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ORIGINAL ARTICLE

Allergen-Specific Immunotherapy and Biologics

The effectiveness of pollen allergen immunotherapy on allergic rhinitis over 18 years: A national cohort study in Denmark

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Abstract

Background: Because long-term effectiveness of pollen allergen immune therapy (AIT) for allergic rhinitis (AR) is not well-described, we studied effectiveness over 18 years in Denmark.

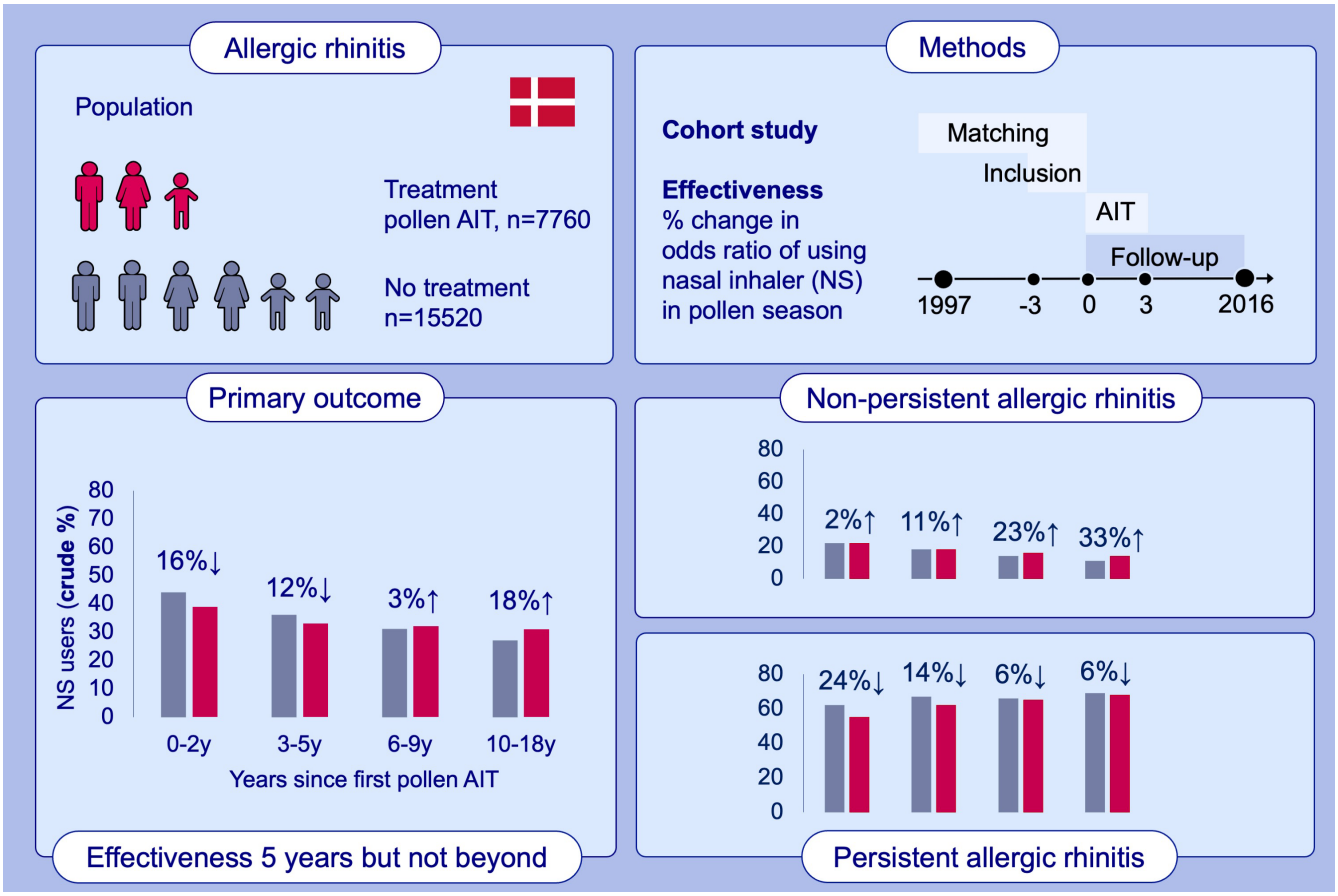
Methods: A register-based cohort study using data on filled prescriptions, 1995–2016, Denmark. In a cohort of 1.1 million intranasal corticosteroid inhaler users (proxy for AR), we matched users treated with grass, birch or mugwort AIT 1:2 with non-treated users on baseline year and 24 characteristics in the 3 years prior to baseline. The primary outcome was the odds ratio (OR) of using anti-allergic nasal inhaler during the pollen season in the treated versus non-treated group by years since baseline.

Results: Among 7760 AR patients treated with pollen AIT, the OR of using nasal inhaler 0–5 years after baseline was reduced when compared with 15,520 non-treated AR individuals (0–2 years, OR 0.84 (0.81–0.88); 3–5 years, OR 0.88 (0.84–0.92)), but was close to unity or higher thereafter (6–9 years, OR 1.03 (0.97–1.08); 10–18 years, OR 1.18 (1.11–1.26)). In post hoc analyses, results were more consistent for those who already had 3 of 3 baseline years of use, and in patients using nasal inhaler in the latest pollen season (0–2 years, OR 0.76 (0.72–0.79); 3–5 years OR 0.86 (0.81–0.93); 6–9 years, OR 0.94 (0.87–1.02); 10–18 years, OR 0.94 (0.86–1.04)) as opposed to no such use.

Conclusions: Patients treated with pollen AIT in routine care to a higher degree stopped using anti-allergic nasal inhaler 0–5 years after starting the standard 3 years of therapy, and not beyond 5 years. Post hoc analyses suggested effectiveness was more consistent among patients with persistent AR.

KEYWORDS
allergic rhinitis, anti-allergic medication, epidemiology, grass pollen, immunotherapy, nasal corticosteroids, observational study

Abbreviation: AIT, allergen immunotherapy; AR, allergic rhinitis; GBM, grass-birch-mugwort; GP, general practitioner.; INS, intranasal corticosteroid inhaler; NS, nasal inhaler



GRAPHICAL ABSTRACT

This analysis of Danish national prescription data over 18 years shows that pollen allergen immunotherapy reduces allergic rhinitis (AR) medication users up to 5 years after start of the standard 3 years of therapy, but not beyond 5 years. Post hoc analyses suggests this effectiveness is more consistent among patients with persistent allergic rhinitis.

Abbreviation: AIT, allergen immunotherapy; NS, nasal inhaler

1 | INTRODUCTION

Allergic rhinitis (AR) is a common chronic upper respiratory tract illness, characterized by running nose, sneezing, nasal blockage, as well as itchy, and watery eyes. In the majority, these symptoms are caused by IgE-mediated hypersensitivity to plant pollen, and thus triggered in pollen seasons. Allergen-immunotherapy (AIT) with sublingual or subcutaneous repeated administration of larger amounts of the offending pollen allergen is the only treatment with evidence of being disease-modifying,[1–4] and having long-term effects.[5–12] AIT may take months or years to act on symptoms and most AR sufferers therefore rely on faster acting medications such as nasal inhalers with corticosteroid or antihistamine, oral antihistamines, and eye drops. Long term effects of AIT are therefore important to study. Clinical trials demonstrated sustained reductions in symptoms and symptom-relieving medication use, for example, use of nasal inhalers, up to 2 years after ending 3 years AIT in AR patients (i.e., total 5 years).[13–16] Although the clinical trial design is gold standard, follow-up time is restricted by resources and patient compliance. In contrast, observational study designs using already available routine care data (e.g., patient registries, claims insurance data, prescription data) can produce longer follow-up. Recent observational studies[5–12] were advantaged by better methodology[17,18] than previously,[19] and has provided a maximum of 9-years follow-up, all showing AIT effectiveness in reducing AR medication use. However, a systematic review noted great heterogeneity between the studies, both in terms of duration, allergens, control population (if any), and outcome measures.[20] In general, outcome data are less precise. For example, the main outcome data are nasal haler prescriptions filled during a pollen season—whereas clinical trials collect diary data on *daily* use of the nasal inhaler(s) throughout a pollen season, which is also the outcome data recommended by regulatory authorities to use to detect clinical effect and qualify the AIT product for marketing approval.[21] In addition, sample sizes were large and this may drive statistical significance. For example, reductions in nasal inhaler fills may be significant but small and not clinical meaningful.[22] In the present study, we took advantage of a longer follow-up (18 years) and focused on a perhaps more clinically meaningful outcome by looking for reductions in the proportion of fillers ("users") each year, rather than reductions in number of fills as in previous studies. We used prescription and

register data since 1994 for the entire country of Denmark, in a large, unselected, national AR patient population treated with pollen AIT (grass, birch, or mugwort), comparing with well-matched AR controls even on income and educational level (not included in previous studies), and also avoiding exclusions for example, of AR patients with certain comorbidities or low adherence to therapy.

2 | METHODS

2.1 | Data sources

The study was based on Danish national registers described elsewhere (see Table S1–S5).[23–28] Specifically, data were obtained from the Register of Medicinal Product Statistics, which contains daily individual information about filled prescriptions at all pharmacies since 1994 (e.g., AR medication and AIT packages), including filling date, number of dispensed packages, unique Danish product code for each medicine package type, and international Anatomic Therapeutic Chemical (ATC) classification system code (www.medstat.dk/en).[24]

2.2 | Ethics

The study was approved by the Danish Data Protection Agency (no. 15/09765) and the Danish Health and Medicines Authority (no. 15/09765). Due to the nature of the research, there was no involvement of patients or members of the public in the design or reporting of this study. Direct dissemination to study participants is not possible. According to National legislation, ethics approval is exempt for such research, cf. implementing decree 2020-09-01, number 1338, about scientific regulatory procedure of health science research projects and health data scientific research projects. The article only contains aggregated results and no personal data. The article is therefore not covered by the European General Data Protection Regulation.

2.3 | Pollen AIT treatment

In Denmark, primarily specialized physicians administer pollen AIT to eligible patients with moderate–severe AR, after referral from their general practitioner. While these services are not consistently registered as part of AIT, the AIT prescriptions are. Thus, the allergen extracts/tablets, are prescribed to the patient, who then fills the prescription at a pharmacy (registration) and bring the dispensed AIT packages for the treatment visit. AIT is only partly reimbursed by the otherwise free public health system. Currently, the only three types of pollen AIT marketed in Denmark are for grass (Phleum pratense), birch (Betula verrucosa), and mugwort (Artemisia vulgaris) allergens, mainly prescribed as subcutaneous immunotherapy (SCIT; injections), but for grass also as sublingual immunotherapy (SLIT; melting tablets) since 2007 (Table S1). There is only one pharmaceutical company with registered AIT products on the Danish market.

2.4 | Source population

The combined pollen season for grass, birch, and mugwort (GBM) in Denmark ranged from April until August in the study period.[29,30] From the entire Danish population, we identified individuals with GBM-induced AR (hereafter denoted "AR individuals" or "INS users") as individuals >5 years old living in Denmark between 1997 and 2013, who had filled a prescription for intranasal corticosteroid spray (INS, ATC = R01AD) in the GBM pollen season, or 2 months before, starting 1 February and ending 31 August (hereafter denoted "a pollen season").

We included INS prescriptions as way to define AR individuals, because INS is the most common recommended medication that is specific for AR, while other common AR medications are not likewise specific in the Danish register-based context. For example, the majority of INS requires a prescription from a doctor, while several oral antihistamines are sold over-the-counter and also used for short-term treatment of common cold and influenza symptoms. A small validation study of Danish register-data among children with allergic diseases suggested ≥1 or >2 INS prescriptions in any year of childhood (mean age 15 years), respectively, has a relatively good sensitivity (84% and 86%) and specificity (66% and 80%), but a lower positive predictive value (PPV) (53% and 65%) for a clinical diagnosis of AR.[31] INS is however also a first-line treatment for chronic rhinosinusitis, perennial AR and non-AR. We conservatively chose to define individuals with pollen-induced AR by INS use during the pollen season, regardless of any use or not outside the pollen season.

2.5 | Identification of the pollen AIT treated group

Individuals who were both pollen AIT treated (patients) and had AR (INS users) were identified. To take into account that most patients started pollen AIT in the autumn before next year's pollen season, we defined an uneven year unit, a baseline sampling year, starting 1 September and ending 31 August. For each baseline sampling year, we included patients with AR, older than 5 years on 1 September, with at least one filled prescription of INS in the three preceding pollen seasons, and then excluded those who in the three preceding sampling years had severe or perennial asthma (defined by hospitalization/medication), lived outside of Denmark, or had ever received other AITs. We did not exclude INS users if they had INS use both in and outside the three preceding pollen seasons (See Figure 1, and in Table S2 also a list of the details of all the aforementioned inclusion and exclusion criteria).

2.6 | Identification of the non-treated group (no history of AIT)

Individuals who had no history of receiving AIT and had AR (INS users) were identified for each baseline sampling year according to the same in/exclusion criteria as for the pollen AIT treated group

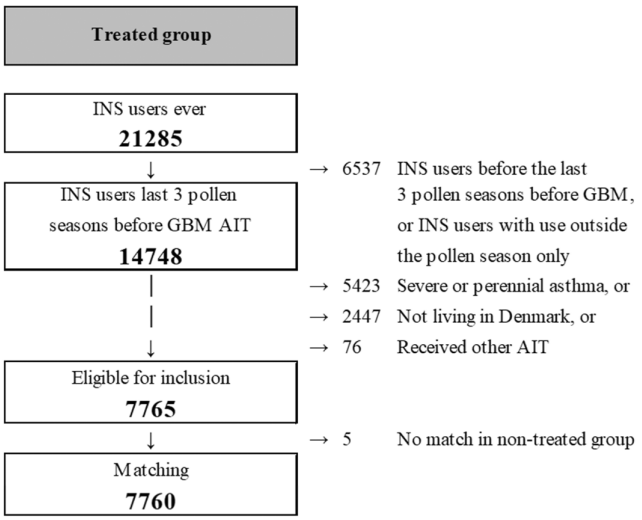


FIGURE 1 Flow-chart for identification of the pollen Allergen Immunotherapy (AIT) treated group, Denmark 1994–2016 (total data period).

(see section above or Table S3). This was done to allow follow-up of treated and non-treated subjects through the same pollen seasons since baseline.

2.7 | Matching

To account for differences in baseline characteristics between pollen AIT treated and non-treated individuals with AR, a propensity score was computed for each baseline sampling year based on socio-demographic characteristics, detailed use of AR medication for the last three pollen seasons, family history of asthma and AR, data on medication use and hospitalizations related to non-severe asthma and atopic dermatitis, contacts to own doctor and number of medication groups used (ATC main groups A to V).[32] Propensity scores were computed for a total of 24 characteristics (see Table S4). Both total AR medication use in latest three pollen seasons and AR medication use in the immediately preceding pollen season were included in the propensity score model because we after first attempt at matching data found that the pollen AIT group was characterized by a particular high proportion of users of medication in the last pollen season before study entry. Number of contacts to own doctor and number of different ATC main groups of prescription medication used were included with an interaction with age. For each baseline sampling year, each pollen AIT treated patient with AR was matched with two non-treated individuals with AR using optimal matching on the logit of the propensity score (see Table S3). The matched groups were considered well-balanced if the standardized differences were below 10%.[33] The matched individuals were followed from the date of the treated individual's/patient's first filled prescription of pollen AIT (date of baseline or "index date") to 31 August 2016, death, or migration, whichever came first. Individuals from the pollen AIT group were also eligible as non-treated individuals but only in the years before starting on pollen AIT and were thus censored as non-treated individuals the day before they started on pollen AIT on the index date (This was the case for 392 patients).

2.8 | Outcome (AR medication users)

The primary outcome was use of at least one nasal inhaler in the pollen season (i.e., users, vs. non-users), and two secondary outcomes were similarly defined for use of oral antihistamines (at least one package of tablets) and anti-allergic eye drops (at least one container) (Table S5). Anti-allergica in nasal inhalers included INS or for example, antihistamine (see Table S5). There is only one nasal inhaler or one eye drop container in a prescribed package.

2.9 | Statistical analysis

Individuals contributed with information on AR medication for each pollen season during their follow-up. The odds of using AR medication in pollen AIT treated versus non-treated were modelled as an odds ratio (OR) by a logistic generalized estimating equations analysis using an autoregressive correlation structure and adjusted for years since baseline (1 year categories). The autoregressive correlation structure was applied to enable inclusion of observations of several pollen seasons from the same person. The correlation structure takes potential within-subject correlation into account by assuming within-subject dependency between observations of AR medication from two pollen seasons, and assuming that the correlation was stronger the closer in time the two pollen seasons were.[34] The main analysis estimated the effectiveness of pollen AIT on each of the three outcomes of AR medication use (with nasal inhaler use being the primary outcome) within four time intervals since baseline: 0–2, 3–5, 6–9, and 10–18 years. The intervals were chosen because in the 0–2 years interval, up-dosing and maintenance dosing takes place (see Table S1), in the 3–5 years interval a proportion of patients continue dose maintenance, while the 6–9 and 10–18 years intervals would represent the long-term effectiveness of interest, that is, continuing after end of therapy. All analyses (except a restriction analysis) was performed on the intention-to-treat population, which we defined as all individuals starting treatment (or "exposed population", i.e., those having at least one filled prescription for pollen AIT starting on the index date), and the matched non-treated individuals. The main as well as several additional analyses were performed for the primary outcome nasal inhaler users and then also for the secondary outcome eye drops and oral antihistamine users. Figure S1 provides an overview of all analyses divided into `a priori´ and post hoc analyses, and their justification. The á priori analyses were sensitivity analyses to the main analysis; one stratified the main analysis by type of pollen AIT allergen (Grass, Birch, Mugwort and Mixed) by introducing an interaction term in the model, and one restricted the main analysis to individuals most likely to have complied with AIT (i.e., those treated with four or more pollen AIT packages the

TABLE 1 Baseline characteristics in the propensity-score matched study population, Denmark 1994–2016. See full definitions of variables in Table S4.

Baseline characteristic		Propensity-score matched sample (1:2)		
		Pollen AIT treated	Not treated	Std. diff.
Total number of AR individuals		7760	15,520	
Baseline sampling years (dates 1 September to 31 August each year)				
	1998–2001	20.8%	20.8%	0.00
	2002–2005	27.8%	27.8%	0.00
	2006–2009	22.2%	22.2%	0.00
	2010–2013	29.2%	29.2%	0.00
Demographic characteristics				
Women		43.9%	44.3%	−0.01
Age at 1 September in baseline sampling year	5–9 years	9.8%	9.1%	0.02
	10–14 years	17.9%	18.5%	−0.01
	15–24 years	20.2%	20.9%	−0.01
	25–34 years	22.3%	22.4%	−0.00
	35–44 years	18.2%	18.4%	−0.01
	45+ years	8.2%	8.0%	0.01
Time since first prescription of INS	0–1 years	32.5%	31.9%	0.01
	2–4 years	31.4%	31.7%	−0.01
	5–9 years	24.5%	24.5%	−0.00
	10+ years	11.6%	11.8%	−0.01
Use of AR medicine in last three pollen seasons (prebaseline use)				
Nasal inhaler, persistence	1 year out of 3	44.9%	45.3%	−0.01
	2 years out of 3	30.5%	30.5%	−0.00
	3 years out of 3	24.5%	24.1%	0.01
Nasal inhaler, number of packages in last three pollen seasons	0–1 pkgs.	34.6%	35.2%	−0.01
	2 pkgs.	24.3%	24.8%	−0.01
	3–4 pkgs.	24.4%	24.1%	0.00
	5+ pkgs.	16.6%	15.9%	0.02
Nasal inhaler, number of packages in last pollen season	0 pkgs.	26.8%	26.9%	−0.00
	1 pkg.	45.2%	46.0%	−0.01
	2–3 pkgs.	22.9%	22.1%	0.01
	4+ pkgs.	5.2%	5.0%	0.01
		Propensity-score matched sample (1:2)		
		Pollen AIT treated	**Not treated**	**Std. diff.**
Eye drops, number of last three pollen seasons where eye drops were used	0 years out of 3	24.2%	23.7%	0.01
	1 year out of 3	28.7%	30.0%	−0.02
	2 years out of 3	22.8%	22.8%	0.00
	3 years out of 3	24.3%	23.5%	0.02
Eye drops, number of packages in last three pollen seasons	0 pkgs.	24.2%	23.7%	0.01
	1 pkg.	22.7%	23.9%	−0.02
	2 pkgs.	16.3%	16.6%	−0.01
	3–4 pkgs.	19.1%	19.2%	−0.00
	5+ pkgs.	17.7%	16.6%	0.03

TABLE 1 (Continued)

		Propensity-score matched sample (1:2)		
		Pollen AIT treated	Not treated	Std. diff.
Eye drops, number of packages in last pollen season	0 pkgs.	42.7%	43.5%	−0.01
	1 pkg.	32.4%	32.6%	−0.00
	2 pkgs.	14.1%	14.1%	0.00
	3–4 pkgs.	10.8%	9.8%	0.03
Oral antihistamines, number of last three pollen seasons where oral antihistamines were used	0 years out of 3	18.5%	17.6%	0.02
	1 year out of 3	26.8%	27.5%	−0.01
	2 years out of 3	25.6%	26.0%	−0.01
	3 years out of 3	29.2%	28.8%	0.01
Oral antihistamines, number of packages in last three pollen seasons	0 pkgs.	18.5%	17.6%	0.02
	1 pkg.	16.6%	17.2%	−0.01
	2 pkgs.	15.5%	16.3%	−0.02
	3–4 pkgs.	23.5%	23.4%	0.00
	5+ pkgs.	26.0%	25.5%	0.01
Oral antihistamines, number of packages in last pollen seasons	0 pkgs.	34.6%	34.2%	0.01
	1 pgk.	29.4%	30.4%	−0.02
	2 pkgs.	18.8%	18.6%	0.00
	3–4 pkgs.	17.2%	16.8%	0.01
Mild/seasonal asthma[a], atopic dermatitis				
Mild/seasonal asthma medication, number of last 3 years where the asthma medication was used	0 years out 3	69.8%	69.5%	0.01
	1 years out 3	19.2%	19.1%	0.00
	2 years out 3	7.4%	7.7%	−0.01
	3 years out of 3	3.6%	3.6%	−0.00

		Propensity-score matched sample (1:2)		
		Pollen AIT treated	Not treated	Std. diff.
Mild/seasonal asthma medication, number of packages in the last 3 years pollen seasons	0 pkgs.	64.9%	64.9%	0.00
	1 pkg.	12.2%	11.9%	0.01
	2 pkgs.	7.6%	7.8%	−0.01
	3+ pkgs.	15.2%	15.4%	−0.00
Mild/seasonal asthma medication, number of packages in last pollen season	0 pkgs.	74.9%	74.8%	0.00
	1 pkg.	11.3%	11.6%	−0.01
	2+ pkgs.	13.8%	13.6%	0.00
Hospital diagnosis of allergic rhinitis		9.2%	8.0%	0.03
Atopic dermatitis (medication and/or hospital contact within last 3 years[b])		5.5%	5.4%	0.00
Parent[c] with allergic rhinitis		56.9%	57.3%	−0.01
Parent[c] with asthma		36.5%	37.0%	−0.01
General health				
Ever admitted to hospital due to respiratory illness (excluding asthma)		28.1%	26.6%	0.03

(Continues)

TABLE 1 (Continued)

		Propensity-score matched sample (1:2)		
		Pollen AIT treated	Not treated	Std. diff.
Average number of different prescriptions drugs over last 3 years	0–1 ATC odes/year	13.5%	13.7%	−0.01
	2–3 ATC odes/year	40.8%	41.6%	−0.01
	4–5 ATC odes/year	28.4%	26.6%	0.03
	6+ ATC codes/year	17.4%	18.0%	−0.01
Average number of contacts to own doctor over last 3 years (in tertiles calculated in full sample)	Lowest	37.2%	38.0%	−0.01
		39.6%	38.9%	0.01
	Highest	23.2%	23.1%	0.00
		Propensity-score matched sample (1:2)		
		Pollen AIT treated	Not treated	Std. diff.
Socio-economic characteristics				
Education[d]	Unknown	22.3%	22.0%	0.01
	Short	21.7%	21.9%	−0.00
	Intermediate	32.2%	32.7%	−0.01
	Long	23.8%	23.4%	0.01
Income[b] (in quartiles calculated in full sample)	Lowest	11.7%	11.5%	0.01
		17.8%	18.0%	−0.01
		25.8%	25.9%	−0.00
	Highest	37.2%	37.2%	−0.00

Abbreviation: Pollen-AIT, grass/birch/mugwort allergen immunotherapy.

[a]Defined as those not using medication for severe asthma and not using perennial asthma medications, also see Table S4.

[b]Using definition from Henriksen et al.[36]

[c]Coding of parent is based on the national CPR registry, Adoption registry, and Medical Birth Registry, and determined in Statistic Denmark's table FTBARN, based on parent–child relation registered shortly after birth in most cases indicate biological parents (see https://www.dst.dk/da/Statistik/dokumentation/Times/fertilitetsdatabasen/far-foed-adop).

[d]Coding of education: Short: Primary education or lower secondary; intermediate: Upper secondary, vocational training, some further education not equivalent of a bachelor's degree; long: Further education equivalent of a bachelor's degree or higher.

first 3 years). Post hoc analyses were performed to (a) explore why negative effectiveness was observed in some years, and (b) to address a sub-hypothesis that pollen AIT might have effectiveness for asthma.[10] The post hoc analyses comprised an analysis of effect modification by prebaseline AR medication (one out of two, two out of two, and three out of three prebaseline years of use), and an analysis conditioning on use of AR medication last pollen season (yes/no)—both investigated by introducing interaction terms in the model. Furthermore, to examine bias from different health seeking behaviour by treatment group, we calculated and plotted over time the mean number of different medication groups that individuals used (main ATC anatomical groups) and the mean number of contacts to G.P, by treatment group. To look at use rather than users, we plotted over time the amount of nasal inhalers dispensed by treatment group. Finally, to look at asthma as outcome, the main analysis was performed with asthma medication as outcome (see definition in Table S11). All analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

3 | RESULTS

We identified 26,949 new pollen AIT treated patients aged >5 years in Denmark in the period 1.9.1997 to 31.8.2013, of which 19,042 had AR (INS users), and among these 7760 were eligible for inclusion in the study (4373 grass, 1374 birch, 60 mugwort, and 2134 a combination of the 3 AITs). Major reasons for exclusion were not being INS user in the last three pollen seasons (55% of all new pollen AIT) or having severe or perennial asthma the last 3 years before baseline (20% of all new pollen AIT) (Figure 1). Each pollen AIT treated individual was successfully matched to two non-treated individuals resulting in a sample of 15,520 non-treated AR individuals. Before matching, the pollen AIT treated group was substantially younger and had a higher use of all types of AR prescription medication than other AR individuals (data not shown). After propensity score matching, the treated and non-treated group were well balanced, with the standardized difference well below 10% for all covariates (Table 1). Assuming one pollen AIT treatment package lasts 6 months, the cumulative percentages of patients ending their last

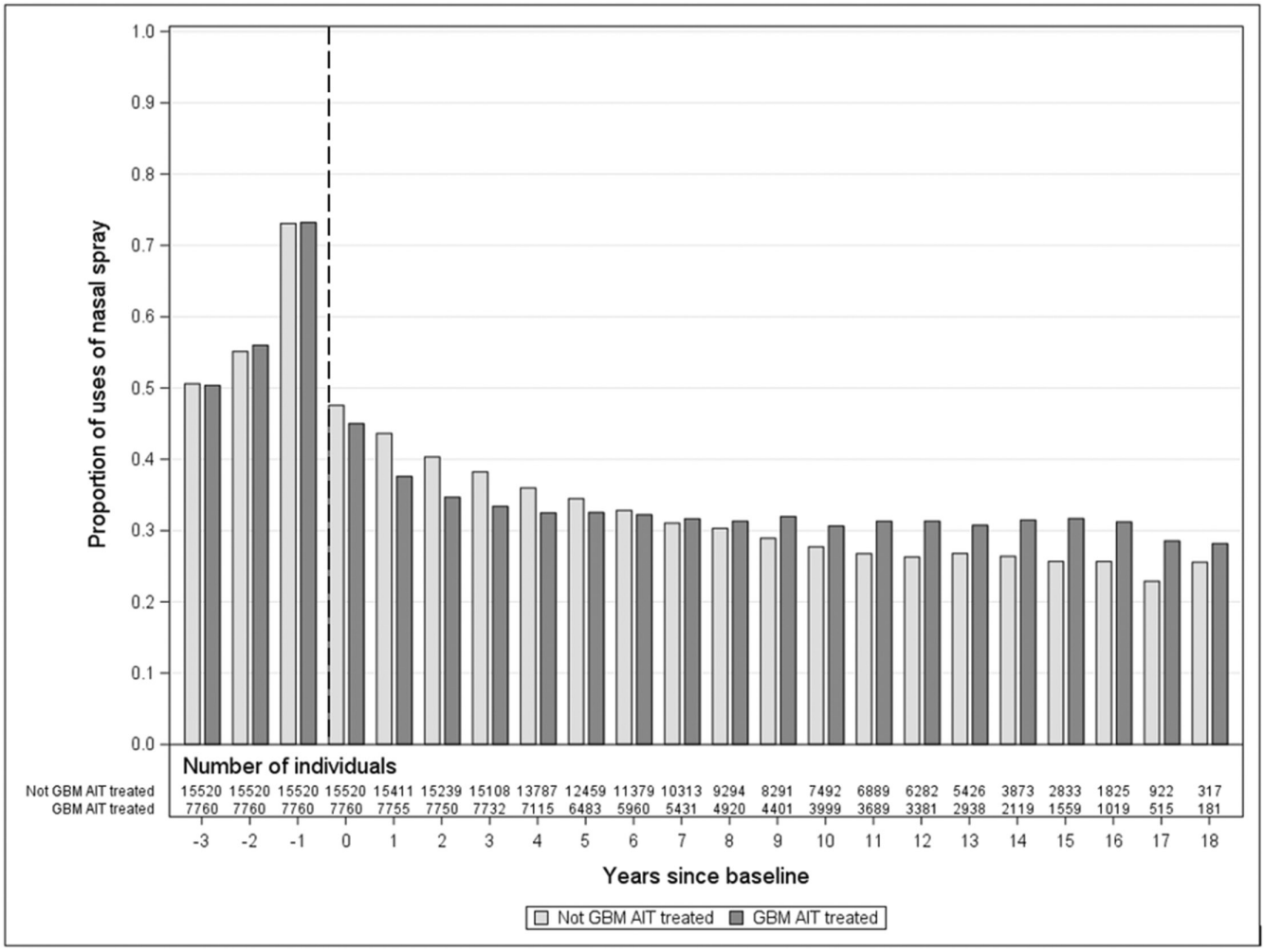


FIGURE 2 Proportion of users of nasal inhaler (in figure "spray") in the pollen season among 7760 pollen AIT treated versus 15,520 matched not pollen AIT treated individuals with AR by year since baseline (dotted line), including 3 years before baseline date, Denmark 1994–2016. Pollen allergens included grass, birch, and mugwort (GBM).

treatment 4, 5, and 6 years after first treatment was 70%, 87%, 94%, respectively (data not shown).

3.1 | Main result

For the primary outcome of nasal inhaler users, Figure 2 shows the proportion who used nasal inhaler in the pollen AIT treatment and the non-treatment group by year including the 3 years before baseline. Overall, in both groups, the proportion of nasal inhaler users increased and peaked in the 3 years before baseline, and then dropped immediately after baseline. In the pollen AIT treated group, the proportion of nasal inhaler users was lower 0-5 years after baseline, when compared with no treatment (0–2 years, OR 0.84, 95% CI 0.81–0.88; 3–5 years, OR 0.88, 95% CI 0.84–0.92), but then remained constant while the proportion in the non-treated group dropped, thereby yielding a relative higher proportion of nasal inhaler users among treated in the later period (6–9 years, OR 1.03, 95% CI 0.97–1.08; 10–18 years, OR 1.18, 95% CI 1.11–1.26) (Figure 2; Table 2).

For the secondary outcome of eye drop users, the results of the main analysis was similar (Table 2). However, for the secondary outcome of oral antihistamine users, the proportion of users was constantly higher in the pollen AIT group, when compared with the non-treated group (0–2 years, OR 1.24, 95% CI 1.18–1.29; 3–5 years, OR 1.19, 95% CI 1.14–1.25), and even higher after 6 or more years (6–9 years, OR 1.29, 95% CI 1.23–1.36; 10–18 years, OR 1.44, 95% CI 1.35–1.54), despite the two groups being well-matched on prebaseline use (Tables 1 and 2).

In an additional analysis, the main result were stratified on years of prebaseline AR medication (see Figure 3; Table S6). For individuals in the strata with 2 of 3 years prebaseline use of nasal inhaler (30.5% of pollen AIT treated), the result (see Figure 3) was similar to the main result. For individuals in the strata with 3 of 3 years prebaseline use of nasal inhaler however (24.5% of pollen AIT treated), the proportion of nasal inhaler users in the treated group was lower 0–9 years after baseline but then became equal to the proportion in the non-treated group (0–2 years, OR 0.59, 95% CI 0.54–0.64; 3–5 years, OR 0.64, 95% CI 0.59–0.71; 6–9 years, OR 0.82, 95% CI 0.75–0.91;

TABLE 2 The OR of using AR medication in 7760 pollen AIT treated versus 15,520 matched not pollen AIT treated individuals with AR by years since baseline and type of AR medication, Denmark, 1994–2016.

Type of AR medication	Years since baseline	Pollen AIT treated		Not pollen AIT treated		OR for using AR medication[b]
		N[a]	%	N[a]	%	
Nasal inhaler	0–2	23,265	39	46,170	44	0.84 (0.81, 0.88)
	3–5	21,330	33	41,354	36	0.88 (0.84, 0.92)
	6–9	20,712	32	39,277	31	1.03 (0.97, 1.08)
	10–18	19,400	31	35,859	27	1.18 (1.11, 1.26)
Eye drops	0–2	23,265	35	46,170	37	0.93 (0.89, 0.98)
	3–5	21,330	28	41,354	30	0.94 (0.89, 0.98)
	6–9	20,712	26	39,277	24	1.12 (1.05, 1.18)
	10–18	19,400	24	35,859	19	1.27 (1.18, 1.36)
Oral antihistamine	0–2	23,265	50	46,170	45	1.24 (1.18, 1.29)
	3–5	21,330	41	41,354	37	1.19 (1.14, 1.25)
	6–9	20,712	37	39,277	31	1.29 (1.23, 1.36)
	10–18	19,400	34	35,859	26	1.44 (1.35, 1.54)

Abbreviations: AR allergic rhinitis, OR, odds ratio; pollen AIT, grass/birch/mugwort allergen immunotherapy.

[a]Number of observations in time intervals. Since each individual contribute with one observation for each year of follow-up, this number is larger than the number of individuals included in the analysis.

[b]The OR for using AR medication is modelled by repeated measure logistic regression using GEE modelling of correlations.

10–18 years, OR 0.95, 95% CI 0.84–1.08) (Figure 3). For individuals in the strata with 1 of 3 years prebaseline use of nasal inhaler (44.9% of pollen AIT treated), the proportion of nasal inhaler users became higher in the pollen AIT treated group already 3 years after baseline. For use of eye drops and oral antihistamine, stratification on prebaseline use yielded a compatible result pattern (Table S6).

Because our main analyses were based on yearly users of AR medication (and not each individual's course of use over the years), we also performed an additional analyses, where we estimated the effectiveness of pollen AIT on use of AR medication every follow-up year conditional on an individual's use of AR medication in the last pollen season (yes/no). Regardless of years since baseline, the proportion of nasal inhaler users was lower in the treated vs non-treated group within patients who used nasal inhaler in the last pollen season (0–2 years, OR 0.76, 95% CI 0.72–0.79; 3–5 years 0.86, 95% CI 0.81–0.93; 6–9 years, OR 0.94, 95% CI 0.87–1.02; 10–18 years, 0.94, 95% CI 0.86–1.04), that is, these patients had a tendency to stop using nasal inhaler, whereas the proportion was higher in the treated vs. non-treated group within patients who did not use nasal inhaler in the last pollen season (0–2 years, OR 1.02, 95% CI 0.95–1.10; 3–5 years 1.11, 95% CI 1.04–1.19; 6–9 years, OR 1.23, 95% CI 1.15–1.32; 10–18 years, 1.33, 95% CI 1.23–1.44), that is, such patients had a tendency to start using nasal inhaler when not having used nasal inhaler in the last pollen season (Table 3). The findings were similar for the proportion of eye drop users, and even for the proportion of oral antihistamine users (Table 3), and even after stratification for prebaseline use (Table S7, shown for nasal inhaler users only). In the latter analysis, however, every year those with the lowest prebaseline use (1 of 3 years) had a tendency to start using nasal inhaler, whereas only some years this was the case for those with higher prebaseline uses (2 or 3, of 3 years) (Table S7).

In sensitivity analyses to the main analysis, we observed that the main result was similar for patients treated only with grass, birch, or mugwort AIT (Tables S8 and S9), or with the recommended 3 years of treatment defined as at least four filled prescriptions of pollen AIT in the first 3 years (Table S10). For patients treated with multiple AITs, the proportion of nasal inhaler users was lower in the first 10 years after baseline and then became equal to the proportion in the non-treated group (Table S8 and S9).

In an alternative outcome analysis, we examined a concern that the pollen AIT might change patients' general health seeking behaviour more than for the non-treated group, by using health registrations in general as outcomes. We observed an almost equal use of the different ATC main anatomical groups of medications (excluding AIT prescriptions) in the pollen AIT treated and non-treated group every year (Figure S2a). Furthermore, the long term use of GP services were also almost equal in the two comparison groups, except in the first 0–5 years after baseline when GP services related to AIT however could not be excluded (Figure S2b). In a final analysis, we used number of prescribed AR medication packages as outcome and depicted the results in Figure S3. Among others, the figure shows that after baseline, less than 50% used at least one nasal inhaler, and less than 20% used at least two nasal inhalers, in a pollen season.

We did a different additional post hoc analysis, and explored the effectiveness of pollen AIT on "new" medication use for the outcome of severe or perennial asthma. The results are presented and

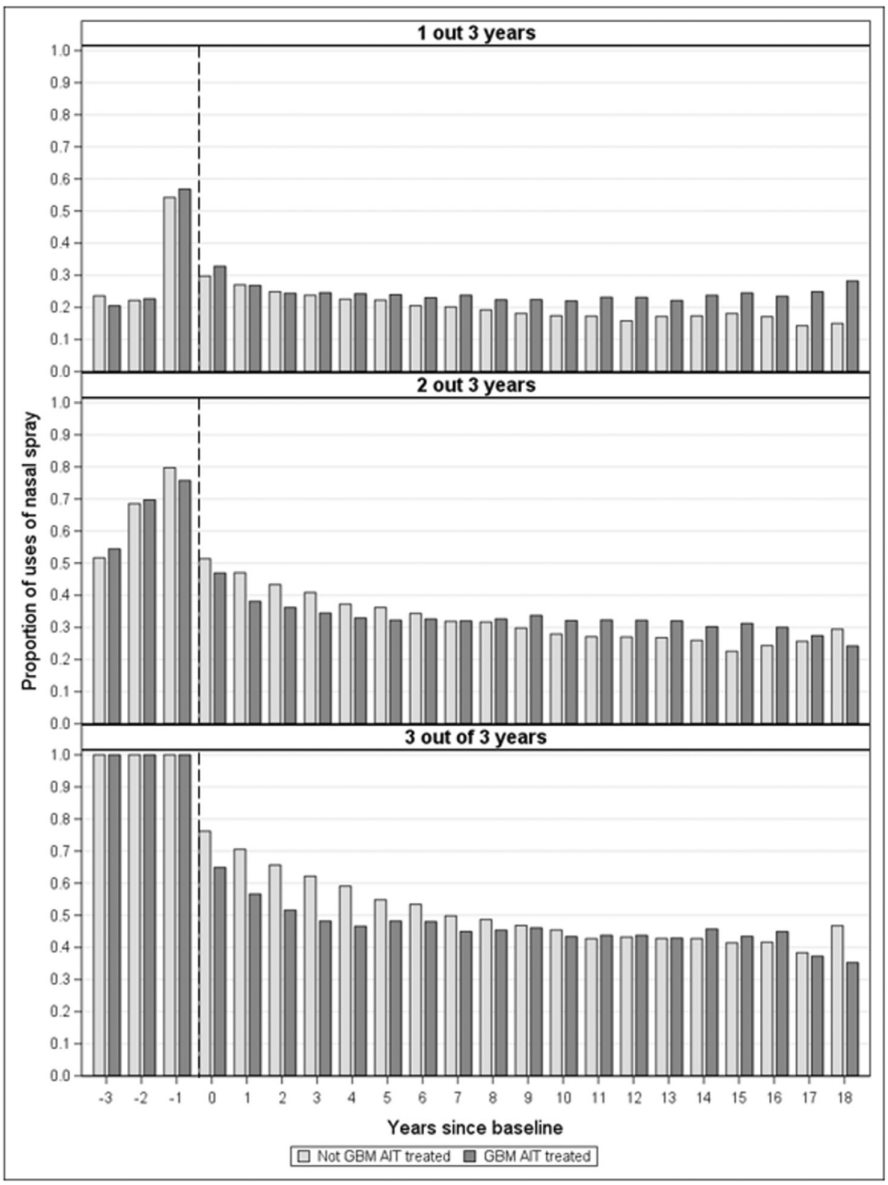


FIGURE 3 Proportion of users of nasal inhaler (in figure "spray") in the pollen season among 7760 pollen AIT treated versus 15,520 matched not pollen AIT treated individuals with AR by years since baseline (dotted line) stratified by prebaseline nasal inhaler use (1, 2, 3 out of 3 years), Denmark 1994–2016. Pollen allergens included grass, birch, and mugwort (GBM). Note that the drop in number of individuals each year is due to end of study in 2016 (truncation) and thus unrelated to treatment group.

discussed in the supplement (see text preceding results in Table S11–S13). This analysis should however be interpreted with caution as the study was not designed to study asthma cases.

4 | DISCUSSION

This longitudinal study of routine care data showed that patients on pollen AIT to a higher degree stopped using nasal inhaler in the first 0–5 years but not later. In post hoc analyses, this finding was more consistent among patients with persistent AR.

4.1 | Interpretation

The observed effectiveness up to 5 years is compatible with findings in clinical trials with a follow-up range of 5 years (<300 pollen AIT patients),[13–16] as well as multiple analyses of regional German and French prescription data with up to 6 years of follow-up (<9000 pollen AIT patients)[7–12] and more recently 9 years of follow-up (>25,000 pollen AIT patients of total 46,024 AIT patients).[5,6]

We also observed that effectiveness was more consistent among patients with persistent AR. This finding was derived during several post hoc analyses (see Figure S1), which we did to explore an unexpected result in the main analysis, notably a constant excess of users of oral antihistamine, and after 6 years also an excess of nasal inhaler and eye drop users (i.e., a negative effectiveness of pollen AIT). This surprising result suggested an additional effect not related to the immunological effect of pollen AIT. To investigate this, we first stratified by prebaseline-levels of AR persistence, and since this did not fully account for the excess use, we conditioned each follow-up year on use or no use in the last pollen season—thereby better capturing changes in individual use. Here, excess users were completely confined to those

TABLE 3 The OR for using nasal inhaler, eye drops, and oral antihistamine in 7760 pollen AIT treated versus 15,520 matched not pollen AIT treated individuals with AR by years since baseline and use of the AR medication type in the latest pollen season (yes/no), Denmark, 1994–2016.

		Use of the AR medication type in the latest pollen season									
		Yes					No				
		Pollen AIT treated		Not pollen AIT treated			Pollen AIT treated		Not pollen AIT treated		
Type of AR medication	Years since baseline	N[a]	%	N[a]	%	OR for using the AR medication	N[a]	%	N[a]	%	OR for using the AR medication
Nasal inhaler	0–2	12,083	55	25,280	62	0.76 (0.72, 0.79)	11,182	22	20,890	22	1.02 (0.95, 1.10)
	3–5	7110	62	15,734	67	0.86 (0.81, 0.93)	14,220	18	25,620	18	1.11 (1.04, 1.19)
	6–9	6624	65	12,654	66	0.94 (0.87, 1.02)	14,088	16	26,623	14	1.23 (1.15, 1.32)
	10–18	6007	68	9664	69	0.94 (0.86, 1.04)	13,393	14	26,195	11	1.33 (1.23, 1.44)
Eye drops	0–2	10,139	58	20,434	64	0.77 (0.73, 0.81)	13,126	17	25,736	15	1.10 (1.02, 1.18)
	3–5	6186	61	13,044	65	0.89 (0.82, 0.96)	15,144	14	28,310	13	1.17 (1.09, 1.26)
	6–9	5544	64	9897	64	0.96 (0.88, 1.04)	15,168	12	29,380	10	1.28 (1.18, 1.38)
	10–18	4690	66	6997	65	0.92 (0.83, 1.02)	14,710	10	28,862	8	1.37 (1.26, 1.50)
Oral antihistamine	0–2	13,143	66	24,407	68	0.86 (0.82, 0.90)	10,122	29	21,763	19	1.72 (1.61, 1.84)
	3–5	9033	66	16,098	69	0.83 (0.78, 0.89)	12,297	22	25,256	16	1.39 (1.30, 1.49)
	6–9	7909	68	12,767	68	0.92 (0.85, 0.99)	12,803	18	26,510	13	1.46 (1.36, 1.57)
	10–18	6705	70	9477	69	0.92 (0.84, 1.01)	12,695	15	26,382	10	1.50 (1.38, 1.63)

Abbreviations: AR, allergic rhinitis; OR, odds ratio; pollen AIT, grass/birch/mugwort allergen immunotherapy.

[a]Number of observation in time intervals. Since each individual contribute with one observation for each year of follow-up, this number is larger than the number of individuals included in the analysis.

with no use last pollen season. The remaining of these post hoc analyses focused on health-seeking behaviour but did not suggest an explanation. An overall conclusion is that AIT effectiveness in patients with less persistent AR may be difficult to detect with observational data. One potential bias in this context, could be that their doctor consulting behaviour, and thus prescribing, could be more variable and modifiable than in persistent AR. As suggested in a population-based study of AR, the perception, which the subject has on the severity of his/her disease, influences the decision whether or not to consult.[35] Other explanations to the additional effects we observed could however also be possible.

The surprising drop in AR medication users immediately after baseline, regardless of pollen AIT, was an unexpected observation. However, pollen AIT is often considered when AR has become chronic, severe, and/or unresponsive to medication. Because this represents a peak in the course of the disease, the number of users may also peak (and this resembles a regression towards the mean phenomenon), and a subsequent drop in AR medication use would be expected, also in the control group because of the matching on a similar duration and severity of AR as in the pollen AIT group.

Our results for pollen AIT effectiveness for 0–5 years are applicable to a selected group of individuals with AR. For example, by our definition about 10% of individuals more than 5 years old in Denmark had AR (i.e., INS use in recent pollen seasons), a proportion somewhat lower than reported for any use of INS.[36] Among the 10%, only 2.2% started on pollen AIT. However, the proportion eligible for pollen AIT is likely larger. For example, 75%–80% of AR patients are estimated to have moderate–severe AR.[35] Further studies are warranted to estimate if a reduction in disease burden and costs could be achieved by treating more AR patients with AIT.

4.2 | Strengths

The study had several strengths. Foremost, the use of real-world data to address long-term effectiveness of pollen AIT over as much as 18 years. In addition, we included detailed individual level data 3 years before baseline. Among others, this allowed us to match pollen AIT patients to non-treated individuals with a similar baseline level of AR medication and history of allergic diseases, thereby strongly reducing potential confounding by a higher baseline severity and persistence of AR in the pollen AIT group.[37]

We acknowledge that AR medication can only be used as proxy for severity and persistence of symptoms. However, since the national register data presented 1.1 million AR individuals (INS users) available for matching, we could match in detail for both number of packages used in the three pollen seasons before baseline (a proxy for severity or intensity of AR) and how many of the three pollen seasons the medication was used (a proxy for persistence of AR), and this was possible for each specific AR medication. The two comparison groups were also matched on income and educational level, because previous reports suggested AIT patients e.g. have a higher education level.[38,39] Such factors were not considered in previous real-world studies of AIT effectiveness, mainly based on German claims databases.[5–12] We

chose a design where comparisons groups were evaluated in the same pollen seasons over time, so that pollen exposure would be relatively equal. We had data to perform several sensitivity analysis of the robustness of results. For example, the main results for pollen AIT were robust for grass, birch, or mugwort AIT received alone or in combinations, and even regardless of a higher number of administered pollen AIT packages. Another (post hoc) analysis showed that markers of the general health seeking behaviour, that is, medication use and primary care, were at the same level for pollen AIT patients and non-treated individuals during follow-up, except for an excess G.P. contacts the first 0–5 years. The last result is likely related to pollen AIT referrals and prescribing (i.e., allergy specialist in Denmark register services as within the G.P. specialty), and is compatible with the German REACT-study finding that subjects treated with AIT were seen more frequently by specialists during the first three to five follow-up years, than non-treated in the prescription database.[5]

4.3 | Limitations

A limitation of the study was the lack of data on clinical diagnosis of AR and sensitization status. However, to identify those suffering from AR we restricted our analysis to individuals using INS, which is the classic common effective and specific medication prescribed for AR. Furthermore, we expected the pollen AIT group to have a diagnosis of AR with moderate-to-severe symptoms and confirmed sensitisation status, because it is a prerequisite for the therapy. In the non-treated group, we cannot rule out some misclassification of AR. However, we matched in detail their AR medication use in the three prebaseline years (including INS), with that of the pollen AIT patients. This algorithm is more valid than one used in the only Danish validation study so far, which differently defined AR by 1 year of INS use only, and reported a positive predictive value of 53% for a clinical AR diagnosis.[31] In addition, a bias from misclassification of AR in the non-treated group would tend to overestimate effectiveness, because of less use in the non-treated group. In contrast, we observed effectiveness was reversed or absent in strata with low prebaseline use, where such bias would be largest, but we also observed that effectiveness was better in the strata with the largest prebaseline use where such bias would be smallest (see Table S6). Thus, our results are not consistent with a bias from misclassification of AR in the non-treated group.

A potential limitation was the lack of data on sensitization status for grass, birch or mugwort pollen allergens. This means that a grass-AIT patient could be matched correctly to a grass-allergic patient but also incorrectly with a birch- or mugwort-allergic patients, and so forth. However, because all three types of pollen allergens were mixed in the AIT group, and since the choice of AR medication do not differ by type of pollen allergy, this is unlikely to bias the results. In addition, we included only prescriptions filled close to or during Denmark's GBM pollen season from April to August.[40]

It might be argued that prescriptions are a proxy for use, and that some over-the-counter medication are not included in the study data. However, AR is considered a chronic disease, and in Denmark individuals with chronic disease are obligated to use prescriptions, for reimbursement purposes. In addition, as also argued previously,[5,41] an increased use of over-the-counter medication over time would impact all AR subjects and is therefore not likely to account for the consistent reductions in AR medication users over time compared to well-matched controls, and is an unlikely source of bias. Also, in Denmark, only 30%–40% of any antihistamine users were from over-the-counter sales up to end of follow-up in 2016 (i.e., using non-individual level national sales data on www.medstat.dk/en).

5 | CONCLUSION

In conclusion, this longitudinal study over 18 years demonstrated that routine care patients who received pollen AIT, compared to non-receivers, had a lower consumption of nasal inhaler medication in the first 0–5 years after starting pollen AIT, and not beyond 5 years. Post hoc analyses suggested results were more consistent for patients with persistent AR.

AUTHOR CONTRIBUTIONS

Drs Bager and Poulsen had full access to all of the data in the study and together with Dr Wohlfahrt take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors. Acquisition, analysis, and interpretation of data: All authors. Drafting of the manuscript: Drs Bager and Poulsen. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Drs Poulsen and Wohlfahrt. Administrative, technical, or material support: All authors. Study supervision: All authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in relation to this work.

DATA AVAILABILITY STATEMENT

The data are available for research upon reasonable request to the Danish Health and Medicines Authority, Statistics Denmark, and

the Research services for the Danish Health Data authority within the framework of the Danish data protection legislation and any required permission from relevant authorities.

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29. Astma-allergiDanmark. Patient Association that among others collects and provides national pollen data for research and surveillance A

database was granted for the study that contains daily pollen and fungal sporecounts from sporetraps in east (Copenhagen) and west (Viborg) Denmark since 1990s Astma-Allergi Danmark wwwastma-allergidk.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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