

# Efficacy of add-on sublingual immunotherapy for adults with asthma A meta-analysis and systematic review

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## ABSTRACT

**Background:** Sublingual immunotherapy (SLIT) reduces symptom scores and the use of rescue medication in children with allergic asthma, but the effect of SLIT therapy in adult patients has not been reported.

**Objective:** To examine the efficacy and adverse effects of SLIT add-on vs conventional medication in adult patients with mild to moderate asthma.

**Methods:** We systematically searched the MEDLINE, Embase, Cochrane, and Central databases. Eligible studies included adult patients with allergic asthma who received either SLIT or standard care. Standard mean differences were used as measures of efficacy in a random-effects model.

**Results:** Twenty trials that included 2,288 patients in the SLIT add-on group and 1,268 patients in the traditional therapy group were identified as eligible for final analysis. Compared with traditional therapy, SLIT add-on therapy was associated with significant improvements in lower and upper airway scores, a higher forced expiratory volume in 1 second, and maximal expiratory flow at 25% of forced vital capacity, and improved bronchial reactivity. Drug consumptions were significantly decreased as well. Airway inflammatory parameters, such as nasal eosinophil infiltration, were markedly improved.

**Conclusion:** The findings of this study suggested that long-term SLIT add-on therapy is a complementary treatment for adults with asthma in addition to conventional medicine. It not only reduces symptom scores but also improves lung function and airway inflammation.

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## Introduction

Allergen specific immunotherapy (SIT) is an immunomodulatory treatment for several types of allergic disease.<sup>1,2</sup> It is complementary to traditional pharmacotherapy because as a biological response modifier SIT not only treats the symptoms but also targets the causes of the disease, thus altering disease progression. Meta-analyses have found that injections of allergens under the skin (subcutaneous immunotherapy

[SCIT]) are effective for treating allergic rhinitis and asthma in children.<sup>3</sup> The benefits may last for years after treatment is stopped.<sup>4,5</sup> However, for those patients who cannot tolerate or are unwilling to undergo an injection, the use of sublingual immunotherapy (SLIT) is an option. Recently, the clinical efficacy of SLIT was confirmed by meta-analyses of rhinitis, but there are few studies that have assessed its effects on inflammation and symptoms of the lower airway, such as asthma.<sup>6–8</sup>

In a meta-analysis by Penagos et al,<sup>9</sup> the selected patients were pediatric patients 3 to 18 years of age. This report found that SLIT reduced symptom scores and medication use in children with asthma. However, another meta-analysis that examined SLIT's effect on asthma was performed by Calamita et al,<sup>10</sup> who found no statistically significant reduction in asthma severity. In addition, several meta-analyses were conducted to assess the efficacy of SLIT vs a placebo rather than evaluating patients treated with SLIT plus medication vs those treated with standard medication.<sup>11,12</sup> In most cases, persistent asthma or moderate asthma was excluded in these clinical trials. In some studies, the inclusion criteria were not restrictive, and adults and children were analyzed together. Thus, the effect of SLIT on adult asthma remains unclear.<sup>13–15</sup> Therefore, in the current study, a systematic review and meta-analysis were performed to evaluate

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the efficacy and safety of SLIT for reduction of adult asthma symptoms, improvement of bronchial hyperreactivity, reduction of medication use, and inhibition of airway allergic inflammation.

## Methods

### Data Sources, Search Strategy, and Selection Criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1).<sup>16</sup> Any study that evaluated the efficacy and safety of SLIT for the treatment of allergic asthma in adult patients was eligible for inclusion in our study, and no restrictions were placed on language or publication status (published or in progress). We searched the MEDLINE, Embase, Cochrane, and CENTRAL databases for articles published through February 2018 using the following core keywords: *sublingual*, *swallow*, *oromucous*, *mucus*, *immunotherapy*, and *desensitization*. The database for abstracts of reviews and the health technology assessment database were used to search for unpublished studies. We conducted manual searches of reference lists from all the relevant original and review articles to identify additional eligible studies. The Medical Subject Heading, methods, patient population, intervention, control, and reported respiratory function outcomes were used to identify relevant studies.

The literature search was independently performed by 2 authors (K.X., Z.D.) using a standardized approach. Any inconsistencies

between the 2 authors were settled by group discussion until a consensus was reached. A study was eligible for inclusion if the following criteria were met: studies with a randomized clinical trial (RCT) or quasi-RCT design, adult patients with allergic asthma with or without rhinitis, patients undergoing SLIT or traditional therapy, and at least 1 of following outcomes: lower respiratory score, upper respiratory score, symptom and medication score (SMS), symptoms score, forced expiratory volume in 1 second (FEV<sub>1</sub>), maximal expiratory flow at 25% of forced vital capacity (MEF<sub>25</sub>), bronchial reactivity, provocative dose causing a 20% decrease in FEV<sub>1</sub> (PD<sub>20</sub>), the use of nasal corticosteroids or bronchodilators, and the presence of nasal eosinophils.

### Data Collection and Quality Assessment

Two reviewers (K.X., Z.D.) independently extracted data from eligible studies using a standardized data extraction table. Any disagreements were settled by group discussion or by a third reviewer (Z.C.) in the absence of a consensus. The following items were extracted: study country, study design, baseline characteristics, interventions, follow-up, loss to follow-up, and outcomes of interest. Individual study quality was independently assessed by 2 reviewers (K.X., Z.D.) according to the Jadad scale,<sup>17</sup> which focuses on randomization (2, 1, or 0), concealment of the treatment allocation (2, 1, or 0), masking (2, 1, or 0), and completeness of follow-up (1 or 0).

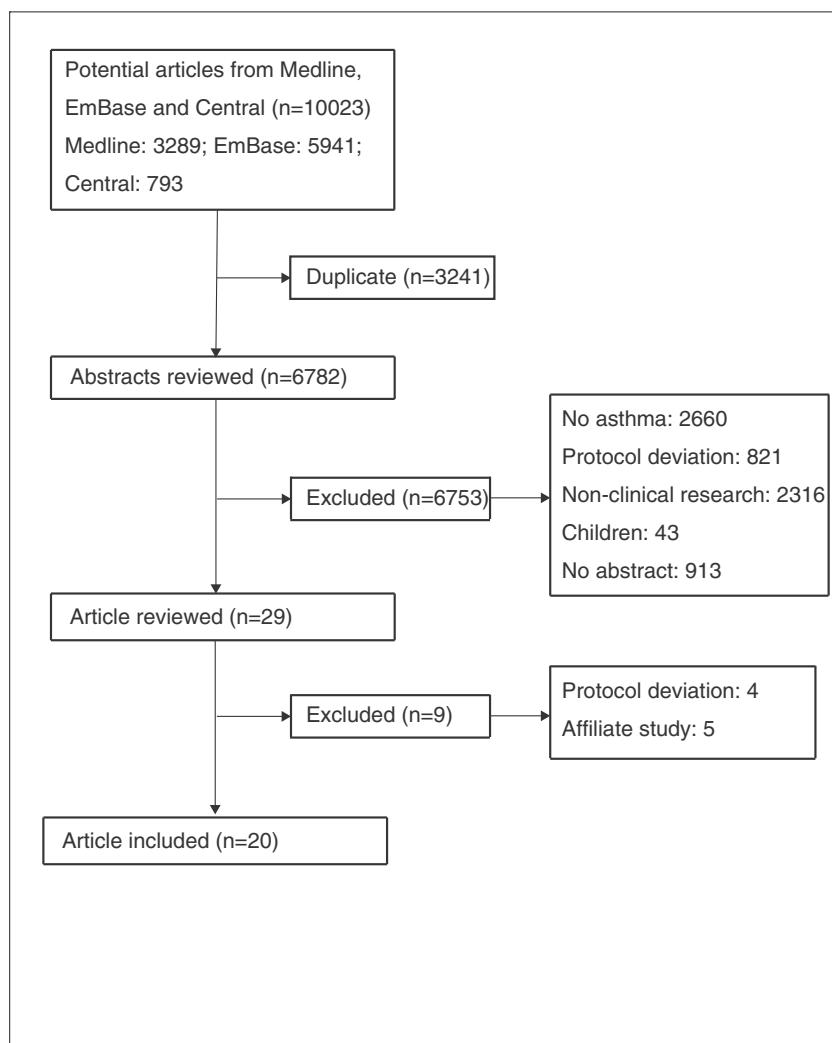


**Figure 1.** Handling of clinical trials identified in a literature search.

## Statistical Analysis

Standard mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using outcomes extracted from each study before data pooling. The summary SMDs with 95% CIs were used to estimate the efficacy of SLIT on the lower respiratory score, upper respiratory score, SMS, symptoms score, FEV<sub>1</sub>, MEF<sub>25</sub>, bronchial reactivity, PD<sub>20</sub>, use of nasal corticosteroids, bronchodilator use, drug consumption, and the presence of nasal eosinophils using a random-effects model.<sup>18</sup> Heterogeneity among trials was investigated using the *Q* statistic. *P* < .10 was indicative of significant heterogeneity.<sup>19</sup> A sensitivity analysis was also conducted to assess the effect of individual trials that contributed the increased heterogeneity of the meta-analysis results.<sup>20</sup> All reported *P* values were 2-sided, and *P* < .05 was considered statistically significant for all included studies. Statistical analyses were performed using STATA software, version 10.0 (StataCorp, College Station, Texas).

## Results

### Literature Search

The results of the study selection process are shown in Figure 1. We identified 10,023 articles in our initial electronic search, of which 6,753 were excluded after duplicates and irrelevant studies were omitted. A total of 29 potentially eligible studies were selected. After detailed evaluations, 20 studies were selected for the final meta-analysis.<sup>21–35</sup> A manual search of the reference lists of these studies did not yield any new eligible studies.

### Study Characteristics

The characteristics of all included studies are listed in Table 1. Seventeen RCTs<sup>21–27,29,30,32,34,35</sup> and 3 quasi-RCTs<sup>28,31,33</sup> with a total of 2,288 patients in the SLIT group and 1,268 patients in the traditional therapy group were included in the final meta-analysis. The sample sizes in each trial ranged from 30 to 834 adult patients with allergic asthma. All trials evaluated SLIT plus traditional drug compared with traditional therapy alone. In most trials, patients had mild intermittent or mild persistent asthma (14 of 20 studies). In 6 of 20 studies, patients with moderate asthma were enrolled. Mild and moderate asthma were diagnosed by the Global Initiative for Asthma guidelines. All studies included patients with asthma or rhinitis, but those patients with only rhinitis were not included in this analysis. All included patients are adults, and adolescents or children were excluded in this analysis. The age range of the participants was 18 to 78 years. Study quality was evaluated using the Jadad scale (Table 1). Overall, 3 studies received a score of 7 of 7, 14 studies received a score of 4 or 5 of 7, and 3 studies received a score of 3 of 7. The score for interrater agreement on methodologic quality was 0.92 (95% CI, 0.78–1.0) (Table 1).

Table 2 lists the characteristics of the treatments. The allergens were common inhalant allergen (*n* = 1), grass or tree pollen (*n* = 10), house dust mite (HDM) (*n* = 7), and grass and tree pollen mixed with HDM (*n* = 2). Soluble tablet was the vehicle most frequently used (*n* = 12). The other trials used glycerol as a vehicle (*n* = 7). The median for SLIT and placebo administration was 2.7 years, with a range of 2 months to 5 years. Pharmacotherapy for asthma was albuterol (*n* = 11), inhaled corticosteroid (ICS) (*n* = 4), or both albuterol and ICS (*n* = 5). Rhinitis was treated with cromolyn, antihistamine<sub>1</sub>, or intranasal corticosteroid.

### Systematic Review

Of all the included studies, 17 of 20 were designed as RCTs, and only 3 studies were quasi-RCTs. Five RCT studies adopted placebo

**Table 1**  
Baseline Characteristic of Studies Included in the Systematic Review and Meta-Analysis

| Study                                   | Design    | Asthma type and severity                           | Diagnosis | No. of interventions | No. of controls | Age, y | Intervention   | Control           | Jadad score |
|-----------------------------------------|-----------|----------------------------------------------------|-----------|----------------------|-----------------|--------|----------------|-------------------|-------------|
| Marogna et al. <sup>21</sup> 2004       | RCT       | Intermittent                                       | R w/wo A  | 319                  | 192             | 15–65  | SLIT plus drug | Drug              | 4           |
| Marogna et al. <sup>22</sup> 2009       | RCT       | Mild persistent                                    | A and R   | 25                   | 26              | 18–65  | SLIT plus drug | Drug              | 5           |
| Marogna et al. <sup>23</sup> 2007       | RCT       | Mild intermittent                                  | A and R   | 36                   | 12              | >18    | SLIT plus drug | Drug              | 5           |
| Marogna et al. <sup>24</sup> 2005       | RCT       | Mild intermittent or persistent                    | R w/wo A  | 39                   | 40              | 18–65  | SLIT plus drug | Drug              | 4           |
| D'Anneo et al. <sup>25</sup> 2008       | RCT       | Mild persistent                                    | R w/wo A  | 45                   | 21              | >18    | SLIT plus drug | Drug              | 3           |
| Passalacqua et al. <sup>26</sup> 2006   | RCT       | Mild persistent                                    | R w/wo A  | 34                   | 34              | 18–50  | SLIT plus drug | Drug plus placebo | 5           |
| Marogna et al. <sup>27</sup> 2010       | RCT       | Moderate persistent                                | A         | 16                   | 17              | 18–65  | SLIT plus drug | Montelukast       | 4           |
| Marogna et al. <sup>28</sup> 2010       | Quasi-RCT | Mild                                               | R w/wo A  | 57                   | 21              | 18–65  | SLIT plus drug | Drug              | 4           |
| D'Anneo et al. <sup>29</sup> 2010       | RCT       | Mild-persistent or moderate persistent             | R w/wo A  | 15                   | 15              | >18    | SLIT plus drug | Drug              | 4           |
| Quercia et al. <sup>30</sup> 2011       | RCT       | Mild intermittent                                  | R w/wo A  | 21                   | 11              | 18–70  | SLIT plus drug | Drug              | 4           |
| Lombardi et al. <sup>31</sup> 2001      | Quasi-RCT | Mild intermittent or mild persistent               | R w/wo A  | 26                   | 25              | 15–48  | SLIT plus drug | Drug              | 3           |
| Leonardi et al. <sup>32</sup> 2010      | RCT       | Mild persistent                                    | R w/wo A  | 21                   | 12              | NA     | SLIT plus drug | Drug              | 4           |
| Marogna and Massolo, <sup>33</sup> 2003 | Quasi-RCT | Intermittent                                       | R w/wo A  | 130                  | 192             | 15–60  | SLIT plus drug | Drug              | 3           |
| Marogna et al. <sup>34</sup> 2010       | RCT       | Intermittent                                       | R and A   | 69                   | 20              | NA     | SLIT plus drug | Drug              | 5           |
| La Grutta et al. <sup>35</sup> 2007     | RCT       | Mild persistent                                    | A w/wo R  | 33                   | 23              | 18–68  | SLIT plus drug | Drug              | 5           |
| Marogna et al. <sup>36</sup> 2013       | RCT       | Mild persistent                                    | R w/wo A  | 63                   | 21              | 18–65  | SLIT plus drug | Drug              | 4           |
| Volitini et al. <sup>37</sup> 2010      | RCT       | Slight intermittent to moderate persistent         | R and A   | 13                   | 9               | >18    | SLIT plus drug | Placebo plus drug | 7           |
| Wang et al. <sup>38</sup> 2013          | RCT       | Mild to moderate persistent                        | A w/wo R  | 308                  | 157             | 16–50  | SLIT plus drug | Placebo plus drug | 5           |
| Mosbech et al. <sup>39</sup> 2014       | RCT       | Mild to moderate                                   | A and R   | 461                  | 143             | >14    | SLIT plus drug | Placebo plus drug | 7           |
| Virchow et al. <sup>40</sup> 2016       | RCT       | Not well controlled by ICSs or combination therapy | A and R   | 557                  | 277             | 17–83  | SLIT plus drug | Placebo plus drug | 7           |

Abbreviations: A, asthma; ICSs, inhaled corticosteroids; NA, not available; R, rhinitis; RCT, randomized clinical trial; SLIT, sublingual immunotherapy; w/wo, with or without.

**Table 2**  
Treatment Descriptions of Studies

| Study                                   | Drug used in both groups                                                                                                         | Allergen                                          | Vehicle/units            | Cumulative dose                                                                        | Outcome                                                                                        | Duration    |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|--------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------|
| Marogna et al, <sup>21</sup> 2004       | For asthma: inhaled albuterol; for rhinitis: nasal cromolyn, oral anti-H <sub>1</sub> , intranasal corticosteroid                | One of the common inhalant allergens <sup>a</sup> | Glycerinated solution/RU | 390 µg of Der p 1/Der p 2; 70 µg of Phl p 1 and Par j 1 and 100 µg of Bet v 1 per year | Mean monthly symptom score; methacholine challenge results                                     | 3 years     |
| Marogna et al, <sup>22</sup> 2009       | For asthma: budesonide, anti-H <sub>1</sub> ; for rhinitis: anti-H <sub>1</sub> , intranasal corticosteroid                      | Grass                                             | Glycerinated solution/RU | 70 g of Phl p 1 per year                                                               | UAS, LAS, nasal eosinophil, PD <sub>20</sub> , bronchodilator, NCSs <sup>a</sup>               | 5 years     |
| Marogna et al, <sup>23</sup> 2007       | For asthma: inhaled albuterol on demand; for rhinitis: anti-H <sub>1</sub> , nasal cromolyn, intranasal corticosteroid           | Birch, grass, or both                             | Glycerinated solution/RU | 100 g of Bet v 1 and 70 g of Phl p 1 per month                                         | SMS, symptom score, drug scores, PD <sub>20</sub> , FEV <sub>1</sub> , eosinophil              | 4 years     |
| Marogna et al, <sup>24</sup> 2005       | For asthma: inhaled albuterol on demand; for rhinitis: anti-H <sub>1</sub> , nasal cromolyn, nasal beclomethasone                | Birch                                             | Glycerinated solution/RU | 102 mg of Bet v 1 per year                                                             | Monthly symptom score, FEV <sub>1</sub> , PD <sub>20</sub> , nasal eosinophil, bronchodilators | 3 years     |
| D'Anneo et al, <sup>25</sup> 2008       | For asthma: inhaled salmeterol; for rhinitis: anti-H <sub>1</sub> , nasal corticosteroid                                         | <i>Parietaria</i>                                 | Soluble tablets/AU       | 1,000 AU/wk or 3,000 AU/wk                                                             | VAS, rescue medication use, PD <sub>20</sub>                                                   | 6 months    |
| Passalacqua et al, <sup>26</sup> 2006   | For asthma: inhaled albuterol; for rhinitis: anti-H <sub>1</sub> , intranasal fluticasone                                        | HDM                                               | Soluble tablets/AU       | 2,000 AU/wk                                                                            | Daily total symptom score, nasal obstruction score, drug intake, 36-Item Short Form            | 2 years     |
| Marogna et al, <sup>27</sup> 2010       | For asthma: fluticasone/salmeterol, montelukast                                                                                  | Birch                                             | Glycerinated solution/RU | 100 µg of Bet v 1 per year                                                             | UAS, LAS, β <sub>2</sub> -agonist intake, PD <sub>20</sub> , FEV <sub>1</sub>                  | 5 years     |
| Marogna et al, <sup>28</sup> 2010       | For asthma: inhaled salmeterol, inhaled beclomethasone; for rhinitis: anti-H <sub>1</sub> , nasal cromolyn, nasal beclomethasone | HDM                                               | Glycerinated solution/RU | 390 mg of Der p 1/Der p 2 per year                                                     | SMS, nasal eosinophil, PD <sub>20</sub> , skin sensitization                                   | 3,4,5 years |
| D'Anneo et al, <sup>29</sup> 2010       | For asthma: inhaled salmeterol, inhaled albuterol on demand; for rhinitis: anti-H <sub>1</sub> , intranasal fluticasone          | HDM                                               | Soluble tablets/AU       | 104,000 AU per year                                                                    | VAS, global symptom score; rescue drug consumption                                             | 1 year      |
| Quercia et al, <sup>30</sup> 2011       | For asthma: inhaled salbutamol, oral prednisone; for rhinitis: anti-H <sub>1</sub> , intranasal fluticasone                      | Grass                                             | Soluble tablets/AU       | 50,000 AU per year                                                                     | VAS, global symptom score, global medication score                                             | 1.5 years   |
| Lombardi et al, <sup>31</sup> 2001      | For asthma: inhaled albuterol, inhaled fluticasone, oral prednisone; for rhinitis: anti-H <sub>1</sub> , nasal fluticasone       | Grass                                             | Soluble tablets/AU       | 36,000 AU per season                                                                   | PD <sub>20</sub> , daily mean symptom score, drug intake score                                 | 3 years     |
| Leonardi et al, <sup>32</sup> 2010      | For asthma: inhaled salmeterol, inhaled albuterol on demand; for rhinitis: anti-H <sub>1</sub> , intranasal corticosteroids      | <i>Olea</i>                                       | Soluble tablets/AU       | 30,000 AU total                                                                        | VAS, drug consumption                                                                          | 2 months    |
| Marogna and Massolo, <sup>33</sup> 2003 | For asthma: inhaled salbutamol, prednisone; for rhinitis: anti-H <sub>1</sub> , intranasal fluticasone propionate                | HDM, grass, or birch                              | Soluble tablets/AU       | 60,000 AU per year                                                                     | Symptom, drug consumption, safety and adherence, BHR, new sensitization                        | 3 years     |
| Marogna et al, <sup>34</sup> 2010       | For asthma: inhaled salbutamol on demand; for rhinitis: anti-H <sub>1</sub> , nasal budesonide                                   | HDM                                               | Soluble tablets/AU       | 1,000, 2000, 3,000 per week                                                            | SMS, FEV <sub>1</sub> , eosinophil, β <sub>2</sub> -agonist, NCS, PD <sub>20</sub>             | 3 years     |
| La Grutta et al, <sup>35</sup> 2007     | For asthma: inhaled salbutamol, oral corticosteroid; for rhinitis: anti-H <sub>1</sub> , nasal fluticasone                       | HDM with or without <i>Parietaria</i>             | Soluble tablets/AU       | 2,000 AU per week                                                                      | PD <sub>20</sub> , daily mean symptom, drug consumption                                        | 1 year      |

(continued)

Table 2 (Continued)

| Study                                | Drug used in both groups                                                                                               | Allergen | Vehicle/units          | Cumulative dose                                     | Outcome                                                                      | Duration  |
|--------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------|------------------------|-----------------------------------------------------|------------------------------------------------------------------------------|-----------|
| Marogna et al., <sup>36</sup> 2013   | For asthma: budesonide, montelukast                                                                                    | Birch    | Soluble tablets/<br>AU | 60,000-AU cumulative<br>annual dose,<br>preseasonal | ACT, SMS, MEF <sub>25</sub> , metacholine                                    | 3 years   |
| Voltolini et al., <sup>37</sup> 2010 | For asthma: bronchial corticosteroid, inhaled bronchodilator; for rhinitis: anti-H <sub>1</sub> , nasal corticosteroid | Birch    | NA/IR                  | 13,800 IR total                                     | Symptom score, number of days with asthma symptoms, asthma severity stepdown | 2 years   |
| Wang et al., <sup>38</sup> 2013      | For asthma: budesonide, salbutamol, prednisolone; for rhinitis: loratadine                                             | HDM      | Solution               | 300 IR daily                                        | Well-controlled asthma, totally controlled asthma, ACQ,                      | 18 months |
| Mosbech et al., <sup>39</sup> 2014   | For asthma: inhaled corticosteroid; or rhinitis: NA                                                                    | HDM      | Soluble tablets        | 1 or 3 or 6 SQ daily                                | Reduction in ICS dose, ACQ, FEV <sub>1</sub> , AQJQ, AE                      | 1 year    |
| Virchow et al., <sup>40</sup> 2016   | For asthma: inhaled corticosteroid and SABA; for rhinitis: NA                                                          | HDM      | Soluble tablets        | 6 or 12 SQ daily                                    | Time to first asthma AE, IgG4, ACQ, AQJQ                                     | 18 months |

Abbreviations: ACQ, Asthma Control Questionnaire; AE, acute exacerbation; AQJQ, Asthma Quality of Life Questionnaire; AU, allergenic units; BHR, bronchial hyperresponsiveness; FEV<sub>1</sub>, forced expiratory volume at 1 second; H<sub>1</sub>, histamine 1; HDM, house dust mite; IR, index of reactivity; LAS, lower airway score; NCS, nasal corticosteroids; PD<sub>20</sub>, provocative dose causing a 20% decrease in FEV<sub>1</sub>; RU, radioallergen sorbent test units; SABA, short-acting bronchodilator; SMS, symptom and medication score; SQ, standard quality; UAS, upper airway score; VAS, visual analog scale.

<sup>a</sup>Common inhalant allergens included HDMs, grasses, *Parietaria*, cat dander, dog dander, birch, olive, ragweed, mugwort, *Alternaria*, and *Cladosporium*.

with similar flavor, appearance, and taste as SLIT tablets, which belong to randomized, double-blind, placebo-controlled trials. Trial populations in these studies are usually fewer than 100, except for 5 studies in which the total number of participants varied from 322 to 834.<sup>21,33,38,39,40</sup> The trial with the biggest population was conducted in 109 European sites from 2011 to 2013 and evaluated the efficacy of HDM SLIT tablet on asthma exacerbation during ICS reduction.<sup>40</sup> The intervention and follow-up duration in most studies are 1 to 5 years, except for 2 studies, by Leonardi et al.<sup>32</sup> and D'Anneo et al.,<sup>29</sup> with 2 and 6 months, respectively.

Leonardi et al.<sup>32</sup> aimed to compare the effect of the coseasonal and preseasonal schemes, with SLIT therapy of 5,000 AU per week for 6 weeks and 3,000 AU per week for 10 weeks, respectively. D'Anneo et al.<sup>29</sup> performed a study starting in the coseasonal period with a 3-day build-up phase and lasting only 6 months, whereas other SLIT therapies had build-up phases of 16 days to 14 weeks. Therefore, the authors concluded that the 6-month SLIT scheme was as effective and safe as long-time therapy. The allergens in SLIT therapy included common inhalant allergen ( $n = 1$  [ $n$  stands for number of studies]), grass and tree pollen ( $n = 10$ ), HDM ( $n = 7$ ), and grass and tree pollen mixed with HDM ( $n = 2$ ). Four of 20 studies treated patients with combination allergens. For instance, in 2007, Marogna et al.<sup>23</sup> described a group of patients sensitized to birch, grass, or both. The patients received SLIT for birch, SLIT for grass, and SLIT for both and found that 2-allergen SLIT produced better clinical results for patients, especially those sensitized to both allergens.<sup>23</sup> In previous years, SLIT therapy for asthma often included patients with intermittent to mild persistent asthma.

Since 2010, 6 studies have evaluated efficacy of SLIT on moderate persistent asthma.<sup>27,28,37,38,39,40</sup> Wang et al.<sup>38</sup> studied 484 adults with asthma and found that HDM SLIT helped reduce the ICS dose of 218.5  $\mu\text{g}$  to 126.2  $\mu\text{g}$  ( $P < .004$ ) in a moderate asthma subgroup. There was no significant treatment difference in the mild asthma subgroup. A study by Virchow et al.<sup>40</sup> found that HDM SLIT add-on therapy reduced asthma exacerbation during ICS reduction and complete withdrawal for patients with asthma not previously well controlled by conventional therapy.

The following are outcomes reported in these studies: (1) symptoms and medications: mean monthly symptom score, upper airway symptom score, lower airway symptom score, SMS, visual analog score, daily total symptom score,  $\beta_2$ -agonist intake, global symptom score, and drug intake score; (2) pulmonary function and airway hyperreactivity: PD<sub>20</sub>, FEV<sub>1</sub>, and MEF<sub>25</sub>; (3) airway inflammation: nasal eosinophils; (4) ICS reduction: reduction in budesonide dose; and (5) risk of acute exacerbation: time to first asthma exacerbation. Although outcomes used in these studies were varied, SLIT add-on therapy achieved a statistically significant performance in most of the RCT studies for adults with asthma. Two of 20 studies mentioned negative results as well. Lombardi et al.<sup>31</sup> investigated the preseasonal and perennial regimen effects and found no differences in symptom score and drug intake score by the end of the first year. There was no improvement in methacholine dosage by the end of the first and second years. In the study by Wang et al.,<sup>38</sup> SLIT add-on therapy had no advantages on mild asthma disease control and ICS dose reduction relative to conventional therapy.

Other issues were also discussed regarding preseasonal vs coseasonal scheme, including the effect of a different maintenance dose and the protective role against the development of rhinitis to asthma. Leonardi et al.<sup>32</sup> compared the preseasonal scheme and the coseasonal scheme. Allergoid SLIT was as effective and safe in the coseasonal regimen as in the preseasonal regimen.<sup>32</sup> A study by Marogna et al.<sup>34</sup> compared 3 different weekly maintenance doses in the SLIT regimen (1,000, 3,000, and 5,000 AU) and found that monomeric allergoid SLIT produced clinical significant results across a wide range of doses. Marogna et al.<sup>33</sup> observed 107 patients with asthma undergoing SLIT plus drug therapy for 3 years and concluded that SLIT had a protective action against

the progression of rhinitis to asthma and the appearance of new form of sensitization.

### Meta-analysis

The pooled analyses found that SLIT add-on therapy improved not only the upper airway symptoms but also the lower airway symptoms with lower 3-year lower airway scores (SMD,  $-10.07$ ; 95% CI,  $-12.40$  to  $-7.74$ ;  $P < .001$ ) (Fig 2), 3-year upper airway scores (SMD,  $-5.60$ ; 95% CI,  $-7.69$  to  $-3.51$ ;  $P < .001$ ) (Fig 2), 5-year lower airway scores (SMD,  $-12.36$ ; 95% CI,  $-20.38$  to  $-4.34$ ;  $P = .003$ ) (Fig 2), 5-year upper airway scores (SMD,  $-7.65$ ; 95% CI,  $-10.98$  to  $-4.32$ ;  $P < .001$ ) (Fig 2), and SMSs (SMD,  $-14.25$ ; 95% CI,  $-24.97$  to  $-3.52$ ;  $P = .009$ ) (Fig 2). Furthermore, the summary SMDs revealed that patients who received SLIT also exhibited improved long-term function, such as FEV<sub>1</sub> (SMD,  $6.32$ ; 95% CI,  $1.10$ – $11.53$ ;  $P = .02$ ) (Fig 3) and 3-year PD<sub>20</sub> (SMD,  $4.18$ ; 95% CI,  $1.40$ – $6.97$ ;  $P = .003$ ) (Fig 3). In addition, the effect of SLIT on quantitative drug consumption was evaluated in several trials, and we noted that SLIT was associated with lower levels of 3-year nasal corticosteroid use (SMD,  $-7.65$ ; 95% CI,  $-11.09$  to  $-4.20$ ;  $P < .001$ ) (Fig 4), 5-year nasal corticosteroid use (SMD,  $-7.88$ ; 95% CI,  $-11.91$  to  $-3.85$ ;  $P < .001$ ) (Fig 4), 3-year bronchodilator use (SMD,  $-9.58$ ; 95% CI,  $-10.88$  to  $-8.29$ ;  $P < .001$ ) (Fig 4), and 5-year bronchodilator use (SMD,  $-10.36$ ; 95% CI,  $-17.22$  to  $-3.49$ ;  $P = .003$ ) (Fig 4). The persistence of nasal inflammation could explain the unsatisfactory asthma control because 5 of 15 trials detected long-term airway inflammation scores and found both 3-

year nasal eosinophil infiltration (SMD,  $-5.32$ ; 95% CI,  $-8.65$  to  $-1.99$ ;  $P = .002$ ) (Fig 4) and 5-year nasal eosinophil infiltration scores (SMD,  $-9.32$ ; 95% CI,  $-10.88$  to  $-7.76$ ;  $P < .001$ ) (Fig 4) were significantly reduced. Finally, SLIT may exert a beneficial effect on symptom scores (SMD,  $-3.98$ ; 95% CI,  $-5.50$  to  $-2.45$ ;  $P < .001$ ), MEF<sub>25</sub> (SMD,  $5.42$ ; 95% CI,  $4.09$ – $6.76$ ;  $P < .001$ ), bronchial reactivity (SMD,  $4.90$ ; 95% CI,  $3.67$  to  $6.13$ ;  $P < .001$ ), 5-year PD<sub>20</sub> (SMD,  $5.66$ ; 95% CI,  $4.34$ – $6.97$ ;  $P < .001$ ), and drug consumption (SMD,  $-2.94$ ; 95% CI,  $-4.20$  to  $-1.67$ ;  $P < .001$ ), although only one study reported these indexes.<sup>21,22,27,31,34–36</sup>

### Adverse Events

In addition, systemic analysis of adverse events was difficult because most studies reported few adverse effects. Marogna et al<sup>28</sup> reported that patients who received SLIT experienced 5 transient oral itching events and 2 generalized itching events. Furthermore, Marogna and Massolo<sup>33</sup> indicated that 19 patients reported generalized itching in response to SLIT therapy. Marogna et al<sup>34</sup> indicated that only 1 patient reported generalized itching when treated with SLIT. Finally, Passalacqua et al<sup>26</sup> reported that patients who received SLIT reported similar adverse effects, such as cough, asthma attacks, rhinitis, flulike syndrome, otitis, and traumatic fracture, compared with those of controls. Neither lethal nor severe systemic reactions were registered in the included studies. No severe asthma attack was reported in these studies.

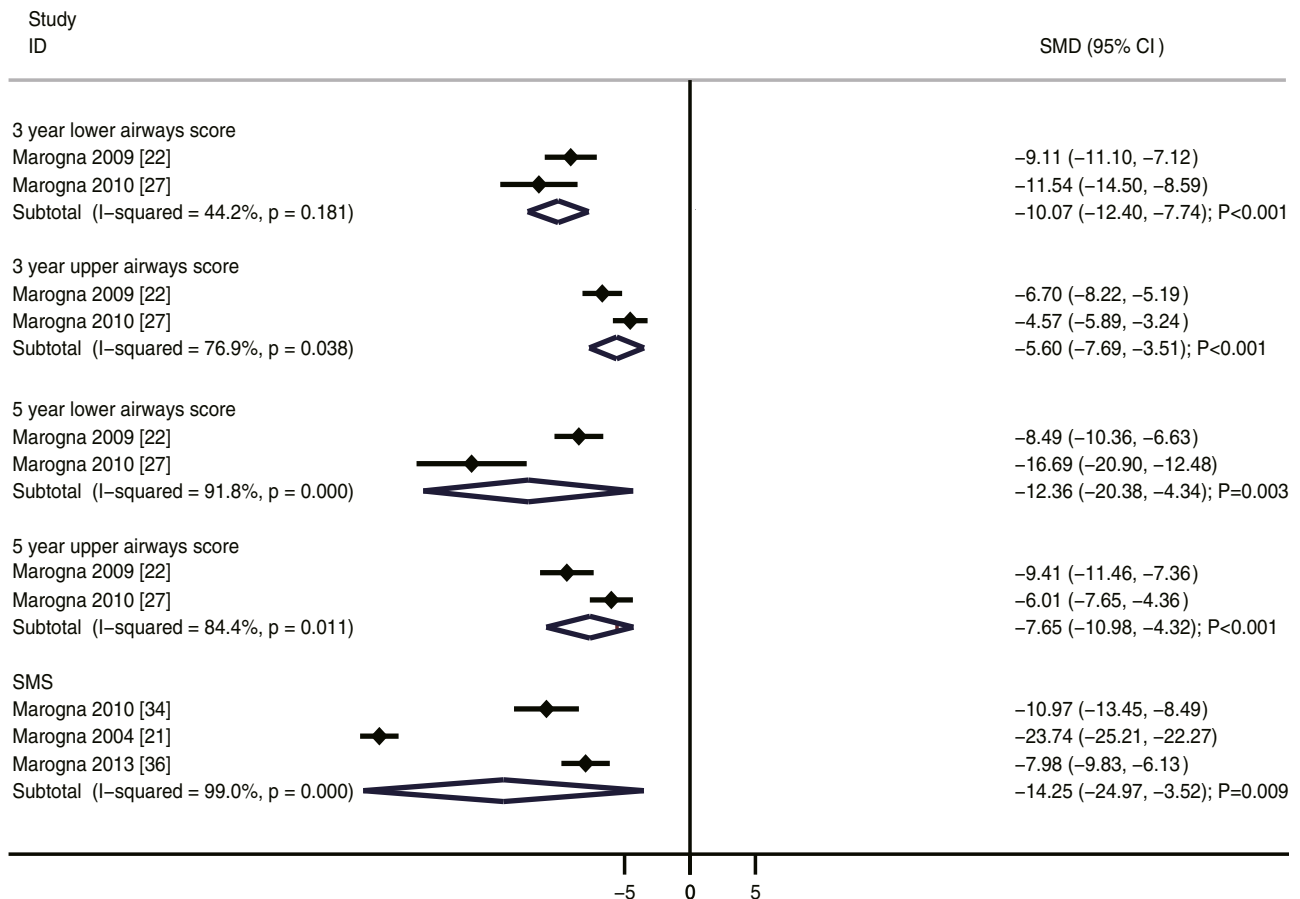


**Figure 2.** Outcome: asthma symptom scores. Upper airway scores include nasal itching, discharge, sneezing, and obstruction. Each symptom was scored from 0 (absent) to 3 (severe). The possible maximum monthly score was therefore 360. Lower airway scores include cough, wheezing, chest tightness, and nocturnal symptoms. SMS (symptom + medication scores): symptom scores include cough, wheezing, dyspnea, nasal obstruction, nasal itching, rhinorrhea, sneezing, conjunctive itching, redness, and watery eyes. Each dose of salbutamol, nasal budesonide was scored 1 point. The mean monthly SMS score was calculated.

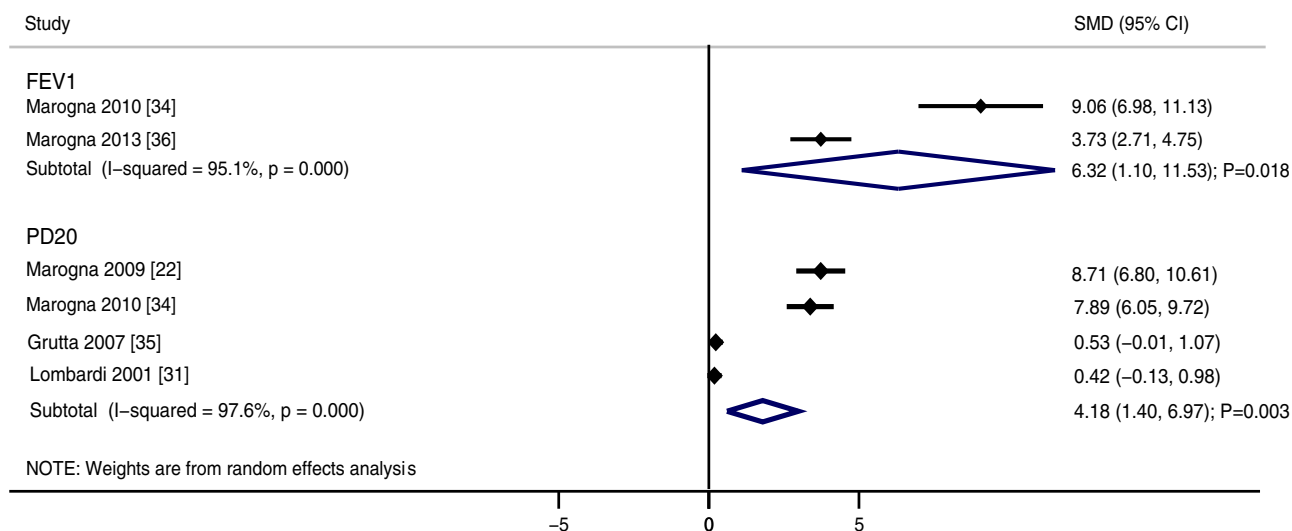


**Figure 3.** Outcome: pulmonary function improvement. FEV<sub>1</sub>, forced expiratory volume at one second (%); PD<sub>20</sub>, methacholine provocation dose in mg.

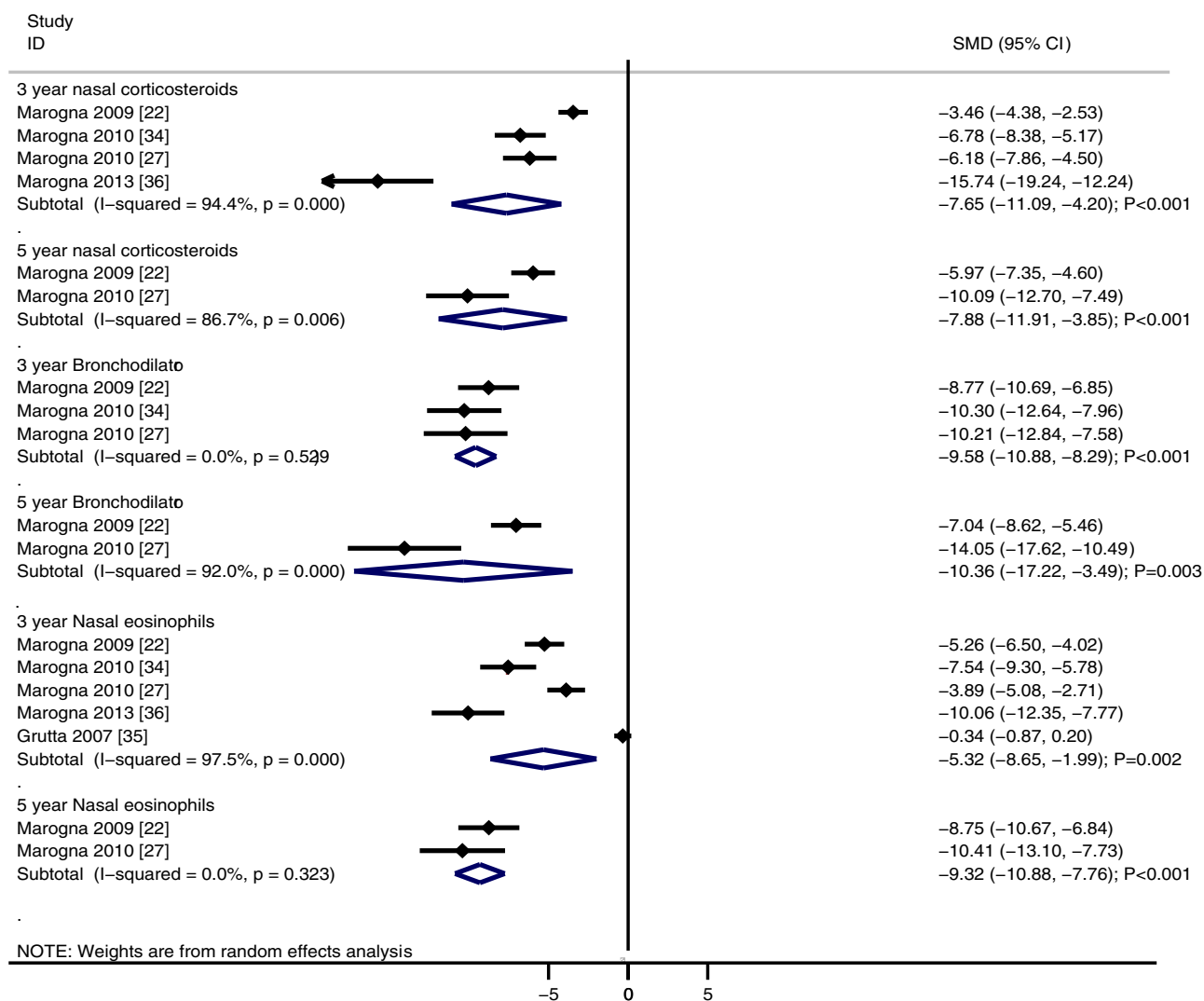


**Figure 4.** Outcome: medication use and airway inflammation scores. Nasal corticosteroid, intake of nasal corticosteroid in the research period; bronchodilator, intake of bronchodilator in the research period; nasal eosinophils, nasal eosinophils (%).

## Discussion

Previous studies<sup>41–43</sup> have suggested that SLIT significantly improves clinical symptoms in patients with allergic rhinitis, but few studies have assessed the effects of SLIT on inflammation and the lower airways. In a recent study,<sup>9</sup> SLIT was recommended as an option for the treatment of allergic asthma in pediatric patients. However, little evidence exists to support the recommendation of SLIT in adults with allergic asthma. Our systematic review and meta-analysis demonstrated that not only symptoms but also respiratory function and drug consumption were significantly improved in adult patients who received SLIT. This systematic review also found that 6 months of SLIT was associated with a significant clinical benefit in adult patients, and a 4-year duration of SLIT was the optimal treatment duration.<sup>25,28</sup>

Our review includes 20 studies of 3,556 patients, of whom 2,282 patients received SLIT plus medication therapy and 1,268 patients received medication therapy only. Any study that examined SLIT vs placebo, studied children, or was not an RCT was excluded from our evaluation. We selected only those trials conducted with rigorous methods to provide solid conclusions. Our study included 3 quasi-RCTs and 17 RCTs. Most of the studies ( $n = 15$ ) were not masked for multiple reasons, such as lack of placebo supply by sponsors, long-term follow-up, and consideration of low adherence if placebo is administered to a control group. However, there is a trend to adopt double-blind RCTs to perform clinical trials in the SLIT area as well.<sup>26,37–40</sup> Placebo was provided in the form of similar appearance, taste, and smell with SLIT tablets.

In our current meta-analysis, we used the SMD as a summary indicator because of the substantial heterogeneity from widely different scoring systems. From our pooled data, not only upper airway symptoms scores but also lower airway symptoms scores were significantly decreased. The drug consumption's deductions were paralleled by symptom improvements. For example, nasal corticosteroid and bronchodilator use were reduced. Notably, 19 of 20 trials selected patients with asthma with or without rhinitis, and only 1 of 20 studies selected patients with pure asthma. This approach suggests that patients with allergic asthma combined with allergic rhinitis may be the optimal population for SLIT. SLIT benefits the upper and lower airway and is expected to decrease allergen-specific inflammation in organs.

The effects of SLIT are not limited to symptoms but also involve local inflammation and bronchial responses. However, recent publications have not reported consistent conclusions on SLIT's effects on lung functions. Two RCTs<sup>31,35</sup> reported that SLIT failed to show superior efficacy in improving the PD<sub>20</sub> after 3 years compared with that of traditional therapy. The limitations of these 2 studies<sup>31,35</sup> were small sample size and specific selection criteria. In our systemic review and meta-analysis, we found that SLIT significantly increased PD<sub>20</sub> compared with that of traditional therapy in most of studies. The number of nasal eosinophils decreased markedly as well. Thus, long-term SLIT is beneficial for adults with asthma with regard to nasal inflammation and nonspecific bronchial responsiveness.

The treatment of moderate to severe asthma still has unmet need. The proportion of well-controlled asthma is relatively low because of unsatisfactory adherence to ICS therapy. Recent studies provided an option to reduce the dose of ICS by adding SLIT to traditional therapy.<sup>37–40</sup> More patients with moderate to severe asthma are being included in SLIT clinical trials to change the belief that SLIT is suitable only for intermittent and mild persistent asthma. Acute exacerbation is an opportunity to evaluate asthma control and severity. It has been used as a primary outcome to assess SLIT add-on therapy for asthma that is not well controlled and achieve positive results.<sup>40</sup> Until now, only 6 published studies on SLIT add-on therapy involved adults with moderate to severe asthma, and the long-term efficacy and safety need to be proved by larger subpopulation studies.<sup>27,29,37–40</sup>

The safety profile of SLIT is much better than that of SCIT based on data derived from clinical trials and postmarketing surveillance. Systemic and anaphylactic reactions are virtually absent in SLIT.<sup>39</sup> Only 9 of 20 included studies described adverse events. Local reactions, such as oral itching, rhinitis, and otitis, were the most commonly reported events. When systemic reactions were evaluated, 61 events were reported (generalized itching, 22 events; asthma, 22 events; flulike syndrome, 17 events). All the adverse events were mild. No patient required hospitalization, and life-threatening or fatal reactions were not reported.

Two strengths of our study should be highlighted. First, the large sample size allowed us to qualitatively and quantitatively assess the efficacy of SLIT for treatment of patients with allergic asthma vs that of traditional pharmacotherapy; thus, our findings were potentially more robust than those of any individual study. Second, the study reported the results of adult patients with allergic asthma, which has not been previously investigated in a meta-analysis.

The limitations of our study are as follows: (1) in a meta-analysis of published studies, publication bias is an inevitable problem; (2) the analysis used pooled data (individual data were not available); (3) several studies only reported *P* values of symptoms, and the data were not available for pooling; and (4) this meta-analysis includes a small numbers of studies, and heterogeneity is therefore a necessary consequence.

The results of this study suggested that long-term SLIT is a complementary treatment for adults with allergic asthma in addition to conventional medical treatment. Considering its favorable safety profile and its potential in modifying the evolution of disease, SLIT has the potential to be recommended more widely in clinical practice.

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