

Original article

Are risk factors of childhood asthma predicting disease persistence in early adulthood different in the developing world?

Background: Predictive factors of childhood asthma for favorable prognosis may differ between populations where a variety of genetic and environmental factors are present.

Objectives: To document the factors predicting disease persistence in early adulthood in Turkey.

Methods: An outpatient cohort ($n = 115$) with a mean follow-up duration of 11.4 ± 0.2 years was evaluated. Complete remission was defined as no asthma symptoms, no use of controller medication, no airflow limitation and no airway hyper-responsiveness, and clinical remission as no symptoms and no use of controller medication, within the past year.

Results: The mean ages during referral and at the final visit were 5.8 ± 0.2 and 17.1 ± 0.2 years, respectively. Thirty-one (27%) were in complete remission, and a further 30 (26%) in clinical remission. In multivariate logistic models, diminished airflow [forced expiratory volume in 1 s (FEV_1) $< 80\%$ vs $\geq 80\%$] at the initial lung function test predicted current diminished airflow (8.422; 2.202–32.206) (odds ratio; 95% confidence interval), and presence of obstructive pattern (FEV_1 /forced vital capacity (FVC) $< 80\%$ vs $\geq 80\%$) predicted current obstructive pattern (29.333; 3.022–284.724). Furthermore, female gender appeared to predict persistence of asthma symptoms (3.330; 1.250–8.333) and absence of clinical remission (2.398; 1.038–5.254); eosinophilia predicted persistence of symptoms (4.271; 1.080–16.889) and presence of airway hyper-responsiveness (3.723; 1.129–12.278).

Conclusions: Diminished airflow, female gender and eosinophilia appear to predict an adverse outcome of childhood asthma, supporting the concept that variability may exist between populations.

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Characteristics of asthmatic children may be used to predict the subsequent likelihood of having asthma in adult life or the resolution of the disease. This information is especially valuable in planning treatments and, potentially, in preventive interventions, in giving information to parents regarding prognosis, and finally, in improving our understanding of the asthma mechanism and its phenotypes. This information can be gained by following cohorts over a period of time that encompasses the transition from childhood to adult life (1). To date, there have been relatively few studies (1–9), and the available information has been gained from cohorts based on asthma outpatients (2–4) or on general populations (1, 5–9); all studies have been conducted in western countries. The results of these studies are consistent regarding the increasing severity of disease, lessening the likelihood of disease resolution (9). Presence of atopy (1), bronchial hyper-reactivity (1, 4, 10, 11), airway obstruction (1, 4) and female gender (2, 3, 6, 9, 12, 13) also appear to predict the persistence of childhood

asthma. However, the roles of age at initial symptoms (2, 14, 15), eosinophilia (16) and treatment (4, 13) are far less consistent between studies.

According to our current understanding, in addition to the major role of genetic factors, environmental factors may also contribute to the development and possibly progression of allergy and asthma phenotypes (17). Thus, studies to determine the risk factors for persisting disease need to be conducted in developing or underdeveloped countries, and the results generated will hopefully broaden or at least confirm our current understanding. Turkey is situated between Europe and Asia within the Balkan and Middle East regions and is the second most populous country in Europe. Several investigations using questionnaires adopted from the The International Study of Asthma and Allergies in Childhood (ISAAC) yielded a prevalence rate of asthma in children in Turkey between 2.8% and 14.5% (18, 19). However, there is a lack of data regarding outcome and risk factors for the persistence of childhood asthma in Turkey as well as in countries within

the region, which we believe holds critical importance in terms of understanding differences and similarities in asthma and its progression between different countries/cultures. This study was conducted in a group of Turkish children to determine which risk factors during childhood may predict the persistence of asthma in early adulthood.

Material and methods

In this study, asthmatic children of an outpatient clinic with regular follow-up data were evaluated retrospectively. However, to determine current status, a final visit including a questionnaire and clinical work-up was required, and therefore only those providing consent were included in the study.

Patients

The study was conducted in a single allergy-asthma outpatient clinic in Ankara, Turkey, which is the largest of its kind catering to pediatrics in the country. While the clinic serves as a referral center for the entire country, patients may also be admitted upon request; thus, it functions as both a primary and secondary health care service. One hundred and fifteen children (45 girls, 70 boys) with asthma, regularly followed up between 1990 and 2000 by the outpatient clinic were selected according to the following inclusion criteria: (i) spirometry could be properly performed; (ii) patients were followed up by regular visits (i.e. at least one visit every 2-year period) for a duration of at least 6 years; (iii) patients were aged ≥ 16 years and (iv) patients provided a written informed consent to participate in the study. All patients had a history of recurrent wheezing and dyspnea and had been diagnosed with asthma according to the American Thoracic Society criteria (20). All were documented to have reversible airway obstruction with spirometry, and other obstructive airway disorders had been excluded by relevant investigations if required. Presence of current individual and/or parental smoking habit was not a prerequisite for selection. The exclusion criteria were: (i) upper and lower respiratory tract infection in the previous 8 weeks; and (ii) presence of any other respiratory diseases (cystic fibrosis, primary ciliary dyskinesia, tuberculosis) or other seriously interfering diseases. Before all visits, patients had to discontinue their asthma medication for a specified amount of time (short-acting beta-2 agonists, anticholinergics: 8 h; cromolyn sodium, antileukotrienes, inhaled corticosteroids: 12 h; theophylline, long-acting beta-2 agonists: 24 h; and antihistamines: 5 days).

All parents provided written informed consent to participate in the trial, which was approved by Hacettepe University's Ethics Committee.

Study design

According to the patient follow-up protocol of our outpatient clinic, a detailed entry questionnaire (including demographics, time of onset of the disease, family history, presence of other atopic diseases, symptom frequencies and triggers) and a clinical work-up (serum total IgE, blood eosinophil count, skin-prick tests, spirometry) were carried out for each patient. Asthmatics are usually seen two or three times a year at scheduled visits and are allowed unscheduled visits whenever required. Spirometric evaluation is a routine procedure for asthmatics in both scheduled and unsched-

uled visits, and reports are retained in the patient's file as well as in a database program of the lung function laboratory, which facilitated the retrospective review.

The file records of these subjects were reviewed, and data obtained at the initial visit were collected, including demographics, age at onset of disease, personal and family history of atopic disease, serum total IgE, blood eosinophil count, and skin-prick test and spirometry results. Follow-up data included only spirometry results, and an end-study visit was conducted for all of the subjects included. Patients were invited specifically for spirometry, skin-prick and methacholine challenge testing, and determination of serum total IgE and blood eosinophil count. Data on current demographics, symptom frequencies, asthma medications, and number of attacks, emergency admittances and hospitalizations for asthma experienced during the past 12 months were also recorded.

Spirometry

Forced expiratory maneuvers were recorded on a dry rolling spirometer (2130 Spirometer; Sensor Medics Co, Yorba Linda, CA, USA). The data were presented as the percentage of predicted value, and adjusted for race, sex and height. If a patient had more than one spirometry result for a certain year, the best pre-bronchodilator test result [highest sum of forced expiratory volume in 1 s (FEV₁) and FVC] of that year was selected for analysis. Lung function test results of all visits were used to plot, in graphic form, visual and statistical analysis of trends; results of initial visit and end visit were used for multivariate regression analyses. If a patient was not able to perform a satisfactory spirometry at the initial visit, the first appropriate spirometry test results were included.

Methacholine challenge

Methacholine challenge was performed to measure airway hyper-responsiveness as described previously (21), which is a slight modification of Cockcroft's method (22). The airway response to inhaled methacholine was expressed as the concentration that caused a decrease in FEV₁ of 20% (PC₂₀). To avoid diurnal variation, all tests were performed in the morning (8:00–10:00 hours).

Skin-prick tests

Skin-prick tests with common allergens, including house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), pollens (grass, weed, and tree), molds (*Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*), animal dander (cat, dog, and horse), and food (cow's milk, egg, peanut, wheat, fish, and soy) were performed on the volar side of the forearm with commercially available extracts (ALK, Allergologisk Laboratorium A/S, Hørsholm, Denmark), saline solution and histamine control (10 mg/ml) using a bifurcated needle (Lincoln Diagnostics, Decatur, IL, USA). A positive skin-prick test response was defined as a wheal 3 mm larger than the wheal of a negative control.

Blood eosinophil counts and serum total IgE levels

Blood eosinophil counts were expressed as cells per cubic millimeter. Serum total IgE levels were measured using a commercially available fluorometric enzyme immunoassay according to the manufacturer's instruction (CAP-FEIA; Pharmacia-Upjohn, Uppsala, Sweden).

Statistical analysis

Results were expressed as either mean $\pm$ SEM or percentages of the responses to each question. The distributions of the variables were checked for normality by Kolmogorov–Smirnov test, and serum total IgE, methacholine PC₂₀ and blood eosinophil counts were log-transformed to obtain normal distribution. In the analysis of follow-up data, Student's *t*- and Mann–Whitney *U*-tests were used for normally distributed and skewed data, respectively. Univariate logistic regression models included age, age at onset of asthma, gender, atopy, untreated period from onset of asthma, lung functions (FEV₁, FVC, FEV₁/FVC), serum total IgE, eosinophil count, parental asthma/atopy, perennial/seasonal allergy, mono-/multi-allergy, and presence/absence of comorbid atopic disease. Complete remission of asthma was defined as no asthma symptoms, no use of controller medication, no airflow limitation (FEV₁ $\geq$ 80%), and no airway hyper-responsiveness (PC₂₀ $\geq$ 8 mg/dl), and clinical remission as no asthma symptoms and no use of controller medication, within the past year. Logistic regression analyses were performed to investigate the independent effects of different variables on the two types of remission in addition to the separate components used in defining remission of asthma. Initially, the crude association between risk factors and dependent variables was analyzed. Variables that were associated with the outcomes in the univariate analysis at a *P*-value of <0.25 were examined in the multivariate logistic regression models. A backward reduction modeling strategy was used. Backward elimination started with all the variables in the model. Then, at each step, variables were evaluated for entry and removal. The score statistic was always used for determining whether variables should be removed from the model. Wald statistic was used to select variables for removal (by default 0.10). The size of the effect of each of the risk factors was measured using the odds ratios (ORs) and 95% confidence intervals (CIs).

For all hypothesis tests, two-sided *P*-values <0.05 were regarded as statistically significant; all analyses were performed using the SPSS software version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

According to our database, we see almost 1000 asthmatics annually. Most of these were seen only once and the visit was usually requested by local physicians for allergy work-up and/or confirmation of reasons for asthma. Between 1990 and 2000, there were 672 patients with at least 2 years of follow-up. Of the 672 patients, 270 fulfilled the exclusion–inclusion criteria of the study. Of these, 100 could not be contacted (change of residence or other reasons), 51 refused to participate in the study [response rate 67.6% (115/170)] primarily because of lack of time (almost 80%) and another four were excluded because of loss of their patient files. Of the remaining 115 patients (male/female: 70/45) with mean clinical and lung function follow-up durations of 11.4 ± 0.2 and 9.2 ± 0.2 years, respectively, all presented for final visit work-up, but 11 refused methacholine inhalation test because of their concerns for bronchospasm. Their characteristics at the initial and end visits are summarized in Tables 1 and 2. Their ages during the

Table 1. Patient characteristics at enrollment and end visit

Characteristics	
Sex (female/male)	70/45
Age at initial asthma symptoms, year*	2.8 ± 0.2
Age at asthma diagnosis, year*	5.8 ± 0.2
Period between initial asthma symptoms and initiation of asthma-specific treatment, year*	2.9 ± 0.2
Duration of follow-up, year*	11.4 ± 0.2
Duration of lung function follow-up, year*	9.2 ± 0.2
Age at the end visit, year*	17.1 ± 0.2
Atopy, <i>n</i> (%)	
At enrollment	90 (78.3)
At end visit	78 (67.8)
Presence of co-morbid disease, <i>n</i> (%)	52 (45.2)
Familial atopic disease, <i>n</i> (%)	30 (26.1)
Complete remission, <i>n</i> (%)	31 (27)
Clinical remission, <i>n</i> (%)	30 (26)
Airway hyper-responsiveness at the end visit, <i>n</i> (%)	
Absence (methacholine PC ₂₀ >8 mg/ml)	43 (41.3)
Presence (methacholine PC ₂₀ ≤ 8 mg/ml)	61 (58.7)
Current use of asthma controller <i>n</i> (%)	30 (26.1)
Presence of reported current <i>n</i> (%)	
Asthma symptoms	35 (30.4)
Use of rescue medication	32 (27.8)
Emergency admittance	4 (3.5)
Hospitalization	–

PC₂₀ provocative concentration causing 20% decline in FEV₁.

*Mean $\pm$ SEM.

Table 2. Lung function and laboratory test results at enrollment and end visit

	At enrollment* (mean $\pm$ SEM)	End visit (mean $\pm$ SEM)
FVC %†	97.2 ± 1.7	113.3 ± 1.6
FEV ₁ %†	98.0 ± 2.0	100.2 ± 1.6
FEV ₁ /FVC	87.3 ± 0.7	80.3 ± 0.9
FEF _{25–75} %†	79.9 ± 2.5	87.4 ± 2.6
PEF %†	123.3 ± 3.7	97.2 ± 1.6
VC %†	–	113.8 ± 1.6
TLC %†	–	139.5 ± 4.2
RV %†	–	118.5 ± 1.8
RV/TLC	–	0.25 ± 0.01
sGaw %†	–	94.6 ± 3.7
PC ₂₀ (mg/ml)	–	7.9 ± 0.6
Total IgE	$362.4 \pm 43.6^\ddagger$	$450.7 \pm 66.8§$
Eosinophil count (per mm ³)	403.6 ± 35.3	255.0 ± 20.0

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FEF_{25–75}, forced expiratory flow; PEF, peak expiratory flow; VC, vital capacity; TLC, total lung capacity; RV, residual volume; sGaw, specific conductance.

*If patient was unable to perform satisfactory lung function test at enrollment, the first appropriate test of that patient was included as the initial test.

†Percent of predicted.

‡In kU/L.

§In IU/ml.

initial visit ranged between 6 months and 12 years (mean age 5.8 ± 0.2 years), and the mean age at asthma diagnosis was 5.8 ± 0.2 years. Although 78.3% were

atopic at the first visit, this rate fell to 67.8% at the end visit.

At the end visit, 31 of these subjects (27%) were in complete remission of asthma and a further 30 (26%) were in clinical remission. Approximately 30% ($n = 35$) and 28% ($n = 32$) reported asthma symptoms and use of short-acting beta-2 agonist, respectively, within the last year. Approximately 26% ($n = 30$) were on regular prophylactic medication and 43 (41.3%) had a $PC_{20} > 8$ mg/ml. No one reported current or ever smoking.

FEV₁-time graphs

Grouping of study subjects according to enrollment characteristics, i.e. gender, presence/absence of atopy or other atopic disease, family history, perennial/seasonal allergy, and onset of asthma symptoms before and after the age of 3 years showed overlapping trends on FEV₁-time graphs. Grouping of subjects according to initial FEV₁ ($\geq 80\%$ and $< 80\%$) and FEV₁/FVC ($\geq 80\%$ and $< 80\%$), however, showed that characteristics of each group consistently persisted throughout the follow-up (Fig. 1). FEV₁-time graphs constructed by grouping subjects according to end-visit characteristics, i.e. presence/absence of airway hyper-responsiveness, being symptomatic/asymptomatic, presence/absence of atopy or other atopic disease, air trapping (residual volume/total lung capacity [RV/TLC]) $\geq 25\%$ or $< 25\%$, and perennial/seasonal allergy, again showed overlapping trends, whereas grouping subjects according to final FEV₁ ($\geq 80\%$ and $< 80\%$) and FEV₁/FVC ($\geq 80\%$ and $< 80\%$) again showed that characteristics of each group had persisted (Fig. 2).

Risk factors

Results of univariate analysis are shown in Table 3. Backward multivariate logistic regression analyses showed that diminished airflow (FEV₁ $< 80\%$ vs $\geq 80\%$) at the initial lung function test predicted current diminished airflow (FEV₁ $< 80\%$ vs $\geq 80\%$) (OR; 95% CI: 8.422; 2.202–32.206), and obstructive pattern (FEV₁/FVC $< 80\%$ vs $\geq 80\%$) predicted current obstructive pattern (29.333; 3.022–284.724). Furthermore, initial FEV₁/FVC predicted current obstructive pattern (FEV₁/FVC $< 80\%$ vs $\geq 80\%$) (1.156; 1.054–1.267), diminished airflow (FEV₁ $< 80\%$ vs $\geq 80\%$) (1.109; 1.019–1.209) and air trapping (RV/TLC $\geq 25\%$ vs $< 25\%$) (1.070; 1.017–1.126). Female gender appeared to be a predictor of persistence of asthma symptoms (3.330; 1.250–8.333) and absence of clinical remission (2.398; 1.038–5.254); and eosinophilia a predictor of persistence of symptoms (4.271; 1.080–16.889) and presence of airway hyper-responsiveness (3.723; 1.129–12.278). There was no predictive childhood characteristic for complete remission during early adulthood.

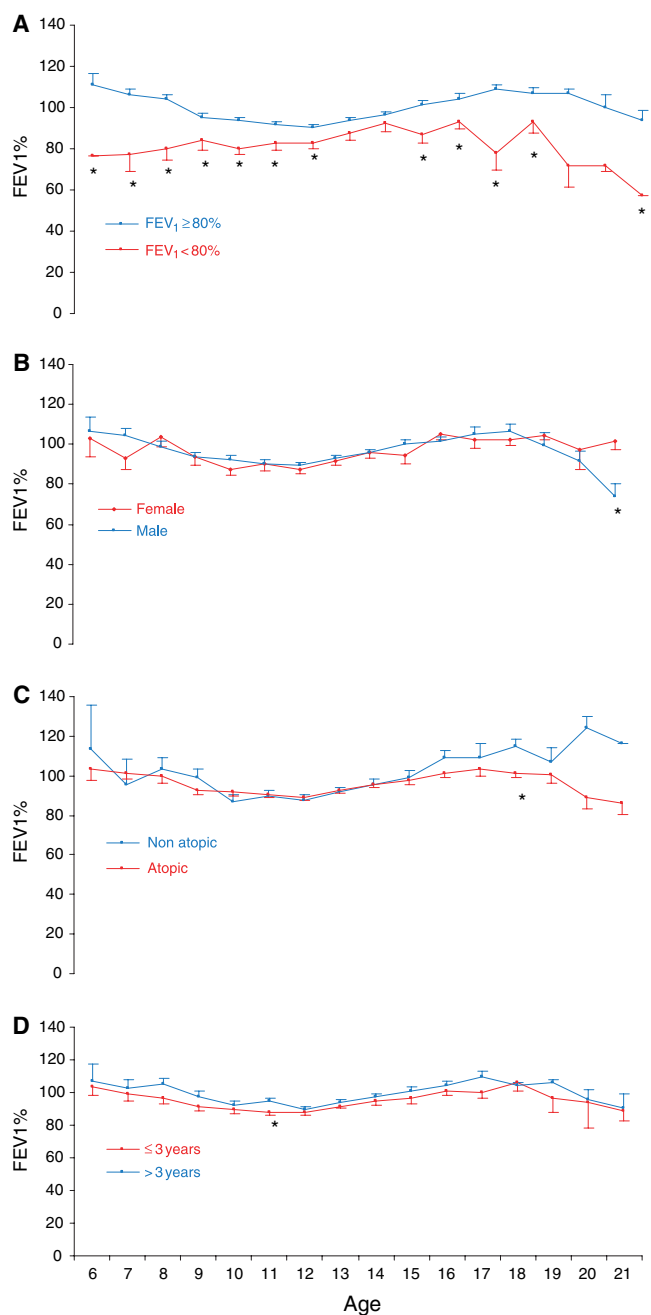


Figure 1. Time trend of forced expiratory volume in 1 s (FEV₁) according to various initial characteristics. (A) First FEV₁ $\geq 80\%$ vs $< 80\%$; (B) males vs females; (C) atopics vs non-atopics; (D) onset of asthma symptoms before vs after the age of 3 years. * $P < 0.05$.

Discussion

We characterized 115 children with asthma over a follow-up period of 10 years and found that 31 (27%) and a further 30 (26%) of the 115 patients were in complete and clinical remission, respectively, during early adulthood. Childhood characteristics of female gender, eosinophilia,

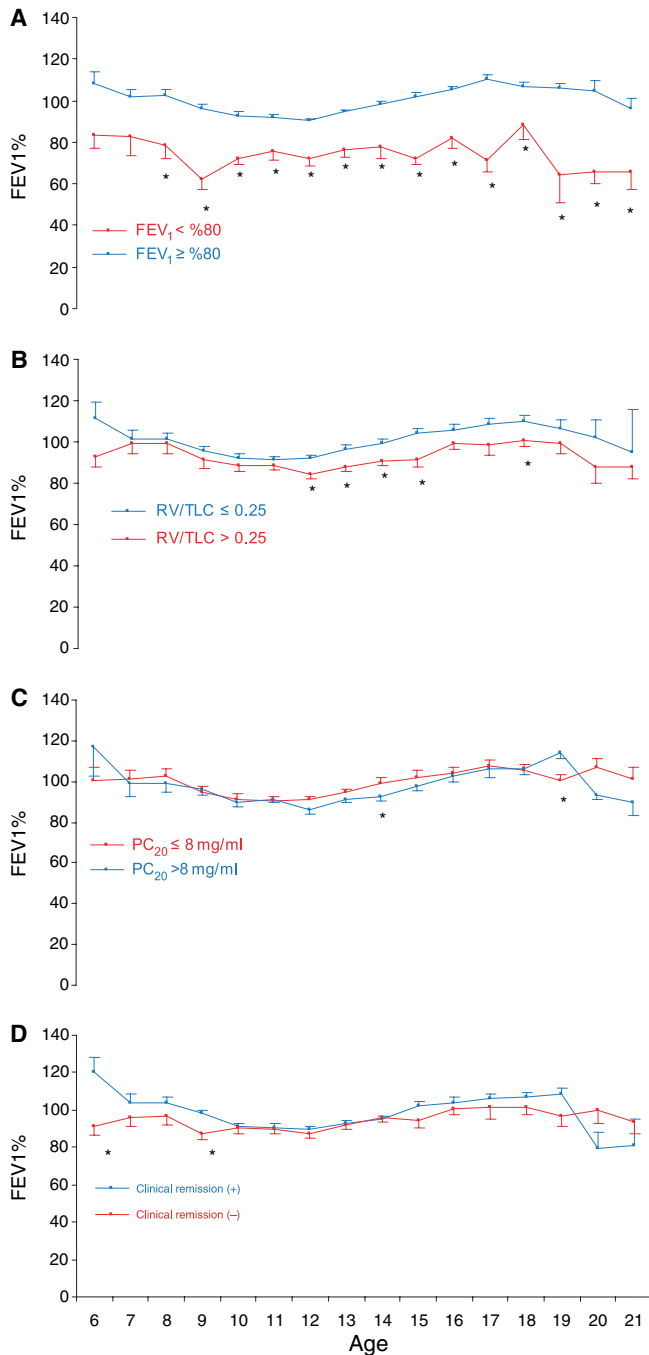


Figure 2. Time trend of forced expiratory volume in 1 s (FEV_1) according to various final visit characteristics. (A) Final $FEV_1 \geq 80\%$ vs $< 80\%$; (B) residual volume (RV)/total lung capacity (TLC) ≤ 0.25 vs > 0.25 ; (C) PC_{20} (provocative concentration causing 20% decline in FEV_1) ≤ 8 vs > 8 mg/ml; (D) presence (+) vs absence (-) of clinical remission. * $P < 0.05$.

diminished airflow, and presence of obstructive pattern appeared to predict adverse outcome of childhood asthma. Although gender and lung function data were consistent with previous longitudinal studies conducted in

Table 3. Results of six univariate logistic regression analyses

	Absence of complete remission 84 vs 31			Absence of clinical remission 54 vs 61			Presence of AHR 61 vs 43			Presence of air trapping 51 vs 64			Presence of diminished airflow ($FEV_1 < 80\%$) 13 vs 102			Presence of obstructive pattern ($FEV_1/FVC < 80$) 18 vs 97		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.02	0.84–1.24	0.834	1.08	0.91–1.29	0.354	1.03	0.85–1.26	0.784	1.21	1.02–1.45	0.034	1.27	0.98–1.64	0.068	1.13	0.90–1.42	0.278
Female gender	1.84	0.75–0.46	0.181	2.39	1.11–5.13	0.026	1.44	0.64–3.26	0.383	0.74	0.35–1.57	0.432	1.39	0.43–4.42	0.589	1.16	0.12–1.27	0.119
Age of asthma-onset	1.23	0.99–0.51	0.052	1.13	0.96–1.32	0.143	1.12	0.94–1.35	0.218	1.05	0.90–1.23	0.534	1.15	0.91–1.45	0.233	1.01	0.81–1.25	0.962
Having asthma after the age of 3 years	1.58	0.67–3.69	0.295	1.24	0.59–2.60	0.566	1.39	0.63–3.06	0.419	1.13	0.54–2.36	0.754	0.79	0.24–2.59	0.699	0.60	0.21–1.74	0.348
Log IgE (at enrollment)	1.90	0.91–3.99	0.089	1.75	0.86–3.54	0.123	1.67	0.80–3.42	0.173	1.13	0.57–2.23	0.719	0.47	0.17–1.25	0.130	0.66	0.27–1.62	0.366
Log eosinophil count (at enrollment)	1.52	0.52–4.40	0.445	1.87	0.69–5.09	0.222	3.17	1.06–9.20	0.039	0.94	0.36–2.48	0.899	0.59	0.13–2.50	0.474	0.35	0.10–1.26	0.108
Personal atopy (+)	2.75	1.08–6.99	0.034	1.44	0.58–3.53	0.432	1.97	0.78–4.20	0.149	1.56	0.62–3.39	0.334	1.60	0.33–7.74	0.558	1.47	0.39–5.53	0.572
Being multi-sensitive (>2) at enrollment	0.83	0.30–2.31	0.726	1.18	0.50–2.79	0.705	0.81	0.31–2.10	0.669	1.12	0.48–2.65	0.793	1.52	0.46–5.42	0.521	1.19	0.38–3.69	0.769
Familial atopic disease (+)	0.87	0.28–2.70	0.805	1.75	0.62–4.98	0.292	0.67	0.22–2.06	0.482	1.14	0.41–3.19	0.808	1.06	0.21–5.24	0.948	0.30	0.03–2.40	0.255
Initial FEV_1 (%)	1.01	0.99–1.02	0.616	1.01	0.96–1.03	0.112	0.99	0.97–1.01	0.425	1.01	0.99–1.02	0.001	1.06	1.02–1.10	0.001	1.04	0.01–1.07	0.006
Initial FEV_1 (< 80)	2.29	0.72–7.30	0.163	2.29	0.72–7.30	0.163	3.75	0.42–33.31	0.236	1.79	0.73–4.38	0.203	7.91	2.30–27.13	0.001	3.72	1.28–10.81	0.016
Initial FEV_1/FVC	1.03	0.98–1.09	0.260	1.03	0.98–1.20	0.192	0.98	0.93–1.04	0.534	1.07	1.12–1.13	0.007	1.16	1.07–1.27	0.001	1.19	1.09–1.29	0.001
Initial FEV_1/FVC (< 80)	2.42	0.28–20.74	0.672	4.80	0.52–44.34	0.167	0.34	0.03–3.89	0.387	1.94	0.31–12.06	0.478	15.00	2.24–100.65	0.005	27.43	2.86–263.35	0.004
Period between initial symptom and diagnosis	0.84	0.67–1.04	0.110	0.96	0.79–1.17	0.673	0.83	0.67–1.02	0.081	0.98	0.80–1.19	0.828	0.95	0.70–1.31	0.772	0.94	0.71–1.24	0.642

Absence of complete remission ($n = 84$); absence of clinical remission ($n = 54$); presence of airway hyper-responsiveness (AHR) ($n = 61$); presence of air trapping ($n = 51$); forced expiratory volume in 1 s (FEV_1); presence of diminished airflow ($n = 13$); forced vital capacity (FVC) and presence of obstructive pattern ($n = 18$).

western countries, the predictor value of blood eosinophil count in our population suggests the existence of variability between populations. The present study further showed that the presence of predictive characteristics were not symmetrical in their impact on risk of asthma outcomes.

Many *in vivo* and *in vitro* laboratory studies have been conducted to highlight the etiopathogenesis of asthma. However, the complex and multifactorial nature of the disease makes it obligatory to observe real-life scenarios and, in this respect, there is a need for a significant contribution of epidemiology to the study of chronic disorders like asthma (23). It is also clear that there are several advantages of longitudinal studies over cross-sectional observations, the most important of which are that the predictive power of early factors can be assessed and age effects clarified (11). To our knowledge, this is the first study to describe childhood asthma outcome and its predictive characteristics in Turkey as well as in this region. As in most of the developing countries, a westernized life style predominates in most central urban districts. Nevertheless, many neighborhoods within the central urban districts includes a significant number of people of low socioeconomic class with a predominantly oriental life style like that seen in the rural areas. Again, as is the case in most developing countries, there is heavy emigration from rural to urban regions because of industrialization, resulting in a life style change from oriental to more western. The main characteristics of an oriental life style include wheat-based food products, overcrowded housing, early exposure to sibling or child partners, pre- and postnatal exposure to smoking, bedroom sharing, wool pillows/beds, relatively low hygiene and maintenance of animals (e.g. chicken, turkey, duck, dog and sheep) in the yard. Furthermore, in the last few decades, air pollution has substantially increased because of motor vehicle exhaust emission, particularly in central districts of the cities, and the use of poor-quality charcoal in underprivileged districts.

Limitations

Several limitations of this study may be highlighted. Perhaps the most relevant is the inclusion of an outpatient cohort, which could be limited in reflecting the trends in our population. Several outpatient cohorts have been published, and they have often been criticized for examining patients at the more severe end of the disease-severity spectrum and reporting lower rates for asthma remission (2, 3). This was not the case in our cohort, however, with almost 70% reporting no current asthma symptoms and 80% having normal lung functions in early adulthood. The most probable reasons for the differences observed in our cohort include: (i) as our outpatient clinic accepts patient admissions in addition to referrals, there is increased likelihood of the inclusion of mild asthmatics in the cohort; and (ii) as asthma is

generally accepted in the Turkish population as a disease with unfavorable prognosis, parents usually prefer that their children be treated in the most experienced clinics. We believe that inclusion of patients who reflect a wider range of asthma severity is an advantage of this study. While it does not completely eliminate the possibility of a selection bias, we believe that our results may better reflect the trends in the Turkish population. Another remarkable limitation of the study was the inclusion of only 115 of 270 eligible patients. However, the reason in the majority of cases was inability to establish contact rather than refusal to participate. Finally, because of the nature of the study, there was no comparison with a group of children without asthma and therefore our study cannot address whether persistence factors are different or similar to factors which might influence the onset of asthma.

Lung function as a risk factor

Several studies investigating childhood risk factors for asthma outcome have consistently shown that better lung function was significantly associated with better prognosis during adulthood (6, 14). In our study, we showed that diminished airflow and presence of obstructive pattern during childhood predicted the presence of obstructive pattern and decreased airflows in early adulthood, respectively. These results are in line with the previous findings in western countries. Although we characterized our study groups twice over a follow-up period of 10 years, we monitored lung function throughout the study period and demonstrated that patients with reduced airflows and/or obstructive pattern during childhood persisted on this trend throughout the study period. The diminished functions are not, however, a consequence of their ongoing lung disease process during the school years, rather they were already present by the age of 6 years.

Allergy as a risk factor

There is convincing evidence that childhood asthma constitutes a spectrum of different phenotypes with different prognoses. It has also recently become clear that children who progress to develop persistent wheezing beyond infancy and early childhood usually have a family history of asthma and allergies and present with allergic symptoms very early in life (24). According to current understanding, the expression of allergy and atopy, while primarily genetically determined, is also dependent on exposure to certain environmental factors. Although they are clearly shown as risk factors for the development of persistent asthma in infants and young children (25), available findings, as well as those of our present study, are far from conclusive that they contribute to the risk profile for developing adulthood asthma (13, 26). Furthermore, we were unable to demonstrate the contribu-

tion of various characteristics of allergy and atopy to prognosis, i.e. perennial/seasonal allergy, mono-/multi-allergy, and presence/absence of comorbid atopic disease. This supports the concept (13) that once asthma has become established in the child, inflammation appears to run its own course, irrespective of the subject's atopic status. However, our findings might have been influenced by the asthma diagnosis practices of our physicians, as most of our children were atopic. In some studies, a favorable prognosis is found in children with negative skin tests or positive test to only a few allergens, whereas the most extensive atopic asthmatic subjects had the worst asthma prognosis (27).

Eosinophilia as a risk factor

Logically, identification of specific inflammatory markers is a necessary future step to predict disease persistence. In young children, eosinophil cationic protein and interleukin-2 receptor were reported to be helpful in predicting asthma outcome, as increased levels were associated with a persistence of symptoms (28, 29). Very recently, high levels of exhaled nitric oxide were shown in adolescents with a past history of asthma but in complete clinical remission during the preceding year (30). The discrepancy between clinical evaluation and levels of inflammatory markers has led to the suggestion that markers of inflammation might be of little help in predicting the clinical and long-term course of asthma (13). However, in our study, we demonstrated that high blood eosinophil count, an indirect marker of airway inflammation, was predictive for the persistence of symptoms as well as for the presence of airway hyper-responsiveness. Airway infiltration by eosinophils and T lymphocytes is recognized as being central to the pathophysiology of asthma (31), and peripheral eosinophilia is a frequent finding in a large proportion of subjects with asthma. However, very little evidence supports the predictive value of blood eosinophilia in relation to asthma outcome; most of the studies failed to report a predictive value for blood eosinophilia. Ulrik (16, 32) reported that a higher eosinophil count in childhood might be associated with a lower FEV₁ in early adulthood. Longitudinal studies of adult asthmatics have revealed a borderline association between eosinophil count at enrollment and subsequent decline in FEV₁ (33). A possible explanation is that the peripheral eosinophil count is related to the severity of current asthma, which suggests an association between increasing eosinophil count, i.e. severity of asthma, and unfavorable disease prognosis.

Gender as a risk factor

With respect to gender, available data in the literature are consistent in showing that the male predominance in asthmatic children gradually diminishes, disappearing

after puberty. After the age of 20 years, asthma incidence and severity are greater in females than in males, suggesting that prognosis in girls is worse (2, 9, 34). Weiss et al. (12) demonstrated that males had a higher incidence rate of asthma but female patients had a greater deficit, suggesting poorer long-term prognosis in women. In our study, female gender appeared to be predictive for the persistence of symptoms but not for diminished lung functions. Poorer prognosis in women has been suggested to relate to differences in lung growth and changes in relative airway diameter and parenchymal size between the sexes. In addition, hormonal differences may potentially influence airway inflammation and airway smooth muscle function; gender-related perception differences might also have a role.

Airway hyper-responsiveness and treatment

Airway hyper-responsiveness was present in 61 asthmatics at the end visit, and this was associated with a higher eosinophil count in the blood at enrollment. Previously, more severe airway responsiveness was suggested to be associated with a lower FEV₁, atopy (34), and higher IgE (3) at enrollment. In contrast to the findings of previous studies (35–37), we observed no relationship in our study group between serum total IgE levels, allergic skin test reactivity and airway hyper-responsiveness. Although the underlying mechanism has yet to be determined, we showed that higher eosinophil counts in blood appear to constitute a risk for persistence of airway hyper-responsiveness. Unfortunately, in our study population, airway responsiveness was not assessed in early life and we therefore were unable to determine its predictive value. However, the Perth Infant Asthma Follow-up Study (11) reported that the initial level of airway responsiveness is the best predictor of respiratory outcome during childhood. Furthermore, in prospective studies, the degree of airway responsiveness in childhood was one of the few variables significantly predicting persistent symptoms in adulthood (2, 6, 34). In most of these clinical studies, nearly half of the symptomatic young adults remained hyper-responsive. In subjects without current symptoms in adulthood, this proportion was much lower (2, 38).

The effect of treatment on asthma outcome has not been addressed in this paper for two reasons: first, in our clinic, although asthma treatment is conducted in line with the recommendations of the Global Initiative for Asthma (GINA) guidelines, there is no uniform treatment regimen. Patients were generally treated with very flexible protocols, including numerous dose changes and seasonal cessations of prophylactic drugs. Secondly, we believe that the records of recommended drugs available in patient files do not necessarily reflect the patient's consumption because of the well-known compliance issue, which we believe detracts from an appropriate analysis. Although certain asthma treatments

have been reported to provide better asthma control, there is not enough evidence that they improve the natural history of asthma (39), and thus it is less likely that treatment effects impacted our results.

Conclusion

Though it remains difficult to predict the outcome of asthma in an individual patient, we have described a number of factors that enable a reasonable prediction of the prognosis in our population. Although most of our findings are in line with the previous findings that lung function and female gender predict a poor prognosis, we showed that blood eosinophil count, an indirect marker of airway inflammation, may also be predictive. This latter finding also supports the concept that variability may exist between populations.

Contributors' list

- BE Sekerel had primary responsibility for protocol development, outcome assessment, and manuscript

preparation, and participated in preliminary data analysis.

- E Civelek participated in the development of the protocol and analytic framework for the study, had primary responsibility for review of files, patient screening, enrollment, and data entry, and contributed to manuscript preparation.
- S Yildirim contributed to patient screening, enrollment, data analysis and manuscript preparation.
- E Karabulut had primary responsibility for data analysis and contributed to manuscript preparation.
- A Tuncer and G Adalioglu supervised the design and execution of the study, and contributed to the final data analysis and manuscript preparation.

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