

# Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy

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**Background:** Subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT) are safe and effective treatments of allergic rhinitis, but high levels of compliance and persistence are crucial to achieving the desired clinical effects.

**Objective:** Our objective was to assess levels and predictors of compliance and persistence among grass pollen, tree pollen, and house dust mite immunotherapy users in real life and to estimate the costs of premature discontinuation.

**Methods:** We performed a retrospective analysis of a community pharmacy database from The Netherlands containing data from 6486 patients starting immunotherapy for 1 or more of the allergens of interest between 1994 and 2009. Two thousand seven hundred ninety-six patients received SCIT, and 3690 received SLIT. Time to treatment discontinuation was analyzed and included Cox proportional hazard models with time-dependent covariates, where appropriate.

**Results:** Overall, only 18% of users reached the minimally required duration of treatment of 3 years (SCIT, 23%; SLIT, 7%). Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively ( $P < .001$ ). Other independent predictors of premature discontinuation were prescriber, with patients of general practitioners demonstrating longer persistence than those of allergologists and other medical specialists; single-allergen immunotherapy, lower socioeconomic status; and younger age. Of the persistent patients, 56% were never late in picking up their medication from the pharmacy. Direct medication costs per nonpersistent patient discontinuing in the third year of treatment were €3800, an amount that was largely missed.

**Conclusion:** Real-life persistence is better in SCIT users than in SLIT users, although it is low overall. There is an urgent need for further identification of potential barriers and measures that

will enhance persistence and compliance. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

**Key words:** allergic rhinitis, specific allergen immunotherapy, subcutaneous, sublingual, subcutaneous allergen immunotherapy, sublingual allergen immunotherapy, persistence, compliance, adherence, cost

Allergic rhinitis, or rhinoconjunctivitis, is a prevalent and exceedingly common condition associated with significant morbidity and substantial costs.<sup>1,2</sup> Today, subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT) are established treatment modalities for patients with moderate-to-severe allergic rhinitis. Evidence for efficacy has been demonstrated in many randomized controlled trials and in several meta-analyses.<sup>1-4</sup> At least 3 years of treatment is required to obtain the long-term benefits and disease-modifying effects of immunotherapy.<sup>5,6</sup> However, both clinical trials and real-life studies have shown that treatment persistence and compliance are frequently problematic, particularly in real-life studies.<sup>7-13</sup> This will jeopardize the effectiveness of immunotherapy and implies that a significant proportion of scarce resources is invested without achieving the maximum benefit. Many studies were done in subgroups of patients,<sup>10,11</sup> used telephone interviews,<sup>14</sup> or had a small sample size.<sup>15,16</sup> Moreover, prior studies focused on compliance and persistence in either SCIT users or SLIT users but not in both. Therefore a joint analysis for both SCIT and SLIT in one large real-life database was warranted.

In The Netherlands both SCIT and SLIT can be initiated and administered by general practitioners and specialists. General practitioners act as gatekeepers to specialized care, which implies that patients with allergic rhinitis need a referral from their general practitioner before they can visit the allergologist. Patients with more complex conditions are more likely to be referred than patients with less complex conditions. Because of the general practitioner's important role in the health care system, prescription of allergen immunotherapy, referral to specialized care, or both are subjected to widely implemented guidelines on the diagnosis and treatment of allergic rhinitis. These guidelines state that a positive skin prick test, the presence of specific IgE, or both to clinically relevant allergens in the presence of sufficient complaints and insufficient response to symptomatic medication are required to warrant the initiation of allergen immunotherapy.<sup>17</sup> Community pharmacies function as a distribution point for immunotherapy; the drugs are picked up by the patient and, in the case of SCIT, handed over to her or his treating physician. Although specialists are mainly hospital based, until recently, most prescriptions have been handled by community pharmacies. Immunotherapy is being reimbursed by insurance companies. Depending on the individual sensitization pattern, up to 3 allergens

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*Abbreviations used*

|       |                                     |
|-------|-------------------------------------|
| GP:   | Grass pollen                        |
| HDM:  | House dust mite                     |
| HR:   | Hazard rate                         |
| SCIT: | Subcutaneous allergen immunotherapy |
| SES:  | Socioeconomic status                |
| SLIT: | Sublingual allergen immunotherapy   |
| TP:   | Tree pollen                         |
| WHO:  | World Health Organization           |

are usually administered, although SCIT with 3 allergens is generally administered at the office of the allergologist.

We performed an analysis of a retrospective database containing real-life dispensing data from Dutch community pharmacies. The aim of the study was 3-fold. The first goal was to assess the persistence and compliance with immunotherapy for grass pollen (GP), tree pollen (TP), and/or house dust mite (HDM) allergy. The second goal was to identify independent predictors of persistence and compliance among the variables available in the database. Finally, we aimed to estimate the costs of immunotherapy among those prematurely discontinuing treatment.

## METHODS

### Patients and setting

Using the World Health Organization (WHO) Anatomical and Therapeutic Class code for allergen immunotherapy, V01A, we identified all patients aged 18 years or older in the PHARMO Record Linkage System who first started immunotherapy between January 1, 1994, and December 31, 2009 ( $n = 7851$ ). No prescription of immunotherapy in the 3 years preceding the start of the first course (the index course) of immunotherapy was allowed to avoid any role of long-term effects of previous courses of immunotherapy. The PHARMO Record Linkage System is a network of linked databases providing drug-dispensing records from community pharmacies. In 2011, the database contained data from 350 community pharmacies throughout The Netherlands and more than 3.2 million residents. The PHARMO database covers roughly one eighth of the total Dutch population, being representative of the entire country.<sup>18,19</sup> From the initial group of patients using immunotherapy, we selected all patients ( $n = 6486$ ) using immunotherapy for the most frequently occurring and regularly treated sensitizations occurring in Europe<sup>20</sup>: HDM ( $n = 831$ ), GP ( $n = 2082$ ), and TP ( $n = 1154$ ). Two thousand four hundred nineteen patients used a combination of the aforementioned extracts, either premixed or as separate drugs. Selection of allergens was also made according to national and international guidelines and excluded the use of immunotherapy aimed at venoms, weeds, and (domestic) animals.<sup>17,21</sup> Roughly one quarter of all patients receiving SCIT ( $n = 2796$ ) were treated with more than 1 allergen administered in separate injections ( $n = 735$ ), whereas 37% of patients receiving SLIT ( $n = 3690$ ) were treated with premixed combinations (mixtures of GPs and TPs,  $n = 1362$ ). Patients were followed until they ended immunotherapy, left the study cohort, died, or met the end of the observation period, December 31, 2009. Only the first course of immunotherapy was included in the analysis.

### Data

The PHARMO database contained data on age, sex, postal code, dates of pharmacy visits, dispensed brand of immunotherapy, amount of the preparation dispensed, route of administration, Anatomical and Therapeutic Class code, prescriber, and retail price of the preparation. The latter included a markup to cover pharmacy expenses. The last known prescribing physician was used to define the indicator variable "prescriber" because in practice she or he is the physician involved in the largest portion of the treatment period. In the few cases that the PHARMO database was unclear about the amount of drugs prescribed, detailed information on the exact nature and amount of drug

dispensed (eg, a bottle of 5-mL injection fluid and 5 sterile injection syringes) was obtained from the database of the Dutch Royal Pharmaceutical Society. For each preparation, a dosing scheme was obtained from the manufacturer. The database was linked to a database from the Social and Cultural Planning Agency, which contained information on the socioeconomic status (SES) of the postal code of residence.<sup>22</sup> Because the PHARMO database contained no diagnostic codes, the presence of allergic rhinitis was implicitly assumed from the use of allergen immunotherapy.

### Persistence and compliance

The method of continuous measurement of medication gaps was used to study compliance and persistence.<sup>23</sup> For each preparation, a maximum permissible gap between 2 pharmacy visits was defined based on the dosing scheme and taking into account potential dose reductions in case of side effects. The latter had to remain within the recommendations of the pharmaceutical company with respect to the dosing scheme. The actual time between 2 consecutive pharmacy visits to collect immunotherapy was compared with the permissible gap. When patients visited the pharmacy early (ie, before the end of the permissible gap), we added the amount of medication that was not yet used to the newly collected amount of medication. In this way patients could build up an extra drug stock, which could contain a maximum of 3 months of medication. Three months was chosen because Dutch physicians are generally not allowed to prescribe drug amounts for more than 3 months. The extra drug stock was used when a patient exceeded the maximum permissible gap (ie, to extend the permissible gap). A patient was labeled as nonpersistent when she or he did not reach the minimum treatment duration of 3 years. If a patient ceased to pick up any further prescriptions from the pharmacy for 3 months (plus the number of days' worth the drugs they have in stock, if applicable), after the end date of the last permissible gap, the course of immunotherapy was considered discontinued. The active treatment duration was then calculated as the sum of the days receiving active treatment (ie, the days that fell within the maximum permissible gap). A patient was labeled as noncompliant when she or he ever exceeded the permissible gap and thus had at least 1 late pharmacy visit (Fig 1). By definition, a nonpersistent patient was noncompliant. Because a meaningful comparison of the number of late pharmacy visits (noncompliance) is only relevant in patients with an equal duration of treatment, we investigated the degree of noncompliance (ie, the number of late pharmacy visits) only in persistent patients using 1 allergen. The total costs of immunotherapy in nonpersistent patients were calculated by using retail drug prices that were recorded in the PHARMO database.

### Statistical analysis

We investigated which of the following variables that were available in the database were independently associated with nonpersistence and noncompliance:

1. age, sex, SES, and geographic location of residence;
2. route of administration: SCIT versus SLIT;
3. allergen: immunotherapy for GP (reference category) versus that for TP, HDM, or a combination of these (no distinction between premixed or nonpremixed combination therapy was made); and
4. prescriber: general practitioner (reference category) versus allergologist and other medical specialists (ear, nose, and throat physicians and pulmonologists).

Interaction effects between these variables, if relevant, were also reported.

We hypothesized that apart from demographic variables, the route of administration, allergen group, and prescriber might influence persistence and compliance. It is conceivable that office-based treatment with SCIT is accompanied by better compliance and persistence than SLIT, and although the route of administration clearly plays a role, the direction of the effect appears to be unclear.<sup>24</sup> Combinations of allergens might serve as a proxy of a greater allergy burden influencing compliance and persistence positively.<sup>8</sup> The rationale for including the prescribing physician as a predictor was provided by Osterberg and Blaschke.<sup>25</sup> We expected that compliance and persistence would be better with allergologists because they might see the most severely affected

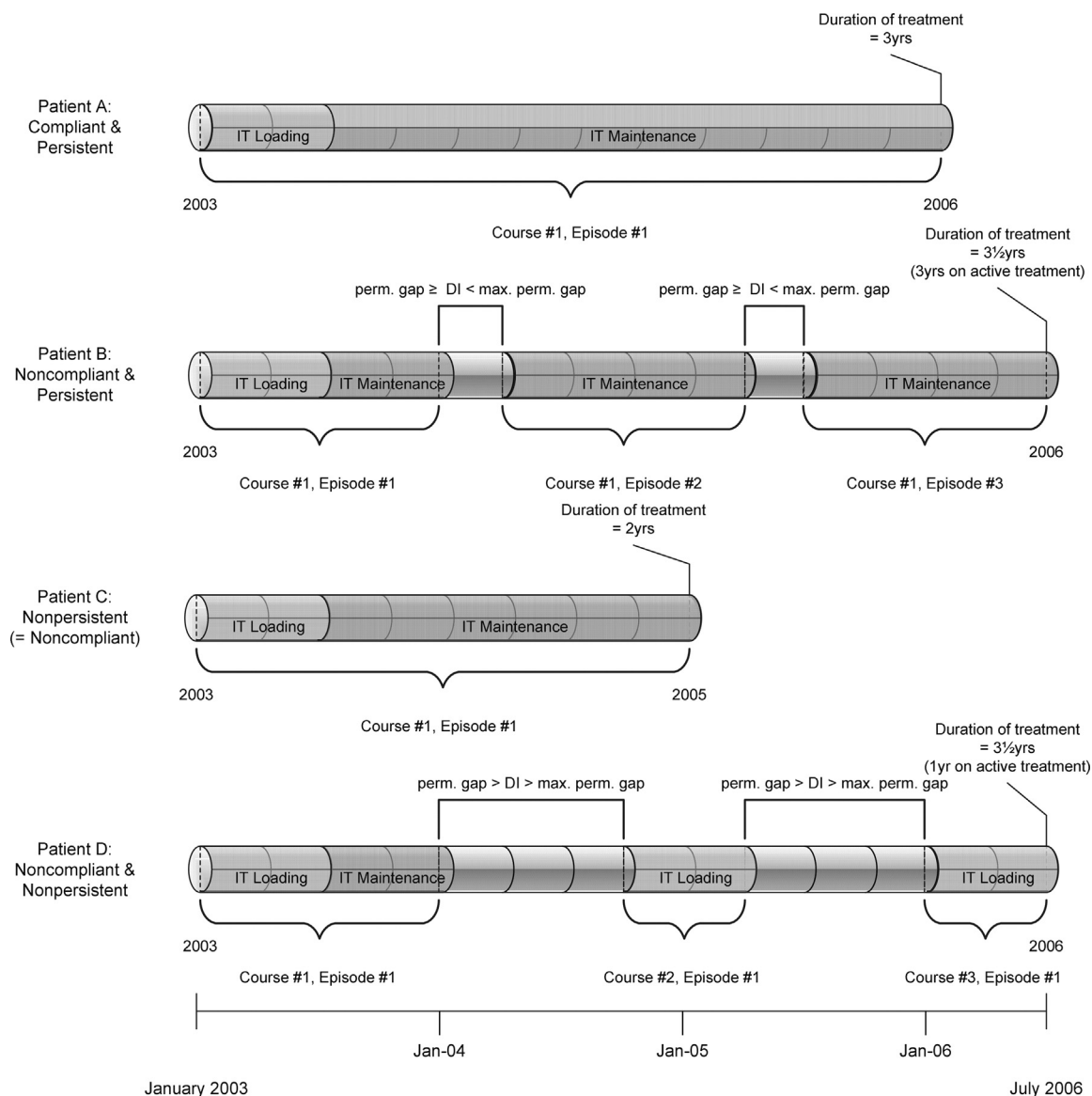


**FIG 1.** Behavior in 4 patients attempting to fulfill a full 3-year course of immunotherapy (IT; simplified). Each vertical marker equals 3 months or one quarter of a year, which in this example equals 1 package of immunotherapy vials or tablets. *DI*, Dispensing interval; (*max.*) *perm. gap*, (maximum) permissible gap. Patient A is both compliant and persistent. Patient B is noncompliant but persistent. Patient C is nonpersistent and therefore noncompliant. Patient D is both noncompliant and nonpersistent.

patients who are likely to benefit most from treatment; alternatively, the short distance to the GP would favor compliance and persistence in primary care.

First, Kaplan-Meier curves of the time to treatment discontinuation were constructed for all variables listed above, and log rank tests were performed. Because patients were considered nonpersistent if they did not complete a treatment duration of 3 years, the time to treatment discontinuation was cut off at a maximum of 3 years for all persistent patients.

Second, Cox proportional hazard models were constructed to investigate whether there was an independent association between the abovementioned variables and premature discontinuation of treatment. Because log-log plots indicated that the effect of various factors differed between the first year after the start of treatment and the 2-year period thereafter, separate Cox models were constructed to estimate hazard rates for the first year and the next 2 years.

Third, binary logistic regression was used to investigate the probability of becoming noncompliant while receiving treatment. This was done in persistent patients only. Additionally, the number of late pharmacy visits was calculated.

Analyses were performed with SAS 9.2 (SAS Institute, Cary, NC) and SPSS 19 (Chicago, Ill) software.

## Sensitivity analysis

In a sensitivity analysis the drug stock, which could be filled with up to 90 days' worth of medication by means of timely pharmacy visits, was disregarded. By doing so, early pharmacy visits could no longer be used to compensate for late pharmacy visits (ie, the analysis of compliance and persistence became more stringent).

## RESULTS

### Patient and treatment characteristics

Immunotherapy users were, on average, in their fourth decade of life, with a slight predominance of female sex. Users had a slightly higher SES than the general population ( $P < .001$ ), as

displayed in Table I. Sixty-eight percent of SCIT prescriptions and 83% of SLIT prescriptions came from general practitioners, whereas 14% of SCIT prescriptions and 1% of SLIT prescriptions came from allergologists ( $P < .001$ ). SCIT was more frequently prescribed for GP allergy, whereas SLIT was more frequently prescribed for HDM allergy and a combination of allergies ( $P < .001$ ). A greater proportion of SCIT users lived in the more populous and urbanized western part of The Netherlands, whereas SLIT users were more likely to live in the more rural south ( $P < .001$ ).

### Univariable analysis of persistence: Kaplan-Meier curves

Overall, 891 (13.8%) of the patients starting immunotherapy were fully persistent. Median time to treatment discontinuation was 1.0 year. Stratification for route of administration resulted in median time until discontinuation of 1.7 years for SCIT and 0.6 years for SLIT. Including discontinuation times beyond 3 years, the mean time until discontinuation was 3.7 years for SCIT and 1.5 years for SLIT. Premature discontinuation of treatment among SLIT users was most prominent around 3 months after the start of treatment, whereas discontinuation among SCIT users was most noticeable 1 year after the start of treatment (Fig 2, A, and Table II). After 1 year, 62% had stopped using SLIT compared with 20% who had stopped using SCIT. At 3 years, these figures were 93% and 77%, respectively.

Stratification by allergen showed that GP immunotherapy users, TP immunotherapy users, or both had a median treatment duration of 1.0 year compared with 0.7 years for HDM immunotherapy users. Both GP and TP immunotherapy users showed a prominent decrease in persistence at 1 year (Fig 2, B, and Table II). This was not seen among HDM immunotherapy users and users of combination therapy.

Stratification by prescriber showed that persistence was worse when immunotherapy was prescribed by other medical specialists, such as ear, nose, and throat physicians and pulmonologists (Fig 2, C, and Table II). Patients receiving their medication from an allergologist have a median time until treatment discontinuation of 1.2 years compared with 1 year for the general practitioners and 0.7 years for other medical specialists. Older patients were more persistent than younger patients, and patients from the southern and western parts of The Netherlands had a higher 1-year persistence than patients from the eastern and northern parts. SES was significantly related to persistence, but sex was not (Table II and see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Multivariable analysis of persistence: Cox model

A time-dependent Cox regression model was constructed because the proportional hazards assumption was not satisfied for a number of variables. Separate hazard rates (HRs) before and after 1 year of treatment were calculated (Table III). The HR of route of administration (SLIT vs SCIT) displayed a significant ( $P < .001$ ) time-dependent relationship: during the first year, the HR of premature discontinuation of patients taking SLIT versus SCIT was 2.60, decreasing to 1.82 after 1 year.

The hazard of premature discontinuation was higher among patients treated by allergologists than among patients treated by general practitioners, with an HR of approximately 1.34, which was not time-dependent. The HR of other medical specialists

**TABLE I.** Individual and therapy-related characteristics of studied SCIT and SLIT users

|                         | SCIT (N = 2796)  | SLIT (N = 3690)  | Total (N = 6486) |
|-------------------------|------------------|------------------|------------------|
| Mean age (y)            | 46 (SD, 13)      | 43 (SD, 12)      | 44               |
| Male sex (%)            | 45               | 43               | 44               |
| SES*                    | -0.20 (SD, 0.85) | -0.16 (SD, 0.85) | -0.18            |
| Prescriber (%)          |                  |                  |                  |
| General practitioner    | 68               | 83               | 76               |
| Allergologist           | 14               | 1                | 7                |
| Other specialist        | 18               | 16               | 17               |
| Allergen (%)            |                  |                  |                  |
| GP                      | 41               | 25               | 32               |
| TP                      | 20               | 16               | 18               |
| HDM                     | 8                | 17               | 13               |
| Combination†            | 31               | 42               | 37               |
| Geographic location (%) |                  |                  |                  |
| West                    | 42               | 27               | 33               |
| East                    | 19               | 16               | 17               |
| South                   | 33               | 52               | 43               |
| North                   | 7                | 6                | 6                |

\*Mean residential SES factor scores. Negative SES factor scores indicate a higher status than the population mean, and higher SES factor scores indicate a lower status.

†Combination = premixed and/or nonpremixed combination therapy.

versus general practitioners was also positive and time-dependent, with an HR of 1.43 during the first year and 1.28 thereafter.

Use of combination therapy displayed a time-dependent relationship with premature discontinuation (ie, the direction of the effect changed from being a hazard-reducing factor in the first year [HR, 0.82] to being a neutral factor [HR, 1.02] in years 2 and 3).

Increased age was negatively associated with premature discontinuation, and persistence increased with each subsequent age quartile. This association was not time-dependent. The lowest SES quartile showed a time-dependent relationship with premature discontinuation: an HR of 1.12 for the first year of treatment, switching to a value of 0.87 for years 2 and 3. Also, an important but non-time-dependent interaction was found between route of administration and allergen group: the HR of SLIT versus SCIT was 2.50 for GP immunotherapy, 2.14 for TP immunotherapy, 2.52 for HDM immunotherapy, and 3.17 for combination immunotherapy.

### Analysis of compliance

Of the persistent monotherapy users ( $n = 565$ ), 56% were fully compliant (ie, they had no late pharmacy visits). In the remaining 249 noncompliant patients, the mean number of late pharmacy visits was 1.4 (95% CI, 1.2-1.7). One hundred sixteen patients (47% of all noncompliant cases) were late once, and 49 patients (20% of all noncompliant cases) were late twice. The remaining 84 patients were late 3 times or more. The mean number of late pharmacy visits was 0.6 in those receiving SCIT and 3.7 in those receiving SLIT. In a logistic regression of compliance, the route of administration was found to be the main predictor of noncompliance: SLIT users had a crude odds ratio of 2.79 when compared with SCIT users ( $P < .001$ ). Sixty-two percent of SLIT users were not compliant compared with 37% of SCIT users. When the same predictors as in the Cox regression model of persistence were entered into the logistic regression model, the odds ratio of the SLIT versus SCIT groups was found

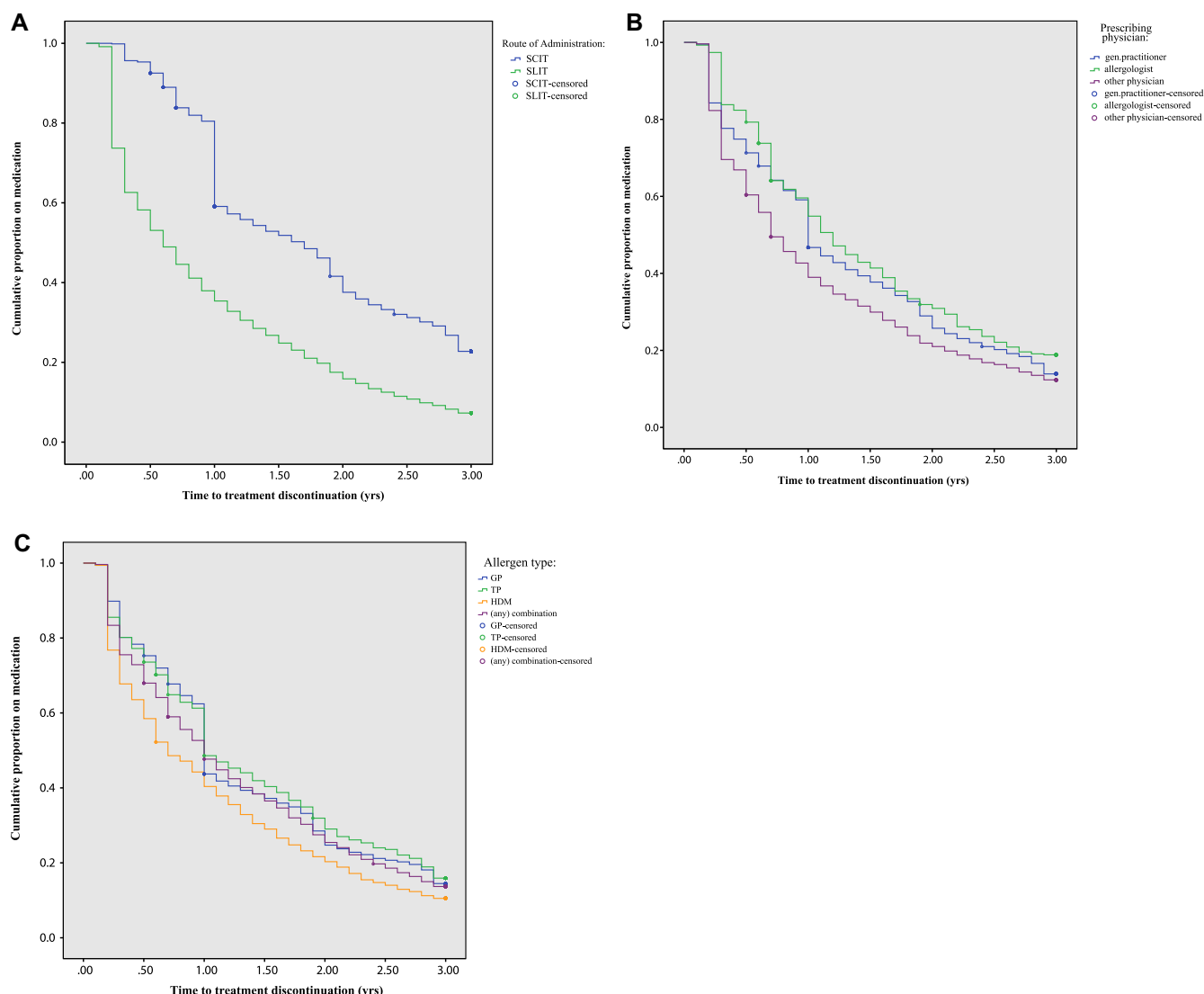


**FIG 2.** Kaplan-Meier curves and summaries of time to treatment discontinuation by route of administration (A), allergen (B), and prescriber (C). *P* values of predictor level distribution equality are less than .001 (right censored for deceased and relocated cases).

to be 1.93 in patients with GP allergy, 2.58 in patients with TP allergy, and 16.91 in patients with HDM allergy. A second interaction effect existed between the allergen and the prescriber: the odds ratio of HDM users versus GP users was 0.28 in general practitioners, 1.16 in allergologists, and 2.96 in other specialists. The odds ratios of TP versus GP were 0.91 in general practitioners, 0.33 in allergologists, and 2.72 in other specialists. Also, patients from the eastern and northern parts of The Netherlands were at increased risk of becoming noncompliant when compared with patients from the western part, with odds ratios of 1.98 and 2.22, respectively. Sex, age, and SES were not found to be significant predictors of noncompliance (see Table E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Costs of nonpersistence

The entire study cohort (both persistent and nonpersistent patients) had total direct pharmaceutical costs of €14.2 million or

€2214 per patient during their first (combined) course of immunotherapy, regardless of its duration. Mean costs per patient completing 3 to 5 years of immunotherapy were €4530, whereas the mean costs per patient not completing at least 3 years of immunotherapy were €1812. The costs of immunotherapy among nonpersistent patients increased from €1015 per patient for those who discontinued treatment in the first year to €3824 for those who discontinued in the third year of treatment. The cumulative total costs of all patients who did not complete 3 years of immunotherapy amounted to €10.04 million (Table IV).

### Sensitivity analysis

Disregarding the “drug stock” did not significantly alter the results. The proportion of nonpersistent patients changed from 891 (13.7%) to 808 (12.5%), and the median time to treatment discontinuation remained unchanged at 1.0 years. The variables that were independently associated with nonpersistence remained the same.

**TABLE II.** Summaries of univariable time to treatment discontinuation, persistence rates, and *P* values

| Variable                 | Median time to treatment discontinuation (y) | Time to treatment discontinuation: First quartile (y) | Time to treatment discontinuation: Third quartile (y) | Patients (no.) | 1-y Persistence rate (%) | 3-y Persistence rate (%) | <i>P</i> value, log rank test |
|--------------------------|----------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|----------------|--------------------------|--------------------------|-------------------------------|
| Route of administration  |                                              |                                                       |                                                       |                |                          |                          | <.001                         |
| SCIT                     | 1.70                                         | 2.90                                                  | 1.00                                                  | 2796           | 80                       | 23                       |                               |
| SLIT                     | 0.60                                         | 1.50                                                  | 0.20                                                  | 3690           | 38                       | 7                        |                               |
| Allergen type            |                                              |                                                       |                                                       |                |                          |                          | <.001                         |
| GP                       | 1.00                                         | 2.00                                                  | 0.60                                                  | 2082           | 62                       | 14                       |                               |
| TP                       | 1.00                                         | 2.40                                                  | 0.50                                                  | 1154           | 61                       | 16                       |                               |
| HDM                      | 0.70                                         | 1.70                                                  | 0.30                                                  | 831            | 44                       | 11                       |                               |
| Any combination          | 1.00                                         | 2.10                                                  | 0.40                                                  | 2398           | 53                       | 14                       |                               |
| Prescriber               |                                              |                                                       |                                                       |                |                          |                          | <.001                         |
| General practitioner     | 1.00                                         | 2.10                                                  | 0.40                                                  | 4801           | 59                       | 14                       |                               |
| Allergologist            | 1.20                                         | 2.40                                                  | 0.60                                                  | 420            | 59                       | 19                       |                               |
| Other prescriber         | 0.70                                         | 1.80                                                  | 0.30                                                  | 1045           | 43                       | 12                       |                               |
| Age                      |                                              |                                                       |                                                       |                |                          |                          | <.001                         |
| Quartile I: ≤34 y        | 0.90                                         | 1.70                                                  | 0.30                                                  | 1422           | 48                       | 9                        |                               |
| Quartile II: 35 to 43 y  | 1.00                                         | 2.00                                                  | 0.40                                                  | 1570           | 55                       | 12                       |                               |
| Quartile III: 44 to 51 y | 1.00                                         | 2.20                                                  | 0.40                                                  | 1571           | 57                       | 14                       |                               |
| Quartile IV: ≥52 y       | 1.10                                         | 2.60                                                  | 0.50                                                  | 1923           | 63                       | 19                       |                               |
| SES*                     |                                              |                                                       |                                                       |                |                          |                          | .001                          |
| Quartile I               | 1.00                                         | 2.00                                                  | 0.40                                                  | 1705           | 56                       | 13                       |                               |
| Quartile II              | 1.00                                         | 2.20                                                  | 0.50                                                  | 1634           | 59                       | 16                       |                               |
| Quartile III             | 1.00                                         | 2.10                                                  | 0.50                                                  | 1511           | 57                       | 14                       |                               |
| Quartile IV              | 1.00                                         | 2.00                                                  | 0.30                                                  | 1542           | 53                       | 13                       |                               |
| Geographic location      |                                              |                                                       |                                                       |                |                          |                          | <.001                         |
| West                     | 1.00                                         | 2.30                                                  | 0.50                                                  | 2157           | 59                       | 17                       |                               |
| East                     | 1.00                                         | 2.10                                                  | 0.50                                                  | 2810           | 53                       | 12                       |                               |
| South                    | 1.00                                         | 2.00                                                  | 0.30                                                  | 398            | 65                       | 14                       |                               |
| North                    | 1.00                                         | 2.00                                                  | 0.50                                                  | 1115           | 58                       | 13                       |                               |
| Sex                      |                                              |                                                       |                                                       |                |                          |                          | .693                          |
| Male                     | 1.00                                         | 2.10                                                  | 0.50                                                  | 2820           | 58                       | 14                       |                               |
| Female                   | 1.00                                         | 2.10                                                  | 0.40                                                  | 3666           | 55                       | 14                       |                               |

Truncated times to discontinuation, median, and first and third quartiles are shown.

\*SES quartiles around median sample factor score. Lower SES quartiles indicate a higher status than the population mean, and higher SES quartiles indicate a lower status than the population mean.

## DISCUSSION

The main conclusion from this study is that real-life persistence and compliance with immunotherapy for the most commonly treated allergens in The Netherlands is low. Median treatment duration is far less than the 3 years that are recommended to achieve long-term health benefits. Even the persistent patients, who do reach at least 3 years of treatment, frequently have late pharmacy visits. Persistence and compliance were better in SCIT users than in SLIT users, in patients treated by general practitioners compared with those treated by medical specialists, in patients receiving treatment for a combination of allergens (only during first year), in older patients, and in patients with a higher SES. The strength of this study is that with almost 6500 patients, it is the largest real-life study of persistence and compliance with immunotherapy for different allergens thus far. The database that was used is representative for the entire population of patients receiving immunotherapy for these allergens. However, as is common in observational research of existing databases, the database does not contain details on diagnosis, severity of disease, side effects, or other medical factors that might influence persistence and compliance. This information could not be obtained retrospectively.

This lack of medical details is unlikely to affect the overall conclusion that persistence is low, but it might have influenced

some of the predictors. Currently, we can only speculate on why persistence is worse in SLIT users than in SCIT users. It might be that oral side effects play a role or lower efficacy. It might also be related to the fact that SCIT is being administered by a physician, whereas SLIT is taken by the patient at home. As a consequence, SCIT users have more frequent opportunities to discuss their experience with a physician, who can offer support and encouragement to continue treatment. In this light the official position of the WHO–Allergic Rhinitis and its Impact on Asthma working group advising SLIT in case of noncompliance with SCIT is put in a somewhat different perspective.<sup>1</sup>

It is worth discussing that the prescriber was found to be an independent predictor of persistence. After correction for the other variables that were available in the database, persistence was better in patients treated by general practitioners than in patients treated by medical specialists. In contrast to our prior expectations, this might be because medical specialists treat more severely ill and more complex patients. It might also be related to a practicality, such as the greater travel distance to medical specialists. On average, Dutch citizens live at a distance of 1.1 km (0.7 miles) from their general practitioner's office and 7 km (4.3 miles) from the nearest hospital.<sup>26</sup> By Dutch standards, these are notable distances, which can be even greater in rural areas. Most

**TABLE III.** Premature discontinuation: Cox regression model

| Variable                                                          | HR, year 1 | 95% CI    | P value | HR, years 2-3 | 95% CI    | P value | P value,<br>HR comparison* |
|-------------------------------------------------------------------|------------|-----------|---------|---------------|-----------|---------|----------------------------|
| Route of administration (SLIT vs SCIT [reference])                | 2.60       | 2.41-2.81 | <.001   | 1.82          | 1.66-2.01 | <.001   | <.001                      |
| Prescriber (overall)                                              |            |           | <.001   |               |           | .007    |                            |
| Prescriber (allergologist vs general practitioner [reference])    | 1.37       | 1.17-1.61 | <.001   | 1.31          | 1.09-1.57 | .004    | .697                       |
| Prescriber (other specialist vs general practitioner [reference]) | 1.43       | 1.31-1.56 | <.001   | 1.13          | 0.99-1.28 | .078    | .003                       |
| Allergen (overall)                                                |            |           | <.001   |               |           | .717    |                            |
| Allergen (TP vs GP [reference])                                   | 0.90       | 0.81-1.00 | .044    | 0.99          | 0.86-1.14 | .898    | .258                       |
| Allergen (HDM vs GP [reference])                                  | 0.96       | 0.86-1.07 | .443    | 1.08          | 0.93-1.27 | .305    | .200                       |
| Allergen (combination therapy vs GP [reference])                  | 0.82       | 0.75-0.89 | <.001   | 1.02          | 0.91-1.14 | .726    | .002                       |
| Patient sex (female vs male [reference])                          | 1.03       | 0.96-1.10 | .458    | 0.94          | 0.86-1.03 | .192    | .137                       |
| Age (overall)                                                     |            |           | <.001   |               |           | <.001   |                            |
| Age, quartile II vs quartile I (reference)                        | 0.91       | 0.83-1.00 | .041    | 0.89          | 0.78-1.01 | .069    | .787                       |
| Age, quartile III vs quartile I (reference)                       | 0.83       | 0.75-0.91 | <.001   | 0.79          | 0.70-0.90 | <.001   | .567                       |
| Age, quartile IV vs quartile I (reference)                        | 0.77       | 0.70-0.85 | <.001   | 0.70          | 0.62-0.80 | <.001   | .299                       |
| SES (overall)                                                     |            |           | .006    |               |           | .072    |                            |
| SES, quartile II vs quartile I (reference)                        | 1.00       | 0.91-1.11 | .952    | 0.87          | 0.77-0.99 | .033    | .089                       |
| SES, quartile III vs quartile I (reference)                       | 0.95       | 0.86-1.05 | .308    | 0.87          | 0.77-0.99 | .028    | .279                       |
| SES, quartile IV vs quartile I (reference)                        | 1.12       | 1.02-1.24 | .017    | 0.87          | 0.77-1.00 | .42     | .002                       |

Multivariable Cox regression results regarding premature discontinuation separately for the period of the first year and the period 2 to 3 years after start of treatment are shown. Data shown are HRs with 95% CIs and *P* values. Predictors of premature discontinuation of treatment with reference categories are also shown. Age quartile I ( $\leq 34$  years of age [reference]) is compared with quartiles II (35-43 years), III (44-51 years), and IV ( $\geq 52$  years). SES quartile I (reference) is compared with quartiles II, III, and IV. SES quartiles are around the median sample factor score of  $-1.64$ . The lower quartiles have the highest status, and the higher quartiles have the lowest status. This model also included a significant ( $P < .005$ ), although non-time-dependent, interaction effect between route of administration and allergen group: the HR of SLIT versus SCIT was 2.50 for users of GP immunotherapy, 2.14 for users of TP immunotherapy, 2.52 for users of HDM immunotherapy, and 3.17 for users of combination immunotherapy.

\*Comparison of HRs in year 1 versus HRs in years 2 to 3.

**TABLE IV.** Immunotherapy: cost of nonpersistence

| Year of treatment discontinuation | Annual total costs (€) | Cumulative total costs (€) | Cumulative mean costs per nonpersistent patient (€) |
|-----------------------------------|------------------------|----------------------------|-----------------------------------------------------|
| 1                                 | 2.88M                  | 2.88M                      | 1015                                                |
| 2                                 | 3.74M                  | 6.62M                      | 2069                                                |
| 3                                 | 3.42M                  | 10.04M                     | 3824                                                |

immunotherapy was prescribed by general practitioners and not by allergologists, reflecting the relatively small number of allergologists in The Netherlands. Greater burden of disease during a larger part of the year might also explain why persistence during the first year is better among patients who receive combination treatment compared with patients who receive monoimmunotherapy for GP allergies.

Even when patients were persistent, they still had frequent late pharmacy visits. The odds of having at least 1 late pharmacy visit (the definition of being noncompliant) were higher for SLIT users than for SCIT users. The odds of becoming noncompliant increased considerably when HDM immunotherapy was administered in sublingual form compared with subcutaneous form. One might hypothesize that lack of efficacy plays a role because the evidence for the efficacy of sublingual HDM immunotherapy is less strong than for the other allergies.<sup>4,27</sup>

This study has also clearly shown that the drug costs of immunotherapy in nonpersistent patients were high. These costs will be even higher when including the costs of physician's office visits and absence from work because of treatment, as is the case in SCIT. Of note is the fact that in The Netherlands these costs were and are largely borne by health insurers, and because there are no long-term benefits as a return on these investments,

nonpersistence seriously jeopardizes the (cost-) effectiveness of immunotherapy.

An important question is whether these Dutch results are transferable to other countries. In The Netherlands both medical specialists and general practitioners can initiate SCIT, but in reality, it frequently starts at the specialist's office and is taken over by the general practitioner. In contrast, general practitioners can easily initiate SLIT themselves without further requirements to their practice procedures, which explains their preference for SLIT. To our knowledge, the contribution of general practitioners to the management of allergen immunotherapy is characteristic of Dutch clinical practice. Apparently, the contribution of Dutch general practitioners does not negatively affect compliance or persistence. On the contrary, taking the better persistence into account, our findings support an active involvement of general practitioners, especially in the treatment of patients with less complex conditions. However, even though medical practice patterns can differ and the specific mixture of patients and types of immunotherapy can vary between countries, the transferability of our results is supported by other studies carried out in completely different health care systems, which also report premature discontinuation of SCIT<sup>11,12</sup> and SLIT<sup>12</sup> at rates as high as 67% and 49%, respectively. However, comparison of compliance data is hampered by differences in definitions.

In conclusion, allergen immunotherapy in real life is characterized by a strikingly low level of compliance and persistence, particularly when using SLIT. There is an urgent need for further identification of potential barriers and measures that will enhance persistence and compliance.

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**Clinical implications: Efforts to increase persistence with allergen immunotherapy in real life are urgently needed because large amounts of money are currently being misspent as a result of premature discontinuation of treatment.**

## REFERENCES

- Bousquet J, Khaltaev N, Cruz A, Denburg J, Fokkens W, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008. *Allergy* 2008;63:8-160.
- van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. *European Academy of Allergology and Clinical Immunology*. *Allergy* 2000;55:116-34.
- Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Cochrane review: allergen injection immunotherapy for seasonal allergic rhinitis. *Evid Based Child Health* 2010;5:1279-379.
- Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010;12:CD002893.
- Durham SR, Walker SM, Varga E, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468-75.
- Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JGR, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010;125:131-8.e7.
- Vita D, Caminiti L, Ruggeri P, Pajno G. Sublingual immunotherapy: adherence based on timing and monitoring control visits. *Allergy* 2010;65:668-9.
- Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 1993;91:734-7.
- Tinkelman D, Smith F, Cole WQ 3rd, Silk HJ. Compliance with an allergen immunotherapy regime. *Ann Allergy Asthma Immunol* 1995;74:241-6.
- Hankin CS, Cox L, Lang D, Levin A, Gross G, Eavy G, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J Allergy Clin Immunol* 2008;121:227-32.
- Donahue JG, Greineder DK, Connor-Lacke L, Canning CF, Platt R. Utilization and cost of immunotherapy for allergic asthma and rhinitis. *Ann Allergy Asthma Immunol* 1999;82:339-47.
- Sieber J, De Geest S, Shah-Hosseini K, Moosges R. Medication persistence with long-term, specific grass pollen immunotherapy measured by prescription renewal rates. *Curr Med Res Opin* 2011;27:855-61.
- Senna G, Ridolo E, Calderon M, Lombardi C, Canonica GW, Passalacqua G. Evidence of adherence to allergen-specific immunotherapy. *Curr Opin Allergy Clin Immunol* 2009;9:544.
- Lombardi C, Gani F, Landi M, Falagiani P, Bruno M, Canonica GW, et al. Quantitative assessment of the adherence to sublingual immunotherapy. *J Allergy Clin Immunol* 2004;113:1219-20.
- Passalacqua G, Musarra A, Pecora S, Amoroso S, Antonicelli L, Cadario G, et al. Quantitative assessment of the compliance with a once-daily sublingual immunotherapy regimen in real life (EASY Project: Evaluation of A novel SLIT formulation during a Year). *J Allergy Clin Immunol* 2006;117:946-8.
- Passalacqua G, Musarra A, Pecora S, Amoroso S, Antonicelli L, Cadario G, et al. Quantitative assessment of the compliance with once-daily sublingual immunotherapy in children (EASY Project: Evaluation of A novel SLIT formulation during a Year). *Pediatr Allergy Immunol* 2007;18:58-62.
- Sachs A, Berger M, Lucassen P, Wal J, Balen J, Verduijn M. NHG-Standaard Allergische en niet-allergische rhinitis. NHG-Standaarden voor de huisarts 2009;980-98.
- PHARMO: Institute for drug outcome research. PHARMO Institute homepage: community pharmacy database (CPD). Available at: <http://www.pharmo.nl/research/page/CPDdatabase>. Accessed January 12, 2012.
- Herings RMC, Pedersen L. Pharmacy-based medical record linkage systems. In: Strom BL, Kimmel SE, Hennessy S, editors. *Pharmacoepidemiology*. 5th ed. London: Wiley-Blackwell; 2012. p. 270.
- Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997;99:314-22.
- Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
- Sociaal & Cultureel Planbureau (SCP). Rangorde naar sociale status van postcodegebieden in Nederland. Available at: <http://www.scp.nl/content.jsp?objectid=default:20133>. Accessed June 19, 2011.
- Peterson AM, Nau DP, Cramer JA, Benner J, Gwady-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* 2007;10:3-12.
- Incorvaia C, Mauro M, Ridolo E, Puccinelli P, Liuzzo M, Scurati S, et al. Patient's compliance with allergen immunotherapy. *Patient Prefer Adherence* 2008;2:247-51.
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-97.
- Hakkaart-van Roijen L, Tan S, Bouwmans C. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. 2010.
- de Bot C, Moed H, Berger MY, Röder E, Hop WCJ, de Groot H, et al. Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol* 2012;23:150-8.

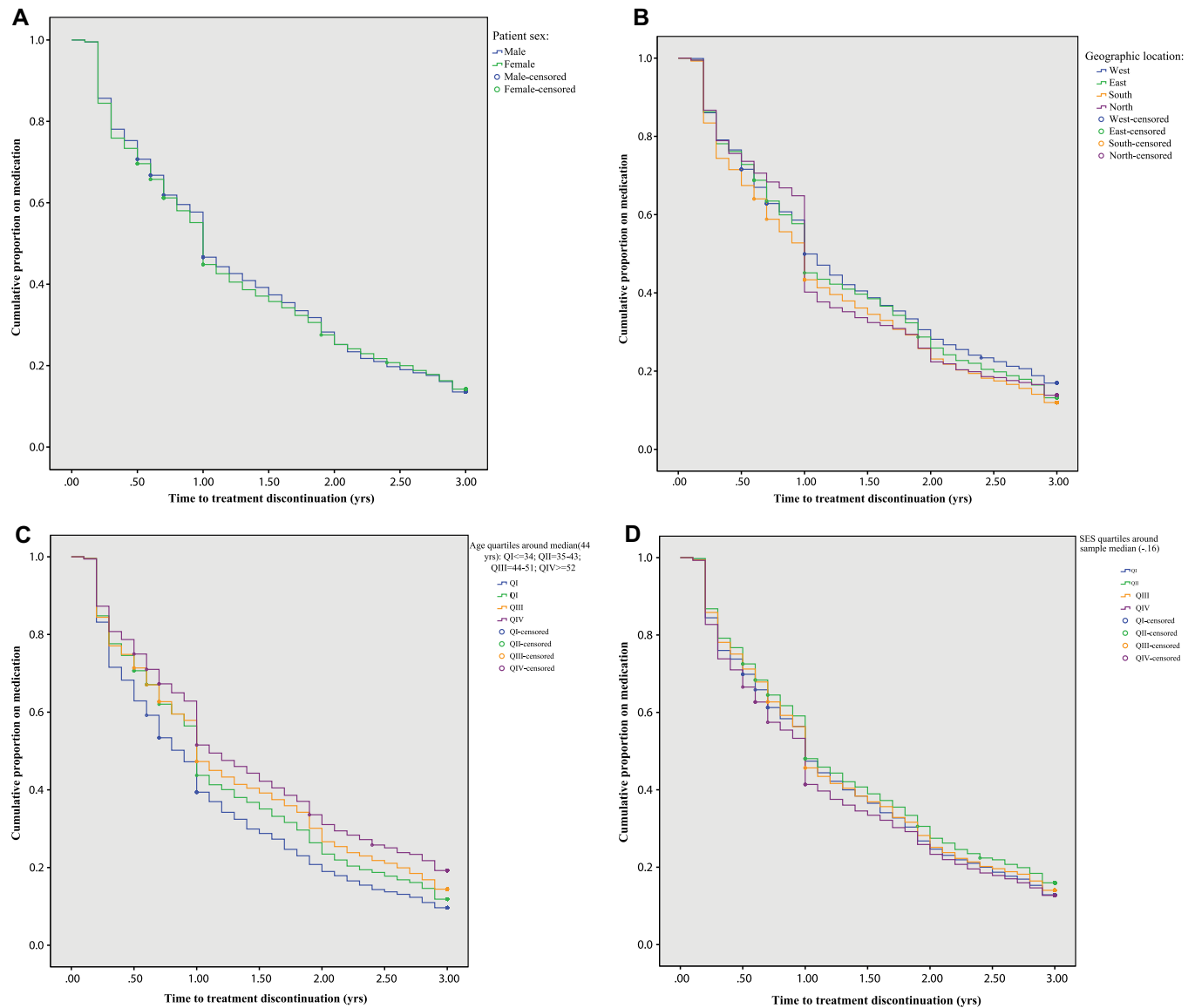


**FIG E1.** **A**, Kaplan-Meier curves and summaries of time to treatment discontinuation by sex (right censored for deceased and relocated cases). **B**, Kaplan-Meier curves and summaries of time to treatment discontinuation by geographic location of residence (right censored for deceased and relocated cases). **C**, Kaplan-Meier curves and summaries of time to treatment discontinuation by age quartile. Quartiles around sample median (44 years) are as follows: quartile I, 33 years or less; quartile II, 35 to 43 years; quartile III, 44 to 51 years, and quartile IV, 53 years or greater (right censored for deceased and relocated cases). **D**, Kaplan-Meier curves and summaries of time to treatment discontinuation by SES factor score. Quartiles are around the sample median ( $-1.64$ ), with the first quartile as the reference category (0) compared with quartiles 2 through 4 (1). Higher quartile numbers have lower SES (factor score).

**TABLE E1.** Binary logistic regression of predictors of noncompliance

| Variables in the equation                                         | OR    | 95% CI for OR |       | P value |
|-------------------------------------------------------------------|-------|---------------|-------|---------|
|                                                                   |       | Lower         | Upper |         |
| Route of administration (SLIT vs SCIT [reference])                | 1.93  | 1.03          | 3.62  | .04     |
| Prescriber (overall)                                              |       |               |       | .04     |
| Prescriber (allergologist vs general practitioner [reference])    | 2.50  | 0.68          | 9.12  | .17     |
| Prescriber (other specialist vs general practitioner [reference]) | 0.36  | 0.14          | 0.95  | .04     |
| Allergen (overall)                                                |       |               |       | .08     |
| Allergen (TP vs GP [reference])                                   | 0.91  | 0.53          | 1.56  | .72     |
| Allergen (HDM vs GP [reference])                                  | 0.28  | 0.09          | 0.85  | .02     |
| Patient sex (female vs male sex [reference])                      | 0.88  | 0.60          | 1.27  | .48     |
| Age (overall)                                                     |       |               |       | .60     |
| Age, quartile II vs quartile I (reference)                        | 1.07  | 0.55          | 2.06  | .85     |
| Age, quartile III vs quartile I (reference)                       | 0.76  | 0.40          | 1.43  | .39     |
| Age, quartile IV vs quartile I (reference)                        | 0.83  | 0.45          | 1.53  | .55     |
| SES (overall)                                                     |       |               |       | .14     |
| SES, quartile II vs quartile I (reference)                        | 0.80  | 0.47          | 1.36  | .40     |
| SES, quartile III vs quartile I (reference)                       | 0.54  | 0.30          | 0.96  | .04     |
| SES, quartile IV vs quartile I (reference)                        | 0.59  | 0.33          | 1.05  | .07     |
| Geographic location (overall)                                     |       |               |       | .05     |
| Geographic location, east vs west (reference)                     | 1.98  | 1.14          | 3.44  | .02     |
| Geographic location, south vs west (reference)                    | 1.45  | 0.89          | 2.36  | .13     |
| Geographic location, north vs west (reference)                    | 2.22  | 1.05          | 4.70  | .04     |
| Interaction term: Allergen * route of administration (overall)    |       |               |       | .01     |
| Interaction term: TP * SLIT                                       | 1.34  | 0.54          | 3.35  | .53     |
| Interaction term: HDM * SLIT                                      | 8.77  | 2.08          | 37.02 | .00     |
| Interaction term: allergen * prescriber (overall)                 |       |               |       | .05     |
| Interaction term: TP * allergologist                              | 0.37  | 0.06          | 2.30  | .29     |
| Interaction term: TP * other specialist                           | 3.00  | 0.79          | 11.45 | .11     |
| Interaction term: HDM * allergologist                             | 4.21  | 0.37          | 47.50 | .25     |
| Interaction term: HDM * other specialist                          | 10.74 | 1.71          | 67.51 | .01     |

Data represent binary logistic regression of predictors of noncompliance in persistent users of noncombination immunotherapy (final model). Data shown are odds ratios with 95% CIs and *P* values. Predictors of noncompliance to treatment are shown with reference categories. Age quartile I ( $\leq 34$  years, reference) was compared with quartiles II (35–43 years), III (44–51 years), and IV ( $\geq 52$  years). SES quartile I (reference) was compared with quartiles II, III, and IV. SES quartiles are around the median sample factor score of  $-1.64$ . The lower quartiles have the highest status, and the higher quartiles have the lowest status.

OR, Odds ratio.