Four subtypes of childhood allergic rhinitis identified by latent class analysis

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Abstract

Background: Childhood allergic rhinitis (AR) is clinically highly heterogeneous. We aimed to identify distinct subgroups amongst children with AR, and to ascertain their association with patterns of symptoms, allergic sensitization and concomitant physician-diagnosed asthma. Methods: We recruited 510 children with physician-diagnosed AR, of whom 205 (40%) had asthma. Latent class analysis (LCA) was performed to identify latent structure within the data set using 17 variables (allergic conjunctivitis, eczema, asthma, family history of asthma, family history of allergic rhinitis, skin sensitization to 8 common allergens, tonsillectomy, adenoidectomy). Results: A four-class solution was selected as the optimal model based on statistical fit. We labeled AR latent classes as: (1) AR with grass mono-sensitization and conjunctivitis (n=361, 70.8%); (2) AR with house dust mite sensitization and asthma (n=75, 14.7%); (3) AR with pet and grass polysensitization and conjunctivitis (n=35, 6.9%) and (4) AR among children with tonsils and adenoids removed (n=39, 7.6%). Perennial AR was significantly more common among children in Class 2 (OR 5.83, 95%CI 3.42-9.94, p<0.001) and Class 3 (OR 2.88, 95%CI 1.36-6.13, p=0.006). Mild and intermittent AR symptoms were significantly more common in children in Class 3 compared to those in Class 1. AR was more severe in Class 1, compared to other 3 classes, indicating that upper respiratory symptoms are more severe among children with isolated seasonal rhinitis, than in those with rhinitis and coexisting asthma. Conclusion: We have identified 4 phenotypes in school-age children with AR, which were associated with different patterns of clinical symptoms and comorbidities.

INTRODUCTION

Allergic rhinitis (AR) is one of the most common chronic diseases of childhood(1) and its symptoms can have a major effect on quality of life (QOL), emotional well-being, sleep, daily activities, and productivity of children and adolescents, especially when they are poorly controlled(2).

For many years classification of AR was based on the temporal pattern of symptoms as seasonal and perennial. Several other attempts were also made to classify patients according to sensitization patterns and co-morbidities(3-5). Following the introduction of ARIA guidelines, the classification was mainly based on symptom severity and persistence(6). ARIA guidelines have additionally emphasized the link between allergic rhinitis and asthma, and introduced the concept of "one airway, one disease"(6).

In addition to these classical, mainly consensus-driven classifications, novel epidemiologic approaches resorting to data-driven phenotyping strategies have recently emerged to identify phenotypes of allergic diseases(7). These methods allow analysis of large datasets without prior hypotheses, and identify latent structures within such datasets which cannot be detected by traditional approaches. This approach has been successfully used

to identify subtypes of childhood wheezing(8), asthma(9), allergic sensitization(10, 11), atopic dermatitis(12), and allergic rhinitis in adults(13, 14).

We aimed to identify distinct subgroups amongst children with AR, and to ascertain their association with clinical patterns of symptoms, allergic sensitization and concomitant physician-diagnosed asthma.

METHODS

Study design, setting and participants

The Gulhane Asthma and Allergic Rhinitis Study (GAARS) is a cross-sectional study established in 2011 in Ankara, Turkey. We recruited 510 consecutive children aged 5 to 17 who presented to the Pediatric Allergy and Asthma Unit of Gulhane Military School of Medicine and received a diagnosis of AR between 2011 and 2017. The study was approved by the institutional review board of Gulhane Military School of Medicine and written informed consent was obtained from parents. Details of the study protocol can be found elsewhere(15).

Data sources

Symptoms, medication, doctor's diagnoses of allergic diseases and environmental exposures were assessed using interviewer-administered questionnaires. Information on sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work and presence of troublesome symptoms was collected to define the severity of AR. Data regarding tonsillectomy and adenoidectomy were collected from the medical records.

All children underwent skin prick testing (SPT) to common aeroallergens for our region(16), including house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass pollen mix (Phleum pratense, Poa pratensis, Dactylis glomerata, Lolium perenne, Festuca pratensis, and Avena eliator) weed pollen mix (Artemisia, Urtica, Taraxacum, Plantago) tree pollen mix (Alnus glutinosa, Corylus avellane, Populus alba, Ulmus minor, Betula alba) molds (Alternaria, Cladosporium, Penicillium, and Aspergillus) and animal dander (cat and dog). Histamine (10 mg/ml of histamine phosphate) and 0.9% saline were used as positive and negative controls, respectively. Total serum IgE level was measured using ImmunoCAP (Phadia AB, Uppsala, Sweden).

Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter, Fullerton, CA, USA) leucocyte measurements.

Pulmonary function tests were performed using Zan 100 spirometer (Nspire Health, Oberthulba, Germany) according to recommendations by the European Respiratory Society(17). Three best efforts were recorded, and the highest value (presented as percent predicted according to age, gender, weight, and height(18)) was used in the analysis.

Definitions of outcomes

Allergic rhinitis was diagnosed by a pediatric allergy specialist using the following criteria: (1) Current upper respiratory symptoms (nasal blockage, rhinorrhea, nasal itching and sneezing after allergen exposure); (2) At least one positive SPT to common inhalant allergens. The symptoms were classified as *"seasonal"* when they were limited to a certain period or a season, and as *"perennial"*when they occurred throughout the year. Duration of the symptoms was classified according to ARIA guidelines(6) as "*Intermittent* " (the symptoms present less than 4 days a week or for less than 4 consecutive weeks) or "*Persistent* " (present more than 4 days a week and for more than 4 consecutive weeks). AR was classified as "*mild* " when none of the severity items (sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work and presence of troublesome symptoms) was present, and as "*moderate/severe* " in patients with one or more of the aforementioned items.

Allergic conjunctivitis: Defined as the presence of current ocular symptoms (tearing, burning, itching and redness in the eyes) and positive SPT.

Physician-diagnosed asthma: Defined as current symptoms (wheeze and cough) and positive bronchodilator responsiveness (improvement of FEV_1 by 12% or more following administration of 200 mcg salbutamol), and/or a positive response to a trial of therapy with inhaled or oral corticosteroids(19).

Atopic dermatitis: Current pruritus and a relapsing eczematous rash typically found over flexor surfaces.

Allergic sensitization: SPT mean wheal diameter at least 3 mm greater compared to the negative control.

Parental asthma and *parental allergic rhinitis* were determined by questionnaire at enrollment.

Statistical Methods

Normally-distributed continuous data (age, age at diagnosis, lung function measures) were expressed as mean and standard deviation, and not-normally distributed continuous data (eosinophil counts and total IgE values) as median and interquartile ranges (IQR). Group comparisons carried out using student´s t-test, Mann–Whitney U-test, ANOVA or Kruskal Wallis test as appropriate for the continuous, and the chi-square test or Fisher test for categorical variables.

Latent class analysis (LCA) was performed to identify patterns of clinical clusters using 17 variables (allergic conjunctivitis, eczema, asthma, family history of asthma, family history of allergic rhinitis, skin sensitization to 8 common allergens, tonsillectomy, adenoidectomy). Starting with a latent model including 2 classes, we compared models with increasing numbers of classes using the Bayesian information criterion (BIC). The expectation maximization algorithm was used to estimate relevant parameters, with 100 000 iterations and 500 replications. The optimal number of classes was selected based on the lowest BIC, and interpretability.

Association of LCA-driven classes with clinical outcomes was examined using regression models adjusted for potential confounders, including gender and maternal history of allergic rhinitis. The odds ratio (OR) and 95% confidence interval (CI) were reported. Analyses were performed using SPSS Statistics v21.0 (IBM, Chicago, IL, USA), Stata 16 (StataCorp, College Station, TX), MPlus 8, and R (http://www.r-project.org/).

RESULTS

Descriptive statistics

A total of 510 children with AR (352 male [69%]; mean age [+- SD] 10.5 [+-3.1] years) were recruited in this study. Of these, 117 (22.9%) had mild intermittent, 92 (18.0%) mild persistent, 63 (12.4%) moderate-severe intermittent, and 238 (46.7%) moderate-severe persistent AR. 205 children (40% of study population; 35 female and 180 male patients; 9.8 +- 2.9 years) had asthma. Table 1 summarizes the demographic and clinical characteristics of all participants, and among those with and without coexisting asthma. Persistent (52 vs. 73%, $p<0.001$) and moderate-severe AR (48 vs. 67%, $p<0.001$), coexisting conjunctivitis (71 vs. 80%, $p=0.012$) and grass pollen sensitization (81 vs. 90%, $p=0.005$) were more frequent in children without asthma, whereas house dust mite (26.8 % vs. 17.4 %, $p=0.01$) and mold sensitizations (13% vs. 5%, $p=0.001$) were more common (13.2 % vs. 4.9 %, $p=0.001$) in those with asthma.

All measures of lung function were significantly lower among children with asthma (Table 1).

Latent classes of children with AR

Figure 1 shows assignment of children into AR phenotypes over a sequence of latent class analysis models with two- to five- classes based on most likely membership class. We selected a four-class solution as the optimal model based on statistical fit (BIC: two-class=6552, three-class=6512, four-class=6496, five-class=6568). Figure 2 shows the distribution of variables across classes. Based on this and clinical interpretation, the latent classes were labeled as: (1) AR with grass mono-sensitization and conjunctivitis (n=361, 70.8%); (2) AR with house dust mite sensitization and asthma (n=75, 14.7%); (3) AR with pet and grass polysensitization and conjunctivitis (n=35, 6.9%) and (4) AR among children with tonsils and adenoids removed (n=39, 7.6%).

Clinical characteristics of latent classes

Table 2 shows the clinical features of patients in each latent class. The results of the multinomial logistic regression analysis comparing the temporal pattern of AR, its duration and severity, as well as the family history of allergic diseases between different classes are shown in Table 3. We found significant differences in the duration, severity and temporal patterns of AR, and allergic conjunctivitis between the four latent classes. Boys were more likely to be in Class 3 (AR with pet and grass polysensitization and conjunctivitis; OR 2.51, 95%CI 1.08-5.80, p=0.03). Perennial AR was markedly and significantly more common among children in Class 2 (AR with house dust mite sensitization and asthma; OR 5.83, 95%CI 3.42-9.94, p<0.001) and Class 3 (AR with pet and grass polysensitization and conjunctivitis; OR 2.88, 95%CI 1.36-6.13, p=0.006). Mild and intermittent AR symptoms were significantly more common in children in Class 3 compared to those in Class 1. Maternal history of allergic rhinitis was significantly more common among children in Class 1, compared to children assigned to other clusters. AR was more severe in Class 1, compared to other 3 classes, indicating that upper respiratory symptoms are more severe among children with isolated seasonal rhinitis than in those with rhinitis and coexisting asthma.

DISCUSSION

Key findings

In this cross-sectional study, we performed latent class analysis to identify distinct subgroups of children allergic rhinitis in a large number of clinically well-defined patients with physician-diagnosed AR. The optimal solution identified four latent classes characterized by different patterns of allergic sensitization, clinical presentations and comorbidities. The largest class consisted of 361 children (70.8% of the study population) who were predominantly monosensitized to grass pollens and had concomitant ocular symptoms. Although upper airway symptoms were the most severe in this latent class (albeit seasonal), the prevalence of coexisting asthma was significantly lower compared to all other classes. 75 children (14.7%) were allocated in the AR class characterized by predominantly house dust mite sensitization and co-existing asthma. In this group, AR symptoms were significantly milder, intermittent and perennial. In the third cluster, there were 39 children (%7.6) who underwent Tonsillectomy & Adenoidectomy. The fourth cluster included 35 children (6.9%) sensitized to cats and/or dogs along with grass pollens. This pattern was associated with male gender and seasonal symptoms.

Limitations and strengths

One limitation of this cross-sectional study is the absence of longitudinal evaluation that would allow phenotype-specific trends in disease progression and pulmonary functions to be monitored over time. We also acknowledge that definitions of symptoms, medication use and environmental exposures used in our models are based on parental reporting using interviewer-administered questionnaires, and that this may reduce the accuracy of the results by introducing bias in the responses of the study parents (e.g. inaccurate recall, misreported information and/or interaction between respondent and interviewer).

The key advantage of our study is the availability of data from a large study population with similar characteristics, a well-defined clinical diagnosis and objective measures such as SPT. LCA enabled us to identify novel clinical clusters in children with AR.

Interpretation

It is well-established that atopy and allergic diseases are more frequent in prepubertal boys. In adolescence, in contrast to asthma and eczema prevalence that shifts toward females, AR continues to affect more males up to the age of 20 years(20). In our study, boys outnumbered the girls (69% vs 31%). However, male gender was not associated with asthma presence or AR severity. In agreement with previous childhood studies, allergic conjunctivitis was the most frequent (76.5%) co-morbidity amongst our patients with AR. Zicari et al.(3) have included 1200 Italian children with AR, and conjunctivitis were present in 51.7% of them, whereas Ibanez et al.(21) have reported a prevalence of 53.6% in 1275 Spanish children. However, the prevalence of conjunctivitis in our cohort was significantly higher. We note that the proportion of patients with moderate-severe persistent AR was substantially higher in our cohort compared to previous childhood

studies(3, 21), and this may account for a higher proportion of those with ocular symptoms.

According to the united airway disease concept, AR and asthma are common diseases that frequently occur together, and patients share common immunopathological features including increased bronchial hyperresponsiveness and reactivity to a variety of stimuli(6). Consistent with previous data, asthma was present in 40% of our patients(3, 19, 21). Previous epidemiological studies have predominantly emphasized the worsening effect of AR on symptoms of asthma, and it has been shown that severe and uncontrolled rhinitis symptoms were associated with severe and uncontrolled asthma in children and adolescents(22, 23). However, the impact of asthma on the severity and persistence pattern of AR symptoms in children and adolescents has rarely been investigated. In our study, in contrast with the asthma-oriented studies, the rhinitis symptoms were more severe and persistent in children without asthma(24).

Results of several studies indicated aeroallergen sensitization, particularly to HDM and Aspergillus, as one of the independent risk factors for asthma in children(25, 26). In a recent study, Chiu et al. have found significant association between HDM sensitization and various urinary metabolites which were significantly associated with childhood asthma development(27). In our study, the prevalence of HDM and mold sensitizations was significantly higher in children with asthma whereas grass pollen sensitization was lower in this group. In the cross-sectional study by Bousquet et al.(24) which included 591 adults with AR, HDM allergy was associated with perennial and milder symptoms (consistent with our results), and - in contrast to our data - persistent rhinitis. In the study by Zicari *et al.* which included 2319 Spanish children with AR, no difference was found in terms of temporal pattern and severity between HDM and grass pollen allergic children(3). The results of these studies are based on investigator-led-assignments whilst our sensitization patterns are data-driven. Boulet et al. have concluded that patients with HDM sensitizations are more prone to have asthma as a co-morbidity than those with outdoor allergy(28). In accordance with their findings, lung function parameters were significantly reduced in this group, and there was a significant association with asthma. Bertelsen et al.(4) have speculated that perennial exposure to allergens can be more related to asthma, when compared to pollen exposure which occurs only during a limited time period.

Allergy to pets is regarded as a major risk factor for asthma(29). In the study of Konradsen et al.(30), children with severe asthma had higher levels of IgE antibodies towards furry animals including cat, dog and horse. Nevertheless, the number of the studies which investigated the features of pet allergy in children with AR is limited. Zicari et al.(3) reported the prevalence of pet sensitization only in 2.5% of patients, without any clinical relevance to AR symptoms. However, in the Environment and Childhood Asthma birth cohort study, pet allergens (dog and cat) were the second most prevalent sensitizing agent in children with AR and the investigators documented two major sensitization groups (grass pollen monosensitization vs. grass pollen/furry pets polysensitization)(4). When they compared the co-morbidities and clinical characteristics, in contrast to our findings, asthma prevalence and the severity of bronchial hyperreactivity were greater in children with pet sensitization. However, in accordance with our findings, pet sensitization was associated with milder and perennial AR symptoms.

Adenoid hypertrophy (AH) is one of the most frequent co-morbidities in children with allergic rhinitis(21, 31). Results of previous studies have reported mold sensitization as a risk factor for adenoid hypertrophy in children with AR(32, 33). In agreement with this finding, sensitization to molds was significantly higher in our cluster consisted of children who underwent tonsillectomy and adenoidectomy when compared with patients in the grass-sensitized patients with conjunctivitis. Dogru et al.(33) have found an association between AH and the severity of AR in children. However, this relationship was not demonstrated in our study. The plausible explanation for the lack of this association may be that the children in this cluster were already operated and the symptom severity could be relieved due to the surgery.

Several clinical implications can be extracted from our findings. Asthma symptoms should be queried and lung function tests can be performed especially in children with house dust mite and mold sensitizations. Severe and persistent symptoms should be expected in children with grass pollen monosensitization, therefore, physicians can consider early initiation of the allergen immunotherapy in such children. Pet sensitization can accompany grass pollen sensitization especially in boys. A referral to otorhinolaryngologist in order

to exclude adenoid hypertrophy should be considered particularly in children with severe and treatment-resistant nasal obstruction and snoring.

In conclusion, we have identified four different subgroups of children with AR using LCA in this cross-sectional study, which were associated with different patterns of clinical symptoms and comorbidities.

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Tables

Table 1. Demographic data of the study population and comparison according to asthma

	Study Population (n=510)	**Children with asthma (n=205)**	**Children without asthma (n=305)**	p*
Age (y)	10.5 ± 3.1	9.8 ± 2.9	11.0 ± 3.1	< 0.001
Sex (male)	69.0	72.2	66.9	.20
Age at AR symptoms start (y)	7.0 ± 3.1	6.2 ± 2.9	7.4 ± 3.2	< 0.001
Temporal pattern - Seasonal - Perennial	77.2 22.8	74.6 25.4	79.0 21.0	.25
Duration - Intermittent - Persistent	35.3 64.7	47.5 52.5	27.1 72.9	<0.001
Severity - Mild - Moderate/severe	40.9 59.1	52.0 48.0	33.1 66.9	< 0.001
Environmental characteristics - Pet exposure - ETS exposure	11.7 39.9	10.3 42.9	12.7 37.9	.41 .27
Family history of allergic disease				
- Maternal asthma	9.8	12.3	8.2	.13
- Paternal asthma	5.1	6.4	4.3	.29
- Maternal allergic rhinitis	25.1	23.5	26.2	.49
- Paternal allergic rhinitis	17.7	16.7	18.4	.62
Co-morbid conditions - Allergic conjunctivitis - Atopic dermatitis - Tonsillectomy - Adenoidectomy - Tonsillectomy & Adenoidectomy	76.5 11.8 8.6 14.1 7.8	70.7 14.1 8.8 14.1 7.8	80.3 10.2 8.5 14.1 7.9	.012 .17 .92 .98 .98
Sensitization - Grass pollens - Tree pollens - Weed pollens - House dust mites - Cat - Dog - Molds **Monosensitization**	86.7 8.4 6.1 21.1 15.3 8.4 2.9 62.4	81.5 8.3 3.9 26.8 16.1 8.8 13,2 58.5	90.2 8.5 7.5 17.4 14.8 8.2 4.9 64.9	.005 .93 .09 .01 .68 .82 .001 .15
Total IgE (kU/L)	92 (34-183)	88 (37-202)	96 (34-170)	.70
Blood eosinophils (%)	4.3 (2.7-7-0)	4.0 (2.3-7.4)	4.5 (2.8-6.9)	.12

Blood eosinophils (/mm^3)	290 (180-497)	295 (173-518)	290 (190-485)	.86
FEV$_1$ % predicted	97 ± 15	87 ± 13	104 ± 11	< 0.001
FVC % predicted	94 ± 13	89 ± 14	98 ± 11	< 0.001
FEV$_1$/FVC %	90 ± 7	87 ± 8	91 ± 6	< 0.001
PEF % predicted	90 ± 17	82 ± 16	95 ± 16	< 0.001
FEF$_{25\text{-}75}$ % predicted	94 ± 21	77 ± 19	108 ± 20	< 0.001
ETS = Environmental tobacco smoke. Continuous variables are given as mean and standard deviation or median (interquartile range) and binary variables are given as frequency (%). *: The p value denoted the difference between children with and without asthma	ETS = Environmental tobacco smoke. Continuous variables are given as mean and standard deviation or median (interquartile range) and binary variables are given as frequency (%). *: The p value denoted the difference between children with and without asthma	ETS = Environmental tobacco smoke. Continuous variables are given as mean and standard deviation or median (interquartile range) and binary variables are given as frequency (%). *: The p value denoted the difference between children with and without asthma	ETS = Environmental tobacco smoke. Continuous variables are given as mean and standard deviation or median (interquartile range) and binary variables are given as frequency (%). *: The p value denoted the difference between children with and without asthma	ETS = Environmental tobacco smoke. Continuous variables are given as mean and standard deviation or median (interquartile range) and binary variables are given as frequency (%). *: The p value denoted the difference between children with and without asthma

Table 2. Clinical features of patients according to classes

	AR with grass mono-sensitization and conjunctivitis (70.8 %)	**AR with pet and grass polysensitization and conjunctivitis (6.9 %)**	**AR with house dust mite sensitization and asthma (14.7 %)**	**AR among children with tonsils and adenoids removed (7.6%)**	p*
N	361	35	75	39	
Age (y)	10.5 ± 3.1	11.2 ± 2.9	10.2 ± 2.9	11.1 ± 3.2	.31
Sex (male)	66.8	82.9	72.0	71.8	.22
Age at AR symptoms start (y)	7.0 ± 3.1	6.8 ± 2.7	6.8 ± 3.2	7.2 ± 3.4	.89
Temporal pattern					<.001
-Seasonal	85.0	65.7	48.0	71.8	
-Perennial	15.0	34.3	52.0	28.2	
Duration					<.001
- Intermittent	30.8	40.0	60.0	25.6	

- Persistent	69.2	60.0	40.0	74.4	
Severity					0.04
- Mild	37.6	42.9	53.3	43.6	
- Moderate/severe	62.4	57.1	46.7	56.4	
Environmental characteristics					
- Pet exposure	10.4	14.3	18.9	8.1	0.21
- ETS exposure	38.5	55.9	35.1	48.6	0.12
Family history of allergic disease					
- Maternal asthma	10.3	2.9	8.0	15.4	.23
- Paternal asthma	5.3	2.9	6.7	2.6	.83
- Maternal allergic rhinitis	29.4	14.3	17.3	10.3	.005
- Paternal allergic rhinitis	18.1	14.3	16.0	20.5	.88
Co-morbid conditions					
- Asthma	36.0	37.1	60.0	43.6	.002
- Allergic conjunctivitis	83.7	85.7	41.3	69.2	<.001
- Atopic dermatitis	11.9	5.7	14.7	10.3	.59
- Tonsillectomy	0	11.4	1.3	100	<.001
- Adenoidectomy	7.2	11.4	5.3	100	<.001
- Tonsillectomy & Adenoidectomy	0	5.2	0	100	<.001
Sensitization					
- Grass pollens	100.0	85.7	25.3	82.1	<.001
- Tree pollens	9.7	8.6	2.7	7.7	.26
- Weed pollens	6.6	11.4	0.0	7.7	.07
- House dust mites	8.3	22.9	82.7	20.5	<.001
- Cat	8.0	100.0	16.0	5.1	<.001
- Dog	1.7	100.0	1.3	2.6	<.001
- Molds	4.2	20.0	17.3	17.9	<.001
Monosensitization	67.3	0.0	65.3	66.7	<.001
Total IgE (kU/L)	91 (35-196)	118 (59-203)	85 (31-184)	58 (27-160)	.39

Blood eosinophils (%)	4.3 (2.7-7.6)	4.2 (2.5-6.2)	4.1 (2.7-6.2)	4.3 (2.3-5.7)	.77
Blood eosinophils ($/mm^3$)	290 (180-540)	300 (190-380)	300 (185-465)	255 (163-390)	.71
FEV_1 % predicted	97 ± 15	99 ± 14	93 ± 14	100 ± 15	.08
FVC % predicted	94 ± 13	95 ± 11	93 ± 12	98 ± 13	.24
FEV_1/FVC %	90 ± 7	89 ± 6	89 ± 7	89 ± 8	.48
PEF % predicted	90 ± 17	90 ± 15	88 ± 17	91 ± 23	.72
FEF_{25-75} % predicted	95 ± 25	95 ± 24	89 ± 23	96 ± 27	.38
Continuous variables are given as mean and standard deviation and binary variables are given as frequency (%). *p-values are computed using chi-square test for categorical variables and one-way analysis of variance or Kruskal-Wallis for continuous variables.	Continuous variables are given as mean and standard deviation and binary variables are given as frequency (%). *p-values are computed using chi-square test for categorical variables and one-way analysis of variance or Kruskal-Wallis for continuous variables.	Continuous variables are given as mean and standard deviation and binary variables are given as frequency (%). *p-values are computed using chi-square test for categorical variables and one-way analysis of variance or Kruskal-Wallis for continuous variables.	Continuous variables are given as mean and standard deviation and binary variables are given as frequency (%). *p-values are computed using chi-square test for categorical variables and one-way analysis of variance or Kruskal-Wallis for continuous variables.	Continuous variables are given as mean and standard deviation and binary variables are given as frequency (%). *p-values are computed using chi-square test for categorical variables and one-way analysis of variance or Kruskal-Wallis for continuous variables.	Continuous variables are given as mean and standard deviation and binary variables are given as frequency (%). *p-values are computed using chi-square test for categorical variables and one-way analysis of variance or Kruskal-Wallis for continuous variables.

Table 3. Univariate multinomial logistic regression results (reference category: AR with grass monosensitization and conjunctivitis)

Classes	**Classes AR with house dust mite sensitization and asthma**	**Classes AR with house dust mite sensitization and asthma**	**Classes AR with pet and grass polysensitization and conjunctivitis**	**Classes AR with pet and grass polysensitization and conjunctivitis**	**Classes AR among children with tonsils & adenoids removed**	**Classes AR among children with tonsils & adenoids removed**
	Relative Risk Ratio (95%CI)	*p*	*Relative Risk Ratio (95%CI)*	*p*	*Relative Risk Ratio (95%CI)*	*p*
Sex						

Male gender	1.30 (0.75-2.25)	0.35	2.51 (1.08-5.80)	0.03	1.26 (0.61-2.62)	0.53
AR Temporal pattern (reference class: Seasonal)	**AR Temporal pattern** (reference class: Seasonal)	**AR Temporal pattern** (reference class: Seasonal)	**AR Temporal pattern** (reference class: Seasonal)	**AR Temporal pattern** (reference class: Seasonal)		
Perennial	5.83 (3.42-9.94)	< 0.001	2.88 (1.36-6.13)	0.006	1.91 (0.88-4.13)	0.10
AR Duration (reference class: Intermittent)	**AR Duration** (reference class: Intermittent)	**AR Duration** (reference class: Intermittent)	**AR Duration** (reference class: Intermittent)	**AR Duration** (reference class: Intermittent)		
Persistent	0.29 (0.17-0.48)	< 0.001	0.66 (0.32-1.35)	0.26	1.28 (0.60-2.72)	0.52
AR Severity (reference class: mild)	**AR Severity** (reference class: mild)	**AR Severity** (reference class: mild)	**AR Severity** (reference class: mild)	**AR Severity** (reference class: mild)		
Moderate/severe	0.55 (0.33-0.90)	0.02	0.81 (0.40-1-64)	0.56	0.79 (0.40-1.54)	0.49
Family history of allergic disease	**Family history of allergic disease**	**Family history of allergic disease**	**Family history of allergic disease**	**Family history of allergic disease**	**Family history of allergic disease**	**Family history of allergic disease**
Maternal allergic rhinitis	0.71 (0.52-0.98)	0.04	0.51 (0.33-0.85)	0.03	0.28 (0.09-0.79)	0.02

Figure Legends

Figure 1: Assignment of 510 children into distinct classes over a sequence of latent class model with two, three, four and five classes based on most likely class membership

Ellipse nodes show class membership whilst the values along the arrow represent the % of children moving from one class to another in models with an increasing number of classes.

Figure 2: AR subtypes identified by latent class analysis in 510 children

Class proportions shown in the figure are computed based on most likely class membership.