]	2015
Demoly	2.9	2.27	297	3.3	2.27	296	4.4%	-0.18 [-0.34, -0.01]	2016
Total (95% CI)			**1260**			**1128**	**100.0%**	**-1.23 [-1.74, -0.73]**	

Heterogeneity: Tau² = 1.51; Chi² = 643.59, df = 24 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.79 (P < 0.00001)

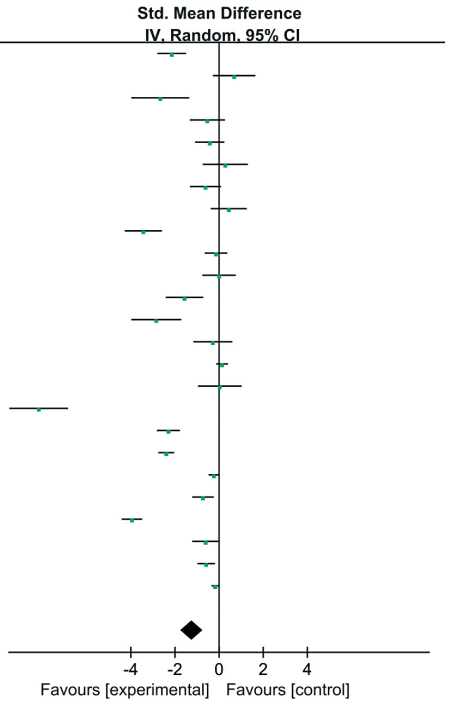

Fig. 4. Nasal symptom scores.

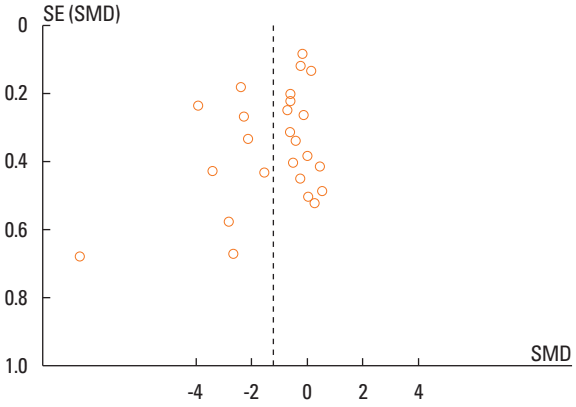

Fig. 5. Funnel plot for nasal symptom scores.

statistically significant for AR symptoms and rhinitis medication (Table 3).

Publication bias

Funnel plots showed some visual indications of asymmetry for SLIT symptom scores and medication scores. Egger regression produced *P* values of 0.046 and 0.061 for SLIT symptom scores and medication scores, respectively. Thus, the regression did not provide evidence of publication bias for the studies investigating SLIT medication scores; however, there was evidence of potential publication bias or asymmetry for SLIT symptom scores. The number of studies (25 for symptom scores and 15 for medication scores) also could limit the power of the Egger regression.

DISCUSSION

The present systematic review and meta-analysis was based on 25 RCTs examining the efficacy of SLIT for perennial AR that included 3,631 patients. In 2009, Compalati *et al.*[20] published the first–to our knowledge–meta-analysis examining SLIT for PAR, mentioned limitations and the contrasting results, recommended the more persuasive data are required. Our meta-analysis showed that, in perennial allergic rhinitis, treatment with SLIT provides an improvement of AR symptoms (SMD=1.23; 95% CI=1.74 to 0.73; $P<0.001$) and a reduction of symptomatic medication use (SMD=1.39; 95% CI=1.90 to 0.88; $P<0.001$) compared with placebo. Although a review[46] of studies found no consensus on basic treatment parameters and questioned the efficacy of SLIT, a considerable number of our included studies support our results. Moreover, multiple systematic reviews[47-49] have resulted in recommendations for the use of SLIT in the management of perennial AR. The author of a recent review[49] also highlighted evidence supporting the efficacy of SLIT in the management of allergic respiratory diseases.

From forest plots for the subgroup of age (Supplementary Figure, we detected SLIT produced significant reductions in adult patients with AR, but not in children ($P=0.060$). Interestingly, if open-label randomized controlled trials were excluded, this tendency should more obviously ($P=0.160$). This may be due to the following reasons, suggested in the publications included

in the present analysis: lack of effectiveness due to low dosage, poor compliance of children, and the small numbers of patients. The authors of another review[50] argued that the severity of disease in patients included in some studies was insufficient to enable the detection of treatment effects. Thus, as has been suggested,[46] more trials are needed for the development of recommendations regarding the use of SLIT for pediatric AR caused by dust mites.

The results of subgroup analysis demonstrated that SLIT administration in drop ($P<0.001$) or tablet ($P=0.002$) form resulted in significant differences in symptom scores. Most SLIT tablet studies showed significantly reduced AR symptoms. However, many of the included SLIT drop studies were unsatisfactory

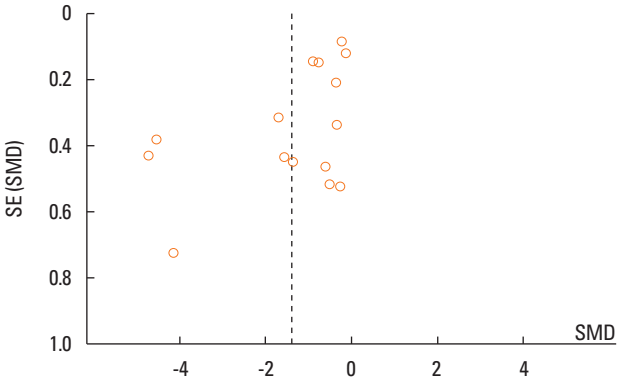

Fig. 7. Funnel plot for nasal medication scores.

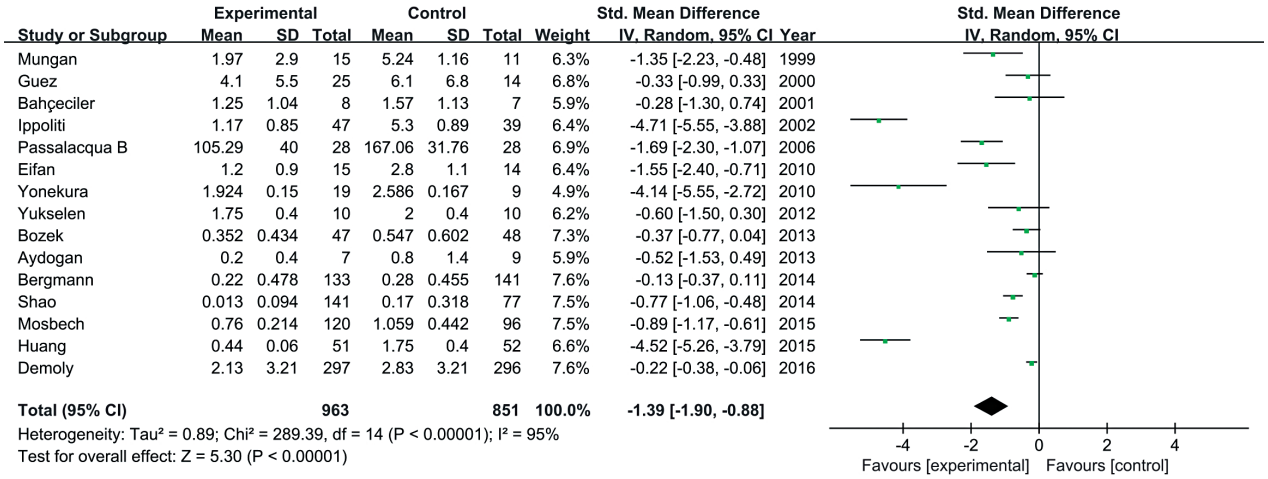

Fig. 6. Nasal medication scores.

Table 2. Subgroupanalysis of efficacy according to treatment characteristics

Subanalysis	Symptom score				Medication score			
	No. of studies	No. of patients	SMD (95% CI)	*P* value	No. of studies	No. of patients	SMD (95% CI)	*P* value
Children only	12	737	-0.70 [-1.43, 0.03]	0.06	7	359	-1.66 [-2.60, -0.71]	0.006
Adults only	10	1,311	-1.02 [-1.53, -0.52]	<0.0001	6	1,147	-1.31 [-2.12, -0.51]	0.001
Children+adults	3	340	-4.13 [-7.50, -0.76]	0.02	2	255	-0.69 [-1.22, -0.16]	0.01
Tablets	6	1,228	-1.81 [-2.94, -0.68]	0.002	4	1,139	-0.65 [-1.13, -0.18]	0.007
Drops	19	1,213	-1.06 [-1.67, -0.44]	0.0007	11	622	-1.66 [-2.47, -0.84]	<0.0001

CI, confidence interval; SMD, standardized mean difference.

Table 3. Sensitivity analysis of efficacy

Sensitivity analysis	Symptom score			Medication score		
	No. of studies	SMD (95% CI)	*P* value	No. of studies	SMD (95% CI)	*P* value
Fixed-effects model	25	-0.69 [-0.78, -0.60]	<0.00001	15	-0.57 [-0.67, -0.47]	<0.00001
Excluded small studies (n<30)	15	-1.62 [-2.28, -0.96]	<0.00001	9	-1.31 [-1.89, -0.74]	<0.00001
Excluded open label trials	22	-1.19 [-1.74, -0.65]	<0.0001	12	-1.00 [-1.42, -0.58]	<0.00001
Excluded high drop out rate (≤20%)	20	-1.16 [-1.73, -0.59]	<0.0001	13	-1.53 [-2.09, -0.97]	<0.00001

CI, confidence interval; SMD, standardized mean difference.

in terms of symptom scores. Doubtless, the immunologic mechanism of different SLIT modalities (drops and tablets) is similar, and the efficacy depends on allergen type, maintenance and cumulative dose. The information obtained from the literature on SLIT drop studies suggests they are undesirable, may due to the dosage is not applied under guidance and the short duration of immunotherapy-treatment period. Moreover, SLIT tablet studies are associated significantly with symptom relief and decreased rescue medication use in PAR. Unfortunately, the number of SLIT tablet studies is limited (n=6), so the efficacy of SLIT tablets requires further verification in additional, larger clinical trials, as suggested by others.[46,48]

Immunotherapy is generally considered more effective in monosensitised than polysensitised patients. Our meta-analysis confirms this point of view because almost all studies of polysensitised children show insignificant results in terms of efficacy.

Reported treatment-related AEs occurred at comparable rates in patients receiving SLIT and a placebo. Oral pruritus and throat irritation were the most common treatment-related AEs, and no case of malignancy was reported. One review[47] showed that SLIT was safer than SCIT, with no death reported during 23 years of testing and clinical use. Although anaphylactic reactions fall within the range of rare, life-threatening events, very large samples are required for their appropriate assessment, and their quantification requires the use of passive and active surveillance systems.

Our study has certain limitations. Initially, differences in the baseline severity of perennial 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 bias due to inter-study heterogeneity, we used a random effects model. Furthermore, language and publication biases should be considered in analyses of efficacy trials. In our study, publication bias may have been attributable to the preferential publication of positive results, bias against the publication of negative results, and analyses of small samples in RCTs. Additionally, caution should be exercised in interpreting the results because the sensitivity analysis erased the statistical significance. Lastly, although the majority of eligible trials were double-blinded and placebo-controlled, the reporting of measures taken to safeguard the blinding process was far from adequate in the trials analysed, resulting in considerable uncertainty regarding important methodological aspects of these studies.

This meta-analysis demonstrates that SLIT was associated with significant symptom relief and decreased rescue medication use in patients. Finally, we stress the concept that SLIT for perennial AR would be more effective with homogeneity. Moreover, we assessed large numbers of clinical trials and explored the effects with statistics, objectivity, and consistency. Additional, large clinical trials are needed to address the effective doses of HDM allergen extracts.

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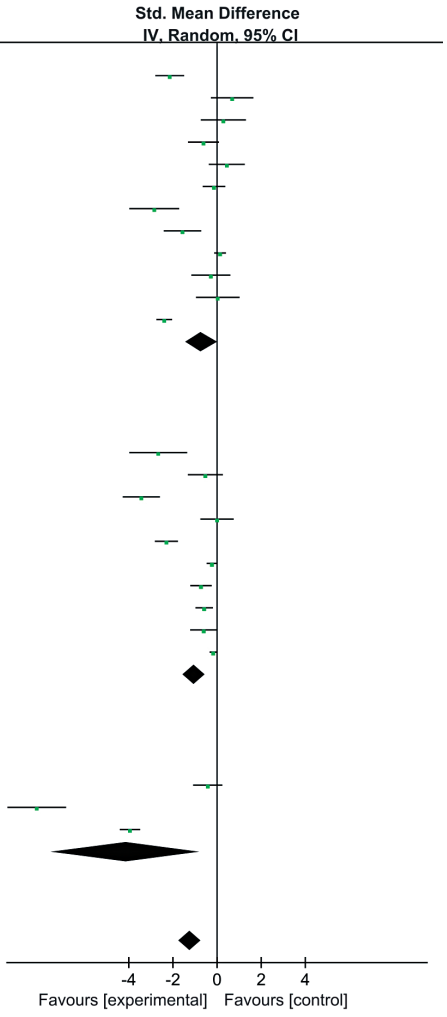
REFERENCES

1. Salo PM, Calatroni A, Gergen PJ, Hoppin JA, Sever ML, Jaramillo R, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2011;127:1226-1235.e7.
2. Bousquet PJ, Chinn S, Janson C, Kogevinas M, Burney P, Jarvis D, et al. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. Allergy 2007;62:301-9.
3. Linneberg A, Henrik Nielsen N, Frølund L, Madsen F, Dirksen A, Jørgensen T, et al. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. Allergy 2002;57:1048-52.
4. Calderón MA, Linneberg A, Kleine-Tebbe J, De Blay F, Hernandez Fernandez de Rojas D, Virchow JC, et al. Respiratory allergy caused by house dust mites: What do we really know? J Allergy Clin Immunol 2015;136:38-48.
5. Miyazawa H, Sakaguchi M, Inouye S, Ikeda K, Honbo Y, Yasueda H, et al. Seasonal changes in mite allergen (Der I and Der II) concentrations in Japanese homes. Ann Allergy Asthma Immunol 1996;76:170-4.
6. Meltzer EO, Bukstein DA. The economic impact of allergic rhinitis and current guidelines for treatment. Ann Allergy Asthma Immunol 2011;106:S12-6.
7. Yoo KH, Ahn HR, Park JK, Kim JW, Nam GH, Hong SK, et al. Burden of respiratory disease in Korea: an observational study on allergic rhinitis, asthma, COPD, and rhinosinusitis. Allergy Asthma Immunol Res 2016;8:527-34.
8. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126:466-76.
9. Burks AW, Calderon MA, Casale T, Cox L, Demoly P, Jutel M, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2013;131:1288-1296.e3.
10. Jutel M, Kosowska A, Smolinska S. Allergen immunotherapy: past, present, and future. Allergy Asthma Immunol Res 2016;8:191-7.
11. Morjaria JB, Caruso M, Rosalia E, Russo C, Polosa R. Preventing progression of allergic rhinitis to asthma. Curr Allergy Asthma Rep 2014;14:412.
12. Dong X, Huang N, Li W, Hu L, Wang X, Wang Y, et al. Systemic reactions to dust mite subcutaneous immunotherapy: a 3-year follow-up study. Allergy Asthma Immunol Res 2016;8:421-7.
13. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2009. Allergy 2009;64 Suppl 91:1-59.

14. Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. J Allergy Clin Immunol 2013;132:1322-36.
15. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6.
16. Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. BMJ 2006;333:782.
17. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. JAMA Intern Med 2015;175:1301-9.
18. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev 2010:CD002893.
19. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy 2005;60:4-12.
20. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. Allergy 2009;64:1570-9.
21. Aydogan M, Eifan AO, Keles S, Akkoc T, Nursoy MA, Bahceciler NN, et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. Respir Med 2013;107:1322-9.
22. Bahçeciler NN, Işik U, Barlan IB, Başaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol 2001;32:49-55.
23. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. J Allergy Clin Immunol 2014;133:1608-1614.e6.
24. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. Clin Exp Allergy 2013;43:242-8.
25. de Bot CM, Moed H, Berger MY, Röder E, Hop WC, de Groot H, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. Pediatr Allergy Immunol 2012;23:150-8.
26. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016;137:444-451.e8.
27. Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010;40:922-32.
28. Guez S, Vatrinet C, Fadel R, André C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. Allergy 2000;55:369-75.
29. Hirsch T, Sähn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Pediatr Allergy Immunol 1997;8:21-7.
30. Huang S, Xie X, Chen Y, Wu L, Li R, Shen F, et al. Study on the efficacy and safety of sublingual immunotherapy with standardized Dermatophagoides farinae drops for allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2015;29:618-21.
31. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, et al. Immunomodulation during sublingual therapy in allergic children. Pediatr Allergy Immunol 2003;14:216-21.
32. Marcucci F, Sensi L, Frati F, Bernardini R, Novembre E, Barbato A, et al. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. Allergy 2003;58:657-62.
33. Mosbech H, Canonica GW, Backer V, de Blay F, Klimek L, Broge L, et al. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. Ann Allergy Asthma Immunol 2015;114:134-40.
34. Mungan D, Misirligil Z, Gürbüz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma--a placebo controlled study. Ann Allergy Asthma Immunol 1999;82:485-90.
35. Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol 2015;135:1494-1501.e6.
36. O'Hehir RE, Gardner LM, de Leon MP, Hales BJ, Biondo M, Douglass JA, et al. House dust mite sublingual immunotherapy: the role for transforming growth factor-beta and functional regulatory T cells. Am J Respir Crit Care Med 2009;180:936-47.
37. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. Lancet 1998;351:629-32.
38. Passalacqua G, Pasquali M, Ariano R, Lombardi C, Giardini A, Baiardini I, et al. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. Allergy 2006;61:849-54.
39. Potter PC, Baker S, Fenemore B, Nurse B. Clinical and cytokine responses to house dust mite sublingual immunotherapy. Ann Allergy Asthma Immunol 2015;114:327-34.
40. Shao J, Cui YX, Zheng YF, Peng HF, Zheng ZL, Chen JY, et al. Efficacy and safety of sublingual immunotherapy in children aged 3–13 years with allergic rhinitis. Am J Rhinol Allergy 2014;28:131-9.
41. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. Allergol Immunopathol (Madr) 1990;18:277-84.
42. Tseng SH, Fu LS, Nong BR, Weng JD, Shyur SD. Changes in serum specific IgG4 and IgG4/IgE ratio in mite-sensitized Taiwanese children with allergic rhinitis receiving short-term sublingual-swallow immunotherapy: a multicenter, randomized, placebo-controlled trial. Asian Pac J Allergy Immunol 2008;26:105-12.
43. Wang DH, Chen L, Cheng L, Li KN, Yuan H, Lu JH, et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. Laryngoscope 2013;123:1334-40.
44. Yonekura S, Okamoto Y, Sakurai D, Horiguchi S, Hanazawa T, Nakano A, et al. Sublingual immunotherapy with house dust extract for house dust-mite allergic rhinitis in children. Allergol Int 2010;59:381-8.

45. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. Int Arch Allergy Immunol 2012;157:288-98.
46. Nelson HS. Update on house dust mite immunotherapy: are more studies needed? Curr Opin Allergy Clin Immunol 2014;14:542-8.
47. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. J Allergy Clin Immunol 2006;117:1021-35.
48. Klimek L, Mosbech H, Zieglmayer P, Rehm D, Stage BS, Demoly P. SQ house dust mite (HDM) SLIT-tablet provides clinical improvement in HDM-induced allergic rhinitis. Expert Rev Clin Immunol 2016;12:369-77.
49. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA 2013;309:1278-88.
50. Larenas-Linnemann D, Blaiss M, Van Bever HP, Compalati E, Baena-Cagnani CE. Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009-2012. Ann Allergy Asthma Immunol 2013;110:402-15.e9.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.3.1 Children									
Tari	8	1.56	30	12	2.1	28	4.1%	-2.14 [-2.80, -1.49]	1990
Hirsch	0.84	0.975	8	0.34	0.35	10	3.8%	0.68 [-0.28, 1.65]	1997
Bahçeciler	0.53	0.4	8	0.41	0.39	7	3.7%	0.29 [-0.74, 1.31]	2001
Ippoliti	0.39	0.71	18	0.82	0.65	15	4.0%	-0.61 [-1.32, 0.09]	2002
Marcucci	5.6	2.25	13	4.4	3	11	3.9%	0.44 [-0.37, 1.26]	2003
Tseng	1.72	1.78	28	1.98	1.9	31	4.2%	-0.14 [-0.65, 0.37]	2008
Yonekura	1.224	0.146	19	1.652	0.146	9	3.6%	-2.85 [-3.98, -1.72]	2010
Eifan	1.5	1	15	2.9	0.7	14	3.9%	-1.57 [-2.41, -0.72]	2010
de Bot	2.26	1.84	108	2.02	1.67	111	4.3%	0.14 [-0.13, 0.40]	2012
Yukselen	3.74	1.4	10	4.15	1.4	10	3.9%	-0.28 [-1.16, 0.60]	2012
Aydogan	3.4	2.7	7	3.3	3	9	3.8%	0.03 [-0.95, 1.02]	2013
Shao	0.41	1.535	141	3.5	0.605	77	4.3%	-2.39 [-2.75, -2.03]	2014
Subtotal (95% CI)			**405**			**332**	**47.5%**	**-0.70 [-1.43, 0.03]**	
Heterogeneity: Tau² = 1.51; Chi² = 187.15, df = 11 (P < 0.00001); I² = 94%									
Test for overall effect: Z = 1.89 (P = 0.06)									
1.3.2 Adults									
Passalacqua A	54.89	11.28	10	108.27	25.19	9	3.4%	-2.67 [-3.98, -1.36]	1998
Mungan	0.5	0.37	15	0.67	0.2	11	4.0%	-0.53 [-1.32, 0.26]	1999
Passalacqua B	1.737	0.135	28	2.281	0.175	28	3.9%	-3.43 [-4.27, -2.59]	2006
O'Hehir	36.59	22	13	36.6	29.5	14	4.0%	-0.00 [-0.76, 0.75]	2009
Bozek	2.656	0.634	47	3.977	0.501	48	4.2%	-2.30 [-2.82, -1.77]	2013
Bergmann	2.6	2.25	133	3.13	2.317	141	4.3%	-0.23 [-0.47, 0.01]	2014
Nolte	5.47	2.69	36	7.45	2.69	34	4.2%	-0.73 [-1.21, -0.24]	2015
Huang	3.89	2.01	51	5.2	2.43	52	4.3%	-0.58 [-0.98, -0.19]	2015
Potter	5.25	1.22	32	6	1.22	16	4.1%	-0.60 [-1.22, 0.01]	2015
Demoly	2.9	2.27	297	3.3	2.27	296	4.4%	-0.18 [-0.34, -0.01]	2016
Subtotal (95% CI)			**662**			**649**	**40.8%**	**-1.02 [-1.53, -0.52]**	
Heterogeneity: Tau² = 0.55; Chi² = 124.80, df = 9 (P < 0.00001); I² = 93%									
Test for overall effect: Z = 3.99 (P < 0.0001)									
1.3.3 children and adults									
Guez	2.3	1.9	25	3.2	2.4	14	4.1%	-0.42 [-1.08, 0.24]	2000
Wang	3.293	0.267	48	6.086	0.414	37	3.4%	-8.17 [-9.50, -6.84]	2013
Mosbech	0.41	0.061	120	0.745	0.107	96	4.2%	-3.95 [-4.41, -3.49]	2015
Subtotal (95% CI)			**193**			**147**	**11.7%**	**-4.13 [-7.50, -0.76]**	
Heterogeneity: Tau² = 8.67; Chi² = 131.55, df = 2 (P < 0.00001); I² = 98%									
Test for overall effect: Z = 2.40 (P = 0.02)									
Total (95% CI)			**1260**			**1128**	**100.0%**	**-1.23 [-1.74, -0.73]**	
Heterogeneity: Tau² = 1.51; Chi² = 643.59, df = 24 (P < 0.00001); I² = 96%									
Test for overall effect: Z = 4.79 (P < 0.00001)									
Test for subgroup differences: Chi² = 3.93, df = 2 (P = 0.14), I² = 49.1%									



Supplementary Figure. Subgroup analysis of efficacy according to age.