

Multiallergen Immunotherapy for Polysensitized Patients with Allergic Rhinitis: A Systematic Review and Meta-Analysis

Yu Shi , Zhouxian Pan , Xinyu Tian, Lisha Li , Kai Guan

Department of Allergy, Beijing Key Laboratory of Precision Medicine for Diagnosis and Treatment on Allergic Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Kai Guan, Department of Allergy, Beijing Key Laboratory of Precision Medicine for Diagnosis and Treatment on Allergic Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing, 100730, People's Republic of China, Email dr_guankai@126.com

Background: Polysensitization occurs in 80% of allergic patients. Allergen immunotherapy (AIT) formulations with multiple allergens remain debated for polysensitized patients.

Objective: This study aims to evaluate the clinical effectiveness and safety profile of multiallergen AIT in polysensitized allergic rhinitis (AR) patients.

Methods: We searched for polysensitized AR patients treated with multiple allergens in immunotherapy in PubMed, Embase, Web of Science and Cochrane Library until June 5, 2025.

Results: Seven randomized clinical trials and 7 nonrandomized studies were included. Multiallergen immunotherapy significantly reduced combined symptom and medication scores versus placebo from baseline (SMD: -3.75 , 95% CI $(-5.85, -1.65)$; $p < 0.001$). Compared to single-allergen AIT, symptom score changes were no difference (SMD: -0.34 , 95% CI $(-1.21, 0.52)$; $p = 0.44$), while medication scores showed slight superiority (SMD: -1.36 , 95% CI $(-2.44, -0.28)$; $p = 0.01$). But both scores at the last follow-up were significantly reduced compared with single-allergen treatment (SMD: -1.75 , $p = 0.01$; SMD: -1.30 , $p = 0.007$). Systematic review highlighted superior outcomes with dual-allergen AIT in some studies. The multiallergen group had a safer profile in randomized studies (OR 0.58, 95% CI 0.35, 0.96, $p = 0.03$). No significant differences were found in adverse events due to AIT treatment among non-randomized studies (OR 0.86, 95% CI 0.64, 1.15, $p = 0.3$). Multiallergen AIT demonstrated enhanced immune tolerance and modulation of the type 2 immune response similar to single-allergen treatment.

Conclusion: Based on current evidence, multiallergen AIT demonstrates no significant difference in efficacy, a comparable safety profile, and equivalent immunological modulation compared to single-allergen AIT for the treatment of polysensitized allergic rhinitis. Dual-allergen approaches may optimize benefits in clinically relevant cases, though study heterogeneity necessitates standardized trials.

Plain Language Summary:

1. Multiallergen immunotherapy is effective in symptom improvement and medication reduction for polysensitized patients with allergic rhinitis.
2. Multiallergen immunotherapy has comparable efficacy than single-allergen therapy in polysensitized AR patients, dual-allergen might be optimal.
3. Multiallergen immunotherapy does not increase the risk of adverse effects.

Keywords: polysensitization, multiallergen immunotherapy, allergen immunotherapy, allergic rhinitis, systematic review and meta-analysis

Introduction

Allergen immunotherapy (AIT) is the only treatment targeting the underlying cause to modify the disease course in patients with IgE-mediated allergic diseases such as allergic rhinitis (AR) or rhinoconjunctivitis with or without allergic asthma. It has been studied for more than a century ever since Noon et al¹ first demonstrated its potential as a promising therapeutic option and showed its effectiveness in the management of airway allergic diseases^{2,3} Although many innovations have been implemented to improve clinical efficacy and tolerability of AIT, there are still many unmet needs.

Polysensitization is more prevalent than monosensitization. Data from several large-scale epidemiological studies in the US and Europe have consistently shown a higher proportion of polysensitization in the general population and patients consulting allergists.^{4–6} However, published practice guidelines by the American Academy of Allergy, Asthma and Immunology⁷ and the European Academy of Allergy and Clinical Immunology⁸ regarding AIT formulations in polysensitized patients differ substantially. Most of the US formulations contain multiple allergens, while fewer than 10% of European formulations contain more than 1 non-cross-reacting allergen.⁹ Allergists in the US prefer to include all clinically relevant allergens due to concerns over the time investment required for AIT, particularly during the build-up phase. The prevailing view in Europe is to select a most troublesome allergen because polysensitization does not necessarily mean poly-allergy.

Multiallergen AIT (whether with mixed allergens or with the separate administration of multiple allergen extracts) has long been acknowledged as an effective therapy for allergic respiratory disease and has been implemented in double-blind, placebo-controlled trials since the mid-1960s.¹⁰ It was also conducted in several rigorously conducted clinical trials evaluating the effect on bronchial hyperreactivity and quality of life.^{11,12} The primary immunological mechanism of AIT involves a profound modulation of the adaptive immune system, characterized by shifting the immune response away from a T helper cell (Th) 2 phenotype toward a regulatory T and Th1 response.¹³ Given that a head-to-head comparison of single and multiallergen AIT would be expensive and time-consuming, the number of well-controlled trials focusing on this issue has been relatively scarce. However, recent clinical research conducted over the past few decades provides an opportunity to aggregate new evidence on the efficacy and safety profile of multiallergen AIT.

In this context, polysensitization indicates sensitization to two or more distinct allergens, demonstrated by a positive skin prick test (SPT) with a wheal diameter of ≥ 3 mm, and/or an allergen-specific IgE (sIgE) level of >0.35 KUA/L. Single-allergen immunotherapy includes the use of extracts containing several closely related allergens, and that multi-allergen immunotherapy refers to mixtures with little or no cross-reactivity such as grass pollen, tree pollen, weed pollen, house dust mite (HDM), etc.

The use of multiallergen AIT for polysensitized patients remains one of the biggest debates in clinical practice. This systematic review and meta-analysis aim to collect and analyze available data to provide more relatively high-quality evidence for the multiallergen debate. Additionally, a review of the relevant literature can help identify the research gaps within this field and highlight areas that require further investigation.

Methods

Search Strategy and Eligibility Criteria

A comprehensive search was conducted in PubMed, Embase, Web of Science, and Cochrane Library databases to identify relevant studies on polysensitized AR with or without mild/controlled comorbid asthma treated with multi-allergen AIT until June 5, 2025 following the PRISMA guidelines.¹⁴ The eligibility criteria to include in our systematic review were as follows: (1) Randomized controlled trials (RCTs), cohort studies, and case-control studies; (2) polysensitized patients treated with multiallergen AIT; (3) Clinical outcomes including assessment of symptoms and medication use or safety profile. Search terms used were “immunotherapy” OR “subcutaneous immunotherapy” OR “sublingual immunotherapy” OR “SCIT” OR “SLIT” AND “multiallergen” OR “multi-allergen” OR “polysensitization” OR “polysensitized”. The search strings employed are detailed in the [Supplementary Table S1](#). Relevant articles were manually identified and reviewed. We also searched for clinical trials on Clinicaltrials.gov to include any data that may have been missing from the previous search but found no relevant data. Only studies focusing AR were included in the systematic review. This systematic review was registered on PROSPERO (ID: CRD42024567545).

Inclusion Criteria for Meta-Analysis

To be included in this meta-analysis, study outcomes had to entail data on one or more of the following parameters: (1) combined or separated symptom score and medication score. (2) adverse events after administering AIT, and number of patients discontinued AIT treatment due to adverse effect. The detailed inclusion criteria were presented in the [Supplementary Table S2](#).

Data Extraction

Two authors independently extracted data and used a standardized data extraction form including first and corresponding author, year of publication, study type, disease type, age, gender, disease duration, type of allergens, number of patients and controls, administration, follow-up duration, assessment of outcome and adverse events. Discrepancies identified during data extraction were resolved by consensus meetings of the authors.

Bias Assessment

Quality and risk of bias of included RCTs were assessed by the Cochrane Risk-of-Bias version 2 (RoB 2). The tool consists of five domains, each containing a list of questions linked to specific aspects of the RCT. An algorithm marks the risk of bias in each domain as “low”, “some concerns”, or “high” depending on the answers to the questions. Non-randomized studies were assessed by Newcastle-Ottawa Scale (NOS).

Data Synthesis and Statistical Analysis

The mean and standard deviation (SD) of symptom score and medication score at baseline and post-treatment were extracted from each study in all groups. Some studies reported post-treatment scores at several time points, the last time point (maximum 2 years) was extracted for further analysis. Obtaining SDs for group of means were calculated from 95% confidence intervals (CIs) by using equations from the Cochrane Handbook¹⁵ chapter 6.5.2.2 when the group SDs were not provided directly [$SD = \sqrt{n} \times (\text{upper limit} - \text{lower limit}) / 3.92$]. When scores were provided in medians and 25th–75th percentile, we converted these into means by Luo et al,¹⁶ and SDs by using the equation by Wan et al (Cochrane Handbook chapter 6525).¹⁵ Furthermore, when not reported, change-from-baseline SDs were estimated using the equation by Follmann et al assuming a correlation coefficient of 0.50 between baseline and post-intervention values

[Cochrane Handbook chapter 6.5.2.8, 2: $SD_{E,\text{change}} = \sqrt{SD_{E,\text{baseline}}^2 + SD_{E,\text{post}}^2 - (2 \times 0.50 \times SD_{E,\text{baseline}} \times SD_{E,\text{post}})}$].^{15,17}

To verify the robustness of our findings, sensitivity analyses were performed by re-running the models using alternative correlation coefficients ($r = 0.25$ and $r = 0.75$). Statistical analyses were performed using Review Manager (RevMan) v5.4 (the Cochrane Collaboration, Copenhagen, Denmark) and R statistical software, version 4.3.1 (<http://www.R-project.org/>). Pooled results were estimated using 9a random-effects model due to the heterogeneity of included studies. The risk of publication bias was assessed visually by funnel plots symmetry and quantitatively by Egger’s test, with a p value <0.05 indicating statistically significant publication bias. Heterogeneity was tested using I^2 , with values $>50\%$ indicating heterogeneity among studies. A p -value of <0.05 was considered statistically significant. Sensitivity analysis was performed by removing one single study at a time to evaluate its impact on the overall results.

Results

Literature Search and Characteristics of Included Studies

A flow chart presenting the search and selection process is shown in [Figure 1](#). A total of 14 studies met the eligibility criteria and were included in this systematic review, of which 7 were RCTs, 1 pilot study, and 6 non-randomized studies. [Figure 2](#) presents the risk-of-bias assessment of the included RCTs, while [Table 1](#) summarizes the quality assessment of cohort and case-control studies using the Newcastle-Ottawa Scale (NOS). Random-effect models were used. Bar graphs illustrating the relative contributions of RCTs with each risk-of-bias judgement are shown in [Supplementary Figure S1](#).

The 14 studies analyzed 1692 polysensitized patients with AR in 5 countries. Dust mites, tree pollen, and grass pollen were the most common allergens in these polysensitized patients. Seven, and 10 of the included treatment protocols were meta-analyzed for treatment effects, safety of multiallergen AIT. The characteristics of the included studies are

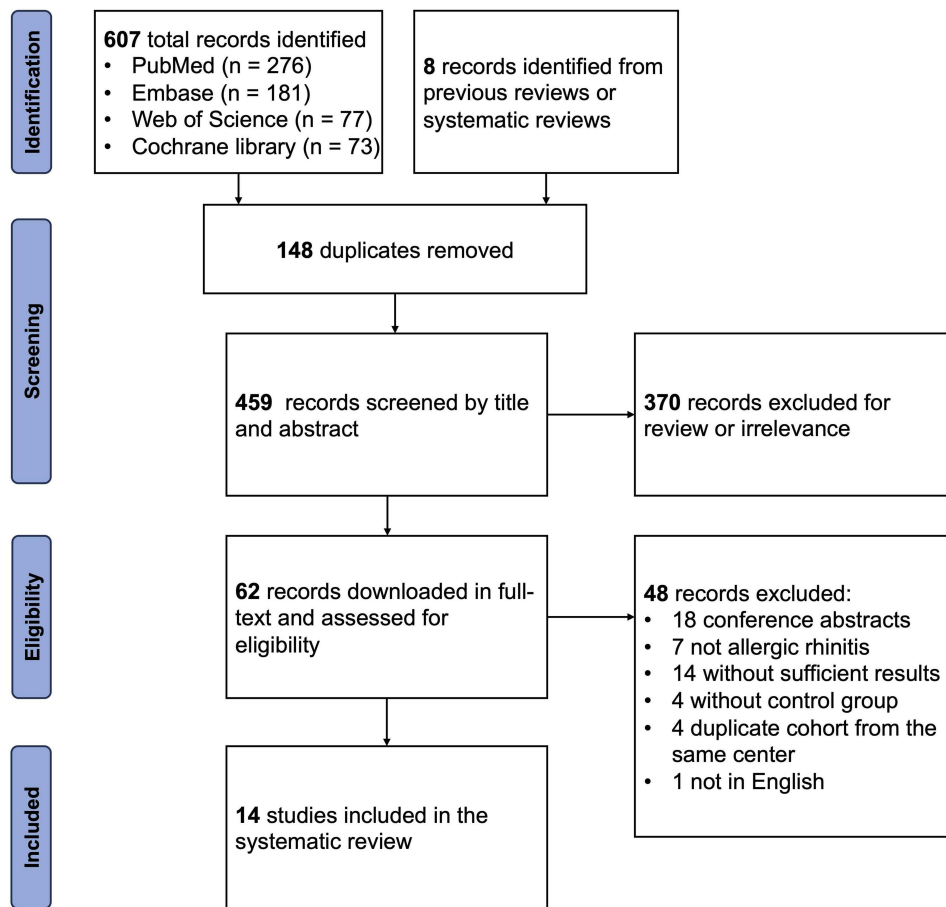


Figure 1 Flow diagram of the search and selection process.

| Study ID | Experimental | Comparator | D1 | D2 | D3 | D4 | D5 | Overall | |
|-------------------------|--------------------|------------|----|----|----|----|----|---------|---|
| Gotoh et al, 2020(37) | HDM+JCP | HDM | + | + | + | + | ! | ! | |
| Marogna et al, 2007(21) | Birch+grass | Birch | + | + | + | ! | ! | ! | |
| Maloney et al, 2016(39) | Ragweed+grass | Grass | ! | + | + | + | ! | ! | D1 Randomisation process |
| Tversky et al, 2023(46) | Multiple allergens | Placebo | + | + | + | + | ! | ! | D2 Deviations from the intended interventions |
| Swamy et al, 2012(20) | Dual SLIT | Placebo | + | + | - | + | ! | - | D3 Missing outcome data |
| Pfaar et al, 2013 (48) | Mixed pollen AIT | Placebo | + | + | + | + | ! | ! | D4 Measurement of the outcome |
| | | | | | | | | | D5 Selection of the reported result |

Figure 2 Assessment of risk of bias using Cochrane Risk-of-Bias tool 2 for randomized trials.

summarized in Table 2. Among the 7 RCTs, 5 were conducted with a placebo group or drug therapy only group, while 2 of them, and other than those, a pilot study compared AIT of multiple allergens and single allergen. All nonrandomized studies compared multiallergen AIT and AIT using single allergen. In only 5 studies were patients administered AIT treatment via subcutaneous injection, the other via sublingual tablets. One of the included RCT was deemed to have a relatively high risk of bias due to a notable proportion of missing outcomes, which could potentially affect the accuracy of the study results. According to the funnel plot, there appeared to be a publication bias in favor of single-allergen AIT (Supplementary Figure S2A), which was further confirmed by Egger’s linear regression test (p = 0.0014). Visual asymmetry was also examined in the funnel plots for the symptom scores (Supplementary Figure S2B), medication

Table 1 Assessment of Risk of Bias in Non-Randomized Studies Using Newcastle-Ottawa Scale

| | Newcastle-Ottawa Scale | | | |
|-------------------------------------|------------------------|---------------|----------|-------------|
| Cohort Studies | Selection | Comparability | Outcome | Total Score |
| Wang et al, 2017 ¹⁸ | **** | ** | *** | 9 |
| Reiber et al, 2016 ¹⁹ | **** | ** | ** | 8 |
| Case-control studies | Selection | Comparability | Exposure | Total score |
| Roder et al, 2009 ²⁰ | *** | * | ** | 6 |
| Lombardi et al, 2008 ²¹ | *** | * | ** | 6 |
| Fujii et al, 2022 ²² | *** | * | ** | 6 |
| Agostinis et al, 2008 ²³ | *** | / | ** | 5 |

Notes: Each asterisk (*) represents one star (point) awarded within the respective domain of the Newcastle-Ottawa Scale.

Table 2 Characteristics of the Included Studies

| First Author, Year (Location) | Study Type | Disease | Treatment Regimen | Number of Patients | Time Frame (Months) | Outcomes Studied |
|---|-----------------------------|---|---|----------------------|---------------------|--|
| Tversky, 2023 (United States) ²⁴ | RCT | Allergic rhinitis | Multiallergen immunotherapy SCIT; Placebo; | 16 14 | 3 | Symptom score, daily combined score, mini-RQLQ, adverse events |
| Gotoh, 2020 (Japan) ²⁵ | RCT | Allergic rhinitis | HDM SLIT first and HDM + JCP SLIT; JCP SLIT first and JCP + HDM SLIT; Placebo | 54 55 N/A | 3 | Adverse events, sIgE, sIgG ₄ |
| Ortiz, 2018 (United States) ²⁶ | Pilot study | Allergic rhinoconjunctivitis | All sensitized allergens (6+) SLIT; 3 allergens SLIT; Single allergen SLIT; Placebo | 5 5 6 N/A | 9 | Symptom score, mini-RQLQ, medication score |
| Maloney, 2016 (Germany) ²⁷ | Multicenter clinical trials | Allergic rhinitis with or without conjunctivitis and asthma | Grass and ragweed SLIT; Grass SLIT; Placebo | 102 102 N/A | 1.5 | Adverse events |
| Pfaar, 2013 (Germany) ²⁸ | RCT | Allergic rhinoconjunctivitis | Grass and birch SCIT; Placebo; | 175 94 | 24 | Symptom and medication score, RQLQ, sIgE, adverse events |
| Swamy, 2012 (United States) ²⁹ | RCT | Allergic rhinitis | DM + Timothy grass SLIT; Placebo; | 20 10 | 24 | Symptom score, medication score, tSPT, nasal provocation test, sIgE, sIgG ₄ , CD203c, Treg function |
| Amar, 2009 (United States) ³⁰ | RCT | Allergic rhinitis with or without well-controlled asthma | Timothy + 9 additional pollen extracts SLIT Timothy extract SLIT Placebo | 20 19 19 | 15 | Symptom and medication score, titrated nasal challenge, sIgE, sIgG ₄ , adverse events, cytokine release |
| Marogna, 2007 (Italy) ³¹ | RCT | Allergic rhinitis and bronchial hypersensitivity | Birch + grass SLIT; Birch SLIT; Grass SLIT; Drug therapy alone; | 13 11 12 12 | 48 | Symptom and medication score, PD ₂₀ , N-EOS% |
| Fujii, 2022 (Japan) ²² | Case-control | Allergic rhinitis | HDM + JCP SLIT; JCP SLIT; | 16 9 | 12 | Separated symptom scores and adverse events |

(Continued)

Table 2 (Continued).

| First Author, Year (Location) | Study Type | Disease | Treatment Regimen | Number of Patients | Time Frame (Months) | Outcomes Studied |
|---------------------------------------|--------------------|---|--|--------------------|---------------------|--|
| Wang, 2017 (China) ¹⁸ | Prospective cohort | Allergic rhinitis | HDM + other clinically relevant allergens SCIT; HDM SCIT; | 34 34 | 12 | Symptom score, medication score, IL-4 levels |
| Reiber, 2016 (Germany) ¹⁹ | Prospective cohort | Allergic rhinitis with or without conjunctivitis and asthma | Grass SLIT and concomitant SLIT or SCIT; Grass SLIT; | 160 21 | 3 | Adverse events |
| Röder, 2009 (Germany) ²⁰ | Prospective cohort | Allergic rhinoconjunctivitis | Birch + grass SCIT; Birch SCIT; Grass SCIT; | 29 25 23 | 12 | Adverse events |
| Lombardi, 2008 (Italy) ²¹ | Case-control | Allergic rhinitis with or without asthma | 2 or 3 tree/grass allergens SLIT; Single allergen SLIT; | 83 76 | 3 | Adverse events |
| Agostinis, 2008 (Italy) ²³ | Case-control | Allergic rhinitis with or without asthma | Multiple tree/grass allergens SLIT; Single allergen SLIT; | 254 179 | 24 | Adverse events |

Notes: N/A: Not applicable (the respective study did not include this treatment arm/group).

Abbreviations: RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; RQLQ, rhinoconjunctivitis quality of life questionnaire; HDM, house dust mite; JCP, Japanese cedar pollen; tSPT, titrated skin prick test; PD, provocation dose; EOS, eosinophil; IL, interleukin.

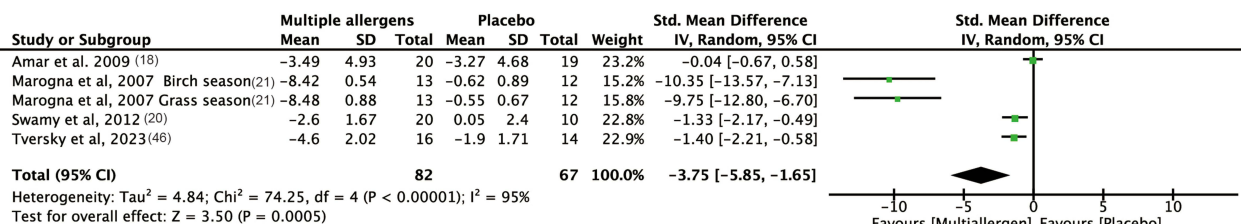
scores ([Supplementary Figure S2C](#)), adverse events of randomized studies ([Supplementary Figure S2D](#)), and adverse events of non-randomized studies ([Supplementary Figure S2E](#)).

Efficacy of Multiallergen AIT on Polysensitized Patients

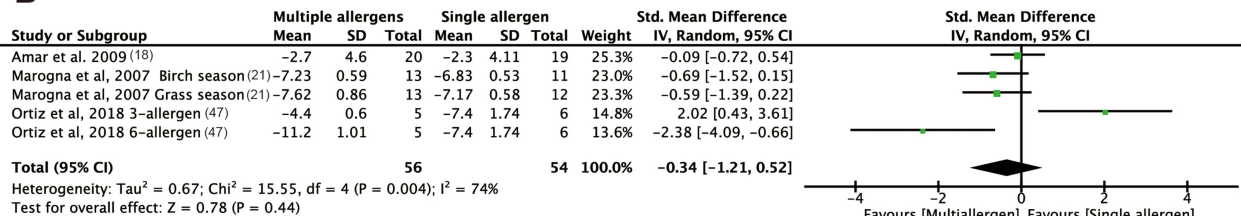
First, the efficacy of multiallergen AIT was established by comparing combined symptom and medication score at the last follow-up with placebo or drug therapy only in 5 RCTs, which yielded a standardized mean difference (SMD) of -2.85 (95% CI $-4.24, -1.46$; $p < 0.001$, [Supplementary Figure S3A](#)). Due to a lack of baseline information, the mean change of combined scores of multiallergen group from baseline was analyzed in 4 RCTs. Results also showed a significantly lower SMD than the control group (SMD -3.75 , 95% CI $-5.85, -1.65$; $p < 0.001$, [Figure 3A](#)). Sensitivity analyses using correlation coefficients of $r = 0.25$ and $r = 0.75$ yielded consistent results, indicating the robustness of the pooled SMDs. Although calculated I^2 indicated high heterogeneity between studies. Then, we performed separate analysis on mean change of symptom score and medication score in randomized trials for multiallergen AIT compared with AIT of single allergen. The SMD of individual studies for symptom scores mostly lie on the side that favors multiallergen AIT, but total SMD and 95% CI was -0.34 ($-1.21, 0.52$) with a p value of 0.44 ([Figure 3B](#)). Multiallergen AIT showed a slightly bigger reduction in medication score with a total SMD of -1.36 (95% CI $-2.44, -0.28$, $p = 0.01$; [Figure 3C](#)). Symptom score and medication score at the last follow-up showed a significant reduction in multiallergen AIT (SMD -1.75 , 95% CI $-3.16, -0.34$; $p = 0.01$, [Supplementary Figure S3B](#); SMD -1.30 , 95% CI $-2.18, -0.43$; $p = 0.007$, [Supplementary Figure S3C](#)). Sensitivity analyses showed robustness of the synthesized result. Several studies included titrated nasal challenge and SPT after AIT treatment, but the results differed greatly in their presented form to perform a meta-analysis.^{29–31}

The included studies employed a heterogeneous array of allergen types, with combinations such as perennial allergens with tree pollen, perennial allergens with grass pollen, and tree pollen with grass pollen, etc. As a result, it was not feasible to conduct separate discussions based on distinct allergen categories. Nevertheless, studies utilizing dual-allergen approaches in multiallergen immunotherapy yielded noteworthy findings. Specifically, two studies investigated dual-allergen AIT: one RCT compared birch and grass pollen combination therapy against single-allergen SLIT,³¹ while another case-control study contrasted HDM and Japanese cedar pollen dual therapy with single Japanese cedar pollen therapy.²² Both studies demonstrated that dual-allergen AIT resulted in significantly greater reductions in symptom

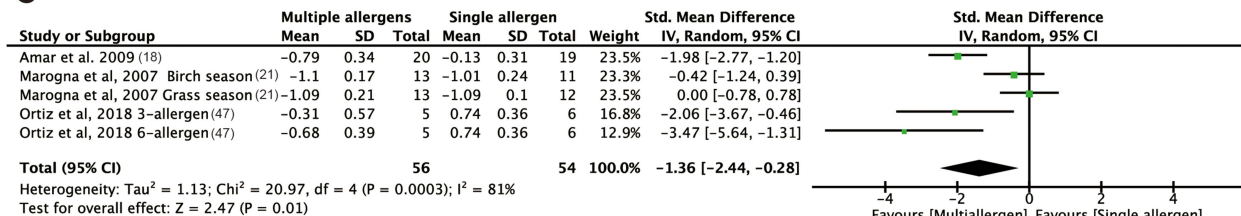
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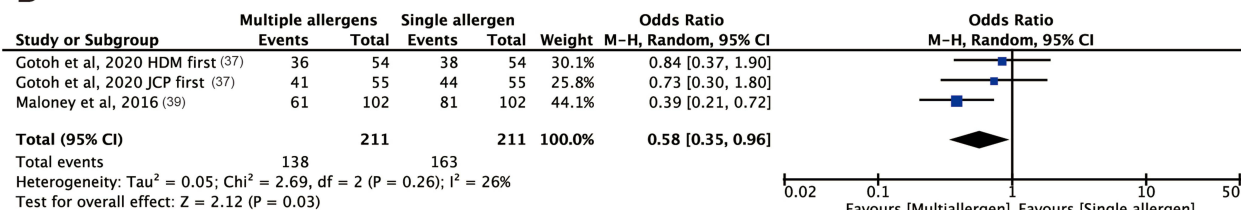
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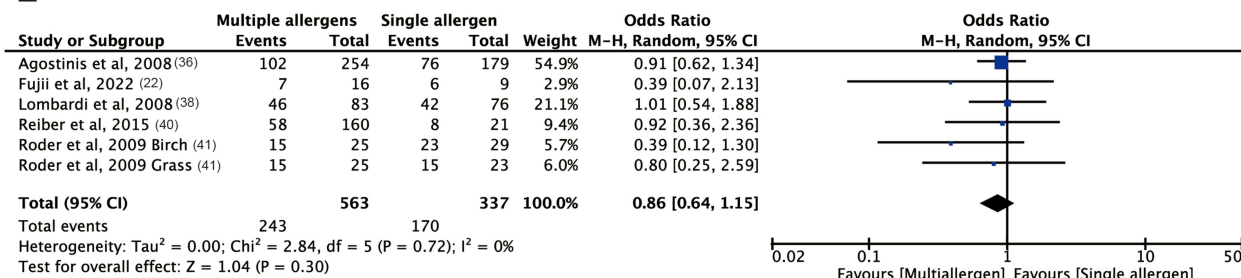


Figure 3 Meta-analysis of (A) mean change of combined symptom and medication score; (B) mean change of symptom score; (C) mean change of medication score; (D) adverse events of randomized studies; (E) adverse events of non-randomized studies between multiallergen immunotherapy and placebo or single allergen.

Abbreviations: CI, confidence interval; HDM, house dust mite; IV, inverse variance; JCP, Japanese cedar pollen; M-H, Mantel-Haenszel; OR, odds ratio; SD, standard deviation; SMD, standardized mean difference.

scores among patients with AR. Other studies comparing dual-allergen AIT with single-allergen AIT consistently reported similar outcomes.

Safety and Immunological Profile of Multiallergen AIT on Polysensitized Patients

The majority of reported adverse events were mild or localized events associated with routes of administration including injection site wheal, oral irritation, mouth swelling, throat irritation, etc. Randomized studies and non-randomized studies were analyzed separately. In both analyses, the multiallergen AIT group and the single allergen group had a similar incidence of adverse events. Among randomized studies, the meta-analysis revealed an odds ratio (OR) of 0.58 (95% CI 0.35, 0.96, $p = 0.03$; [Figure 3D](#)). The multiallergen group had a slightly safer profile because of the Maloney study. Regarding non-randomized studies, the OR was 0.86 (95% CI 0.64, 1.15, $p = 0.3$; [Figure 3E](#)). The incidence of discontinuation due to adverse events was also similar between the two groups in both randomized and non-randomized studies (data not shown). The calculated I^2 values were below 50%, indicating a high level of homogeneity. Adverse events leading to discontinuation recorded in the studies include persistent oral itching, lip and mouth swelling.

Multiallergen AIT induced notable immunological changes in polysensitized patients with AR. Studies by Amar and Gotoh both reported elevated levels of sIgE, whereas Gotoh's study also demonstrated this elevation in allergen-specific IgG₄ (sIgG₄). Additionally, Wang and Amar observed reductions in interleukin-4 (IL-4) and interferon- γ (IFN- γ) levels, suggesting enhanced immune tolerance and modulation of the type 2 immune response. Compared with single-allergen AIT, multiallergen approaches demonstrated comparable effects on IL-4 suppression and sIgE/sIgG₄ elevations. However, certain indicators like IFN- γ showed attenuated responses in multiallergen groups, potentially due to antigen competition.

Discussion

To our knowledge, this is the first and most comprehensive systematic review and meta-analysis summarizing the efficacy and safety of multiallergen AIT compared to single-allergen AIT. The results suggest that multiallergen AIT is effective in the treatment of polysensitized AR patients. There was no clear or definitive indication that the clinical efficacy of multiallergen AIT was superior to that of single-allergen AIT, although formulations of multiple allergens do not seem to cause more adverse events. This study covers different categories of allergen and routes of administration including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), though they were not analyzed separately due to the limited number of studies.

Numerous studies have examined the efficacy of single-allergen AIT in both mono- and polysensitized patients. Several cohort studies investigating the clinical effectiveness of short-term dust mite AIT found no significant difference between polysensitized and monosensitized patients.^{32,33} A post-hoc analysis of a clinical trial with grass pollen SLIT³⁴ separately analyzed monosensitized patients and pollen polysensitized patients. The results showed significant reductions in symptom and medication use, regardless of their sensitization profile. Similar results were reported by another post-hoc analysis by Malling et al³⁵ of a sublingual tablet containing 5 related grass pollens. An Italian team published consecutive trials with possibly overlapping patients that confirmed primarily single-allergen SLIT improved symptom and quality of life in polysensitized patients.^{36–39} However, the course of treatment was relatively short and the time of symptom evaluation was not clear enough to draw a conclusion whether AIT of a certain seasonal allergen could improve symptoms caused by allergens in different season or perennial allergens. A review on multiallergen AIT for patients with AR and asthma published by Nelson⁴⁰ identified 13 studies between 1961 and 2007 in which 2 or more unrelated allergens were simultaneously administered. Although results were not reported separately for single or multiple allergens in several studies, and the population was not clarified to be polysensitized patients, the findings of this review strongly suggest that the simultaneous delivery of multiple unrelated allergens can be clinically effective.

The selection of multiple allergens for AIT should be approached with caution. First of all, the clinically relevant allergens must be properly identified, defined as those with demonstrable sIgE positivity and clinical relevance. According to the US practice update,⁷ “inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective”. The premise of mixing multiple allergens is to ensure the effective

concentration of each allergen. Also, certain allergens containing cockroach or mold extracts have a risk of proteolytic degradation of other allergen extracts.^{41,42} Formulations containing cockroach or mold extracts should be administered separately. Appropriately chosen allergens, correct dosage, and pharmaceutical stability could be hard to achieve, potentially affecting the efficacy of multiallergen AIT.

Safety issues were raised by some case reports that prescribed AIT of multiple allergen extracts and led to severe adverse effects.^{43,44} Some of the included studies sought to determine whether multiallergen AIT increases the risk of adverse events.^{19–23,25,27} It turned out the majority of the studies observed no significant differences in safety profile between the groups, and our meta-analysis had the same conclusion with low heterogeneity. Available evidence suggests that appropriately administered AIT utilizing standardized extracts, when prescribed at clinically validated dosages and limited to an appropriate number of allergens, does not appear to elevate the incidence of adverse events in polysensitized patients compared to single-allergen protocols.

Whether the change of sIgE or sIgG₄ could be used as a biomarker of AIT has been controversial. Yang et al⁴⁵ conducted a case-control study and found the changes of sIgE, sIgG₄, sIgE/sIgG₄ ratio had no correlations with the improvement of combined symptom and medication score after AIT. While a subgroup of RCT showed evidence for coordinated sIgE and sIgG₄ responses in subjects benefiting the most from AIT.⁴⁶ However, there is evidence that polysensitized patients present distinct immune responses. Prigione et al⁴⁷ found that peripheral blood mononuclear cells from patients who remained mono-sensitized produced higher levels of IFN- γ than cells from patients who had become polysensitized. The different immune reactivity made it complicated to determine interpretation of the changed immunological parameters.

Integrating the findings from our meta-analysis and narrative synthesis, multiple studies comparing dual-allergen AIT with single-allergen AIT have demonstrated superior outcomes for the dual approach, potentially offering enhanced efficacy in polysensitized patients with AR while maintaining comparable safety profiles. Balancing the economic implications of incorporating additional allergens into AIT regimens, the current evidence leans toward recommending dual-allergen AIT using clinically relevant allergens for polysensitized individuals, as this strategy may optimize therapeutic benefits without substantial increases in risk or cost.

Given the limited number and variability of studies, the results of this meta-analysis should be interpreted with caution. The lack of standardization of study protocols concerning AIT poses a difficulty in forming high quality clinical trials and meta-analysis. Another limitation involves the potential dilution and degradation within mixed formulations. As studies rarely assessed the precise final active concentrations, the therapeutic efficacy of multiallergen formulations might have been underestimated. Additionally, publication bias may have been an issue, as negative results may not have been reported. The included studies exhibited a wide range of follow-up duration, introducing inherent clinical heterogeneity. This should be considered when interpreting our findings. Also, our findings regarding safety outcomes warrant careful consideration, as the inclusion of non-randomized cohort and case-control studies introduces inherent confounding bias.

Conclusion

In conclusion, findings from our systematic review demonstrate that multiallergen AIT exhibits no significant difference in therapeutic efficacy compared to single-allergen therapy in polysensitized patients with AR. Moreover, multiallergen AIT does not appear to increase the incidence of overall adverse events or treatment discontinuation due to side effects. However, significant heterogeneity across studies, particularly in administer routes, treatment protocols, and the format in which results are presented, calls for more robust clinical trials to further clarify the optimal approach for treating polysensitized patients with AIT.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

Ethical approval was not required for this systematic review and meta-analysis as it involved the synthesis of previously published data and did not include new data collection from human participants. This systematic review was registered on PROSPERO (ID: CRD42024567545).

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Disclosure

The authors declare no conflicts of interest in this work.

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