

# Sublingual immunotherapy for allergic respiratory diseases: An evaluation of meta-analyses

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**Background:** Five published meta-analyses (MAs) seem to prove the efficacy of sublingual immunotherapy in allergic asthma and rhinoconjunctivitis.

**Objective:** We aimed to assess the consistency, magnitude, and robustness of the results of these MAs.

**Methods:** The data reported in the MAs were checked with the data reported in the original studies. Funnel plots were performed to test for potential publication bias, and the trim-and-fill method was used to assess and correct the estimate of the effects if asymmetry was present.

**Results:** The 5 MAs included 43 studies; 17 were used in more than one MA. There were discrepancies among the MAs in the data reported from the same original studies: the MAs reported different estimates for the same outcome or the same estimates for different outcomes in 16 of those 17 studies. The MAs evaluated 15 main outcomes, 10 of which showed benefits that reached statistical significance. Funnel plots showed asymmetry in 7 outcomes, and correction by using the trim-and-fill method led to a decrease in their effect estimates and even to a loss of statistical significance in 4 of the previously significant outcomes. There was inconsistency among the MAs in the benefits when considering age, disease, allergen, or symptoms and medication use.

**Conclusion:** Because of discrepancies, inconsistencies, and lack of robustness, the MAs on sublingual immunotherapy do not provide enough evidence to support its current routine management in patients with allergic asthma or rhinoconjunctivitis. Sensitivity to potential publication bias should be tested and reported in all MAs. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

**Key words:** Allergy, asthma, bias, funnel plot, immunotherapy, meta-analysis, rhinoconjunctivitis, sublingual, trim and fill

There has been a steady increase in the prevalence of allergic diseases in the last 20 years. The etiologic treatment of these diseases is based on avoidance measures and, when indicated, immunotherapy. Because of the high prevalence of allergy, the

## Abbreviations used

MA: Meta-analysis

SLIT: Sublingual immunotherapy

potential target population for immunotherapy is very large. Subcutaneous injections of allergen have been used for almost 100 years. Although they have been proved efficacious, they can be time consuming and inconvenient.

Thus other routes for immunotherapy have been explored, and lately, the sublingual route is being increasingly used in European countries and is viewed with interest in the United States.<sup>1</sup> Its efficacy is a matter of discussion, and 5 meta-analyses (MAs) have been published that seem to prove its value in randomized studies.<sup>2-7</sup>

The aim of our study was to evaluate results published in MAs of sublingual immunotherapy (SLIT) and to assess their consistency, the magnitude of the effects, and the robustness of their conclusions.

## METHODS

Five MAs on SLIT<sup>2-7</sup> were identified through a Medline search. They were all the MAs on SLIT published in the English language until June 2008. Systematic reviews not following the MA methodology were not included. The MAs analyzed original, randomized, mostly double-blind placebo-controlled studies in children, adults, or both with allergic asthma, rhinoconjunctivitis, or both. The original studies included in the MAs were scrutinized, and their data on the analyzed outcomes were compared with their reported correspondent data on the different MAs to check consistency in reports.

To assess potential publication bias in the MAs, their results on the different outcomes were used to generate funnel plot graphs by using the Review Manager 4.2 software (Cochrane Reviews). The methods of Begg and Mazumdar<sup>8</sup> and Egger et al<sup>9</sup> were performed, as was the trim-and-fill method,<sup>10</sup> which also allows correction of the effect estimate when potential bias is present, to test for significant asymmetry. Stata 9.1 software (StataCorp, College Station, Tex) was used.

Briefly, the funnel plot is a graph that plots the effect estimate of each original study in the x-axis and its precision in the y-axis. As a measure of precision, it might use the number of patients included in the study or, more commonly, the inverse of the SE of the effect estimate. The smaller the precision of the studies, the wider the variation of the effect estimates across the different studies, and conversely, the higher the precision, the narrower the amplitude in variation of effect estimates. Thus the plot will have the shape of an inverted funnel, which must have a roughly symmetric appearance. In case there is a publication bias (eg, studies with negative results are not published), the funnel plot will be truncated in one side and will show an asymmetric appearance. The trim-and-fill method assesses asymmetry and, through a nonparametric procedure, estimates the number of potentially missing studies,

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**TABLE I.** Examples of discrepancies

| Study                                          | Source                             | SLIT       |      |      | Placebo    |      |      | SMD   | CILL  | CIUL  | Outcome                                            |
|------------------------------------------------|------------------------------------|------------|------|------|------------|------|------|-------|-------|-------|----------------------------------------------------|
|                                                |                                    | No.        | Mean | SD   | No.        | Mean | SD   |       |       |       |                                                    |
| Vourdas et al, 1998 <sup>E14</sup>             | Original                           | 34 → 34    | –    | –    | 32 → 32    | –    | –    |       |       |       |                                                    |
|                                                |                                    | 1R 33AR    |      |      | 3R 29AR    |      |      |       |       |       |                                                    |
|                                                | Wilson et al, 2003 <sup>4</sup>    | 34         | 1.38 | 2.01 | 32         | 1.07 | 1.63 | 0.17  | –0.32 | 0.65  | Allergic rhinitis symptom score                    |
|                                                | Penagos et al, 2006 <sup>5</sup>   | 34         | 0.88 | 0.25 | 32         | 1.24 | 0.35 | –1.18 | –1.70 | –0.65 | Nasal score, rhinitis                              |
| Rolinck-Werninghaus et al, 2004 <sup>E10</sup> | Olaguibel et al, 2005 <sup>2</sup> | 34         | 0.98 | 1.31 | 32         | 1.34 | 1.78 | –0.23 | –0.71 | 0.26  | Nasal symptom score                                |
|                                                | Original                           | 49 → 39    | 2.54 | 3.58 | 48 → 38    | 2.85 | 3.87 |       |       |       |                                                    |
|                                                |                                    | 29RC 20ARC |      |      | 29RC 19ARC |      |      |       |       |       |                                                    |
|                                                | Calamita et al, 2006 <sup>6</sup>  | 39         | 2.54 | 3.58 | 38         | 2.85 | 3.87 | –0.08 | –0.53 | 0.36  | Reductions of medication use to allergies, general |
|                                                | Penagos et al, 2006 <sup>5</sup>   | 39         | 2.54 | 3.58 | 38         | 2.85 | 3.87 | –0.08 | –0.53 | 0.36  | Medication score, rhinitis                         |
|                                                | Penagos et al, 2008 <sup>7</sup>   | 20         | 2.54 | 3.58 | 19         | 2.85 | 3.87 | –0.08 | –0.71 | 0.55  | Medication score (asthma)                          |

In the first study different data are reported by 3 MAs for the same outcome. In the second study 3 MAs report the same data for different outcomes.

SMD, Standardized mean difference; CILL, 5% to 95% CI lower limit; CIUL, 5% to 95% confidence interval upper limit. →, number of patients who initiate → finish treatment; R, rhinitis; A, asthma; C, conjunctivitis.

adjusts for them by using “mirrored” data of the most extreme present studies, and recalculates the effect estimate.

Finally, we calculated the estimates of the effects of SLIT on several major outcomes if the data of all the studies included in the 5 MAs were used to perform a new MA. The results were also tested with the Begg and Mazumdar,<sup>8</sup> Egger et al,<sup>9</sup> and trim-and-fill<sup>10</sup> methods by using the Stata 9.1 software.

## RESULTS

The 5 MAs cited 43 references (see the reference list in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org)): 2 studies were apparently included in some MAs, but their numeric data were not used for analysis. One study had 2 references, one as an abstract and the other as a journal publication; 26 studies were included in only one MA, and 17 (39.5%) studies were included in 2 to 5 MAs. The overlapping of studies is shown in [Tables E1 and E2](#) in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org). The MA by Wilson et al has been published in a journal<sup>3</sup> and in the Cochrane Library<sup>4</sup>; there were numerous differences between both sources in the figures provided, probably because of misprints in the editing process because the final result was the same, and therefore the results published in the Cochrane Library were used for evaluation.

There were discrepancies not caused by errata or rounding among the original studies, the MAs, or both in the reported data concerning the number of patients, mean effect, and SD in the active and placebo groups and hence in the standardized mean difference and its 5% to 95% CIs. Some discrepancies regarding the number of patients were due to the fact that 2 MAs<sup>2,4</sup> evaluated all initially included patients and included an intent-to-treat assessment, whereas the other 3 MAs<sup>5–7</sup> evaluated patients who actually finished the study. This pattern was not uniformly followed, and MAs 1<sup>2</sup> and 2<sup>4</sup> in some cases evaluated the number of patients who finished instead of those who initiated the treatment, and conversely, MAs 3<sup>5</sup> and 5<sup>7</sup> occasionally did the opposite. The MA by Calamita et al<sup>6</sup> evaluated patients who finished treatment for the outcomes of symptoms, medication, or their combination but evaluated patients who initiated treatment for a dichotomous outcome of “worse of asthma.”

There were more important discrepancies in the effect estimates in the active and control groups, with reported values in one MA that were up to 8 times the reported values for the same outcome in another MA. In as many as 27 instances, the original study did not report all the values required for analysis: authors of MAs 3<sup>5</sup> and 5<sup>7</sup> occasionally calculated them through image analysis of the figures, but all 5 MAs included trials in which they had to obtain the values by asking the authors of the original study. The discrepancies in the effect estimates led to discrepancies among MAs in the standardized mean difference and its CIs, with differences that reached up to 1.35 standardized z units.

In some results in which no apparent numeric discrepancy was found, the outcome was different for one MA when compared with another MA and with the original study (eg, MA 2<sup>4</sup> used data for rhinitis symptoms, whereas the original study and MA 4<sup>6</sup> had the same results for a combined asthma plus rhinitis plus conjunctivitis symptom score). [Table I](#) shows 2 examples of discrepancies between the reported values in the original articles and their values as reported in the MAs. The results of all the studies are shown in [Tables E3 to E6](#) in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org).

In the 15 main outcomes of the MAs, as shown in [Table II](#) (left side), 10 significantly favored active treatment over placebo, whereas in 5 the 95% CI interval of the effect crossed the line of no effect. We found a negative correlation (Spearman rho = 0.54,  $P = .037$ ), as shown in [Fig E1](#) in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org), of the benefit with the number of studies in each MA, and therefore the MAs with the highest number of evaluated studies showed the smallest benefits.

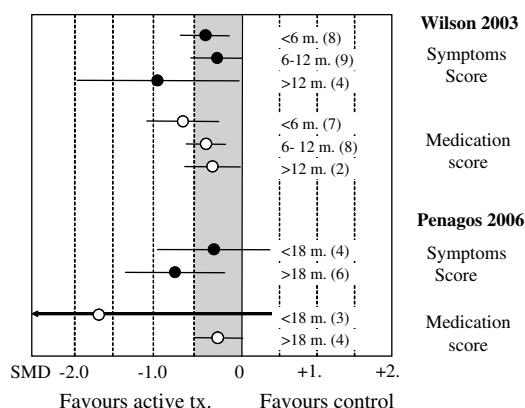
The MAs showed results of some subanalyses according to duration of SLIT, allergen, and age of patients. Regarding duration ([Fig 1](#)), MA 2<sup>4</sup> found a trend toward improvement of rhinitis symptoms with increasing duration, but at the same time, there was a decrease in the benefits in the rhinitis medication score. Likewise, MA 3<sup>5</sup> found a significant benefit in the symptom score, but not in the use of medication for rhinitis in children receiving more than 18 months of SLIT, although the number of studies included in these subanalyses was low.

For allergens, MA 2<sup>4</sup> found no benefit with perennial (mainly mites) allergens, and small benefits were found with pollens in

**TABLE II.** Results of the estimates for continuous outcomes in the 5 MAs and corrected estimates using the trim-and-fill method in estimates in which asymmetry was found

| MA no.         | Outcome scores        | Results of the 5 MAs |                        |         | Trim-and-fill evaluation |                                  |         |
|----------------|-----------------------|----------------------|------------------------|---------|--------------------------|----------------------------------|---------|
|                |                       | No. of studies       | Estimate, SMD (95% CI) | P value | No. of missing studies   | Corrected estimate, SMD (95% CI) | P value |
| 1 <sup>2</sup> | Nasal symptoms        | 6                    | −0.44 (−1.22 to 0.35)  | .27     | 0                        | No change                        |         |
|                | Bronchial symptoms    | 5                    | −1.42 (−2.61 to −0.34) | .01     | 0                        | No change                        |         |
|                | Ocular symptoms       | 2                    | −1.49 (−3.69 to 0.72)  | .19     | 1                        | −0.383 (−2.67 to 1.90)           | .74     |
|                | Medication            | 4                    | −1.01 (−2.06 to 0.04)  | .06     | 0                        | No change                        |         |
| 2 <sup>4</sup> | Nasal symptoms        | 21                   | −0.43 (−0.69 to −0.16) | .002    | 3                        | −0.24 (−0.57 to 0.09)            | .15     |
|                | Nasal medication      | 17                   | −0.31 (−0.45 to −0.17) | <.0001  | 5                        | −0.22 (−0.43 to −0.01)           | .04     |
| 3 <sup>5</sup> | Nasal symptoms        | 10                   | −0.66 (−1.01 to −0.10) | .02     | 0                        | No change                        |         |
|                | Nasal medication      | 7                    | −0.76 (−1.46 to −0.06) | .03     | 0                        | No change                        |         |
| 4 <sup>6</sup> | Asthma symptoms       | 9                    | −0.38 (−0.79 to 0.03)  | .07     | 2                        | −0.15 (−0.62 to 0.33)            | .54     |
|                | Asthma medication     | 6                    | −0.91 (−1.94 to 0.12)  | .08     | 0                        | No change                        |         |
|                | Allergic symptoms     | 10                   | −1.18 (−1.93 to −0.43) | .002    | 3                        | −0.43 (−1.33 to 0.47)            | .35     |
|                | Allergic medication   | 10                   | −0.82 (−1.26 to −0.39) | .0002   | 4                        | −0.39 (−0.87 to 0.08)            | .11     |
|                | Symptoms + medication | 7                    | −0.78 (−1.34 to −0.23) | .006    | 0                        | No change                        |         |
| 5 <sup>7</sup> | Asthma symptoms       | 9                    | −1.14 (−2.10 to −0.18) | .02     | 1                        | −0.88 (−1.86 to 0.11)            | .08     |
|                | Asthma medication     | 7                    | −1.63 (−2.83 to −0.44) | .007    | 0                        | No change                        |         |

Negative results in estimate (standardized mean difference [SMD] and 95% CI) favor active treatment over placebo.

**FIG 1.** Effect estimates according to duration in months of treatment with SLIT. The shaded area indicates that results are statistically significant but of modest clinical benefit. The number of studies included for that outcome is shown in parentheses. The medication score in the MA by Penagos et al<sup>5</sup> has been calculated from the results they show. SMD, Standardized mean difference.

children and adults with rhinitis. MA 3<sup>5</sup> found benefits for pollen but not for mites in children with rhinitis, but the same authors, in MA 5,<sup>7</sup> found benefit for mites but not for pollen in children with asthma.

With regard to age and disease, as shown in Table III, there were also inconsistent findings: MA 3,<sup>5</sup> which studied only children with rhinitis, found a benefit for them, whereas MA 1,<sup>2</sup> which also studied only children, found a benefit for asthma but not for rhinitis. MA 2,<sup>4</sup> which studied rhinitis in children and adults, found a benefit for the latter but not for the former, and MA 4<sup>6</sup> did not find differences between children and adults. MA 4<sup>6</sup> found a benefit in a “worse of asthma” outcome but not in asthma symptoms or asthma medication scores.

The assessment of asymmetry of funnel plots by using the methods of Begg and Mazumdar<sup>8</sup> and Egger et al<sup>9</sup> is shown in Table E7 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). Two of the most representative funnel plots of the different

outcomes in which asymmetry was identified are shown in Fig 2. Figs E2 to E16 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org) show the graphs of all the funnel plots with correction by using the trim-and-fill method, where applicable. Some outcomes included too few studies to have reliable results, but they are shown anyway. In the case of outcomes with the highest number of included studies, when there was an asymmetric plot, it was always with truncation in the side of negative studies. The trim-and-fill method was used for all outcomes, even in those with a very low number of studies, although it is less reliable in these studies: results are summarized in Table II (right side), which shows the change in the magnitude of the effect, with the new estimates corrected for potential publication bias.

The estimates of the effect of SLIT if all 43 original studies were used for a new synthetic MA are shown in Table E8 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org), as well as the correction by using the trim-and-fill method. The assessment of asymmetry of these estimates with the methods of Begg and Mazumdar<sup>8</sup> and Egger et al<sup>9</sup> is shown in Table E9 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org).

## DISCUSSION

Immunotherapy, as declared by the World Health Organization,<sup>11</sup> is the only treatment able to modify the natural course of allergic diseases. The sublingual route, as an alternative to subcutaneous administration, has been the focus of much attention lately. Its efficacy is a matter of debate, although published MAs seem to prove its efficacy.<sup>2-7</sup>

In a recent letter some concerns about methodological issues in MA 4<sup>6</sup> were raised, regarding the number and type of patients included.<sup>12</sup> In some outcomes of asthma in this MA, patients with rhinoconjunctivitis but without asthma were included for evaluation. This criticism led to a response by the authors of the MA, who explained their reasons for doing so.<sup>13</sup> The other 4 MAs also occasionally included patients with only rhinitis for outcomes of asthma or *vice versa*. The method is open to argument,

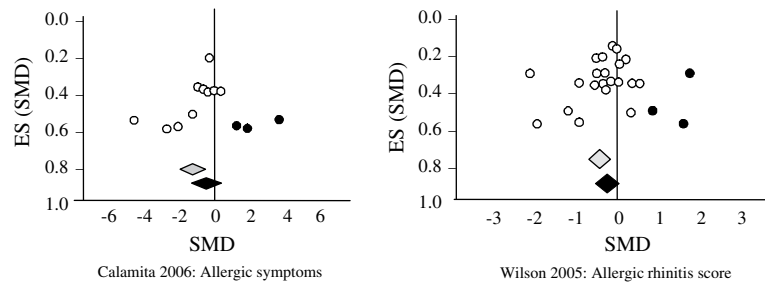


**FIG 2.** Funnel plots of symptom scores in MAs 4<sup>6</sup> (left) and 2.<sup>4</sup> Open circles indicate the estimates of each individual study; the shaded diamond indicates the global estimate of the MA. Solid circles indicate the estimates of the potential missing studies according to the trim-and-fill method; solid diamonds indicate the corrected estimate if the missing studies are included.

**TABLE III.** Statistically significant benefits found in the MAs, according to age and disease

|          | MA no.         | Asthma     | Rhinoconjunctivitis |
|----------|----------------|------------|---------------------|
| Children | 1 <sup>2</sup> | Benefit    | No benefit          |
|          | 2 <sup>4</sup> |            | No benefit          |
|          | 3 <sup>5</sup> |            | Benefit             |
|          | 4 <sup>6</sup> | No benefit | Benefit*            |
|          | 5 <sup>7</sup> | Benefit    |                     |
| Adults   | 2 <sup>4</sup> |            | Benefit             |
|          | 4 <sup>6</sup> | No benefit | Benefit*            |

MAs 1, 3, and 5 did not include adults.

Blank boxes, Not evaluated in the MA.

\*Benefits for composite asthma-rhinitis-conjunctivitis.

but the approach should be uniform for all studies in an MA, and this was not always the case, with inclusion or exclusion of different patients across studies in the same MA.

We have found numerous discrepancies in the data used for the MAs. In many instances the results used differed from the original study to those used for the MA or across MAs. These discrepancies were of 2 types: differences in the values used for the same outcome and different outcomes with the same values. The exact values were not reported in some original studies, and therefore authors of MAs had to find them out mainly through contact with authors of the original studies, but these authors might have failed to provide the same data to the authors of different MAs. This clearly demands the standardization of reports of clinical trials according to Consolidated Standards of Reporting Trials statements<sup>14</sup> or, more specifically, to recommendations for studies on immunotherapy.<sup>15</sup> Meanwhile, and whatever the causes and the solutions, the discrepancies make the results of these MAs less reliable.

In the assessment of MAs, and for their clinical application, both the magnitude of the effect and its CIs have to be considered. It has been estimated that the benefit of a treatment is clinically and not just statistically significant when there is a reduction of at least a 0.5 standardized mean difference in effect. These reductions were found in the mean estimates of several outcomes, although the benefit was lowest in the MAs with the highest number of included studies.

Publication bias has long been recognized as a shortcoming for the practice of evidence-based medicine. Studies with so-called negative results are more often not submitted for publication<sup>16</sup> or for report to regulatory authorities,<sup>17</sup> take longer to be published,<sup>18,19</sup> and have a lower impact factor,<sup>20</sup> although they do

not seem to be rejected more often by editors of journals.<sup>16</sup> Thus the absence of negative studies in MAs might lead to an overestimation of beneficial effects.

Potential publication bias in MAs can be roughly estimated with the use of funnel plots: as depicted in Figs E2 through E16, some of the outcomes of the evaluated MAs had an asymmetric appearance, suggesting possible publication bias. To assess asymmetry, several methods have been developed that do not always yield the same result. The method of Begg and Mazumdar<sup>8</sup> is claimed to be fairly powerful for MAs with 75 component studies but has little power for MAs with 25 component studies, and therefore bias cannot be ruled out if the test is not significant. One of the 5 MAs we have evaluated included 21 studies,<sup>4</sup> whereas the other 4 included 10 studies or less. The method of Egger et al<sup>9</sup> also has a low capacity to detect bias when MAs include a limited number of small trials, just as happened in the evaluated MAs. The trim-and-fill method<sup>10</sup> has been proposed as a method to correct for publication bias. When applying this method to the evaluated MAs, the benefits in several outcomes lost statistical significance or decreased dramatically, whereas in other outcomes they remained unchanged.

Publication bias is not the only reason for asymmetry. The assessment of asymmetry should better be used to examine the effect of small studies, which tend to be of lower quality than large studies. Asymmetry is not a proof of bias, but it should lead us to question the interpretation of the effect estimates in MAs.<sup>21</sup> In the case of SLIT, in addition to asymmetry, there were discrepancies among the MAs concerning benefits: some found benefit for asthma but not for rhinitis and *vice versa*. Likewise, discrepancies were found regarding age and allergen too. Also, if patients have fewer symptoms, they should be expected to need less relief medication, but there was divergence in these outcomes, as shown in Fig 2. This lack of consistency makes it difficult to support the current use of this kind of immunotherapy as a first-line treatment for allergic diseases.

We have calculated the estimates of the effect of SLIT if the 43 original studies were used for a new MA. Nevertheless, we had to face the same difficulties regarding the lack of explicit data in some original articles and the effect of the potentially missing studies, and moreover, we did not select the studies but relied on the selection made by the authors of the 5 MAs. They, however, have used different criteria for inclusion of studies, as, in fact, some studies that were included in an MA were excluded from others. Thus these results should be viewed with as much or even more caution than those of the 5 evaluated MAs.

The price of SLIT, up to 5 times that of subcutaneous immunotherapy, and the frequent schedule of administration (3-7 times a week) can affect the compliance with this long treatment and reduce its effects. In the case of subcutaneous immunotherapy, the need for administration in a medical setting can turn into an advantage regarding compliance and especially regarding access to emergency treatment in case of a reaction. Although SLIT is considered generally safe, severe asthmatic or even anaphylactic reactions have been described,<sup>22-25</sup> even in studies used for the MAs. When reactions appear, rapid assessment and treatment are essential, but they are not available in the homes of the patients where SLIT is self-administered.

A recent comprehensive review pointed at dose, treatment schedule, and duration as the main current unanswered questions about SLIT, although it described SLIT as effective.<sup>1</sup> The data presented in this article, however, cast doubt on its efficacy because of inconsistencies and lack of robustness of the MAs. If efficacy is not remarkable in the controlled conditions of clinical trials, its effectiveness in the more unstable conditions of real life will be even more impaired.

In conclusion, the current MAs do not provide robust enough evidence to support the use of SLIT in the practical routine treatment of allergy. The concerns raised are not specific to MAs on SLIT but rather reflect the general difficulties with all MAs, and therefore for publication of these, analyses to test their robustness through assessment of asymmetry or other methods should be required.

**Clinical implications: Current evidence is not strong enough to support the routine treatment with SLIT because the MAs supporting it show features suggesting publication bias and reach inconsistent and discrepant conclusions.**

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The 5 MAs cited 43 references. References E36 and E43 were apparently included, but their numeric results were not used in any of the outcomes. The study by Niu et al was referenced twice (as E16 and E33), once as an abstract and once in a journal. The study by Andre et al (E17) was referenced as an abstract in the MA by Wilson, although it was later published as a journal article.

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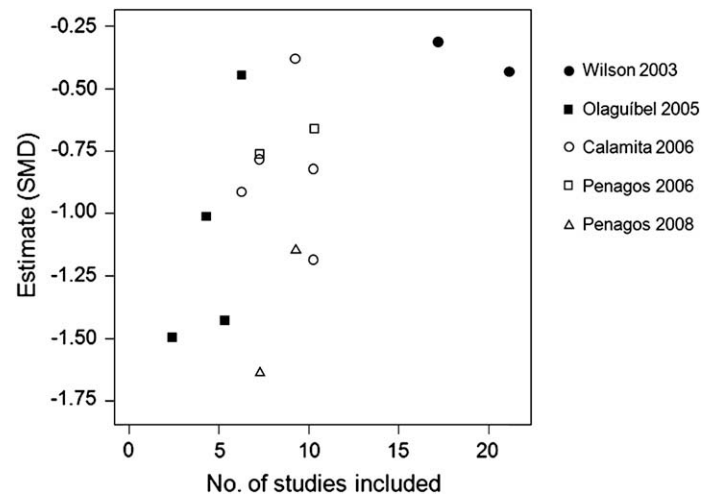


**FIG E1.** Correlation of the effect estimate (reduction of scores in standardized mean differences [SMD]) and the number of studies included in the MAs for each outcome (Spearman's rho = 0.54,  $P = .037$ ).

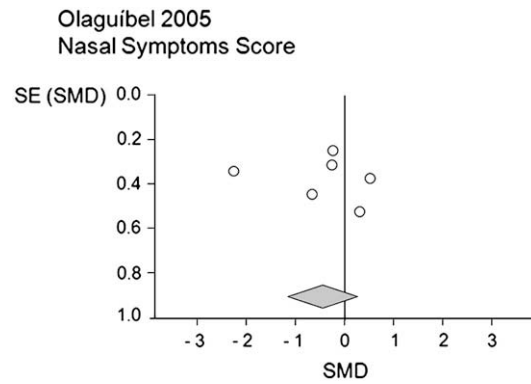


**FIG E2.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA. *SMD*, Standardized mean difference.

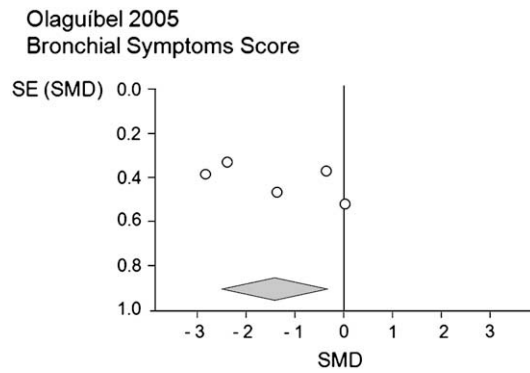


**FIG E3.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA. *SMD*, Standardized mean difference.

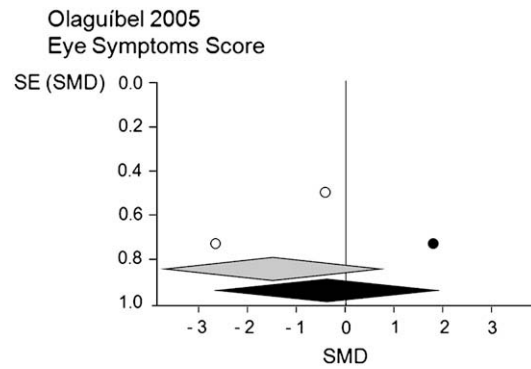


**FIG E4.** Funnel plot. *Open circles* indicate the estimates of each individual study, and the *shaded diamond* indicates the global estimate of the MA. The *solid circle* indicates the estimate of one potential missing study according to the trim-and-fill method. The *solid diamond* indicates the corrected estimate if the missing study is included. *SMD*, Standardized mean difference.

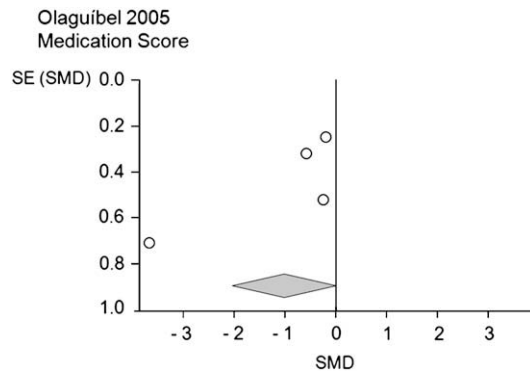


**FIG E5.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA. *SMD*, Standardized mean difference.

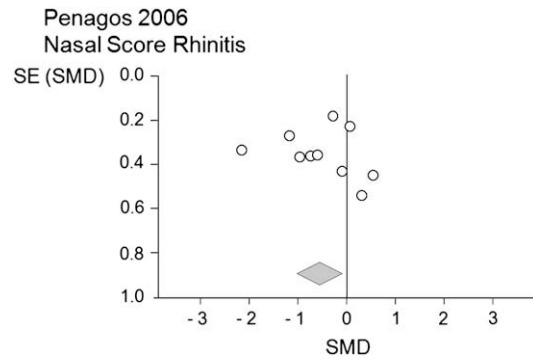


**FIG E6.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA.

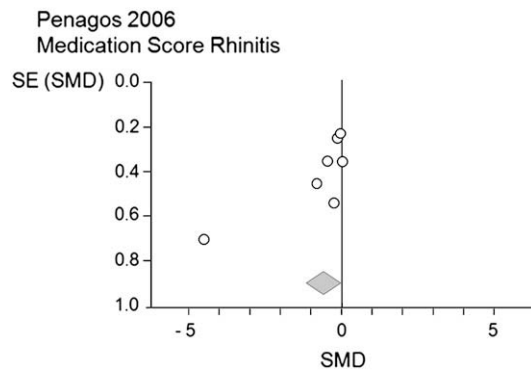


**FIG E7.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA. *SMD*, Standardized mean difference.

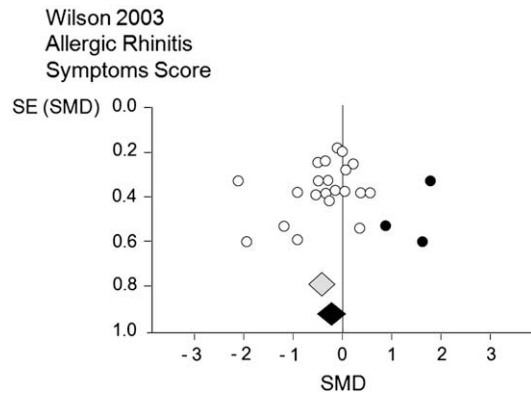


**FIG E8.** Funnel plot. *Open circles* indicate the estimates of each individual study, and the *shaded diamond* indicates the global estimate of the MA. *Solid circles* indicate the estimates of the potential missing studies according to the trim-and-fill method. The *solid diamond* indicates the corrected estimate if the missing studies are included. *SMD*, Standardized mean difference.

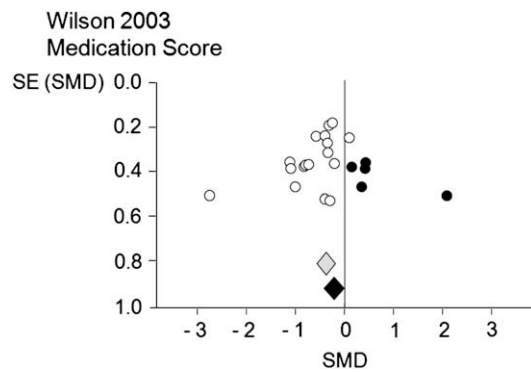


**FIG E9.** Funnel plot. *Open circles* indicate the estimates of each individual study, and the *shaded diamond* indicates the global estimate of the MA. *Solid circles* indicate the estimates of the potential missing studies according to the trim-and-fill method. The *solid diamond* indicates the corrected estimate if the missing studies are included. *SMD*, Standardized mean difference.

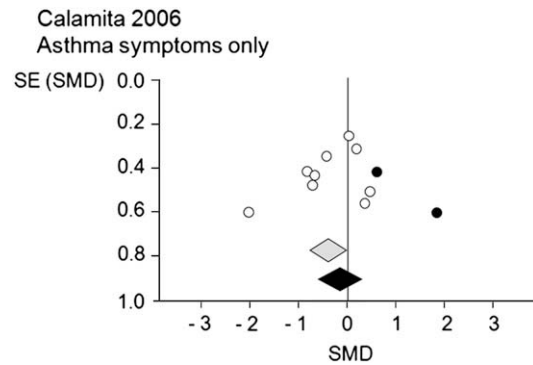


**FIG E10.** Funnel plot. *Open circles* indicate the estimates of each individual study, and the *shaded diamond* indicates the global estimate of the MA. *Solid circles* indicate the estimates of the potential missing studies according to the trim-and-fill method. The *solid diamond* indicates the corrected estimate if the missing studies are included. *SMD*, Standardized mean difference.

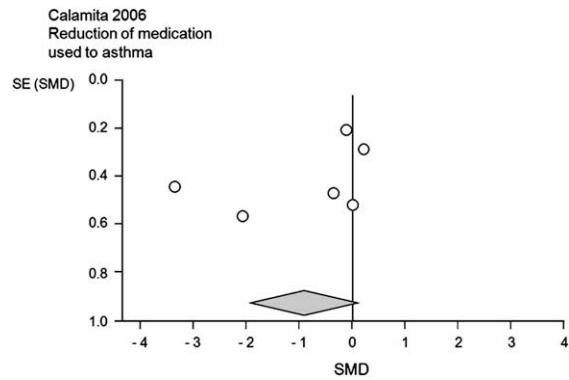


**FIG E11.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA. *SMD*, Standardized mean difference.

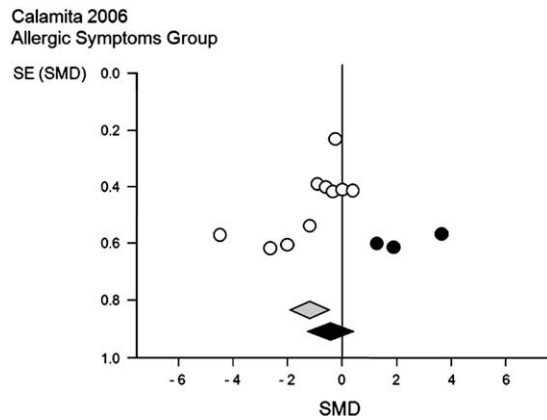


**FIG E12.** Funnel plot. *Open circles* indicate the estimates of each individual study, and the *shaded diamond* indicates the global estimate of the MA. *Solid circles* indicate the estimates of the potential missing studies according to the trim-and-fill method. The *solid diamond* indicates the corrected estimate if the missing studies are included. *SMD*, Standardized mean difference.

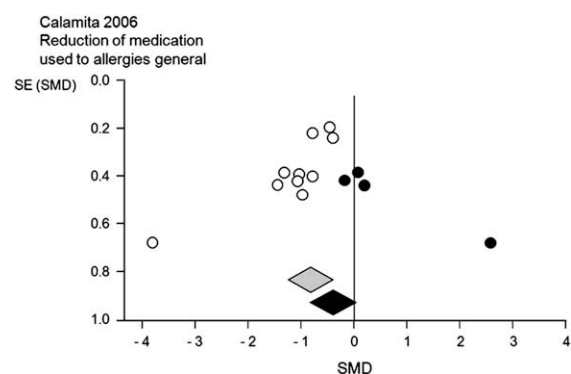


**FIG E13.** Funnel plot. *Open circles* indicate the estimates of each individual study, and the *shaded diamond* indicates the global estimate of the MA. *Solid circles* indicate the estimates of the potential missing studies according to the trim-and-fill method. The *solid diamond* indicates the corrected estimate if the missing studies are included. *SMD*, Standardized mean difference.

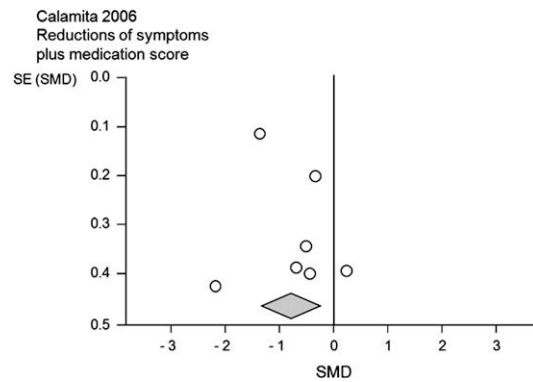


**FIG E14.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA. *SMD*, Standardized mean difference.

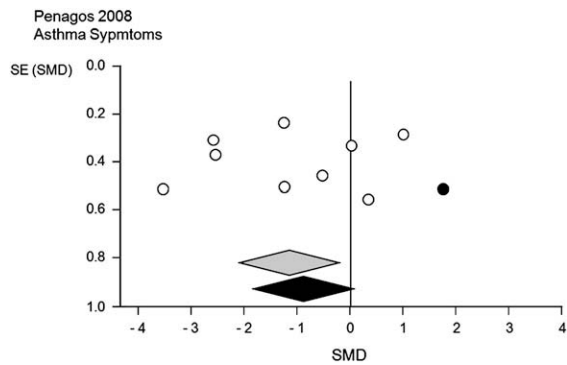


**FIG E15.** Funnel plot. *Open circles* indicate the estimates of each individual study, and the *shaded diamond* indicates the global estimate of the MA. The *solid circle* indicates the estimate of one potential missing study according to the trim-and-fill method. The *solid diamond* indicates the corrected estimate if the missing study is included. *SMD*, Standardized mean difference.

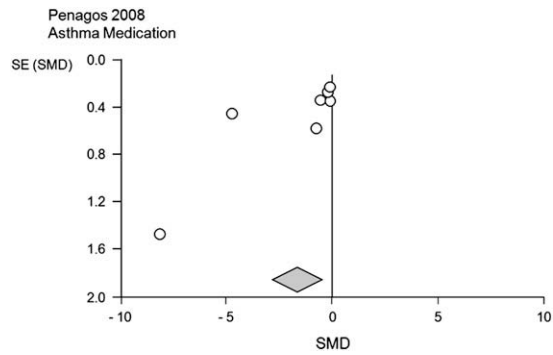


**FIG E16.** Funnel plot. *Circles* indicate the estimates of each individual study, and the *diamond* indicates the global estimate of the MA.

**TABLE E1.** Distribution of studies in the different meta-analysis

|                         |              |    |
|-------------------------|--------------|----|
| No. of studies included | Only in 1 MA | 26 |
|                         | In 2 Mas     | 10 |
|                         | In 3 Mas     | 3  |
|                         | In 4 Mas     | 2  |
|                         | In 5 Mas     | 2  |
| Total                   |              | 43 |

| Online reference no. | Included in:  |             |              |                |              |
|----------------------|---------------|-------------|--------------|----------------|--------------|
| E1                   | Calamita 2006 | Wilson 2005 |              |                |              |
| E2                   | Calamita 2006 | Wilson 2005 | Penagos 2006 | Olaguíbel 2005 | Penagos 2008 |
| E3                   | Calamita 2006 | Wilson 2005 |              |                |              |
| E4                   | Calamita 2006 | Wilson 2005 | Penagos 2006 | Olaguíbel 2005 | Penagos 2008 |
| E5                   | Calamita 2006 | Wilson 2005 |              |                | Penagos 2008 |
| E6                   | Calamita 2006 | Wilson 2005 |              |                |              |
| E7                   | Calamita 2006 | Wilson 2005 |              |                |              |
| E8                   | Calamita 2006 | Wilson 2005 |              |                |              |
| E9                   | Calamita 2006 | Wilson 2005 |              |                |              |
| E10                  | Calamita 2006 |             | Penagos 2006 |                | Penagos 2008 |
| E11                  | Calamita 2006 | Wilson 2005 |              |                |              |
| E12                  |               | Wilson 2005 | Penagos 2006 | Olaguíbel 2005 |              |
| E13                  |               | Wilson 2005 | Penagos 2006 | Olaguíbel 2005 | Penagos 2008 |
| E14                  |               | Wilson 2005 | Penagos 2006 | Olaguíbel 2005 | Penagos 2008 |
| E15                  |               |             | Penagos 2006 | Olaguíbel 2005 |              |
| E16                  |               |             |              |                | Penagos 2008 |
| E17                  |               | Wilson 2005 |              |                |              |
| E18                  | Calamita 2006 |             |              |                |              |
| E19                  | Calamita 2006 |             |              |                |              |
| E20                  |               |             | Penagos 2006 |                |              |
| E21                  |               |             | Penagos 2006 |                | Penagos 2008 |
| E22                  |               | Wilson 2005 |              |                |              |
| E23                  | Calamita 2006 |             |              |                |              |
| E24                  |               | Wilson 2005 |              |                |              |
| E25                  |               |             | Penagos 2006 |                | Penagos 2008 |
| E26                  |               | Wilson 2005 |              |                |              |
| E27                  |               | Wilson 2005 |              |                |              |
| E28                  | Calamita 2006 |             |              |                |              |
| E29                  | Calamita 2006 |             |              |                |              |
| E30                  |               | Wilson 2005 |              |                |              |
| E31                  | Calamita 2006 |             |              |                |              |
| E32                  |               | Wilson 2005 |              |                |              |
| E33                  | Calamita 2006 |             |              |                |              |
| E34                  | Calamita 2006 |             |              |                |              |
| E35                  | Calamita 2006 |             |              |                |              |
| E36 (*)              | Calamita 2006 |             |              |                |              |
| E37                  | Calamita 2006 |             |              |                |              |
| E38                  |               | Wilson 2005 |              |                |              |
| E39                  | Calamita 2006 |             |              |                |              |
| E40                  | Calamita 2006 |             |              |                |              |
| E41                  |               | Wilson 2005 |              |                |              |
| E42                  | Calamita 2006 |             |              |                |              |
| E43 (#)              |               | Wilson 2005 |              |                |              |

(\*) Included in Calamita 2006, but data not used in the analysis

(#) Included in Wilson 2005, but data not used in the analysis

**TABLE E2.** Number of original studies included in 1 or more meta-analyses. Each of the numbers in the *yellow boxes* along the diagonal indicates the number of studies included only in that meta-analysis. Each of the numbers in the other boxes indicates the number of studies included in the 2 corresponding crossing meta-analysis. Some studies are included in up to the five meta-analyses (see table E1) and Thus in up to ten boxes. References listed in the online repository list

|                |   | A             | B           | C            | D              | E            |
|----------------|---|---------------|-------------|--------------|----------------|--------------|
|                |   | Calamita 2006 | Wilson 2005 | Penagos 2006 | Olaguibel 2005 | Penagos 2008 |
| Calamita 2006  | 1 | 14            | 9           | 3            | 3              | 4            |
| Wilson 2005    | 2 |               | 10          | 5            | 5              | 4            |
| Penagos 2006   | 3 |               |             | 1            | 6              | 7            |
| Olaguibel 2005 | 4 |               |             |              | 0              | 5            |
| Penagos 2008   | 5 |               |             |              |                | 1            |

| References included in Box # |     |     |     |     |
|------------------------------|-----|-----|-----|-----|
| 1A                           | 1B  | 1C  | 1D  | 1E  |
| E18                          | E1  | E2  | E2  | E2  |
| E19                          | E2  | E4  | E4  | E4  |
| E23                          | E3  | E10 | E5  | E5  |
| E28                          | E4  |     |     | E10 |
| E29                          | E6  |     |     |     |
| E31                          | E7  |     |     |     |
| E33                          | E8  |     |     |     |
| E34                          | E9  |     |     |     |
| E35                          | E11 |     |     |     |
| E36                          |     |     |     |     |
| E37                          |     |     |     |     |
| E39                          |     |     |     |     |
| E40                          |     |     |     |     |
| E42                          |     |     |     |     |
|                              | 2B  | 2C  | 2D  | 2E  |
|                              | E17 | E2  | E2  | E2  |
|                              | E22 | E4  | E4  | E4  |
|                              | E24 | E12 | E12 | E13 |
|                              | E26 | E13 | E13 | E14 |
|                              | E27 | E21 | E21 |     |
|                              | E30 |     |     |     |
|                              | E32 |     |     |     |
|                              | E38 |     |     |     |
|                              | E41 |     |     |     |
|                              | E43 |     |     |     |
|                              |     | 3C  | 3D  | 3E  |
|                              |     | E20 | E2  | E2  |
|                              |     |     | E4  | E4  |
|                              |     |     | E12 | E10 |
|                              |     |     | E13 | E13 |
|                              |     |     | E14 | E14 |
|                              |     |     | E15 | E21 |
|                              |     |     |     | E25 |
|                              |     |     | 4D  | 4E  |
|                              |     |     |     | E2  |
|                              |     |     |     | E4  |
|                              |     |     |     | E5  |
|                              |     |     |     | E14 |
|                              |     |     |     | E41 |
|                              |     |     |     | 5E  |
|                              |     |     |     | E16 |

**TABLE E3.** Outcomes on symptoms of asthma, rhinitis, rhinoconjunctivitis, or their combination. The source identifies the data as reported in the original publication and in the meta-analysis in which it was included. See footnotes for explanation

| Study                      | Source         | Outcome                               | Active SLIT                |        |        | Placebo                    |        |        | SMD (5% to 95%CI) |       |       |
|----------------------------|----------------|---------------------------------------|----------------------------|--------|--------|----------------------------|--------|--------|-------------------|-------|-------|
|                            |                |                                       | No.                        | Mean   | SD     | No.                        | Mean   | SD     | SMD               | 5%    | 95%   |
| 1. ARIANO 2001             | Original       | Symptoms score (ARC composite)        | 10 -> 10<br>2A/8RC         | 1.80   | 1.75   | 10 -> 10<br>1A/9RC         | 5.38   | 1.57   |                   |       |       |
|                            | Calamita 2006  | Allergic symptoms group               | 10                         | 1.80   | 1.75   | 10                         | 5.38   | 1.57   | -2.06             | -3.19 | -0.93 |
|                            | Wilson 2003    | Allergic rhinitis symptoms scores     | 10                         | 1.80   | 1.75   | 10                         | 5.38   | 1.57   | -2.06             | -3.19 | -0.93 |
| 2. BAHÇECILER 2001         | Original       | Asthma score                          | 8 -> 8<br>8AR              |        |        | 7 -> 7<br>7AR              |        |        |                   |       |       |
|                            | Calamita 2006  | Asthma symptoms only                  | 8                          | 0.42   | 0.45   | 7                          | 0.29   | 0.26   | 0.33              | -0.70 | 1.35  |
|                            | Penagos 2008   | Asthma score                          | 7                          | 0.42   | 0.45   | 7                          | 0.29   | 0.26   | 0.33              | -0.73 | 1.39  |
|                            | Olaguibel 2005 | Bronchial symptoms scores             | 8                          | 0.25   | 0.75   | 7                          | 0.24   | 0.40   | 0.02              | -1.00 | 1.03  |
|                            | Original       | Rhinitis Score                        | 8 -> 8                     |        |        | 7 -> 7                     |        |        |                   |       |       |
|                            | Wilson 2003    | Allergic rhinitis symptoms score      | 8                          | 0.53   | 0.40   | 7                          | 0.40   | 0.38   | 0.31              | -0.71 | 1.34  |
|                            | Olaguibel 2005 | Nasal symptoms scores                 | 8                          | 0.53   | 0.40   | 7                          | 0.40   | 0.38   | 0.31              | -0.71 | 1.34  |
|                            | Penagos 2006   | Nasal score rhinitis                  | 7                          | 0.53   | 0.40   | 7                          | 0.41   | 0.39   | 0.28              | -0.77 | 1.34  |
| 3. FELIZIANI 1995          | Original       | Symptoms score (ARC composite)        | 18 -> 18<br>18RC±A         | 109.70 |        | 16 -> 16<br>16RC±A         | 209.40 |        |                   |       |       |
|                            | Calamita 2006  | Allergic symptoms group               | 18                         | 109.70 | 103.90 | 16                         | 209.40 | 103.90 | -0.94             | -1.65 | -0.22 |
|                            | Wilson 2003    | Allergic rhinitis symptoms scores     | 18                         | 109.70 | 92.46  | 16                         | 215.80 | 114.20 | -1.00             | -1.72 | -0.28 |
| 4. HIRSCH 1997             | Original       | Nasal symptoms                        | 15 -> 14<br>3A/3R/9AR      |        |        | 15 -> 15<br>5A/5R/5AR      |        |        |                   |       |       |
|                            | Wilson 2003    | Allergic rhinitis symptoms scores     | 15                         | 0.99   | 1.13   | 15                         | 0.52   | 0.47   | 0.53              | -0.20 | 1.26  |
|                            | Olaguibel 2005 | Nasal symptoms scores                 | 15                         | 0.99   | 1.13   | 15                         | 0.52   | 0.47   | 0.53              | -0.20 | 1.26  |
|                            | Penagos 2006   | Nasal score rhinitis                  | 11                         | 0.99   | 1.13   | 10                         | 0.52   | 0.47   | 0.51              | -0.36 | 1.39  |
|                            | Original       | Pulmonary symptoms                    | 15 -> 14                   |        |        | 15 -> 15                   |        |        |                   |       |       |
|                            | Calamita 2006  | Asthma symptoms only                  | 12                         | 0.07   | 0.27   | 10                         | 0.28   | 0.27   | -0.75             | -1.62 | 0.13  |
|                            | Olaguibel 2005 | Bronchial symptoms scores             | 15                         | 0.03   | 0.70   | 15                         | 0.28   | 0.60   | -0.37             | -1.10 | 0.35  |
|                            | Penagos 2008   | Asthma score                          | 11                         | 0.17   | 0.30   | 10                         | 0.42   | 0.58   | -0.53             | -1.40 | 0.35  |
| 5. PAJNO 2000              | Original       | Score for nighttime symptoms (Asthma) | 12 -> 12<br>12A            | 6.00   |        | 12 -> 9<br>12A             | 13.20  |        |                   |       |       |
|                            | Calamita 2006  | Asthma symptoms only                  | 12                         | 6.00   | 3.34   | 9                          | 13.20  | 3.34   | -2.07             | -3.18 | -0.96 |
|                            | Olaguibel 2005 | Bronchial symptoms scores             | 12                         | 6.00   | 3.40   | 12                         | 13.20  | 6.20   | -1.39             | -2.30 | 0.48  |
|                            | Original       | Visual Analogue Scale                 | 12 -> 12                   | 2.50   |        | 12 -> 9                    | 6.60   |        |                   |       |       |
|                            | Penagos 2008   | Asthma score                          | 12                         | 2.50   | 0.14   | 9                          | 6.60   | 4.88   | -1.24             | -2.20 | -0.28 |
| 6. PASSALACQUA 1998        | Original       | Symptoms score (ARC composite)        | 10 -> 10<br>7RC/3ARC       |        |        | 10 -> 9<br>7RC/3ARC        |        |        |                   |       |       |
|                            | Calamita 2006  | Allergic symptoms group               | 10                         | 59.60  | 27.80  | 9                          | 109.10 | 45.70  | -1.27             | -2.28 | -0.26 |
|                            | Wilson 2003    | Allergic rhinitis symptoms scores     | 10                         | 59.60  | 27.80  | 9                          | 109.10 | 45.70  | -1.27             | -2.28 | -0.26 |
| 7. PASSALACQUA 1999        | Original       | Rhinoconjunctivitis plus asthma score | 15 -> 14<br>6ARC/9RC       | 189.20 |        | 15 -> 13<br>7ARC/8RC       | 191.00 |        |                   |       |       |
|                            | Calamita 2006  | Allergic symptoms group               | 14                         | 189.20 | 93.10  | 13                         | 191.00 | 88.1   | -0.02             | -0.77 | 0.74  |
|                            | Wilson 2003    | Allergic rhinitis symptoms scores     | 15                         | 189.00 | 113.00 | 15                         | 191.00 | 108.00 | -0.02             | -0.73 | 0.70  |
| 8. PRADALIER 1999          | Original       | No. days with asthma symptoms         | 63 -> 62 -> 60<br>45R/17AR | 1.10   | 3.57   | 63 -> 61 -> 59<br>36R/25AR | 4.20   | 9.28   |                   |       |       |
|                            | Calamita 2006  | Asthma symptoms only                  | 17                         | 1.10   | 3.57   | 25                         | 4.20   | 8.28   | -0.40             | -1.03 | 0.22  |
|                            | Original       | Rhinitis symptoms                     | 63 -> 62 -> 60             | 2.33   | 1.61   | 63 -> 61 -> 59             | 2.65   | 1.97   |                   |       |       |
|                            | Wilson 2003    | Allergic rhinitis symptoms score      | 63                         | 2.33   | 1.60   | 63                         | 2.65   | 2.00   | -0.18             | -0.53 | 0.17  |
| 9. PURELLO D'AMBROSIO 1999 | Original       | Not clearly disclosed (Asthma?)       | 14 -> 14<br>7RC/7ARC       |        |        | 16 -> 16<br>8RC/8ARC       |        |        |                   |       |       |
|                            | Calamita 2006  | Asthma symptoms only                  | 14                         | 10.35  | 19.92  | 16                         | 90.50  | 122.87 | -0.86             | -1.61 | -0.10 |
|                            | Original       | Not clearly disclosed (Rhinitis?)     |                            |        |        |                            |        |        |                   |       |       |
|                            | Calamita 2006  | Allergic symptoms group               | 14                         | 509.00 | 514.22 | 16                         | 897.06 | 678.19 | -0.62             | -1.36 | 0.12  |
|                            | Wilson 2003    | Allergic rhinitis symptoms scores     | 14                         | 509.00 | 514.20 | 16                         | 897.06 | 678.20 | -0.62             | -1.36 | 0.12  |

(Continued)

TABLE E3. (Continued)

| Study                        | Source         | Outcome                                                      | Active SLIT                |        |        | Placebo                    |        |       | SMD (5-95%CI) |       |       |
|------------------------------|----------------|--------------------------------------------------------------|----------------------------|--------|--------|----------------------------|--------|-------|---------------|-------|-------|
|                              |                |                                                              | No.                        | Mean   | SD     | No.                        | Mean   | SD    | SMD           | 5%    | 95%   |
| 10. ROLINCK-WERNINGHAUS 2004 | Original       | Bronchi symptoms score                                       | 49 -> 39<br>29RC/20ARC     | 2.54   | 5.00   | 48 -> 38<br>29RC/19ARC     | 2.50   | 5.06  |               |       |       |
|                              | Calamita 2006  | Asthma symptoms only                                         | 39                         | 2.54   | 5.00   | 38                         | 2.50   | 5.06  | 0.01          | -0.44 | 0.45  |
|                              | Penagos 2008   | Asthma score                                                 | 20                         | 2.54   | 5.00   | 19                         | 2.50   | 5.06  | 0.01          | -0.62 | 0.64  |
|                              | Original       | Nose symptoms score                                          | 39                         | 13.71  | 23.12  | 38                         | 12.66  | 21.65 |               |       |       |
|                              | Penagos 2006   | Nasal score rhinitis                                         | 39                         | 13.71  | 23.12  | 38                         | 12.66  | 21.65 | 0.05          | -0.40 | 0.49  |
| 11. VOLTOLINI 2001           | Original       | Symptoms score (ARC composite)                               | 15 -> 14<br>6RC/9ARC       | 129.64 |        | 15 -> 13<br>6RC/9ARC       | 83.23  |       |               |       |       |
|                              | Calamita 2006  | Allergic symptoms group                                      | 14                         | 129.64 | 153.88 | 13                         | 83.23  | 78.82 | 0.36          | -0.40 | 1.13  |
|                              | Wilson 2003    | Allergic rhinitis symptoms scores                            | 15                         | 130.00 | 154.00 | 15                         | 83.00  | 79.00 | 0.37          | -0.35 | 1.10  |
| 12. LA ROSA 1999             | Original       | Rhinitis symptoms score                                      | 20 -> 16<br>20RC±A         |        |        | 21 -> 17<br>21RC±A         |        |       |               |       |       |
|                              | Wilson 2003    | Allergic rhinitis symptoms scores                            | 20                         | 1.21   | 1.66   | 21                         | 1.61   | 1.56  | -0.24         | -0.86 | 0.37  |
|                              | Olaguibel 2005 | Nasal symptoms scores                                        | 20                         | 1.21   | 1.66   | 21                         | 1.61   | 1.56  | -0.24         | -0.86 | 0.37  |
|                              | Penagos 2006   | Nasal score rhinitis                                         | 16                         | 0.19   | 0.44   | 17                         | 0.72   | 0.88  | -0.75         | -1.46 | -0.04 |
| 13. TARI 1990                | Original       | Nose, Eyes, and Lung Symptom Score (separate)                | 34 -> 30<br>R and/or A     |        |        | 32 -> 28<br>R and/or A     |        |       |               |       |       |
|                              | Wilson 2003    | Allergic rhinitis symptoms scores                            | 34                         | 8.00   | 1.50   | 32                         | 12.00  | 2.00  | -2.25         | -2.87 | -1.62 |
|                              | Penagos 2006   | Nasal score rhinitis                                         | 30                         | 8.00   | 1.56   | 28                         | 12.00  | 2.10  | -2.14         | -2.80 | -1.49 |
|                              | Olaguibel 2005 | Nasal symptoms scores                                        | 30                         | 8.00   | 1.50   | 28                         | 12.00  | 2.00  | -2.24         | -2.91 | -1.58 |
|                              | Original       |                                                              | 34 -> 30                   |        |        | 32 -> 28                   |        |       |               |       |       |
|                              | Olaguibel 2005 | Bronchial symptoms scores                                    | 30                         | 6.00   | 1.50   | 28                         | 9.70   | 1.00  | -2.84         | -3.59 | -2.10 |
|                              | Penagos 2008   | Asthma score                                                 | 30                         | 6.00   | 1.62   | 28                         | 9.44   | 0.96  | -2.53         | -3.23 | -1.83 |
| 14. VOURDAS 1998             | Original       | Dyspnea, Eyes redness, Rhinitis Symptoms (separate)          | 34 -> 33<br>1R/33AR        |        |        | 32 -> 31<br>3R/29AR        |        |       |               |       |       |
|                              | Wilson 2003    | Allergic rhinitis symptoms scores                            | 34                         | 1.38   | 2.01   | 32                         | 1.07   | 1.63  | 0.17          | -0.32 | 0.65  |
|                              | Penagos 2006   | Nasal score rhinitis                                         | 34                         | 0.88   | 0.25   | 32                         | 1.24   | 0.35  | -1.18         | -1.70 | -0.65 |
|                              | Olaguibel 2005 | Nasal symptoms scores                                        | 34                         | 0.98   | 1.31   | 32                         | 1.34   | 1.78  | -0.23         | -0.71 | 0.26  |
|                              | Original       |                                                              | 34 -> 33                   |        |        | 32 -> 31                   |        |       |               |       |       |
|                              | Olaguibel 2005 | Bronchial symptoms scores                                    | 34                         | 0.15   | 0.07   | 32                         | 0.32   | 0.07  | -2.40         | -3.04 | -1.76 |
| 15. WÜTHRICH 2003            | Original       | Symptoms Score (ARC composite)                               | 14 -> 10<br>RD             |        |        | 14 -> 12<br>5RC/7ARC       |        |       |               |       |       |
|                              | Penagos 2006   | Nasal score rhinitis                                         | 10                         | 94.70  | 88.95  | 12                         | 103.5  | 59.86 | -0.11         | -0.95 | 0.73  |
|                              | Olaguibel 2005 | Nasal symptoms scores                                        | 10                         | 110.00 | 21.86  | 12                         | 125.00 | 21.86 | -0.66         | -1.53 | 0.21  |
| 16. NIU 2006                 | Original       | Asthma scores                                                | 56 -> 49<br>56A            | 0.04   |        | 54 -> 48<br>54A            | 0.06   |       |               |       |       |
|                              | Penagos 2008   | Asthma score                                                 | 49                         | 0.04   | 0.01   | 48                         | 0.06   | 0.02  | -1.26         | -1.70 | -0.82 |
| 17. ANDRE 2002 (Abstract)    | Original       | Symptoms score (RC + A?)                                     | 55 -> 48 -> 41<br>55RC±A   |        |        | 55 -> 51 -> 49<br>55RC±A   |        |       |               |       |       |
|                              | Wilson 2003    | Allergic rhinitis symptoms score                             | 55                         | 3.78   | 2.74   | 55                         | 3.95   | 2.66  | -0.06         | -0.44 | 0.31  |
| 18. ARIANO 2005              | Original       | Symptom scores (ARC composite)                               | 20 -> 20<br>4A/13R/3C      | 4.95   | 2.16   | 10 -> 10<br>2A/6R/2C       | 10.40  | 1.96  |               |       |       |
|                              | Calamita 2006  | Allergic symptoms group                                      | 20                         | 9.30   | 3.03   | 10                         | 10.40  | 1.96  | -0.39         | -1.16 | 0.37  |
| 19. BOUSQUET 1999            | Original       | Nighttime asthma                                             | 42 -> 32 -> 23<br>24A/18AR | 0.17   | 0.51   | 43 -> 33 -> 27<br>26A/17AR | 0.11   | 0.35  |               |       |       |
|                              | Calamita 2006  | Asthma symptoms only                                         | 23                         | 0.17   | 0.51   | 27                         | 0.11   | 0.35  | 0.14          | -0.42 | 0.69  |
| 20. BUFE 2004                | Original       | Clinical Index Score (Composite Symptoms + Medication Index) | 82 -> 64<br>33A/79R/76C    |        |        | 79 -> 68<br>35A/76R/73C    |        |       |               |       |       |
|                              | Penagos 2006   | Nasal score rhinitis                                         | 63                         | 1.47   | 0.94   | 63                         | 1.77   | 1.01  | -0.31         | -0.66 | 0.05  |
| 21. CAFFARELLI 2000          | Original       | Bronchial Symptoms                                           | 24 -> 24<br>ARC            | 2.40   | 2.70   | 24 -> 20<br>C              | 4.60   | 3.50  |               |       |       |
|                              | Penagos 2008   | Asthma score                                                 | 23                         | 2.39   | 0.50   | 20                         | 4.60   | 0.73  | -3.51         | -4.50 | -2.53 |
|                              | Original       | Nasal symptoms                                               | 24 -> 24                   |        |        | 24 -> 20                   |        |       |               |       |       |
|                              | Penagos 2006   | Nasal score rhinitis                                         | 17                         | 4.40   | 1.60   | 17                         | 6.00   | 1.60  | -0.98         | -1.69 | -0.26 |

(Continued)

TABLE E3. (Continued)

| Study                       | Source        | Outcome                                                    | Active SLIT            |         |         | Placebo                |         |         | SMD (5-95%CI) |       |       |
|-----------------------------|---------------|------------------------------------------------------------|------------------------|---------|---------|------------------------|---------|---------|---------------|-------|-------|
|                             |               |                                                            | No.                    | Mean    | SD      | No.                    | Mean    | SD      | SMD           | 5%    | 95%   |
| 22. CASANOVAS 2000          | Original      | Symptom score                                              | 10 -> 9<br>10RC        |         |         | 10 -> 6<br>10RC        |         |         |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 9                      | 5.46    | 3.56    | 6                      | 10.98   | 7.10    | -1.00         | -2.11 | 0.12  |
| 24. HORDIJK 1998            | Original      | Symptoms score                                             | 35 -> 27 -> 24<br>27RC | 3.21    | 3.05    | 36 -> 30 -> 30<br>30RC | 5.13    | 3.60    |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 35                     | 3.21    | 3.05    | 36                     | 5.13    | 3.60    | -0.57         | -1.04 | -0.09 |
| 25. IPPOLITI 2003           | Original      | Asthma Scores                                              | 47 -> 47<br>29A/18ARC  | 1.28    |         | 39 -> 39<br>24A/15ARC  | 3.15    |         |               |       |       |
|                             | Penagos 2008  | Asthma score                                               | 47                     | 1.28    | 0.77    | 39                     | 3.15    | 0.66    | -2.57         | -3.14 | -1.99 |
|                             | Original      | Rhinitis Scores                                            | 47 -> 47               | 0.39    |         | 39 -> 39               | 0.82    |         |               |       |       |
|                             | Penagos 2006  | Nasal score rhinitis                                       | 18                     | 0.39    | 0.71    | 15                     | 0.82    | 0.65    | -0.61         | -1.32 | 0.09  |
| 26. GUEZ 2000               | Original      | Total (nasal) Symptoms score                               | 36 -> 25<br>36RC±A     | 2.30    | 1.90    | 36 -> 14<br>36RC±A     | 3.20    | 2.40    |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 36                     | 2.30    | 1.90    | 36                     | 3.20    | 2.40    | -0.41         | -0.88 | 0.06  |
| 27. LIMA 2002               | Original      | Symptoms score (ARC composite?)                            | 28 -> 26<br>28RC±A     |         |         | 28 -> 23<br>28RC±A     |         |         |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 28                     | 2494.00 | 2326.00 | 28                     | 2465.00 | 1537.00 | 0.01          | -0.51 | 0.54  |
| 29. MAROGNA 2005            | Original      | Monthly symptom score (ARC composite)                      | 39 -> 29<br>39AR       |         |         | 40 -> 23<br>40AR       |         |         |               |       |       |
|                             | Calamita 2006 | Allergic symptoms group                                    | 29                     | 48.51   | 11.29   | 23                     | 148.65  | 29.93   | -4.57         | -5.64 | -3.51 |
| 30. NELSON 1993             | Original      | Symptom Scores (ARC composite)                             | 22 -> 20<br>17RC/3ARC  | 12.15   | 1.94    | 22 -> 21<br>18RC/3ARC  | 18.67   | 2.96    |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 20                     | 12.15   | 8.68    | 21                     | 18.67   | 13.56   | -0.56         | -1.18 | 0.07  |
| 32. MUNGAN 1999             | Original      | Rhinitis Scores                                            | 15 -> 15<br>15AR       | 0.50    |         | 11 -> 11<br>11AR       | 0.67    |         |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 15                     | 0.50    | 0.45    | 11                     | 0.67    | 0.58    | -0.32         | -1.11 | 0.46  |
| 34. NOVEMBRE 2004           | Original      | Symptoms Score (ARC composite)                             | 54 -> 47 (*)<br>54R    |         |         | 59 -> 50 (*)<br>59R    |         |         |               |       |       |
|                             | Calamita 2006 | Allergic symptoms group                                    | 47                     | 89.8    | 94.84   | 50                     | 125.16  | 142.54  | -0.29         | -0.69 | 0.11  |
| 35. PAJNO 2003              | Original      | Chest symptoms                                             | 15 -> 14<br>15ARC      |         |         | 15 -> 13<br>15ARC      |         |         |               |       |       |
|                             | Calamita 2006 | Asthma symptoms only                                       | 14                     | 6.94    | 4.43    | 13                     | 11.27   | 6.96    | -0.73         | -1.51 | 0.06  |
| 37. PATRIARCA 2002          | Original      | Symptoms score (ARC composite after mucous challenge test) | 12 -> 12<br>8A/4RC/10U | 0.25    | 0.70    | 12 -> 12<br>9A/6RC/8U  | 2.75    | 1.05    |               |       |       |
|                             | Calamita 2006 | Allergic symptoms group                                    | 12                     | 0.25    | 0.70    | 12                     | 2.75    | 1.05    | -2.71         | -3.36 | -1.55 |
| 38. PURELLO D'AMBROSIO 1996 | Original      | Symptoms Score (ARC composite)                             | 20 -> 15<br>12RC/3ARC  | 4352.00 |         | 20 -> 15<br>11RC/4ARC  | 6134.00 |         |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 15                     | 290.00  | 258.00  | 15                     | 408.90  | 315.35  | -0.40         | -1.13 | 0.32  |
| 41. TROISE 1995             | Original      | Symptoms Score                                             | 15 -> 15<br>15R        | 86.90   |         | 16 -> 16<br>16R        | 102.20  |         |               |       |       |
|                             | Wilson 2003   | Allergic rhinitis symptoms scores                          | 15                     | 87.00   | 76.00   | 16                     | 102.00  | 58.00   | -0.22         | -0.92 | 0.49  |
| 42. YUKSEL 1999             | Original      | Symptoms Scores for Asthmatics                             | 21 -> 21<br>11A/10R    |         |         | 18 -> 18<br>8A/10R     |         |         |               |       |       |
|                             | Calamita 2006 | Asthma symptoms only                                       | 11                     | 13.00   | 9.90    | 8                      | 9.00    | 6.80    | 0.44          | -0.49 | 1.36  |

A: Asthma; R: Rhinitis; C: Conjunctivitis; D: Atopic dermatitis; U: Urticaria-angioedema

No. of patients at initiation -&gt; (evaluable) -&gt; finish

In green, discrepancy surely due to rounding

In red, discrepancy in numerical data compared to the original or to other meta-analyses

In orange, discrepancy in outcome compared to the original or to other meta-analyses

In blue, the meta-analysis makes intention to treat analysis, but in marked study it uses patients who finish treatment, or viceversa.

(Continued)

**TABLE E3.** (Continued)

|                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| In gray, the meta-analysis includes patients with asthma for rhinitis outcomes, or viceversa, opposite to what it makes in other studies on the same outcome                          |
| Meta-analysis #1, Olaguibel et al. Respiratory allergy. Intention to treat analysis                                                                                                   |
| Meta-analysis #2, Wilson et al. Allergic rhinitis. Intention to treat analysis                                                                                                        |
| Meta-analysis #3, Penagos et al, 2006. Allergic rhinitis. It analyzes patients who finish treatment.                                                                                  |
| Meta-analysis #4, Calamita et al. Asthma and other respiratory allergies. It analyzes patients who finish treatment.                                                                  |
| Meta-analysis #5, Penagos et al, 2008. Allergic asthma. It analyzes patients who finish treatment.                                                                                    |
| Study 10 and study 14 : The meta-analysis by Penagos et al 2008 assumes that all drop-outs were patients with rhinitis but not with asthma                                            |
| Study 18: Error in the original with different values for active group in table and text.<br>Correct values in the text; the meta-analysis by Calamita et al uses values in the table |
| Study 30: Standard error instead of standard deviation in the original                                                                                                                |
| Study 34: Data of number of patients differ from algorithm to table in the original                                                                                                   |
| Study 38: Open study. Results expressed as total for the group instead of means in the original                                                                                       |

**TABLE E4.** Outcomes on use of medication for asthma, rhinitis, rhinoconjunctivitis, or their combination. The source identifies the data as reported in the original publication and in the meta-analyses in which it was included. See footnotes for explanation

| Study                        | Source         | Outcome                                           | Active SLIT                |       |       | Placebo                    |        |        | SMD (5% to 95%CI) |        |       |
|------------------------------|----------------|---------------------------------------------------|----------------------------|-------|-------|----------------------------|--------|--------|-------------------|--------|-------|
|                              |                |                                                   | No.                        | Mean  | SD    | No.                        | Mean   | SD     | SMD               | 5%     | 95%   |
| 1. ARIANO 2001               | Original       | Medication Score (ARC composite)                  | 10 -> 10<br>2A/8RC         | 2.50  | 2.10  | 10 -> 10<br>1A/9RC         | 5.30   | 4.90   |                   |        |       |
|                              | Calamita 2006  | Reductions of medication use to allergies general | 10                         | 2.50  | 2.10  | 10                         | 5.30   | 4.90   | -0.71             | -1.62  | 0.20  |
|                              | Wilson 2003    | Medication scores                                 | 10                         | 2.50  | 2.10  | 10                         | 5.30   | 4.90   | -0.71             | -1.62  | 0.20  |
| 2. BAHÇECILER 2001           | Original       | β2-Mimetic Use                                    | 8 -> 8<br>8AR              |       |       | 7 -> 7<br>7AR              |        |        |                   |        |       |
|                              | Calamita 2006  | Reduction of medication use to asthma             | 8                          | 0.11  | 0.17  | 7                          | 0.11   | 0.12   | 0.00              | -1.01  | 1.01  |
|                              | Penagos 2008   | Medication score                                  | 7                          | 2.13  | 0.83  | 7                          | 3.14   | 1.57   | -0.75             | -1.85  | 0.35  |
|                              | Original       | Intranasal budesonide dose                        | 8 -> 8                     |       |       | 7 -> 7                     |        |        |                   |        |       |
|                              | Wilson 2003    | Medication scores                                 | 8                          | 1.25  | 1.04  | 7                          | 1.57   | 1.25   | -0.26             | -1.28  | 0.76  |
|                              | Olaguibel 2005 | Medication scores                                 | 8                          | 1.25  | 1.04  | 7                          | 1.57   | 1.25   | -0.26             | -1.28  | 0.76  |
| 3. FELIZIANI 1995            | Original       | Drug Score (ARC composite)                        | 18 -> 18<br>18RC±A         | 24.05 |       | 16 -> 16<br>16RC±A         | 76.00  |        |                   |        |       |
|                              | Calamita 2006  | Reductions of medication use to allergies general | 18                         | 24.05 | 45.47 | 16                         | 76.00  | 45.47  | -1.12             | -1.85  | -0.39 |
|                              | Wilson 2003    | Medication scores                                 | 18                         | 24.06 | 25.72 | 16                         | 75.90  | 50.30  | -1.29             | -2.04  | -0.54 |
| 5. PAJNO 2000                | Original       | Medication Score                                  | 12 -> 12<br>12A            | 82.68 |       | 12 -> 9<br>12A             | 205.20 |        |                   |        |       |
|                              | Calamita 2006  | Reduction of medication use to asthma             | 12                         | 82.68 | 56.80 | 9                          | 205.20 | 56.80  | -2.07             | -3.18  | -0.96 |
|                              | Olaguibel 2005 | Medication scores                                 | 12                         | 82.68 | 32.38 | 12                         | 205.20 | 32.38  | -3.65             | -5.04  | -2.27 |
|                              | Penagos 2008   | Medication scores                                 | 12                         | 82.60 | 11.73 | 9                          | 205.20 | 17.68  | -8.10             | -10.95 | -5.25 |
| 7. PASSALACQUA 1999          | Original       | Drug Intake score (ARC composite)                 | 15 -> 14<br>6ARC/9RC       | 42.30 |       | 15 -> 13<br>7ARC/8RC       | 83.00  |        |                   |        |       |
|                              | Calamita 2006  | Reductions of medication use to allergies general | 14                         | 42.30 | 25.50 | 13                         | 83.00  | 64.80  | -0.81             | -1.60  | -0.02 |
|                              | Wilson 2003    | Medication Scores                                 | 15                         | 42.00 | 49.50 | 15                         | 83.00  | 65.00  | -0.69             | -1.43  | 0.05  |
| 8. PRADALIER 1999            | Original       | Global Medication score (ARC composite)           | 63 -> 62 -> 60<br>45R/17AR | 1.77  | 2.27  | 63 -> 61 -> 59<br>36R/25AR | 2.13   | 2.74   |                   |        |       |
|                              | Calamita 2006  | Reductions of medication use to allergies general | 60                         | 1.77  | 2.27  | 59                         | 2.13   | 2.74   | -0.14             | -0.50  | 0.22  |
|                              | Wilson 2003    | Medication scores                                 | 63                         | 1.77  | 2.30  | 63                         | 2.13   | 2.70   | -0.14             | -0.49  | 0.21  |
| 9. PURELLO D'AMBROSIO 1999   | Original       | Not clearly disclosed (ARC composite?)            | 14 -> 14<br>7RC/7ARC       |       |       | 16 -> 16<br>8RC/8ARC       |        |        |                   |        |       |
|                              | Calamita 2006  | Reductions of medication use to allergies general | 14                         | 48.16 | 46.61 | 16                         | 124.37 | 121.08 | -0.79             | -1.54  | -0.04 |
|                              | Wilson 2003    | Medication scores                                 | 14                         | 48.10 | 46.6  | 16                         | 124.37 | 121.00 | -0.79             | -1.54  | -0.04 |
| 10. ROLINCK-WERNINGHAUS 2004 | Original       | Medication Score (ARC composite)                  | 49 -> 39<br>29RC/20ARC     | 2.54  | 3.58  | 48 -> 38<br>29RC/19ARC     | 2.85   | 3.87   |                   |        |       |
|                              | Calamita 2006  | Reductions of medication use to allergies general | 39                         | 2.54  | 3.58  | 38                         | 2.85   | 3.87   | -0.08             | -0.53  | 0.36  |
|                              | Penagos 2006   | Medication score rhinitis                         | 39                         | 2.54  | 3.58  | 38                         | 2.85   | 3.87   | -0.08             | -0.53  | 0.36  |
|                              | Penagos 2008   | Medication score (asthma)                         | 20                         | 2.54  | 3.58  | 19                         | 2.85   | 3.87   | -0.08             | -0.71  | 0.55  |
| 11. VOLTOLINI 2001           | Original       | Drug Score (ARC composite)                        | 15 -> 14<br>6RC/9ARC       | 21.93 |       | 15 -> 13<br>6RC/9ARC       | 38.85  |        |                   |        |       |
|                              | Calamita 2006  | Reductions of medication to allergies general     | 14                         | 21.93 | 29.96 | 13                         | 38.85  | 33.94  | -0.51             | -1.28  | 0.26  |
|                              | Wilson 2003    | Medication scores                                 | 15                         | 22.00 | 30.00 | 15                         | 39.00  | 34.00  | -0.52             | -1.25  | 0.21  |
| 12. LA ROSA 1999             | Original       | Antirhinitis medication Scores                    | 20 -> 16<br>20RC±A         |       |       | 21 -> 17<br>21RC±A         |        |        |                   |        |       |
|                              | Wilson 2003    | Medication scores                                 | 20                         | 2.28  | 3.89  | 21                         | 2.36   | 3.95   | -0.02             | -0.63  | 0.59  |
|                              | Penagos 2006   | Medication scores rhinitis                        | 16                         | 0.39  | 0.80  | 17                         | 0.40   | 1.19   | -0.01             | -0.69  | 0.67  |
|                              | Olaguibel 2005 | Medication scores                                 | 20                         | 1.48  | 2.04  | 21                         | 3.29   | 3.73   | -0.59             | -1.21  | 0.04  |
| 14. VOURDAS 1998             | Original       | Medication Score (composite)                      | 34 -> 33<br>1R/33AR        |       |       | 32 -> 31<br>3R/29AR        |        |        |                   |        |       |
|                              | Wilson 2003    | Medication scores                                 | 34                         | 1.77  | 3.85  | 32                         | 1.39   | 3.41   | 0.10              | -0.38  | 0.59  |
|                              | Olaguibel 2005 | Medication scores                                 | 34                         | 1.12  | 2.27  | 32                         | 1.64   | 3.01   | -0.19             | -0.68  | 0.29  |
|                              | Penagos 2006   | Medication score rhinitis                         | 34                         | 1.12  | 2.27  | 32                         | 1.64   | 3.01   | -0.19             | -0.68  | 0.29  |
|                              | Penagos 2008   | Medication scores (asthma)                        | 34                         | 1.12  | 2.27  | 32                         | 1.64   | 3.01   | -0.19             | -0.68  | 0.29  |

(Continued)

TABLE E4. (Continued)

| Study                     | Source        | Outcome                                           | Active SLIT                    |         |         | Placebo                     |         |         | SMD (5-95%CI) |       |       |
|---------------------------|---------------|---------------------------------------------------|--------------------------------|---------|---------|-----------------------------|---------|---------|---------------|-------|-------|
|                           |               |                                                   | No.                            | Mean    | SD      | No.                         | Mean    | SD      | SMD           | 5%    | 95%   |
| 15, WÜTHRICH 2003         | Original      | Drug consumption (ARC composite)                  | 14 -> 10<br>5RC/4ARC/1ARD      |         |         | 14 -> 12<br>5RC/7ARC        |         |         |               |       |       |
|                           | Penagos 2006  | Medication score rhinitis                         | 10                             | 21.20   | 27.48   | 12                          | 65.33   | 62.35   | -0.85         | -1.74 | 0.03  |
| 16, NIU 2006              | Original      | Inhaled $\beta_2$ -agonists                       | 56 -> 49<br>56A                | 0.02    | 0.31    | 54 -> 48<br>54A             | 0.05    | 0.27    |               |       |       |
|                           | Penagos 2008  | Medication score                                  | 49                             | 0.02    | 0.31    | 48                          | 0.05    | 0.27    | -0.10         | -0.50 | 0.30  |
| 17, ANDRE 2002 (Abstract) | Original      | Medication score (RC + A?)                        | 55 -> 48 -> 41<br>55RC±A       |         |         | 55 -> 51 -> 49<br>55RC±A    |         |         |               |       |       |
|                           | Wilson 2003   | Medication scores                                 | 55                             | 3.90    | 6.91    | 55                          | 8.68    | 11.46   | -0.50         | -0.88 | -0.12 |
| 18, ARIANO 2005           | Original      | Drug consumption scores (ARC composite)           | 20 -> 20<br>4A/13R/3C          | 3.00    | 1.03    | 10 -> 10<br>2A/6R/2C        | 7.20    | 1.06    |               |       |       |
|                           | Calamita 2006 | Reductions of medication use to allergies general | 20                             | 3.00    | 1.03    | 10                          | 7.20    | 1.06    | 6.05          | -5.24 | -2.62 |
| 19, BOUSQUET 1999         | Original      | Use of inhaled $\beta_2$ -agonists                | 42 -> 32 -> 23<br>24A/18AR     | 122.00  | 235.00  | 43 -> 33 -> 27<br>26A/17AR  | 79.00   | 136.00  |               |       |       |
|                           | Calamita 2006 | Reduction of medication use to asthma             | 23                             | 122.00  | 235.00  | 27                          | 79.00   | 136.00  | 0.23          | -0.33 | 0.78  |
| 21, CAFFARELLI 2000       | Original      | Drug consumption (ARC composite)                  | 24 -> 24<br>7A/1R<br>3AR/13ARC |         |         | 24 -> 20<br>3A/3AR<br>14ARC |         |         |               |       |       |
|                           | Penagos 2008  | Medication score (asthma)                         | 23                             | 8.37    | 1.51    | 20                          | 9.15    | 1.37    | -0.53         | -1.14 | 0.08  |
|                           | Penagos 2006  | Medication score rhinitis                         | 17                             | 8.40    | 1.50    | 17                          | 9.15    | 1.37    | -0.51         | -1.19 | 0.17  |
| 22, CASANOVAS 2000        | Original      | Daily medication (ARC composite)                  | 10 -> 9<br>10RC                |         |         | 10 -> 6<br>10RC             |         |         |               |       |       |
|                           | Wilson 2003   | Medication score                                  | 9                              | 1.69    | 2.46    | 6                           | 2.13    | 2.22    | -0.17         | -1.21 | 0.86  |
| 24, HORDIJK 1998          | Original      | Anti-allergic medication                          | 35 -> 27 -> 24<br>27RC         | 0.16    | 0.37    | 36 -> 30 -> 30<br>30RC      | 0.31    | 0.45    |               |       |       |
|                           | Wilson 2003   | Medication score                                  | 35                             | 0.16    | 0.37    | 36                          | 0.31    | 0.45    | -0.36         | -0.83 | 0.11  |
| 25, IPPOLITI 2003         | Original      | ND                                                | 47 -> 47<br>29A/18ARC          |         |         | 39 -> 39<br>24A/15ARC       |         |         |               |       |       |
|                           | Penagos 2008  | Medication score                                  | 47                             | 1.41    | 0.73    | 39                          | 5.04    | 0.80    | -4.72         | -5.56 | -3.88 |
|                           | Penagos 2006  | Medication score rhinitis                         | 18                             | 1.17    | 0.85    | 15                          | 5.30    | 0.89    | -4.64         | -6.02 | -3.26 |
| 26, GUEZ 2000             | Original      | Weekly (total nasal) medication score             | 36 -> 25<br>36RC±A             | 4.10    | 5.50    | 36 -> 14<br>36RC±A          | 6.10    | 6.80    |               |       |       |
|                           | Wilson 2003   | Medication score                                  | 36                             | 4.10    | 5.50    | 36                          | 6.10    | 6.80    | -0.32         | -0.79 | 0.15  |
| 27, LIMA 2002             | Original      | Medication score (ARC composite?)                 | 28 -> 26<br>28RC±A             |         |         | 28 -> 23<br>28RC±A          |         |         |               |       |       |
|                           | Wilson 2003   | Medication score                                  | 28                             | 2334.00 | 2616.00 | 28                          | 2837.00 | 2052.00 | -0.21         | -0.74 | 0.31  |
| 29, MAROGNA 2005          | Original      | Beta2 intake                                      | 39 -> 29<br>39AR               |         |         | 40 -> 23<br>40AR            |         |         |               |       |       |
|                           | Calamita 2006 | Reduction of medication use to asthma             | 29                             | 1.73    | 0.64    | 23                          | 11.68   | 4.35    | -3.35         | -4.22 | -2.49 |
| 32, MUNGAN 1999           | Original      | Medication Scores (ARC composite)                 | 15 -> 15<br>15AR               | 1.97    |         | 15 -> 11<br>11AR            | 5.24    |         |               |       |       |
|                           | Wilson 2003   | Medication score                                  | 15                             | 1.97    | 1.40    | 11                          | 5.20    | 1.60    | -2.10         | -3.10 | -1.11 |
| 33, NIU 2004 (Abstract)   | Original      | ND                                                | A                              |         |         | A                           |         |         |               |       |       |
|                           | Calamita 2006 | Reduction of medication use to asthma             | 49                             | 0.02    | 0.31    | 48                          | 0.05    | 0.27    | -0.10         | -0.50 | 0.30  |
| 34, NOVEMBRE 2004         | Original      | Medication Score (ARC composite)                  | 54 -> 47<br>54R                |         |         | 59 -> 50<br>59R             |         |         |               |       |       |
|                           | Calamita 2006 | Reduction of medication used to allergies general | 47                             | 15.32   | 20.06   | 50                          | 28.09   | 28.46   | -0.51         | -0.92 | -0.11 |
| 35, PAJNO 2003            | Original      | Drug intake score                                 | 15 -> 14<br>15ARC              |         |         | 15 -> 13<br>15ARC           |         |         |               |       |       |
|                           | Calamita 2006 | Reductions of medication use to allergies general | 14                             | 10.27   | 7.26    | 13                          | 26.27   | 16.50   | -1.23         | -2.07 | -0.40 |

(Continued)

TABLE E4. (Continued)

| Study                          | Source        | Outcome                               | Active SLIT           |        |       | Placebo               |         |       | SMD (5-95%CI) |       |      |
|--------------------------------|---------------|---------------------------------------|-----------------------|--------|-------|-----------------------|---------|-------|---------------|-------|------|
|                                |               |                                       | No.                   | Mean   | SD    | No.                   | Mean    | SD    | SMD           | 5%    | 95%  |
| 38, PURELLO<br>D'AMBROSIO 1996 | Original      | Drug Score (composite ARC)            | 20 -> 15<br>12RC/3ARC | 895.00 |       | 20 -> 15<br>11RC/4ARC | 1024.00 |       |               |       |      |
|                                | Wilson 2003   | Medication score                      | 15                    | 59.70  | 83.00 | 15                    | 68.30   | 75.30 | -0.11         | -0.82 | 0.61 |
| 41, TROISE 1995                | Original      | Drug Score                            | 15 -> 15<br>15R       | 17.10  |       | 16 -> 16<br>16R       | 32.90   |       |               |       |      |
|                                | Wilson 2003   | Medication score                      | 15                    | 17.00  | 21.00 | 16                    | 33.00   | 33.00 | -0.56         | -1.28 | 0.16 |
| 42, YUKSEL 1999                | Original      | β2 agonist consumption rate           | 21 -> 21<br>11A/10R   |        |       | 18 -> 18<br>8A/10R    |         |       |               |       |      |
|                                | Calamita 2006 | Reduction of medication use to asthma | 11                    | 4.00   | 2.10  | 8                     | 4.80    | 2.40  | -0.34         | -1.26 | 0.58 |

A: Asthma; R: Rhinitis; C: Conjunctivitis; D: Atopic dermatitis

No. of patients at initiation -&gt; (evaluable) -&gt; finish

In green, discrepancy surely due to rounding

In red, discrepancy in numerical data compared to the original or to other meta-analyses

In orange, discrepancy in outcome compared to the original or to other meta-analyses

In blue, the meta-analysis makes intention to treat analysis, but in marked study it uses patients who finish treatment, or viceversa.

In gray, the meta-analysis evaluates rhinitis, but in marked study it includes also patients with asthma, or viceversa, opposite to what it makes in other studies on the same outcome

Meta-analysis #1, Olaguibel et al. Respiratory allergy. Intention to treat analysis

Meta-analysis #2, Wilson et al. Allergic rhinitis. Intention to treat analysis

Meta-analysis #3, Penagos et al, 2006. Allergic rhinitis. It analyzes patients who finish treatment.

Meta-analysis #4, Calamita et al. Asthma and other respiratory allergies. It analyzes patients who finish treatment.

Meta-analysis #5, Penagos et al, 2008. Allergic asthma. It analyzes patients who finish treatment.

Study 3 and study 4: Same SD in active and placebo groups

Study 33 (abstract): Data can be obtained in the journal publication of the same investigation in study 16

Study 34: Data of number of patients differ from algorithm to table in the original

Study 38: Open study. Results expressed as total for the group instead of means in the original

**TABLE E5.** Outcome on combination of symptoms and medication. See footnotes for explanation. The source identifies the data as reported in the original publication and in the meta-analysis by Calamita et al.<sup>6</sup>

| Study                      | Source        | Outcome                                                          | Active SLIT               |        |        | Placebo                  |         |        | SMD (5% to 95%CI) |       |       |
|----------------------------|---------------|------------------------------------------------------------------|---------------------------|--------|--------|--------------------------|---------|--------|-------------------|-------|-------|
|                            |               |                                                                  | No.                       | Mean   | SD     | No.                      | Mean    | SD     | SMD               | 5%    | 95%   |
| 7. PASSALACQUA 1999        | Original      | Symptoms + Drugs intake Score                                    | 15 --> 14<br>6ARC/9RC     | 231.5  |        | 15 --> 13<br>7ARC/8RC    | 274.30  |        |                   |       |       |
|                            | Calamita 2006 | Reduction of symptoms + medication score (*)                     | 14                        | 231.5  | 82.60  | 13                       | 274.30  | 94.20  | -0.47             | -1.24 | 0.30  |
| 9. PURELLO D'AMBROSIO 1999 | Original      | Symptoms+drugs score                                             | 14 -->14<br>7ARC/7RC      |        |        | 16 -->16<br>8ARC/8RC     |         |        |                   |       |       |
|                            | Calamita 2006 | Reduction of symptoms + medication score (*)                     | 16                        | 557.08 | 526.99 | 14                       | 1021.43 | 726.07 | -0.72             | -1.46 | 0.02  |
| 11. VOLTOLINI 2001         | Original      | Total (drugs + symptoms scores)                                  | 15 --> 14<br>9ARC/6RC     | 151.57 |        | 15 --> 13<br>9ARC/6RC    | 122.08  |        |                   |       |       |
|                            | Calamita 2006 | Reduction of symptoms + medication score (*)                     | 14                        | 151.57 | 161.51 | 13                       | 122.08  | 95.74  | 0.21              | -0.54 | 0.97  |
| 23. DRACHENBERG 2001       | Original      | Combined Symtoms-Medication Score                                | 49 --> 37<br>49 RC±A      | 0.31   | 0.37   | 19 --> 12<br>19 RC±A     | 0.53    | 0.49   |                   |       |       |
|                            | Calamita 2006 | Reduction of symptoms + medication score (*)                     | 37                        | 0.31   | 0.37   | 12                       | 0.53    | 0.49   | -0.54             | -1.20 | -0.12 |
| 28. MAROGNA 2004           | Original      | Monthly clinical score (Composite AR Symptoms-Medication Scores) | 319 --> 271<br>128R/191AR | 54.70  | 2.80   | 192 --> 170<br>72R/120AR | 121.00  | 3.8    |                   |       |       |
|                            | Calamita 2006 | Reduction of symptoms + medication score (*)                     | 271                       | 54.70  | 46.09  | 170                      | 121.00  | 49.51  | -1.40             | -1.61 | -1.18 |
| 34. NOVEMBRE 2004          | Original      | Symptoms plus medication scores                                  | 54 --> 47<br>54R          |        |        | 59 --> 50<br>59R         |         |        |                   |       |       |
|                            | Calamita 2006 | Reduction of symptoms + medication score (*)                     | 47                        | 106.12 | 104.77 | 60                       | 153.25  | 154.25 | -0.36             | -0.76 | 0.04  |
| 40. SAMBUGARO 2003         | Original      | Symptoms + medication usage score                                | 43 --> 43<br>43 RC±A      |        |        | 10 --> 10<br>10 RC±A     |         |        |                   |       |       |
|                            | Calamita 2006 | Reduction of symptoms + medication score (*)                     | 43                        | 2.48   | 1.30   | 10                       | 5.50    | 1.50   | -2.22             | -3.04 | -1.41 |

A, Asthma; R: Rhinitis; C: Conjunctivitis

No. of patients at initiation --&gt; finish

Metanalysis #4, Calamita et al. Analysis of patients who finish treatment in this outcome.

Outcome: Reductions of symptoms plus medication score together of allergy in general asthma, rhinitis, conjunctivitis

In red: discrepancy in numerical data compared to the original

Study 9: Error in the meta-analysis: 16 and 14 should be 14 and 16 respectively.

The correct SMD (95%CI) should be -0.70 (-1.45 0.04)

Study 28: Standard error instead of standard deviation in the original

Study 34: Error in the meta-analysis: 60 should be 50. The correct SMD (95%CI) should be -0.35 (-0.75 0.05)

**TABLE E6.** Outcome on "worse asthma". See footnotes for explanation. The source identifies the data as reported in the original publication and in the meta-analysis by Calamita et al.<sup>6</sup>

| Study                   | Source        | Outcome                                 | Active SLIT                 |         | Placebo                     |         | RR (5% to 95% CI) |      |      |
|-------------------------|---------------|-----------------------------------------|-----------------------------|---------|-----------------------------|---------|-------------------|------|------|
|                         |               |                                         | No.                         | Results | No.                         | Results | RR                | 5%   | 95%  |
| 4. HIRSCH 1997          | Original      | Better health status                    | 15 -> 14<br>3A/3R/9AR       | 4/15    | 15<br>5A/5R/5AR             | 8/15    |                   |      |      |
|                         | Calamita 2006 | Worse of asthma                         |                             | 5/15    |                             | 8/15    | 0.63              | 0.26 | 1.47 |
| 8. PRADALIER 1999       | Original      | No. of patients who had asthma symptoms | 63 -> 62 -> 60?<br>45R/17AR | 5+4/17  | 63 -> 61 -> 59?<br>36R/25AR | 16+7/25 |                   |      |      |
|                         | Calamita 2006 | Worse of asthma                         |                             | 9/17    |                             | 23/25   | 0.58              | 0.36 | 0.91 |
| 28. MAROGNA 2004        | Original      | Positive methacoline Test               | 319 -> 271<br>128R/191AR    | 63      | 192 -> 170<br>72R/120AR     | 95      |                   |      |      |
|                         | Calamita 2006 | Worse of asthma                         |                             | 63/319  |                             | 95/192  | 0.40              | 0.31 | 0.52 |
| 31. NOVEMBRE 1991       | Original      | Physician's overall evaluation          | 11 -> 9<br>11A              | 2/11    | 9 -> 4<br>9A                | 3/9     |                   |      |      |
|                         | Calamita 2006 | Worse of asthma                         |                             | 2/11    |                             | 3/9     | 0.55              | 0.11 | 2.59 |
| 33. NIU 2004 (Abstract) | Original      | ND                                      | 56 -> 49<br>56A             | ?       | 54 -> 48<br>54A             | ?       |                   |      |      |
|                         | Calamita 2006 | Worse of asthma                         |                             | 23/56   |                             | 29/54   | 0.76              | 0.51 | 1.14 |
| 34. NOVEMBRE 2004       | Original      | % of children with asthma               | 54 -> 48 -> 47?<br>54R      | 8/54    | 59 -> 49 -> 50?<br>59R      | 18/59   |                   |      |      |
|                         | Calamita 2006 | Worse of asthma                         |                             | 8/54    |                             | 18/59   | 0.49              | 0.23 | 1.02 |
| 39. RODRIGUEZ 2004      | Original      | PEF values < 80% of predicted           | 25 -> 25<br>25A             | 6/25    | 25 -> 25<br>25A             | 19/25   |                   |      |      |
|                         | Calamita 2006 | Worse of asthma                         |                             | 6/25    |                             | 19/25   | 0.32              | 0.15 | 0.66 |

A: Asthma; R: Rhinitis

No. of patients at initiation -&gt; (evaluable) -&gt; finish

Metanalysis #4, Calamita et al. Intention to treat analysis in this outcome.

Outcome: "worse of asthma" includes worse of symptoms, respiratory function, broncho-provocation, increase of medication use

In red: discrepancy in numerical data compared to the original

In orange, discrepancy in outcome compared to the original

No patient had asthma at inclusion in study 34

All patients had asthma in studies 31, 33 and 39

Denominator excludes patients without asma in study 8

Denominator includes patients without asma in studies 4 and 28

Study 8: Numerator includes 4 and 7 patients without asthma at inclusion, although this kind of patients are excluded from the denominator

Study 33 (abstract): Data can be obtained in the journal publication of the same investigation in study 16

Study 39: Errata in table in the original. Correct result in text and in the meta-analysis

**TABLE E7.** Assessment of funnel plot asymmetry by using the methods of Begg and Mazumdar<sup>8</sup> and Egger et al<sup>9</sup>

| MA                                 | Outcome               | Begg and Mazumdar <sup>8</sup> |                | Egger et al <sup>9</sup> |                |
|------------------------------------|-----------------------|--------------------------------|----------------|--------------------------|----------------|
|                                    |                       | <i>z</i>                       | <i>P</i> value | <i>t</i>                 | <i>P</i> value |
| Olaguibel et al, 2005 <sup>2</sup> | Nasal symptoms        | −0.19                          | .85            | −0.14                    | .90            |
|                                    | Bronchial symptoms    | −0.49                          | .62            | −1.15                    | .33            |
|                                    | Ocular symptoms       | 1                              | .32            | —                        | —              |
|                                    | Medication            | 1.36                           | .17            | 1.72                     | .23            |
| Wilson et al, 2003 <sup>4</sup>    | Nasal symptoms        | 0.97                           | .33            | 1.28                     | .21            |
|                                    | Nasal medication      | 2.64                           | .008           | 2.89                     | .01            |
| Penagos et al, 2006 <sup>5</sup>   | Nasal symptoms        | −0.63                          | .53            | 0.20                     | .85            |
|                                    | Nasal medication      | 1.95                           | .051           | 2.37                     | .064           |
| Calamita et al, 2006 <sup>6</sup>  | Asthma symptoms       | 1.04                           | .30            | 1.39                     | .21            |
|                                    | Asthma medication     | 0.94                           | .35            | 1.32                     | .26            |
|                                    | Allergic symptoms     | 2.06                           | .04            | 2.36                     | .046           |
|                                    | Allergic medication   | 2.41                           | .016           | 3.92                     | .004           |
|                                    | Symptoms + medication | 0.45                           | .65            | −1.21                    | .28            |
| Penagos et al, 2008 <sup>7</sup>   | Asthma symptoms       | 0.21                           | .84            | 0.40                     | .70            |
|                                    | Asthma medication     | 2.25                           | .024           | 2.13                     | .086           |

*P* values of less than .05 are associated with statistically significant asymmetry.

**TABLE E8.** Estimates of the effect of SLIT on several major outcomes using the data of all the studies included in the 5 evaluated MAs and the corrected estimates using the-trim and-fill method

| Outcome scores          | Results of the MAs |                        |         | Trim-and-fill evaluation |                                  |         |
|-------------------------|--------------------|------------------------|---------|--------------------------|----------------------------------|---------|
|                         | No. of studies     | Estimate, SMD (95% CI) | P value | No. of missing studies   | Corrected estimate, SMD (95% CI) | P value |
| Asthma symptoms         | 18                 | −0.92 (−1.44 to −0.40) | .001    | 0                        | No change                        |         |
| Asthma medication       | 11                 | −1.08 (−1.92 to −0.25) | .011    | 0                        | No change                        |         |
| Rhinitis symptoms       | 26                 | −0.44 (−0.66 to −0.22) | <.001   | 0                        | No change                        |         |
| Rhinitis medication     | 21                 | −0.54 (−0.78 to −0.29) | <.001   | 6                        | −0.28 (−0.56 to 0.01)            | .06     |
| Allergic symptoms       | 10                 | −1.22 (−1.99 to −0.45) | .002    | 3                        | −0.43 (−1.33 to 0.47)            | .35     |
| Allergy medication      | 13                 | −0.71 (−1.06 to −0.37) | <.0001  | 5                        | −0.34 (−0.72 to 0.04)            | .07     |
| Symptoms and medication | 7                  | −0.80 (−1.35 to −0.24) | .005    | 0                        | No change                        |         |
| Eye symptoms            | 2                  | −1.51 (−3.74 to 0.73)  | .19     | 1                        | −0.38 (−2.67 to 1.90)            | .74     |

SMD, Standardized mean difference.

**TABLE E9.** Assessment of funnel plot asymmetry by the methods of Begg and Mazumdar<sup>8</sup> and Egger et al<sup>9</sup> in a hypothetical MA (shown in Table E8) with all the studies included in the 5 evaluated MAs

| Outcome                 | Begg and Mazumdar <sup>8</sup> |                | Egger et al <sup>9</sup> |                |
|-------------------------|--------------------------------|----------------|--------------------------|----------------|
|                         | <i>z</i>                       | <i>P</i> value | <i>t</i>                 | <i>P</i> value |
| Asthma symptoms         | −0.87                          | .384           | −0.76                    | .461           |
| Asthma medication       | 1.95                           | .052           | 1.80                     | .105           |
| Rhinitis symptoms       | 0.99                           | .321           | 1.49                     | .150           |
| Rhinitis medication     | 3.68                           | <.001          | 4.02                     | .001           |
| Allergic symptoms       | 2.06                           | .040           | 2.36                     | .046           |
| Allergy medication      | 2.32                           | .020           | 3.55                     | .005           |
| Symptoms and medication | 0.45                           | .652           | 1.21                     | .281           |
| Eye symptoms            | 1.00                           | .317           | –                        | –              |

*P* values of less than .05 are associated with statistically significant asymmetry. *SMD*, Standardized mean difference.