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ORIGINAL RESEARCH

Asthma Prevalence and Phenotyping in the General Population: The LEAD (Lung, hEart, sociAl, boDy) Study

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Background: Asthma is a chronic heterogeneous respiratory disease involving differential pathophysiological pathways and consequently distinct asthma phenotypes.

Objective and Methods: In the LEAD Study, a general population cohort (n=11.423) in Vienna ranging from 6–82 years of age, we addressed the prevalence of asthma and explored inflammatory asthma phenotypes that included allergic and non-allergic asthma, and within these phenotypes, an eosinophilic (eosinophils ≥300 cells/μL, or ≥150 cells/μL in the presence of ICS medication) or non-eosinophilic (eosinophils <300 cells/μL, or <150 cells/μL in the presence of ICS) phenotype. In addition, we compared various factors related to biomarkers, body composition, lung function, and symptoms in control subjects versus subjects with current asthma (current doctor's diagnosis of asthma).

Results: An overall prevalence of 4.6% was observed for current asthma. Furthermore, an age-dependent shift from allergic to non-allergic asthma was found. The non-eosinophilic phenotype was more prominent. Obesity was a prevalent condition, and body composition including visceral adipose tissue (VAT), is affected in current asthma versus controls.

Conclusion: This broad-aged and large general population cohort identified differential patterns of inflammatory asthma phenotypes that were age-dependent. The presence of eosinophilia was associated with worse asthma control, increased asthma medication, increased VAT, and lower lung function, the opposite was found for the presence of an allergic asthma.

Keywords: asthma, prevalence, phenotyping, pulmonary function testing, spirometry, general population, body composition

Introduction

Asthma is a chronic heterogeneous disease characterized by chronic airway inflammation, variable expiratory airflow limitation and respiratory symptoms including wheeze, shortness of breath, chest tightness and cough that may vary over time and in intensity.[1]

The prevalence of asthma increased in the last decades and asthma is presently a highly prevalent disease affecting over 399 million people globally, or 4.3% of the population.[1–3] However, these figures range from 1–22% dependent on country and/or age ranges studied.[3] In children, (allergic) asthma is the highest prevalent chronic respiratory condition and is studied extensively;[4] conversely, data on asthma prevalence in the elderly are more scarce[5] although it is associated with increased morbidity[6] and mortality.[7]

Differential underlying pathophysiological pathways in asthma are associated with distinct asthma phenotypes. These phenotypes can be classified by their clinical phenotype, such as early-onset, late-onset, and obesity-associated asthma, or by their inflammatory phenotype, including allergic and non-allergic eosinophilic (Th2-high) or non-eosinophilic (Th2-

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low) asthma,[8,9] and are largely derived from cohorts that included participants with severe asthma.[10–12] As such, these phenotypes are poorly studied in primary care,[13] and data on these phenotypes in the general population are lacking. International GINA recommendations[14] suggest asthma can be characterized by different stages of severity, ranging from mild to severe asthma and by variable asthma control being either well-controlled, partly-controlled, or uncontrolled.[3]

In this study, we sought to determine the prevalence of asthma and inflammatory asthma phenotypes in the general population between 6 and 82 years. In addition, the presence of asthma was related to asthma control, medication use and body composition.

Methods

Study Design and Participants

The LEAD (Lung, hEart, sociAl, boDy) Study (NCT01727518; http://clinicaltrials.gov) is a single-centered longitudinal, observational, population-based cohort study that aims to provide a comprehensive database of measured parameters of the function of the respiratory, cardiovascular, and metabolic system in a general population. In the first study phase, from 2012 to 2016, a random sample (stratified by age, gender, and residential area) of 11,423 subjects (males 47.6%, females 52.4%), aged 6–82 years, from Vienna and lower Austria has been investigated. A detailed study protocol is available online.[15] Ever asthma was defined as doctor's diagnosis (Positive response to the following question: "Has a doctor or other health professional ever told you that you have asthma?") and current asthma defined by a current doctor's diagnosis (Positive response to the following question: "Do you still have the diagnosis of asthma?").[16,17] Control subjects were all subjects with complete lung function data (pre- and post-bronchodilation (BD)) excluding those diagnosed with COPD, emphysema, or chronic bronchitis and current/ever asthma. The Asthma Control Test™ was performed according to the guidelines.[18] The presence of asthma medication was used as a proxy to assess severity of asthma according to GINA, with intake of at least one of the following: inhaled corticosteroids (ICS), short-acting (SABA) and long-acting beta agonist (LABA), and short-acting (SAMA) and long-acting muscarinic antagonist (LAMA). In addition, antihistamine medication was recorded.

Ethics

The local Ethics committee of Vienna (Ethikkommission der Stadt Wien) approved the study (protocol number: EK-11-117-0711). Participants signed informed consent, and informed consent for children under the age of 18 had to be signed by their parents or legal representative. The manuscript was conducted in accordance with the Declaration of Helsinki.

Measurements

All measurements were performed at the LEAD study center of the Ludwig Boltzmann Institute for Lung Health at the Clinic Penzing in Vienna, Austria. Lung function measurements included pre- and post-BD spirometry following international guidelines.[19,20] Quality control of spirometry was ensured by employment of trained personnel and standard operating procedures, and lung function parameter (forced expiratory volume in 1 second, FEV1; forced vital capacity, FVC) results were related to the Global Lung Initiative (GLI) reference equations.[21,22] Reversibility was defined as the difference of post-BD minus pre-BD FEV1 >12% and >0.2 L in participants ≥19 years; in participants <19 years: ≥12% difference in pre- vs post-BD FEV1.[23]

For more detailed information regarding the collection of parameters (including questionnaires) collected in this study, refer to[15] and Table S1.

Assessment of Atopic State, Eosinophils, and Body Composition

Atopic state was defined by skin prick allergen testing: a positive skin prick test was defined as the presence of a reaction ≥3mm to aero-allergens.[24] In brief, antihistamines or glucocorticoids were withdrawn for at least 48h before testing. The following aero-allergens were tested: ash tree, tree pollen mix (hazel, alder, birch), grass mix (Anthoxantum, Dactylis, Lolium, Phleum and Poa), mugwort, ragweed, ribwort, mites mix (Dermatophagoides Farinae and Dermatophagoides Pteronyssinus), mildew, and dog and cat dander. All allergens were obtained from the company "Alk-Abello". Positive

(0.1% histamine) and negative (0.9% sodium chloride) controls were included in the test panel.[24] Additionally, doctor's diagnosis of allergy and atopy were recorded, as well as questionnaires on the presence of atopic symptoms. Venous blood was collected from each participant, processed, and blood plasma was analysed for eosinophil counts using the Sysmex XN1000 hematology analyzer, performed by specialists at the Institute for Laboratory Medicine at Klinik Penzing, Vienna, Austria.

Body height and weight were measured with a stadiometer and a high precision scale, respectively. BMI was calculated as weight (kg) divided by height (m^2), and obesity was defined as a BMI >30 kg/m^2 and +2 standard deviations (SD) in those aged <19 years.[25] Body composition measurements were performed with a Lunar Prodigy™ (GE Healthcare©, USA) dual x-ray absorptiometry (DXA) scan. Whole-body scans were performed, and main body composition parameters including visceral adipose tissue (VAT) mass and volume were subsequently analyzed with enCORE™ v17. Quality control and calibration were conducted daily, as detailed elsewhere.[26] The fat mass index (FMI) and lean mass index (LMI) were derived from the fat mass and lean mass respectively and were corrected for height. Additionally, z-scores were accounted for age and sex.

Asthma Phenotyping

In subjects with current asthma, we determined phenotypes as following: allergic (positive skin prick, in combination with at least 1 of the following: doctor`s diagnosis of allergy, atopic symptoms, neurodermitis/atopic eczema) or non-allergic (Absence of positive skin prick with at least 1 of the following: doctor`s diagnosis of allergy, atopic symptoms, neurodermitis/atopic eczema) asthma. Within allergic and non-allergic asthma, we defined an eosinophilic (eosinophils ≥300 cells/μL, or ≥150 cells/μL in the presence of current ICS medication) or non-eosinophilic (eosinophils <300 cells/μL, or <150 cells/μL in the presence of current ICS medication) phenotype based on GINA 2021.[27,28]

Statistical Analysis

Statistics were performed in SPSS Statistics, version 27.[29] Differences between the control population and (current or ever) asthmatics, between age groups in current asthmatics (children/adolescents, 6-<20 years; adults, 20–60 years; elderly, 60+ years; and overall study population, age 6–82), or between the different asthma phenotypes, were analyzed using either ANOVA or Chi-square (Fisher's Exact). P-values < 0.05 were considered significant.

Results

Study Population

From the total LEAD study population of 11,423 participants aged 6–82 years, 11,249 participants had valid spirometry. From these 11,249 subjects, 9,920 were defined as controls (436 exclusions due to COPD, and for the analysis of current asthma, 401 ever asthmatics were excluded), 492 with current asthma (7 with invalid spirometry; Figure 1A) and 893 with ever asthma (11 with invalid spirometry; Figure 1B).

Prevalence of Doctor's Diagnosed Asthma

The overall prevalence of current asthma was 4.4% (4.3% male, 4.8% female; Figure 1C), and the highest prevalence was observed in the age group 40-<50 years, with 5.3% (5.2% male, 5.9% female). In the current asthma group, 52 subjects (61.5% male) were <20 years, whereas 447 subjects (43.0% male) were ≥20 years. The highest prevalence for males was observed at age group 60-<70 (5.7% male) and for females at age group 50-<60 (6.0% female). The overall prevalence of ever asthma was 7.9% (8.3% male, 8.8% female; Figure 1D). Prevalence of ever asthma declined more substantially at older age (>60 years).

Baseline characteristics as well as other factors for current and ever asthma are shown in Table 1. The current asthma population were older than controls (mean±SD: 46.7±17.8 versus 44.10±19.6 years; p<0.01). Both ever and current asthmatics weighed more, had increased BMI, and had increased pack years compared to respective controls. Current and ever asthmatics had increased symptoms (cough, sputum, wheezing and dyspnea) and had significantly lower lung function, pre- and post-BD (in liters, and %pred GLI) in all forced expiratory spirometric lung function parameters

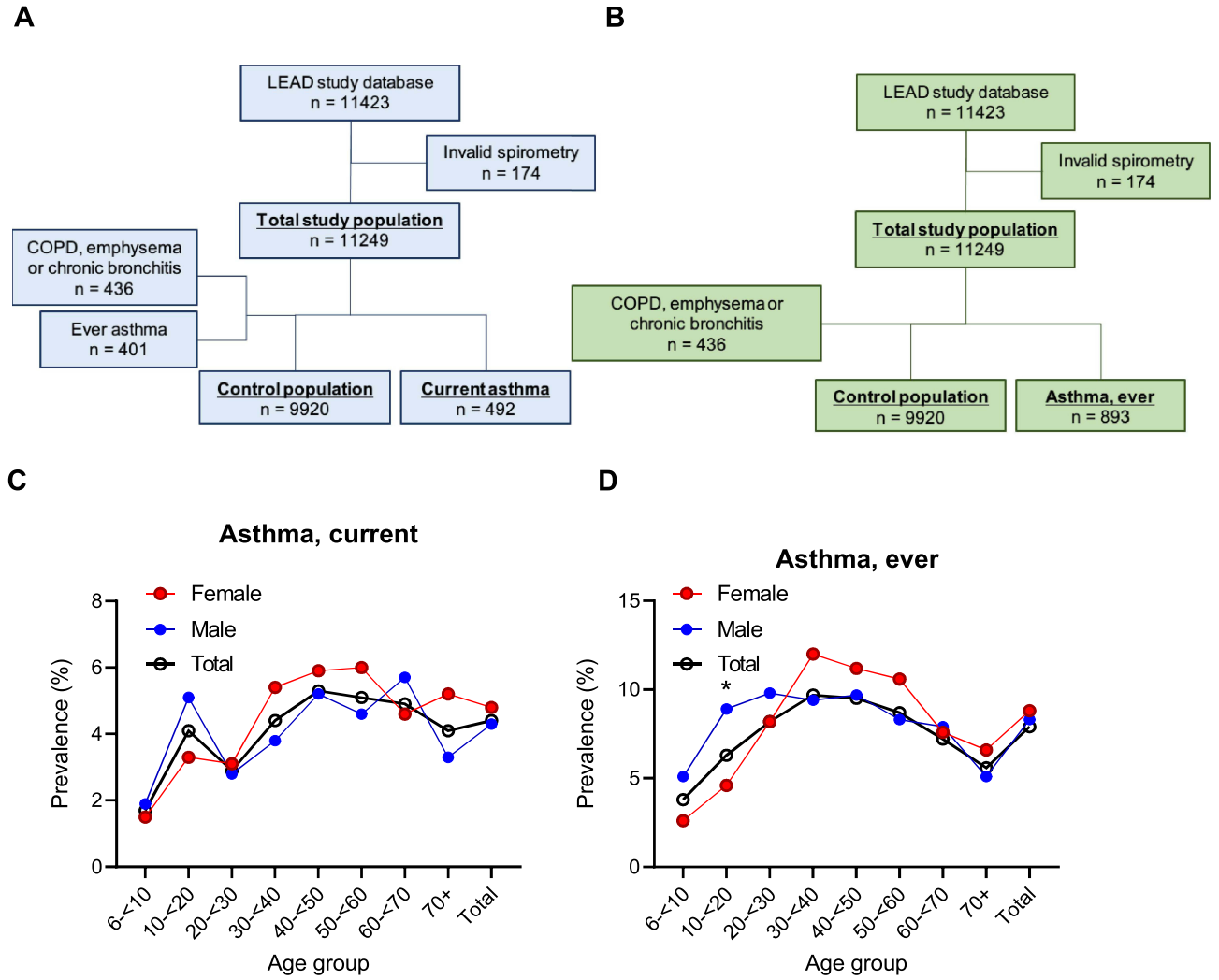

Figure 1 Flowchart of study population of current ((**A**); n=492) and ever ((**B**); n=893) asthma within the LEAD study cohort following exclusion criteria, including the prevalence of current (**C**) and ever (**D**) asthma. * $p < 0.05$.

(FEV1, FVC and FEV1/FVC) compared to controls. These lung function parameters were lower in all age groups with current asthma but did not reach statistical significance in the children/adolescents with current asthma versus controls (Table 2). The adult asthma population revealed significant lower numbers in all lung function parameters, but the largest reductions were observed in the elderly asthmatics.

Table 1 Baseline Characteristics Analysis Including Anthropometrics, as Well as Lung Function, Body Composition, Inflammation Markers, and Other Blood Biomarkers in the LEAD Study for Control and Asthma Subjects

Parameter	Control		Current Asthma		Ever Asthma		p-value	
	Total, n=9920		Total, n=492		Total, n=893		Ctl vs.	
	Mean or N	SD or %	Mean or N	SD or %	Mean or N	SD or %	Current	Ever
Male sex	4722	47.6	223	45.3	415	46.5	ns	ns
Age, years	44.1	19.6	46.7	17.8	44.4	17.4	**	ns
Height, cm	168.1	12.7	168.4	10.8	168.8	11.2	ns	ns
Weight, kg	71.8	19	74.7	17.4	74.6	18.3	****	****

(*Continued*)

Table 1 (Continued).

Parameter	Control		Current Asthma		Ever Asthma		p-value	
	Total, n=9920		Total, n=492		Total, n=893		Ctl vs.	
	Mean or N	SD or %	Mean or N	SD or %	Mean or N	SD or %	Current	Ever
BMI, kg/m^2	25.1	5.2	26.2	5.4	26	5.4	****	****
Low SES	791	8	43	8.7	73	8.2	ns	ns
Smoking habits and environment								
Pack years	8.3	16.7	10.2	21.4	9.6	19.1	*	*
Never smoker	5083	51.2	250	50.8	434	48.6	ns	ns
Former smoker	2756	27.8	144	29.3	260	29.1	ns	ns
Current smoker	2078	20.9	98	19.9	199	22.3	ns	ns
SHS, ever	5466	55.1	308	62.6	526	58.9	***	*
MS during pregnancy	442	4.5	40	8.1	64	7.2	****	****
Urban	8337	84	418	85	756	84.7	ns	ns
Asthma symptoms								
Coughing	1104	11.1	180	36.6	250	28	****	****
Sputum	822	8.3	164	33.3	225	25.2	****	****
Wheezing	666	6.7	253	51.4	313	35.1	****	****
Dyspnea	228	2.3	93	18.9	119	13.3	****	****
Lung function								
FEV1 pre, L	3.2	0.9	2.8	0.9	3	0.9	****	****
% pred, GLI	98.6	13.5	86	17.2	89.5	16.2	****	****
FEV1 post, L	3.3	0.9	3	0.9	3.1	0.9	****	****
% pred, GLI	101.4	13.3	91.4	16.5	94.2	15.6	****	****
FVC pre, L	4	1.1	3.8	1.1	4	1.1	****	ns
% pred, GLI	100	12.8	95.2	14.3	96.8	13.7	****	****
FVC post, L	4	1.1	3.9	1.1	4	1.1	****	ns
% pred, GLI	100.4	12.7	97.5	13.6	98.4	13.1	****	****
FEV1/FVC pre, %	80	7.4	72.6	10.1	74.8	9.3	****	****
% pred, GLI	98.2	7.6	89.6	11.1	91.8	10.2	****	****
FEV1/FVC post, %	82	7.1	75.5	9.9	77.5	9.2	****	****
% pred, GLI	100.6	7.2	93.1	10.6	95.1	9.7	****	****
Reversibility	264	2.7	84	17.1	103	11.5	****	****

Notes: *p < 0.05, **p < 0.01, ****p < 0.0001.

Abbreviations: SES, socioeconomic status; BMI, body mass index; SHS, secondhand smoking; MS, maternal smoking; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

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Table 2 Categorical Analysis in the LEAD Study for Control and Asthma Subjects, Separated by Age (<20 Years, 20–60 Years, 60+ Years) Including Anthropometrics, Body Composition, Lung Function, and Asthma Medication

Parameter	Control						Current Asthma						p-value		
	<20 Years, n=1406		20–60 Years, n=6008		60+ Years, n=2506		<20 Years, n=51		20–60 Years, n=310		60+ Years, n=131		Ctl vs Asthma		
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	<20	20–60	60+
Male sex	726	51.6	2824	47.0	1172	46.8	31	60.8	129	41.6	63	48.1	ns	ns	ns
Age, years	13.0	3.9	41.1	11.4	68.7	5.2	14.0	3.8	43.1	10.3	68.1	4.8	ns	**	ns
Height, cm	153.8	18.6	171.8	9.4	167.4	9.2	159.5	17.0	170.5	9.1	167.0	9.4	*	*	ns
Weight, kg	48.0	18.1	74.8	16.4	78.1	15.0	54.9	17.1	76.4	16.2	78.6	15.2	**	ns	ns
BMI, kg/m^2	19.5	4.0	25.3	4.7	27.8	4.6	21.1	4.0	26.3	5.2	28.2	5.0	***	****	ns
Lung function															
FEV1 pre, L	2.8	1.1	3.5	0.8	2.7	0.6	2.9	1.0	3.0	0.8	2.1	0.7	ns	****	****
% *pred, GLI*	97.9	11.9	97.8	12.0	101.0	16.9	92.6	15.0	87.5	14.9	79.9	21.0	***	****	****
FEV1 post, L	2.9	1.1	3.6	0.8	2.7	0.6	3.1	1.0	3.2	0.8	2.3	0.7	ns	****	****
% *pred, GLI*	100.9	12.2	100.4	11.9	103.9	16.5	98.3	13.2	92.9	13.9	85.5	21.1	ns	****	****
FVC pre, L	3.2	1.2	4.4	1.0	3.5	0.8	3.5	1.2	4.2	1.0	3.1	0.9	ns	****	****
% *pred, GLI*	98.1	11.5	99.6	11.5	101.8	15.8	97.2	12.2	96.4	12.6	91.6	18.0	ns	****	****
FVC post, L	3.2	1.2	4.4	1.0	3.5	0.8	3.6	1.2	4.2	1.0	3.3	0.9	*	****	***
% *pred, GLI*	98.9	11.6	99.7	11.5	102.7	15.3	99.0	11.4	98.3	12.0	95.1	17.3	ns	*	****
FEV1/FVC pre, %	87.2	6.8	79.8	6.6	76.4	6.5	82.5	9.0	73.5	9.1	66.7	9.2	****	****	****
% *pred, GLI*	99.3	7.6	97.8	7.3	98.7	8.3	94.4	10.0	90.3	10.6	86.0	11.7	****	****	****
FEV1/FVC post, %	89.1	6.2	82.0	6.2	78.0	6.4	86.1	7.2	76.6	8.5	68.9	9.5	***	****	****
% *pred, GLI*	101.4	6.9	100.4	6.8	100.6	8.1	98.6	7.8	94.1	9.7	88.8	12.0	**	****	****
Delta FEV1 (mL)	82.4	145.3	97.0	134.3	76.4	119.0	175.1	177.5	187.3	170.8	146.3	158.9	****	****	****
FEV1 change (%)	3.2	5.8	2.9	4.1	3.2	5.0	7.0	7.7	6.7	6.9	7.9	8.7	****	****	****
Reversibility	73	5.2	115	1.9	77	3.1	9	17.6	46	14.8	29	22.1	****	****	****

Body composition															
Waist circumference (cm)	71.4	11.7	91.1	13.3	100.6	12.4	76.8	12.0	93.7	14.1	102.1	12.5	***	***	ns
Adiposity	41	2.9	859	14.3	675	26.9	2	3.9	62	20.0	40	30.5	ns	**	ns
Central obesity	244	17.4	1994	33.2	1635	65.2	12	23.5	132	42.6	88	67.2	ns	****	ns
Medication															
Antihistamine	28	2.0	197	3.3	78	3.1	13	25.5	73	23.5	24	18.3	****	****	****
Asthma medication	26	1.8	48	0.8	44	1.8	27	52.9	173	55.8	88	67.2	****	****	****
ICS	7	0.5	21	0.3	22	0.9	13	25.5	126	40.6	76	58.0	****	****	****

Notes: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

Abbreviations: BMI, Body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids.

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Nearly a fifth (17.1%) of the current asthma population and a tenth (11.5%) of the ever asthma population showed reversibility (Table 1). More specifically, it was observed in 17.6%, 14.8% and 22.1% of the children/adolescents, adults, and the elderly population with current asthma, respectively (Table 2).

Asthma Control and Medication

The asthma control test (ACT) indicated that 73.4% of the asthmatics were found to have well-controlled asthma, 18.5% partly-controlled asthma, and 8.2% uncontrolled asthma (Figure 2), which was not affected by sex. In addition, a visible shift in the ACT was observed between children and adults with asthma, with children having a higher percentage of partly-controlled or uncontrolled asthma (partly-controlled: 24.4%, vs 15.4% in adults; uncontrolled: 17.1%, vs 7.3% in adults; p-value = 0.027). In the elderly, the prevalence of partly-controlled asthma increased again compared to the adult population (25.3%), whereas uncontrolled asthma remained relatively stable (6.3%). Overall, 288 out of 492 (58.5%) current asthmatics had a medication for their asthma, of which 214 (74%) subjects indicated taking ICS.

Phenotyping of Current Asthma

Allergic and non-allergic asthma was observed in 301 (64.6%) and 165 (35.4%) asthmatics, respectively. Within allergic asthma, 40.2% were eosinophilic (26.2% of asthmatics), whereas 59.8% were non-eosinophilic (38.8% of asthmatics). In non-allergic asthma, 44.0% (15.4% of asthmatics) displayed an eosinophilic and 56.0% (19.6% of asthmatics) a non-eosinophilic phenotype, respectively. Eosinophilic and non-eosinophilic asthma was present in 189 (41.5%) and 266 (58.5%) asthmatics, respectively (Figure 3A). Of note, ICS intake in eosinophilic and non-eosinophilic asthma was 74.6% and 20.7%, respectively (Table 3).

Significant age-related differences in these phenotypes were found in our study. Allergic asthma was the most prominent phenotype in children/adolescents (81.6%) and adults (73.4%; Figure 3B) but revealed an age-related decrease with a concomitant increase in non-allergic asthma, which was more prominent in elderly asthmatics (64.2%). In allergic asthmatics, a non-eosinophilic phenotype was more prominent, and this increased with age (Figure 3C; 47.4%, 60.9% and 65.1% for children/adolescents, adults, and the elderly respectively) with a concomitant decrease in eosinophilic allergic asthma. In non-allergic asthma, the non-eosinophilic phenotype, while more prominent, decreased with age (Figure 3D; 66.7%, 57.9% and 52.7% for children/adolescents, adults, and the elderly respectively). Allergic asthma revealed a higher prevalence of male gender, lower age, increased height, and lower BMI (Table 3). These subjects had better lung function, less secondhand smoking (SHS) exposure and a higher proportion of never smokers.

Compared to non-eosinophilic asthma, a worse outcome in asthma control was measured in eosinophilic asthma concordant with increased ICS/asthma medication intake (Table 3). They also had significantly lower lung function both pre- and post-BD (FEV1, FVC, FEV1/FVC %pred, and ratio FEV1/FVC) as well as a higher prevalence of reversibility compared to non-eosinophilic asthma subjects.

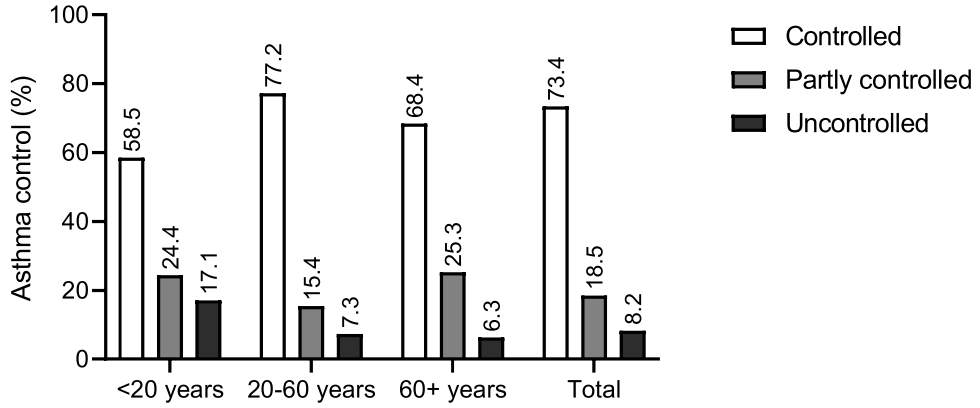

Figure 2 Asthma control according to the Asthma Control Test (ACT) in the current asthma population, separated by age groups (<20 years, 20 to 60 years, 60+ years). A significant difference (p=0.027) was found for ACT between the age groups <20 years versus 20 to 60 years.

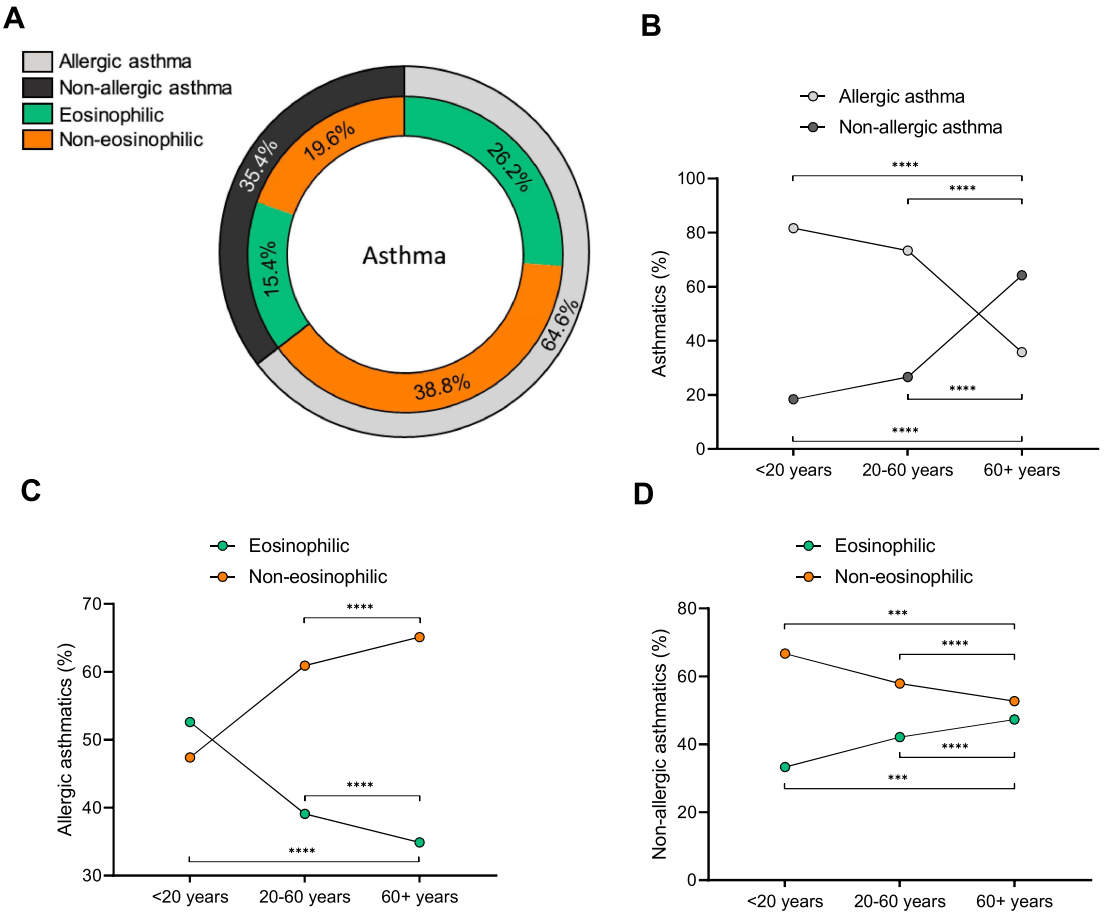

Figure 3 The percentage of LEAD study asthma subjects (n=492 total, n=26 with missing allergic status, and another n=11 with missing eosinophil counts) with (**A** and **B**) allergic asthma (64.6%) or non-allergic asthma (35.4%), either (**C** and **D**) eosinophilic (26.6% with allergic, 15.4% with non-allergic) or non-eosinophilic (38.8% with allergic, 19.6% with non-allergic), separated by age (<20 years of age, and 20 years to 60, or 60+). *** $p < 0.001$, **** $p < 0.0001$.

Asthma and Obesity

Obesity was prevalent in current asthma: 21.1% or 104 of 492 were obese, which was also significantly higher than in controls (16.0%: p=0.002; Table 1). In children/adolescents, obesity was detected by both significant increases in BMI and waist circumference, whereas in the adult asthma population, obesity was additionally recognized by central obesity, which was significantly higher than respective controls (Table 2). Absolute visceral adipose tissue (VAT) mass was increased in the adult and elderly asthma population, whereas VAT volume and mass (z-score) were only increased in the elderly asthma population (Table S2). The fat mass index (absolute and z-scores) was significantly increased in the children/adolescent and adult asthma population.

Within the asthma phenotypes, obesity was significantly higher prevalent in non-allergic compared to allergic asthmatics (26.7% versus 17.9%, p=0.028), and increased by age (Figure 4A). Moreover, allergic asthma revealed lower FMI and VAT (mass, volume and z-scores) compared to non-allergic asthmatics. Within the categories of allergic/non-allergic, the differentiation between eosinophilic and non-eosinophilic did not have an impact on the prevalence of obesity (Figure 4B; allergic eosinophilic, 17.6%; non-eosinophilic, 18.1%; non-allergic eosinophilic 25.7%; non-eosinophilic 25.8%) but increased with age (Figure 4C).

Discussion

The current study covering a lifespan between 6 and 82 years highlights a 4.4% prevalence of current asthma which is age-dependent with its peak prevalence from 40 years onwards without any sex dependence in the general population. Additionally, we were able to differentiate between allergic/non-allergic as well as eosinophilic/non-eosinophilic asthma

Table 3 Comparison of Asthma Phenotypes (Allergic (A), Non-Allergic (NA), Eosinophilic (E), Non-Eosinophilic (NE)) for Anthropometrics, as Well as Exposures, Smoking, Symptoms, Lifestyle, Lung Function and Body Composition

	A	n=301	NA	n=165	p-value	E	n=189	NE	n=266	p-value
	N or Mean	% or SD	N or Mean	% or SD	A vs NA	N or Mean	% or SD	N or Mean	% or SD	E vs NE
Male gender	148	49.2	64	38.8	*	95	50.3	115	43.2	ns
Age	42.2	16.5	54.6	17.3	****	46.0	18.9	47.0	16.9	ns
Height	169.6	10.8	166.6	10.8	**	167.7	11.6	169.3	10.4	ns
Weight	74.5	17.8	75.2	17.0	ns	73.7	17.6	75.6	17.5	ns
BMI	25.7	5.3	27.0	5.4	*	26.1	5.5	26.2	5.3	ns
Urban	258	85.7	138	83.6	ns	165	87.3	222	83.5	ns
Smoking										
Pack years	14.7	25.8	14.7	25.8	****	9.2	18.5	11.1	23.7	ns
Never smoker	166	55.1	69	41.8	**	93	49.2	136	51.1	ns
Former smoker	75	24.9	63	38.2		58	30.7	76	28.6	
Current smoker	60	19.9	33	20.0		38	20.1	54	20.3	
SHS, ever	169	56.1	123	74.5	****	121	64.0	166	62.4	ns
MS during pregnancy	23	7.6	16	9.7	ns	16	8.5	23	8.6	ns
Symptoms										
Coughing	97	32.2	72	43.6	*	92	48.7	72	27.1	ns
Sputum	90	29.9	66	40.0	*	69	36.5	81	30.5	ns
Wheezing	158	52.5	78	47.3	ns	103	54.5	126	47.4	ns
Dyspnea	40	13.3	45	27.3	****	37	19.6	44	16.5	ns
ACT, controlled	191	76.7	81	68.6	ns	106	67.9	161	79.3	*
ACT, partly controlled	40	16.1	29	24.6		37	23.7	30	14.8	
ACT, uncontrolled	18	7.2	8	6.8		13	8.3	12	5.9	
Medication										
ICS	123	40.9	77	46.7	ns	141	74.6	55	20.7	****
Asthma medication	177	58.8	92	55.8	ns	157	83.1	107	40.2	****
Antihistamine	81	26.9	16	9.7	****	43	22.8	52	19.5	ns
Body composition										
Obesity	54	17.9	44	26.7	*	39	20.6	55	20.7	ns
FMI, kg/m^2	8.8	3.9	10.3	4.0	****	9.3	4.1	9.3	4.0	ns
FMI, z-score	0.1	1.0	0.2	1.1	ns	0.2	1.1	0.1	1.1	ns
LMI, kg/m^2	16.1	2.5	16.0	2.4	ns	16.0	2.5	16.2	2.4	ns
LMI, z-score	0.1	1.0	0.1	1.2	ns	0.0	1.1	0.1	1.1	ns
VAT mass	929.7	837.2	1230.0	946.3	***	1165.1	981.2	959.3	824.6	*

(*Continued*)

Table 3 (Continued).

	A	n=301	NA	n=165	p-value	E	n=189	NE	n=266	p-value
	N or Mean	% or SD	N or Mean	% or SD	A vs NA	N or Mean	% or SD	N or Mean	% or SD	E vs NE
VAT volume	1001.3	893.4	1284.9	983.0	**	1230.5	1023.8	1034.1	879.5	ns
VAT mass, z-score	0.0	1.2	0.1	1.1	ns	0.1	1.2	0.0	1.1	ns
Lung function										
FEV1 pre, % GLI	87.1	16.4	84.5	18.5	ns	80.9	17.7	90.0	15.9	****
FEV1 post, % GLI	92.6	15.3	90.0	18.3	ns	87.0	17.6	95.0	15.0	****
FVC pre, % GLI	95.9	14.0	94.5	15.1	ns	91.4	14.5	98.1	13.8	****
FVC post, % GLI	98.0	13.2	97.2	14.4	ns	94.6	14.0	99.7	13.1	****
FEV1/FVC pre, % GLI	90.2	10.7	88.5	11.9	ns	87.6	12.0	91.2	10.1	***
FEV1/FVC post, % GLI	93.9	9.8	91.9	11.9	*	91.2	11.7	94.7	9.6	***
FEV1/FVC pre	73.7	9.7	70.7	10.7	**	71.2	11.1	73.9	9.2	**
FEV1/FVC post	76.8	9.3	73.4	10.8	***	74.1	11.0	76.7	9.0	**
Reversibility	57	18.9	24	14.5	ns	42	22.2	36	13.5	*

Notes: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.
Abbreviations: BMI, body mass index; SHS, secondhand smoking; MS, maternal smoking; ACT, asthma control test; FMI, fat mass index; LMI, lean mass index; VAT, visceral adipose tissue; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids.

phenotypes. We found that asthma, compared to the general population, has higher indices of obesity, including BMI, central obesity and visceral fat mass, the latter of which was related to the elderly. Furthermore, asthma in adulthood is associated with lower lung function even though current asthma within a general population reflects milder asthma. In addition, the overall analysis of asthmatics compared to controls reveal that symptoms and lung function impairment pre- and post-BD not only in current, but also ever asthmatics, are significantly higher than in the general population. Lastly, asthma phenotyping reveals that eosinophilic asthma has the lowest lung function pre-and post-BD.

According to the World Health Survey (WHS), the global prevalence of doctor diagnosed asthma is 4.3%, and varied significantly among 70 countries.[3] In the US, the prevalence of asthma among adults is 7.6%, but rates vary dramatically among different ethnic groups.[30] A survey of UK healthcare records reported that the prevalence was marginally higher at 6.5%.[31] They additionally reported that prevalence was highest at age 12–17, then declined gradually up to the group aged 45–54 years, where the prevalence slightly started increasing again.[31] Our prevalence data based on current asthma fit very well with the global prevalence. Nevertheless, we also have a significant proportion of 401 individuals (44.4% of total asthma population) with an asthma diagnosis but without symptom persistence, and as such, the prevalence of ever asthma is significantly higher, and may partially explain the differential findings between studies using different definitions.

Research indicates that asthma is common in the elderly[32,33] and has been associated with increased morbidity and mortality rates,[34] and is often underdiagnosed or confused with COPD.[5] However, general population data are scarce in this older population: one study demonstrated a prevalence of 7.8% in male and 7.1% in female aged >65 years based on an asthma diagnosis and symptoms.[35] Here we provide evidence that asthma is indeed common in the elderly, and is distinct from asthma during adolescence or in adults regarding phenotype, and body composition as discussed below.

Phenotyping of the current asthma population revealed that in children/adolescents, allergic asthma is the dominant phenotype, and an age-dependent shift from allergic asthma to non-allergic asthma.

In allergic asthma, a non-eosinophilic profile became the major phenotype from adulthood onward, whereas in non-allergic asthma, the inflammatory profiles remained stable with increasing age and with a slight predominance of the non-eosinophilic phenotype. This is in line with previous studies that describe a decrease of childhood and early-onset allergic

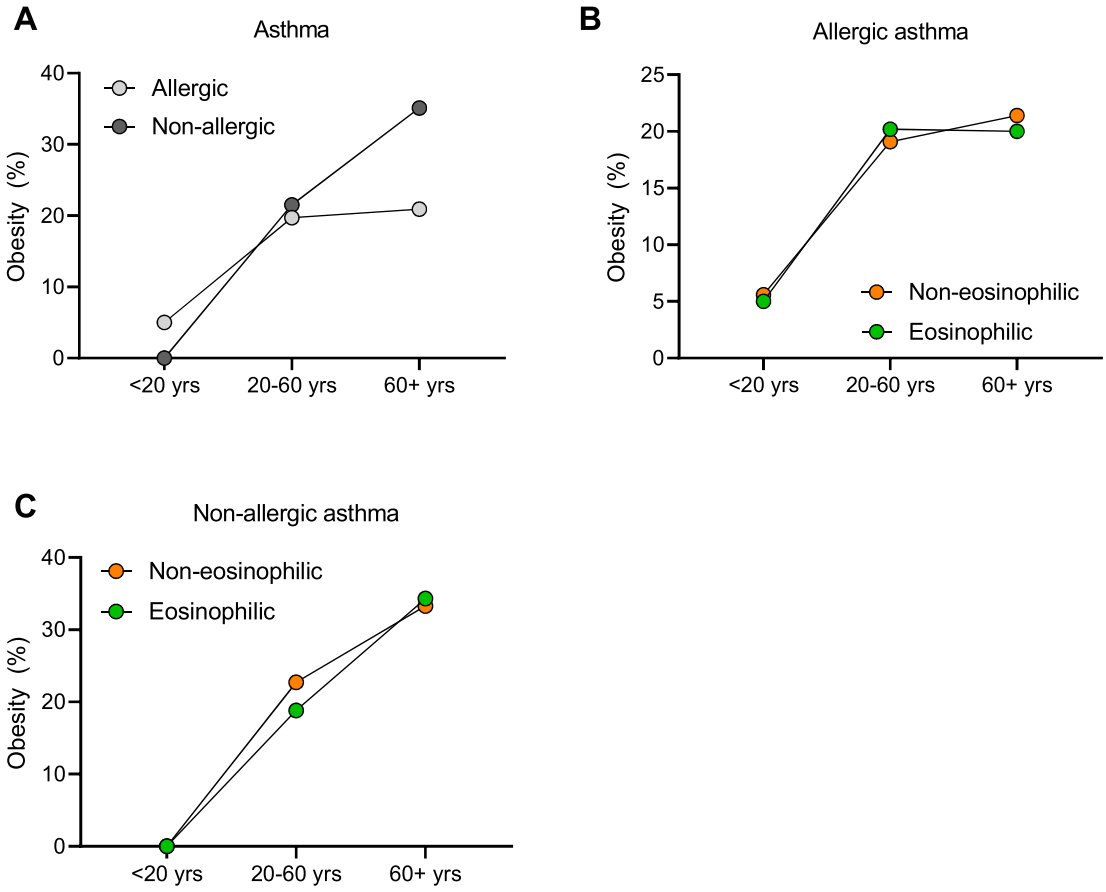

Figure 4 (**A**) Prevalence of current asthmatics with obesity (BMI ≥ 30 kg/m^2 or participants aged ≤19 years old: ≥ + 2 SD) having either an allergic or non-allergic asthma. Prevalence of obesity within allergic (**B**) or non-allergic (**C**) asthma for the eosinophilic (green) or non-eosinophilic (Orange) phenotype.

asthma and increased non-allergic asthma (less atopy, lower serum IgE, lower blood/sputum eosinophil levels) with increasing age, especially in late-onset asthma/asthma in the elderly.[36,37] Similar observations were reported in a Finnish cohort study.[38] As for non-eosinophilic asthma, our current findings are in line with previous studies that have suggested about 50% of asthmatics display a non-eosinophilic asthma,[39,40] a finding that was also observed in molecular signature studies, where 20 of 42 participants with asthma had Th2-low asthma.[41] The age-dependent increase in non-eosinophilic asthma may be related to extrinsic and intrinsic factors.[40,42] Another important question is whether the allergic/eosinophilic asthma phenotype disappears with increasing age, or whether this is the emergence of a new disease; however, our cross-sectional analysis cannot elaborate on this.

The differences in the asthma phenotypes are multifaceted and are in line with previous survey studies,[43,44] and indicate significant differences regarding sex, anthropometrics, medication intake, symptoms, lung function and reversibility, as well as smoking behavior and body composition. The presence of eosinophilia was associated with worse asthma control, ICS intake, asthma medication, increased VAT,[26] and lower lung function. The presence of an allergic asthma was associated with being male, younger, taller, lower BMI, less obesity, lower FMI and VAT, less symptoms, better lung function and more antihistamine intake. These data indicate that typing in eosinophilic and non-eosinophilic asthma may contribute to experienced disease burden and trait differentiation.

Our definition of the presence of an eosinophilic phenotype is based on commonly used cut-off levels (≥300 cells/μL, or ≥150 cells/μL in the presence of ICS medication) to guide treatment with currently approved biologic agents.[27,28] Interestingly, a recent meta-analysis on eosinophils as a biomarker in asthma addressed blood eosinophil ranges and distribution, which revealed median ranges of 157–280 and 200–400 cells/μL for asthma and severe asthma, respectively.[45] The current study observed similar eosinophil levels in asthmatics: with ICS intake 285.6±240.1 cells/

µL (95% CI: 199.1–241.6, median 220.0) versus 220.4±177.3 cells/µL in asthmatics without ICS intake (95% CI: 253.1–318.2, median 170.0). As such, the current analysis may overestimate eosinophilic asthma using a cut-off of 150 cells/µL in the presence of ICS intake and highlights the need to assess eosinophil count following ICS treatment.

Our data furthermore clearly demonstrate the importance of body composition in asthma. Obesity was more prevalent in current asthmatics, a finding that has been demonstrated previously from epidemiological studies and meta-analyses,[46,47] and a recent large scale study observed that asthmatics have a higher risk of developing obesity than non-asthmatics, particularly those that are non-atopic,[48] have longer disease duration or are on oral corticosteroids.[49] In line with these findings, we here observed that obesity was more prevalent in non-allergic/non-atopic asthmatics versus allergic asthmatics. An important observation is that changes in body composition types were already present in children (increased BMI, FMI) that are known to modify asthma[50] and may reflect worse long-term prognosis (lung function, airflow obstruction) if not treated. Our data furthermore indicate that in the elderly asthmatics, VAT is mainly impacted, and VAT was recently shown to increase with age in both males and females.[26] Intriguingly, visceral fat may contribute to airway narrowing in asthma.[51,52] Overall, obese asthma has been linked with increased (adipose tissue) inflammation and asthma morbidity.[53]

Our data indicate that the pattern of asthma control was relatively similar with a large proportion having good asthma control in the different age groups, although in children/adolescents, and to a lesser extent the elderly, asthma was less controlled than in adults, which paralleled with the use of ICS. This is in line with previous studies that highlight a difficult-to-control asthma in the elderly[34] as well as in children/adolescents.

Other general population cohorts have found similar rates of asthma control, although definitions were different to the current study[54] and often times involved severe asthma.[55–58]

While reversibility testing is advised in all guidelines,[59] a Canadian general population study observed that reversibility was found in only 16.3% in study participants with a doctor's diagnosis of asthma and current asthma symptoms,[60] a finding that is similar to the prevalence of 17.1% in current asthmatics in our study as well as a 17.3% reversibility in current asthmatics as found by a study with combined data from three large population studies.[61] Collectively, this would suggest that reversibility testing is not sufficient to diagnose asthma in the general population and would require further assessment for accurate asthma diagnosis.

The primary strengths of our study are the population-based design with a large sample and broad age range of participants representative for the general Austrian population.[15] Another strength is atopy testing in all participants of this general population cohort. Additionally, all analyses of spirometry and body composition, based on state-of-The-art DXA, were performed by trained technicians using standardized operational procedures.

A limitation of this study is that prescribed medication adherence was assessed by self-reporting. Additionally, the data was collected between 2012 and 2016, before the era of current biologic treatments. Furthermore, there were no direct measurements of inflammation relevant to asthma (eg interleukins and FeNO). Since induced sputum was not obtained, we cannot draw any conclusions on sputum-derived eosinophil levels to further elucidate eosinophilic asthma. We recognize that not all asthmatics with a positive skin prick necessarily have allergic asthma,[62] although we extended on the definition of allergic asthma by including at least a diagnosis of allergy, or atopy symptoms in addition to a positive skin prick. Lastly, as this study was cross-sectional in design, we cannot draw any causal inference between the parameters addressed in the current study and asthma.

Overall, the present study on current asthma in the general population highlighted a prevalence of 4.4% in a large cohort with a broad age range, which is associated with lower lung function. In addition, our findings advance the knowledge on asthma in that 1) there is an age-dependent shift from allergic to non-allergic asthma, in both of which a non-eosinophilic profile was more prominent. 2) Eosinophilic asthma is strongly associated with asthma symptoms, asthma control, asthma medication and impaired lung function, whereas allergic status is associated with male sex, body composition and body morphometry. 3) Obesity is prevalent, and asthma has major associations with body composition with indices of increased fat mass in both children and adults, central obesity in adults, and VAT in the elderly.

Summary

There are differential asthma phenotypes in the general population; eosinophilic asthma is strongly associated with the lowest lung function and asthma control, and symptoms. Furthermore, asthma has major association with body composition.

Abbreviation

LEAD Study, Lung, Heart, Social, Body Study; FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; GLI, Global Lung Initiative; DXA, Dual-energy X-ray absorptiometry; SES, Socioeconomic status; SHS, secondhand smoking; MS, Maternal smoking; FMI, Fat mass index; LMI, Lean mass index; VAT, visceral adipose tissue; SHS, Second-hand smoking; BMI, Body mass index; BD, bronchodilation; Th2, T helper 2; COPD, Chronic obstructive pulmonary disease; ACT, Asthma Control Test; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; SABA, short-acting beta agonist; LABA, long-acting beta agonist; SAMA, short-acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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