

Medical care and treatment of allergic rhinitis: a population-based cohort study based on routine healthcare utilization data

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Abstract

Background: Health services research on medical care and treatment of allergic rhinitis (AR) is scarce.

Objectives: To investigate the prevalence, incidence, comorbidities, and treatment of AR in a realistic setting.

Methods: A cohort of 1 811 094 German National Health Insurance beneficiaries in 2005 was followed until 2011. To avoid misclassification, the ICD-10 code for AR (J30) had to be documented at least twice to classify patients as having AR. Descriptive statistics and logistic regression models were used to describe the burden, comorbidities, and treatment of AR.

Results: A total of 111 394 patients (6.2%) had prevalent AR in 2005/2006. In another 60 145 individuals (3.3%), AR was newly diagnosed in 2007 to 2011 (incident cases). Patients with prevalent AR were three times more likely to develop asthma compared to patients without AR (age and sex-adjusted risk ratio (RR) 3.04; 95% confidence interval (95%CI) 2.98–3.10). Newly diagnosed recurrent depressive disorder (RR 1.61; 95%CI 1.55–1.68), anxiety disorder (RR 1.52; 95%CI 1.48–1.56), and ADHD (RR 1.21; 95%CI 1.13–1.29) were also related to prevalent AR. Approximately 20% of children and 36% of adults with AR were exclusively treated by general practitioners. Allergy immunotherapy (AIT) was prescribed for 16.4% of patients with AR. Subcutaneous immunotherapy was most frequently used (80% of AIT).

Conclusions: This study highlights the significant burden of AR. Despite the established benefits of AIT to treat AR and prevent asthma, this study suggests significant undertreatment. Future research is necessary to develop and implement adequate measures to increase guideline adherence.

Epidemiological studies suggest that approximately 10 to 20% of school-age children and adolescents suffer from allergic rhinitis (AR) with wide regional variations in disease occurrence and a general increase in disease prevalence over time (1–3). AR is associated with a substantial impairment of quality of life and loss of productivity for the affected patients (4, 5). Medical care for patients with AR in Germany is provided by general practitioners and allergy specialists from various disciplines such as otolaryngologists (ENT), dermatologists, pediatricians, or pneumologists. Studies on the prevalence and burden of AR in adults are scarce, as well

as studies from the field of health services research that are needed to document healthcare utilization, medical care by the different disciplines involved, and the provision and effectiveness of treatments for AR in realistic clinical settings.

It is well established that AR is associated with other atopic conditions, that is, asthma and atopic dermatitis (6). Following the model of the atopic march, children with AR are more likely to develop asthma (7, 8). Importantly, AR is also a major risk factor for the development of asthma (9). In addition to allergic symptoms and comorbidities, a recently published biopsychological investigation also indicated that

AR may induce cognitive impairments like reduced information processing speed and attention control following allergen exposure (10). Patients with atopy in general are also more likely to suffer from mental disorders than individuals, who are not affected from an atopic disease (11, 12). Concerning mental health comorbidities, however, most research focused in atopic dermatitis or asthma or atopy in general, and specific investigations on AR are still limited (13–16). Most comorbidity studies also focused on children and/or relied on selected clinical cohorts. Population-based comorbidity studies from multidisciplinary settings are missing.

In contrast to the vast majority of chronic disorders, a causal treatment option is available for AR. As recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, allergy immunotherapy (AIT) is indicated for patients with persistent AR and for patients with intermittent AR and moderate-to-severe symptoms (17–19). AIT may effectively induce long-term remission of AR and asthma, and may also prevent new sensitizations (17, 20). A recently published cohort study indicated that AIT also prevents incident asthma in patients with AR in a routine care setting (21).

Routine data on healthcare utilization are a valuable and powerful resource for health services research. This study aims to describe and analyze the epidemiology, healthcare utilization, and medical care of AR in a realistic setting based on comprehensive information of a large cohort of patients followed for 7 years.

Specific objectives of this study were to describe the prevalence and incidence of AR, atopic and mental health comorbidities, treatment, and medical care of patients with AR with a specific focus on AIT. We hypothesized that AR is associated with a high healthcare utilization burden characterized by high prevalence and significant atopic and mental health comorbidities. Analyses on AIT use were exploratory.

Methods

Study design and data source

We conducted a cohort study including all German National Health Insurance beneficiaries insured by the AOK PLUS (Saxony) from January 1st, 2005 until December 31st, 2011 or death, whatever occurred first.

The AOK Saxony database (22–24) is an anonymized population-based administrative healthcare database with comprehensive information on outpatient health care including demographic characteristics (age (years), sex, 3 digits of zip code) of patients, diagnoses (according to the International Statistical Classification of Diseases-10 (ICD-10)), treatments (prescribed and filled in prescriptions; classification of treatments according to Anatomical Therapeutic Chemical Classification code (ATC code)), information on procedures of medical consultations, and medical specialty of treating physicians.

The study base represents approximately 55% of the population from the federal state of Saxony, Germany (25, 26). In terms of age and sex distribution, the study base is highly representative for the federal state of Saxony and also for the

German general population. The database only holds anonymized information. The identification of specific individuals by the research team was impossible. All individuals who included in the study base that were insured from January 1st, 2005 until death or December 31st, 2011 at the AOK PLUS were included in the study. The study was performed in accordance with the declaration of Helsinki and all other relevant legal and regulatory requirements.

Study collectives and identification of patients with AR

To minimize misclassification bias with consecutive overestimation of disease prevalence and incidence, 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 measure of internal case validation is in accordance with the guidelines for 'good practice secondary data analysis' (27).

To describe and analyze the prevalence, incidence, comorbidities, and treatments of AR, the following four study collectives were defined:

- Cohort of all individuals insured with the AOK PLUS Saxony from January 1st, 2005 until death or December 31st, 2011 (total cohort).
- Cohort of patients with *prevalent AR in 2005/2006*: All individuals from the overall cohort, who have been diagnosed as having AR (ICD-10 Code J30) at least twice during the period of 2005 to 2011 and at least once within 2005 or 2006 (with the last documentation of the diagnoses not being a diagnosis of exclusion).
- Cohort of patients with *incident AR in 2007–2011*: All individuals from the overall cohort, who have not been diagnosed as having AR (ICD-10 Code J30) in 2005/2006 and have been diagnosed as having AR (ICD-10 Code J30) at least twice during the period of 2007–2011 (with the last documentation of the diagnoses not being a diagnosis of exclusion).
- *Control cohort* of individuals without prevalent or incident AR according to the criteria defined above.

Comorbidities of AR

Incident and prevalent atopic and mental health comorbidities of AR were assessed applying the same methods for the definition of prevalent and incident cases as described above. Patients were considered as affected from comorbid disease if the corresponding ICD-10 code for asthma (J45), atopic dermatitis (L20), attention-deficit/hyperactivity disorder (ADHD) (F90), depressive episode (F32), recurrent depressive disorder (F33), and/or anxiety disorder (F40-F41) has been coded at least twice within the relevant time period (27).

Classification of AIT therapy

Detailed information on prescribed AIT was used to classify patients with AR as exposed and unexposed to AIT. If patients filled in an AIT prescription, they were considered as treated for ≤ 1 year. With each filled in prescription for the

same AIT as the initial prescription, the estimated treatment duration was prolonged for 1 year. For the majority of type I allergens, both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) treatments are available. Additionally, SLIT with tablets for grass pollen allergy has been available since 2006, so that SLIT was further stratified into SLIT drops and SLIT tablets. Further stratifications of AIT were done to differentiate between AIT targeted at seasonal vs perennial allergen(s) and AIT preparation (i.e. native allergens vs allergoids (modified allergens)).

Statistical methods

The overall cohort served as the basis to describe the frequency of the documentation of the diagnosis AR in general, the prevalence, and the incidence of AR (total and stratified by age and sex).

The cohorts of patients with prevalent AR and of patients with incident AR have served as the basis for the analyses of healthcare epidemiology, healthcare provision, and medical treatment. Special attention was paid to the treatment of an AR with allergy immunotherapy, by analyzing single drugs and their characteristics (dosage, combination of allergens, modifiers, mode of application) and the duration of treatment. The frequency and risk of comorbidities have been compared between patients with prevalent AR vs the control cohort of patients without AR. Atopic diseases (allergic asthma, atopic dermatitis) as well as mental disorders (depression, ADHD, anxiety disorder) were considered for these analyses using generalized linear models adjusted for age (years) and sex to estimate risk ratios (RR) and corresponding 95% confidence intervals (95%CI). All analyses were carried out using STATA (StataCorp LP, College Station, Texas, USA).

Results

The overall cohort consists of 1 811 094 individuals, with a mean age of 45.3 years (± 23.5) and 54.1% ($n = 979 171$)

being female. In total, 14.3% of the study population ($n = 258 047$) were younger than 20 years, and 347 147 individuals (20.7%) were between age 20 and 39 years. A total of 508 982 (28.1%) and 669 891 (37.0%) individuals from the study population were between 40 and 59 years and ≥ 60 years, respectively. In total, 2 102 302 outpatient visits due to AR were documented in the cohort, representing approximately 2% of all outpatient visits (due to any reason) during the evaluation period. The number of visits per year remained rather stable in the evaluation period from 2005 until 2011.

Prevalence and incidence of allergic rhinitis—healthcare utilization burden

A total of 111 394 patients met the prespecified criteria for prevalent AR in 2005/2006 resulting in an overall 2-year prevalence of 6.2%. The prevalence was slightly higher in females (6.6%; $n = 64 212$) than in males (5.7%; $n = 47 182$). Among children younger than 6 years, the AR prevalence was 5.9% in girls and 8.5% in boys. In children age 6 to 12 years, 11.5% of the girls and 15.8% of the boys were classified as having prevalent AR. Prevalence of AR peaked in adolescents age 13 to 18 years (females 13.6%, males 14.3%). Among young adults age 19 to 24 years, 9.9% of the women and 7.8% of the men utilized health care due to AR. In adults, AR prevalence generally decreased with age, but remained considerably high even in elderly patients >75 years with still 2.2% of the population ($n = 5334$) being affected. Figure 1 summarizes the prevalence of AR in different age strata and by sex. Healthcare utilization prevalence of AR was higher in males during childhood and adolescence. In contrast, female adults more frequently utilized health care due to AR compared to males.

Figure 2 shows the incidence of AR by sex in different age strata. A total of 60.145 patients (3.3%) without documentation of AR in 2005/2006 utilized healthcare services due to AR in 2007 to 2011. Incidence of AR decreased with age. Among children 5 years or younger, 11.4% of the boys and

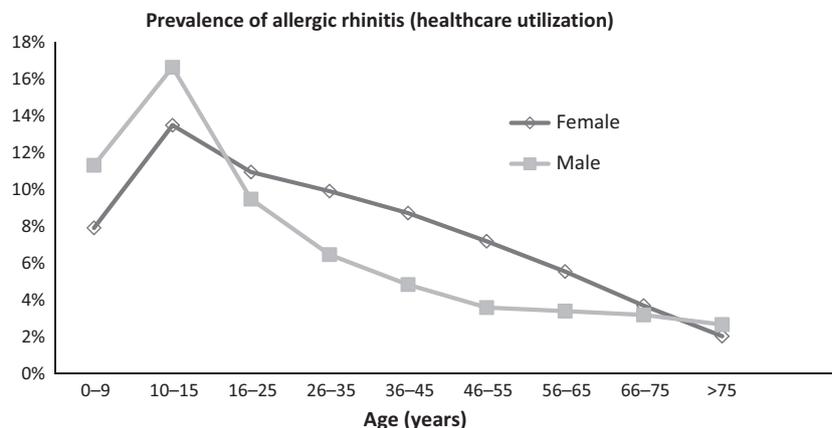


Figure 1 Prevalence of AR by age and sex (healthcare utilization).

8.7% of the girls were classified as incident cases of AR. Incidence among children age 6 to 12 years was 7.7% in girls and 8.1% in boys. In adolescents (age 13 to 18 years), 6.4% of the females and 4.9% of the males were classified as incident cases of AR. Further information on the incidence of AR in adults is summarized in Fig. 2.

Both incidence and prevalence indicate a high burden of AR for patients of all age groups, that is, a high proportion of individuals seeking care due to AR. The sum of both cohorts (incident and prevalent AR cases) may be interpreted as the 7-year period prevalence. In total, 171 539 patients (9.5%) sought medical care at least twice within the observation period.

Atopic and mental health comorbidities

Patients with prevalent AR frequently suffered from other atopic diseases. In 30.6% and 19.7% of patients with AR, comorbid asthma and atopic dermatitis were documented, respectively. Compared to patients without AR, patients with AR were about 8-times and 4 times as likely to have asthma and atopic dermatitis, respectively.

Mental health problems such as ADHD, depressive episode, recurrent depressive disorder, and anxiety disorder were also much more prevalent among patients with AR compared to individuals without prevalent AR ($P < 0.001$ for all comparisons) (Fig. 3). ADHD was related to AR particularly among children. Among children below age 6 years at baseline, 17.4% of children with AR compared to 12.7% of children without AR utilized health care due to ADHD (RR 1.37; 95%CI 1.31–1.41). In the age group 6 to 12 years, ADHD prevalence was 15.0% vs 11.8% among children with AR vs without AR (RR 1.27; 95%CI 1.21–1.32). In adolescents age 13 to 18 years at baseline, 3.1% of patients with AR compared to 2.3% of individuals without AR were classified as having ADHD (RR 1.38; 95%CI 1.26–1.50).

These cross-sectional analyses document substantial allergic and mental health comorbidities of AR, but do not allow conclusions about temporal relationships. We therefore also compared the risk for incident comorbidities in 2007 to 2011 dependent of AR prevalence in 2005/2006. Adjusting for age and sex, patients with prevalent AR were at significantly increased risk for incident asthma (RR 3.04; 95%CI 2.98–3.10) and atopic dermatitis (RR 1.65; 95%CI 1.60–1.70), as

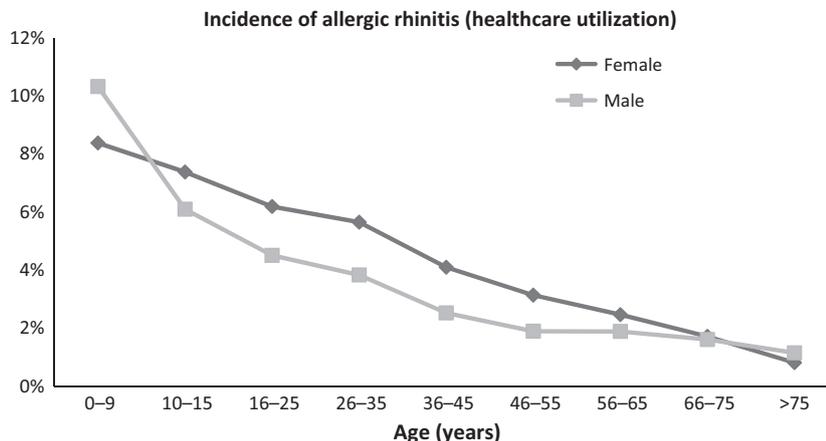


Figure 2 Incidence of AR by age and sex (healthcare utilization).

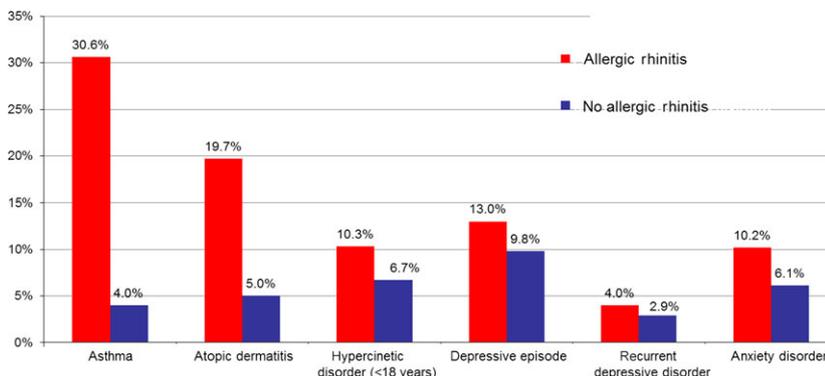


Figure 3 Comorbidities of patients with prevalent AR vs patients without AR (2005–2011; $n = 111\ 394$).

well as for all mental health comorbidities investigated: Newly diagnosed recurrent depressive disorder (RR 1.61; 95%CI 1.55–1.68), anxiety disorder (RR 1.52; 95%CI 1.48–1.56), and ADHD (RR 1.21; 95%CI 1.13–1.29) were significantly related to prevalent AR ($P < 0.001$ for all comparisons) (Table 1).

Medical disciplines providing care for patients with AR

Over the 7-year period, the majority of children and adults with prevalent or incident AR ($n = 171\ 539$) were treated for AR by physicians from more than one medical specialty. (Figs 4 and 5) ENT physicians were involved in AR treatment of 20.7% and 31.7% of pediatric and adult patients

Table 1 Results of the multivariate regression analyses on the risk of atopic and mental health problems in patients with prevalent AR vs patients without AR

Incident comorbidity in 2007–2011 (ICD-10 code)	Multivariate analysis (adjusted for age in years and sex): Risk ratio (RR) of outcome in patients with prevalent AR vs patients without AR		
	Risk Ratio	(95%CI)	<i>P</i> -value
Asthma (J45)	3.04	2.98–3.10	<0.001
Atopic dermatitis (L20)	1.65	1.60–1.70	<0.001
ADHD (F90)	1.21	1.13–1.29	<0.001
Depressive episode (F32)	1.40	1.37–1.43	<0.001
Recurrent depressive disorder (F33)	1.61	1.55–1.68	<0.001
Anxiety disorder (F40-F41)	1.52	1.48–1.56	<0.001

with AR, respectively. Dermatologists were involved in AR care in about 9% of affected children/adolescents and in about 16% of affected adults, respectively. Approximately 20% of children and 36% of adults with AR were exclusively treated by general practitioners.

Treatment of AR with antihistamines

From the cohort of patients with prevalent AR ($n = 111\ 394$), 5.3% ($n = 5854$) were prescribed sedative antihistamines. Nonsedative antihistamines were prescribed for 36.0% of patients with prevalent AR at least once. Because antihistamines are over-the-counter medications in Germany, these numbers have to be interpreted with caution. The majority of patients receiving a prescription for sedative antihistamines ($n = 47\ 353$; 2.8% of all individuals without AR) and nonsedative antihistamines ($n = 87\ 526$; 5.2% of all individuals without AR) were not classified as having AR.

Treatment of AR with AIT

A total of 20 202 patients with prevalent and 8007 patients with incident AR were treated with AIT at least once within the observation period. This corresponds to a proportion of patients with prevalent and incident AR treated with AIT of 18.1% and 13.3%, respectively. From all 171 539 patients with prevalent or incident AR, 16.4% filled in at least one prescription for AIT ($n = 28\ 209$) between 2005 and 2011. Table 2 summarizes the kind of AIT prescribed in these 28 209 patients with AR. With more than 80%, SCIT was the most frequently used kind of AIT to treat AR. AIT only targeting perennial and only targeting seasonal allergens were administered in 45.0% ($n = 12\ 699$) and 38.8% ($n = 10\ 954$) of all AR patients with AIT prescription. A total of 4556 patients (16.2%) received both AIT for perennial and AIT

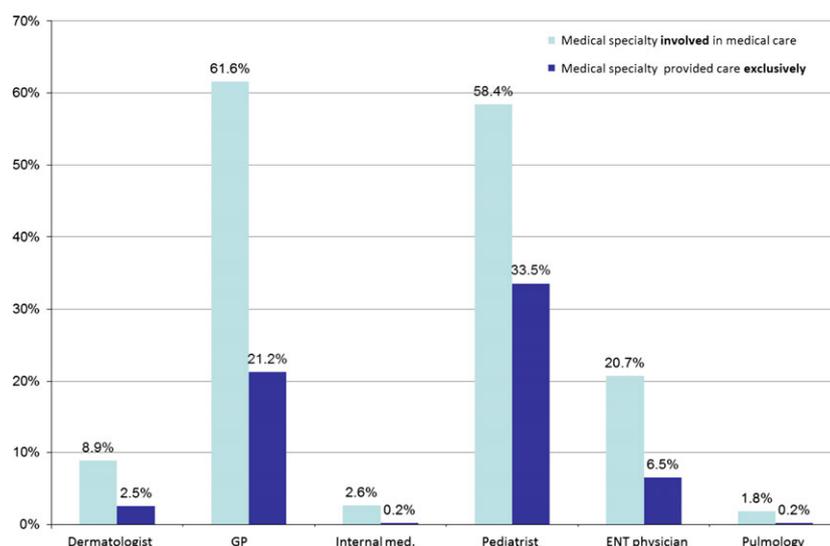


Figure 4 Treatments for AR per medical specialty in children and adolescents (2005–2011).

for seasonal allergens. Only AIT-containing allergoids were utilized in 38.7% of patients treated with AIT ($n = 10\,913$), while only intact allergens were used in 23.6% of AIT-treated patients ($n = 6670$). Both AIT-containing allergoids and AIT-containing intact allergens were used in 18.3% ($n = 5159$) patients. In the remaining cases ($n = 5567$; 19.4%), AIT could not be classified in this regard. Duration of AIT treatment is shown in Table 3. A total of 3.33% of the patients received AIT for 3 years or longer, whereas 67% of patients received AIT for less than 3 years. Gender differences in the duration of AIT treatment were not observed.

Discussion

This cohort study describes the healthcare utilization burden, healthcare provision, and medical treatment of AR in routine care, as well as comorbidities of allergic rhinitis in a large population-based sample. The utilization of routine data from German statutory health insurance allowed us to efficiently extend previous health services research on AR. Our study indicates that AR constitutes a very high medical burden: Approximately 2% of all outpatient healthcare contacts within the medical system are related to allergic rhinitis.

Our study has important strengths: Firstly, it is based on a high, relatively unselected proportion of individuals from the general population in Saxony, Germany. Although individuals with very high income are underrepresented in the German statutory healthcare system, we assume high generalizability of our results. In another cohort study based on administrative data that included patients from all regions of Germany, approximately 7.3% of the total population were classified as having prevalent AR within a 2-year observation period (28).

Table 2 Kind of AIT used to treat patients with AR ($n = 28\,209$)

Kind of AIT	Patients treated (n)	Proportion of patients treated (%)
SCIT	22 704	80.48%
SLIT (drops)	3127	11.09%
SLIT (tablet)	844	2.99%
SCIT + SLIT (classic)	999	3.54%
SCIT + SLIT (tablet)	342	1.21%
SLIT (classic) + SLIT (tablet)	144	0.51%
SCIT + SLIT (classic) + SLIT (tablet)	49	0.17%
Total	28 209	100.00

In our cohort, the 2-year prevalence of AR was 6.2%. These similar findings suggest that our findings are representative at least for the German healthcare system. We adhered to established methods of internal case validation of administrative healthcare data as recommended by the guidelines for good practice secondary data analysis (27). The prevalence rates estimated in our cohort are similar to the ones from primary epidemiological studies (1–3) so that we assume that the case validation methods were adequate and our results valid. However, despite these efforts, we cannot rule out the possibility for false-positive or false-negative classification of AR status in individual patients from the cohort investigated. There may also be individuals with AR who do not consult a physician. When interpreting our results, it therefore has to be considered that—in contrast to epidemiological studies which aim to estimate disease occurrence in a population—our health services research study investigated treatment utilization due to AR as a proxy for disease burden. A potential limitation also arises from the use of ICD-10 codes for case

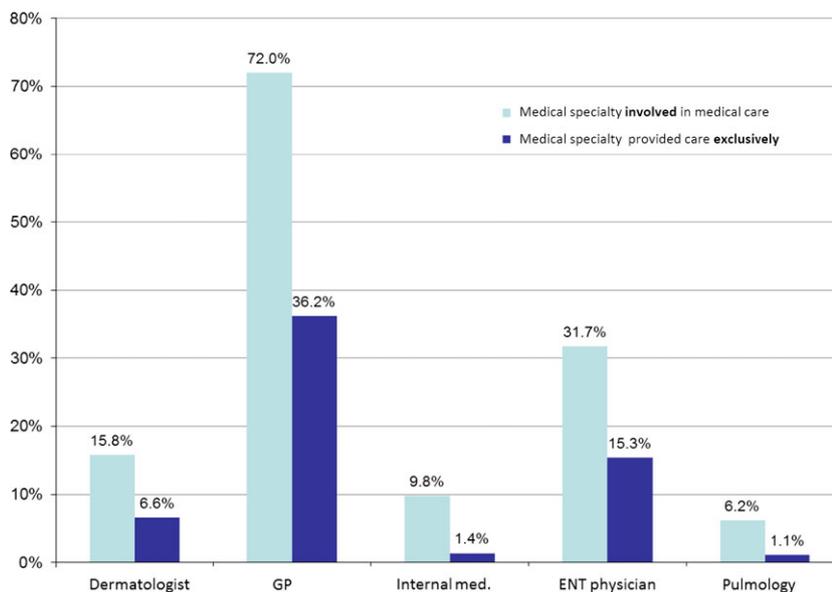


Figure 5 Treatments for AR per medical specialty in adults (2005–2011).

Table 3 Duration of AIT treatment in 28 209 patients with AR

Duration (years)*	Female patients (n; %)	Male patients (n; %)	Total (n; %)
1 year	6603; 43.63%	5303; 40.56%	11 906; 42.21%
2 years	3626; 23.96%	3247; 24.83%	6873; 24.36%
3 years	3083; 20.37%	2795; 21.38%	5878; 20.84%
≥4 years	1821; 12.03%	1731; 13.24%	3552; 12.59%
Total	15 133; 100%	13 076; 100%	28 209; 100%

*Consecutive years with at least one AIT prescription.

definition. ICD-10 codes are not specific for allergic diseases, that is, patients with vasomotor rhinitis may have been misclassified as AR cases and patients with asthma and AR may have only received the ICD-10 code J45 and may thus have been misclassified as not having AR. However, potential bias introduced by misclassification of AR would lead to an underestimation of the true risk ratio for comorbidities and cannot explain the observed increased risk of patients with AR for mental health comorbidities.

With a 7-year period prevalence of 9.5%, AR is among the most prevalent conditions inducing the utilization of outpatient medical care at all. Prevalence and incidence peak in childhood and adolescence. In adults, the 2-year prevalence declines from 10% in young adults to approximately 3% in the elderly. Interestingly, males sought medical care more frequently due to AR in childhood and adolescents, whereas females tended to utilize the healthcare system more often due to AR in adults. Our study indicates that the majority of patient with AR is treated by general practitioners, while approximately 30% of patients receive treatment from ENT specialists. A high proportion of patients with AR are not treated by a specialist, even if the disease is chronic. This indicates that not only medical disciplines specialized to treat patients with allergies need to be approached to improve medical care by guidelines, but that general practitioners also need to be better educated and informed on treatment options. Furthermore, general physicians also need to be included in intervention studies and clinical registries, in order to gain insights on treatment pathways and outcomes in routine care.

Previous studies indicated that AIT as a causal treatment option may effectively induce long-term remission of AR and asthma, and may also prevent the onset of new sensitizations (17, 20). The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines therefore recommend initiating AIT for patients with persistent AR and for patients with intermittent AR and moderate-to-severe symptoms for at least 3 years (17, 18). An important finding of our study is the significant undertreatment of AR patients with AIT in routine care. Only 18% or patients with prevalent AR in 2005/2006 received AIT treatment within the 7-year observation period. For patients with incident AR, the corresponding proportion of patients with AIT therapy was only 13%. These low numbers are possibly even an overestimation, because we cannot exclude that some of these patients did not receive AIT for AR, but for potential comorbid asthma or hymenoptera

venom allergy. In our cohort, AIT was not only initiated in a small proportion of patients, but was also discontinued within the first year in a substantial proportion of those patients receiving AIT. The reasons for the observed AIT undertreatment and low guideline adherence remain speculative, but challenge further qualitative and quantitative health services research in this field.

A previous investigation of the same cohort of patients with AR clearly indicates that AIT effectively prevents the development of asthma in patients with AR (21). Patients with AR exposed to AIT had a 40% decreased risk for incident asthma compared to patients with AR in whom AIT was not initiated. The preventive effects were strongest and significant for SCIT and AIT including native allergens, whereas chemically modified allergens (allergoids) showed a trend toward asthma prevention failing to reach statistical significance. AIT is generally more effective when provided for ≥3 years than AIT for less than 3 years (21). In light of these findings, the current undertreatment of AIT has an adverse impact on the overall morbidity of patients with AR and leads to increased healthcare cost and patient burden. Reasons for this undertreatment with AIT have been discussed controversially; inadequate remuneration of treating allergy patients may be a main reason in Germany. In addition, in light of the asthma preventive effect of AIT and its potential to save healthcare costs by preventing the onset of asthma, a main task for the medical community should be the development of measures that are able to increase patients' adherence to AIT (19).

Our study also clearly indicates that AR is associated with a high burden of disease not only due to its high healthcare utilization prevalence, but also due to atopic and mental health comorbidities of affected patients. Patients with AR more frequently suffer from comorbid depression, anxiety disorder, and ADHD. These comorbidities are clinically relevant as they lead to increased healthcare utilization as an indicator for patient bother. Although our study is not suitable to investigate causal relationship, the cohort analysis clearly indicates that patients with AR are at significantly increased risk to develop incident mental disease. Regression analyses were adjusted for age and sex, but other potential confounders such as socioeconomic status, life events, or behavioral factors could not be considered based on the data source used. A recently published biopsychological study (10) indicated that this relationship might be causal by showing significant impairments in information processing and

changes in attentional control adjustments in patients with seasonal AR when exposed to individually relevant allergens, that is, during the allergy season.

Our findings related to the broad spectrum of mental health comorbidities are very important from a public health perspective, as mental health problems constitute a major economic burden to our healthcare system and society. Further exploratory analyses based on large patient cohorts are needed to fully understand the spectrum of clinically relevant comorbidities of AR. Additionally, future health services research needs to further explore this association and investigate whether adequate treatment of AR may decrease the risk of comorbidities compared to the current status quo. A main public health task is to improve the treatment situation with AIT of patients with AR in routine care.

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Conflicts of interest

JS received funding for investigator-initiated research from Novartis, ALK-Abelló, MSD, Pfizer, Abbott; ES none; DK none; EW is besides the affiliation to Dresden university employee of ALK-Abelló and holds stock.

Author contributions

J Schmitt, E Stadler, D Küster, and E Wüstenberg designed and performed the study concept; J Schmitt involved in the acquisition of data; J Schmitt, E Stadler, D Küster, and E Wüstenberg involved in analysis and interpretation of data; J Schmitt and D Küster drafted the manuscript; E Stadler and E Wüstenberg carried out critical revision of the manuscript for important intellectual content; E Stadler and J Schmitt carried out statistical analysis; J Schmitt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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