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Healthcare costs associated with allergic rhinitis, asthma and allergy immunotherapy

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Key words

Allergic rhinitis; allergy treatment; asthma treatment; cost analysis; immunotherapy.

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Summary

Allergic rhinitis (AR) and asthma are chronic diseases in which the airways become inflamed in response to allergens. Allergy immunotherapy (AIT) is recommended for those unable to manage symptoms using pharmacotherapy. This study estimated healthcare costs and utilisation for patients with AR and asthma. Mean annual outpatient visits, pharmaceutical costs and inpatient hospitalisations were calculated for 2010 and 2014, with pharmaceutical and inpatient costs stratified by AIT use. AR and asthma patients had a 35% higher mean number of physician visits and up to 90% higher mean pharmaceutical costs compared to controls. The cost of pharmaceuticals and inpatient hospitalisations were 54% lower in those prescribed AIT. Further research is recommended to understand the reasons for these cost differences.

List of abbreviations

ADHD – Attention deficit hyperactivity disorder.
AIT - Allergy immunotherapy.
AR – Allergic rhinitis.
ENT – Ear nose and throat.
ICD - International Classification of Diseases.
NPP – Named patient product.
OTC – Over the counter.
TAO - Therapy Allergen Ordinance.

Introduction

Allergic rhinitis (AR) affects 17 to 26% of the population in Europe, with prevalence expected to rise (1). Although symptoms such as blocked and itchy nasal passages, frequent sneezing, and inflamed eyes, are sometimes seen as trivial, evidence indicates that they have a detrimental impact on quality of life and work productivity (2,3). Moreover, accumulating evidence indicates that asthma, with more 'serious' symptoms including restricted airways (4), can develop as a consequence of AR. As one of the strongest independent risk factors for asthma development (5), evidence has shown that AR increases the risk of adult-onset asthma 3-fold (6). Researchers have hypothesised that AR and asthma are different expressions of the same disease, with chronic inflammation of a 'united airway', occurring in the upper airway in AR, and in the lower airway in asthma (7). Indeed, more than 80% of asthma patients have comorbid AR, while 20 to 60% of AR patients have comorbid asthma (5).

Both AR and asthma present cost burdens to the healthcare sectors, with costs for both usually incurred through a combination of pharmaceutical treatments and outpatient visits to assess disease management. In addition, asthma may also require inpatient hospitalisation for serious asthma exacerbations. Recommended first-line treatments such as anti-histamines and nasal steroids in AR, and inhaled steroids in asthma, aim only to alleviate the symptoms of the diseases, rather than treating the underlying immune response. Depending on the pattern of exposure and allergen sensitivity, an individual may require daily

treatment during particular seasons, or all year round, and once developed remission is rare, meaning both diseases commonly require lifelong treatment (4,8).

Over 90% of individuals with seasonal AR use symptom-relieving pharmacotherapy, with the majority using more than one form of medication, most commonly to evoke a more effective nasal response (9). Even so, dissatisfaction with symptom management is commonly reported (9), and evidence has shown that the resource use and costs associated with treating those sensitive to perennial allergens is higher than for seasonal AR, due to increased requirements for pharmaceuticals (10,11).

Despite the relatively low costs of the available symptom-relieving pharmacotherapy, the high prevalence and chronic nature of AR corresponds to a high economic burden of disease at the population level. For example, in Europe, a Swedish questionnaire study analysed the direct and indirect costs related to self-reported AR in a random population of residents between the ages of 18-65 (12). The study found that pharmacological treatment (most commonly oral antihistamines, nasal steroids and nasal sprays), along with health care consultations for AR cost €210 per individual annually, while productivity loss due to absenteeism and presenteeism at work cost €751 per individual annually. In total, this gave an average cost per year for an individual with AR of €961. Costs also varied depending on the severity of AR, with the cost of those suffering from moderate to severe persistent AR being four times higher than those with mild persistent disease (€1757 per year and €464 per year respectively). Due to the prevalence of AR being reported at 24% in the survey, it was estimated that the total cost of AR in Sweden is €1.3 billion euros (12).

Further studies have also assessed costs of AR in the US, for instance, a 2001 review of cost-of-illness studies for AR showed direct costs (those associated directly with disease management) in the US estimated to be between $1.2 billion in a study conducted in 1990, to $4.5 billion in a 1997 study. Overall costs of treating allergic rhinitis in 2005 were estimated at $11.2 billion, nearly double the $6.1 billion spent in 2000 (in 2005 dollars); more than half was spent on prescription medications (13). On top of these costs, indirect costs associated in particular with lost productivity at work have been estimated to be between $86 million and $7.7 billion (14). Asthma is more expensive still, with a more recent study estimating a total annual cost of $82 billion in the USA in 2013, of which $50 billion were medical costs and a further $32 billion costs were due to productivity losses resulting from missed work and school days and asthma-related mortality (15). Per person annual medical costs were estimated at $3,266; 56% incurred for pharmaceuticals, 25% for hospitalisations and emergency room admissions, and 19% for outpatient assessments in primary and secondary care. Moreover, another study demonstrated how in asthmatic children who had been hospitalised, co-morbid AR increased the hazard of asthma-related readmissions by 1.72 times, and predicted significantly more days in hospital (16).

Allergy immunotherapy (AIT) is a treatment option that is recommended for patients with moderate-to-severe persistent AR who are unable to manage their disease using symptom-relieving pharmacotherapy (17). AIT can be administered both subcutaneously (via injection) as well as sublingually (in both tablet and drop formulations). Uniquely, AIT aims to desensitise the immune response to trigger allergens. Not only has evidence shown AIT to effectively reduce AR symptoms, but when administered in childhood, it can reduce the risk of experiencing asthma symptoms and using asthma medication 5 years after initiation of a 3-year AIT treatment programme (i.e. 2 years after treatment completion) (18). In addition to health benefits, treatment of the underlying disease is likely to reduce resource use, a perspective supported by a Cochrane systematic review published in 2010, which reported that subcutaneous AIT effectively reduced not only symptoms, but also medication use (19). One study demonstrated that among children, pharmacy, outpatient and inpatient costs and resource use were significantly reduced for AR patients compared with pre-AIT levels (20).

It is generally accepted worldwide that AIT can reduce the long term economic burden of allergic disease, particularly following the first six years following the start of treatment (21). However, certain regulatory issues have come into fruition with regards to immunotherapy in the last ten years (21). It is now necessary, as a medicinal product, for this kind of treatment to obtain a marketing authorization in Europe by proving its safety, efficacy and quality (22). This has led to withdrawals of many Named Patient Products (NPPs), including allergen immunotherapy. For instance, in Germany more than 6400 NPPs have been removed from the market due to these regulations (known as Therapy Allergen Ordinance or TAO) (23).

To illustrate the actual economic impact born by health insurance payers, this project aimed to show the resource use and costs associated with allergic rhinitis, asthma and immunotherapy treatment in adults and children, but without considering causality links such as comorbidities and socioeconomic status.

Methods and materials

Data source

An anonymised dataset of all German National Health Insurance beneficiaries insured by the AOK PLUS healthcare fund in Saxony between January 1st 2005 and December 31st 2014 was accessed at the Centre for Evidence-based Healthcare, TU Dresden. The database was used previously for several analyses in the field of allergy and other disease areas (24,25). This dataset included, for each patient: demographic characteristics, ICD-10 (International Classification of Diseases – 10) diagno-

ses, prescription data (ATC-code, volume, price, pack size and defined daily doses), outpatient physicians assessments and inpatient hospitalisation costs (diagnoses, DRG-codes and any other broad costs covered by the hospital budget). Data for inpatient hospitalisations were only available from 2008 onwards.

Population

The total cohort comprised all individuals insured consecutively with AOK PLUS Saxony between 2005 and 2014, or until death if death occurred within this time period. ICD-10 codes for AR (ICD-10 J30) and asthma (ICD-10 J45) were used to identify six subgroups:
1. prevalent AR;
2. prevalent asthma;
3. prevalent AR and asthma;
4. controls - no AR;
5. controls - no asthma;
6. controls - no AR or asthma.

Prevalent groups were defined, in accordance with good practice guidelines (26) as including all cases where ICD codes (J30 for AR; J45 for asthma) were recorded at least twice in four consecutive quarters between 2005 and 2006. For prevalent asthma, cases were only categorised as prevalent if they had also filled two prescriptions of inhaled corticosteroids in the same time period, alongside the ICD reference. Control cohorts were defined as all individuals from the overall cohort who were not diagnosed with the relevant ICD codes (and, for asthma, had not filled two prescriptions of inhaled corticosteroids) twice in any four consecutive quarters across the full observation period of 2005 to 2014.
AR and asthma cohorts are not mutually exclusive, thus individual patients may be included in more than one cohort.

Analysis methods

Analyses were completed using Stata V13.1. Sample characteristics were calculated for the total cohort and each subgroup. Frequency statistics for annual outpatient healthcare visits to all physicians, ear nose and throat (ENT) specialists, and pulmonologists were calculated (total and stratified by age group in 2005; <12 years, 12 to 17 years, 18 to 50 years, 50 years and over).
Mean (standard deviation) annual direct costs were calculated for pharmaceutical and inpatient hospitalisations (total and stratified by subgroup and age group). For each prevalent group, costs were further stratified into those patients who had filled at least one prescription for AIT, and those who had not filled any prescriptions for AIT. These statistics are reported for 2014, the most recent year available, as well as for 2010 to give an indication of the consistency of the findings.

Sensitivity analyses (see Supplementary Material) were performed where appropriate to exclude outlying data (top 1%) that may have skewed the pattern of results.

Results

Population

The total cohort included a total of 1,739,440 individuals (54% female), with a mean age of 49 years (SD= 24; see **table I** for full sample characteristics of the study population). The sample comprised approximately 7% children (younger than 12 years), 5% adolescents (12 to 17 years), 37% younger adults (18 to 50 years) and 52% older adults (older than 50 years). Approximately 4% of the overall cohort (n = 74,642) were defined as having prevalent AR, approximately 2% (n = 34,362) were defined as having prevalent asthma, and approximately 0.6% (n = 9,832) were defined as having co-morbid prevalent AR and asthma. Of the prevalent subgroups, 23% (n = 17,289) of those with prevalent AR, 10% (n = 3,460) of those with prevalent asthma, and 25% (n = 2,488) of those with prevalent AR + asthma had filled at least one prescription for AI.

Outpatient care utilisation

Across both years, and all age groups and physician types, patients in prevalent AR and/or asthma subgroups had, on average, 5.1 (35%) more outpatient physician contacts than their respective control subgroups. Physician contacts were an average of 19% higher in the prevalent subgroups with asthma (17% higher for prevalent AR + asthma; 22% higher for prevalent asthma) than in the prevalent AR subgroup. All Mean (SD) outpatient physician contacts in prevalent and control subgroups for the whole cohort and stratified by physician type and age group are presented in **table II**.

Healthcare costs

Comparing prevalent and control subgroups

Mean costs for pharmaceuticals and inpatient hospitalisations are presented for each subgroup in **table III**. Patients in the prevalent asthma subgroup incurred the highest healthcare costs, averaging around €2500 per year per patient. For the prevalent asthma subgroup, both pharmaceutical and inpatient costs were higher than for the no asthma control subgroup, with pharmaceutical costs 90% higher, and inpatient costs 38% higher. For the prevalent AR and prevalent AR + asthma subgroups, although costs of pharmaceuticals were generally higher than their respective control groups (by 3% in the prevalent AR group, and 75% in the AR + asthma group), inpatient

Table I *- Sample characteristics of the study population.*

	Overall cohort	Prevalent AR	Prevalent asthma	Prevalent asthma + AR	Control AR	Control asthma	Control asthma + AR
Total, *n*	1,739,440	74,642	34,362	9832	1,477,433	1,656,319	1,433,533
Male, *n* (%)	792,605 (45.6)	31,065 (41.6)	14,727 (42.9)	4178 (42.5)	689,804 (46.5)	758,329 (45.8)	671,603 (46.9)
Female, *n* (%)	946,835 (54.4)	43,577 (58.4)	19,635 (57.1)	5654 (57.5)	787,629 (53.3)	897,990 (54.2)	761,930 (53.2)
Age, Mean/(SD)	49.1 (23.2)	39.4 (21.6)	48.47 (24.0)	39,25 (22.1)	50.76 (23.0)	49.30 (23.2)	50.71 (23.0)
Age groups							
<12 years, *n* (% of all)	122,714 (7.1)	7,137 (9.6)	3,527 (10.3)	1274 (13.0)	94,547 (6.4)	112,638 (6.8)	90,963 (6.4)
12-17 years, *n* (% of all)	79,785 (4.6)	8,456 (11.3)	2,077 (6.0)	1059 (10.8)	57,105 (3.9)	75,008 (4.5)	55,681 (3.9)
18-50 years, *n* (% of all)	637,411 (36.6)	34,302 (46.0)	10,157 (29.6)	4024 (40.9)	517,910 (35.1)	609,391 (36.8)	506,367 (35.3)
>50 years, *n* (% of all)	899,530 (51.7)	24,747 (33.2)	18,601 (54.1)	3475 (35.3)	807,871 (54.7)	859,282 (51.9)	780,522 (54.5)
Total by year							
2005, *n*	1,739,440	74,642	34,362	9,832	1,477,433	1,659,535	1,433,533
2006, *n*	1,739,440	74,642	34,362	9,832	1,477,433	1,659,535	1,433,533
2007, *n*	1,705,296	74,237	33,615	9,771	1,443,705	1,626,161	1,400,282
2008, *n*	1,671,594	73,786	32,875	9,704	1,410,628	1,593,316	1,367,824
2009, *n*	1,637,546	73,303	32,145	9,651	1,377,686	1,560,284	1,367,824
2010, *n*	1,603,667	72,770	31,446	9,580	1,345,432	1,527,508	1,335,667
2011, *n*	1,570,536	72,200	30,783	9,512	1,314,349	1,495,573	1,304,289
2012, *n*	1,537,416	71,633	30,108	9,421	1,283,602	1,463,771	1,274,167
2013, *n*	1,503,573	71,015	29,344	9,337	1,252,650	1,431,452	1,244,274
2014, *n*	1,471,716	70,400	28,700	9,247	1,223,879	1,401,076	1,214,749

costs did not follow such a consistent pattern, with higher costs more commonly observed in control subgroups than in prevalent subgroups.

Comparing costs for those prescribed AIT and not prescribed AIT in prevalent subgroups

Collapsing across all subgroups, total costs were on average €753 (54%) lower for those prescribed AIT than those not prescribed AIT. **Figure 1** demonstrates that in the prevalent AR subgroup, costs of both pharmaceuticals and inpatient hospitalisations were lower for patients prescribed AIT than those not prescribed AIT (€153 (29%) lower for pharmaceuticals; €510 (48%) lower for inpatient costs). A similar pattern was observed for both the prevalent asthma subgroup (see **figure 2**) and the prevalent asthma + AR subgroup (see **figure 3**). The pattern of results remained the same when the cost of the AIT pharmaceuticals themselves was both included and excluded from the analysis.

For the prevalent asthma subgroup, the cost difference was highest. Pharmaceutical costs were an average of €303 (34%) lower, and costs of inpatient hospitalisations an average of €777 (115%) lower for patients prescribed AIT, than those not prescribed AIT (see **figure 2**).

Finally, for the prevalent asthma + AR subgroup, pharmaceuticals were an average of €239 (28%) lower, and costs of inpatient hospitalisations an average of €430 (65%) lower for patients prescribed AIT, than those not prescribed AIT (see **figure 3**).

Table II *- Mean (SD) outpatient physician contacts in prevalent and control subgroups in 2010 and 2014, for the whole cohort and stratified by physician type and age group.*

	Prevalent AR		Control AR		Prevalent asthma		Control asthma		Prevalent AR + asthma		Control AR + asthma	
	2010	**2014**	**2010**	**2014**	**2010**	**2014**	**2010**	**2014**	**2010**	**2014**	**2010**	**2014**
All physicians	18.0 (15.4)	18.7 (16.0)	16.6 (16.2)	17.3 (16.6)	22.2 (17.9)	22.7 (18.1)	16.4 (15.9)	17.2 (16.4)	21.1 (17.5)	21.7 (17.3)	13.3 (15.0)	12.9 (15.4)
<12 years	11.0 (8.3)	10.4 (9.1)	8.0 (6.8)	8.1 (7.9)	12.2 (8.5)	10.8 (9.1)	8.2 (6.9)	8.3 (8.0)	13.5 (9.2)	11.6 (9.8)	7.1 (6.5)	7.1 (7.5)
12-17 years	11.0 (9.5)	11.3 (11.0)	9.4 (9.6)	9.9 (10.6)	12.6 (10.7)	12.4 (11.8)	9.6 (9.5)	10.1 (10.6)	12.7 (9.8)	12.5 (11.2)	7.7 (8.4)	8.1 (9.4)
18-50 years	15.6 (13.8)	17.0 (14.4)	11.7 (13.1)	13.1 (14.1)	18.1 (16.4)	19.7 (16.7)	11.9 (13.1)	13.3 (14.0)	19.5 (16.2)	20.5 (15.8)	9.0 (11.3)	10.5 (12.6)
>50 years	25.6 (17.5)	26.7 (17.9)	21.4 (17.5)	22.8 (17.9)	27.9 (18.7)	29.2 (18.8)	21.4 (17.4)	22.7 (17.8)	29.7 (19.6)	30.3 (18.9)	17.2 (16.9)	15.4 (17.4)
ENT	3.4 (3.6)	2.9 (3.0)	2.3 (2.2)	2.1 (1.9)	3.0 (3.2)	2.7 (2.7)	2.4 (2.4)	2.3 (2.1)	3.5 (3.7)	3.1 (3.1)	2.2 (2.1)	2.1 (1.8)
<12 years	3.6 (3.9)	3.0 (3.3)	2.4 (2.2)	1.9 (1.7)	3.2 (3.6)	2.8 (3.0)	2.6 (2.5)	2.3 (2.4)	3.9 (4.5)	3.0 (3.3)	2.4 (2.2)	1.9 (1.7)
12-17 years	3.4 (3.9)	3.1 (3.5)	2.0 (2.0)	1.9 (1.8)	2.9 (3.2)	2.7 (3.0)	2.4 (2.7)	2.3 (2.6)	3.2 (3.4)	2.9 (3.1)	2.0 (2.0)	1.9 (1.8)
18-50 years	3.7 (4.1)	3.2 (3.4)	2.2 (2.3)	2.1 (2.1)	3.5 (3.9)	3.1 (3.5)	2.5 (2.8)	2.4 (2.5)	3.8 (4.1)	3.2 (3.4)	2.2 (2.2)	2.1 (2.0)
>50 years	3.1 (3.0)	2.7 (2.4)	2.3 (2.2)	2.1 (1.7)	2.8 (2.8)	2.5 (2.2)	2.3 (2.2)	2.2 (1.8)	3.2 (3.2)	3.0 (2.6)	2.2 (2.05)	2.1 (1.7)
Pulmonology	3.2 (2.7)	3.0 (2.4)	2.7 (2.8)	2.7 (2.7)	3.4 (2.5)	3.2 (2.3)	2.6 (2.9)	2.5 (2.8)	3.4 (2.59)	3.2 (2.4)	2.5 (3.0)	2.5 (2.8)
<12 years	3.1 (2.8)	2.5 (2.3)	1.9 (1.3)	1.9 (1.5)	2.7 (2.5)	2.4 (2.1)	2.3 (2.3)	1.9 (2.1)	3.2 (2.6)	2.2 (1.5)	1.7 (1.3)	1.6 (1.1)
12-17 years	3.0 (2.9)	2.6 (2.5)	2.1 (1.7)	2.2 (1.9)	2.9 (2.7)	2.8 (2.7)	2.1 (2.3)	1.97 (2.0)	3.2 (2.9)	2.8 (2.8)	1.8 (1.6)	1.6 (1.2)
18-50 years	3.3 (3.0)	3.1 (2.7)	2.5 (2.3)	2.6 (2.7)	3.4 (2.8)	3.3 (2.6)	2.4 (2.5)	2.4 (2.9)	3.4 (2.9)	3.2 (2.7)	2.2 (2.2)	2.3 (2.9)
>50 years	3.2 (2.4)	3.0 (2.1)	2.8 (2.9)	2.8 (2.7)	3.5 (2.3)	3.3 (2.1)	2.6 (3.1)	2.6 (2.8)	3.2 (2.4)	3.3 (2.2)	2.6 (3.2)	2.6 (2.8)

Note: visits to ENTs and Pulmonologists were only reported for those patients who visited this specialty at least once in the respective year.

Discussion

Findings and implications

This study describes the healthcare utilisation and costs associated with allergic rhinitis and asthma in a large population-based cohort. Overall, the pattern of findings found higher costs and resource use in prevalent subgroups than controls, with the highest costs and resource use in the prevalent asthma subgroup. Of interest, within prevalent subgroups, mean costs were, on average, 54% lower for those prescribed AIT than for those not. This data is important as it shows the actual costs to the healthcare system for these different patient groups. The study did not aim to explore the reason for these cost differences, and this could be an area of future research.

Comparison of prevalent and control subgroups

Outpatient contacts and pharmaceutical costs were greater in prevalent subgroups than in control subgroups. This is in

Table III *- Mean (SD) direct costs (Euros) for pharmaceuticals and inpatient hospitalisations in all subgroups in 2010 and 2014, overall and stratified by patient age.*

	Prevalent AR		**Control AR**		**Prevalent asthma**		**Control asthma**		**Prevalent AR + asthma**		**Control AR + asthma**	
	2010	**2014**	**2010**	**2014**	**2010**	**2014**	**2010**	**2014**	**2010**	**2014**	**2010**	**2014**
Pharmaceutical treatments	625 (2615)	675 (3140)	621 (2686)	641 (3488)	1217 (2729)	1104 (3354)	597 (2672)	623 (3473)	1038 (2867)	997 (3505)	577 (2540)	588 (3137)
<12 years in 2005	348 (1596)	287 (2948)	136 (1426)	157 (2199)	486 (1954)	405 (4146)	144 (1392)	169 (2088)	636 (2155)	581 (6593)	121 (1323)	143 (2116)
12-17 years in 2005	229 (3684)	248 (3766)	130 (1392)	171 (3330)	373 (1737)	303 (1524)	141 (1938)	182 (3582)	350 (1224)	293 (974)	115 (1386)	155 (3490)
18-50 years in 2005	471 (2354)	581 (2941)	337 (2782)	455 (3861)	913 (2425)	1019 (3397)	332 (2773)	450 (3861)	881 (2482)	936 (2918)	303 (2728)	408 (3580)
>50 years in 2005	1055 (2697)	1063 (3182)	903 (2772)	856 (3343)	1616 (3015)	1373 (3275)	883 (2748)	843 (3336)	1576 (3667)	1434 (2877)	842 (2554)	787 (2876)
Inpatient hospitalisations	723 (3307)	871 (4186)	1005 (4677)	1063 (5702)	1328 (5148)	1419 (5987)	967 (4561)	1026 (5559)	899 (3655)	1064 (4990)	974 (4590)	1010 (5350)
<12 years in 2005	319 (2145)	512 (3990)	332 (2766)	414 (3087)	459 (2426)	483 (2797)	320 (2673)	410 (3096)	430 (2423)	486 (3129)	303 (2509)	387 (2993)
12-17 years in 2005	326 (1888)	430 (2049)	262 (2706)	440 (2599)	415 (2035)	520 (2275)	347 (2554)	431 (2496)	336 (1656)	491 (1927)	331 (2537)	405 (2523)
18-50 years in 2005	480 (2312)	651 (3528)	535 (3557)	668 (5883)	789 (4260)	943 (4362)	522 (3448)	654 (5690)	681 (2918)	848 (4328)	503 (3373)	629 (5199)
>50 years in 2005	1309 (4743)	1429 (5395)	1443 (5504)	1445 (5951)	1890 (6063)	1957 (7286)	1420 (5451)	1423 (5871)	1496 (4937)	1701 (6587)	1403 (5450)	1374 (5765)

Figure 1 *- Mean direct costs (Euros) for pharmaceuticals (all and non-AIT) and inpatient hospitalisations in prevalent AR, stratified by AIT use, in the years 2010 and 2014.*

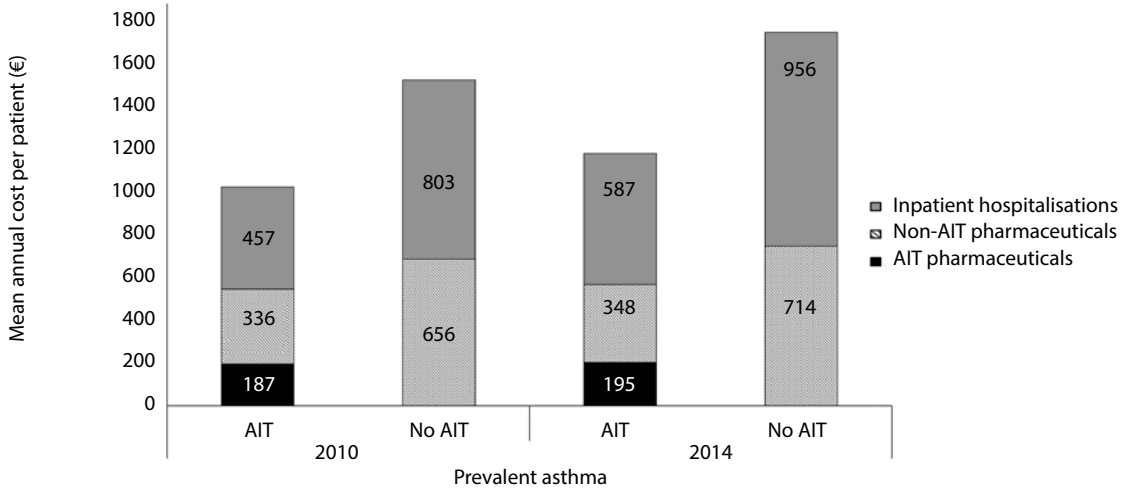


Figure 2 *- Mean direct costs (Euros) for pharmaceuticals (all and non-AIT) and inpatient hospitalisations in prevalent asthma, stratified by AIT use, in the years 2010 and 2014.*

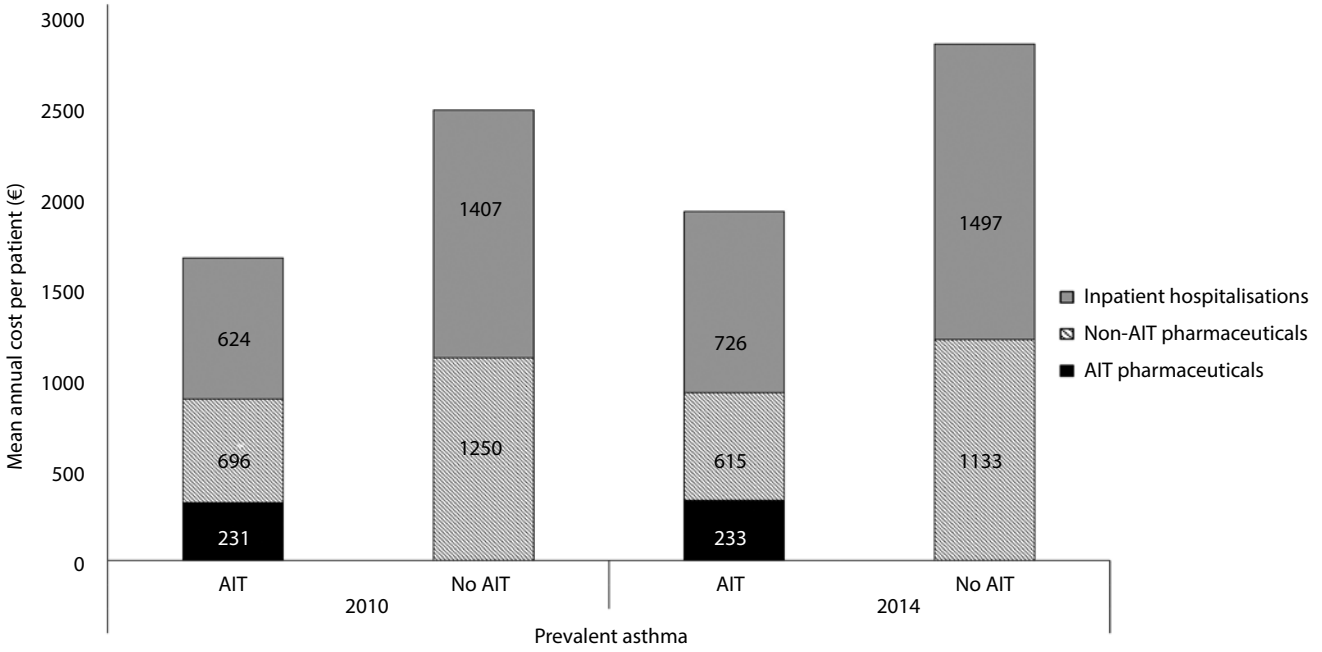
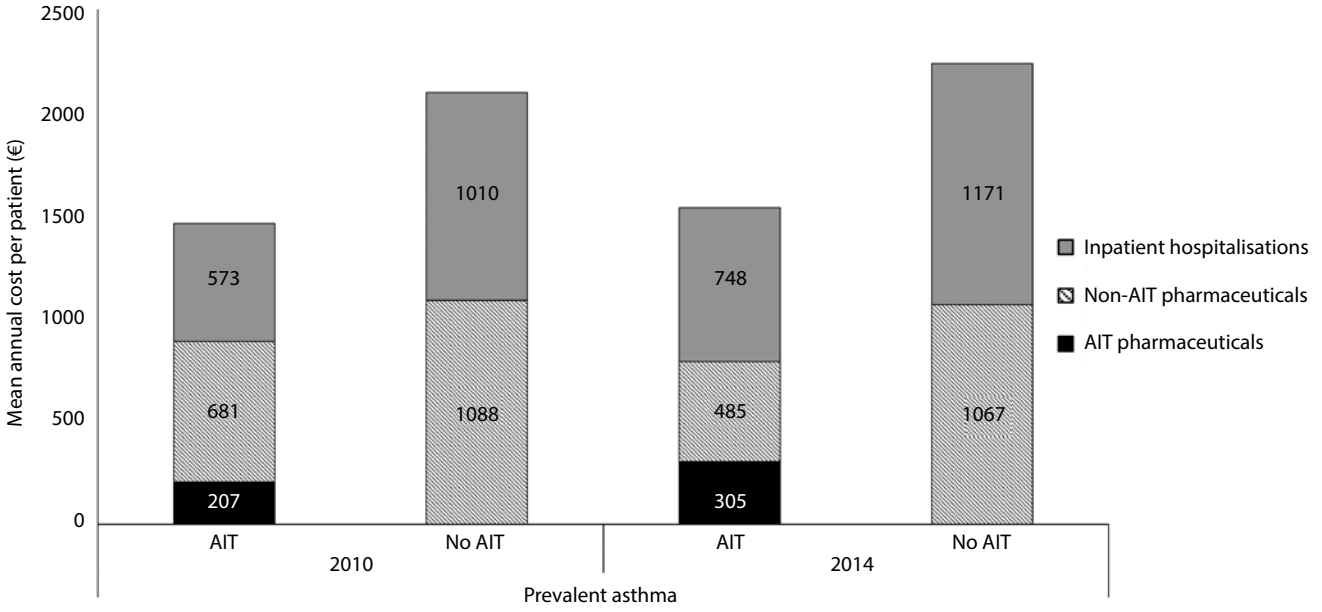


Figure 3 *- Mean direct costs (Euros) for pharmaceuticals (all and non-AIT) and inpatient hospitalisations in prevalent asthma + AR, stratified by AIT use, in the years 2010 and 2014.*



line with expectations, given that both diseases require ongoing pharmaceutical management, thus incurring costs for the pharmaceutical treatments themselves, as well as outpatient appointments for prescribing and monitoring purposes, that would not be incurred by people without these diseases. However, for inpatient costs, the pattern was less consistent. While inpatient costs for the prevalent asthma subgroup were consistently higher than those for the no asthma control subgroup, for the other two prevalent subgroups inpatient costs were, in many cases, lower than for the respective control subgroups. The reasons for this are unknown. Inpatient hospitalisations are rarely required for the management of AR, so inpatient costs in the prevalent AR subgroup are likely incurred due to co-morbid health problems. As such, we speculate that co-morbid health problems may be more easily identified and treated in prevalent cohorts due to regular contact with physicians, thus reducing the risk for costly inpatient visits. In contrast, inpatient hospitalisations are more common in the management of asthma (16), particularly in patients with uncontrolled asthma, thus a proportion of the inpatient costs in the prevalent asthma subgroup are likely directly related to asthma treatment. Accordingly, this subgroup is therefore likely to incur greater inpatient costs than those with no asthma.

One unexpected finding was that resource utilisation and costs were generally lower in the co-morbid prevalent AR with asthma subgroup than in the prevalent asthma subgroup. This may appear contrary to the logic of treating two diseases compared with treating one, but we consider it likely to be related to the nature of disease classification. In co-morbid cases where asthma is considered severe, or predates the onset of AR, the diagnostic code for AR may not be applied to patient notes (16), resulting in underreporting of AR in more severe (and more expensive) cases of asthma. In contrast, the prevalent AR + asthma subgroup may be more likely to include a large proportion of patients with AR who have only recently begun showing signs and symptoms of asthma, and therefore as a cohort, the asthma may be better controlled, requiring fewer outpatient contacts, less medication and being associated with a lower risk of asthma-related hospitalisation.

Comparison of costs for those prescribed AIT and not prescribed AIT in prevalent subgroups

Examination of healthcare costs demonstrated that the costs of both pharmaceutical treatments and inpatient hospitalisations were lower in patients prescribed AIT than those not prescribed AIT. One consideration when interpreting these findings, is that the overall healthcare utilisation and costs associated with pharmaceuticals and inpatient hospitalisations were not specific to those associated with the treatment of AR or asthma, and instead, refer to all-cause healthcare use. As such, the costs will reflect treatment for co-morbid health conditions in addition to that for the diseases of interest. If co-morbid health problems are caused, or mediated, by AR and/or asthma, better disease control in these disease areas may also reduce healthcare resource use in the co-morbid disease(s). A further consideration is that the data shows the actual cost to payers for different subpopulations patients, and there are many reasons why these costs may differ. It is possible that patients who receive AIT have different comorbidities and AR and AA disease severity to those who do not receive AIT. Further research would be needed to establish why the costs are different in each patient population.

Strengths and limitations

The study benefits from the use of a large insurance database as the data source. While this may somewhat under-represent high income patients who may be less likely to use statutory healthcare, we consider this sample relatively unselected and highly representative of the general population in Germany (28), thus the results are likely to be widely generalizable.

While use of an insurance database provides many strengths, it is limited in terms of the data available. As for all insurance claims databases, pharmaceutical costs only include those for which prescriptions were provided, and likely under-represent those incurred privately for over-the-counter (OTC) medications. This is likely to particularly affect the costs associated with AR pharmaceuticals, for which OTC medications are readily available at low cost. However, as OTC costs are paid by patients, the costs reported here are relevant when considering the burden for healthcare systems. Relatedly, it is possible that self-treating patients may not have consulted a physician and, without an ICD-10 diagnosis code, they would not have met criteria for inclusion in the AR prevalent group, thus resulting in misclassification. However, if these patients self-treat, the misclassification will not affect the resource use and costs incurred by statutory health services, thus it can be argued that such a limitation does not alter the conclusions of this study.

It was also discussed that the costs for inpatient hospitalisations and pharmaceutical costs in this study are not limited to the costs of AR and asthma only. It is therefore possible that non-related, co-morbid diseases could have influenced the cost calculations reported. However, this was equally biased for both AR and asthma patients and was therefore unlikely to have influenced the differences found in the costs reported. Additionally, co-morbid diseases found in asthma and AR patients in the study may also be found in the real-world population. Therefore, the costs reported reflect potential real-life circumstances that may be faced when treating these conditions.

It should be noted that a conservative approach to defining AIT use was implemented, with any patient who had filled at least

one prescription for AIT stratified to the AIT group. Given evidence-based recommendations that AIT should be used for at least 3 years (29), it is likely that the AIT group includes a proportion of patients who may not have received full clinical benefit, which may have resulted in an underestimation the cost differences between the AIT and no AIT groups.

The study design cannot provide evidence for a causal relationship between reduced cost and treatment with AIT. It is possible that higher costs for non-AIT subgroup may have been observed, for example, due to a high proportion of patients with complications that both contraindicate treatment with AIT and result in higher costs.

Conclusions

AR and asthma were associated with increased outpatient visits and pharmaceutical costs. Asthma also incurred greater inpatient costs compared with controls, reinforcing the importance of AR treatments that reduce the risk of developing asthma, such as AIT (30). Within prevalent populations, pharmaceutical and inpatient costs were lower for those prescribed AIT than for those not prescribed AIT.

Conflict of interests

AD, TSG, LE and EW were all employees of ALK Abelló while conducting this work; EW reports holding stock options for ALK Abelló; DK, FT and JS report an institutional grant from ALK Abelló for the submitted work; JS reports institutional grants from ALK Abelló, Novartis, Pfizer and Sanofi outside the submitted work.

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