APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

House dust mite allergen immunotherapy for monosensitized versus polysensitized patients with allergic rhinitis: A systematic review and meta-analysis

Phichayut Phinyo,[1,2,3] Thanachit Krikeerati,[4] Pakpoom Wongyikul,[2] Mongkol Lao-Araya,[5] Torpong Thongngarm[4]

Abstract

Background: Most patients with allergic rhinitis are polysensitized. The efficacy of house dust mite (HDM) allergen immunotherapy (AIT) compared between monosensitized and polysensitized patients remains limited.

Objective: To systematically review the efficacy and safety of HDM AIT compared between monosensitized and polysensitized patients with allergic rhinitis.

Methods: We searched PubMed/MEDLINE, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) until June 2022. The primary outcome was the changes from baseline in total nasal symptom score (TNSS). Secondary outcomes were changes from baseline in total medication score (TMS), combined symptom and medication score (CSMS), visual analog scale (VAS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score, immunological parameters, and adverse events (AEs).

Results: Of 13 eligible studies, 10 prospective cohorts, 2 retrospective cohorts, and 1 matched cohort, we identified 10 studies for quantitative synthesis. There were 1,113 patients with allergic rhinitis, 566 with HDM monosensitization and 547 with polysensitization to HDM and other allergens. There was no significant difference in the pooled mean changes of the 2 groups in TNSS (SMD -0.05, 95%CI: -0.22 to 0.11, p = 0.532) and VAS (SMD -0.20, 95%CI: -0.42 to 0.01, p = 0.060) with moderate certainty of evidence. The changes in TMS, CSMS, and RQLQ were similar between the 2 groups with very low certainty of evidence. The AEs were mild and comparable between the 2 groups. The immunological indices remained inconsistent and were not predictive of clinical responses.

Conclusion: A single HDM AIT similarly improved clinical outcomes in monosensitized and polysensitized patients with allergic rhinitis.

Key words: allergen immunotherapy, allergic rhinitis, effectiveness, efficacy, house dust mite, monosensitized, polysensitized, subcutaneous immunotherapy, sublingual immunotherapy

Citation:
Phinyo, P., Krikeerati, T., Wongyikul, P., Lao-Araya, M., Thongngarm, T. House dust mite allergen immunotherapy for monosensitized versus polysensitized patients with allergic rhinitis: A systematic review and meta-analysis. *Asian Pac J Allergy Immunol*. https://doi.org/10.12932/ap-190822-1440

Affiliation:
[1] Department of Family Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
[2] Center for Clinical Epidemiology and Clinical Statistics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
[3] Musculoskeletal Science and Translational Research (MSTR) Center, Chiang Mai University, Chiang Mai, Thailand
[4] Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[5] Division of Allergy and Clinical Immunology, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Corresponding author:
Torpong Thongngarm
Division of Allergy and Clinical Immunology,
Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University
2 Wanglang Rd., Bangkok Noi, Bangkok 10700, Thailand
E-mail: torallergy@gmail.com

Abbreviations:

AEs	Adverse events
AIT	Allergen immunotherapy
AR	Allergic rhinitis
CSMS	Combined symptom and medication score
Der p	Dermatophagoides pteronyssinus
Der f	Dermatophagoides farinae
HDM	House dust mite
RCT	Randomized controlled trial
RQLQ	Rhinitis Quality of Life Questionnaire
SCIT	Subcutaneous immunotherapy
sIgE	Specific immunoglobulin E
sIgG4	Specific immunoglobulin G4
SLIT	Sublingual immunotherapy
TMS	Total medication score
TNSS	Total nasal symptom score
VAS	Visual analog scale

Introduction

Patients with allergic rhinitis can be sensitized to a single (monosensitized) or multiple (polysensitized) allergens. Polysensitization accounts for 27.5-74.3% of patients in the United States and European populations.[1-4] Of importance, the more significant number of allergens being sensitized, the more severe the allergic diseases.[5] Strategies for treating polysensitized patients with allergen immunotherapy (AIT) vary among clinicians. In the United States, polysensitized patients are generally treated with multi-allergen AIT, whereas in Europe, with a single or 2 most clinically relevant allergens.[6,7] The disparity of both concepts remains debated.

Ortiz et al[8] found that the efficacy of single-, pauci- and multi-allergens sublingual immunotherapy (SLIT) was comparable in improving nasal symptoms and quality of life in polysensitized patients. If the majority of sensitization had been pollens, the cross-reactivity of allergenic proteins would have explained the efficacy of a single allergen AIT. However, the study did not report the sensitization pattern of enrolled patients. Kim et al[9] showed that multi-allergen AIT treating polysensitized asthmatic children was less effective than a single house dust mite (HDM) AIT for monosensitized ones. In contrast, Zhang et al[10] have recently reported that a single HDM SLIT was as clinically effective as multi-allergen AIT for treating polysensitized patients with asthma.

The results from the randomized controlled trials (RCTs), of which 66-90% of the recruited patients with allergic rhinitis were polysensitized, have demonstrated the efficacy of HDM SLIT tablets in improving clinical symptoms.[11-15] The pooled analysis from 2 of those RCTs showed that HDM SLIT tablets effectively improved total combined rhinitis score of -1.20 (95%CI; -2.0 to -0.5) in the monosensitized group and -0.9 (95%CI; -1.3 to -0.4) in polysensitized group, compared with placebo.[16] Although those RCTs excluded patients with clinically relevant allergens other than HDM to avoid their polysensitization being a confounder, HDM-induced perennial symptoms may still conceal clinical symptoms caused by other allergens. Taking the findings of those studies into account, the issue of whether a single HDM AIT may be beneficial for polysensitized patients is of interest.

Herein, we conducted a systematic review and meta-analysis to assess the efficacy of HDM AIT in monosensitized versus polysensitized patients with allergic rhinitis on total nasal symptom score (TNSS), total medication score (TMS), combined symptom and medication score (CSMS), visual analog scale (VAS), Rhinitis Quality of Life Questionnaire (RQLQ) score, immunologic parameters, and adverse events (AEs).

Methods

This systematic review and meta-analysis was conducted following the Cochrane Handbook for Systematic Reviews of Intervention[17] and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020.[18] The review protocol was registered on PROSPERO (CRD42022332703).

Data sources and search strategy

A pre-specified search strategy was used to search for relevant literature from its inception to the end of June 2022. Electronic medical databases included PubMed/MEDLINE, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). A search strategy for each database is provided in **eTable 1** to **eTable 4**. A search for grey literature was conducted through Google scholar and Clinical Trial Registry.[19] The authors also reviewed the previous list of references from previously reported systematic reviews and/or meta-analyses on the same topic.

Study selection and outcomes

The study inclusion was based on the following criteria: 1) a longitudinal study (e.g., cohort or case-control); 2) patients with allergic rhinitis of all ages prescribed with HDM AIT for maintenance treatment for at least 3 months; and 3) patients were categorized into monosensitized and polysensitized groups according to their sensitization status using standard tests, and the outcomes of interest were reported for each group. Exclusion criteria were non-English studies, studies with no abstract or available full text, duplicated studies, and studies that excluded polysensitized patients.

The primary outcome of interest was the changes from baseline in TNSS. The secondary outcomes were the changes from baseline in TMS, CSMS, VAS, RQLQ score, immunologic parameters, and AEs.

Screening

Two screening procedures were employed in this review. Firstly, two investigators (TK and PW) screened records using Rayyan.[20] Secondly, one investigator (PP) screened through the rearranged records using ASReview, an open-source machine learning for prioritized screening.[21] The screening was stopped after the investigator had screened 50% of the records. The results of the two procedures were combined. Disagreements during the screening process were resolved through discussion with a clinical expert in allergy (TT).

Data extraction

Two authors (TK and PW) independently extract the following data from each study: study characteristics, country/location including environmental factors, study design, inclusion and exclusion criteria, population type (i.e., children, or adults), patient demographics, including age and gender, and potential effect modifiers. Any discrepancy was resolved through discussion with a clinical expert (TT).

For continuous outcomes, we extracted the mean change values and their standard deviation (SD) for each treatment arm. For studies that did not directly report the mean values of the outcomes, the methods proposed by Luo et al[22] and Wan et al[23] were employed to estimate the mean values. If the SDs were not reported, we followed the methods suggested by the Cochrane Handbook to impute these values.[17] Digitizelt was used to extract data from graphs if needed. The total number of patients and events within each treatment arm were collected for the categorical endpoint. We contacted the corresponding authors for studies with incomplete outcome data.

Risk-of-bias assessment

Two authors (TK and PW) independently evaluated the quality of each included study using the Newcastle-Ottawa Scale (NOS).[24] NOS assessed the study quality based on three domains: subject selection, comparability, and outcome assessment. Studies were rated as good, fair, or poor quality according to the number of stars received within each domain. Any disagreement was resolved by consulting with a clinical expert in allergy (TT) and a clinical methodologist (PP).

Data synthesis and analysis

All analyses were performed using Stata 17 (StataCorp). *P*-values < 0.05 were considered statistically significant. Tabulation methods were used to assess the similarity across studies in terms of clinical questions prior to meta-analysis. A pairwise meta-analysis was performed using DerSimonian and Laird random-effects model. Heterogeneity was evaluated using the Cochrane Q test and the I-squared statistics. For continuous outcomes, we pooled the estimates as standardized mean difference (SMD). A treatment effect with an SMD of 0.2, 0.5, and 0.8 was considered a small, medium, and large effect.[25]

For the efficacy outcomes, we focused on the changes in TNSS, TMS, CSMS, VAS, and RQLQ after being treated with HDM AIT for at least 3 months. Only studies reporting score change from 12 months onwards after treatment initiation were included. For studies that provide the data on only TNSS and TMS but did not report CSMS, we calculated the CSMS according to the standard formula: TNSS/4 + TMS.[26]

Subgroup analyses were performed using the quality of study according to the NOS. Sensitivity analyses were conducted by excluding studies with baseline imbalance. A leave-one-out sensitivity analysis was performed to examine the robustness of the main results. Publication bias was not evaluated as the number of included studies was less than 10.

Quality and certainty of evidence

Two authors (PW and PP) rated the certainty and quality of synthesized evidence following the Grading of Recommended Assessment, Development, and Evaluation (GRADE) approach.[27] The quality of evidence depends on study design, risk of bias, consistency, directness, and precision of the findings. Each outcome was graded as having very low, low, moderate, or high quality of evidence. A team discussion with all other authors was used to resolve any disagreements.

Results

Search results

A total of 2,929 records were identified from a systematic search. Thirty studies were identified from manual screening, and another was identified from ASReview. However, we could not retrieve full-text articles for 6 studies. Thus, only 28 full-text articles were assessed. Fifteen studies were excluded, 13 were conference abstracts, and the other two studies[28,29] were published in Chinese. Finally, 13 studies were included in this systematic review, but only 10 of them had sufficient outcome data for meta-analysis. The PRISMA 2020 flow diagram is shown in **Figure 1**.

Characteristics of the included studies

A total of 13 studies were included in this systematic review, 9 prospective cohorts,[30-38] 3 retrospective cohorts,[39-41] and 1 matched cohort.[42] Eight studies were from China, 3 from Korea, 1 from Turkey, and 1 from Italy. The summary of characteristics and the main findings of each study are presented in **Table 1**. This systematic review included a total of 1,113 patients, 566 with HDM monosensitization and 547 with polysensitization (HDM and other allergens sensitized). Details on the inclusion criteria, exclusion criteria, number, and reasons for withdrawals of each study are shown in **eTable 5**. One study[34] included polysensitized patients who were not polyallergic, 1 study[40] included those who were polyallergic, and the remaining 11 studies did not report the status of their polysensitized patients. Allergens besides HDM sensitized in the polysensitized group of each study are shown in **eTable 6**. Details on the outcome of interest, point of outcome measurements, and definitions of outcomes are shown in **eTable 7**. Nine studies[30,31,35,37-42] treated patients with HDM SLIT, while 4[32-34,36] used HDM subcutaneous immunotherapy (SCIT). All studies had 1 year or greater duration except for the one[34] from Turkey. Both monosensitized and polysensitized patients in all included studies experienced a similar improvement in clinical symptoms during the treatment period, with no significant differences between the 2 groups. However, 1 study followed patients 5 more years after cessation of a 2-year HDM SLIT and found a more sustained clinical benefit, favoring the monosensitized group only at year 5 of the total 7-year study duration.[31] Three studies compared the degree of responses to HDM AIT between monosensitized and polysensitized patients and found no significant difference between the 2 groups.[30,35,41]

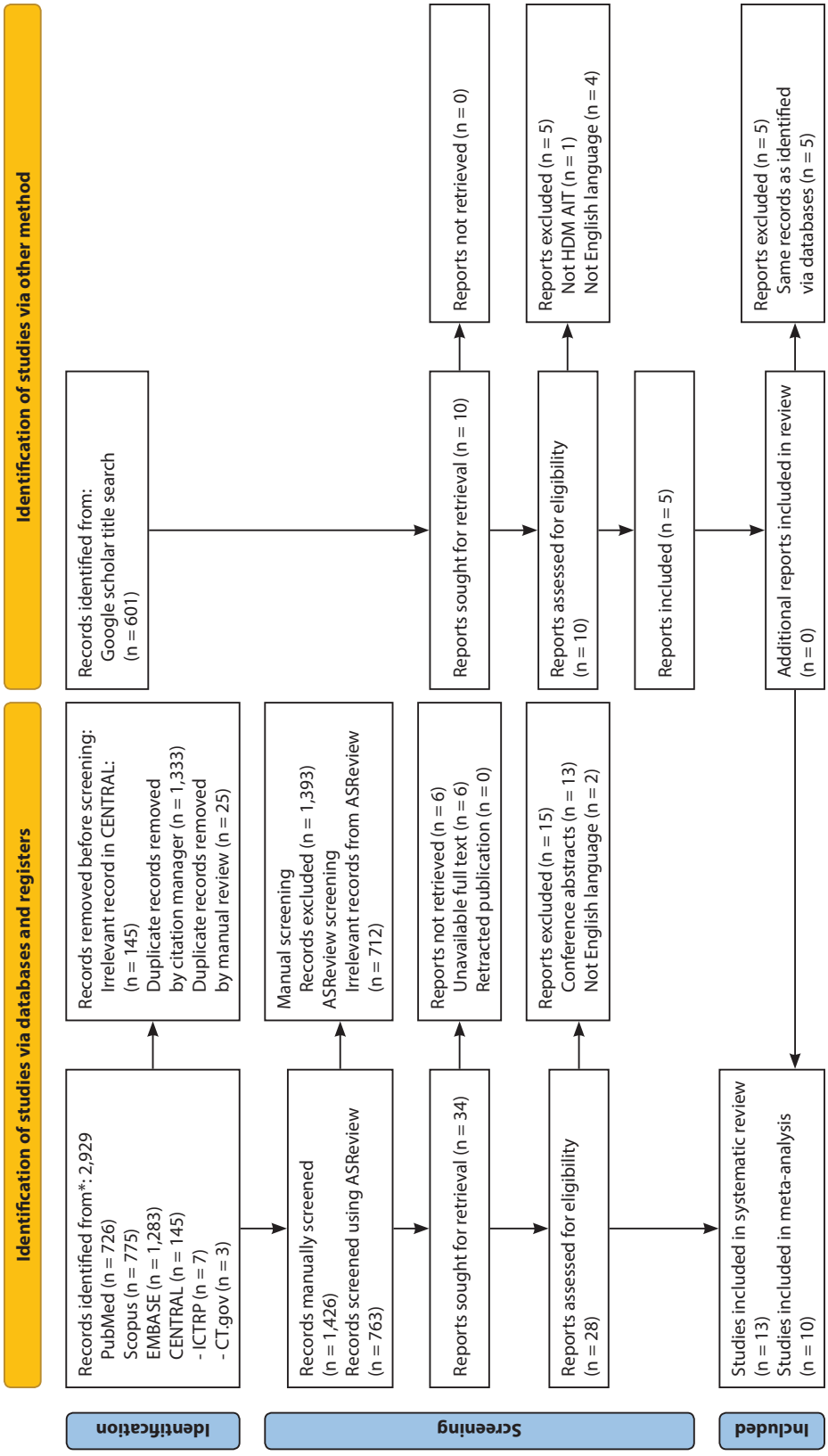


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of included and excluded studies.

Table 1. Characteristics of included studies of house dust mite allergen immunotherapy in monosensitized versus polysensitized patients with allergic rhinitis

Studies	Site of studies	Type/duration of studies	Study size (n)	Route of HDM AIT	Dose of HDM AIT[c]	Patients, n	Age (y)	Pre-TNSS	Post-TNSS	Pre-TMS	Post-TMS	Pre-CSMS	Post-CSMS
Ma 2021[39]	China	Retrospective cohort/12 mo	68	SLIT-D daily	Der f[d] 100 μg/d (Adult) 50 μg/d (< 14 y)	Monosensitized AR, 36	21.7 ± 15.1	6.70 ± 2.44	2.63 ± 2.22	2.32 ± 1.07	0.51 ± 0.95	4.00 ± 1.68[f]	1.17 ± 1.51[f]
						Polysensitized AR, 32	16.5 ± 9.9	6.94 ± 2.22	2.28 ± 2.41	2.44 ± 1.14	0.21 ± 0.58	4.18 ± 1.70[f]	0.78 ± 1.18[f]
Gao 2020[30]	China	Prospective cohort/36 mo	110	SLIT-D daily	Der f[d] 100 μg/d (Adult) 50 μg/d (< 14 y)	Monosensitized AR, 68	16.89 ± 13.33	NR	NR	NR	NR	6.33 ± 0.55	1.12 ± 0.73
						Polysensitized AR, 42 (≤ 3 allergens)		NR	NR	NR	NR	6.48 ± 0.54	1.01 ± 0.71
Cui 2019[31]	China	Prospective cohort/24 mo	80	SLIT-D daily	Der f[d] 50 μg/d	Monosensitized AR, 40	7.10 ± 2.09	NR	NR	NR	NR	4.31 ± 0.51	1.22 ± 0.3
						Polysensitized AR, 40 (≤ 3 allergens)	6.62 ± 1.63	NR	NR	NR	NR	4.30 ± 0.51	1.20 ± 0.36
Tu 2019[32]	China	Prospective cohort/24 mo	58	SCIT q 6 wk	9.8 μg Der p1	Monosensitized AR, 35	11[a] (5-53)	7.00[b] (6.00, 9.75)	2.00[b] (0.00, 4.00)	3.7 (median)	1.4 (median)	NR	NR
						Polysensitized AR, 23		10.00[b] (7.75, 11.00)	2.00[b] (1.50, 4.00)			NR	NR
Zhang 2019[40]	China	Retrospective cohort/24 mo	183	SLIT-D daily	HDM[d] (unspecified species) 50 μg/d	Monosensitized AR, 65	7.5 ± 1.3	11.27 ± 1.50	3.48 ± 1.5	1.67 ± 0.43	0.52 ± 0.4	4.49 ± 0.81[f]	1.39 ± 0.78[f]
						Polysensitized AR, 118	7.1 ± 1.4	11.54 ± 1.42	3.56 ± 1.56	1.64 ± 0.44	0.55 ± 0.41	4.53 ± 0.80[f]	1.44 ± 0.80[f]
Kim 2019[41]	Korea	Retrospective cohort/24 mo	80	SLIT-D daily	200 STU/d	Monosensitized AR, 22	10.6 ± 6.2	8.6 ± 2.1	4.06 ± 2.43	NR	NR	NR	NR
						Polysensitized AR, 58	13.1 ± 8.8	8.0 ± 2.9	2.78 ± 2.03	NR	NR	NR	NR
Song 2018[33]	China	Prospective cohort/60 mo	106	SCIT q 6 wk	4.5 μg Der p1	Monosensitized AR, 89	9.1 ± 4.3	NR	NR	0.49 ± 0.09	0.23 ± 0.08	NR	NR
						Polysensitized AR, 17		NR	NR			NR	NR

Table 1. (Continued)

Studies	Site of studies	Type/duration of studies	Study size (n)	Route of HDM AIT	Dose of HDM AIT[c]	Patients, n	Age (y)	Pre-TNSS	Post-TNSS	Pre-TMS	Post-TMS	Pre-CSMS	Post-CSMS
Soyyigit 2016[34]	Turkey	Prospective cohort/20 wk	43	SCIT q 4 wk	9.8 µg Der p1	Monosensitized AR, 19	33.57 ± 10.19	NR	NR	0.19	0.22	NR	NR
						Polysensitized AR, 24	31.4 ± 8.88	NR	NR	0.19	0.20	NR	NR
Xu 2015[35]	China	Prospective cohort/12 mo	50	SLIT-D daily	Der f[d] 150 µg/d (Adult)[e] 50 µg/d (< 14 y)[e]	Monosensitized AR, 20	42 ± 11	NR	NR	NR	NR	NR	NR
						Polysensitized AR, 30	43 ± 12	NR	NR	NR	NR	NR	NR
Kim 2014[36]	Korea	Prospective cohort/24 mo	60	SCIT q 1-3 mo	HDM (unspecified dose and species)	Monosensitized AR, 30	23 (17-39)	11.3 ± 1.2	3.2 ± 1.2	11.6 ± 0.9	2.91 ± 1.02	14.43 ± 1.20[f]	3.71 ± 1.34[f]
						Polysensitized AR, 30	26 (15-42)	11.8 ± 1.1	3.8 ± 1.31	13.7 ± 0.5	4.10 ± 1.15	16.65 ± 0.78[f]	5.05 ± 1.52[f]
Li 2014[37]	China	Prospective cohort/12 mo	112	SLIT-D daily	Der f[d] 150 µg/d (Adult) 50 µg/d (< 14 y)	Monosensitized AR, 56	6.80 ± 2.77	4.85 ± 2.08	0.95 ± 0.19	2.01 ± 1.18	0.05 ± 0.09	3.22 ± 1.70[f]	0.29 ± 0.14[f]
						Polysensitized AR, 56	7.06 ± 2.22	4.31 ± 2.63	0.95 ± 0.19	2.36 ± 1.51	0.34 ± 0.09	3.44 ± 2.17[f]	0.58 ± 0.14[f]
De Castro 2013[42]	Italy	Matched prospective cohort/36 mo	29	SLIT-T (allergoid) daily	Combined 50% Der p 1 + 50% Der f 1 of 5.4-13.5 µg/d	Monosensitized, 16	10.46 ± 3	NR	NR	NR	NR	NR	NR
						Polysensitized, 13		NR	NR	NR	NR	NR	NR
Lee 2011[38]	Korea	Prospective cohort/12 mo	134	SLIT-D 3 times weekly	250 STU/dose	Monosensitized AR, 70	14.3 ± 9.9	11.4 ± 4.1	5.7 ± 3.31	96.9 ± 27.4	47.5 ± 17	NR	NR
						Polysensitized AR, 64	15.3 ± 10.4	10.2 ± 4.6	4.6 ± 3.55	93.6 + 28.4	42.8 ± 17.1	NR	NR

Numbers are mean ± SD unless stated otherwise; [a]Median (range); [b]Median (interquartile 25,75)
[c]The dose recommended by the manufacturer
[d]Dose calculated by estimating 1 drop = 0.05 mL
[e]No manufacturer name or recommended dose mentioned
[f]The CSMS presented in this systematic review was calculated from the reported TNSS and TMS based on following the equation: CSMS = TNSS/4 + TMS.
Abbreviations: AR, allergic rhinitis; CSMS, combined symptom and medication score; HDM, house dust mite; mo, month; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT-D, sublingual immunotherapy drop; STU, standard therapeutic unit; TMS, total medication score; TNSS, total nasal symptom score; wk, week

Quality of included studies

According to the NOS, 7 studies were rated high quality, and 6 were rated low quality (**eTable 8**). According to the NOS, 7 studies were rated high quality, and 6 were rated low quality. All included studies did not show any serious concern regarding the selection of population and ascertainment of exposure. The lack of comparability was the most common reason that affected the quality of studies, followed by outcome assessment and adequacy of follow-up.

Changes from baseline in TNSS following HDM AIT

Seven studies reported the changes in TNSS from baseline to post-treatment in monosensitized and polysensitized patients.[32,36-41] Both groups showed a decreasing trend in TNSS from baseline to post-treatment. There was no significant difference in the pooled effect size of the 2 groups in TNSS changes (SMD -0.05, 95% Confidence interval (CI): -0.22 to 0.11, p = 0.532) with non-significant level of heterogeneity (I^2 = 15.23%, P-value = 0.314) (**Figure 2A**).

A subgroup analysis by the quality of the study was conducted for TNSS changes, and no significant difference was revealed (P = 0.230) (**eFigure 1**). A sensitivity analysis was performed by removing Tu et al[32] study due to the imbalance in pre-treatment TNSS. The result after removal remained unchanged (SMD -0.01, 95%CI: -0.17 to 0.15, P = 0.937). The results of the leave-one-out sensitivity analysis for TNSS changes did not differ from the main results (**eFigure 2**).

Changes from baseline in TMS following HDM AIT

Five studies, including 300 polysensitized and 257 monosensitized patients, were assessed for the difference in TMS changes from baseline to post-treatment.[36-40] Following AIT, both groups showed a decrease in TMS. The overall effect of sensitization status on the TMS changes was insignificant (SMD -0.05, 95%CI: -0.36 to 0.27, p = 0.767) with moderate level of heterogeneity (I^2 = 69.15%, P-value = 0.011) (**Figure 2B**).

A subgroup analysis by the study quality did not reveal a significant difference (P = 0.986) (**eFigure 3**). A leave-one-out sensitivity analysis result did not differ from the main result (**eFigure 4**).

Changes from baseline in CSMS following HDM AIT

The overall difference in CSMS changes was pooled from six studies involving 593 patients with AR.[30,31,36,37,39,40] Like TNSS and TMS, the CSMS showed a decremental trend following treatment in both groups, and there was no significant difference in the mean changes of CSMS from baseline between the 2 groups (SMD -0.12, 95%CI: -0.38 to 0.15, p = 0.384) (**Figure 2C**). The pooled result was, however, affected by significant heterogeneity (I^2 = 58.20%, P-value = 0.035). All studies for CSMS changes were rated as high-quality; hence, subgroup analysis was not performed. No significant difference from the main result was identified from leave-one-out sensitivity analysis for CSMS (**eFigure 5**).

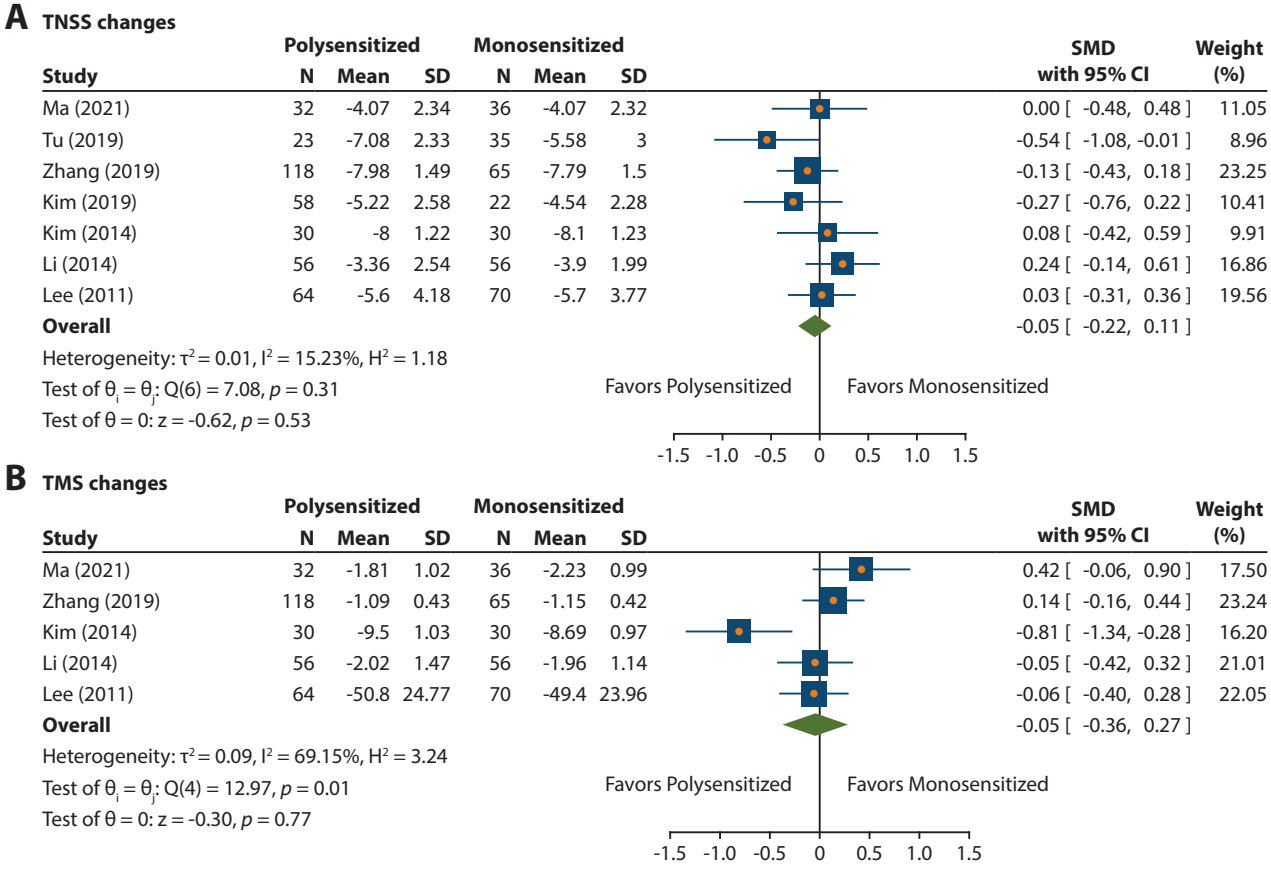


Figure 2. Changes from baseline in each clinical outcome following house dust mite allergen immunotherapy between monosensitized and polysensitized patients. (A) total nasal symptom score. (B) total medication score. (C) combined symptom and medication score. (D) visual analog scale.

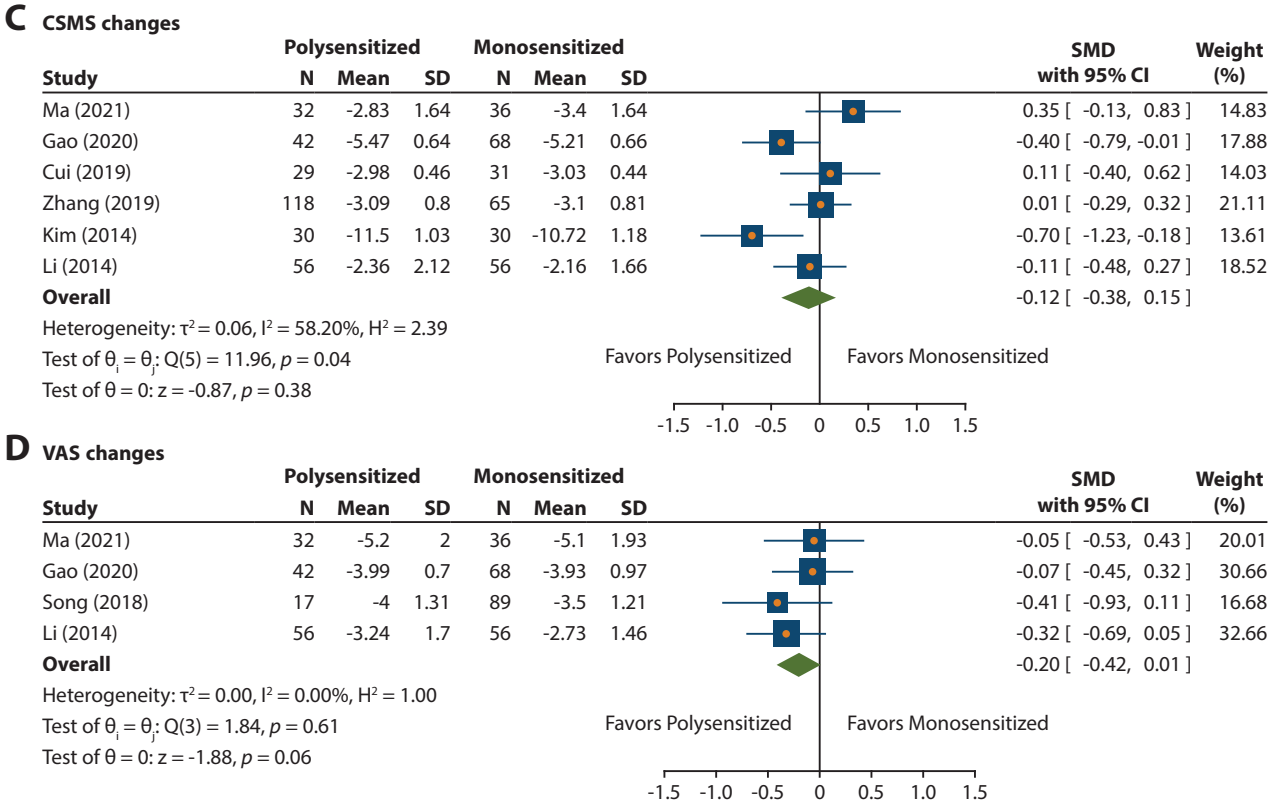


Figure 2. (Continued)

Changes from baseline in VAS following HDM AIT

Four studies compared the changes in VAS after HDM AIT.[30,33,37,39] The pooled mean changes from baseline in VAS were not significantly different between polysensitized and monosensitized groups (SMD -0.20, 95%CI: -0.42 to 0.01, p = 0.060) with no statistical evidence of heterogeneity (I^2 = 0.00%, P = 0.605) (**Figure 2D**).

A subgroup analysis by the quality of the study was conducted for VAS changes, and no significant group difference was revealed (P = 0.402) (**eFigure 6**). When we excluded Song et al[33] and Li et al[37] studies due to an imbalance in the baseline VAS, the main result was unaffected (SMD -0.06, 95%CI: -0.36 to 0.24, p = 0.687). The results were consistent in the leave-one-out sensitivity analysis when Ma et al[39] and Gao et al[30] studies were excluded (**eFigure 7**).

Changes from baseline in RQLQ following HDM AIT

The data on RQLQ changes were reported in two studies.[33,36] Both studies had balanced RQLQ at baseline. No statistically significant changes from baseline in RQLQ following treatment were identified (SMD 0.24, 95%CI: -0.13 to 0.60, p = 0.201) (**eFigure 8**). The test of heterogeneity revealed non-significant results (I^2 = 0.00%, P-value = 0.641).

GRADE Quality of the pooled evidence

Table 2 shows the overall quality rating according to GRADE. The primary outcome was rated as moderate certainty. Thus, the conclusion can be made that the difference in sensitization status probably results in little to no difference in TNSS changes. For secondary outcomes, VAS was rated as moderate certainty, while others were rated as very low certainty.

Immunologic indices and their changes from baseline following HDM AIT

Total IgE, sIgE, and sIgG4 and their alteration following HDM AIT were summarized in **Table 3**. At baseline, sIgE and IgG4 levels were similar between monosensitized and polysensitized groups except for Zhang et al[40] and Kim et al 2019[41] studies. Polysensitized patients in Zhang et al[40] study had more significant levels of total IgE, sIgE, and sIgG4, while those in Kim et al 2019[41] had a higher *Der p* sIgE level than the monosensitized one. Following HDM AIT, both groups showed an increase in sIgE and sIgG4 in most studies. Of note, Soyyigit et al[34] found that the sIgE/total IgE ratio was significantly higher in polysensitized patients, while Kim et al 2019[41] found more significant changes in *Der p* sIgG4 and *Der f* sIgG4 in the monosensitized groups; however, neither of those findings correlated with clinical response.

Soyyigit et al[34] also found that at baseline, the polysensitized group had higher CD203c expression on basophils than the monosensitized one. The more CD203c expression in the polysensitized group remained persistent after receiving a 14-week HDM SCIT. Zhang et al[40] demonstrated that IL-2 and TGF-β1 significantly increased, whereas IL4 and IL17α significantly decreased in both groups following a 2-year HDM SLIT.

Table 2. GRADE (Grading of Recommended Assessment, Development, and Evaluation) quality rating of the pooled evidence.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polysensitized	Monosensitized	Relative (95% CI)	Absolute (95% CI)		
TNSS changes (follow-up: 12+ months; assessed with: TNSS)												
7	observational studies	not serious[a]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed[b]	381	314	-	SMD **0.05 SD lower** (0.22 lower to 0.11 higher)	⊕⊕⊕◯ Moderate	CRITICAL
TMS changes (follow-up: 12+ months; assessed with: TMS)												
5	observational studies	not serious	serious[c]	not serious	not serious	none	300	257	-	SMD **0.05 SD lower** (0.36 lower to 0.27 higher)	⊕◯◯◯ Very low	IMPORTANT
CSMS changes (follow-up: 12+ months; assessed with: CSMS)												
6	observational studies	not serious	serious[c]	not serious	not serious	none	307	286	-	SMD **0.12 SD lower** (0.38 lower to 0.15 higher)	⊕◯◯◯ Very low	IMPORTANT
VAS changes (follow-up: 12+ months; assessed with: VAS)												
4	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed[b]	147	249	-	SMD **0.2 SD lower** (0.42 lower to 0.01 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
RQLQ changes (follow-up: 12+ months; assessed with: RQLQ)												
2	observational studies	serious[d]	not serious	not serious	serious[e]	none	47	119	-	SMD **0.24 SD higher** (0.13 lower to 0.6 higher)	⊕◯◯◯ Very low	IMPORTANT

Abbreviations: CI, confidence interval; CSMS, combined symptom and medication score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TMS, total medication score; TNSS, total nasal symptoms score; SMD, standardized mean difference; VAS, visual analog scale.

Explanations:

[a]Three out of seven studies were rated as low quality. Both subgroup analysis and sensitivity analysis confirmed that the primary result was robust.

[b]Subgroup analysis by study quality showed that studies with a high risk of bias (low-quality study) reported spurious treatment effects.

[c]There was a moderate to a high level of heterogeneity across studies.

[d]One of the studies was rated as low quality

[e]Only two studies were included. Widened confidence intervals.

Table 3. Specific IgE, total IgE, and specific IgG4 changes from baseline following house dust mite allergen immunotherapy.

Immunological indices	Groups	Baseline	6 mo	12 mo	24 mo	Changes from baseline	*P*-values within the group
sIgG4							
Zhang 2019[40]	Polysensitized (n = 118)	713.6 (22.7)	NR	NR	1208.1(31.3)	+494.5 (28.0)	***P* < 0.01**
	Monosensitized (n = 65)	681.5 (19.4)	NR	NR	1175.4 (34.9)	+439.9 (30.3)	***P* < 0.01**
	P-values between the groups	***P* < 0.001**			***P* < 0.001**	***P* < 0.001**	
Soyyigit 2016[34]	Polysensitized (n = 24)	0.07 (0.01, 0.41)[a]	0.68 (0.04, 6.21)[a]	NR	NR	NR	***P* < 0.025**
	Monosensitized (n = 19)	0.08 (0.01, 2.63)[a]	0.18 (0.03, 18.4)[a]	NR	NR	NR	NR
	P-values between the groups	NR	NR				
***Der p* sIgG4**							
Kim 2019[41]	Polysensitized (n = 58)	0.21 (0.02, 0.80)[b]	NR	NR	0.33 (0.04, 1.20)b	0.11 (-0.46, 0.89)[b]	NR
	Monosensitized (n = 22)	0.22 (0.04, 0.80)[b]	NR	NR	0.42 (0.10, 1.78)b	0.22 (-0.24, 1.41)[b]	NR
	P-values between the groups	*P* = 0.510			*P* = 0.140	***P* = 0.020**	
***Der f* sIgG4**							
Kim 2019[41]	Polysensitized (n = 58)	0.26 (0.06, 1.61)[b]	NR	NR	0.36 (0.04, 2.52)[b]	0.07 (-0.80, 2.13)[b]	NR
	Monosensitized (n = 22)	0.23 (0.04, 1.18)[b]	NR	NR	0.43 (0.11, 2.67)[b]	0.19 (-0.12, 1.57)[b]	NR
	P-values between the groups	*P* = 0.327			*P* = 0.308	***P* = 0.005**	
sIgE							
Zhang 2019[40]	Polysensitized (n = 118)	72.9 (4.5)	NR	NR	74.7 (6.9)	+1.8 (6.1)	***P* < 0.05**
	Monosensitized (n = 65)	68.3 (3.8)	NR	NR	71.9 (4.1)	+3.6 (4.0)	***P* < 0.01**
	P-values between the groups	***P* < 0.001**			***P* = 0.003**	***P* = 0.034**	
Kim 2014[36]	Polysensitized (n = 30)	216.4 (96.2)	NR	NR	232.8 (95.8)	+16.4 (96.0)	NR
	Monosensitized (n = 30)	225.7 (92.3)	NR	NR	247.3 (78.9)	+21.6 (86.4)	NR
	P-values between the groups	*P* = 0.704			*P* = 0.525	*P* = 0.826	
Soyyigit 2016[34]	Polysensitized (n = 24)	1.65 (0.01, 52.6)[a]	5.47 (0.4, 90.3)[a]	NR	NR	NR	***P* < 0.05**
	Monosensitized (n = 19)	0.75 (0.01, 39.1)[a]	1.47 (0.01, 49.2)[a]	NR	NR	NR	NR
	P-values between the groups	NR	NR				

Table 3. (Continued)

Immunological indices	Groups	Baseline	6 mo	12 mo	24 mo	Changes from baseline	*P*-values within the group
***Der p* sIgE**							
Kim 2019[41]	Polysensitized (n = 58)	28.9 (0.2, 160.0)[b]	NR	NR	45.2 (0.2, 365.0)[b]	12.2 (-8.2, 271.1)[b]	NR
	Monosensitized (n = 22)	13.3 (1.9, 68.9)[b]	NR	NR	40.0 (6.1, 98.8)[b]	22.0 (-14.6, 81.7)[b]	NR
	P-values between the groups	**P = 0.010**			*P* = 0.442	*P* = 0.614	
Kim 2014[36]	Polysensitized (n = 30)	216.4 (96.2)	NR	NR	232.8 (95.8)	+16.4 (96.0)	NR
	Monosensitized (n = 30)	222.4 (75.2)	NR	NR	252.8 (65.8)	+30.4 (71.0)	NR
	P-values between the groups	*P* = 0.704			*P* = 0.525	*P* =0.826	
***Der f* sIgE**							
Kim 2019[41]	Polysensitized (n = 58)	53.1 (0.3, 363.0)[b]	NR	NR	68.8 (0.16, 913.0)[b]	8.5 (-29.9, 550.0)[b]	NR
	Monosensitized (n = 22)	31.6 (3.2, 180.0)[b]	NR	NR	71.2 (8.1, 354.0)[b]	28.1 (-9.3, 271.9)[b]	NR
	P-values between the groups	*P* = 0.437			*P* = 0.692	*P* = 0.095	
Kim 2014[36]	Polysensitized (n = 30)	225.7 (92.3)	NR	NR	247.3 (78.9)	+21.6 (86.4)	NR
	Monosensitized (n = 30)	214.7 (62.3)	NR	NR	237.3 (58.9)	+22.6 (60.7)	NR
	P-values between the groups	*P* = 0.591			*P* = 0.580	*P* = 0.959	
Total IgE							
Zhang 2019[40]	Polysensitized (n = 118)	72.9 (4.5)	NR	NR	74.7 (6.9)	+1.8 (6.1)	**P < 0.05**
	Monosensitized (n = 65)	68.3 (3.8)	NR	NR	71.9 (4.1)	+3.6 (4.0)	**P < 0.01**
	P-values between the groups	**P < 0.001**			**P = 0.003**	**P = 0.034**	
Soyyigit 2016[34]	Polysensitized (n = 24)	90.1 (26.1, 702.0)[a]	161 (18.8, 816.0)[a]	NR	NR	NR	**P < 0.025**
	Monosensitized (n = 19)	84.6 (23.2, 1250.0)[a]	107.0 (21.0, 1764.0)[a]	NR	NR	NR	NR
	P-values between the groups	NR	NR				
Kim 2014[36]	Polysensitized (n = 30)	216.4 (96.2)	NR	NR	232.8 (95.8)	+16.4 (96.0)	NR
	Monosensitized (n = 30)	225.7 (92.3)	NR	NR	247.3 (78.9)	+21.6 (86.4)	NR
	P-values between the groups	*P* = 0.704			*P* = 0.525	*P* = 0.826	

Numbers are mean ± SD unless stated otherwise; [a]Median (range); [b]Median (IQR)
Der f, *Dermatophagoides farinae*; *Der p*, *Dermatophagoides pteronyssinus*; IQR, interquartile range; mo, months; NR, not reported; sIgE, specific immunoglobulin E, sIgG4, specific immunoglobulin G4

Table 4. Summary of adverse events reported from included studies.

Study	Ma 2021[a]		Gao 2020[a]		Cui 2019[a]		Tu 2019[b]		Zhang 2019[a]		Kim 2019[a]		Song 2018[b]		Soyyigit 2016[b]		Xu 2015[a]		Kim 2014[b]		Li 2014[a]		De Castro 2013[a,c]		Lee 2011[a]	
AEs	Mono (36)	Poly (32)	Mono (68)	Poly (42)	Mono (39)	Poly (21)	Mono (35)	Poly (23)	Mono (65)	Poly (118)	Mono (22)	Poly (58)	Mono (89)	Poly (17)	Mono (19)	Poly (24)	Mono (20)	Poly (30)	Mono (30)	Poly (30)	Mono (41)	Poly (35)	Mono (16)	Poly (13)	Mono (70)	Poly (64)
Local AEs	36 (52.9%)	64 (50%)	28 (8.5%)[¶]		6 (1.4%)	5 (1.2%)	NR	NR	21 (5.7%)	45 (12.3%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10 (13.2%)[¶]	7 (9.2%)[¶]	8 (4.2%) **		11 (8.2%)	
Systemic AEs not requiring epinephrine treatment			5 (1.5%)[¶]		0	0	25/1740 (1.4%)[†] (gr 1, 20; gr 2, 5)		0	1* (0.3%)	NR	NR	264/5406 (1.6%)[¥] (gr1, 253; gr3, 11)		NR	NR	NR	NR	NR	NR			6 (3.1%) **		26 (19.4%)	
Severe systemic AEs requiring epinephrine treatment	0	0	0	0	0	0	0	0	NR	NR	NR	NR	0	0	NR	NR	NR	NR	NR	NR	0	0	0	0	0	0

AEs, adverse events; Mono, monosensitized group; NR, not reported; Poly, polysensitized group
The reported numbers are the number of adverse events unless stated otherwise. The percentage is the incidence rate of adverse events per 100 person-years.
[a]Sublingual immunotherapy; [b]Subcutaneous immunotherapy; [c]Monomeric allergoid tablet
[¶]The numbers indicate the number of subjects with reported adverse events. The percentage is the incidence rate of subjects with AEs per 100 person-years.
[†]The number of adverse events per total injection; Percentage is an incidence rate of adverse events per administrations-year; grade 1, localized urticaria, rhinitis or mild asthma (PEF < 20% decrease from baseline); grade 2, slow onset (> 15 min) of generalized urticaria, moderate asthma (PEF < 40% decrease from baseline).
[¥]The number of adverse events per total injection: grade 1, one organ system such as cutaneous, upper respiratory or conjunctival; grade 2, either lower respiratory (< 40% PEF or FEV1 drop), gastrointestinal or uterine cramps; grade 3, lower respiratory (asthma with 40% PEF or FEV1 drop, not responding to inhaled bronchodilator) or upper respiratory (laryngeal, uvula, or tongue edema); grade 4, respiratory failure or cardiovascular (hypotension) with or without loss of consciousness; grade 5, death.
*This patient developed wheezing, which recovered after symptomatic treatment. The wheezing reoccurred with subsequent immunotherapy and led to the discontinuation of treatment.
**The numbers indicate the reported AEs that were not classified by type of SLIT received (either grass or HDM).

Adverse events

HDM AIT was generally well-tolerated in both monosensitized and polysensitized groups, irrespective of the route of administration. Overall reported AEs were comparable between the two groups, ranging from 0.3% to 52.9% of the subjects (**Table 4**). Only Tu et al[32] and Song et al[33] studies reported AEs per administration on HDM SCIT with an incidence rate of 1.4% and 1.6%, respectively. Song et al[33] reported 11 grade 3 AEs (0.2%), including asthma attack and airway hyper-responsiveness, which responded well to a single dose of dexamethasone. Ma et al[39] reported the decline of AE incidence over time following HDM AIT from 44.4%-50% at 1 month to 12.5%-16.7% at 12 months. Only Zhang et al[40] study reported that a polysensitized patient who developed 2 episodes of wheezing recovered well with symptomatic medications; however, these AEs led to discontinuing the AIT. None of the studies reported severe systemic AEs resulting in epinephrine administration.

Discussion

This systematic review included 13 studies conducted on patients with allergic rhinitis. HDM AIT in polysensitized patients with allergic rhinitis was as effective in improving TNSS, TMS, CSMS, VAS, and RQLQ as in monosensitized ones. The AEs were mild and comparable between the 2 groups. The immunological indices remained inconsistent and were not predictive of clinical responses. Before implementing this approach to clinical practice, specific issues have to be addressed and considered.

Polysensitization can be categorized into 2 distinct subgroups: cross-reactivity/cross-sensitization and co-sensitization. Cross-reactivity refers to common structures of different allergens that bind to the same sIgE, whereas co-sensitization indicates the concurrent presence of different sIgE that bind to their allergen epitopes. HDM has been known for being cross-reactive with cockroaches and mugwort but not with other non-homologous allergens.[43] Therefore, the simultaneous presence of sIgE to HDM, animal danders, and pollens tends to be co-sensitization rather than cross-reactivity.

HDM allergy in polysensitized patients could be classified into 3 subgroups: 1) HDM as the only clinically relevant allergen and other allergens only being co-sensitized; 2) HDM being major and other non-homologous allergens being minor and relatively less significant in contributing to patient' symptoms; 3) Both HDM and other non-homologous allergens being clinically relevant in contributing to patient' symptoms. The efficacy of HDM AIT should be highest in the first subgroup, diminishing in the second subgroup, and likely least effective in the third subgroup, whose symptoms may fluctuate when exposed to other causal allergens. Based on the details of included studies, polysensitized patients but not polyallergic in Soyyigit et al[34] study were consistent with the first subgroup. In contrast, those in Zhang et al[40] study who were obviously polyallergic were likely consistent with the second subgroup as their clinical responses to HDM AIT were not significantly different from those of monosensitizied ones. In the remaining studies, polysensitized patients with unreported polyallergy status also responded favorably to HDM AIT, indicating that they likely belonged to either the first or the second subgroups.

Adequate maintenance dose of HDM AIT directly affects the clinical effectiveness. The HDM SCIT dosages used in Soyyigit et al,[34] Song et al,[33] and Tu et al[32] studies were close to the dose being demonstrated the efficacy by a controlled clinical trial.[44] The dosages of HDM SLIT drops containing HDM allergens of 50 to 100 μg in most of our included studies were close to the dose being demonstrated the efficacy by a well-designed RCT.[45] Although the SLIT drops used in Kim et al 2019[41], Lee et al[38] studies, and allergoid SLIT tablets in the De Castro et al[42] study differed from those in the remaining studies; they followed the dosing regimens recommended by the manufacturers.

Baseline immunologic indices and their alteration following HDM AIT have been investigated in 4 studies.[34,36,40,41] One of the basophil surface biomarkers reflecting its degranulation in the early phase of allergic reaction is CD203c.[46] At baseline and after HDM AIT, the level of CD203c expression in polysensitized patients was higher than in monosensitized ones, indicating a higher baseline level of allergic inflammation.[34] In addition, polysensitized patients have demonstrated their immunologic shift toward predominant type 2 cytokines, as evidenced by an increase in IL4 and a decrease in IL10 and IFNγ levels.[47,48] Of interest, a reduction in type 2 cytokines following HDM AIT was observed by Zhang et al[40] study with no difference between monosensitized and polysensitized patients.

Biomarkers associated with clinical responses following AIT have been extensively studied, some of which were assessed in our included studies. Soyyigit et al[34] reported that the sIgE/total IgE ratio was significantly higher in polysensitized patients; however, no correlation was found between the ratio and clinical responses. The sIgE/total IgE ratio was reported to be a valuable biomarker for predicting effective responses to HDM AIT in monosensitized patients, with a sensitivity and specificity of 97.9 % and 93.1 %, respectively.[49] However, another open-labeled RCT was unable to replicate the benefits of this ratio.[50] An additional potential biomarker is allergen sIgG4, a blocking antibody that competes with allergens for binding with sIgE on mast cells and basophils.[51] The studies examining the relationship between increased sIgG4 and improved clinical outcomes following HDM AIT showed inconclusive results.[52,53] Of note, a more significant increase in sIgG4 in monosensitized subjects in Kim et al 2019[41] was not predictive of AIT responders.

This systematic review and meta-analysis carry some limitations. First, all of the included studies were observational in design. Thus, the meta-analytic results were subjected to confounding and should be interpreted with caution. We have provided the summary tables with ratings on the quality of evidence according to GRADE to emphasize the certainty of each pooled outcome. Second, the clinical efficacy of AIT in monosensitized and polysensitized patients was evaluated without placebo as a control group. However, the superiority of HDM AIT over placebo has been repeatedly demonstrated by previous RCTs.[45,54] Therefore. the efficacy

of HDM AIT, which may differ between the 2 groups, could be evaluated through non-randomized studies in which the monosensitized patients would serve as a control group. In addition, substantial real-world evidence from non-randomized studies will complement RCTs with rigorous methodology.[55] Third, the total number of patients included within the quantitative synthesis was relatively low and may not contain sufficient power to identify minimal clinically important differences in treatment effects. A trial sequential analysis was one alternative to help conclude the futility of the results;[56] however, owing to statistical reasons, the trial sequential analysis could not be performed for the standardized mean difference.[57] Finally, several outcome values used during analysis were not directly reported in the included original articles and, therefore, had to be extracted from graphs, imputed, or calculated from other reported values. This certainly affects the quality of data and the pooled results. However, we believed that the effects would be minimal as standard methods were used as references, and leave-one-out sensitivity analyses of all outcomes showed robust and consistent results.

In conclusion, since HDM allergens may play a dominant role in specific subgroups of polysensitized patients, thus, carefully selecting clinically relevant HDM-allergic patients to be treated with HDM AIT could be a reasonable treatment option as opposed to being restricted to monosensitized ones.

Acknowledgement

We thank Professor Harold S. Nelson, MD, for his valuable comments on the manuscript. This study was partially supported by the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, and the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Conflict of interests

The authors declare the following financial interests/relationships which may be considered as a potential conflict of interests:

- P. Phinyo, T. Krikeerati, and P. Wongyikul declare no conflict of interests;
- M. Lao-Araya has received honoraria for scientific lectures from Abbott, A. Menarini, Astra-Zeneca, GSK, Novartis, Organon, Takeda, and Viatris
- T. Thongngarm has received honoraria for scientific lectures from A. Menarini, Astra-Zeneca, GSK, Novartis, Sanofi, Takeda, and Viatris; research supports from Abbott and Sanofi; has served on the advisory board for Sanofi and Viatris.

Funding

No funding has been received for this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

T. Krikeerati is an essentially intellectual contributor involving in research design, data analysis, data interpretation, result summary, comprehensive comments, and writing the manuscript.

Ethics approval

Ethics approval was considered exempt due to the nature of systematic review and meta-analysis.

References

1. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol. 2005;116:377-83.
2. Migueres M, Fontaine JF, Haddad T, Grosclaude M, Saint-Martin F, Bem David D, et al. Characteristics of patients with respiratory allergy in France and factors influencing immunotherapy prescription: a prospective observational study (REALIS). Int J Immunopathol Pharmacol. 2011;24:387-400.
3. Navarro A, Colas C, Anton E, Conde J, Davila I, Dordal MT, et al. Epidemiology of allergic rhinitis in allergy consultations in Spain: Alergologica-2005. J Investig Allergol Clin Immunol. 2009;19 Suppl 2: 7-13.
4. Ciprandi G, Cirillo I. Monosensitization and polysensitization in allergic rhinitis. Eur J Intern Med. 2011; 22:e75-9.
5. Ciprandi G, Alesina R, Ariano R, Aurnia P, Borrelli P, Cadario G, et al. Characteristics of patients with allergic polysensitization: the POLISMAIL study. Eur Ann Allergy Clin Immunol. 2008;40:77-83.
6. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127:S1-55.
7. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2018;73:765-98.
8. Ortiz AS, McMains KC, Laury AM. Single vs multiallergen sublingual immunotherapy in the polysensitized patient: a pilot study. Int Forum Allergy Rhinol. 2018;8:490-4.
9. Kim KW, Kim EA, Kwon BC, Kim ES, Song TW, Sohn MH, et al. Comparison of allergic indices in monosensitized and polysensitized patients with childhood asthma. J Korean Med Sci. 2006;21:1012-6.
10. Zhang AZ, Liang ME, Chen XX, Wang YF, Ma K, Lin Z, et al. Clinical Evaluation for Sublingual Immunotherapy With Dermatophagoides farinae in Polysensitized Allergic Asthma Patients. Front Med (Lausanne). 2021;8:645356.
11. Nolte H, Bernstein DI, Nelson HS, Kleine-Tebbe J, Sussman GL, Seitzberg D, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2016;138:1631-8.
12. 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;135:1494-501e6.
13. 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;137:444-51e8.

14. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA. 2016;315:1715-25.
15. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2014;134:568-75e7.
16. Bernstein DI, Kleine-Tebbe J, Nelson HS, Bardelas JA Jr, Sussman GL, Lu S, et al. SQ house dust mite sublingual immunotherapy tablet subgroup efficacy and local application site reaction duration. Ann Allergy Asthma Immunol. 2018;121:105-10.
17. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester: Wiley; 2019.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
19. Haddaway NR, Collins AM, Coughlin D, Kirk S. The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching. PLoS One. 2015;10:e0138237.
20. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
21. van de Schoot R, de Bruin J, Schram R, Zahedi P, de Boer J, Weijdema F, et al. An open source machine learning framework for efficient and transparent systematic reviews. Nat Mach Intell. 2021;3: 125–33.
22. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27:1785-805.
23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
24. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa: Ottawa Hospital Research Institute; c2021 [cited 2022 Jul 21]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
25. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York: Routledge; 1988.
26. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014;69:854-67.
27. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.
28. Li P, Fa M, Huang ZH, Xie LS, Xu Y, Chen WB, et al. [The efficacy of sublingual specific immunotherapy in children with allergic rhinitis]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2016;30(7):546-51. Chinese.
29. Xing QB, Chen S, Chen B, Li HF, Chen LL. [Efficacy of sublingual immunotherapy with Dermatophagoides farina drops in monosensitized and polysensitized children with allergic rhinitis and asthma]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2017;31(3):204-8. Chinese.
30. Gao Y, Lin X, Ma J, Wei X, Wang Q, Wang M. Enhanced Efficacy of Dust Mite Sublingual Immunotherapy in Low-Response Allergic Rhinitis Patients after Dose Increment at 6 Months: A Prospective Study. Int Arch Allergy Immunol. 2020;181:311-9.
31. Cui L, Li J, Li Y, Xia Z. Long-Term Efficacy of Sublingual Mite Immunotherapy in Monosensitized and Polysensitized Children with Allergic Rhinitis: A 7-Year Prospective Study. Int Arch Allergy Immunol. 2019;180:144-9.
32. Tu Y, Zhang H, Zhao L, Jin P, Zi X, Li T, et al. The changes in different symptom scores during subcutaneous immunotherapy in Chinese house dust mite allergic patients: a two-year, observational study. J Laryngol Otol. 2019;133:213-9.
33. Song Y, Long J, Wang T, Xie J, Wang M, Tan G. Long-term efficacy of standardised specific subcutaneous immunotherapy in children with persistent allergic rhinitis due to multiple allergens including house dust mites. J Laryngol Otol. 2018;132:230-5.
34. Soyyigit S, Guloglu D, Ikinciogullari A, Secil D, Oztuna D, Mungan D, et al. Immunologic alterations and efficacy of subcutaneous immunotherapy with Dermatophagoides pteronyssinus in monosensitized and polysensitized patients. Ann Allergy Asthma Immunol. 2016; 116:244-51e2.
35. Xu CX, Zhang ML, Li BZ, He Y, Zou ZH, Wu QR, et al. Efficacy of Sublingual Immunotherapy with Dermatophagoides farinae Extract in Monosensitized and Polysensitized Patients with Allergic Rhinitis: Clinical Observation and Analysis. Biomed Res Int. 2015;2015:187620.
36. Kim SH, Shin SY, Lee KH, Kim SW, Cho JS. Long-term Effects of Specific Allergen Immunotherapy Against House Dust Mites in Polysensitized Patients With Allergic Rhinitis. Allergy Asthma Immunol Res. 2014;6:535-40.
37. Li P, Li Q, Huang Z, Chen W, Lu Y, Tian M. Efficacy and safety of house dust mite sublingual immunotherapy in monosensitized and polysensitized children with respiratory allergic diseases. Int Forum Allergy Rhinol. 2014;4:796-801.
38. Lee JE, Choi YS, Kim MS, Han DH, Rhee CS, Lee CH, et al. Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis. Ann Allergy Asthma Immunol. 2011;107:79-84.
39. Ma X, Zhang Y, Gu X, Wu G, Liu J, Lu J, et al. A Retrospective Cohort Study of Sublingual Immunotherapy with Standardized Dermatophagoides farinae Drops for Allergic Rhinitis. Adv Ther. 2021; 38:2315-22.
40. Zhang YZ, Luo J, Wang ZH, Wang J. Efficacy and safety of sublingual dust mite drops in children with mono- or polysensitized allergic rhinitis. Am J Otolaryngol. 2019;40:755-60.
41. Kim JY, Han DH, Won TB, Kim HJ, Lee CH, Rhee CS, et al. Immunologic modification in mono- and poly-sensitized patients after sublingual immunotherapy. Laryngoscope. 2019;129:E170-E7.
42. De Castro G, Zicari AM, Indinnimeo L, Tancredi G, di Coste A, Occasi F, et al. Efficacy of sublingual specific immunotherapy on allergic asthma and rhinitis in children's real life. Eur Rev Med Pharmacol Sci. 2013;17:2225-31.
43. Zhao L, Zhang Y, Zhang S, Zhang L, Lan F. The effect of immunotherapy on cross-reactivity between house dust mite and other allergens in house dust mite -sensitized patients with allergic rhinitis. Expert Rev Clin Immunol. 2021;17:969-75.
44. Tabar AI, Arroabarren E, Echechipia S, Garcia BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. J Allergy Clin Immunol. 2011;127:57-63, e1-3.
45. 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.
46. Buhring HJ, Streble A, Valent P. The basophil-specific ectoenzyme E-NPP3 (CD203c) as a marker for cell activation and allergy diagnosis. Int Arch Allergy Immunol. 2004;133:317-29.
47. Pene J, Rivier A, Lagier B, Becker WM, Michel FB, Bousquet J. Differences in IL-4 release by PBMC are related with heterogeneity of atopy. Immunology. 1994;81:58-64.
48. Prigione I, Morandi F, Tosca MA, Silvestri M, Pistoia V, Ciprandi G, et al. Interferon-gamma and IL-10 may protect from allergic polysensitization in children: preliminary evidence. Allergy. 2010;65:740-2.
49. Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. J Allergy Clin Immunol. 2009;123:1103-10, 10e1-4.
50. 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.
51. van Neerven RJ, Wikborg T, Lund G, Jacobsen B, Brinch-Nielsen A, Arnved J, et al. Blocking antibodies induced by specific allergy vaccination prevent the activation of CD4+ T cells by inhibiting serum-IgE-facilitated allergen presentation. J Immunol. 1999;163: 2944-52.

52. Gomez E, Fernandez TD, Dona I, Rondon C, Campo P, Gomez F, et al. Initial immunological changes as predictors for house dust mite immunotherapy response. Clin Exp Allergy. 2015;45:1542-53.
53. Potapova E, Bordas-Le Floch V, Schlederer T, Vrtala S, Huang HJ, Canonica GW, et al. Molecular reactivity profiling upon immunotherapy with a 300 IR sublingual house dust mite tablet reveals marked humoral changes towards major allergens. Allergy [Preprint]. 2022 [cited 2022 Jul 3]. Available from: https://onlinelibrary.wiley.com/doi/10.1111/all.15327.
54. Bozek A, Starczewska-Dymek L, Jarzab J. Prolonged effect of allergen sublingual immunotherapy for house dust mites in elderly patients. Ann Allergy Asthma Immunol. 2017;119:77-82.
55. Paoletti G, Di Bona D, Chu DK, Firinu D, Heffler E, Agache I, et al. Allergen immunotherapy: The growing role of observational and randomized trial "Real-World Evidence". Allergy. 2021;76:2663-72.
56. Clephas PRD, Kranke P, Heesen M. How to perform and write a trial sequential analysis. Anaesthesia [Preprint]. 2022 [cited 2022 Jul 13]. Available from: https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/abs/10.1111/anae.15811.
57. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA) [Internet]. Copenhagen: Copenhagen Trial Unit; c2017 [cited 2022 Jun 6]. Available from: https://ctu.dk/tsa.

Supplemental material

eTable 1. Search strategy from PubMed.

Components	Step	Search algorithm	Items found
Domain	#1	Allergic rhinitis	30,996
	#2	AR	222,591
	#3	Respiratory allergic rhinitis	3
	#4	Perennial allergic rhinitis	7,829
	#5	Persistent allergic rhinitis	351
	#6	Pollen allergy	3,946
	#7	Antiallergic agent*	351
	#8	House dust allergen	87
	#9	Dermatophagoides	8,023
	#10	Dermatophagoides pteronyssinus	3,349
	#11	Dermatophagoides farinae	2,119
	#12	Dust mite extract*	333
	#13	House dust mite*	7,096
	#14	HDM*	2,843
	#15	HDM extract	188
	#16	House dust mite immunotherapy	47
	#17	House dust mite allergen immunotherapy	9
	#18	HDM AIT	18
	#19	Sublingual immunotherapy	1,827
	#20	SLIT	21,473
	#21	Subcutaneous immunotherapy	994
	#22	SCIT	826
	#23	Allergen-specific immunotherapy	1,612
	#24	ASIT	319
	#25	Allergy immunotherapy	412
	#26	Allergen immunotherapy	2,082
	#27	AIT	5,001
	#28	Immunotherapy	383,530
	#29	Desensitization	41,044
	#30	"Respiratory Hypersensitivity" [Mesh]	166,222
	#31	"Rhinitis, Allergic" [Mesh]	22,923

eTable 1. (Continued)

Components	Step	Search algorithm	Items found
	#32	"Rhinitis, Allergic, Seasonal" [Mesh]	13,840
	#33	"Dermatophagoides pteronyssinus" [Mesh]	701
	#34	"Dermatophagoides farinae" [Mesh]	538
	#35	"Antigens, Dermatophagoides" [Mesh]	3,420
	#36	"Sublingual Immunotherapy" [Mesh]	653
	#37	"Desensitization, Immunologic" [Mesh]	12,247
	#38	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 #35 OR #36 OR #37	819,746
Exposure	#39	"monoallergen sensiti*"	4
	#40	"polyallergen sensiti*"	4
	#41	polysensiti*	669
	#42	monosensiti*	520
	#43	#39 OR #40 OR #41 OR #42	1,031
Outcomes	#44	Rhinitis	48,788
	#45	Rhinitis symptom*	1,045
	#46	Visual analogue scale*	31,844
	#47	Visual analog scale*	36,352
	#48	VAS	61,821
	#49	Nasal symptom score*	848
	#50	Total nasal symptom score*	533
	#51	TNSS	347
	#52	Medication score*	820
	#53	Total medication score*	36
	#54	TMS	14,662
	#55	Combined symptom and medication score*	36
	#56	CSMS	296
	#57	Antiallergic medication score*	1,581
	#58	AMS	16,304
	#59	Rhinitis quality of life questionnaire*	5
	#60	RQLQ	340
	#61	Quality of life	395,657
	#62	Clinical outcome*	210,869
	#63	Treatment outcome*	1,140,433
	#64	Clinical effectiveness	15,729
	#65	PNIF	256
	#66	Peak Nasal Inspiratory flow	358
	#67	Acoustic rhinometry	1,151
	#68	Eosinophil*	92,432
	#69	ECP	4,783

eTable 1. (Continued)

Components	Step	Search algorithm	Items found
	#70	Immunoglobulin*	385,466
	#71	Ig*	57,884
	#72	Dp Specific Ig*	27
	#73	Df Specific Ig*	29
	#74	Dp sIg*	29
	#75	Df sIg*	46
	#76	Der p sIg*	6
	#77	Der f sIg*	1
	#78	Regulatory T*	29,883
	#79	Treg*	59,875
	#80	Regulatory B*	8,925
	#81	Breg*	7,273
	#82	BAT	24,438
	#83	Basophil*	20,074
	#84	Skin prick test*	9,119
	#85	SPT	5,934
	#86	Intradermal test*	4,558
	#87	IDT	1,121
	#88	Nasal provocation test	323
	#89	NPT	2,278
	#90	Environmental exposure chamber	49
	#91	EEC	3,350
	#92	Asthma control*	7,761
	#93	Asthma symptom*	5,751
	#94	Total asthma symptom score	24
	#95	TASS	420
	#96	ACQ	1,153
	#97	ACT	350,445
	#98	Asthma quality of life questionnaire*	881
	#99	AQLQ	552
	#100	Asthma exacerbation	2,815
	#101	Asthma attack	1,271
	#102	Lung function*	39,712
	#103	Pulmonary function*	36,135
	#104	FEV1*	34,403
	#105	TGF*	83,190
	#106	Transforming growth factor*	105,771
	#107	IL*	652,469
	#108	Interleukin*	390,763

eTable 1. (Continued)

Components	Step	Search algorithm	Items found
	#109	"Interleukins" [Mesh]	259,867
	#110	"Transforming Growth Factor beta" [Mesh]	66,125
	#111	"Pulmonary Ventilation" [Mesh]	45,802
	#112	"Nasal Provocation Tests" [Mesh]	1,622
	#113	"Skin Tests" [Mesh]	65,276
	#114	"Intradermal Tests" [Mesh]	3,641
	#115	"Basophils" [Mesh]	7,890
	#116	"Basophil Degranulation Test" [Mesh]	478
	#117	"B-Lymphocytes, Regulatory" [Mesh]	838
	#118	"T-Lymphocytes, Regulatory" [Mesh]	35,626
	#119	"Immunoglobulin G4-Related Disease" [Mesh]	958
	#120	Immunoglobulins [Mesh]	950,987
	#121	"Eosinophil Cationic Protein" [Mesh]	697
	#122	"Eosinophils"[Mesh]	25,370
	#123	"Rhinometry, Acoustic"[Mesh]	577
	#124	"Treatment Outcome"[Mesh]	1,193,284
	#125	"Quality of Life"[Mesh]	241,159
	#126	OR #44 OR # 45 OR #46 OR #47 OR #48 OR#49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR # 58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR 96# OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125	4,154,265
	#127	#126 AND #38 AND #43	726

eTable 2. Search strategy from Scopus.

Component	Step	Search algorithm	Items found
Domain	#1	TITLE-ABS-KEY (allergic AND rhinitis)	46,078
	#2	TITLE-ABS-KEY (ar)	230,110
	#3	TITLE-ABS-KEY (respiratory AND allergic AND rhinitis)	10,865
	#4	TITLE-ABS-KEY (perennial AND allergic AND rhinitis)	8,363
	#5	TITLE-ABS-KEY (persistent AND allergic AND rhinitis)	1,994
	#6	TITLE-ABS-KEY (pollen AND allergy)	16,677
	#7	TITLE-ABS-KEY (antiallergic AND agent*)	8,846
	#8	TITLE-ABS-KEY (house AND dust AND allergen)	11,503
	#9	TITLE-ABS-KEY (dermatophagoides)	11,262
	#10	TITLE-ABS-KEY (dermatophagoides AND pteronyssinus)	6,412
	#11	TITLE-ABS-KEY (dermatophagoides AND farinae)	3,519
	#12	TITLE-ABS-KEY (dust AND mite AND extract*)	2,683
	#13	TITLE-ABS-KEY (house AND dust AND mite*)	10,713

eTable 2. (Continued)

Component	Step	Search algorithm	Items found
	#14	TITLE-ABS-KEY (hdm*)	9,207
	#15	TITLE-ABS-KEY (hdm AND extract)	637
	#16	TITLE-ABS-KEY (house AND dust AND mite AND immunotherapy)	1,812
	#17	TITLE-ABS-KEY (house AND dust AND mite AND allergen AND immunotherapy)	1,685
	#18	TITLE-ABS-KEY (hdm AND ait)	77
	#19	TITLE-ABS-KEY (sublingual AND immunotherapy)	3,470
	#20	TITLE-ABS-KEY (slit)	75,380
	#21	TITLE-ABS-KEY (subcutaneous AND immunotherapy)	8,093
	#22	TITLE-ABS-KEY (scit)	976
	#23	TITLE-ABS-KEY (allergen-specific AND immunotherapy)	3,175
	#24	TITLE-ABS-KEY (asit)	850
	#25	TITLE-ABS-KEY (allergy AND immunotherapy)	14,350
	#26	TITLE-ABS-KEY (allergen AND immunotherapy)	13,229
	#27	TITLE-ABS-KEY (ait)	8,241
	#28	TITLE-ABS-KEY (immunotherapy)	215,188
	#29	TITLE-ABS-KEY (desensitization)	45,448
	#30	(TITLE-ABS-KEY (allergic AND rhinitis)) OR (TITLE-ABS-KEY (ar)) OR (TITLE-ABS-KEY (respiratory AND allergic AND rhinitis)) OR (TITLE-ABS-KEY (perennial AND allergic AND rhinitis)) OR (TITLE-ABS-KEY (persistent AND allergic AND rhinitis)) OR (TITLE-ABS-KEY (pollen AND allergy)) OR (TITLE-ABS-KEY (antiallergic AND agent*)) OR (TITLE-ABS-KEY (house AND dust AND allergen)) OR (TITLE-ABS-KEY (dermatophagoides)) OR (TITLE-ABS-KEY (dermatophagoides AND pteronyssinus)) OR (TITLE-ABS-KEY (dermatophagoides AND farinae)) OR (TITLE-ABS-KEY (dust AND mite AND extract*)) OR (TITLE-ABS-KEY (house AND dust AND mite*)) OR (TITLE-ABS-KEY (hdm*)) OR (TITLE-ABS-KEY (hdm AND extract)) OR (TITLE-ABS-KEY (house AND dust AND mite AND immunotherapy)) OR (TITLE-ABS-KEY (house AND dust AND mite AND allergen AND immunotherapy)) OR (TITLE-ABS-KEY (hdm AND ait)) OR (TITLE-ABS-KEY (sublingual AND immunotherapy)) OR (TITLE-ABS-KEY (slit)) OR (TITLE-ABS-KEY (subcutaneous AND immunotherapy)) OR (TITLE-ABS-KEY (scit)) OR (TITLE-ABS-KEY (allergen-specific AND immunotherapy)) OR (TITLE-ABS-KEY (asit)) OR (TITLE-ABS-KEY (allergy AND immunotherapy)) OR (TITLE-ABS-KEY (allergen AND immunotherapy)) OR (TITLE-ABS-KEY (ait)) OR (TITLE-ABS-KEY (immunotherapy)) OR (TITLE-ABS-KEY (desensitization))	632,131
Exposure	#31	TITLE-ABS-KEY (monosensiti*)	493
	#32	TITLE-ABS-KEY (monoallergen AND sensiti*)	7
	#33	TITLE-ABS-KEY (polysensiti*)	736
	#34	TITLE-ABS-KEY (polyallergen AND sensiti*)	4
	#35	(TITLE-ABS-KEY (monosensiti*)) OR (TITLE-ABS-KEY (monoallergen AND sensiti*)) OR (TITLE-ABS-KEY (polysensiti*)) OR (TITLE-ABS-KEY (polyallergen AND sensiti*))	1,091
Outcome	#36	TITLE-ABS-KEY (rhinitis)	69,530
	#37	TITLE-ABS-KEY (rhinitis AND symptom*)	21,962
	#38	TITLE-ABS-KEY (visual AND analogue AND scale*)	109,545
	#39	TITLE-ABS-KEY (visual AND analog AND scale*)	109,535
	#40	TITLE-ABS-KEY (vas)	127,924
	#41	TITLE-ABS-KEY (nasal AND symptom AND score*)	5,674
	#42	TITLE-ABS-KEY (total AND nasal AND symptom AND score*)	2,397
	#43	TITLE-ABS-KEY (tnss)	406
	#44	TITLE-ABS-KEY (medication AND score*)	49,950

eTable 2. (Continued)

Component	Step	Search algorithm	Items found
	#45	TITLE-ABS-KEY (total AND medication AND score*)	15,185
	#46	TITLE-ABS-KEY (tms)	147,626
	#47	TITLE-ABS-KEY (combined AND symptom AND medication AND score*)	1,329
	#48	TITLE-ABS-KEY (csms)	648
	#49	TITLE-ABS-KEY (antiallergic AND medication AND score*)	194
	#50	TITLE-ABS-KEY (ams)	260,584
	#51	TITLE-ABS-KEY (rhinitis AND quality AND of AND life AND questionnaire*)	1,957
	#52	TITLE-ABS-KEY (rqlq)	352
	#53	TITLE-ABS-KEY (quality AND of AND life)	814,890
	#54	TITLE-ABS-KEY (clinical AND outcome*)	2,382,721
	#55	TITLE-ABS-KEY (treatment AND outcome*)	2,221,600
	#56	TITLE-ABS-KEY (clinical AND effectiveness)	498,689
	#57	TITLE-ABS-KEY (pnif)	269
	#58	TITLE-ABS-KEY (peak AND nasal AND inspiratory AND flow)	967
	#59	TITLE-ABS-KEY (acoustic AND rhinometry)	1,365
	#60	TITLE-ABS-KEY (eosinophil*)	132,725
	#61	TITLE-ABS-KEY (ecp)	8,306
	#62	TITLE-ABS-KEY (immunoglobulin*)	756,593
	#63	TITLE-ABS-KEY (ig*)	1,012,477
	#64	TITLE-ABS-KEY (dp AND specific AND ig*)	377
	#65	TITLE-ABS-KEY (df AND specific AND ig*)	287
	#66	TITLE-ABS-KEY (dp AND sig*)	25,481
	#67	TITLE-ABS-KEY (df AND sig*)	23,178
	#68	TITLE-ABS-KEY (der AND p AND sig*)	10,788
	#69	TITLE-ABS-KEY (der AND f AND sig*)	2,389
	#70	TITLE-ABS-KEY (regulatory AND t*)	871,644
	#71	TITLE-ABS-KEY (treg*)	28,629
	#72	TITLE-ABS-KEY (regulatory AND b*)	857,050
	#73	TITLE-ABS-KEY (breg*)	5,954
	#74	TITLE-ABS-KEY (bat)	46,356
	#75	TITLE-ABS-KEY (basophil*)	29,483
	#76	TITLE-ABS-KEY (skin AND prick AND test*)	16,331
	#77	TITLE-ABS-KEY (spt)	13,212
	#78	TITLE-ABS-KEY (intradermal AND test*)	13,346
	#79	TITLE-ABS-KEY (idt)	5,149
	#80	TITLE-ABS-KEY (nasal AND provocation AND test)	3,386
	#81	TITLE-ABS-KEY (npt)	6,557
	#82	TITLE-ABS-KEY (environmental AND exposure AND chamber)	4,467
	#83	TITLE-ABS-KEY (eec)	12,389

eTable 2. (Continued)

Component	Step	Search algorithm	Items found
	#84	TITLE-ABS-KEY (asthma AND control*)	105,169
	#85	TITLE-ABS-KEY (asthma AND symptom*)	48,621
	#86	TITLE-ABS-KEY (total AND asthma AND symptom AND score)	1,925
	#87	TITLE-ABS-KEY (tass)	754
	#88	TITLE-ABS-KEY (acq)	1,999
	#89	TITLE-ABS-KEY (act)	1,026,873
	#90	TITLE-ABS-KEY (asthma AND quality AND of AND life AND questionnaire*)	4,710
	#91	TITLE-ABS-KEY (aqlq)	592
	#92	TITLE-ABS-KEY (asthma AND exacerbation)	23,409
	#93	TITLE-ABS-KEY (asthma AND attack)	8,516
	#94	TITLE-ABS-KEY (lung AND function*)	340,775
	#95	TITLE-ABS-KEY (pulmonary AND function*)	189,875
	#96	TITLE-ABS-KEY (fev1*)	36,052
	#97	TITLE-ABS-KEY (tgf*)	114,761
	#98	TITLE-ABS-KEY (transforming AND growth AND factor*)	170,908
	#99	TITLE-ABS-KEY (il*)	3,975,596
	#100	TITLE-ABS-KEY (interleukin*)	668,808
	#105	((TITLE-ABS-KEY (rhinitis)) OR (TITLE-ABS-KEY (rhinitis AND symptom*)) OR (TITLE-ABS-KEY (visual AND analogue AND scale*)) OR (TITLE-ABS-KEY (visual AND analog AND scale*)) OR (TITLE-ABS-KEY (vas)) OR (TITLE-ABS-KEY (nasal AND symptom AND score*)) OR (TITLE-ABS-KEY (total AND nasal AND symptom AND score*)) OR (TITLE-ABS-KEY (tnss)) OR (TITLE-ABS-KEY (medication AND score*)) OR (TITLE-ABS-KEY (total AND medication AND score*)) OR (TITLE-ABS-KEY (tms)) OR (TITLE-ABS-KEY (combined AND symptom AND medication AND score*)) OR (TITLE-ABS-KEY (csms)) OR (TITLE-ABS-KEY (antiallergic AND medication AND score*)) OR (TITLE-ABS-KEY (ams)) OR (TITLE-ABS-KEY (rhinitis AND quality AND of AND life AND questionnaire*)) OR (TITLE-ABS-KEY (rqlq)) OR (TITLE-ABS-KEY (quality AND of AND life)) OR (TITLE-ABS-KEY (clinical AND outcome*)) OR (TITLE-ABS-KEY (treatment AND outcome*)) OR (TITLE-ABS-KEY (clinical AND effectiveness)) OR (TITLE-ABS-KEY (pnif)) OR (TITLE-ABS-KEY (peak AND nasal AND inspiratory AND flow)) OR (TITLE-ABS-KEY (acoustic AND rhinometry)) OR (TITLE-ABS-KEY (eosinophil*)) OR (TITLE-ABS-KEY (ecp)) OR (TITLE-ABS-KEY (immunoglobulin*)) OR (TITLE-ABS-KEY (ig*)) OR (TITLE-ABS-KEY (dp AND specific AND ig*))) OR ((TITLE-ABS-KEY (df AND specific AND ig*)) OR (TITLE-ABS-KEY (dp AND sig*)) OR (TITLE-ABS-KEY (df AND sig*)) OR (TITLE-ABS-KEY (der AND p AND sig*)) OR (TITLE-ABS-KEY (der AND f AND sig*)) OR (TITLE-ABS-KEY (regulatory AND t*)) OR (TITLE-ABS-KEY (treg*)) OR (TITLE-ABS-KEY (regulatory AND b*)) OR (TITLE-ABS-KEY (breg*)) OR (TITLE-ABS-KEY (bat)) OR (TITLE-ABS-KEY (basophil*)) OR (TITLE-ABS-KEY (skin AND prick AND test*)) OR (TITLE-ABS-KEY (spt)) OR (TITLE-ABS-KEY (intradermal AND test*)) OR (TITLE-ABS-KEY (idt)) OR (TITLE-ABS-KEY (nasal AND provocation AND test))) OR ((TITLE-ABS-KEY (npt)) OR (TITLE-ABS-KEY (environmental AND exposure AND chamber)) OR (TITLE-ABS-KEY (eec)) OR (TITLE-ABS-KEY (asthma AND control*)) OR (TITLE-ABS-KEY (asthma AND symptom*)) OR (TITLE-ABS-KEY (total AND asthma AND symptom AND score)) OR (TITLE-ABS-KEY (tass)) OR (TITLE-ABS-KEY (acq)) OR (TITLE-ABS-KEY (act)) OR (TITLE-ABS-KEY (asthma AND quality AND of AND life AND questionnaire*)) OR (TITLE-ABS-KEY (aqlq)) OR (TITLE-ABS-KEY (asthma AND exacerbation))) OR ((TITLE-ABS-KEY (asthma AND attack)) OR (TITLE-ABS-KEY (lung AND function*)) OR (TITLE-ABS-KEY (pulmonary AND function*)) OR (TITLE-ABS-KEY (fev1*)) OR (TITLE-ABS-KEY (tgf*)) OR (TITLE-ABS-KEY (transforming AND growth AND factor*)) OR (TITLE-ABS-KEY (il*)) OR (TITLE-ABS-KEY (interleukin*)))	11,545,333

eTable 2. (Continued)

Component	Step	Search algorithm	Items found
All	#106	((TITLE-ABS-KEY (allergic AND rhinitis)) OR (TITLE-ABS-KEY (ar)) OR (TITLE-ABS-KEY (respiratory AND allergic AND rhinitis)) OR (TITLE-ABS-KEY (perennial AND allergic AND rhinitis)) OR (TITLE-ABS-KEY (persistent AND allergic AND rhinitis)) OR (TITLE-ABS-KEY (pollen AND allergy)) OR (TITLE-ABS-KEY (antiallergic AND agent*)) OR (TITLE-ABS-KEY (house AND dust AND allergen)) OR (TITLE-ABS-KEY (dermatophagoides)) OR (TITLE-ABS-KEY (dermatophagoides AND pteronyssinus)) OR (TITLE-ABS-KEY (dermatophagoides AND farinae)) OR (TITLE-ABS-KEY (dust AND mite AND extract*)) OR (TITLE-ABS-KEY (house AND dust AND mite*)) OR (TITLE-ABS-KEY (hdm*)) OR (TITLE-ABS-KEY (hdm AND extract)) OR (TITLE-ABS-KEY (house AND dust AND mite AND immunotherapy)) OR (TITLE-ABS-KEY (house AND dust AND mite AND allergen AND immunotherapy)) OR (TITLE-ABS-KEY (hdm AND ait)) OR (TITLE-ABS-KEY (sublingual AND immunotherapy)) OR (TITLE-ABS-KEY (slit)) OR (TITLE-ABS-KEY (subcutaneous AND immunotherapy)) OR (TITLE-ABS-KEY (scit)) OR (TITLE-ABS-KEY (allergen-specific AND immunotherapy)) OR (TITLE-ABS-KEY (asit)) OR (TITLE-ABS-KEY (allergy AND immunotherapy)) OR (TITLE-ABS-KEY (allergen AND immunotherapy)) OR (TITLE-ABS-KEY (ait)) OR (TITLE-ABS-KEY (immunotherapy)) OR (TITLE-ABS-KEY (desensitization))) AND ((TITLE-ABS-KEY (monosensiti*)) OR (TITLE-ABS-KEY (monoallergen AND sensiti*)) OR (TITLE-ABS-KEY (polysensiti*)) OR (TITLE-ABS-KEY (polyallergen AND sensiti*))) AND (((TITLE-ABS-KEY (rhinitis)) OR (TITLE-ABS-KEY (rhinitis AND symptom*)) OR (TITLE-ABS-KEY (visual AND analogue AND scale*)) OR (TITLE-ABS-KEY (visual AND analog AND scale*)) OR (TITLE-ABS-KEY (vas)) OR (TITLE-ABS-KEY (nasal AND symptom AND score*)) OR (TITLE-ABS-KEY (total AND nasal AND symptom AND score*)) OR (TITLE-ABS-KEY (tnss)) OR (TITLE-ABS-KEY (medication AND score*)) OR (TITLE-ABS-KEY (total AND medication AND score*)) OR (TITLE-ABS-KEY (tms)) OR (TITLE-ABS-KEY (combined AND symptom AND medication AND score*)) OR (TITLE-ABS-KEY (csms)) OR (TITLE-ABS-KEY (antiallergic AND medication AND score*)) OR (TITLE-ABS-KEY (ams)) OR (TITLE-ABS-KEY (rhinitis AND quality AND of AND life AND questionnaire*)) OR (TITLE-ABS-KEY (rqlq)) OR (TITLE-ABS-KEY (quality AND of AND life)) OR (TITLE-ABS-KEY (clinical AND outcome*)) OR (TITLE-ABS-KEY (treatment AND outcome*)) OR (TITLE-ABS-KEY (clinical AND effectiveness)) OR (TITLE-ABS-KEY (pnif)) OR (TITLE-ABS-KEY (peak AND nasal AND inspiratory AND flow)) OR (TITLE-ABS-KEY (acoustic AND rhinometry)) OR (TITLE-ABS-KEY (eosinophil*)) OR (TITLE-ABS-KEY (ecp)) OR (TITLE-ABS-KEY (immunoglobulin*)) OR (TITLE-ABS-KEY (ig*)) OR (TITLE-ABS-KEY (dp AND specific AND ig*))) OR ((TITLE-ABS-KEY (df AND specific AND ig*)) OR (TITLE-ABS-KEY (dp AND sig*)) OR (TITLE-ABS-KEY (df AND sig*)) OR (TITLE-ABS-KEY (der AND p AND sig*)) OR (TITLE-ABS-KEY (der AND f AND sig*)) OR (TITLE-ABS-KEY (regulatory AND t*)) OR (TITLE-ABS-KEY (treg*)) OR (TITLE-ABS-KEY (regulatory AND b*)) OR (TITLE-ABS-KEY (breg*)) OR (TITLE-ABS-KEY (bat)) OR (TITLE-ABS-KEY (basophil*)) OR (TITLE-ABS-KEY (skin AND prick AND test*)) OR (TITLE-ABS-KEY (spt)) OR (TITLE-ABS-KEY (intradermal AND test*)) OR (TITLE-ABS-KEY (idt)) OR (TITLE-ABS-KEY (nasal AND provocation AND test))) OR ((TITLE-ABS-KEY (npt)) OR (TITLE-ABS-KEY (environmental AND exposure AND chamber)) OR (TITLE-ABS-KEY (eec)) OR (TITLE-ABS-KEY (asthma AND control*)) OR (TITLE-ABS-KEY (asthma AND symptom*)) OR (TITLE-ABS-KEY (total AND asthma AND symptom AND score)) OR (TITLE-ABS-KEY (tass)) OR (TITLE-ABS-KEY (acq)) OR (TITLE-ABS-KEY (act)) OR (TITLE-ABS-KEY (asthma AND quality AND of AND life AND questionnaire*)) OR (TITLE-ABS-KEY (aqlq)) OR (TITLE-ABS-KEY (asthma AND exacerbation))) OR ((TITLE-ABS-KEY (asthma AND attack)) OR (TITLE-ABS-KEY (lung AND function*)) OR (TITLE-ABS-KEY (pulmonary AND function*)) OR (TITLE-ABS-KEY (fev1*)) OR (TITLE-ABS-KEY (tgf*)) OR (TITLE-ABS-KEY (transforming AND growth AND factor*)) OR (TITLE-ABS-KEY (il*)) OR (TITLE-ABS-KEY (interleukin*))))	775

eTable 3. Search strategy from Embase.

Component	Step	Search algorithm	Item founds
Domain	#1	'Allergic rhinitis':ti,ab,kw,de	43,122
	#2	'AR':ti,ab,kw,de	81,958
	#3	'Respiratory allergic rhinitis':ti,ab,kw,de	5
	#4	'Perennial allergic rhinitis':ti,ab,kw,de	1,451
	#5	'Persistent allergic rhinitis':ti,ab,kw,de	581
	#6	'Pollen allergy':ti,ab,kw,de	19,940
	#7	'Antiallergic agent*':ti,ab,kw,de	6,362
	#8	'House dust allergen':ti,ab,kw,de	6,102
	#9	'Dermatophagoides':ti,ab,kw,de	14,412
	#10	'Dermatophagoides pteronyssinus':ti,ab,kw,de	6,710

eTable 3. (Continued)

Component	Step	Search algorithm	Items founds
	#11	'Dermatophagoides farinae':ti,ab,kw,de	3,562
	#12	'Dust mite extract*':ti,ab,kw,de	1,030
	#13	'House dust mite*':ti,ab,kw,de	11,871
	#14	'HDM*':ti,ab,kw,de	10,932
	#15	'HDM extract':ti,ab,kw,de	410
	#16	'House dust mite immunotherapy':ti,ab,kw,de	72
	#17	'House dust mite allergen immunotherapy':ti,ab,kw,de	16
	#18	'HDM AIT':ti,ab,kw,de	52
	#19	'Sublingual immunotherapy':ti,ab,kw,de	3,814
	#20	'SLIT':ti,ab,kw,de	40,634
	#21	'Subcutaneous immunotherapy':ti,ab,kw,de	2,787
	#22	'SCIT':ti,ab,kw,de	1,685
	#23	'Allergen-specific immunotherapy':ti,ab,kw,de	2,711
	#24	'ASIT':ti,ab,kw,de	427
	#25	'Allergy immunotherapy':ti,ab,kw,de	715
	#26	'allergen immunotherapy':ti,ab,kw,de	3,551
	#27	'AIT':ti,ab,kw,de	4,382
	#28	'immunotherapy':ti,ab,kw,de	248,782
	#29	'desensitization':ti,ab,kw,de	42,872
	#30	'allergic rhinitis'/exp	52,961
	#31	'perennial rhinitis'/exp	4,056
	#32	'antiallergic agent'/exp	440,704
	#33	'dust mite extract'/exp	618
	#34	'house dust allergen'/exp	6,609
	#35	'Dermatophagoides pteronyssinus'/exp	5,577
	#36	'Dermatophagoides farinae'/exp	2,769
	#37	'sublingual immunotherapy'/exp	2,798
	#38	'subcutaneous immunotherapy'/exp	2,139
	#39	'desensitization'/exp	25,926
	#40	'house dust allergy'/exp	2,802
	#41	'pollen allergy'/exp	19,300
	#42	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	891,466
Exposure	#43	'Monosensiti*':ti,ab,kw,de	1,035
	#44	'Monoallergen sensiti*':ti,ab,kw,de	5
	#45	'Polysensiti*':ti,ab,kw,de	1,323
	#46	'polyallergen sensiti*':ti,ab,kw,de	6
	#47	'monosensitization'/exp	11

eTable 3. (Continued)

Component	Step	Search algorithm	Items founds
	#48	'polysensitization'/exp	47
	#49	#43 OR #44 OR #45 OR #46 OR #47 OR #48	2,029
Outcome	#50	'rhinitis':ti,ab,kw,de	69,252
	#51	'Rhinitis symptom*':ti,ab,kw,de	1,672
	#52	'Visual analogue scale*':ti,ab,kw,de	48,892
	#53	'Visual analog scale*':ti,ab,kw,de	116,778
	#54	'VAS':ti,ab,kw,de	96,658
	#55	'Nasal symptom score*':ti,ab,kw,de	1,406
	#56	'Total nasal symptom score*':ti,ab,kw,de	981
	#57	'TNSS':ti,ab,kw,de	688
	#58	'medication score*':ti,ab,kw,de	1,385
	#59	'Total medication score*':ti,ab,kw,de	49
	#60	'TMS':ti,ab,kw,de	20,724
	#61	'Combined symptom and medication score*':ti,ab,kw,de	111
	#62	'csms':ti,ab,kw,de	385
	#63	'Antiallergic medication score*':ti,ab,kw,de	1
	#64	'AMS':ti,ab,kw,de	10,739
	#65	'rhinitis quality of life questionnaire*':ti,ab,kw,de	114
	#66	'RQLQ':ti,ab,kw,de	629
	#67	'Quality of life':ti,ab,kw,de	682,843
	#68	'Clinical outcome*':ti,ab,kw,de	456,970
	#69	'Treatment outcome*':ti,ab,kw,de	969,944
	#70	'clinical effectiveness':ti,ab,kw,de	171,980
	#71	'pnif':ti,ab,kw,de	396
	#72	'peak nasal inspiratory flow':ti,ab,kw,de	758
	#73	'Acoustic rhinometry':ti,ab,kw,de	1,398
	#74	'Eosinophil*':ti,ab,kw,de	153,196
	#75	'ECP':ti,ab,kw,de	6,493
	#76	'Immunoglobulin*':ti,ab,kw,de	835,049
	#77	'Ig*':ti,ab,kw,de	652,609
	#78	'Dp Specific Ig*':ti,ab,kw,de	39
	#79	'Df Specific Ig*':ti,ab,kw,de	46
	#80	'Dp sIg*':ti,ab,kw,de	138
	#81	'Df sIg*':ti,ab,kw,de	73
	#82	'Der p sIg*':ti,ab,kw,de	27
	#83	'Der f sIg*':ti,ab,kw,de	9
	#84	'Regulatory T*':ti,ab,kw,de	90,091
	#85	'Treg*':ti,ab,kw,de	47,151

eTable 3. (Continued)

Component	Step	Search algorithm	Items founds
	#86	'Regulatory B*':ti,ab,kw,de	3,511
	#87	'Breg*':ti,ab,kw,de	3,557
	#88	'BAT':ti,ab,kw,de	25,177
	#89	'Basophil*':ti,ab,kw,de	30,456
	#90	'Skin prick test*':ti,ab,kw,de	17,531
	#91	'SPT':ti,ab,kw,de	10,009
	#92	'Intradermal test*':ti,ab,kw,de	3,170
	#93	'IDT':ti,ab,kw,de	1,534
	#94	'Nasal provocation test':ti,ab,kw,de	553
	#95	'NPT':ti,ab,kw,de	2,608
	#96	'Environmental exposure chamber':ti,ab,kw,de	196
	#97	'EEC':ti,ab,kw,de	4,718
	#98	'Asthma control*':ti,ab,kw,de	15,134
	#99	'Asthma symptom*':ti,ab,kw,de	8,965
	#100	'total asthma symptom score':ti,ab,kw,de	36
	#101	'TASS':ti,ab,kw,de	331
	#102	'ACQ':ti,ab,kw,de	2,551
	#103	'ACT':ti,ab,kw,de	377,755
	#104	'Asthma quality of life questionnaire*':ti,ab,kw,de	1,678
	#105	'AQLQ':ti,ab,kw,de	1,295
	#106	'Asthma exacerbation':ti,ab,kw,de	5,286
	#107	'Asthma attack':ti,ab,kw,de	1,921
	#108	'lung function*':ti,ab,kw,de	160,986
	#109	'Pulmonary function*':ti,ab,kw,de	57,387
	#110	'FEV1*':ti,ab,kw,de	35,297
	#111	'TGF*':ti,ab,kw,de	147,269
	#112	'Transforming growth factor*':ti,ab,kw,de	185,641
	#113	'IL*':ti,ab,kw,de	2,164,965
	#114	'Interleukin*':ti,ab,kw,de	806,222
	#115	'visual analog scale'/exp	106,600
	#116	'nasal symptom score'/exp	33
	#117	'rhinitis quality of life questionnaire'/exp	12
	#118	'clinical outcome'/exp	232,622
	#119	'treatment outcome'/exp	2,005,341
	#120	'clinical effectiveness'/exp	159,507
	#121	'peak nasal inspiratory flow'/exp	592
	#122	'acoustic rhinometry'/exp	536
	#123	'eosinophil cationic protein'/exp	3,445
	#124	'immunoglobulin e'/exp	91,132

eTable 3. (Continued)

Component	Step	Search algorithm	Items founds
	#125	'immunoglobulin g'/exp	201,516
	#126	'regulatory t lymphocyte'/exp	81,504
	#127	'regulatory b lymphocyte'/exp	1,584
	#128	'basophil activation test'/exp	1,276
	#129	'prick test'/exp	23,837
	#130	'intracutaneous test'/exp	4,088
	#131	'nose provocation test'/exp	1,256
	#132	'exposure chamber'/exp	236
	#133	'asthma control'/exp	34
	#134	'asthma control test'/exp	2,163
	#135	'asthma attack'/exp	40
	#136	'lung function test'/exp	220,613
	#137	'transforming growth factor'/exp	166,507
	#138	'interleukin 13'/exp	32,059
	#139	'interleukin 4'/exp	92,796
	#140	interleukin 5'/exp	33,495
	#141	#50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140	6,925,879
Combined		#42 AND #49 AND #141	1,283

eTable 4. Search strategy from CENTRAL.

Component	Step	Search algorithm	Item founds
Domain	#1	Allergic rhinitis	8,408
	#2	AR	17,811
	#3	Respiratory allergic rhinitis	1,375
	#4	Perennial allergic rhinitis	1,779
	#5	Persistent allergic rhinitis	580
	#6	Pollen allergy	2,672
	#7	Antiallergic agent*	1,038
	#8	House dust allergen	806
	#9	Dermatophagoides	1,038
	#10	Dermatophagoides pteronyssinus	545
	#11	Dermatophagoides farinae	244
	#12	Dust mite extract*	438
	#13	House dust mite*	1,441
	#14	HDM*	1,046

eTable 4. (Continued)

Component	Step	Search algorithm	Items founds
	#15	HDM extract	114
	#16	House dust mite immunotherapy	535
	#17	House dust mite allergen immunotherapy	303
	#18	HDM AIT	42
	#19	Sublingual immunotherapy	1,194
	#20	SLIT	2,674
	#21	Subcutaneous immunotherapy	1,152
	#22	SCIT	337
	#23	Allergen-specific immunotherapy	518
	#24	ASIT	133
	#25	Allergy immunotherapy	2,860
	#26	Allergen immunotherapy	1,615
	#27	AIT	764
	#28	Immunotherapy	12,070
	#29	Desensitization	3,293
	#30	MeSH descriptor: [Rhinitis, Allergic] explode all trees	3,216
	#31	MeSH descriptor: [Rhinitis, Allergic, Seasonal] explode all trees	2,048
	#32	MeSH descriptor: [Anti-Allergic Agents] explode all trees	836
	#33	MeSH descriptor: [Pyroglyphidae] explode all trees	263
	#34	MeSH descriptor: [Antigens, Dermatophagoides] explode all trees	286
	#35	MeSH descriptor: [Sublingual Immunotherapy] explode all trees	119
Exposure	#36	MeSH descriptor: [Desensitization, Immunologic] explode all trees	1,003
	#37	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	42,747
	#38	Monosensiti*	103
Outcome	#39	Monoallergen sensiti*	4
	#40	Polysensiti*	80
	#41	Polyallergen sensiti*	3
	#42	#38 OR #39 OR #40 OR #41	157
	#43	Rhinitis	10,678
	#44	Rhinitis symptom*	5,507
	#45	Visual analogue scale*	57,185
	#46	Visual analog scale*	57,152
	#47	VAS	42,244
	#48	Nasal symptom score*	2,761
	#49	Total nasal symptom score*	1,723
	#50	TNSS	479
	#51	Medication score*	25,180
	#52	Total medication score*	11,082

eTable 4. (Continued)

Component	Step	Search algorithm	Items founds
	#53	TMS	5,404
	#54	Combined symptom and medication score*	2,067
	#55	CSMS	97
	#56	Antiallergic medication score*	150
	#57	AMS	803
	#58	Rhinitis quality of life questionnaire*	842
	#59	RQLQ	377
	#60	Quality of life	141,695
	#61	Clinical outcome*	470,274
	#62	Treatment outcome*	415,956
	#63	Clinical effectiveness	148,725
	#64	PNIF	173
	#65	Peak Nasal Inspiratory flow	462
	#66	Acoustic rhinometry	270
	#67	Eosinophil*	5,838
	#68	ECP	836
	#69	Immunoglobulin*	15,334
	#70	Ig*	39,176
	#71	Dp Specific Ig*	120
	#72	Df Specific Ig*	406
	#73	Dp sIg*	4,830
	#74	Df sIg*	5,737
	#75	Der p sIg*	9,508
	#76	Der f sIg*	2,887
	#77	Regulatory T*	9,984
	#78	Treg*	1,420
	#79	Regulatory B*	9,917
	#80	Breg*	365
	#81	BAT	922
	#82	Basophil*	827
	#83	Skin prick test*	2,035
	#84	SPT	858
	#85	Intradermal test*	1,171
	#86	IDT	70
	#87	Nasal provocation test	389
	#88	NPT	404
	#89	Environmental exposure chamber	473
	#90	EEC	609
	#91	Asthma control*	36,004

eTable 4. (Continued)

Component	Step	Search algorithm	Items founds
	#92	Asthma symptom*	10,802
	#93	Total asthma symptom score	1,245
	#94	TASS	71
	#95	ACQ	1,082
	#96	ACT	15,041
	#97	Asthma quality of life questionnaire*	2,236
	#98	AQLQ	678
	#99	Asthma exacerbation	3,599
	#100	Asthma attack	804
	#101	Lung function*	27,370
	#102	Pulmonary function*	22,541
	#103	FEV1*	14,390
	#104	TGF*	2,226
	#105	Transforming growth factor*	1,611
	#106	IL*	143,670
	#107	Interleukin*	22,773
	#108	MeSH descriptor: [Visual Analog Scale] explode all trees	1,024
	#109	MeSH descriptor: [Quality of Life] explode all trees	28,372
	#110	MeSH descriptor: [Treatment Outcome] explode all trees	151,827
	#111	MeSH descriptor: [Rhinometry, Acoustic] explode all trees	74
	#112	MeSH descriptor: [Eosinophils] explode all trees	838
	#113	MeSH descriptor: [Immunoglobulins] explode all trees	28,895
	#114	MeSH descriptor: [T-Lymphocytes, Regulatory] explode all trees	323
	#115	MeSH descriptor: [B-Lymphocytes, Regulatory] explode all trees	3
	#116	MeSH descriptor: [Basophil Degranulation Test] explode all trees	11
	#117	MeSH descriptor: [Basophils] explode all trees	143
	#118	MeSH descriptor: [Intradermal Tests] explode all trees	136
	#119	MeSH descriptor: [Nasal Provocation Tests] explode all trees	340
	#120	MeSH descriptor: [Respiratory Function Tests] explode all trees	24,818
	#121	MeSH descriptor: [Forced Expiratory Volume] explode all trees	5,396
	#122	MeSH descriptor: [Transforming Growth Factors] explode all trees	29
	#123	MeSH descriptor: [Interleukins] explode all trees	6,718
	#124	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123	886,876
Combined	#125	#37 AND #42 AND #124	146
		Cochrane review identified (excluded)	1
Total		Trials from CENTRAL (Embase, PubMed, ICTRP, and CT.gov)	145

eTable 5. Inclusion criteria, exclusion criteria, and intervention withdrawal of included studies.

Studies	Inclusion criteria	Exclusion criteria	Numbers of withdrawals in each group (n)	Reasons for withdrawals (n)
Ma 2021	1) Patients diagnosed with moderate-to-severe persistent AR 2) sIgE of dust mites and/or HDM were positive and were ++ or greater, with or without 1–2 other allergens sensitized.	1) Patients with active malignancy, AIDS, immunodeficiency, severe cardiovascular disease 2) Patients receiving β-blockers or ACEI 3) Pregnancy	Monosensitized (0) Polysensitized (0)	NA
Gao 2020	1) Patients aged 4-60 yr with moderate-to-severe AR 2) sensitization to *Der f* and/or *Der p* confirmed by sIgE > 0.7 kU/L.	1) Patients with severe systemic diseases such as poorly controlled cardiovascular diseases, immune diseases, or malignancies 2) Patients receiving β-blockers or ACEI 3) Serious psychological barriers or failure to understand the risks and limitations of treatment 4) Pregnancy or lactation, or planning pregnancy within 1 yr	Overall (25)	- Withdrew consent (7) - Lost to follow-up (6) - Non-compliant (5) - Other reasons (7)
Cui 2019	1) Patients with a clinical history of allergy and/or typical symptoms of rhinitis 2) sensitization to *Der f* and/or *Der p* assessed by sIgE > 0.7 kU/L 3) FEV1 > 70% of predicted	1) Patients with uncontrolled asthma or other systemic immunological disorders 3) Patients receiving β-blockers in the previous 6 mo	Monosensitized (9) Polysensitized (11)	- Lost to follow-up (7) - Poor adherence (2) - Lost to follow-up (8) - Poor adherence (3)
Tu 2019	1) Patients with a history of mite-induced allergy requiring treatment 2) Typical symptoms and signs of AR 3) Positive SPT to *Der p* and a positive sIgE to *Der p* ≥ 0.7 kU/L	1) Patients with severe or uncontrolled asthma, significant cardiovascular diseases, immune system disorders, malignancy, pregnancy, nasal polyps and chronic sinusitis 2) Patients receiving β-blockers or ACEI 3) Patients receiving AIT within the past three year	Monosensitized (0) Polysensitized (0)	NA
Zhang 2019	1) AR patients aged ≤ 15 yr 2) Having sIgE to *Der p* or *Der f* ≥ 0.35 IU/L, or a positive SPT to *Der p* or *Der f* (+++ or above) 3) Polysensitized AR was defined as having at least another allergen by sIgE or SPT besides HDM 4) Patient symptoms associated with HDM remained despite allergen avoidance 5) Patient symptoms were worse in spring and autumn or exposure to dog fur.	1) Patients with asthma, severe deviation of nasal septum and severe adenoid hypertrophy (the ratio of adenoid to nasopharyngeal cavity width > 0.71) 2) Patients with diseases in gastroenterology, liver, renal, cardiovascular, brain, lung, and hematologic systems.	Monosensitized (8) Polysensitized (14)	- Not effective (2) - No improvement of symptoms (1) - Non-adherence to treatment (5) - Not effective (4) - No improvement of symptoms (2) - Non-adherence to treatment (8)
Kim 2019	1) Patients with AR sensitized to HDM by SPT with wheal diameter of ≥ 3 mm 2) Treated with HDM SLIT	1) Patients with asthma or atopic dermatitis who required regular medication. 2) Pregnant or lactating women 3) Subjects who had immunologic or hematologic disorders	Monosensitized (0) Polysensitized (0)	NA
Song 2018	1) AR patients, aged 5-14 yr 2) Postive SPT to *Der p* and/or *Der f* with or without other allergens.	NR	Overall (14)	- Lost to follow-up (9) - Incomplete data (5)

eTable 5. (Continued)

Studies	Inclusion criteria	Exclusion criteria	Numbers of withdrawals in each group (n)	Reasons for withdrawals (n)
Soyyigit 2016	1) AR patients with a positive SPT to *Der p* and/or *Der f* with or without other allergens. 2) Patients were not clinically polyallergic.	Patients previously used AIT or had contraindication for AIT.	Monosensitized (3)	Withdrew during the placebo period (2) and in the second week of the maintenance phase (1)
			Polysensitized (0)	NA
Kim 2014	Patients with AR with positive response to *Der p* and/or *Der f* with or without other allergens	Patients with chronic rhinosinusitis, nasal polyposis, or asthma	Monosensitized (0)	NA
			Polysensitized (0)	
Xu 2015	1) Patients aged 4-60 yr with moderate-to-severe AR 2) Having positive SPT to HDM allergens 3) Having dust mite sIgE > 0.35 kU/L 4) Having SLIT duration ≥ 1 yr 5) Willing to follow-up and stop treatment for 1-2 yr	Patients with acute or chronic sinusitis, organic nasal disease, nonallergic autoimmune disease, malignancies, chronic infection, or mental disorder	Monosensitized (0)	NA
			Polysensitized (0)	NA
Li 2014	1) Patients with moderate-to-severe or persistent AR without severe asthma 2) Having a clinical history of mite allergy and positive SPT to *Der f* and/or *Der p* 3) FEV1 ≥ 70% of predicted	1) Patients suffering from other immune diseases. 2) Patients previously received AIT	Monosensitized (15)	NR
			Polysensitized (21)	NR
De Castro 2013	1) Patients with AR and/or controlled asthma, aged > 6 yr 2) Having positive SPT and sIgE to grass pollen or HDM 3) Have never received AIT	NR	Monosensitized (NR)	NR
			Polysensitized (NR)	
Lee 2011	1) Patients having > 2 AR symptoms, including sneezing, itching, rhinorrhea, and nasal congestion with or without eye symptoms 2) Sensitization to *Der p* and/or *Der f*, defined as sIgE ≥ class 2 or positive SPT 3) SLIT with HDM ≥ 1 yr	Patients who received immunotherapy in the preceding 3 years or had systemic immunologic disorders were excluded.	Overall (48)	NR

ACEI, angiotensin-converting enzyme inhibitors; AIT, allergen immunotherapy; AR, allergic rhinitis; *Der f*, *Dermatophagoides farinae*; *Der p*, *Dermatophagoides pteronyssinus*; FEV1, forced expiratory volume in 1 second; HDM, house dust mite; NA, not applicable; NR; not reported; sIgE, specific immunoglobulin E; SPT, skin prick test; yr, year

eTable 6. Sensitized allergens other than house dust mite in polysensitized patients of included studies.

Studies	Sensitized allergens other than house dust mite				
	Insects	Animals	Fungi	Pollens	Other allergens and remarks
Ma 2021	NR				NR
Gao 2020	NR				NR
Cui 2019	NR				NR
Tu 2019	None	None	*Alternaria spp.* (NR)	Unspecified pollen (NR)	None
Zhang 2019	Dog Fur or Cockroach or Mold or Shrimp (4.2%)			Artemisia powder (36.4%), phoenix tree pollen(36.4%), birch pollen (16.1%), Artemisia powder and phoenix tree pollen (6.9%)	None *Polysensitized patients were polyallergic to HDM and seasonal allergens or animals.
Kim 2019	NR				None
Song 2018	Cockroaches (70.5%)	Cat hair (5.9%)	Unspecified fungi (11.8%)	Unspecified Pollens (11.8%)	None
Soyyigit 2016	NR	Cat (4.2%)	Unspecified Mold (4.2%)	Unspecified Pollens (62.5%)	Pollens and cat (8.3%), Pollen and mold (12.5%), Pollens, cat, and latex (4.2%), Pollens, mold, cat, and latex (4.2%) *Polysensitized patients were not clinically polyallergic.
Xu 2015	Cockroach (83%), Moth (50%), Honey Bee (43%)	Animal dander (duck, chicken, rabbit, porcine, and goose) (53%), Dog hair (30%), Cat hair (40%)	NR	Winter pollens (70%), autumn pollen (50%), summer pollens (43%), spring pollens (33%), Amaranth thorn (43%)	Silk (63%), house dust (37%), padding (23%), cocoon filament (23%)
Kim 2014	NR	NR	NR	White Oak (20%), birch alder mix (20%), goldenrod (16%), mugwort (13%), dandelion (13%), bermuda (10%), ragweed (7%)	None
Li 2014	Blomia tropicalis (53.6%), american cockroach (5.4%)	Dog (12.5%), Cat (8.9%)	None	Unspecified pollens (3.6%),	None
De Castro 2013	NR	NR	NR	Unspecified grass (100%)	None
Lee 2011	NR	Unspecified animals (51.6%)	Unspecified fungi (37.5%)	Unspecified tree (26.6%), Unspecified grass (17.2%)	House dust (21.9%)

The percentage of sensitized allergens was calculated from the number of distributed sensitizations divided by the number of polysensitized patients.

eTable 7. Interested outcomes of included studies.

Studies	Interested outcomes	Points of Measurement										Definition of interested outcomes
		Baseline	1 mo	3 mo	5 mo	6 mo	12 mo	24 mo	3 yr	5 yr	7 yr	
Ma 2021	TNSS	✓	✓	✓	NA	✓	✓	NA				TNSS was a sum of sneezing, runny nose, stuffy nose, and itchy nose scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.
	TMS	✓	✓	✓	NA	✓	✓	NA				TMS was the sum of medication used scores as 1 for nasal, ophthalmic, or oral antihistamines, 2 for ICS or INCS, and 3 points for OCS.
	VAS	✓	✓	✓	NA	✓	✓	NA				VAS was a 0–10 point horizontal scale rated by patients: 0, no symptoms; 10, the most severe symptoms.
Gao 2020	CSMS	✓	NA			✓	✓	✓	✓	NA		CSMS = TNSS/4 + TMS
	TNSS	✓	NA			✓	✓	✓	✓	NA		TNSS was the sum of the four symptom scores, each ranged 0 to 3; sneezing (number/day, ≤ 2 = 0, 3–5 = 1, 6–10 = 2, ≥ 11 = 3), rhinorrhea (times/day, none = 0, 1–4 = 1, 5–9 = 2, ≥10 = 3), nasal itching (no symptom = 0, intermittent itching = 1, tolerable itching = 2, intolerable itching = 3), and nasal obstruction (no symptom = 0, congestion without mouth breathing = 1, severe congestion with occasional mouth breathing = 2, severe congestion with mouth breathing almost all day = 3)
	TMS	✓	NA			✓	✓	✓	✓	NA		TMS was the sum of medication used scores as 0 for none, 1 for oral antihistamines or antileukotrienes, 2 for topical glucocorticoid, and 3 for OCS.
	VAS	✓	NA			✓	✓	✓	✓	NA		VAS was a 0–10 point horizontal scale rated by patients: 0, no symptoms; 10, the most severe symptoms.
Cui 2019	TNSS	✓	NA				✓	✓	✓	✓	✓	TNSS was a sum of sneezing, runny nose, stuffy nose, and itchy nose scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.
	TMS	✓	NA				✓	✓	✓	✓	✓	TMS was the sum of medication used scores as 0 for none, 1 for antihistamine or antileukotrienes, 2 for topical corticosteroid and 3 for OCS.
	CSMS	✓	NA				✓	✓	✓	✓	✓	CSMS was calculated with the following formula: CSMS = TNSS/4 + TMS

eTable 7. (Continued)

Studies	Interested outcomes	Points of Measurement										Definition of interested outcomes
		Baseline	1 mo	3 mo	5 mo	6 mo	12 mo	24 mo	3 yr	5 yr	7 yr	
Tu 2019	VAS	✓	NA			✓	✓	✓	NA			VAS was a 0–10 point horizontal scale rated by patients: 0, no symptoms; 10, the most severe symptoms.
	TMS	✓	NA			✓	✓	✓	NA			TMS was the total score for all medications scored as 1 point for oral or intranasal antihistamines and SABA, 2 points for INCS or ICS and 3 points for OCS.
	TNSS	✓	NA			✓	✓	✓	NA			TNSS was a sum of sneezing, runny nose, stuffy nose, and itchy nose scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.
	RQLQ	✓	NA			✓			NA			RQLQ measured the health status by focusing on seven domains (nasal symptoms, eye symptoms, non-hay fever symptoms, practical problems, emotional function, activities limitation and sleep), rated 0-6 points on each domain. The higher the RQLQ scores, the worse the quality of life.
	TASS	✓	NA			✓	✓	✓	NA			TASS was the sum of daytime and night-time asthma symptom scores. Daytime asthma symptoms were scored from 0, no symptoms, to 5, the severest symptoms. Night-time asthma symptom scores ranged from 0, no awakening by asthma, to 4, awake all night.
	AQLQ	✓	NA			✓	✓	✓	NA			AQLQ focused on four domains (activity limitations, symptoms, emotional function and exposure to environmental stimuli), rated 1–7 points on each domain. The higher AQLQ scores, the better the quality of life.
Zhang 2019	TNSS	✓	NA					✓	NA			TNSS was a sum of sneezing, runny nose, stuffy nose, and itchy nose scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.
	TMS	✓	NA					✓	NA			TMS was the sum of medication used scores as 1 for antihistamines, 2 for INCS and 3 points for OCS.
	IL2	✓	NA					✓	NA			Serum markers were detected by ELISA with commercially available kits (Shanghai WesTang Bio-Tech Co., LTD, Shanghai, China). The lower detection limits were 4 pg/ml for IL-2, 1.95 pg/ml for IL-4, 7.8 pg/ml for IL-17α and 15.6 pg/ml for TGF-β1, respectively.
	IL4	✓	NA					✓	NA			
	IL17a	✓	NA					✓	NA			
	TGFβ1	✓	NA					✓	NA			
	sIgE	✓	NA					✓	NA			
	sIgG4	✓	NA					✓	NA			

eTable 7. (Continued)

Studies	Interested outcomes	Points of Measurement										Definition of interested outcomes
		Baseline	1 mo	3 mo	5 mo	6 mo	12 mo	24 mo	3 yr	5 yr	7 yr	
Kim 2019	TNSS	✓	NA					✓	NA			TNSS was a sum of sneezing, runny nose, stuffy nose, and itchy nose scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.
	Der p sIgE	✓	NA					✓	NA			- Total IgE, sIgE for *Der p* and *Der f*, sIgG4 for *Der p* and *Der f*, and eosinophil cationic protein (ECP) were measured using ImmunoCAP (ThermoFisher Scientific Uppsala, Sweden). - Peripheral blood eosinophils were counted by XE-2100 analyzer (Sysmex, Kobe, Japan)
	Der f sIgE	✓	NA					✓	NA			
	Der p sIgG4	✓	NA					✓	NA			
	Der f sIgG4	✓	NA					✓	NA			
	Total IgE	✓	NA					✓	NA			
	Eosinophil count	✓	NA					✓	NA			
	ECP	✓	NA					✓	NA			
Song 2018	VAS	✓	NA			✓	✓	NA	✓	✓	NA	VAS was a 0–10 point horizontal scale rated by patients: 0, no symptoms; 10, the most severe symptoms.
	RQLQ	✓	NA			✓	✓	NA	✓	✓	NA	RQLQ was evaluated using the Rhinoconjunctivitis Quality of Life Questionnaire.
	TMS	✓	NA			✓	✓	NA	✓	✓	NA	TMS was scored as 1 point each for oral antihistamine, ICS, SABA; 0.75 points for INCS; 0.25 points for intranasal antihistamine; 2 points for ICS plus β-2 agonists.

eTable 7. (Continued)

Studies	Interested outcomes	Points of Measurement										Definition of interested outcomes
		Baseline	1 mo	3 mo	5 mo	6 mo	12 mo	24 mo	3 yr	5 yr	7 yr	
Soyyigit 2016	TNSS	✓	NA	NA	✓	NA						TNSS was a sum of sneezing, runny nose, stuffy nose, and itchy nose scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.
	TASS	✓	NA	NA	✓	NA						TASS was a sum of dyspnea, cough, and wheezing; each ranged 0, nil; 3, severe.
	TSS	✓	✓	✓	✓	NA						TSS was a combination of TNSS and TASS.
	TMS	✓	✓	✓	✓	NA						TMS was the sum of medication used scores as 1 point for SABA and antihistamines, 2 points for ICS or INCS, and 3 points for antileukotriene or OCS.
	VAS	✓	✓	✓	✓	NA						VAS was a 0–10 point horizontal scale rated by patients: 0, no symptoms; 10, the most severe symptoms.
	RQLQ	✓	NA		✓	NA						RQLQ was assessed using Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ).
	AQLQ	✓	NA		✓	NA						AQLQ was assessed using Asthma Quality of Life Questionnaire (AQLQ).
	NPT	✓	NA		✓	NA						The Der p extract was delivered in 3 consecutive doses (2, 4, and 8 BU/mL; ALK-Abello) every 10 minutes via a metered nasal spray in both nostrils. A combined total nasal and ocular symptom score of ≥ 6 was considered a positive result.
	sIgE	✓	NA		✓	NA						The levels of total IgE, sIgE, and sIgG4 were quantified using a CAP fluoroenzyme immunoassay (Phadia, Uppsala, Sweden).
	sIgG4	✓	NA		✓	NA						
	Total IgE	✓	NA		✓	NA						
	Basophil activation by measured CD203c expression	✓	NA		✓	NA						The results were expressed as the percentage of activated basophils and as mean fluorescence intensity according to the up-regulation of CD203c expression.

eTable 7. (Continued)

Studies	Interested outcomes	Points of Measurement									Definition of interested outcomes
		Baseline	1 mo	3 mo	5 mo	6 mo	12 mo	24 mo	3 yr	5 yr	7 yr	
Xu 2015	TNSS	✓	NA				✓	NA				Treatment effectiveness was measured using the percentage of symptom improvement from baseline.
Kim 2014	TNSS	✓	NA					✓	NA			TNSS was a sum of sneezing, runny nose, stuffy nose, and itchy nose scores, each ranging: 0, nil; 1, mild; 2, moderate; 3, severe.
	TMS	✓	NA					✓	NA			TMS was a sum of medication used scores as 1 point for INCS at a minimum of 1 per day every week, 2 points for the previous therapy plus 1 tablet of levocetirizine at a minimum of 1 per day, 3 points for the previous therapies plus a 4 mg tablet of methylprednisolone at a minimum of 1 per day.
	RQLQ	✓	NA					✓	NA			RQLQ measured the health status by focusing on 7 domains: activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional well-being. Each question was scored using an impairment rating scale of 0-6, with higher scores indicative of more severe impairment of quality of life.
	sIgE	✓	NA					✓	NA			IgE level was measured by ImmunoCAP system (Thermo Scientific, Uppsala, Sweden)
	Eosinophil count	✓	NA					✓	NA			Peripheral blood eosinophils were analyzed using a Coulter automated hematology analyzer (Hialeah FL, Miami, FL, USA).
Li 2014	TNSS	✓	✓	✓	✓	✓	✓	NA				TNSS was a sum of sneezing, rhinorrhea, nasal itching, and obstruction, each ranging from 0 to 3 points.
	TASS	✓	✓	✓	✓	✓	✓	NA				TASS was a sum of daytime and nocturnal asthma symptom scores. The daytime asthma symptoms were scored from 0 to 5 points according to the general severity of wheeze, shortness of breath, dyspnea, and cough. The nocturnal symptoms were scored from 0 to 4 points according to nocturnal and early morning awakening due to asthma.
	TMS	✓	✓	✓	✓	✓	✓	NA				TMS was a sum of medication used scores as 1 for antihistamine or antileukotrienes or SABA, 2 for topical corticosteroid, and 3 for OCS.
	VAS	✓	✓	✓	✓	✓	✓	NA				VAS was a 0–10 point horizontal scale rated by patients: 0, no symptoms; 10, the most severe symptoms.
	Grade of skin reaction	✓	NA	NA	NA	NA	✓	NA				The wheal area of allergens was graded based on the ratio (%) of wheal area between allergen and positive control as follows: grade 1 = 1% to 49%; grade 2 = 50% to 99%; grade 3 = 100% to 199%; and grade 4 ≥ 200%.

eTable 7. (Continued)

Studies	Interested outcomes	Points of Measurement									Definition of interested outcomes
		Baseline	1 mo	3 mo	5 mo	6 mo	12 mo	24 mo	3 yr	5 yr	7 yr
De Castro 2013	TNSS	✓	NA		NA	NA	✓	✓	✓	NA	NA	TNSS was a sum of sneezing, rhinorrhea, nasal itching, and obstruction, each ranging from 0 to 3 points. TASS was a sum of wheezing, dyspnea, cough and exercise-induced asthma, each ranging from 0, no symptoms to 3, severe symptoms. TMS was a sum of medication used scores as 1 for antihistamine, nasal corticosteroid, inhaled corticosteroid, inhaled β2 agonists, 2 for OCS and antileukotrienes.
	TASS	✓	NA		NA	NA	✓	✓	✓	NA	NA	
	TMS	✓	NA		NA	NA	✓	✓	✓	NA	NA	
	FEV1	✓	NA	NA	NA	NA	NA	NA	✓	NA	NA	
Lee 2011	TNSS	✓	NA		NA	NA	✓	NA	NA	NA	NA	TNSS was defined as the sum of the scores for 4 nasal symptoms: rhinorrhea, sneezing, nasal obstruction, and itchy nose (range, 0–20).
	AMS	✓	NA		NA	NA	✓	NA	NA	NA	NA	The antiallergic medication score (AMS) was calculated as 1 for oral antihistamine and 2 points for INCS.

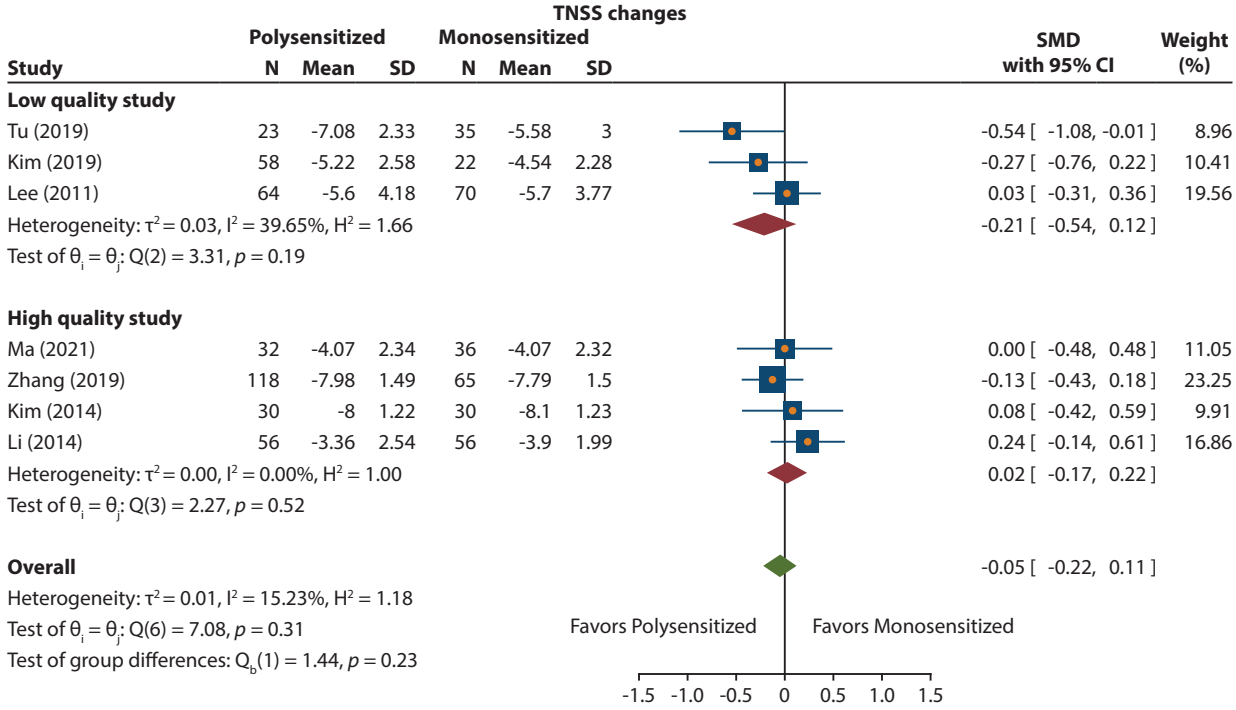
AQLQ, asthma quality of life questionnaire; CSMS; combined symptom and medication score; *Der f*, *Dermatophagoides farinae*; *Der p*, *Dermatophagoides pteronyssinus*; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; INCS, intranasal corticosteroid; mo, month; NA, not applicable; OCS, oral corticosteroid; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SABA, short-acting β2 agonist; sIgE, specific immunoglobulin E; sIgG4, specific immunoglobulin G4; TASS, total asthma symptom score; TMS, total medication score, TNSS, total nasal symptom score; VAS, visual analog scale; yr, year

Asian Pac J Allergy Immunol DOI 10.12932/AP-190822-1440

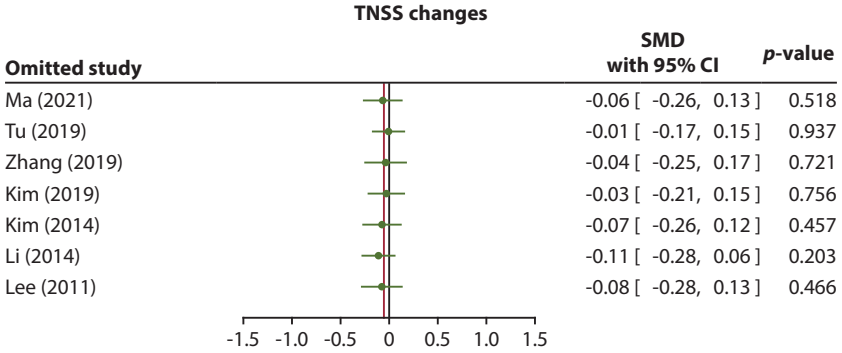
eTable 8. Newcastle-Ottawa Quality Assessment Scale for cohort studies included in the systemic review.

Author (year)	Selection				Comparability	Outcome			Total score	Quality of study
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts		
Ma (2021)	*	*	*	*	*	*	*	*	8	High
Gao (2020)	*	*	*	*	**		*	*	8	High
Cui (2019)	*	*	*	*	**		*	*	8	High
Tu (2019)	*	*	*	*			*	*	6	Low
Zhang (2019)	*	*	*	*	*	*	*	*	8	High
Kim (2019)	*	*	*	*		*	*	*	7	Low
Song (2018)	*	*	*	*			*	*	6	Low
Soyyigit (2016)	*	*	*	*	**	*		*	8	High
Xu (2015)	*	*	*	*			*	*	6	Low
Kim (2014)	*	*	*	*	**		*	*	8	High
Li (2014)	*	*	*	*	**	*	*	*	9	High
De Castro (2013)	*	*	*	*	*		*		6	Low
Lee (2011)	*	*	*	*		*	*		6	Low

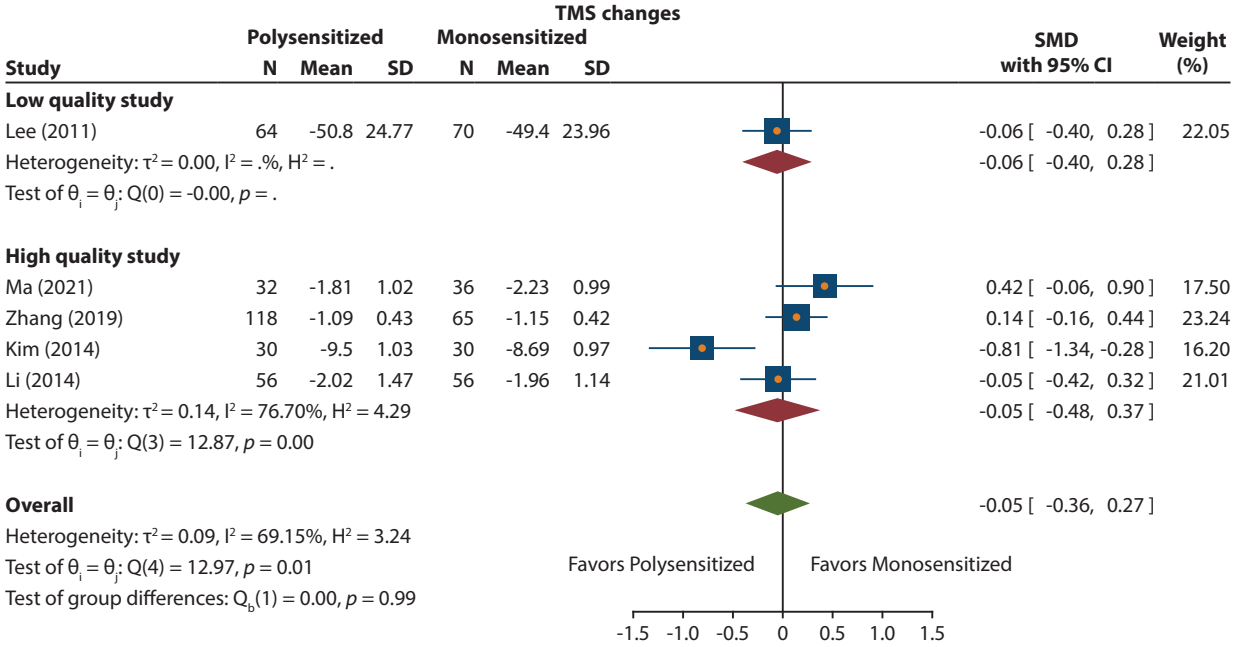
*This symbol represents the number of stars given to each category according to the star-based scoring systems employed to assess the quality of each study as detailed in the section "Assessment of Quality" in the main text.



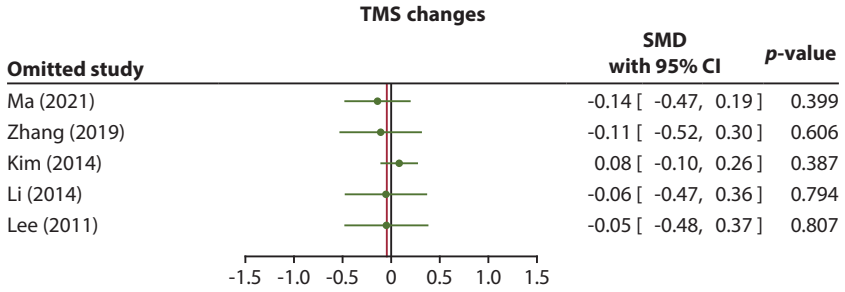
eFigure 1. Subgroup analysis by the quality of the study of changes from baseline in total nasal symptom score following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.



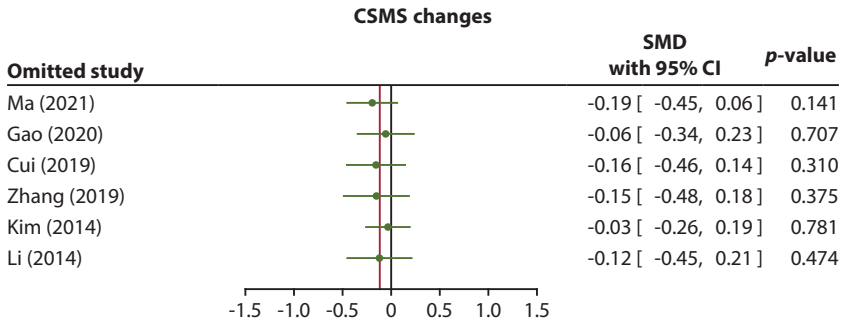
eFigure 2. The leave-one-out sensitivity analysis of changes from baseline in total nasal symptom score following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.



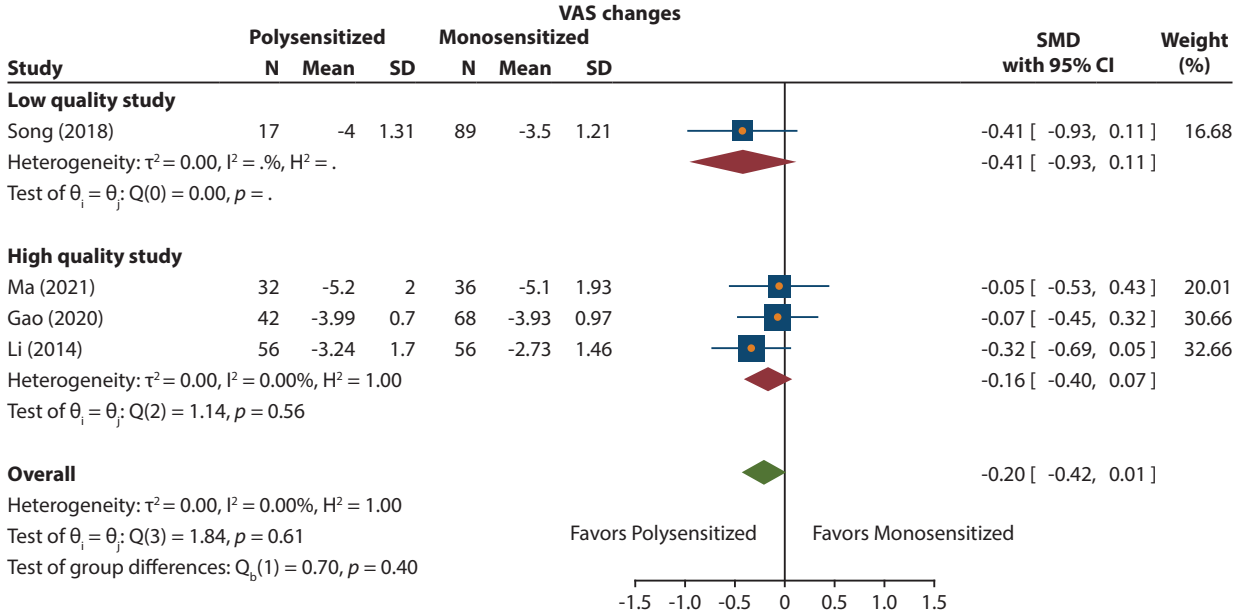
eFigure 3. Subgroup analysis by the quality of the study of changes from baseline in total medication score following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.



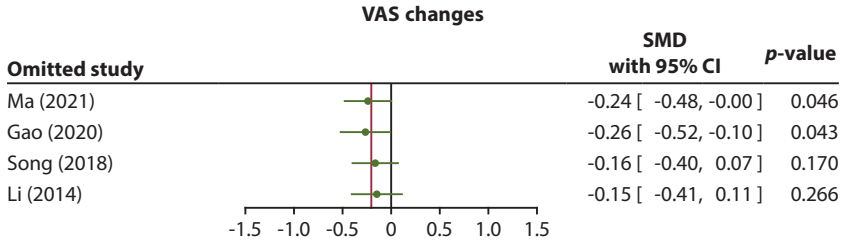
eFigure 4. The leave-one-out sensitivity analysis of changes from baseline in total medication score following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.



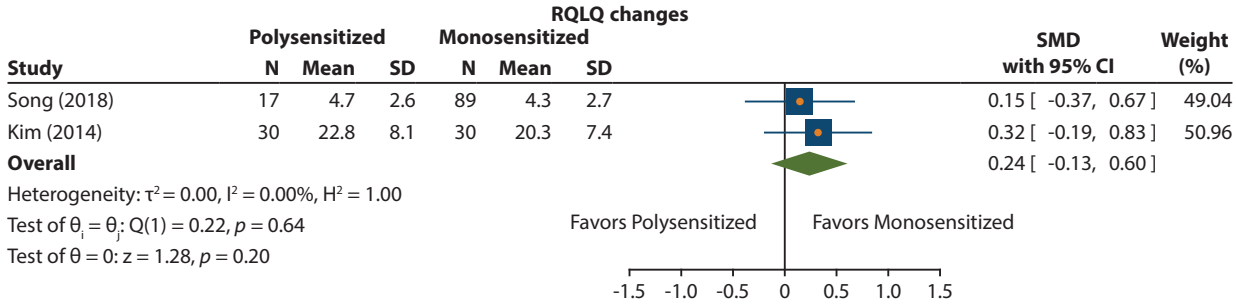
eFigure 5. The leave-one-out sensitivity analysis of changes from baseline in combined symptom and medication score following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.



eFigure 6. Subgroup analysis by the quality of the study of changes from baseline in visual analog scale following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.



eFigure 7. The leave-one-out sensitivity analysis of changes from baseline in visual analog scale following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.



eFigure 8. Changes from baseline in Rhinoconjunctivitis Quality of Life Questionnaire score following house dust mite allergen immunotherapy between monosensitized and polysensitized patients.