

Care with allergen immunotherapy for allergic respiratory diseases in Germany—Predictors and deficits

Frederik Valbert¹  | Silke Neusser¹ | Oliver Pfaar²  | Ludger Klimek³ | Annette Sperl³ | Thomas Werfel⁴ | Eckard Hamelmann⁵ | Cordula Riederer⁶ | Stefanie Wobbe-Ribinski⁶ | Vivienne Hillerich¹ | Anja Neumann¹ | Jürgen Wasem¹ | Janine Biermann-Stallwitz¹

¹Institute for Healthcare Management and Research, University Duisburg-Essen, Essen, Germany

²Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

³Center for Rhinology and Allergology, Wiesbaden, Germany

⁴Clinic for Dermatology, Allergology and Venerology, Hannover Medical School, Hanover, Germany

⁵Department for Pediatrics, Children's Center Bethel, University Bielefeld, Bielefeld, Germany

⁶Department of Health Services Research, DAK-Gesundheit, Hamburg, Germany

Correspondence

Frederik Valbert, Institute for Healthcare Management and Research, University Duisburg-Essen, Essen, Germany.
Email: frederik.valbert@medman.uni-due.de

Funding information

Innovation Fund (Fund of the Federal Joint Committee, "Gemeinsamer Bundesausschuss", funding code: 01VSF17042)

Abstract

Background: Allergen immunotherapy (AIT) represents the only possibility of causal therapy for allergic respiratory diseases. Although the prevailing high prevalence of allergic diseases and restrictions in the daily lives of patients, AIT is offered to a sub-optimal number of patients in Germany.

Methods: Insured patients with documented allergic respiratory disease of one of the largest statutory health insurances in Germany, 'DAK-Gesundheit', were contacted by postal mail and asked to participate in the study. In case of written consent, primary and secondary data of patients were collected and analysed. Patient characteristics, predictors of being offered AIT, predictors of performing AIT and guideline-compliant care were analysed.

Results: 2505 subjects were included in the VerSITA study. Allergy to tree pollen and native speaking were identified as predictors, which increase the probability of being offered AIT. The probability was significantly decreased by the characteristics allergic rhinitis only, allergic asthma only, age in years, non-German citizenship, no graduation and lower secondary qualification. Significant positive predictors for an AIT to be actually performed were: Allergy to tree pollen and male sex. Predictors that decrease the likelihood that AIT is performed were: only allergic asthma, current smoker, former smoker, age and non-German citizenship. Furthermore, it was possible to identify characteristics in which guideline-compliant patients differed significantly from the rest of the study population.

Conclusions: Based on statutory health insurance data and patient survey data, the VerSITA study provides a broad and in-depth overview of the care situation with regard to AIT in Germany and identifies deficits.

KEYWORDS

epidemiology, rhinitis, immunotherapy and tolerance induction, regulatory aspects, prevention

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Clinical & Experimental Allergy* published by John Wiley & Sons Ltd.

1 | INTRODUCTION

As one of the most frequent chronic conditions allergic respiratory diseases such as allergic rhinitis and allergic asthma can interfere with all people regardless of age, gender or social class. The burden of these diseases is a relevant issue from a social and economic perspective.¹ The only possible causal therapy—apart from allergen avoidance, which is not possible in most cases, and the symptomatic treatment with drugs—is allergen immunotherapy (AIT).^{2–4} This therapy can be conducted as periodic subcutaneous injections (subcutaneous immunotherapy) or sublingual application (sublingual immunotherapy).^{5–7} The S2k-guideline of the German, Austrian and Swiss specialist societies for allergy indicates AIT for at least five-year-old patients with a diagnosed allergy, which cannot be avoided or adequately controlled by drugs.⁸ If conducted correctly AIT can reduce the severity of symptoms, the use of pharmaceuticals as well as potential consequences such as loss of productivity or the manifestation of bronchial asthma.^{8–11} However, to achieve these purposes the adherence of the patient is a crucial requirement.^{12,13} In addition, the availability of certified allergen extracts as well as the probability of a therapy success and efficacy are important aspects to be considered before starting an AIT.^{4,8} In case of premature discontinuation of therapy, the costs are not offset by adequate benefits.⁸ This underlines the clinical need to evaluate if AIT is offered to patients with allergic respiratory diseases when indicated under real life conditions. Currently, in Germany the documented rate of this type of therapy is estimated to be rather low, although it is known that the course of respiratory allergies can be positively influenced by choosing the right treatment.^{14,15} Detailed systematic analyses of AIT supply in Germany are rare so far.¹⁶

Therefore, this analysis aimed at a detailed and up to date examination of the care situation in term of allergic respiratory diseases with focus of AIT in Germany.

2 | METHODS

The study 'Analysis of the care situation with regard to the specific immunotherapy in cases of allergic respiratory diseases' (VerSITA) is conducted by the Institute for Healthcare Management and Research of the University Duisburg-Essen, the DAK-Gesundheit (DAK) and representatives of the German Allergy League (Deutsche AllergieLIGA).

An explanation of the selection of study participants (taking into account different sectors of care) and a description of the used questionnaire can be found in the corresponding Appendix S1. The standardized questionnaire was sent to a sample of 21,901 insured patients of the DAK. The survey started in May 2019 and ended in February 2020. Only responses with valid consent forms were taken into account. In addition, informed consent was obtained for the DAK to transmit routine data of the insured (secondary data) for analysis in pseudonymized form.

Key Messages

- Characteristics of people with allergic respiratory diseases in Germany could be described.
- Partly non-clinical factors were identified that significantly influence the probability of an AIT offer/performance.
- Certain social groups seem to be disadvantaged with regard to access to AIT.

The routine data transmitted concern the period 01/01/2014 to 06/30/2018 (routine data period). The data cover the following areas: patient characteristics, outpatient care, hospital stays, rehabilitation, drugs, sickness benefits, therapeutic appliances and medical devices.

Based on patient information in the survey (primary data), study participants were divided into three study groups according to their allergic respiratory disease: Patients with allergic rhinitis only, patients with allergic asthma only and patients with both allergic rhinitis and allergic asthma.

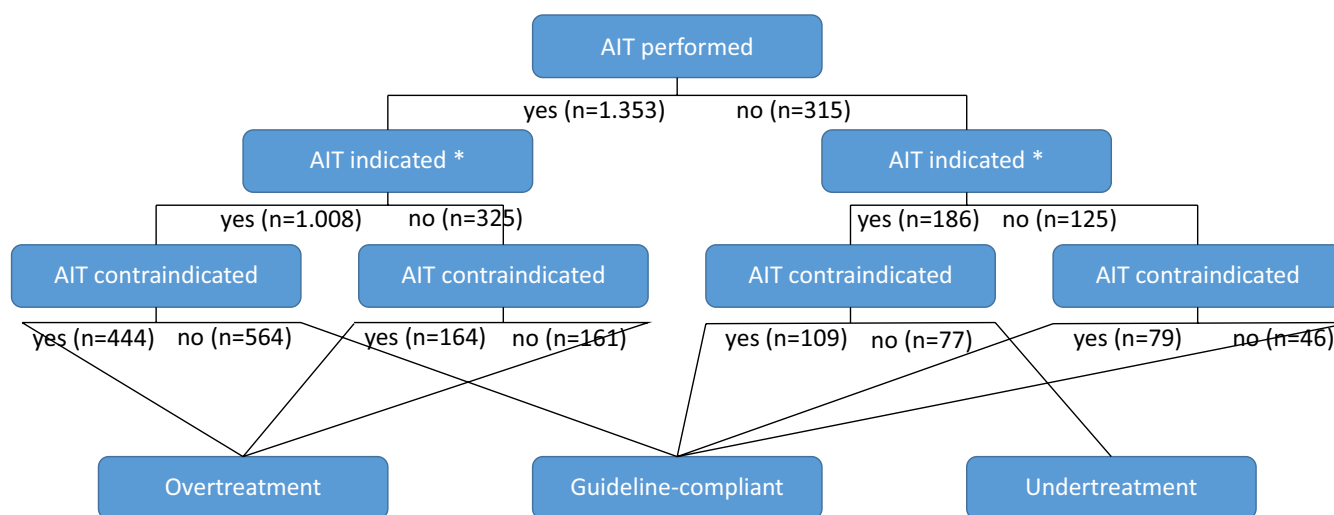
The aim of the analyses presented here was (I) to present the proportion and characteristics of patients with suspected undertreatment, overtreatment of AIT and guideline-compliant care with regard to AIT and (II) to identify predictors for the following situations: offer of AIT and performance of AIT.

In order to identify guideline-based treatment in the study population, indications and contraindications for AIT had to be operationalized. Basis for this was the German guideline valid at the time of the study.⁸ However, this was limited by data availability, so not every criteria of the guidelines could be operationalized (for example the available data do not allow determination of asthma control at the time of AIT). Table 1 shows the criteria, which were used to identify indication and contraindication regarding AIT. In part, the criteria are derived from routine data, in part from the patient survey. While the criteria for indication have to be fulfilled cumulatively for an indication for AIT, the fulfilment of a single contraindication is sufficient for AIT to be considered contraindicated in this study. The next step in the analysis of care was to identify patients who had never received AIT according to the patient survey. Validation was performed on the drug prescription information in the routine data (routine data period). If the patient did not show AIT offer to either data set, he was defined as potentially undertreated for the purposes of the study. The indications and contraindications described in Table 1 were hereafter used to identify those within this population who were undertreated in terms of AIT for the purposes of the study. All study participants for whom AIT was documented in the outpatient fee schedule positions (GOP) or in the drug prescription data in the routine data for routine data period are considered as potentially overtreated in this period. Potentially overtreated study participants for whom AIT was not indicated or for whom AIT was contraindicated are considered overtreated here. Study participants

TABLE 1 Operationalization of criteria for indication/contraindication to AIT in the VerSITA study

	Criteria	Data source
Indication (have to be fulfilled cumulatively)	Physician-diagnosed allergy to grass pollen or tree pollen or ragweed or mugwort pollen or house dust mites	Patient survey
	Moderate or poor success with allergen abstinence	Patient survey
	Age >5 years	Inclusion criterion
Contraindication (are also valid singularly)	Administration of immunosuppressants	Routine data—drug prescriptions (PZN codes)
	Administration of beta-blockers	Routine data—drug prescriptions (PZN codes)
	Diagnosis of tuberculosis	Routine data—diagnosis from outpatient care or hospital stays (ICD codes)
	Hepatic dysfunction	Routine data—diagnosis from outpatient care or hospital stays (ICD codes)
	Renal dysfunction	Routine data—diagnosis from outpatient care or hospital stays (ICD codes)
	Tumour disease	Routine data—diagnosis from outpatient care or hospital stays (ICD codes)
	Autoimmune disease/deficiency	Routine data—diagnosis from outpatient care or hospital stays (ICD codes)

Abbreviations: PZN, Pharmacy Central Number ('Pharma zentral nummer'; German pharmaceutical registration number); ICD, International Classification of Diseases.



*Smaller n than in the previous level due to non-replaceable missing values.

FIGURE 1 Categorization in overtreated, undertreated and Guideline-compliant care

who are potentially undertreated but for whom AIT is not indicated or contraindicated and study participants who are potentially overtreated but for whom AIT is indicated and not contraindicated are considered to have received guidelines-based care. For the purposes of the study, AIT is considered to be offered if the patient indicates in the primary data that he has already been recommended AIT by a physician at some point. It is considered to be performed in the time frame of the routine data if it is documented there in codes for medication or GOP. This procedure is summarized in Figure 1.

Statistical analyses were performed using IBM SPSS Statistics version 25. Depending on the scale level, differences are tested for significance using the Mann-Whitney U test or the chi-square test. Predictors were calculated using logistic regression models (a

detailed overview of the independent variables used in the regression models can also be found in the Appendix S1). A test for multicollinearity was performed using the Variance Inflation Factor (VIF) (threshold = 10). The threshold in all performed statistical analyses is a significance level of $p < .05$.

The study was registered in the German Clinical Trials Register (DRKS) (DRKS00017316) and an ethic approval has been obtained from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (19-8598-BO). VerSITA is financed exclusively by the Innovation Fund (Fund of the Federal Joint Committee, 'Gemeinsamer Bundesausschuss', funding code: 01VSF17042).

A more detailed description of the study protocol including a figure showing the principal flow of the study is published elsewhere.¹⁷

3 | RESULTS

2505 of the 21,901 insured patients contacted responded with analysable data and a valid consent form (in addition, there were 169 responses without valid informed consent and 189 responses with questionnaires that could not be analysed [for example, due to explicit statement that there was no allergic respiratory disease or questionnaires returned empty]). These 2505 patients corresponded to 11% of the patients contacted. All in all, this were 0.5% of all people who were insured by DAK and could fulfil the inclusion criteria. Table 2 shows characteristics of included patients like the average of 48.3 years (standard deviation [SD] = 20.6, minimum = 6 years, maximum = 89 years) and the 67.1% proportion of female patients. This population includes 2218 adults (age $\geq$ 18 years) and 287 minors (age < 18 years). 91.6% of the study participants held German citizenship. For comparison, 489,996 people were potentially eligible for the sample. Their average age was 47.5 years and the proportion of women/German citizens were 62.9%, respectively, 88.2%. Furthermore, it was shown in which variables the patients in the groups 'allergic rhinitis only', 'allergic asthma only' and 'allergic rhinitis and allergic asthma' differed significantly from the respective rest. In addition, further characteristics and an overview of the frequency of various allergens in the groups and the proportions of mono-, duo- and polyallergic patients are shown in Table 2. Most study participants were non-smokers (63.1%) and German native speaker (96.2%). 8.5% of study participants had a migration background. Most frequently reported highest school degree and highest completed professional training were higher education entrance qualification (37.3%), respectively, apprenticeship (36.9%). It can be seen that in all groups tree (66.3–82.9%) and grass pollen (66.7–80%) were the most common allergens and that in all of these groups study participants were very frequent polyallergic patients (48.1–75.6%).

AIT was coded in 54% of the 2505 individuals in the routine data period (as mentioned above, overall a AIT rate of 4.9% was estimated). Inversely, after validation of the primary data with routine data (28 cases were removed from this classification because primary data indicated they were never offered AIT, while secondary data documented that AIT was performed), only 13% of the study participants were never offered AIT. For the remaining study participants, there was either an AIT according to primary data, but this was outside the period covered by the routine data or an AIT was offered but not carried out or they were not evaluable in this regard.

According to the logistic regression model used to examine which factors could be identified as predictors of an allergy patient being offered AIT (number of cases [n] = 2125, Nagelkerkes-R-square = 15%) the following characteristics significantly favoured the likelihood of being offered AIT (Table 3): Allergy to tree pollen (regression coefficient [B] = 0.564) and native speaker (B = 0.824). The likelihood of being offered AIT was significantly lowered by the characteristics only allergic rhinitis (B = -0.397), only allergic asthma (B = -0.942), age in years (B = -0.019), non-German citizenship (B = -0.572), no graduation (B = -1.795) and lower secondary qualification (B = -0.425). So, elderly patients with a non-German

citizenship, not German as their native language, a low educational status and only allergic rhinitis or only allergic asthma that is not due to an allergy to tree pollen were especially unlikely to be offered AIT.

As it is shown in Table 4 significant positive predictors an AIT were performed in the second logistic regression model (n = 1442, Nagelkerkes-R-square = 19.4%) were: Allergy to tree pollen (B = 0.531) and sex: male (B = 0.381). Predictors that decreased the likelihood that AIT was performed were: only allergic asthma (B = -0.73), current smoker (B = -0.602), former smoker (B = -0.415), age in years (B = -0.038) and non-German citizenship (B = -0.582).

Characteristics of patients with undertreatment, overtreatment and guideline-compliant care can be seen in Table 5. In addition, data showed in which characteristics patients from one of these three groups differed from the rest of the entire study population. In this analysis (n = 1644), most patients were in the 'guideline-compliant care' group (n = 798), closely followed by the 'overtreated' group (n = 769). The 'undertreated' group was far behind in terms of the number of cases (n = 77). Undertreated patients were significantly younger than the mean from the rest of the study population, and they also had significantly lower mean external control beliefs and were significant more frequently allergic to mould. Patients in the group overtreated had significantly more often a German citizenship than the average of the remaining study population. Patients with guideline-compliant care had a significantly different distribution with respect to allergy group (allergic rhinitis only, allergic asthma only, allergic rhinitis + allergic asthma), their highest school degree and their professional training. In addition, patients in this group were significantly younger and less likely to be female. With regard to allergens, grass pollen and ragweed were mentioned more frequently here, 'other' allergens were mentioned less frequently.

4 | DISCUSSION

Data on the current care situation could be comprehensively collected and interpreted.

The findings regarding the likelihood of being offered an AIT can be explained well in causal terms. The fact that an allergy to tree pollen significantly increases the likelihood of being offered AIT is probably due to the fact that this is a very common and therefore well-known allergy.¹⁸ It is remarkable that an allergy to grass pollen is not also a significant predictor. A hypothetical explanation for this observation is that patients with grass pollen allergy in our analysis population on average react to substantially more allergens, thus had a higher degree of polysensitization, compared to patients without grass pollen allergy. This might result in a higher percentage of patients with poorly or uncontrolled asthma among the group of grass allergic patients explaining a smaller number of patients meeting the indication for AIT. The lower likelihood in rhinitis patients may result from the lower disease burden compared with the reference group (allergic rhinitis + allergic asthma). Nevertheless, it should be emphasized that allergic rhinitis alone may also be a valid reason for AIT. The stronger negative effect on the likelihood in the allergic

TABLE 2 Patient characteristics

	Number of cases (n = 2505)			
	Only allergic rhinitis	Only allergic asthma	Allergic rhinitis + allergic asthma	Overall
Number of cases	560	893	1052	2505
Age (years) (MV, SD)	46.6 (21.2)**	49.7 (21.7)**	48 (19.3)	48.3 (20.6)
Sex female (n, %)	356 (63.6)**	564 (63.2)**	761 (72.3)**	1681 (67.1)
German citizenship (n, %)	520 (92.9)	805 (90.1)**	970 (92.2)	2295 (91.6)
Highest school degree (n, %):		**	**	
No specification	6 (1.1)	23 (2.6)	21 (2)	50 (2)
Still in school education	57 (10.2)	90 (10.1)	90 (8.6)	237 (9.5)
No graduation	2 (0.4)	9 (1)	2 (0.2)	13 (0.5)
Lower secondary qualification	70 (12.5)	203 (22.7)	135 (12.8)	408 (16.3)
Upper secondary qualification	182 (32.5)	289 (32.4)	391 (37.2)	862 (34.4)
Higher education entrance qualification	243 (43.4)	279 (31.5)	413 (39.3)	935 (37.3)
Highest completed professional training (n, %):		**	**	
No specification	26 (4.6)	64 (7.2)	48 (4.6)	138 (5.5)
Still in training	35 (6.3)	57 (6.4)	51 (4.8)	143 (5.7)
None	47 (8.4)	88 (9.9)	58 (5.5)	193 (7.7)
Apprenticeship	195 (34.8)	334 (37.4)	396 (37.6)	925 (36.9)
Technical college	98 (17.5)	128 (14.3)	199 (18.9)	425 (17)
University of applied science	42 (7.5)	59 (6.6)	80 (7.6)	181 (7.2)
University	91 (16.3)	98 (11)	144 (13.7)	333 (13.3)
Other	26 (4.6)	65 (7.3)	76 (7.2)	167 (6.7)
Smoking status (n, %)				
No specification	1 (0.2)	12 (1.3)	11 (1)	24 (1)
Non-smoker	362 (64.6)	561 (62.8)	657 (62.5)	1580 (63.1)
Former smoker	145 (25.9)	245 (27.4)	289 (27.5)	679 (27.1)
Active smoker	52 (9.3)	75 (8.4)	95 (9)	222 (8.9)
Migration background (n, %)*	52 (9.4)	81 (9.3)	80 (7.7)	213 (8.5)
Native speaker (n, %)*	531 (95.8)	840 (96)	1003 (96.4)	2374 (96.2)
Allergy to (n, %)	^a	^b	^c	^d
Tree pollen	404 (75.4)	498 (66.3)	852 (82.9)	1754 (75.8)
Grass pollen	363 (67.7)	501 (66.7)	822 (80)	1686 (72.8)
Dust mites	237 (44.2)	451 (60.1)	647 (62.9)	1335 (57.7)
Animals (not dust mites)	160 (29.9)	315 (41.9)	546 (53.1)	1021 (44.1)
Mould	85 (15.9)	186 (24.8)	344 (33.5)	615 (26.6)
Mugwort pollen	109 (20.3)	130 (17.3)	332 (32.3)	571 (24.7)
Ragweed (ambrosia)	59 (11)	75 (10)	187 (18.2)	321 (13.9)
Other	84 (15.7)	147 (19.6)	280 (27.2)	511 (22.1)
Number of sensitizations:	^a	^b	^c	^d
Monoallergic	124 (23.1)	148 (19.7)	84 (8.2)	356 (15.4)
2 allergens	154 (28.7)	177 (23.6)	167 (16.2)	498 (21.5)
3 or more allergens	258 (48.1)	426 (56.7)	777 (75.6)	1461 (63.1)

Note: lower secondary = 'Haupt-/Volksschulabschluss'; upper secondary qualification = 'Realschulabschluss oder gleichwertig'; higher education entrance qualification = '(Fach-)Hochschulreife'; * In case of migration background, 44 study participants cannot be evaluated, in case of native speaker 36; for these variables % = valid %; ** Significant difference from the rest of the study population according to Mann-Whitney U test or chi-square test (significance level: 0.05).

^a24 cases with missing data, % = valid %.

^b142 cases with missing data, % = valid %.

^c24 cases with missing data, % = valid %.

^d190 cases with missing data, % = valid %.

TABLE 3 Predictors to get an AIT offer

	Regression coefficient B	Sig.	Exp(B)
Only allergic rhinitis	-0.397	0.007	0.672
Only allergic asthma	-0.942	0.000	0.390
Grass pollen	0.220	0.073	1.246
Tree pollen	0.564	0.000	1.758
Ragweed (ambrosia)	-0.220	0.237	0.802
Mugwort pollen	0.144	0.348	1.155
Mould	-0.215	0.116	0.807
Dust mites	0.065	0.587	1.067
Animals (not dust mites)	-0.041	0.736	0.960
Other allergens	-0.050	0.698	0.951
Current smoker	-0.331	0.076	0.718
Former smoker	-0.236	0.053	0.789
User of alternative medical procedures	-0.081	0.466	0.922
Age (years)	-0.019	0.000	0.981
Non-German citizenship	-0.572	0.005	0.564
Sex (male)	0.069	0.574	1.071
Insured status	0.122	0.591	1.130
Migration background	0.187	0.453	1.206
Native speaker	0.824	0.019	2.279
Still in school education	-0.299	0.378	0.742
No graduation	-1.795	0.049	0.166
Lower secondary qualification	-0.425	0.030	0.654
Upper secondary qualification	-0.235	0.140	0.791
Still in professional training	-0.039	0.903	0.962
No completed professional training	-0.014	0.959	0.986
Technical college	0.070	0.643	1.072
University of applied science	0.215	0.388	1.240
University	0.100	0.641	1.105
Other completed professional training	-0.014	0.948	0.986
High external control beliefs	0.004	0.974	1.004
High internal control beliefs	-0.115	0.297	0.892
Constant	1.499	0.001	4.478

Note: Nagelkerkes-R-square: 15%, number of cases in the regression model = 1215; Reference categories for categorical variables: allergic rhinitis + allergic asthma, never smoked, university entrance qualification, apprenticeship.

All coefficients with statistically significant influence are bold.

asthma only group is explained by the contraindicating character of uncontrolled asthma.⁸ The regression coefficient shows a clear graduation between no graduation and lower secondary qualification. Thus, no graduation has a stronger lowering effect than a lower

secondary qualification. Low educational status may correlate with lower awareness of the disease and a lack of knowledge about how to counter it. The likelihood of contraindicating diseases increases with age, so the lowering effect of age seems plausible here. The higher likelihood among native speakers corresponds to the lower likelihood among people with non-German citizenship. Possible explanations here may be language barriers, lack of knowledge about health care in Germany among people from other cultural backgrounds, and possibly discrimination. This partly coincides with findings of Razum et al. who reported reduced access to the German health care system for migrants, for example, due to communication problems.¹⁹ It is remarkable that a migration background (which can also be second-generation) does not have a significant influence as an independent variable in this model. Probably, some of the above-mentioned problems no longer have any effect at all, or at least a weaker effect, on people who have lived in Germany for a long time (or even lived there since birth).

The contraindicating nature of uncontrolled asthma (according to the guideline valid at the time of the study) is also evident in the regression model for predictors that AIT will be performed. Also the effects of an allergy to tree pollen, a higher age and a citizenship other than German work in the same direction as described above and with the same presumed causality. In view of the regression in Table 3, the significant effects among active and former smokers in Table 4 are not explained by the fact that they may be offered AIT less frequently. Rather, the willingness to perform AIT appears to be lower among smokers, possibly due to less health-oriented behaviour. This is consistent with the observation that the coefficient lowers the likelihood more for current smokers than for former smokers. The significant influence of sex in this model may result from clinical differences between male and female participants. For example, the proportion of individuals with allergic asthma (exclusively or comorbidly) in this study population is significantly higher in female study participants than in male study participants.

While several studies have already addressed compliance barriers to AIT, a focus on barriers to offering AIT is rare. One barrier mentioned several times internationally are difficulties in reimbursement/financing of AIT.^{20,21} This can be a discouragement to physicians, as well as patients. Due to different health care systems, this point is barely transferable between countries. Reports on other physician-side barriers cannot be compared with the presented results, as the focus here was on patients. On the patient side, lack of awareness has already been identified as a barrier to AIT.²¹ This corresponds to the effect of a low education status observed in the presented regression (Table 3).

When analysing with regard to the care situation, the composition of the study population must be taken into account. Primarily due to the selection process described in the Appendix S1, the study population has a high AIT rate, which is higher than that which can be assumed for the German health care situation (compared to the rate in the potential study population). Thus, considerably more study participants show potential to detect an overtreatment than an undertreatment. Thus, the number of cases in each category does

TABLE 4 Predictors that AIT is performed

	Regression coefficient B	Sig.	Exp(B)
Only allergic rhinitis	-0.037	0.860	0.964
Only allergic asthma	-0.730	0.000	0.482
Grass pollen	0.196	0.257	1.216
Tree pollen	0.531	0.003	1.701
Ragweed (ambrosia)	-0.472	0.062	0.624
Mugwort pollen	0.278	0.203	1.321
Mould	-0.367	0.053	0.693
Dust mites	-0.056	0.742	0.946
Animals (not dust mites)	0.116	0.499	1.123
Other allergens	-0.182	0.317	0.834
Current smoker	-0.602	0.017	0.548
Former smoker	-0.415	0.014	0.660
User of alternative medical procedures	-0.233	0.136	0.792
Age (years)	-0.038	0.000	0.962
Non-German citizenship	-0.582	0.037	0.559
Sex (male)	0.381	0.034	1.464
Insured status	0.093	0.769	1.098
Migration background	-0.098	0.779	0.907
Native speaker	0.091	0.852	1.096
Still in school education	0.090	0.865	1.095
No graduation	-0.547	0.545	0.579
Lower secondary qualification	-0.257	0.360	0.773
Upper secondary qualification	-0.289	0.203	0.749
Still in professional training	-0.358	0.459	0.699
No completed professional training	-0.641	0.086	0.527
Technical college	0.052	0.805	1.053
University of applied science	0.128	0.722	1.136
University	-0.157	0.600	0.855
Other completed professional training	0.157	0.622	1.170
High external control beliefs	0.020	0.899	1.020
High internal control beliefs	-0.148	0.340	0.862
constant	3.707	0.000	40.712

Note: Nagelkerkes-R-square: 19.4%, number of cases in the regression model = 1442; Reference categories for categorical variables: allergic rhinitis + allergic asthma, never smoked, university entrance qualification, apprenticeship.

All coefficients with statistically significant influence are bold.

not show high external validity. The characteristics of the study participants in the various groups, on the other hand, appear to be generalizable.

The identification of contraindicating diseases is subject to the following limitation: Since an exact end of illness cannot be derived

from routine data, even the single occurrence of the events described above was defined as contraindicating. This is simplifying, but due to the often long or persistent duration of the disease and the actual AIT prescription behaviour, it fits well to the real care situation.

The definition of 'undertreatment' and 'overtreatment' should be viewed with the caveat that the treating physician may be aware of (for example) contraindicating information that is not detectable in the data collected, but may also be influenced by factors like efficacy and availability of AIT commercial products.²² The standardized evaluation of a large amount of data makes corresponding individual case decisions impossible.

That undertreated patients are significantly younger may be explained by the fact that a shorter previous life provides fewer opportunities for AIT (combined with less opportunities due to only infrequent physician contacts). In addition, young people are less likely to have contraindicating comorbidities. In this group, the diagnosis of allergy to moulds is also significantly more frequent. A plausible cause could be that the allergic reaction to moulds is considered difficult to treat in clinical practice. It fits with the results of the previous regressions in which non-German citizenship significantly reduces the chance of being offered/performing AIT, that overtreated patients are significantly more frequently of German citizenship. The significantly lower age in the guideline-compliant treated group probably results from the lower likelihood of comorbidities in the group, which reduces the risk of therapy despite contraindication. As described above, female study participants are more likely to have asthma. This could explain why their proportion is significantly lower in the guideline-compliant treated group. More common allergens (especially grass pollen, but also ragweed) are significantly more frequent here, while non-specific 'other' allergens are rare. Thus, allergies to common allergens are more likely to be treated according to guidelines than uncommon ones.

Especially when explaining the effects of asthma, it should be noted that the study was conducted with the guideline valid at the time of VerSITA study.⁸ In the currently planned update, AIT will also be increasingly recommended for asthmatics. In the current asthma-guideline for Germany (09/2020) AIT is recommended in allergic patients with controlled asthma when indicated and efficacy has been demonstrated in the clinical documentation.¹⁰

Other limitations are inherent in the data themselves. For example, routine data have the risk of being susceptible to miscoding and do not include data on people who have no contact with the health care system despite being ill, while primary data are for example possibly subject to recall bias. However, by using primary and secondary data, the data sets could be used to validate each other. For example, study participants were only grouped to be undertreated if no AIT (offer) was documented in both their primary and routine data. Thus, cumulatively, a more valid database could be generated than in studies which only use one of the two sources of data. Due to the selection process described in the Appendix S1 the data set used also has the specificity of a high AIT rate, which prevents generalizability of some results. This has already been discussed at the

TABLE 5 Characteristics of patients with undertreatment, overtreatment and guideline-compliant care

	Cases in the analysis <i>n</i> = 1644		
	Non-guideline-compliant care		Guideline-compliant care
	Undertreatment	Overtreatment	
Number of cases (<i>n</i>)	77	769	798
Group membership (<i>n</i>)			*
Only allergic rhinitis	18	176	191
Only allergic asthma	33	255	251
Allergic rhinitis + allergic asthma	26	338	356
Age (years) (MV, SD)	42.9 (17.7)*	47.5 (19.4)	42.1 (21.7)*
Sex female (<i>n</i> , %)	58 (75.3)	526 (68.4)	513 (64.3)*
German citizenship (<i>n</i> , %)	73 (94.8)	720 (93.6)*	720 (90.2)
Highest school degree (<i>n</i> , %)			*
No specification	1 (1.3)	16 (2.1)	15 (1.9)
Still in school education	6 (7.8)	71 (9.2)	124 (15.5)
No graduation	1 (1.3)	4 (0.5)	7 (0.9)
Lower secondary qualification	10 (13)	107 (13.9)	106 (13.3)
Upper secondary qualification	34 (44.2)	266 (34.6)	236 (29.6)
Higher education entrance qualification	25 (32.5)	305 (39.7)	310 (38.8)
Highest completed professional training (<i>n</i> , %)			*
No specification	4 (5.2)	36 (4.7)	60 (7.5)
Still in training	4 (5.2)	46 (6.0)	69 (8.6)
None	8 (10.4)	56 (7.3)	89 (11.2)
Apprenticeship	30 (39)	266 (34.6)	259 (32.5)
Technical college	15 (19.5)	150 (19.5)	98 (12.3)
University of applied science	3 (3.9)	55 (7.2)	53 (6.6)
University	9 (11.7)	107 (13.9)	119 (14.9)
Other	4 (5.2)	53 (6.9)	51 (6.4)
External control beliefs (MV, SD)	41.6 (22.9) ^{a,*}	44.2 (19.5) ^b	42.5 (18.5) ^c
Internal control beliefs (MV, SD)	75 (11.8) ^a	70.7 (13) ^d	71.1(12.2) ^e
Allergy to (multiple choice possible) (<i>n</i> , %)		^f	^g
Tree pollen	59 (76.6)	573 (74.5)	589 (73.8)
Grass pollen	54 (70.1)	545 (70.9)	592 (74.2)*
Dust mites	48 (62.3)	422 (54.9)	464 (58.1)
Animals (not dust mites)	40 (51.9)	328 (42.7)	341 (42.7)
Mould	30 (39)*	191 (24.8)	208 (26.1)
Mugwort pollen	22 (28.6)	179 (23.3)	186 (23.3)
Other	21 (27.3)	167 (21.7)	142 (17.8)*
Ragweed (ambrosia)	13 (16.9)	95 (12.4)	125 (15.7)*

Note: *Significant difference from the rest of the whole study population (significance level: .05).

^a*n* = 73 (due to non-evaluable scores).

^b*n* = 741 (due to non-evaluable scores).

^c*n* = 773 (due to non-evaluable scores).

^d*n* = 749 (due to non-evaluable scores).

^e*n* = 778 (due to non-evaluable scores).

^f*n* = 754 (due to missing data).

^g*n* = 775 (due to missing data).

points concerned. Even though the use of samples is common in scientific studies, a limitation is inherent in this. It cannot be ruled out that certain subgroups are not represented or underrepresented in the sample (especially due to the selection process). Since no valid statements can be made about the representativeness of this sample, the external validity of the findings is limited. Also, the extent of the used routine data is limited. For example, no statements can be made about the specialty of physicians who provided AIT.

In some cases, for example contraindicating comorbidities may not be recorded, as individual study participants had missing time in the routine data. However, this effect is estimated to be minor because missed times are infrequent and the contraindicating illnesses are likely to recur in routine data over a longer period of time. So if a chance to capture it is missed, it will probably be identified on another chance.

The VerSITA study provides a comprehensive overview of the care situation of people in Germany with allergic respiratory diseases under 'real life' conditions. It becomes apparent that certain groups are underprivileged in the health care system with regard to optimal care of their allergic respiratory disease. This should be counteracted with respect to the equity of care, for example, with multilingual documents that serve to inform patients or through training, especially in the field of primary care physicians. In addition, the study provides a detailed characterization of patients with allergic respiratory diseases in Germany. Further analyses on patient reported outcomes such as health-related quality of life, symptom severity and health economics will follow in a series of reports of VerSITA.

AUTHOR CONTRIBUTIONS

Frederik Valbert, Silke Neusser, Oliver Pfaar, Ludger Klimek, Annette Sperl, Thomas Werfel, Eckard Hamelmann, Cordula Riederer, Stefanie Wobbe-Ribinski, Vivienne Hillerich, Anja Neumann, Jürgen Wasem and Janine Biermann-Stallwitz: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Drafting the work or revising it critically for important intellectual content, Final approval of the version to be published, Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Dr. Klimek reports grants and personal fees from Allergopharma, grants and personal fees from MEDA/Mylan, personal fees from HAL Allergie, grants from ALK Abelló, grants and personal fees from LETI Pharma, grants from Stallergenes, grants from Quintiles, grants and personal fees from Sanofi, grants from ASIT biotech, grants from Lofarma, personal fees from Allergy Therapeut., grants from AstraZeneca, grants from GSK, grants from Immunotk, personal fees from Cassella med, outside the submitted work; and Membership: AeDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV, GPA, EAACI.

Dr. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from GlaxoSmithKline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from ROXALL Medizin, personal fees from Novartis, personal fees from Sanofi-Aventis and Sanofi-Genzyme, personal fees from Med Update Europe GmbH, personal fees from streamedup! GmbH, grants from Pohl-Boskamp, grants from Immunotek S.L., personal fees from John Wiley and Sons, AS, personal fees from Paul-Martini-Stiftung (PMS), personal fees from Ingress-Health HWM, personal fees from Regeneron Pharmaceuticals Inc., outside the submitted work.

The remaining authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

For reasons of privacy and contractual obligations, the data analysed here cannot be made publicly available.

ETHICAL APPROVAL

The study was registered in the German Clinical Trials Register (DRKS) (DRKS00017316) and an ethic approval has been obtained from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (19-8598-BO). VerSITA is financed exclusively by the Innovation Fund (Fund of the Federal Joint Committee, 'Gemeinsamer Bundesausschuss', funding code: 01VSF17042).

ORCID

Frederik Valbert  <https://orcid.org/0000-0003-0061-5841>

Oliver Pfaar  <https://orcid.org/0000-0003-4374-9639>

REFERENCES

1. Bousquet J, Khaltaev N, Cruz 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(86):8-160. doi:10.1111/j.1398-9995.2007.01620.x
2. Muraro A, Robert G, Halken S, et al. EAACI guidelines on allergen immunotherapy: executive statement. *Allergy*. 2018;73(4):739-743. doi:10.1111/all.13420
3. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136:556-568
4. Pfaar O, Angier E, Muraro A, Halken S, Roberts G. Algorithms in allergen immunotherapy in allergic rhinoconjunctivitis. *Allergy*. 2020;75(9):2411-2414. doi:10.1111/all.14270
5. Klimek L, Brehler R, Hamelmann E, et al. Evolution of subcutaneous allergen immunotherapy (part 1): from first developments to

- mechanism-driven therapy concepts. *Allergo J Int*. 2019;28(3):78-95. doi:10.1007/s40629-019-0092-4
6. Klimek L, Brehler R, Hamelmann E, et al. Development of subcutaneous allergen immunotherapy (part 2): preventive aspects and innovations. *Allergo J Int*. 2019;28(4):107-119. doi:10.1007/s40629-019-0097-z
 7. Roberts G, Pfaar O, Akdis CA, et al. EAACI guidelines on Allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy*. 2017;73(4):765-779. doi:10.1111/all.13317
 8. Pfaar O, Bachert C, Buffe A, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases. *Allergo J Int*. 2014;23:282-319. doi:10.1007/s40629-014-0032-2
 9. Bachert C, Borchard U, Wedi B, et al. Leitlinie der DGAI zur allergischen Rhinokonjunktivitis. *Allergo J*. 2003;12:182-194.
 10. Schulz M, Martin E, Dalhoff K, et al. Nationale Versorgungsleitlinie Asthma. 4. Auflage. AWMF online. doi:10.6101/AZQ/000469
 11. Romano M, James S, Farrington E, et al. The impact of perennial allergic rhinitis with/without allergic asthma on sleep, work and activity level. *Allergy Asthma Clin Immunol*. 2019;15(81):1-10. doi:10.1186/s13223-019-0391-9
 12. Distler A, Pappelendam D. 13-year overview of serious adverse drug reactions following subcutaneous specific immunotherapy with a chemically modified allergen preparation. *Allergo J Int*. 2015;24(8):294-302. doi:10.1007/s40629-015-0084-y
 13. Rabe U, Altengarten J, Benke E, et al. Long-term efficacy of specific subcutaneous, short-term MPL adjuvant immunotherapy over three treatment and three follow-up years, as measured by quality of life. *Allergo J Int*. 2017;26(5):147-154. doi:10.1007/s40629-017-0029-8
 14. Biermann J, Merk H, Wehrmann W, et al. Allergic disorders of the respiratory tract—findings from a large patient sample in the German statutory health insurancesystem. *Allergo J*. 2013;22:366-373. doi:10.1007/s15007-013-0350-6
 15. Weschenfelder A-K, Wasem J, Biermann J. Versorgung von Patienten mit allergischer Rhinitis – eine Analyse von Routinedaten einer gesetzlichen Krankenversicherung. *Allergologie*. 2015;38(5):252-259. doi:10.5414/ALX01749
 16. Weschenfelder A-K, Klimek L, Mülleneisen N, et al. Course of respiratory allergy by treatment strategy based on German routine data. *Allergo J Int*. 2017;26(6):195-203. doi:10.1007/s40629-017-0027-x
 17. Valbert F, Neusser S, Riederer C, et al. Health care situation in patients with allergic respiratory diseases with special focus on specific immunotherapy. *Allergo J Int*. 2021;30(1):39-45. doi:10.1007/s40629-020-00149-z
 18. Haftenberger M, Laußmann D, Ellert U, et al. Prävalenz von Sensibilisierungen gegen Inhalations- und Nahrungsmittelallergene. *Bundesgesundheitsblatt*. 2013;56:687-697. doi:10.1007/s00103-012-1658-1
 19. Razum O, Geiger I, Zeeb H, et al. Gesundheitsversorgung von Migranten. *Deutsches Ärzteblatt*. 2004;101(43):A2882-A2887.
 20. Ryan D, Gerth van Wijk R, Angier E, et al. Challenges in the implementation of the EAACI AIT guidelines: a situational analysis of current provision of allergen immunotherapy. *Allergy*. 2017;73(4):827-836. doi:10.1111/ALL.13264
 21. Hellings PW, Pugin B, Mariën G, et al. Stepwise approach towards adoption of allergen immunotherapy for allergic rhinitis and asthma patients in daily practice in Belgium: a BelSACI-Abeforcal-EUFOREA statement. *Clin Transl Allergy*. 2019;9(1):1-7. doi:10.1186/s13601-019-0243-1
 22. Brehler R, Klimek L, Vogelberg C, Werfel T, Pfaar O, Hamelmann E. Evidence vs. efficacy in allergen-specific immunotherapy: considerations using the example of tradable products in Germany. *Allergo J Int*. 2016;25(2):38-43. doi:10.1007/s40629-016-0096-2

SUPPORTING INFORMATION

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

How to cite this article: Valbert F, Neusser S, Pfaar O, et al. Care with allergen immunotherapy for allergic respiratory diseases in Germany—Predictors and deficits. *Clin Exp Allergy*. 2022;52:1422-1431. doi: [10.1111/cea.14172](https://doi.org/10.1111/cea.14172)