Original Article

Efficacy of Subcutaneous and Sublingual Immunotherapy for House Dust Mite Allergy: A Network Meta-Analysis–Based Comparison

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What is already known about this topic? Subcutaneous and sublingual allergen immunotherapies are effective therapeutic arms for house dust mite allergy, but comparisons between modalities are limited.

What does this article add to our knowledge? To the authors' knowledge, this is the first meta-analysis to provide an indirect comparison of the clinical efficacy of immunotherapy modalities with house dust mite extracts. Subcutaneous immunotherapy has been shown to be more effective than sublingual immunotherapy in reducing allergic rhinitis symptoms.

How does this study impact current management guidelines? This study provides both direct and indirect evidence to assist clinicians in selecting an immunotherapy modality for the treatment of house dust mite allergy. Well-powered, direct, head-to-head trials are needed to validate current results.

BACKGROUND: Meta-analyses comparing the efficacy of sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) for house dust mite allergy are lacking.
OBJECTIVE: To compare the efficacy of SLIT drops, SLIT tablets, and SCIT in patients with perennial allergic rhinitis through network analysis.
METHODS: Frequentist network meta-analyses estimated the standardized mean difference (SMD) across the three immunotherapy modalities on allergic rhinitis symptom and medication score data from double-blind randomized clinical trials. Random effects models were investigated.
RESULTS: We included 26 double-blind randomized clinical trials in this meta-analysis for the symptom score and 18 for the medication score. In the direct pairwise meta-analysis, a significant reduction of the symptom score was observed for all immunotherapy modalities compared with the placebo: pooled SMDs of −0.461 (95% confidence interval [CI], −0.795 to −0.127) for SLIT drop, −0.329 (95% CI, −0.426 to −0.231) for SLIT tablet, and −1.669 (95% CI, −2.753 to −0.585) for SCIT. For the medication score, a significant reduction was observed for all modalities. In network meta-analysis, the clinical efficacy of SCIT based on the symptom score was greater than for SLIT drop or SLIT tablet (SMD: −0.697, 95% CI, −1.105 to −0.288; and SMD: −0.819, 95% CI, −1.242 to −0.397). However, there was no significant difference in the symptom score between SLIT drop and SLIT tablet.
CONCLUSIONS: This study demonstrated the clinical efficacy of all house dust mite immunotherapy modalities and suggests that SCIT may be more effective than SLIT drops or tablets in controlling symptoms of allergic rhinitis. © **2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Allergen immunotherapy; Allergic rhinitis; House dust mites; Immunologic desensitization; Meta-analysis; Subcutaneous immunotherapy; Sublingual immunotherapy*

INTRODUCTION

Allergic rhinitis (AR) is a common IgE-mediated disease, and its prevalence has gradually increased over the past several decades. Pharmacotherapy, including nonsedating oral antihistamines, topical nasal antihistamines, and intranasal corticosteroids, is administered to manage the symptoms of AR. Although pharmacotherapy is generally considered effective, some population surveys have reported that 62% of adults and 29% of children experience merely partial or poor relief of symptoms through pharmacotherapy alone.[1,2] Therefore, for patients with uncontrolled AR, allergen-specific immunotherapy (AIT) should be considered.[3] Allergen-specific immunotherapy is

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication June 4, 2021; revised July 20, 2021; accepted for publication August 13, 2021.
Available online ■■
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2213-2198

https://doi.org/10.1016/j.jaip.2021.08.018

Abbreviations used
AIT- Allergen-specific immunotherapy
AR- Allergic rhinitis
DBRCT- Double-blind randomized clinical trial
HDM- House dust mite
NMA- Network meta-analysis
PMA- Pairwise meta-analysis
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy
SLIT drop- Sublingual immunotherapy drop formulation
SLIT tablet- Sublingual immunotherapy tablet formulation
SMD- Standardized mean difference

an established treatment tool for AR to modify the underlying immunologic mechanism.

The most common administration routes for AIT in clinical practice are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) (drop [SLIT drop] or tablet [SLIT tablet] formulation). Subcutaneous immunotherapy is considered the conventional modality and is highly effective.[4,5] However, SCIT is occasionally associated with systemic adverse effects, which raises safety concerns.[6] More recently, SLIT has been prescribed worldwide as a promising alternative to SCIT, and meta-analyses have highlighted its efficacy in parallel to lesser systemic adverse effects.[7,8]

Although the efficacy of both SCIT and SLIT has been well established compared with placebo, the relative efficacy of the two has yet to be determined for improved AIT selection. In a previous double-blind randomized clinical trial (DBRCT) of direct head-to-head comparisons between SCIT and SLIT,[9-13] no significant difference was found between the two modalities. However, these studies had the limitation of a small study population. A number of systematic reviews compared the clinical efficacy of different immunotherapy modalities for grass pollen allergies, although with conflicting results.[14-16] In contrast, there is a lack of systematic reviews and meta-analyses comparing the efficacy of SLIT and SCIT for house dust mite (HDM) allergy. The aim of this study was to compare SLIT drop, SLIT tablet, and SCIT efficacy in patients with HDM-associated perennial AR through network analysis.

METHODS

Search strategy

We conducted a comprehensive search of the PubMed, Cochrane Library, and EMBASE databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to identify studies published up to November 12, 2020 containing data suitable for inclusion in the meta-analysis. We sought to include DBRCTs of AIT for the treatment of HDM-induced perennial AR. Two investigators (J.Y. Kim and D. H. Han) independently conducted the literature search to identify all available studies using the following search terms: rhin* AND ("immunotherapy" or "desensitization" or "immunologic") AND ("mite" or "perennial") AND controlled. Only studies published in English were considered.

Data extraction

Data were extracted into standardized forms and independently confirmed by the two investigators. For each article, we noted information on the following aspects: the name of the first author, the publication year, the form of AIT, the country where the study was conducted, the diagnosis of enrolled subjects, age, treatment duration and cumulative dose, assessed outcome, total sample size, and the number of subjects in AIT and placebo groups. Data were requested from authors of articles in which the means and SDs of clinical outcome scores were not reported. The revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the quality of identified trials.[17] Each item was classified as having low, some, or a high risk of bias. Studies with a high risk of bias were excluded.

Statistical analysis

The primary outcome was the nasal symptom score, and the secondary outcome was the medication score. For studies presenting the means and SDs only in figures, means and SDs were drawn from the figures. For studies reporting medians and interquartile range, means and SDs were estimated through an equation.[18] Because different scoring systems and measures for symptom and medication scores were used across studies, the treatment effect was calculated using the standardized mean difference (SMD). The SMD is calculated based on the difference in the symptom or medication score between the AIT and placebo groups.

Both direct pairwise meta-analysis (PMA) and network meta-analysis (NMA) were performed. We first conducted a PMA to estimate pooled SMDs and 95% confidence intervals (CIs) for direct comparisons between each modality (SLIT drop, SLIT tablet, and SCIT) and placebo. Heterogeneity was assessed using the I^2 statistic, which ranges between 0% and 100%, in which higher values indicate greater degrees of variability across study results. I^2 values of 25%, 50%, and 75% have been suggested to indicate low, moderate, and high heterogeneity, respectively.[19] Second, NMA was conducted using a frequentist approach to estimate pooled SMDs with 95% CIs for comparisons among modalities (SLIT drop vs SLIT tablet, SLIT drop vs SCIT, and SLIT tablet vs SCIT). Figure 1 shows a schematic of the practical approach for NMA. In both PMA and NMA, we selected a random-effects model to account for heterogeneity when substantial heterogeneity was observed ($I^2 > 50\%$) and applied a fixed-effects model for lower I^2 values.

We evaluated inconsistency between direct and indirect evidence using the design-by-treatment interaction model as a global test for inconsistency across the network, and the node-splitting method for each comparison (node) as a local approach.[20,21] Sensitivity analysis was performed by restricting analysis to studies determined as having a low risk of bias. The leave-one-out method for the direct pairwise comparison was used to assess the influence of an individual study on pooled SMDs by removing one study at a time. A comparison-adjusted funnel plot and Egger's test were employed to identify possible small-study effects in the network meta-analysis.[20,22] All analyses were conducted using the meta, metafor, and netmeta packages in R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 2427 citations initially identified through the search strategy, we included 26 DBRCTs for meta-analysis (Figure 2). Table I lists the characteristics of the 26 included studies.[9,10,23-46] The 26 DBRCTs (12 with 766 patients for SLIT drop,[9,10,26,27,30-35,37,39] 10 with 5744 patients for SLIT tablet,[25,29,36,38,41-46] six with 233 patients for SCIT,[9,10,23,24,28,40] and two studies[9,10] including both SLIT drop and SCIT) included a total of 3331 patients treated with immunotherapy and 3412 controls who received placebo. Of the

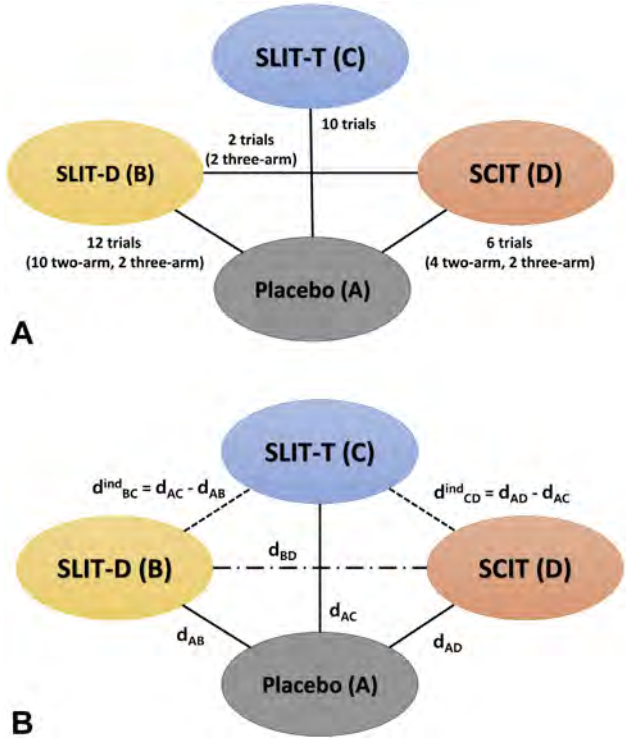

FIGURE 1. Schematic of practical approach for network meta-analysis (NMA). (**A**) Available trials for direct comparison. (**B**) Network diagram. The solid line indicates a weighted average of direct and indirect estimates with direct evidence dominantly contributing to NMA estimates. Dotted and solid line indicates a weighted average of direct and indirect estimates with indirect evidence dominantly contributing to NMA estimates. Dotted line indicates indirect estimates. Relative treatment effects compared with the placebo were used to calculate indirect comparisons ($d^{ind}BC$ and $d^{ind}CD$). Other NMA estimates (dAB, dAC, dAD, and dBD) were calculated from weighted averages of direct and indirect estimates. *D*, drops; *T*, tablets; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy

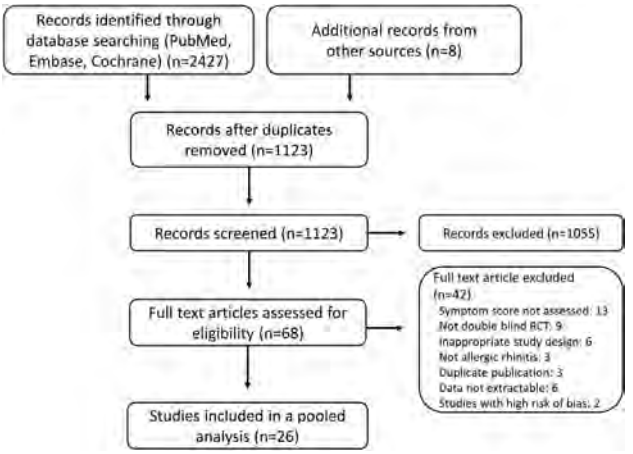

FIGURE 2. Study selection diagram. *RCT*, randomized controlled trial.

26 studies, both the symptom and medication scores were evaluated in 18 studies, and the symptom scores alone were evaluated in eight studies. Thirteen studies were performed in Europe, nine in Asia, one in North America, one in Africa, one in Oceania, and one in multiple continents. Twelve of 26 studies (three of 12 in SLIT drop and nine of 10 in SLIT tablet) were conducted in multiple centers, whereas the rest were conducted in single centers. Immunotherapy with HDM extract was performed in all except for two studies[25,29] in which allergoid was used for immunotherapy. The duration of AIT ranged from 6 months to 3 years. The risk of bias for all studies is shown in Figure E1, (in this article's Online Repository at www.jaci-inpractice.org).

Direct pairwise meta-analysis

The clinical efficacy of HDM immunotherapy for the symptom score is shown in Figure 3. Direct pairwise meta-analysis revealed a significant reduction in the symptom score in each immunotherapy group relative to the placebo group, with pooled SMDs of −0.461 (95% CI,−0.795 to −0.127) for SLIT drop, −0.329 (95% CI, −0.426 to −0.231) for SLIT tablet, and −1.669 (95% CI, −2.753 to −0.585) for SCIT (Figure 3). Severe heterogeneity was in SLIT drop and SCIT studies (I^2 = 77% and 91%, respectively), and high heterogeneity was found in SLIT tablet studies (I^2 = 64%).

When we restricted the pooled analysis to studies with a low risk of bias, it included five studies with 374 patients for SLIT drop, six studies with 3825 patients for SLIT tablet, and four studies with 175 patients for SCIT. Whereas sensitivity analysis of studies with a low risk of bias revealed a significant reduction in symptom score for SLIT tablet relative to the placebo by direct pairwise comparison, no significant differences were observed for SLIT drop and SCIT with pooled SMDs of −0.156 (95% CI, −0.472 to 0.159) for SLIT drop, −0.302 (95% CI, −0.366 to −0.238) for SLIT tablet, and −0.990 (95% CI, −2.076 to 0.097) for SCIT (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Because the sensitivity analysis included only studies with a low risk of bias, heterogeneity among SLIT drop and SLIT tablet studies was moderate and low, respectively (I^2 = 38% and 0%, respectively), whereas that among SCIT studies was still severe (I^2 = 90%). Sensitivity analysis omitting each study is shown in Figure E3, *A-C* (in this article's Online Repository at www.jaci-inpractice.org).

Figure 4 shows the clinical efficacy of HDM immunotherapy based on the medication score. Among the 26 studies, 18 evaluated the medication score. A significant reduction in medication score for each immunotherapy group relative to the placebo group was identified by direct pairwise meta-analysis: pooled SMDs of −0.546 (95% CI, −0.860 to −0.232) for SLIT drop, −0.227 (95% CI, −0.371 to −0.083) for SLIT tablet, and −0.697 (95% CI, −1.039 to −0.355) for SCIT (Figure 4). The degree of heterogeneity was moderate, severe, and low among SLIT drop, SLIT tablet, and SCIT studies, respectively (I^2 = 47%, 85%, and 0%, respectively). Sensitivity analysis omitting each study is shown in Figure E3, *D-E* (in this article's Online Repository at www.jaci-inpractice.org).

Network meta-analysis

In NMA, there was no significant difference in symptom score between SLIT drop and SLIT tablet (SMD, −0.123; 95% CI,

TABLE I. Double-blind randomized controlled trials included in meta-analysis

First author (year)	Country	N*	Diagnosis	Age, y†	Treatment duration, mo	Cumulative dose	Outcome assessed
Sublingual immunotherapy drop formulation							
Guez (2000)[26]	France	36	R with or without A	29.6 ± 12.4	24	90,000 IR	SS, MS
Bahceciler (2001)[27]	Turkey	8	R with A	12.4 (7.8-18)	6	7,000 IR	SS, MS
Tseng (2008)[30]	Taiwan¶	28	R with or without A	9.7 ± 3.3	6	37,312 IR	SS, MS
O'Hehir (2009)[31]	Australia	13	R with or without A	28.5 ± 8.2	12	NR	SS
Yonekura (2010)[32]	Japan¶	19	R with or without A	9.4 ± 2.2	10	NR	SS
de Bot (2012)[33]	Netherlands	110	R with or without A	11.8 ± 3.1	24	435 μg	SS
Yukselen (2012)[9]	Turkey	10	R with A	9.2 ± 3.4	12	173,733 TU	SS, MS
Bozek (2013)[34]	Poland	47	R with or without A	65.8 ± 4.9	36	421,200 IR	SS, MS
Wang (2013)[35]	China¶	48	R with or without A	22.7 ± 10.9	6	NR	SS
Potter (2015)[37]	South Africa	32	R with or without A	33.7 (18-60)	24	96,600 IR	SS
Wang (2016)[39]	China	25	R without A	6-14	12	NR	SS, MS
Xian (2020)[10]	China	27	R with or without A	24.2 ± 14.3	12	118.2 μg	SS, MS
Sublingual immunotherapy tablet formulation							
Passalacqua (1998)[25],‡	Italy	10	R with or without A	25 (15-37)	24	NR	SS
Passalacqua (2006)[29],‡	Italy¶	28	R with or without A	30.6 (18-49)	24	NR	SS, MS
Bergmann (2014)[36]	7 European countries¶	141	R with or without A	29.0 ± 8.5	12	109,200 IR	SS, MS
Demoly (2016)[38]	12 European countries¶	284	R with or without A	32.1 ± 10.6	12	4380 SQ	SS, MS
Nolte (2016)[46]	United States and Canada¶	740	R with or without A	35 ± 14	12	4380 SQ	SS, MS
Okamoto (2017)[41]	Japan¶	315	R without A	30.0 ± 11.8	12	109,200 IR	SS, MS
Okubo (2017)[42]	Japan¶	285	R without A	27.2 ± 12.0	12	2190 SQ	SS
Masuyama (2018)[43]	Japan¶	209	R with or without A	10.8 ± 2.9	12	2190 SQ	SS, MS
Okamoto (2019)[44]	Japan¶	205	R with or without A	10.3 ± 2.7	12	109,200 IR	SS
Demoly (2020)[45]	13 countries¶	586	R with or without A	29.5 ± 13.1	12	109,200 IR	SS, MS
Subcutaneous immunotherapy							
McHugh (1990)[23]	United Kingdom	28	R with or without A	17-52	12	NR	SS, MS
Pichler (1997)[24]	Switzerland	16	R with or without A	28.8 (20-46)	12	NR	SS
Varney (2003)[28]	United Kingdom	15	R with or without A	33 (19-48)	12	106 μg	SS, MS
Yukselen (2012)[9]	Turkey	10	R with A	10.9 ± 3.2	12	43,770 TU	SS, MS
Bozek (2017)[40]	Poland	30	R without A	68.1 ± 5.9	24	560,500 BAU	SS
Xian (2020)[10]	China	26	R with or without A	21.1 ± 12.0	12	81.2 μg	SS, MS

A, asthma; *MS*, medication score; *NR*, not reported; *R*, allergic rhinitis; *SS*, symptom score.
*N indicates the number of patients treated with immunotherapy in the individual studies.
†Age is presented as mean ± SD, mean (range), or range.
‡Allergoid was used for immunotherapy.
¶Multicenter study.

−0.428 to 0.182) (Figure 5, *A*). The SCIT had greater clinical efficacy in the symptom score compared with SLIT drop or SLIT tablet (SMD: −0.697, 95% CI, −1.105 to −0.288; and SMD: −0.819, 95% CI, −1.242 to −0.397). Direct comparisons estimated by NMA indicated that all AIT modalities had significant clinical efficacy based on the symptom score compared with the placebo, which was in agreement with pairwise comparisons. The sensitivity analysis of studies with a low risk of bias revealed no significant difference in the symptom score between SLIT drop and SLIT tablet (SMD, 0.070; 95% CI, −0.283 to 0.424) (see Figure E4 in this article's Online Repository at www.jaci-inpractice.org), which is consistent with NMA results. In addition, sensitivity analysis suggested that the clinical efficacy of SCIT for the symptom score was greater than that of SLIT drop or SLIT tablet (SMD: −0.518, 95% CI, −0.937 to −0.099; and SMD: −0.448, 95% CI, −0.863 to −0.032).

The medication score was not significantly different between studies with SLIT drop and SLIT tablet (SMD, −0.254; 95% CI, −0.552 to 0.044) (Figure 5, *B*). The improvement in medication score was greater for SCIT than for SLIT tablet (SMD, −0.517; 95% CI, −0.914 to −0.121) but not significantly different than that for SLIT drop (SMD, −0.263; 95% CI, −0.664 to 0.137). Direct comparisons estimated by NMA demonstrated that all AIT modalities had significant clinical efficacy based on the medication score compared with the placebo, which was in agreement with pairwise comparisons.

Additional analyses

We assessed potential publication bias using a comparison-adjusted funnel plot (see Figure E5 in this article's Online Repository at www.jaci-inpractice.org). In the comparison-adjusted Egger's test, there was no evidence of significant publication bias

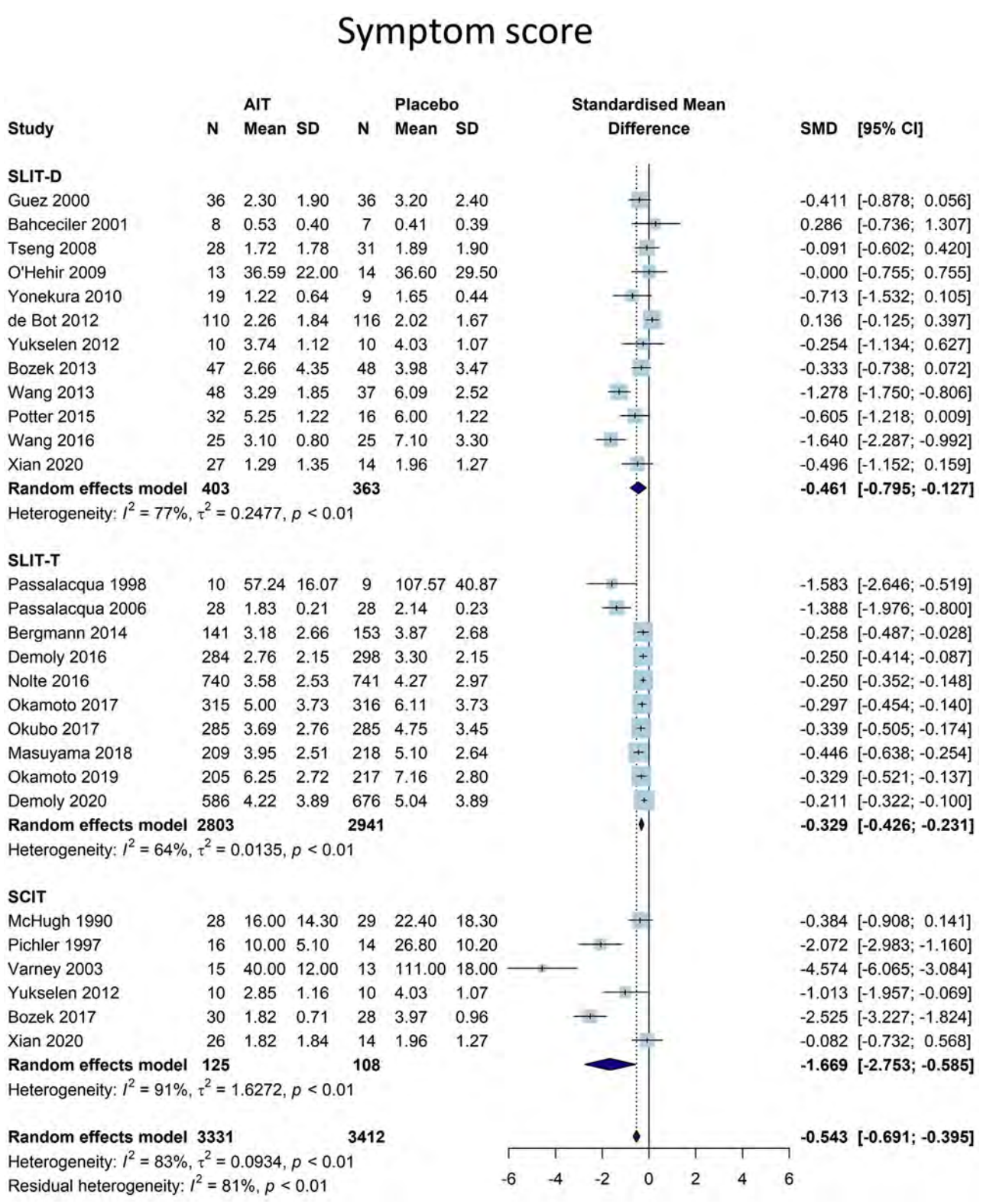

FIGURE 3. Direct pairwise comparison for symptom scores of immunotherapy modalities versus placebo. *AIT,* allergen-specific immunotherapy; *CI*, confidence interval; *D*, drops; *SCIT,* subcutaneous immunotherapy; *SLIT,* sublingual immunotherapy; *SMD*, standardized mean difference; *T,* tablets.

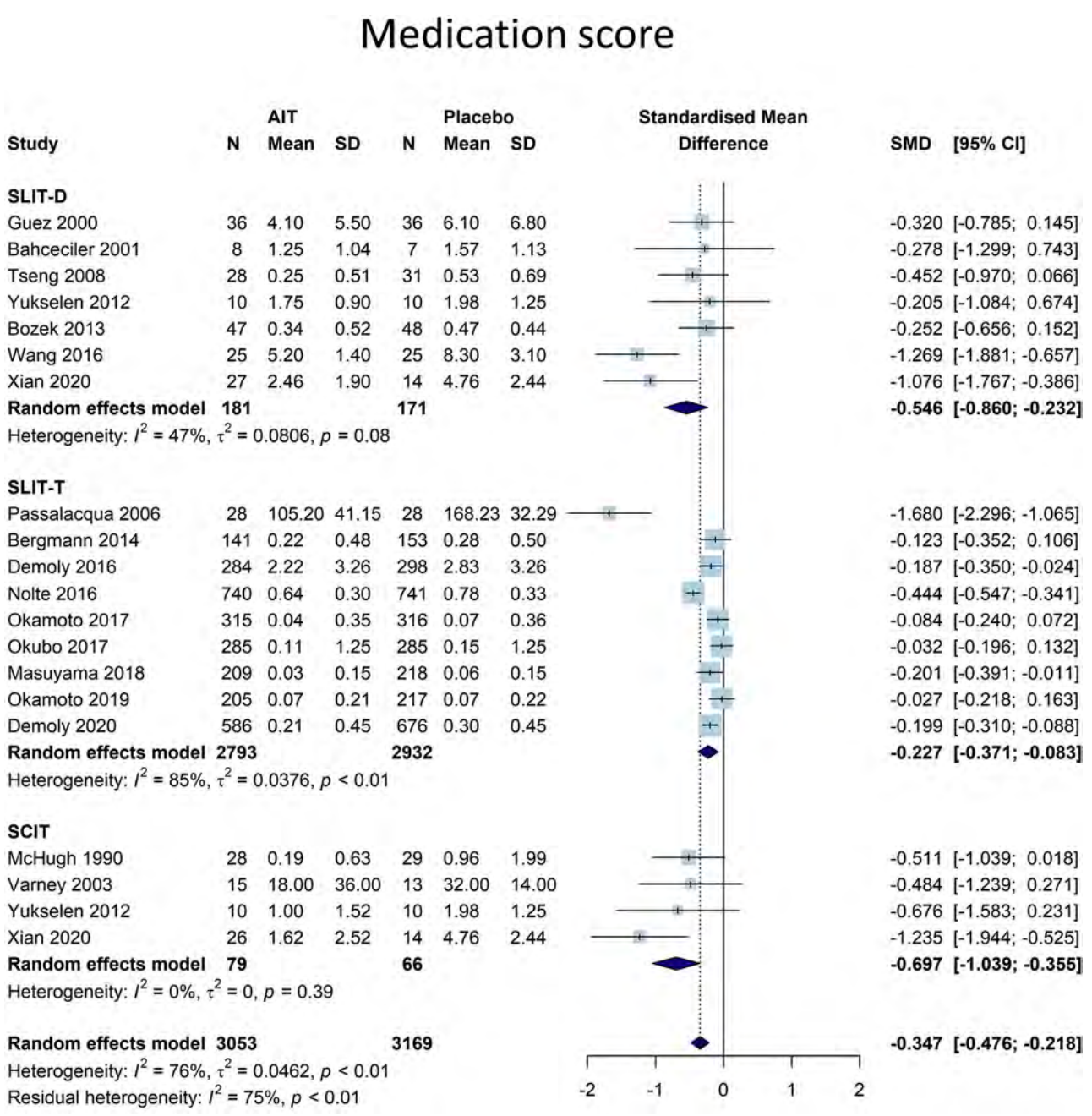

FIGURE 4. Direct pairwise comparison for medication scores of immunotherapy modalities versus placebo. *AIT*, allergen-specific immunotherapy; *CI*, confidence interval; *D*, drops; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy; *SMD*, standardized mean difference; *T*, tablets.

with regard to symptom and medication scores ($P = .089$ and .842, respectively). Concerning network inconsistency, significant inconsistency was detected between direct and indirect evidence by the design-by-treatment interaction model ($P = .003$) and node-splitting method (SLIT drop vs placebo, $P < .001$; SCIT vs SLIT drop, $P = .008$) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) in the analysis of the symptom score. However, no significant inconsistency was detected by the design-by-treatment interaction model ($P = .369$) and node-splitting method (see Table E2 in this article's Online Repository at www.jaci-inpractice.org) in the medication score analysis.

DISCUSSION

In this meta-analysis, 12 studies for SLIT drop,[9,10,26,27,30-35,39] 10 for SLIT tablet,[25,29,36-38,41-46] and six for SCIT[9,10,23,24,28,40] were pooled, and clinical efficacy was compared among the different AIT modalities. Direct comparison versus placebo through pairwise and network analysis indicated that all

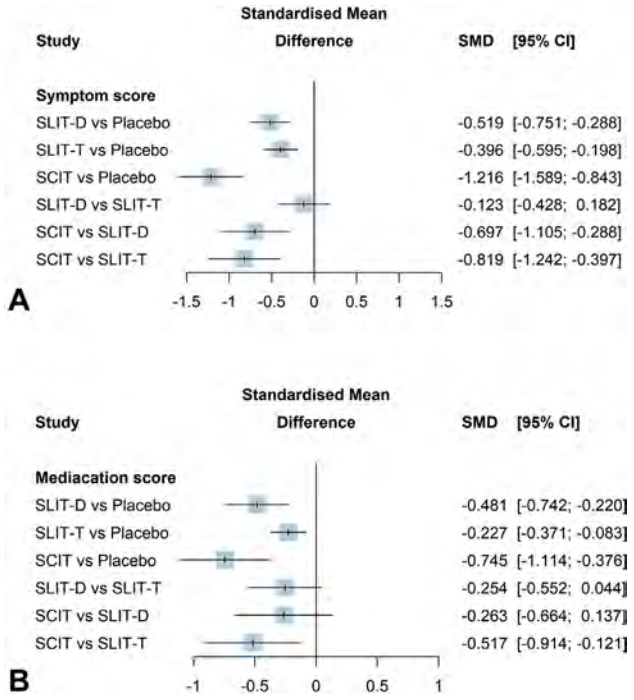

FIGURE 5. Results of network meta-analysis. Direct and indirect comparison of (**A**) the symptom score and (**B**) the medication score. *CI*, confidence interval; *D*, drops; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy; *SMD*, standardized mean difference; *T*, tablets.

modalities exhibited significant clinical efficacy on symptom and medication scores. Indirect comparison via NMA suggested that the clinical efficacy of SCIT on symptom scores was greater than that of SLIT drop or SLIT tablet, whereas theirs were comparable. There have been discrepancies among systematic reviews and meta-analyses comparing SCIT and SLIT for seasonal AR.[14-16] Chelladurai et al[14] reported that moderate-grade evidence supports the greater efficacy of SCIT than SLIT for nasal and/or eye symptom reduction in a systematic review. In addition, Di Bona et al[47] conducted a meta-analysis of randomized clinical trials for the efficacy of SCIT and SLIT for seasonal AR and suggested a greater clinical efficacy of SCIT in reducing AR symptoms compared with SLIT drop or SLIT tablet, which is consistent with the current findings. However, a network meta-analysis performed by Nelson et al[16] revealed no significant difference for both symptom and medication scores between SLIT drop and SCIT, nor between SLIT tablet and SCIT. In addition, they reported no significant difference in symptom score between SLIT drop and SLIT tablet, which is also consistent with the current results.[16]

When we restricted the PMA to studies with a low risk of bias, we observed no significant difference in studies of SLIT drop and SCIT, which may be explained by the small number of patients and lower pooled SMDs. In addition, the NMA of studies with a low risk of bias revealed a significant difference in symptom score for SLIT tablet and SCIT, but not for SLIT drop, compared with placebo. The symptom score of SLIT drop was not significantly different from that of placebo in sensitivity analyses from both direct pairwise comparison and NMA. There are two possible explanations for the lack of clinical efficacy indicated by the sensitivity analysis of SLIT drop. First, in studies on SLIT drop, a large number (10 of 12) had no significant clinical efficacy, and some (three of nine) did not show a trend favoring SLIT drop versus placebo. In contrast, all publications for SLIT tablet and most for SCIT (four of six) indicated significant clinical efficacy. Two studies for SCIT demonstrated a trend favoring SCIT over placebo, albeit without significant clinical efficacy. Despite the inconsistent results of studies for SLIT drop, two studies[35,39] with high SMDs might have led to the significant clinical efficacy of SLIT drop versus placebo in reducing the symptom score in the pooled analysis. However, both[35,39] did not satisfy criteria for the low risk of bias and were omitted in sensitivity analysis. The second reason may be that the number of patients in the sensitivity analysis of SLIT drop might be insufficient to provide evidence for its clinical efficacy.

With regard to network inconsistency, significant inconsistency was identified by the design-by-treatment interaction model and node-splitting method in symptom score analysis. To identify designs that cause inconsistency, network inconsistency was calculated when each design was detached, which revealed that holding out two-arm trials comparing SCIT and placebo resulted in nonsignificant inconsistency ($P = .817$). The inconsistent result from two three-arm trials[9,10] may also have contributed to the inconsistency. The symptom score of SLIT drop was much lower than that of SCIT in the study by Xian et al.[10] Therefore, large head-to-head trials are necessary to strengthen evidence for a direct comparison among different AIT modalities.

There were some limitations to the current meta-analysis. First, although all included studies were DBRCTs, study characteristics varied. Most studies for SLIT tablet were multicenter DBRCTs performed with a large population, and there were 2803 SLIT tablet—treated patients for pooling. In contrast, most studies for SLIT drop and SCIT were single-center DBRCTs with a small study population, and there were 403 and 125 SLIT drop—and SCIT-treated patients, respectively, for pooling. Second, the different result of two three-arm trials might have had a considerable effect on NMA. Finally, because no universal scoring system has been established for AIT, inconsistent scoring systems for symptom and medication scores might have led to significant heterogeneity across studies. In addition, different characteristics of the individual studies (demographics, type of HDM extracts and allergen concentration, and severity of AR) might also have contributed to significant heterogeneity across studies.

Taken together, NMA of 26 DBRCTs in patients treated with AIT for HDM allergies revealed that the therapeutic effect of SCIT in controlling AR symptoms was greater than those of SLIT drop or SLIT tablet. The clinical efficacy of SLIT drop and SLIT tablet with regard to symptom score was comparable. Direct comparisons versus placebo by PMA and NMA demonstrated the clinical efficacy of SLIT drop, SLIT tablet, and SCIT to reduce symptom and medication scores in perennial AR. Despite certain limitations, including differences between study designs and significant heterogeneity across studies, this NMA may provide useful evidence for comparing different AIT modalities for perennial AR.

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TABLE E1. Assessment of local inconsistency in network using node-splitting method for symptom score

Comparison	Studies providing direct evidence, n	Proportion*	Network meta-analysis estimate†	Direct estimate†	Indirect estimate†	Difference‡	*P*¶
SLIT drop vs placebo	12	97%	−0.519	−0.445	−2.830	2.385	<.001
SLIT tablet vs placebo	10	100%	−0.398	−0.398			
SCIT vs placebo	6	89%	−1.216	−1.309	−0.495	−0.813	.175
SLIT drop vs SLIT tablet	0	0%	−0.123		−0.123		
SCIT vs SLIT drop	2	42%	−0.697	−0.043	−1.163	1.120	.008
SCIT vs SLIT tablet	0	0%	−0.819		0.819		

*Proportion of direct evidence.
†Standardized mean difference values.
‡Difference between standardized mean difference values for direct and indirect comparison.
¶*P* value of test for disagreement (direct vs indirect comparison).

TABLE E2. Assessment of local inconsistency in network using node-splitting method for medication score

Comparison	Studies providing direct evidence, n	Proportion*	Network meta-analysis estimate†	Direct estimate†	Indirect estimate†	Difference‡	*P*¶
SLIT drop vs placebo	7	95%	−0.481	−0.524	0.270	−0.794	.180
SLIT tablet vs placebo	9	100%	−0.227	−0.227			
SCIT vs placebo	4	85%	−0.745	−0.746	−0.734	−0.012	.982
SLIT drop vs SLIT tablet	0	0%	−0.254		−0.254		
SCIT vs SLIT drop	2	53%	−0.263	−0.431	−0.073	−0.358	.382
SCIT vs SLIT tablet	0	0%	−0.517		−0.517		

*Proportion of direct evidence.
†Standardized mean difference values.
‡Difference between standardized mean differences for direct and indirect comparison.
¶*P* value of test for disagreement (direct vs indirect comparison).

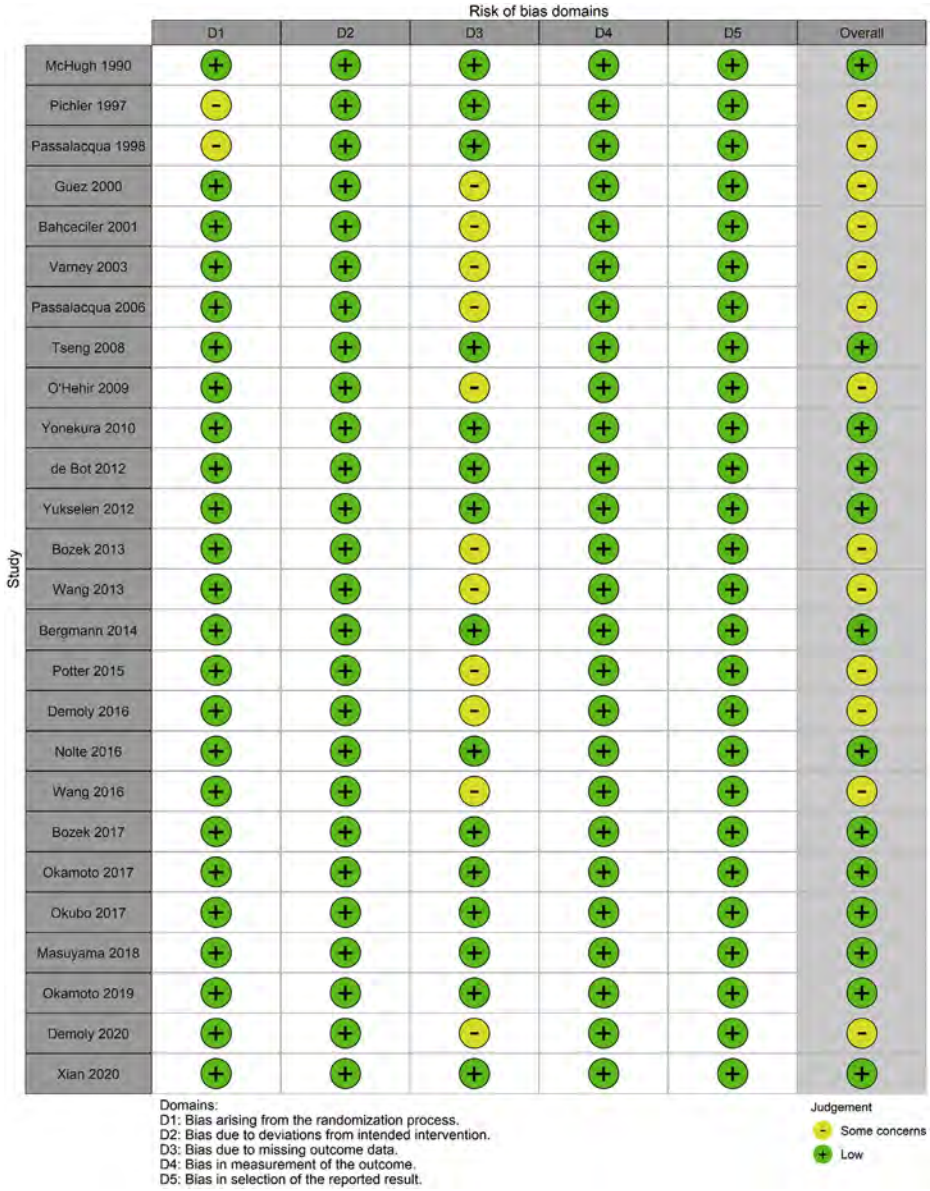

FIGURE E1. Assessment of risk of bias.

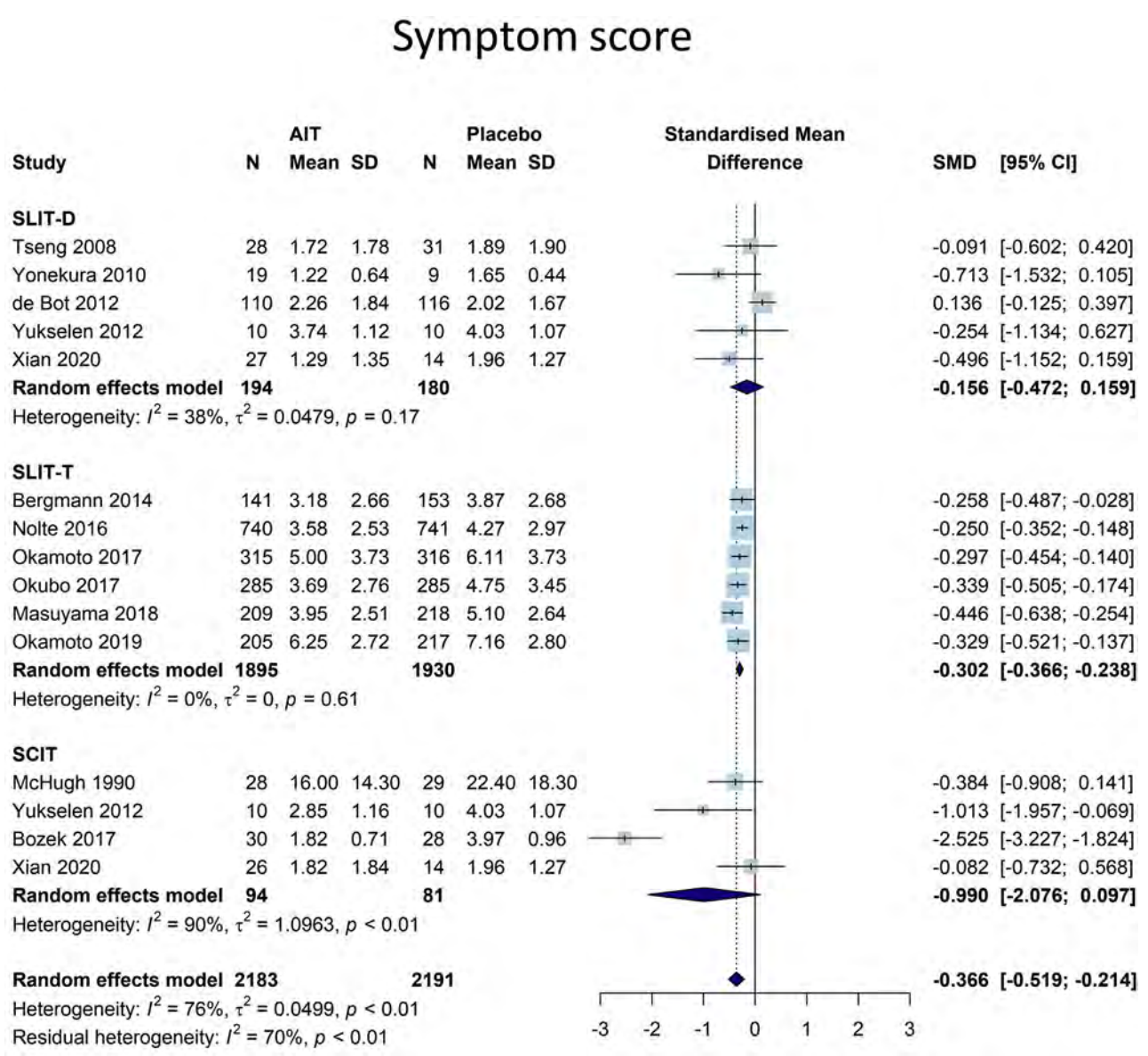

FIGURE E2. Sensitivity analysis of studies with low risk of bias for direct pairwise comparison between immunotherapy modalities versus placebo based on symptom score. *AIT,* allergen-specific immunotherapy; *CI*, confidence interval; *D*, drops; *SCIT,* subcutaneous immunotherapy; *SLIT,* sublingual immunotherapy; *SMD*, standardized mean difference; *T,* tablets.

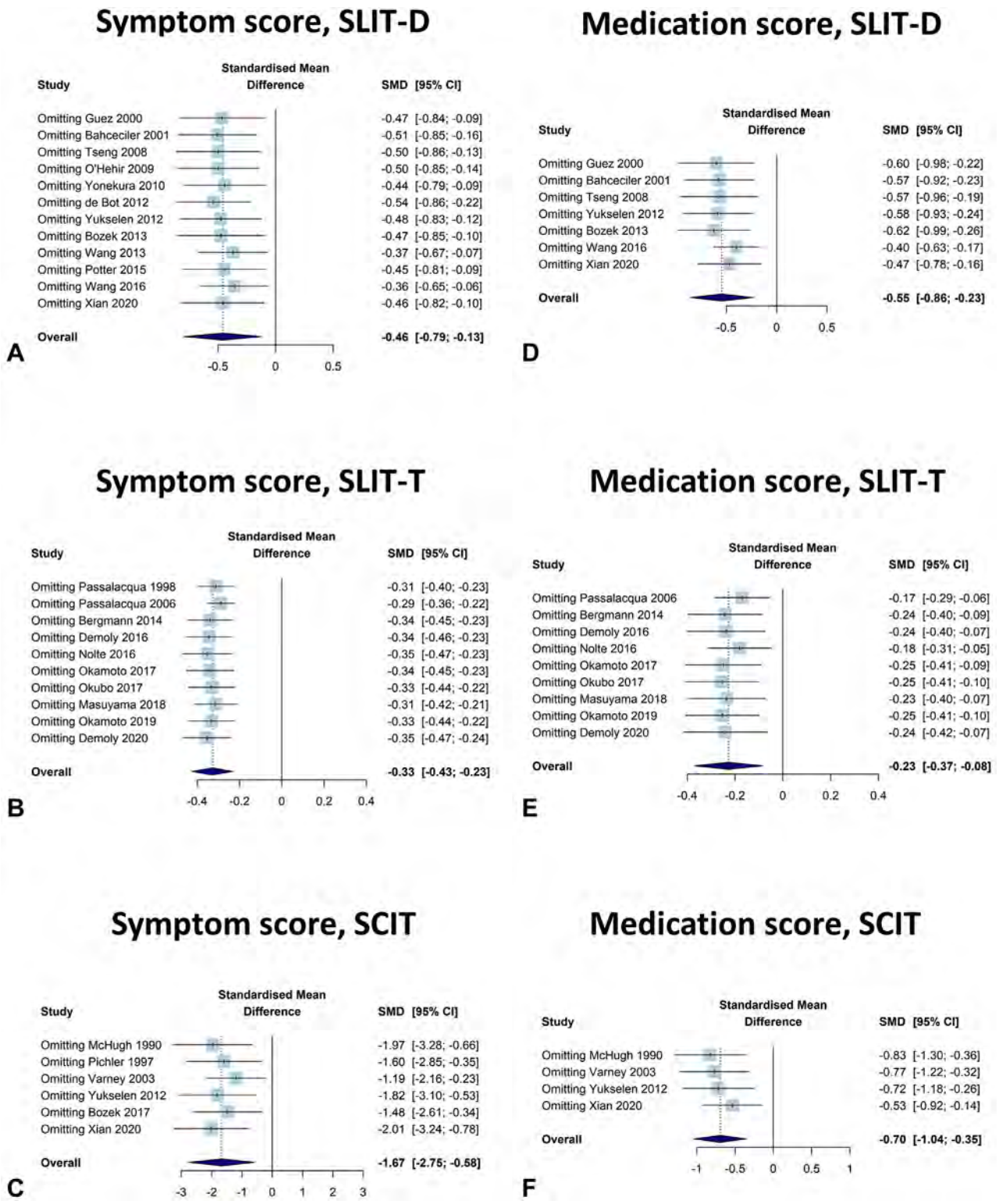

FIGURE E3. Sensitivity analysis omitting each study for direct pairwise comparison between immunotherapy modalities and placebo based on symptoms and medication scores. (**A**) Symptom score for sublingual immunotherapy (SLIT) drop. (**B**) Symptom score for SLIT tablet. (**C**) Symptom score for subcutaneous immunotherapy (SCIT). (**D**) Medication score for SLIT drop. (**E**) Medication score for SLIT tablet. (**F**) Medication score for SCIT. *CI*, confidence interval; *SMD*, standardized mean difference.

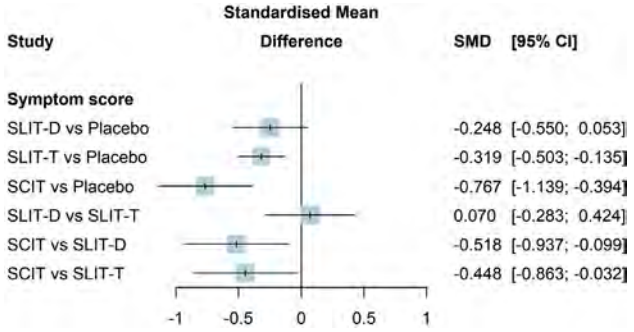

FIGURE E4. Sensitivity analysis of studies with low risk of bias for network meta-analysis of symptom scores. *CI*, confidence interval; *D*, drops; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy; *SMD*, standardized mean difference; *T*, tablets.

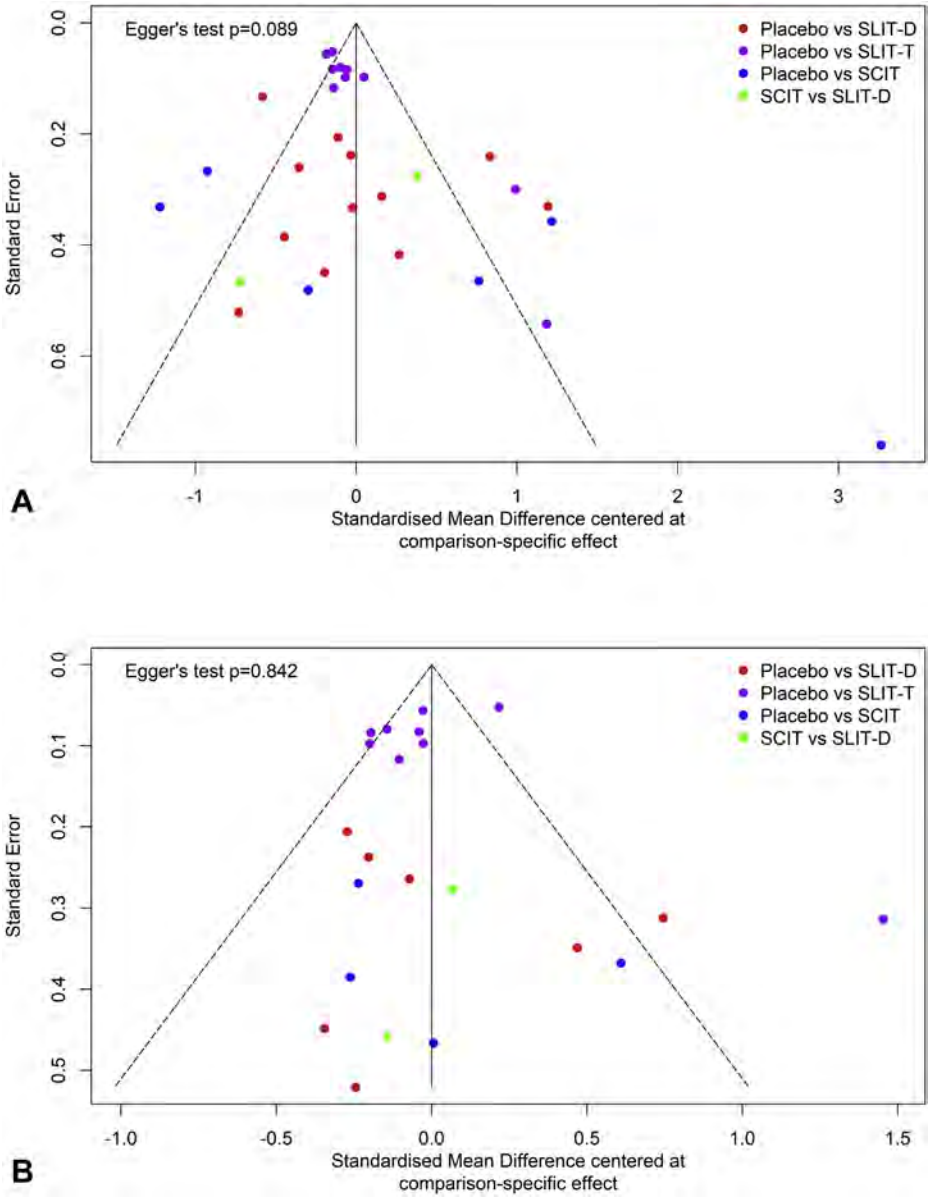

FIGURE E5. Funnel plot of symptom and medication score for each modality of immunotherapy. (**A**) Symptom score. (**B**) Medication score. *D*, drops; *SCIT*, subcutaneous immunotherapy; *SLIT*, sublingual immunotherapy, *T*, tablets.