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Development of rhinitis may be an indicator for the persistence of childhood asthma[☆]

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ABSTRACT

Objectives: Results of previous studies have established several factors related with the natural course of childhood asthma. The aim of this study is to investigate the prognosis of childhood asthma and to determine possible risk factors for disease persistence.

Methods: An outpatient cohort with a median (interquartile range) follow-up duration of 19.4 (17.7–21.8) years was re-evaluated. Current clinical remission (CR) was defined as no asthma symptoms and no use of controller medication within the past year.

Results: Out of 115 patients, 78 could be surveyed with questionnaire and 46 patients with a median age of 25.3 (23.9–27.0) years were further investigated with clinical work-up. Nineteen (24.4%) patients were in CR in both visits (adolescence and young adulthood). A further 7 patients (9.0%) who were not in CR at adolescence were in CR at the young adulthood visit. However, 21 patients (26.9%) who were in CR at adolescence were not in CR at the young adulthood visit. Thirty-one patients (39.7%) with persistent symptoms at adolescence were not in CR at young adulthood, either. In multivariate logistic models, the presence of obstructive pattern (forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) <80% vs. ≥80%) in pulmonary function tests during the adolescence period (odds ratio; [95% confidence interval] (6.71 [1.65–27.29]; $p = 0.008$) and later-onset rhinitis (10.27 [1.18–89.13]; $p = 0.035$) predicted the absence of CR at young adulthood.

Conclusion: A substantial number of patients who were in CR during adolescence have re-emerging disease. The presence of obstructive pattern in adolescence and later-onset rhinitis were associated with the absence of CR in young adults with asthma. Awareness of risk factors along with early interventions may provide better results in childhood asthma.

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1. Introduction

Asthma, which is one of the most common chronic diseases worldwide, predominantly begins in childhood and may persist for a lifetime in a substantial part of patients [1,2]. Prediction of patients with persistent asthma in adulthood may help clinicians

dealing with asthmatic children and adolescents in terms of treatment planning, application of preventive interventions and informing parents regarding prognosis. Moreover, this data may improve our understanding of the mechanisms of the disease and precisely documentation of different phenotypes.

Results of a number of longitudinal cohort studies in different populations have established several childhood risk factors for disease persistence in adulthood. Along with the well determined features such as severity of initial symptoms [3,4], the presence of airway hyperresponsiveness [3,5,6] and degree of airway obstruction [3,7], there are several findings such as atopy, female sex, eosinophilia which are relatively less confirmed due to inconsistent results between studies [3,8]. In addition to initial risk factors present in early childhood, results of several studies have also revealed some recent risk factors such as rhinitis and eczema emerging during adolescence and early adulthood [9–12].

[☆] This study is presented as thematic poster presentation at the EAACI Congress 2012, 16–20 June, Geneva, Switzerland and awarded with an abstract prize.

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To investigate the prognosis of childhood asthma and to determine possible risk factors in childhood and adolescence for disease persistence, we re-evaluated our outpatient cohort of young adults with physician-diagnosed asthma after 10 years, which was the second of a series of survey in the same population.

2. Methods

In this study, an outpatient cohort, enrolled during preschool period and followed at least up to adolescence period, was re-evaluated 10 years after the adolescence visit [13] and the natural course of the disease was further investigated. To determine current status, a visit including a questionnaire and clinical work-up was performed, and therefore only those who can be contacted and providing consent were included in the study.

2.1. Definitions

Current clinical remission (CR) of asthma was defined as no asthma symptoms and no use of controller medication, within the past year.

Co-morbid rhinitis was defined by an affirmative response in the questionnaire to the following question “Do you ever get attacks of ‘hay fever’ (that is sneezing, running or blocked nose, sometimes with itchy eyes or nose)?”

Later-onset rhinitis was defined as rhinitis, which was not present in childhood and developed during adolescence or early adulthood.

2.2. Patients

The study patients and method was defined previously [13]. Briefly, the study was conducted in a single allergy-asthma outpatient clinic in Ankara, Turkey, which is the largest of its kind catering to paediatrics in the country. One hundred and fifteen children (45 girls, 70 boys) with asthma, regularly followed up between 1990 and 2006 by the outpatient clinic were allocated and needed to fulfil the following inclusion criteria: (i) spirometry could be properly performed; (ii) patients were aged >18 years and (iii) patients provided a written informed consent to participate in the study. All patients had a history of recurrent wheezing and dyspnoea and had been diagnosed with asthma according to the American Thoracic Society criteria [14]. The clinical work-up was performed in the absence of upper and lower respiratory tract infection in the previous 8 weeks; and any other respiratory diseases (cystic fibrosis, primary ciliary dyskinesia, tuberculosis) or other seriously interfering diseases. Before the visit, patients had to discontinue their asthma medication for a specified amount of time (short-acting beta-2 agonists, anticholinergics: 8 h; antileukotrienes, inhaled corticosteroids: 12 h; long-acting beta-2 agonists: 24 h; and antihistamines: 5 days).

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

2.3. Study design

According to the study protocol, a detailed questionnaire (including demographics, time of onset of the disease, family history, the presence of other atopic diseases, symptom frequencies and triggers) and a clinical work-up (serum total IgE, blood eosinophil count, skin-prick tests, spirometry, bronchial provocation test with methacholine) were carried out for each patient. 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.

2.4. Spirometry

A spirometry test using the ZAN100 spirometry system (nSpire Health, Longmont, CO, USA) to measure the prebronchodilator forced expiratory volume in one second (FEV₁), FEV₁/FVC (forced vital capacity), and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25–75}) was performed in patients. Results were compared with references and reported as a percentage of the predicted value [15].

2.5. Methacholine challenge

Methacholine challenges (MCCs) were performed according to a protocol described by Cockcroft et al. [16] as detailed previously [17]. Briefly, after saline inhalation, doubling concentrations of methacholine were inhaled during 2-min tidal breathing period every 5 min, starting with 0.06 mg/ml up to 16 mg/ml or until a fall in FEV₁ of at least 20% was obtained. The concentration of agents producing 20% fall in FEV₁ (PC₂₀) was calculated by linear interpolation on the log dose-response curve. A PC₂₀ ≤ 8 was considered to represent a positive test. The aerosols were generated by the DeVilbiss Model 646 (DeVilbiss Co., Somerset, PA, USA) nebulizer attached to an air compressor (Pulmo-Aide, DeVilbiss Co., Somerset, PA, USA), with an output of 0.25 ml/min. The same nebulizer was used for each challenge. Duplicate spirometry was performed at 0.5 and 1.5 min after each inhalation. As suggested [18], methacholine was diluted in saline. Albuterol metered dose inhaler (MDI) was given to reverse bronchospasm. Spirometry was repeated 15 min post-bronchodilator administration to verify reversal of the bronchospasm.

2.6. Skin-prick tests

All participants were skin prick tested with common allergens, including house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), pollens (grass, weed, and tree), moulds (*Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*), animal dander (cat, dog, and horse) and histamine (10 mg/ml of histamine phosphate) as positive and 0.9% sterile saline as negative controls. The tests were applied on the volar surface of both forearms and recorded after 15 min, and considered as positive if the mean wheal diameter was ≥3 mm compared to the negative control. “Aeroallergen sensitization” was defined as “having at least one positive skin test response” to one of the aeroallergens tested whereas “Multiaeroallergen sensitization” was defined as “having more than one positive skin test response”.

2.7. Blood eosinophil counts and serum total IgE levels

Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter, Fullerton, CA, USA) leucocyte measurements. Serum total IgE levels were measured with the ImmunoCAP system (Phadia AB, Uppsala, Sweden) according to the manufacturer's instructions.

2.8. Statistical analysis

The PASW Statistics software package version 18.0 (SPSS Inc., Chicago, IL, USA) was used for all calculations. The distributions of all variables, including age, age at initial symptoms, age at asthma diagnosis, total IgE levels, eosinophil counts and lung function parameters were skewed; thus, results were summarized as medians and interquartile ranges. Group comparisons were

established using Mann–Whitney tests for medians (and ranges) and the chi-square test for categorical variables.

The association between demographic, laboratory and spirometric parameters and CR was analyzed using logistic regression modelling. Variables with a p value < 0.20 in univariable analysis were used for multivariable analysis. Major independent variables tested in univariable models were; age, age at onset of asthma, gender, aeroallergen sensitization, untreated period from onset of asthma, lung functions (FEV_1 , FVC, FEV_1/FVC), serum total IgE, eosinophil count, parental asthma/atopy, perennial/seasonal allergy, mono-/multi aeroallergen sensitization, and the presence/absence of co-morbid rhinitis. The strength of association between the absence of CR and risk factors was measured using the odds ratios (ORs) and 95% confidence intervals (CIs). The diagnostic performances of eosinophil counts to predict the absence of CR were determined by receiver operating characteristics (ROC) curve analysis. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for selected cut-off points.

A p level < 0.05 was considered significant.

3. Results

3.1. Patient characteristics

Of the 115 patients who have been regularly followed between pre-school and adolescence period for at least 10 years were invited for another clinical work-up in 2012. 37 of the patients could not be contacted (34 change of residence, 2 military services, 1 death due to intracranial haemorrhage). Remaining 78 patients (male/female: 45/33) had a median (interquartile range) clinical follow-up duration of 19.4 (17.7–21.8) years. During the young adulthood visit, only 26 (33.3%) of the study population were in CR, whereas 17.9% and 47.4% were on regular prophylactic and

on-demand rescue treatment during the past year, respectively. A total of 14 (17.9%) patients reported at least one emergency admission along with 3 (3.8%) hospitalization.

Of the 78 patients contacted, 46 presented for young adulthood visit (year 2012) work-up. In 32 patients, only questionnaire was performed predominantly due to lack of time or unwillingness to participate in to the clinical work up. The difference between the two groups was not statistically significant in terms of age, gender, smoking status, the presence of atopy or co-morbid rhinitis in the previous visit. However, as expected, current CR for asthma was present in only 6 (13%) of 46 patients in whom clinical work-up was performed whereas in 20 (62.5%) of 32 patients who refused to have a clinical work-up and only performed questionnaire ($p < 0.001$).

Characteristics of the study population during visits of pre-school period (enrollment), adolescence period (year 2002) and young adulthood period (year 2012) are summarized in Table 1.

When queried for preventive asthma therapy, only 14 (26.9%) out of 52 patients without current CR were on regular prophylactic treatment. Furthermore, 27 out of 37 patients with co-morbid rhinitis were not using any medication in the last year; whereas 3 patients taking antihistamines only; 2 patients taking nasal corticosteroids and 5 patients taking a combination of antihistamines and nasal corticosteroids for the treatment of rhinitis. Moreover, 10 of 15 patients with later-onset rhinitis were not taking any medication for rhinitis treatment in the last year.

3.2. Clinical remission patterns

During the young adulthood visit, only 26 (33.3%) of the study population were in CR. The percentage of patients with CR during adolescence was higher in the group with current CR [19 (73.1%)] when compared to patients without current CR [21 (40.4%)] ($p = 0.006$) at early adulthood. Later-onset rhinitis was more

Table 1
Demographical characteristics of patients.

	At enrollment (pre-school)	2002 (adolescence)	2012 (young adulthood)
N	115	115	78
Sex (female/male), n (%)	45/70 (39.1/60.9)	45/70 (39.1/60.9)	33/45 (42.3/57.7)
Age at initial symptoms, year	2.0 (0.9–5.0)	2.0 (0.9–5.0)	2.0 (1.0–5.0)
Age at asthma diagnosis, year	6.0 (4.0–7.0)	6.0 (4.0–7.0)	6.0 (4.0–7.1)
Period between initial symptoms and initiation of asthma-specific treatment, year	2.5 (1.5–4.2)	2.5 (1.5–4.2)	3.0 (1.2–4.2)
Family history of atopic disease	30 (26.1)	30 (26.1)	19 (24.3)
Age at the visit, year	6.1 (5.8–6.6)	16.9 (15.2–18.6)	25.3 (23.9–27.0)
Duration of follow-up, year	0	11.3 (9.0–13.4)	19.4 (17.7–21.8)
Co-morbid rhinitis	Data not available	52 (45.2)	37 (47.4)
Current clinical remission	0	61 (53.0)	26 (33.3)
Current use of asthma controller	115 (100)	30 (26.1)	14 (17.9)
Presence of reported current			
Asthma symptoms	115 (100)	35 (30.4)	45 (57.7)
Use of rescue medication	115 (100)	30 (26.1)	37 (47.4)
Emergency admittance	Data not available	4 (3.5)	14 (17.9)
Hospitalization	Data not available	0 (0)	3 (3.8)
Tobacco smoking	0	–	21 (26.9)
Aeroallergen sensitization	90 (78.3)	78 (67.8)	34 (73.9) ^a
Eosinophil count (mm^{-3})	350 (150–586)	200 (100–300)	300 (100–350) ^a
Total IgE (kU/L)	258 (78–543)	196 (82–548)	117 (32–237) ^a
FVC (%)	98 (86–108)	115 (102–122)	95 (88–107) ^a
FEV_1 (%)	87 (84–111)	100 (91–111)	92 (83–101)
FEV_1/FVC	88 (81–93)	82 (74–87)	82 (76–92)
FEF_{25-75}	81 (61–97)	90 (70–104)	70 (52–98)
PEF (%)	116 (95–149)	97 (86–109)	84 (73–93)
Airway hyperresponsiveness	Data not available	61 (58.7)	22 (55.0) ^b
PC ₂₀ (mg/ml)	Data not available	5.0 (1.0–16.0)	3.4 (1.3–16.0)

Data are presented as number (percentage) or median (interquartile range) unless otherwise stated.

^a Skin prick tests, eosinophil counts, total IgE measurements and pulmonary function tests were performed in 46 patients at young adulthood visit.

^b Bronchial provocation tests were performed in 40 patients.

Table 2

Patient characteristics according to clinical remission status.

	CR (+) (young adulthood)	CR (–) (young adulthood)	<i>p</i>	CR (+) (adolescence and/or young adulthood)	CR (–) (adolescence and young adulthood)	<i>p</i>
<i>N</i>	26	52		47	31	
Sex (female/male)	12/14 (46%/54%)	21/31 (40%/60%)	.627	18/29 (38.3/61.7)	15/16 (48.4/51.6)	.377
Age at, years						
Initial symptoms	1.8 (0.7–5.0)	2.3 (1.0–4.8)	.749	2.0 (0.5–4.0)	2.5 (1.0–5.0)	.179
Asthma diagnosis	6.0 (4.8–7.3)	5.8 (4.0–7.0)	.803	6.0 (4.0–7.0)	5.2 (4.0–8.0)	.842
Symptoms before age 3	15 (57.7)	29 (55.8)	.872	27 (57.4)	17 (54.8)	.820
Current tobacco smoking	5 (19.2)	16 (30.8)	.279	11 (23.4)	10 (32.3)	.388
Age at, years						
Adolescence visit	17.4 (15.1–18.8)	16.7 (15.4–18.5)	.820	17.2 (16.0–18.3)	16.7 (15.1–19.0)	.736
Family history of atopic disease	7 (26.9)	12 (23.1)	.709	12 (25.5)	7 (22.6)	.766
CR at adolescence visit	19 (73.1)	21 (40.4)	.006			
Current use of asthma controller	0 (0)	14 (26.9)	.003	3 (6.4)	11 (35.5)	.001
Aeroallergen sensitization						
Pre-school visit	22 (84.6)	40 (76.9)	.428	39 (83.0)	23 (74.2)	.347
Adolescence visit	17 (65.4)	35 (67.3)	.865	31 (66.0)	21 (67.7)	.870
Multi aeroallergen sensitization						
Pre-school visit	9 (34.6)	15 (28.8)	.704	14 (29.8)	10 (32.3)	.817
Adolescence visit	6 (23.1)	18 (34.6)	.298	13 (27.7)	11 (35.5)	.464
Co-morbid rhinitis						
Adolescence visit	13 (50)	22 (42.3)	.520	24 (51.1)	11 (35.5)	.176
Later-onset rhinitis	1 (3.8)	15 (28.8)	.01	6 (12.8)	10 (32.3)	.037
Airway hyperresponsiveness						
Adolescence visit	11/24 (45.8)	33/48 (68.8)	.060	23/45 (51.1)	21/27 (77.8)	.025
PC ₂₀						
Adolescence visit	16.0 (1.2–16.0)	2.7 (0.5–16.0)	.081	6.4 (1.0–16.0)	2.6 (0.5–7.2)	.061
Total IgE (kU/L)						
Pre-school visit	178 (57–320)	299 (72–567)	.272	201 (61–535)	372 (138–511)	.349
Adolescence visit	126 (76–266)	219 (78–665)	.111	146 (70–295)	388 (90–746)	.051
Eosinophil counts (mm ^{–3})						
Pre-school visit	300 (100–550)	300 (100–488)	.990	250 (100–400)	350 (200–700)	.039
Adolescence visit	110 (100–200)	220 (100–400)	.013	150 (100–245)	300 (140–420)	.009
FEV ₁ (%)						
Pre-school visit	94 (79–112)	95 (84–109)	.857	101 (87–114)	90 (78–101)	.046
Adolescence visit	103 (98–111)	99 (90–109)	.093	102 (96–111)	94 (80–105)	.022
FEV ₁ < 80						
Pre-school visit	7 (26.9)	11 (21.2)	.569	9 (19.1)	9 (29.0)	.311
Adolescence visit	2 (7.7)	9 (17.3)	.319	3 (6.4)	8 (25.8)	.022
FEV ₁ /FVC (%)						
Pre-school visit	88 (82–90)	88 (81–95)	.734	89 (82–94)	85 (78–91)	.086
Adolescence visit	85 (81–90)	80 (73–85)	.013	84 (79–87)	78 (69–85)	.011
FEV ₁ /FVC < 80						
Pre-school visit	4 (15.4)	12 (23.1)	.428	6 (12.8)	10 (32.3)	.037
Adolescence visit	4 (15.4)	24 (46.2)	.008	12 (25.5)	16 (51.6)	.019
FEF _{25–75} (%)						
Pre-school visit	80 (61–88)	76 (53–95)	.890	82 (72–93)	69 (44–93)	.022
Adolescence visit	99 (83–112)	81 (65–100)	.025	96 (90–106)	74 (50–101)	.026
FEF _{25–75} < 70						
Pre-school visit	7 (26.9)	20 (38.5)	.313	10 (21.3)	17 (54.8)	.002
Adolescence visit	3 (11.5)	16 (30.8)	.062	5 (10.6)	14 (45.2)	.001

Data are presented as number (percentage) or median (interquartile range) unless otherwise stated. CR, clinical remission.

frequent in patients without current CR [15 (28.8%)] when compared to patients with current CR [1 (3.8%)] ($p = 0.01$) at the young adulthood visit. The median level of eosinophil counts (median, interquartile range) [220 (100–400)] during adolescent period was significantly higher in patients without current CR than patients with current CR at young adulthood [110 (100–200)] ($p = 0.013$). Spirometry parameters including forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) and forced expiratory flow 25–75% (FEF_{25–75}) during adolescent period were

lower in patients without current CR at young adulthood when compared to patients with current CR. Data of the demographic and laboratory features of patients with or without current CR at the young adulthood visit are presented in Table 2.

In multivariable logistic models, the presence of obstructive pattern FEV₁/FVC < 80% vs. ≥ 80% at the adolescent period lung function test (odds ratio; [95% confidence interval] [6.7 [1.7–27.3]; $p = 0.008$), and later-onset rhinitis (10.3 [1.2–89.1]; $p = 0.035$) predicted the absence of current CR (Table 3) in young adulthood.

Table 3

Multivariable logistic regression analysis for the absence of clinical remission at young adulthood visit.

	CR (+)	CR (–)	<i>p</i>	OR	95% CI	<i>p</i>
Later-onset rhinitis	1 (3.8)	15 (28.8)	.01	10.27	1.18–89.13	.035
FEV ₁ /FVC < 80 at adolescence visit	4 (15.4)	24 (46.2)	.008	6.71	1.65–27.29	.008

OR, odds ratio; CI, confidence interval; CR, clinical remission. Variables included in analysis were later-onset rhinitis, FEV₁/FVC < 80 at adolescence visit, eosinophil counts at adolescence visit and the absence of CR at adolescence visit.

Table 4
Clinical remission patterns of patients in respective visits ($n = 78$).

	Adolescence	
	CR (+)	CR (–)
Young adulthood		
CR (+)	19 (24.4)	7 (9.0)
CR (–)	21 (26.9)	31 (39.7)

Data are presented as number (percentage). CR, clinical remission.

Nineteen (24.4%) patients were in CR in both adolescence and young adulthood periods (years 2002 and 2012, respectively). A further 7 patients (9.0%) who were not in CR during adolescence were in CR at the young adulthood period. However, 21 patients (26.9%) who were in CR during adolescence were not in CR at the young adulthood period. A group consisted of 31 patients (39.7%) with persistent symptoms during adolescence were not in CR at young adulthood, either (Table 4 and Fig. 1).

Analysis using ROC curves identified the role of childhood eosinophil counts in predicting the absence of CR in adolescence or young adulthood (AUC: 0.64 95% CI: 0.51–0.77, $p = 0.04$). When analyzed for the best cut-off value with the highest combined sensitivity and specificity, a cut-off value of 575 mm^{-3} for eosinophil counts was obtained with sensitivity, specificity, PPV and NPV of 33.3%, 88.4%, 66.7% and 65.5%, respectively. In multivariable logistic models, the presence of obstructive pattern in mid-expiratory flow (forced expiratory flow 25–75%, $\text{FEF}_{25-75} < 70\%$ vs. $\geq 70\%$) at the childhood lung function test (4.9 [1.6–15.4]; $p = 0.006$), later-onset rhinitis (4.8 [1.3–17.5]; $p = 0.017$) and high eosinophil counts in pre-school period ($> 575 \text{ mm}^{-3}$) (3.4 [1.1–12.6]; $p = 0.039$) predicted the absence of ever CR in adolescence or young adulthood (Table 5).

4. Discussion

In the present study, our results demonstrated that CR was absent in two third of patients with asthma in young adulthood and patients with CR at adolescence were more likely to have CR at young adulthood. Almost 50% of patients whose asthma was in CR

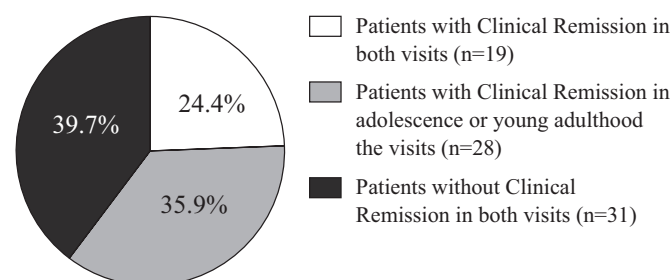


Fig. 1. Clinical remission patterns of the study group.

Table 5
Multivariable logistic regression analysis for the absence of ever clinical remission.

	OR	%95 CI	p
Later-onset rhinitis	4.80	1.32–17.48	.017
Eosinophilia ($> 575 \text{ mm}^{-3}$) at pre-school visit	3.38	1.12–12.59	.039
$\text{FEF}_{25-75} < 70$ at pre-school visit	4.94	1.58–15.40	.006

OR, odds ratio; CI, confidence interval. Variables included in analysis were later-onset rhinitis, $\text{FEF}_{25-75} < 70$ at pre-school visit, eosinophilia ($> 575 \text{ mm}^{-3}$) at pre-school visit and $\text{FEV}_1/\text{FVC} < 80$ at pre-school visit.

during adolescence had remittent disease pattern. Moreover, we found out that the presence of obstructive pattern in adolescence and later-onset rhinitis were associated with the absence of CR in young adults with asthma.

Previous longitudinal studies on the outcomes of childhood asthma have consistently established the association between the severity of asthma symptoms in childhood and lack of CR in adulthood [19–26]. In addition to this finding, we have shown in our study that the severity of asthma during adolescence period was related with adult asthma prognosis in a similar extent. Those who were asymptomatic in adolescence period are likely to be found asymptomatic in early adulthood, too. However, our results highlighted that nearly one fourth of patients who were under CR in adolescence period were symptomatic in young adulthood. Furthermore, there was a sub-group who were symptomatic in adolescence but without CR in young adulthood. Those findings seem to be related with the variability of the natural course of asthma. Besides, recent genetic studies indicate the underlying heterogeneity of the disease in terms of endophenotypes [27,28]. Further genetic based clustering studies may provide better identification of childhood asthma phenotypes and may allow accurate prediction of the asthma prognosis.

One of the most striking results of our study was the relationship of later-onset allergic rhinitis and poor asthma prognosis. Review of the literature revealed that Burgess et al. have initially established the association between accompanying or later-onset atopic diseases – such as allergic rhinitis and atopic eczema – and persistence of childhood asthma when they analyzed the data of Tasmanian Longitudinal Health Study after nearly 4 decades [9,10]. Results of our study confirmed the association of allergic rhinitis with persistence of childhood asthma in the early adulthood. Although there are major structural differences between the nasal and the bronchial mucosa, it is known that the epithelial–mesenchymal trophic unit exists from the nose to the bronchiolar–alveolar junction and that the same inflammatory cells are present throughout the airways suggesting a continuum of disease [29]. Therefore, allergic rhinitis and asthma are characterized by means of a similar inflammatory process and previous studies showed that nasal allergen exposure in patients with allergic rhinitis results in generalized airway inflammation including lower airways through upregulation of adhesion molecules and eosinophil recruitment [30,31]. Those mutual inflammatory responses may explain the association between rhinitis development and asthma persistence.

Only a quarter of the patients with accompanying rhinitis were taking regular medication including antihistamine and/or nasal corticosteroids. Querying of rhinitis symptoms in the follow-up of patients with asthma may prevent the underdiagnosis along with the undertreatment and the early and proper interventions may not only ameliorate the rhinitis symptoms, but also may contribute to a better prognosis of childhood asthma.

Results of previous studies have conflicting results about the association of blood eosinophils with the prognosis of childhood asthma [3]. Gerritsen et al. [32] had investigated 101 patients with childhood asthma 16 years later and could not find any association between eosinophilia and outcome of asthma in adulthood, whereas another follow-up study by Ulrik [33] regarding children with asthma found a correlation between the blood eosinophil count in childhood and severity of symptoms along with lower levels of FEV_1 in early adulthood. We have re-confirmed our finding in terms of the relationship of childhood eosinophilia and adverse outcome of childhood asthma at adolescence and early adulthood as well [13]. Blood eosinophil counts are well known to be associated with the severity of current asthma, that may suggest an association between

increasing eosinophil activation, i.e. severity of the inflammation at airways, and poor longitudinal changes in lung function of patients with asthma [3]. However, the evidence for such a relationship, possibly owing to the effect of corticosteroids on eosinophil inflammation in the airways is quiet limited and further studies may help providing better data.

Previous longitudinal studies primarily investigating the relationship of adulthood symptoms and childhood lung function values have clearly established an association between poor lung functions [22,34], particularly FEV₁ levels [21,24] and FEV₁/FVC ratio [35] with the adverse outcome of asthma at adulthood. Our results have revealed that in contrast to the FEV₁ values, FEV₁/FVC ratio along with FEF_{25–75} values in childhood and adolescence were significantly related with lack of CR at adulthood in patients with asthma. The association of obstruction in small airways in childhood with the poor prognosis in adulthood is a novel finding and further studies may establish the prominent role of FEF_{25–75} in predicting childhood asthma prognosis better than FEV₁ which did not emerge as a significant predictor in our study.

A relatively low number of study subjects particularly who were admitted for clinical work-up due to the unavailability to contact all patients is one of the major limitations of our study. Moreover, as we did not perform regular yearly clinical visits, our results represent a “snapshot” of the clinical status of our patients after a decade from adolescence period. The variable nature of the illness must be taken into account when interpreting our results and various fluctuations in CR status may have been overlooked.

Our study has several strengths. First of all, although we could not contact all patients of the initial study, number of the subjects who were recruited were quite satisfactory for data analysis. Furthermore, medical literature regarding outcome of childhood asthma has been dominated by developed Western countries. Considering the different exposures and treatment protocols, we think that a longitudinal data from a developing country might be an important addition.

In conclusion, we would like to indicate that a substantial number of patients with asthma who were in CR during early adulthood have re-emerging disease. The presence of obstructive pattern at lung function test and high eosinophil counts at the initial visit, and development of allergic rhinitis during adolescence/early adulthood appear to predict an adverse outcome of childhood asthma. Awareness of risk factors along with early interventions such as early diagnosis and treatment of rhinitis may provide better results in childhood asthma.

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Authors contributions

- B. Sekerel had primary responsibility for protocol development and analytic framework of the study, outcome assessment, and manuscript preparation.
- S.T. Yavuz 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 prepared the manuscript with B. Sekerel.
- E. Civelek, U.M. Sahiner and B. Buyuktiryaki had contributed to data generation, patient screening, data analysis and prepared the manuscript with B. Sekerel.
- A.F. Kalyoncu, A. Tuncer and S. Comert had contributed to protocol development, data analysis, patient follow-up and preparation and revision of the manuscript.

References

- [1] Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, *Lancet* 351 (1998) 1225–1232.
- [2] M.I. Asher, S. Montefort, B. Björkstén, C.K. Lai, D.P. Strachan, S.K. Weiland, et al., Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys, *Lancet* 368 (2006) 733–743.
- [3] C.S. Ulrik, Outcome of asthma: longitudinal changes in lung function, *Eur. Respir. J.* 13 (1999) 904–918.
- [4] W.J. Kelly, I. Hudson, P.D. Phelan, M.C. Pain, A. Olinsky, Childhood asthma in adult life: a further study at 28 years of age, *Br. Med. J. (Clin. Res. Ed.)* 294 (1987) 1059–1062.
- [5] M.R. Sears, J.M. Greene, A.R. Willan, E.M. Wiecek, D.R. Taylor, E.M. Flannery, et al., A longitudinal, population-based, cohort study of childhood asthma followed to adulthood, *N. Engl. J. Med.* 349 (2003) 1414–1422.
- [6] B.G. Toelle, W. Xuan, J.K. Peat, G.B. Marks, Childhood factors that predict asthma in young adulthood, *Eur. Respir. J.* 23 (2004) 66–70.
- [7] J.M. Vonk, D.S. Postma, H.M. Boezen, M.H. Grol, J.P. Schouten, G.H. Koeter, et al., Childhood factors associated with asthma remission after 30 year follow up, *Thorax* 59 (2004) 925–929.
- [8] R.A. Panettieri Jr., R. Covar, E. Grant, E.V. Hillyer, L. Bacharier, et al., Natural history of asthma: persistence versus progression – does the beginning predict the end, *J. Allergy Clin. Immunol.* 121 (2008) 607–613.
- [9] J.A. Burgess, E.H. Walters, G.B. Byrnes, M.C. Matheson, M.A. Jenkins, C.L. Wharton, et al., Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study, *J. Allergy Clin. Immunol.* 120 (2007) 863–869.
- [10] J.A. Burgess, S.C. Dharmage, G.B. Byrnes, M.C. Matheson, L.C. Gurrin, C.L. Wharton, et al., Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age, *J. Allergy Clin. Immunol.* 122 (2008) 280–285.
- [11] J.A. Burgess, M.C. Matheson, L.C. Gurrin, G.B. Byrnes, K.S. Adams, C.L. Wharton, et al., Factors influencing asthma remission: a longitudinal study from childhood to middle age, *Thorax* 66 (2011) 508–513.
- [12] P.E. Martin, M.C. Matheson, L. Gurrin, J.A. Burgess, N. Osborne, A.J. Lowe, et al., Childhood eczema and rhinitis predict atopic but not nonatopic adult asthma: a prospective cohort study over 4 decades, *J. Allergy Clin. Immunol.* 127 (2011) 1473–1479, e1471.
- [13] B.E. Sekerel, E. Civelek, E. Karabulut, S. Yildirim, A. Tuncer, G. Adaloglu, Are risk factors of childhood asthma predicting disease persistence in early adulthood different in the developing world, *Allergy* 61 (2006) 869–877.
- [14] Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986, *Am. Rev. Respir. Dis.* 136 (1987) 225–244.
- [15] Standardization of spirometry, 1994 update. American Thoracic Society, *Am. J. Respir. Crit. Care Med.* 152 (1995) 1107–1136.
- [16] D.W. Cockcroft, D.N. Killian, J.J. Mellon, F.E. Hargreave, Bronchial reactivity to inhaled histamine: a method and clinical survey, *Clin. Allergy* 7 (1977) 235–243.
- [17] B.E. Sekerel, Y. Saraclar, A. Tuncer, G. Adaloglu, F. Cetinkaya, Standardization of methacholine inhalation challenge, *Turk. J. Pediatr.* 39 (1997) 165–172.
- [18] P.J. Sterk, L.M. Fabbri, P.H. Quanjer, D.W. Cockcroft, P.M. O’Byrne, S.D. Anderson, et al., Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report working party standardization of lung function tests, European Community for Steel and Coal. Official statement of the European Respiratory Society, *Eur. Respir. J. Suppl.* 16 (1993) 53–83.
- [19] P.D. Phelan, C.F. Robertson, A. Olinsky, The Melbourne asthma study: 1964–1999, *J. Allergy Clin. Immunol.* 109 (2002) 189–194.
- [20] A.J. Martin, L.A. McLennan, L.I. Landau, P.D. Phelan, The natural history of childhood asthma to adult life, *Br. Med. J.* 280 (1980) 1397–1400.
- [21] J. Gerritsen, G.H. Koeter, D.S. Postma, J.P. Schouten, K. Knol, Prognosis of asthma from childhood to adulthood, *Am. Rev. Respir. Dis.* 140 (1989) 1325–1330.
- [22] M.A. Jenkins, J.L. Hopper, G. Bowes, J.B. Carlin, L.B. Flander, G.G. Giles, Factors in childhood as predictors of asthma in adult life, *BMJ* 309 (1994) 90–93.
- [23] H. Oswald, P.D. Phelan, A. Lanigan, M. Hibbert, J.B. Carlin, G. Bowes, et al., Childhood asthma and lung function in mid-adult life, *Pediatr. Pulmonol.* 23 (1997) 14–20.
- [24] D.J. Godden, S. Ross, M. Abdalla, D. McMurray, A. Douglas, D. Oldman, et al., Outcome of wheeze in childhood. Symptoms and pulmonary function 25 years later, *Am. J. Respir. Crit. Care Med.* 149 (1994) 106–112.
- [25] D.S. Postma, M.D. Lebowitz, Persistence and new onset of asthma and chronic bronchitis evaluated longitudinally in a community population sample of adults, *Arch. Intern. Med.* 155 (1995) 1393–1399.
- [26] D.P. Strachan, J.M. Griffiths, I.D. Johnston, H.R. Anderson, Ventilatory function in British adults after asthma or wheezing illness at ages 0–35, *Am. J. Respir. Crit. Care Med.* 154 (1996) 1629–1635.
- [27] H. Bisgaard, K. Bonnelykke, Long-term studies of the natural history of asthma in childhood, *J. Allergy Clin. Immunol.* 126 (2010) 187–197, quiz 189–198.
- [28] J.W. Holloway, S.H. Arshad, S.T. Holgate, Using genetics to predict the natural history of asthma? *J. Allergy Clin. Immunol.* 126 (2010) 200–209, quiz 210–201.
- [29] J. Bousquet, N. Khaltaev, A.A. Cruz, J. Denburg, W.J. Fokkens, A. Togias, et al., Allergic rhinitis and its impact on asthma (ARIA) 2008, *Allergy* 63 (Suppl. 86) (2008) 8–160.

- [30] G.J. Braunstahl, A. Kleinjan, S.E. Overbeek, J.B. Prins, H.C. Hoogsteden, W.J. Fokkens, Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients, *Am. J. Respir. Crit. Care Med.* 161 (2000) 2051–2057.
- [31] G.J. Braunstahl, S.E. Overbeek, A. Kleinjan, J.B. Prins, H.C. Hoogsteden, W.J. Fokkens, Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways, *J. Allergy Clin. Immunol.* 107 (2001) 469–476.
- [32] J. Gerritsen, G.H. Koeter, J.G. de Monchy, K. Knol, Allergy in subjects with asthma from childhood to adulthood, *J. Allergy Clin. Immunol.* 85 (1990) 116–125.
- [33] C.S. Ulrik, Peripheral eosinophil counts as a marker of disease activity in intrinsic and extrinsic asthma, *Clin. Exp. Allergy* 25 (1995) 820–827.
- [34] B. Kjellman, B. Hesselmar, Prognosis of asthma in children: a cohort study into adulthood, *Acta Paediatr.* 83 (1994) 854–861.
- [35] J. Kokkonen, O. Linna, The state of childhood asthma in young adulthood, *Eur. Respir. J.* 6 (1993) 657–661.