

Allergy immunotherapy for allergic rhinitis effectively prevents asthma: Results from a large retrospective cohort study

Jochen Schmitt, MD, MPH,^a Kristin Schwarz,^a Erich Stadler,^a and Eike Gunther Wüstenberg, MD^b *Dresden, Germany*

Background: Allergic rhinitis (AR) is a main risk factor for the development of asthma. Two randomized open-label trials indicated that allergy immunotherapy (AIT) prevents the onset of asthma in patients with AR. However, these trials have methodological limitations, and it is unclear to what extent this experimental efficacy translates into clinical effectiveness.

Objectives: We sought to investigate the effectiveness of AIT to prevent asthma in patients with AR.

Methods: Using routine health care data from German National Health Insurance beneficiaries, we identified a consecutive cohort of 118,754 patients with AR but without asthma who had not received AIT in 2005. These patients were stratified into one group starting AIT in 2006 and one group receiving no AIT in 2006. Both groups were observed regarding the risk of incident asthma in 2007 to 2012. Risk ratios (RRs) were calculated with generalized linear models by using a Poisson link function with robust error variance and adjustment for age, sex, health care use because of AR, and use of antihistamines.

Results: In a total of 2431 (2.0%) patients, AIT was started in 2006. Asthma was newly diagnosed from 2007-2012 in 1646 (1.4%) patients. The risk of incident asthma was significantly lower in patients exposed to AIT (RR, 0.60; 95% CI, 0.42-0.84) compared with patients receiving no AIT in 2006. Sensitivity analyses suggested significant preventive effects of subcutaneous immunotherapy (RR, 0.54; 95% CI, 0.38-0.84) and AIT including native (nonallergoid) allergens (RR, 0.22; 95% CI, 0.02-0.68). AIT for 3 or more years tended to have stronger preventive effects than AIT for less than 3 years.

Conclusion: AIT effectively prevents asthma in patients with AR in a real-world setting. Confounding by indication cannot be excluded but would lead to an underestimation of the true preventive effects of AIT. (*J Allergy Clin Immunol* 2015;■■■■:■■■-■■■.)

Key words: Allergic rhinitis, allergy immunotherapy, asthma, cohort study, epidemiology, prevention, effectiveness

Abbreviations used

AIT:	Allergy immunotherapy
AR:	Allergic rhinitis
ATC:	Anatomical Therapeutic Chemical
ICD-10:	International Statistical Classification of Diseases, 10th edition
PAT:	Preventive Allergy Treatment
RR:	Risk ratio
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy

Affecting 15% to 20% of the population in Western countries, allergic rhinitis (AR) is among the most frequent chronic multifactorial diseases.¹⁻³ The prevalence of AR peaks in younger adulthood between 20 and 40 years of age.⁴ AR not only frequently causes substantial problems in everyday life and in terms of work productivity loss^{5,6} but might also induce significant adverse cognitive alterations, such as reduced processing speed or anxious mood after allergen exposure.⁷

Most importantly, AR is a major risk factor for asthma development.^{3,8} Because of the considerable burden of asthma, resulting morbidity, adverse effect on quality of life, and cost,^{9,10} it is of the utmost importance to prevent asthma in patients with AR.

As a causal treatment option, allergy immunotherapy (AIT) might effectively induce long-term remission of AR and asthma and might also prevent the onset of new sensitizations.^{11,12} Therefore the Allergic Rhinitis and its Impact on Asthma guidelines recommend considering AIT for patients with persistent AR and for those with intermittent AR and moderate-to-severe symptoms.^{12,13} AIT is usually differentiated into subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SLIT can be differentiated into SLIT drops and SLIT tablets. For SCIT and SLIT, the allergens in the products can be delivered as natural (intact) allergens, or they can be modified by using aldehydes as so-called allergoids.^{3,12}

Although clinical efficacy (ie, reduction of symptoms, medication use, or both) is established for several AIT products, trial evidence that AIT prevents the manifestation of asthma in patients with AR is less strong.¹¹ More than 10 years ago, a randomized open-label trial suggested that pollen SCIT reduces the risk of asthma in children with AR.¹⁴ Another smaller, randomized, but unblinded trial concluded that pollen SLIT drops can reduce asthma risk in children with AR.¹⁵ However, these trials have methodological limitations, and it is unclear to what extent the observed experimental efficacy translates into clinical effectiveness. Because disease-modifying aspects are the main benefits of AIT compared with symptomatic treatment,¹⁶ it is of

From ^athe Center for Evidence-based Healthcare and ^bthe Department for Otorhinolaryngology, Medical Faculty Carl Gustav Carus, TU Dresden.

Disclosure of potential conflict of interest: J. Schmitt has received research support from Novartis, ALK-Abelló, MSD, Pfizer, and Abbott. E. G. Wüstenberg is employed by and has stock/stock options in ALK-Abelló. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 20, 2015; revised July 10, 2015; accepted for publication July 20, 2015.

Corresponding author: Jochen Schmitt, MD, MPH, Center for Evidence-based Healthcare, Medical Faculty Carl Gustav Carus at the TU Dresden, Fetscherstr. 74, D-01307 Dresden, Germany. E-mail: jochen.schmitt@uniklinikum-dresden.de.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2015.07.038>

utmost importance to investigate to what extent these preventive benefits of AIT can also be achieved in routine care.

Hypothesizing that patients receiving AIT in routine care have a lower risk of incident asthma than patients with AR not receiving AIT, we investigated a large cohort of patients with AR in a realistic setting based on secondary data received from the health care system.

METHODS

Study design and participants

This retrospective cohort study used the AOK Saxony database,¹⁷⁻¹⁹ a pseudonymized population-based administrative health care database that holds complete information on outpatient health care (diagnoses according to the International Statistical Classification of Diseases, 10th edition [ICD-10] and treatments according to the Anatomical Therapeutic Chemical [ATC] classification code) and sociodemographic characteristics (age, sex, and 3 digits of the ZIP code) of approximately 55% of the population from the federal state of Saxony, Germany. The study base consisted of all subjects insured from January 1, 2005, until December 31, 2012, or until death ($n = 1,811,094$; mean age, 48 years; 54% female). From this study base, we selected all patients with AR in 2005 without comorbid asthma, without AIT in 2005, and without first AIT in 2007 or later.

In accordance with the guidelines on good practice for secondary data analysis,²⁰ we defined *a priori* that the ICD-10 code for AR (J30) had to be documented at least twice to classify patients as having AR. This double classification was done as a measure to minimize misclassification. A total of 171,539 patients met these criteria (mean age, 36 years; 57% female), resulting in a 1-year prevalence of AR of 9.5% in 2005. A total of 36,216 (21%) patients had comorbid asthma at baseline (ICD-10 code J45 documented at least twice plus ≥ 2 prescriptions of inhalant steroids) and were therefore excluded from the cohort under investigation. From the remaining 135,323 patients (mean age, 37 years; 58% female), a total of 16,569 subjects currently received AIT in 2005 or first AIT in 2007 or later. These patients were also excluded from the study, resulting in a cohort under investigation of 118,754 patients (mean age, 37 years; 58% female) with chronic AR, without asthma, and without AIT in 2005 and without first AIT in 2007 or later (Fig 1).

Exposure and confounding variables

The exposure of interest was AIT in 2006. Detailed and complete information on prescribed AIT was available through prescription data available in the data set used. Every patient from the cohort under investigation who received at least 1 prescription of AIT in 2006 was classified as “exposed.” AIT was further stratified as SCIT, SLIT drops, SLIT tablets, and combinations by using the corresponding ATC classification codes. Further stratifications of AIT were done for the kind of allergen targeted by AIT (most common seasonal allergen or allergens [grasses/trees], most common perennial allergen or allergens [mites], and both seasonal and perennial allergens), duration of AIT (<3 vs ≥ 3 years), and AIT preparation (ie, modified allergens [allergoids], native allergens, and combinations). Trees, grasses, and mites are by far the dominant allergens in central Europe. Allergen products containing these allergens are mostly registered products. Comparably rare allergen preparations were rated as “not classified” to avoid dilution with these allergen preparations (eg, cat, molds, *Alternaria* species, and storage mites) that are most frequently produced individually on a named patient basis. This information was based on prescription data on the summary of characteristics for the respective products.

Age (continuously) and sex were considered confounders. One potential threat to internal validity is confounding by indication. The Allergic Rhinitis and its Impact on Asthma guidelines recommend that AIT is indicated for patients in whom antihistamines and moderate-dose glucocorticoids insufficiently control symptoms.¹³ Therefore it can be assumed that patients with more severe AR and higher asthma risk are more likely to receive AIT. Therefore we attempted to deal with unmeasured disease severity by stratification of patients with AR

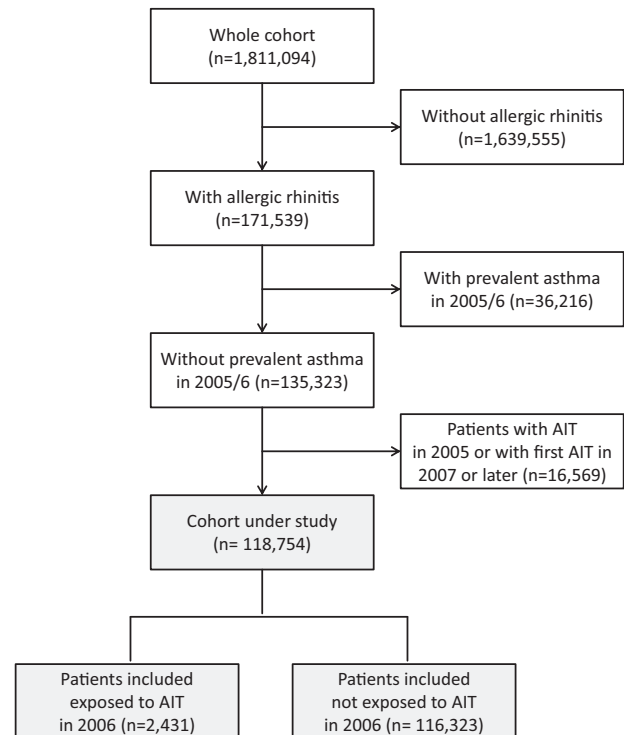


FIG 1. Patient flow chart.

based on the amount of systemic antihistamines they were prescribed into 5 categories: no antihistamines prescribed and the first to fourth quartiles of total defined daily dosages of antihistamines prescribed. Only antihistamine prescriptions that were filled were considered. The role of AR-specific health care use was assessed by modeling the number of physician's office visits because of AR (also in quartiles).

Primary outcome

The primary outcome of interest was incident asthma in 2007 to 2012. Incident asthma was defined as no documentation of the corresponding ICD-10 code in 2005 and 2006, at least 2 documented physician contacts because of asthma (ICD-10 code J45) in 2007 to 2012, and at least 2 prescriptions of inhalant corticosteroids (ATC classification code R03BA) in 2007 to 2012. Because inhalant corticosteroids are the standard treatment of bronchial asthma according to the Global Initiative for Asthma guidelines,²¹ they were used as a marker for bronchial asthma. In accordance with the good practice of secondary data analysis,²⁰ this specific internal case validation method of asthma was applied to avoid misclassification bias.

Statistical analysis

Counts and percentages were calculated for each confounding, outcome, and exposure variable. Risk ratios (RRs) were calculated by using generalized linear models with a logarithmic link function and binomial distribution for the residual (log-binomial regression) and adjustment for age, sex, health care use because of AR, and use of antihistamines. The primary analysis compared patients exposed to AIT in 2006 versus patients not exposed to AIT in 2006. Sensitivity analyses explored the role of the kind of AIT (SCIT, SLIT, and combinations), duration of AIT (<3 vs ≥ 3 years), AIT preparation (modified allergens [allergoids], native allergens, not classified, and combinations), and kind of allergen targeted by AIT (seasonal, perennial, and both seasonal and perennial allergen). In addition, effect modification by age and sex was investigated by inclusion of interaction terms of age and exposure to AIT in 2006 or of sex and exposure to AIT in 2006.

TABLE I. Characteristics of the study population stratified by exposure to AIT in 2006 (*n* = 118,754 patients with AR, no asthma, no exposure to AIT in 2005, and no first exposure to AIT in 2007 or later)

Characteristic	Exposed to AIT (<i>n</i> = 2,431)	Not exposed to AIT (<i>n</i> = 116,323)
Female sex, no. (%)	1,353 (55.7)	67,686 (58.2)
Age (y), mean (SD)	28.6 (16.1)	38.4 (22.5)
Prescriptions of antihistamines, no. (%)		
None	1,234 (50.8)	82,381 (70.8)
First quartile	102 (4.2)	4,947 (4.3)
Second quartile	351 (14.4)	11,877 (10.2)
Third quartile	343 (14.1)	8,913 (7.7)
Fourth quartile	401 (16.5)	8,205 (7.1)
Health care use because of AR, no. (%)		
First quartile	51 (2.1)	28,977 (24.9)
Second quartile	123 (5.1)	25,986 (22.3)
Third quartile	604 (24.8)	32,853 (28.2)
Fourth quartile	1,653 (68.0)	28,507 (24.5%)

We used the Akaike information criterion to decide whether the log-binomial model fits better than the Poisson model with robust error variance and whether our models fit better than models with less confounding variables. The Akaike information criterion values of our models were smaller compared with those of the alternative models, indicating better fit.²² Outliers were detected by calculating the Cook distance after regression. Cook distances of greater than 1 are considered influential. All Cook D values of our final models were less than 1.²² All *P* values were 2-sided, and *P* values of less than .05 were considered statistically significant. Data were analyzed with STATA version 12 software (StataCorp, College Station, Tex).

RESULTS

Fig 1 summarizes the patient flow. All patients (*n* = 118,754) from the underlying cohort with confirmed AR but without comorbid asthma at baseline who had not received any AIT in 2005 and who did not newly receive AIT in 2007 or later were included in the study. From this cohort, a total of 2,431 (2.1%) patients newly received AIT in 2006. Patients exposed to AIT in 2006 were younger, were more likely to receive antihistamines, and had more physician contacts for AR compared with patients not exposed to AIT in 2006 (Table I).

Incident asthma during follow-up was observed in 1646 (1.4%) patients. On average, patients with newly diagnosed asthma received higher dosages of antihistamines and had more physician contacts caused by AR than patients who were not given a diagnosis of asthma during follow-up. The raw asthma incidence did not differ between patients exposed to AIT and patients not exposed to AIT (Table II).

As summarized in Table III, SCIT was the most frequent type of AIT, followed by SLIT drops. SLIT tablets were launched in late 2006 in Germany and therefore prescribed to only 10 patients from the study cohort, none of whom had asthma during follow-up. More than half of the patients starting AIT in 2006 continued treatment for less than 3 years. In general, patients who received different kinds of AIT and AIT against both perennial and seasonal allergens tended to be more likely to have incident asthma than patients with a single kind of AIT or AIT against either perennial or seasonal allergens (Table III).

TABLE II. Incidence of asthma during follow-up (*n* = 118,754 patients with AR)

Characteristic	Incident asthma (<i>n</i> = 1,646)	No incident asthma (<i>n</i> = 117,108)
Female sex, no. (%)	866 (52.6)	68,173 (58.2)
Prescriptions of antihistamines, no. (%)		
None	702 (42.6)	82,913 (70.8)
First quartile	205 (12.5)	4,844 (4.1)
Second quartile	280 (17.0)	11,948 (10.2)
Third quartile	241 (14.6)	9,015 (7.7)
Fourth quartile	218 (13.2)	8,388 (7.2)
Health care use because of AR, no. (%)		
First quartile	267 (16.2)	28,761 (24.6)
Second quartile	337 (20.5)	25,772 (22.0)
Third quartile	597 (36.3)	32,860 (28.1)
Fourth quartile	445 (27.0)	29,715 (25.4)
Exposure to AIT in 2006, no. (%)		
Exposure	33 (2.0)	2,398 (2.0)
No exposure	1,613 (98.0)	114,710 (98.0)

TABLE III. Specification of AIT exposure stratified by incidence of asthma during follow-up (*n* = 2,431 patients with AR exposed to AIT in 2006)

Characteristic	No incident asthma (<i>n</i> = 2,398)	Incident asthma (<i>n</i> = 33)
Route of administration, no. (%)		
SCIT	2,005 (83.6)	25 (75.8)
SLIT drops	245 (10.2)	3 (9.1)
SLIT tablets	10 (0.4)	0 (0.0)
Combinations	138 (5.8)	5 (15.2)
Kind of allergen, no. (%)		
Seasonal	1,190 (49.6)	15 (45.5)
Perennial	723 (30.2)	8 (24.2)
Combinations	485 (20.2)	10 (30.3)
AIT preparation, no. (%)		
Modified allergens (allergoids)	735 (30.7)	10 (30.3)
Native allergens	637 (26.6)	3 (9.1)
Combinations	443 (18.5)	10 (30.3)
Not classified	583 (24.3)	10 (30.3)
Duration, no. (%)		
<3 y	1,307 (54.5)	18 (54.5)
≥3 y	1,091 (45.5)	15 (45.5)

Regression analyses indicated that the risk of incident asthma was significantly less in patients with AR exposed to AIT compared with that in patients not exposed to AIT (RR, 0.60; 95% CI, 0.42-0.84; *P* = .003). The risk of asthma also significantly increased with decreasing age, with increasing intake of antihistamines as a proxy for the severity of AR and with increasing health care use caused by AR (Table IV).

Sensitivity analyses suggested significant preventive effects of SCIT (RR, 0.57; 95% CI, 0.38-0.84; *P* = .005) and AIT, including native allergens (RR, 0.22; 95% CI, 0.02-0.68; *P* = .009), whereas the effects of SLIT drops (RR, 0.43; 95% CI, 0.14-1.33) and combinations of SCIT and SLIT (RR, 1.22; 95% CI, 0.52-2.99) did not reach statistical significance (Table IV). AIT for 3 or more years tended to have stronger preventive effects than AIT for less than 3 years (RR, 0.62; 95% CI, 0.39-0.98 vs 0.57; 95%

TABLE IV. Results of multivariate regression analysis: RRs of asthma in patients with AR

Exposure variable (reference)	Multivariate analysis (adjusted for age, sex, health care use because of AR, and prescribed antihistamines)		
	RR	95% CI	P value
Male sex (female)	1.09	0.99-1.20	.07
Age (per y)	0.98	0.97-0.98	<10 ⁻¹⁷
Prescriptions of antihistamines (none)			
First quartile	2.85	2.43-3.34	<10 ⁻¹⁷
Second quartile	1.99	1.74-2.28	<10 ⁻¹⁷
Third quartile	2.21	1.92-2.55	<10 ⁻¹⁷
Fourth quartile	2.26	1.95-2.63	<10 ⁻¹⁷
Health care use because of AR (first quartile)			
Second quartile	1.31	1.12-1.54	.00088
Third quartile	1.77	1.53-2.04	<10 ⁻¹⁷
Fourth quartile	1.83	1.57-2.15	<10 ⁻¹⁷
Exposure to AIT in 2006 (not exposed)	0.60	0.42-0.84	.003
Route of administration of SIT (no AIT)			
SCIT	0.57	0.38-0.84	.005
SLIT drops	0.43	0.14-1.33	.14
Combinations	1.22	0.52-2.90	.65
Kind of allergen of AIT (no AIT)			
Seasonal	0.54	0.33-0.90	.02
Perennial	0.49	0.25-0.98	.04
Combinations	0.88	0.47-1.63	.68
Preparation of AIT (no AIT)			
Modified allergens (allergoids)	0.59	0.32-1.09	.09
Native allergens	0.22	0.02-0.68	.009
Combinations	0.90	0.48-1.66	.73
Not classified	0.73	0.39-1.35	.31
Duration of AIT (no AIT)			
<3 y	0.62	0.39-0.98	.04
≥3 y	0.57	0.34-0.94	.03

CI, 0.34-0.94). The only subgroup of patients exposed to AIT in which no preventive effect could be demonstrated was the group of patients receiving both SCIT and SLIT (Table IV). No evidence for effect modification by age and sex was observed (all *P* for interaction > .05).

DISCUSSION

Clinical efficacy of AIT products is usually evaluated in clinical trials as required for registration purposes.¹⁶ However, clinical trials are performed in select patient groups with strict inclusion and exclusion criteria and with medical procedures and monitoring that are frequently different from routine care. On the other hand, clinical effectiveness evaluates the effect of an intervention in routine care. Such real-life studies are necessary to investigate whether and to what extent trial evidence translates into realistic clinical settings.

Whereas clinical efficacy (ie, reduction of symptoms, medication use, or both) has been established for many AIT products, trial evidence that AIT prevents the manifestation of asthma in patients with AR is weak.¹² The assumption of the asthma-preventive effect of AIT is based on 2 studies, one of them the so-called Preventive Allergy Treatment (PAT) study.¹⁴ This study was performed with an SQ standardized SCIT product containing intact pollen allergens. It demonstrated a risk reduction for asthma development with an odds ratio of approximately

2.5 in favor of SCIT after 3 years of treatment with this specific product compared with symptomatic treatment.¹⁴ This effect was maintained after treatment's end for a further 7 years.²³ However, this study is prone to bias because it was performed in an unblinded fashion. A second smaller but also unblinded study was performed with SLIT drops.¹⁵ Both studies consistently indicated that AIT might have preventive effects on the onset of asthma. Currently, a large double-blind, placebo-controlled study including more than 800 children and investigating the asthma-preventive effect of AIT by using an SQ grass SLIT tablet containing an intact allergen is being performed.²⁴ First data from this study are expected by the end of 2015.

This large cohort study extends previous research by indicating that AIT prevents asthma in patients with AR in routine care. Our study confirms previous research from clinical trials indicating that AIT prevents the manifestation of asthma in patients with AR also in a real-life setting. AIT in general demonstrated an RR of 0.60, indicating a 40% risk reduction for patients with AR for the development of asthma. For SCIT and SLIT drops, this effect was even stronger, whereas statistical significance was reached only for SCIT, most likely because of the relatively low number of cases in the SLIT group. Because only 10 patients in the cohort were treated in 2006 with SLIT grass tablets, which had just been approved at this time, these patients were not included in the regression analysis, but none of these patients had asthma in the follow-up period from 2007-2012. Combinations of SLIT and SCIT were only done in a few cases in which no asthma prevention could be shown. A possible explanation could be that the allergic disease of patients who have an indication for multiple AITs might be too progressed to achieve the preventive effects of AIT, confirming the recommendations of the AIT guidelines to start AIT early in the course of disease.^{12,13} However, it is also possible that combination AIT is inherently less effective than single-allergen AIT.

Looking at the kind of allergy for both seasonal and perennial allergens, a significant reduction of asthma risk was shown for both groups. This reduction was numerically even more pronounced in the perennial allergen group. The strongest preventive effect was observed for AIT with native allergens, with a relative reduction of asthma risk of 78% compared with that seen in patients with AR not receiving AIT. The PAT study,²³ which was performed with a product containing native allergens, fits these findings quite well. Despite being prescribed more frequently compared with native allergens, allergoids showed a trend toward asthma prevention without statistical significance. Even if the original allergoid concept claims that it is possible to reduce B-cell reactivity while maintaining T-cell reactivity, this concept is still considered controversial. Several *in vitro* studies indicate that a decrease in B-cell reactivity is usually accompanied by a reduction in T-cell reactivity as well,^{25,26} a possible explanation of the lower preventive effect compared with native allergens.

Our data suggest that an AIT treatment duration of 3 years or more seems to have slightly better preventive effects on the development of asthma than AIT treatment for a shorter time. However, it cannot be ruled out that AIT provides temporary relief that is extended by extended use. Clinical data with respect to the optimal treatment duration are rare. First data for the long-term efficacy of AIT were published in 1999.²⁷ The PAT study showed an asthma-preventive effect after 3 years of treatment that was maintained for a further 7 years.^{14,23,28} In a long-term trial with an SQ grass SLIT tablet, a sustained effect

resulting in reduced symptom and medication scores compared with placebo has been demonstrated at 2 years of follow-up after a 3-year course of continuous AIT treatment.²⁹ Therefore the limited clinical data also support a treatment duration of 3 years or more.

Study strengths and limitations

This study has several limitations. A major limitation is that the administrative data set used does not contain information on allergen sensitization, which limits the interpretation of AR phenotype, AIT treatment, and the generalizability of the findings. Missing information on the exact spectrum of type 1 sensitizations also harbors a risk for residual misclassification, despite our efforts for internal case validation according to the guidelines for good practice secondary data analysis.²⁰ It is most likely that such misclassification would be differential and more prominent in the group of patients not receiving AIT and thus lead to an underestimation of the true preventive effectiveness of AIT. Patients with multiple sensitizations might be more likely to request AIT and be recommended to receive AIT than monosensitized patients. Such residual confounding would most likely bias the results in favor of the control group (ie, underestimate the true preventive effect of AIT).

Although we adjusted for antihistamine prescriptions and health care use because of AR as surrogate markers of AR severity, residual confounding by indication is a possible source of bias in our study; that is, the more severely affected patients with AR who are more likely to have asthma are also more likely to receive AIT. However, this bias would lead to an underestimation of the true preventive effectiveness of AIT and cannot explain the observed risk reduction in patients exposed to AIT. The database used does not include the exact time from AIT exposure to asthma onset, and therefore we did not perform time-to-event analyses. We defined asthma as documentation of ICD-10 code J45 at least twice plus at least 2 prescriptions of inhalant steroids to avoid misclassification bias.²⁰ This might have led to the inclusion of patients with mild intermittent asthma at baseline, and therefore we cannot exclude that AIT prevented progress from mild intermittent asthma to persistent asthma in a subgroup of patients. This also suggests that the results can be generalized to patients with AR without persistent asthma before AIT treatment.

It cannot be ruled out that higher antihistamine prescription is not only an indicator of more severe AR but also of better access to care by an allergy/respiratory care specialist and thus exposure to AIT. Access to care by an allergy/respiratory care specialist is also most likely related to greater likelihood that asthma is not undiagnosed/missed, resulting in an underestimation of the true preventive effectiveness of AIT. Compared with clinical studies, no symptom or medication scores were measured because these scores are not available in health care databases. This was also not the aim of this study.

In addition to these limitations, our study has several strengths. To our knowledge, this is the first study that used routine data based on data from the health care system to assess the preventive effectiveness of AIT in patients with AR. A major strength of our study is that it includes all patients with AR from the underlying cohort who used medical care. This allowed us to capture a comprehensive and complete picture of the course of AR and asthma in a large and relatively unselected population of more

than 100,000 patients with low risk of selection and recall bias. In addition, we adjusted for *a priori*-defined confounders, including age, sex, and health care use.

In another large cohort study including patients from all regions of Germany that was also based on data from the German health care system, approximately 7.3% and 2.5% of the total population were classified as having AR and asthma, respectively.³⁰ In our database we had approximately 9% with AR and approximately 2% classified as having asthma. Because of the similar data between these 2 cohort studies, we believe that our data from a more limited database are representative of even larger databases.

Implications for future research

Based on our data, the same analysis could be repeated with nationwide or even Europe-wide health care databases. This would also allow investigation of the asthma-preventive effect of AIT for single products; for this, our available database was too small. In addition, the analysis should be repeated approximately 5 years from now to obtain first data about the asthma-preventive effect of the new AIT tablets in routine use.

Implications for clinicians and health policymakers

AIT effectively prevents the progression of AR to asthma in a real-life setting. This asthma-preventive effect is strongest in products containing native allergens. By reducing the risk for asthma, significant health care costs can be saved. AIT should be initiated early in the allergic disease and be continued for at least 3 years.

We thank the Saxony Compulsory Health Insurance AOK PLUS for their cooperation in data use and technical support.

Clinical implications: In patients with AR, AIT should be considered to prevent asthma.

REFERENCES

1. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008;19:110-24.
2. Maziak W, Behrens T, Brasky TM, Duhme H, Rzehak P, Weiland SK, et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. *Allergy* 2003;58:572-9.
3. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med* 2015;372:456-63.
4. Yonekura S, Okamoto Y, Horiguchi S, Sakurai D, Chazono H, Hanazawa T, et al. Effects of aging on the natural history of seasonal allergic rhinitis in middle-aged subjects in South Chiba, Japan. *Int Arch Allergy Immunol* 2012;157:73-80.
5. Meltzer EO, Bukstein DA. The economic impact of allergic rhinitis and current guidelines for treatment. *Ann Allergy Asthma Immunol* 2011;106(suppl):S12-6.
6. Miraglia Del GM, Marseglia A, Leonardi S, La RM, Salpietro C, Brunese FP, et al. Allergic rhinitis and quality of life in children. *Int J Immunopathol Pharmacol* 2011;24(suppl):25-8.
7. Trikojat K, Buske-Kirschbaum A, Schmitt J, Plessow F. Altered performance in attention tasks in patients with seasonal allergic rhinitis: seasonal dependency and association with disease characteristics. *Psychol Med* 2015;45:1289-99.
8. Greiner AN, Hellings PW, Rotiroli G, Scadding GK. Allergic rhinitis. *Lancet* 2011;378:2112-22.
9. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. *BMC Pulm Med* 2013;13:70.
10. Croisant S. Epidemiology of asthma: prevalence and burden of disease. *Adv Exp Med Biol* 2014;795:17-29.
11. Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol* 2007;119:881-91.

12. Bousquet J, Schunemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, et al. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* 2012;130:1049-62.
13. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63(suppl 86):8-160.
14. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109:251-6.
15. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004;114:851-7.
16. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) and Efficacy Working Party (EWP): guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf. Accessed April 2015.
17. Schmitt J, Romanos M, Schmitt NM, Meurer M, Kirch W. Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. *JAMA* 2009;301:724-6.
18. Schmitt J, Romanos M, Pfennig A, Leopold K, Meurer M. Psychiatric comorbidity in adult eczema. *Br J Dermatol* 2009;161:878-83.
19. Schmitt J, Maywald U, Schmitt NM, Meurer M, Kirch W. Cardiovascular comorbidity in patients with chronic inflammatory skin diseases: a case-control study utilising a population-based administrative database. *Ital J Public Health* 2008;5:187-93.
20. [Good practice of secondary data analysis, first revision]. *Gesundheitswesen* 2008; 70:54-60.
21. Global Initiative for Asthma. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Available at: <http://www.ginasthma.org/>. Accessed April 2015.
22. Rosner B. *Fundamentals of Biostatistics*. 5th ed. Pacific Grove (CA): Duxbury; 2000.
23. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006;61:855-9.
24. Valovirta E, Berstad AK, de BJ, Bufer A, Eng P, Halken S, et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Ther* 2011; 33:1537-46.
25. Henmar H, Lund G, Lund L, Petersen A, Wurtzen PA. Allergenicity, immunogenicity and dose-relationship of three intact allergen vaccines and four allergoid vaccines for subcutaneous grass pollen immunotherapy. *Clin Exp Immunol* 2008;153:316-23.
26. Heydenreich B, Bellinghausen I, Lorenz S, Henmar H, Strand D, Wurtzen PA, et al. Reduced in vitro T-cell responses induced by glutaraldehyde-modified allergen extracts are caused mainly by retarded internalization of dendritic cells. *Immunology* 2012;136:208-17.
27. Durham SR, Walker SM, Varga EM, 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.
28. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943-8.
29. Durham SR, Emminger W, Kapp A, De Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-25.
30. Biermann J, Merk H, Wehrmann W. Allergic disorders of the respiratory tract—findings from a large patient sample in the German statutory health insurance system. *Allergo J* 2013;22:366-73.