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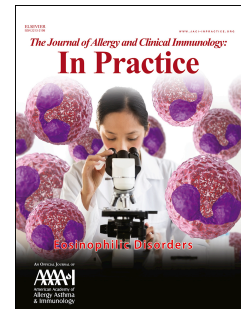
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Original Article

Persistent asthma from childhood to adulthood presents a distinct phenotype of adult asthma

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33 **Conflicts of Interest Statement:**

34 All authors have reported that no potential conflicts of interest exist in regard to this article.

ABSTRACT

Background: In approximately 30% of children with asthma, the condition persists into adulthood. The longer duration of asthma in these patients is a risk factor for poor asthma control. However, the characteristics of adult patients with asthma that has persisted since childhood are not well documented.

Objective: We sought to compare the clinical characteristics among patients with adult-onset asthma, patients who outgrew childhood asthma but relapsed, and patients with persistent asthma since childhood.

Methods: We conducted a cross-sectional study of adult patients with asthma who visited our hospital. We classified them into three groups: those with adult-onset asthma (adult-onset), those who had remitted childhood asthma which relapsed (relapsed), and those who had asthma that had persisted since childhood (persistent). The clinical characteristics of these groups were compared.

Results: A total of 1443 patients were enrolled. The persistent group was younger and included fewer patients with a smoking history. There were statistically significant differences among the three groups in the percentages of patients with a family history of asthma and comorbidities of allergic rhinitis and atopic dermatitis. The proportion of patients with severe asthma differed among the three groups (31% in the adult-onset group, 34% in the relapsed group, and 40% in the persistent group; $p=0.015$). The values of FEF_{75} were lower in the persistent group than the relapsed or adult-onset group. A multivariable logistic regression analysis (dependent variable: severe asthma) in each group revealed that the factors associated with severe asthma differed among the adult-onset, relapsed, and persistent groups. When we established an overall model that included interaction terms of cohort-by-other factors, there was a trend that comorbidity of allergic rhinitis affected the

severity of asthma differently in the relapsed group compared to the other groups.

Conclusions: The clinical phenotype of asthma that persists from childhood to adulthood seems to be a distinct phenotype of adult asthma.

Keywords:

adult asthma, childhood asthma, duration of asthma, family history of asthma, persistence of asthma from childhood, phenotype of asthma, severe asthma

ABBREVIATIONS

BMI: body mass index

FEF₅₀: forced expiratory flow at 50% of vital capacity

FEF₇₅: forced expiratory flow at 75% of vital capacity

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroids

IgE: immunoglobulin E

PEF: peak expiratory flow

Highlights box*1. What is already known about this topic?*

In approximately 30% of children with asthma, the condition persists into adulthood, comprising a significant patient population. The characteristics of these patients are not well documented.

2. What does this article add to our knowledge?

Adult patients with asthma that has persisted from childhood to adulthood have poorer lung function and more severe asthma in adulthood than those with adult-onset asthma.

3. How does this study impact current management guidelines?

The finding that asthma which persists from childhood to adulthood presents a distinct clinical phenotype should be considered in order to improve personalized asthma treatment.

INTRODUCTION

Although most individuals with childhood asthma are expected to outgrow their asthma before adulthood, the actual remission rate is lower than generally thought. This rate was approx. 30% from 1950 to 1960.¹ A long-term study over 35 years from 1964 demonstrated that the remission rate was approximately 30% for all childhood asthma and 10% for severe childhood asthma.² The remission rate for all childhood asthma was reported to be approximately 70% in more recent studies.^{3,4} Thus, the asthma of approximately 30% of individuals with childhood asthma persists into their adult years. This population comprises a rather large number of patients.

Adult patients whose asthma persisted from childhood have a longer duration of asthma, which is a risk factor for increased severity and poor asthma control⁵ and airway remodeling induced by persistent airway inflammation.^{6,7} Saglani et al. showed that children (6–16 years) with recurrent wheeze and reversible airflow obstruction already had basement membrane thickening in the bronchial mucosa.⁸ The persistent airway inflammation from childhood asthma further increases the airway remodeling over time, presumably leading to the difficulty of treating childhood asthma that persists into adulthood.

Adult asthma that has persisted from childhood asthma is thus potentially difficult to treat and is a distinct clinical phenotype. However, the characteristics of adult patients with asthma that has persisted from childhood are not well documented. We conducted the present study to determine the clinical characteristics of patients with adult-onset asthma, patients whose asthma remitted and then relapsed, and patients with persistent asthma since childhood.

PATIENTS AND METHODS

Study population

The study population consisted of patients with adult asthma (≥ 18 years old) who visited the outpatient clinic of the Department of Allergy and Respiratory Medicine at The Fraternity Memorial Hospital between October and December 2015. Our department is one of the largest for the treatment of allergic diseases in Japan, with a capacity of approximately 1,500 patients with asthma per month. The inclusion criteria were (1) asthma diagnosed using the Global Initiative for Asthma (GINA) guidelines; (2) fulfillment of the definition of 'relapsed,' 'persistent,' or 'adult-onset' described below in the *Study design* section; (3) visiting our hospital regularly and regular use of controller medication for asthma for ≥ 2 years before enrollment; (4) available spirometry data taken under stable conditions; and (5) no other respiratory diseases potentially affecting the spirometry data, for example, old tuberculosis, diffuse emphysema, bronchiolitis, interstitial lung disease or diffuse lung diseases.

Study design

We performed a cross-sectional study using clinical and laboratory data obtained from electronic medical records (EMRs). We classified the patients into three groups: those with adult-onset asthma (adult-onset group), those who had remitted childhood asthma but then relapsed in adulthood (relapsed group), and those with persistent asthma from childhood (persistent group). The clinical characteristics of the groups were compared. 'Adult-onset' was defined as asthma diagnosed at ≥ 18 years old with no previous diagnosis at ≤ 17 years old. 'Relapsed' was defined as the resolution of childhood asthma at ≤ 16 years old (patient-reported history) and the relapse of asthma symptoms at ≥ 18 years old. 'Persistent' was

defined as asthma that was first diagnosed at ≤ 16 years old, with symptoms or regular medication that continued until the time of enrollment. This study was approved by The Fraternity Memorial Hospital Research Ethics Committee and was performed in accordance with the Declaration of Helsinki.

Data collection

All data were obtained from EMRs. Demographic data, comorbidities, latest spirometry data (pre-bronchodilator values), laboratory data, characteristics of asthma, types of controller used under stable conditions, and the number of severe acute exacerbations per year were recorded on a standardized data-collection sheet. “Domestic exposure to pet” means that patients own pets currently and/or owned them previously. Comorbid allergic diseases and aspirin sensitivity were diagnosed by clinical diagnosis based on history. Duration of asthma was based on the patient-reported data. Eosinophil numbers were tested under stable conditions of asthma. Allergen-specific IgE measurement was performed by fluorimetric enzyme-linked immunoassay. Patients were considered positive for allergen-specific IgE when the IgE score was 0.035UA/mL or higher. Severe asthma was defined based on the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines for severe asthma.⁹ High-dose inhaled corticosteroids (ICSs) were defined based on the GINA guidelines. “Severe acute exacerbation of asthma” was defined¹⁰ as an event requiring an emergency room visit and/or hospitalization for treatment with systemic corticosteroids or increased systemic corticosteroids from a stable maintenance dose for ≥ 3 days. Spirometry was performed by trained medical technologists based on the guidelines of the American Thoracic Society in clinical settings. The definition of obesity for Japanese established by the Japan Society for the Study of Obesity was used: BMI ≥ 25 kg/m².¹¹

163

164 *Statistics*

165 Data were compared using the Mann-Whitney U-test or Kruskal-Wallis test with a post-hoc
166 Dunn's test. Fisher's exact test or the Chi-square test was used for comparisons of
167 proportions for categorical variables.

168 A multivariable logistic regression analysis was performed using severe asthma as the
169 dependent variable to investigate which variables were independently associated with severe
170 asthma. Age, sex, duration of asthma, %FEV₁, and comorbidity of allergic rhinitis were
171 entered as independent variables in the analysis. We also established an overall model that
172 included interaction terms of cohort-by-other factors (persistent asthma-by-obesity,
173 relapsed-by-obesity, persistent-by-allergic rhinitis and relapsed-by-allergic rhinitis).
174 A p-value <0.05 was considered significant. For the pairwise multiple comparisons of
175 categorical variables, a p-value <0.016 was considered significant with Bonferroni
176 correction. All statistical analyses were performed using SPSS ver. 24 software (IBM,
177 Armonk, NY).

178

179 **RESULTS**180 *Demographic data*

181 A total of 1443 patients met the inclusion criteria. Their demographic characteristics and
182 comorbidities are summarized in Tables I and II. There were statistically significant
183 differences among the three groups in terms of age, sex, smoking history, and the
184 percentages of patients with a family history of asthma and comorbidities of allergic rhinitis
185 and atopic dermatitis. The persistent group had male predominance, and the other two
186 groups had female predominance. By pairwise comparison using Fisher's exact test, the

percentage of patients with a family history of asthma was higher in the persistent group than in the adult-onset or relapsed group ($p<0.001$) (Tables I and V). The comorbidities of allergic rhinitis ($p<0.001$) and atopic dermatitis ($p<0.001$) were higher in the persistent group than in the adult-onset group (Tables I and V).

Disease characteristics and therapy

The disease characteristics and therapy for asthma are summarized in Table III. As expected, the duration of asthma was longer in the persistent group ($p<0.001$). The percentages of patients with severe asthma differed among the three groups (31% in the adult-onset group, 34% in the relapsed group, and 40% in the persistent group, $p=0.015$). When the pairwise comparisons were performed, the percentage of patients with severe asthma in the persistent group was higher than that in the adult-onset group ($p=0.005$), but not higher than that in the relapsed group ($p=0.238$) (Table V). There were no differences in the percentage of patients with severe asthma between the relapsed and adult-onset groups ($p=0.499$) (Tables III and V). There were also differences among the groups in the percentage of patients using high-dose ICSs ($p=0.004$), and the percentage having one or more severe acute exacerbations per year ($p=0.022$, Table III). When the pairwise comparisons were performed (Table V), the percentage of patients using high-dose ICSs in the persistent group was higher than that in the adult-onset group ($p=0.001$), but not higher than that in the relapsed group ($p=0.240$). The percentage of patients using high-dose ICSs was not different between the relapsed and adult-onset groups ($p=0.283$).

Pulmonary function tests and laboratory data

The results of the pulmonary function tests and laboratory data are summarized in Tables II

and IV. The %FEF₇₅ values were lower in the persistent group compared to the adult-onset ($p<0.001$) and relapsed groups ($p<0.05$), and the %FEV₁ and %FEF₅₀ values were lower in the persistent group than in the adult-onset group ($p<0.001$). The peripheral eosinophil count was also higher in the persistent group than in the adult-onset group ($p<0.01$), and the total IgE values were higher in both the persistent group ($p<0.01$) and the relapsed groups ($p<0.01$) than in the adult-onset group. Differences in allergen-specific IgE data were also detected among the three groups (House dust: $p<0.001$; Mite: $p<0.001$; Cat: $p<0.001$; Dog: $p<0.001$; Candida: $p=0.001$; Aspergillus: $p<0.001$) (Tables II and V).

Differences in factors associated with severe asthma among the persistent, relapsed and adult-onset groups

Based on the results described above, we speculated that patients with adult asthma that persists from childhood have distinct clinical characteristics and have more severe disease. We next investigated factors associated with severe asthma in each group. We divided the patients in each group into two sub-groups: those with severe asthma (SA) and those with non-severe asthma (NSA), and we compared these groups' variables.

In the adult-onset group, statistically significant differences were revealed between the SA and NSA patients in BMI, the percentage of obese subjects, the duration of asthma, spirometry data, and the total IgE level. In the relapsed group, statistically significant differences were observed between the SA and NSA patients in BMI, comorbidity of allergic rhinitis, comorbidity of food allergy, and the duration of asthma. In the persistent group, statistically significant differences were observed in age, family history of asthma, duration of asthma and spirometry data between the SA and NSA patients (Tables E1–E3).

The multivariable logistic regression analysis of the adult-onset group showed that

age, obesity, the duration of asthma, and %FEV₁ were independently associated with severe asthma in the adult-onset group (Table VI). In the relapsed group, the duration of asthma and allergic rhinitis were independently associated with severe asthma (Table VI). In the persistent group, %FEV₁ was independently associated with severe asthma (Table VI). We next established an overall model that included interaction terms of cohort-by-other factors, e.g. persistent asthma-by-obesity, *etc.* (Table VII). There was a trend that comorbidity of allergic rhinitis affected the severity of asthma differently in the relapsed group compared to the other groups.

DISCUSSION

We examined the clinical characteristics of 1443 patients with adult asthma. Our findings showed that adult patients with asthma that had persisted from their childhood had asthma more atopic in nature (more frequent allergen sensitization and comorbidities of allergic diseases), poorer lung function, and a higher incidence of severe asthma compared to patients with adult-onset asthma. Small airway closure measured by FEF₇₅ was also more severe in the persistent group compared to the adult-onset and relapsed groups. These findings are largely in agreement with previously published studies. For example, adult asthma patients with a history of childhood asthma were previously shown to be male-predominant and to have a higher rate of family history of asthma, more frequent asthma attacks, lower lung function (especially function related to the small airways) and more frequent allergen sensitization.^{12, 13} In a study that enrolled only patients with severe asthma, those with late-onset asthma (diagnosed after 12 years old) had lower lung function while those with early-onset asthma (diagnosed before 12 years old) had more allergen sensitization and allergic symptoms.¹⁴

An important finding in this study is that the percentage of patients with severe asthma was higher in the persistent group than that in the adult-onset group. This result is consistent with a previous study.¹³ One of the causes of this phenomenon may be the longer duration of asthma in these patients, since longer asthma duration would induce remodeling of the bronchial walls, which can lead to difficult-to-treat asthma⁸ and has been associated with severe asthma.⁵ In addition, it is speculated that the severity of asthma in childhood might affect the severity of asthma in adulthood. Other studies have reported that severe asthma symptoms, poor lung function, and higher airway hypersensitiveness in childhood are all predictors of persistence of childhood asthma to adulthood.^{15, 16}

Another interesting finding in this study is that the %FEF₇₅ was lower in the persistent group compared to both the adult-onset and relapsed groups while other spirometry parameters were lower in the persistent group compared to the adult-onset group but not compared to the relapsed group. Because %FEF₇₅, %FEF₅₀ and %FEF₂₅₋₇₅ are all used as markers for small airway dysfunction,¹⁷⁻¹⁹ these results suggest that the impairment of the small airways was greater in the persistent group than the other two groups, which is in agreement with a previous report.¹³ The reason for this is unclear, but small airway diseases seem to be present despite mild asthma symptoms and normal spirometry in children with asthma,²⁰ implying that the small airways of children may be more fragile and sensitive to airway inflammation. Small airway dysfunction in patients with asthma is also associated with airway hyperresponsiveness²¹ and is strongly related to an increase in dyspnea,²² which indicates that the small airway asthma phenotype may be associated with severer asthma.^{18,}

^{23, 24}

It is noteworthy that patients with adult asthma that persists from childhood have poorer lung function and more severe asthma in adulthood than those with adult-onset

asthma (Tables III, VI and V), although not all early-onset asthmatic patients are severe and have poor lung function. In fact, several studies have demonstrated that patients with late-onset asthma are more severe and have poorer lung function.^{25, 26} Other investigations have demonstrated that the results of lung function tests and the prevalence of severe asthma in early-onset asthma and late-onset asthma were similar.^{27, 28} A serious limitation of those studies is that the early-onset asthma groups seemed to contain both patients whose asthma persisted from childhood and patients with early-onset asthma that remitted but relapsed in adulthood. The former and the latter show different characteristics; the latter is less severe. Regarding the typical course of early-onset asthma, it is reported that early-onset asthma with normal lung function and good control tends to remit before adulthood, and conversely, early-onset asthma with poor lung function and severe symptoms tends to persist into adulthood.^{29, 16, 30} It is thus reasonable that the population (early-onset of asthma that persists into adulthood) shows a more severe phenotype.

Our analyses and previous studies demonstrated that adult patients with asthma that had persisted from childhood had distinct clinical characteristics compared to other adult asthma patients. Based on the information, we performed a multivariable logistic regression analysis to investigate which variables were independently associated with severe asthma in each group (adult-onset, relapsed, or persistent). As independent variables, we entered the same variables (duration of asthma⁵, %FEV₁⁹, obesity³¹ and comorbidity of allergic rhinitis^{32, 33}) in each group, which are all reported to be associated with increased severity of asthma. The results showed that the factors associated with severe asthma differed among the adult-onset, relapsed and persistent groups. Next, we established an overall model that included interaction terms of cohort-by-other factors: persistent asthma-by-obesity, relapsed-by-obesity, persistent-by-allergic rhinitis and relapsed-by-allergic rhinitis. We

chose the factors, obesity and allergic rhinitis, because they are physiological factors reported to be associated with increased severity of asthma^{31, 32, 33} and showed association with severe asthma in only one cohort (obesity in Adult-onset, allergic rhinitis in relapsed) in the data shown in Table VI. In our analysis, statistically significant differences in the interactions between severe asthma and clinical factors among the adult-onset, relapsed and persistent groups were not detected. With the results from the two analyses, although we detected differences in the clinical factors associated with severe asthma among the three groups, differences in the mechanisms of increased severity of asthma in the three groups were not demonstrated in an overall model that included interaction terms of cohort-by-other factors.

A key strength of this study was that all of the patients were diagnosed with asthma by trained allergy specialists or physicians under training to be allergy specialists, based on the GINA guidelines. However, certain limitations should also be considered when interpreting our results. First, in this cross-sectional study, we could not collect data regarding the treatment or control of asthma in childhood. Nonetheless, the treatment and control of asthma could have affected the asthma severity in adulthood. Second, this study was performed at a specialist hospital, and no patients who received medical attention at a primary care clinic were included. In fact, the percentage of severe asthma was 48% in this study population while the percentage of severe asthma is typically around 5%.^{34,35} This might have caused a sample selection bias. However, in Japan, patients with mild asthma who would get their medical care at a primary care clinic in other countries sometimes visit a specialist hospital and receive medical attention from specialists. Therefore, any potential sample selection bias would be relatively minimal. Third, we enrolled only patients who had received regular medication for ≥ 2 years before enrollment in order to exclude patients with

poor adherence to medication. However, we could not check whether all prescribed medication was used properly in all patients, and thus unrecognised patients with poor medication adherence might have been accidentally included. Fourth, as mentioned above, we enrolled only patients who had received regular medication for ≥ 2 years before enrollment. This means that patients with very mild asthma—such as patients at GINA therapy step 1—were excluded.

CONCLUSION

Adult patients with asthma that has persisted from childhood to adulthood have poorer lung function and more severe asthma in adulthood than those with adult-onset asthma based on our findings. Asthma that persists from childhood to adulthood seems to present a distinct clinical phenotype of adult asthma, and this should be considered when clinicians attempt to optimize treatment for their adult patients with asthma.

Author Contributions: MT and YT participated in the conception and design of the study. MT, RT, OK, SY, SS, YK, YK, NH, IK, and YT participated in the acquisition, analysis, and interpretation of data. MT, KH, and YT participated in the writing and critical revision of the manuscript. All authors are accountable for the accuracy and integrity of the work.

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453

Table I. Demographic data of the adult-onset, relapsed, and persistent asthma groups

	Adult-onset	Relapsed	Persistent	p^s
n	1037	143	263	
Age, yrs	62 (48-72)	46 (38-58) ^{***}	42 (35-49) ^{***,++}	<0.001
Sex, male, n (%)	380 (37%)	66 (46%)	147 (56%)	<0.001
Smokers, Ex & current	350 (37%)	50 (39%)	58 (25%)	0.002
Domestic exposure, pet	443 (49%)	59 (49%)	92 (42%)	0.221
Family history of asthma	356 (36%)	67 (52%)	157 (64%)	<0.001
Obesity ^x	287 (28%)	45 (31%)	92 (35%)	0.057

Data are the median (interquartile range) or n (%).

^sp-values for Kruskal-Wallis tests or Chi-square tests. ***p<0.001 compared to the adult-onset group by post-hoc test (Dunn's test). ++p<0.01 compared to the relapsed group by post-hoc test (Dunn's test).

^xAs calculated using the definition of obesity for Japanese established by the Japan Society for the Study of Obesity (obesity = BMI ≥ 25 kg/m²). BMI, body mass index.

Table II. Comorbidities and laboratory test data

	Adult-onset	Relapsed	Persistent	p ^s
Comorbidities:				
Allergic rhinitis	666 (64%)	104 (73%)	202 (77%)	<0.001
Atopic dermatitis	68 (7%)	36 (25%)	78 (30%)	<0.001
Food allergy	71 (7%)	15 (10%)	17 (6%)	0.255
Drug allergy	100 (10%)	10 (7%)	18 (7%)	0.256
Chronic sinusitis	104 (10%)	13 (9%)	14 (5%)	0.060
Peripheral blood:				
Eosinophils/ μ L	213 (121–393)	264 (145–442)	288 (160–440)**	<0.001
IgE, IU/mL	129 (45–379)	238 (90–547) ***	306 (124–892) ***	<0.001
Allergen-specific IgE-positive:				
House dust	431 (47%)	116 (85%)	242 (98%)	<0.001
Mites	418 (46%)	111 (83%)	241 (98%)	<0.001
Cat	67 (28%)	20 (50%)	73 (57%)	<0.001
Dog	62 (25%)	20 (48%)	56 (50%)	<0.001
Candida	43 (18%)	12 (26%)	31 (38%)	0.001
Aspergillus	29 (12%)	10 (22%)	27 (35%)	<0.001

Data are the median (interquartile range) or n (%).

^sp-values for Kruskal-Wallis tests or Chi-square tests. ***p<0.001 compared to the adult-onset group by post-hoc test (Dunn's test), **p<0.01 compared to the adult-onset group by post-hoc test (Dunn's test).

House dust: actual house dust containing cotton dust, soil, sand, hair, scurf, pet hair, fungus, mites and so on. Mites: *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farina*.

IgE, Immunoglobulin E.

Table III. Characteristics of asthma and its treatments

	Adult-onset	Relapsed	Persistent	p^s
Duration of asthma, yrs	11 (5–21)	11 (4–23)	36 (30–44) ^{***, +++}	<0.001
Aspirin sensitivity	49 (5%)	4 (3%)	8 (3%)	0.320
Severe asthma	317 (31%)	48 (34%)	105 (40%)	0.015
Asthma therapy:				
High-dose ICS	302 (29%)	48 (34%)	104 (40%)	0.004
Daily use of OCS	43 (4%)	6 (4%)	12 (5%)	0.956
Omalizumab	32 (3%)	9 (6%)	14 (5%)	0.063
Severe acute exacerbations/year:				
0	775 (75%)	105 (74%)	186 (71%)	0.022
1	81 (8%)	3 (2%)	18 (7%)	
>1	181 (17%)	35 (24%)	59 (22%)	

Data are the median (interquartile range) or n (%).

^sp-values for Kruskal-Wallis tests or Chi-square tests. ***p<0.001 compared to the adult-onset group by post-hoc test (Dunn's test). +++p<0.001 compared to the relapsed group by post-hoc test (Dunn's test). ICS, inhaled corticosteroids; OCS, oral corticosteroids.

Table IV. Pulmonary function test results

	Adult-onset	Relapsed	Persistent	p ^s
FVC, L	2.66 (2.09–3.27)	3.02 (2.42–3.61)***	3.17 (2.63–3.98)***	<0.001
%FVC %	89 (78–100)	88 (76–99)	89(80–99)	0.639
FEV ₁ , L	2.14 (1.64–2.70)	2.53 (2.07–2.98)***	2.55 (2.14–3.21)***	<0.001
%FEV ₁ , %	89 (77–101)	86 (73–97)	85 (70–94)***	<0.001
FEV ₁ /FVC, %	82.6 (76.3–88.0)	82.8 (75.6–89.2)	82.4 (75.1–86.7)	0.222
%PEF, %	84 (69–100)	83 (69–99)	86 (70–98)	0.881
%FEF ₅₀ , %	79 (54–104)	75 (52–100)	68 (46–85)***	<0.001
%FEF ₇₅ , %	65 (46–91)	63 (40–99)	56 (36–77)***,†	<0.001

Data are the median (interquartile range).

^sp-values for Kruskal-Wallis tests. ***p<0.001 compared to the adult-onset group by post-hoc test (Dunn's test). †p<0.05 compared to the relapsed group by post-hoc test (Dunn's test). FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; FEF₅₀, forced expiratory flow at 50% of the vital capacity; FEF₇₅, forced expiratory flow at 75% of the vital capacity.

Table V. Multiple comparisons of categorical variables

	Adult-onset vs Relapsed	Relapsed vs Persistent	Adult-onset vs Persistent
Sex, male, n(%)	0.034	0.062	<0.001
Smokers, Ex & Current	0.697	0.006	<0.001
Obesity [*]	0.372	0.511	0.023
Family history of asthma	0.001	0.020	<0.001
Comorbidity:			
Allergic rhinitis	0.049	0.399	<0.001
Atopic dermatitis	<0.001	0.357	<0.001
Severe asthma	0.499	0.238	0.005
High-dose ICS	0.283	0.240	0.001
Severe acute exacerbations/year	0.010	0.117	0.171
Allergen-specific IgE-positive:			
House dust	<0.001	<0.001	<0.001
Mites	<0.001	<0.001	<0.001
Cat	0.009	0.470	<0.001
Dog	0.005	0.857	<0.001
Candida	0.233	0.175	<0.001
Aspergillus	0.093	0.157	<0.001

p-values for Fisher's exact test are presented. For the multiple comparisons, a p-value <0.016 was considered significant with Bonferroni correction. *As calculated using the definition of obesity for Japanese established by the Japan Society for the Study of Obesity (BMI ≥ 25 kg/m²).

House dust: actual house dust containing cotton dust, soil, sand, hair, scurf, pet hair, fungus, mites and so on. Mites: *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farina*.

IgE, Immunoglobulin E.

Table VI. Differences in the factors associated with severe asthma among the persistent, relapsed, and adult-onset groups

	All		Adult-onset		Relapsed		Persistent	
	Adjusted OR (95% CI)	p [§]	Adjusted OR (95% CI)	p [§]	Adjusted OR (95% CI)	p [§]	Adjusted OR (95% CI)	p [§]
Age	0.99 (0.98-1.00)	0.019	0.99 (0.98-1.00)	0.006	0.98 (0.95-1.01)	0.227	1.02 (0.98-1.06)	0.248
Sex (male)	0.93 (0.73-1.18)	0.558	0.96 (0.72-1.29)	0.800	1.19 (0.54-2.63)	0.666	0.76 (0.44-1.30)	0.316
Duration of asthma	1.03 (1.02-1.04)	<0.001	1.03 (1.01-1.04)	<0.001	1.06 (1.02-1.10)	0.003	1.02 (0.98-1.06)	0.299
%FEV ₁	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	0.001	1.00 (0.98-1.03)	0.726	0.98 (0.96-0.99)	0.009
Obesity	1.69 (1.32-2.16)	<0.001	1.86 (1.38-2.50)	<0.001	1.68 (0.74-3.83)	0.214	1.15 (0.66-1.66)	0.625
Allergic rhinitis	1.29 (1.00-1.67)	0.048	1.17 (0.87-1.57)	0.300	2.72 (1.13-7.22)	0.033	1.47 (0.78-2.83)	0.240

FEV₁, forced expiratory volume in 1 second; CI, confidence interval.[§]p-values for multivariate logistic regression analyses.

Table VII. An overall model including the interaction terms of cohort-by-other factors

	Adjusted odds ratio (95% CI)	p [§]
Age	0.99 (0.98-1.00)	0.017
Sex (male)	0.94 (0.73-1.19)	0.589
Duration of asthma	1.03 (1.02-1.04)	0.000
%FEV ₁	0.99 (0.98-0.99)	<0.001
Obesity	1.87 (1.38-2.52)	<0.001
Allergic rhinitis	1.18 (0.88-1.58)	0.276
Persistent x obesity	0.67 (0.37-1.23)	0.196
Relapsed x obesity	0.92 (0.40-2.13)	0.844
Persistent x allergic rhinitis	1.11 (0.57-2.20)	0.760
Relapsed x allergic rhinitis	2.32 (0.93-6.30)	0.082

FEV₁, forced expiratory volume in 1 second; CI, confidence interval.

[§]p-values for multivariate logistic regression analyses.

Table E3. Comparison of pulmonary function tests between non-severe asthma and severe asthma in each group (Adult-onset, Relapsed, and Persistent)

	Adult-onset			Relapsed			Persistent		
	non-severe asthma	severe asthma	p ^s	non-severe asthma	severe asthma	p ^s	non-severe asthma	severe asthma	p ^s
FVC, L	2.68 (2.11–3.32)	2.57 (2.05–3.19)	0.098	3.02 (2.46–3.61)	2.97 (2.38–3.66)	0.826	3.36 (2.74–4.12)	3.07 (2.52–3.65)	0.004
%FVC, %	90 (79–101)	87 (75–97)	0.004	88 (74–99)	90 (77–101)	0.721	91 (83–100)	87 (74–98)	0.011
FEV ₁ , L	2.17 (1.67–2.73)	2.06 (1.56–2.63)	0.017	2.57 (2.12–2.96)	2.48 (1.82–3.03)	0.623	2.66 (2.31–3.32)	2.34 (1.92–2.85)	<0.001
%FEV ₁ , %	91 (78–102)	85 (72–98)	<0.001	86 (73–97)	87 (74–98)	0.974	86 (77–96)	80 (65–92)	0.001
FEV ₁ /FVC, %	83.1 (77.2–88.3)	81.0 (73.3–87.1)	0.006	82.2 (77.2–89.3)	84.6 (7.19–89.2)	0.307	83.3 (76.6–86.7)	79.3 (71.3–87.1)	0.016
%PEF, %	85 (71–101)	80 (65–98)	0.016	81 (71–97)	88 (62–101)	0.715	89 (75–100)	77 (64–91)	0.001
%FEF ₅₀ , %	82 (60–107)	68 (46–96)	<0.001	76 (55–101)	75 (40–105)	0.526	73 (52–87)	61 (41–83)	0.002
%FEF ₇₅ , %	68 (49–95)	59 (38–84)	<0.001	63 (41–104)	64 (36–98)	0.665	60 (43–81)	46 (29–70)	0.002

Data are the median (interquartile range).

^sp-values for Mann-Whitney U-test. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; FEF₅₀, forced expiratory flow at 50% of the vital capacity; FEF₇₅, forced expiratory flow at 75% of the vital capacity.

Online Repository Tables

Persistent asthma from childhood to adulthood presents a distinct phenotype of adult asthma**Table E1.** Comparison of demographic data between non-severe asthma and severe asthma in each group (Adult-onset, Relapsed, and Persistent)

	Adult-onset			Relapsed			Persistent		
	non-severe asthma	severe asthma	p ^s	non-severe asthma	severe asthma	p ^s	non-severe asthma	severe asthma	p ^s
n	720	317		95	48		158	105	
Age, yrs	63 (47–73)	61 (48–71)	0.354	46 (38–57)	46 (38–63)	0.884	41 (32–48)	44 (37–53)	0.001
Sex, male, n (%)	260 (36%)	120 (38%)	0.624	42 (44%)	24 (50%)	0.595	90 (57%)	57 (54%)	0.705
Smokers, Ex & current	241 (37%)	109 (38%)	0.714	33 (39%)	17 (40%)	1.000	34 (24%)	24 (27%)	0.536
Domestic exposure, pet	229 (47%)	144 (53%)	0.148	38 (46%)	21 (57%)	0.324	60 (45%)	32 (39%)	0.399
Family history of asthma	243 (35%)	113 (38%)	0.427	46 (52%)	21 (51%)	1.000	85 (58%)	72 (74%)	0.010
Obesity ^x	173 (24%)	114 (36%)	<0.001	26 (27%)	19 (40%)	0.182	51 (32%)	41 (39%)	0.292

Data are the median (interquartile range) or n (%).

^sp-values for Mann-Whitney U-test or Fisher's exact test. ^xAs calculated using the definition of obesity for Japanese established by the Japan Society for the Study of Obesity (BMI ≥25 kg/m²). BMI, body mass index.

Table E2. Comparison of comorbidities, laboratory test data and characteristics of asthma between non-severe asthma and severe asthma in each group (Adult-onset, Relapsed, and Persistent)

	Adult-onset			Relapsed			Persistent		
	non-severe asthma	severe asthma	p ^s	non-severe asthma	severe asthma	p ^s	non-severe asthma	severe asthma	p ^s
Comorbidity:									
Allergic rhinitis	454 (63%)	212 (67%)	0.261	64 (67%)	40 (83%)	0.048	119 (75%)	83 (79%)	0.552
Atopic dermatitis	49(7%)	19 (6%)	0.684	27 (28%)	9 (19%)	0.228	46 (29%)	32 (30%)	0.890
Food allergy	45 (6%)	26(8%)	0.285	6 (6%)	9 (19%)	0.039	11 (7%)	6 (6%)	0.801
Drug allergy	69 (10%)	31 (10%)	0.910	8(8%)	2 (4%)	0.496	10 (6%)	8 (8%)	0.804
Chronic sinusitis	73 (10%)	31 (10%)	0.911	9 (9%)	4 (8%)	1.000	9 (6%)	5 (5%)	1.000
Peripheral blood:									
Eosinophils/ μ L	207 (120–372)	226 (125–455)	0.119	252 (143–466)	267 (150–383)	0.679	293 (168–437)	288 (157–489)	0.642
IgE, IU/mL	117 (40–344)	162 (54–453)	0.001	271 (97–611)	173 (80–515)	0.220	282 (123–782)	373 (124–1164)	0.262
Allergen-specific IgE:									
House dust	281 (45%)	150 (50%)	0.122	79 (88%)	37 (80%)	0.308	141 (97%)	101 (99%)	0.652
Mites	271 (44%)	147 (49%)	0.156	73 (83%)	38 (83%)	1.000	141 (97%)	100 (99%)	0.405
Cat	46 (29%)	21 (26%)	0.761	12 (43%)	8 (67%)	0.301	45 (55%)	28 (61%)	0.579
Dog	43 (27%)	19 (23%)	0.642	14 (47%)	6 (50%)	1.000	35 (49%)	21 (53%)	0.844
Candida	20 (15%)	23 (23%)	0.124	8(25%)	4 (27%)	1.000	16 (38%)	15 (38%)	1.000
Aspergillus	15(10%)	14 (14%)	0.423	9 (29%)	1 (7%)	0.137	11 (28%)	16 (43%)	0.161
Characteristics of asthma:									
Duration of asthma, yrs	11 (5–19)	14 (7–25)	<0.001	8 (4–20)	15 (9–26)	0.007	32 (25–42)	40 (32–49)	0.001
Aspirin sensitivity	30 (4%)	19 (6%)	0.207	3 (3%)	1 (2%)	1.000	3 (2%)	5 (5%)	0.272

Data are the median (interquartile range) or n (%).

^sp-values for Mann-Whitney U-test or Fisher's exact test. House dust: actual house dust containing cotton dust, soil, sand, hair, scurf, pet hair, fungus, mites and so on. Mites: *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farina*. IgE, Immunoglobulin E.