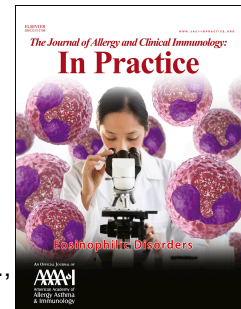


Journal Pre-proof

Characterization of asthma trajectories from infancy to young adulthood

Maria Ödling, M.Sc., Gang Wang, M.D., Niklas Andersson, M.Sc., Jenny Hallberg, Ph.D., Christer Janson, M.D., Ph.D., Anna Bergström, Ph.D., Erik Melén, M.D., Ph.D., Inger Kull, Ph.D.



PII: S2213-2198(21)00187-2

DOI: <https://doi.org/10.1016/j.jaip.2021.02.007>

Reference: JAIP 3432

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 26 November 2020

Revised Date: 3 February 2021

Accepted Date: 3 February 2021

Please cite this article as: Ödling M, Wang G, Andersson N, Hallberg J, Janson C, Bergström A, Melén E, Kull I, Characterization of asthma trajectories from infancy to young adulthood, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.02.007>.

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Characterization of asthma trajectories from infancy to young adulthood

Maria Ödling, M.Sc.¹, Gang Wang, M.D.^{1,2,3}, Niklas Andersson, M.Sc.³, Jenny Hallberg, Ph.D.^{1,4}, Christer Janson, M.D., Ph.D.⁵, Anna Bergström, Ph.D.^{3,6}, Erik Melén, M.D., Ph.D.^{1,3,4} & Inger Kull, Ph.D.^{1,4}

1. Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden;
2. Department of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University, Sichuan, China;
3. Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden;
4. Sachs' Children and Youth Hospital, Stockholm, Sweden;
5. Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden;
6. Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden.

Corresponding author

Maria Ödling
Forskningscentrum
Södersjukhuset
SE-118 83 Stockholm, Sweden
Telephone: +468 524 800 02
E-mail: Maria.Odling@ki.se

E-mail addresses

Wanggang-cn@foxmail.com
Niklas.Andersson@ki.se
Jenny.Hallberg@ki.se
Christer.Janson@medsci.uu.se
Anna.Bergstrom@ki.se
Erik.Melen@ki.se
Inger.Kull@ki.se

Acknowledgment of funding

This study was supported by grants from the Swedish Research Council, the Swedish Research Council for Health, Working Life and Welfare, Formas, Swedish Asthma and Allergy research foundation, the Swedish Heart-Lung Foundation, the European Research Council (TRIBAL, grant agreement 757919), Region Stockholm (ALF project, and for cohort and database maintenance), and the program for doctoral education in healthcare science at Karolinska Institutet. Thermo Fisher Scientific kindly provided reagents for IgE analyses.

Disclosure of potential conflict of interest

E. Melén reports personal fees from AstraZeneca, Chiesi, Sanofi and Novartis outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Word count

Abstract:	248/250
A total word count:	3,519/3,500

Abstract

Background: Development of asthma is complicated by the multidimensional nature of the disease.

Objective: To identify and characterize trajectories of asthma from infancy to young adulthood, and their associations with lung function and inflammatory and respiratory markers in adolescence and young adulthood.

Methods: A latent class analysis was performed in a population-based cohort (N = 4,089). Parental and self-reported symptoms of asthma were used to investigate asthma development. We characterized background factors, allergic co-morbidity, and immunoglobulin E sensitization, and investigated associations with asthma markers.

Results: A 4-class solution of asthma trajectories was identified: never/infrequent (n = 3,291, 80.4%), early-onset transient (n = 307, 7.5%), adolescent-onset (n = 261, 6.4%), and persistent asthma (n = 230, 5.6%).

Uncontrolled asthma was equally prevalent in the adolescent-onset and persistent asthma trajectory groups, at both 16 (41.7% vs. 42.4%, $p = 0.90$) and 24 years of age (53.7% vs. 52.4%, $p = 0.81$). The persistent asthma trajectory group had a higher proportion of eosinophil counts ≥ 0.3 (10^9 cells/L) at 24 years of age compared with the adolescent-onset trajectory group (31.0% vs. 18.5%, $p < 0.01$).

Conclusions: The adolescent-onset and persistent asthma trajectory groups had equal burdens of asthma control in adolescence and young adulthood. However, the persistent asthma trajectory group showed more signs of type 2 inflammation than the adolescent-onset trajectory group. This unbiased approach highlights the need of identifying patients with adolescent asthma to optimize care, as they suffer the same lack of asthma control as those with persistent asthma.

Highlights box

1. What is already known about this topic?

Asthma has many underlying biological pathways that lead to different disease trajectories.

2. What does this article add to our knowledge?

Subjects in the adolescent-onset and persistent asthma trajectory groups have equal burdens of asthma control and severity in adolescence and young adulthood.

3. How does this study impact current management guidelines?

Through the defined and characterized asthma trajectories, we found that the adolescent-onset and persistent asthma trajectory groups are vulnerable groups that healthcare professionals need to identify, to optimize care.

Key words

adolescents,
asthma,
age at onset,
birth cohort,
cluster analysis,
eosinophil counts,
inflammatory markers,
longitudinal analysis,
lung function,
phenotype.

99 **Abbreviations**

100	BAMSE:	Barn/Child, Allergy, Milieu, Stockholm, Epidemiology
101	ERS/ATS:	European Respiratory Society and American Thoracic Society
102	FeNO:	Exhaled nitric oxide
103	FEV ₁ :	Forced expiratory volume in 1 second
104	FVC:	Forced vital capacity
105	GINA:	Global Initiative for Asthma
106	GLI:	Global Lung function Initiative
107	ICS:	Inhaled corticosteroids
108	LABA:	Long-acting β 2-agonists
109	LCA:	Latent class analysis
110	LLN:	Lower limit of normal
111	IgE:	Immunoglobulin E

Introduction

Asthma is a heterogeneous disease with clinical manifestations that typically vary with the stage of life (1). Asthma, eczema, and rhinitis often co-occur, and can be classified as allergic co-morbidities (2). Asthma, eczema, and rhinitis are complex diseases, with genetic and environmental factors interlinked through both immunoglobulin E (IgE)-associated and non-IgE-associated mechanisms (3).

The development of asthma is a dynamic process (4). For some patients, asthma starts early, while it debuts later in life for others (5). The disease may progress, remit, or relapse over time (6). The goal of asthma treatment is to achieve and maintain asthma control and minimize exacerbations and lung function loss (7, 8). Most patients with asthma have mild or moderate disease, but one group has poor outcomes across the spectrum of disease severity (9, 10). Asthma has many underlying biological pathways that lead to different disease trajectories (7). Previous research by Martinez et al. had impact when they studied the natural history of wheezing in the first six years of life (11). Later, similar research has been supplemented by unbiased data-driven approaches, such as latent class analysis (LCA) (12). The number of asthma trajectories identified and their specific patterns vary somewhat between populations and different lengths of follow-up (13). A recent meta-analysis of wheeze trajectories, including thirteen cohorts from the general and at-risk populations, identified five distinct trajectories (14). The follow-ups varied between 3 and 18 years with a mean length of about 10 years. The authors concluded that longer follow-ups were needed to improve evidence for causal inference (14). Unlike most prior studies (7, 14-19), present study provided the possibility to cover a period from infancy up to 24 years of age in a population-based cohort. This includes adolescence, which is a crucial period in the natural course of asthma (16).

136 Investigating asthma trajectories provides a foundation for gaining increased knowledge
137 on asthma development and associated markers, and disease outcomes can thereby be
138 improved (20, 21). Thus, the aim of this study was to identify and characterize trajectories of
139 asthma from infancy to young adulthood, and the association with lung function,
140 inflammatory, and respiratory markers in adolescence and young adulthood using LCA.

Methods

Study design

During 1994–1996, parents to all newborns living in predefined areas of Stockholm, the capital of Sweden, including inner city, urban, and suburban districts, were asked to participate in the longitudinal population-based birth cohort BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) (22, 23). The ongoing cohort includes 4,089 participants, who have been followed since birth with repeated follow-ups. At 2 months of age, a baseline questionnaire was filled out, where information on background factors was obtained. When the participants were approximately 1, 2, 4, 8, 12, and 16 years old, parents completed follow-up questionnaires. Follow-up response rates were 96%, 94%, 91%, 84%, 82%, and 78%, respectively. At 12, 16, and 24 years, participants were also asked to complete a questionnaire themselves. Follow-up response rates were 68%, 76%, and 75% respectively. Following the completion of questionnaires, the participants were invited to undergo clinical examinations at approximate ages 4, 8, 16, and 24 years.

Definition of asthma

Based on questionnaire data from all the follow-ups, *current asthma* at approximate ages 1, 2, 4, 8, 12, 16, and 24 years, was defined as fulfilling at least two of the following three criteria (10): Symptoms of wheeze and/or breathing difficulties in the 12 months preceding the follow-up, ever doctor's diagnosis of asthma and/or use of asthma medication occasionally or regularly in the 12 months preceding the follow-up.

Allergic co-morbidity and IgE sensitization

The assessments of allergic co-morbidity and IgE sensitization were based on questionnaire and clinical data from the 4-, 8-, 16-, and 24-year follow-ups. Information on the definitions

of *eczema* and *rhinitis*, as well as on IgE sensitization to common *inhalant* and *food allergens*, has been given in detail elsewhere (24-26), and is provided in this article's Online Repository at www.jaci-inpractice.org.

Lung function

Lung function was measured through spirometry using a Jaeger MasterScreen-IOS system (Carefusion Technologies) at the 16- and 24-year clinical follow-ups. All subjects performed repeated maximal expiratory flow volume measurements (27). The highest values of *forced vital capacity* (FVC) and *forced expiratory volume in 1 second* (FEV₁) were extracted and used for analysis in accordance with the European Respiratory Society and American Thoracic Society (ERS/ATS) criteria (28). FEV₁/FVC data were converted to z-scores based on Global Lung Function Initiative (GLI) reference values (29). *Airflow limitation* was defined as the FEV₁/FVC ratio z-score below the lower limit of normal (LLN), defined as the lowest 5th percentile in the never asthmatic population.

Inflammatory markers

The assessments of inflammatory markers were based on clinical data from the 16- and 24-year follow-ups. Values for blood *eosinophil* cell count were regarded as above reference for all ages if ≥ 0.3 (10^9 cells/L) (30). Values for blood *neutrophil* cell count outside normal were based on the highest tertile (tertile 3) (31): > 3.9 (10^9 cells/L) for 16-year data, and > 4.1 (10^9 cells/L) for 24-year data.

Exhaled nitric oxide (FeNO) ≥ 25 ppb indicated the presence of eosinophilic inflammation and was measured with a chemiluminescence analyzer (EcoMedics Exhalyzer[®], and Circassia NIOX VERO[®]). The procedure was performed in accordance with published guidelines (27, 32).

Respiratory markers

The assessments of respiratory markers were based on questionnaire and clinical data from the 16- and 24-year follow-ups. Information on pharmacy-dispensed asthma medication within the 18 months preceding the 16- and 24-year follow-ups was obtained by linkage to the Swedish Prescribed Drug Register (33). *Severe asthma* was based on ERS/ATS and Global Initiative for Asthma (GINA) guidelines (8, 9). It was defined as a) asthma with high daily doses of inhaled corticosteroids (ICS), ≥ 800 μ g budesonide or equivalent, ≥ 500 μ g fluticasone, as ICS separately or as fixed combinations of ICS and long-acting β_2 -agonists (LABA), b) plus dispensed LABA (together with ICS separately) and/or leukotriene receptor antagonists at least once to prevent the asthma from becoming or remaining uncontrolled despite therapy (34). Uncontrolled asthma was defined as fulfilling at least one of the following four criteria, based on data from the respective follow-ups: 1) *Uncontrolled asthma* based on the modified GINA definition (8, 10). 2) Having taken cortisone tablets dissolved in water for asthma or respiratory symptoms ≥ 3 days in a row the last 12 months prior to the 16- or 24-year follow-ups. 3) Having sought acute medical care because of respiratory symptoms the last 12 months prior to the 16- or 24-year follow-ups. 4) FEV₁ below 80% of predicted; measured through spirometry at the 16- or 24-year clinical follow-ups.

Respiratory markers such as “*episodes of breathing difficulties*” and “*respiratory symptoms following physical exertion*” were based on self-reported information regarding the 12 months preceding each respective follow-up.

Statistical analysis

To investigate trajectories of asthma from infancy to young adulthood, the LCA was performed in the BAMSE cohort (N = 4,089) (Table E1 in this article’s Online Repository at

www.jaci-inpractice.org). Data on current asthma, as defined in this study, from all follow-ups were included (approximate ages 1, 2, 4, 8, 12, 16, and 24 years). The R software (version 4.0.2) and package “depmixS4” was used. The models were compared for goodness-of-fit using the Bayesian information criterion and the number of clusters was confirmed. A sensitivity analysis was performed in the same way, but this included current asthma only up to the 16-year follow-up.

To analyze differences between proportions of background factors, allergic comorbidity, IgE sensitization, airflow limitation, inflammatory, and respiratory markers of the participants in the results of the LCA, Pearson’s chi-squared tests and Fisher’s exact tests were used. Differences between mean age at puberty, mean values of FEV₁, FVC, and FEV₁/FVC based on GLI reference values were investigated using one-way analysis of variance. Differences between mean values of lung function volume were analyzed with multiple linear regression, adjusted for gender, height, age, and weight. P values of < 0.05 were considered statistically significant. These analyses were performed with the STATA statistical software (release 14.2; College Station, TX, USA).

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. All participants and parents provided informed consent to participate in the study.

Results

Trajectories of asthma from infancy to young adulthood

A total of 4,089 participants were included in the LCA with data on asthma symptoms up to the 24-year follow-up. Evaluations were done for 2-, 3-, 4-, 5-, 6-, and 7-class solutions; the 4-class solution was chosen as the best fit (Bayesian information criterion: 14,344.8) and resulted in four distinct asthma trajectory groups (Figure 1). Class 1 had a predominant profile of never/infrequent asthma ($n = 3,291$, 80.4%). Class 2 had a predominant profile of early-onset transient asthma, with debut of asthma at 1, 2, or 4 years of age, but no asthma in later years ($n = 307$, 7.5%). Class 3 had a predominant profile of adolescent-onset asthma with a debut of asthma after age 8 years ($n = 261$, 6.4%). Class 4 encompassed participants with predominantly persistent asthma ($n = 230$, 5.6%). Figure 1 presents the probability of latent class membership for each class in the 4-class LCA model.

A separate LCA including information of asthma symptoms only up to the 16-year follow-up showed similar trajectories (Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Characterization of the identified trajectory groups

The distribution of background factors differed between the identified asthma trajectory groups (Table I). The never/infrequent asthma trajectory group had the highest proportion of exclusive breastfeeding for 4 months or more ($n = 2,536$, 80.7%). The highest proportion of parental smoking ($n = 82$, 26.7%) was seen in the early-onset transient asthma trajectory group. The adolescent-onset asthma trajectory group had the highest proportion of females ($n = 148$, 56.7%), and the persistent asthma trajectory group had the lowest ($n = 92$, 40.0%). In the persistent asthma trajectory group, almost half of the participants had a family history of allergic disease.

258

259 Allergic co-morbidity and IgE sensitization in the identified trajectory groups

260 The distribution of allergic co-morbidity and IgE-sensitization differed between the identified
261 asthma trajectory groups (Table II). Sensitization to inhalant allergens increased with age in
262 all trajectories. In the never/infrequent asthma trajectory group, 38.4% (n = 679) were
263 sensitized to inhalant allergens at age 24 years, which was comparable to the proportion in the
264 early-onset transient asthma trajectory group. In contrast, over 75.0% (n = 135) of those in the
265 adolescent-onset trajectory group and 71.3% (n = 82) of those in the persistent asthma
266 trajectory group were sensitized to inhalant allergens at age 24 years. Moreover, the
267 prevalence of allergic comorbidity was highest in the adolescent-onset and persistent asthma
268 trajectory groups, about one third had eczema at age 4 years, and about two thirds had rhinitis
269 at age 24 years. Sensitization to food allergens was most common in the persistent asthma
270 trajectory group (n = 35, 30.4% at 24 years of age).

271

**272 Lung function, inflammatory, and respiratory markers in the identified trajectory
273 groups**

274 The distribution of lung function, inflammatory, and respiratory markers differed between the
275 identified asthma trajectory groups (Table III. Table E2 and E3 in this article's Online
276 Repository at www.jaci-inpractice.org). For example, in the early-onset transient asthma
277 trajectory group, 8.2% (n = 13) had airflow limitation (FEV_1/FVC z-score < LLN) at age 16
278 years, and 7.2% (n = 11) at age 24 years, which was comparable to the numbers in the
279 adolescent-onset trajectory group, but lower than in the persistent asthma trajectory group
280 (Table III). Moreover, those in the persistent asthma trajectory group had the lowest mean
281 value of FEV_1 (expressed as z-scores based on GLI reference values) at ages 16 and 24 years.
282 Mean differences of lung function volume showed a similar pattern. Severe asthma at 16 and

24 years of age was most prevalent in the adolescent-onset asthma trajectory group, albeit quite uncommon ($n = 8$, 4.1% at 24 years of age). In the adolescent-onset and persistent asthma trajectory groups, about half had uncontrolled disease at 24 years of age. The persistent asthma trajectory group had the highest proportions of airflow limitation at 16 and 24 years of age (18.1% and 14.2%, respectively), FeNO value ≥ 25 ppb (41.7% and 34.3%, respectively), and eosinophil count ≥ 0.3 (10^9 cells/L) (38.7% and 31.0%, respectively). The proportions of high neutrophils were the same in the adolescent-onset and persistent asthma trajectory groups at both 16 and 24 years of age.

A separate comparison between the adolescent-onset and persistent asthma trajectory groups showed that there were few statistically significant differences with respect to respiratory markers such as asthma control or severity at 16 or 24 years of age. The persistent asthma trajectory group had lower mean values of FEV₁ and FEV₁/FVC, as well as a higher proportion of airflow limitation at age 16 years, lower mean value of FEV₁, and a higher proportion of eosinophils, at age 24 years (Figure 2 and Table E2). The other lung function and inflammatory variables did not show any significant differences between the adolescent-onset and persistent asthma trajectory groups at 16 or 24 years of age.

Discussion

In the population-based BAMSE cohort, an unbiased LCA based on asthma symptom data from infancy to young adulthood resulted in four distinct asthma trajectories: never/infrequent, early-onset transient, adolescent-onset, and persistent asthma. This solution of asthma trajectories provided insights about the origins and characteristics of asthma, as the adolescent-onset and persistent asthma trajectory groups seemed to have equal burdens of respiratory markers, such as asthma control and severity in adolescence and young adulthood. However, compared with the adolescent-onset trajectory group, the persistent asthma trajectory group showed more signs of lung function impairment, for example lower mean values of FEV₁, in adolescence and young adulthood. Further, the four asthma trajectory groups showed differences in established background factors, allergic co-morbidity, and IgE sensitization.

In line with our results, other studies have identified similar classes to describe childhood asthma trajectories (14). The unbiased studies have consistently identified 3 to 5 trajectory groups. In the recent meta-analyses by Owora et al. (14) with 5 identified trajectory groups, the intermediate-onset trajectory group occurred between 3–5 years which is similar to our results of the early-onset transient asthma trajectory group, with a debut of asthma at 1, 2, or 4 years of age. Further, in the meta-analysis the late-onset occurred between 5–8 years of age, which is a bit earlier than in the adolescent-onset asthma trajectory group in our results, with a debut of asthma after age 8 years. The variations in the number of identified trajectories could be explained by differences in asthma definitions, sample size, type of population, or frequency and timing of data collection (15). To our knowledge, the present study on asthma is one of few population-based cohort studies with a follow-up length of more than approximately 24 years.

In the natural course of asthma, one clear manifestation is the “sex switch” in asthma prevalence, from male asthma predominance in early childhood to mid-childhood, to female predominance in adolescence (10, 35). This was confirmed in our results. Adolescence is also a time of changes in lifestyle, as well as biological and physiological processes (36). In the present study, we therefore compared the adolescent-onset and persistent asthma trajectory groups, and they seemed to have equal burdens of respiratory markers at adolescence and young adulthood, although the adolescent-onset trajectory group had a more recent onset of disease. Our results showed that four out of ten in the adolescent-onset and persistent asthma trajectory groups had uncontrolled disease in adolescence, and more than half in young adulthood. However, the persistent asthma trajectory group, with the highest proportions of FeNO and high eosinophil counts, tended to have more signs of type 2 inflammation (37) than the adolescent-onset trajectory group. Further, our results showed that the persistent asthma trajectory group had lower mean values of FEV₁ and FEV₁/FVC, as well as a higher proportion of airflow limitation in adolescence. Our results are in line with a previous study showing that asthma patients with increased FeNO and eosinophil counts had a higher prevalence of impaired lung function (FEV₁ < 80% predicted, FEV₁/FVC < LLN) and uncontrolled asthma compared with patients with normal levels of these inflammatory markers (30). Their results remained statistically significant after adjusting for sex, age, atopy, smoking habits, and asthma medicines. A previous study showed that FeNO levels and eosinophil counts were independently associated with both inhalant (furred animals and mold) and food allergens (38), indicating that inhalant and food allergens should also be mapped to increase understanding of inflammation patterns in asthma. The eosinophilic inflammation and degree of atopy seems to be of importance in asthma, as the National Heart, Lung and Blood Institute’s Severe Asthma Research Program found that children with severe asthma

overall had a high degree of atopy reflected by increased blood eosinophils and higher concentrations of total serum IgE compared with children with non-severe asthma (39).

During adolescence, asthma management encompasses the transition process from pediatric to adult healthcare. Successful support during this period could minimize excess morbidity and mortality risk (36). However, in our previous studies, we found that young adults felt left out of the system, and that healthcare consultations decreased after the transition to adult healthcare (34, 40). Generally, there is a lack of adult allergy services. Through defined asthma trajectories, management could be individualized and multidisciplinary, to ensure the best possible outcomes (36). Opportunely, the European Academy of Allergy and Clinical Immunology recently developed a clinical practice guideline to provide evidence-based recommendations for healthcare professionals to support the transitional care of adolescents and young adults with asthma (36).

In this study, we identified several established background factors associated with trajectories of asthma, such as that family history of allergic disease seemed to be associated with a persistent wheeze trajectory in childhood (41). Our results also showed that a higher proportion of parental smoking at baseline characterized the early-onset transient asthma trajectory group. Environmental tobacco smoke exposure is known to increase asthma risk in children and adults (42). Our results showed that eight percent in the early-onset transient asthma trajectory group had airflow limitation as adolescents. Recent studies have found that a low childhood lung function trajectory is associated with risk of future chronic obstructive pulmonary disease (43, 44). Recent results from our cohort showed that irreversible airflow limitation was present already in young adulthood, and was observed despite most being non-smokers or ever-smokers having smoked on average less than one pack-year (45).

Our results were in line with the concept of the atopic march, where allergic diseases start in early life with eczema, progress through food allergy and culminate as hay fever and

asthma (46-48). We showed that participants with early allergic co-morbidity fell into the adolescent-onset and persistent asthma trajectory groups. About one third of the participants in the adolescent-onset and persistent asthma trajectory groups had eczema and were sensitized to food allergens at early ages. Further, more than two thirds were sensitized to inhalant allergens in adolescence and young adulthood.

Strengths and limitations

Important strengths of the present study include the prospective population-based design and the large and well-characterized study sample. Moreover, we chose to use LCA, as asthma classification is complicated. We used asthma symptoms reported on up to 7 occasions (from approximately 12 months to 24 years of age) in this data-driven approach to derive asthma trajectory groups, so that preconceptions about trajectory structure did not affect the derived groups. With the asthma symptom variables used in our LCA analysis assessed from infancy to young adulthood, we were able to study the temporal stability of the identified latent classes and transition over time. The long period of asthma symptoms was sufficient for examination of the role of puberty and sex hormones, shown to impact airway responsiveness and asthma prevalence at a population level (7).

Nonetheless, there are some limitations with the LCA approach. The classes are dependent on the study population and when the variables are entered. However, collecting data at critical timepoints might help counterbalance the effects of suboptimal conditions (7, 15). In our sensitivity analysis including asthma symptoms up to only adolescence, the asthma trajectory groups were similar. Moreover, results showed that participants in the never/infrequent asthma trajectory group also had symptoms in adolescence and young adulthood. This could be explained by the use of LCA: a participant's probability of

belonging to any of the other classes was also calculated, and a decision was then made as to the class membership that each participant would ultimately be allotted.

Further, asthma control was based on information for the 12 months preceding each questionnaire, but the GINA guidelines base asthma control on information from the last 4 weeks (8). This could lead to an overestimation in our data of the proportion of adolescents and young adults with uncontrolled asthma.

Conclusions

This analysis resulted in four distinct asthma trajectory groups: never/infrequent, early-onset transient, adolescent-onset, and persistent asthma. Comparisons showed that the adolescent-onset and persistent asthma trajectory groups seemed to have equal burdens of respiratory markers in adolescence and young adulthood. However, the persistent asthma trajectory group showed more signs of lung function impairment, and type 2 inflammation, compared with the adolescent-onset trajectory group.

Acknowledgements

We thank all the participants and parents participating in the BAMSE cohort and the staff involved in the study through the years.

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Figure legends and footnotes

Figure 1. Trajectories of asthma from infancy to young adulthood using latent class analysis in the BAMSE cohort (N = 4,089).

Figure 2. A separate comparison between the adolescent-onset and persistent asthma trajectory groups in relation to airflow limitation, inflammatory and respiratory markers in adolescence and young adulthood (N = 4,089).

^aThe forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio z-score below the lower limit of normal (LLN), defined as the lowest 5th percentile in the never-asthmatic population.

^bExhaled nitric oxide (FeNO) $\geq$ 25 ppb.

^cBlood eosinophil cell count $\geq 0.3 \times 10^9$ cells/L.

^dBlood neutrophil cell count were based on the highest tertile. At age 16 years $> 3.9 \times 10^9$ cells/L, and at age 24 years $> 4.1 \times 10^9$ cells/L.

^eSevere asthma was defined as asthma with high daily doses of inhaled corticosteroids (ICS), as ICS separately or as fixed combinations of ICS and long-acting β 2-agonists (LABA), plus dispensed LABA (together with ICS separately) and/or leukotriene receptor antagonists at least once to prevent the asthma from becoming or remaining uncontrolled despite therapy.

^fUncontrolled asthma defined as at least 1 of 4 symptoms: daytime asthma, nocturnal asthma, activity limitation or symptom reliever in the last 12 months preceding the 16- or 24-year follow-up.

^gMore than 12 episodes of breathing difficulties in the preceding 12 months.

^hRespiratory symptoms following physical exertion in the preceding 12 months.

Table E1. Selected background characteristics in the BAMSE cohort.

<i>Background characteristics</i>	BAMSE cohort N = 4,089	
	n	%
Female gender	2,024	49.5
Mother's age < 25 years at birth	319	7.8
Parent born outside Sweden	718	21.1
Family history of allergic disease^a	1,200	29.7
Parental education - University^b	2,161	52.9
Parental smoking at baseline^c	855	21.0

^aMother and/or father with doctor's diagnosis of asthma and use of asthma medication and/or doctor's diagnosis of hay fever in combination with reported allergy to furred animals and/or pollen at the time of the baseline questionnaire.

^bAt least university or college degree/other education at the time of the baseline questionnaire.

^cAny of the parents smoked at least one cigarette per day at the time of the baseline questionnaire.

Table E2. Lung function expressed as z-scores based on Global Lung Function Initiative reference values in adolescence and young adulthood in the identified asthma trajectory groups (N = 4,089).

	Class 1 Never/infrequent asthma n = 3,291, 80.4%		Class 2 Early-onset transient asthma n = 307, 7.5%		Class 3 Adolescent-onset asthma n = 261, 6.4%		Class 4 Persistent asthma n = 230, 5.6%		Difference between classes 1 – 4	Difference between classes 3 and 4
Lung function	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p value ^b	p value ^b
Forced expiratory volume in 1 second (FEV₁)^a										
- at age 16 years	0.03	0.9	-0.3	0.9	-0.2	0.9	-0.5	0.9	< 0.01	< 0.01
- at age 24 years	-0.2	0.8	-0.4	0.9	-0.3	0.9	-0.6	0.9	< 0.01	< 0.01
Forced vital capacity (FVC)^a										
- at age 16 years	0.2	0.9	0.1	1.0	0.2	0.9	0.07	0.9	0.55	0.20
- at age 24 years	-0.06	0.8	-0.03	0.9	0.04	0.9	-0.1	0.9	0.32	0.09
FEV₁/FVC^a										
- at age 16 years	-0.2	0.9	-0.6	0.9	-0.6	1.0	-0.9	1.1	< 0.01	0.04
- at age 24 years	-0.3	0.9	-0.6	0.9	-0.6	1.0	-0.7	1.0	< 0.01	0.24

^aThe forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) data were converted to z-scores based on Global Lung Function Initiative reference values.

^bP values obtained using one-way analysis of variance indicated differences between classes 1 – 4 and classes 3 and 4.

Table E3. Mean differences in lung function volume in adolescence and young adulthood in the identified asthma trajectory groups (N = 4,089).

	Class 1 Never/infrequent asthma n = 3,291, 80.4%		Class 2 Early-onset transient asthma n = 307, 7.5%		Class 3 Adolescent-onset asthma n = 261, 6.4%		Class 4 Persistent asthma n = 230, 5.6%		Difference between classes 1 – 4	Difference between classes 3 and 4
<i>Lung function</i>	Adjusted mean ^a	95% CI	Adjusted mean ^a	95% CI	Adjusted mean ^a	95% CI	Adjusted mean ^a	95% CI	p value ^b	p value ^b
FEV₁ (ml)										
- at age 16 years	Ref.	–	-152.2	-222.6; -81.9	-120.1	-187.6; -52.7	-296.9	-375.1; -218.8	< 0.01	< 0.01
- at age 24 years	Ref.	–	-88.7	-158.1; -19.3	-67.4	-133.1; -1.7	-208.5	-290.7; -126.2	< 0.01	0.01
FVC (ml)										
- at age 16 years	Ref.	–	-53.0	-131.9; 25.9	0.2	-75.4; 75.8	-117.1	-204; -29.5	< 0.01	0.04
- at age 24 years	Ref.	–	31.3	-52.8; 115.5	41.8	-37.9; 121.5	-74.9	-174.6; 24.9	< 0.01	0.06
FEV₁/FVC (%)										
- at age 16 years	Ref.	–	-2.1	-3.1; -1.1	-2.4	-3.4; -1.5	-4.2	-5.4; -3.1	< 0.01	0.01
- at age 24 years	Ref.	–	-2.2	-3.1; -1.2	-2.0	-2.9; -1.1	-2.9	-4.1; -1.8	< 0.01	0.20

^aAdjusted for gender, height, age, and weight at the respective follow-ups.^bP values obtained using multiple linear regression on the mean indicated differences between classes 1 – 4 and between classes 3 and 4.

19 **Figure legend**

20

21 **Figure E1.** Trajectories of asthma from infancy to adolescence using latent class analysis in
22 the BAMSE cohort (N = 4,089).

Online Repository

Characterization of asthma trajectories from infancy to young adulthood

Maria Ödling, M.Sc.¹, Gang Wang, M.D.^{1,2,3}, Niklas Andersson, M.Sc.³, Jenny Hallberg, Ph.D.^{1,4}, Christer Janson, M.D., Ph.D.⁵, Anna Bergström, Ph.D.^{3,6}, Erik Melén, M.D., Ph.D.^{1,3,4} & Inger Kull, Ph.D.^{1,4}

1. Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden;
2. Department of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University, Sichuan, China;
3. Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden;
4. Sachs' Children and Youth Hospital, Stockholm, Sweden;
5. Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden;
6. Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden.

Corresponding author

Maria Ödling
Forskningscentrum
Södersjukhuset
SE-118 83 Stockholm, Sweden
Telephone: +468 524 800 02
E-mail: Maria.Odling@ki.se

Methods

Allergic co-morbidity and IgE sensitization

The assessments of allergic co-morbidity and IgE sensitization were based on questionnaire and clinical data from the 4-, 8-, 16-, and 24-year follow-ups.

Definitions of eczema

At age 4 years: Parental report of dry skin and itchy skin rash for ≥ 2 weeks in specific locations (face or arm/leg extension surfaces or arm/leg flexures or wrists/ankles) within the preceding 12 months and/or doctor's diagnosis of eczema after age 2 years and up to the date of the 4-year questionnaire.

At age 8 years: Parental report of dry skin and itchy skin rash for ≥ 2 weeks in specific locations (face or arm/leg flexures or wrists/ankles or neck) within the preceding 12 months and/or doctor's diagnosis of eczema after age 4 years up to age 8 years.

At age 16 years: Adolescent-reported dry skin and itchy skin rash in specific locations (arm/leg flexures or wrists/ankles or neck) within the preceding 12 months.

At age 24 years: Participant's report of itchy rash in the preceding 12 months in combination with at least 3 out of 4 of the following criteria: 1) Dry skin in the preceding 12 months. 2) Eczema onset below age 2 years. 3) History of flexural eczema at any follow-up. 4) Personal history of asthma and/or rhinitis at any follow-up from age 4 years.

Definitions of rhinitis

At age 4 years: Parental report of symptoms from eyes/nose (suspected or evident) after exposure to furred animals or pollen (from age 2 years) and/or doctor's diagnosis of allergic rhinitis from age 2 years and up to the date of the 4-year questionnaire.

At age 8 years: Parental report of symptoms of sneezing, a runny or blocked nose, and/or itchy, red, and watery eyes after exposure to furred animals or pollen (from age 4 years) and/or doctor's diagnosis of allergic rhinitis from age 4 years and up to the date of the 8-year questionnaire.

At age 16 years: Parental report of symptoms of sneezing, a runny or blocked nose, and/or itchy, red, and watery eyes after exposure to furred animals or pollen (in the preceding 12 months) and/or doctor's diagnosis of allergic rhinitis from age 12 years up to the date of the 16-year questionnaire.

At age 24 years: Participant's report of symptoms of sneezing, a runny or blocked nose, and/or itchy, red, and watery eyes after exposure to furred animals or pollen (in the preceding 12 months) and/or doctor's diagnosis of allergic rhinitis ever up to the date of the 24-year questionnaire.

IgE sensitization

IgE sensitization to common *inhalant* and *food allergens* was analyzed using the ImmunoCAP System (Thermo Fisher/Phadia AB, Uppsala, Sweden) with Phadiatop[®] (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum*), and fx5[®] (cow's milk, peanut, hen's egg, wheat, soybean, and fish). IgE values greater than 0.35 kU_A/L were regarded as positive.

Table I. Background factors in the identified asthma trajectory groups (N = 4,089).

	Class 1 Never/infrequent asthma n = 3,291, 80.4%		Class 2 Early-onset transient asthma n = 307, 7.5%		Class 3 Adolescent-onset asthma n = 261, 6.4%		Class 4 Persistent asthma n = 230, 5.6%		Difference between classes 1 – 4 p value ^g
<i>Background factors</i>	n	%	n	%	n	%	n	%	
Female gender	1,659	50.4	125	40.7	148	56.7	92	40.0	< 0.01
Gestational age < 37 weeks	169	5.1	26	8.5	17	6.5	15	6.5	0.07
Mother's age at birth < 25 years	229	7.0	47	15.3	18	6.9	25	10.9	< 0.01
Exclusively breastfed ≥ 4 months	2,536	80.7	219	73.2	194	76.7	167	74.6	< 0.01
Family history of allergic disease^a	871	26.8	109	35.7	113	44.0	107	47.8	< 0.01
Any older siblings at baseline^b	1,563	47.5	180	58.6	115	44.1	122	53.0	< 0.01
Had a furred animal at baseline^c	503	15.3	62	20.2	36	13.8	28	12.2	0.05
Parent born outside Sweden	589	21.6	42	16.9	48	20.3	39	20.1	0.37
Parental education – University^d	1,781	54.1	139	45.3	146	55.9	95	41.3	< 0.01
Parental smoking at baseline^e	670	20.5	82	26.7	45	17.4	58	25.6	< 0.01
Age at puberty – years^f	Mean	Max	Mean	Max	Mean	Max	Mean	Max	p value ^h
Females – first menarche	12.7	16	12.7	16	12.6	16	12.4	16	0.39
Males – voice change	13.6	17	13.5	16	13.7	16	13.9	16	0.02

^aMother and/or father with doctor's diagnosis of asthma and use of asthma medication and/or doctor's diagnosis of hay fever in combination with reported allergy to furred animals and/or pollen at the time of the baseline questionnaire.

^bAny older siblings in the household/family at the time of the baseline questionnaire.

^cCurrently had a furred animal (cat, dog, and/or rodent) at home at the time of the baseline questionnaire.

^dAt least university or college degree/other education.

^eAny of the parents smoked at least one cigarette per day at the time of the baseline questionnaire.

^fBased on self-reported information from the 16-year follow-up.

^gP values obtained using Pearson's chi-squared test indicated differences between classes 1 – 4.

^hP values obtained using one-way analysis of variance indicated differences between classes 1 – 4.

Table II. Allergic co-morbidity and IgE-sensitization in the identified asthma trajectories (N = 4,089).

	Class 1 Never/infrequent asthma		Class 2 Early-onset transient asthma		Class 3 Adolescent-onset asthma		Class 4 Persistent asthma		Difference between classes
	n = 3,291, 80.4%		n = 307, 7.5%		n = 261, 6.4%		n = 230, 5.6%		1 – 4
Allergic co-morbidity	n	%	n	%	n	%	n	%	p value ^c
Eczema^a									
- at age 4 years	533	17.9	76	27.3	84	33.5	76	34.7	< 0.01
- at age 8 years	361	13.5	59	24.5	59	25.0	64	34.2	< 0.01
- at age 16 years	197	8.0	19	8.0	45	19.6	36	20.3	< 0.01
- at age 24 years	366	15.0	40	17.9	76	33.8	61	35.9	< 0.01
Rhinitis^a									
- at age 4 years	217	7.4	41	15.0	46	18.6	82	37.7	< 0.01
- at age 8 years	246	9.1	34	13.8	97	40.9	76	39.6	< 0.01
- at age 16 years	509	20.5	48	21.2	136	59.9	96	54.2	< 0.01
- at age 24 years	674	27.9	71	32.3	148	66.1	107	62.9	< 0.01
IgE sensitization^b									
Inhalant allergens									
- at age 4 years	223	10.9	24	11.5	75	42.4	78	45.9	< 0.01
- at age 8 years	391	20.3	39	21.4	122	64.9	85	55.9	< 0.01
- at age 16 years	772	38.3	80	42.6	150	76.9	105	70.0	< 0.01
- at age 24 years	679	38.4	65	38.7	135	75.0	82	71.3	< 0.01
Food allergens									
- at age 4 years	267	13.0	25	12.0	62	35.0	60	35.3	< 0.01
- at age 8 years	316	16.4	30	16.5	82	43.9	62	40.5	< 0.01
- at age 16 years	209	10.4	20	10.6	53	27.2	52	34.7	< 0.01
- at age 24 years	100	5.7	17	10.1	44	24.4	35	30.4	< 0.01

^aThe definitions of eczema and rhinitis are provided in this article's Online Repository at www.jacionline.org.

^bImmunoglobulin E (IgE) sensitization to inhalant allergens (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum*), and food allergens (cow's milk, peanut, hen's egg, wheat, soybean, and fish) at the respective follow-ups.

^cP values obtained using Pearson's chi-squared test indicated differences between classes 1 – 4.

Table III. Airflow limitation, inflammatory and respiratory markers in adolescence and young adulthood in the identified asthma trajectory groups (N = 4,089).

	Class 1 Never/infrequent asthma		Class 2 Early-onset transient asthma		Class 3 Adolescent-onset asthma		Class 4 Persistent asthma		Difference between classes 1 – 4
	n = 3,291, 80.4%		n = 307, 7.5%		n = 261, 6.4%		n = 230, 5.6%		
	n	%	n	%	n	%	n	%	p value ^f
Lung function									
Airflow limitation									
(FEV₁/FVC z-score < LLN)^a									
- at age 16 years	73	4.6	13	8.2	18	10.3	23	18.1	< 0.01
- at age 24 years	68	4.2	11	7.2	17	9.9	15	14.2	< 0.01
Inflammatory markers									
Exhaled nitric oxide (FeNO) ≥ 25 ppb									
- at age 16 years	308	18.8	32	21.2	59	36.7	55	41.7	< 0.01
- at age 24 years	183	12.2	18	12.0	47	28.3	35	34.3	< 0.01
Blood eosinophil cell count									
≥ 0.3 × 10⁹ cells/L									
- at age 16 years	295	15.4	37	20.4	58	30.7	55	38.7	< 0.01
- at age 24 years	169	9.8	23	13.9	33	18.5	35	31.0	< 0.01
Blood neutrophil cell count^b									
- at age 16 years > 3.9 × 10 ⁹ cells/L	611	31.9	48	26.5	66	34.9	48	33.8	0.33
- at age 24 years > 4.1 × 10 ⁹ cells/L	572	33.1	45	27.1	62	34.8	48	42.5	0.06
Respiratory markers									
Severe asthma^c									
- at age 16 years	2	0.1	0	0.0	13	6.9	9	6.5	< 0.01
- at age 24 years	1	0.06	0	0.0	8	4.1	3	2.2	< 0.01
Uncontrolled asthma^d									
- at age 16 years	69	2.9	8	3.5	93	41.7	72	42.4	< 0.01
- at age 24 years	252	10.4	33	14.9	117	53.7	86	52.4	< 0.01
> 12 episodes of breathing difficulties^e									
- at age 16 years	14	0.6	1	0.4	22	9.7	14	8.0	< 0.01
- at age 24 years	68	2.8	6	2.7	35	15.7	21	12.4	< 0.01
Respiratory symptoms following physical exertion^f									
- at age 16 years	427	17.5	51	21.6	167	72.6	114	64.4	< 0.01
- at age 24 years	214	8.8	32	14.4	112	51.1	78	47.6	< 0.01

^aThe forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio z-score below the lower limit of normal (LLN), defined as the lowest 5th percentile in the never-asthmatic population.

^bBlood neutrophil cell count were based on the highest tertile at the respective follow-up.

^cSevere asthma was defined as asthma with high daily doses of inhaled corticosteroids (ICS), as ICS separately or as fixed combinations of ICS and long-acting β₂-agonists (LABA), plus dispensed LABA (together with ICS separately) and/or leukotriene receptor antagonists at least once to prevent the asthma from becoming or remaining uncontrolled despite therapy.

^dUncontrolled asthma defined as at least 1 of 4 symptoms: daytime asthma, nocturnal asthma, activity limitation or symptom reliever in the last 12 months preceding the 16- or 24-year follow-up.

^eMore than 12 episodes of breathing difficulties in the preceding 12 months.

^fRespiratory symptoms following physical exertion in the preceding 12 months.

^gP values obtained using Pearson's chi-squared test and Fisher's exact test indicated differences between classes 3 and 4.

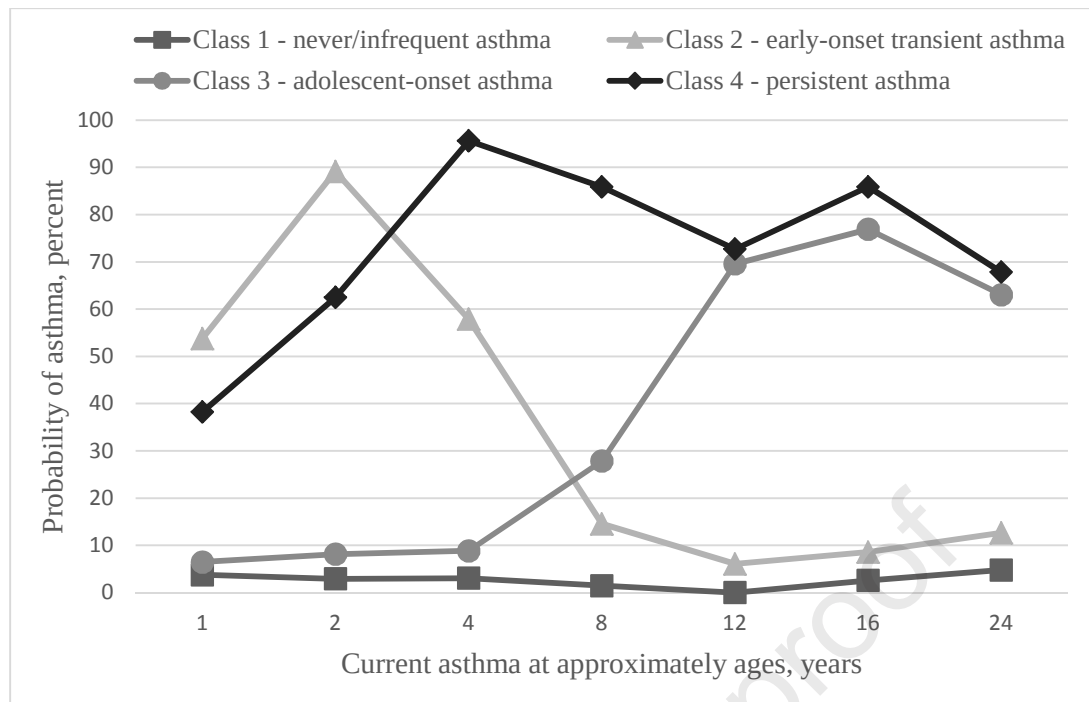
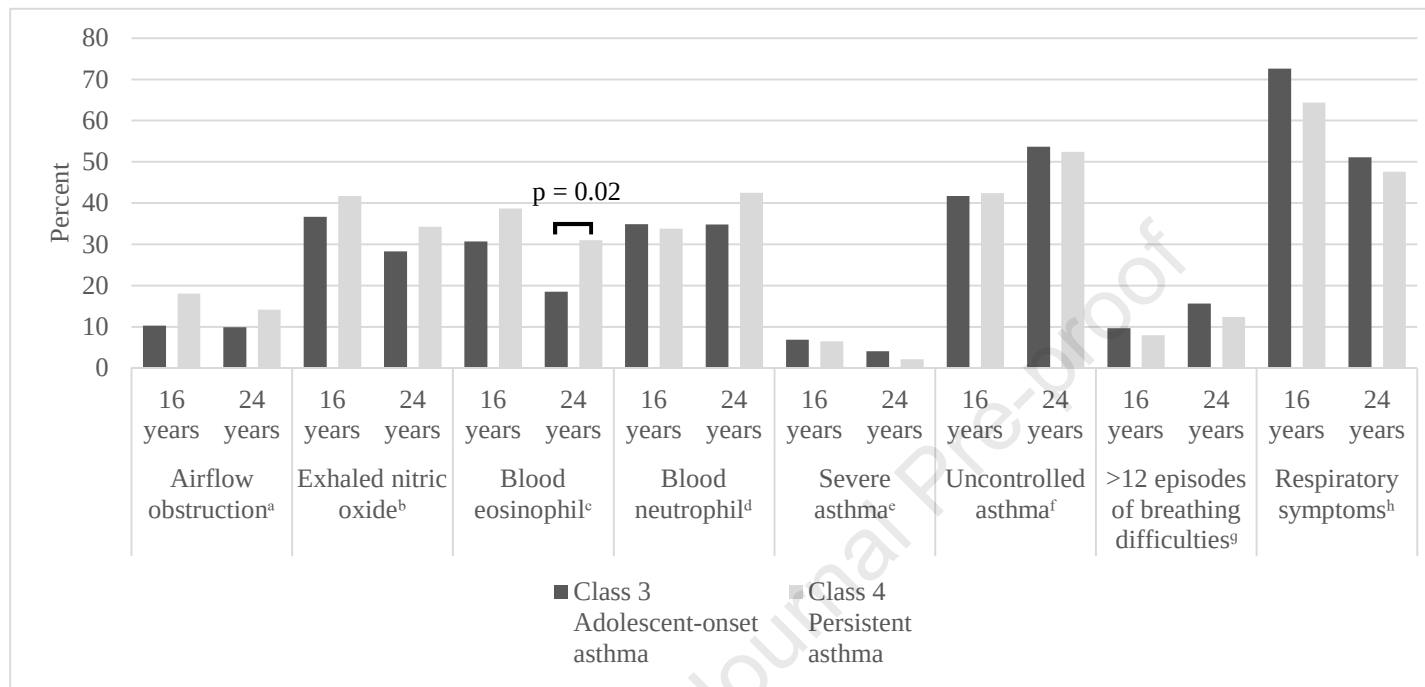


Figure 1.

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2

3 **Figure 2.**

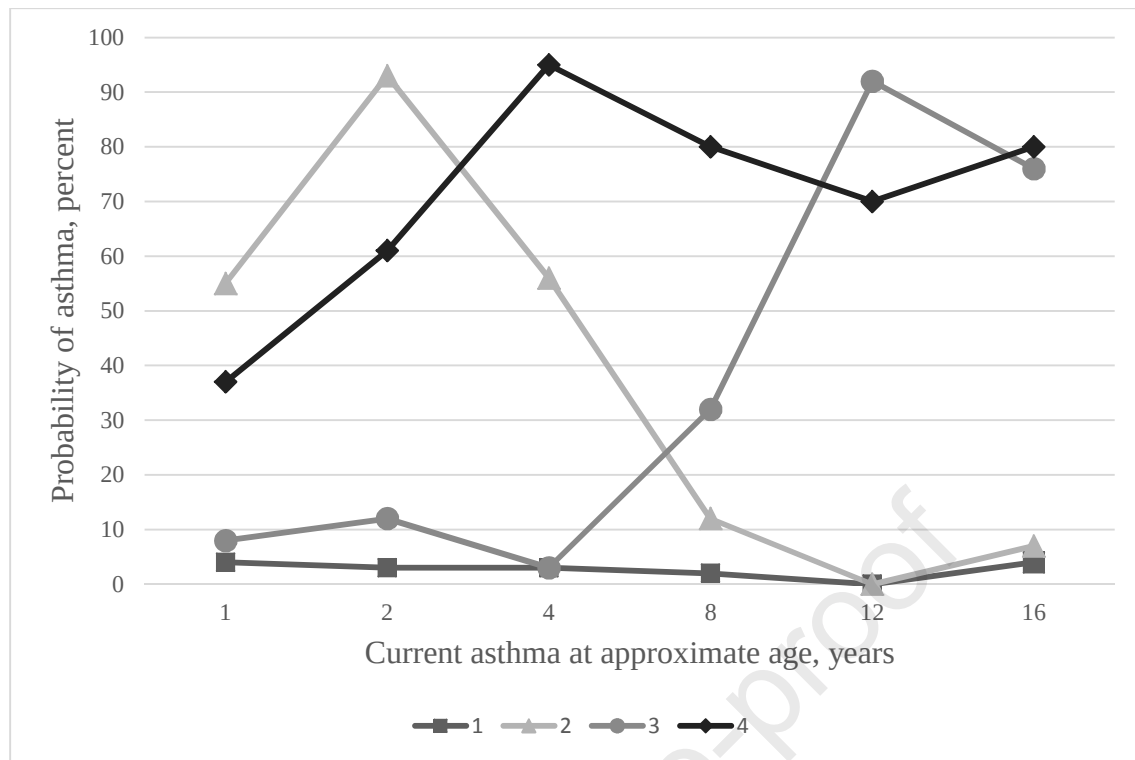


Figure E1.