

REVIEW ARTICLE

Allergen immunotherapy for asthma prevention: A systematic review and meta-analysis of randomized and non-randomized controlled studies

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Abstract

Background: Allergen immunotherapy (AIT) is a disease-modifying treatment for IgE-mediated diseases. Randomized controlled trials (RCTs) support AIT's potential role in asthma prevention but evidence from non-randomized studies of interventions (NRSI) and longitudinal observational studies has been poorly addressed. Therefore, we aimed to conduct a systematic review and meta-analysis to assess clinical data from all study types to evaluate quantitatively the preventive role of AIT in asthma onset.

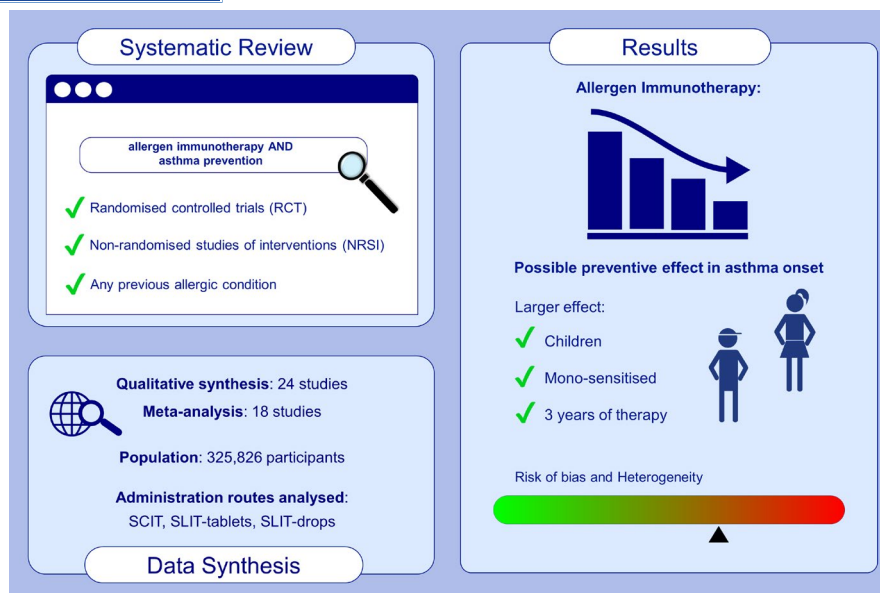
Methods: We search three databases. Studies were screened, selected and evaluated for quality using risk-of-bias (ROB) tools. Data were descriptively summarized and meta-analysed using random effects. We performed a sensitivity, influence and subgroup analyses. Publication bias and heterogeneity were assessed.

Results: From the 4549 identified studies, 24 (12 RCTs and 12 NRSI) were included in the qualitative synthesis and 18 underwent meta-analysis. One study was at low ROB, seven had moderate ROB, and 15 were proven of high ROB. Random-effects analysis showed a significant decrease in the risk of developing asthma following AIT by 25% (RR, 95% CI: 0.75, 0.64–0.88). This effect was not significant in the sensitivity analysis. Publication bias raised concerns, together with the moderate heterogeneity between studies ($I^2 = 58\%$). Subgroup analysis showed a remarkable preventive effect of AIT in children (RR, 95% CI: 0.71, 0.53–0.96), when completing 3 years of therapy (RR, 95% CI: 0.64, 0.47–0.88), and in mono-sensitized patients (RR, 95% CI: 0.49, 0.39–0.61).

Conclusions: Our findings support a possible preventive effect of AIT in asthma onset and suggest an enhanced effect when administered in children, mono-sensitized, and for at least 3 years, independently of allergen type.

KEYWORDS

allergen immunotherapy, allergy treatment, asthma, prevention, rhinitis



GRAPHICAL ABSTRACT

This systematic review and meta-analysis included 18 studies (RCT and NRSI) in the quantitative synthesis. Our findings support a possible preventive effect of AIT in asthma onset. This effect might be enhanced when administered in children, mono-sensitised, and for at least three years, independently of allergen type. NRSI, non-randomised studies of intervention; RCT, randomised controlled trial; SCIT, subcutaneous immunotherapy, SLIT, sublingual immunotherapy.

1 | INTRODUCTION

Allergen immunotherapy (AIT), administered either by the sublingual (SLIT) or the subcutaneous (SCIT) route, has been used to treat some IgE-mediated allergic diseases for many decades.^{1,2} Recent literature has highlighted the importance of studying allergic conditions using a multimorbidity framework instead of the classic transition from one disease to another, allowing for a mechanism-based treatment approach, such as AIT.^{3–5} However, it is not fully understood how IgE profiles and other underlying allergic (and non-allergic) mechanisms in multimorbidities relate to better treatment response and prognosis, including the risk of developing other allergic conditions.^{3,5,6} Atopic sensitization is a risk factor for the development of allergic multimorbidities,^{4,6,7} and the presence of allergic diseases, such as food allergy, atopic dermatitis, rhinitis and rhinoconjunctivitis, is a significant risk factor for asthma development.⁸ Children with allergic rhinitis have a higher risk of developing asthma later in life, and the co-existence of these diseases is very frequent since both share common pathophysiological features.^{7,9}

Allergen immunotherapy induces allergen-specific immune tolerance and suppresses allergic inflammation by inducing changes in the profile of T- and B-cell responses to allergens, by decreasing activation and degranulation of effector cells, and by reducing effector cells pro-inflammatory mediators in mucosal tissues.^{10,11} Studies evaluating the effectiveness of AIT in patients with allergic rhinitis suggest a reduction in the risk of developing asthma.^{12,13}

Asthma affects more than 300 million people worldwide and it is expected to increase in the upcoming years, being one of the most common non-communicable diseases with a high impact on patient's

lives and healthcare systems.¹⁴ Thus, there is interest in gathering information from all studies investigating this potential preventive effect of AIT in asthma onset. In 2017, the European Academy of Allergy and Clinical Immunology (EAACI) conducted a systematic review (SR) to assess the effectiveness of AIT in the prevention of asthma and the development of new sensitizations using randomized controlled trials (RCTs).¹² This study showed a significant reduction in the short-term risk of patients with allergic rhinitis developing asthma (RR: 0.40; 95% CI: 0.29–0.54) when data from six RCTs were combined.

In this SR, we aimed to assess and update the current knowledge in this field by assembling and presenting new evidence, not limited to RCTs, but including non-randomized studies of interventions (NRSI) and longitudinal observational studies. The outcome of interest in this SR is the development of asthma. Different outcome definitions were considered to achieve a comprehensive analysis.

2 | METHODS

2.1 | Search strategy and study selection

A search was performed in Pubmed, Scopus and Cochrane databases for articles published until 6 April 2021 using the following search terms: (immunotherapy OR vaccine OR allergy shot) AND asthma* AND (prevent* OR risk). During the search, we selected studies conducted in humans and published in English, Spanish or Portuguese. No data restrictions were employed, and the search algorithm was repeated in the final stage of the review (date: 30.12.2021) to confirm whether new papers were

available. Duplicates were removed, and two independent reviewers screened the search results based on the title and abstract. Any original study that evaluated the effect of AIT on the development of asthma in healthy subjects or subjects with other allergic diseases was included. Two independent reviewers read the full text of the previous selected studies and those accomplishing the inclusion criteria were selected for data extraction. In case of disagreement, a third reviewer was consulted. References were managed with EndNote X9 Software (Clarivate). A manual search of the reference lists from all the relevant original studies and review articles to identify additional eligible studies was performed.

2.2 | Inclusion criteria

Inclusion criteria were defined following the PICOS framework. We were interested in studies conducted on subjects of any age, either healthy or with allergic conditions such as rhinitis, atopic dermatitis or rhinoconjunctivitis. AIT studies including subjects with comorbid asthma were included if data were available for the outcome of interest in those without asthma. The intervention was AIT with any allergen administered through any route, SLIT or SCIT. The comparator group included placebo or no intervention (control group). The outcome of interest was the development of asthma. Different asthma definitions were considered for the inclusion of studies to guarantee a comprehensive analysis: asthma symptoms and/or asthma medication, and GINA-based or medical diagnosis. RCTs and NRSI (cross-sectional, retrospective or prospective) were considered for selection and data extraction.

2.3 | Data extraction and synthesis

One reviewer extracted the main characteristics of eligible studies (study design, population characteristics, intervention, comparator, follow-up, baseline allergic conditions, asthma definition and outcome of interest) onto a customized data extraction sheet in Microsoft Excel. A descriptive summary and data tables were produced to summarize the literature. The outcome of interest was extracted, when possible, as the absolute number of subjects developing asthma (event rate data). When not reported, this number was estimated if the percentage of subjects developing the outcome was available or by contacting the authors of the study. If none of the previous data was reported, the study was only considered for the qualitative synthesis. The data available for the intention-to-treat population were preferable and, if not reported, the per-protocol population was extracted.

2.4 | Quality assessment

The revised Cochrane Risk of Bias tool (RoB2) for randomized trials¹⁵ was used to assess the risk of bias (ROB) of the included

RCTs. The ROB was judged as low, moderate, high or unclear for each domain: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and overall bias. This assessment was performed independently by the two reviewers and discussed if results differed across the evaluations. The Risk of Bias tool for non-randomized studies of interventions (ROBINS-I) was used to assess the ROB of the included observational studies.¹⁶ The domains included in this tool are divided according to the stage of the intervention: pre-intervention (bias due to confounding, bias in selection of participants into the study), at intervention (bias in classification of interventions) and post-intervention (bias due to deviations from intended interventions, bias due to missing data, bias in measuring outcomes and bias in a selection of the reported result). The domains and the overall ROB were judged as low, moderate, high (included serious and critical judgements) or unclear.

2.5 | Data analysis

Meta-analysis using the random-effects model approach was performed in the available data provided by 18 studies and using RStudio software v3.4.2 (R Foundation). For dichotomous variables, the event rate data were pooled as risk ratio (RR) with a 95% confidence interval using the Der Simonian-Laird estimator.^{17,18} The magnitude of heterogeneity between the included studies was estimated using the Higgins I^2 statistic, Cochran's Q, tau-squared and prediction interval. Outlier and influential analyses were performed to improve the robustness of the results. Publication bias was assessed through the creation of a funnel plot and using Egger's test.¹⁹ In case of publication bias, Thuvail & Tweedie's trim-and-fill procedure was applied to estimate the effect size if missing small studies have been published.²⁰

Sensitivity analysis was performed according to the risk of bias/quality of evidence by comparing the summary estimates obtained by excluding studies to be at high risk of bias with those considered at low and moderate risk. Subgroup analyses were undertaken according to the type of study (RCT vs. NRSI), AIT administration route (SLIT tablets vs. SLIT drops; any SLIT vs. SCIT), population (children vs. adults), asthma definition, follow-up and therapy duration, type of outcome analysis (primary or secondary outcomes/endpoints), allergen (grass pollen vs. house-dust mites), history of sensitization (mono- vs. poly-sensitized) and funding (pharmaceutical industry vs. academic/other).

2.6 | Registration and reporting

This systematic review was reported per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist 2020 and the Cochrane Handbook for Systematic Reviews of Interventions Version 6.1.^{17,21} This review is registered with PROSPERO registration number: CRD42021251166.

3 | RESULTS

3.1 | Study selection and characterization

In this systematic review, we identified 4549 potentially eligible studies after the removal of duplicates. During the screening of titles and abstracts using the prespecified inclusion criteria, 4482 studies were rejected, yielding 67 studies for a complete revision. Each of those studies was then reviewed. Forty-three studies were later excluded. Thus, 24 studies were included for the qualitative analysis and 18 for the quantitative analysis. Figure 1 shows the flow diagram of the search and selection process.

Regarding study design, 12 RCTs were included.^{22–33} Of these, three publications are from the PAT study (the Preventive Allergy Treatment study) but with different updates according to the follow-up duration; after 3 years of therapy,²⁸ and after 2 and 7 years of therapy discontinuation.^{26,27} Twelve studies were NRIS.^{34–45} Of these, six studies used secondary data from healthcare databases; one analysed real-world data from a population-based administrative healthcare database,³⁶ while five used real-world data from a health insurance prescription database.^{35,42–44,46} Three studies were not eligible for meta-analysis; one due to the single-arm design (no comparator group)⁴⁰ and two studies used a mixed population (with

asthma and/or rhinitis) but did not present the data for those only with rhinitis at baseline.^{25,32} Additionally, due to different follow-up times of the same population, three studies were also not included in the main meta-analysis.^{26,27,41}

The population in each study varied significantly, ranging from 28 subjects (14 in the intervention group vs. 14 in the comparator group) up to 118,754 subjects (2431 in the intervention group vs. 116,323 in the comparator group). Eleven studies were performed only in children, one in adolescents, one in adults and eleven in a mixed population (children and adults). Most studies were performed in a population with allergic rhinitis ($n = 12$), followed by rhinoconjunctivitis ($n = 9$), atopic dermatitis ($n = 2$) and healthy individuals ($n = 1$). Eleven studies also included participants with allergic asthma; nine presented the data for the subpopulation without asthma at baseline. Eight only included participants mono-sensitized to the specific allergen under investigation. Asthma onset was the primary outcome/endpoint only in seven publications.

SLIT was evaluated in thirteen studies, SCIT in eight, and both in three studies of which two studies presented data separately according to the administration route. The allergens used for AIT were grass pollen (7 studies), house dust mites (5 studies), birch pollen (2 studies) and *Parietaria judaica* (1 study). Nine studies evaluated more than one allergen but results were not presented separately

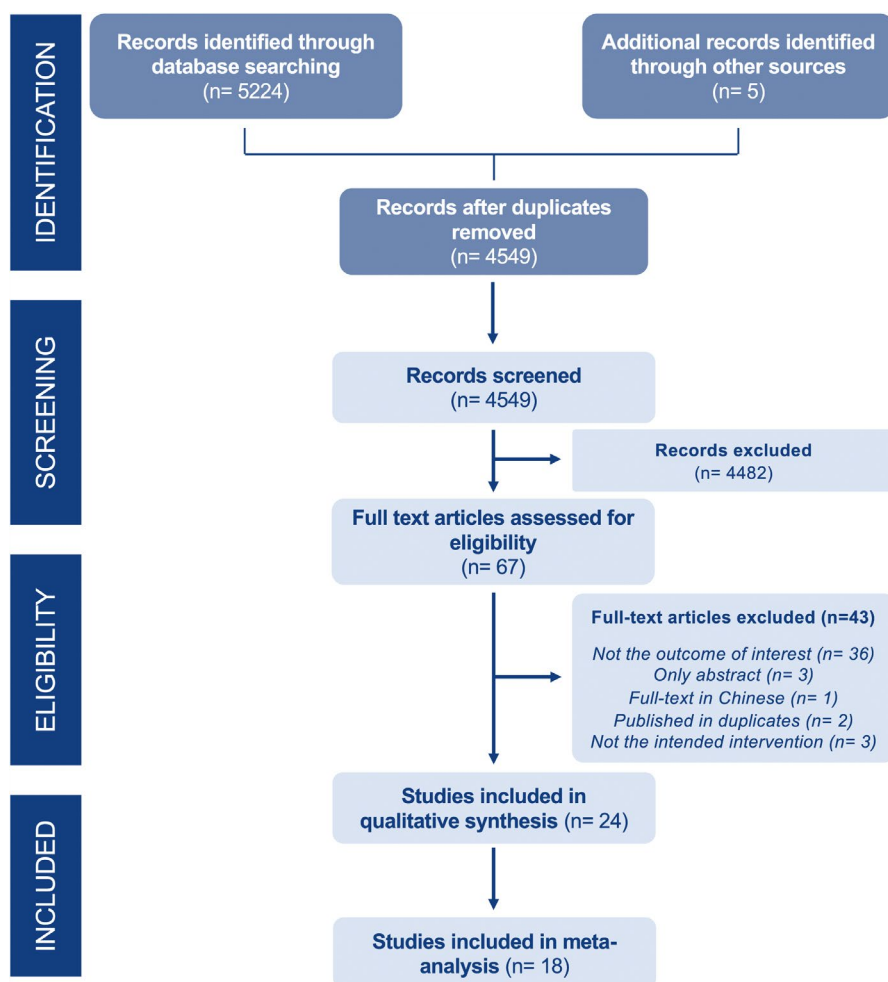


FIGURE 1 PRISMA flow diagram of the studies included

according to the type of allergen used for AIT. The follow-up after treatment discontinuation varied from 9 months to 12 years, while some studies did not conduct a follow-up of participants after discontinuation.

The definition of the outcome (asthma) varied between studies, and it was grouped as follows: a) asthma symptoms, presence of one or more symptoms of asthma (nine studies); b) asthma medication, prescription and use of asthma medication (5 studies); c) asthma symptoms and medication use; d) the combination of the previous definitions and the presence of both to define asthma (4 studies); e) and mixed criteria, according to symptoms, lung function and medication use or following the GINA guidelines (5 studies).

The key characteristics and main findings are presented in Table 1. Risk-of-bias results are detailed in the Appendix S1.

3.2 | Random-effects meta-analysis and sensitivity analysis

Random-effects meta-analysis of studies demonstrated a significant decrease in the risk of developing asthma following AIT by 25% (RR, 95% CI: 0.75, 0.64–0.88; $N = 17$) (Figure 2). The three indicators of between-study heterogeneity show moderate-to-high heterogeneity between the pooled studies (Figure 2). The broad prediction interval (0.53–1.08), which surpasses the value one, does not allow to overly confidence in the preventive effect of the intervention, meaning that AIT may not be protective in every context. In addition, after excluding studies with high risk of bias the result did not remain significant (RR, 95% CI: 0.76, 0.45–1.27; $N = 7$; $I^2 = 27\%$). When including the study considered an outlier (Fritzching et al, 2021) and when excluding influential studies from the analysis (Fritzching et al, 2021 and Wahn et al, 2018), the results remained significant and similar (Figures S3, S4, S5, S6) showing the robustness of these findings. The evidence of publication bias needs to be considered since the funnel plot (Figure 3) shows substantial asymmetry and the Egger's test is statistically significant ($p < .01$), denoting that small studies without a significant effect might be missing. When performing the trim-and-fill analysis to impute data from missing studies, the result remained marginally significant (RR, 95% CI: 0.82, 0.68–0.98) and the heterogeneity remained moderate-to-high ($I^2 = 59.7\%$). The analysis by study design evidenced the protective effect of AIT in preventing asthma onset in RCTs (RR, 95% CI: 0.59, 0.40–0.88; $I^2 = 17\%$), while in NRSI studies, the effect was not significant (RR, 95% CI: 0.82, 0.66–1.02; $I^2 = 86\%$). The between-study heterogeneity in RCTs was low ($I^2 = 17\%$), and the prediction interval remained wide (0.31–1.12); thus, these results need to be interpreted with caution.

3.3 | Subgroup analysis

Given the number of studies needed to perform the subgroup analysis to evaluate AIT in different contexts, we decided to perform the analysis combining all types of studies independently of the design.

This analysis showed that AIT is beneficial in specific circumstances (Table 2): a) studies conducted only in children (RR 95% CI: 0.71, 0.53–0.96; N studies = 8); b) mono-sensitized patients (RR 95% CI: 0.49, 0.39–0.61; $N = 6$); c) AIT administration for at least 3 years (RR 95% CI: 0.64, 0.47–0.88; $N = 8$); d) follow-up after AIT discontinuation for up to 3 years (RR 95% CI: 0.74, 0.62–0.88; $N = 14$); and e) evidence from academic/or studies (RR 95% CI: 0.68, 0.53–0.88; $N = 10$). When asthma was defined by symptoms, medication and lung function (mixed criteria) or only by medication, the results did not remain significant. The AIT administration route did not influence the results since results were significant for both SCIT and SLIT. We were able to pool the results for grass pollen and HDM studies and results were significant for both. Concerning SLIT administration, both drops and tablets were statistically significant, with a larger effect observed when administering SLIT in drops. The subgroup analysis was further stratified according to SLIT and SCIT administration, but there were some limitations due to the low number of studies considered in each group, and results need to be interpreted cautiously (Table 2).

4 | DISCUSSION

This meta-analysis suggests a preventive effect of allergen immunotherapy in asthma development, confirming the association found in previous studies. The preventive effect of AIT was noteworthy in children, mono-sensitized patients, and when administered for at least 3 years, independently of the allergen (grass pollen or HDM) and administration route (SCIT, SLIT tablets or SLIT drops), indicating an overall effect of this therapy on the outcome of interest. The results were robust for the short-term (3 years of follow-up). This is the first meta-analysis combining all the evidence, independently of study design, since both RCTs and NRSI were reviewed, analysed and included in the analysis whenever possible. Thus, it was possible to pool the data from eighteen studies, achieving a relevant number of participants while having moderate heterogeneity.

There are several strengths of this study. First, the comprehensive search strategy and eligibility criteria with the inclusion of evidence from NRSI provide new insights on the preventive effect of AIT supported by real-world evidence (RWE) data from a larger number of studies and, consequently, participants. The inclusion of non-randomized studies, specifically retrospective cohorts of prescriptions and/or routine healthcare databases, was important to counterpart evidence from RCTs because these studies reflect the complexity of clinical settings.⁴⁷ AIT results in clinical practice depend on the population's characteristics such as patients' preferences, comorbidities, lifestyle, personal expectations and priorities, and the accessibility to correct diagnosis and treatment. Second, the overall heterogeneity between studies was moderate, supporting the meta-analysis using a random-effects model methodology. The heterogeneity may be explained by differences in study design, therapy duration, time of follow-up and population considered across studies. Third, the detailed subgroup analysis allowed the scrutiny of

TABLE 1 Characteristics and main results of the original studies including in the systematic review

Author, year, country	Design	Participants, allergic disease(s), sensitization	Intervention group	Comparator group
Zhou et al, 2021, China ⁴⁵	NRSI	Mixed (adults and children, 5–45 years old); Atopic dermatitis and Rhinitis; mono- or poly-sensitized	N = 91. SCIT (HDM, Allergovit, maintenance dose: 5000 TU/ml)	N = 116. control
Fritzsche et al (REACT study), 2021, Germany ⁴⁴	NRSI	Mixed (children and adults); Rhinitis; mono- or poly-sensitized	N = 27,039. SCIT, SLIT drops, or SLI tablets (against HDM, grass, tree, or other).	N = 27,039. Controls, selected using propensity matching scores
Jutel et al, 2020, Germany ⁴³	NRSI	Mixed (adults and children, 5–50 years old); Rhinitis; mono- or poly-sensitized	^a N = 1492. SCIT (HDM extract, Acaroid®, 1000 or 10 000 TU/ml)	^a N = 38,219. Control
Alviani et al, 2020, UK ²²	RCT	Children (aged 6–12 months); Healthy; No sensitization	N = 54. SLIT drops (HDM extract, ALK Abelló, 2000 standard treatment units per day)	N = 53. Placebo
Devillier et al, 2019, France ³⁴	NRSI	Mixed (adults and children over 5 years old); Rhinitis, asthma; mono- or poly-sensitized	^a N = 686. SLIT tablets (grass pollen; oralair, Stallergenes Greer; or grazax, ALK Abelló)	^a N = 16,699. Control
Wahn et al, 2018 ⁴²	NRSI	Mixed (adults and children over 5 years old); Rhinitis, asthma; mono- or poly-sensitized	^a N = 6349. SLIT drops (N = 634) or SCIT (N = 5715) (birch pollen; natural SLIT drops, natural SCIT or allergoid SCIT preparations)	^a N = 31,683. Control
Zielen et al, 2018, Germany ³⁵	NRSI	Mixed (adults and children over 5 years old); Rhinitis, asthma; mono- or poly-sensitized	^a N = 2191. SLIT tablets (grass pollen, grazax or oralair, ALK Abelló or Stallergenes Greer)	^a N = 53,718. control

Therapy duration; follow-up	Asthma, N of events	Asthma definition	Risk of bias	Main findings
Therapy: 3 years; Follow-up: 2 years	Int: 19; Cp: 45	Allergic asthma (no more specifications)	High	New asthma onset was a secondary endpoint. Among patients with atopic dermatitis and rhinitis at baseline (but not asthma), the RR of asthma diagnosis for the control group was 1.86 (95% CI: 1.17–2.95), considering an interval of 5 years (3 of intervention +2 follow-up).
Therapy: at least 1 year; Follow-up: at least 1 year (and up to 9 years)	Int: 1148; Cp: 950	At least one asthma diagnosis (coded at database) and two prescriptions of SABA/ICS	High	New asthma onset was a secondary endpoint. Time-to-first onset of asthma showed an increased risk for the AIT group (HR: 1.22; 95% CI: 1.12–1.32). In the non-asthma cohort, the number of prescriptions for asthma medication over time was low and remained stable for the AIT group across the 9 follow-up years, but prescriptions tended to increase in the control group (indicating reporting bias). Data were not presented separately according to administration route, allergen or population (children vs. adults).
Therapy: at least 1 year; Follow-up: at least 2 years	Int: 208; Cp: 6829	Prescription data of asthma medication	High	New asthma onset was a secondary endpoint. After covariate adjustment in the regression analysis, the probability of asthma development was significantly lower in the patients receiving HDM allergoid (OR = 0.81; 95% CI: 0.70–0.95). When considering only children, the adjusted OR was 0.83 (95% CI: 0.69–1.00). Number of asthma events presented separately for children (used in meta-analysis, for the sensitivity analysis).
Therapy: 1 year; Follow-up: 5 years	Int: 1; Cp: 5	Based on symptoms, medication, and lung function	Mod.	Asthma development was the primary outcome. Early-life administration of HDM SLIT may reduce childhood asthma. Only RCT investigating primary prevention of asthma and atopy using AIT.
Therapy: at least 2 years; Follow-up: at least 1 year	Int: 94; Cp: 2836	Prescription data of asthma medication	High	New asthma onset was a secondary endpoint. The number of patients with a dispensed prescription for asthma medication (those who had not been treated for asthma at index date) was lower in the SLIT group (13.7%) than in the control group (17.0%). The data presented is for the primary analysis reported by the authors (No age-matching). For the secondary analysis, with age-matching of participants, adjusted OR was 0.549 (95% CI: 0.431–0.700). SLIT tablets on AR may have a potential effect in reducing asthma onset and asthma progression in routine clinical practice, using medication dispensing as a proxy.
Therapy: at least 2 years; Follow-up: at least 2 years	Int: 793 (SLIT = 61; SCIT: 732); Cp: 4159	Prescription data of asthma medication	High	New asthma onset was a secondary endpoint. During treatment, new-onset asthma risk was significantly reduced in the AIT vs. non-AIT group (OR: 0.83; $p = .001$). During the follow-up/post-treatment period, the OR for the AIT group was close to equality and therefore not significant (OR: 1.02, $p = .77$). Number of asthma events were presented separately for SCIT and SLIT drops (used in meta-analysis, for the sensitivity analysis). Birch pollen AIT demonstrated real-world benefits up to 6 years post-treatment cessation through significantly decreased risk of new-onset asthma medication use on-treatment.
Therapy: at least 2 Tx cycles; Follow-up: at least 2 years	Int: 208; Cp: 6222	Prescription of asthma medication	High	New asthma onset was a secondary endpoint. After adjustment for covariates, the odds ratio for new asthma onset evidenced a reduction in the risk of asthma onset in the SLIT tablet group in all analytical periods (OR: 0.696, 95% CI: 0.552–0.877). Real-world treatment of AR patients with grass pollen SLIT tablets was associated with less frequent asthma onset.

TABLE 1 (Continued)

Author, year, country	Design	Participants, allergic disease(s), sensitization	Intervention group	Comparator group
Valovirta et al (GAP study), 2018, Europe (11 countries) ^{23b}	RCT	Children (5–12 years old); RC; mono- or poly-sensitized	N = 398. SLIT tablets (grass pollen, grazax, ALK Abelló)	N = 414. Placebo
Schmitt et al, 2015, Germany ³⁶	NRSI	Mixed; Rhinitis; mono- or poly-sensitized	N = 2431. Any SLIT, SLIT drops (N = 248) or SCIT (N = 2030) (any allergen type was included in the analysis)	N = 11,6323. Control
Peng et al, 2013, China ³⁷	NRSI	Mixed; Rhinitis, asthma; only HDM sensitized	^a N = 55. SCIT (standardized mite depot-allergen extract, Allergopharma)	^a N = 23. Control
Holt et al, 2013, Australia and USA ²⁴	RCT	Children (12 months old); Atopic dermatitis; sensitization to ≥ 1 food allergen	N = 25. SLIT drops (mixture of soluble allergens of HDM, cat, and timothy grass)	N = 25. Placebo
Milani et al (EFESO trial), 2008, Italy ³⁸	NRSI	Adolescents (mean aged 22 years old); Rhinitis; mono- or poly-sensitized	N = 154. SLIT drops (SLITone, any allergen type, ALK Abelló)	N = 151. control
Marogna et al, 2008, Italy ^{25c}	RCT	Children (5–17 years old); Rhinitis, intermittent asthma; mono- or poly-sensitized	N = 144. SLIT (Any allergen type, Anallergo)	N = 72. Control
Jacobsen et al (PAT study, 10 years), 2007, Europe ^{26d}	RCT	Children (6–14 years old); RC, mild seasonal asthma; only sensitized to grass or birch	^a N = 79. SCIT (grass and/or birch pollen, Alutard or Aquagen, ALK Abelló). Sample size after follow-up: 64	^a N = 72. Control. Sample size after follow-up: 53
Niggemann et al (PAT study, 5 years), 2006, Europe ^{27d}	RCT	Children (6–14 years old); RC, mild seasonal asthma; only sensitized to grass or birch	^a N = 79. SCIT (grass and/or birch pollen, Alutard or Aquagen, ALK Abelló). Sample size after follow-up: 95.	^a N = 72. Control. Sample size after follow-up: 88.
Moller et al (PAT study, 3 years), 2002, Europe ^{28d}	RCT	Children (6–14 years old); RC, asthma; only sensitized to grass or birch	^a N = 79. SCIT (grass and/or birch pollen, Alutard or Aquagen, ALK Abelló)	^a N = 72. Control

Therapy duration; follow-up	Asthma, N of events	Asthma definition	Risk of bias	Main findings
Therapy: 3 years; Follow-up: 2 years	Int: 34; Cp: 39	Based on symptoms, medication, and lung function	Low	Asthma onset was the primary outcome. Asthma according to symptoms or medication intake was a secondary outcome. Treatment reduced the risk of experiencing asthma symptoms and using asthma medication. HR (95% CI) for asthma onset: 0.90 (0.57–1.43). OR (95% CI), and for asthma symptoms and medication used: 0.67 (0.46–0.97). Treatment with SLIT tablets reduced the risk of experiencing asthma symptoms and using asthma medication.
Therapy: at least 1 prescription; Follow-up: up to 6 years	Int: 33 (SLIT drops: 3; SCIT: 25); Cp: 1613	Diagnoses according to the ICD-10 code and at least 2 prescriptions of ICS	Mod.	Asthma onset was de primary outcome. AIT demonstrated an RR of 0.60 (95% CI: 0.42–0.84), indicating a 40% risk reduction for patients with AR for the development of asthma. Our data suggest that Tx duration of 3 years or more have slightly better preventive effects on the development of asthma. Number of asthma events presented separately for SCIT and SLIT drops (used in meta-analysis, for the sensitivity analysis).
Therapy: 3 years; Follow-up: 2 years.	Int: 6; Cp: 7	Based on GINA guidelines	High	The outcome of asthma development showed an OR of 3.57 (1.05–12.19; $p < .05$) in favour of the hypothesis that SCIT can prevent the development of asthma meaning that the risk of developing asthma was 3.57 times higher in the control group.
Therapy: 1 year; Follow-up: 3 years	Int: 4; Cp: 4	Asthma symptoms.	Mod.	Asthma onset was a secondary endpoint. It is not possible to draw firm conclusions concerning the potential efficacy of this overall approach for allergy prophylaxis. OR (95% CI): 1.00 (0.16–6.1).
Therapy: 2 years; Follow-up: 0	Int: 13; Cp: 30	Asthma symptoms (ISAAC questionnaire: 'Have you had wheezing or whistling in the chest in the last 12 months?')	High	Asthma onset was a secondary outcome. SLIT was associated with a lower incidence of asthma-related symptoms, such as wheezing, and new sensitizations at the end of the observational period in comparison with allergic patients not treated with SLIT. Age, sex distribution, duration of allergy symptoms and type of AR and poly-sensitized patients were equally distributed in the two groups.
Therapy: 3 years; Follow-up: 0	No data for subjects without asthma at baseline	Based on GINA guidelines (intermittent or mild asthma).	High	Asthma onset was the primary outcome. This study shows a preventive effect on the onset of mild persistent asthma and remained statistically significant even after the worst-case analysis.
Therapy: 3 years; Follow-up: 7 years	Int: 16; Cp: 24.	Asthma symptoms and response to B2-agonists.	High	Asthma development was the primary outcome. This 10-year follow-up study demonstrates that SCIT for 3 years shows the persistent long-term effect on clinical symptoms and a preventive effect on the later development of asthma in children with seasonal RC. Asthma development showed an OR of 2.5 (95% CI: 1.1–5.9) in favour of the hypothesis that SCIT could prevent the long-term development of asthma.
Therapy: 3 years; Follow-up: 2 years	Int: 15; Cp: 29.	Asthma symptoms and response to B2-agonists.	High	Asthma development was the primary outcome. This follow-up study indicates that SIT for 3 years had a long-term effect on symptoms and a reduction of the risk of developing asthma in children. OR (95% CI) of 2.68 (1.3–5.7, $p < .05$) in favour of the hypothesis that SCIT can prevent the long-term development of asthma.
Therapy: 3 years; Follow-up: 0	Int: 19; Cp: 32.	Asthma symptoms and use of B2-agonists.	High	Asthma development was the primary outcome. A 3-year course of SIT in children with allergic RC significantly reduces the risk of developing clinical asthma and improves BHR.

(Continues)

TABLE 1 (Continued)

Author, year, country	Design	Participants, allergic disease(s), sensitization	Intervention group	Comparator group
Eng et al, 2006, Switzerland ^{39e}	NRSI	Children (5–16 years old); RC; only sensitized to grass or tree	N = 14. SCIT (grass pollen, Allergovit, Allergopharma)	N = 14. Control
Eng et al, 2002, Switzerland ^{41e}	NRSI	Children (5–6 years old); RC; only sensitized to grass or tree	N = 14. SCIT (grass pollen, Allergovit, Allergopharma)	N = 14. Control
Crimi et al, 2004, Italy ²⁹	RCT	Adults (20–54 years old); Rhinitis; mono-sensitized only	N = 15. SCIT (Parietaria judaica, Alutard, ALK Abelló)	N = 15. Placebo
Novembre et al, 2004, Italy ³⁰	RCT	Children (5–14 years old); RC; only mono-sensitized	N = 54. SLIT drops (grass pollen, ALK Abelló). After follow-up: 47	N = 59. Control. After follow-up: 50
Madonini et al, 2003, Italy ^{40b}	NRSI	Mixed (2–68 years old); Rhinitis, asthma	N = 281. SLIT (Any allergen type, Allergopharma)	No comparator
Grembiale et al, 2000, UK ³¹	RCT	Mixed (10–38 years old); Rhinitis; mono-sensitized only	N = 22. SCIT (HDM, Conjuvac, Bayer)	N = 22. Placebo
Pradalier et al, 1999, France ^{32b}	RCT	Mixed (>6 years old); Seasonal rhinitis, RC, mild asthma; sensitized to grass pollen only	N = 62. SLIT (5- grass pollen, Stallergenes Greer)	N = 61. Placebo
Moller et al, 1986, Sweden ³³	RCT	Children (8–16 years old); RC; mono or poly-sensitized	N = 16. SLIT tablets (birch pollen capsules)	N = 16. Placebo

Note: Studies presenting quantitative results regarding the effects of AIT on asthma were included in the meta-analysis (if data available on the column 'Asthma, N of events').

Abbreviations: AIT, Allergen immunotherapy; AR, allergic rhinitis; CI, confidence interval; Cp, Comparator group; HDM, house-dust mite; ICD-10, International Statistical Classification of Diseases; ICS, inhaled corticosteroids; Int, Intervention group; Mod., Moderate; N, number of cases; NA, not applicable; NRSI, non-randomized studies of interventions; OR, odds ratio; RC, rhinoconjunctivitis; RCT, randomized controlled trial; SABA, short-acting beta agonists; SCIT, subcutaneous immunotherapy; SLIT, sublingual Immunotherapy; Tx, treatment.

^a Data were presented (sample size) for individuals without asthma at baseline.

^b The primary outcome data were used in the meta-analysis.

^c Not included in the meta-analysis.

^d PAT study articles. For the meta-analysis, we used Moller et al, 2002. When considering the subgroup analysis by time of follow-up, we considered also Jacobsen 2007 due to the longer follow-up time.

^e Studies with same population but different follow-up times (both, long-term follow-up, >6 years). For the meta-analysis, we used Eng et al, 2006.

Therapy duration; follow-up	Asthma, N of events	Asthma definition	Risk of bias	Main findings
Therapy: 3 years; Follow-up: 12 years	Int: 4; Cp: 7	Asthma symptoms.	High	Asthma onset was a secondary endpoint. This prospective controlled long-term follow-up study demonstrates that both the clinical efficacy and the preventive capacity of grass pollen SCIT are evident 12 years after the end of SIT when compared with seasonal pharmacotherapy alone. This study is the continuation of Eng et al, 2002.
Therapy: 3 years; Follow-up: 6 years	Int: 3; Cp: 7	Asthma symptoms.	High	Asthma onset was a secondary endpoint. It demonstrates that SIT in children with monovalent pollen allergy prevents the development of new sensitization, reduces the prevalence of subsequent asthma and therefore has the potential to modify the natural course of the allergic disease.
Therapy: 3 years; Follow-up: 0.	Int: 2; Cp: 7	Asthma symptoms.	Mod.	Asthma onset was a secondary outcome. The preventive effect of SIT did not reach significance ($p = .056$) but a trend was apparent; 47% of subjects in the placebo group developed asthma symptoms by the end of the study, compared to 14% in the SIT group.
Therapy: 3 years; Follow-up: 0.	Int: 8; Cp: 18	Asthma symptoms and medication use.	High	Asthma development was not defined as the primary or secondary outcome. The results of this study show that it can prevent the onset of asthma in children with RC.
Therapy: 26 (mean) months; Follow-up: 9 months (mean)	Int: 2	Asthma symptoms.	NA	Not specified if asthma is a primary or secondary outcome. Despite the limitations of a retrospective, uncontrolled study, the results point to the long-term and preventive effects of SLIT benefits.
Therapy: 2 years; follow-up: 0.	Int: 0; Cp: 2	Asthma symptoms.	Mod.	Asthma was a secondary outcome. This pilot study, although not designed to detect differences in the incidence of asthma between the SCIT and placebo groups, suggests that individuals with allergic rhinitis should undergo testing of their bronchial reactivity to identify those with BHR and to provide a window of opportunity in which SCIT may be effective at preventing progression to asthma.
Therapy: 6 months. Follow-up: 0.	No data for subjects without asthma at baseline	Asthma symptoms.	Mod.	Asthma onset was a secondary outcome. The proportion of patients who experienced asthma symptoms at least once during the pollen season was significantly smaller ($p = .005$) in the active treatment group (15%) than in the placebo group (38%). Adjusting for a personal history of asthma did not abolish the significant between-group differences.
Therapy: 10 months; Follow-up: 0.	Int: 0; Cp: 5	Lung symptoms.	Mod.	Asthma onset was a secondary outcome. AIT would appear to have protected against the development of asthma during this period.

data, unravelling important clinical implications and supporting the consistency of the main results. For the first time, a meta-analysis pooled separate effect estimates for SLIT tablets and SLIT drops. Finally, the influence analysis was important to identify high impact studies driving the results and to increase the robustness of findings.

The main limitation is the low number of high-quality studies; specifically, only one was considered of low risk of bias. The sensitivity analysis supports the importance of this gap since it led to imprecise results. However, the biological plausibility of AIT effects in allergic diseases and the absence of studies pointing for a statistically significant increased risk of using AIT as a prevention strategy support the results presented. Most RCTs were conducted using small samples contributing to imprecision (wider confidence intervals) of individual studies. The effect estimate generated in NRSI was based on the raw results presented in each study. However, four studies presented the adjusted relative risk ratio which was systematically lower than the relative risk obtained in this meta-analysis; thus, the results provided by observational studies on the pooled meta-analysis might be underestimated. Nevertheless, NRSI results should be analysed cautiously having in mind the risk-of-bias and confounder factors. Another limitation is the fact that in very few studies asthma onset was a primary or a secondary endpoint, highlighting the need for studies specifically designed for the assessment of asthma onset. Additionally, asthma definition should follow GINA guidelines whenever possible to guarantee precise results and allow better comparisons across studies; specifically, when using a more complete definition of asthma (including symptoms, medication and lung function assessments), in a subgroup analysis, the results on asthma prevention were not significant, although the results suggest publication bias further evaluation using a trim-and-fill method to compute and estimate the impact of small studies missing in the analysis did not change the estimate, supporting their consistency. Finally, the subgroup analysis according to SLIT administration routes (drops vs. tablets) was hampered by the small number of studies.

The evidence provided by RCTs is more robust when compared to NRSI studies because of the randomization process which make results less prone to bias compared to NRSI. Furthermore, therapy compliance and treatment duration according to recommendations tended to be better accomplished and evaluated in RCTs, which could contribute to the observed positive effects of asthma prevention in these studies. However, some RCTs included in this review raise some concerns due to the unblinding of participants and outcome assessors, contributing to a lower quality of the evidence.^{26-28,30,39,41} Authors justified the lack of use of controls due to ethical issues concerning the use of placebo in children for a long time and the difficulties in justifying its use to parents when asthma is a possible outcome.^{30,41} However, more studies in this age group are needed despite the anticipated limitations and challenges regarding blinding. Still, the recent high-quality RCT conducted by Valovirta et al. in children used a large placebo group.²³ The study was primarily designed to detect differences in asthma onset according to different criteria. Despite not being significant for the time of asthma onset strictly defined by symptoms, medication and

lung function, the adjusted odds ratio was statistically significant when considering asthma defined by symptoms and medication use, indicating a reduction of 33% in the risk of developing asthma, which corroborates with our findings.²³

Non-randomized studies of interventions reflect better the real-world effectiveness of AIT but raises serious concerns regarding the selection of participants, reporting bias and confounders. Allergic patients receiving AIT are generally from higher socioeconomic status, with facilitated access to healthcare specialists, overestimating the effect. However, better access to the healthcare system reduces the likelihood of undiagnosed asthma in the intervention group, which may be the opposite in patients with less access or in the control group, underestimating the results. Another limitation is the incomplete or absence of data on relevant prognostic variables, especially in retrospective studies, such as multiple sensitization status, severity and duration of allergic disease for which AIT is being prescribed, and previous history of asthma. The previous variables may underestimate the results because patients requesting AIT usually have a longer and more severe disease, a previous or familiar history of asthma, and are multiple sensitized. The retrospective study conducted by Schmitt et al. was considered of moderate quality due to efforts in minimizing bias and confounding, such as the criteria to select controls and adjustment of the effect measure for *a priori*-defined confounder (age, sex, healthcare use, antihistamines use), as well as the outcome definition reliably.³⁶ Asthma was defined according to reporting of the ICD-10 code on the administrative database, at least two times, and prescription of asthma medication. At baseline, AIT patients were more likely to have higher prescriptions of antihistamines and healthcare use because of allergic rhinitis, being more likely to be diagnosed with asthma, which may underestimate the results.³⁶ Some studies might have reported overestimated results since control patients had more severe disease (higher number of allergic rhinitis prescriptions).^{34,35} The study by Schmitt et al. reported a markedly decrease in the adjusted relative risk of 40% in developing asthma compared with the conservative result calculated by the random-effects meta-analysis that was based on raw event counts without any adjustments for covariates. Still, the adjusted association measure highlighted a higher preventive effect for SCIT, independently of allergen (seasonal or perennial) and duration of AIT.³⁶ Finally, we cannot rule out indication bias, which is inherent to these studies designs, as well as reporting bias since patients adhering to AIT are more carefully accompanied by physicians over time and asthma diagnosis can be reported more frequently. The study considered as an outlier showed different effects on asthma prevention.⁴⁴ The results were explained by the authors to be due to reporting bias since patients from the intervention group visit more frequently specialists and asthma definition required a medical diagnosis coded onto the database. This reasoning was supported by the major conclusions of the study that pointed a preventive effect of AIT in asthma progression from mild to severe.⁴⁴

Treating allergic multimorbidities may prevent the onset of asthma because of induced allergen-specific immune tolerance, impacting underlying mechanisms of asthma development.¹¹ However,

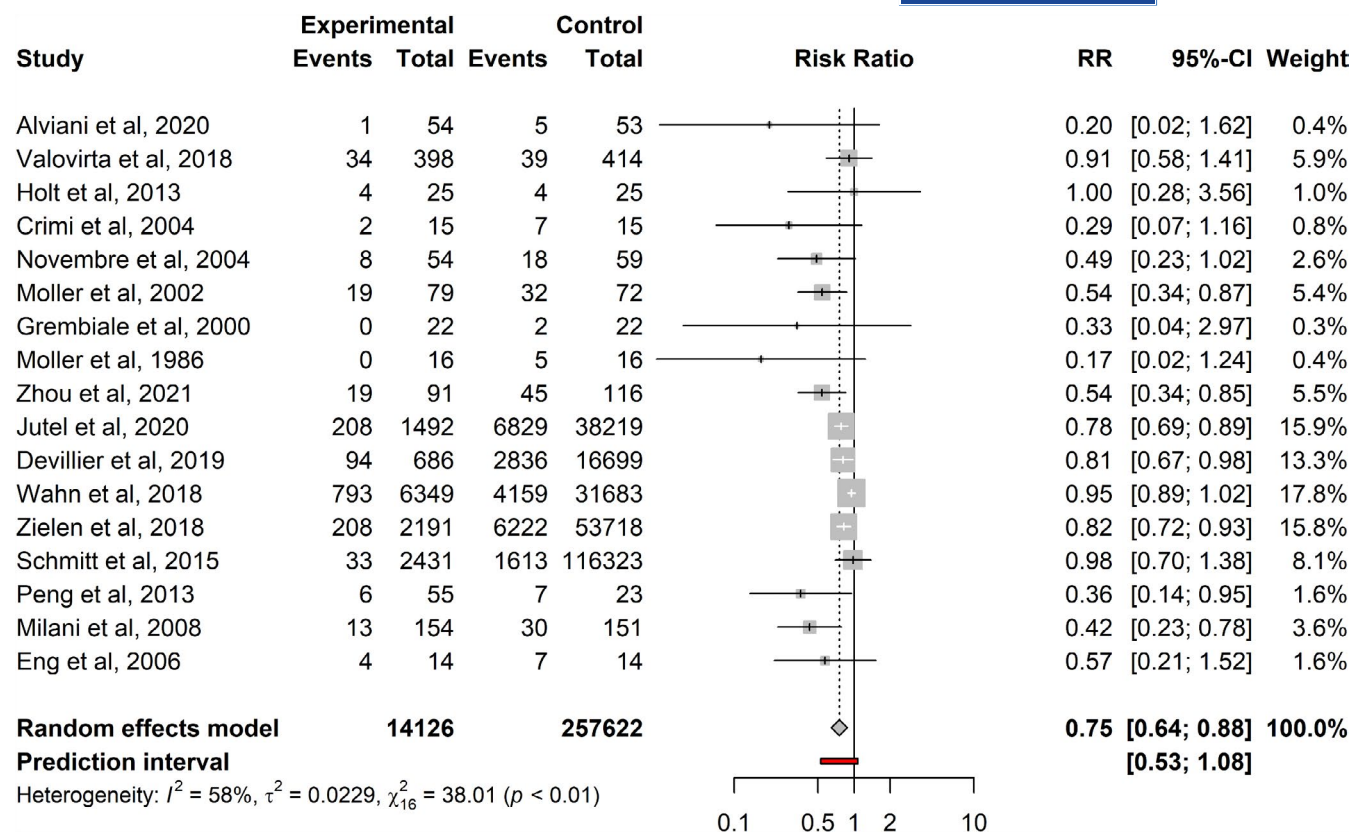
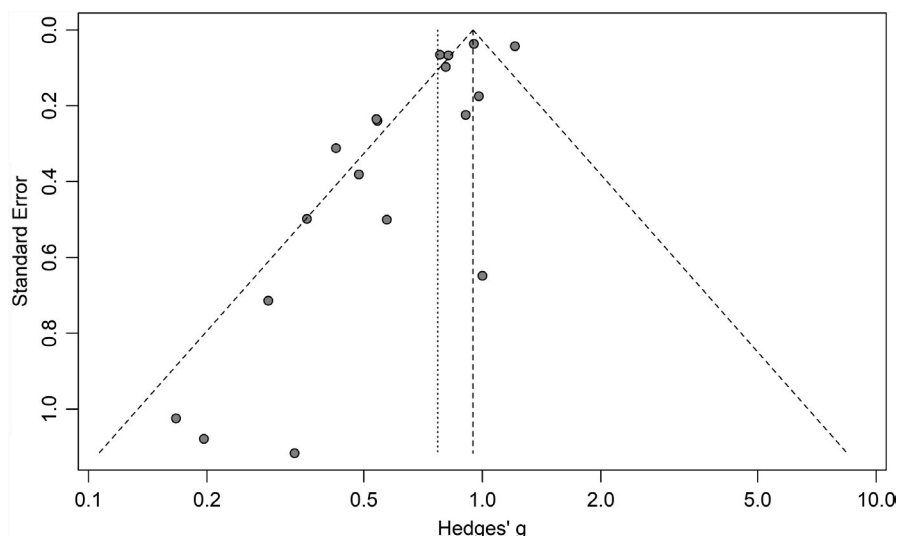


FIGURE 2 Random-effects meta-analysis of effectiveness of AIT in the prevention of asthma (N of studies =17). Diamond: pooled effect; grey square: represents study weight; black horizontal line: study confidence interval

FIGURE 3 Publication bias assessed by funnel plot



it is important to unravel the underlying mechanisms conferring higher risk of developing asthma and who will better respond to AIT, highlighting the importance of discovering treatable traits using the multimorbidity framework. Furthermore, it should be noted that AIT is not currently recommended in healthy individuals nor with atopic dermatitis because the link between atopic dermatitis and asthma development is not clear and studies are generally inconclusive.⁴⁸ Still, this work included evidence from studies conducted in the

aforementioned population to ensure a comprehensive analysis of the literature.

Our data have important clinical and research implications. In terms of clinical practice, they may contribute to the further improvement of guidelines by extending the efficacy results of AIT in treating allergic diseases to its secondary preventive role in asthma.⁴⁹ Moreover, it might be an additional reason for patients to initiate AIT and to be more compliant, although future expectations

TABLE 2 Meta-analysis when combining all studies, all studies except the outlier (*Fritzsche et al, 2021*), and by AIT administration route (SLIT or SCIT)

	All studies	All studies except the outlier	SLIT	SCIT
Meta-analysis, RR (95% CI)	0.77 (0.64; 0.92)	0.75 (0.64; 0.88)	0.77 (0.66; 0.89)	0.72 (0.56; 0.93)
Heterogeneity: I ² ; Q	79.5%; 20.63	58%; 38.01	17%; 10.79	70%; 26.37
N of studies analysed	18	17	10^a	9^a
Sensitivity, RR (95% CI)	0.76 (0.45; 1.27)	0.76 (0.45; 1.27)	0.77 (0.39; 1.54)	0.62 (0.13; 2.94)
Heterogeneity: I ² ; Q	27%; 8.25	27%; 8.25	12%; 4.56	33%; 2.97
N of studies analysed	7	7	5	3
Subgroup analysis				
Study design				
RCT, RR (95% CI)	0.59 (0.40; 0.88)	0.59 (0.40; 0.88)	0.63 (0.29; 1.35)	0.50 (0.27; 0.93)
Heterogeneity: I ² ; Q	17%; 8.44;	17%; 8.44	33%; 5.93	0%; 0.87
N of studies analysed	8	8	5	3
NRSI, RR (95% CI)	0.82 (0.66–1.02)	0.79 (0.66; 0.94)	0.78 (0.66; 0.93)	0.78 (0.59; 1.04)
Heterogeneity: I ² ; Q	86%; 65.41;	67%; 24.08	15%; 4.71	73%; 18.41
N of studies analysed	10	9	5	6
Outcome				
Primary analysis, RR (95% CI)	0.84 (0.67; 1.06)	0.84 (0.67; 1.06)	0.76 (0.57; 1.03)	0.83 (0.59; 1.17)
Heterogeneity: I ² ; Q	64%; 13.89	64%; 13.89	0%; 2.35	78%; 13.75
N of studies analysed	6	6	4	4
Secondary analysis, RR (95% CI)	0.67 (0.50; 0.89)	0.65 (0.52; 0.82)	0.73 (0.54; 1.00)	0.48 (0.36; 0.65)
Heterogeneity: I ² ; Q	83%; 63.74	38%; 16.08	40%; 8.38	0%; 1.34
N of studies analysed	12	11	6	5
Population				
Children, RR (95% CI)	0.71 (0.53; 0.96)	0.71 (0.53; 0.96)	0.63 (0.29; 1.35)	0.71 (0.37; 1.38)
Heterogeneity: I ² ; Q	30%; 10.04	30%; 10.04	33%; 5.93	48%; 3.81
N of studies analysed	8	8	5	3
Adults, RR (95% CI)	0.75 (0.56; 1.01)	0.75 (0.56; 1.01)	0.78 (0.58; 1.05)	0.54 (0.21; 1.35)
Heterogeneity: I ² ; Q	45%; 10.89	45%; 10.89	30%; 4.28	43%; 5.24
N of studies analysed	7	7	4	4
Therapy duration				
<3 years, RR (95% CI)	0.85 (0.67; 1.07)	0.81 (0.68; 0.96)	0.76 (0.61; 0.94)	0.87 (0.59; 1.36)
Heterogeneity: I ² ; Q	85%; 60.37	62%; 20.82	32%; 8.77	79%; 9.69
N of studies analysed	10	9	7	3
≥3 years, OR (95% CI)	0.64 (0.47; 0.88)	0.64 (0.47; 0.88)	0.78 (0.35; 1.74)	0.60 (0.42; 0.85)
Heterogeneity: I ² ; Q	42%; 12.01	42%; 12.01	2%; 2.04	22%; 6.43
N of studies analysed	8	8	3	6
Follow-up after treatment discontinuation				
Short-term (≤3 years), RR (95% CI)	0.74 (0.62; 0.88)	0.74 (0.62; 0.88)	0.77 (0.65; 0.91)	0.70 (0.50; 0.97)
Heterogeneity: I ² ; Q	63%; 34.92	63%; 34.92	23%; 9.12	77%; 25.55
N of studies analysed	14	14	8	7
Long-term (>3 years), RR (95% CI)	0.88 (0.51; 1.49)	0.73 (0.38; 1.40)	Not enough data	0.76 (0.42; 1.37)
Heterogeneity: I ² ; Q	67%; 11.93	33%; 4.47		0%; 1.62
N of studies analysed	5	4		3
Funding				
Pharma, RR (95% CI)	0.84 (0.64; 1.11)	0.79 (0.62; 1.02)	0.77 (0.63; 0.95)	Not enough data
Heterogeneity: I ² ; Q	87%; 51.91	68%; 18.54	32%; 7.37	
N of studies analysed	8	7	6	
Academic/others, RR (95% CI)	0.68 (0.53; 0.88)	0.68 (0.53; 0.88)	0.59 (0.27; 1.31)	0.69 (0.53; 0.91)
Heterogeneity: I ² ; Q	29%; 12.58	29%; 12.58	0%; 2.43	24%; 7.94
N of studies analysed	10	10	4	6
Asthma definition				
^b Mixed criteria, RR (95% CI)	0.77 (0.34; 1.73)	0.77 (0.34; 1.73)	0.85 (0.36; 2.03)	Not enough data
Heterogeneity: I ² ; Q	46%; 5.57	46%; 5.57	0%; 1.95	
N of studies analysed	4	4	3	

TABLE 2 (Continued)

	All studies	All studies except the outlier	SLIT	SCIT
Symptoms + medication, RR (95% CI)	0.52 (0.45; 0.60)	0.52 (0.45; 0.60)	0.50 (0.40; 0.61)	Not enough data
Heterogeneity: I ² ; Q	0%; 0.07	0%; 0.07	0%; 0	
N of studies analysed	3	3	2	
Medication, RR (95% CI)	0.91 (0.72; 1.14)	0.85 (0.73; 0.99)	0.80 (0.71; 0.91)	Not enough data
Heterogeneity: I ² ; Q	92%; 47.42	70%; 9.96	0%; 0.65	
N of studies analysed	5	6	3	
Symptoms, RR (95% CI)	0.45 (0.29; 0.72)	0.45 (0.29; 0.72)	0.47 (0.10; 2.24)	0.44 (0.16; 1.16)
Heterogeneity: I ² ; Q	0%; 3.24	0%; 3.24	20%; 2.51	0%; 0.73
N of studies analysed	6	6	3	3
SLIT administration route				
Drops, RR (95% CI)	-	-	0.65 (0.48; 0.89)	-
Heterogeneity: I ² ; Q			5%; 5.28	
N of studies analysed			6	
Tablets, RR (95% CI)	-	-	0.82 (0.70; 0.96)	-
Heterogeneity: I ² ; Q			0%; 2.65	
N of studies analysed			4	
Previous sensitization				
Only mono-sensitized, RR (95% CI)	0.49 (0.39; 0.61)	0.49 (0.39; 0.61)	Not enough data	0.49 (0.36; 0.66)
Heterogeneity: I ² ; Q	0%; 1.36	0%; 1.36		0%; 1.36
N of studies analysed	6	6		5
Mono- or poly-sensitized, RR (95% CI)	0.85 (0.70; 1.03)	0.81 (0.70; 0.95)	0.79 (0.69; 0.90)	0.83 (0.58; 1.17)
Heterogeneity: I ² ; Q	84%; 63.43	61%; 22.85	15%; 7.53	79%; 14.04
N of studies analysed	11	10	8	4
Allergen				
Grass pollen, RR (95% CI)	0.79 (0.68; 0.92)	0.79 (0.68; 0.92)	0.81 (0.71; 0.94)	0.55 (0.42; 0.72)
Heterogeneity: I ² ; Q	5%; 5.28	5%; 5.28	0%; 2.09	0%; 0.01
N of studies analysed	6	6	4	2
House dust mite, RR (95% CI)	0.60 (0.38; 0.96)	0.60 (0.38; 0.96)	Not enough data	0.63 (0.38; 1.05)
Heterogeneity: I ² ; Q	40%; 6.63	40%; 6.63		41%; 5.10
N of studies analysed	5	5		4

Note: For each output, we report the corresponding RR (95% CI), the heterogeneity parameters, and the number of studies included. Results for sensitivity analysis and subgroup analysis are also included.

Abbreviations: CI, confidence interval; I², Higgins & Thompson's I² Statistic; N, number of studies; NRSI, non-randomized studies of interventions; Q, Cochran's Q; RCT, randomized controlled trial; RR, risk ratio; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

^aTwo studies presented data for both SLIT and SCIT administration routes. The study by *Fritzching et al, 2021*, presented mixed data for both SLIT and SCIT but not separated by each administration route and, thus, was not included in these analyses.

^bMixed criteria were defined as a combination of symptoms, medication and lung function assessments to diagnose asthma; thus, in these studies, asthma diagnosis was more accurate because it followed a more complete and strict criteria. One of these studies reported an asthma diagnosis based on the GINA guidelines.

Bold values denote statistical significance at the $p < 0.05$ level.

must be managed carefully as it is not fully understood how to select patients that will benefit the most from the preventive effect of AIT. Concerning research implications, our study reveals the lack of high-quality well-powered studies, independent of study design, especially for the long-term effects after AIT discontinuation. Evidence for implementation is also lacking. RWE provided by health-related nationwide and representative databases may overcome such limitations; however, researchers must ensure a suitable and comparable control group of patients and minimize, whenever possible and employ appropriate methodologies, confounding effects.⁴⁷ This study also provides data and highlights the importance of including asthma prevention outcomes in cost-effectiveness models.⁵⁰

5 | CONCLUSIONS

This systematic review with meta-analysis suggests a possible preventive role of AIT in the short-term reinforcing the body of evidence and highlights a more pronounced effect in children, mono-sensitized, and for the patients completing 3 years of therapy, independently of allergen used for AIT. However, we should be aware that this effect was observed when considering the diagnosis of asthma based on symptoms or medication, which may indicate that AIT can prevent the onset of asthma-like symptoms and the use of asthma medication. It may be argued that secondary prevention of asthma using AIT has its best chance in stopping the progression

of allergic multimorbidities when administered early in life and at the beginning of the allergic disease and sensitization. Results were more noticeable for SCIT and SLIT drops, but SCIT tablets also demonstrated protective effects.

This work highlights the importance of gathering data from different sources, both RCTs and NRSI, allowing for a comprehensive analysis of different perspectives and reflecting the real-world complexity and preferences of populations. Future implications of using AIT as a secondary allergy prevention strategy while treating allergic rhinitis, atopic dermatitis, or rhinoconjunctivitis, depends on the availability of high-quality evidence, compliance and adherence of participants, and costs.

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CONFLICT OF INTEREST

None of the other authors report any conflict of interest in relation to this work.

AUTHOR CONTRIBUTIONS

AM, JCR and MF conceptualized the work and performed the literature search. AM, IA and MS discussed and approved the clinical aspects and conclusions as medical experts in this field. MF and JCR selected, extracted the data and evaluated the risk of bias of the studies. MF summarized data and conducted the meta-analysis. All authors discussed the results and were involved in the manuscript drafting and writing. All authors revised critically the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Appendix S1

Results

1. Assessment of Risk of Bias

During the risk of bias evaluation, only one study was classified as having high quality (low risk of bias), followed by seven of moderate quality, and 15 of low quality (high risk of bias). Regarding RCTs, we considered five to be at high risk of bias mainly due to the use of a control group instead of a placebo group, which raises concerns due to unblinding of participants and assessors when measuring the outcome; and missing data of participants that were lost to the follow-up, usually without specifying the reasons and if the dropouts were balanced or unbalanced between the groups. As expected, the risk of bias was higher in non-randomised studies of intervention (NRSI) mainly due to indication, selection, and detection bias reflecting the real-world nature of these studies, and consequently, confounding. We considered one non-randomized study of moderate quality due to the appropriate measures taken to minimize bias and confounding (matching, multivariate modelling) and the proper definition and assessment of the outcome reliably. A risk-of-bias diagram is presented in figure S1 and S2.

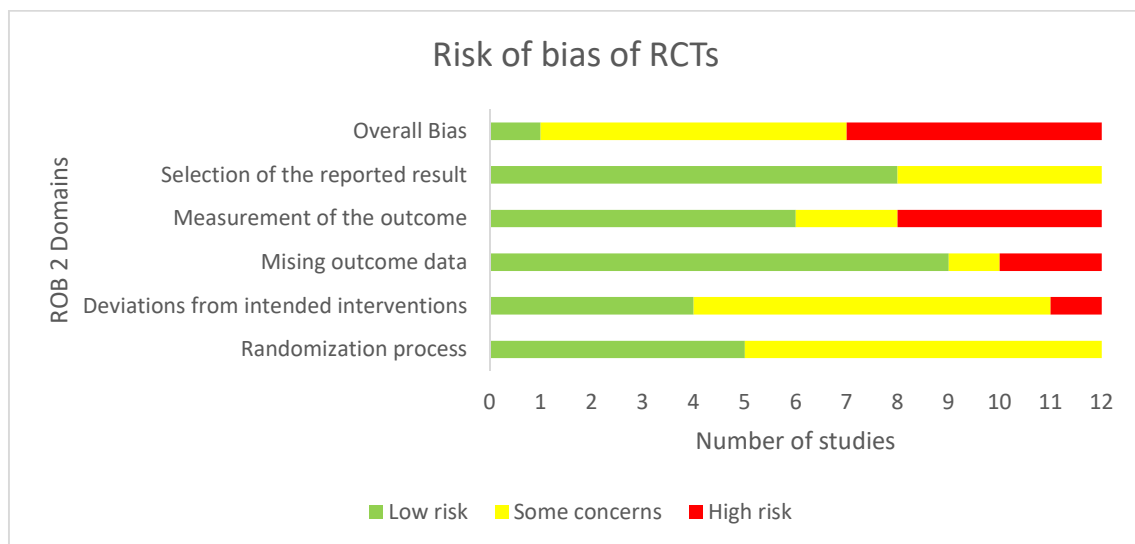


Figure S1 - Risk of Bias Assessment of randomised clinical trials (RCTs) using the ROB 2 Tool.

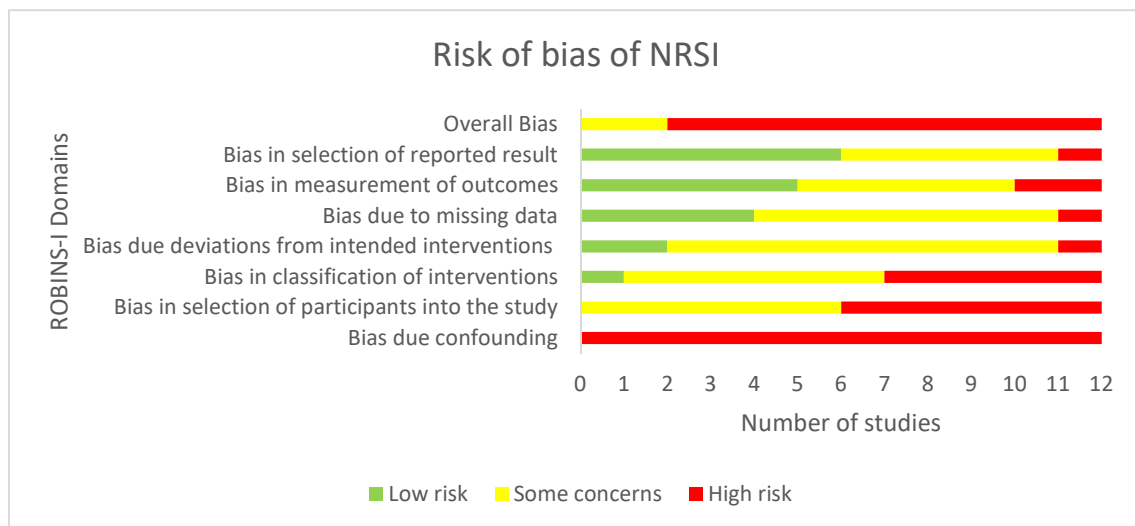


Figure S2 - Risk of Bias Assessment of non-randomised studies of intervention (NRSI) using ROBINS-I Tool.

2. Meta-analysis

2.1. Outlier analysis

By visual inspection, a study can be an outlier if its confidence interval does not overlap with the confidence interval of the pooled effect. In this meta-analysis, we can identify one outlier case: Fritzsching et al, 2021. The pool effect size with that study is presented in the figure below.

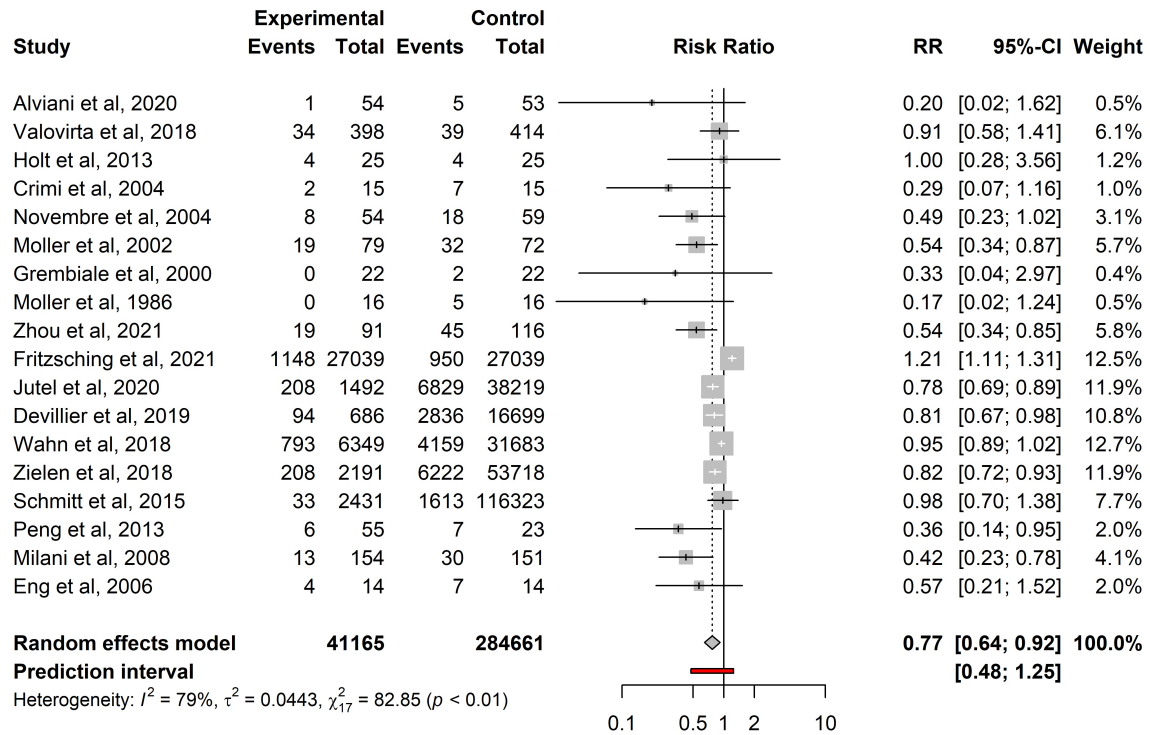


Figure S3 – Forest plot including all studies in the meta-analysis. Fritzsching et al, 2021. is an outlier case.

2.2. Influential analysis

Influential analysis is used to know if the pooled effect estimate we found is robust, meaning that it does not depend heavily on one single study. Therefore, we also want to know whether there are studies which heavily push the effect of our analysis into one direction. The following graphs highlight two influential studies: Fritzsching et al, 2021. and Wahn et al, 2018.

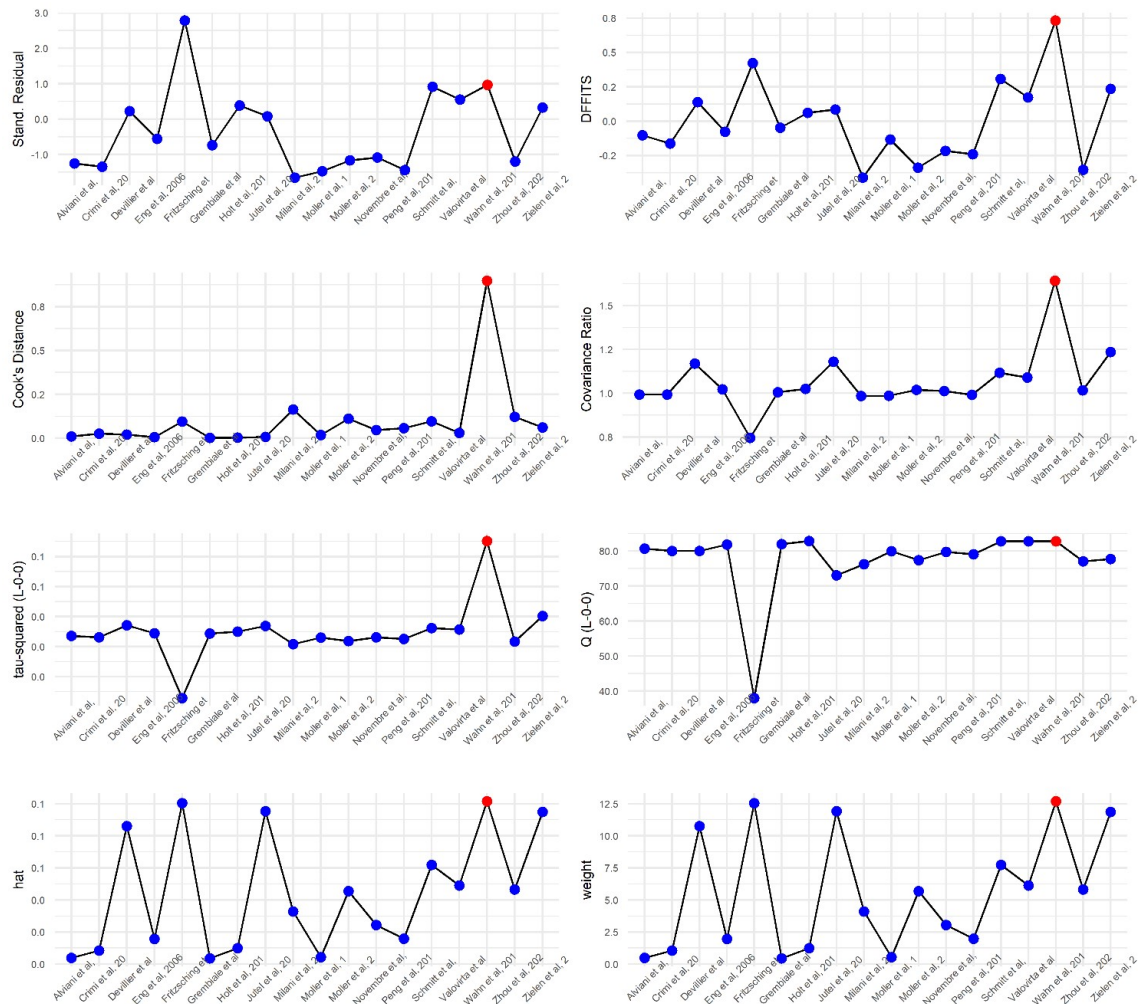


Figure S4 - Influence analysis according to different influence measures. Influential cases (in red) are those with very extreme values in graphs.

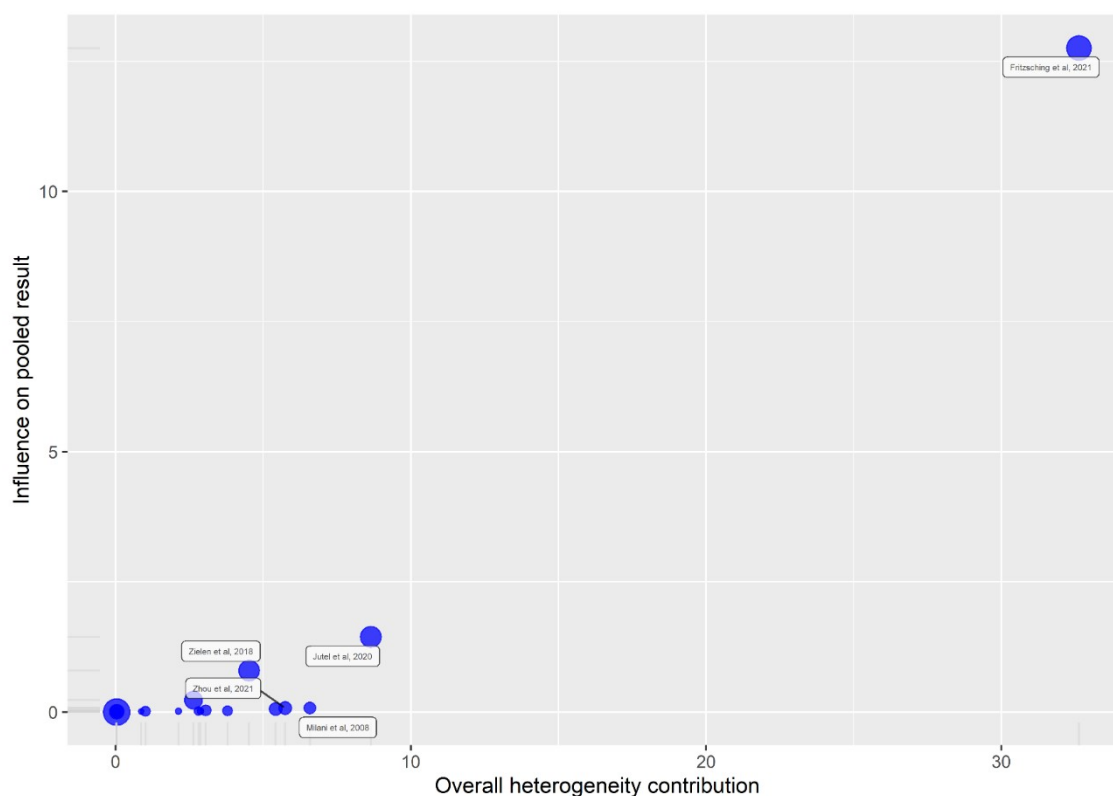


Figure S5 - Baujat Plot. Diagnostic plot to detect studies contributing to heterogeneity (those at the right side of the plot), Fritzsching et al, 2021.

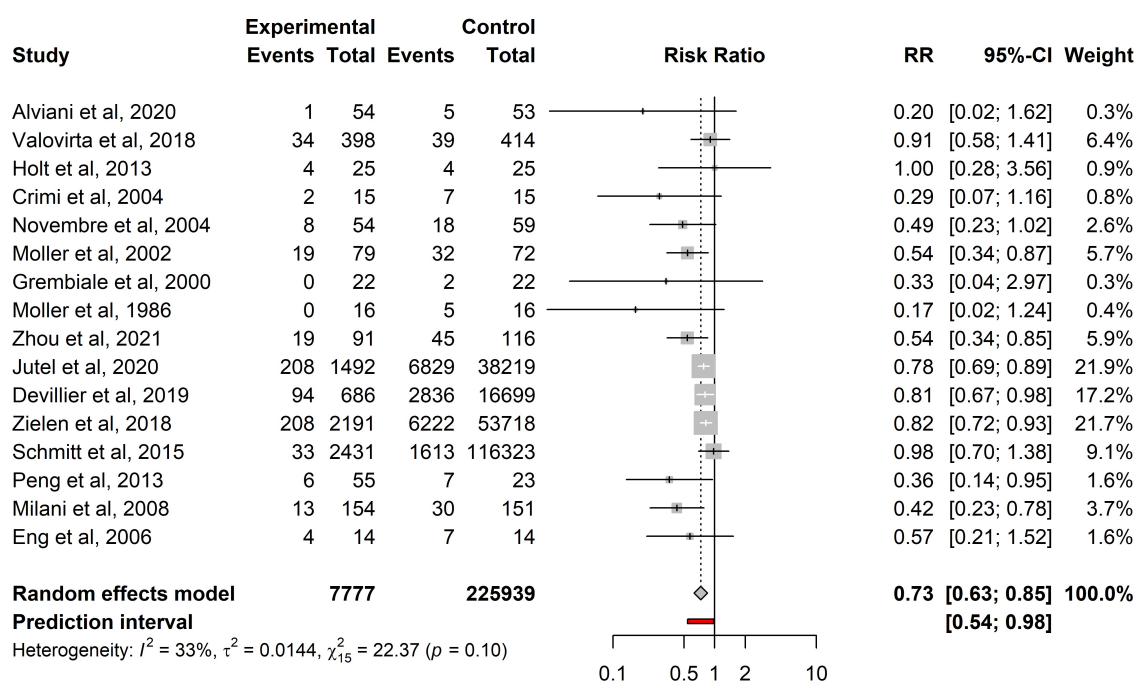


Figure S6 – Forest plot without influential cases (Fritzsching et al, 2021. and Wahn et al, 2018.).