Allergen immunotherapy for atopic dermatitis: Systematic review and meta-analysis of benefits and harms

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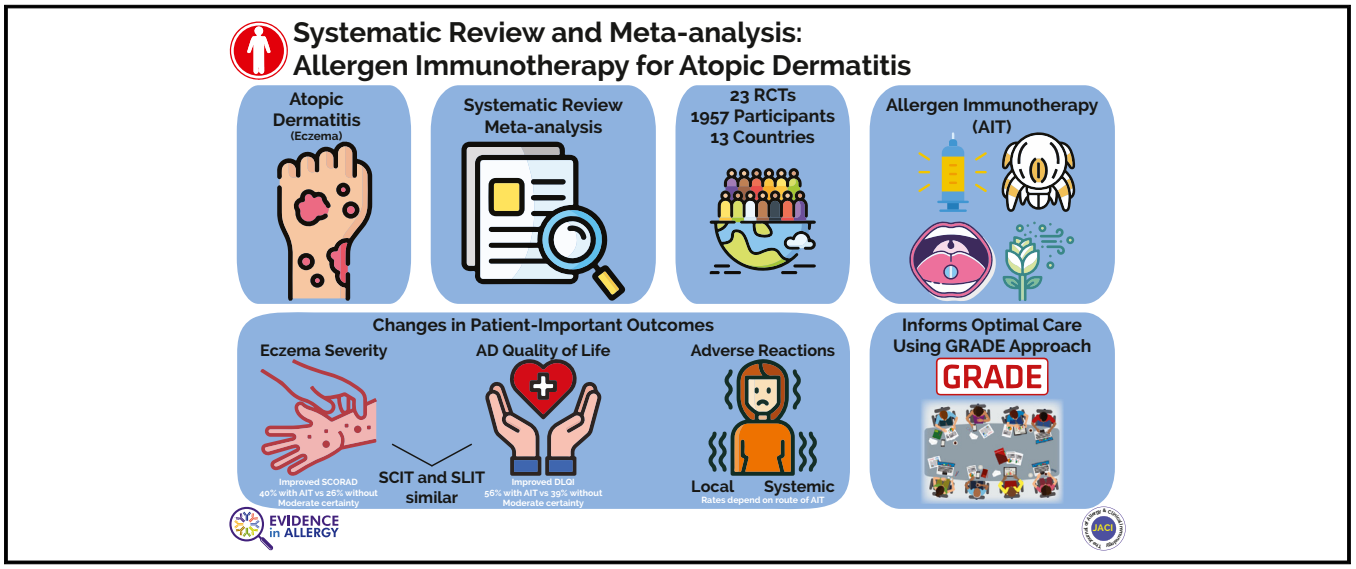
GRAPHICAL ABSTRACT



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Background: Atopic dermatitis (AD, eczema) is driven by a combination of skin barrier defects, immune dysregulation, and extrinsic stimuli such as allergens, irritants, and microbes. The role of environmental allergens (aeroallergens) in triggering AD remains unclear.

Objective: We systematically synthesized evidence regarding the benefits and harms of allergen immunotherapy (AIT) for AD.

Methods: As part of the 2022 American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters AD Guideline update, we searched the MEDLINE, EMBASE, CENTRAL, CINAHL, LILACS, Global Resource for Eczema Trials, and Web of Science databases from inception to December 2021 for randomized controlled trials comparing subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), and/or no AIT (placebo or standard care) for guideline panel–defined patient-important outcomes: AD severity, itch, AD-related quality of life (QoL), flares, and adverse events. Raters independently screened, extracted data, and assessed risk of bias in duplicate. We synthesized intervention effects using frequentist and Bayesian random-effects models. The GRADE approach determined the quality of evidence.

Results: Twenty-three randomized controlled trials including 1957 adult and pediatric patients sensitized primarily to house dust mite showed that add-on SCIT and SLIT have similar relative and absolute effects and likely result in important improvements in AD severity, defined as a 50% reduction in SCORing Atopic Dermatitis (risk ratio [95% confidence interval] 1.53 [1.31-1.78]; 26% vs 40%, absolute difference 14%) and QoL, defined as an improvement in Dermatology Life Quality Index by 4 points or more (risk ratio [95% confidence interval] 1.44 [1.03-2.01]; 39% vs 56%, absolute difference 17%; both outcomes moderate certainty). Both routes of AIT increased adverse events (risk ratio [95% confidence interval] 1.61 [1.44-1.79]; 66% with SCIT vs 41% with placebo; 13% with SLIT vs 8% with placebo; high certainty). AIT's effect on sleep disturbance and eczema flares was very uncertain. Subgroup and sensitivity analyses were consistent with the main findings.

Conclusions: SCIT and SLIT to aeroallergens, particularly house dust mite, can similarly and importantly improve AD severity and QoL. SCIT increases adverse effects more than SLIT. These findings support a multidisciplinary and shared decision-making approach to optimally managing AD. (J Allergy Clin Immunol 2023;151:147-58.)

Key words: *Atopic dermatitis (atopic eczema), allergy, allergen immunotherapy (AIT), aeroallergen, house dust mite, subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), systematic review, meta-analysis, GRADE approach, multidisciplinary, evidence-based medicine, SCORAD, DLQI, quality of life, itch (pruritus), sleep disturbance, adverse events*

Atopic dermatitis (AD), also referred to as atopic eczema, flexural eczema, or neurodermatitis, is a chronic and relapsing disease characterized by intense itching and skin inflammation.[1] It affects 15% to 20% of children and 3% to 5% of adults.[2] Some world regions report increasing prevalence.[3] Direct costs of AD in the United States are estimated to be more than $5 billion per year.[4] Especially when lesions are visible and symptoms are not controlled, AD negatively impacts quality of life (QoL), emotional health, and socialization.[5]

AD pathogenesis is driven by a combination of intrinsic skin barrier defects, immune dysregulation, and extrinsic stimuli like allergens, irritants, and microbes.[2,6,7] However, the precise role that environmental allergens (aeroallergens like house dust mite [HDM] or pollens) play in driving AD remains unclear. For example, AD's strong association with allergic rhinitis, allergic asthma, and allergic sensitization to dust mites[8-11] has not led to robust treatments for AD that specifically address allergy.

Allergen immunotherapy (AIT), also called specific desensitization, allergen-specific immunotherapy, or hyposensitization, involves the administration of increasing amounts of a specific allergen to an allergic patient in order to (temporarily) induce tolerance to it.[12-14] AIT includes subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Both are well established as safe and effective treatments to address allergies to aeroallergens for allergic rhinitis and allergic asthma, and they also have possible long-term disease-modifying benefits.[15,16] Previous studies of AIT for AD, however, found mixed results, so the benefits and harms remain uncertain.[17-20] As part of the American Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI) Joint Task Force on Practice Parameters 2022 AD guideline update, we systematically reviewed the effectiveness and safety of AIT (SCIT and SLIT) versus no AIT (placebo or standard care) for patients with AD.

METHODS

We conducted this systematic review according to Cochrane[21] and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidance,[22] registered it (https://osf.io/cqngx/?view_only=625970c13c06412f86318fe934f17c34), and report it according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[23] This work is linked to the development of the 2022 AAAAI/ACAAI Joint Task Force on

atopic dermatitis. The funder contributed to defining the scope of the review but otherwise had no role in study design and data collection. Data were interpreted and the report drafted and submitted without funder input. The funder was provided a copy of the report at time of submission. The review team had the ability, but not obligation, to consider the funder's feedback. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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Abbreviations used

AAAAI: American Academy of Allergy, Asthma & Immunology
ACAAI: American College of Allergy, Asthma and Immunology
AD: Atopic dermatitis
AIT: Allergen immunotherapy
CI: Confidence interval
Der f: *Dermatophagoides farinae*
Der p: *Dermatophagoides pteronyssinus*
DLQI: Dermatology Life Quality Index
GRADE: Grades of Recommendation Assessment, Development, and Evaluation
HDM: House dust mite
QoL: Quality of life
RCT: Randomized controlled trial
RoM: Ratio of means
RR: Risk ratio
SCIT: Subcutaneous immunotherapy
SCORAD: SCORing Atopic Dermatitis
SLIT: Sublingual immunotherapy

Practice Parameters AD Management Guidelines[24] and new evidence on bleach bath,[25] diet,[26] topical, and systemic treatments.

Search strategy and selection criteria

We searched the MEDLINE, EMBASE, CENTRAL, CINAHL, LILACS, and Global Resource for Eczema Trials (GREAT) databases, without language restrictions, from database inception until August 2021, followed by forward and backward citation analysis using all databases in Web of Science to December 12, 2021, for published or unpublished randomized controlled trials (RCTs) comparing the efficacy and/or safety of AIT for the treatment of AD against no AIT (placebo or standard care) (see Supplement E1 in the Online Repository at www.jacionline.org). We then manually searched reference lists of relevant studies and review articles, and we discussed with the guideline panel to find and monitor for other relevant references.

Data collection

We screened, independently and in duplicate, titles and abstracts, and reviewed full texts of potentially eligible records using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Reviewers extracted data independently and in duplicate using standardized prepiloted forms. We resolved disagreements by consensus and involved a third reviewer (D.K.C. or J.J.Y.N.) if necessary. We collected information on study identifiers, design, setting, population characteristics, intervention and comparator characteristics, outcomes, and sources of funding. In the case of multiple records pertaining to the same trial, we collected all relevant data and analyzed them as a single study. We cross-referenced data from published reports with results available on corresponding clinical trial registries. In cases of discrepancies, we used the most complete data set. Conversely, if a single record reported on more than 1 randomized trial, we treated each trial as a separate study in the analysis.

Outcomes

We focused on outcomes that the 2022 AAAAI/ACAAI AD guideline panel of patients and caregivers, front-line clinicians, and allergy and AD experts[24] deemed, after consideration of the Harmonizing Outcome Measures for Eczema (HOME) initiative,[27-29] to be important to patients: clinician-reported severity (eg, validated scales such as the clinician-adjudicated domains of SCORing Atopic Dermatitis [SCORAD][27,28] or Eczema Area and Severity Index were prioritized over investigator global assessment), patient-reported severity (eg, patient-oriented eczema measure[30]), itch, sleep, eczema-related QoL (eg, Dermatology Life Quality Index [DLQI][31]), and adverse events. Supplement E2 in the Online Repository at www.jacionline.org provides further details.

Risk of bias assessment

Reviewers independently and in duplicate rated risk of bias per outcome for each study using version 1 of the CLARITY-revised Cochrane Risk of Bias tool as being at low risk of bias, probably low risk of bias, probably high risk of bias, or high risk of bias.[32,33] We considered a study to be at high risk of bias if at least 1 domain was high or probably high risk. If discrepancies remained after discussion, a third reviewer (D.K.C. or J.J.Y.N.) resolved them.

Data analysis

We analyzed outcomes according to the intention-to-treat principle (patients analyzed according to the arm to which they were originally assigned). In the main analyses, we performed pairwise meta-analysis using DerSimonian-Laird random effects models. Because we anticipated variability in the baseline severity of AD across included studies, we calculated the probability to improve by panel-defined patient-important differences—for example, a 50% reduction from baseline in clinician-reported severity. Supplement E2 provides additional details. For harm outcomes in which there were insufficient data among the AD trials to generate an informative estimate to support development of recommendations, we judged that adverse effects of AIT would be similar when used to treat allergic rhinitis and allergic asthma, and therefore, following GRADE and recent guidance,[34,35] we supplemented the AD harm estimates with those systematically reviewed[36-42] from these 2 related conditions. We pooled dichotomous outcomes using risk ratio (RR) with accompanying 95% confidence interval (CI).

Unless otherwise specified, time points chosen for analysis reflect the longest duration of continuous treatment with the intervention with all outcome data available. We conducted prespecified subgroup analyses with tests for interaction and appraised statistically significant findings using ICEMAN,[43] including the following: severity of the disease; age (hypothesized to be more effective with younger age); route of allergenic immunotherapy administration (SCIT hypothesized to be more effective than SLIT); duration of treatment (hypothesized to be more effective with time); type of allergen (dust mites hypothesized to be more effective vs pollen or animal allergens); risk of bias (high risk of bias hypothesized to report larger benefits and less harms compared to low risk of bias); and funding source (industry-sponsored studies hypothesized to report larger benefits and less harms compared to nonindustry or mixed funding). The panel requested additional subgroup analyses by geography (no direction specified), allergen sensitization pattern (monosensitized to be more effective than polysensitized), and co-interventions (presence of background topical therapies hypothesized to be more effective than monotherapy).

Sensitivity analyses included using Hartung-Knapp-Sidik-Jonkman models,[44] using ratio of means (RoM)[45,46] and mean differences after converting within-group changes in continuous outcomes to a common scale using GRADE guidance,[45,46] using fixed-effect meta-analysis, leaving out any one study, and restricting estimates to studies with a sample size of 70 or greater; and performing Bayesian analyses using blocked hybrid Metropolis-Hastings sampling with Gibbs updates, 4 chains, a minimum of 10,000-sample burn-in, 50,000 Markov chain Monte Carlo samples, thinning of 100, informative heterogeneity hyperpriors,[47,48] and model inspection (trace plots, autocorrelation plots, histograms, kernel density estimates, acceptance, Gelman-Rubin statistics) to inform posterior distribution mean estimates of effect and associated 95% credible intervals. We performed the analyses using Stata 14.3 and Stata 17.0 (StataCorp, College Station, Tex), and R 4.0.2 (R Project; www.r-project.org).

Certainty of evidence

The GRADE approach, in which randomized trials start as high-certainty evidence but then can be rated down to moderate, low, or very low for risk of bias, imprecision, inconsistency, indirectness, and publication bias informed

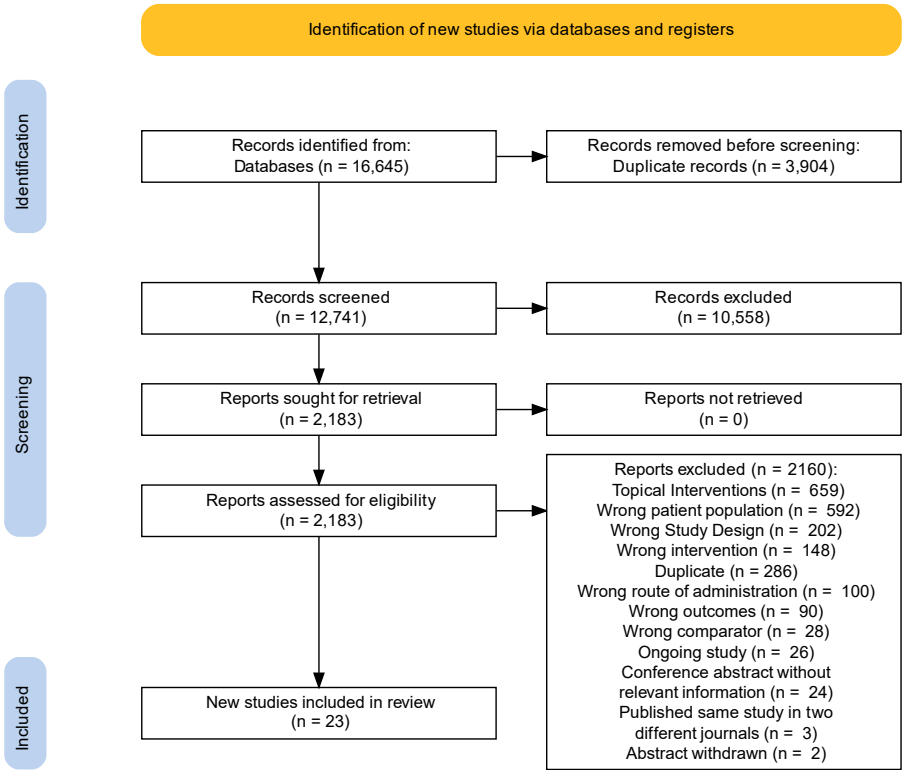

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

our evaluation of certainty (quality) of evidence.[22,49] We used a minimally contextualized approach in which we rated our certainty in whether effects were greater or less than minimal important differences[50] established by the guideline panel. We evaluated inconsistency on the basis of similarity of point estimates and degree of overlap of CIs,[51] with less emphasis on I^2, which can be misleading when analyzing continuous outcomes or estimates with narrow CIs.[51-53] We assessed publication bias using the GRADE approach, including inspecting for small-study effects through funnel plots, and evaluating the relation between study findings and funding. We evaluated risk of bias due to missing participant data by sensitivity analysis using plausible worst-case scenarios.[54,55]

We present the findings using standardized language expressing the magnitude of effect estimates and certainty of the body of evidence.[49,56] We created tables summarizing the findings tables using GRADEpro GDT (McMaster University and Evidence Prime, Hamilton, Ontario, Canada).

RESULTS

The systematic search initially yielded 12,741 unique records, with 23 RCTs (n = 1957 patients)[57-78] (EUCTR2005-004675-37) reported in 26 records (Fig 1).

Table I summarizes the study characteristics of included RCTs. The trials were conducted in 13 countries across 4 continents (Asia, Europe, North America, South America) and in general included a mixture of children, adolescents, and adults (median of study mean ages, 19 years; range of means, 4-34 years), about half of whom where women, with baseline moderate to severe AD (median on SCORAD scale[27] [0-103, higher worse], 42; range of means, 12-64). Most RCTs (n = 15) used placebo controls. The studies added either AIT or placebo to standard care with topical treatments (eg, midpotency topical steroids or topical calcineurin inhibitors). SCIT and SLIT comprised an approximately equal proportion of the included RCTs. Most studies desensitized patients to HDM allergens (*Dermatophagoides pteronyssinus* [Der p] and/or *Dermatophagoides farinae* [Der f]), and 4 (17%) RCTs either addressed pollens or did not specify the allergen or allergens used. The reports described the doses used to be based on efficacy in allergic rhinitis. AIT was provided for a median (range) of mean duration among studies of 12 (3-36) months. SLIT was administered as liquid extracts (eg, Staloral [Greer, Lenoir, NC], SLITone [ALK, Horsholm, Denmark], Chanallergen [Zheijang Wolwo, Huzhou, China]) in all studies.

Applicable to all outcomes analyzed, 10 studies were at high or probably high risk of bias as a result of a lack of blinding (9 studies[57,58,60,61,69,71,73,74,78]) or missing outcome data (2 studies[62,74]) (see Fig E1 in the Online Repository at www.jacionline.org). One study[67] reported QoL data from *post hoc* analyses of a subgroup showing statistically significant results, but not the nonsignificant results from the main analysis, leading this study's outcome to be at high risk for selective reporting bias. We did not detect effect modification by risk of bias for any outcome (see Table E2 in the Online Repository). There was no strong evidence of publication bias (see Fig E2 in the Online Repository).

Effects of interventions

Table II presents the GRADE summary of findings.

AD severity. Twenty-two RCTs[57-74,76-78] (EUCTR2005-004675-37) (n = 1801) compared AIT versus no AIT and addressed a combination of clinician-reported AD severity and patient-reported itch and sleep disturbance. AIT likely improved the probability to reduce baseline AD severity by 50% or more

TABLE I. Characteristics of included studies

Study	Country	Sample size	Age (years), mean (SD)	% Women	Baseline severity	AIT route	Allergen (brand) [organism]	Starting dose [final dose]	Background therapy	Polysensitized allowed?	Funding source
Di Rienzo 2014[57]	Italy	57	11.3 (4.4)	37	Mild, moderate	SLIT	HDM (SLITone) [Der f, Der p]	NR; 200 STU [0.9 + 0.4 μg Der f + p 1 + 2][103]	Moisturizers	Yes	Industry (ALK)
EUCTR2005-004675-37[104]	Germany	152	29.2 (9.4)	49	Mild to severe	SCIT	HDM (Alutard SQ) [Der f, Der p]	NR; 4.9 μg Der p 1 + 6.9 μg Der f 1	TCS/TCI	Yes	Industry (ALK)
Galli 1994[58]	Italy	34	4.2 (2.6)	42	Mild to severe	SLIT	HDM [Der p]	NR [250 STU]	Topicals	Yes	NR
Glover 1992[59]	United Kingdom	26	10.3 (2.8)	42	Severe	SCIT	HDM [Der p]	4 Noon units[12,105] [400 Noon units]	Topicals, OAH	Yes	Mixed (Beecham)
Hajdu 2021[60]	Hungary	14	19.0 (8.3)	50	Mild, moderate	SLIT	HDM (Staloral) [Der p, Der f]	NR [300 IR]	Topicals, OAH	No	Government
Huang 2021[61]	China	440	7.3 (2.6)	38	Mild to severe	SLIT	HDM (Chanllergen) [Der f]	0.04 μg protein [40 μg protein]	Topicals, OAH	Yes	Mixed (Zhejiang Bio)
Kaufman 1974[62]	United States	52	19.3 (13.1)	54	Mild to severe	SCIT	HDM, dander, molds, pollens	0.1 PNU[15] [400 PNU]	Topicals, OAH	Yes	Industry (Dome Las)
Langer 2021[63]	Brazil	91	19.6 (14.3)	91	Moderate, severe	SLIT	HDM [Der p]	3E-7 μg Der p 1 + 2 [0.3 μg Der p 1 + 2]	Topicals, DMARDs	Yes	Mixed (IPI-ASAC Brasil)
Leroy 1992[64]	Belgium	24	31.1 (13.5)	44	Moderate, severe	IDT	HDM [Der p]	60 μg + 240 μg Ab [60 μg + 240 μg Ab]	Topicals, OAH, OCS	Yes	Industry (Baxter)
Liu 2019[65]	China	239	31.5 (10.8)	52	Mild, moderate	SLIT	HDM (Chanllergen) [Der f]	0.04 μg protein [40-80 μg protein]	Topicals, OAH, Abx	Yes	Mixed (Zhejiang Bio)
Luna-Pech 2013[66]	Mexico	68	Range 4-10 years	NR	Moderate, severe	SLIT	HDM [Der p]	NR	NR	No	NR
Novak 2012[67]	Germany	168	33.8 (11.6)	46	Moderate, severe	SCIT	HDM (Depigold) [Der f, Der p]	2 DPP units [50 DPP units]	Topicals, OAH	Yes	Industry (LETI pharma)
Pajno 2007[68]	Italy	56	10.5 (2.8)	52	Mild to severe	SLIT	HDM [Der f, Der p]	1E-3 μg Der p 1 + 2 [1 μg Der p 1 + 2]	TCS, OAH	Yes	Industry (Stallergenes)
Qin 2014[69]	China	107	27.3 (8.2)	41	Moderate	SLIT	HDM (Chanllergen) [Der f]	0.04 μg protein [80 μg protein]	TCS, OAH	Yes	Industry (Zhejiang Bio)
Ring 1982[70]	Germany	2	10	100	Severe	SCIT	Grass	NR	Topicals	Yes	NR
SanchezCaraballo 2012[71]	Colombia	65	9.4 (5.2)	50	Mild to severe	SCIT	HDM [Der f, Der p]	2 DPP units [50 DPP units]	Topicals, OAH	Yes	NR
Silny 2006[72]	Poland	20	Range 5-40 years	75	Moderate, severe	SCIT	HDM or grass	NR	Topicals	Yes	Industry (Nexter)
Slavyanskaya 2013[73]	Russia	61	Range 5-17 years	NR	Moderate	SLIT	NR	1 mg (NOS)	"Basic therapy" NOS	NR	NR
Song 2020[74]	South Korea	60	8.8 (2.7)	48	Mild to severe	SLIT	HDM (Staloral) [Der p, Der f]	NR (300 IR?)	NR	Yes	NR
Warner 1978[75]	United Kingdom	20	NR	NR	NR	SCIT	HDM (Migen) [Der p]	4 Noon units [400 Noon units]	NR	Yes	Industry (Beechams)
Wen 1992[76]	China	56	24.8 (8.1)	33	NR	SCIT	HDM [Der f]	0.4 μg/mL protein [19 μg/mL protein]	NR	NR	NR
Werfel 2006[77]	Germany	89	NR	53	Moderate, severe	SCIT	HDM (Alutard SQ) [Der f, Der p]	0.1 μg Der p + f 1 [1-1.4 μg Der p + f 1]	Topicals, OAH	Yes	Industry (ALK)
Yu 2021[78]	China	96	26.5 (4.5)	55	Mild, moderate	SLIT	HDM (Chanllergen) [Der f]	0.04 μg protein [40-80 μg protein]	TCS, OAH	Yes	Industry (Zheijang Bio)

DPP, Depigmented polymerized units; *IDT*, intradermal immunotherapy; *IR*, index of reactivy; *NOS*, not otherwise specified; *NR*, not reported; *OAH*, oral antihistamine; *OIT*, oral immunotherapy; *PNU*, protein nitrogen units; *RAST*, radioallergosorbent test; *SPT*, skin prick test; *STU*, Stallergenes units; *TCI*, topical calcineurin inhibitors; *TCS*, topical corticosteroids; *Topicals*, topical steroids, calcineurin inhibitors, and/or topical antibiotics.
See Supplement E1 for details.

compared to no AIT (40% vs 26%, RR 1.53 [95% CI, 1.31-1.78], moderate certainty, Fig 2) with similar estimates of effect for SCIT and SLIT ($P_{interaction}$ = .63). Median (range) time to effect was 5 (1-12) months. In sensitivity analyses, the corresponding pooled relative AD severity among patients receiving AIT compared to no AIT was a RoM 0.67 (95% CI, 0.59-0.76) (see Fig E3 and Table E1 in the Online Repository at www.jacionline.org).

AD-related QoL. Eight RCTs[60,63,65,67-69,74,78] (n = 629) addressed the impact of AIT versus no AIT on health-related QoL (measured using DLQI and a minimally important difference of 4[79]). AIT probably improved DLQI by 4 or more points compared to no AIT (56% vs 39%, RR 1.44 [95% CI, 1.03-2.01], moderate certainty, Fig 3). The corresponding pooled relative AD-related QoL among patients receiving AIT compared to no AIT was a RoM 0.75 (95% CI, 0.64-0.89) (Fig E3, Table E2).

Itch. Three RCTs[59,63,64] (n = 113) addressed AIT's impact versus no AIT on itch (pruritus). AIT may reduce itch by 50% from baseline compared to no AIT, but the evidence is uncertain (25% vs 19%, RR 1.29 [95% CI, 0.84-1.98], low certainty, Fig 4). Findings were similar when the data were interpreted using fixed effect analyses (RR 1.43 [95% CI, 0.95-2.17], Table E2) or, because itch is a domain within SCORAD, a Bayesian approach assuming itch would improve similarly to the overall AD severity intervention effects (28% vs 19%, RR 1.46 [95% credible interval, 1.12-1.89], Fig 4). The corresponding pooled relative itch severity among patients receiving AIT compared to no AIT was a RoM of 0.79 (95% CI, 0.64-0.99, Fig E3, Table E2).

TABLE II. Summary of findings for AIT using SCIT or SLIT compared to no AIT for AD

Outcome	No. of participants (no. of studies)	Relative effect (95% CI)	Absolute effects (95% CI) for: Without AIT (placebo)	With AIT	Difference	Certainty	Plain-language summary
AD severity, improvement of 50% from baseline (SCORAD [0-103, higher worse], combination of clinician-reported severity and patient-reported sleep disturbance and itch)	1801 (22 RCTs)	RR 1.53 (1.31-1.78), RoM 0.67 (0.59-0.86)	26%	40% (34-46)	14% more (8 to 20 more)	⊕⊕⊕◯ Moderate*	AIT using SCIT or SLIT probably results in an important improvement in AD severity.
QoL improvement in DLQI, MID (4 or more; scale 0-30, higher worse)	629 (8 RCTs)	RR 1.44 (1.03-2.01), RoM 0.75 (0.64-0.89)	39%	56% (40-79)	17% more (1 to 40 more)	⊕⊕⊕◯ Moderate*†	AIT using SCIT or SLIT probably results in an important improvement in AD-related QoL.
Flares leading to systemic steroid therapy	165 (4 RCTs)	RR 0.94 (0.30-2.94)	22%	20% (7-65)	2% fewer (15 fewer to 43 more)	⊕◯◯◯ Very low*‡	The effect of AIT on AD flares is highly uncertain.
Adverse events	1041 (12 RCTs) (AIT in ARC and asthma reviews [87 RCTs])	RR 1.61 (1.44-1.79)	SCIT 41%, SLIT 8%	SCIT 66% (59-73), SLIT 13% (12-14)	SCIT 25% more (18 to 32 more), SLIT 5% more (4 to 6 more)	⊕⊕⊕⊕ High	AIT increases adverse events.
Systemic reactions	857 (11 RCTs) (AIT in ARC and asthma reviews [59 RCTs])	RR 1.37 (1.15-1.64)	SCIT 8%, SLIT 0.1%[106]	SCIT 11% (9-13), SLIT 0.14% (0.12-0.16)	SCIT 3% more (1 to 5 more), SLIT 0.04% more (0.02 to 0.06 more)	⊕⊕⊕◯ Moderate§	AIT using SCIT probably results in an important increase in systemic allergic reactions and probably has little to no increase with SLIT.
Adverse events causing therapy discontinuation	1608 (14 RCTs) (AIT in ARC reviews [14 RCTs])	RR 1.39 (0.94-2.05)	SCIT 7% SLIT 0.9%	10% (7-14) 1.2% (0.8-1.8)	3% more (0.4 fewer to 7 more) 0.3% more (0.05 fewer to 0.9 more)	⊕⊕⊕◯ Moderate‡	AIT using SCIT likely increases adverse events causing discontinuation SLIT results in little to no increase in adverse events causing discontinuation.

Population was AD or atopic eczema. Intervention was AIT by SCIT or SLIT. Comparison was no AIT. The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Baseline risks are median of the control arms among the included trials unless otherwise specified.

ARC, Allergic rhinitis (and/or conjunctivitis); *MID,* minimally important difference. GRADE Working Group grades of evidence are as follows: *High,* we are very confident that the true effect lies close to that of the estimate of the effect; *moderate,* we are moderately confident in the effect estimate: the true effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different; *low,* our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect; and *very low,* we have very little confidence in the effect estimate, so the true effect is likely to be substantially different from the estimate of effect.

*Risk of bias. Multiple studies were at risk of bias as a result of outcome assessors and/or patients not always being blinded to group allocation, and as a result of missing outcome data. Although we did not find a significant difference between studies that had high or low risk of bias, we conservatively chose to rate down the certainty of the evidence.

†Indirectness. Because all but 1 RCT used SLIT, the evidence is more indirect for SCIT, and overall certainty could be lower. The improvements in SCORAD, however, supported not rating down.

‡Imprecision. We noted wide CIs that included important benefit and harm (all instances of note), and low information size (flare).

§Indirectness. Systemic allergic reactions captured in the studies were a mix of immediate (eg, generalized urticaria and anaphylaxis) and delayed (anaphylaxis or eczematous eruptions). Information from non-AD populations (rhinitis and asthma) provide increased confidence in the estimate—more so for urticarial and anaphylactic allergic systemic reactions than for the potential eczematous eruptions that might also occur in AD with AIT.

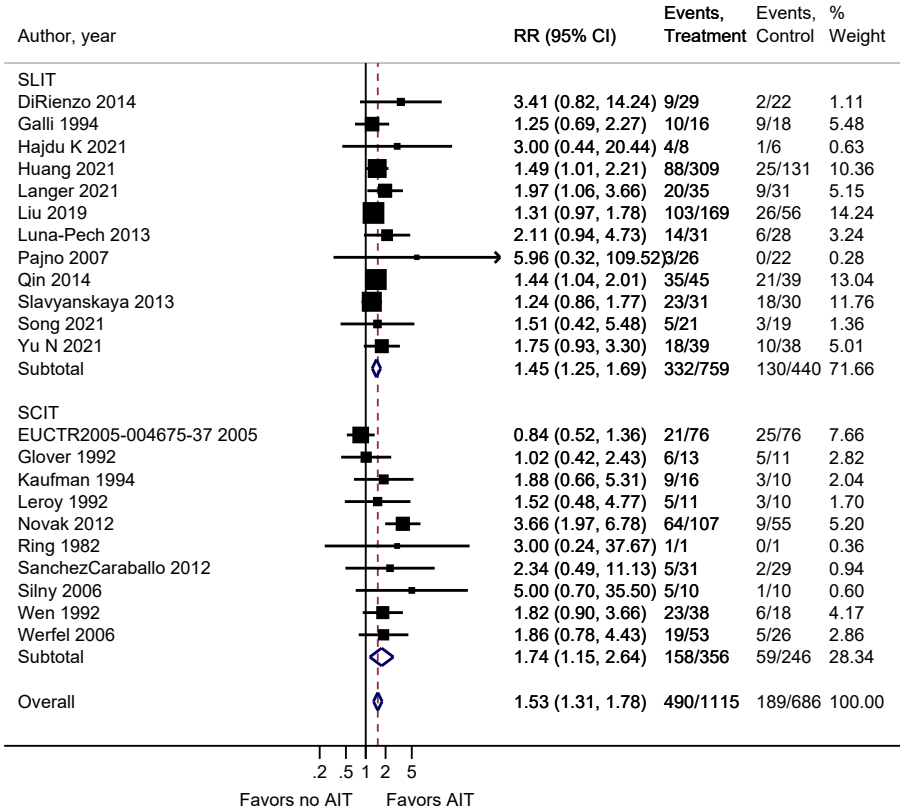

FIG 2. Impact of AIT on AD (eczema) severity. Meta-analysis of probabilty to improve by 50% from baseline.

Sleep disturbance. One study[63] (n = 66) reported sleep loss on a visual analog scale (0 to 10, higher worse) as an estimated mean (SD) change from baseline of −2.81 (2.42) in the AIT group and −2.74 (2.58) in the no-AIT group for a between group mean (95% CI) difference of −0.07 (−1.28 to 1.14, Fig E3). Another RCT[59] collected data on sleep disturbance but did not report the data. The effect of AIT compared to no AIT on sleep loss in patients with AD is therefore very uncertain (very low-certainty evidence).

AD flares. Four RCTs[62,64,68,71] (n = 165) addressed flares leading to systemic corticosteroid therapy. The effect of AIT, compared to no AIT, was very uncertain (20% vs 22%, RR 0.94 [95% CI, 0.30-2.94], very low certainty, Fig E3).

Adverse events. Adverse events estimated from the AD trials alone were often insufficient to meaningfully inform decision making and were therefore pooled in frequentist and Bayesian frameworks[35] with systematic reviews of AIT used similarly for allergic rhinitis and asthma[36-42] (Fig 5, Fig E3).

Twelve RCTs[57-59,64,65,67-69,71,72,78] (EUCTR2005-004675-37) (n = 1041) in AD and 87 RCTs in rhinitis and asthma[36-42] addressed adverse events from AIT and were described as primarily local reactions. The local reactions in SCIT were primarily reported as injection site reactions. The local reactions in SLIT were primarily oropharyngeal symptoms, such as transient pruritus and irritation. Compared to placebo, AIT increased local adverse events (RR 1.65 [95% CI, 1.48-1.64], high certainty) with similar relative effects for SCIT and SLIT ($P_{interaction}$ = .42) and different absolute effects (SCIT, 66% vs 41%; SLIT, 13% vs 8%).

Eleven RCTs[57,59,64,65,67-72,78] (n = 857) in AD and 59 RCTs in rhinitis and asthma[36-42] addressed systemic allergic events from AIT. Compared to placebo, AIT increased systemic reactions (RR 1.37 [95% CI, 1.15-1.64], moderate certainty) with similar relative effects for SCIT and SLIT ($P_{interaction}$ = .18) but different absolute effects (SCIT, 11% vs 8%; SLIT, 0.14% vs 0.1%). One reason we rated the certainty of the evidence down is because the systemic reactions reported in the AD studies were a mix of immediate (eg, generalized urticaria and anaphylaxis) and delayed reactions (eg, eczematous eruptions). Information from non-AD populations (rhinitis and asthma) provide increased confidence in the estimate for urticarial and anaphylactic allergic systemic reactions rather than the potential eczematous eruptions that might also occur in AD with AIT, and therefore the overall certainty of the evidence was rated down to moderate.

Fourteen RCTs[57-59,61,63-65,67-69,71,77,78] (EUCTR2005-004675-37) (n = 1608) in AD and 14 RCTs in rhinitis[39,40] (no robust systematic review examined AIT's effect on this outcome in asthma) addressed adverse events causing discontinuation from AIT. Compared to placebo, AIT probably increased adverse effects severe enough to cause discontinuation (RR 1.39 [95% CI, 0.94-2.05], moderate certainty) with similar relative effects for SCIT and SLIT $P_{interaction}$ = .38), but different absolute effects (SCIT, 10% with SCIT vs 7% with placebo; SLIT, 1.2% with SLIT vs 0.9% with placebo).

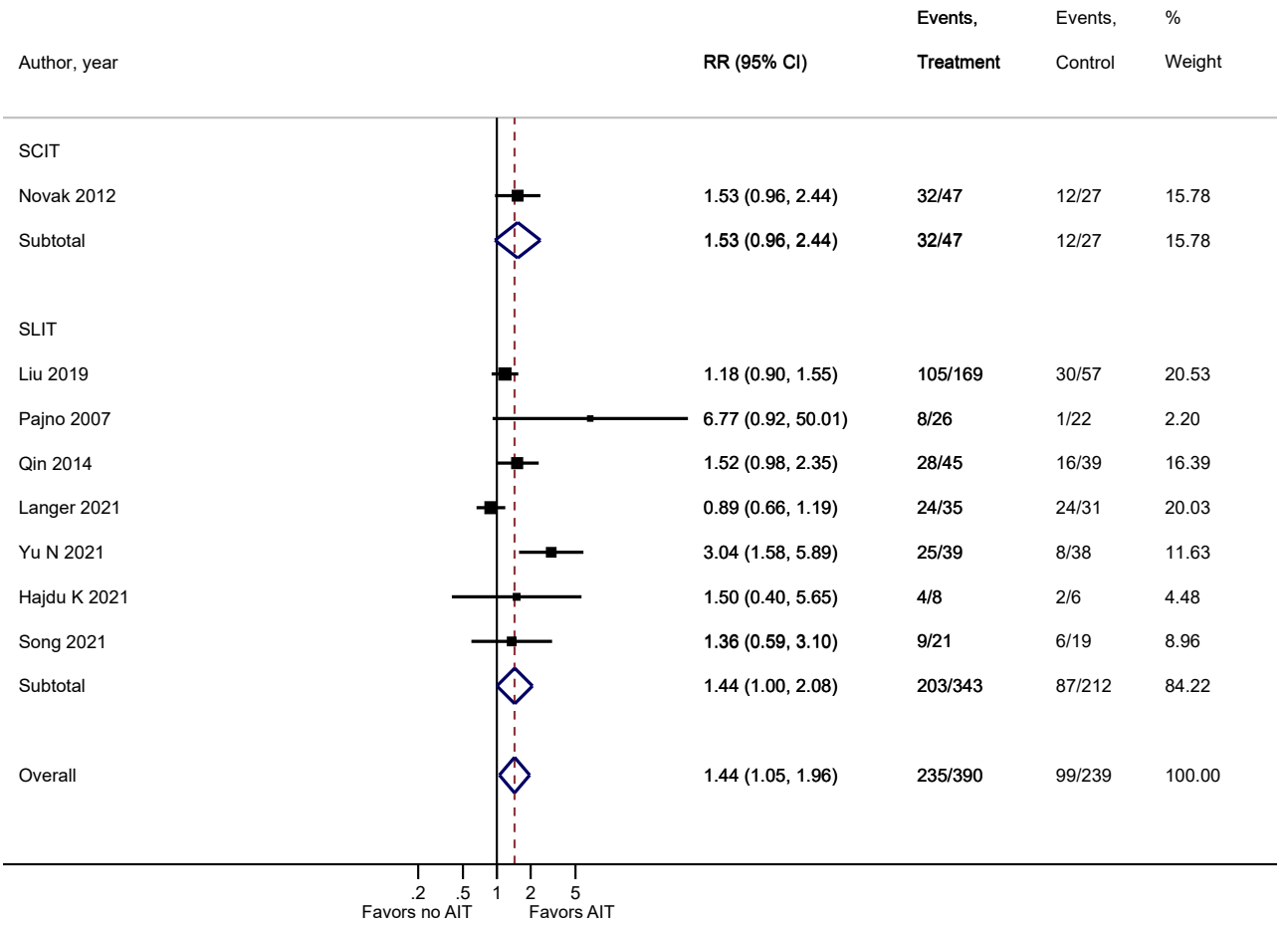

FIG 3. Impact of AIT on AD (eczema)-related QoL. Improvement measured by DLQI by minimally important difference of 4.

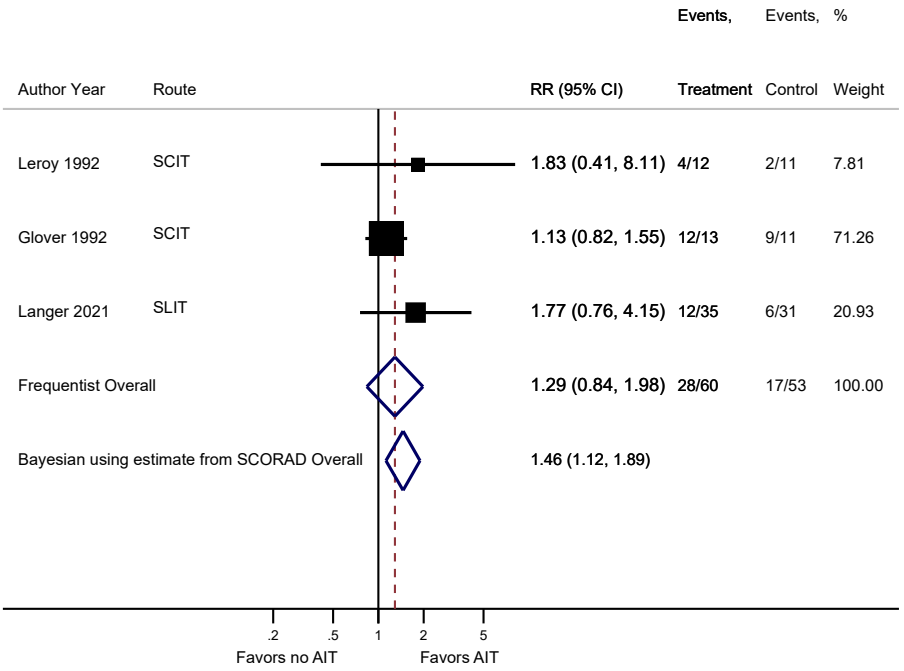

FIG 4. AIT impact on itch (pruritus).

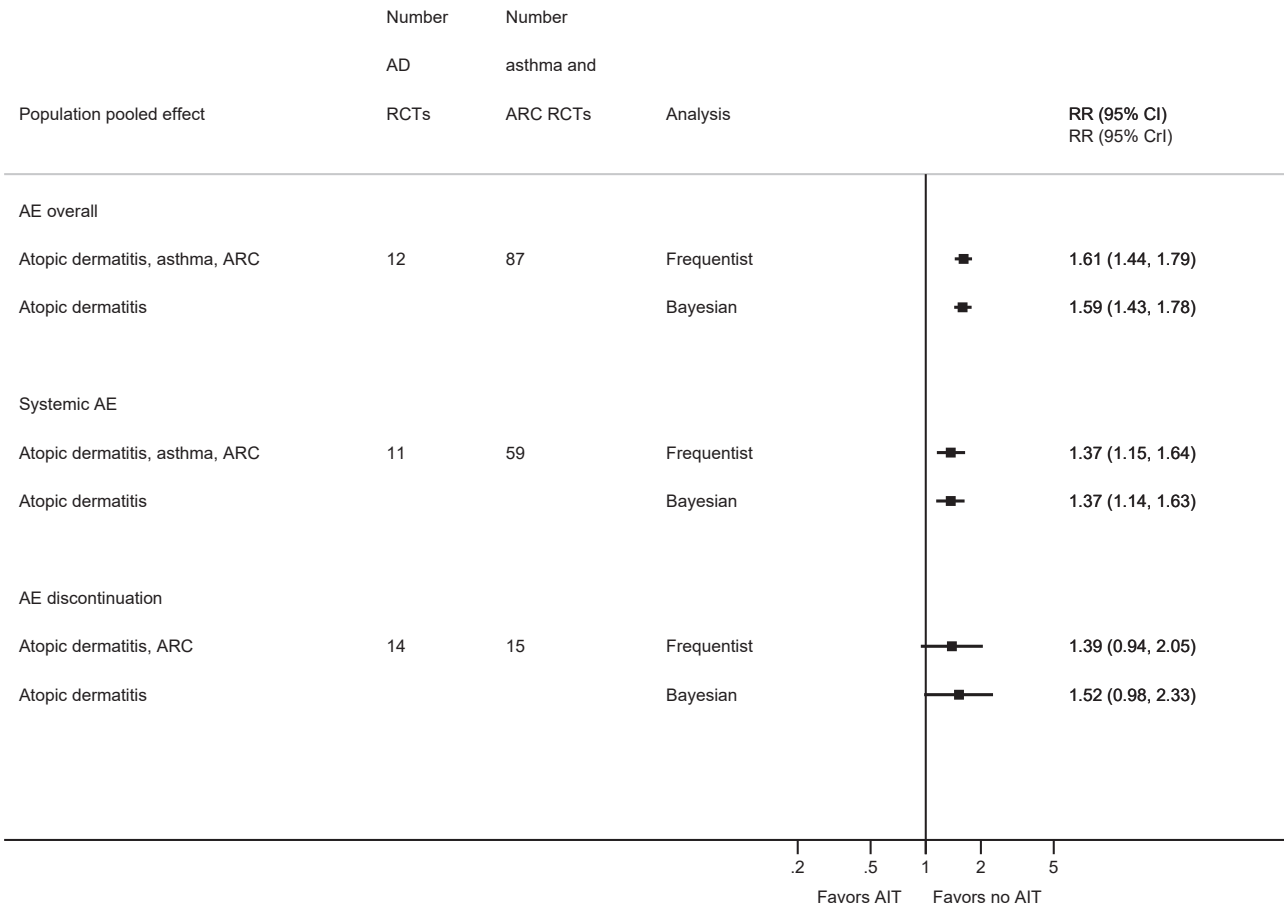

FIG 5. AIT impact on adverse events.

Additional analyses

The findings were supported by sensitivity analyses including fixed effect models, Bayesian analyses, excluding any one study, making plausible assumptions for missing outcome data, using different analytic approaches (eg, RoM), restricting analyses to RCTs with a sample size of 70 or more, and using Hartung-Knapp-Sidik-Jonkman models (Table E2).

Subgroup analyses showed no relative effect modification among outcomes for age, drug administration route (SCIT vs SLIT), AIT duration, country of study conduct, latitude from equator, baseline AD severity, comparator (placebo or unblinded standard care), dust mite species used, monoallergen versus multiallergen AIT, formulation, commercial versus noncommercial funding, monosensitized versus polysensitized patients, source of funding, published versus unpublished report, or risk of bias (Table E2).

DISCUSSION

This systematic review of 23 RCTs including 1957 patients with AD shows with moderate certainty that AIT importantly improves AD severity and QoL. The relative benefits were similar among SCIT and SLIT, among children and adults, and across AD severities. SCIT likely and importantly increases adverse events (primarily injection site reactions followed by systemic reactions and adverse events important enough to cause drug discontinuation), whereas the small increase in adverse events (primarily transient oropharyngeal reactions) with SLIT may be, on average, unimportant. The impact of immunotherapy on long-term AD control, flares, and patient-reported AD severity (and the specific domains of itch and sleep quality) are less certain. The overall evidence is best for immunotherapy to HDM rather than other environmental allergens, though the specific species (Der p and/or Der f) and formulations did not modify the effects seen. AIT took months to take effect.

Our findings support an important role for allergy in contributing to AD outcomes. Allergens such as HDM may drive innate and adaptive inflammatory processes through specific cellular and humoral mechanisms[80,81] beyond contributing to epidermal barrier disruption via their allergen-intrinsic enzymatic activity[82-85] and direct innate cell activation.[86-88] These mechanisms could lead to the elaboration of multiple cytokines including IL-4 and IL-13 from T cells, and local production of thymic stromal lymphopoietin, IL-25, IL-33, and granulocyte-macrophage colony-stimulating factor[89-91] by multiple cellular sources that promote skin inflammation and itch. Conversely, AIT's multiple anti-inflammatory, immunomodulatory, and protolerogenic mechanisms,[92-94] including induction of IL-10 production by innate cells, epithelial repair, and modulation of the JAK-STAT pathway,[95] might explain the clinical benefits observed in this meta-analysis. Additional research is needed to better understand the mechanisms by which allergens and AIT affect AD and might interact with the other factors that drive disease.

The clinical implications of our findings suggest that the effectiveness, wide availability, safety in pregnancy,[15,96,97] and

relatively low cost of AIT compared to some other modalities must be carefully considered against its harms (likely similar to those for rhinitis and asthma[98]) and well-recognized burdens in terms of time commitment and inconveniences (eg, daily SLIT dosing or weekly to monthly SCIT injections). Second, an established role for allergy in AD implies that optimal AD outcomes might be best achieved through multidisciplinary care. Differentiating allergy from clinically irrelevant sensitization in AD, however, can be challenging and could be addressed using a combination of clinical history (eg, exacerbation after allergen exposure), considering the most likely relevant allergen exposures in a patient's environment, and judicious testing. Third, the improvements in AD's severity (SCORAD, a combination of clinical-reported severity and patient-reported itch and sleep disturbance) being on a relative scale implies that the magnitude of absolute changes on the SCORAD scale will vary depending on the baseline AD severity, albeit the AAAAI/ACAAI guideline panel, and studies suggest a reduction in SCORAD by 50% is likely to be important for many patients with AD. Those with milder AD, however, might accept a smaller absolute magnitude of AD improvement depending on if they also importantly experience allergic rhinitis and/or allergic asthma and would expect all conditions to improve with AIT. Clinicians and decision makers will have to carefully navigate these common and probably preference-sensitive scenarios in order to optimally treat patients with AD.

Our findings of moderate- to high-certainty evidence in 5 of 8 patient-important outcomes suggests that future research should clarify the impact of AIT on long-term AD control and flares, and whether patient-reported AD severity (eg, using a patient-oriented eczema measure), itch, and sleep disturbance fully align with those captured by SCORAD's total score.[99] Robust RCTs are required to clarify the effect of AIT using allergens other than HDM, optimal dose, or formulations such as sublingual tablets on short-term (months) and long-term (years) AD outcomes. Many patients might also favor AIT should it prove capable of inducing long-term improvements in disease, including remission, similar to how it has for allergic rhinitis and asthma.[100,101] Sample size estimates informed by our study's findings suggest a 352-participant RCT or RCTs might robustly address these now open questions (see Supplement E3 in the Online Repository at www.jacionline.org).

Strengths of this review include using structured GRADE and Cochrane methods, incorporating multidisciplinary and patient and caregiver perspectives through the AAAAI/ACAAI 2022 guideline panel and its patient partners, and performing a comprehensive search to synthesize 10 more RCTs and over 1200 more patients compared to previous systematic reviews, which were unable to draw clear conclusions regarding efficacy and safety.[17-20]

There are potential limitations. First, not all populations had the same baseline severity of AD. We addressed this using relative changes from baseline, a common measure among modern AD trials, along with structured assessment and tests for interaction to evaluate for credible effect modifiers. (We found none.) Second, we included conference abstracts,[102] which some might question the appropriateness of, although their inclusion might mitigate against publication bias, and we found no modification of our estimates by including them. Third, the data are sparse for some outcomes like itch, sleep, and flares, which we addressed using structured appraisal of imprecision using GRADE, Bayesian sensitivity analyses, standardized language to express uncertainty, and directed calls for future research. Future studies should ensure that all patient-important outcomes are reported and that when collected, all measures are fully reported. For example, if total SCORAD is captured, then the subdomains objective SCORAD, itch, and sleep should also be reported. Similarly, although we did not detect differences in effects between studies at high versus low risk of bias, we opted to conservatively rate down the certainty of the evidence to moderate. Fourth, time-to-effect analyses are crude estimates, and future studies must formally address this. Fifth, there was sparse direct AD evidence addressing adverse events, which we addressed by incorporating AIT's extensive safety data from rhinitis and asthma using frequentist and Bayesian frameworks; we found similar adverse event rates across indications. Future studies should clearly document whether systemic reactions after AIT for AD are immediate (eg, anaphylaxis) or delayed (eg, eczematous eruption or AD flare). Sixth, no study addressed AIT's potential long-term immunomodulatory effects.

This synthesis of current best evidence shows that aeroallergen AIT improves AD outcomes in patient-important ways that must be balanced by a modest increase in harms; some may be important for SCIT but unimportant for SLIT. These findings support patients, caregivers, clinicians, and other decision makers in achieving optimal AD care.

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Clinical implications: Moderately certain evidence from 23 RCTs including 1957 patients shows that adjunctive AIT improves AD (eczema) severity and QoL. High-certainty evidence shows that AIT increases adverse events.

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