SUPPLEMENTARY MATERIAL

Table S1. Search strategy.

Search number	Query	Results
5	#1 AND #2 AND #3 AND #4	187
4	((rct) OR (randomized controlled trial*)) OR (placebo-controlled)	927,58
3	(grass) OR (grass pollen)	179,26
2	((sublingual immunotherapy) OR (AIT)) OR (SLIT)	29,302
1	(((rhinoconjunctivitis) OR (rhinitis)) OR (allergic rhinitis)) OR (asthm*)	253,61

Table S2. Sensitivity analysis for symptom and medication scores.

Symptom Score	n	Point estimate (95%CI)	I^2
REM w/o influential studies	540	-0.36 (-0.53, -0.18)	0%
FEM w/o influential studies	540	-0.36 (-0.53, -0.18)	0%
With duplicated controls	**621**	**-0.34 (-0.62, -0.06)**	61%
Without duplicated controls	549	-0.33 (-0.51, -0.16)	71%
Sample size ≥57	433	-0.39 (-0.59, -0.20)	0%
Sample size <57	188	-0.36 (-1.00, 0.27)	77%
High quality studies	169	-0.68 (-1.26, -0.11)	67%
Studies with low quality or some concerns	452	-0.18 (-0.47, 0.12)	53%
Available data	538	-0.25 (-0.49, -0.02)	38%
Estimated data	83	-1.08 (-2.73, 0.57)	89%

Medication Score	n	Point estimate (95%CI)	I^2
REM w/o influential studies	289	-0.46 (-0.80, -0.12)	45%
FEM w/o influential studies	289	-0.45 (-0.68, -0.21)	45%
With duplicated controls	**507**	**-0.54 (-0.97, -0.10)**	79%
Without duplicated controls	445	-0.43 (-0.80, -0.07)	65%
Sample size ≥57	375	-0.26 (-0.63, 0.11)	66%
Sample size <57	132	-0.83 (-1.72, 0.06)	82%
High quality studies	169	-0.68 (-1.46, 0.10)	82%
Studies with low quality or some concerns	338	-0.39 (-0.94, 0.15)	79%
Available data	482	-0.52 (-1.00, -0.04)	92%
Estimated data	25	-0.71 (-1.53, 0.10)	0%

REM, random effects model; FEM, fixed effects model; CI, confidence interval.

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Table S3. Evidence summary.

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLIT	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Symptom Score (follow-up: mean 19 months; assessed with: SMD)												
8	randomized trials	serious [a]	not serious [b]	not serious	Serious [c]	all plausible residual confounding would reduce the demonstrated effect	336	260	-	SMD **0.26 SD lower** (0.47 lower to 0.06 lower)	⨁⨁⨁◯ Moderate [a,b,c]	Critical
Medication Score (follow-up: mean 20 months; assessed with: SMD)												
6	randomized trials	serious [d]	not serious [e]	not serious	very serious [f]	all plausible residual confounding would reduce the demonstrated effect	275	197	-	SMD **0.34 SD lower** (0.68 lower to 0)	⨁⨁◯◯ Low [d,e,f]	Critical

The certainty assessment was performed after removing one influential study for the SS analysis (Kaluzinska 2011) and one influential study for the MS analysis (Stelmach-pre/co 2012). The Stelmach 2012 study was treated as two separate studies: Stelmach-cont. 2012 and Stelmach-pre/co 2012 (see Figures 2 and 4). CI: confidence interval; SMD: standardized mean difference.

Explanations

a. 3/8 studies have moderate risk of bias (some concerns according to RoB2), while 1/8 study has high risk of bias. The remaining 4/8 studies have low risk of bias.

b. After removing the outlying study of Kaluzinska 2011, the CIs of individual studies overlap, leading to a rating of "not serious" for inconsistency.

c. The CIs of six studies cross the threshold of no effect/small effect. These CI spans from the thresholds of moderate to small effect, according to Cohen's criteria (Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.). Optimal Information Threshold (OIT) is met.

d. 2/6 studies have moderate risk of bias (some concerns according to RoB2), while 1/6 studies have high risk of bias, and the remaining 3/6 studies have low risk of bias.

e. After removing the outlying study of Stelmach-pre/co 2012, the CIs of individual studies overlap, allowing the inconsistency to be rated as "not serious".

f. The CIs of four studies cross the threshold of no effect/small effect. The CI of those studies spans from the thresholds of large to small effect. OIT is met.

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Table S4. Incidence of adverse events and discontinuation rates.

	SLIT	Placebo	Chi^2	*P*
Patients (n)	335	217		
Patients with AE, n (%)	69 (20.6)	38 (17.5)	0.55	0.46
Discontinuation for reason other than AE, n (%)	8 (2.4)	13 (6.0)	4.29	0.04
Discontinuation for AE, n (%)	10 (3.0)	4 (1.8)	0.66	0.41

AE, adverse events; n, number

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