

EXERCISE INDUCED BRONCHOSPASM

Positive Exercise Test and Obstructive Spirometry in Young Male Conscripts Associated with Persistent Asthma 20 years Later

IRMELI LINDSTRÖM, M.D.,^{1,*} HILLE SUOJALEHTO, M.D.,¹ HARRI LINDHOLM, M.D.,²
PAULA PALLASAHO, M.D., PH.D.,¹ RITVA LUUKKONEN, PH.D.,³ JOUKO KARJALAINEN, M.D, PH.D.,⁴
ANTTI LAUERMA, M.D, PH.D.,⁵ AND ANTTI KARJALAINEN, M.D, PH.D.⁶

¹Control of Hypersensitivity Diseases, Finnish Institute of Occupational Health, Helsinki, Finland.

²Physical Work Capacity, Finnish Institute of Occupational Health, Helsinki, Finland.

³Statistical Services Team, Finnish Institute of Occupational Health, Helsinki, Finland.

⁴Centre of Military Medicine, Helsinki, Finland.

⁵Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland.

⁶Surveillance of Working Conditions Team, Finnish Institute of Occupational Health, Helsinki, Finland.

Background. Asthma often begins in childhood or early adulthood and is a common disease among conscripts. The identification of long-term predictive factors for persistent asthma may lead to improved treatment opportunities and better disease control. **Objective.** Our aim was to study the prognostic factors of the severity of asthma among 40-year-old male conscripts whose asthma began in youth. **Methods.** We studied 119 conscripts who were referred to the Central Military Hospital during 1987–1990 due to asthma and who attended a follow-up visit approximately 20 years later. Asthma severity was evaluated during military service according to the medical records, and 20 years later during a follow-up visit using Global Initiative for Asthma guidelines. We used the results of lung function and allergy tests at baseline as predictors of current persistent asthma. **Results.** Compared with baseline, asthma was less severe at follow-up: 11.8% of subjects were in remission, 42.0% had intermittent asthma, 10.9% had mild persistent asthma, and 35.3% had moderate/severe persistent asthma ($p < .001$). In multivariate models, a positive exercise test at baseline yielded an odds ratio (OR) of 3.2 (95% CI 1.0–9.8, $p = .046$), a decreased FEV₁/FVC % predicted an OR of 4.0 (95% CI 1.7–9.3, $p = .002$), and a decreased FEF_{50%} % predicted an OR of 2.8 (95% CI 1.3–6.4, $p = .012$) for current persistent asthma. **Conclusions.** About half of the men had persistent asthma at the 20-year follow-up. Positive exercise tests and obstructive spirometry results were related to the persistence of asthma and may be useful long-term prognostic factors for asthma severity.

Keywords asthma, epidemiology, exercise test, forced expiratory flow rate at 50% of vital capacity, prognostic factors, spirometry

INTRODUCTION

Asthma is a common disease among the working-age adults (1, 2), often beginning in childhood or early adulthood. Only limited information about the long-term predictive factors for persistent asthma is available concerning asthmatics in early adulthood. In a longitudinal birth cohort study, smoking and airway hyperresponsiveness to a methacholine challenge at the age of 21 predicted wheezing 5 years later (3). In the same study, atopy and decreased forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) ratio at the age of 18 years were associated with a later relapse of asthma in a subgroup of asthmatics in clinical remission at 18 years of age (4). In the European Community Respiratory Health Survey, early deterioration of lung function, high serum Immunoglobulin E (IgE), and persistent cough/mucus hypersecretion predicted moderate or severe persistent asthma (5).

Many studies have associated obstructive spirometry, for example, a decreased FEV₁/FVC ratio in asthmatic children, with poorer asthma prognosis (3, 6–8). In adult studies, a

decreased FEV₁ has predicted more severe asthma later (5, 9). Only limited knowledge exists on how the exercise test or small airway function parameters, for example, forced expiratory flow rate at 50% of vital capacity (FEF_{50%}) predict the long-term prognosis of asthma. However, in general terms, the peripheral airways have been described as playing a significant role in airway inflammation, hyperresponsiveness, and asthma control (10).

The aim was to study the severity of asthma at the age of around 40 among males who had asthma during their military service at the age of about 20. We analyzed the impact of individual characteristics and lung function tests at this age as risk factors for current persistent asthma. The identification of young men at risk of persistent asthma can lead to improved treatment opportunities and better disease control.

METHODS

Subjects

The study population originates from the Finnish Defence Forces' register and is described in detail in a recent article (11) and in Figure 1. In Finland, it is obligatory for all young men of sufficiently good health to perform either military or civil service. During 1987–1990, about 90% of

*Corresponding author: Irmeli Lindström, Control of Hypersensitivity Diseases, Finnish Institute of Occupational Health, Topeliuksenkatu 41aA, 00250 Helsinki, Finland; Tel: +358 304742136; Fax: +358 30474 2149; E-mail: irmeli.lindstrom@ttl.fi

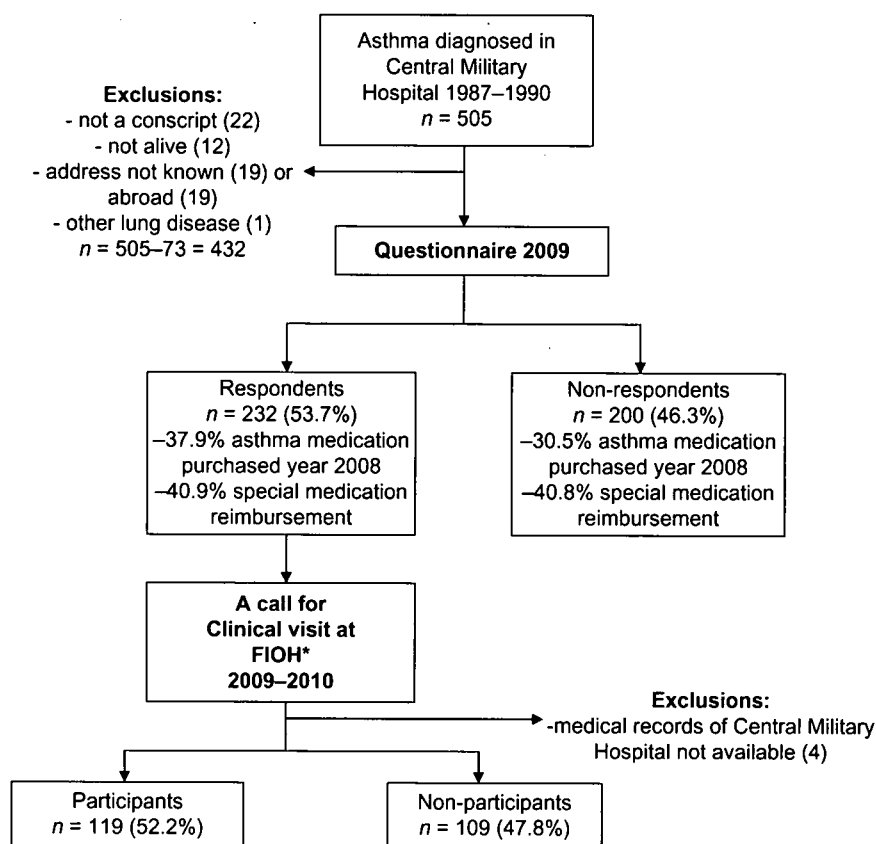


FIGURE 1.—Description of the study. The comparison of the respondents and the non-respondents was based on the nationwide registers of Finnish Social Insurance Institution.

Note: *FIOH; Finnish Institute of Occupational Health.

young men, typically at the age of 19–21 years, carried out 8–11 months of military service. Mild or moderate asthma did not provide exemption. Men with severe asthma at the age of 18 were exempted from the military service and were not included in this survey. Our study population ($n = 505$) consisted of subjects who were referred during their military service in 1987–1990 to the Central Military Hospital due to asthma. These represented an unselected population of men with mostly mild or moderate asthma, living in southern and central parts of Finland at the age of 18–27 years. A total of 232 (54%) men answered the follow-up questionnaire in spring 2009.

We used the nationwide registers of the Finnish Social Insurance Institution to obtain information on the non-respondents of the follow-up questionnaire. There was no significant difference between the proportion of respondents and non-respondents with special medication reimbursement rights for asthma medication (see (12) for details of the definition and criteria of these rights) or who had bought asthma medication in 2008 (Figure 1). In addition, the number of sick leave days due to respiratory disease did not differ between respondents and non-respondents.

All 232 respondents of the follow-up questionnaire were invited to clinical tests at the Finnish Institute of Occupational Health (FIOH). A total of 119 (51.3%) respondents accepted and attended the tests between August 2009 and April 2010, that is, approximately

20 years (18–23 years, mean 21.1 years) after their military service. The study was approved by the Ethical Committee of the Department of Medicine of Helsinki University Central Hospital. Written informed consent was obtained from the study subjects.

Collection of Data at Baseline

All clinical investigations were carried out in the Central Military Hospital between 1987 and 1990. Information on height, weight, the results of pulmonary function tests and allergy tests, the use of asthma medication, and asthma symptoms and exacerbations were elicited from the medical records. The medical records of four subjects were not available; thus, these individuals did not participate in the follow-up visit.

Ventilatory function was measured by a flow-volume spirometer (Pneumoscreen, Eric Jaeger, Germany) according to the guidelines (12), using predicted values for the Finnish population (13). In this study, the cut-off values for decreased spirometric parameters were based on the lower limits of normal and were <81 for FEV_1 % predicted, <88 for FEV_1/FVC % predicted, and <62 for $FEF_{50\%}$ % predicted. A significant reversibility of airway obstruction was defined as an increase of at least 12% and 200 ml in FEV_1 after bronchodilator administration.

Airway hyperresponsiveness to histamine was assessed using Laitinen's method (14). It was classified as severe if

the concentration of histamine causing a 15% decrease in the FEV₁ or peak expiratory flow (PEF) values (PD₁₅) was ≤ 0.10 mg, moderate for PD₁₅ values of 0.11–0.39 mg, and mild for PD₁₅ values of 0.40–1.60 mg.

A standardized "field exercise" test was performed using an 8-minute free running test outdoors on a 150-m circular track between 9 and 11 AM (15). Running speed was adjusted by monitoring the subject's heart rate with a Sport Tester™ PE 3000 heart rate meter (Polar Electro Ky, Kempele, Finland). Subjects raised their heart rate to 85% of the predicted maximal rate during a 2-minute run-in and maintained it at that level for the remaining 6 minutes of the test. The PEF values were measured just before the exercise and immediately, 5, 10, 20, and 30 minutes after, using Wright's peak flow meter. The highest value of the three successive PEF measurements obtained on each occasion was recorded for analysis. A positive exercise response was defined by a fall of at least 15% in PEF in the 30-minute follow-up after exercise. The response to the exercise challenge was the maximum percentage fall in PEF (Δ PEF%) after exercise: $\% \text{ fall in PEF} = [\text{PEF}(\text{baseline}) - \text{PEF}(\text{after})] / \text{PEF}(\text{baseline}) \times 100$. Air temperature ranged from -19°C to $+24^{\circ}\text{C}$, mean 5.4°C . Therefore, for all exercise challenges, Δ PEF% was adjusted to a temperature of 5.4°C using the regression coefficient (-0.327) between air temperature ($^{\circ}\text{C}$) and Δ PEF%, as in one previous study (16). The regression coefficient was obtained by linear regression from similar outdoor exercise tests in 1809 conscripts with asthma (17). These exercise tests were performed during 1985–1998, in temperatures ranging from -25°C to $+26^{\circ}\text{C}$.

Serial PEF recordings showing either a diurnal variation of $\geq 20\%$ or a bronchodilatation effect of $\geq 15\%$ at least three times were considered diagnostic of asthma.

Skin prick tests (SPTs) were performed using both a negative and positive control and a panel of 10 common perennial and seasonal allergens with standardized allergen extracts (ALK, Abello, Copenhagen, Denmark). A wheal diameter of at least 3 mm and at least 50% histamine control in SPT was considered positive.

The definition of asthma was based on the 1986–1990 Military Hospital medical records. One hundred and nineteen follow-up participants had been diagnosed with asthma in the Internal Medicine Unit of the Central Military Hospital. A total of 48 (40.3%) men were already suffering from asthma when they entered the military service and were admitted to the Central Military Hospital to restart or increase medication, or for an evaluation of service ability. Sixty-seven (56.3%) men had a new onset of asthma and came for confirmation of diagnosis, while in four cases it was unclear whether asthma had begun during or before military service. Asthma was verified by a significant reversibility of bronchial obstruction in spirometry ($n = 2$), moderate/severe airway hyperresponsiveness to histamine challenge ($n = 7$), a positive exercise test ($n = 48$), a diagnostic PEF recording ($n = 1$), more than one of these tests being diagnostic for asthma ($n = 24$), or clinical evidence of earlier diagnosed asthma ($n = 6$). In 31 (26.1%) men asthma diagnosis was

based on borderline diagnostic findings such as mild hyperresponsiveness ($n = 11$), a PEF decrease of 10–14% in the exercise test ($n = 9$), both of these ($n = 4$), obstructive spirometry ($n = 2$), or a history of childhood asthma or typical asthma symptoms ($n = 5$).

Collection of Data at Follow-Up

All clinical investigations were carried out at FIOH. A period of 4 weeks without respiratory infections and exposure to seasonal allergens before the visit was required.

Flow-volume spirometry was performed using a Medikro spirometer according to the guidelines (18) and the same predicted values were used as those at baseline. The patients filled in the questionnaire, which included validated questions about asthma symptoms and medications used (19). SPTs were performed similarly to those at baseline, using corresponding allergen extracts. A respiratory physician (IL/HS) examined every subject.

Assessment of Asthma Severity

We used the Global Initiative for Asthma (GINA) (20) to evaluate current asthma severity. Two independent GINA classifications were combined, the first based on symptoms and FEV₁ and the second on current medication, in order to construct a final "symptom-FEV₁-medication" classification as described earlier (21) and in Table 1. Clinical severity was classified as one of four grades according to the frequency of diurnal and nocturnal symptoms in the last 12 months and the prebronchodilator FEV₁ of predicted values. Treatment was also classified as one of four grades, according to the reported daily medication use. Finally, asthma severity was based on the independent classifications of clinical severity and medication, according to the GINA. The following categories were used: remission, intermittent, mild persistent, moderate persistent, and severe persistent. Remission was defined as having no asthma symptoms and using no asthma medication in the last 3 years. Classification was carried out by two physicians (IL and HS) separately, and the results proved congruent with each other. The kappa coefficient between the two observations was 0.90.

In the risk factor analyses, the subjects with mild, moderate, and severe persistent asthma were categorized as having persistent asthma and were compared with those whose asthma was in remission or intermittent.

Asthma severity during military service was evaluated according to the modified GINA guidelines and classified as intermittent, mild persistent, or moderate/severe persistent. We did not use treatment step classes, because most subjects had no treatment, and the medication used differed from the current treatment guidelines.

Statistical Analysis

Our data set consisted of both continuous and categorical variables. In our preliminary study, we wanted to check whether those who participated in examinations differed from those who did not. We then applied chi-squared tests for categorical variables and one-way ANOVA for continued variables. The same tests were applied when

TABLE 1.—Asthma severity was evaluated by combining the current severity of the asthma treatment (horizontal axis) and the current severity of asthma based on symptoms and lung function (vertical axis).

		Current treatment			
		Intermittent Only when needed	Mild Persistent Inhaled corticosteroid < 800 µg/day ^b or leukotriene modifier	Moderate persistent Inhaled corticosteroid > 800 µg/day ^b or inhaled corticosteroid 100–800 µg/day plus long- acting inhaled β ₂ -agonist or inhaled corticosteroid 100–800 µg/day plus leuco- triene modifier/theophylline	Severe persistent Inhaled corticosteroid > 1000 µg/day ^b with or without long-acting inhaled β ₂ -agonist plus one or more of the following, if needed: -theophylline -leukotriene modifier -oral corticosteroid
Symptoms and lung function ^a	Definitive severity				
Intermittent -Symptoms < once a week -Nocturnal symptoms ≤ twice a month -FEV ₁ ≥ 80% -PEF variability < 20%	Intermittent		Mild persistent	Moderate persistent	Severe persistent
Mild persistent -Symptoms ≥ once a week but < once a day -nocturnal symptoms > twice a month but ≤ once a week -FEV ₁ ≥ 80% -PEF variability 20–30%	Mild persistent		Moderate persistent	Severe persistent	Severe persistent
Moderate persistent -daily-nocturnal symptoms > once a week -60% < FEV ₁ < 80% -PEF variability > 30%	Moderate persistent		Severe persistent	Severe persistent	Severe persistent
Severe persistent -frequent exacerbations -frequent nocturnal asthma symptoms -limitation of physical activities -FEV ₁ ≤ 60% -PEF variability > 30%	Severe persistent		Severe persistent	Severe persistent	Severe persistent

Note: ^aWorst feature determines severity classification.

^bDoses of inhaled corticosteroids are equivalent to Beclomethasone dipropionate (BDP).

examining the associations between potential predictors and asthma severity. When comparing the baseline results to the follow-up results of those who had participated in both examinations, we used statistical tests for repeated measurements. The correlation between FEV₁/FVC % predicted and FEF_{50%} % predicted was estimated by using the Spearman's correlation coefficient (ρ). The same coefficient was also used when examining the relationship between PD₁₅ in histamine challenge and PEF decrease (%) in exercise test. A p -value of < .05 was considered statistically significant.

We used logistic regression analyses when examining the associations between different spirometry values, exercise test results, and asthma severity. We then calculated the odds ratios (ORs) and their 95% confidence intervals (95% CIs).

All analyses were carried out using the Statistical Analysis System 9.1 program (SAS Institute Cary, NC, USA).

RESULTS

Comparison of Non-Participants and Participants

The baseline characteristics of 119 subjects participating in clinical visits between 2009 and 2010, and of the 109 subjects who responded to the questionnaire but who did not participate in the clinical tests, are shown in Table 2. There were no statistically significant differences between these two groups, but the proportion of smokers was somewhat higher among the non-participants.

TABLE 2.—Characteristics of non-participants at baseline and participants at baseline and follow-up.

	Non-participants	Participants		P-value ^b
	Baseline 1987–1990 ^a	Baseline 1987–1990 ^a	Follow-up 2009–2010	
<i>n</i>	109	119	119	
Age, mean, years (SD)	20.2 (1.1)	20.1 (1.4)	41.2 (1.9)	
Smoking ^c				0.002
Non-smoker	43.5% (47)	52.9% (63)	65.5% (78)	
Ex-smoker	9.3% (10)	10.9% (13)	14.3% (17)	
Smoker	47.2% (51)	36.1% (43)	20.2% (24)	
BMI, mean, kg/m ² , (SD)	23.4 (3.3)	22.9 (3.0)	27.7 (5.1)	<0.001
Skin prick tests ^c				0.026
0 positive	22.9% (24)	13.8% (15)	13.6% (16)	
1–3 positive	28.6% (30)	25.7% (28)	14.4% (17)	
≥4 positive	48.6% (51)	60.5% (66)	72.0% (85)	
Prebronchodilator spirometry ^c				
FVC% predicted, mean (SD)	100.1 (9.9)	98.2 (11.6)	93.7 (11.4)	<0.001
FEV ₁ % predicted, mean (SD)	88.4 (12.6)	88.3 (12.0)	88.5 (13.3)	0.827
FEV ₁ /FVC% predicted, mean (SD)	87.8 (10.7)	89.7 (9.6)	94.3 (9.1)	<0.001
FEF _{50%} % predicted, mean (SD)	60.8 (19.3)	62.7 (16.6)	74.4 (23.9)	<0.001
Histamine challenge ^c			ND	
PD ₁₅ > 1.6mg	31.5% (24)	30.7% (27)		
0.40mg ≤ PD ₁₅ ≤ 1.6mg	36.8% (28)	40.9% (36)		
PD ₁₅ < 0.40mg	36.8% (28)	28.4% (25)		
Exercise test			ND	
PEF decrease <10%	25.7% (28)	23.5% (28)		
PEF decrease 10.0%–14.9	18.3% (20)	20.2% (24)		
PEF decrease ≥15%	56.0% (61)	56.3% (67)		
Asthma severity				<0.001
Remission	0% (0)	0% (0)	11.8% (14)	
Intermittent	33.0% (36)	33.6% (40)	42.0% (50)	
Mild persistent	20.2% (22)	19.3% (23)	10.9% (13)	
Moderate/severe persistent	46.8% (51)	47.0% (56)	35.3% (42)	
Using inhaled corticosteroid	0	0	22.7% (27)	

Note: Data provided as % (n) unless otherwise stated.

^a None of the differences between participants and non-participants at baseline were statistically significant (*p*-values not shown). ^b *P*-values refer to comparisons between participants at baseline and follow-up, ^c due to some missing data the number of subjects differs from 119 among participants and from 109 among non-participants.

BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEF_{50%}, forced expiratory flow rate at 50% of vital capacity; PD, provocative dose; PEF, peak expiratory flow; ND, not done.

Characteristics of Participating Subjects

The mean age of the subjects was 20.1 years at baseline and 41.2 years at follow-up (Table 2). At follow-up, current smoking was less frequent, mean BMI was higher, and more subjects had at least four positive reactions to SPTs compared with baseline status. The mean FVC % predicted decreased (from 98.2% to 93.7%) and that of FEF_{50%} % predicted increased (from 62.7% to 74.4%) during the follow-up. At the time of baseline evaluation, none of the subjects, and at follow-up 22.7% of the subjects, regularly used inhaled corticosteroids.

At baseline, 27.7% of the participants had a decreased FEV₁ % predicted, 37.8% had a decreased FEV₁/FVC % predicted, and 53.4% had a decreased FEF_{50%} % predicted (Table 2). FEV₁/FVC % predicted values and FEF_{50%} % predicted values were clearly correlated with each other ($\rho = 0.850$, *p*-value < .001). The spirometry result of one subject was missing; the other 118 subjects had successfully performed spirometry measurements. A total of 56.3% of the men had positive exercise test results and, additionally, 20.2% of the men had PEF decrease by 10–14% in the test. Only a weak negative correlation was detected between the PD₁₅ value in histamine challenge

and PEF decrease in exercise test ($\rho = -0.320$, *p*-value < .001).

Asthma was less severe at follow-up than at baseline (Table 2). At follow-up, 11.8% of the men were in remission, 42.0% had intermittent asthma, 10.9% had mild persistent asthma, and 35.3% had moderate/severe persistent asthma.

Prognostic Factors for Persistent Asthma

Smoking (*p* = .050), decreased FEV₁ % predicted (*p* = .001), decreased FEV₁/FVC % predicted (*p* < .001), decreased FEF_{50%} % predicted (*p* = .001), a PEF decrease of ≥10% in exercise tests (*p* = .011), and more severe asthma (*p* = .028) at baseline showed a statistically significant correlation with persistent asthma at follow-up (Table 3). No significant associations were found between asthma severity at follow-up and the age of asthma onset, positive skin prick tests, or airway hyperresponsiveness to a histamine challenge at baseline.

Modeling the Predictive Value of Spirometric Parameters and Exercise Tests

Table 4 reports the univariate and multivariate models that assess the predictive value of spirometry and

TABLE 3.—Distribution of current asthma severity by baseline characteristics.

Characteristics at baseline		Current asthma severity		P-value
	Subject, <i>n</i>	Remission or intermittent <i>n</i> = 64 (54.8%)	Persistent asthma (mild/moderate/severe) <i>n</i> = 55 (46.2%)	
Age of asthma onset	119			0.179
<12 years	36	44.0% (16)	56.0% (20)	
≥12 years	83	57.8% (48)	42.2% (35)	
Smoking	119			0.050
Current smoker	43	41.9% (18)	58.1% (25)	
Ex- or non-smoker	76	60.5% (46)	39.5% (30)	
BMI				0.757
<25	95	54.7% (52)	45.3% (43)	
<25 BMI <30	21	47.6% (10)	52.4% (11)	
>30	3	66.7% (2)	33.3% (1)	
Skin prick tests	109			0.769
0 positive	15	53.3% (8)	46.7% (7)	
1–3 positive	28	46.4% (13)	53.6% (15)	
≥4 positive	66	54.5% (36)	45.5% (30)	
Prebronchodil. spirometry	118			
FEV ₁ % predicted ≥81	85	64.3% (54)	35.7% (31)	0.001
FEV ₁ % predicted <81	33	30.3% (10)	69.7% (23)	
FEV ₁ /FVC % predicted ≥88	73	68.5% (50)	31.5% (23)	<0.001
FEV ₁ /FVC % predicted <88	45	31.1% (14)	68.9% (31)	
FEF _{50%} % predicted ≥62	54	70.4% (38)	29.6% (16)	0.001
FEF _{50%} % predicted <62	64	40.6% (26)	59.4% (38)	
Histamine challenge	88			0.970
PD ₁₅ > 1.6 mg	27	59.3% (16)	40.7% (11)	
0.40 mg ≤ PD ₁₅ ≤ 1.6 mg	36	58.3% (21)	41.7% (15)	
PD ₁₅ < 0.40 mg	25	56.0% (14)	44.0% (11)	
Exercise test	119			0.011
PEF decrease <10%	28	71.4% (20)	28.6% (8)	
PEF decrease 10.0–14.9%	24	66.7% (16)	33.3% (8)	
PEF decrease ≥15%	67	41.8% (28)	58.2% (39)	
Asthma severity	119			0.028
Intermittent	40	62.5% (25)	37.5% (15)	
Mild persistent	23	69.5% (16)	30.4% (7)	
Moderate/severe persistent	56	41.1% (23)	58.9% (33)	

Note: Data provided as % (*n*). *n*, number of subjects with data; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{50%}, forced expiratory flow rate at 50% of vital capacity; PD, provocative dose; PEF, peak expiratory flow.

exercise test findings at baseline for persistent asthma at follow-up. Decreased FEV₁ % predicted, decreased FEV₁/FVC % predicted, decreased FEF_{50%} % predicted, and a positive exercise test at baseline all

indicated an increased risk of persistent asthma at follow-up. The risk remained after adjusting for smoking and asthma severity at baseline, with ORs of between 2.8 and 4.0.

TABLE 4.—Risk of current persistent asthma according to spirometry and exercise test findings at baseline.

Predictors at baseline	Univariate model			Adjusted for smoking at baseline			Adjusted for asthma severity at baseline			Adjusted for both		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Spirometry, <i>n</i> = 118												
FEV ₁ % predicted ≥81	1	reference		1	reference		1	reference		1	reference	
FEV ₁ % predicted <81	4.0	1.7–9.5	0.002	4.2	1.7–10.0	0.002	3.0	1.2–7.7	0.023	3.3	1.3–8.7	0.016
FEV ₁ /FVC % predicted ≥88	1	reference		1	reference		1	reference		1	reference	
FEV ₁ /FVC % predicted <88	4.8	2.2–10.7	<0.001	4.6	2.0–10.2	<0.001	4.1	1.8–9.3	0.001	4.0	1.7–9.1	0.001
FEF _{50%} % predicted ≥62	1	reference		1	reference		1	reference		1	reference	
FEF _{50%} % predicted <62	3.5	1.6–7.5	0.002	3.4	1.6–7.4	0.002	2.8	1.3–6.2	0.012	2.8	1.3–6.4	0.012
Exercise test, <i>n</i> = 119												
PEF decrease <10%	1	reference		1	reference		1	reference		1	reference	
PEF decrease 10.0–14.9%	1.2	0.4–4.1	0.420	1.2	0.4–4.1	0.430	1.3	0.4–4.4	0.554	1.3	0.4–4.4	0.541
PEF decrease ≥15 %	3.5	1.3–9.0	0.004	3.4	1.3–9.0	0.005	3.2	1.1–9.3	0.022	3.2	1.1–9.5	0.021

Note: Significant OR values are shown in boldface. FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{50%}, forced expiratory flow rate at 50% of vital capacity; PEF, peak expiratory flow.

TABLE 5.—Final multivariate model on risk of current persistent asthma according to baseline spirometric and exercise test findings.

Predictors at baseline	OR	95% CI	p-value
Exercise test + FEV₁/FVC			
PEF decrease <10%	1	reference	
10–14 %	1.5	0.4–5.4	0.758
>15 %	3.2	1.0–9.8	0.046
FEV ₁ /FVC % predicted ≥88	1	reference	
FEV ₁ /FVC % predicted <88	4.0	1.7–9.3	0.002

Note: The model is adjusted for smoking, asthma severity at baseline and the other predictors studied in the model. Significant OR values are shown in boldface. PEF, peak expiratory flow; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{50%}, forced expiratory flow rate at 50% of vital capacity.

In a final multivariate model (Table 5), exercise test results and FEV₁/FVC % predicted results at baseline were adjusted for each other as well as for smoking and asthma severity at baseline. The OR for current persistent asthma was 3.2 (95% CI 1.0–9.8, $p = .046$) in subjects with a positive exercise test and 4.0 (95% CI 1.7–9.3, $p = .002$) in subjects with a decreased FEV₁/FVC ratio.

DISCUSSION

We studied the prognostic factors of current persistent asthma. A positive exercise test at baseline associated with current persistent asthma and proved to be independent of obstructive spirometry. Baseline lung function parameters, a decreased FEV₁, a decreased FEV₁/FVC ratio, and a decreased FEF_{50%} in prebronchodilator spirometry were also significant risk factors for current persistent asthma. As these spirometric parameters are closely correlated, we used only one of them in the adjusted final model (Table 5). Our study population of young male conscripts whose asthma had begun in childhood or early adulthood represented the main atopic phenotype (22) and the different severity forms of asthma. During the baseline evaluation, about half of the subjects had intermittent or mild persistent asthma, while the rest had either moderate or severe persistent asthma. All subjects were steroid naïve and their asthma symptoms had worsened, which corresponds to real life situations in which clinicians usually meet asthmatics. After 20 years, about half of the subjects (46.2%) had persistent asthma, while the asthma of the rest of the subjects was either in remission or in intermittent. During the follow-up evaluation, 22.7% of the men used inhaled corticosteroids, which probably affected their spirometry results.

Current Asthma Severity

The outcome variable of this study was current asthma severity, which was defined by using the 2002 version of the GINA guidelines (20) as in previous epidemiological studies (5). This classification relies on three dimensions: (1) perceived symptoms, (2) lung function, and (3) type of asthma treatment and is a reliable determinant of asthma morbidity. The current distribution of asthma severity in

our study was in line with a previous population-based report on asthmatics of the same age (5).

Role of Exercise Test

A positive exercise test associated with asthma persistence in our study, but airway hyperresponsiveness to a histamine challenge had no effect on asthma prognosis. All study subjects underwent an exercise test; while about three quarters of them underwent a histamine challenge, possibly affecting its predictive value. The challenge was not performed on some subjects due to obstructive spirometry. The exercise test is an indirect challenge test and acts by causing the release of endogenous mediators that cause airway smooth muscle contraction. The histamine challenge is a direct challenge test, in which the stimulus acts directly on a specific smooth muscle receptor. Both the exercise test and the histamine challenge measure airway hyperresponsiveness. Comparative studies of these tests have demonstrated that exercise tests have higher specificity, but lower sensitivity in diagnosing asthma (23). In another study, adding the inhalation of cold air increased the sensitivity of the exercise test, while still maintaining specificity (24).

As the severity of exercise-induced bronchoconstriction depends on the level of ventilation and on the temperature of the inspired air, the exercise tests in this study were heart rate conducted and temperature adjustments for PEF calculations were included. Exercise tests were performed outdoors in all seasons, so despite temperature adjustments, the complex effect of the season on the exercise test results cannot be ruled out. In an earlier Finnish study, aggravated exercise-induced asthma response was reported in asthmatics with pollen allergy, when the outdoor exercise test was performed during the pollen season rather than in wintertime (25). However, in subjects with non-allergic asthma, exercise-induced bronchoconstriction was attenuated in spring time probably due to more humid, warmer weather. Goldberg *et al.* reported a lower proportion of positive exercise test results during the summer than in other seasons (26) and suggested that this was related to the lower activity of asthma during the summer. However, this study is from Israel, where, contrary to Finland, summer is not a pollen season.

Airway hyperresponsiveness to methacholine or histamine in childhood has previously been connected to the persistence of asthma symptoms or their onset in adult life (3, 7). Moreover, less severe airway hyperresponsiveness has predicted the development of irreversible airflow limitation (27). Little is known about the effect of positive exercise tests on the long-term prognosis of asthma, although exercise-related respiratory symptoms predicted persistent asthma in children in the study of Frank *et al.* (28).

Small Airway Obstruction

In addition to other spirometry parameters, a decreased FEF_{50%} at baseline was related to persistent asthma at follow-up. Small airways (airways of < 2mm in internal

diameter) are a major site of airflow limitation in asthma, but have proved difficult to study (29). FEF_{25–75%} and FEF_{50%} are the spirometric variables most commonly cited as indicators of small airway obstruction, although they have been criticized as having a marked measurement variability and poor correlation with other measures of air trapping (30). Small airways have been associated with recurrent exacerbations of asthma (31), nocturnal asthma (32), and also milder asthma (33). In a 5-year follow-up, exhaled NO predicted a lung function decline in severe asthmatics with normal FEV₁ at baseline, suggesting that this was related to small airways (34).

Advantages and Limitations

The study population at baseline was homogenous in age and sex, and represented unselected men from southern and central parts of Finland with different severity forms of asthma at the age of 19–21 years. At the time of the follow-up 21 years later, these participants came from different parts of Finland, including the northernmost regions. All lung function tests at baseline were performed by qualified technicians using uniform, validated methods in the clinical physiology laboratory of the Central Military Hospital, which had strict quality control procedures. The repeatability of maneuvers in spirometry was always controlled according to guidelines (12,18), and measurements with excessively large variability were not accepted in between-maneuver evaluation.

One of the limitations was the loss of many subjects during follow-up. We analyzed the subjects who did not respond to the questionnaire and those who answered the questionnaire without participating in the clinical tests. Smokers might be underrepresented among the participants, which may underestimate current asthma severity. Otherwise, these analyses showed only minor differences between the respondents and non-respondents, as well as between the participants and non-participants, and do not indicate the selection of specific types of asthmatics for the final study population. Our results cannot be generalized to females, asthma which begins after early adulthood, or non-atopic asthma.

CONCLUSIONS

To summarize, in this study we found that about half of the male conscripts suffering from different severity forms of asthma at the age of around 20 had persistent asthma approximately 20 years later. A positive exercise test, a decreased FEV₁/FVC, and a decreased FEF_{50%} were related to persistence of asthma. The FEV₁/FVC ratio and FEV₁ decreased in only a minority of subjects, while over half of the subjects had a decreased FEF_{50%} and a positive exercise test. Both of the latter parameters might be clinically meaningful in males with atopic asthma that began at a young age, and clinicians should not ignore this. The measurement variability of FEF_{50%} probably limits its use in clinical practice, because quality of spirometries varies. The exercise test was superior to the histamine challenge in predicting the persistence of asthma, and it

could be useful in evaluating long-term asthma prognosis, although further studies are needed to confirm this.

ACKNOWLEDGMENTS

The authors thank Outi Fisher and the study nurses.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This study was supported by the The Finnish Work Environment Fund, Finnish Defence Forces, and Ida Montin Foundation.

REFERENCES

1. Pallasaho P, Juusela M, Lindqvist A, Sovijärvi A, Lundback B, Ronmark E. Allergic rhinoconjunctivitis doubles the risk for incident asthma—Results from a population study in Helsinki, Finland. *Respir Med* 2011; 105:1449–1456.
2. Gershon AS, Guan J, Wang C, To T. Trends in Asthma Prevalence and Incidence in Ontario, Canada, 1996–2005; A Population Study. *Am J Epidemiol* 2010; 172:728–736.
3. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; 349:1414–1422.
4. Taylor DR, Cowan JO, Greene JM, Willan AR, Sears MR. Asthma in remission: can relapse in early adulthood be predicted at 18 years of age? *Chest* 2005; 127:845–850.
5. de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, Carolei A, Cazzoletti L, Corsico A, Gislason D, Gulsvik A, Jogi R, Marinoni A, Martinez-Moratalla J, Pin I, Janson C. Prognostic factors of asthma severity: A 9-year international prospective cohort study. *J Allergy Clin Immunol* 2006; 117:1249–1256.
6. Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, Sears MR. Risk factors for airway remodeling in asthma manifested by a low postbronchodilator FEV₁/vital capacity ratio: A longitudinal population study from childhood to adulthood. *Am J Respir Crit Care Med* 2002; 165:1480–1488.
7. Toelle BG, Xuan W, Peat JK, Marks GB. Childhood factors that predict asthma in young adulthood. *Eur Respir J* 2004; 23:66–70.
8. Vonk JM, Postma DS, Boezen HM, Grol MH, Schouten JP, Koeter GH, Gerritsen J. Childhood factors associated with asthma remission after 30 year follow up. *Thorax* 2004; 59:925–929.
9. Panhuysen CI, Vonk JM, Koeter GH, Schouten JP, van Altena R, Bleecker ER, Postma DS. Adult patients may outgrow their asthma: A 25-year follow-up study. *Am J Respir Crit Care Med* 1997; 155:1267–1272.
10. Gelfand EW, Kraft M. The importance and features of the distal airways in children and adults. *J Allergy Clin Immunol* 2009; 124:S84–87.
11. Lindstrom I, Pallasaho P, Luukkainen R, Suojalehto H, Karjalainen J, Lauerman A, Karjalainen A. Reduced work ability in middle-aged men with asthma from youth—a 20-year follow-up. *Respir Med* 2011; 105:950–955.
12. Standardization of spirometry. 1987. update. Statement of the American Thoracic Society. *Am Rev Respir Dis* 1987; 136:1285–1298.
13. Viljanen A. Reference values for spirometric, pulmonary diffusing capacity and body plethysmographic studies. *Scand J Clin Invest* 1982; 42:S1–50.
14. Laitinen LA. Histamine and methacholine challenge in the testing of bronchial reactivity. *Scand J Respir Dis* 1975; 86:S1–48.
15. Karjalainen J. Exercise response in 404 young men with asthma: No evidence for a late asthmatic reaction. *Thorax* 1991; 46:100–104.

16. Rouhos A, Ekroos H, Karjalainen J, Sarna S, Sovijarvi AR. Exhaled nitric oxide and exercise-induced bronchoconstriction in young male conscripts: Association only in atopics. *Allergy* 2005; 60:1493–1498.
17. Latvala J, Karjalainen J, Remes J, Hassi J. Exercise-induced asthma and weather (abstract) XXXIII International Congress of Military Medicine, Helsinki; Finland, June 25–30, 2000.
18. Miller MR, Hankinson J, Brusasco V et al. et al. Standardisation of spirometry. *Eur Respir J* 2005; 26:319–338.
19. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Validation of a new questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults. *Allergy* 2001; 56:377–384.
20. Global Initiative for Asthma (GINA). Available at: <http://www.ginasthma.com>. 2002.
21. Liard R, Leynaert B, Zureik M, Beguin FX, Using Global NF. Initiative for Asthma guidelines to assess asthma severity in populations. *Eur Respir J* 2000; 16:615–620.
22. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, Aldington S, Beasley R. Distinct clinical phenotypes of airways disease defined by cluster analysis. *Eur Respir J* 2009; 34:812–818.
23. Cockcroft DW. Direct challenge tests: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010; 138:S18–24.
24. Carlsen KH, Engh G, Mork M, Schroder E. Cold air inhalation and exercise-induced bronchoconstriction in relationship to methacholine bronchial responsiveness: Different patterns in asthmatic children and children with other chronic lung diseases. *Respir Med* 1998; 92:308–315.
25. Karjalainen J, Lindqvist A, Laitinen LA. Seasonal variability of exercise-induced asthma especially outdoors. Effect of birch pollen allergy. *Clin Exp Allergy* 1989; 19:273–278.
26. Goldberg S, Schwartz S, Izbicki G, Hamami RB, Picard E. Sensitivity of Exercise testing for Asthma in Adolescents is halved in the summer. *Chest* 2005; 128:2408–2411.
27. Vonk JM, Jongepier H, Panhuysen CI, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003; 58:322–327.
28. Frank PI, Morris JA, Hazell ML, Linehan MF, Frank TL. Long term prognosis in preschool children with wheeze: longitudinal postal questionnaire study 1993–2004. *BMJ* 2008; 21:1423–1426.
29. Burgel PR. The role of small airways in obstructive airway diseases. *Eur Respir Rev* 2011; 20:23–33.
30. Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, Curran-Everett D, Erzurum SC, Gaston BM, Israel E, Jarjour NN, Moore WC, Peters SP, Teague WG, Wenzel SE. Lung function in adults with stable but severe asthma: Air trapping and incomplete reversal of obstruction with bronchodilation. *J Appl Physiol* 2008; 104:394–403.
31. in't Veen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. *Am J Respir Crit Care Med*. 2000;161:1902–1906.
32. Lehtimäki L, Kankaanranta H, Saarelainen S, Turjanmaa V, Moilanen E. Increased alveolar nitric oxide concentration in asthmatic patients with nocturnal symptoms. *Eur Respir J* 2002; 20:841–845.
33. Beigelman-Aubry C, Capderou A, Grenier PA, Straus C, Becquemin MH, Similowski T, Zelter M. Mild intermittent asthma: CT assessment of bronchial cross-sectional area and lung attenuation at controlled lung volume. *Radiology* 2002; 223:181–187.
34. van Veen IH, Ten Brinke A, Sterk PJ, Sont JK, Gauw SA, Rabe KF, Bel EH. Exhaled nitric oxide predicts lung function decline in difficult-to-treat asthma. *Eur Respir J* 2008; 32(2):344–349.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.