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Picturing asthma in Turkey: results from the Turkish adult asthma registry

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ABSTRACT

Introduction: National data on asthma characteristics and the factors associated with uncontrolled asthma seem to be necessary for every country. For this purpose, we developed the Turkish Adult Asthma Registry for patients with asthma aiming to take a snapshot of our patients, thereby assigning the unmet needs and niche areas of intervention.

Methods: Case entries were performed between March 2018 and March 2022. A web-based application was used to record data. Study outcomes were demographic features, disease characteristics, asthma control levels, and phenotypes.

Results: The registry included 2053 patients from 36 study centers in Turkey. Female subjects dominated the group ($n=1535$, 74.8%). The majority of the patients had allergic ($n=1158$, 65.3%) and eosinophilic ($n=1174$, 57.2%) asthma. Six hundred nineteen (32.2%) of the patients had obese asthma. Severe asthma existed in 670 (32.6%) patients. Majority of cases were on step 3–5 treatment (n: 1525; 88.1%). Uncontrolled asthma was associated with low educational level, severe asthma attacks in the last year, low FEV_1, existence of chronic rhinosinusitis and living in particular regions.

Conclusion: The picture of this registry showed a dominancy of middle-aged obese women with moderate-to-severe asthma. We also determined particular strategic targets such as low educational level, severe asthma attacks, low FEV_1, and chronic rhinosinusitis to decrease uncontrolled asthma in our country. Moreover, some regional strategies may also be needed as uncontrolled asthma is higher in certain regions. We believe that these data will guide authorities to reestablish national asthma programs to improve asthma service delivery.

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Asthma; severe asthma; asthma control; ACT; uncontrolled asthma; allergic asthma; eosinophilic asthma; N-ERD; ACO

Introduction

Asthma is one of the most common chronic diseases, affecting as many as 262 million people worldwide (1,2). It is a cause of substantial burden of disease, including both premature death and reduced quality of life, in people of all ages, in all parts of the world (1,2). In Turkey, asthma has been estimated to affect around 3 million people and is the second most common reason for outpatient admission to hospitals among chronic respiratory diseases.

Patient-specific factors such as geographic location and environmental risk factors, as well as genotypes and phenotypes, may all influence the burden of asthma. With this, some features of asthma may vary between countries and also among the regions of countries; each country and each region may have its own characteristic features of asthma.

Some countries have developed national asthma registries to collect information on asthma and risk factors (1,3–5). These registries are important to provide valuable country-specific information about the disease so that each country can determine its own strategies to decrease asthma costs and burden accordingly. In this regard, national data on asthma demographics, comorbidities, the severity of patients, medications, and the factors associated with uncontrolled asthma seem to be necessary. Currently, there is no adult asthma registry program in Turkey to investigate risk factors, medication use, and treatment outcomes.

Although both global and national guidelines are prominent in the treatment and follow-up of patients with asthma, it is increasingly important to combine these guidelines with real-world data for individualized medicine practices. For this reason, the Turkish Adult Asthma Registry (TAAR) study, the first largest adult asthma registry in Turkey, was designed to produce a multicenter real-world study that would provide country-specific scientific evidence for adult patients with asthma. In the TAAR study, we aimed to take a snapshot of patients with asthma in Turkey by documenting the risk factors, demographic parameters, and clinical characteristics of adult patients with asthma. Another important aim was to be able to assign the unmet needs and niche areas of intervention in Turkey.

We believe that these data will guide authorities to reestablish national asthma programs to improve asthma service delivery including standard patient management, engaging with their professional societies, civil society, asthma patient organizations, and health services, and consequently tracking improvements in diagnosis and reductions in emergency visits and hospital admissions.

Material and methods

Study design

This study presents the data of a national registry on adult asthma in which patient entries were performed between March 15th, 2018, and March 15th, 2022, in Turkey.

After establishing the idea of a national asthma registry for adult patients, first, an invitation letter was e-mailed to all members of the email group of the Asthma Working Group of the Turkish Thoracic Society (TTS) (Figure 1). The requirement for inclusion as a study center was being a secondary or tertiary hospital that provided regular health care services for adult patients with asthma. A total of 36 centers participated in the registry (Supplemental Figure 1). The study was approved by Ankara University Ethics Committee (Approval no: 16-101 I-I7/2017).

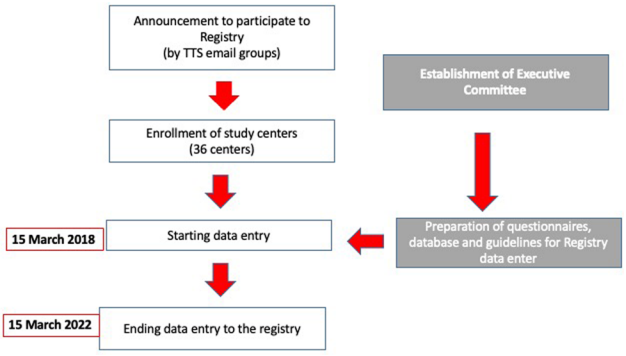


Figure 1. Study design.

Registry

On the initiation of the study, an Executive Committee for the Registry was established (Figure 1). This group established a questionnaire to determine several aspects of asthma such as demographics, and characteristics (see below for details).

A web-based application, a modular medical data management and analysis system called "Epikriz" was used to record medical data (www.epikriz.com). Written instructions on how to register the patients on the database as well as a video recording were shared with all investigators by email. Confidentiality was strictly maintained by all partners and each center agreed to the confidentiality of the database. Data entries started on March 15th, 2018, and lasted till March 15th, 2022.

The main outcome of this registry was writing a frame manuscript on asthma demographics and characteristics in Turkey. However, considering the aim of establishing this database, we also wanted to get more detailed and analyzed data to obtain more specific data to develop strategies for dealing with asthma in our country. In this manuscript, adult asthma in Turkey will be discussed in general to put the perspective of the disease in our country. More details will be discussed in separate manuscripts as already stated above.

Study patients

The patients who were diagnosed as having asthma and had regular visits due to asthma to the study centers between March 15th, 2018, and March 15th, 2022, were included in the study. Asthma diagnosis was based on both Global Initiative for Asthma (GINA) (6) and national asthma guidelines (7).

Study parameters and definitions

All study variables and outcomes were defined in a standardized way based on guidelines by the study executive committee and written instructions about this information were emailed to all study investigators before data enrollment to the registry. Non-standardized data were neither entered nor accepted. Patient records were used as the data source. Demographic features included age; sex; living region; education; smoking history; body mass index (BMI); disease characteristics

such as a family history of asthma, disease duration, age at onset of asthma; comorbidities; asthma control level; and phenotypes. Laboratory evaluations included atopy status, pulmonary function tests (spirometry, reversibility testing, and nonspecific bronchial provocation tests with methacholine), peripheral blood eosinophil count, radiologic examinations [chest X-ray, chest computed tomography (CT) scans, and paranasal sinus CT scans if necessary].

Pulmonary function tests

Spirometric measurements [forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), and maximum mid-expiratory flow (MMF)] were performed using a spirometry device (ZAN 100, Germany) and evaluated according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (8). The best of three attempts within a 5% range was recorded.

Assessment of atopy

Atopy was defined as a positive result in a skin prick test (SPT) or serum-specific immunoglobulin (Ig)-E. SPTs were performed using a standardized panel including house dust mites (HDM) (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae)*, grass, tree, weed pollen, cat, dog, cockroach, *Aspergillus*, *Alternaria*, and *Cladosporium* antigens (ALK/Allergo Pharma/Germany). A wheal diameter of 3 mm or larger than the negative control was considered positive.

Asthma control

Asthma control was defined in two ways. The first was asthma symptom control in the last 4 wk, which was assessed through asthma control tests (ACT) (6,7). ACTs were considered well controlled if the score was ≥20, not well controlled if the score was between 6–19 and very poorly controlled if the score was less than 16. For multivariate factor analysis, comparison of controlled (ACT ≥ 20) and uncontrolled (ACT ≤ 19) asthma was performed. Secondly, asthma control in the last year was assessed using the number of asthma attacks requiring at least 3 days of oral corticosteroids (OCS) and the number of hospitalizations due to asthma. The number of admission to emergency care, the number of admissions to the intensive care unit, scheduled physician visits due to asthma, and unscheduled physician visits due to asthma were also recorded.

Comorbidities

Both allergic and systemic comorbidities diagnosed by a physician were recorded. Allergic comorbidities were allergic rhinitis, drug and food allergy, urticaria, angioedema, anaphylaxis, bee venom allergy, and latex allergy. Systemic comorbidities were hypertension, diabetes mellitus, thyroid disease failure, and others.

Assessment of phenotypes (6,7)

Eosinophilic asthma was defined as a peripheral blood eosinophil count of over 150 cells/μL at least in the last year or at the time of assessment. Patients with an eosinophil count of fewer than 150 cells/μL but were taking mepolizumab or regular OCS at the time of enrollment were also considered as having eosinophilic asthma. *Allergic asthma* was defined as a positive allergy test (skin prick, or specific IgE) compatible with clinical presentation. *Asthma COPD overlap* (ACO) was defined as a post-bronchodilator FEV_1/FVC level of less than 70% and the presence of clinical findings compatible with both diseases. *Obese asthma* was defined as a BMI over 30 kg/m^2 in the study patients. *Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD)* was defined as at least two documented positive reactions following the use of aspirin and/or other NSAIDs.

Assessment of severe asthma

Before making a diagnosis of severe asthma, all subjects were evaluated by their physicians in terms of the reasons for uncontrolled asthma (confirmation of diagnosis, correction of compliance and inhaler device techniques, treatment of comorbidities, environmental exposures) (6,7). After corrections of these factors, patients who still had uncontrolled asthma despite high-dose ICS/long-acting bronchodilator inhaler (LABA) treatment or only controlled with high-dose ICS/LABA or OCS and lose control after the dose was tapered were considered as having *severe asthma*. Patients who were on biologic treatments or regular OCS because of asthma were also considered as having *severe asthma*.

Statistical analysis

A total of 1825 patients with a diagnosis of asthma were calculated to be required with a 95% CI ($d = 0.01$) and the knowledge of the prevalence rate of asthma

being 5% in Turkey. No stratification was performed as the characteristics of the patients were regarded as similar.

Data were described using either frequency (percent) for categorical data or mean ± standard deviation (minimum-maximum) for metric variables. Student's t-test was used for the comparison of two independent groups. $p < 0.05$ was considered statistically significant. Multivariable logistic regression was used to define the risk factors (age, sex, education, living region, disease duration, smoking history, atopy, FEV_1, phenotypes, severe asthma, and severe asthma attacks in the last year, comorbidities, use of omalizumab and use of mepolizumab) for uncontrolled asthma. For the significant effect of risk factors, odds ratio with its 95% confidence interval was given. The entry and removal criteria used were p values of 0.10 for entry and p values of 0.20 for variable removal in logistic regression analysis.

Results

The patients

Demographics

The registry included a total of 2053 patients from 36 study centers in Turkey (Table 1). Most of the patients were living in the Marmara ($n = 779$, 40.8%) and Central Anatolia regions ($n = 513$, 26.9%). Female subjects dominated the group ($n = 1535$, 74.8%). The majority of the patients ($n = 795$, 41%) were housewives and had a primary school education level ($n = 766$, 39.9%). The majority of the patients were born ($n = 1136$; 58.7%) and had been living ($n = 1854$; 94.1%) in cities. Six hundred nineteen (32.2%) patients were obese. The minority of the patients ($n = 228$; 11.4%) were still active smokers. The onset of asthma was after the age of 18 years in the majority of the patients ($n = 1564$, 83.8%). The majority of the patients ($n = 1158$, 65.3%) were allergic, mostly allergic to HDMs ($n = 882$, 50.8%). Pollen and mold allergies were more prominent in patients living in the Aegean region ($n = 99$, 40.2% and $n = 48$; 19.7%, respectively) (Table 1) (Figure 2). Cockroach allergy was more common in East Anatolia ($n = 8$; 14.8%) and Mediterranean ($n = 8$; 16.7%) regions. In terms of regions, eosinophilia was most common in patients living in Southeastern Anatolia ($n = 36$; 62%).

Comorbidities

Chronic rhinosinusitis and gastroesophageal reflux were the most common systemic comorbidities [$n = 601$ (32.1%) and $n = 497$ (26.4%), respectively]. Concerning allergic comorbidities, allergic rhinitis ($n = 1254$, 64.2%) was the most common, followed by NSAID hypersensitivity ($n = 227$, 12.2%) (Table 2). Concerning regions, chronic rhinosinusitis without nasal polyps were higher in patients living in Central Anatolia ($n = 193$; 38.7%), Marmara ($n = 247$; 32.2%), and Southeastern Anatolia ($n = 22$, 37.9%) regions. Allergic rhinitis was more common in patients living in the Marmara ($n = 610$; 78.8%) and Aegean ($n = 179$; 68.1%) regions, whereas N-ERD was more frequent in those living in the Central Anatolia ($n = 82$; 16.1%) and Southeastern Anatolia ($n = 13$, 23.2%) regions.

Asthma phenotypes. The majority of the patients had allergic ($n = 1158$, 65.4%) and eosinophilic asthma ($n = 1174$, 57.2%). N-ERD and ACO existed in 12.1% ($n = 249$) of patients and 3.7% ($n = 76$) of patients, respectively (Figure 3). Six hundred nineteen (32.2%) of the patients had obese asthma. Most of the allergic patients were living in the Aegean ($n = 182$; 70.2%), Marmara ($n = 544$; 75.4%), and Black Sea ($n = 50$; 72.4%) regions (Supplemental Figure 2).

Treatment and underlying severity of asthma. The majority of the patients were using ICS/LABA combinations ($n = 1811$, 88%) (Table 3). The majority of the patients were on GINA step 3–5 treatments [$n = 443$ (25.6%), $n = 388$ (22.4%), and $n = 694$ (40.1%), respectively] (Supplemental Figure 3).

Severe asthma. Severe asthma existed in 670 (32.6%) patients (mean age: 50.2 ± 0.48 years), the majority of whom were female ($n = 498$, 74.3%). Two hundred forty patients (37.8%) were obese and had allergic and eosinophilic phenotypes (Figure 3). Among the severe asthmatics, 471 (70.2%) and 137 (20.4%) patients were on omalizumab and mepolizumab, respectively, and 38 (2.2%) patients were on aspirin treatment after aspirin desensitization (ATAD).

Asthma control. Concerning symptom control in the last 4 wk, asthma was controlled in the majority of the patients ($n = 981$, 59%) based on ACTs (Table 4). The majority of the patients had no severe asthma attacks in the last year ($n = 1329$, 75.5%), and no hospitalizations due to asthma ($n = 1572$; 91.3%) (Table 4). Poorly controlled asthma (ACT between 5–15) was more common in patients living in the Southeastern ($n = 22$, 43.1%) and East Anatolia ($n = 6$, 42.9%) regions. A similar trend was also observed in the rate of patients with ≥2 severe asthma attacks in the last

Table 1. Demographics and disease characteristics of the study group ($n = 2053$).

Variable	Overall	Mediterranean	Eastern Anatolia	Aegean	Central Anatolia	Black Sea	Marmara	Southeastern Anatolia	p
Sex (Female)	1535 (74.82)	106 (72.6)	24 (72.7)	215 (72.1)	393 (76.6)	68 (85)	585 (75.1)	41 (70.7)	NS
Age (year)*	46.68 ± 14.76 (18–100)	50.21 ± 14.02 (18–82)	48.67 ± 15.55 (23–100)	51.01 ± 13.72 (18–80)	45.65 ± 15.28 (18–83)	49.54 ± 15.01 (18–78)	45.09 ± 14.73 (18–87)	41.72 ± 11.54 (20–61)	<0.001
Education									<0.001
No school, no literate	83 (4.3)	10 (12)	7 (21.9)	14 (4.8)	11 (2.2)	9 (12.2)	23 (3)	7 (12.3)	
No school, literate	30 (1.6)	2 (2.4)	–	6 (2.1)	4 (0.8)	–	14 (1.8)	1 (1.8)	
Primary school	766 (39.9)	25 (30.1)	15 (46.9)	131 (45)	195 (38.7)	31 (41.9)	302 (39.6)	21 (36.8)	
High School	451 (23.5)	21 (25.3)	3 (9.4)	68 (23.4)	114 (22.6)	16 (21.6)	184 (24.1)	13 (22.8)	
Collage/University	588 (30.7)	25 (30.1)	7 (21.9)	72 (24.7)	180 (35.7)	18 (24.3)	239 (31.4)	15 (26.3)	
Occupation									<0.001
Government officer	279 (14.4)	12 (13.8)	5 (15.2)	27 (9.3)	81 (16.1)	9 (11.7)	108 (14)	14 (24.1)	
Self-employment	256 (13.2)	12 (13.8)	5 (15.2)	40 (13.8)	80 (15.9)	5 (6.5)	91 (11.8)	5 (8.6)	
Housewife	795 (41.0)	33 (37.9)	20 (60.6)	114 (39.3)	205 (40.8)	40 (51.9)	307 (39.9)	29 (50)	
Student	147 (7.6)	5 (5.7)	–	8 (2.8)	54 (10.7)	4 (5.2)	70 (9.1)	–	
Retired	189 (9.7)	10 (11.5)	–	52 (17.9)	43 (8.5)	6 (7.8)	64 (8.3)	1 (1.7)	
Not working	93 (4.8)	8 (9.2)	3 (9.1)	14 (4.8)	26 (5.2)	4 (5.2)	30 (3.9)	3 (5.2)	
Other	181 (9.3)	7 (8.0)	–	35 (12.1)	14 (2.8)	9 (11.7)	99 (12.9)	6 (10.3)	
Borning place									0.011
Urban	1136 (58.7)	54 (50)	15 (45.5)	170 (57.6)	309 (64.2)	38 (48.7)	451 (58.6)	38 (66.7)	
Rural	800 (41.3)	54 (50)	18 (54.5)	125 (42.4)	172 (35.8)	40 (51.3)	318 (41.4)	19 (33.3)	
Living place									<0.001
Urban	1854 (94.1)	99 (90)	25 (75.8)	268 (90.8)	499 (97.5)	60 (75.5)	753 (97.7)	48 (84.2)	
Rural	117 (5.9)	11 (10)	8 (24.2)	27 (9.2)	13 (2.5)	19 (24.1)	18 (2.3)	9 (15.8)	
Body Mass Index									0.021
≤18.49 (Lean)	38 (2.0)	2 (1.5)	1 (3.1)	5 (1.7)	12 (2.6)	–	17 (2.3)	–	
18.50-24.99 (Normal weight)	569 (29.7)	44 (32.1)	7 (21.9)	61 (21)	144 (30.9)	13 (17.3)	245 (32.5)	19 (33.9)	
25-29.99 (Overweight)	693 (36.1)	44 (32.1)	16 (50)	126 (43.4)	160 (34.3)	24 (32)	264 (35)	19 (33.9)	
≥30 (Obese)	619 (32.2)	47 (34.3)	8 (24.9)	98 (33.8)	150 (32.2)	38 (50.7)	229 (30.3)	18 (32.2)	
Smoking history									0.003
Never smoker	1364 (68.1)	83 (61)	24 (72.7)	180 (60.8)	347 (69.3)	57 (71.2)	551 (71.2)	40 (69)	
Currently smoker	228 (11.4)	28 (20.6)	6 (18.2)	39 (13.2)	57 (11.4)	10 (12.5)	71 (9.2)	4 (6.9)	
Past smoker	410 (20.5)	25 (18.4)	3 (9.1)	77 (26)	97 (19.4)	13 (16.2)	152 (19.6)	14 (24.1)	
Amount of smoking (packs-year)*	14.0 ± 22.2	24.2 ± 58.2	4.2 ± 3.8	16.4 ± 15.4	13.7 ± 11.6	15.4 ± 14	11.1 ± 17.8	12.3 ± 8.1	0.013
Age of disease onset									0.003
<12 years	157 (8.4)	5 (4.7)	–	14 (5.2)	38 (7.9)	8 (11)	77 (10.5)	8 (14.3)	
>12-18 years	146 (7.8)	3 (2.8)	4 (12.9)	19 (7)	40 (8.4)	8 (11)	57 (7.8)	7 (12.5)	
>18-39 years	901 (48.3)	50 (46.7)	13 (41.9)	122 (45)	244 (50.9)	28 (38.4)	359 (49.1)	30 (53.6)	
40-64 years	630 (33.7)	44 (41.1)	14 (45.2)	112 (41.3)	151 (31.5)	27 (37)	225 (30.8)	11 (19.6)	
>65 years	33 (1.8)	5 (4.7)	–	4 (1.5)	6 (1.3)	2 (2.7)	13 (1.8)	–	
Disease duration (year)*	12.9 ± 10.34 (0.5-70)	11.9 ± 10.6 (0.5-40)	11.5 ± 9.9 (0.5-40)	15.2 ± 11.5 (1–70)	12.6 ± 9.7 (0.5-50)	15.4 ± 11.8 (1–58)	12.7 ± 10.1 (0.5-55)	14.5 ± 11.2 (1–40)	0.004
Atopy rate	1158 (65.3)	42 (65.6)	13 (59.1)	182 (70.3)	227 (47.8)	50 (72.5)	544 (75.5)	35 (62.5)	<0.001
House dust mites	882 (50.8)	31 (53.4)	10 (45.5)	119 (47)	104 (22.6)	40 (58.8)	507 (70.5)	29 (51.8)	<0.001
Cockroaches	144 (8.6)	8 (16.7)	–	24 (10)	22 (4.8)	8 (12.5)	66 (9.4)	8 (14.8)	<0.001
Molds	166 (9.9)	4 (8.7)	2 (9.5)	48 (19.7)	18 (3.9)	8 (12.3)	68 (9.7)	6 (11.1)	<0.001
Pollens	474 (27.8)	13 (25)	6 (27.3)	99 (40.2)	96 (20.9)	18 (27.7)	202 (28.6)	17 (30.9)	0.001
Cat dander	167 (9.9)	7 (14.6)	2 (9.1)	26 (10.7)	37 (8.1)	6 (9.2)	73 (10.4)	5 (9.3)	<0.001
Dog dander	118 (7)	2 (4.4)	2 (9.1)	22 (9.1)	19 (4.2)	7 (10.8)	58 (8.3)	2 (3.6)	<0.001
Food	30 (.8)	2 (4.4)	–	6 (2.5)	6 (1.3)	2 (3.1)	13 (1.9)	1 (1.8)	<0.001

FEV_1 (L)*	2.31 ± 0.84 (0.35-5.81)	2.13 ± 0.81 (0.51-4.30)	2.18 ± 0.77 (0.73-3.42)	2.16 ± 0.84 (0.41-5.11)	2.36 ± 0.79 (0.59-5.12)	2.14 ± 0.83 (0.68-4.76)	2.38 ± 0.88 (0.56-5.81)	2.23 ± 0.80 (0.73-3.92)	0.001
FEV_1 (%)*	82.1 ± 20.3 (13-147)	76.1 ± 18.7 (32-126)	77.4 ± 20.6 (48-119)	80.2 ± 21.1 (22-133)	86 ± 18.5 (34-135)	81.7 ± 24.8 (25-147)	81.9 ± 20.1 (27-143)	72.9 ± 21.7 (28-114)	<0.001
FEV_1/FVC (%)*	76.09 ± 11.7 (22-131)	74.1 ± 12.3 (22–103)	72.3 ± 12.8 (48-112)	74.6 ± 10.4 (44–105)	76.8 ± 9.3 (43-108)	77.9 ± 12.2 (41–100)	76.5 ± 13.1 (38-131)	75.3 ± 11.8 (47–95)	0.021
Eosinophil count (cell/μL)*	417.23 ± 459.62 (0-4800)	348.17 ± 305.52 (0-1690)	363 ± 414.02 (10-1800)	383.89 ± 441.94 (0-3790)	408.72 ± 443.23 (0-3140)	378.69 ± 370.45 (0-1630)	426.20 ± 490.74 (0-4800)	651.50 ± 538.64 (40-2400)	0.002
Eosinophil (%)*	5.11 ± 5.90 (0-112)	4.15 ± 3.29 (0-18.3)	3.72 ± 3.76 (0.10-15.3)	4.49 ± 4.60 (0-30)	5.24 ± 7.04 (0-112)	6.38 ± 12.72 (0-87)	5.34 ± 5.22 (0-37.1)	6.67 ± 4.63 (0.10-17.2)	0.027
Blood eosinophil level (cell/μL)									0.022
<150	462 (28.6)	36 (29)	9 (42.9)	84 (32.8)	119 (27)	15 (27.8)	165 (30.1)	13 (22.4)	
150-300	434 (26.9)	33 (26.6)	3 (14.3)	64 (25)	126 (28.6)	17 (31.5)	144 (26.2)	9 (15.5)	
>300-1000	587 (36.3)	49 (39.5)	8 (38.1)	91 (35.5)	162 (36.7)	19 (35.2)	195 (35.5)	22 (37.9)	
>1000	132 (8.2)	6 (4.8)	1 (4.8)	17 (6.6)	34 (7.7)	3 (5.6)	45 (8.2)	14 (24.1)	

Note. For the variables with *, [Mean ± SD (min-max)] was used as descriptive statistics, otherwise frequency (percent).

year in the same regions ($n = 10$; 45.5% in Southeastern Anatolia and $n = 24$; 42.1% in Southeastern Anatolia regions) (Table 4).

Based on the ACTs, uncontrolled asthma was associated with low educational level, having severe asthma attacks in the last year, disease duration, low FEV_1 values (<80%), having chronic rhinosinusitis without nasal polyps and living in particular geographic regions (Table 5). In terms of regions, most of the poorly controlled patients were living in the Southeastern and East Anatolia regions (Table 4). Uncontrolled asthma was higher in patients with $FEV_1 \leq 80\%$ in all regions but Aegean region (Supplemental Table 1).

Discussion

TAAR is a national standardized database study that allows for analyzing real-life asthma patients with a good representation of all geographic regions for the first time in our country. This study provided a picture of patients with asthma who were followed up in 36 secondary and tertiary care clinics. A significant female dominance was noticed in all regions. The majority of the patients were overweight or obese. Allergic and eosinophilic asthma were the most common phenotypes. Concerning regional characteristics, HDM allergy was a significant problem in the Northern coastal areas of Turkey, whereas pollen allergy was more prevalent in the Aegean region. Majority of the cases were on step 3–5 treatment. Importantly, asthma was well controlled in 59% of patients. The particular factors related to uncontrolled asthma were lower educational status, having lower FEV_1, severe asthma attacks in the last year, chronic rhinosinusitis without nasal polyps and living in particular geographic regions in the country. Severe asthma was diagnosed in around 32% of the patients.

Regarding demographics, as in many previous multicenter studies on asthma in our country and around the world, asthma was predominant in female subjects in our group. The incidence and severity of asthma were reported to increase in women (9). Female sex hormones have been shown to increase type 2-mediated airway inflammation (9–11). In our study, the fact that the majority of women were housewives and they were frequently exposed to cleaning chemicals at home, may cause inflammation in the respiratory tract, concordant with previous studies (8).

Recent studies focused more on the assessment of phenotypes of asthma to provide individualized specific treatments such as biologics (12–15). In our group, allergic and eosinophilic asthma phenotypes

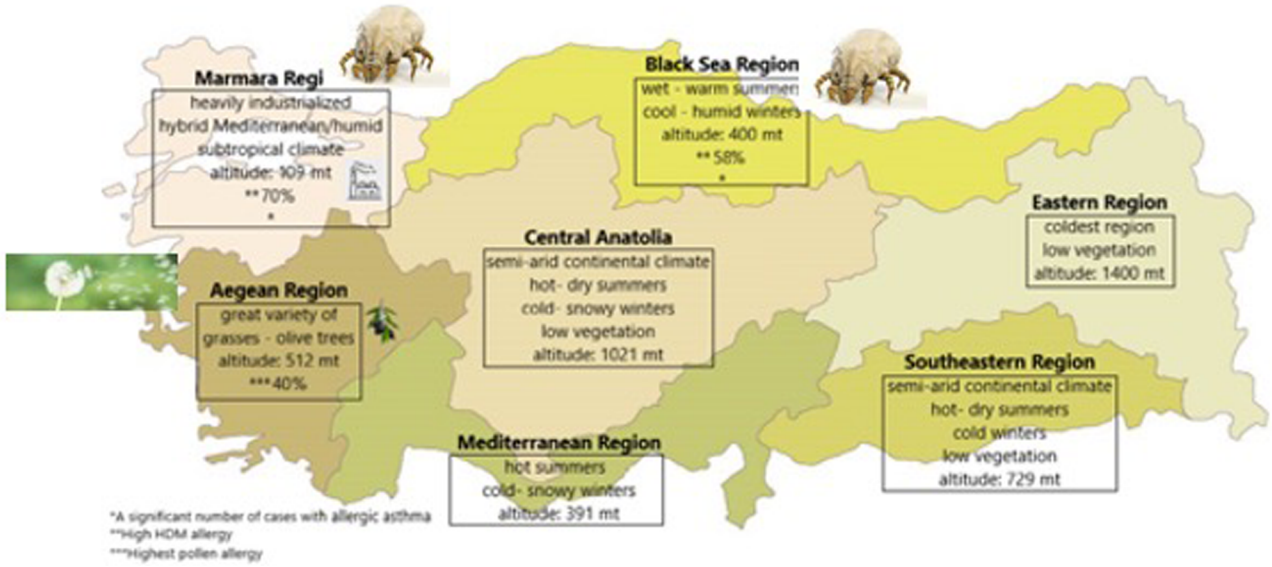


Figure 2. Distribution of allergen sensitization in the study group based on the characteristics of the regions.

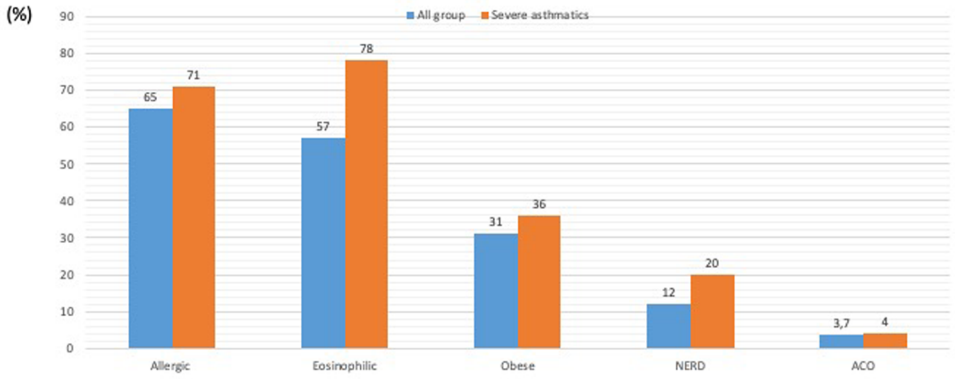
Table 2. Comorbidities in the study group.

Variables	Overall	Mediterranean	Eastern Anatolia	Aegean	Central Anatolia	Black Sea	Marmara	Southeastern Anatolia	p
Systemic comorbidities									
Chronic rhinosinusitis without nasal polyps	601 (32.1%)	29 (27.6%)	4 (12.9%)	42 (21.3%)	193 (38.7%)	15 (20%)	247 (32.2%)	22 (37.9%)	<0.001
Gastro-oesophageal reflux disease	497 (26.4%)	39 (37.5%)	5 (15.6%)	56 (28.1%)	102 (20.3%)	15 (19.2%)	227 (29.4%)	16 (27.6%)	<0.001
Chronic rhinosinusitis with nasal polyps	378 (19.9%)	18 (17.3%)	7 (21.9%)	51 (23.7%)	122 (24.2%)	15 (19.5%)	118 (15.3%)	16 (27.6%)	0.002
Cardiac diseases	358 (18.8%)	31 (27.9%)	1 (3.1%)	71 (32.3%)	77 (15.3%)	21 (26.9%)	122 (15.9%)	9 (15.5%)	<0.001
Thyroid disorders	286 (15.2%)	17 (15.9%)	4 (12.5%)	47 (23.4%)	82 (16.4%)	9 (11.8%)	106 (13.8%)	5 (8.8%)	0.024
Diabetes mellitus	255 (13.6%)	20 (18.7%)	4 (12.5%)	51 (25.1%)	55 (11%)	9 (11.7%)	93 (12.2%)	7 (12.1%)	<0.001
Psychiatric diseases	142 (7.6%)	10 (9.7%)	6 (18.8%)	18 (9.2%)	49 (9.8%)	7 (9%)	38 (4.9%)	3 (5.2%)	0.004
Migraine	115 (6.2%)	10 (9.8%)	3 (9.7%)	9 (4.7%)	19 (3.8%)	1 (1.3%)	51 (6.6%)	8 (13.8%)	0.005
Obstructive sleep apnea syndrome (OSAS)	70 (3.8%)	5 (5%)	3 (9.4%)	6 (3.2%)	15 (3%)	2 (2.6%)	32 (4.2%)	–	NS
Bronchiectasis	39 (2.1%)	1 (1%)	–	5 (2.7%)	10 (2%)	3 (4%)	16 (2.1%)	1 (1.7%)	NS
Allergic diseases and disorders									
Allergic rhinitis	1254 (64.2%)	40 (39.2%)	11 (34.4%)	179 (68.1%)	265 (52.6%)	44 (56.4%)	610 (78.8%)	32 (56.1%)	<0.001
Non-steroidal anti-inflammatory drug hypersensitivity	227 (12.2%)	5 (5.1%)	3 (9.4%)	15 (7.9%)	82 (16.1%)	7 (9.1%)	86 (11.2%)	13 (23.2%)	0.001
Urticaria/angioedema	161 (8.6%)	11 (11.2%)	3 (9.4%)	12 (6.1%)	55 (10.9%)	5 (6.4%)	60 (7.8%)	2 (3.6%)	NS
Atopic dermatitis	82 (4.4%)	3 (3.1%)	1 (3.1%)	3 (1.6%)	19 (3.8%)	8 (10.3%)	41 (5.3%)	1 (1.8%)	0.038
Beta-lactam allergy	75 (4.1%)	1 (1%)	1 (3.1%)	10 (5.3%)	18 (3.6%)	2 (2.6%)	36 (4.7%)	4 (7.1%)	NS
Food allergy	74 (4.0%)	8 (8.2%)	1 (3.1%)	7 (3.7%)	21 (4.2%)	3 (3.9%)	30 (3.9%)	–	NS
Venom allergy	52 (2.8%)	4 (4.2%)	2 (6.2%)	6 (3.2%)	24 (4.8%)	5 (6.5%)	11 (1.4%)	–	0.006
Contact dermatitis	23 (2.2%)	2 (3.9%)	2 (7.7%)	2 (20%)	3 (1.1%)	1 (1.7%)	12 (2.4%)	–	0.001
Anaphylaxis	18 (1.7%)	–	1 (3.8%)	–	3 (1.1%)	2 (3.5%)	12 (2.4%)	–	NS
Latex allergy	23 (1.2%)	3 (3.1%)	2 (6.2%)	4 (2.1%)	5 (1%)	1 (1.3%)	7 (0.9%)	–	NS

Note. Cells represent frequency (percent).

were the most common. Therefore, evaluations of allergy with clinical history and allergy testing, as well as assessment of eosinophil counts in asthma, also seem to be particularly important in our country. However, the rate of allergic asthma in our group was found to be higher than in a previous study (16) performed 10 years ago in our country. In that study, allergic asthmatics constituted 36.5% of the patients, lower than our result of 65%. Owing to the increased number of courses on allergy in the pulmonology area in our country in recent years, performing more allergy tests in our study centers could have led to better identification of patients with allergic phenotypes. Moreover, many of the study centers also had allergy departments.

On the other hand, ACO was less frequently reported in our series which requires a special look at the symptoms and correlations with laboratory data (17,18). Suggesting this, in our registry, only 157 patients had post bronchodilatory FEV_1/FVC results,



Abbreviations: N-ERD: Nonsteroidal antiinflammatory drugs exacerbated respiratory disease, ACO: Asthma COPD overlap

Figure 3. Distribution of asthma phenotypes in all groups and severe asthma.

Table 3. Use of medications by the patients in all study groups.

Medications n (%)	Overall	Mediterranean	Eastern Anatolia	Aegean	Central Anatolia	Black Sea	Marmara	Southeastern Anatolia	p
ICS alone n (%)	187 (11.3%)	12 (9,6%)	4 (12,9%)	22 (7,8%)	83 (16,7%)	7 (9,2%)	28 (3,8%)	7 (12,1%)	<0,001
ICS/LABA fixed combinations n (%)	1811 (88%)								
Fluticasone/Salmeterol	422 (25.5%)	21(16,8%)	10 (32,3%)	84 (29,7%)	7 (14,9%)	15 (19,7%)	174 (23,8%)	14 (24,1%)	<0,001
Budesonide/Formeterol	701 (42.4%)	48 (38,4%)	11 (35,5%)	94 (33,2%)	189 (38%)	30 (39,5%)	229 (31,4%)	24 (41,4%)	0,177
BDP/Formoterol	535 (32.3%)	31 (24,8%)	8 (25,8%)	39 13,8%)	147 (29,6%)	17 (22,4%)	227 (31,1%)	21 (36,2%)	<0,001
Fluticasone/Vilanterol	153 (9.2%)	11 (8,8%)	1 (3,1%)	24 (8,5%)	23 (4,6%)	4 (5,3%)	80 (11%)	4 (6,9%)	0,006
Anti-leukotriene receptor antagonist n (%)	1268 (61.2%)	35(28%)	10 (32,3%)	119 (42%)	190 (38,2%)	26 (34,2%)	194 (26,6%)	21 (36,2%)	<0,001
Long-acting muscarinic agent n (%)	220 (13.3%)	6 (4,8%)	3 (9,7%)	31 (11%)	44 (8,9%)	6 (7,9%)	112 (15,3%)	17 (29,3%)	<0,001
Omalizumab n (%)	471 (28%)	15 (15,5%)	3 (15%)	88 (37,9%)	38 (8,4%)	10 (20,4%)	257 (35,4%)	25 (48,1%)	<0,001
Mepolizumab n (%)	137 (8.2%)	1 (1,1%)	3 (15%)	18 (9,3%)	30 (6,7%)	5 (10,2%)	58 (8%)	13 (26,5%)	<0,001

which are the diagnostic hallmark for ACO in the presence of compatible symptoms. Thus, in accordance with previous studies, we believe that ACO is underreported in our series.

Another endophenotype, N-ERD, also requires a carefully assessed clinical history, as well as a specific provocation test for diagnosis (19–22), which may not be available in many centers. Suggesting this, only 58 were diagnosed based on a positive aspirin provocation test whereas 160 patients were diagnosed in the presence of strong clinical history. Therefore, we may assume that N-ERD is underreported as well. As another important phenotype, in our cohort, one-third of patients were obese. The obesity prevalence observed in this study is in line with previous data from our country (16,23). Considering the relationship between obesity and poor outcomes of asthma, obesity should be kept in mind as an important treatable trait in asthma management.

Our results on the allergic profile of the patients provided some outstanding regional data. In this sense, the discrepancy in vegetation and climate seems to have an impact on allergic sensitization. In our group, the patients living particularly in the Marmara, Black Sea, and Aegean regions had more allergic asthma in comparison with those living in other regions. The Marmara and Black Sea regions are located on the north coast of the country and are good hosts for HDM growth due to their high humidity and relatively more temperate climates in comparison to other coastal regions of the Aegean and Mediterranean regions, which have high humidity/temperatures, killing HDMs but accommodating for patients with pollen allergy. Previous studies showed that HDM decreased in number with altitude (24,25). Compared with coastal regions, at higher altitudes (900–1000 m), the number of mites decreases by 90% (26). Another explanation for the higher rate of HDM sensitization in coastal regions of Turkey (Marmara and Black Sea) may be the fact that the altitude of most cities in Eastern and Central Anatolia is higher than 900 meters (Figure 2) (26,27). Accordingly, physicians who follow up on patients with asthma in these particular regions should be aware of regional allergen load and patients should be closely followed up for the effect of allergen

Table 4. Asthma Control: Assessment of 4 wk of asthma symptom control and asthma attacks/hospitalizations in the last year.

Last year									
Variable (Number of asthma episodes)	Overall	Mediterranean ($n=146$)	Eastern Anatolia ($n=33$)	Aegean ($n=298$)	Central Anatolia ($n=513$)	Black Sea ($n=80$)	Marmara ($n=779$)	Southeastern Anatolia ($n=58$)	p
Severe asthma attacks requiring at least 3 days of OCS in the last year									
0	1329 (75.5)	78 (75)	8 (36.4)	218 (78.7)	315 (77.6)	47 (71.2)	567 (79.4)	24 (42.1)	<0.001
1	188 (10.7)	14 (13.5)	4 (18.2)	29 (10.5)	46 (11.3)	8 (12.1)	55 (7.7)	9 (15.8)	
≥2	243 (13.8)	12 (11.5)	10 (45.5)	30 (10.8)	45 (11.1)	11 (16.7)	92 (12.9)	24 (42.1)	
Admission to emergency care service due to asthma in the last year									
0	1285 (72.7)	75 (68.2)	9 (40.9)	213 (76.9)	327 (79.8)	36 (55.4)	528 (74.4)	23 (42.6)	<0.001
1	171 (9.7)	15 (13.6)	2 (9.1)	22 (7.9)	45 (11)	7 (10.8)	58 (8.2)	4 (7.4)	
≥2	311 (17.6)	20 (18.2)	11 (50)	42 (15.2)	38 (9.3)	22 (33.8)	124 (17.5)	27 (50)	
Hospitalization due to asthma in the last year									
0	1572 (91.3)	95 (89.6)	9 (45)	256 (92.4)	365 (92.4)	56 (87.5)	658 (94.7)	41 (77.4)	<0.001
1	102 (5.9)	9 (8.5)	5 (25)	16 (5.8)	22 (5.6)	3 (4.7)	27 (3.9)	9 (17)	
≥2	48 (2.8)	2 (1.9)	6 (30)	5 (1.8)	8 (2)	5 (7.8)	10 (1.4)	3 (5.7)	
Unscheduled visits due to asthma in the last year									
0	1244 (70.4)	75 (70.8)	5 (21.7)	239 (86.9)	321 (78.5)	36 (52.2)	464 (64.4)	31 (59.6)	<0.001
1	185 (10.5)	16 (15.1)	2 (8.7)	10 (3.6)	44 (10.8)	12 (17.4)	90 (12.5)	2 (3.8)	
≥2	338 (19.1)	15 (14.2)	16 (69.6)	26 (9.5)	44 (10.8)	21 (30.4)	166 (23.1)	19 (36.5)	
LAST 4 WEEKS									
Asthma Control Test									
Well controlled	981 (59.0)	41 (42.7)	6 (42.9)	193 (69.4)	288 (63.9)	36 (48.6)	339 (56.5)	22 (43.1)	<0.001
Not well controlled	343 (20.6)	26 (27.1)	2 (14.3)	42 (15.1)	87 (19.3)	16 (21.6)	141 (23.5)	7 (13.7)	
Very poorly controlled	339 (20.4)	29 (30.2)	6 (42.9)	43 (15.5)	76 (16.9)	22 (29.7)	120 (20)	22 (43.1)	

exposure and individualized precautions should be implemented.

Uncontrolled asthma has a significant effect on the burden of asthma and the causes are usually preventable (e.g. nonadherence to treatment, incorrect diagnosis, inadequate control of environmental factors) (28–30). In our group, regardless of the underlying severity, asthma symptoms were well controlled in 59% of the subjects, being higher than in previous studies (33.7%, 51%) from our country (31,32). We may assume that the improvement of asthma control level in our study can be explained, at least in part, by the effect of increased awareness and physicians following the recommendations of the national asthma guidelines. In fact, following the introduction of updated national asthma guidelines in our country, launch meetings have been held for implementation. Moreover, the increased number of available asthma medications in our country could be another reason. On the other hand, lower educational level, living in certain regions, severe asthma attacks in the last year, chronic rhinosinusitis and low FEV_1 (<80%) were found to be related to uncontrolled asthma in our series. Concerning the living area of the patients, asthma was poorly uncontrolled in the Southeastern and East Anatolia regions. Although it is difficult to make a specific comment on these data, this finding may reflect a problem in healthcare service for patients with asthma in both regions because we were unable to show any region-specific factors such as a specific allergen sensitization to contribute to this uncontrolled asthma. Therefore, special attention should be paid to why asthma is uncontrolled in these particular regions and what kind of strategies should be implemented.

Severe asthmatics, who constitute around 5–10% of asthmatics, require high healthcare use and have high medication needs, causing a burden on the patient and society (31–33). These patients are vulnerable to burdensome symptoms, limitations to their exercise capacity, and asthma attacks that can be frightening and potentially life-threatening. In our group, there were 670 (32.6%) patients with severe asthma, somewhat higher than in previous reports published from our country (16,31,32). Moreover and importantly, severe asthma was not found to be related to uncontrolled asthma, contrary to previous studies (31–33). In our recent asthma guidelines, severe asthma is recommended to be referred to centers with physicians experienced with severe asthma and followed up by these centers (6). As a general approach, the patients referred to the centers experienced with severe asthma are studied for phenotyping and appropriate biologics are introduced. In our country, omalizumab and mepolizumab are available and these medicines are introduced in indicated severe asthma

Table 5. Demographics and asthma characteristics based on asthma symptom control.

		Controlled			
	Variable	(ACT:20-25)	Uncontrolled (ACT:5-19)	**p****	OR (95% CI)
Sex	Male	254 (63.2)	148 (36.8)	NS	–
	Female	727 (57.7)	534 (42.3)		
Age (year)*		47.26 ± 14.65	45.95 ± 14.78	0.061	0.987 (0.974-1.001)
Education	Illiterate	32 (47.1)	36 (52.9)	0.002	REF
	≤8 years of education	379 (56.9)	287 (43.1)		2.016 (0.841-4.833)
	>8 years of education	528 (62)	323 (38)		1.929 (1.327-2.804)
Region	Mediterranean	41 (42.7)	55 (57.3)	<0.001	6.781 (1.680-27.370)
	Eastern Anatolia	6 (42.9)	8 (57.1)		4.838 (0.743-31.513)
	Aegean	193 (69.4)	85 (30.6)		REF
	Central Anatolia	288 (63.9)	163 (36.1)		2.730 (1.377-5.415)
	Black Sea	36 (48.6)	38 (51.4)		2.896 (0.856-9.797)
	Marmara	339 (56.5)	261 (43.5)		5.413 (2.838-10.322)
	Southeastern	22 (43.1)	29 (56.9)		2.989 (1.111-8.041)
Smoking history	Never smoker	683 (60.9)	439 (39.1)	NS	–
	Past smoker	196 (57.1)	147 (42.9)		
	Currently smoker	91 (52.3)	83 (47.7)		
Disease duration, year*		13.69 ± 10.39	12.51 ± 10.4	0.018	0.979 (0.962-0.996)
Atopy rates	Negative	330 (61.3)	208 (38.7)	NS	–
	Positive	574 (59.4)	392 (40.6)		
House dust mites	Negative	452 (59.9)	302 (40.1)	NS	–
	Positive	436 (60.1)	290 (39.9)		
Pollens	Negative	626 (59.3)	430 (40.7)	NS	–
	Positive	247 (62.5)	148 (37.5)		
Cockroach	Negative	687 (59.5)	467 (40.5)	NS	–
	Positive	80 (63.5)	46 (36.5)		
Mold	Negative	783 (61.2)	497 (38.8)	NS	–
	Positive	76 (55.5)	61 (44.5)		
Cat	Negative	734 (60.1)	488 (39.9)	NS	–
	Positive	81 (57.9)	59 (42.1)		
FEV_1 (%)	≥80%	549 (68)	258 (32)	<0.001	REF
	<80%	265 (46.7)	302 (53.3)		2.128 (1.500-3.018)
Allergic asthma	Negative	330 (61.3)	208 (38.7)	NS	–
	Positive	574 (59.4)	392 (40.6)		
Eosinophilic asthma	Negative	391 (59)	272 (41)	0.004	REF
	Positive	590 (59)	410 (41)		0.589 (0.410-0.845)
Obese asthma	Negative	670 (59.4)	458 (40.6)	NS	–
	Positive	311 (58.1)	224 (41.9)		
N-ERD	Negative	865 (59.5)	590 (40.5)	NS	–
	Positive	116 (55.8)	92 (44.2)		
Severe asthma	Negative	689 (62.6)	411 (37.4)	NS	–
	Positive	292 (51.9)	271 (48.1)		
Severe asthma attack in the last year	None	765 (69)	344 (31)	<0.001	REF
	At least one	119 (33.7)	234 (66.3)		5.819 (3.802-8.905)
Chronic rhinosinusitis without nasal polyps	Absent	655 (63.7)	373 (36.3)	0.011	REF
	Present	261 (53.7)	225 (46.3)		1.599 (1.115-2.293)
Chronic rhinosinusitis with nasal polyps	Absent	747 (61)	478 (39)	NS	–
	Present	183 (57.5)	135 (42.5)		
Psychiatric diseases	Absent	855 (60.9)	548 (39.1)	NS	–
	Present	61 (53)	54 (47)		
Allergic rhinitis	Absent	347 (62.6)	207 (37.4)	NS	–
	Present	603 (58.1)	434 (41.9)		
Patients receiving omalizumab	No	680 (62.7)	404 (37.3)	NS	–
	Yes	207 (53.4)	181 (46.6)		
Patients receiving mepolizumab	No	818 (62.2)	498 (37.8)	NS	–
	Yes	51 (45.5)	61 (54.5)		

Notes. *For the variables with *, the descriptive statistics is mean ± standard deviation, otherwise frequency (percent).
**Multivariate p.
OR: Odds ratio, CI: confidence interval, REF: reference category.

cases. Therefore, we may assume that the increased rate of severe asthma in our cohort as well as increased asthma control in our severe asthma cases can partly be explained by increased awareness of the physicians who deal with uncontrolled asthma, a good working referral system recommended by the national guideline, and the use of biologics in indicated cases. Moreover, eosinophilic asthma phenotype seems to be protective for uncontrolled asthma in our results as well. Concerning good responses to corticosteroid based inhaled treatments as well as mepolizumab in severe cases in eosinophilic asthma could partly explain this finding.

Having the most representative data on adult asthma in our country is one of the most important strengths of our study. To avoid bias, and the retrospective design of the study, all of the study variables and outcomes

were defined in a standardized way based on guidelines, and written instructions about this information were emailed to all study investigators before data enrollment to the registry. Moreover, many online meetings were held to present how to register data online. Non-standardized data were not entered, so this procedure might have caused some missing data in our analysis. Missing data were not included in the analysis. Moreover, the COVID-19 pandemic could also have caused some missing data because some patients could visit the hospitals. In this paper, we only provided a general overview of the asthma picture in our country. Many details are not given because these data will be discussed in separate manuscripts.

In conclusion, the results of this registry provided important details of the adult asthma picture in secondary and tertiary care clinics in Turkey. The figures dominating our picture are middle-aged overweight or obese women with moderate-to-severe asthma. Importantly, our database showed improved asthma control in comparison with previous years, highlighting the importance of implementing national asthma guidelines into clinical practice. However, patients with low educational level, low FEV_1 values, severe asthma attacks in the last year, chronic rhinosinusitis without nasal polyps and living in certain regions seem to require particular attention because these factors were found to be associated with uncontrolled asthma in our population. The reasons for higher rates of poorly controlled asthma in patients living in particular regions deserve to be defined carefully and regional strategies need to be taken. Concerning high sensitization rates, particularly to HDMs in certain coastal regions, early diagnosis and management of these patients are necessary to prevent disease progression because the majority of the patients with severe asthma were allergic. In terms of phenotyping, although allergic and eosinophilic phenotypes were well recognized and diagnosed by the physicians in our series, underreporting of ACO and N-ERD seems to have particular importance; therefore, much attention should be given to the diagnosis of both conditions and other phenotypes and centers dealing with patients with severe asthma should be equipped with necessary diagnostic tools. Importantly, regarding increased asthma control even in severe asthma cases, strategies to increase referral of these cases to experienced centers to receive individualized phenotyping treatments seem to be a good strategy to improve asthma control. We believe the results of this registry will guide authorities to reestablish national asthma programs to improve asthma service delivery.

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Authors' contribution statement

GEC and OA were the coordinator and vice coordinators of this study, respectively. They were responsible from conceptualized the scope of the project, general planning and task distribution, all correspondences, and following all works. GEC; OA AU, YN, FOE, ZCS, IK, AB; ED, SK, and MK form the questionnaire for the development of the registry based on the scope of the article. DG and YY performed statistics. The draft manuscript was written by GEC and OA and sent to all authors. Following the feedback and contribution of the authors, GEC, OA, AY, BD, AFK, FY, IB, IY, ED, AU, SKO, ZCS, YN, MK, SAY, TY, and GKB reviewed and combined the contributions from all authors and finalized the manuscript. After finalization, all authors approved the manuscript.

Declaration of interest

None of the authors declare conflicts of interest in relation to this work.

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