Original Article

Cluster Analysis of Finnish Population-Based Adult-Onset Asthma Patients

Pinja Ilmarinen, PhD[a,b], Anna Julkunen-Iivari, Lic Odont, PhD[c,d], Marie Lundberg, MD, PhD[e], Annika Luukkainen, MD, PhD[f], Mikko Nuutinen, DSc[c,g], Jussi Karjalainen, MD, PhD[b,h], Heini Huhtala, MSci[i], Juha Pekkanen, MD, PhD[j,k], Hannu Kankaanranta, MD, PhD[a,b,l], and Sanna Toppila-Salmi, MD, PhD[c,g,m]
Seinäjoki, Tampere, Helsinki, and Kuopio, Finland; and Gothenburg, Sweden

What is already known about this topic? Several clusters of adult-onset asthma have been identified in previous studies by using clinical cohorts. The clusters were based on atopy, sex, obesity, smoking, inflammation type, and disease severity.

What does this article add to our knowledge? We were able to replicate in part these clusters in a population-based setting and also identified novel clusters that were related to different childhood conditions and infection history.

How does this study impact current management guidelines? These results will help to understand the development of different adult-onset asthma phenotypes and in planning individualized management strategies.

BACKGROUND: Phenotypes of adult asthma have been identified in previous studies but rarely in population-based settings.

OBJECTIVE: To identify clusters of adult-onset asthma in a Finnish population-based study on subjects born before 1967.

METHODS: We used population-based data from 1350 asthmatics with adult-onset asthma (Adult Asthma in Finland) from Finnish national registers. Twenty-eight covariates were selected based on literature. The number of covariates was reduced by using factor analysis before cluster analysis.

RESULTS: Five clusters (CLU1-CLU5) were identified, 3 clusters with late-onset adult asthma (onset ≥40 years) and 2 clusters

with onset at earlier adulthood (<40 years). Subjects in CLU1 (n = 666) had late-onset asthma and were nonobese, symptomatic, and predominantly female with few respiratory infections during childhood. CLU2 (n = 36) consisted of subjects who had earlier-onset asthma, were predominantly female, obese with allergic asthma, and had recurrent respiratory infections. Subjects in CLU3 (n = 75) were nonobese, older, and predominantly men with late-onset asthma, smoking history, comorbidities, severe asthma, least allergic diseases, low education, many siblings, and childhood in rural areas. CLU4 (n = 218) was a late-onset cluster consisting of obese females with comorbidities, asthma symptoms, and low education level.

aDepartment of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

bFaculty of Medicine and Health Technology, Tampere University, Tampere, Finland

cDepartment of Allergy, Skin and Allergy Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

dDepartment of Oral and Maxillofacial Diseases, University of Helsinki, Helsinki, Finland

eDepartment of Otorhinolaryngology—Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

fInflammation Center, Department of Infectious Diseases, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

gHaartman Institute, Medicum, University of Helsinki, Helsinki, Finland

hAllergy Centre, Tampere University Hospital, Tampere, Finland

iFaculty of Social Sciences, Tampere University, Tampere, Finland

jDepartment of Public Health, University of Helsinki, Helsinki, Finland

kEnvironmental Health Unit, National Institute for Health and Welfare, Kuopio, Finland

lDepartment of Internal Medicine and Clinical Nutrition, Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

mDepartment of Pulmonary Medicine, Heart and Lung Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

---

Abbreviations used
   AC- Allergic conjunctivitis
   AD- Atopic dermatitis
   AERD- Nonsteroidal anti-inflammatory drug—exacerbated
      respiratory disease
   AR- Allergic rhinitis
   BMI- Body mass index
   CLU- Cluster
   COPD- Chronic obstructive pulmonary disease
   CRSwNP- Chronic rhinosinusitis with nasal polyps
   FEV1- Forced expiratory volume during the first second
   HC- Hierarchical clustering
   ICS- Inhaled corticosteroid
   OCS- Oral corticosteroid
   PEF- Peak expiratory flow
   SABA- Short-acting β-agonist
   SD- Standard deviation

Subjects in CLU5 (n = 260) had earlier onset asthma, were nonobese, and predominantly allergic females.
CONCLUSIONS: Our population-based adult-onset asthma clusters take into account several critical factors such as obesity and smoking, and identified clusters that partially overlap with clusters identified in clinical settings. Results give us a more profound understanding of adult-onset asthma phenotypes and support personalized management.   © 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). (J Allergy Clin Immunol Pract 2023;11:3086-96)

Asthma is a heterogeneous disease, and among the various asthma characteristics involved in the disease's phenotypic heterogeneity, both clinical observations and statistical cluster-based approaches have identified age at asthma onset as a key differentiating factor.[1-4] Asthma symptoms may start during childhood or adulthood, but adult-onset asthma has gained less attention in literature. In adult- or late-onset asthma, patients are less often allergen sensitized, less responsive to inhaled corticosteroid (ICS) treatment, and have a poorer prognosis compared with childhood-onset asthma.[5,6] Adult-onset asthma demonstrates multiple phenotypes and endotypes.[7,8] Severe adult-onset asthma has increased morbidity and mortality.[9] By identifying phenotypes and personalizing treatment, one can avoid suffering and unnecessary costs.

We have previously identified 5 clusters based on longitudinal data from hospital-level adult-onset asthmatics.[7] These clusters were (1) non-rhinitic, controlled, or partially controlled asthma; (2) older men with heavy smoking history, poor lung function, and persistent obstruction; (3) nonsmoking females with good lung function; (4) obese and symptomatic patients with additional comorbidities; and (5) atopic patients with earliest onset of asthma, blood eosinophilia, and forced expiratory volume in the first second (FEV1) reversibility. However, limited cluster study information is available on population-based level of phenotypes of adult-onset asthma. Hence, our aim was to identify clusters in a large population-based case control study on late-onset asthma.

METHODS
Study design
This is a cross-sectional population-based study of adult-onset asthma in Finland. We used questionnaire study data of childhood and adulthood factors. The questionnaire was performed between 1996 and 1997.

Study population
We used subjects of asthma of the Adult Asthma in Finland study, which is a population-based study of asthmatics older than 30 years and was conducted in 1997 (Figure 1) as previously described.[9-11] This study collected information from only the late-onset asthmatics. The total number of patients with asthma was 1350. They all were older than 30 years with an asthma diagnosis. Of this asthma population, 182 asthmatics were from the longitudinal, population-based Mini Finland Health Survey and 1168 were recently diagnosed asthmatics randomly drawn from the Finnish Drug Reimbursement register maintained by Social Insurance Institution of Finland.[12] All asthmatics fulfilled the following criteria for doctor-diagnosed asthma in this register: typical history, clinical features, and asthma course, and at least one of the following physiologic criteria: (1) a variation of 20% or greater in diurnal peak expiratory flow (PEF) recording (reference to maximal value), (2) an increase of 15% or greater in PEF or FEV1 with β-agonist, or (3) a decrease of 15% or greater in PEF or FEV1 in exercise testing. This method of case ascertainment has been validated earlier.[13,14] In addition, the asthmatics had self-reported onset of asthma symptoms and/or asthma diagnosis after 15 years of age. The questionnaire consisted of demographic questions and asthma-specific questions. The proportion of responders in asthma group was 84.6%. Approval for the study was obtained from the ethical committee at Tampere University Hospital (2/1996), and a written consent was obtained from all subjects.

Covariates
Twenty-eight covariates associated with asthma were initially selected based on the literature:

- Personal characteristics (n = 3): sex,[15-17] age (<50 vs ≥50 years and <60 vs ≥60 years),[18] body mass index (BMI) (<30 vs ≥30).[19,20]
- Socioeconomic characteristics (n = 2): education level (baccalaureate/secondary vs primary school) and professional training (completed professional college/university/courses/completed trade school vs no).[21-23]
- Lifestyle factors (n = 1): smoking (never vs ever).[15,24,25]
- Early-life factors (n = 7): season of birth (July-December vs January-June),[26] growing up in countryside/farm,[27] parental smoking,[28] parental asthma and/or allergies,[29] severe childhood infections (pneumonia before or during school age and/or hospitalization due to infection at ≤3 years of age),[30] number of siblings (<2 vs ≥2),[10] and birth order (first vs other).[10,31,32]
- Asthma characteristics (n = 8): nonsteroidal anti-inflammatory drug—exacerbated disease (AERD),[33] age at asthma onset (<40 vs ≥40 years).[6,34-37] Severe asthma, which was defined as self-reported severe asthma and asthma symptoms causing much harm and regular impairment, and ≥1 oral corticosteroid (OCS) course per year or continuous OCS use, or waking up in the night due to asthma symptoms/wheezing ≥ a few times/month[38]: a medication-based definition of severe asthma (daily ICS +
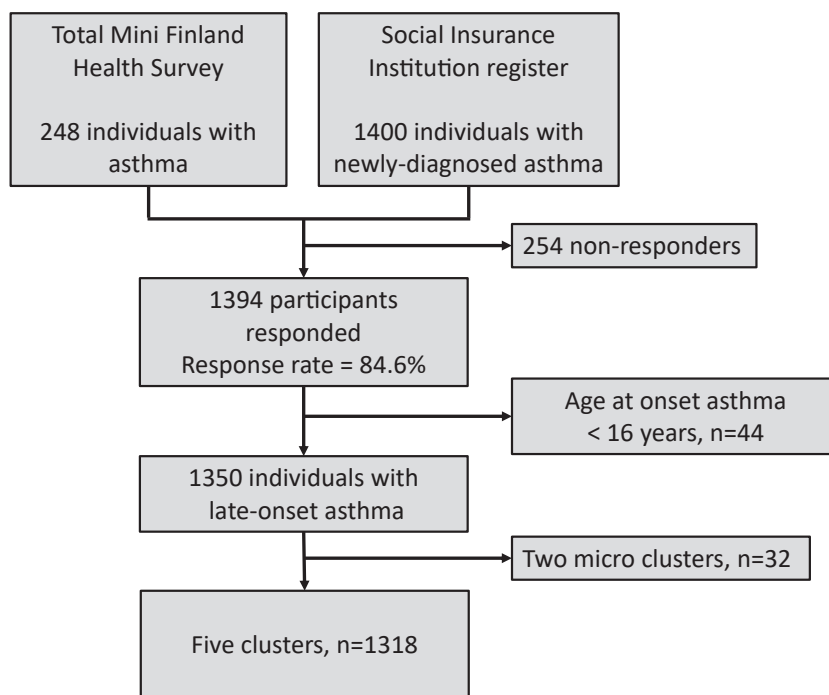
FIGURE 1. Flow chart of the study population. Asthmatics drawn from the Finnish Drug Reimbursement register were older than 30 years. A total of 248 asthmatics were from the longitudinal, population-based Mini-Finland Health Survey. In total, 1400 asthmatics had recently (in 2 years) diagnosed asthma. The asthma was defined to be adult onset if the subject responded that the onset of asthma symptoms and/or the age of asthma diagnosis was 16 years or more.

short-acting β-agonist [SABA]) was given by the report of regular use of inhaled ICS and daily use of SABA.[38]
- Multimorbidity (n = 7): ≥1 other chronic disease,[9,15,25] allergic rhinitis (AR), allergic conjunctivitis (AC), atopic dermatitis (AD), ≥2 other allergic diseases ever (eg, AR/AC/AD),[10,22] and nasal polyps;[39] allergic multimorbidity was defined as ≥1 allergic disease (eg, AR/AC/AD).[10]

Information on other chronic diseases was obtained by the following questions: Do you have any of the following doctor-diagnosed conditions: hypertension, coronary artery disease, rheumatoid arthritis, psychiatric disorder, diabetes, ocular hypertension, back disease, and arthritis? Has your doctor diagnosed you with any of the following lung diseases: chronic bronchitis, emphysema, bronchiectasis, and allergic bronchopulmonary aspergillosis (empyema was only included)? Do you have any other doctor-diagnosed chronic diseases? (bronchitis/bronchiectasis was excluded).

Statistical analysis

Input covariates for cluster analysis were selected based on factor analysis. The 28 covariates were entered into factor analysis to reduce the number of covariates. We selected the components (numbers 1-8) having eigenvalue >1.0. Rotated component matrix was used to select the covariates characterizing components 1 to 8. The 9 variables that were selected for hierarchical cluster analysis had the first (age, sex, BMI, season of birth, number of siblings, and number of allergic diseases) and second highest (smoking status and severe asthma) loading of each of the components and/or were basic variables (such as age, sex, and age of asthma onset). Our method of selecting variables has been previously used in cluster analyses.[7,40] Altogether 9 variables were entered into hierarchical cluster

analysis and they were age (<50 vs ≥50 years), sex, smoking status (never vs ever), BMI (<30 vs ≥30), number of siblings (<2 vs ≥2), number of allergic diseases (0-1 vs 2-3), age of asthma onset (<40 vs ≥40 years), severe asthma (yes vs no), and season of birth (July-December vs January-June). First, to pre-evaluate the number of clusters, average linkage hierarchical cluster analysis was performed by using the agglomerative (bottom-up) method[41] between-groups linkage and using the squared Euclidean distance. We performed group comparisons by using the Kruskal-Wallis test (continuous variables) or the χ^2 test (dichotomous variables) for the set of variables of study (51 variables). These 51 variables are different versions from the variables (n = 28) used for the factor analysis (different thresholds, original continuous variables, etc). Statistically significant results were expected for most of the comparisons because the objective of the cluster analysis was to differentiate the participants into distinct phenotypes of adult-onset asthma. Statistical significance was assessed as $P < .05$. Statistics were performed with SPSS Base 24 Statistical Software Package (Released 2016, IBM SPSS Statistics for Windows, Version 24.0; IBM Corp, Armonk, NY). Missing values were omitted in the factor analysis and hierarchical cluster analyses. The proportion of missing values in the hierarchical cluster analysis was 5.9%, and they were present in 3 of the 9 variables: BMI, number of siblings, and ≥2 allergic diseases. Validation hierarchical cluster analyses were performed by using BMI and age as continuous variables.

RESULTS
Population description

The study flow chart is shown in Figure 1. Subject characteristics are shown in Table I. The total number of adult-onset

TABLE I. Self-reported demographic factors of the asthma population (n = 1350)

Demographic factors	n (%)
Personal characteristics	
Female sex	838 (62.1)
Age (y), mean (SD)	54.4 (12.2)
BMI[a], mean (SD)	26.9 (4.7)
Socioeconomic characteristics	
Baccalaureate/secondary school	488 (36.1)
Professional training	895 (66.2)
Lifestyle factors	
Ever smokers	794 (58.8)
Early-life factors	
Born January-June	750 (55.6)
First child	385 (28.5)
≥2 siblings	1018 (75.4)
Growing in countryside/farm	1014 (75.1)
Severe childhood infections[b]	228 (16.9)
Parental smoking	764 (56.6)
Parental asthma and/or allergy	466 (34.5)
Asthma characteristics	
Age asthma onset ≥40 y	1014 (75.1)
AERD	143 (10.6)
Daily ICS users	1132 (83.9)
Regular OCS or ≥1 course/y	395 (29.3)
Regular OCS or ≥2 courses/y	226 (16.7)
Severe asthma	100 (7.4)
Daily ICS+SABA	276 (20.4)
Work impairment days/y, mean (SD)	9.6 (43.5)
Multimorbidity	
CRSwNP	152 (11.3)
AR	685 (50.7)
AC	549 (40.7)
AD	457 (33.9)
≥1 other disease[c]	929 (68.8)
≥1 other allergic disease (AR/AC/AD)	907 (67.2)

P values by the χ^2 test (dichotomous) or the t-test (continuous variables). P values less than .05 were considered significant.

Education level = baccalaureate/secondary versus primary school; professional training = completed professional college/university/courses/completed trade school versus no. Severe asthma was defined as self-reported severe asthma AND asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/y or regular oral corticosteroids AND/OR wake up in the night due to asthma symptoms/wheezing attach ≥ a few times/mo). Severe medication-based asthma (daily ICS+SABA) was defined by the report of regular use of inhaled glucocorticosteroid and daily use of short-acting β-agonist.

AC, Allergic rhinoconjunctivitis; *AD*, atopic dermatitis; *AERD*, patient-reported NSAID-exacerbated respiratory disease; *AR*, allergic rhinitis; *BMI*, body mass index; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *ICS*, inhaled corticosteroid; *NSAID*, nonsteroidal anti-inflammatory drug; *OCS*, oral corticosteroid; *SABA*, short-acting β-agonist; *SD*, standard deviation.

[a]BMI data were missing from 6 (6.0%) severe asthmatics and 29 (2.3%) nonsevere asthmatics.

[b]Pneumonia before or during school age and/or hospitalization due to infection at ≤3 years of age.

[c]Hypertension (n = 298), coronary artery disease (n = 120), rheumatoid arthritis (n = 60), psychiatric disease/disorder (n = 86), diabetes (n = 54), glaucoma (n = 49), musculoskeletal disease/back pain (n = 367), arthritis (n = 244), emphysema (n = 106), and other chronic disease(s) except chronic bronchitis/bronchiectasis (n = 449).

asthma cases with available data was 1350. The mean age (standard deviation [SD], minimum-maximum) was 54 (12, 31-93) years. The proportion of females was 62.1%, and 59% had a smoking history. The proportion of subjects reporting at least secondary school level of education was 36.1%. Eighty-four percent of subjects were daily ICS users, and 7.4% fulfilled questionnaire-based definition of severe asthma.

Cluster analysis

Five good-sized clusters, including a total of 1255 cases, were identified by hierarchical cluster analysis, 3 clusters (CLU1, CLU3, CLU4) with age at asthma onset ≥40 years ("late-onset") and 2 clusters (CLU2, CLU5) with onset at earlier adulthood (<40 years) ("early adulthood-onset"). The basic characteristics of these clusters are shown in Table II.[42]

Two microclusters (n = 16 cases) were excluded from further analyses. The mean (±SD) age of patients in the microclusters was 42 (±7) years, and the mean age of asthma onset was 37 (±7) years. These clusters consisted of 56% females, 69% smokers, and 94% with at least 1 allergic disease.

Cluster 1: late onset, nonobese, female predominant with nonsevere asthma symptoms, and less respiratory infections during childhood (n = 666). All subjects of cluster 1 (n = 666) reported asthma onset ≥40 years of age. None had a BMI ≥30. Sixty-one percent were female (Table II). This cluster showed the highest median age of asthma onset (Figure 2). They had low proportion reporting a history of childhood respiratory infections as compared with the other clusters (Table II). Of the subjects, 28% were regular OCS users or had ≥1 OCS burst per year, which was third highest among all clusters, but least frequent among late-onset clusters (Figure 2).

Cluster 2: early adulthood onset, female predominant, obese with allergic asthma, and recurrent respiratory infections (n = 36). Cluster 2 was the smallest cluster. All subjects reported asthma onset <40 years of age. The proportion of females was 89% (Table II). All subjects were obese (BMI >30). A high proportion of subjects were reporting respiratory infections during childhood as compared with the other clusters (Table II, Figure 3). The proportion of AR, AC, and AD was 83%, 69%, and 56%, respectively (Table II). Fifty-six percent of the subjects of this cluster reported being first-born, which was the highest percentage compared with the other clusters (Figure 3). Of the patients, 22% were regular OCS users and/or had needed OCS bursts for asthma but 17% used daily ICS and SABA, being the highest proportion among early-onset clusters.

Cluster 3: late onset, older men with smoking history, comorbidities and severe asthma, least allergic diseases, low education, many siblings, and childhood in countryside (n = 75). Cluster 3 (n = 75) consisted of severe asthmatics defined by questionnaire (100%) and by medication (44%). This cluster was male predominant (59%) and had the highest median age, 63 years (Figure 2). Seventy-seven percent had smoked. This cluster had high prevalence of

TABLE II. Basic characteristics of the 5 clusters (CLU1-CLU5)

Variables	CLU 1: Late onset, nonsymptomatic, nonobese	CLU 2: Early-onset female predominant, obese, allergic, respiratory infections	CLU 3: Late-onset older men with severe asthma and comorbidities	CLU 4: Late-onset female predominant, obese, low education, comorbidities	CLU 5: Early-onset female predominant, allergic, nonobese	P_{All}
Subjects, n	666	36	75	218	260	
Personal characteristics						
Female, n (%)	404 (61)	32 (89)	31 (41)	138 (63)	184 (71)	<.001
Age, median (Q1-Q3)	57 (50-65)	39 (34-50)	61 (54-67)	57 (50-63)	38 (34-44)	<.001
Age ≥50 y, n (%)	505 (76)	9 (25)	69 (92)	166 (76)	51 (20)	<.001
BMI, median (Q1-Q3)	26 (24-28)	34 (31-37)	26 (23-29)	32 (31-35)	24 (22-27)	<.001
BMI ≥30, n (%)	0 (0)	36 (100)	16 (21)	218 (100)	0 (0)	<.001
Socioeconomic characteristics, n (%)						
Primary school or less	457 (69)	12 (33)	57 (79)	162 (75)	76 (29)	<.001
No professional training	175 (28)	3 (9)	29 (43)	68 (35)	28 (11)	<.001
Lifestyle factors, n (%)						
Ever smoking	397 (60)	20 (56)	58 (77)	122 (56)	146 (56)	.01
Current exposure to tobacco smoke at home	31 (5)	3 (8)	5 (7)	12 (6)	10 (4)	.68
Early-life factors, n (%)						
Childhood maternal/paternal smoking	375 (59)	21 (60)	47 (65)	133 (64)	139 (55)	.32
First child	179 (27)	20 (56)	18 (24)	74 (34)	78 (30)	.002
Siblings ≥2	525 (79)	18 (50)	67 (89)	174 (80)	180 (69)	<.001
Siblings ≥4	334 (49)	5 (14)	39 (53)	105 (49)	90 (35)	<.001
Birth order ≥2	269 (40)	13 (36)	27(36)	81 (37)	103 (40)	.87
Born in winter or in spring	358 (54)	23 (64)	50 (67)	118 (54)	152 (59)	.15
Parental allergy and/or asthma	198 (31)	22 (65)	19 (26)	86 (41)	114 (44)	<.001
Childhood in country	524 (79)	20 (56)	60 (82)	168 (77)	166 (64)	<.001
Childhood in farm	283 (43)	9 (25)	31 (41)	102 (47)	69 (27)	<.001
Severe childhood infections[a]	117 (18)	11 (31)	7 (10)	38 (18)	44 (17)	.11
Much respiratory infections before/in school age	108 (16)	15 (42)	16 (21)	43 (20)	85 (33)	<.001
Much respiratory infections <7 y	31 (5)	6 (17)	4 (5)	12 (6)	34 (13)	<.001
Much respiratory infections at school age	101 (15)	14 (39)	14 (19)	39 (18)	78 (30)	<.001
Childhood wheeze	639 (99)	35 (97)	72 (99)	210 (99)	244 (95)	<.001
Childhood exposure to tobacco smoke	375 (59)	21 (60)	47 (65)	133 (64)	139 (55)	.32
Current exposure to tobacco smoke	31 (5)	3 (8)	5 (7)	12 (6)	10 (4)	.68
Asthma characteristics, n (%)						
Asthma onset ≥40 y	663 (100)	0 (0)	69 (92)	210 (96)	0 (0)	<.001
Severe asthma[b]	0 (0)	0 (0)	75 (100)	0 (0)	0 (0)	<.001
Regular OCS and/or ≥1 course/y	185 (28)	8 (22)	45 (60)	65 (30)	60 (23)	<.001
Regular OCS and/or ≥2 courses/y	104 (16)	4 (11)	33 (44)	45 (21)	25 (10)	<.001
Daily ICS+SABA	136 (20)	6 (17)	34 (45)	43 (20)	25 (10)	<.001
Sick leave ≥20 days/y	61 (9)	2 (6)	13 (17)	27 (12)	16 (6)	.020
Use of ICS	564 (85)	28 (78)	67 (90)	183 (84)	183 (84)	.45
Asthma symptoms, n (%)						
Asthma causes quite/very much harm	114 (17)	4 (11)	75 (100)	47 (22)	25 (10)	<.001
Wake up due to asthma at least a few times/mo	212 (32)	9 (25)	67 (89)	90 (41)	58 (22)	<.001
Asthma is severe (patient's own assessment)	27 (4)	0 (0)	75 (100)	8 (4)	11 (4)	<.001
Asthma causes constant harm in daily life	163 (25)	1 (3)	75 (100)	57 (26)	26 (10)	<.001
Asthma symptoms are very harmful	8 (1)	2 (6)	33 (44)	3 (1)	3 (1)	<.001
Allergic diseases, n (%)						
Allergic diseases ≥2	242 (36)	26 (72)	18 (24)	84 (39)	147 (57)	<.001
AR	305 (47)	30 (83)	28 (39)	111 (52)	175 (69)	<.001
AC	232 (37)	25 (69)	23 (32)	91 (45)	144 (57)	<.001
AD	213 (34)	20 (56)	17 (24)	67 (33)	116 (46)	.001
no AR/AC/AD	252 (38)	3 (8)	30 (40)	68 (31)	43 (17)	<.001

(continued)

TABLE II. *(Continued)*

Variables	CLU 1: Late onset, nonsymptomatic, nonobese	CLU 2: Early-onset female predominant, obese, allergic, respiratory infections	CLU 3: Late-onset older men with severe asthma and comorbidities	CLU 4: Late-onset female predominant, obese, low education, comorbidities	CLU 5: Early-onset female predominant, allergic, nonobese	P_{All}
Multimorbidity, n (%)						
Other than respiratory disease(s)[c]	467 (70)	27 (75)	65 (87)	172 (79)	124 (48)	<.001
AERD	66 (10)	2 (6)	14 (19)	20 (9)	33 (13)	.092
CRSwNP	88 (15)	3 (9)	6 (11)	14 (8)	30 (13)	.10
Self-reported acute rhinosinusitis	105 (16)	11 (31)	7 (9)	33 (15)	57 (22)	.009
Doctor-diagnosed acute rhinosinusitis	84 (13)	11 (31)	7 (9)	34 (16)	52 (20)	.002
Recurrent respiratory infections in adulthood	388 (58)	23 (64)	45 (60)	134 (62)	173 (67)	.23
Pneumonia ever	205 (31)	13 (36)	29 (39)	70 (32)	66 (25)	.17
Febris/flu any	189 (28)	16 (44)	19 (25)	64 (29)	107 (41)	<.001
Arthrosis	137 (21)	2 (6)	21 (28)	50 (23)	19 (7)	<.001

P values by the χ^2 test (dichotomous) or 1-way analysis of variance (continuous variables). *P* values less than .05 were considered significant. Education level = baccalaureate/secondary versus primary school, professional training = completed professional college/university/courses/completed trade school versus no.

Questions used for the variables: Ever Smoking = if at least one of the following questions was true: Have you ever smoked? Have you ever smoked regularly? How old were you when starting smoking regularly? How many years have you smoked? How many cigarettes/pipes/cigars are you smoking? Or did you smoke before quitting per day? Do you smoke now? When have you smoked for the last time? Childhood maternal/paternal smoking = Did anyone regularly smoke indoors when you were a child? No; Yes; Don't know. Current exposure to tobacco smoke = Is someone else currently smoking indoors at your home? No; Yes. Self-reported/doctor-diagnosed acute sinusitis = Have you had the following respiratory infections during the past 12 months: flu without fever/common cold with fever/tonsillitis/otitis/maxillary sinusitis/bronchitis/pneumonia/other what? How many times? How many of them have been doctor diagnosed? Recurrent respiratory infections = Have you ever had recurrent common colds or other respiratory infections? No; Yes (before school age, at school age, in adulthood); Don't know. Arthrosis = Do you have doctor-diagnosed diseases (hypertension/coronal artery disease/rheumatoid arthritis/mental problems/diabetes/glaucoma/back disease/arthrosis)?: No; Yes; I use regular medication for it. Childhood wheeze = Have you ever had cough or attack of dyspnea with wheeze? No; Yes (choose 1 option) only in childhood; only in adulthood; both in adulthood and in childhood.

The following variables have previously been reported: education and training,[42] parental allergy/asthma, childhood in country/farm, AR/AC/AD and severe childhood infections,[10] asthma causes quite/very much harm, wake up due to asthma at least a few times/month, asthma is severe (patient's own assessment), asthma causes constant harm in daily life, asthma symptoms are quite/very harmful, severe asthma, regular OCS and daily ICS+SABA, other than respiratory disease(s), AERD, CRSwNP, birth order, number of siblings.[34]

AC, Allergic rhinoconjunctivitis; *AD*, atopic dermatitis; *AERD*, patient-reported NSAID-exacerbated respiratory disease; *AR*, allergic rhinitis; *BMI*, body mass index; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *ICS*, Inhaled corticosteroid; *NSAID*, nonsteroidal anti-inflammatory drug; *OCS*, oral corticosteroid; *SABA*, short-acting β-agonist; *SD*, standard deviation.

[a]Severe childhood infection = pneumonia before or during school age and/or hospitalization due to infection at ≤3 years of age.

[b]Severe asthma was defined as self-reported severe asthma AND asthma symptoms causing much harm AND regular impairment AND (≥1 oral corticosteroid course/y or regular oral corticosteroids AND/OR wake up in the night due to asthma symptoms/wheezing attach ≥ a few times/mo).

[c]Other than respiratory diseases were hypertension (n = 273), coronary artery disease (n = 111), rheumatoid arthritis (n = 52), psychiatric disease/disorder (n = 81), diabetes (n = 46), glaucoma (n = 42), musculoskeletal disease/back pain (n = 337), arthritis (n = 229), and other chronic disease(s) except chronic bronchitis/bronchiectasis (n = 410).

AERD (19%) and ≥1 other disease (87%). All subjects reported asthma symptoms causing much and constant harm, and all subjects considered their asthma as severe. Also, OCS use was the most frequent of all clusters (60%). Fifty-three percent of the subjects of this cluster had ≥4 siblings, and 80% grew up in the countryside. Seventy-nine percent reported having a low education.

Cluster 4: late onset, older obese females with comorbidities, and low education (n = 218).

Ninety-two percent of subjects of cluster 4 (n = 218) reported asthma onset ≥40 years of age. This cluster included mainly females (63%), and all subjects reported BMI >30. This cluster had high prevalence of other disease(s) (79%). Seventy-five percent reported low education (primary school or less). In this cluster, 30% had used OCS, and asthma symptoms were the second most common among all clusters.

Cluster 5: early adulthood onset, female predominant, allergic, and nonobese (n = 260).

All subjects of cluster 5 (n = 260) reported asthma onset <40 years of age. All had BMI <30. None fell into the group of severe asthma. Sixty-nine percent reported having ≥2 siblings, and 70% had one or more older siblings. Twenty-seven percent reported childhood in farm. This cluster had the second highest proportion of chronic rhinosinusitis with nasal polyps (CRSwNP) (13%) and the second highest proportion of AERD (13%), as compared with the other clusters (Table II).

Validation analysis

To analyze the stability of the clusters, we performed cluster analysis in 2 subgroups that were randomly divided from the population by 50% to 50% basis. The numbers of subjects who were entered into cluster analyses were 620 and 650, respectively. The percentages of subjects who fell into the same clusters were 94% and 89%, respectively, which reflects good stability of the clusters.

Validation hierarchical clustering (HC) analyses were performed to analyze the effect of dichotomizing continuous variables. Using BMI as a continuous value, there was a strong correlation between the original and new clusters ($P < .01$, r = 0.81 by Spearman's rank correlation test). When age was also added to this model as a continuous variable, the correlation between these new clusters and the original clusters remained good ($P < .01$, r = 0.71).
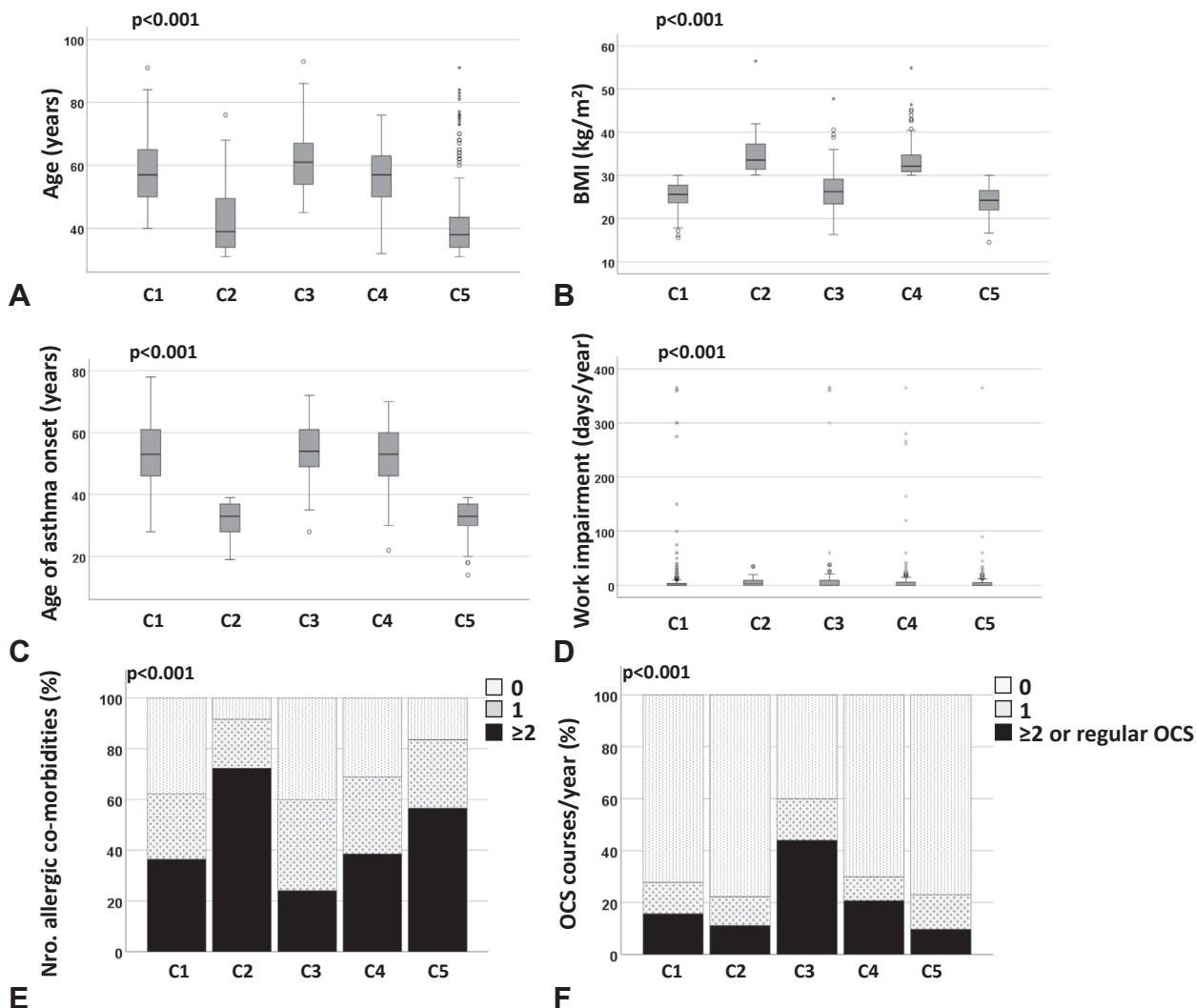
FIGURE 2. Distribution of (**A**) age, (**B**) BMI, (**C**) self-reported age of asthma onset, (**D**) work impairment due to asthma, (**E**) allergic comorbidities, and (**F**) use of oral corticosteroids in the 5 clusters (C1-C5). P values by the Kruskal-Wallis test (**A-D**) or the Pearson χ^2 test (**E, F**). Allergic comorbidities are allergic rhinitis, allergic conjunctivitis, and atopic dermatitis. *BMI*, Body mass index; *OCS*, oral corticosteroid.

DISCUSSION

In this population-based study of adult-onset asthma, we identified 5 clusters: 3 with late-onset asthma (onset ≥40 years) and 2 female predominant with onset at earlier adulthood (<40 years). CLU1 (n = 666) consisted of subjects with late-onset asthma. They were nonobese, symptomatic, predominantly female, with few respiratory infections during childhood. Subjects in CLU2 (n = 36) had asthma onset at early adulthood and were predominantly female, obese, with allergic asthma, and recurrent respiratory infections. CLU3 (n = 75) was a late-onset cluster consisting of old men with smoking history, comorbidities, severe asthma, least allergic diseases, low level of education, many siblings, and childhood in the countryside. CLU4 (n = 218) included late-onset obese females with comorbidities, asthma symptoms, and low education level. Subjects in CLU5 (n = 260) had early adulthood-onset asthma, were often female, allergic, and nonobese.

Previous clustering studies have mostly focused on childhood-onset asthma. To the best of our knowledge, 2 previous studies have focused on adult- or late-onset asthma.[7] Late/adult-onset clusters that have been recurrently identified in previous studies are obese, noneosinophilic asthma, eosinophilic asthma, severe and obstructive asthma, asthma in smokers (in those studies that do not exclude patients based on smoking history), and milder form of adult-onset asthma.[43] Most studies include adult patients with both childhood- and adult-onset asthma. In 2021, Cunha et al[44] published a systematic review including 68 studies on asthma phenotypes derived by data-driven methods. Variables identified were clinical, personal, and functional. The most frequent phenotypes were based on atopy, sex, and disease severity, but phenotypes varied according to variables included, sample's characteristics, and data availability. They concluded that more population-based studies are warranted as only 7 studies were population based.
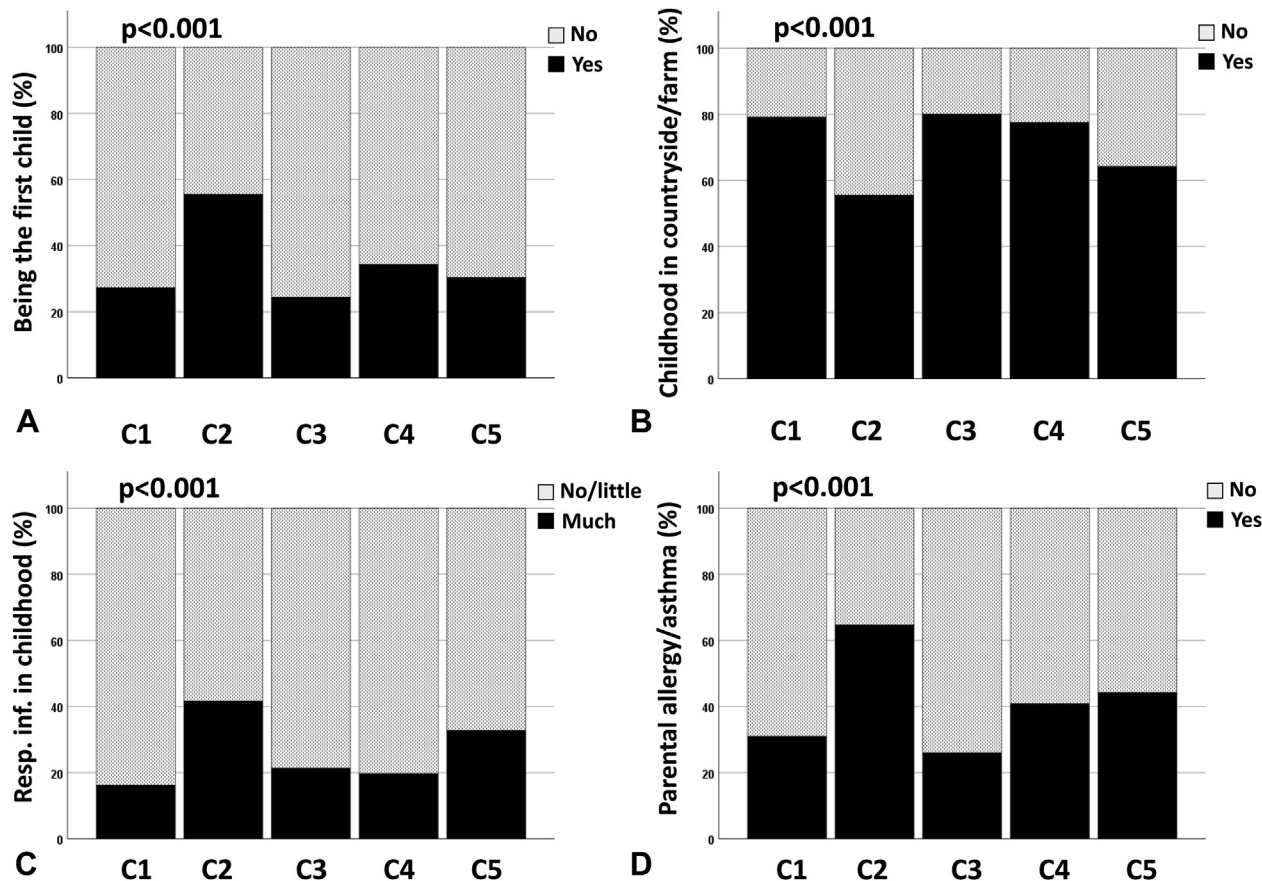
FIGURE 3. Bar plots showing the distribution of (**A**) being the first child, (**B**) childhood in countryside or farm, (**C**) a history of respiratory infections before and/or in school age, and (**D**) a history of parental allergy and/or asthma in the 5 clusters (C1-C5). *P* values by the Pearson χ^2 test.

We carried out cluster analysis in population-based setting and focusing on late-onset asthma. Our cluster analysis showed both similarities and differences in relation to the previous cluster analyses, which may mainly be due to including partially different covariates into the classification algorithm. Smoking and severe asthma identified a late-onset cluster in our study (CLU3), as well as obesity (CLU4). Smoking identified a cluster in at least 3 previous studies based on patients recruited from a hospital setting,[7,45,46] and a female-predominant, late-onset, obese cluster has been identified in several clustering studies.[7,46] In our cluster of smokers, subjects were highly symptomatic and 87% had nonrespiratory comorbidities. The cluster resembled that of our previous clinical study, where 84% of patients had uncontrolled asthma and the median number of comorbidities was 3.[7] AERD was most common in our cluster with severe asthma in smokers (19%), which is consistent with previous findings showing that AERD is associated with severe asthma,[33,47] and cumulative exposure including smoking is a risk factor for AERD.[48] AERD was not included as a variable in the previous cluster analyses identifying clusters with smoking asthmatics. Regarding the background factors, childhood in the countryside or at a farm was common in both smoking and late-onset obese clusters, and a previous population-based study has interestingly suggested that childhood in a farm predisposes to late-onset asthma even though protects from early-onset allergic

asthma.[34] Other studies have shown that farm environments represent a source of fungi and increase asthma risk and that sensitization to fungi might be related to severe asthma.[49]

The third and the largest late-onset cluster in the study was CLU1, consisting of nonobese, predominantly female subjects. Even though asthma in this cluster seems milder compared with the other late-onset groups, the CLU1 patients were on average more symptomatic than any of the early-onset clusters. We also saw a trend for highest prevalence of CRSwNP, known to be associated with severe asthma.[39] However, in our material, CRSwNP was not associated with severe asthma.[38] Cluster with nonobese females with good lung function but still relatively high use of health care was identified in our previous analysis[7] and some other studies,[45] showing resemblance with CLU1 in the current study. Females in CLU1 had the lowest amount of respiratory tract infections during childhood compared with other clusters. There is no or little previous evidence of an effect of childhood infections on adult-onset asthma. The topic is challenging due to recall issues and as the direction of association might depend on the infectious agent. For example, pertussis and measles were associated with new-onset asthma after childhood, but a greater infectious load has also been negatively associated with persisting asthma at all ages.[29] Therefore, it is difficult to assess the significance of childhood respiratory infections in the context of our clusters.

Our previous study showed that the presence of AR and/or AC is more prevalent among younger asthmatic adults,[10] which is in line with our current findings. In the current study, we identified 2 clusters with onset before 40 years of age, both with high prevalence of allergic multimorbidity. The clusters were relatively similar in regard to asthma symptoms but differed by factors such as BMI, comorbidities, childhood infections, and number of siblings. Subjects in CLU2 had predominantly grown up as the oldest of siblings. Allergic multimorbidity and AR were more common than in other clusters, as well as recurrent respiratory infections during childhood. Seventy-eight percent used ICS and asthma was rarely severe, suggesting that disease had good steroid responsiveness. This cluster highly resembles the classical early-onset allergic asthma, despite beginning in early adulthood. Another early-onset cluster, CLU5, differed from CLU2 by a high number of siblings, despite that asthma-related parameters that were available in this study were highly similar. In agreement with the hygiene hypothesis, a number of siblings have been suspected to protect against the development of childhood asthma[50,51] and other atopic diseases.[52] On the other hand, the number of siblings might be a risk factor for asthma, and decreased lung function might lead to increased contact with pathogens causing lower respiratory infections and thus lead to be exacerbated asthma, especially in genetically predisposed individuals.[42,52,53] It could also be speculated that the presence of more than 2 siblings could reflect poorer early living conditions predisposing patients to lower socioeconomic status in adulthood,[50] which thus may have an impact on asthma self-care behavior.[21] Whether the endotypes or lung function tests are similar in CLU2 and CLU5 remains unknown.

The early-onset CLU2 in this study consisted of obese, allergic subjects as compared with the other early-onset CLU5, which contained allergic nonobese subjects. It has been postulated that obesity-related asthma breaks out into at least 2 phenotypes: conventional early-onset allergic asthma modulated by obesity and late-onset phenotype that arises due to the presence of obesity.[54] We were able to identify both obesity-related phenotypes in our study and could see that the late-onset obese asthma had 6-fold higher prevalence compared with the early adulthood-onset variant. The patients were also more symptomatic as in the early-onset, obese phenotype, despite higher percentage subjects reporting that they were using ICS medication daily (84% vs 78%). This suggests that late-onset obese type is less steroid responsive, as has been previously shown.[55] Use of daily rescue medication was, however, similar in both obese phenotypes and higher than in allergic, nonobese phenotypes. Consistently, in a previous study, obesity predicted higher SABA use in patients with adult-onset asthma.[56]

Phenotypes that were shown in our population-based cohort differ from phenotypes identified in previous population-based cohorts. Three population-based, low-risk bias studies have been published (Amaral et al,[44] Boudier et al,[57] and Siroux et al[4]). In the study of Amaral, patients largely had milder childhood-onset asthma, rarely used ICS (11%), and were clustered based on their allergy profiles and symptoms.[44] Similar input variables (respiratory symptoms, allergic status, and pulmonary function) were used in the study of Boudier et al,[57] who performed a longitudinal follow-up, showing that cluster stability was 54% to 88%. Siroux et al[4] used age of asthma onset as an input variable in addition to symptoms, allergic status, and

pulmonary function resulting in clusters of which 2 had active asthma: the childhood-onset, allergic type and adult-onset, mostly female type, and 2 inactive or mild asthma types that were distinguished based on atopy status. Obesity or smoking was not reported in the 2 latter studies. Results are difficult to compare with ours due to such a different approach.

Differences to previous studies may mainly be explained by different covariates included in factor/cluster analyses. For example, early-life factors have not been included in most previous cluster analyses. Another reason for the differences seen may be different population included, for example, young adult asthmatics with mild disease may be missing from some hospital-based settings but be present in this population-based setting.

The strengths of this study include population-based setup and that we focused on adults who had lung-function-test–confirmed, doctor-diagnosed asthma with onset at 16 years of age or after. Other strengths are high age range and responder rate.

Many epidemiological studies aiming at identifying risk factors have not fully been able to account for heterogeneity of adult-onset asthma phenotypes, which may affect interpretation and comparison of results between studies.

We acknowledge that we lacked lung-function tests or other clinical or biomarker data. We acknowledge that a small portion of asthmatics might have had childhood-onset asthma that relapsed in adulthood. In addition, a memory bias in the report of risk factors might have occurred. We acknowledge limited accuracy in the assessment of some dichotomized variables (BMI and age), as well as such variables as smoking, which does not take into account the amount and the duration of smoking. However, when validating the HC analyses by using BMI and age as continuous variables, the clusters were strongly correlated with the original ones. The reduced correlation, after adding age to this validation model, might be related to decreased power and the population that was composed of asthmatics older than 30 years. Despite the efforts to validate the clusters as well as to use variables that have previously shown to be associated with asthma, we acknowledge that the data provided us limited possibilities to perform validation analyses and that some important variables (such as that of chronic obstructive pulmonary disease [COPD]) were lacking from the data. Hence, we cannot exclude if part of smoking patients have concurrent COPD. In addition, the weaknesses of our study include self-reported nature of study data. Average linkage with square Euclidean distance was used as it is a well-known algorithm used to cluster categorical and numerical data. Further research could be to apply some other clustering method, such as, for example, latent class analysis, and other interval methods, such as Gower's distance. We acknowledge that we did not use flexible imputation method as it was not available. However, because the proportion of missing values was small, it can be assumed that performing analyses by omitting the missing values is an appropriate method.

CONCLUSIONS

Our population-based adult-onset asthma clusters take into account several critical factors such as obesity and smoking, and identified clusters that partially overlap with clusters identified in clinical settings. These clusters also take into account childhood conditions and infection history. Thus, these results could be

useful to understand the development of different adult-onset asthma phenotypes as well as in developing novel personalized management strategies.

REFERENCES

1. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. J Allergy Clin Immunol 2019;144:1-12.
2. Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet 2006; 368:804-13.
3. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 2012;18:716-25.
4. Siroux V, Basagaña X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. Identifying adult asthma phenotypes using a clustering approach. Eur Respir J 2011;38:310-7.
5. Tuomisto LE, Ilmarinen P, Kankaanranta H. Prognosis of new-onset asthma diagnosed at adult age. Respir Med 2015;109:944-54.
6. Honkamäki J, Piirilä P, Hisinger-Mölkänen H, Tuomisto LE, Andersén H, Huhtala H, et al. Asthma remission by age at diagnosis and gender in a population-based study. J Allergy Clin Immunol Pract 2021;9:1950-9.
7. Ilmarinen P, Tuomisto LE, Niemelä O, Tommola M, Haanpää J, Kankaanranta H. Cluster analysis on longitudinal data of patients with adult-onset asthma. J Allergy Clin Immunol Pract 2017;5(4):967-78.
8. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 2019;56:219-33.
9. Lemmetyinen RE, Karjalainen JV, But A, Renkonen RLO, Pekkanen JR, Toppila-Salmi SK, et al. Higher mortality of adults with asthma: a 15-year follow-up of a population-based cohort. Allergy 2018;73:1479-88.
10. Toppila-Salmi S, Chanoine S, Karjalainen J, Pekkanen J, Bousquet J, Siroux V. Risk of adult-onset asthma increases with the number of allergic multi-morbidities and decreases with age. Allergy 2019;74:2406-16.
11. Pasternack R, Huhtala H, Karjalainen J. Chlamydophila (Chlamydia) pneumoniae serology and asthma in adults: a longitudinal analysis. J Allergy Clin Immunol 2005;116:1123-8.
12. Backman H, Räisänen P, Hedman L, Stridsman C, Andersson M, Lindberg A, et al. Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016-results from three population surveys. Clin Exp Allergy 2017;47:1426-35.
13. Karjalainen A, Kurppa K, Martikainen R, Klaukka T, Karjalainen J. Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. Am J Respir Crit Care Med 2001;164:565-8.
14. Kauppi P, Laitinen LA, Laitinen H, Kere J, Laitinen T. Verification of self-reported asthma and allergy in subjects and their family members volunteering for gene mapping studies. Respir Med 1998;92:1281-8.
15. Engelkes M, de Ridder MA, Svensson E, Berencsi K, Prieto-Alhambra D, Lapi F, et al. Multinational cohort study of mortality in patients with asthma and severe asthma. Respir Med 2020;165:105919.
16. Kisiel MA, Zhou X, Sundh J, Ställberg B, Lisspers K, Malinovschi A, et al. Data-driven questionnaire-based cluster analysis of asthma in Swedish adults. NPJ Prim Care Respir Med 2020;30:1-9.
17. Leynaert B, Sunyer J, Garcia-Esteban R, Svanes C, Jarvis D, Cerveri I, et al. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based cohort. Thorax 2012;67:625-31.
18. Hirano T, Matsunaga K. Late-onset asthma: current perspectives. J Asthma Allergy 2018;9:19-27.
19. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol 2010;126:926-38.
20. Tashiro H, Shore SA. Obesity and severe asthma. Allergol Int 2019;68: 135-42.
21. Temam S, Chanoine S, Bédard A, Dumas O, Sanchez M, Boutron-Ruault MC, et al. Low socioeconomic position and neighborhood deprivation are associated with uncontrolled asthma in elderly. Respir Med 2019;158:70-7.
22. Lee E, Lee SH, Kwon JW, Kim YH, Yoon J, Cho HJ, et al. Persistent asthma phenotype related with late-onset, high atopy, and low socioeconomic status in school-aged Korean children. BMC Pulm Med 2017;17:45.
23. Ekerljung L, Sundblad B-M, Rönmark E, Larsson K, Lundbäck B. Incidence and prevalence of adult asthma is associated with low socio-economic status. Clin Respir J 2010;4:147-56.
24. Jaakkola JJK, Hernberg S, Lajunen TK, Sripaijboonkij P, Malmberg LP, Jaakkola MS. Smoking and lung function among adults with newly onset asthma. BMJ Open Respir Res 2019;6:e000377.
25. Tommola M, Ilmarinen P, Tuomisto LE, Lehtimäki L, Niemelä O, Nieminen P, et al. Cumulative effect of smoking on disease burden and multimorbidity in adult-onset asthma. Eur Respir J 2019;54:1801580.
26. Koskinen A, Lemmetyinen R, Luukkainen A, Kankaanranta H, Ilmarinen P, Karjalainen J, et al. Season of birth affects the risk of adult-onset asthma in Finland. Allergy 2023;78:555-8.
27. Karvonen AM, Lampi J, Keski Nisula L, Auvinen J, Toppila Salmi S, Järvelin MR, et al. Farm environment during pregnancy and childhood and polysensitization at the age of 31—prospective birth cohort study in Finland. J Investig Allergol Clin Immunol 2019;31:44-51.
28. Toppila-Salmi S, Luukkainen AT, Xu B, Lampi J, Auvinen J, Dhaygude K, et al. Maternal smoking during pregnancy affects adult onset of asthma in offspring: a follow up from birth to age 46 years. Eur Respir J 2020;55: 1901857.
29. Paaso EMS, Jaakkola MS, Rantala AK, Hugg TT, Jaakkola JJK. Allergic diseases and asthma in the family predict the persistence and onset-age of asthma: a prospective cohort study. Respir Res 2014;15:152.
30. Burgess JA, Abramson MJ, Gurrin LC, Byrnes GB, Matheson MC, May CL, et al. Childhood infections and the risk of asthma: a longitudinal study over 37 years. Chest 2012;142:647-54.
31. Ziyab AH. Prevalence of food allergy among schoolchildren in Kuwait and its association with the coexistence and severity of asthma, rhinitis, and eczema: a cross-sectional study. World Allergy Organ J 2019;12:100024.
32. Kikkawa T, Yorifuji T, Fujii Y, Yashiro M, Okada A, Ikeda M, et al. Birth order and paediatric allergic disease: a nationwide longitudinal survey. Clin Exp Allergy 2018;48:577-85.
33. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. J Allergy Clin Immunol 2015;135:676-81.
34. Andersén H, Ilmarinen P, Honkamäki J, Tuomisto LE, Hisinger-Mölkänen H, Backman H, et al. Influence of childhood exposure to a farming environment on age at asthma diagnosis in a population-based study. J Asthma Allergy 2021;14: 1081-91.
35. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther 2017;43:39-45.
36. Turrin M, Rizzo M, Bonato M, Bazzan E, Cosio MG, Semenzato U, et al. Differences between early-and late-onset asthma: role of comorbidities in symptom control. J Allergy Clin Immunol Pract 2022;10:3196-203.
37. Won HK, Kim YC, Kang MG, Park HK, Lee SE, Kim MH, et al. Age-related prevalence of chronic rhinosinusitis and nasal polyps and their relationships with asthma onset. Ann Allergy Asthma Immunol 2018;120:389-94.
38. Toppila-Salmi S, Lemmetyinen R, Chanoine S, Karjalainen J, Pekkanen J, Bousquet J, et al. Risk factors for severe adult-onset asthma: a multi-factor approach. BMC Pulm Med 2021;21:214.
39. Canonica GW, Malvezzi L, Blasi F, Paggiaro P, Mantero M, Senna G, et al. Severe Asthma Network Italy (SANI). Chronic rhinosinusitis with nasal polyps impact in severe asthma patients: evidences from the Severe Asthma Network Italy (SANI) registry. Respir Med 2020;166:105947.
40. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008;178:218-24.
41. Deliu M, Sperrin M, Belgrave D, Custovic A. Identification of asthma subtypes using clustering methodologies. Pulm Ther 2016;2:19-41.
42. Loisel DA, Du G, Ahluwalia TS, Tisler CJ, Evans MD, Myers RA, et al. Genetic associations with viral respiratory illnesses and asthma control in children. Clin Exp Allergy 2016;46:112-24.
43. Ilmarinen P, Tuomisto LE, Kankaanranta H. Phenotypes, risk factors, and mechanisms of adult-onset asthma. Mediators Inflamm 2015;2015:514868.

44. Cunha F, Amaral R, Jacinto T, Sousa-Pinto B, Fonseca JA. A systematic review of asthma phenotypes derived by data-driven methods. Diagnostics (Basel) 2021;11:644.

45. Kim TB, Jang AS, Kwon HS, Park JS, Chang YS, Cho SH, et al. Identification of asthma clusters in two independent Korean adult asthma cohorts. Eur Respir J 2013;41:1308-14.

46. Lefaudeux D, De Meulder B, Loza MJ, Peffer N, Rowe A, Baribaud F, et al. U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics. J Allergy Clin Immunol 2017;139:1797-807.

47. Kowalski ML, Agache I, Bavbek S, Bakirtas A, Blanca M, Bochenek G, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)—a EAACI position paper. Allergy 2019;74:28-39.

48. Andersén H, Ilmarinen P, Honkamäki J, Tuomisto LE, Hisinger-Mölkänen H, Backman H, et al. NSAID-exacerbated respiratory disease: a population study. ERJ Open Res 2022;8:00462-2021.

49. Buil JB, Meijer EFJ, Denning DW, Verweij PE, Meis JF. Burden of serious fungal infections in the Netherlands. Mycoses 2020;63:625-31.

50. Forastiere F, Agabiti N, Corbo GM, Dell'Orco V, Porta D, Pistelli R, et al. Socioeconomic status, number of siblings, and respiratory infections in early life as determinants of atopy in children. Epidemiology 1997;8:566-70.

51. Almqvist C, Olsson H, Fall T, Lundholm C. Sibship and risk of asthma in a total population: a disease comparative approach. J Allergy Clin Immunol 2016;138: 1219-1222.e3.

52. Koopman LP, Smit HA, Heijnen ML, Wijga A, van Strien RT, Kerkhof M, et al. Respiratory infections in infants: interaction of parental allergy, child care, and siblings—the PIAMA study. Pediatrics 2001;108:943-8.

53. Bobolea I, Arismendi E, Valero A, Agustí A. Early life origins of asthma: a review of potential effectors. J Investig Allergol Clin Immunol 2019;29:168-79.

54. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, et al. Obesity and asthma: an association modified by age of asthma onset. J Allergy Clin Immunol 2011;127:1486-1493.e2.

55. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, et al. Cluster analysis of obesity and asthma phenotypes. PLoS One 2012;7: e36631.

56. Vähätalo I, Lehtimäki L, Tuomisto LE, Karjalainen J, Niemelä O, Ilmarinen P, et al. Long-term use of short-acting β2-agonists in patients with adult-onset asthma. J Allergy Clin Immunol Pract 2022;10:2074-2083.e7.

57. Boudier A, Curjuric I, Basagaña X, Hazgui H, Anto JM, Bousquet J, et al. Ten-year follow-up of cluster-based asthma phenotypes in adults. A pooled analysis of three cohorts. Am J Respir Crit Care Med 2013;188:550-60.