

## Asthma phenotypes in Turkey: a multicenter cross-sectional study in adult asthmatics; PHENOTURK study

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### Abstract

**Background and Aims:** To evaluate asthma phenotypes in patients with asthma from different regions of Turkey.

**Methods:** A total of 1400 adult asthmatic patients (mean (SD) age: 44.0 (13.9) years, 75% females) from 14 centers across Turkey were included in this study and a standard questionnaire was applied between the time period of February 2011–January 2012.

**Results:** The disease onset  $\geq 40$  years of age was higher percentage in obese vs. normal/overweight patients and nonallergic vs. allergic patients ( $P < 0.01$ ). The percentage of patients who had FEV1 values over 80% was higher in allergic than nonallergic and normal/overweight than obese patients ( $P < 0.01$ ). Uncontrolled asthmatics have more severe disease ( $P < 0.01$ ). There were more frequent hospital admissions in nonallergic and uncontrolled asthmatics ( $P < 0.01$ ). Chronic rhinosinusitis was the leading comorbid disorder in normal/overweight and allergic asthma, while gastroesophageal reflux disorder was more frequent in nonallergic and uncontrolled asthma ( $P < 0.01$ ). Asthma control rate was the highest (39.0%) in patients from Marmara region among all geographical regions ( $P < 0.05$ ).

**Conclusion:** In conclusion, our findings revealed existence of clinical/trigger related phenotypes based on BMI, allergic status, control level and geographical region with more frequent respiratory dysfunction and/or adverse health outcomes in uncontrolled, obese and nonallergic phenotypes.

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### Conflict of interest

The authors declare that they have no conflict of interest related to this study.

### Key words

allergy – asthma – control level – disease onset – obesity – phenotypes – severity

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### Authorship and contributorship

Fusun Yildiz is responsible for collection of data and writing of manuscript. Dilsad Mungan, Bilun Gemicioglu and A. Fuat Kalyoncu are responsible for editing of manuscript. Arzu Yorgancioglu, Berna Dursun, Ferda Oner Erkekol, Candan Ogus, Haluk Turktas, Gunhan Bogatekin, Fusun Topcu, Figen Deveci, Hasan Bayram and Meltem Tor are also responsible for the collection of data.

### Ethics

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the 'Declaration of Helsinki' and approved by the institutional ethics committee.

## Introduction

Asthma has been recognized as a heterogeneous disorder with a multifaceted phenotype in which complex interactions between environmental and genetic factors cause bronchial inflammation with variable, reversible airflow obstruction, airway hyper-responsiveness and airway inflammation that produces characteristic clinical symptoms (1–3). Considerable overlap among several clinical variants and phenotypes described in both genders and in all ethnic groups has been considered to make an accurate and comprehensive phenotyping in asthma quite challenging with difficulties to identify a particular phenotype and direct appropriate treatment strategies (3).

To date, many different clinical phenotypes of asthma have been described in the literature that can be classified into broad categories including phenotyping based on causation or trigger factor (atopy, aspirin, infection, occupation, exercise, obesity), differing pattern of airflow obstruction (Brittle asthma, irreversible/fixed airflow obstruction), disease severity (mild-moderate asthma, severe refractory asthma, corticosteroid-insensitive asthma), radiologic pattern (airway dilatation, bronchial wall thickening, air trapping and type of airway inflammation) and the nature of airway inflammation (eosinophilic, neutrophilic, combined/mixed inflammatory) (3, 4).

Although the diagnosis and phenotyping of asthma could be used to apply specifically directed therapies to specific phenotypes (3). We are lack of large-scale studies on characterizing the phenotype distribution of asthma in Turkey. Therefore, this study was designed to evaluate the distribution of clinical and trigger related asthma phenotypes for the first time in patients with asthma from different regions of Turkey.

## Materials and methods

### Study population

A total of 1400 adult asthmatic patients (mean (SD) age: 44.0 (13.9) years, 75% females) from 14 centers of different geographic locations across Turkey were included in this study and a standard questionnaire was applied between the time period of February 2011–January 2012.

Female or male outpatients aged  $\geq 18$  years, diagnosed with persistent asthma at least for the last six months according to the Global Initiative for Asthma (GINA) criteria (5), followed-up for at least 6 months prior to the study were included. Presence of confirmed or suspected pregnancy, breastfeeding, comorbid Chronic Obstructive Pulmonary Disease (COPD),

hospitalization because of symptomatic respiratory infection of asthma within the last eight weeks, chronic diseases that likely affect the prognosis negatively (e.g. carcinoma), chronic alcohol consumption and substance abuse were the exclusion criteria.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the 'Declaration of Helsinki' and approved by the institutional ethics committee.

### Data collection

Following the patients' eligibility check in terms of inclusion/exclusion criteria, data on patient demographics, smoking status, body mass index (BMI), asthma age, asthma severity, allergic status, comorbid disorders, asthma triggers and asthma control were recorded in each patient to determine asthma phenotypes in the overall population as well as in relation to gender, BMI (normal/overweight vs. obese patients), allergic status (allergic vs. nonallergic patients), disease control (controlled vs. partially controlled and uncontrolled asthma) and geographical region at the single enrollment visit based on application of standard questionnaire form.

### Asthma control and severity

Asthma control level was classified as controlled, partially controlled and uncontrolled based on Asthma Control Test (ACT) which is one of the standard tests that have been developed for reflecting the patient's perspective for his/her disease and enables to determine asthma control levels, to predict exacerbations and to optimize the therapies of the patients (6). In this study, ACT<sup>TM</sup> filled in by patients was used to assess the level of asthma control in the 4 weeks preceding the enrollment considering an overall score of 25 indicating the controlled asthma, 20–24 for partially controlled asthma and a score  $\leq 19$  indicating the uncontrolled asthma.

Asthma severity was categorized into four groups as mild intermittent, mild persistent, moderate persistent and severe persistent according to GINA guidelines (5).

### BMI classification

Patients with BMI values ( $\text{kg}/\text{m}^2$ ) of 18.5–24.9  $\text{kg}/\text{m}^2$  were classified under the category of normal weight, 25.0–29.9  $\text{kg}/\text{m}^2$  as overweight and BMI of  $\geq 30$   $\text{kg}/\text{m}^2$  as obese according to WHO criteria (7).

## Allergy evaluation

Skin prick tests was performed with a standardized panel of airborne allergens including *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*; grass, tree and weed pollens; molds and cat and dog allergens. Histamine dihydrochloride (10 mg/mL) and glycerol diluent were used as positive and negative controls, respectively. A wheal size larger than 3 mm or greater than that produced by the control solution was considered a positive reaction.

## Statistical analysis

Statistical analysis was made using computer software (SPSS version 13.0, SPSS Inc. Chicago, IL, USA). Chi-square ( $\chi^2$ ) test for the comparison of categorical data and Mantel-Haenszel test was used for the analysis of linear relationship between ordinal variables. ANOVA and *post hoc* Tukey test were used for the parametric variables. Data were expressed as 'mean (standard deviation; SD)', median (minimum-maximum) and percent (%) where appropriate.  $P < 0.05$  was considered statistically significant.

## Results

### Asthma phenotypes in the overall population

Study population was comprised of 1054 females (75.3%, mean(SD) age: 45.0(13.0) years) and 346 males (24.7%, mean(SD) age: 43.0(15.7) years), while 66.0% of patients were nonsmokers, 22.0% were ex-smokers and 12.0% were active smokers (Table 1).

Obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>) composed 36.0% of all study patients with mean(SD) asthma age of 9.0(9.1) years; 43.0% of obese patients were suffering from asthma for 1–5 years and the onset of the disease was at the age of 18–39 years in 51.0% (Table 1).

Mild (40.0%) or moderate (38.0%) persistent asthma was evident in most patients. ACT revealed that asthma was partially controlled in 50.0% of patients and uncontrolled in 28.0% FEV1 measurements were  $>80\%$  in 60.0% and peak expiratory flow values were  $>80\%$  in 54.0% of patients (Table 1).

Chronic rhinitis/rhino-sinusitis (48.6%) was the most common comorbid disease, while perennial allergens (41.9%) and psychological factors (25.1%) were the most common asthma triggers (Table 1).

In 27.9% of patients, there was asthma related hospital admissions within the last year including emergency admission ending in hospitalization, being taken into ICU and use of systemic steroids in majority of patients (Table 1).

Allergic asthma phenotype consisted 36.4% of the study population with mite sensitivity in 58.0% and grass sensitivity in 52.0% of patients with positive skin test (Table 1).

### Asthma phenotypes with respect to gender

There was significant gender influence on obesity and asthma control level with significantly higher percentage of obese patients among females than males (42.0 vs. 19.0%,  $P < 0.01$ ), higher percentage of patients with controlled asthma among males than females (29.0 vs. 19.0%,  $P < 0.01$ ) and higher percentage of patients with uncontrolled asthma in females than males (31.0 vs. 22.0%,  $P < 0.01$ ) (Table 1).

### Asthma phenotypes with respect to BMI (normal/overweight vs. obese patients)

In 55.0% of obese patients vs. 37.0% of normal/overweight patients, the disease onset was  $\geq 40$  years of age ( $P < 0.01$ ), the percentage of patients with earlier disease onset ( $<40$  years of age) was significantly higher among the normal/overweight patients than obese patients (63.0 vs. 45.0%,  $P < 0.01$ ). Normal/overweight patients had significantly higher FEV1 values (over 80%) than obese patients (56.0 vs. 45.0%,  $P < 0.01$ ) and chronic rhinitis/rhino-sinusitis were more common comorbidities (47.5 vs. 36.3%,  $P < 0.01$ ).

### Asthma phenotypes with respect to allergic status (allergic vs. nonallergic patients)

In 47.0% of nonallergic patients vs. 29.0% of allergic patients, the disease onset was  $\geq 40$  years of age ( $P < 0.01$ ). Allergic patients had significantly higher percent of mild persistent asthma than non allergic asthmatics (47.0 vs. 35.0%,  $P < 0.01$ ) and FEV1 values over 80% (70.0 vs. 54.0%,  $P < 0.01$ ). Chronic rhinitis/rhino-sinusitis was determined to be significantly more common in allergic than nonallergic patients (62.3 vs. 40.7%,  $P < 0.01$ ) while gastroesophageal reflux disorder (GERD) was more common in nonallergic asthmatics (36.8 vs. 29.1%,  $P < 0.01$ ). Hospital admissions in the last year were more frequent among nonallergic asthmatics than allergic asthmatics (30.5 vs. 23.2%,  $P < 0.01$ ) (Table 2).

### Asthma phenotypes with respect to disease control

Significantly higher percent of uncontrolled patients (68.0%) had an early onset of disease when compared with controlled (56.0%) and partially controlled (57.0%) asthma patients ( $P < 0.01$ ). The mild persistent asthma was significantly higher in controlled than

**Table 1.** Asthma phenotypes in the overall population with respect to gender

|                                  | Gender                     |                       | Overall (n = 1400)    |
|----------------------------------|----------------------------|-----------------------|-----------------------|
|                                  | Female (n = 1054)          | Male (n = 346)        |                       |
|                                  | Mean(SD); median(min-max)  |                       |                       |
| <b>Age (years)</b>               | 45.0(13.2); 45(14–87)      | 43.0(15.7); 43(16–84) | 44.0(13.9); 45(14–87) |
| <b>Smoking status</b>            | n(%)                       |                       |                       |
| Non-smoker                       | 768(73.0)                  | 162(47.0)             | 930(66.0)             |
| Ex-smoker                        | 168(16.0)                  | 134(39.0)             | 302(22.0)             |
|                                  | Mean(SD); median(min-max)  |                       |                       |
| <i>Years since quitting</i>      | 7.3(6.3); 5(1–29)          | 10.4(8.7); 10(1–60)   | 8.7(7.6); 7(1–60)     |
| <i>Pack-years</i>                | 11.7(11.2); 8(1–63)        | 15.5(13.8); 10(1–60)  | 13.4(12.5); 10(1–63)  |
|                                  | n(%)                       |                       |                       |
| Active smoker                    | 118(11.0)                  | 50(14.0)              | 168(12.0)             |
|                                  | Mean(SD); median(min-max)  |                       |                       |
| <i>Pack-years</i>                | 11.0(8.6); 10(1–45)        | 12.5(12.6); 9(1–60)   | 11.5(9.9); 10(1–60)   |
| <b>BMI (kg/m<sup>2</sup>)</b>    | 28.8(6.3); 28(17–62)       |                       | 28.2(5.9); 28(15–62)  |
|                                  | n(%)                       |                       |                       |
| Normal weight (BMI < 24.9)       | 81(25.0)                   | 42(37.0)              | 123(28.0)             |
| Overweight (BMI = 25.0–29.9)     | 110(33.0)                  | 49(43.0)              | 159(36.0)             |
| Obese (BMI ≥ 30)                 | 138(42.0)*                 | 22(20.0)              | 160(36.0)             |
| Missing data                     | 725                        | 233                   | 958                   |
|                                  | Mean(SD); median(min-max)  |                       |                       |
| <b>Asthma age (years)</b>        | 9.0(9.1); 6(1–61)          | 8.7(8.7); 6(1–63)     | 9.0(9.0); 6(1–63)     |
|                                  | n(%)                       |                       |                       |
| New diagnosis                    | 102(10.0)                  | 44(13.0)              | 146(11.0)             |
| 1–5 years                        | 441(44.0)                  | 137(41.0)             | 578(43.0)             |
| 6–9 years                        | 141(14.0)                  | 50(15.0)              | 191(14.0)             |
| 10–19 years                      | 207(21.0)                  | 63(19.0)              | 270(20.0)             |
| 20–29 years                      | 78(8.0)                    | 28(8.0)               | 106(8.0)              |
| ≥30 years                        | 38(4.0)                    | 9(3.0)                | 47(4.0)               |
| Missing data                     | 47                         | 15                    | 62                    |
| <b>Age at disease onset</b>      |                            |                       |                       |
| <18 years                        | 65(7.0)                    | 43(13.0)              | 108(8.0)              |
| 18–39 years                      | 520(52.0)                  | 155(48.0)             | 675(51.0)             |
| 40–60 years                      | 370(37.0)                  | 106(33.0)             | 476(36.0)             |
| >60 years                        | 42(4.0)                    | 20(6.0)               | 62(5.0)               |
| Missing data                     | 57                         | 22                    | 79                    |
| <b>Family history</b>            |                            |                       |                       |
| Asthma                           | 453(43.0)                  | 122(35.0)             | 575(41.0)             |
| AR disorders                     | 81(8.0)                    | 24(7.0)               | 105(8.0)              |
| Drug allergy                     | 37(4.0)                    | 6(2.0)                | 43(3.0)               |
| None                             | 557(53.0)                  | 208(60.0)             | 765(55.0)             |
| <b>Asthma severity</b>           | n(%)                       |                       |                       |
| Mild intermittent                | 80(9.0)                    | 33(11.0)              | 113(10.0)             |
| Mild persistent                  | 347(39.0)                  | 128(43.0)             | 475(40.0)             |
| Moderate persistent              | 352(40.0)                  | 98(33.0)              | 450(38.0)             |
| Severe persistent                | 107(12.0)                  | 40(13.0)              | 147(12.0)             |
| Missing data                     | 168                        | 47                    | 215                   |
| <b>Asthma control status</b>     | Mean(SD); median (min-max) |                       |                       |
| Overall                          | 20.0(4.9); 22(1–26)        | 22.0(4.1); 23(3–25)   | 21.0(4.8); 22(1–26)   |
|                                  | n(%)                       |                       |                       |
| Controlled (ACT ≥ 25)            | 179(19.0)*                 | 88(29.0)              | 267(22.0)             |
| Partially controlled (ACT 20–24) | 467(50.0)                  | 151(49.0)             | 618(50.0)             |
| Uncontrolled (ACT ≤ 19)          | 285(31.0)*                 | 67(22.0)              | 352(28.0)             |
| Missing data                     | 123                        | 40                    | 163                   |

Table 1. Continued

|  | Gender                    |                        | Overall (n = 1400)     |
|--|---------------------------|------------------------|------------------------|
|  | Female (n = 1054)         | Male (n = 346)         |                        |
| <b>FEV1 values (%)</b>                             |                           |                        |                        |
| <30  | 7(1.0)                    | 2(1.0)                 | 9(1.0)                 |
| 30–59  | 122(12.0)                 | 38(12.0)               | 160(12.0)              |
| 60–80  | 275(28.0)                 | 79(25.0)               | 354(27.0)              |
| >80  | 586(59.0)                 | 197(62.0)              | 783(60.0)              |
| Missing data                                       | 64                        | 30                     | 94                     |
| <b>PEF values (%)</b>                              |                           |                        |                        |
| Overall  | Mean(SD); median(min-max) |                        |                        |
|  | 80.0(22.5); 82(11–162)    | 82.8(23.0); 85(16–157) | 80.6(22.7); 83(11–162) |
|  | n(%)                      |                        |                        |
| <30  | 12(1.0)                   | 4(2.0)                 | 16(1.0)                |
| 30–59  | 141(17.0)                 | 35(13.0)               | 176(16.0)              |
| 60–80  | 229(28.0)                 | 71(27.0)               | 300(28.0)              |
| >80  | 432(53.0)                 | 152(58.0)              | 584(54.0)              |
| Missing data                                       | 240                       | 84                     | 324                    |
| <b>Co-morbid disorders/triggers</b>                |                           |                        |                        |
| GERD   | 388(36.8)                 | 88(25.4)               | 476(34.0)              |
| Brittle asthma                                     | 4(0.4)                    | 3(0.9)                 | 7(0.5)                 |
| Chronic rhinitis/rhino-sinusitis                   | 534(50.7)                 | 146(42.2)              | 680(48.6)              |
| Nasal polyp  | 104(9.9)                  | 40(11.6)               | 144(10.3)              |
| Analgesic allergy                                  | 117(11.1)                 | 25(7.2)                | 142(10.1)              |
| Diabetes mellitus                                  | 85(8.1)                   | 21(6.1)                | 106(7.6)               |
| Hypertension                                       | 194(18.4)                 | 34(9.8)                | 228(16.3)              |
| Vocal cord dysfunction                             | 24(2.3)                   | 5(1.4)                 | 29(2.1)                |
| Animal breeding                                    | 138(13.1)                 | 42(12.1)               | 180(12.9)              |
| <i>Past</i>  | 79(7.5)                   | 30(8.7)                | 109(7.8)               |
| <i>Current</i>                                     | 59(5.6)                   | 12(3.5)                | 71(5.1)                |
| Beta blockers within the last 2 years              | 46(4.4)                   | 15(4.3)                | 61(4.4)                |
| Sleep related conditions                           | 149(14.1)                 | 35(10.1)               | 184(13.1)              |
| Food allergy                                       | 55(5.2)                   | 13(3.8)                | 68(4.9)                |
| Mold in living or work environment                 | 83(7.9)                   | 25(7.2)                | 108(7.7)               |
| Psychological state                                | 309(29.3)                 | 42(12.1)               | 351(25.1)              |
| Increase in premenstrual symptoms                  | 74(7.0)                   | –                      | 74(5.3)                |
| Increase in symptoms at work                       | 55(5.2)                   | 46(13.3)               | 101(7.2)               |
| Increase in seasonal symptoms                      | 449(42.6)                 | 138(39.9)              | 587(41.9)              |
| Thyroid disorder                                   | 133(12.6)                 | 9(2.6)                 | 142(10.1)              |
| <b>Comorbid disorders/not triggers</b>             | 72(6.8)                   | 46(13.3)               | 118(8.4)               |
| <b>AR-hospital admissions within the last year</b> | 311(29.5)                 | 79(22.8)               | 390(27.9)              |
| <b>Skin prick test positivity</b>                  |                           |                        |                        |
| To one type of allergen                            | 201(19.0)                 | 88(25.0)               | 289(21.0)              |
| To more allergens                                  | 148(14.0)                 | 34(10.0)               | 182(13.0)              |
| Missing  | 705                       | 224                    | 929                    |
| <b>Type of allergy</b>                             |                           |                        |                        |
| Mite mix   | 215(62.0)                 | 59(48.0)               | 274(58.0)              |
| Mold mix   | 68(19.0)                  | 16(13.0)               | 84(18.0)               |
| Cockroach  | 47(13.0)                  | 13(11.0)               | 60(13.0)               |
| Cat  | 54(15.0)                  | 11(9.0)                | 65(14.0)               |
| Grass pollen mix                                   | 186(53.0)                 | 61(50.0)               | 247(52.0)              |

\* $P < 0.01$  compared to males

ACT, asthma control test; AR, asthma related; BMI, body mass index; FEV1, Forced expiratory volume in one second; GERD, Gastro-esophageal reflux disease; PEF, peak expiratory flow; SD, standard deviation

**Table 2.** Asthma phenotypes with respect to body mass index and allergic status

|   | Body mass index (kg/m <sup>2</sup> ) |                              | Allergic status          |                          |
|---|--------------------------------------|------------------------------|--------------------------|--------------------------|
|   | Obese (n = 160)                      | Normal/over-weight (n = 282) | Non-allergic (n = 891)   | Allergic (n = 509)       |
|   | Mean(SD); median(min-max)            |                              |                          |                          |
| <b>Age (years)</b>                        | 49.0(11.3);<br>50(18–87)             | 42.0(14.1);<br>41(16–75)     | 46.0(13.7);<br>47(14–87) | 41.0(13.5);<br>40(16–84) |
| <b>Smoking status</b>                     | n(%)                                 |                              |                          |                          |
| Non-smoker                                | 112(70.0)                            | 181(64.0)                    | 576(65.0)                | 354(70.0)                |
| Ex-smoker                                 | 35(22.0)                             | 64(23.0)                     | 192(22.0)                | 110(22.0)                |
|   | Mean(SD); median(min-max)            |                              |                          |                          |
| <i>Years since quitting</i>               | 10.9(8.4);<br>10(1–31)               | 8.8(6.8);<br>9(1–30)         | 9.2(8.2);<br>8(1–60)     | 7.8(6.3);<br>6(1–27)     |
| <i>Pack-years</i>                         | 13.4(11.0);<br>10(1–40)              | 11.2(12.7);<br>5(1–60)       | 14.3(13.0);<br>10(1–63)  | 11.8(11.5);<br>7(1–60)   |
|   | n(%)                                 |                              |                          |                          |
| Active smoker                             | 13(8.0)                              | 37(13.0)                     | 123(12.0)                | 45(14.0)                 |
|   | Mean(SD); median(min-max)            |                              |                          |                          |
| <i>Pack-years</i>                         | 12.7(9.9);<br>8(1–30)                | 9.6(8.4);<br>9(1–45)         | 12.2(10.6);<br>10(1–60)  | 9.5(7.5);<br>8(1–35)     |
| <b>Body mass index (kg/m<sup>2</sup>)</b> |                                      |                              |                          |                          |
| Overall                                   | 34.1(4.8);<br>33(30–62)              | 24.8(3.3);<br>25(15–29)      | 28.6(6.1);<br>28(15–62)  | 27.1(5.4);<br>27(17–49)  |
|   | n(%)                                 |                              |                          |                          |
| Normal weight (BMI<24.9)                  | –                                    | 123(44.0)                    | 74(25.0)                 | 49(35.0)                 |
| Overweight (BMI=25.0–29.9)                | –                                    | 159(56.0)                    | 105(35.0)                | 54(38.0)                 |
| Obese (BMI≥30)                            | 160(100.0)                           | –                            | 121(40.0)                | 39(27.0)                 |
| Missing data                              | –                                    | –                            | 591                      | 367                      |
| <b>Asthma age</b>                         | Mean(SD); median(min-max)            |                              |                          |                          |
| Overall                                   | 9.0(8.1);<br>7(1–47)                 | 9.6(9, 7);<br>6(1–63)        | 8.4(8.6);<br>5(1–63)     | 9.8(9.5);<br>6(1–58)     |
|   | n(%)                                 |                              |                          |                          |
| New diagnosis                             | 18(11.0)                             | 47(17.0)                     | 99(12.0)                 | 47(10.0)                 |
| 1–5 years                                 | 63(40.0)                             | 105(38.0)                    | 380(45.0)                | 198(41.0)                |
| 6–9 years                                 | 24(15.0)                             | 41(15.0)                     | 120(14.0)                | 71(15.0)                 |
| 10–19 years                               | 35(22.0)                             | 47(17.0)                     | 170(20.0)                | 100(21.0)                |
| 20–29 years                               | 14(9.0)                              | 28(10.0)                     | 63(7.0)                  | 43(9.0)                  |
| ≥30 years                                 | 5(3.0)                               | 12(4.0)                      | 19(2.0)                  | 28(6.0)                  |
| Missing data                              | 1                                    | 2                            | 40                       | 22                       |
| <b>Age at disease onset</b>               |                                      |                              |                          |                          |
| <18 years                                 | 7(5.0)                               | 30(11.0)                     | 50(6.0)                  | 58(12.0)                 |
| 18–39 years                               | 63(41.0)                             | 143(52.0)                    | 392(47.0)                | 283(59.0)                |
| 40–60 years                               | 75(48.0)                             | 95(35.0)                     | 342(41.0)                | 134(28.0)                |
| >60 years                                 | 10(6.0)                              | 7(3.0)                       | 55(7.0)                  | 7(1.0)                   |
| Missing data                              | 5                                    | 7                            | 52                       | 27                       |
| <40 years                                 | 70(45.0)*                            | 173(63.0)                    | 445(53.0) <sup>q</sup>   | 342(71.0)                |
| ≥40 years                                 | 85(55.0)*                            | 102(37.0)                    | 394(47.0) <sup>q</sup>   | 140(29.0)                |
| <b>Family history</b>                     |                                      |                              |                          |                          |
| Asthma                                    | 75(47.0)                             | 122(43.0)                    | 332(37.0)                | 243(48.0)                |
| AR disorders                              | 11(7.0)                              | 20(7.0)                      | 48(5.0)                  | 57(11.0)                 |
| Drug allergy                              | 6(4.0)                               | 5(2.0)                       | 26(3.0)                  | 17(3.0)                  |
| None                                      | 79(49.0)                             | 151(54.0)                    | 534(60.0)                | 231(45.0)                |
| <b>Asthma severity</b>                    |                                      |                              |                          |                          |
| Mild intermittent                         | 18(14.0)                             | 34(15.0)                     | 74(10.0)                 | 39(8.0)                  |
| Mild persistent                           | 54(41.0)                             | 101(44.0)                    | 249(35.0) <sup>q</sup>   | 226(47.0)                |

Table 2. Continued

|  | Body mass index (kg/m <sup>2</sup> ) |                              | Allergic status           |                           |
|--|--------------------------------------|------------------------------|---------------------------|---------------------------|
|  | Obese (n = 160)                      | Normal/over-weight (n = 282) | Non-allergic (n = 891)    | Allergic (n = 509)        |
| Moderate persistent  | 47(36.0)                             | 68(30.0)                     | 292(41.0)                 | 158(33.0)                 |
| Severe persistent  | 12(9.0)                              | 25(11.0)                     | 90(13.0)                  | 57(12.0)                  |
| Missing data   | 29                                   | 54                           | 186                       | 29                        |
| <b>Asthma control status</b>                                   | Mean(SD); median(min-max)            |                              |                           |                           |
| Overall  | 20.0(4.9);<br>22(6–25)               | 20.0(5.0);<br>21(1–26)       | 20.0(4.8);<br>22(2–25)    | 21.0(4.7);<br>22(1–26)    |
|  | n(%)                                 |                              |                           |                           |
| Controlled (ACT ≥25)   | 24(16.0)                             | 52(19.0)                     | 150(20.0)                 | 117(25.0)                 |
| Partially controlled (ACT 20–24)                               | 75(49.0)                             | 126(46.0)                    | 395(51.0)                 | 223(48.0)                 |
| Uncontrolled (ACT ≤19)   | 55(36.0)                             | 96(35.0)                     | 224(29.0)                 | 128(27.0)                 |
| Missing data   | 6                                    | 8                            | 122                       | 41                        |
| <b>FEV1 values (%)</b>   |                                      |                              |                           |                           |
| <30  | 3(2.0)                               | 4(1.0)                       | 6(1.0)                    | 3(1.0)                    |
| 30–59  | 27(18.0)                             | 48(18.0)                     | 116(14.0)                 | 44(9.0)                   |
| 60–80  | 53(35.0)                             | 68(25.0)                     | 253(31.0)                 | 101(21.0)                 |
| >80  | 69(45.0)*                            | 153(56.0)                    | 444(54.0) <sup>q</sup>    | 339(70.0)                 |
| Missing data   | 8                                    | 9                            | 72                        | 22                        |
| <b>PEF values (%)</b>  | Mean(SD); median(min-max)            |                              |                           |                           |
| Overall  | 72.0(26.3);<br>71(19–138)            | 75.4(25.8);<br>76(11–134)    | 78.2(23.0);<br>79(16–162) | 84.5(21.6);<br>86(11–134) |
|  | n(%)                                 |                              |                           |                           |
| <30  | 1(1.0)                               | 5(2.0)                       | 12(2.0)                   | 4(1.0)                    |
| 30–59  | 41(36.0)                             | 58(27.0)                     | 115(17.0)                 | 61(15.0)                  |
| 60–80  | 31(27.0)                             | 58(27.0)                     | 217(33.0)                 | 83(20.0)                  |
| >80  | 42(37.0)                             | 93(43.0)                     | 320(48.0)                 | 264(64.0)                 |
| Missing data   | 45                                   | 68                           | 227                       | 97                        |
| <b>Co-morbid disorders/triggers</b>                            |                                      |                              |                           |                           |
| Gastro-esophageal reflux disease                               | 82(51.3)*                            | 129(45.7)                    | 328(36.8) <sup>q</sup>    | 148(29.1)                 |
| Brittle asthma   | –                                    | 4(1.4)                       | 4(0.4)                    | 3(0.6)                    |
| Chronic rhinitis/rhino-sinusitis                               | 58(36.3)*                            | 134(47.5)                    | 363(40.7) <sup>q</sup>    | 317(62.3)                 |
| Nasal polyp  | 12(7.5)                              | 26(9.2)                      | 103(11.6)                 | 41(8.1)                   |
| Analgesic allergy  | 16(10.0)                             | 32(11.3)                     | 79(8.9)                   | 63(12.4)                  |
| Diabetes mellitus  | 27(16.9)                             | 17(6.0)                      | 70(7.9)                   | 36(7.1)                   |
| Hypertension   | 49(30.6)                             | 50(17.7)                     | 168(18.9)                 | 60(11.8)                  |
| Vocal cord dysfunction   | 1(0.6)                               | 5(1.8)                       | 17(1.9)                   | 12(2.4)                   |
| Animal breeding  | 17(10.6)                             | 51(18.1)                     | 107(12.0)                 | 73(14.3)                  |
| <i>Past</i>  | 6(3.8)                               | 31(11.0)                     | 64(7.2)                   | 45(8.8)                   |
| <i>Current</i>   | 11(6.9)                              | 20(7.1)                      | 43(4.8)                   | 28(5.5)                   |
| Beta blockers within the last 2 years                          | 9(5.6)                               | 19(6.7)                      | 39(4.4)                   | 22(11.8)                  |
| Sleep related conditions                                       | 20(12.5)                             | 43(15.2)                     | 124(13.9)                 | 60(13.4)                  |
| Food allergy   | 7(4.4)                               | 21(7.4)                      | –                         | 68(17.0)                  |
| Mold in living or work environment                             | 12(7.5)                              | 23(8.2)                      | 57(6.4)                   | 51(10.0)                  |
| Psychological state  | 54(33.8)                             | 97(34.4)                     | 246(27.6)                 | 105(20.6)                 |
| Increase in premenstrual symptoms                              | 9(5.6)                               | 16(5.7)                      | 46(5.2)                   | 28(5.5)                   |
| Increase in symptoms at work                                   | 10(6.3)                              | 29(10.3)                     | 59(6.6)                   | 42(8.3)                   |
| Increase in seasonal symptoms                                  | 71(44.4)                             | 145(51.4)                    | 346(38.8) <sup>†</sup>    | 241(47.3)                 |
| Thyroid disorder   | 23(14.4)                             | 31(11.0)                     | 86(9.7)                   | 56(11.0)                  |
| <b>Comorbid disorders/not triggers</b>                         | 13(8.1)                              | 17(6.0)                      | 94(10.5)                  | 24(4.7)                   |
| <b>Asthma related hospital admissions within the last year</b> | 50(31.3)                             | 86(30.5)                     | 272(30.5) <sup>†</sup>    | 118(23.2)                 |

**Table 2.** Continued

|                                   | Body mass index (kg/m <sup>2</sup> ) |                              | Allergic status        |                    |
|-----------------------------------|--------------------------------------|------------------------------|------------------------|--------------------|
|                                   | Obese (n = 160)                      | Normal/over-weight (n = 282) | Non-allergic (n = 891) | Allergic (n = 509) |
| <b>Skin prick test positivity</b> | n(%)                                 |                              |                        |                    |
| To one type of allergen           | 17(11.0)                             | 57(20.0)                     | –                      | 289(57.0)          |
| To more allergens                 | 18(11.0)                             | 35(12.0)                     | –                      | 182(36.0)          |
| Missing                           | 125                                  | 190                          | –                      | 38(7.0)            |
| Total                             | 160(100.0)                           | 282(100.0)                   | 891                    | 509                |
| <b>Type of allergy</b>            |                                      |                              |                        |                    |
| Mite mix                          | 22(63.0)                             | 52(57.0)                     | –                      | 274(58.0)          |
| Mold mix                          | 12(34.0)                             | 18(20.0)                     | –                      | 84(18.0)           |
| Cockroach                         | 8(23.0)                              | 15(16.0)                     | –                      | 60(13.0)           |
| Cat                               | 3(9.0)                               | 14(15.0)                     | –                      | 65(14.0)           |
| Grass pollen mix                  | 14(40.0)                             | 50(54.0)                     | –                      | 247(52.0)          |

\* $P < 0.01$  compared to normal/overweight patients

<sup>‡</sup> $P < 0.01$  compared to allergic patients

ACT, asthma control test; AR, asthma related; FEV<sub>1</sub>, Forced expiratory volume in one second; PEF, peak expiratory flow; SD, standard deviation

partially controlled and uncontrolled asthma (57.0% vs. 42.0 and 25.0%, respectively,  $P < 0.01$ ). In the controlled group GERD was significantly less frequent than in other groups (23.6 vs. 33.8 and 45.5%, respectively,  $P < 0.01$ ). Perennial allergens (49.7%) and psychological (36.1%) triggers were most common factors in uncontrolled patients. Hospital admission in the last year was more frequent among patients with uncontrolled (38.9%) than partially controlled (23.8%) and controlled (16.9%) asthma ( $P < 0.01$ ) (Table 3).

### Asthma phenotypes with respect to geographical region

The percentages of active smokers in Eastern and Southeastern region (18.0%,  $P < 0.01$ ) were significantly higher compared to other geographical regions. Early disease onset was (under age of 40) significantly higher in patients from Central Anatolia (61.0%), Eastern-Southeastern (63.0%,  $P < 0.05$ ) parts than Mediterranean (47.0%,  $P < 0.05$ ) regions. Severe persistent asthma was more common in Eastern-Southeastern (16.0%,  $P < 0.05$ ) and Marmara (16.0%,  $P < 0.05$ ) regions when compared to Aegean (4.0%) region. The percentage of patients with allergy was significantly higher in Black Sea (58.0%) and Marmara (45.0%) regions compared to Eastern-Southeastern (28.0%) and Mediterranean (17.0%) regions ( $P < 0.05$  for each). GERD in Mediterranean (40.0%) and Central Anatolia (26.0%,  $P < 0.05$ ) and chronic rhinitis/rhino-sinusitis in Mediterranean (18.0%,  $P < 0.05$ ) region were less common compared to other regions. Pet keeping and sleep related conditions were more common in Aegean (19.0% and  $P < 0.05$  for each) and

Eastern-Southeastern (18.0 and 20.0%, respectively,  $P < 0.05$  for each) regions. Psychological triggers and increase in seasonal symptoms were least common in Aegean (3.0 and 16.0%, respectively,  $P < 0.05$ ) and Mediterranean (7.0 and 18.0%, respectively,  $P < 0.05$ ) regions compared with other regions. Asthma related hospital admissions within the last year were significantly more common in Eastern-Southeastern than Marmara region (36.0 and 21.0%, respectively,  $P < 0.05$ ). Marmara (39.0%) and Central Anatolia (27.0%) regions were associated with the highest asthma control compared with other regions ( $P < 0.05$ ) (Table 4).

### Discussion

Representing the first study on integration of data from a detailed clinical questionnaire in a large number ( $n = 1400$ ) of asthmatic patients in Turkey to evaluate phenotypes, our findings revealed preponderance of females (75.3%), mild to moderate persistent asthma (78.0%), presence of several comorbidities with onset of disease at age of 18–39 years (51.0%) mostly by perennial triggers (41.9%) and total asthma control in 22.0% of study population.

Earlier onset ( $< 40$  years of age), milder forms of disease, higher FEV<sub>1</sub> values, perennial symptoms and concomitant chronic rhinitis/rhino-sinusitis were more common in allergic than nonallergic asthmatics, whereas higher frequency of hospital admissions and GERD were notable among nonallergic asthmatics.

Our findings of lesser hospital admissions and higher FEV<sub>1</sub> function in allergic asthmatics seem compatible with the statement that patients with allergic



**Table 3.** Asthma phenotypes with respect to disease control

|                               | Asthma control level                      |   |   |
|-------------------------------|---|---|---|
|                               | Controlled<br>(ACT $\geq$ 25; $n = 267$ ) | Partially controlled<br>(ACT 20–24; $n = 618$ ) | Uncontrolled<br>(ACT $\leq$ 19; $n = 352$ ) |
|                               | Mean(SD); median(min-max)                 |   |   |
| <b>Age (years)</b>            | 43.0(13.7); 43(17–77)                     | 44.0(13.9); 45(14–84)                           | 44.0(13.4); 43(16–87)                       |
| <b>Smoking status</b>         | n(%)                                      |   |   |
| Non-smoker                    | 174(65.0)                                 | 402(66.0)                                       | 239(68.0)                                   |
| Ex-smoker                     | 70(26.0)                                  | 124(20.0)                                       | 71(20.0)                                    |
|                               | Mean(SD); median(min-max)                 |   |   |
| <i>Years since quitting</i>   | 9.3(7.9); 7(1–31)                         | 8.3(7.0); 6(1–30)                               | 8.4(6.0); 8(1–28)                           |
| <i>Pack-years</i>             | 12.8(13.2); 8(1–60)                       | 14.6(12.8); 10(1–63)                            | 10.2(8.7); 7(1–40)                          |
|                               | n(%)                                      |   |   |
| Active smoker                 | 23(9.0)                                   | 92(15.0)  | 42(12.0)                                    |
|                               | Mean(SD); median(min-max)                 |   |   |
| <i>Pack-years</i>             | 9.4(9.1); 5(1–30)                         | 10.3 (9.2); 8(1–45)                             | 13(8.3); 10(1–30)                           |
| <b>BMI (kg/m<sup>2</sup>)</b> | 27.6(5.5); 27(17–49)                      | 28.3(5.3); 28(18–49)                            | 28.0(6.4); 28(15–50)                        |
|                               | n(%)                                      |   |   |
| Normal weight (BMI <24.9)     | 26(34.0)                                  | 47(23.0)  | 47(31.0)                                    |
| Overweight (BMI=25.0–29.9)    | 26(34.0)                                  | 79(39.0)  | 49(32.0)                                    |
| Obese (BMI $\geq$ 30)         | 24(32.0)                                  | 75(37.0)  | 55(36.0)                                    |
| Missing data                  | 191                                       | 417   | 201   |
|                               | Mean(SD); median(min-max)                 |   |   |
| <b>Asthma age (years)</b>     | 7.3(7.7); 4(1–36)                         | 8.6(9.1); 5(1–35)                               | 10.2(9.0); 8(1–58)                          |
|                               | n(%)                                      |   |   |
| New diagnosis                 | 23(9.0)                                   | 72(12.0)  | 30(9.0)                                     |
| 1–5 years                     | 141(55.0)                                 | 261(44.0)                                       | 123(36.0)                                   |
| 6–9 years                     | 29(11.0)                                  | 87(15.0)  | 57(16.0)                                    |
| 10–19 years                   | 40(16.0)                                  | 112(19.0)                                       | 89(26.0)                                    |
| 20–29 years                   | 19(7.0)                                   | 43(7.0)   | 33(10.0)                                    |
| $\geq$ 30 years               | 6(2.0)                                    | 18(3.0)   | 14(4.0)                                     |
| Missing data                  | 9   | 25  | 6   |
| <b>Age at disease onset</b>   |   |   |   |
| <18 years                     | 23(9.0)                                   | 47(8.0)   | 29(8.0)                                     |
| 18–39 years                   | 121 (47.0)                                | 286(49.0)                                       | 205(60.0)                                   |
| 40–60 years                   | 102(40.0)                                 | 218(37.0)                                       | 99(29.0)                                    |
| >60 years                     | 10(4.0)                                   | 33(6.0)   | 10(3.0)                                     |
| Missing data                  | 11  | 34  | 9   |
| <40 years                     | 143(56.0)*                                | 333(57.0)*                                      | 233(68.0)                                   |
| $\geq$ 40 years               | 112(44.0)*                                | 251(43.0)*                                      | 110(32.0)                                   |
| <b>Family history</b>         |   |   |   |
| Asthma                        | 125(47.0)                                 | 235(38.0)                                       | 158(45.0)                                   |
| AR disorders                  | 19(7.0)                                   | 45(7.0)   | 31(9.0)                                     |
| Drug allergy                  | 3(1.0)                                    | 15(2.0)   | 18(5.0)                                     |
| None                          | 134(50.0)                                 | 352(57.0)                                       | 181(51.0)                                   |
| <b>Asthma severity</b>        |   |   |   |
| Mild intermittent             | 38(16.0)                                  | 60(11.0) <sup>q</sup>                           | 11(3.0) <sup>q</sup>                        |
| Mild persistent               | 139(57.0)                                 | 227(42.0) <sup>q</sup>                          | 79(25.0) <sup>q</sup>                       |
| Moderate persistent           | 62(25.0)                                  | 201(37.0)                                       | 151(48.0)                                   |
| Severe persistent             | 6(2.0)                                    | 52(10.0)  | 74(23.0)                                    |
| Missing data                  | 22  | 78  | 37  |
| <b>FEV1 values (%)</b>        |   |   |   |
| <30                           | 1(0.)                                     | 2(0.)   | 6(2.0)                                      |
| 30–59                         | 11(4.0)                                   | 70(12.0)  | 66(19.0)                                    |
| 60–80                         | 40(16.0)                                  | 159(26.0)                                       | 114(33.0)                                   |

**Table 3.** Continued

|  | Asthma control level  |   |   |
|--|---|---|---|
|  | Controlled<br>(ACT $\geq$ 25; <i>n</i> = 267)                       | Partially controlled<br>(ACT 20–24; <i>n</i> = 618) | Uncontrolled<br>(ACT $\leq$ 19; <i>n</i> = 352) |
| >80  | 206(80.0)   | 372(62.0)   | 161(46.0)                                       |
| Missing data   | 9   | 15  | 5   |
| <b>PEF values (%)</b>  | Mean(SD; median; min-max)<br>89.3(19.7); 90(22–144)<br><i>n</i> (%) | 81.5(21.9); 83(16–162)                              | 73.4(23.0); 75(11–134)                          |
| <30  | 1(0.)   | 5(1.0)  | 8(3.0)  |
| 30–59  | 13(6.0)   | 74(15.0)  | 79(25.0)  |
| 60–80  | 42(20.0)  | 136(28.0)   | 106(33.0)                                       |
| >80  | 150(73.0)   | 272(56.0)   | 127(40.0)                                       |
| Missing data   | 61  | 131   | 32  |
| <b>Co-morbid disorders/triggers</b>                            |   |   |   |
| GERD   | 63(23.6)  | 209(33.8) <sup>q</sup>                              | 160(45.5) <sup>q</sup>                          |
| Brittle asthma   | 1(0.4)  | 2(0.3)  | 4(1.1)  |
| Chronic rhinitis/rhino-sinusitis                               | 130(48.7)   | 311(50.3)   | 191(54.3)                                       |
| Nasal polyp  | 27(10.1)  | 68(11.0)  | 34(9.7)   |
| Analgesic allergy  | 22(8.2)   | 64(10.4)  | 48(13.6)  |
| Diabetes mellitus  | 17(6.4)   | 45(7.3)   | 30(8.5)   |
| Hypertension   | 34(12.7)  | 90(14.6)  | 73(20.7)  |
| Vocal cord dysfunction   | 2(0.7)  | 9(1.5)  | 16(4.5)   |
| Animal breeding  | 38(14.2)  | 69(11.2)  | 58(16.5)  |
| <i>Past</i>  | 18(6.7)   | 43(7.0)   | 37(10.5)  |
| <i>Current</i>   | 20(7.5)   | 26(4.2)   | 21(6.0)   |
| Beta blockers within the last 2 years                          | 6(2.2)  | 22(3.6)   | 30(8.5)   |
| Sleep related conditions                                       | 14(5.2)   | 67(10.8)  | 88(25.0)  |
| Food allergy   | 8(3.0)  | 25(4.0)   | 27(7.7)   |
| Mold in living/work environment                                | 16(6.0)   | 46(7.4)   | 36(10.2)  |
| Psychological state  | 42(15.7)  | 154(24.9) <sup>q</sup>                              | 127(36.1) <sup>q</sup>                          |
| Increase in premenstrual symptoms                              | 12(4.5)   | 30(4.9)   | 27(7.7)   |
| Increase in symptoms at work                                   | 14(5.2)   | 42(6.8)   | 34(9.7)   |
| Increase in seasonal symptoms                                  | 113(42.3)*  | 250(40.5)*  | 175(49.7)                                       |
| Thyroid disorder   | 17(6.4)   | 64(10.4)  | 41(11.6)  |
| <b>Comorbid disorders/not triggers</b>                         | 26(9.7)   | 53(8.6)   | 11(3.1)   |
| <b>Asthma related hospital admissions within the last year</b> | 45(16.9)  | 147(23.8) <sup>q</sup>                              | 137(38.9) <sup>q</sup>                          |
| <b>Skin prick test positivity</b>                              |   |   |   |
| To one type of allergen  | 76(28.0)  | 130(21.0)   | 63(18.0)  |
| To more allergens  | 38(14.0)  | 76(12.0)  | 52(15.0)  |
| Missing  | 153   | 412   | 237   |
| <b>Type of allergy</b>   |   |   |   |
| Mite mix   | 64(56.0)  | 110(53.0)   | 78(68.0)  |
| Mold mix   | 17(15.0)  | 37(18.0)  | 23(20.0)  |
| Cockroach  | 10(9.0)   | 30(15.0)  | 13(11.0)  |
| Cat  | 14(12.0)  | 27(13.0)  | 16(14.0)  |
| Grass pollen mix   | 61(54.0)  | 106(51.0)   | 59(51.0)  |

\**P* < 0.01 compared to uncontrolled asthma<sup>q</sup>*P* < 0.01 compared to controlled asthmaACT, asthma control test; AR, asthma related; BMI, body mass index; FEV<sub>1</sub>, Forced expiratory volume in one second; GERD, gastroesophageal reflux disorder; PEF, peak expiratory flow; SD, standard deviation

**Table 4.** Asthma phenotypes with respect to geographic region

|                                     | Geographical region       |                               |                          |                            |                                       |                          |
|-------------------------------------|---------------------------|-------------------------------|--------------------------|----------------------------|---------------------------------------|--------------------------|
|                                     | Marmara<br>(n = 179)      | Central Anatolia<br>(n = 720) | Aegean<br>(n = 115)      | Mediterranean<br>(n = 125) | Eastern-<br>Southeastern<br>(n = 228) | Black Sea<br>(n = 33)    |
| <b>Age (years)</b>                  | Mean(SD); median(min-max) |                               |                          |                            |                                       |                          |
|                                     | 45.4(14.9);<br>45(17–77)  | 43.3(13.3);<br>44(14–83)      | 43.9(12.7);<br>44(17–71) | 53.0 (13.5);<br>53(22–84)  | 42.4(13.7);<br>43(15–84)              | 44.4(15.9);<br>42(20;87) |
| <b>Smoking status</b>               | n(%)                      |                               |                          |                            |                                       |                          |
| Non-smoker                          | 118(66.0)                 | 492(68.0)                     | 78(68.0)                 | 72(58.0)                   | 150(66.0)                             | 20(61.0)                 |
| Ex-smoker                           | 43(24.0)                  | 143(20.0)                     | 30(26.0)                 | 38(30.0)                   | 37(16.0)                              | 11(33.0)                 |
| Active smoker                       | 18 (10.0)                 | 85(12.0)                      | 7(6.0)                   | 15(12.0)                   | 41(18.0)**                            | 2(6.0)                   |
| <b>BMI (kg/m<sup>2</sup>)</b>       | Mean(SD); median(min-max) |                               |                          |                            |                                       |                          |
|                                     | 27.8(5.3);<br>28(17–42)   | 30.6(10.1);<br>29(20–62)      | 27.9(5.5);<br>28(19–50)  | 28.6(5.0);<br>28(18–44)    | 28.4(6.2);<br>28(15–49)               | 27.7(4.7);<br>28(18–38)  |
|                                     | n(%)                      |                               |                          |                            |                                       |                          |
| Normal weight (BMI <24.9)           | 34(31.0)                  | 5 (25.0)                      | 32(28.0)                 | 22(20.0)                   | 45(27.0)                              | 7(21.0)                  |
| Overweight (BMI=25.0–29.9)          | 36(31.0)                  | 6 (30.0)                      | 45(39.0)                 | 49(44.0)                   | 58(35.0)                              | 14(42.0)                 |
| Obese (BMI ≥30)                     | 41(37.0)                  | 9 (45.0)*                     | 37(32.0)                 | 41(37.0)                   | 61(37.0)                              | 12(36.0)                 |
| Missing data                        | 68                        | 700                           | 1                        | 13                         | 64                                    | –                        |
| <b>Age at disease onset</b>         |                           |                               |                          |                            |                                       |                          |
| <18 years                           | 20(11.0)                  | 48(7.0)                       | 6(5.0)                   | 5(5.0)                     | 24(11.0)                              | 5(15.0)                  |
| 18–39 years                         | 80(46.0)                  | 361(54.0)                     | 58(52.0)                 | 45(42.0)                   | 114(52.0)                             | 17(52.0)                 |
| 40–60 years                         | 68(39.0)                  | 236(35.0)                     | 45(41.0)                 | 44(41.0)                   | 74(34.0)                              | 9(27.0)                  |
| >60 years                           | 7(4.0)                    | 29(4.0)                       | 2(2.0)                   | 14(13.0)                   | 8(4.0)                                | 2(6.0)                   |
| Missing data                        | 4                         | 46                            | 4                        | 17                         | 8                                     | –                        |
| <40 years                           | 100(57.0)                 | 409(61.0) <sup>+</sup>        | 64(58.0)                 | 50(46.0)                   | 138(63.0) <sup>+</sup>                | 22(67.0)                 |
| ≥40 years                           | 75(43.0)                  | 265(39.0)                     | 47(42.0)                 | 58(54.0)                   | 82(37.0)                              | 11(33.0)                 |
| <b>Family history</b>               |                           |                               |                          |                            |                                       |                          |
| Asthma                              | 78(44.0)                  | 297(41.0)                     | 49(43.0)                 | 42(34.0)                   | 93(41.0)                              | 16(48.0)                 |
| AR                                  | 8(4.0)                    | 57(8.0)                       | 10(9.0)                  | 2(2.0)                     | 25(11.0)                              | 3(9.0)                   |
| Drug allergy                        | 1(1.0)                    | 29(4.0)                       | 3(3.0)                   | 1(1.0)                     | 8(4.0)                                | 1(3.0)                   |
| None                                | 95(53.0)                  | 392(54.0)                     | 60(52.0)                 | 82(66.0)                   | 119(52.0)                             | 17(52.0)                 |
| <b>Asthma severity</b>              |                           |                               |                          |                            |                                       |                          |
| Mild intermittent                   | 22(13.0)                  | 52(8.0) <sup>w</sup>          | 26(23.0)                 | 1(3.0)                     | 9(6.0) <sup>w</sup>                   | 3(9.0)                   |
| Mild persistent                     | 81(49.0)                  | 251(37.0)                     | 49(43.0)                 | 18(46.0)                   | 62(41.0)                              | 14(42.0)                 |
| Moderate persistent                 | 38(23.0)                  | 293(43.0) <sup>t</sup>        | 34(30.0)                 | 16(41.0)                   | 56(37.0)                              | 13(39.0)                 |
| Severe persistent                   | 26(16.0) <sup>w</sup>     | 84(12.0)                      | 5(4.0)                   | 4(10.3)                    | 25(16.0) <sup>w</sup>                 | 3(9.1)                   |
| Missing data                        | 12                        | 40                            | 1                        | 86                         | 76                                    | –                        |
| <b>FEV1 values (%)</b>              |                           |                               |                          |                            |                                       |                          |
| <30                                 | 0(0.0)                    | 2(0.0)                        | 0(0.0)                   | 0(0.0)                     | 7(3.0)                                | 0(0.0)                   |
| 30–59                               | 18(11.0)                  | 55(8.0)                       | 17(15.0)                 | 12(16.0)                   | 55(24.0)                              | 3(9.0)                   |
| 60–80                               | 55(33.0)                  | 180(26.0)                     | 18(16.0)                 | 33(44.0)                   | 63(28.0)                              | 5(16.0)                  |
| >80                                 | 94(56.0)                  | 458(66.0)                     | 76(68.0)                 | 30(40.0)*                  | 101(45.0)*                            | 24(75.0)                 |
| Missing data                        | 12                        | 25                            | 4                        | 50                         | 2                                     | 1                        |
| <b>Co-morbid disorders/triggers</b> |                           |                               |                          |                            |                                       |                          |
| Gastro-esophageal reflux disease    | 61(34.0)                  | 188(26.0)*                    | 56(49.0)                 | 34(27.0)*                  | 117(51.0)                             | 20(61.0)                 |
| Chronic rhinitis/rhino-sinusitis    | 85(47.0)                  | 407(57.0)                     | 51(44.0)                 | 22(18.0)*                  | 95(42.0)                              | 20(61.0)                 |
| Nasal polyp                         | 16(9.0)                   | 96(13.0)                      | 9(8.0)                   | 5(4.0)                     | 14(6.0)                               | 4(12.0)                  |
| Analgesic allergy                   | 17(9.0)                   | 75(10.0)                      | 11(10.0)                 | 2(2.0)                     | 33(14.0)                              | 4(12.0)                  |
| Diabetes mellitus                   | 20(11.0)                  | 44(6.0)                       | 9(8.0)                   | 16(13.0)                   | 16(7.0)                               | 1(3.0)                   |
| Hypertension                        | 42(23.0)                  | 84(12.0)                      | 26(23.0)                 | 30(24.0)                   | 36(16.0)                              | 10(30.0)                 |
| Thyroid disease                     | 14(8.0)                   | 64(9.0)                       | 17(15.0)                 | 12(10.0)                   | 28(12.0)                              | 7(21.0)                  |
| Animal breeding                     | 13(7.0)                   | 88(12.0)                      | 22(19.0) <sup>t</sup>    | 14(11.0)                   | 41(18.0) <sup>t</sup>                 | 2(6.0)                   |
| Sleep related conditions            | 1(1.0)*                   | 104(14.0)                     | 22(19.0)                 | 8(6.0)                     | 45(20.0)                              | 4(12.0)                  |

**Table 4.** Continued

|  | Geographical region       |                               |                         |                            |                                   |                        |
|--|---------------------------|-------------------------------|-------------------------|----------------------------|-----------------------------------|------------------------|
|  | Marmara<br>(n = 179)      | Central Anatolia<br>(n = 720) | Aegean<br>(n = 115)     | Mediterranean<br>(n = 125) | Eastern-Southeastern<br>(n = 228) | Black Sea<br>(n = 33)  |
| Mold in living/work environment                                | 7(4.0)                    | 66(9.0)                       | 19(17.0)*               | 1(1.0)                     | 12(5.0)                           | 3(9.0)                 |
| Psychological state  | 6(3.0)*                   | 182(25.0)                     | 48(42.0)                | 9(7.0)*                    | 94(41.0)                          | 12(36.0)               |
| Increase in symptoms at work                                   | 5(3.0)                    | 56(8.0)                       | 18(16.0)*               | 4(3.0)                     | 11(5.0)                           | 7(21.0)                |
| Increase in seasonal symptoms                                  | 28(16.0)                  | 319(44.0)                     | 73(63.0)                | 22(18.0)                   | 119(52.0)                         | 26(79.0)               |
| <b>Asthma related hospital admissions within the last year</b> | 38(21.0)                  | 185(26.0)                     | 33(29.0)                | 39(31.0)                   | 81(36.0) <sup>†</sup>             | 14(42.0)               |
| <b>Skin prick test positivity</b>                              | 81(45.0) <sup>‡</sup>     | 291(40.0) <sup>‡</sup>        | 34(30.0)                | 21(17.0)                   | 63(28.0)                          | 19(58.0) <sup>‡</sup>  |
|  | Mean(SD); median(min-max) |                               |                         |                            |                                   |                        |
| <b>Asthma control status (ACT score)</b>                       | 22.9(2.9);<br>24(10–25)   | 21.4(4.1);<br>23(2–25)        | 17.7 (5.7);<br>19(2–26) | 18.0(8.2);<br>22(2–25)     | 19.2(4.7);<br>20(1–25)            | 16.9(4.8);<br>18(7–25) |
|  | n(%)                      |                               |                         |                            |                                   |                        |
| Controlled (ACT ≥25)   | 66(39.0)*                 | 174(27.0)*                    | 7(6.0)                  | 4(9.0)                     | 15(7.0)                           | 1(3.0)                 |
| Partially controlled (ACT 20–24)                               | 83(49.0)                  | 335(51.0)                     | 45(40.0)                | 30(65.0)                   | 114(52.0)                         | 11(33.0)               |
| Uncontrolled (ACT ≤19)   | 22(13.0)                  | 145(22.0)                     | 60(54.0)                | 12(26.0)                   | 92(42.0)                          | 21(64.0)               |
| Missing data   | 8                         | 66                            | 3                       | 79                         | 7                                 | –                      |

\* $P < 0.05$  and \*\* $P < 0.01$  compared to other regions, <sup>†</sup> $P < 0.05$  compared to Mediterranean region, <sup>‡</sup> $P < 0.05$  compared to Aegean region, <sup>§</sup> $P < 0.05$  compared to Marmara region, <sup>¶</sup> $P < 0.05$  compared to Mediterranean and Eastern-Southeastern regions

ACT, asthma control test; BMI, body mass index; FEV1, Forced expiratory volume in one second; PEF, peak expiratory flow; SD: standard deviation

asthma have a better response to steroids, and a greater FEV1 (8, 9).

Higher incidence of GERD, frequent hospitalizations, poor respiratory function and late onset disease in our nonallergic asthmatics are consistent with a late onset and more severe form of the airway disease, which is more commonly triggered by GERD, besides infections irritants, and stress reported in patients with intrinsic or nonatopic asthma (3, 8, 9).

In line with higher frequency of milder form of the disease in allergic than nonallergic phenotype in our study population, fewer subjects with severe asthma were reported to have positive skin prick tests to  $\geq 1$  allergens (10) while patients with severe asthma had reduced allergic responses compared with those with milder disease (11) with fewer positive tests in severe asthmatics than those from mild and moderate asthmatics (10, 12). The atopy rate and the allergen spectrum of the research participants were compatible with the previous multi-center national asthma research findings (13).

Besides, early age at onset in our patients with allergic asthma supports that early age at onset may reasonably define a distinct group of asthmatics in which allergic factors contribute to a large portion of their symptoms and disease (4).

Given the increased likelihood of hospital admissions and pronounced deterioration of respiratory

functions in nonallergic asthmatics alike to be seen in uncontrolled asthmatics in our study population, it seems notable to emphasize that, besides frequent hospital admissions, both phenotypes were also associated with higher incidence of GERD rather than chronic rhinitis/rhino-sinusitis, while the onset of asthma was at a later age ( $\geq 40$  years) in nonallergic asthma but earlier ( $< 40$  years) in the uncontrolled asthma.

In relation to concurrent increases in the prevalence of obesity and asthma along with emerging data on potential overlapping pathologic mechanisms, albeit the exact nature has not yet been clarified, a link has been suggested between these diseases with a significant public health effect (14, 15). In our study population obese asthmatics (36.0%) were mostly female with higher likelihood of later ( $\geq 40$  years) onset of the disease while normal/overweight asthmatics were determined to have better FEV1 values and higher ratio of chronic rhinitis/rhino-sinusitis. Similarly, increase in the risk of asthma, more severe or difficult-to-control asthma phenotype and altered response to asthma controller therapy were considered to be more likely among obese asthmatics, which emphasize that weight loss in obese asthmatic subjects can lead clinical and physiologic improvement (15, 16).

Given the similar asthma control rates between normal/overweight and obese asthmatics, while poor respiratory function parameters in the latter group in

our study population, our findings are consistent with the indication that increased BMI was not a clinically significant modifier of impairment but associated with a modest reduction of therapeutic efficacy of ICS-containing regimens based on indices of airway inflammation and lung function in mild-to-moderate asthma (15).

Hence alike to allergic asthmatics, normal/overweight asthmatics were also associated with earlier onset of the disease, better respiratory function and increased likelihood of chronic rhinitis/rhino-sinusitis in the present study compared to nonallergic and obese asthmatics.

Predominance of female gender, earlier onset of the disease, lesser ratio of GERD, higher incidence of perennial and psychological triggers and more frequent hospital admissions were the main characteristics in patients with uncontrolled asthma (28.0%), while milder form of the disease and higher FEV1 values were identified in controlled asthmatics (22.0%).

Earlier onset of the disease (<40 years of age, 59.0%) was specific to normal/overweight, allergic and uncontrolled asthmatics, while later onset ( $\geq$ 40 years of age, 41.0%) was identified primarily in obese and nonallergic asthmatics.

Pulmonary function tests (FEV1 and FVC) were reported to be marginally lower in late-onset disease than in early, in the past studies, despite the reported duration of illness being significantly less in late-onset asthma (4, 8). Consistently, in our study population the later age of onset in nonallergic and obese asthmatics, these two phenotypes were associated with lower FEV1 values which may indicate a more rapid decline in lung function in late-onset disease (4).

Consistent with published data on the higher frequency of GERD in severe asthma (10), our findings revealed that uncontrolled and nonallergic types showed higher frequency of GERD and poorer respiratory function. Moreover, in another research on asthma and its comorbidities in Turkey, hypertension, diabetes mellitus, GERD, psychological disorders, obesity, and hyperlipidaemia were significantly more prevalent in the asthmatic group. Interestingly, coronary artery disease (CAD) and congestive heart failure (CHF) were more common in the analgesic exacerbated respiratory disease (AERD) group; CAD/CHF was associated with AERD (OR: 4.5; 95% confidence interval: 1.206–16.93) (17).

Based on increased likelihood of poor lung function and more severe forms of the disease leading frequent hospitalizations in certain phenotypes such as nonallergic and uncontrolled asthma, our findings emphasize the consideration of specific characteristics of

asthma phenotypes in identification of patients at risk for persistent lung function abnormalities and/or adverse health outcomes.

Notably, our findings indicate an alteration in asthma related phenotypic characteristics specific to certain geographical regions. Achievement of asthma control was remarkably higher in Central Anatolia and Marmara regions which host Ankara as the second largest city and capital of Turkey and Istanbul as the largest city of Turkey, respectively. Hence, higher number of tertiary care centers including university hospitals in these regions along with specialist physicians and educational sessions seems to have a role in better asthma control rates in patients from these regions. In this regard, patients from Eastern-Southeastern regions, where the educational level as well as the number of hospitals and specialists are lower than other regions of Turkey, were shown to be associated with more severe forms of the disease and higher number of asthma related hospital admissions within the last year besides higher rate of active smoking.

Interestingly, despite achievement of highest asthma control rate, Marmara region was also associated with more severe forms of the disease and higher number of asthma related hospital admissions within the last year. This finding may be explained by the fact that Marmara region is the Turkey's main industrial region and the most developed area.

Current descriptions of asthma phenotypes are limited by subjectivity and poor coherence with considerable overlapping between clinical and pathological phenotypes in recent classifications. Therefore, it seems challenging to recognize a particular phenotype in asthma and direct treatment strategies accordingly (3). Nevertheless, using clinical and physiologic characteristics combined with the knowledge of biomarkers have been recommended for physicians to guide the treatment of asthma, especially in case of severe, persistent, or refractory forms of the disease (3).

Hence, as many asthmatic patients from different geographic regions of Turkey have involved in this presented study, evaluation of comprehensive data on the clinical overlaps seem to contribute to improve phenotype characterization and to increase our understanding of disease pathogenesis and to tailor effective therapies in the clinical practice.

With the help of data from genetic, immunologic and pathological studies (18) enabling identification of possible markers that should differentiate phenotypes from each other, introduction of special phenotype related asthma treatment seems likely (19). Accordingly, it was indicated that data from cohorts of asthmatic subjects enrolled in prospective clinical trials

may provide an opportunity for more robust cross-sectional and longitudinal assessment of the asthma given the detailed phenotypic characterization of asthma in these studies (15).

In conclusion, our findings related to evaluation of phenotypes for the first time in a cohort of adult asthma patient population in Turkey revealed existence of clinical/trigger related phenotypes based on BMI, allergic status, control level and geographical location with more frequent respiratory function abnormalities and/or adverse health outcomes in uncontrolled, obese and nonallergic phenotypes and particularly among females. In this regard, our findings emphasize that differentiating asthma based on BMI, presence of allergy, triggering factors, control level and geographical location seems to contribute to effort in isolation of genetic differences, clarify the pathophysiology and enable selection of more appropriate therapeutic approaches.

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