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Identifying the Heterogeneity of Young Adult Rhinitis through Cluster Analysis in the Isle of Wight Birth Cohort

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Abstract

Introduction—Rhinitis affects many young adults and often shows comorbidity with asthma.

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

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Contributor Statement

RJK contributed to study design and conduct, conceived the idea for the paper, contributed to data analysis, and wrote the first draft of the manuscript.

HZ contributed to study design, conducted data analysis, and contributed to manuscript preparation.

AR contributed to study conduct, data analysis, and manuscript preparation.

VP conducted data analysis and contributed to manuscript preparation.

WK contributed to study design and manuscript preparation.

SE contributed to study design and manuscript preparation.

SHA contributed to study design, data analysis, manuscript preparation and acts as guarantor for the study. As corresponding author, SHA confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing Interest Declaration:

"All authors have completed the Unified Competing Interest form at www.icmje.org/coidisclosure.pdf (available on request from the corresponding author) and declare that (1) RJK, HZ, VP, AR, WK, SE and SHA have no support from any company for the submitted work; (2) RJK, HZ, VP, AR, WK, SE and SHA have no relationship to any company that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no specified financial relationships that may be relevant to the submitted work; and (4) RJK, HZ, VP, AR, WK, SE and SHA have no non-financial interests that may be relevant to the submitted work".

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

Results—Four clusters were identified;

Cluster 1 (n=128; 27.4%). Moderate-childhood-onset-rhinitis: They had high atopy and eczema prevalence, high total IgE but low asthma prevalence. They showed best lung function at 18-years with normal FeNO (Fractional Exhaled Nitric Oxide), low BHR (Bronchial Hyper-responsiveness) and low BDR (Bronchodilator Reversibility) but high rhinitis symptoms and treatment.

Cluster 2 (n=199; 42.5%). Mild-adolescent-onset-female-rhinitis: They had lowest prevalence of comorbid atopy, asthma and eczema. They showed normal lung function, low BHR, BDR, FeNO and total IgE plus low rhinitis symptoms, severity and treatment.

Cluster 3 (n =59; 12.6%). Severe-earliest-onset-rhinitis-with-asthma: They had youngest rhinitis onset plus highest comorbid asthma (of simultaneous onset) and atopy. They showed most obstructed lung function with high BHR, BDR and FeNO plus high rhinitis symptoms, severity and treatment.

Cluster 4 (n=82; 17.5%). Moderate-childhood-onset-male-rhinitis-with-asthma: Their prevalence of atopy was high, asthma was intermediate and eczema was low. They had impaired lung function with high FeNO and total IgE, but intermediate BHR and BDR. They showed moderate rhinitis symptoms.

Conclusion—Clinically distinctive adolescent rhinitis clusters are apparent with varying sex and asthma associations plus differing rhinitis severity and treatment needs.

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.

Keywords

Asthma; Cluster Analysis; Morbidity; Rhinitis; Wheezing

Introduction

Rhinitis is a common condition that rises in prevalence through childhood and adolescence to affect a substantial proportion of individuals in young adulthood [1]. Frequently under-recognized, it may 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 may 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 understanding of the diversity of wheezing disorders. Cluster analysis has identified wheeze clusters with strong [11,12] or little [13] associations to atopy, impaired lung function [11,12], severe bronchial

hyper-responsiveness [11,14], high [11,13] or low [12] 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 non-atopic 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 physiological change. It is also a period which 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 paper we describe a cluster analysis of young adult 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 (UK) in 1989 to study the natural history of allergic disease. Participants were assessed at 1-, 2-, 4-, 10- and 18-years. Methodology for the first decade of follow-up has been published previously [17–20].

18-Year Follow-Up Methodology

The Local Research Ethics Committee (06/Q1701/34) approved follow-up at 18-years. Participants gave informed consent and provided information on respiratory, nasal and dermatological symptoms. Study-specific plus International Study of Asthma and Allergies in Childhood (ISAAC) [21] questionnaires were used. Questions about specific exposures are provided in the online supplement.

Participation at age 18 was in person, by telephone or by post. Participants attending in person also performed spirometry, fractional exhaled nitric oxide (FeNO) measurement, methacholine challenge test, skin prick test (SPT) and provided blood for total IgE measurement. Identical methodology, published previously [20], was used for spirometry and methacholine challenge testing at 10- and 18-years. FeNO (Nioxmino, ®Aerocrine AB, Solna, Sweden) and SPT to 14 common aero- and food allergens (ALK-Abello, Horsholm, Denmark) were performed as reported previously [20]. Relevant methodology at 10 and 18-years is summarised in the online supplement.

Definitions

Rhinitis at 10 and 18-years was defined by “have you ever had a problem with sneezing, runny or blocked nose in the absence of cold or flu” plus “symptoms in the last 12 months”. Seasonality of rhinitis was defined as perennial (+/– seasonal exacerbation) or seasonal only. Asthma at 10 and 18-years was defined as “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 was defined by “have you ever been diagnosed with eczema” plus “having an itchy rash in the past 12 months”. Diagnostic definitions used at early life follow-ups are given in the online supplement. Atopy was defined by positive SPT (mean wheal diameter 3 mm

negative control) to at least one allergen. Age of rhinitis onset was defined as “childhood” (<12-years) or “adolescent” (12-years).

BDR (Bronchodilator Reversibility) was defined as percentage change in FEV₁ (Forced Expiratory Volume in 1 Second) after inhaling 600 micrograms salbutamol. Not all subjects undergoing methacholine challenge testing demonstrate a 20% fall in FEV₁ that enables PC20 calculation to indicate BHR (Bronchial Hyper-Responsiveness). Therefore at both 10 and 18-years, a continuous dose-response slope (DRS) measure of BHR was estimated by least-square regression of percentage change in FEV₁ upon 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 using the SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA). Cluster analysis was performed on the population reporting rhinitis within the past 12 months at age 18 (n=468). Cluster variables were selected that defined clinical characteristics at 18-years. These included both questionnaire-derived data and variables from objective testing. Thirteen variables were selected for the cluster analyses; atopic status at 18, asthma at 18, eczema at 18, age that rhinitis appeared, seasonality of rhinitis symptoms, total IgE (log 10), BDR, BHR DRS, mean FeNO (log10), FEV₁, FVC (Forced Vital Capacity), FEV₁/FVC, FEF₂₅₋₇₅ (Forced Expiratory Flow 25–75%).

As in linear regressions, clustering methods are sensitive to the scale of the variables. To put every continuous variable on a common scale, each variable was standardized by subtracting its mean and dividing by its standard deviation. To remove gender and height effect on FEV₁, FVC, and FEF₂₅₋₇₅, we regressed these variables on gender and height; the residuals with gender and height effects excluded were used in the analyses. We used this approach in preference to using % predicted lung function values. The use of % predicted values is dependent on values estimated from existing formulas based on reference populations. Those reference ranges may not apply to all populations and would not necessarily reflect the relevance of individual lung function measures at the age studied in our cohort. Due to 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 (Table E1), between continuous and binary variables (Table E2), and between binary variables (Table E3).

The method of K-means (PROC FASTCLUS in SAS) was used for cluster analysis. To determine cluster number, we used two criteria; cubic clustering criterion (CCC) [22] and 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 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 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 R^2 statistic measuring between cluster variations (the larger the better) (Table E4).

To evaluate each clustering variable across the clusters, ANOVA was used for continuous variables and Chi-Square tests for binary variables. Pairwise t-tests with Bonferonni multiple testing correction were applied to continuous variables, and pairwise proportion tests were applied to binary variables with the overall significance level set at $\alpha=0.05$. Having defined distinct clusters, we sought to further characterize those clusters by assessing morbidity parameters for them. These included rhinitis symptom frequency, severity and rhinitis therapy with assessment by Chi-Square 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, 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, and Body Mass Index (BMI) at 18-years. Identical methods as for morbidity variables were used to compare risk factors between different clusters.

Results

High cohort follow-up was achieved at 10-years (94%; n= 1373) and 18-years (90%; n= 1313). 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 and 5.4% (n=80) were seen at 18-years but not at 10. Of subjects seen for a Centre Visit at 18-years (n=864), 90.5% (n=762) were also seen at 10-years. Previously published data [24] demonstrated that participants attending the centre for a “full visit” (n=864) at 18-years did not differ significantly from the overall cohort participation (Supplementary Table E5). Statistical summary of standardised variables is in the online supplement (Table E6). At 18-years, whole population prevalence of diagnosed rhinitis was 35.8% (468/1309), asthma was 17.9% (234/1306), eczema was 12.3% (161/1306) and atopy was 41.3% (352/853).

Clustering Outcome

Cluster analysis on the population (n= 468) with rhinitis at 18-years identified four clusters. Their characteristics based on cluster variables are outlined in Table 1. Separation of clusters by cluster variables using ANOVA for continuous variables or Chi-Squared tests for binary variables is provided in Table 1 (last column) and resulting cluster variable based characterization is summarised below. The proportion of these clusters within the rhinitis population varied; cluster 1 (27.4%), cluster 2 (42.5%), cluster 3 (12.6%), 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, high total IgE but low prevalence of asthma. They showed highest lung function at 18-years. They also had normal FeNO, low BHR and low BDR all of which were comparable to values for the whole population seen at 18-years.

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

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

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 most impairment of FEV₁ and FVC with high FeNO and total IgE, 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-adolescent-onset-female-rhinitis*) (Table 2). Persistent rhinitis symptom frequency (Figure 1) at 18-years differed significantly between clusters, being highest for cluster 3 (*severe-earliest-onset-rhinitis-with-asthma*) and lowest for cluster 2 (*mild-adolescent-onset-female-rhinitis*). The same pattern of association emerged for high degree of impairment of daily activity due to rhinitis (Table 2). Cluster 3 (*severe-earliest-onset-rhinitis-with-asthma*) had highest prevalence of impairment of daily activity, cluster 1 (*moderate-childhood-onset-rhinitis*) had highest prevalence of little impairment of daily activity while cluster 4 (*moderate-childhood-onset-male-rhinitis-with-asthma*) had highest prevalence of moderate impairment. Other rhinitis associated morbidity, such as eye symptoms and sleep disturbance, were broadly similar across the 4 clusters (Table 2).

Asthma Comorbidity

Asthma comorbidity varied significantly between rhinitis clusters (Table 1), being significantly higher for cluster 3 (*severe-earliest-onset-rhinitis-with-asthma*) than cluster 2 (*mild-adolescent-onset-female-rhinitis*). Cluster 3 (*severe-earliest-onset-rhinitis-with-asthma*) also showed most impaired lung function with high BHR, BDR and FeNO. The mean age of asthma onset predated that for rhinitis in all four rhinitis clusters; cluster 1 (*moderate-childhood-onset-rhinitis*; 6.8 years), cluster 2 (*mild-adolescent-onset-female-rhinitis*; 8.1 years), cluster 3 (*severe-earliest-onset-rhinitis-with-asthma*; 6.0 years), cluster 4 (*moderate-childhood-onset-male-rhinitis-with-asthma*; 7.3 years). This pattern was retained where analysis was restricted to individuals with dual asthma and rhinitis, when age of asthma onset was almost identical across the clusters (Figure 2). Furthermore among individuals with dual disease, cluster 3 (*severe-earliest-onset-rhinitis-with-asthma*) had the earliest rhinitis onset with almost simultaneous asthma and rhinitis onset (Figure 2).

Risk Factors

Potential risk factors for rhinitis clusters are shown in Table 3. Female sex was significantly associated with cluster 2 (*mild-adolescent-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 breastfeeding, recurrent chest infections in infancy, personal smoking, maternal, cord IgE at birth and paracetamol use at 18-years) did not show significant association to any particular cluster.

Final Summary Characterization of Rhinitis Clusters

Final summary characterization of the 4 rhinitis clusters is shown in Table 4 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 adulthood rhinitis could be categorized by four distinct clusters with differing associations to asthma, lung function, bronchial hyper-reactivity, 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-adolescent-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 adults [11–14] 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), so when performing cluster analyses, subjects with similar levels of lung function measure 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 mainland England (data on file) and previous findings [17–19] have been similar to 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 two relatively low asthma prevalence rhinitis clusters. Indeed the largest rhinitis cluster (*cluster 2; mild-adolescent-onset-female-rhinitis*) showed asthma prevalence comparable to the general (whole cohort) population (Table 1). 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 elevated 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 Figure 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), while least prevalent, showed highest prevalence of persistent rhinitis and rhinitis morbidity in terms of daily impairment. It therefore emerges as the most clinically significant rhinitis cluster in our population. It also showed highest atopy and asthma prevalence plus most abnormal measures of airway pathophysiology including airflow obstruction, BDR, BHR and exhaled nitric oxide. It is worth noting that for individuals with dual disease, while mean age of asthma onset consistently predated rhinitis onset in the three 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 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 a notion that rhinitis symptoms are often being passively accepted and not being 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 rhinitis disease endotypes that have recently been proposed [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 since 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 18-years. Childhood rhinitis may 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. That may partly reflect the specific population age being assessed in our study. The division of allergic and non-allergic rhinitis has greater importance in older patients, where other disease phenotypes (non-allergic, chronic rhinosinusitis with nasal polyposis, Aspirin Exacerbated Respiratory Disease) have higher prevalence [16]. Therefore, our study findings cannot be extrapolated to all ages. There may also be different association patterns to allergic sensitisation 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 which showed significant association to 2 clusters. The *mild-adolescent-onset-female-rhinitis* cluster (cluster 2) emerged as the commonest cluster but with mildest disease. While 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 non-atopic 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 may 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, which 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 may 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Persistent Rhinitis Symptom Frequency for the Rhinitis Clusters

Prevalence of persistent rhinitis symptoms (>4 days/week and >4 weeks in the past year).

Error bars are standard errors.

Cluster 1: Moderate-childhood-onset-rhinitis.

Cluster 2: Mild-adolescent-onset-female-rhinitis.

Cluster 3: Severe-earliest-onset-rhinitis-with-asthma.

Cluster 4: Moderate-childhood-onset-male-rhinitis-with-asthma.

Figure 2. Age of Asthma v Rhinitis Onset for Subjects with Dual Disease in the Rhinitis Clusters

Age of onset of asthma compared to rhinitis where both coexisted for the rhinitis clusters.

Cluster 1: Moderate-childhood-onset-rhinitis.

Cluster 2: Mild-adolescent-onset-female-rhinitis.

Cluster 3: Severe-earliest-onset-rhinitis-with-asthma.

Cluster 4: Moderate-childhood-onset-male-rhinitis-with-asthma.

Figure 3. Rhinitis Morbidity and Prevalence of Asthma for 18-yr Rhinitis Clusters

Size of the spheres is proportionate to prevalence of clusters.

Asthma prevalence at 18 yr = “ever had asthma” and either of “wheezing in the last 12 months” or “asthma treatment in the last 12 months”

A lot of impairment due to rhinitis at 18 yr reflects % within each cluster reporting yes to this question.

Table 1

Summary Characterisation of Cluster Variables for 18-year Rhinitis Clusters

Variables	Cluster sample (n=468)	Whole Age 18 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)							
FEV1 [*]	-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}}
FEV1/FVC [‡]	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 1 st appeared ^{‡‡} (Years)	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 18	11.38	12.23	25.2	15.1	22.4	7.31	{1,2,3},{2,3,4}
Asthma or wheezing at 18	39.96	24.88	41.4	24.1	72.9	52.4	{1,4},2,{3,4}
Atopy at 18	69.76	41.27	81.2	55.6	96.6	71.0	{1,3},{1,4},{2,4}

Notes:

Figures in bold indicate highest and lowest values across the clusters.

For continuous variables, mean values are shown with standard deviation (SD).

^{*} FEV1 = Forced expiratory volume in first second in litres (L) at 18-years. It is height and gender adjusted.[‡] FVC = Forced vital capacity in litres (L) at 18-years. It is height and gender adjusted.^{‡‡} FEV1/FVC = ratio of FEV1 to FVC at 18-years.[§] FEF25-75% = Forced expiratory flow 25-75% in litres per second (L/s) at 18-years. It is height and gender adjusted.

// BDR refers to %FEV₁ Bronchodilator reversibility: to 600 micrograms inhaled salbutamol at 18-years.

¶ BHR DRS refers to a continuous dose-response (DRS) measure of bronchial hyperresponsiveness (BHR) expressed as Log10 (DRS+10). Higher values infer greater BHR at 18-years.

** FeNO refers to Fractional exhaled Nitric Oxide measured in parts per billion (ppb) at 18-years at 18-years.

†† Log 10 Total IgE at 18-years.

‡‡ Age wheeze 1st appeared (in years; determined from collected data throughout the 18-years of the cohort).

§§ Rhinitis seasonality refers to having seasonal disease only.

/// Atopy refers to positive skin prick test (>3 mm wheal diameter) to at least allergen in standard test panel at 18-years.

¶¶ Numbers included within a pair of curly brackets indicate the statistics within those clusters are not significantly different from each other after adjusting for multiple testing. Numbers in different pairs of curly 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 both of these two clusters showed significant difference with clusters 3 and 4. However, the mean FEV₁ in clusters 3 and 4 are not significantly different.

Table 2

Rhinitis Morbidity Characteristics for Rhinitis Clusters at 18-years

Symptoms & Treatment (% Reporting Yes)	Cluster 1 (n=128) % (count)	Cluster 2 (n=199) % (count)	Cluster 3 (n=59) % (count)	Cluster 4 (n=82) % (count)	p-value
Eye Symptoms	72.66 (93)	68.02 (134)	71.43 (40)	77.78 (63)	0.42
Sleep Disturbance	34.92 (44)	22.80 (44)	42.86 (24)	30.0 (24)	0.014
Rhinitis Treatment	67.20 (84)	56.99 (110)	68.52 (37)	65.38 (51)	0.19
Antihistamine Treatment	62.50 (80)	46.73 (93)	57.63 (34)	58.54 (48)	0.030
Nasal Steroid Treatment	11.72 (15)	9.05 (18)	11.86 (7)	10.98 (9)	0.85
Impairment of daily activity (% Reporting Yes)					0.0003
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	

Notes:

Eye Symptoms refers to presence of associated eye symptoms in the past year at age 18.

Sleep Disturbance refers to disturbance of sleep by rhinitis in the past year at age 18.

Rhinitis Treatment categories refer to need for those rhinitis therapies in the past year at age 18.

Impairment of daily activity refers to impairment of daily activity due to rhinitis in the past year.

The p-values are from Chi-square tests comparing the distribution patterns of a categorical variable in each cluster across the 4 clusters.

Table 3

Risk Factor Association with the Rhinitis Clusters at 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 Gender	50.78(65)	40.20 (80)	47.46 (28)	60.98 (50)	0.013
Family history of rhinitis	83.02 (88)	79.25 (126)	72.34 (34)	73.44 (47)	0.34
Low birth weight	4.03 (5)	1.58 (3)	1.69 (1)	3.80 (3)	0.50
Exclusively breastfed	35.71 (40)	32.54 (55)	22.45 (11)	35.29 (24)	0.39
Chest infection in infancy	15.09 (16)	22.36 (36)	22.73 (10)	17.14 (12)	0.44
Personal smoking	50.79 (64)	48.70 (94)	57.14 (32)	47.50 (38)	0.68
Maternal smoking in pregnancy	32.03 (41)	37.69 (75)	40.68 (24)	29.27 (24)	0.37
Mean Cord log-IgE	-0.72 (0.48)	-0.81 (0.40)	-0.74 (0.46)	-0.73 (0.38)	0.47
Mean Paracetamol use	1.73 (2.54)	2.05 (4.08)	1.61 (2.40)	1.90 (4.81)	0.78
Mean BMI	23.91 (4.70)	23.01 (4.08)	24.31 (5.20)	22.38 (4.00)	0.07

Notes

Family History of rhinitis = Family (parent or sibling) history of rhinitis.

Low Birth weight = Low Birth Weight (<2.5 kg).

Exclusively Breastfed = Exclusively breastfed for > 3 months.

Chest infection in infancy = History of recurrent chest infections at 1 or 2-years.

Personal Smoking = Personal (past or current) history of cigarette smoking.

Maternal Smoking = Maternal smoking history during pregnancy.

Cord IgE = Cord blood IgE at birth.

Paracetamol Use = Paracetamol use at 18-years in average number of times taken per month.

BMI = Body Mass Index (Weight [Kg]/Height² [M]) at 18-years.

The p-values are for the tests comparing the distribution patterns of a categorical variable in each cluster or comparing medians (continuous variables) across the 4 clusters. For categorical variables, chi-square tests were implemented and for continuous variables Kruskal-Wallis tests were used due to the violation of the normality assumption in the residuals.

Table 4

Summary Characterisation 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- adolescent- onset- female- rhinitis.	+	++	+	+	+	+	+	+
3	Severe- earliest- onset- rhinitis- with- asthma.	+++	+++	+++	++	+++	+++	+++	+++
4	Moderate- childhood- onset- male- rhinitis- with- asthma.	++	+	++	+++	++	+	++	+

Notes:

Summary characterisation of clusters by core parameters.

+ = Low

++ = Moderate

+++ = High

BDR = Bronchodilator Reversibility

BHR = Bronchial Hyper-responsiveness