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ORIGINAL ARTICLE

Rhinitis, Sinusitis, and Upper Airway Disease

Natural course of pollen-induced allergic rhinitis from childhood to adulthood: A 20-year follow up

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Abstract

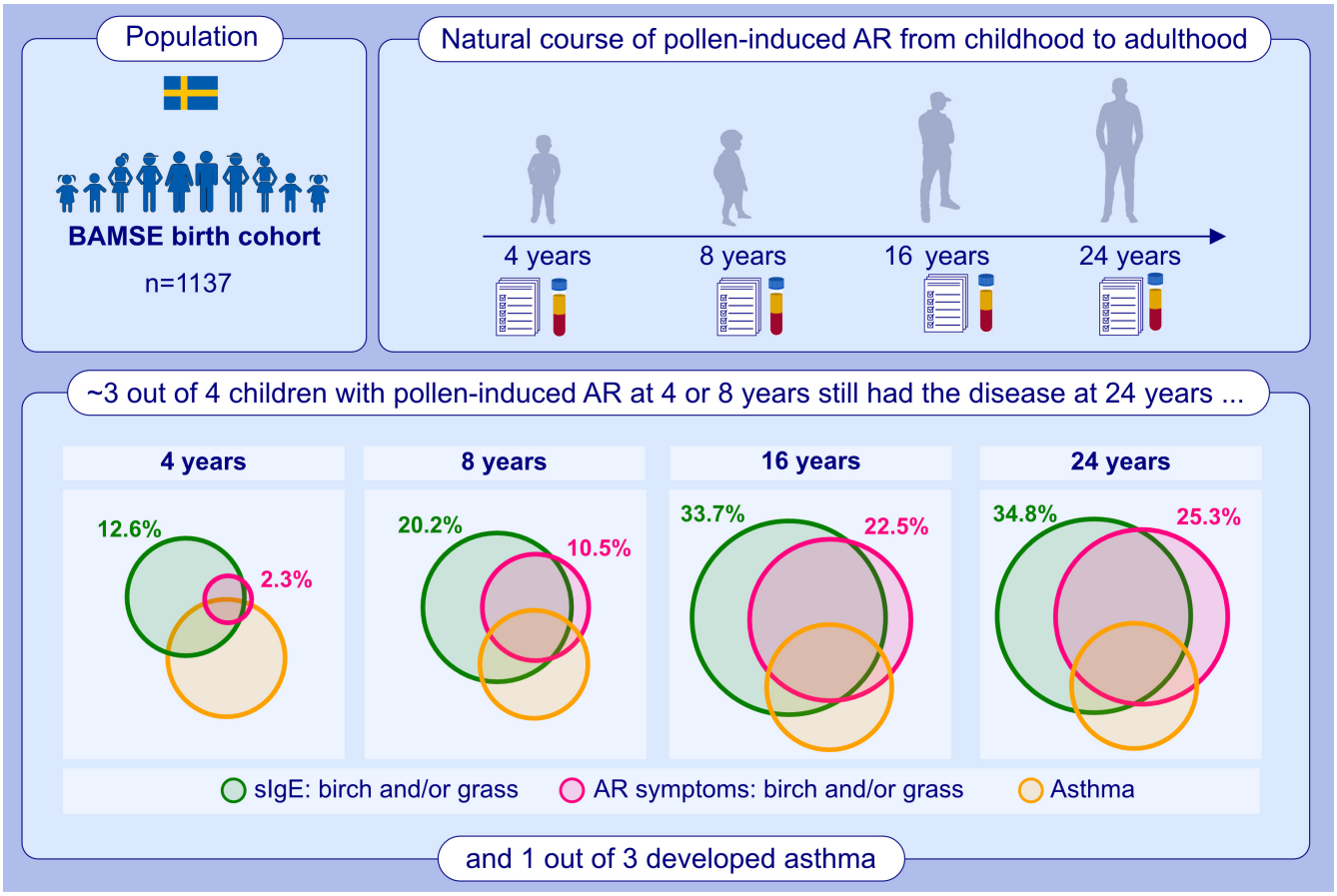
Background: Allergic rhinitis (AR) is one of the most common chronic diseases worldwide. There are limited prospective long-term data regarding persistency and remission of AR. The objective of this study was to investigate the natural course of pollen-induced AR (pollen-AR) over 20 years, from childhood into early adulthood.

Methods: Data from 1137 subjects in the Barn/Children Allergi/Allergy Milieu Stockholm Epidemiologic birth cohort (BAMSE) with a completed questionnaire regarding symptoms, asthma, treatment with allergen immunotherapy (AIT) and results of allergen-specific IgE for inhalant allergens at 4, 8, 16 and 24 years were analyzed. Pollen-AR was defined as sneezing, runny, itchy or blocked nose; and itchy or watery eyes when exposed to birch and/or grass pollen in combination with allergen-specific IgE ≥0.35kU$_A$/L to birch and/or grass.

Results: Approximately 75% of children with pollen-AR at 4 or 8 years had persistent disease up to 24 years, and 30% developed asthma. The probability of persistency was high already at low levels of pollen-specific IgE. The highest rate of remission from pollen-AR was seen between 16 and 24 years (21.5%); however, the majority remained sensitized. This period was also when pollen-specific IgE-levels stopped increasing and the average estimated annual incidence of pollen-AR decreased from 1.5% to 0.8% per year.

Conclusion: Children with pollen-AR are at high risk of persistent disease for at least 20 years. Childhood up to adolescence seems to be the most dynamic period of AR progression. Our findings underline the close cross-sectional and longitudinal relationship between sensitization, AR and asthma.

KEYWORDS
allergic rhinitis, asthma, BAMSE, IgE, pollen allergy



GRAPHICAL ABSTRACT
1137 subjects in the BAMSE birth cohort were followed prospectively over 20 years. Children with pollen induced allergic rhinitis are at high risk of persistent disease for at least 20 years. Childhood up to adolescence seems to be the most dynamic period of AR progression. Abbreviations: AR, allergic rhinitis; BAMSE, Barn/Children Allergi/Allergy Milieu Stockholm Epidemiologic birth cohort; sIgE, specific immunoglobulin E.

1 | INTRODUCTION

The prevalence of allergic rhinitis (AR) has increased in westernized countries during the last decades and is now one of the most common chronic diseases among children and young adults.[1–3] Climate changes, leading to longer pollen seasons and higher pollen counts, may further increase the burden of disease linked to AR for both patients and society.[4,5] Furthermore, AR is strongly associated with concomitant asthma and later onset of asthma.[1,6–9] Sensitization to airborne allergens precedes the development of AR and is a strong risk factor for onset of clinical disease.[10–12] Among children up to adolescence[13,14] and young adulthood,[15] the prevalence of sensitization to tree and grass pollen increases with age and is more common among males. Remission of sensitization is infrequent and seems to be more common among females.[13–15] Multiple sensitizations and high allergen-specific IgE (sIgE) levels increases the risk of allergic respiratory disease.[11,16–18] In fact, there seems to be a dynamic process during childhood with increasing sIgE levels, number of sensitizing allergens and subsequent allergic disease.[11,19]

Regarding clinical manifestation of AR, there are studies among children up to adolescence (16–20 years of age) showing an increasing prevalence with age, also indicating AR to remain for many

years.[17,18,20,21] Studies regarding remission are scarce. In a cohort study from Isle of Wight following subjects up to 18 years of age, the rate of negative transition, between two follow up time points, was lower than the positive transition.[21] Among adults, remission rates of 12%–23% over an 8-year period have been reported.[22,23] In a recent questionnaire-based study among 20- to 44-year-olds followed over 10–20 years, the remission rate was 26% for subjects <45 years of age at follow up and 36% > 58 years.[24]

The aim of this study was to investigate the natural course of pollen induced AR (pollen-AR) by prospectively following the same individuals over 20 years, including the transition from childhood into young adulthood, with respect to prevalence, persistence, remission of disease and development of asthma. An increased understanding of pollen-AR in a long-term perspective could lead to improved recommendations regarding treatment of this large patient group.

2 | METHODS

2.1 | Study population

The Barn/Children Allergi/Allergy Milieu Stockholm Epidemiologic study cohort (BAMSE) is an unselected population-based birth cohort study of 4089 children born during 1994–1996 in Stockholm, Sweden. The complete study design is described elsewhere.[25] In short, children were recruited at a median age of 2 months and have been followed-up repeatedly with questionnaires regarding allergic diseases. At 4 time points, 4, 8, 16 and 24 years, subjects with a completed questionnaire were invited for a clinical follow up including blood samples for sIgE.[26] Included in this study were all children with results from sIgE-tests and complete questionnaire data on AR symptoms, asthma, and treatment with allergen immunotherapy (AIT) at 4, 8, 16 and 24 years of age, $N = 1137$ (Figure S1).

2.2 | Measurements of sensitization

Blood samples were screened for sIgE to inhalant allergens by using Phadiatop® [a mixture of common inhalant allergens: birch, grass (timothy), mugwort, cat, dog, horse, mould (*Cladosporium herbarum*) and house dust mite (*Dermatophagoides pteronyssinus*), Thermo Fisher Diagnostics AB, Uppsala, Sweden]. Sera with a positive Phadiatop®, defined as sIgE ≥0.35 kU_A/L, were analyzed for sIgE to the included airborne allergens (ImmunoCAP™, Thermo Fisher Diagnostics AB, Uppsala, Sweden).

2.3 | Definitions of outcomes

2.3.1 | Pollen induced allergic rhinitis (pollen-AR)

Symptoms of AR to birch- and/or grass pollen, in combination with sensitization to birch and/or grass.

2.3.2 | Sensitization

sIgE ≥0.35 kU_A/L to birch and/or timothy grass.

2.3.3 | Symptoms of pollen-AR

Self-reported sneezing, runny, itchy or blocked nose; and/or itchy or watery eyes when exposed to birch- and/or grass pollen.

2.3.4 | Persistent pollen-AR

4–24 years: pollen-AR at 4 and 24 years.
8–24 years: pollen-AR at 8 and 24 years, no pollen-AR at 4 years.
16–24 years: pollen-AR at 16 and 24 years, no pollen-AR at 4 or 8 years.

2.3.5 | Asthma

MeDALL criteria (Mechanisms of the Development of Allergy).[27] At least two of three criteria should be fulfilled:

1. Symptoms of wheeze in the last 12 months prior to the date of questionnaire.
2. Ever doctors diagnose of asthma.
3. Asthma medicine occasionally or regularly last 12 months prior to the date of questionnaire.

2.3.6 | Eczema at 8 years

Dry skin in combination with itchy rash for 2 weeks or more AND typical localisation (face or arms/legs flexures or wrists/ankles or neck) in the last 12 months prior to the date of questionnaire 8 AND/OR doctor's diagnosis of eczema from 4 years and up to the date of questionnaire at 8 years.

2.3.7 | Pollen-food-syndrome (PFS)

Oral symptoms after ingestion of apple, pear, peach, nectarine or raw carrot; or avoiding these food items due to previous reaction. The question differed slightly over time (Data S1).

Parents answered the questionnaires at 4 and 8 years while subjects answered at 16 and 24 years.

2.4 | Statistical analyses

Calculation of *prevalence* and *average estimated annual incidence* are described in Data S1.

The overlap of sensitization to birch and/or grass, symptoms of pollen-AR and asthma at the different follow ups are illustrated with proportional Venn diagrams. Comparison of proportions between two groups was performed with chi-squared test. sIgE levels are expressed as box plots with median, and interquartile range (IQR). Comparison of median levels was done with Student's *t*-test after logarithmic transformation. Known risk factors for AR in childhood (male sex, family history of AR, high socioeconomic status, sensitization to other inhalant allergens, asthma and eczema) were analyzed with logistic regression, in the aspect of possibly affecting persistent or later pollen-AR at 24 years, stratified on sensitization to birch/grass. All variables were tested in a multivariable model. Predicted probability estimates for later and persistent pollen-AR were plotted according to levels of sIgE, based on results from an unadjusted logistic regression model. Odds ratios (OR) for asthma up to 24 years among subjects without asthma but with pollen-AR at 4 or 8 years compared to those without pollen-AR was calculated with General estimating equations (GEE). Children receiving AIT any time during the 24-year period were excluded in the longitudinal statistical analyses. All statistical analyses were undertaken with STATA Statistical Software (Version 16.1 SE StataCorp).

2.5 | Pollen counts

Data were provided by the Palynological Laboratory, Swedish Museum of Natural History, Stockholm, Sweden.

2.6 | Ethics

Permission was obtained from the Regional Ethical Review board at Karolinska Institutet, Stockholm, Sweden, throughout the study years. Participants (from 18 years) or parents provided informed consent for each follow up.

3 | RESULTS

Baseline characteristics of the study population ($N = 1137$), compared to the original cohort ($N = 4089$), are shown in Table S1. The study population consisted of a somewhat higher proportion of females, and parents with history of allergic disease, while the proportion of mothers smoking during pregnancy was slightly lower compared to the original cohort.

3.1 | Prevalence of pollen induced AR, sensitization and comorbidities

From 4 to 16 years the prevalence of sensitization to birch and/or grass increased from 12.6% to 33.7% (Figure 1). From 16 years the increase levelled off and remained approximately at the same level at 24 years (34.8%). A similar pattern was seen for the prevalence of reported AR-symptoms to birch and/or grass, with an increase from 4 to 16 years (2.3%–22.5%) followed by a minor increase from 16 to 24 years (25.3%). The proportion with pollen AR (sensitized and reporting symptoms), increased from 1.9% at 4 years, 9.0% at

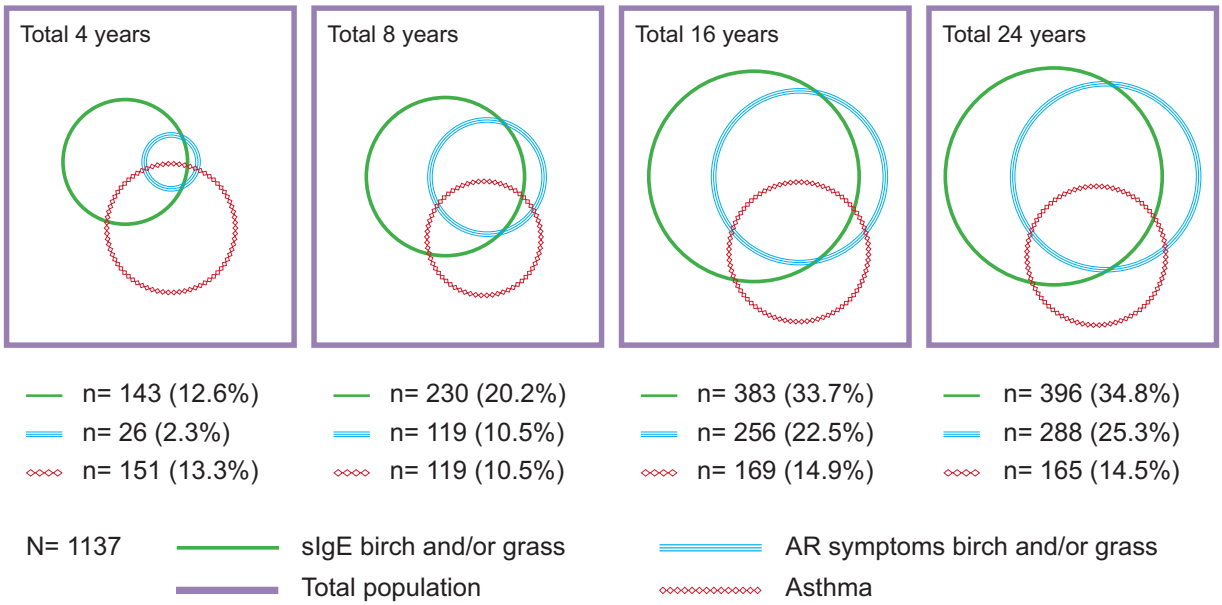


FIGURE 1 Venn diagram describing the overlap of sensitization to birch and/or grass, symptoms of pollen-induced allergic rhinitis and asthma at 4, 8, 16 and 24 years of age.

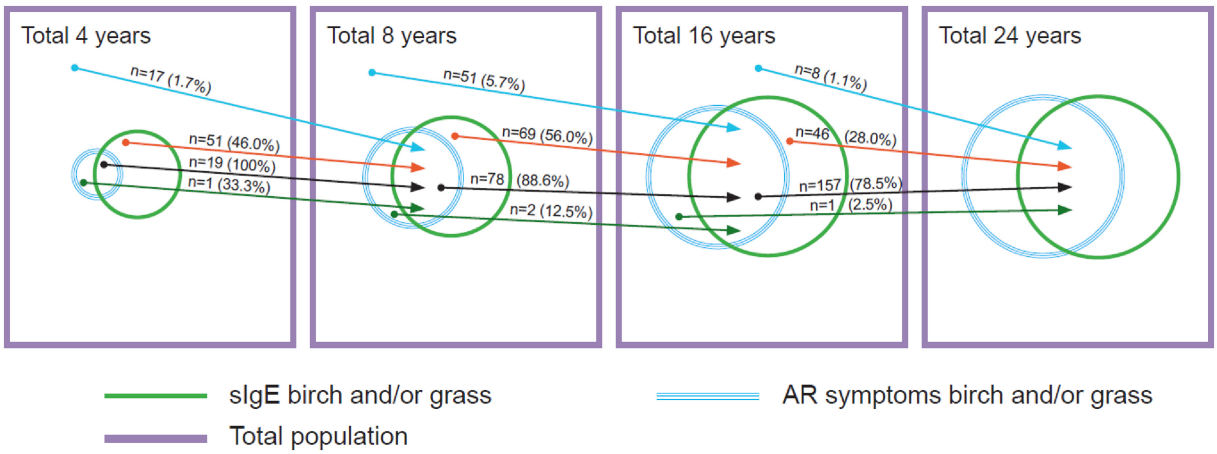


FIGURE 2 Trajectories of sensitization and symptoms of pollen induced allergic rhinitis from 4 to 24 years. Subjects who received AIT at any timepoint up to 24 years are excluded. $N = 1116$.

8 years to 18.9% at 16 years with no further increase seen from 16 to 24 years (20.0%). Pollen counts of grass pollen were on a similar level during the follow up period. Pollen counts of birch normally have biannual fluctuations. This was also seen during the follow up period in this study (Figures S2 and S3).

Asthma was found in 13.3%, 10.5%, 14.9% and 14.5% at 4, 8, 16 and 24 years, respectively. The proportion of subjects with pollen-AR who had concomitant asthma was 36.4% at age 4 years and 30.8% at 24 years. At 4 years of age the proportion of children with asthma who also had pollen-AR was 5.3%. At 8 years of age the corresponding proportion was 30.3%, increasing to 42.4%–43.8% at 16 and 24 years. Among those with AR to birch pollen, the overall proportion of reporting symptoms of pollen-food-syndrome (PFS), was rather similar at 8 years (43.9%) 16 years, (51.0%) and 24 years (47.0%) (Table S2). However, among subjects with pollen-AR from 8 years, a significantly higher proportion of PFS was reported compared to new cases at 16 years (67.1% vs. 37.0%) as well as at 24 years (66.9% vs. 22.7%).

3.2 | Trajectories of sensitization, symptoms and pollen induced AR

Figure 2 illustrates trajectories of pollen-AR, symptoms of pollen-AR only and sensitization only, from age 4, 8, 16 up to 24 years. From 4 to 8 years 100% of subjects with pollen-AR remained with pollen-AR. From 8 to 16 years and 16–24 years 88.6% and 78.5%, respectively, remained with pollen-AR. The highest remission rate of pollen-AR was seen between 16 and 24 years ($n = 43$, 21.5%). The majority of the subjects with remission of pollen-AR at 16 years remained sensitized ($n = 40$, 93.0%). A comparison between the subjects with pollen-AR at 16 years of age who remitted up to 24 years and those with persistent disease, revealed lower levels of IgE to birch and/or grass at 8 years of age (median 6.8 vs. 12.3 kU_A/L, p-value 0.039) (Table S3). A tendency towards lower median IgE levels was seen at 16 and 24 years (no statistical significance). Among subjects sensitized only, at 4 years, 46.0% developed pollen-AR up to 8 years and from 8 to 16 years 56.1%. A lower proportion (28.1%) of the sensitized only developed pollen-AR from 16 to 24 years. Most of the subjects sensitized only remained sensitized throughout the follow up time; however, between 16 and 24 years a somewhat larger proportion (15.2%) were no longer sensitized compared to between 4 and 8 (9.0%) and between 8 and 16 (5.7%) years. Among the 15.2% who remitted between 16 and 24 years, significantly lower levels of IgE to birch and/or grass at 16 years of age were noted, compared to those who remained sensitized or developed pollen AR (Table S4). Sensitization to any other inhalant allergen was less frequent among the remitting subjects compared to those who developed pollen-AR (48.0% vs. 74.0%, p-value .029). No sex differences were noted.

The number of new cases of pollen-AR at 8 years was 69 corresponding to an average estimated annual incidence of 1.5% between 4 and 8 years of age. Between 8 and 16 years of age the average estimated annual incidence was 1.3% and between 16 and 24 years 0.8%.

Among subjects with persistent pollen-AR from age 4 to 24 years there was a significant increase in sIgE levels to birch and/or grass from 4 to 8 years (28.5 vs. 75.7 kU_A/L, $p = .007$) (Figure 3). Between 16 and 24 years the levels seemed to decrease, although not statistically significant (70.1 vs. 48.4 kU_A/L). Among subjects with persistent pollen-AR from age 8 years through 24 years (but not at 4 years), there was a significant increase of sIgE levels from 4 (sensitized only) to 8 years and a decrease in sIgE levels between 16 and 24 years (74.0–39.0 kU_A/L, $p < .001$). Among subjects with pollen-AR from 16 to 24 years (not at 4 or 8 years) there was an increase in sIgE-levels up to 16 years (when sensitized only), but interestingly, from age 16 to 24 years there was a decrease (22.3–16.4 kU_A/L, $p = .035$).

3.3 | Prediction of pollen-induced AR and asthma at 24 years

The probability of persistent pollen-AR for subjects with pollen-AR at age 4–24 years was 73.7%, and from 8 to 24 years 75.0% (Table S5). Among those sensitized only, the probability of later pollen-AR, at

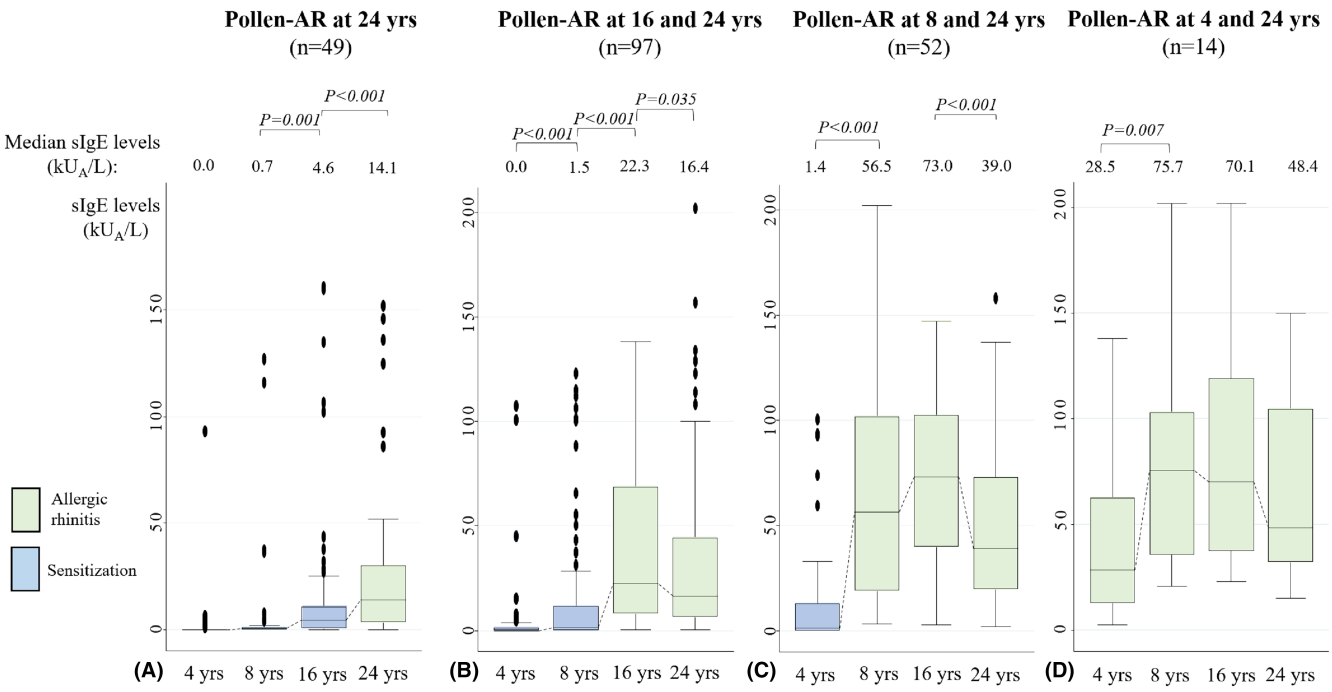


FIGURE 3 Change in sIgE-levels to birch and/or grass over time among subjects with pollen induced allergic rhinitis (pollen-AR) at 24 years (A) new cases of pollen-AR at 24 years, (B) pollen-AR from 16 years, (C) pollen-AR from 8 years, (D) from 4 years. sensitization, sIgE to birch and/or grass.

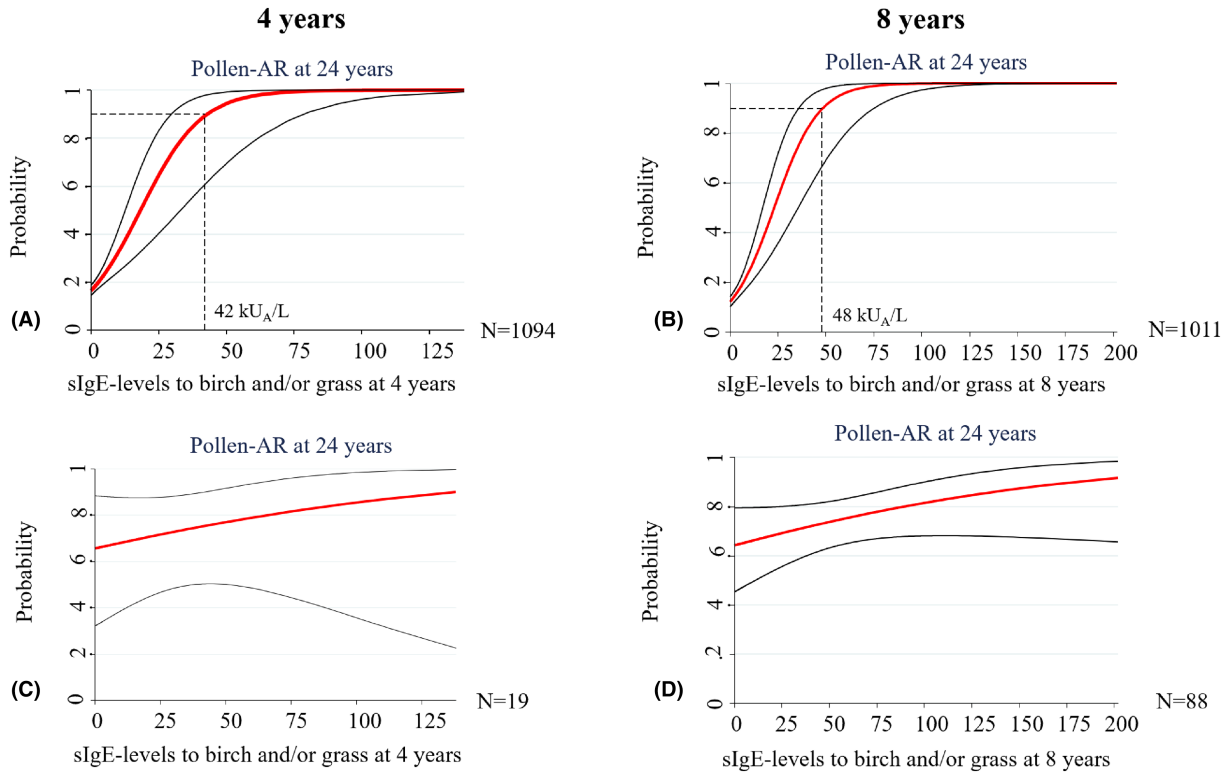


FIGURE 4 Probability of pollen-induced allergic rhinitis (pollen-AR) at 24 years in relation to sIgE levels to birch and/or grass at 4 and 8 years, respectively, among those without pollen-AR at 4 years (A) without pollen-AR at 8 years (B), with pollen-AR at 4 years (C) and with pollen-AR at 8 years (D). $n = 1116$.

TABLE 1 Proportions and odds ratios for developing asthma up to 24 years, among subjects with pollen induced allergic rhinitis, but without asthma, at 4 or 8 years, and 16 years (no pollen-AR at 4 or 8 years), respectively, without asthma at baseline and 8 years. Subjects ever treated with AIT are excluded. n.a. = not applicable.

	Asthma development up to 24 years							
	Overall up to 24 years				16 years		24 years	
Pollen induced allergic rhinitis (pollen-AR)	*n*	%	OR	95% CI	OR	95% CI	OR	95% CI
4 or 8 years								
No ($n=868$)	103	11.9	ref	ref	ref	ref	ref	ref
Yes ($n=54$)	16	29.6	3.1	1.7–5.6	3.9	2.0–7.5	2.5	1.2–5.1
16 years								
No ($n=722$)	24	3.3	ref	ref	n.a.	n.a.	n.a.	n.a.
Yes ($n=80$)	13	16.3	5.6	2.7–11.6	n.a.	n.a.	n.a.	n.a.

24 years, was 66.7% from 4 years and 61.0% from 8 years. No increased rate of pollen-AR at 24 years was seen among subjects with pollen-AR symptoms only, at 4, 8 or 16 years, compared to those without symptoms nor sensitization.

The probability of persistent pollen-AR from 4 or 8 to 24 years, or later symptoms among subjects sensitized, was not affected by sex, parental history of AR, socioeconomic status, current asthma, eczema or sensitization to other inhalant allergens in a logistic regression model. Among children with neither pollen-AR nor sensitization to birch and/or grass at age 8, asthma (adjusted OR 2.8, 95% CI 1.4–5.9) and eczema (adjusted OR 2.0, 95% CI 1.1–3.8) were the only independent risk factors for pollen-AR at 24 years (Table S6).

The probability of having pollen-AR at age 24 years increased with increasing levels of sIgE to birch and/or grass at 4 and 8 years, respectively, among children without pollen-AR at baseline (4 or 8 years) (Figure 4A,B). The 90.0% likelihood of pollen-AR at 24 years was at a sIgE-level of 42.0 kU_A/L at 4 years ($n=13$) and 48.0 kU_A/L at 8 years ($n=15$). Among children with pollen-AR at 4 or 8 years, the probability of pollen-AR at 24 years was high already at low levels of IgE (Figure 4C,D).

Among children with pollen-AR but without asthma at age 4 or 8 years, 29.6% developed asthma up to 24 years, compared to 11.9% among children without pollen-AR (OR 3.1 95% CI 1.7–5.6). From age 16 to 24 years the absolute risk was lower, 16.3%, but the odds ratio was at the same level, OR = 5.6 (95% CI 2.7–11.6) (Table 1).

4 | DISCUSSION

In this prospective long-term follow up of 1137 subjects from 4 to 24 years of age we have thoroughly investigated the natural course of pollen-AR during the transition from childhood to early adulthood. We found that approximately three out of four children with pollen-AR at 4 or 8 years still had the disease at 24 years and one out of three developed asthma. The rate of remission was low and was mostly seen between 16 and 24 years. That was also the period where the pollen-AR prevalence stopped increasing, and levels of IgE to birch and/or grass decreased, indicating that childhood up to adolescence is the most dynamic period of disease development. The risk of persistency of pollen-AR from childhood into adulthood was not much affected by sIgE levels or known risk factors for AR.

In line with findings from other birth cohorts[20,21] the prevalence of pollen-AR in our study increased with age during childhood, but after 16 years of age this increase levelled off. Others have shown that during childhood[11] and from adolescence to adulthood[28] the pollen IgE-levels tend to increase with time. This was also seen in our study, but interestingly, after 16 years of age the IgE levels to pollen seemed to decrease or stay at the same level, regardless of when the disease started. Between 16 and 24 years was also the period with the highest rate of remission of pollen-AR, and the incidence was lower. This was not explained by lower pollen counts at the 24-year follow up compared to the other time points, although, we cannot rule out lower allergen exposure prior to follow up on individual basis, or that young adults report symptoms differently, thereby potentially overestimating remission of symptoms. However, between 16 and 24 years was also the period with the highest remission of sensitization. Remission of AR and sensitization has been described in other cohorts.[14,22,29,30] These studies suggest that remission of sensitization and AR in childhood is uncommon but increases during adulthood. It may be that around 20 years of age is a time-period where this change is starting, supporting the theory that childhood up to adolescence is the most dynamic period of disease progression[31] whereafter natural tolerance becomes more common. We can only speculate regarding the immunological mechanisms. A higher IgG/IgE-ratio has been reported among asymptomatic compared to symptomatic subjects.[32] The lower sIgE-levels among the remitting subjects in our study could be in line with this, though unfortunately, we do not have data on IgG. From AIT-trials it is known that increased IgG levels on group level is associated with decreased symptoms.[33] Thus, it is tempting to speculate that continuous exposure with time, to (high levels of) allergen (cumulated exposure) may result in natural tolerance. It has been proposed that tolerance should be viewed as a dynamic lifelong process and a continuous exposure is needed to maintain or induce tolerance.[34]

The probability of persistence was high already at low levels of pollen-specific IgE. Thus, the sIgE levels were not useful in predicting which children with pollen-AR would have persistent disease. Neither did sex, family history of allergic disease, socioeconomic status, current asthma or sensitization to other inhalant allergens affect the odds. A study from the BAMSE cohort has shown that males are more often sensitized to airborne allergens up to 24 years of age.[15] However, this did not seem useful in predicting persistence of clinical symptoms. A cohort study from Isle of Wight found a stronger positive transition of AR from 10 to 18 years of age among males than females.[21] Possibly the longer follow up time in our study (8 up to 24 years) diminished these sex differences[35] or that there are differences depending on type of allergens or population. It seems as if once pollen-AR is established, the risk of persistent disease is high. This is important to keep in mind when treating patients with pollen-AR as it is well known that the disease has a negative impact on quality of life, school results and work performance.[1]

It is known that sensitization precedes AR and is a strong risk factor for later AR, which was confirmed in this study. None of the other previously known risk factors for AR[10,15,36,37] (sex, socioeconomic status, family history of allergic disease, current asthma, eczema and sensitization to other inhalant allergens) seemed to affect the probability of later symptoms in this long term follow up. Thus, our results support that sensitization is one of the strongest risk factors for later disease, up to adulthood. These findings are in line with data from a recently published cohort study where it was shown that a majority of subjects (84%) sensitized ≤8 years developed either asthma or rhinitis at 19 years of age.[29] Contrary to persistency of pollen-AR, the probability of later pollen-AR increased with increasing levels of IgE to birch and/or grass, at both 4 and 8 years and may thus be useful as a tool for identification of individuals with high-risk of pollen-AR.

Among subjects with pollen-AR the risk of developing later asthma was 3–5 times higher compared to subjects without pollen-AR. The association between AR and asthma is well established[2,38–40] and our findings highlight the importance of this association over time in an unselected population. The proportion of pollen-AR among subjects with asthma was higher in adulthood compared to childhood indicating that allergic manifestations to a larger extent causes asthma in adolescence/adulthood compared with childhood where a larger proportion probably is caused by infections.[41]

The strength of this study is the long follow up period extending from early childhood into adolescence and adulthood, the prospective design and the large number of subjects still providing blood samples in combination with clinical data regarding both sensitization and symptoms. Another strength is data on pollen counts over the entire period. This makes the results less sensitive for misinterpretations due to fluctuations in pollen counts. Furthermore, the population-based design makes the data valid for interpretation into a larger perspective. We chose to focus on the seasonal allergens birch and grass, as they by far are the most common allergens causing AR in Sweden, where house dust mite (HDM) allergy is less frequent than in the majority of European countries. Furthermore, rhinitis symptoms caused by seasonal allergens as compared to perennial allergens are easier to discriminate from infectious rhinitis symptoms, thereby minimizing misclassification. However, this could decrease the generalizability of our findings to other geographical regions where perennial allergens dominate. A limitation is that the study population consisted of only 1137 out of 4089 from the original cohort. When comparing the study population with the original cohort the differences observed were small. The observation of a higher proportion of females at the BAMSE 24-year follow up compared to the original cohort has been previously noted.[15] Also, rhinitis and IgE-sensitization as well as atopic dermatitis, were somewhat more common among those who attended the 24-year follow up, but no differences were seen between males and females. However, these differences might lead to a slight overestimation of the prevalence of pollen-AR at 24 years.

We can conclude that children with pollen-AR are at high risk of persistent disease for at least 20 years and that childhood up to adolescence seems to be the most dynamic period of disease progression. Our findings further underline the close cross-sectional and longitudinal relationship between sensitization, AR and asthma.

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CONFLICT OF INTEREST STATEMENT

M Lindqvist is an employee of ALK Nordic A/S, Kungsbacka, Sweden. E Melén has received lecture and/or advisory board fees from Airsonett, ALK, AstraZeneca, Chiesi, Novartis and Sanofi outside the submitted work. M P Borres is an employee of Thermo Fischer Scientific, Uppsala, Sweden. M van Hage reports personal fees from Thermo Fisher Scientific and AstraZeneca, outside the submitted work. M Westman reports lecture fees from Sanofi and Orion Pharma, personal fees from Viatris and research funding from ALK. Other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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