

Identifying the heterogeneity of young adult rhinitis through cluster analysis in the Isle of Wight birth cohort

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Background: Rhinitis affects many young adults and often shows comorbidity with asthma.

Objective: We hypothesized that young adult rhinitis, like asthma, exhibits clinical heterogeneity identifiable by means of cluster analysis.

Methods: Participants in the Isle of Wight birth cohort (n = 1456) were assessed at 1, 2, 4, 10, and 18 years of age. Cluster analysis was performed on those with rhinitis at age 18 years (n = 468) by using 13 variables defining clinical characteristics.

Results: Four clusters were identified. Patients in cluster 1 (n = 128 [27.4%]; ie, moderate childhood-onset rhinitis) had high atopy and eczema prevalence and high total IgE levels but low asthma prevalence. They showed the best lung function at 18 years of age, with normal fraction of exhaled nitric oxide (FENO), low bronchial hyperresponsiveness (BHR), and low bronchodilator reversibility (BDR) but high rhinitis symptoms and treatment. Patients in cluster 2 (n = 199 [42.5%]; ie, mild-adolescence-onset female rhinitis) had the lowest prevalence of comorbid atopy, asthma, and eczema. They had normal lung function and low BHR, BDR, FENO values, and total IgE levels plus low rhinitis symptoms, severity, and treatment. Patients in cluster 3 (n = 59 [12.6%]; ie, severe earliest-onset rhinitis with asthma) had the youngest rhinitis onset plus the highest comorbid asthma (of simultaneous onset) and atopy. They showed the most obstructed lung function with high BHR, BDR, and FENO values plus high rhinitis symptoms, severity, and treatment. Patient 4 in cluster 4 (n = 82 [17.5%]; ie, moderate childhood-onset male rhinitis with asthma) had high atopy, intermediate asthma, and low eczema. They had impaired lung function with high FENO values and total IgE levels but intermediate BHR and BDR. They had moderate rhinitis symptoms.

Conclusion: Clinically distinctive adolescent rhinitis clusters are apparent with varying sex and asthma associations plus

differing rhinitis severity and treatment needs. (J Allergy Clin Immunol 2014;■■■■:■■■-■■■.)

Key words: Asthma, cluster analysis, morbidity, rhinitis, wheezing

Rhinitis is a common condition that increases in prevalence through childhood and adolescence to affect a substantial proportion of young adults.¹ Frequently under-recognized, it can be associated with considerable morbidity and impaired quality of life.² Comorbidity with other allergic diseases, most notably asthma, is well documented for rhinitis.^{3,4} This has led to increasing acceptance of the concept of “one airway, one disease” in clinical practice.⁵ In turn, rhinitis is recognized as a risk factor for asthma development,⁶⁻⁸ and rhinitis treatment might help reduce asthma morbidity.⁹ Asthma itself has been increasingly characterized as a heterogeneous disorder composed of different phenotypes.¹⁰ Recently, cluster analysis has further enhanced our understanding of the diversity of wheezing disorders. Cluster analysis has identified wheeze clusters with strong^{11,12} or little¹³ association with atopy, impaired lung function,^{11,12} severe bronchial hyperresponsiveness (BHR),^{11,14} high^{11,13} or low¹² disease morbidity, and obesity.¹³ Different forms of rhinitis are also being identified,^{4,15,16} and although rhinitis is regarded as an allergic disorder, both atopic and nonatopic forms exist.¹ However, a deeper understanding of the potential diversity of rhinitis is yet to emerge, and to date, no cluster analysis of rhinitis has been published in the literature.

Adolescence is a crucial developmental phase that represents a period of dynamic physiologic change. It is also a period that sees substantial rhinitis incidence.¹ We hypothesized that a cluster analysis in young adulthood would demonstrate distinctive rhinitis clusters with potential clinical relevance. In this article we describe a cluster analysis of young adults with rhinitis to determine phenotypes without observer bias from the Isle of Wight Birth Cohort.

METHODS

An unselected whole-population birth cohort (n = 1456) was established on the Isle of Wight (United Kingdom) in 1989 to study the natural history of allergic disease. Participants were assessed at 1, 2, 4, 10, and 18 years of age. The methodology for the first decade of follow-up has been published previously.¹⁷⁻²⁰

Eighteen-year follow-up methodology

The local research ethics committee (06/Q1701/34) approved follow-up at 18 years of age. Participants provided informed consent and information on respiratory, nasal, and dermatologic symptoms. Study-specific plus International Study of Asthma and Allergies in Childhood²¹ questionnaires were used. Questions about specific exposures are provided in the [Methods](#) section in this article's Online Repository at www.jacionline.org.

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Abbreviations used

BDR:	Bronchodilator reversibility
BHR:	Bronchial hyperresponsiveness
CCC:	Cubic clustering criterion
DRS:	Dose-response slope
FEF ₂₅₋₇₅ :	Forced expiratory flow at 25% to 75%
FENO:	Fraction of exhaled nitric oxide
FVC:	Forced vital capacity
SPT:	Skin prick test

Participation at age 18 years was in person, by telephone, or by post. Participants attending in person also performed spirometry, fraction of exhaled nitric oxide (FENO) measurement, methacholine challenge tests, and skin prick tests (SPTs) and provided blood for total IgE measurement. Identical methodology published previously²⁰ was used for spirometry and methacholine challenge testing at 10 and 18 years of age. FENO (NIOX MINO; Aerocrine AB, Solna, Sweden) measurement and SPTs to 14 common aeroallergens and food allergens (ALK-Abelló, Hørsholm, Denmark) were performed, as reported previously.²⁰ Relevant methodology at 10 and 18 years is summarized in the [Methods](#) section in this article's Online Repository.

Definitions

Rhinitis at 10 and 18 years of age was defined by the question "Have you ever had a problem with sneezing, runny or blocked nose in the absence of cold or flu?" plus the presence of "symptoms in the last 12 months." Seasonality of rhinitis was defined as perennial (with or without seasonal exacerbation) or seasonal only. Asthma at 10 and 18 years of age was defined as an answer of yes to "ever had asthma" and either of "wheezing in the last 12 months" or "asthma treatment in the last 12 months." Eczema at 10 and 18 years was defined by the question "Have you ever been diagnosed with eczema?" plus "having an itchy rash in the past 12 months." Diagnostic definitions used at early-life follow-up are presented in the [Methods](#) section in this article's Online Repository. Atopy was defined by a positive SPT response (mean wheal diameter, 3 mm $\geq$ negative control) to at least 1 allergen. Age of rhinitis onset was defined as "childhood" (<12 years of age) or "adolescence" ($\geq$ 12 years of age).

Bronchodilator reversibility (BDR) was defined as a percentage change in FEV₁ after inhaling 600 μ g of salbutamol. Not all subjects undergoing methacholine challenge testing demonstrate a 20% decrease in FEV₁ that enables PC₂₀ calculation to indicate BHR. Therefore at both 10 and 18 years of age, a continuous dose-response slope (DRS) measure of BHR was estimated by using least-square regression of the percentage change in FEV₁ on the cumulative methacholine dose for each child. The DRS was transformed as log₁₀ (DRS+10) to satisfy normality and homoscedasticity, with higher values inferring greater BHR.

Statistical methods

All statistical measures were performed with the SAS statistical package, version 9.3 (SAS Institute, Cary, NC). Cluster analysis was performed on the population reporting rhinitis within the past 12 months at age 18 years (n = 468). Cluster variables were selected that defined clinical characteristics at 18 years of age. These included both questionnaire-derived data and variables from objective testing. Thirteen variables were selected for the cluster analyses: atopic status at age 18 years, asthma at age 18 years, eczema at age 18 years, age at which rhinitis appeared, seasonality of rhinitis symptoms, total IgE level (log₁₀), BDR, BHR DRS, mean FENO value (log₁₀), FEV₁, forced vital capacity (FVC), FEV₁/FVC ratio, and forced expiratory flow at 25% to 75% (FEF₂₅₋₇₅).

As in linear regressions, clustering methods are sensitive to the scale of the variables. Each variable was standardized by subtracting its mean and dividing by its SD to put every continuous variable on a common scale. To remove the effect of sex and height on FEV₁, FVC, and FEF₂₅₋₇₅, we regressed these

variables on sex and height; the residuals with sex and height effects excluded were used in the analyses. We used this approach in preference to using percent predicted lung function values. The use of percent predicted values is dependent on values estimated from existing formulas based on reference populations. Those reference ranges might not apply to all populations and would not necessarily reflect the relevance of individual lung function measures at the age studied in our cohort. Because of the skewness of total IgE and FENO measures in the original scale, those variables were log₁₀ transformed to improve normality and homoscedasticity. Correlations were calculated among the continuous variables (see [Table E1](#) in this article's Online Repository at www.jacionline.org), between continuous and binary variables (see [Table E2](#) in this article's Online Repository at www.jacionline.org), and between binary variables (see [Table E3](#) in this article's Online Repository at www.jacionline.org).

The method of K-means (PROC FASTCLUS in SAS) was used for cluster analysis. To determine cluster number, we used 2 criteria: the cubic clustering criterion (CCC)²² and the pseudo F statistic.²³ The CCC criterion is a measure of cluster deviation from the distribution expected if data points were drawn from a uniform distribution. The pseudo F statistic captures cluster homogeneity and is a ratio of the mean sum of squares between groups to the mean sum of squares within group. Larger CCC and pseudo F values indicate a better cluster solution. In our analysis we considered different numbers of clusters and then for each case obtained values for CCC and pseudo F. In general, the patterns of CCC and pseudo F values were quadratic with respect to the number of clusters. The final choice for number of clusters was determined by an overall evaluation of CCC and pseudo F combined with an R² statistic measuring between-cluster variations (the larger the better, see [Table E4](#) in this article's Online Repository at www.jacionline.org).

ANOVA was used for continuous variables and χ^2 tests were used for binary variables to evaluate each clustering variable across the clusters. Pairwise *t* tests with Bonferroni multiple testing correction were applied to continuous variables, and pairwise proportion tests were applied to binary variables, with the overall significance level set at an α value of .05. Having defined distinct clusters, we sought to further characterize those clusters by assessing morbidity parameters for them. These included rhinitis symptom frequency and severity and rhinitis therapy with assessment by using χ^2 analysis for each parameter across the clusters. Potential associations with risk factors recorded prospectively during the lifetime of the cohort were then assessed. These included male sex, family history (parent or sibling) of rhinitis, cord blood IgE level, low (<2.5 kg) birth weight, maternal smoking in pregnancy, exclusive breast-feeding in the first 3 months of life, recurrent chest infections in infancy, past or current personal smoking, paracetamol use at 18 years of age, and body mass index at 18 years of age. Identical methods as for morbidity variables were used to compare risk factors between different clusters.

RESULTS

High cohort follow-up was achieved at 10 (94%, n = 1373) and 18 (90%, n = 1313) years of age. Not all subjects participated at all visits. Of the overall initial cohort of 1456 subjects, 16.8% (n = 210) were seen at 10 but not 18 years of age, and 5.4% (n = 80) were seen at 18 but not 10 years of age. Of subjects seen for a center visit at 18 years of age (n = 864), 90.5% (n = 762) were also seen at 10 years of age. Previously published data²⁴ demonstrated that participants attending the center for a "full visit" (n = 864) at 18 years of age did not differ significantly from the overall cohort participation (see [Table E5](#) in this article's Online Repository at www.jacionline.org). Statistical summary of standardized variables is shown in [Table E6](#) in this article's Online Repository at www.jacionline.org. At 18 years of age, whole population prevalence of diagnosed rhinitis was 35.8% (468/1309), that of asthma was 17.9% (234/1306), that of eczema was 12.3% (161/1306) and that of atopy was 41.3% (352/853).

TABLE I. Summary characterization of cluster variables for 18-year rhinitis clusters

Variables	Cluster sample (n = 468)	Whole age 18-y cohort (n = 864)	Cluster 1 (n = 128)	Cluster 2 (n = 199)	Cluster 3 (n = 59)	Cluster 4 (n = 82)	Separation of the clusters
Mean (SD)							
FEV ₁ *	−0.03 (0.50)	0 (0.46)	0.45 (0.29)	−0.03 (0.28)	−0.56 (0.50)	−0.58 (0.31)	{1,2,{3,4}}
FVC†	0.01 (0.51)	0 (0.51)	0.46 (0.38)	−0.16 (0.33)	0.03 (0.56)	−0.35 (0.51)	{1,{2,3},{2,4}}
FEV ₁ /FVC ratio‡	0.86 (0.08)	0.87 (0.07)	0.88 (0.06)	0.90 (0.06)	0.74 (0.09)	0.81 (0.06)	{{1,2},{3,4}}
FEF ₂₅₋₇₅ §	−0.11 (1.09)	0 (0.98)	0.62 (0.96)	0.13 (0.75)	−1.44 (0.86)	−1.20 (0.49)	{1,2,{3,4}}
BDR	6.03 (7.30)	5.00 (5.78)	5.01 (3.75)	2.57 (5.62)	20.54 (9.49)	8.60 (3.97)	{{1,2},{3,4}}
BHR DRS¶	1.23 (0.41)	1.13 (0.30)	1.17 (0.21)	1.04 (0.23)	2.17 (0.48)	1.27 (0.26)	{{1,2},3,{1,4}}
FENO#	39.71 (42.16)	27.88 (31.92)	49.41 (47.86)	17.89 (11.94)	72.05 (51.39)	62.32 (48.28)	{{1,4},2,{3,4}}
Total IgE**	230.91 (383.96)	174.50 (343.88)	219.36 (266.59)	89.38 (153.01)	162.99 (212.87)	608.04 (660.27)	{{1,3},{2,3},4}
Age rhinitis first appeared†† (y)	10.71 (4.93)	11.86 (4.21)	11.09 (4.82)	12.30 (4.44)	6.30 (4.56)	9.16 (4.30)	{{1,2},{3,4}}
Prevalence (%)							
Rhinitis seasonality‡‡	77.90	76.52	70.4	88.0	71.7	69.6	{{1,3,4},2}
Eczema at age 18 y	11.38	12.23	25.2	15.1	22.4	7.31	{{1,2,3},{2,3,4}}
Asthma or wheezing at age 18 t	39.96	24.88	41.4	24.1	72.9	52.4	{{1,4},2,{3,4}}
Atopy at age 18 y§§	69.76	41.27	81.2	55.6	96.6	71.0	{{1,3},{1,4},{2,4}}

Figures in boldface indicate the highest and lowest values across clusters. For continuous variables, mean values are shown with SDs.

*FEV₁ is shown in liters at 18 years of age. It is height and sex adjusted.

†FVC is shown in liters at 18 years of age. It is height and sex adjusted.

‡The FEV₁/FVC ratio is shown at 18 years of age.

§FEF₂₅₋₇₅ is shown in liters per second at 18 years of age. It is height and sex adjusted.

||BDR indicates percentage FEV₁ bronchodilator reversibility to 600 µg of inhaled salbutamol at 18 years of age.

¶BHR DRS refers to a continuous dose-response measure of bronchial hyperresponsiveness expressed as log₁₀ (DRS + 10). Higher values infer greater BHR at 18 years of age.

#FENO is measured in parts per billion at 18 years of age.

**Log₁₀ total IgE at 18 years of age.

††Determined from data collected throughout the 18 years of the cohort.

‡‡Rhinitis seasonality refers to having seasonal disease only.

§§Atopy refers to a positive SPT response (>3 mm wheal diameter) to at least 1 allergen in the standard test panel at 18 years of age.

|||Numbers included within a pair of brackets indicate the statistics within those clusters are not significantly different from each other after adjusting for multiple testing. Numbers in different pairs of brackets indicate that there is a significant difference between those grouped clusters. For instance, {1,2,{3,4}} for FEV₁ indicate that there was a statistically significant difference between clusters 1 and 2 in the mean of FEV₁ and that both of these clusters showed significant differences to clusters 3 and 4. However, the mean FEV₁ values in clusters 3 and 4 are not significantly different.

Clustering outcome

Cluster analysis on the population (n = 468) with rhinitis at 18 years of age identified 4 clusters. Their characteristics based on cluster variables are outlined in [Table I](#). Separation of clusters by cluster variables using ANOVA for continuous variables or χ^2 tests for binary variables is provided in [Table I](#), and the resulting cluster variable–based characterization is summarized below. The proportion of these clusters within the rhinitis population varied: cluster 1, 27.4%; cluster 2, 42.5%; cluster 3, 12.6%; and cluster 4, 17.5%.

Cluster 1 (n = 128 [27.4%]): Moderate childhood-onset rhinitis. This group showed childhood-onset predominantly seasonal rhinitis. Members of this cluster had high prevalence of atopy and eczema and high total IgE levels but low prevalence of asthma. They showed the highest lung function at 18 years of age. They also had normal FENO values, low BHR, and low BDR, all of which were comparable with values for the whole population seen at 18 years of age.

Cluster 2 (n = 199 [42.5%]): Mild adolescence-onset female rhinitis. This group showed the oldest mean age of rhinitis onset, with predominantly seasonal disease. Members of this cluster had the lowest prevalence of atopy (still greater than that of the whole population at 18 years of age) plus low comorbid asthma and eczema (comparable with the whole-population values). They showed normal lung function with low BHR, BDR, FENO values, and total IgE levels, which were similar to those of the whole population at 18 years of age.

Cluster 3 (n = 59 [12.6%]): Severe earliest-onset rhinitis with asthma. This group had the earliest age of rhinitis onset, with predominantly seasonal disease. The cluster showed high prevalence of eczema and the highest prevalence of both asthma and atopy. It also showed impaired and most obstructed lung function with high BHR, BDR, and FENO values.

Cluster 4 (n = 82 [17.5%]): Moderate childhood-onset male rhinitis with asthma. This group had childhood-onset predominantly seasonal disease. Members of this cluster had high prevalence of atopy, low prevalence of eczema, and intermediate prevalence of asthma. They showed the most impairment of FEV₁ and FVC, with high FENO values and total IgE levels but intermediate BHR and BDR.

Rhinitis morbidity measures

Rhinitis treatment was generally similar across the clusters, except for antihistamine therapy, which was significantly higher for cluster 1 (moderate childhood-onset rhinitis) than cluster 2 (mild adolescence-onset female rhinitis, [Table II](#)). Persistent rhinitis symptom frequency ([Fig 1](#)) at 18 years of age differed significantly between clusters, being highest for cluster 3 (severe earliest-onset rhinitis with asthma) and lowest for cluster 2 (mild adolescence-onset female rhinitis). The same pattern of association emerged for high degree of impairment of daily activity caused by rhinitis ([Table II](#)). Cluster 3 (severe earliest-onset

TABLE II. Rhinitis morbidity characteristics for rhinitis clusters at 18 years of age

	Cluster 1 (n = 128) , % (count)	Cluster 2 (n = 199), % (count)	Cluster 3 (n = 59), % (count)	Cluster 4 (n = 82), % (count)	P value
Symptoms and treatment (% reporting yes)					
Eye symptoms	72.66 (93)	68.02 (134)	71.43 (40)	77.78 (63)	.42
Sleep disturbance	34.92 (44)	22.80 (44)	42.86 (24)	30.0 (24)	.014
Rhinitis treatment	67.20 (84)	56.99 (110)	68.52 (37)	65.38 (51)	.19
Antihistamine treatment	62.50 (80)	46.73 (93)	57.63 (34)	58.54 (48)	.030
Nasal steroid treatment	11.72 (15)	9.05 (18)	11.86 (7)	10.98 (9)	.85
Impairment of daily activity (% reporting yes)					.0003
None	50.79	64.58	46.43	48.72	
A little	33.33	28.13	32.14	43.59	
Moderate	13.49	5.21	8.93	5.13	
A lot	2.38	2.08	12.50	2.56	

Eye symptoms refers to the presence of associated eye symptoms in the past year at age 18 years. *Sleep disturbance* refers to disturbance of sleep caused by rhinitis in the past year at age 18 years. *Rhinitis treatment* categories refer to the need for those rhinitis therapies in the past year at age 18 years. *Impairment of daily activity* refers to impairment caused by rhinitis in the past year. *P* values are from χ^2 tests comparing the distribution patterns of a categorical variable in each cluster across the 4 clusters.

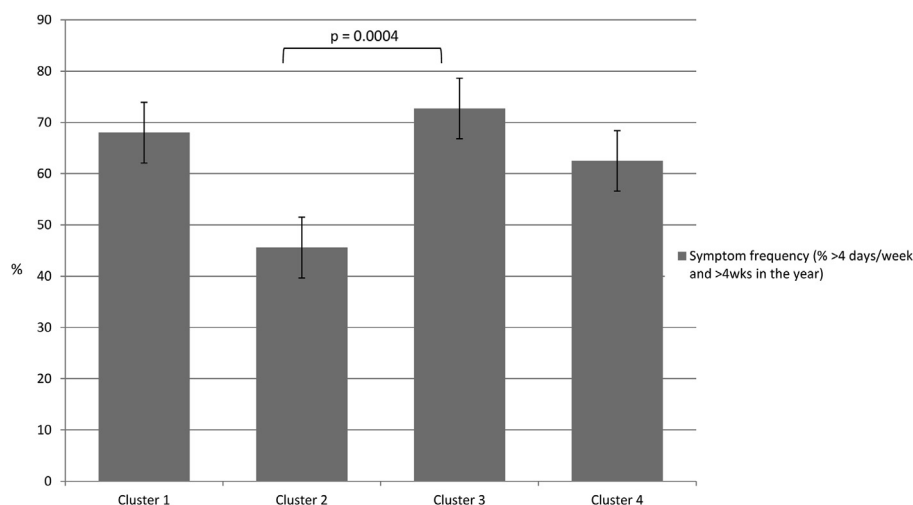


FIG 1. Persistent rhinitis symptom frequency for the rhinitis clusters. The prevalence of persistent rhinitis symptoms (>4 days/week and >4 weeks in the past year) is shown. Error bars are SEs. *Cluster 1*, Moderate childhood-onset-rhinitis; *cluster 2*, mild adolescence-onset female rhinitis; *cluster 3*, severe earliest-onset rhinitis with asthma; *cluster 4*, moderate childhood-onset male rhinitis with asthma.

rhinitis with asthma) had the highest prevalence of impairment of daily activity, cluster 1 (moderate childhood-onset rhinitis) had the highest prevalence of little impairment of daily activity, and cluster 4 (moderate childhood-onset male rhinitis with asthma) had the highest prevalence of moderate impairment. Other rhinitis-associated morbidity, such as eye symptoms and sleep disturbance, were broadly similar across the 4 clusters (Table II).

Asthma comorbidity

Asthma comorbidity varied significantly between rhinitis clusters (Table I), being significantly higher for cluster 3 (severe earliest-onset rhinitis with asthma) than cluster 2 (mild adolescence-onset female rhinitis). Cluster 3 (severe earliest-onset rhinitis with asthma) also showed the most impaired lung function with high BHR, BDR, and FENO values. The mean age of asthma onset predated that for rhinitis in all 4 rhinitis clusters: cluster 1 (moderate childhood-onset rhinitis), 6.8 years; cluster 2, (mild adolescence-onset female rhinitis), 8.1 years;

cluster 3 (severe earliest-onset rhinitis with asthma), 6.0 years; and cluster 4 (moderate childhood-onset male rhinitis with asthma), 7.3 years. This pattern was retained where analysis was restricted to patients with dual asthma and rhinitis when age of asthma onset was almost identical across the clusters (Fig 2). Furthermore, among patients with dual disease, cluster 3 (severe earliest-onset rhinitis with asthma) had the earliest rhinitis onset, with almost simultaneous asthma and rhinitis onset (Fig 2).

Risk factors

Potential risk factors for rhinitis clusters are shown in Table III. Female sex was significantly associated with cluster 2 (mild adolescence-onset female rhinitis) and male sex with cluster 4 (moderate childhood-onset male rhinitis with asthma). Other factors that were assessed (family history of rhinitis, low birth weight, exclusive breast-feeding, recurrent chest infections in infancy, personal smoking, maternal cord IgE level at birth, and paracetamol use at 18 years of age) did not show significant association with any particular cluster.

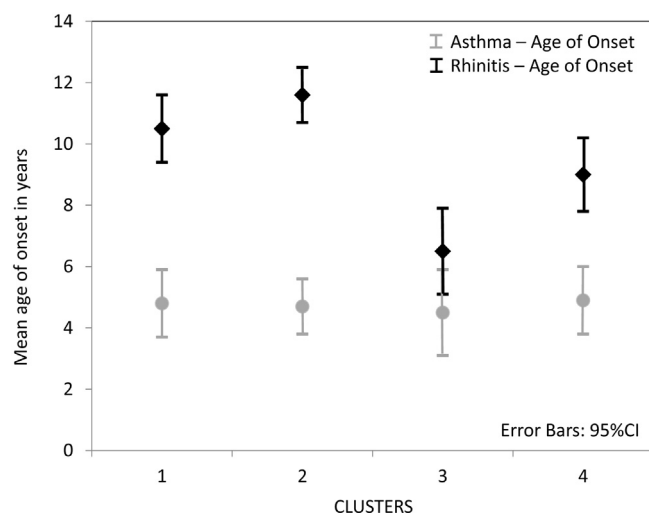


FIG 2. Age of asthma versus rhinitis onset for patients with dual disease in the rhinitis clusters. *Cluster 1*, Moderate childhood-onset-rhinitis; *cluster 2*, mild adolescence-onset female rhinitis; *cluster 3*, severe earliest-onset rhinitis with asthma; *cluster 4*, moderate childhood-onset male rhinitis with asthma.

Final summary characterization of rhinitis clusters

Final summary characterization of the 4 rhinitis clusters is shown in [Table IV](#), incorporating clustering and morbidity characteristics.

DISCUSSION

This is the first study to use cluster analysis in a longitudinal birth cohort to assess the diversity of young adult rhinitis. Rhinitis emerged as a common condition in young adulthood, affecting one third of 18-year-olds. Most rhinitis was seasonal and of childhood onset. However, cluster analysis demonstrated that young adult rhinitis could be categorized by 4 distinct clusters with differing associations with asthma, lung function, bronchial hyperreactivity, sex, age of disease onset, rhinitis morbidity, and rhinitis severity. Milder rhinitis clusters were more prevalent and less strongly associated with atopy. Two clusters showed low asthma comorbidity (*cluster 2* [mild adolescence-onset female rhinitis] and *cluster 1* [moderate childhood-onset rhinitis]). Higher rhinitis severity was associated with higher asthma prevalence and impaired airway physiology (*cluster 3* [severe earliest-onset rhinitis with asthma]).

Cluster analysis potentially offers an assessment of the diversity of rhinitis that is less biased by preconceived assumptions. It has been previously used successfully to describe the nature of wheezing in both adults¹¹⁻¹⁴ and children.^{25,26} To the best of our knowledge, this is the first study using this technique to study the nature of rhinitis during the transition to early adulthood in a longitudinal whole-population birth cohort. The use of longitudinally acquired data enables reliable assessment of patterns of disease development and potential risk factors for these rhinitis clusters, particularly in a study with high long-term follow-up, such as ours. One potential criticism of our study might be the choice of potentially correlated cluster variables, such as lung function, BHR, and BDR. High correlations (≥ 0.7) occurred between FEV₁ and FVC (and FEV₁ and FEF₂₅₋₇₅), and therefore when performing cluster analyses, subjects with similar levels of lung function measures were more likely to be in the same cluster.

To ensure that such collinearity did not bias the cluster patterns, we performed cluster analyses without FVC and FEF₂₅₋₇₅. Similar clustering patterns were obtained (data not shown). This was likely due to the inclusion of many other variables that are not correlated or are only moderately correlated (correlation <0.5).

Another possible criticism of our study is the wider applicability of our findings, given a unique island environment. However, our island population is genetically similar to that of mainland England (data on file), and previous findings¹⁷⁻¹⁹ have been similar to those of other international cohorts. Nonetheless, our present findings require replication in other birth cohorts and larger samples.

Much interest has focused on associations between rhinitis and asthma, leading to the concept of “one airway, one disease.”⁵ This cluster analysis extends understanding of that concept by identifying heterogeneity to this association with demonstration of 2 relatively low-asthma-prevalence rhinitis clusters. Indeed, the largest rhinitis cluster (*cluster 2* [mild adolescence-onset female rhinitis]) showed asthma prevalence comparable with that of the general (whole cohort) population ([Table I](#)). However, our analysis revealed a clear pattern of association for more severe rhinitis clusters with higher asthma prevalence. This reciprocates previous reports of more severe asthma symptoms in groups with higher rhinitis prevalence.^{4,9} In turn, the most increased measures of asthma pathophysiology, such as BHR, BDR, and airflow obstruction, were seen in the rhinitis clusters with greatest rhinitis severity. Taken collectively, our findings indicate that there are different association patterns of asthma and rhinitis in young adulthood. As shown in [Fig 3](#), among more common rhinitis clusters with milder disease, such associations appear less prevalent and less clinically relevant. However, in rarer rhinitis clusters the association between rhinitis and asthma is very strong and appears to signify a mutually detrimental state with respect to both conditions, adding further insight into the concept of “one airway, one disease.”

The severe earliest-onset rhinitis with asthma cluster (*cluster 3*), although least prevalent, showed the highest prevalence of persistent rhinitis and rhinitis morbidity in terms of daily impairment. Therefore it emerges as the most clinically significant rhinitis cluster in our population. It also showed the highest atopy and asthma prevalence plus the most abnormal measures of airway pathophysiology, including airflow obstruction, BDR, BHR, and FENO. It is worth noting that for patients with dual disease, although mean age of asthma onset consistently predated rhinitis onset in the 3 other rhinitis clusters, the severe earliest-onset rhinitis with asthma cluster (*cluster 3*) showed simultaneous onset of rhinitis and asthma. Therefore this higher-severity rhinitis cluster had the earliest onset of rhinitis expression and consequently the longest duration of disease. The presence of longstanding upper and lower airway inflammation could plausibly lead to a mutually detrimental airway disease state by early adulthood. The potential poor clinical implications of that cluster for later adult respiratory health need to be acknowledged. Recent guidance advocates a high index of suspicion for childhood allergic rhinitis in the presence of comorbidities, such as asthma.²⁷ Whether earlier recognition and treatment of both aspects of a conjoined severe airways disease cluster could be mutually beneficial is an important point for clinicians to consider. It is plausible that such early intervention could have significant beneficial clinical implications for later respiratory health. However, a general

TABLE III. Risk factor association with the rhinitis clusters at age 18 years

	Cluster 1 (n = 128), % (count)	Cluster 2 (n = 199), % (count)	Cluster 3 (n = 59), % (count)	Cluster 4 (n = 82), % (count)	P value
Male sex	50.78 (65)	40.20 (80)	47.46 (28)	60.98 (50)	.013
Family history of rhinitis	83.02 (88)	79.25 (126)	72.34 (34)	73.44 (47)	.34
Low birth weight	4.03 (5)	1.58 (3)	1.69 (1)	3.80 (3)	.50
Exclusively breast-fed	35.71 (40)	32.54 (55)	22.45 (11)	35.29 (24)	.39
Chest infection in infancy	15.09 (16)	22.36 (36)	22.73 (10)	17.14 (12)	.44
Personal smoking	50.79 (64)	48.70 (94)	57.14 (32)	47.50 (38)	.68
Maternal smoking in pregnancy	32.03 (41)	37.69 (75)	40.68 (24)	29.27 (24)	.37
Mean cord log IgE	−0.72 (0.48)	−0.81 (0.40)	−0.74 (0.46)	−0.73 (0.38)	.47
Mean paracetamol use	1.73 (2.54)	2.05 (4.08)	1.61 (2.40)	1.90 (4.81)	.78
Mean body mass index	23.91 (4.70)	23.01 (4.08)	24.31 (5.20)	22.38 (4.00)	.07

Family history of rhinitis is defined as a history of rhinitis in a parent or sibling. *Low birth weight* is defined as less than 2.5 kg. *Exclusively breast-fed* is defined as exclusively breast-fed for more than 3 months. *Chest infection in infancy* is defined as a history of recurrent chest infections at 1 or 2 years of age. *Personal smoking* is defined as a personal (past or current) history of cigarette smoking. *Maternal smoking* is defined as history during pregnancy. *Cord IgE* is defined as cord blood IgE at birth. *Paracetamol use* is defined as use at 18 years of age in average number of times taken per month. *Body mass index* is defined as kilograms per meter squared at 18 years of age. *P* values are for tests comparing distribution patterns of a categorical variable in each cluster or comparing medians (continuous variables) across the 4 clusters. For categorical variables, χ^2 tests were implemented, and for continuous variables, Kruskal-Wallis tests were used because of the violation of the normality assumption in the residuals.

TABLE IV. Summary characterization of rhinitis clusters in young adulthood

Cluster	Name	Atopy	Eczema	Asthma	Total IgE	BDR	BHR	Persistent rhinitis	High levels of limitation by rhinitis
1	Moderate childhood-onset rhinitis	+++	+++	+	++	+	+	++	+
2	Mild adolescence-onset female rhinitis	+	++	+	+	+	+	+	+
3	Severe earliest-onset rhinitis with asthma	+++	+++	+++	++	+++	+++	+++	+++
4	Moderate childhood-onset male rhinitis with asthma	++	+	++	+++	++	+	++	+

Summary characterization of clusters was done by core parameters.

+, Low; ++, moderate; +++, high.

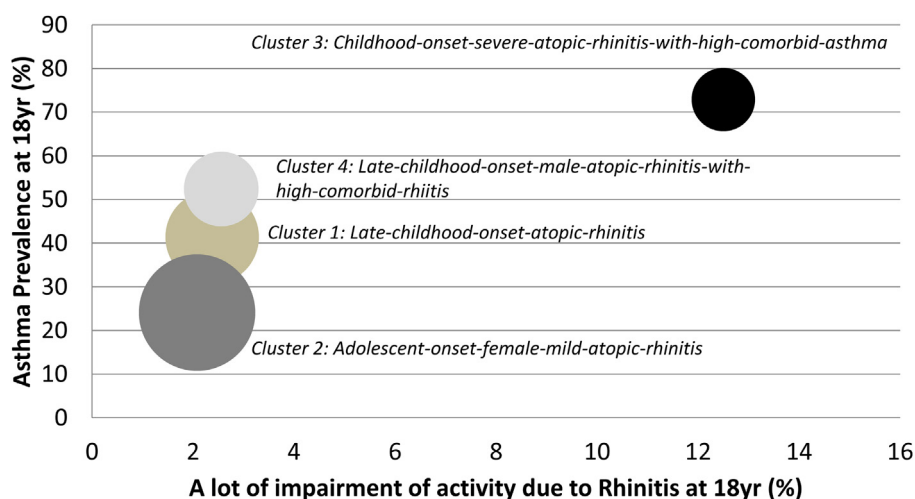


FIG 3. Rhinitis morbidity and prevalence of asthma for 18-year rhinitis clusters. The size of the spheres is proportionate to the prevalence of clusters. *Asthma prevalence at 18yr*, Ever had asthma and either of wheezing in the last 12 months or asthma treatment in the last 12 months. *A lot of impairment of activity due to rhinitis at 18yr*, Percentage within each cluster answering yes to this question.

observation noted across the rhinitis clusters and particularly in this higher-severity cluster was a high prevalence of persistent rhinitis symptoms but relatively low proportion of treatment with nasal corticosteroids in a population who would seem to merit their use. This tends to support the notion that rhinitis symptoms are often passively accepted and not given due recognition as a clinical problem. Our characterization of cluster 3 suggests that such acceptance is mistaken. Future work should aim to

define the pathophysiology of this high-morbidity cluster and its relation to recently proposed rhinitis disease endotypes.¹⁶

Previous studies have proposed that rhinitis is a risk factor for subsequent asthma development.^{4,6-8} Our findings contradict that concept by demonstrating that across all the young adult rhinitis clusters, asthma either predated or developed concomitantly with rhinitis. Recall bias is unlikely to have affected this observation because age of onset for both asthma and rhinitis

was derived from prospective recordings made through the cohort follow-up rather than simply retrospectively collected at age 18 years. Childhood rhinitis might present with atypical symptoms, such as cough, hearing problems, or sleep disturbance.²⁷ It is possible that poor recognition of rhinitis as a problem by the subject, parent, or physician might have led to delayed reporting of that as a clinical problem. Nevertheless, our overall findings lend credence to the concept of a more complex picture of multiple allergic disease trajectories from childhood to young adulthood rather than the previous traditional concept of a simple “allergic march.”²⁸

This cluster analysis approach did not observe rhinitis clusters clearly separated based on previously characterized classification parameters, such as atopy or seasonality. In part, that might reflect the specific population age being assessed in our study. The division of allergic and nonallergic rhinitis has greater importance in older patients, in whom other disease phenotypes (nonallergic, chronic rhinosinusitis with nasal polyposis, and aspirin-exacerbated respiratory disease) have higher prevalence.¹⁶ Therefore our study findings cannot be extrapolated to all ages. There might also be different association patterns to allergic sensitization in different geographic regions, with different prevalent allergens and levels of allergen exposure that limit extrapolation.

We did confirm some previous observations in addition to the concept of asthma and rhinitis comorbidity. Sex proved an important factor that showed significant association with 2 clusters. The mild adolescence-onset female rhinitis cluster (cluster 2) emerged as the most common cluster but with the mildest symptoms. Although still predominantly atopic, this cluster showed the lowest atopy prevalence among the rhinitis clusters. This pattern of less atopic and mainly female rhinitis that develops in adolescence is consistent with previous rhinitis trajectory analysis in our cohort that demonstrated a pattern for girls to grow into nonatopic rhinitis in adolescence.¹ The finding of a childhood-onset male-predominant atopic rhinitis (cluster 4 [moderate childhood-onset male rhinitis with asthma]) cluster in our study can be viewed as consistent with prior suggestions that related conditions, such as asthma, show male predominance prepubertally.²⁹ However, our cluster analysis approach indicates that to suggest that childhood-onset rhinitis is predominantly male is an oversimplification. Thus the earliest-onset rhinitis (severe earliest-onset rhinitis with asthma) cluster (cluster 3) in our study showed no sex predominance. This again highlights the greater insight into the nature of young adult rhinitis that can be revealed by a cluster analysis approach.

In conclusion, a cluster analysis approach in the Isle of Wight Birth Cohort has identified 4 distinct rhinitis clusters in young adulthood that show varying associations to age of disease onset, rhinitis morbidity and severity, asthma prevalence, and severity plus sex. The high-morbidity, severe, earliest-onset rhinitis with asthma cluster might portend more difficult later adult disease, merits early recognition, and should prompt consideration of treatment once detected; future research should focus on better understanding its development.

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assistance with many aspects of the 18-year follow-up of this study. Finally, we would like to highlight the role of the late Dr David Hide in starting this study.

Clinical implications: Recognition that earliest-onset rhinitis is associated with most severe young adult airways disease should focus early treatment efforts that might reduce later development of severe adult rhinitis and asthma.

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METHODS**SPTs at 10 and 18 years of age**

Allergy SPTs were performed by using a standardized method to a panel of common aeroallergens and food allergens: house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, tree pollen mix, cat and dog epithelia, *Alternaria alternata*, *Cladosporium herbarum*, milk, hen's egg, soya, cod, and peanut. Histamine and physiologic saline acted as positive and negative controls (ALK-Abelló). Single-headed lancets were used, skin was pricked at a 90° angle, and wheal diameter recorded at 15 minutes.

FENO measurement at 18 years of age

Participants had their FENO values measured (NIOX MINO, Aerocrine AB), according to American Thoracic Society guidelines. A biofeedback mechanism was used to maintain the expiratory flow rate at 50 mL/s, and subjects exhaled against resistance to prevent upper airway contamination. Measurements were made in a standardized manner with the subject standing without a nose clip; FENO values were measured before spirometric testing. Participants were rescheduled if they had clinical symptoms consistent with either current infection, a recent (within 2 weeks) asthma exacerbation, or required antibiotics or oral steroids in the preceding 2 weeks.

Pulmonary function testing and bronchial challenge at 10 and 18 years of age

Baseline pulmonary function testing, FEV₁, FVC, and peak expiratory flow were measured in all subjects attending the research center by using Koko spirometry software (Pds Instrumentation, Louisville, Colo). Subjects with past or current wheezing (plus a control group of "never wheezers") were also invited to perform a methacholine bronchial challenge to assess BHR with a Koko dosimeter (Pds Instrumentation) with a compressed air source at 8 L/min and nebulizer output of 0.8 L/min. Initial inhalation of 0.9% saline was followed 1 minute later by means of spirometric recording

to obtain a baseline value. Subsequently, incremental concentrations from 0.0625 to 16 mg/mL methacholine were serially administered. The concentration causing a 20% decrease in FEV₁ from the postsaline value was interpolated and expressed as PC₂₀ FEV₁. To perform spirometry or bronchial challenge, subjects were required to be free from respiratory tract infection for 14 days, to be not taking oral steroids, to have not taken a β_2 -agonist for 6 hours, and to have abstained from caffeine intake for at least 4 hours.

Other key questions asked at 10 and 18 years of age
Paracetamol use at age 18 years.

- "On average, how many times a month do you use paracetamol?"

Tobacco smoke exposure at age 18 years.

- "Do you currently smoke?"
- "If yes, how many cigarettes do you smoke a day?"
- "Have you ever smoked?"
- "If yes, how many cigarettes did you used to smoke a day on average?"
- "What age did you start smoking?"
- "What age did you stop smoking?"
- "What made you stop smoking?"

Early-life (1, 2, and 4 years of age) follow-up diagnostic definitions.

- **Asthma:** At least 3 separate episodes of wheezing, each at least 3 days in duration during the past year.
- **Eczema:** Chronic or chronically relapsing itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution.
- **Rhinitis:** Recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes.

TABLE E1. Correlations between the 9 continuous clustering variables

	FEV ₁	FVC	FEV ₁ /FVC ratio	FEF ₂₅₋₇₅	BDR	BHR	FENO	Log ₁₀ total IgE	Age rhinitis first appeared
FEV ₁	0.70 (0.64 to 0.75)		0.51 (0.42 to 0.58)	0.78 (0.74 to 0.82)	−0.43 (−0.52 to −0.34)	−0.28 (−0.40 to −0.15)	−0.13 (−0.26 to 0.005)	−0.05 (−0.21 to 0.11)	0.003 (−0.10 to 0.11)
FVC			−0.23 (−0.33 to −0.12)	0.20 (0.09 to 0.30)	−0.01 (−0.12 to 0.10)	−0.10 (−0.23 to 0.030)	−0.06 (−0.19 to 0.072)	0.04 (−0.12 to 0.20)	−0.04 (−0.15 to 0.070)
FEV ₁ /FVC ratio				0.80 (0.76 to 0.84)	−0.62 (−0.68 to −0.55)	−0.30 (−0.42 to −0.18)	−0.13 (−0.26 to 0.004)	−0.12 (−0.27 to 0.036)	0.07 (−0.037 to 0.18)
FEF ₂₅₋₇₅					−0.53 (−0.61 to −0.44)	−0.29 (−0.41 to −0.16)	−0.09 (−0.22 to 0.045)	−0.08 (−0.23 to 0.077)	0.005 (−0.10 to 0.12)
BDR						0.46 (0.34 to 0.56)	0.27 (0.14 to 0.40)	0.07 (−0.088 to 0.23)	−0.09 (−0.20 to 0.023)
BHR							0.42 (0.27 to 0.55)	0.08 (−0.11 to 0.27)	−0.25 (−0.37 to −0.12)
FENO								0.19 (−0.007 to 0.37)	−0.28 (−0.40 to −0.15)
Log ₁₀ total IgE									−0.09 (−0.24 to 0.056)

Correlations are shown with 95% CIs in brackets. Significant correlations are in boldface.

TABLE E2. Biserial correlations between continuous and binary outcome variables

	Rhinitis seasonality	Eczema	Asthma	Atopy
FEV ₁	0.06 (−0.049 to 0.17)	0.05 (−0.060 to 0.16)	−0.26 (−0.36 to −0.16)	−0.02 (−0.13 to 0.087)
FVC	−0.02 (−0.13 to 0.092)	0.10 (−0.0049 to 0.21)	−0.05 (−0.16 to 0.054)	0.04 (−0.071 to 0.15)
FEV ₁ /FVC ratio	0.13 (0.019 to 0.24)	−0.04 (−0.15 to 0.064)	−0.28 (−0.37 to −0.17)	−0.10 (−0.20 to 0.014)
FEF ₂₅₋₇₅	0.11 (0.0011 to 0.22)	−0.02 (−0.12 to 0.092)	−0.30 (−0.39 to −0.19)	−0.04 (−0.15 to 0.070)
BDR	−0.19 (−0.30 to −0.079)	0.03 (−0.087 to 0.14)	0.28 (0.17 to 0.38)	0.14 (0.024 to 0.24)
BHR	−0.08 (−0.21 to 0.056)	0.12 (−0.0069 to 0.25)	0.34 (0.23 to 0.46)	0.23 (0.10 to 0.35)
FENO	−0.28 (−0.40 to −0.15)	−0.005 (−0.14 to 0.13)	0.30 (0.18 to 0.42)	0.46 (0.35 to 0.56)
Log ₁₀ total IgE	−0.003 (−0.15 to 0.15)	−0.05 (−0.20 to 0.094)	−0.05 (−0.19 to 0.097)	0.31 (0.16 to 0.44)
Age rhinitis first appeared	0.16 (0.065 to 0.25)	−0.03 (−0.12 to 0.064)	−0.17 (−0.25 to −0.078)	−0.29 (−0.38 to −0.18)

Correlations are shown with 95% CIs in brackets.

TABLE E3. Biserial correlations between the binary outcome variables

	Rhinitis seasonality	Eczema	Asthma	Atopy
Rhinitis seasonality		−0.13 (−0.32 to 0.055)	−0.24 (−0.40 to −0.082)	−0.049 (−0.25 to 0.15)
Eczema			0.17 (0.0008 to 0.33)	0.067 (−0.14 to 0.28)
Asthma				0.23 (0.052 to 0.40)

Correlations are shown with 95% CIs in brackets.

TABLE E4. Pseudo F, R^2 , and CCC values for different number of clusters in model

No. of clusters:	2	3	4	5	6
CCC	27.15	29.85	30.23	25.79	28.07
Pseudo F	141.64	121.71	101.90	82.37	77.79
R^2	0.12	0.20	0.25	0.29	0.33

On the basis of the CCC and pseudo F values, a model with 4 clusters was chosen.

TABLE E5. Characteristics of participants attending for a full visit at 18 years of age versus the whole population seen at 18 years of age

	Participants attending in person for full visit at 18 years of age (no.)	Total population at 18-year follow-up (no.)	<i>P</i> value*
Female sex	52.9% (423/799)	50% (660/1313)	.196
Active smoking	24.7% (198/799)	28% (368/1313)	.145
Full-time education	78% (624/799)	68% (898/1313)	<.001
Atopic at age 10 y [†]	26.7% (189/709)	26.9% (279/1036)	.956
Asthma at age 18 y	19.3% (155/799)	17.5% (231/1313)	.6045

*Z test of proportions (2-sided) for comparison between participants analyzed in this study and all those assessed at 18 years of age.

[†]Numbers reflect those who attended at the 10-year and 18-year follow-up.

TABLE E6. Standardized Variables: statistical summary of the standardized variables

Variable	No.	Mean	SD	Minimum	Maximum
Log ₁₀ total IgE at age 18 y	542	1.75	0.65	0.32	3.47
Age at rhinitis onset	468	11.94	4.28	0	18.00
FEV ₁ /FVC ratio at age 18 y	839	0.87	0.07	0.57	1.00
FEV ₁	839	5.14	1.00	1.79	8.63
FVC at age 18 y	838	4.61	0.93	2.30	7.27
FEF ₂₅₋₇₅ at age 18 y	839	4.44	1.13	0.77	9.63
Log ₁₀ FENO at age 18 y	543	1.29	0.34	0.70	2.48
BHR DRS at age 18 y	585	1.13	0.30	−0.61	3.00
BDR at age 18 y	790	5.00	5.78	−28.34	42.55

In the cluster analysis all continuous data were standardized. FEV₁ is shown in liters with SEs. FVC is shown in liters with SEs. FEF_{25-75%} is shown in liters per second with SEs. FENO is measured in parts per billion. BHR DRS refers to a continuous dose-response measure of bronchial hyperresponsiveness expressed as log₁₀ (DRS+10). BDR refers to the percentage of FEV₁ bronchodilator reversibility to 600 µg of inhaled salbutamol.