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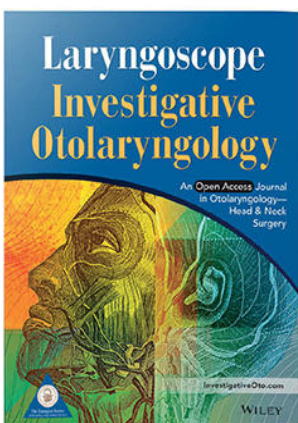


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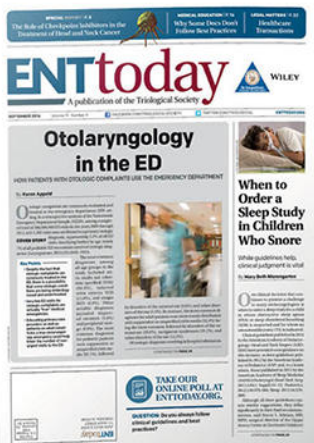


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Subcutaneous Versus Sublingual Immunotherapy for Adults with Allergic Rhinitis: A Systematic Review with Meta-Analyses

Kevin Tie, BS ; Craig Miller, MD; Adam M. Zanation, MD, FACS;
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Objectives: To determine whether subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) better improves patient outcomes and quality of life for adults with allergic rhinitis or rhinoconjunctivitis (AR/C) with or without mild to moderate asthma.

Methods: Systematic review methodology was based on the Cochrane Collaboration handbook and Preferred Reporting Items for Systematic Reviews and Meta-analyses. Four databases (PubMed, Cochrane Library, EMBASE, and Web of Science) were queried from inception to July 30, 2020. Two independent reviewers screened potentially relevant studies and assessed risk of bias. Outcomes of interest were symptom score (SS), medication score (MS), combined symptom medication score (CSMS), and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Meta-analyses with an adjusted indirect comparison were conducted in RevMan 5.4.1.

Results: Seven SCIT versus SLIT randomized controlled trials (RCTs) demonstrated no significant differences for any outcomes, but insufficient data precluded direct meta-analysis. For the adjusted indirect comparison, 46 RCTs over 39 studies were included for SCIT versus placebo ($n = 13$) and SLIT versus placebo ($n = 33$). Statistically significant results favoring SCIT were found for SS (standardized mean difference [SMD] = 0.40; 95% confidence interval [CI] = 0.31–0.49), MS (SMD = 0.26; 95% CI = 0.14–0.39), CSMS (SMD = 0.42; 95% CI = 0.17–0.67), and RQLQ (MD = 0.24; 95% CI = 0.04–0.44). Statistically significant results favoring SLIT were found for SS (SMD = 0.42; 95% CI = 0.32–0.53), MS (SMD = 0.40; 95% CI = 0.28–0.53), CSMS (SMD = 0.37; 95% CI = 0.29–0.45), and RQLQ (MD = 0.32; 95% CI = 0.20–0.43). No significant differences were found between SCIT and SLIT for SS (SMD = –0.02; 95% CI = –0.15 to 0.11), MS (SMD = –0.14; 95% CI = –0.31 to 0.03), CSMS (SMD = 0.05; 95% CI = –0.21 to 0.31), or RQLQ (MD = –0.08; 95% CI = –0.31 to 0.15).

Conclusion: SCIT and SLIT are comparably effective treatments for adults with AR/C. More RCTs analyzing SCIT versus SLIT are needed to directly compare the two.

Key Words: Subcutaneous immunotherapy, sublingual immunotherapy, allergy, allergic rhinitis, allergic rhinoconjunctivitis, patient outcomes, symptom score, medication score, combined symptom medication score, quality of life, Rhinoconjunctivitis Quality of Life Questionnaire, systematic review, meta-analysis, indirect comparison.

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INTRODUCTION

Allergic rhinitis (AR) is a disease characterized by episodes of sneezing, rhinorrhea, and nasal obstruction, which are often accompanied by symptoms such as itchy eyes, itchy nose, postnasal drip, cough, and fatigue.¹ Estimates of AR prevalence are as high as 42%, affecting approximately 58 million people in the United States.² AR also has a significant economic burden with both direct and indirect costs, including loss of work productivity and nearly twice as many average annual prescriptions for affected patients.^{3,4}

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The basic treatment of AR has traditionally been with pharmacotherapy.⁵ However, for patients with refractory symptoms who fail to respond significantly to pharmacotherapy, allergen immunotherapy (AIT) has emerged as an alternative treatment option.⁶ AIT may be administered as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT), both of which have demonstrated efficacy in randomized controlled trials (RCTs).^{7,8} Whereas the vast majority of RCTs have examined SCIT and SLIT separately, only a few RCTs have directly compared the two.^{9,10}

To our knowledge, no meta-analysis to date has analyzed SCIT versus SLIT for AR exclusively in the adult population. The most recent systematic review comparing SCIT versus SLIT across all age groups was performed in 2013, at which time only one RCT directly comparing SCIT versus SLIT was identified.¹¹ Since then, a number of new RCTs on this topic have been published, including several direct comparisons of SCIT versus SLIT.^{7–9,12}

When head-to-head trials of two interventions are lacking, indirect comparisons allow for analyses based on trials comparing each intervention separately.¹³ The objective of this study is to conduct a systematic review

and meta-analysis with an adjusted indirect comparison to answer the following question: Does SCIT or SLIT better improve patient outcomes and quality of life for adults with allergic rhinitis or rhinoconjunctivitis (AR/C) with or without mild to moderate asthma? The results of this paper will update the current literature and help guide immunotherapy treatment decisions for adults with AR.

MATERIALS AND METHODS

Systematic review methodology was based on the Cochrane Collaboration handbook and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).^{14,15}

Study Selection and Evaluation

Four databases (PubMed, Cochrane Library, EMBASE, and Web of Science) were queried from inception to July 30, 2020 for RCTs of SCIT versus placebo, SLIT versus placebo, or SCIT versus SLIT (fully reproducible search strategies can be found in Supporting Information, Table 1 in the online version of this article). Manual searches were performed for potentially relevant articles identified as references during the screening process. Two independent reviewers screened potentially relevant studies, first by title and abstract, and then by full text. Discrepancies were resolved via discussion or a third reviewer.

Eligible studies were RCTs that included only adults with AR/C with or without mild to moderate asthma. The intervention was SCIT compared against placebo, SLIT compared against placebo, or SCIT compared against SLIT. Outcomes of interest were symptom score (SS), medication score (MS), combined symptom medication score (CSMS), or Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score. Studies were excluded if they had pediatric (age < 18) data inseparable from adult data, lacked adequate outcome measures, or lacked adequate data to contribute to analyses involving means and SDs (e.g., a study that only reported median data).

Risk of bias was assessed with the revised Cochrane Risk of Bias 2 tool, which analyzes the following five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.¹⁶ Multiple signaling questions help classify each domain as either low risk of bias, some concerns for bias, or high risk of bias.

Outcome Measures

Symptoms scores were assessed for various domains (e.g., nasal symptoms, ocular symptoms, lung symptoms, other allergic symptoms) most commonly using a four-point severity scale from 0 to 3 for each domain, but some studies used other grading scales, such as a seven-point visual analog scale or a 12-point Lebel symptom score.^{17–19} Studies varied in the number and types of domains assessed and also reported findings differently. For example, some studies reported each domain separately,²⁰ whereas others reported a total symptom score (TSS) that was some combination of the individual domains. Studies also differed in the calculation of the TSS. For example, some studies reported the TSS as a sum of other domains,²¹ whereas others reported a mean of other domains.²²

Medication scores were primarily based on how often patients took certain medications during the course of the study. However, studies varied widely in their determination of MS. Although the World Allergy Organization recommends

calculating a rescue medication score by weighting each medication, weighting remains arbitrary as demonstrated by the wide range of scoring systems used across studies.²³ Some studies determined the MS as a cumulative score, whereas others used a graded scale. The MS scoring system of three different studies are mentioned to highlight this variability. One study calculated MS as the sum of the following drug score designations: 2 points for each cetirizine 10-mg tablet, 4.5 points for each prednisolone 5-mg tablet, and 1 point for each drop of levocabastine per eye.²⁰ Another study calculated MS as the sum of the following drug score designations: 1 point for each eye drop, puff of salbutamol or beclomethasone; 2 points for each cetirizine tablet; and 3 points for each betamethasone tablet.²⁴ Another study assigned a score from 0 to 3 as follows: 0 if no intake of rescue medication, 0.5 for at least one ocular anti-H1 antihistamine intake, 1 for at least one oral anti-H1 antihistamine, 2 for at least one nasal corticosteroid, and 3 for at least one systemic corticosteroid.²²

The CSMS was typically calculated as some combination of the SS and MS. Given the variability of SSs and MSs across studies as discussed above, the CSMSs are expected to inherently differ across studies. Furthermore, studies also calculated the CSMS differently. Some studies calculated the CSMS as the sum of the SS and MS,^{25,26} whereas other studies calculated it as a weighted average of the SS and MS.^{22,27}

The RQLQ is a validated questionnaire widely used to assess quality of life in patients with rhinoconjunctivitis.²⁸ It consists of 28 questions across 7 domains: nose symptoms, eye symptoms, non-nose/eye symptoms, activities limitation, sleep problems, practical problems, and emotional function. Each question is evaluated on a seven-point scale from 0 (not impaired at all) to 6 (severely impaired). The overall RQLQ score is the mean across all questions.

The minimal clinically important difference (MCID) may be defined as the smallest difference in the scores of a measure that is perceived by the patient to be beneficial or harmful.²⁹ Due to the variability in how the SS, MS, and CSMS are assessed and reported across studies, there is currently no consensus on the MCID for these outcome measures. On the other hand, the MCID for the standardized RQLQ has been shown to be approximately 0.5.³⁰ However, one must remember that the MCID represents a clinically relevant change in an outcome measure, implying a comparison between baseline and postintervention, rather than the difference between the intervention and placebo groups.³¹

Statistical Analyses

The following criteria were used to select data for analysis. The standardized mean difference (SMD) was used as the effect measure for SS, MS, and CSMS due to variability in how they were assessed and reported across studies. The mean difference (MD) was used as the effect measure for RQLQ because it is a standardized measure across studies. With regard to timing of data collection during the pollen season, primary endpoints were used. Multiple arms (e.g., different dosing regimens) within the same study were treated as separate data cohorts for inclusion. For studies with outcomes assessed at multiple time points, data were included from the farthest out (i.e., most recent) time point to avoid counting duplicate cohorts. Different articles across the same study investigating the same cohort (e.g., follow-up articles at multiple time points) were excluded as duplicates unless they reported unique outcome measures. Only postintervention data were included, whereas change-from-baseline data were excluded because the two should not be combined when the effect measure is an SMD.³²

We sought to conduct two main statistical analyses for each outcome measure:

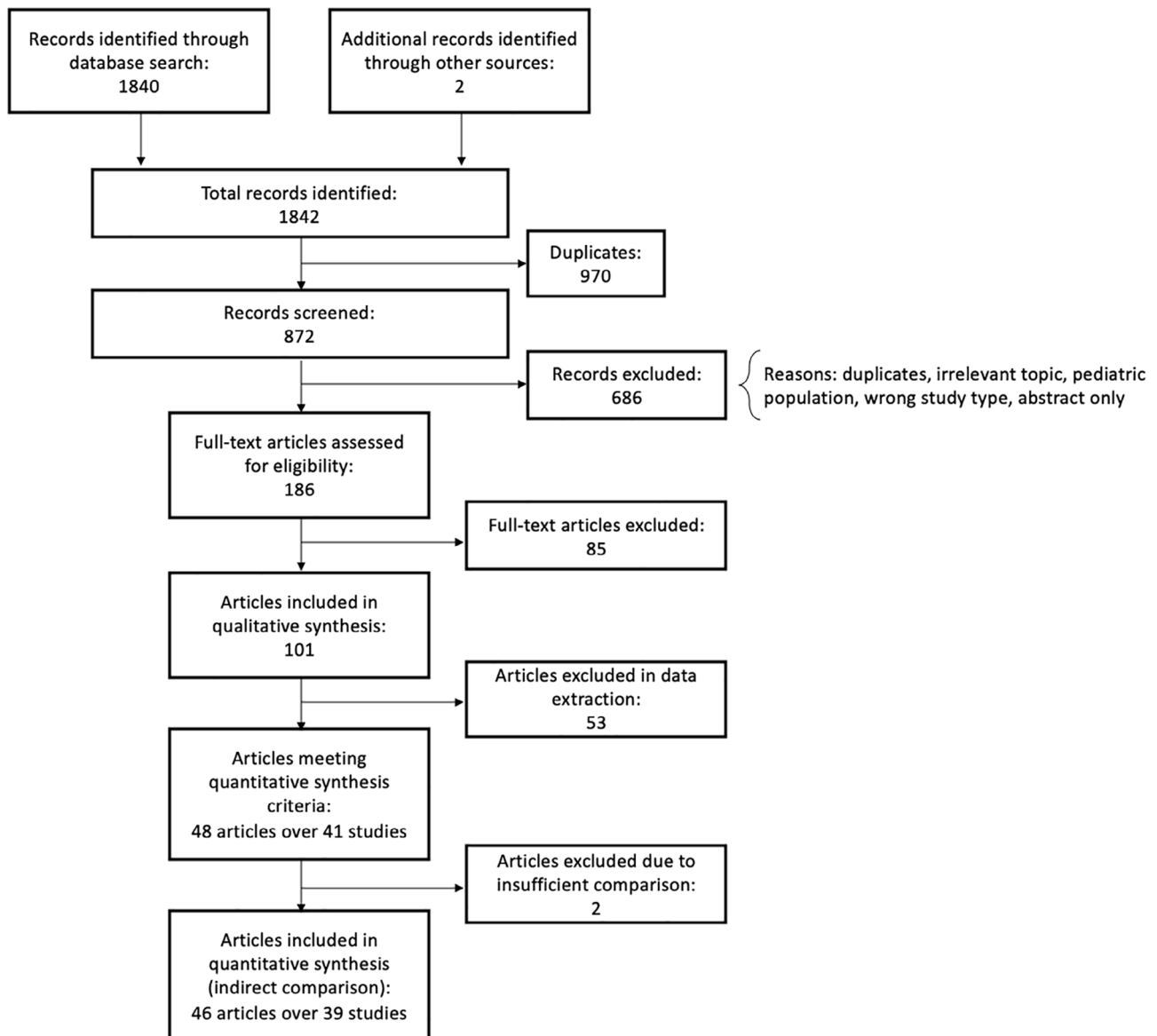


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram of the literature search study selection process.

1. A head-to-head comparison of SCIT versus SLIT (from RCTs directly comparing SCIT versus SLIT)
2. An adjusted indirect comparison (from RCTs comparing SCIT versus placebo against RCTs comparing SLIT versus placebo)

An adjusted indirect comparison estimates the effect of intervention B relative to that of intervention A (effect_{AB}) indirectly by subtracting the direct estimator for the effects of intervention C relative to intervention B (effect_{BC}) from the direct estimator for the effects of intervention C relative to that of intervention A (effect_{AC}).¹³ This may be represented by the following equation: $\text{effect}_{AB} = \text{effect}_{AC} - \text{effect}_{BC}$. The direct estimator effect_{AC} may be found by pooling results (i.e., conducting a meta-analysis) from a group of RCTs analyzing intervention A versus intervention C (effect_{BC} can be found similarly). In this study, intervention A may be represented by SCIT, intervention B by SLIT, and intervention C by placebo. The adjusted indirect comparisons for each outcome were obtained by subtracting the pooled effect size of all SLIT versus placebo

studies from the pooled effect size of all SCIT versus placebo studies. Positive values indicate that SCIT is favored over SLIT, whereas negative values indicate that SLIT is favored over SCIT.

Meta-analyses were conducted in RevMan 5.4.1 using a random-effects model based on the assumption that intervention effects vary across studies.^{33,34} Heterogeneity was assessed, and forest plots and risk of bias tables were generated.

RESULTS

Study Selection and Evaluation

The initial search queries across four databases found 1,840 articles. Two additional articles were later identified: one from a Cochrane trial, and one as a follow-up of another study. After duplicate removal, 872 articles were screened for title and abstract relevance, of which

TABLE I.
Risk of Bias Assessments for SCIT Versus Placebo.

Reference	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Bozek 2017 - SCIT	+	+	+	+	+	+
Charpin 2007	+	+	+	+	+	+
Drachenberg 2001	+	+	+	+	+	+
Frew 2006	+	+	+	+	+	+
Kleine-Tebbe 2014	+	+	+	+	+	+
Klimek 2014	+	+	+	+	+	+
Leynadier 2001	+	+	+	+	+	+
Mosges 2018	+	+	+	+	+	+
Patel 2014	+	+	+	+	+	+
Pfaar 2016 - SCIT	+	+	+	+	+	+
Shamji 2012	+	+	+	+	+	+
Worm 2019	+	+	+	+	+	+
Zielen 2019	+	+	+	+	+	+

Risk of bias assessment for randomized controlled trials comparing subcutaneous immunotherapy to placebo. Risk of bias was assessed using the revised Cochrane Risk of Bias 2 tool.

SCIT = subcutaneous immunotherapy; + = low risk; ? = some concerns; = high risk

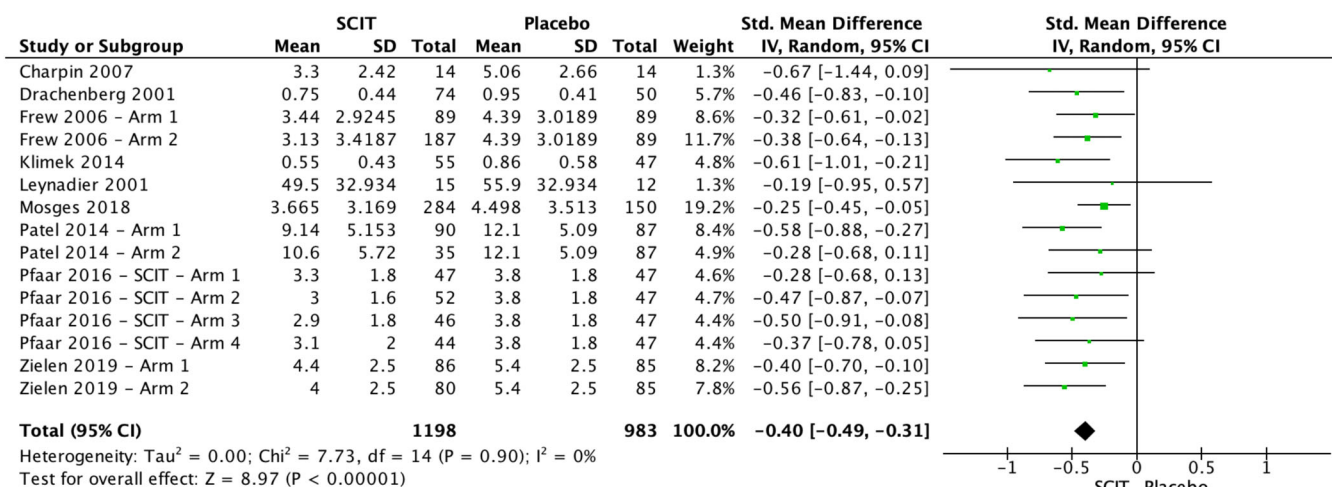
TABLE II.
Risk of Bias Assessments for SLIT Versus Placebo.

Reference	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Amar 2009	+	+	+	+	+	+
Ariano 2005	+	+	+	?	+	!
Bergmann 2014	+	+	+	+	+	+
Bozek 2013	+	+	+	+	+	+
Bozek 2014	+	+	+	+	+	+
Bozek 2017 - SLIT	+	+	+	?	+	!
Bozek 2018	+	+	+	?	+	!
Couroux 2019	+	+	+	+	+	+
Cox 2012	+	+	+	+	+	+
Creticos 2013	+	+	+	+	+	+
Creticos 2014	+	+	+	+	+	+
Dahl 2006 - 1	+	+	+	+	+	+
Dahl 2006 - 2	+	+	+	+	+	+
Demoly 2016	+	+	+	+	+	+
Didier 2009	+	+	+	+	+	+
Didier 2011	+	+	+	+	+	+
Didier 2013	+	+	+	+	+	+
Didier 2015	+	+	+	+	+	+
DiRienzo 2006	+	+	+	+	+	+
Durham 2006	+	+	+	+	+	+
Durham 2010	+	+	+	+	+	+
Durham 2012	+	+	+	+	+	+
Ellis 2018	+	+	+	+	+	+
Horak 2009	+	+	+	+	+	+
Marogna 2013	+	+	+	?	+	!
Murphy 2013	+	+	+	+	+	+
Nelson 2011	+	+	+	+	+	+
Nolte 2013	+	+	+	+	+	+
Pfaar 2016 - SLIT	+	+	+	+	+	+
Pfaar 2019	+	+	+	+	+	+
Quercia 2011	+	+	+	?	+	!
Skoner 2010	+	+	+	+	+	+
Worm 2014	+	+	+	+	+	+

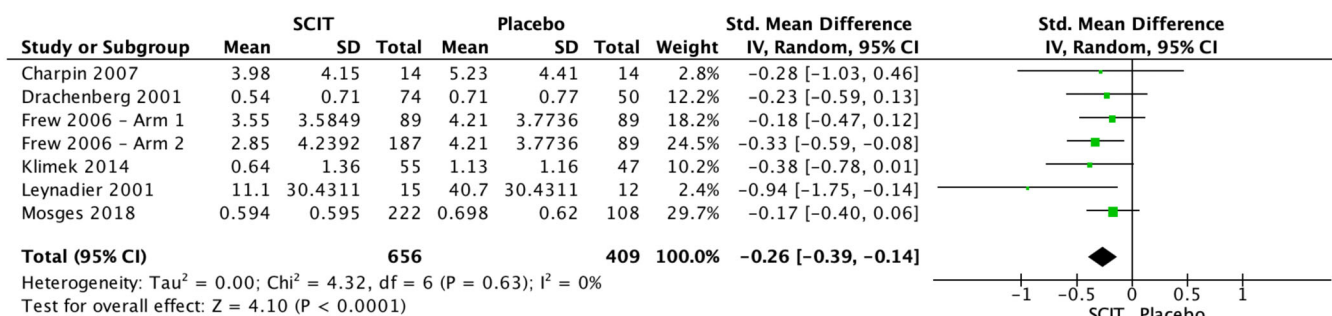
Risk of bias assessment for randomized controlled trials comparing sublingual immunotherapy to placebo. Risk of bias was assessed using the revised Cochrane Risk of Bias 2 tool.

SLIT = sublingual immunotherapy; + = low risk; ? = some concerns; = high risk

A Symptom Score



B Medication Score



C Combined Symptom Medication Score

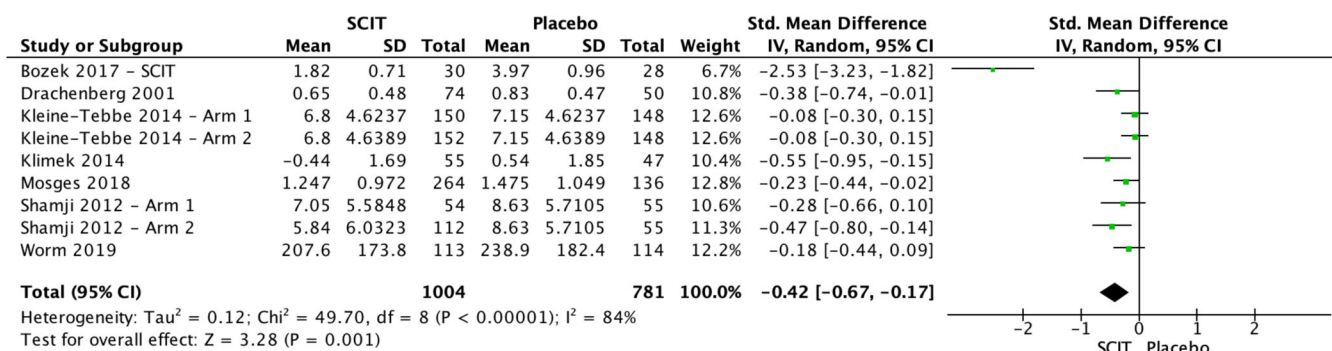


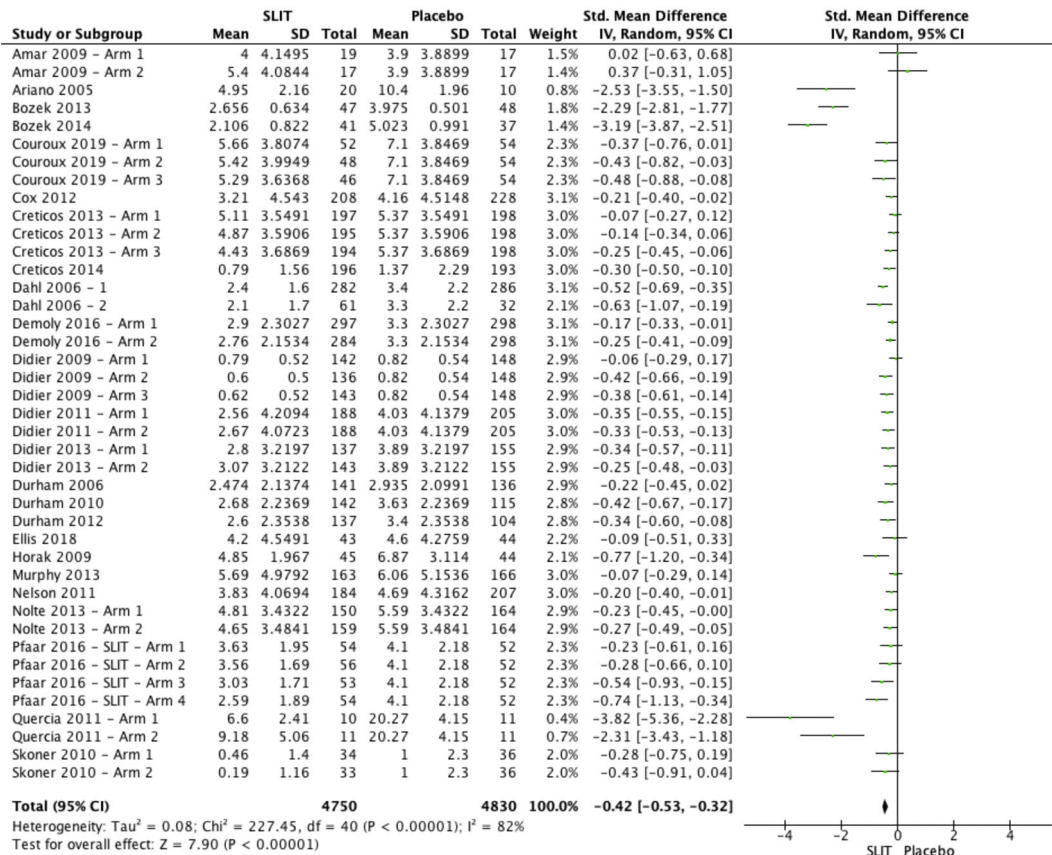
Fig. 2. Forest plots for randomized controlled trials comparing subcutaneous immunotherapy to placebo for symptom score (A), medication score (B), and combined symptom medication score (C). The standardized mean difference (SMD) is reported for symptom score, medication score, and combined symptom medication score. The overall SMD is represented by the black diamond. Heterogeneity and statistical significance are displayed at the bottom. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

186 full-text articles were assessed for eligibility. A total of 101 articles met qualitative synthesis criteria, of which 48 articles over 41 studies met quantitative synthesis criteria. However, the two head-to-head SCIT versus SLIT RCTs reported different outcome measures and were thus excluded from analysis.^{12,35} Ultimately, 46 RCTs over 39 studies were included for the adjusted indirect comparisons, of which 13 RCTs analyzed SCIT

versus placebo,^{19–21,24,36–44} and 33 RCTs analyzed SLIT versus placebo (see Fig. 1 and Supporting Information, Figure 1, in the online version of this article for more details).^{17,22,25–27,45–72}

The 46 RCTs were published between 2001 and 2019 and included single-center and multicenter studies that collected data from sites in Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Finland,

A Symptom Score



B Medication Score

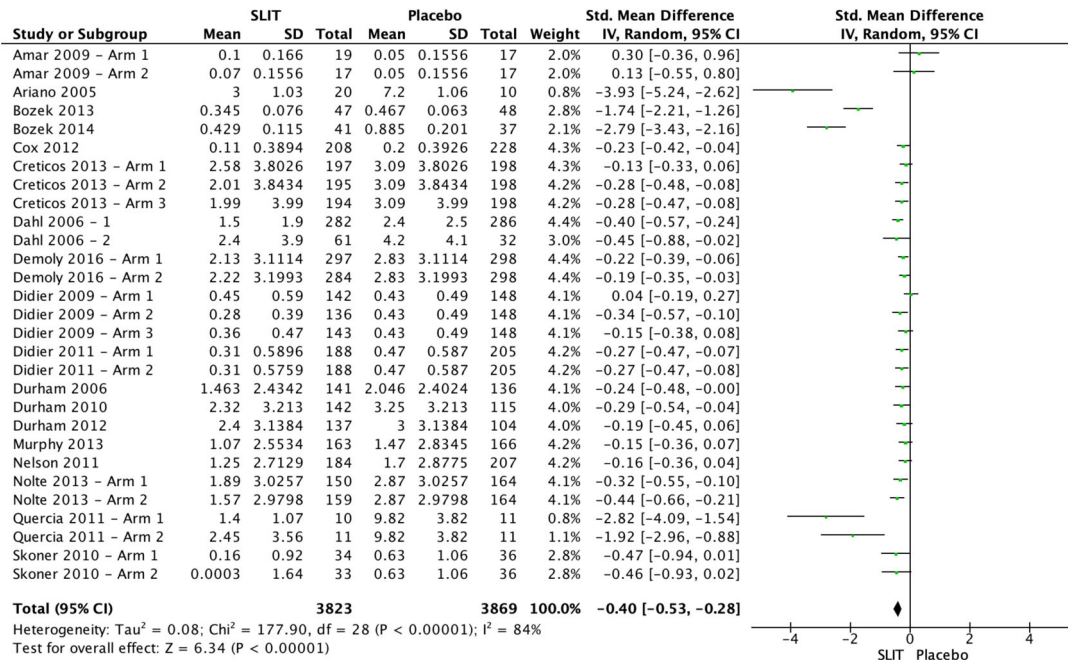
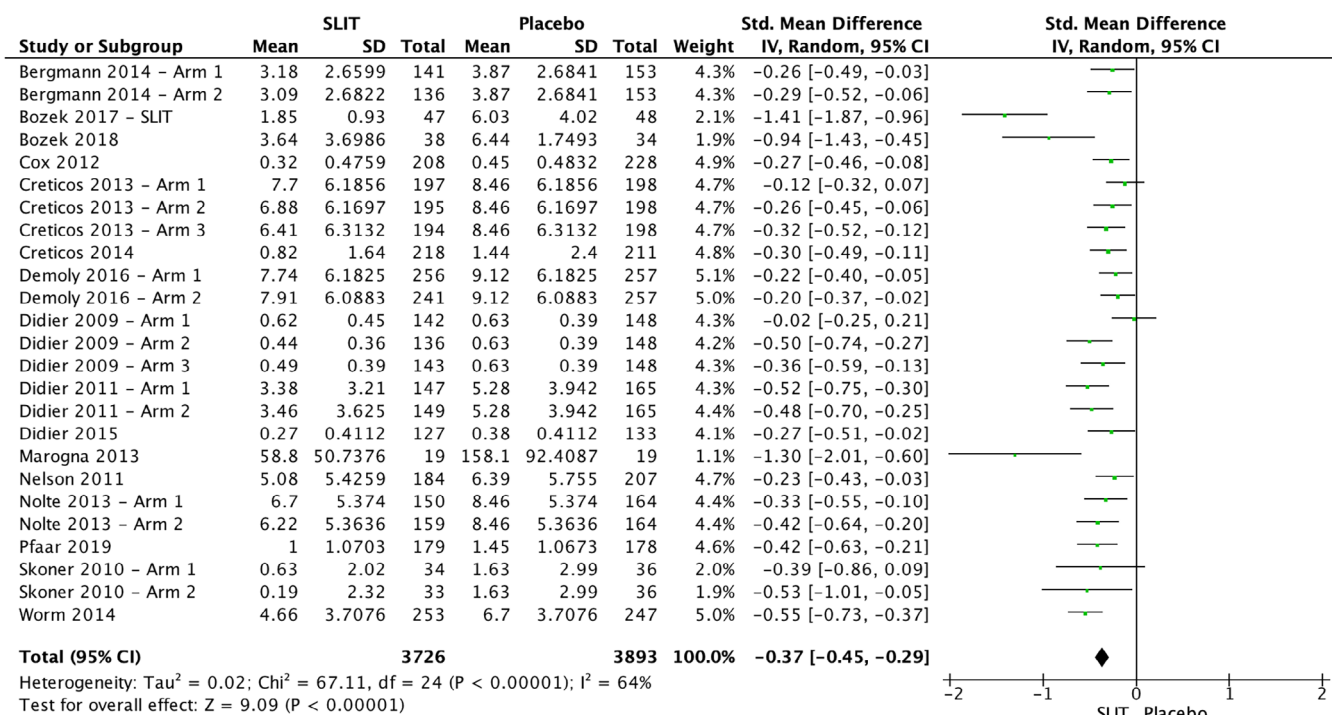


Fig. 3. Forest plots for randomized controlled trials comparing sublingual immunotherapy to placebo for symptom score (A), medication score (B), combined symptom medication score (C), and Rhinoconjunctivitis Quality of Life Questionnaire (D). The standardized mean difference (SMD) is reported for symptom score, medication score, and combined symptom medication score, whereas the mean difference (MD) is reported for RQLQ. The overall SMD or MD is represented by the black diamond. Heterogeneity and statistical significance are displayed at the bottom. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

C Combined Symptom Medication Score



D Rhinoconjunctivitis Quality of Life Questionnaire

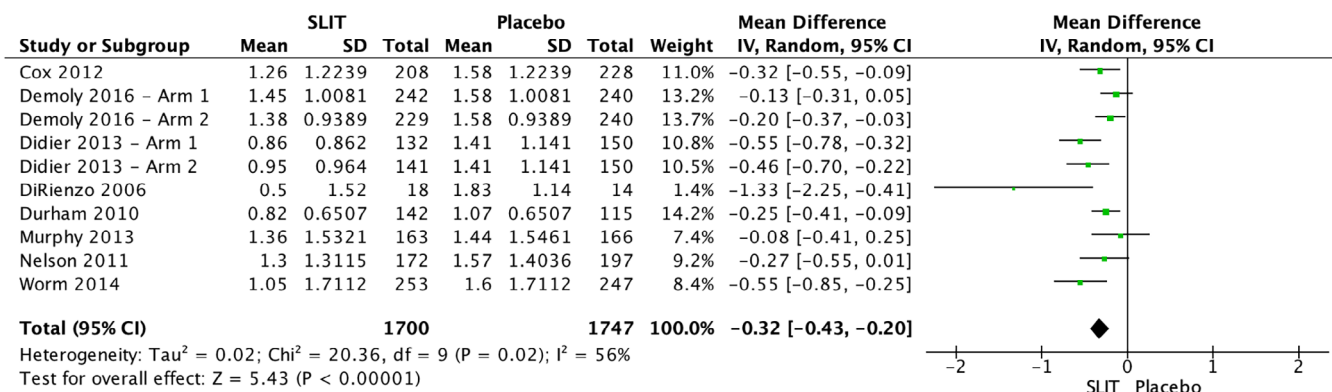


Fig. 3. (Continued) [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Russia, Slovakia, Spain, Sweden, Ukraine, United Kingdom, and United States. The most commonly documented allergens included birch, grass pollen, house dust mites, and ragweed pollen. Details of the study characteristics may be found in Supporting Information, Table 2 in the online version of this article.

Risk of bias was low for all SCIT versus placebo RCTs in all five domains. Risk of bias was low for all SLIT versus placebo RCTs in all five domains except five RCTs that had some concern for bias in the outcome measurement domain. There was no high risk of overall bias for any RCT that would have precluded it from analysis (Tables I and II).

Meta-Analysis Head-to-Head Comparison: SCIT Versus SLIT

A total of seven head-to-head SCIT versus SLIT RCTs met qualitative synthesis criteria,^{9,10,12,35,73-75} five of which were excluded due to inadequate data (either missing [e.g., only reported change-from-baseline data without postintervention data] or reported medians). The remaining two reported different outcome measures, so there were not enough studies to carry out a direct head-to-head comparison meta-analysis for any outcome measure.^{12,35} None of the seven studies reported significant differences between SCIT and SLIT for any of their measured outcomes.

Adjusted Indirect Comparison: Pooled SCIT Versus Placebo

The following SMDs and MDs are reported as absolute values (positive favors SCIT) along with their associated CIs. Statistically significant results favoring SCIT were found for SS (SMD: 0.40; 95% CI: 0.31–0.49; 15 arms across 9 studies; SCIT n = 1,198, placebo n = 983), MS (SMD: 0.26; 95% CI: 0.14–0.39; 7 arms across 6 studies; SCIT n = 656, placebo n = 409), CSMS (SMD: 0.42; 95% CI: 0.17–0.67; 9 arms across 7 studies; SCIT n = 1,004, placebo n = 781), and RQLQ (MD: 0.24; 95% CI: 0.04–0.44; 1 arm across 1 study; SCIT n = 332, placebo n = 170). Heterogeneity among studies varied for SS, MS, and CSMS (Fig. 2). Because there was only one arm from one study for the RQLQ, no meta-analysis was performed, so heterogeneity is not applicable.

Adjusted Indirect Comparison: Pooled SLIT Versus Placebo

The following SMDs and MDs are reported as absolute values (positive favors SLIT) along with their associated CIs. Statistically significant results favoring SLIT were found for SS (SMD: 0.42; 95% CI: 0.32–0.53; 41 arms across 25 studies; SLIT n = 4,750, placebo n = 4,830), MS (SMD: 0.40; 95% CI: 0.28–0.53; 29 arms across 19 studies; SLIT n = 3,823, placebo n = 3,869), CSMS (SMD: 0.37; 95% CI: 0.29–0.45; 25 arms across 16 studies; SLIT n = 3,726, placebo n = 3,893), and RQLQ (MD: 0.32; 95% CI: 0.20–0.43; 10 arms across 8 studies; SLIT n = 1,700, placebo n = 1,747). There was significant heterogeneity among studies for SS, MS, CSMS, and RQLQ (Fig. 3).

Adjusted Indirect Comparison: Pooled SCIT Versus Placebo Against Pooled SLIT Versus Placebo

In the following reported SMDs and MDs, positive values favor SCIT, whereas negative values favor SLIT. Upon comparing pooled data, no significant differences were found between SCIT and SLIT for SS (SMD: –0.02; 95% CI: –0.15 to 0.11), MS (SMD: –0.14; 95% CI: –0.31 to 0.03), CSMS (SMD: 0.05; 95% CI: –0.21 to 0.31), or RQLQ (MD: –0.08; 95% CI: –0.31 to 0.15; see Table III).

TABLE III.
Adjusted Indirect Comparison – Subcutaneous Versus Sublingual Immunotherapy.

	SMD* (95% CI)	P value
SS	–0.02 (–0.15, 0.11)	.77
MS	–0.14 (–0.31, 0.03)	.11
CSMS	0.05 (–0.21, 0.31)	.71
RQLQ	–0.08 (–0.31, 0.15)	.50

*Positive favors SCIT; negative favors SLIT. Standardized mean difference reported for SS, MS, and CSMS; mean difference reported for RQLQ.

CI = confidence interval; CSMS = combined symptom medication score; MS = medication score; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; SMD = standardized mean difference; SS = symptom score.

Adverse Events

Adverse events (AEs) were reported in 11 of the 13 SCIT versus placebo RCTs and 29 of the 33 SLIT versus placebo RCTs. The vast majority of AEs from SCIT were injection site reactions (e.g., pruritus, swelling, edema, erythema, and wheal formation), whereas less common AEs included headaches, fatigue, nasopharyngitis, and tonsillitis. One study reported mild systemic anaphylactic reaction.³⁶ The majority of AEs from SLIT were local reactions (e.g., oral pruritus, oral swelling, mouth edema, facial flushing, throat irritation, and lip paresthesia), whereas less common AEs included headaches, fatigue, nasopharyngitis, pyrexia, angioedema, generalized pruritus, and abdominal cramps.

DISCUSSION

The objective of this study was to conduct a systematic review and meta-analysis with an adjusted indirect comparison to answer the following question: Does SCIT or SLIT better improve patient outcomes and quality of life for adults with AR/C with or without mild to moderate asthma? Although the literature lacked enough RCTs of SCIT versus SLIT to conduct a direct meta-analysis, the results of the adjusted indirect comparison revealed that treatment with either SCIT or SLIT results in comparable patient outcomes.

In recent years, AIT, which may be administered as SCIT or SLIT, has emerged as an alternative treatment option for patients with AR who fail to respond significantly to pharmacotherapy.⁶ Although both SCIT and SLIT have demonstrated efficacy in RCTs, few trials have directly compared the two. To our knowledge, no meta-analysis to date has analyzed SCIT versus SLIT for AR exclusively in the adult population. This study presents a comprehensive systematic review with an adjusted indirect comparison based on meta-analyses to determine whether SCIT or SLIT better improves patient outcomes and quality of life for adults with AR/C with or without mild to moderate asthma.

The first objective to carry out a head-to-head comparison of SCIT versus SLIT was hindered by a paucity of RCTs directly comparing the two that met quantitative inclusion criteria. However, none of the SCIT versus SLIT trials included for qualitative analysis demonstrated a statistically significant difference between the two for any of the outcome measures (SS, MS, CSMS, and RQLQ). Only two new RCTs comparing SCIT versus SLIT were identified since the most recent systematic review across all age groups was conducted in 2013.^{9,11,12}

For the adjusted indirect comparison, a total of 46 RCTs over 39 studies were included for SCIT versus placebo (n = 13) and SLIT versus placebo (n = 33). Meta-analyses pooling the results of SCIT versus placebo found statistically significant results favoring SCIT for all outcome measures (SS, MS, CSMS, and RQLQ). Similarly, meta-analyses pooling the results of SLIT versus placebo found statistically significant results favoring SLIT for all outcome measures. However, the adjusted indirect comparison of SCIT versus SLIT obtained by comparing the

pooled data revealed no statistically significant differences between SCIT and SLIT for any outcome measure. There was significant heterogeneity among SLIT versus placebo trials for all outcome measures, whereas heterogeneity for SCIT versus placebo trials varied.

The results of the adjusted indirect comparison suggest that treatment with either SCIT or SLIT results in comparable patient outcomes. This finding is supported by the seven RCTs directly comparing SCIT versus SLIT. Given their similar clinical efficacies, the decision for choosing between SCIT and SLIT may be guided by other considerations, such as availability, cost, and patient preference.

Although the strengths of this study include its comprehensive search strategy, detailed article screening process, methodical data extraction algorithm, and robust data analysis exclusively involving RCTs, there are some limitations. The variability in outcome measures across studies necessitates the use of SMD as the effect measure, which is difficult to clinically interpret. Although the MCID for RQLQ is well accepted, there is currently no consensus on the MCID for SS, MS, and CSMS due to the variability in how these outcomes are measured, limiting clinical interpretation of the results. The results of our study are generalizable only to adults with AR/C with or without mild to moderate asthma. These findings may not be generalizable to pediatric patients or patients with severe asthma or other allergic conditions. Furthermore, the lack of head-to-head RCTs comparing SCIT versus SLIT precluded the possibility of carrying out a direct meta-analysis. More future head-on RCTs analyzing SCIT versus SLIT are needed to directly compare the two.

CONCLUSION

Both SCIT and SLIT are effective treatment options for adults with pharmacotherapy-refractory AR/C with or without mild to moderate asthma. Based on results from an adjusted indirect comparison, treatment with either SCIT or SLIT results in comparable patient outcomes, so the decision for choosing between the two may be guided by other considerations, such as availability, cost, and patient preference. More future head-on RCTs analyzing SCIT versus SLIT are needed to directly compare the two.

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eTable 1. Database Search Strategy

Database	Search Query for RCTs	Search Query for Cohort Studies
PubMed	• (allerg* OR seasonal allerg* OR hypersensitiv* OR "hay fever" OR pollen allerg* OR pollinos* OR rhinitis OR rhinoconjunctivitis OR "Rhinitis, Allergic, Seasonal"[Mesh] OR Hypersensitivity[Mesh]) • AND • (sublingual immunotherap* OR SLIT OR subcutaneous immunotherap* OR SCIT OR "Sublingual Immunotherapy"[Mesh]) • AND • ("quality of life" OR QOL OR HRQOL OR "life quality" OR patient reported outcome* OR "patient satisfaction" OR symptom scor* OR medication scor* OR "Quality of Life"[Mesh] OR "Patient Reported Outcome Measures"[Mesh] OR "Patient Satisfaction"[Mesh]) • AND • (randomized controlled trial[Publication Type] OR (random*[TIAB] AND control*[TIAB] AND (trial[TIAB] OR study[TIAB])) OR (random*[TIAB] AND (allocat*[TIAB] OR assign*[TIAB])) OR ((single[TIAB] OR double[TIAB] OR triple[TIAB]) AND blind*[TIAB]))	• (allerg* OR seasonal allerg* OR hypersensitiv* OR "hay fever" OR pollen allerg* OR pollinos* OR rhinitis OR rhinoconjunctivitis OR "Rhinitis, Allergic, Seasonal"[Mesh] OR Hypersensitivity[Mesh]) • AND • (sublingual immunotherap* OR SLIT OR subcutaneous immunotherap* OR SCIT OR "Sublingual Immunotherapy"[Mesh]) • AND • ("quality of life" OR QOL OR HRQOL OR "life quality" OR patient reported outcome* OR "patient satisfaction" OR symptom scor* OR medication scor* OR "Quality of Life"[Mesh] OR "Patient Reported Outcome Measures"[Mesh] OR "Patient Satisfaction"[Mesh]) • AND • (cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR (relative[TIAB] AND risk*[TIAB]) OR (relative risk[Text Word]) OR risks[Text Word])
Cochrane Library	• (allerg* OR seasonal NEXT allerg* OR hypersensitiv* OR "hay fever" OR pollen NEXT allerg* OR pollinos* OR rhinitis OR rhinoconjunctivitis) • OR [mh "Rhinitis "] OR [mh Hypersensitivity] • AND • (sublingual NEXT immunotherap* OR SLIT OR subcutaneous NEXT immunotherap* OR SCIT • OR [mh "Sublingual Immunotherapy"]) • AND • ("quality of life" OR QOL OR HRQOL OR "life quality" OR patient NEXT reported NEXT outcome* OR "patient satisfaction" OR symptom NEXT scor* OR medication NEXT scor*) • OR [mh "Quality of Life"] OR [mh "Patient Reported Outcome Measures"] OR [mh "Patient Satisfaction"])	
EMBASE	• (allerg* OR "seasonal allerg*" OR hypersensitiv* OR 'hay fever'/exp OR "pollen allerg*" OR pollinos* OR 'rhinitis'/exp OR 'rhinoconjunctivitis'/exp OR 'hypersensitivity'/exp) • AND • ("sublingual immunotherap*" OR SLIT OR "subcutaneous immunotherap*" OR SCIT OR 'sublingual	• (allerg* OR "seasonal allerg*" OR hypersensitiv* OR 'hay fever'/exp OR "pollen allerg*" OR pollinos* OR 'rhinitis'/exp OR 'rhinoconjunctivitis'/exp OR 'hypersensitivity'/exp) • AND • ("sublingual immunotherap*" OR SLIT OR "subcutaneous immunotherap*" OR SCIT OR 'sublingual immunotherapy'/exp OR 'subcutaneous immunotherapy'/exp)

Database	Search Query for RCTs	Search Query for Cohort Studies
	immunotherapy'/exp OR 'subcutaneous immunotherapy'/exp) • AND • ("quality of life" OR QOL OR HRQOL OR "life quality" OR "patient reported outcome*" OR "patient satisfaction" OR "symptom scor*" OR "medication scor*" OR 'Quality of Life'/exp OR 'Patient Reported Outcome Measures'/exp OR 'Patient Satisfaction'/exp) • AND • [randomized controlled trial]/lim	• AND • ("quality of life" OR QOL OR HRQOL OR "life quality" OR "patient reported outcome*" OR "patient satisfaction" OR "symptom scor*" OR "medication scor*" OR 'Quality of Life'/exp OR 'Patient Reported Outcome Measures'/exp OR 'Patient Satisfaction'/exp) • AND • ('cohort studies'/de OR 'longitudinal studies'/de OR 'follow-up studies'/de OR 'prospective studies'/de OR 'retrospective studies'/de OR cohort:ti,ab OR longitudinal:ti,ab OR prospective:ti,ab OR retrospective:ti,ab OR (relative:ti,ab AND risk*:ti,ab))
Web of Science	• TS = ((allerg* OR "seasonal allerg*" OR hypersensitiv* OR "hay fever" OR "pollen allerg*" OR pollinos* OR rhinitis OR rhinoconjunctivitis) • AND • ("sublingual immunotherap*" OR SLIT OR "subcutaneous immunotherap*" OR SCIT) • AND • ("quality of life" OR QOL OR HRQOL OR "life quality" OR "patient reported outcome*" OR "patient satisfaction" OR "symptom scor*" OR "medication scor*")) • AND • (• TS = ((random* AND control* AND (trial OR study)) OR (random* AND (allocat* OR assign*)) OR ((single OR double OR triple) AND blind*)) • OR • TI = ((random* AND control* AND (trial OR study)) OR (random* AND (allocat* OR assign*)) OR ((single OR double OR triple) AND blind*)) • OR • AB = ((random* AND control* AND (trial OR study)) OR (random* AND (allocat* OR assign*)) OR ((single OR double OR triple) AND blind*)) •)	• TS = ((allerg* OR "seasonal allerg*" OR hypersensitiv* OR "hay fever" OR "pollen allerg*" OR pollinos* OR rhinitis OR rhinoconjunctivitis) • AND • ("sublingual immunotherap*" OR SLIT OR "subcutaneous immunotherap*" OR SCIT) • AND • ("quality of life" OR QOL OR HRQOL OR "life quality" OR "patient reported outcome*" OR "patient satisfaction" OR "symptom scor*" OR "medication scor*")) • AND • (• TS = ("cohort stud*" OR "longitudinal stud*" OR "follow-up stud*" OR "prospective stud*" OR "retrospective stud*" OR "relative risk*") • OR • TI = (cohort OR longitudinal OR prospective OR retrospective OR "relative risk*") • OR • AB = (cohort OR longitudinal OR prospective OR retrospective OR "relative risk*") •)

All searches were carried out from database inception to July 30, 2020.

RCT = randomized controlled trial

eTable 2. Study Characteristics

Study Type	Study	Country	Number of Patients	Female %	Age, mean ± SD (range) ^a	Asthma %	Treatment Allergen	Tx Arms	Treatment Regimen	Evaluation Period	Outcome Measures Included (Specific Measure) ^b
SCIT vs. P	Bozek 2017 – SCIT	Poland	T: 30 P: 28	T: 60 P: 60.7	T: 68.1 ± 5.9 P: 69.2 ± 6.3	0	Purethal Mites	1	D: 20000 AUeq/mL I: 0.1 mL, 0.2 mL, 0.5 mL every week M: 0.5 mL q4w for 24 months	24 months	CSMS (AAdSS)
	Charpin 2007	France	T: 17 P: 15	T: 70.6 P: 46.7	T: 39 (24-52) P: 44 (29-66)	T: 35.3 P: 26.7	Juniperus ashei extract	1	D: 100-IR (54 µg/mL) I: 0.1, 1, 10, 100 IR/mL injections twice weekly over 1-2 months M: 0.30 mL (16.2 µg) monthly for 18 months	18 months	SS (rhinitis TSS), MS (TMS)
	Drachenberg 2001	Austria, Germany	T: 74 P: 50	T: 45.9 P: 46	T: 29.6 ± 8.4 (19-54) P: 27.4 ± 7.8 (18-56)	NR	Mixture of pollen from 12 temperate zone grasses and S. cereale (cultivated rye)	1	2000 SU = 24 µg First 2 injections (1.0 mL) 1 week apart: 300 SU/mL, 800 SU/mL Inj 3 (1.0 mL) 1-4 weeks later: 2000 SU/mL Inj 4 (1.0 mL) 2-4 weeks before start of GPS: 2000 SU/mL CD: 60 µg	9-14 weeks (GPS)	SS (TSS), MS, CSMS
	Frew 2006 ¹	UK	A1: 104 A2: 203 P: 103	A1: 43.3 A2: 45.8 P: 39.8	A1: 36.9 ± 9.0 (19.7-58.2) A2: 38.3 ± 9.1 (18.4-59.7) P: 37.9 ± 9.1 (18.9-59.2)	NR	Grass pollen extract	2	10000 SQ-U = 2 µg A1: 10000 SQ-U A2: 100000 SQ-U I: 15 injections over 8 weeks M: q6±2w until GPS	6-8 months (GPS)	SS, MS
	Kleine-Tebbe 2014	Austria, Germany, Spain	A1: 150 A2: 152 P: 148	51	33 (18-64)	33	Timothy grass (Phleum pratense)	2	A1: 4000 SQ+ A2: 15000 SQ+ I: 5 weekly injections M: 2 weeks later, 4 weeks later, then 9 more injections q6w	64 weeks	CSMS
	Klimek 2014	Germany	T: 55 P: 47	T: 56.4 P: 44.7	T: 37.1 ± 10.4 (18.1-65.4) P: 36.2 ± 10.7 (19.5-69.5)	T: 14.6 P: 6.4	Mixture of 6 grasses and rye pollen	1	D: 10000 TU/mL I: Day 1: 0.1 mL + 0.2 mL; 1 week later: 0.3 mL + 0.5 mL M: 0.5 mL q4w for 1 year	1 year (PPS)	SS (RTSS), MS (TRMS), CSMS
	Leynadier 2001	France	T: 16 P: 13	T: 56.3 P: 46.2	T: 29 (18-44) P: 31 (20-42)	NR	5-grass pollen extract	1	I: 16 injections weekly M: once a month during pollen season (3 months) CD: 220.4 ± 90 IR	29 weeks	SS (RTSS), MS
	Mosges 2018	Belgium, Czech Republic, Germany, France, Italy, Spain	T: 372 P: 182	T: 48.4 P: 42.3	T: 33.6 ± 11.1 P: 34.1 ± 11.6 (18-64)	T: 25.5 P: 21.4	Lolium perenne pollen	1	8 injections at 4 visits over 3 consecutive weeks	PPS	SS (RTSS), MS,

Study Type	Study	Country	Number of Patients	Female %	Age, mean $\pm$ SD (range) ^a	Asthma %	Treatment Allergen	Tx Arms	Treatment Regimen	Evaluation Period	Outcome Measures Included (Specific Measure) ^b
									1: 2x5 μ g; 2: 2x10 μ g; 3: 2x20 μ g; 4: 2x50 μ g CD: 170 μ g		CSMS, RQLQ
	Patel 2014	Canada	A1: 95 A2: 40 P: 93	A1: 52.6 A2: 52.5 P: 58.1	A1: 39 $\pm$ 10.4 A2: 37 $\pm$ 10.2 P: 37 $\pm$ 12.7 (18-65)	NR	Ragweed MATA (short ragweed pollen)	2	A1: Ragweed MATA MPL A2: Ragweed MATA injection 4 weekly 0.5 mL injections (300, 700, 2000, 6000 SU) over 3 weeks	6 weeks	SS (TSS)
	Pfaar 2016 – SCIT	Germany, Austria, Netherlands, Belgium, Spain	A1: 57 A2: 59 A3: 59 A4: 59 P: 56	A1: 52.6 A2: 42.4 A3: 50.8 A4: 59.3 P: 50	A1: 31.6 $\pm$ 9.2 (18-56) A2: 32.1 $\pm$ 10.4 (18-59) A3: 29.4 $\pm$ 8.9 (18-52) A4: 30.5 $\pm$ 10.3 (18-56) P: 30.2 $\pm$ 10.1 (18-58)	NR	HDM mixture of Der p and Der f (1:1)	4	A1: 6667 AUeq/mL A2: 20000 AUeq/mL A3: 50000 AUeq/mL A4: 100000 AUeq/mL I: 6 weekly injections (0.05, 0.1, 0.2, 0.3, 0.4, 0.5 mL) M: 0.5 mL monthly until 12 months	12 months	SS (Lebel symptom score after TNPT)
	Shamji 2012 ¹	UK	A1: 104 A2: 203 P: 103	A1: 43.3 A2: 45.8 P: 39.8	A1: 36.9 $\pm$ 9.0 (19.7-58.2) A2: 38.3 $\pm$ 9.1 (18.4-59.7) P: 37.9 $\pm$ 9.1 (18.9-59.2)	NR	Grass pollen extract	2	10000 SQ-U = 2 μ g A1: 10000 SQ-U A2: 100000 SQ-U I: 15 injections over 8 weeks M: q6 $\pm$ 2w until GPS	6-8 months (GPS)	CSMS
	Worm 2019	Sweden, Finland, Germany, Poland	T: 122 P: 127	T: 56.6 P: 47.2	T: 37.6 $\pm$ 12.2 P: 35.5 $\pm$ 11.2 (18-59)	T: 27.0 P: 22.8	Birch pollen	1	I: weekly injections 0.1, 0.2, 0.4, 0.8 mL (1000 TU/mL) $\rightarrow$ 0.15, 0.3, 0.6 mL (10000 TU/mL) M: individual max dose; q1w $\rightarrow$ q2w $\rightarrow$ q4w Treatments started in October and continued until 2 weeks before birch pollen season of next year (for 2 years)	2 years	CSMS
	Zielen 2019	Austria, Germany, Poland	A1: 86 A2: 80 P: 85	A1: 50 A2: 46.3 P: 45.9	A1: 29.6 $\pm$ 8.5 A2: 30.0 $\pm$ 8.1 P: 31.6 $\pm$ 9.3 (18-50)	A1: 20.9 A2: 21.3 P: 16.5	PQ Grass (mixture of 13 grass species)	2 (Data absent for 2 of 4 arms)	A1: CD 5100 SU A2: CD 35600 SU Weekly intervals of six 1.0 mL injections (over 31-41 days) Concentrations: 300, 800, 900, 2000, 2700, 6000, 8000 SU/mL	10 weeks	SS (TSS)
SLIT vs. Placebo	Amar 2009	USA	A1: 19 A2: 17 P: 17	A1: 73.7 A2: 58.8 P: 52.9	A1: 39.3 A2: 35.6 P: 38.8 (18-70)	A1: 15.8 A2: 11.8 P: 0	A1: Timothy grass A2: Timothy grass + 9 other extracts	2	D: daily 0.25 mL $\rightarrow$ 0.28 mL of 100000 BAU/mL (19 μ g) for 10 months CD: 571 μ g/month	10 months	SS, MS

Study Type	Study	Country	Number of Patients	Female %	Age, mean $\pm$ SD (range) ^a	Asthma %	Treatment Allergen	Tx Arms	Treatment Regimen	Evaluation Period	Outcome Measures Included (Specific Measure) ^b
	Ariano 2005	France, Italy	T: 20 P: 10	T: 30 P: 50	T: 32.70 $\pm$ 11.85 P: 36.20 $\pm$ 12.73	T: 20 P: 20	Cupressus arizonica	1	I: Days 1-8: 500 AU/mL = 25 AU/drop Days 1-4: 1 drop BID Days 5-8: 4 drops BID Days 9-16: 3000 AU/mL Days 9-13: 2 drops BID Days 14-16: 6 drops BID M: 3000 AU/mL 6 drops once a week until 4 months	4 months	SS, MS (DCS)
	Bergmann 2014	Berlin, Germany, France, Netherlands, Spain	A1: 153 A2: 150 P: 163	A1: 55.6 A2: 51.3 P: 49.1	A1: 29.0 $\pm$ 8.52 A2: 30.1 $\pm$ 8.43 P: 30.0 $\pm$ 8.96 (18-50)	A1: 32.0 A2: 28.7 P: 28.8	HDM mixture of Der p and Der f (1:1)	2	A1: 300IR A2: 500IR I: A1: day 1 100IR, day 2 200IR, day 3 300IR A2: days 1-2 100IR, days 3-4 200IR, days 5-6 300IR, days 7-8 400IR, day 9 500IR M: once daily until 12 months	12 months	CSMS (AAdSS)
	Bozek 2013 ²	Poland	T: 51 P: 57	T: 54.9 P: 52.6	T: 65.78 $\pm$ 4.89 P: 66.71 $\pm$ 3.77 (60-75)	T: 11.8 P: 8.8	HDM mixture of Der p and Der f (1:1)	1	I: Days 1-8, increasing 1-8 puffs of 100 IR/mL Days 9-16: 1-8 puffs of 300 IR/mL M: five applications of 18 puffs (1 puff = 30 IR) of 300 IR/mL 5x/week until 36 months	36 months	SS (NSS), MS
	Bozek 2014 ³	Poland	T: 41 P: 37	T: 46.3 P: 48.6	T: 63.18 $\pm$ 3.12 P: 64.13 $\pm$ 2.92 (60-70)	T: 7.3 P: 5.4	5 grass pollen mixture extract	1	I: first 4 days: 30-60-120-240 IR M: 240 IR 5x/week January-May for 3 consecutive years	36 months	SS, MS
	Bozek 2017 – SLIT ²	Poland	T: 51 P: 57	T: 54.9 P: 52.6	T: 65.78 $\pm$ 4.89 P: 66.71 $\pm$ 3.77 (60-75)	T: 11.8 P: 8.8	HDM mixture of Der p and Der f (1:1)	1	I: Days 1-8, increasing 1-8 puffs of 100 IR/mL Days 9-16: 1-8 puffs of 300 IR/mL M: five applications of 18 puffs (1 puff = 30 IR) of 300 IR/mL 5x/week until 36 months	72 months	CSMS (AAdSS)
	Bozek 2018 ³	Poland	T: 41 P: 37	T: 46.3 P: 48.6	T: 63.18 $\pm$ 3.12 P: 64.13 $\pm$ 2.92 (60-70)	T: 7.3 P: 5.4	5 grass pollen mixture extract	1	I: first 4 days: 30-60-120-240 IR M: 240 IR 5x/week January-May for 3 consecutive years	72 months	CSMS
	Couroux 2019	Canada	A1: 55 A2: 54 A3: 54	A1: 45.5 A2: 35.2 A3: 51.9	A1: 40 $\pm$ 11.2 (20-65)	A1: 11 A2: 7 A3: 13	Birch pollen	3	1 DU = 5 μ g A1: 2 DU A2: 7 DU	24 weeks	SS (TSS)

Study Type	Study	Country	Number of Patients	Female %	Age, mean $\pm$ SD (range) ^a	Asthma %	Treatment Allergen	Tx Arms	Treatment Regimen	Evaluation Period	Outcome Measures Included (Specific Measure) ^b
			P: 56	P: 53.6	A2: 42 $\pm$ 10.3 (21-64) A3: 40 $\pm$ 12.3 (18-65) P: 38 $\pm$ 11.9 (18-65)	P: 9			A3: 12 DU Daily for 24 weeks		
	Cox 2012	USA	T: 210 P: 228	T: 51.9 P: 54.8	T: 36.8 $\pm$ 11.27 P: 37.6 $\pm$ 11.64 (18-65)	T: 18.3 P: 21.9	5 grass pollen mixture extract	1	D: 300 IR Daily tablets 4 months before GPS and throughout Average duration: 179.8 $\pm$ 13.69 days	Average: 179.8 $\pm$ 13.69 days	SS (RTSS), MS (RMS), CSMS, RQLQ
	Creticos 2013	USA, Canada, Hungary, Ukraine, Russia	A1: 197 A2: 195 A3: 194 P: 198	A1: 56 A2: 53 A3: 47 P: 49	A1: 36 $\pm$ 9 A2: 37 $\pm$ 9 A3: 36 $\pm$ 9 P: 37 $\pm$ 9 (18-50)	A1: 17 A2: 16 A3: 19 P: 16	Ragweed (Amb a)	3	A1: 1.5 Amb a 1-U A2: 6 Amb a 1-U A3: 12 Amb a 1-U Daily starting 16 weeks before RPS for 52 weeks	52 weeks (PPS)	SS, MS, CSMS
	Creticos 2014	USA, Canada	T: 218 P: 211	T: 58.3 P: 55.5	T: 38.2 $\pm$ 10.6 P: 38.4 $\pm$ 10.1 (18-55)	T: 7.8 P: 9.0	Ragweed liquid extract	1	D: max tolerated Daily starting 8-16 weeks before RPS and throughout	~12 weeks (RPS)	SS, CSMS
	Dahl 2006 – 1 ⁴	Austria, Denmark, Germany, Italy, Netherlands, Spain, Sweden, UK	T: 316 P: 318	T: 43.4 P: 39.3	T: 33.8 $\pm$ 9.6 P: 34.5 $\pm$ 10.0 (18-65)	NR	Timothy grass (Phleum pratense)	1	D: 75000 SQ-T = 15 μ g Phl p 5 Daily starting 16-35 weeks before GPS 2005 and throughout (average 57.8 $\pm$ 13.9 days)	End of GPS	SS (RTSS), MS
	Dahl 2006 – 2	Denmark, Sweden	T: 74 P: 40	T: 28.4 P: 40.0	T: 36.5 $\pm$ 10.6 (18-64) P: 34.1 $\pm$ 9.9 (20-60)	T: 100 P: 100	Timothy grass (Phleum pratense)	1	D: 75000 SQ-T = 15 μ g Phl p 5 Daily starting 10-14 weeks before GPS 2004 and throughout (average 53 $\pm$ 2 days)	End of GPS	SS (RTSS), MS
	Demoly 2016	12 European countries (France, Austria, Denmark, Germany)	A1: 336 A2: 318 P: 338	A1: 50.9 A2: 48.7 P: 50.9	A1: 32.5 $\pm$ 11.2 (18-66) A2: 32.1 $\pm$ 10.6 (18-63) P: 32.2 $\pm$ 10.9 (18-66)	A1: 45 A2: 48 P: 45	HDM mixture of Der p and Der f (1:1)	2	A1: 6 SQ-HDM A2: 12 SQ-HDM Daily for 12 months	12 months	SS, MS, CSMS, RQLQ
	Didier 2009	Austria, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Slovakia, Spain	A1: 157 A2: 155 A3: 160 P: 156	A1: 48.6 A2: 45.6 A3: 37.8 P: 40.5	A1: 29.3 $\pm$ 6.90 A2: 28.7 $\pm$ 7.34 A3: 30.4 $\pm$ 7.45 P: 29.1 $\pm$ 7.60 (18-45)	A1: 9.9 A2: 11.0 A3: 10.5 P: 8.8	5 grass pollen mixture extract	3	A1: 100 IR A2: 300 IR A3: 500 IR Daily starting 4 months before GPS and throughout (~1 month)	~5 months (GPS)	SS (RTSS), MS, CSMS
	Didier 2011 ⁵	Austria, Canada, Czech Republic, Denmark, France, Germany, Italy,	A1: 188 A2: 188 P: 205	A1: 41.0 A2: 35.1 P: 40.5	A1: 30.4 $\pm$ 7.57 (18-51) A2: 30.9 $\pm$ 8.25 (18-49)	A1: 11.7 A2: 14.9 P: 15.6	5 grass pollen mixture extract	2	A1: 300 IR (2 months) A2: 300 IR (4 months) Daily tablet starting 2 months (or 4 months) before GPS and	3 years	SS (RTSS), MS (RMS), CSMS (AAdSS)

Study Type	Study	Country	Number of Patients	Female %	Age, mean $\pm$ SD (range) ^a	Asthma %	Treatment Allergen	Tx Arms	Treatment Regimen	Evaluation Period	Outcome Measures Included (Specific Measure) ^b
		Poland, Russia, Slovakia			P: 30.2 $\pm$ 8.56 (18-49)				throughout for 3 consecutive GPS (2007, 2008, 2009)		
	Didier 2013 ⁵	Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia, Slovakia	A1: 137 A2: 143 P: 155	A1: 38.7 A2: 35.7 P: 39.4	A1: 31.0 $\pm$ 7.93 (18-51) A2: 30.7 $\pm$ 8.38 (18-49) P: 30.0 $\pm$ 8.60 (18-49)	A1: 12.4 A2: 12.6 P: 13.5	5 grass pollen mixture extract	2	A1: 300 IR (2 months) A2: 300 IR (4 months) Daily tablet starting 2 months (or 4 months) before GPS and throughout for 3 consecutive GPS (2007, 2008, 2009)	1 year after 3 years treatment period	SS (RTSS), RQLQ
	Didier 2015 ⁵	Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia, Slovakia	A1: 117 A2: 127 P: 133	A1: 39.3 A2: 36.2 P: 40.6	A1: 30.9 $\pm$ 7.8 (18-51) A2: 30.5 $\pm$ 8.5 (18-49) P: 30.1 $\pm$ 8.7 (18-49)	A1: 11.1 A2: 12.6 P: 14.3	5 grass pollen mixture extract	2	A1: 300 IR (2 months) A2: 300 IR (4 months) Daily tablet starting 2 months (or 4 months) before GPS and throughout for 3 consecutive GPS (2007, 2008, 2009)	2 years after 3 years treatment period	CSMS
	DiRienzo 2006	Italy	T: 19 P: 15	41.2	33.8 $\pm$ 9.5 (18-55)	NR	Juniperus ashei extract	1	I: increasing concentration (10-100-300 IR/mL) over 12 days (starting Dec) M: 300 IR/mL, 8 drops daily until 5 months (Apr)	5 months	RQLQ
	Durham 2006	Belgium, Denmark, Germany, Sweden, Austria, Norway, UK, Canada	T: 141 P: 136	T: 40.4 P: 34.6	T: 37 (19-62) P: 33 (18-61)	NR	Timothy grass (Phleum pratense)	1 (Data absent for 2 of 3 arms)	75000 SQ-T = 15 μ g Phl p 5 Daily starting 8 weeks before GPS and throughout (average Tx duration 18 weeks)	GPS	SS, MS
	Durham 2010 ⁴	Austria, Denmark, Germany, Italy, Netherlands, Spain, Sweden, UK	T: 157 P: 126	T: 36 P: 36	T: 36.4 $\pm$ 9.89 P: 36.8 $\pm$ 9.89 (18-65)	NR	Timothy grass (Phleum pratense)	1	D: 75000 SQ-T/2800 BAU = 15 μ g Phl p 5 Daily starting 16-35 weeks before GPS 2005 until end of GPS 2007	1 year after 3 years of treatment	SS (RTSS), MS, RQLQ
	Durham 2012 ⁴	Austria, Denmark, Germany, Italy, Netherlands, Spain, Sweden, UK	T: 137 P: 104	T: 41 P: NR	T: NR P: NR (18-65)	NR	Timothy grass (Phleum pratense)	1	D: 75000 SQ-T/2800 BAU = 15 μ g Phl p 5 Daily starting 16-35 weeks before GPS 2005 until end of GPS 2007	2 years after 3 years of treatment	SS (RTSS), MS
	Ellis 2018	Canada	T: 47 P: 46	T: 51 P: 50	T: 37.5 $\pm$ 10.8 P: 37.7 $\pm$ 10.9 (18-65)	NR	Timothy grass (Phleum pratense)	1	D: 2800 BAU Daily for 4 months	4 months	SS (RTSS)
	Horak 2009	Austria	T: 45 P: 44	T: 53.3 P: 63.6	T: 27.5 $\pm$ 6.58 (19.7-49.8) P: 27.1 $\pm$ 5.81 (18.6-46.6)	NR	5 grass pollen mixture extract	1	D: 300 IR = 20 μ g Daily for 4 months	4 months	SS (RTSS)
	Marogna 2013	Italy	T: 21 P: 21	NR	24.797 $\pm$ 0.8 (18-43)	T: 100 P: 100	Birch pollen	1 (Tx was	D: 1000 AU I: 4 day build up	3 years	CSMS

Study Type	Study	Country	Number of Patients	Female %	Age, mean $\pm$ SD (range) ^a	Asthma %	Treatment Allergen	Tx Arms	Treatment Regimen	Evaluation Period	Outcome Measures Included (Specific Measure) ^b
								not SLIT for 2 of 3 arms)	M: Daily, 5 days/week, early Feb to late April (≥ 12 weeks), total 3 years CD: 60000 AU/year (214200 μ g/year)		
	Murphy 2013	USA	T: 163 P: 166	T: 54 P: 53	T: 35.9 $\pm$ 11.7 (18-65) P: 35.9 $\pm$ 11.7 (18-62)	T: 28 P: 26	Timothy grass (Phleum pratense)	1	D: 2800 BAU (75000 SQ-T = 15 μ g Phl p 5) Daily starting 8-16 weeks before GPS and throughout (average GPS duration 43 days)	GPS	SS, MS, RQLQ
	Nelson 2011	USA, Canada	T: 213 P: 225	T: 51 P: 50	T: 35.9 (18-63) P: 35.9 (18-61)	T: 21 P: 26	Timothy grass (Phleum pratense)	1	D: 2800 BAU (75000 SQ-T = 15 μ g Phl p 5) Daily starting 16 weeks before GPS and throughout (average GPS duration 53 days)	GPS	SS, MS, CSMS, RQLQ
	Nolte 2013	USA, Canada	A1: 190 A2: 187 P: 188	A1: 44 A2: 58 P: 50	A1: 35.3 (18-50) A2: 34.9 (18-51) P: 35.9 (18-50)	A1: 20 A2: 23 P: 23	Ragweed (Amb a)	2	A1: 6 Amb a 1-U A2: 12 Amb a 1-U Daily starting 12 weeks before RPS and throughout (Tx duration 52 weeks)	PPS	SS, MS, CSMS
	Pfaar 2016 – SLIT	Poland, Czech Republic, Germany	A1: 54 A2: 56 A3: 53 A4: 54 P: 52	A1: 50 A2: 51.8 A3: 52.8 A4: 48.1 P: 46.2	A1: 36.5 $\pm$ 10.2 (19-59) A2: 34.9 $\pm$ 10.0 (18-58) A3: 35.8 $\pm$ 10.0 (19-58) A4: 36.2 $\pm$ 10.8 (19-57) P: 36.4 $\pm$ 10.0 (20-58)	NR	Birch pollen	4	A1: 3333 AUN/mL A2: 10000 AUN/mL A3: 20000 AUN/mL A4: 40000 AUN/mL I: One drop and adding one drop each day until 5 drops/day M: 5 drops/day until 5 months	5 months	SS (Lebel symptom score after TNPT)
	Pfaar 2019	Belgium, Czech Republic, Germany, Poland, Slovakia	T: 208 P: 198	T: 51.0 P: 49.0	T: 37.48 $\pm$ 11.43 (18-65) P: 36.69 $\pm$ 10.77 (18-61)	27	Birch pollen	1	D: 40000 AUN/mL I: Add one drop/day until 5 drops/day M: 5 drops/day for 6 months + BPS (Tx duration 6-9 months)	BPS	CSMS
	Quercia 2011	Italy	A1: 10 A2: 11 P: 11	A1: 60 A2: 27.2 P: 36.4	A1: 26.5 $\pm$ 10.4 A2: 31.6 $\pm$ 11.6 P: 31.2 $\pm$ 8.3 (18-70)	A1: 20 A2: 54.5 P: 54.5	Grass pollen	2	I: 16 days (25, 100, 300, 1000 AU) A1: 1000 AU/week for 2 years A2: 5000 AU/week for 10 weeks/year pre-seasonally for 2 years CD: 50000 AU/year	2 years	SS (GSS), MS (DCS)

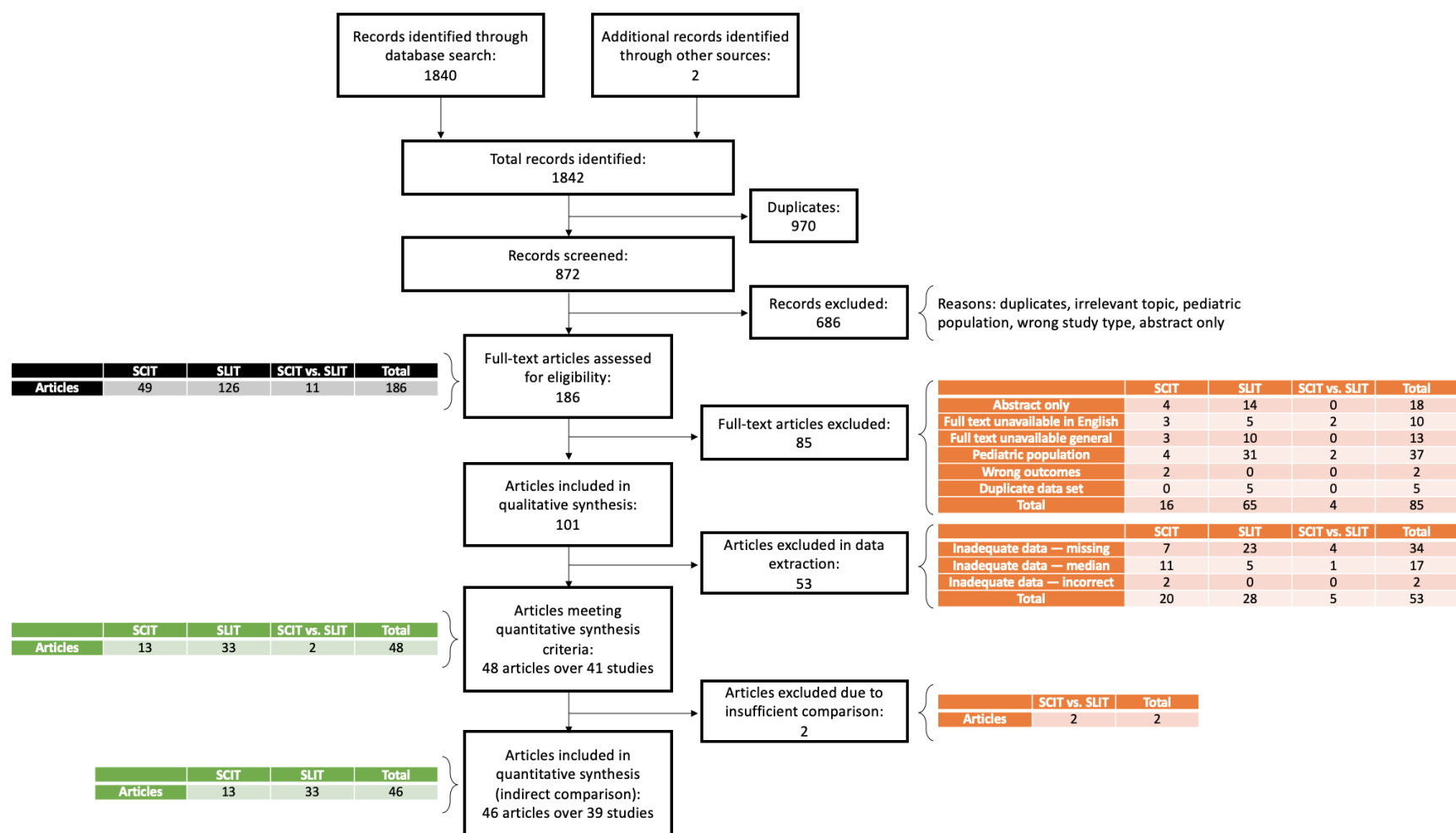
Study Type	Study	Country	Number of Patients	Female %	Age, mean $\pm$ SD (range) ^a	Asthma %	Treatment Allergen	Tx Arms	Treatment Regimen	Evaluation Period	Outcome Measures Included (Specific Measure) ^b
	Skoner 2010	USA	A1: 39 A2: 36 P: 40	A1: 74.4 A2: 66.7 P: 52.5	A1: 34.4 (19-49) A2: 33.6 (20-49) P: 34.9 (20-50)	A1: 7.7 A2: 5.9 P: 7.5	Ragweed (Amb a)	2	A1: 4.8 μ g Amb a 1 daily A2: 48 μ g Amb a 1 daily Average tx duration 17 $\pm$ 3 weeks	17 $\pm$ 3 weeks	SS, MS, CSMS
	Worm 2014	Czech Republic, Denmark, Estonia, Finland, France, Germany, Latvia, Lithuania, Poland, Slovakia, Sweden	T: 253 P: 247	T: 52.2 P: 52.2	T: 38.4 $\pm$ 11.05 P: 36.7 $\pm$ 11.33 (18-65)	T: 21.3 P: 28.3	Birch pollen	1	I: 12 days (1, 2, 4, 6, 8, 10, 30, 60, 120, 180, 240, 300 IR/day) M: 300 IR/mL Daily starting 4 months before BPS and throughout (Tx duration 5 months/year) for 2 consecutive years (7 months no Tx between years)	17 months	CSMS (AAdSS), RQLQ

^{1,2,3,4,5}Articles from the same study.

^aIf only one age range listed, then it applies to all groups.

^bSpecific outcome measure listed only if name differs from generic outcome measure. Note that the same named outcome measure may have different definitions across different studies.

A# = arm #; AAdSS = average adjusted symptom score; BID = twice a day; BPS = birch pollen season; CD = cumulative dose; CSMS = combined symptom medication score; D = dose; DCS = drug consumption score; GPS = grass pollen season; GSS = global symptom score; HDM = house dust mite; I = induction phase; M = maintenance phase; MS = medication score; NR = not reported; NSS = nasal symptom score; P = placebo; PPS = peak pollen season; q#w = every # weeks; RMS = rescue medication score; RPS = ragweed pollen season; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; RTSS = rhinoconjunctivitis total symptom score; SCIT = subcutaneous immunotherapy; SD = standard deviation; SLIT = sublingual immunotherapy; SS = symptom score; T = Tx = treatment; TMS = total medication score; TNPT = titrated nasal provocation test; TRMS = total rescue medication score; TSS = total symptom score; UK = United Kingdom; USA = United States of America



eFigure 1. PRISMA diagram of the literature search study selection process with detailed exclusion and inclusion information.
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy