

Long-term health care resource and cost savings with allergy immunotherapy: REACT study results



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Background: Allergy immunotherapy (AIT) can be administered as subcutaneous immunotherapy (SCIT) injections in the clinic or as sublingual immunotherapy (SLIT) tablets at home after initiation under medical supervision. To achieve long-term, sustained effects, a 3-year treatment duration is recommended.

Objective: Our aim was to assess the association of AIT (SCIT and SLIT tablets) with long-term health care resource use (HRU) and costs in subjects with allergic rhinitis.

Methods: REACT was a retrospective propensity score-matched cohort study using claims data from a German health insurance database (2007-2017), with up to 9 years of follow-up after AIT initiation. HRU and costs were evaluated for hospitalizations, ambulatory care visits, and prescriptions, in subjects who received AIT versus in matched controls with allergic rhinitis who had not received AIT, as well as for SCIT and SLIT tablets. **Results:** Across all 9 years, the subjects who received AIT had a significantly lower incidence of hospitalization than the controls did. Generally, proportions of subjects with ambulatory care visits and hospitalizations were lower, and length of hospitalization was shorter, for those receiving SLIT tablets than those who received SCIT. Total costs were significantly higher with AIT versus for the controls during the treatment period (years 1 to 3), driven by prescriptions and ambulatory care visits, but they were lower in years 4 to 9. During years 1 to 3, prescription costs were generally higher for SLIT tablets than

for SCIT, whereas ambulatory care costs were numerically lower. In most years, hospitalization costs were numerically lower for SLIT tablets than for SCIT.

Conclusion: Initial higher HRU and costs of AIT during the expected treatment period are offset in the long term. At-home administration of SLIT tablets may further reduce ambulatory care costs. (*J Allergy Clin Immunol Global* 2024;3:100197.)

Key words: Allergic rhinitis, allergy immunotherapy, cost, health care resource use, real-world evidence, REACT, subcutaneous immunotherapy, sublingual immunotherapy tablet

INTRODUCTION

The prevalence of respiratory allergy is increasing,¹⁻³ which further affects patients' quality of life, health care resource use (HRU), and costs. Allergy immunotherapy (AIT) is currently the only causal treatment option for allergic disease.^{4,5} AIT can be administered for 3 to 5 years as subcutaneous immunotherapy (SCIT) at specialized clinics or as sublingual immunotherapy (SLIT) tablets at home following initiation under medical supervision.^{4,6}

Data for HRU and costs associated with AIT are scarce. Published evidence shows that there are considerable cost savings to be made with the use of appropriate allergy therapy,⁷ and that AIT use is associated with appreciably lower costs than with no AIT use.⁸ However, such studies have not evaluated whether the long-term benefits of AIT (ie, reductions in hospitalizations and symptomatic pharmacotherapy) are sufficient to offset the short-term costs of the treatment and its administration.

The REAL-world effeCtiveness in allergy immunoTherapy (REACT) study was a retrospective cohort study, evaluating claims data from 5,983,511 individuals in a German health insurance database (2007-2017), of whom 18.7% had allergic rhinitis (AR).⁹ Subjects with AR who had received AIT prescriptions were matched 1:1 (using propensity score matching) with a control group of subjects with AR who had not received a prescription for AIT, and were followed for up to 9 years.⁹ The decision to treat with AIT and the type of AIT to prescribe—SCIT or SLIT—was the responsibility of the prescribing physician. The REACT study demonstrated overall effectiveness of AIT for the treatment of AR (and asthma) in a broad population of 92,048 individuals.⁹ AIT was consistently associated with greater reductions in AR and asthma prescriptions than for the controls, as well as with lower risks of pneumonia, asthma exacerbations, and hospitalizations in subjects with preexisting asthma.⁹

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Ethical review and approval were not required for this secondary analysis of claims data from a German health insurance database. Written informed consent was not required in accordance with the national legislation and the institutional requirements.

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Abbreviations used

AIT:	Allergy immunotherapy
AR:	Allergic rhinitis
HRU:	Health care resource use
REACT:	REAL-world effeCtiveness in allergy immunoTherapy
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy

This analysis expands on the prespecified exploratory HRU and cost outcomes from the REACT study, describing the impact of AIT on long-term HRU and costs in subjects with AR, to determine whether the clinical benefits of AIT observed in the REACT study translate into economic benefits for the health care system. HRU is reported as the proportion of subjects with events by year and the mean length of hospital stay (days). Costs are reported as mean cost (in euros [€]) per subject per year. Hospital inpatient costs are calculated using the German diagnosis-related groups system, which includes summarized costs per hospitalization. Hospital outpatient costs are calculated per case and include procedures, medication, and operations. For ambulatory care costs, procedures and operations are billed by fee schedule items according to the German system of medical remuneration for outpatient services (Einheitlicher Bewertungsmaßstab). The data are compared between subjects who received AIT and controls and are presented descriptively by route of administration (SCIT and SLIT tablet subgroups). Categorical variables for hospitalizations and ambulatory care visits in subjects with an AIT prescription versus in controls are reported as odds ratios with 95% CIs and *P* values (Fisher exact test). To account for the reduction in the sample size over time, data are truncated if the number of patients in a subgroup was fewer than 200 in any follow-up year. To reflect the current value of AIT, discounted costs (3% and 5%) were calculated *post hoc*.

RESULTS AND DISCUSSION

Of the 46,024 subjects in the AIT cohort (matched 1:1 with controls who had not received AIT), 36,927 subjects received prescriptions for SCIT and 3,754 received prescriptions for SLIT tablets. Baseline demographics for the REACT study cohort (subjects who received AIT and controls) and for the subgroup of those who received AIT (SCIT and SLIT tablets) have been published previously.^{9,10} The data were similar across the matched AIT and control groups in the main cohort and were generally similar for the SCIT and SLIT tablet subgroups.^{9,10}

Across the entire 9-year period, AIT was associated with a significantly lower incidence of hospitalization than in the case of the controls (Table 1). In the initial years of treatment, the incidence of ambulatory care visits was significantly higher with AIT (Table 1), which is not unexpected, as clinical guidelines recommend an AIT treatment duration of at least 3 years.⁴ Fig 1, A shows that the increased number of ambulatory visits was driven mainly by SCIT treatment, in which case patients are required to visit the clinic each month for their injections. In contrast, SLIT tablets can be administered at home without the need for regular clinic visits, which is reflected in the numerically lower use of ambulatory care for SLIT tablets versus for SCIT (Fig 1, A). After year 1, the SLIT tablet subgroup also showed a numerically lower proportion of subjects being

hospitalized and a shorter length of hospital stay than the SCIT subgroup did (Fig 1, B and C). Together with a lower incidence of hospitalization, length of stay remained lower with AIT versus the controls throughout the follow-up period (Table 1), potentially thanks to improved symptom control and a reduced incidence of pneumonia and asthma exacerbations.⁹ In year 8, use of AIT was associated with approximately 2 fewer hospital days per subject per year versus controls.

From an economic perspective, total health care costs per subject were significantly greater with AIT than among the controls during the initial years of treatment, but they were significantly lower in subsequent years, including in those after expected treatment completion (Fig 2, A). The initially greater treatment costs for the AIT cohort were driven by the cost of prescriptions and ambulatory care visits (Fig 2, B and C). Supporting the finding that AIT is associated with a lower risk of hospitalization than among the controls who had not received AIT, hospitalization costs were also lower (Fig 2, D). These findings were unaffected by *post hoc* discounting at 3% and 5% (Fig 3), suggesting that the initial higher costs of AIT may be offset in the long term. When examined by route of AIT administration, the cost of prescriptions was generally higher for SLIT tablets than for SCIT in the first 3 years of treatment (Fig 4, B), whereas the cost of ambulatory care visits was numerically lower (Fig 4, C). During most of the 9-year follow-up period, the cost of hospitalizations was lower for those receiving SLIT tablets than for those receiving SCIT (Fig 4, D). The trade-off between the higher prescription costs and the lower costs of ambulatory care visits and hospitalizations resulted in numerically lower total health care costs per subject for SLIT tablets than for SCIT (Fig 4, A).

The REACT cohort included a small subset of subjects with AR and preexisting asthma (31.8% of the total AR group),⁹ reflecting a real-life patient population. Subjects with preexisting asthma who were treated with AIT showed a higher total health care cost than the group of those without asthma who received AIT; the same pattern was observed for the corresponding control groups. This finding is expected because AR subjects with preexisting asthma have an additional comorbidity. However, the data show that AIT delivers long-term cost savings for subjects with AR regardless of asthma status (Fig 5).

The data presented here strengthen the limited economic evidence available for AIT by providing information on HRU and costs based on real-world data from a study with up to 9 years follow-up after AIT initiation. Previous studies have either reported HRU and costs based on estimates only⁷ or reported data for short time periods (1-2 years).⁸ This analysis of real-world data found that the initial added HRU and costs with AIT during the recommended treatment period are offset in the long term during the 9-year follow-up period.

It should be acknowledged that the analysis did not focus on indirect costs, which are a greater contributor to the economic burden of allergy than direct costs.^{11,12} High indirect costs have considerable economic consequences for patients and society.^{11,12} To provide some insight into the indirect costs of AIT, *post hoc* analyses of HRU data from the REACT study were used to estimate the time spent at the hospital per subject, assuming a 3-hour visit for an ambulatory care visit (outside a hospital setting), 4 hours for an outpatient visit (inside a hospital setting), and 8 hours for an inpatient visit. The time estimate was then translated into the cost of lost productivity per subject, assuming a mean hourly wage of €17.23 (Eurostat, 2018

TABLE I. HRU in subjects receiving AIT versus in controls

Year	Ambulatory care visits		Hospitalizations		Length of inpatient stay (d)	
	OR (95% CI)	P value	OR (95% CI)	P value	Mean difference (95% CI)	P value
1	15.38 (11.91-19.85)	<.001	0.73 (0.69-0.76)	<.001	-0.460 (-0.543 to -0.377)	<.001
2	3.78 (3.34-4.27)	<.001	0.80 (0.76-0.83)	<.001	-0.425 (-0.523 to -0.327)	<.001
3	2.15 (1.95-2.38)	<.001	0.85 (0.81-0.89)	<.001	-0.344 (-0.459 to -0.230)	<.001
4	1.46 (1.32-1.61)	<.001	0.82 (0.77-0.87)	<.001	-0.374 (-0.495 to -0.253)	<.001
5	0.99 (0.90-1.10)	.90	0.84 (0.79-0.90)	<.001	-0.541 (-0.694 to -0.387)	<.001
6	0.98 (0.87-1.09)	.69	0.81 (0.75-0.87)	<.001	-0.364 (-0.541 to -0.186)	<.001
7	0.89 (0.78-1.02)	.10	0.81 (0.74-0.89)	<.001	-0.327 (-0.550 to -0.105)	.004
8	0.96 (0.81-1.14)	.69	0.80 (0.71-0.91)	<.001	-0.477 (-0.757 to -0.197)	<.001
9	0.97 (0.71-1.31)	.88	0.77 (0.63-0.94)	.01	-0.326 (-0.674 to 0.022)	.066

An ambulatory care visit was defined as an outpatient medical service provided outside a hospital setting, including visits to specialists (otolaryngologists, pulmonologists, general practitioners, and internists) and nonspecialists (others).

OR, Odds ratio.

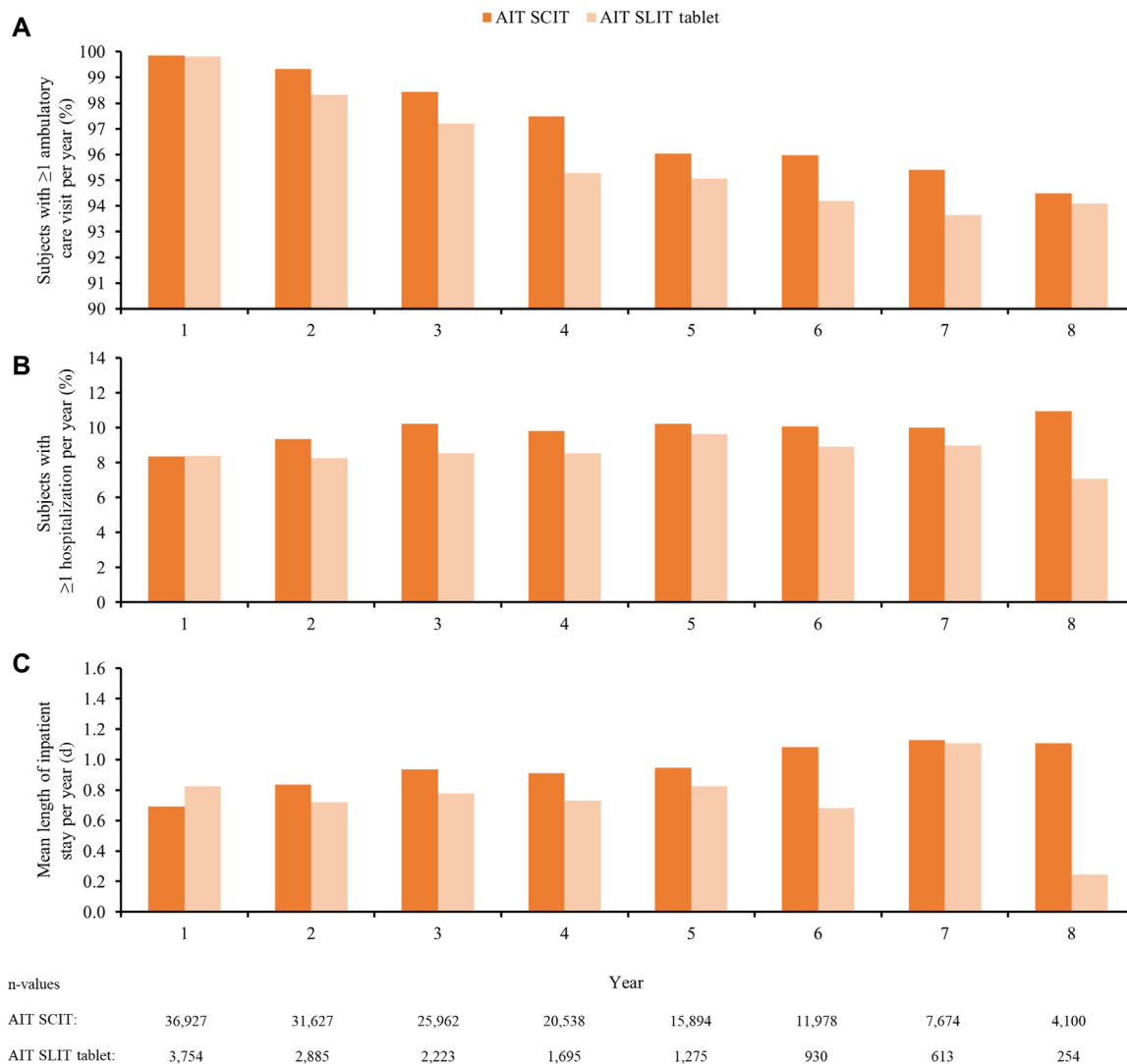


FIG 1. HRU use by route of AIT administration. **A**, Ambulatory care visits. **B**, Hospitalizations. **C**, Mean length of inpatient stay. The data were truncated at year 8 (as $n = 43$ in the SLIT tablet group in year 9). An ambulatory care visit was defined as an outpatient medical service provided outside a hospital setting, including visits to specialists (otolaryngologists, pulmonologists, general practitioners, and internists) and nonspecialists (others).

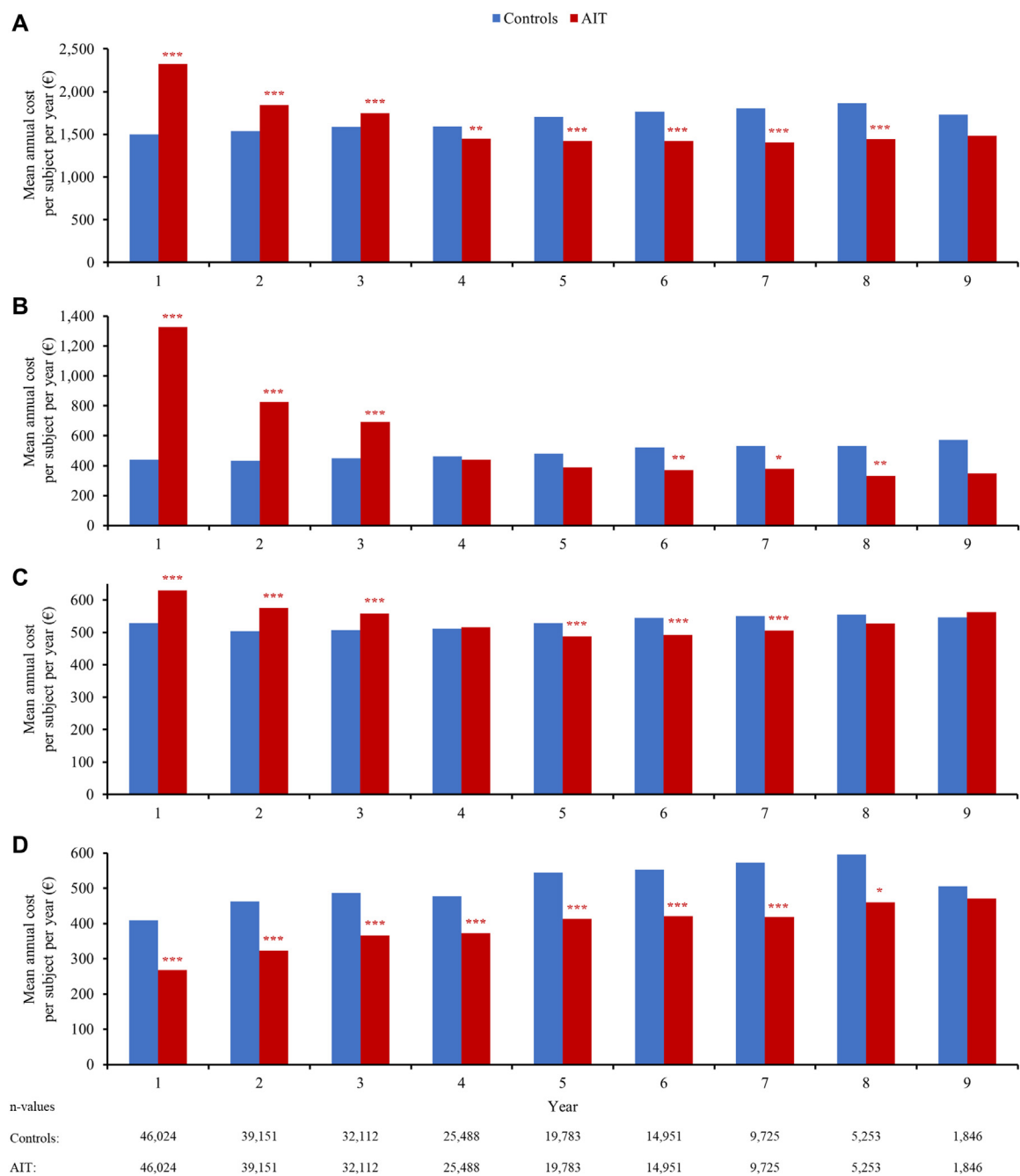


FIG 2. Mean annual cost per subject in subjects with AIT versus in controls. **A**, Total health care. **B**, Prescriptions. **C**, Ambulatory care visits. **D**, Hospitalizations. ****P* < .001; ***P* < .01; **P* < .05 versus controls. An ambulatory care visit was defined as an outpatient medical service provided outside a hospital setting, including visits to specialists (otolaryngologists, pulmonologists, general practitioners, and internists) and nonspecialists (others).

data).¹³ The calculations show that indirect costs for medical consultations per subject at year 8 were €66 lower for those receiving AIT, €51 lower for those receiving SCIT, and €573 lower for those receiving SLIT tablets than for the controls. Furthermore, assuming a mean hourly wage of €17.23¹² and an 8-hour workday, the average estimated costs for sick leave were €122 lower per subject per year with AIT versus controls. Although we acknowledge that these estimates are conservative and that

formal analysis is required, the data show the potential for lower long-term indirect costs with AIT, particularly for SLIT tablets, which require fewer ambulatory visits than SCIT does.

The REACT study showed that AIT is associated with reduced prescriptions for AR and asthma.⁹ Potentially, savings to health care could be achieved by reducing corticosteroid use in these patients.^{14,15} Long-term systemic use of corticosteroids, particularly at high doses, is associated with adverse events (eg, osteoporosis

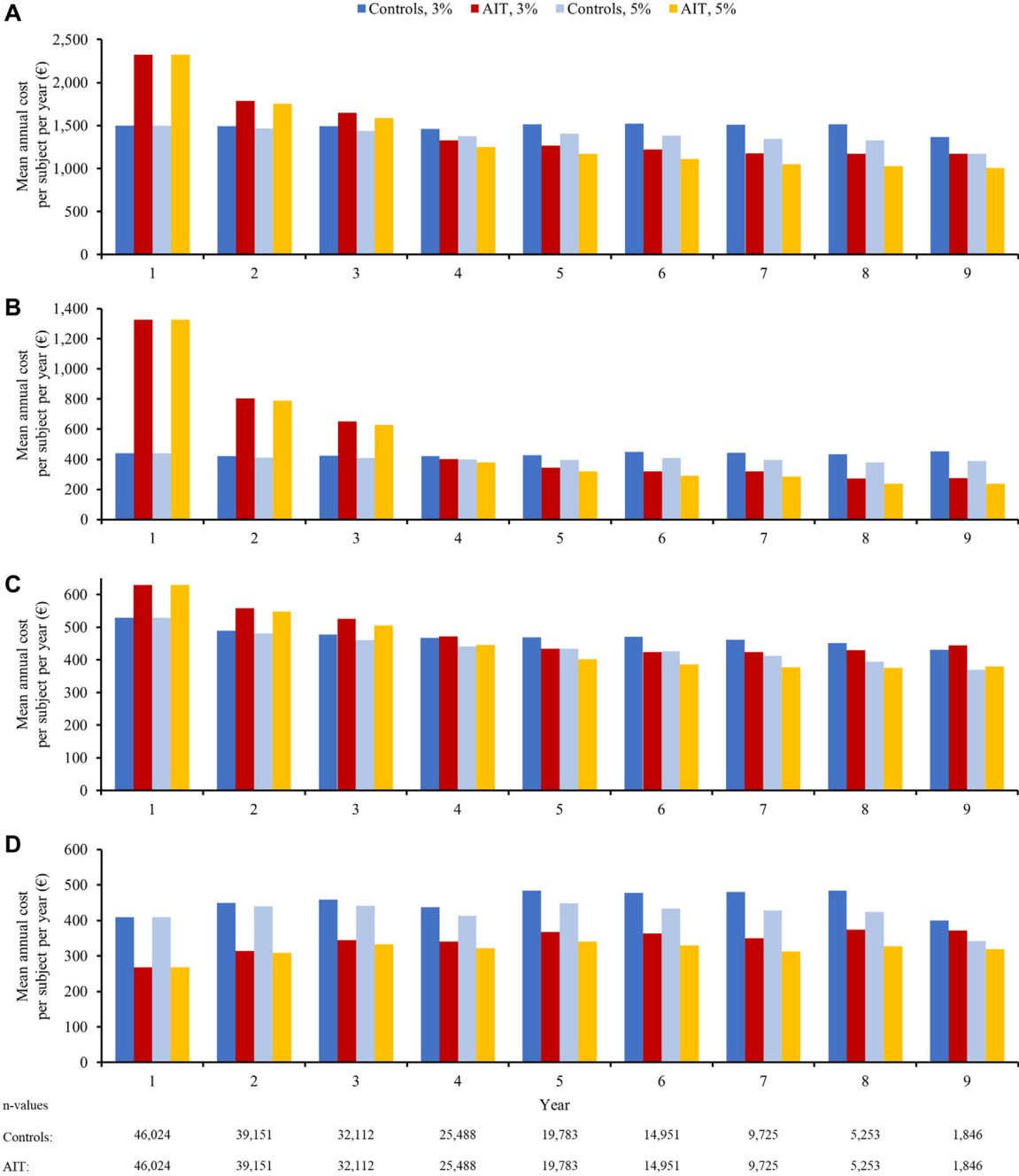


FIG 3. Mean annual cost per subject in subjects with AIT versus in controls, discounted at 3% and 5%. **A**, Total health care. **B**, Prescriptions. **C**, Ambulatory care visits. **D**, Hospitalizations. An ambulatory care visit was defined as an outpatient medical service provided outside a hospital setting, including visits to specialists (otolaryngologists, pulmonologists, general practitioners, and internists) and nonspecialists (others).

and fractures, adrenal suppression, and hyperglycaemia and diabetes).¹⁶ More recent data from a metabolomic profiling study have shown that inhaled corticosteroids result in adrenal suppression,¹⁷ suggesting that the adverse effects of corticosteroids are not restricted to systemic use of these drugs. Given that the management of corticosteroid-related adverse effects considerably increases the cost of treatment for asthma,¹⁸ pharmacologic approaches that may reduce the use of corticosteroids, such as

AIT, could be prioritized. The REACT study showed that AIT is associated with greater reductions than the controls in terms of prescriptions for intranasal corticosteroid use in AR, as well as for inhaled corticosteroids with long-acting β -agonists in asthma.⁹ A limitation of the analysis is that the subjects with AIT were not rematched to form the SCIT and SLIT tablet subgroups. Consequently, although there were no apparent differences between these subgroups at baseline, residual confounding

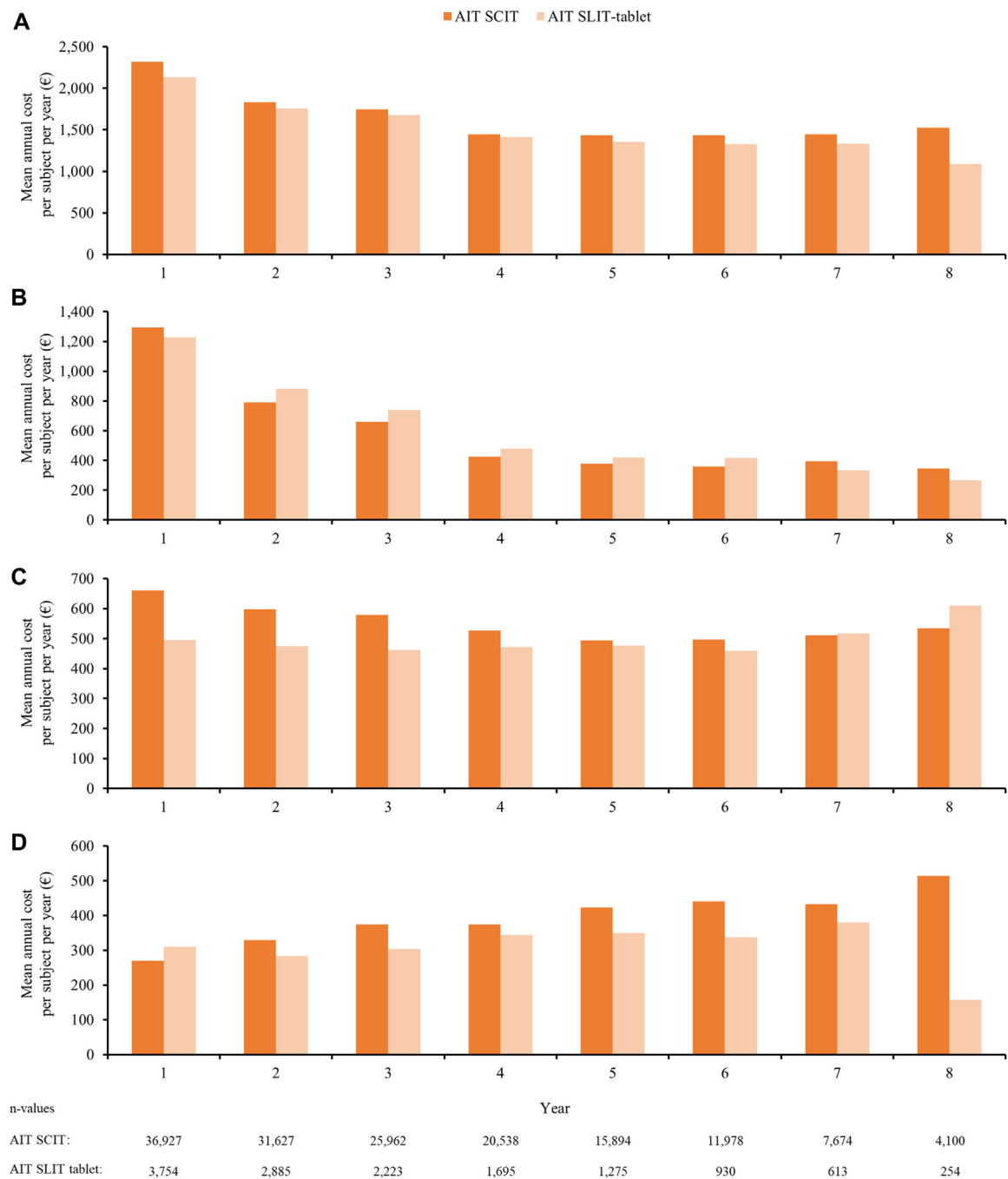


FIG 4. Annual health care costs per subject by route of AIT administration. **A**, Total health care. **B**, Prescriptions. **C**, Ambulatory care visits. **D**, Hospitalizations. The data were truncated at year 8 (as n = 43 in the SLIT tablet group in year 9). An ambulatory care visit was defined as an outpatient medical service provided outside a hospital setting, including visits to specialists (otolaryngologists, pulmonologists, general practitioners, and internists) and nonspecialists (others).

factors may exist; these factors include differences in disease severity between subjects with AIT who were prescribed SCIT and those prescribed SLIT tablets.¹⁰

In conclusion, the findings of the REACT study show that although AIT is initially associated with increased costs, these costs are offset in the longer term. As the only causal treatment for allergic disease,⁴ a 3-year course of AIT is recommended to

provide long-term and sustained disease-modifying effects.⁶ The higher initial outlay for AIT is offset by fewer hospitalizations and associated costs after the expected course of AIT has been completed, as well as by improved health outcomes. Although SCIT requires monthly clinic visits, SLIT tablets can be administered at home (after initiation under medical supervision) and may further reduce ambulatory care costs.

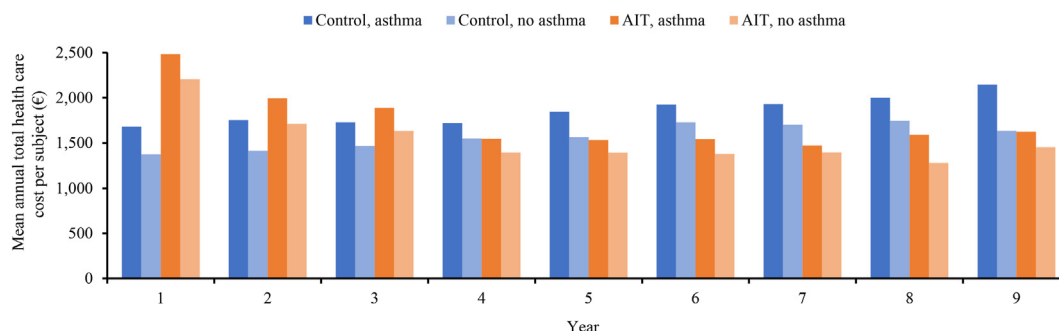


FIG 5. Annual total health care costs per subject in AIT subjects by asthma status. Asthma was defined on the basis of the *International Classification of Diseases, 10th Revision*, diagnostic code J45.x, or J46, and/or at least 2 prescriptions of a short-acting β -agonist or inhaled corticosteroid within an index year.

DISCLOSURE STATEMENT

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Key messages

- Across the 9-year follow-up, AIT was associated with a lower incidence of hospitalization than without use of AIT.
- The initially high HRU and costs of AIT during treatment are offset in the long term.

REFERENCES

- Leth-Møller KB, Skaaby T, Linneberg A. Allergic rhinitis and allergic sensitisation are still increasing among Danish adults. *Allergy* 2020;75:660-8.
- Sasaki M, Morikawa E, Yoshida K, Adachi Y, Odajima H, Akasawa A. The change in the prevalence of wheeze, eczema and rhino-conjunctivitis among Japanese children: findings from 3 nationwide cross-sectional surveys between 2005 and 2015. *Allergy* 2019;74:1572-5.
- Ha J, Lee SW, Yon DK. Ten-year trends and prevalence of asthma, allergic rhinitis, and atopic dermatitis among the Korean population, 2008-2017. *Clin Exp Pediatr* 2020;63:278-83.
- Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018;73:765-98.
- Klimek L, Brehler R, Hamelmann E, Kopp M, Ring J, Treudler R, et al. Evolution of subcutaneous allergen immunotherapy (part 1): from first developments to mechanism-driven therapy concepts. *Allergy J Int* 2019;28:78-95.
- Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;136:556-68.
- Zuberbier T, Lötval J, Simoes S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA²LEN review. *Allergy* 2014;69:1275-9.
- Tesch F, Sydendal Grand T, Wuestenberg E, Elliott L, Schmitt J, Kuster D. Health-care costs associated with allergic rhinitis, asthma allergy immunotherapy. *Eur Ann Allergy Clin Immunol* 2020;52:164-74.
- Fritzsching B, Contoli M, Porsbjerg C, Buchs S, Larsen JR, Elliott L, et al. Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: results from the REACT study, a retrospective cohort study. *Lancet Reg Health Eur* 2022;13:100275.
- Contoli M, Porsbjerg C, Buchs S, Larsen JR, Freemantle N, Fritzsching B. Real-world, long-term effectiveness of allergy immunotherapy in allergic rhinitis: subgroup analyses of the REACT study. *J Allergy Clin Immunol* 2023;152:445-52.e4.
- Colás C, Brosa M, Antón E, Montoro J, Navarro A, Dordal MT, et al. Rhinoconjunctivitis Committee of the Spanish Society of Allergy and Clinical Immunology. Estimate of the total costs of allergic rhinitis in specialized care based on real-world data: the FERIN Study. *Allergy* 2017;72:959-66.
- Cardell LO, Olsson P, Andersson M, Welin KO, Svensson J, Tennvall GR, Hellgren J. TOTALL: high cost of allergic rhinitis - a national Swedish population-based questionnaire study. *NPJ Prim Care Respir Med* 2016;26:15082.
- Eurostat. Data browser. Median hourly earnings, all employees (excluding apprentices) by age. Available at: https://ec.europa.eu/eurostat/databrowser/view/EARN_SES_PUB2A/default/?table?lang=en&category=labour.earn.earn_ses_main.earn_ses_pub.earn_ses_pub2. Accessed June 30, 2022.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Updated 2021. Available at: <https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf>. Accessed June 10, 2022.
- Scadding G. Real world evidence of long-term benefits from allergen-specific immunotherapy (AIT). *Lancet Reg Health Eur* 2021;13:100283.
- Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9:30.
- Kachroo P, Stewart ID, Kelly RS, Stav M, Mendez K, Dahlin A, et al. Metabolic profiling reveals extensive adrenal suppression due to inhaled corticosteroid therapy in asthma. *Nat Med* 2022;28:814-22.
- Canonica GW, Colombo GL, Bruno GM, Di Matteo S, Martinotti C, Blasi F, et al; SANI network. Shadow cost of oral corticosteroids-related adverse events: a pharmacoeconomic evaluation applied to real-life data from the Severe Asthma Network in Italy (SANI) registry. *World Allergy Organ J* 2019;12:100007.