

Follow-up of asthma from childhood to adulthood: Influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood

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The outcome of asthma in 406 children, aged 8 to 12 years, was studied. Follow-up in adulthood was 86%, with a mean age of 24.7 years and a mean interval of follow-up of 14.8 years. The predictive value of gender and various childhood variables on the adult level of pulmonary function (forced expiratory volume in 1 second [FEV₁]) and bronchial responsiveness in adulthood was assessed. An increase in mean percent predicted FEV₁ from childhood to adulthood was found, both in subjects with (76%) and without (24%) current respiratory symptoms. The only childhood variable predictive of adult level of FEV₁ was the level of percent predicted FEV₁ ($p < 0.01$). The proportion of subjects with a histamine provocative concentration causing a 10% decrease in FEV₁ less than or equal to 16 mg/ml decreased significantly in adulthood. The degree of bronchial responsiveness had increased slightly in adults with symptoms ($p = 0.87$), whereas it had decreased significantly in subjects without symptoms ($p < 0.01$). Female subjects were significantly more responsive in adulthood than male subjects ($p = 0.047$). The childhood degree of bronchial responsiveness significantly predicted the presence of bronchial responsiveness in adulthood ($p = 0.02$). We conclude that childhood percent predicted FEV₁ is relevant to predict the outcome of the adult pulmonary function level, whereas female gender and the childhood degree of bronchial responsiveness are important for the prediction of adult degree of bronchial responsiveness among children with asthma (J ALLERGY CLIN IMMUNOL 1994; 93:575-84.)

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The number of studies on the prognosis of childhood asthma with objective data on pulmonary function and bronchial responsiveness, is

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Abbreviations used

CI	Confidence interval
FEV ₁	Forced expiratory volume in 1 second
IVC	Inspiratory vital capacity
PC ₁₀	Provocative concentration causing a 10% decrease in FEV ₁
PC ₂₀	Provocative concentration causing a 20% decrease in FEV ₁

limited.¹⁻¹⁴ Most studies are retrospectively designed, and if objective measurements are done at the end of the study, data on the same parameters at the time of entry are often lacking. In many studies a high proportion of the original study group has been lost to follow-up.

Intermittent bronchial obstruction and increased airway responsiveness to inhaled nonspecific stimuli are main features of asthma. Both the initial degree of bronchial obstruction, represented by forced expiratory volume in 1 second (FEV_1) as a percentage of predicted value, and the level of bronchial responsiveness, measured in a standardized way, reflect the severity of actual disease and may have predictive value for the prognosis of childhood asthma and the prediction of adult disease.^{13, 15}

Therefore we prospectively studied a group of children with asthma to investigate the contribution of childhood level of pulmonary function and degree of bronchial responsiveness in combination with other variables in the prediction of adult level of pulmonary function and bronchial responsiveness.

The contribution of the same childhood variables in the prediction of the outcome of respiratory symptoms will be discussed elsewhere.

METHODS

Study design

This study on the outcome of childhood asthma was designed as a survey of a cohort of children with asthma, who were referred to the outpatient clinic of the Department of Pediatric Pulmonology at the University Hospital of Groningen over a period of 5 consecutive years and who were followed up longitudinally and reinvestigated in adulthood.

Childhood data were collected in the outpatient department at the first visit. In adulthood subjects were seen in the same season of the year as that of the initial visit in childhood to avoid potential seasonal influences.

At each visit, inhaled bronchodilators were withheld for at least 12 hours before the investigations, and xanthine derivatives were withheld for a minimum of 48 hours. If required, maintenance treatment with cromoglycate or inhaled corticosteroids was continued.

Informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the University Hospital of Groningen.

Patients

The original study group consisted of 406 children, aged 8 to 12 years, who were referred to the outpatient clinic of the Department of Pediatric Pulmonology of the University Hospital of Groningen between January 1972 and December 1976. Diagnosis of asthma was based on clinical symptoms and the exclusion of specific respiratory diseases, such as cystic fibrosis, tuberculosis, and bronchiectasis, by a physician. The gender ratio was 1 to 2; there were 133 girls (33%) and 273 boys (67%).

In the second survey a total of 58 subjects (14%) were lost to follow-up: 34 persons (8.4%) could not be

traced; six subjects (1.5%) lived abroad; two persons (0.5%) were hospitalized because of psychiatric illness; and 16 subjects (3.9%) were not cooperative. The remaining 348 persons (86%), now adults aged 20 to 29 years, participated in the follow-up study between June 1987 and December 1990.

Of the original patients, 285 (70%) were reinvestigated in the outpatient clinic with the same methods as in childhood. Sixty-three adults (16%) replied to the questionnaire but were not able or willing to perform the pulmonary function tests.

Questionnaire

The Dutch version of the standardized questionnaire of the British Medical Research Council (Medical Research Council-European Community for Coal and Steel questionnaire) was used in both childhood and adulthood.¹⁶ In both surveys subjects were interviewed by a trained pediatric pulmonologist. Special attention was given to the 3 years before the follow-up visit. The four main categories of respiratory symptoms were: cough, wheeze, dyspnea with exercise, and asthma attacks. Symptoms were scored according to the guidelines of the Medical Research Council-European Community for Coal and Steel questionnaire. Cough was considered to be present if a subject coughed frequently during at least 3 months in a year. Wheezing was considered to be present if chest sounds frequently included wheezing or whistling. Exercise-induced dyspnea was scored as positive if the subject reported having shortness of breath frequently during physical exertion or participation in a sport. Attacks of breathlessness with wheezing in the last 3 years were recorded as asthma attacks.

To assess the severity of symptoms, we used a cumulative scoring system. The symptom score in our study ranges from 0 to 4, which is the sum of the four main categories of symptoms. Each of the symptoms is of equal value in this score.

Pulmonary function

Spirometry was performed with a water-sealed spirometer (Spirograph D75; Lode, Groningen, The Netherlands). Inspiratory vital capacity (IVC) and FEV_1 were measured until three technically satisfactory recordings were produced. The best of these three efforts of baseline pulmonary function measurement was used as the prechallenge value for the histamine provocation test and for statistical analysis.

Reference values of Tammeling,¹⁷ which are based on age, gender, and height, were used. FEV_1 data are expressed as percent predicted $FEV_1 = (FEV_1 \div FEV_1 \text{ predicted}) \times 100\%$.

Histamine inhalation test

A histamine threshold was used to express the degree of bronchial responsiveness. Histamine provocation in children was tested within 3 months after the initial visit to the clinic. In general, the interval between

first visit and histamine provocation was less than 1 week. In adults all pulmonary function tests, including histamine provocation, were performed on a single day.

Histamine provocation was carried out according to the modified method of Tiffeneau, as described by De Vries et al.¹⁸ and Knol.¹⁹ This method meets the guidelines for standardization.²⁰ A 30-second tidal breathing method was used with a Wiesbadener Doppel inhalation device (Doppel Inhalator; Blümel, Wiesbaden, Germany), filled with 4 ml of test solution, with an airflow of approximately 5 L/min. In these conditions the output of the nebulizer is 0.06 ml/min.

After baseline pulmonary function measurement was obtained, an aerosol of buffer solution was inhaled. Then sequential aerosols of histamine biphosphate, ranging from 0.5 to 32 mg/ml (children) or 64 mg/ml (adults) were given. FEV₁ values were measured 30 and 90 seconds after the end of each inhalation step. As soon as a decrease of at least 10% of baseline FEV₁ was reached or when the maximum histamine concentration was given, the test was stopped. The histamine concentration at which there was a decrease in FEV₁ of at least 10% of baseline value was taken as the threshold value. The exact histamine provocative concentration causing a 10% decrease in FEV₁ (PC₁₀) was estimated from the log dose-response curve.²¹

Determination of PC₁₀ was the standard method used to define bronchial responsiveness at the inception of this study and has been retained in adulthood studies to ensure comparability of results. From a previous study it is known that PC₁₀ is as reproducible as the provocative concentration causing a 20% decrease in FEV₁ (PC₂₀) in the assessment of bronchial responsiveness in children.²² A PC₁₀ of 16 mg/ml or less indicates bronchial hyperresponsiveness. A histamine PC₁₀ of 16 mg/ml or less correlates with a presently more conventional histamine PC₂₀ of 32 mg/ml or less.²³

Besides the log of the histamine PC₁₀, the log dose-response slope of O'Connor et al.²⁴ was also included in some of the analyses. This is the slope of the line extending from the origin of FEV₁ of the challenge test to the last data point obtained. Therefore it is also suitable for the expression of bronchial responsiveness for subjects in whom no threshold was reached.

Statistical analysis

Statistical analysis was performed on a personal computer with the Superior Performing Software System for Personal Computers (SPSS-PC+ 4.0) software program (SPSS Inc., Chicago, Ill.). The data for each patient in childhood were compared with the data in adulthood. The study therefore consists of two data points, one collected in childhood and one in adulthood. Cross-sectional analyses were performed on the childhood and adult data separately. In the 285 subjects who were reexamined in adulthood, the childhood data were also used to predict the adult end points of pulmonary function and bronchial responsiveness.

The distribution of the variables was checked for normality, or the variables were log-transformed to

obtain normality. Because the histamine concentrations used for testing bronchial hyperresponsiveness are an exponential sequence, data of PC₁₀ natural log-transformed for analysis. Data of log-transformed variables are expressed as geometric means and 95% confidence intervals (CIs). Other variables are presented as arithmetic means and 95% CIs.

In univariate analyses changes between the two surveys in the proportion of subjects with current respiratory symptoms, as well as in subjects with a measurable histamine threshold of 16 mg/ml or less, were assessed for statistical significance with McNemar's chi square test. Differences in levels of pulmonary function and bronchial responsiveness between groups were analyzed with paired or unpaired Student's *t* tests.

In subjects who were reexamined in adulthood (*n* = 285), the influence and potential predictive value of the following childhood variables were studied with multiple linear and logistic regression analyses: gender, age of onset and duration of respiratory symptoms, symptom score, initial level of percent predicted IVC and percent predicted FEV₁ in childhood, and the degree of bronchial responsiveness (natural logarithm of histamine PC₁₀ [LnPC₁₀]) in childhood. The results were adjusted for the influence of the following potential confounding variables: skin test score, eosinophil count and passive smoking in childhood, adult age, pack-years of active smoking, and the use of medication in adulthood. Outcome variables in adulthood were level of pulmonary function (FEV₁ in milliliters) and presence and degree of bronchial responsiveness (histamine PC₁₀). FEV₁ is a continuous variable. Airway responsiveness in adulthood is considered as a categorical outcome variable (≤ 16 mg/ml or > 16 mg/ml, respectively) or a continuous outcome variable. A *p* value of less than 0.05 was considered significant.

RESULTS

Population characteristics

The childhood data for the subjects who participated in the second survey (*n* = 348) were compared with the data for the children who were lost to follow-up (Table I).

Childhood data were not traceable in 11 of the 58 subjects who were lost to follow-up, which is the reason that they did not participate in the second survey. No significant differences were found between the remaining 47 subjects who were not reexamined and 348 children who were reexamined.

The childhood data for subjects who fully participated in the second survey (*n* = 285) were compared with the data for those who answered a questionnaire only (*n* = 63). In childhood no significant differences were noted between the data for these two groups, except for the proportion of subjects who had had a histamine PC₁₀ of 16 mg/ml or less (59% and 44%, respectively,

TABLE I. Characteristics of 47 children lost to follow-up and 348 subjects who participated in the second survey ($n = 285$ examined and $n = 63$ questionnaire)

Characteristic	Lost to follow-up	Follow-up	
	Childhood data ($n = 47$)	Childhood data ($n = 348$)	Adulthood data ($n = 348$)
Age (yr)*	9.9 (7.0-12.8)	10.1 (7.2-13.0)	24.7 (20.6-28.8)
Male:female (no.)	34:13	239:109	239:109
Interval between first and second survey (yr)*			14.8 (11.7-17.9)
Smoking no. (%)			117 (34)
IVC (% pred)*	95 (58-132)	97 (72-122)	104 (79-129)†‡
FEV ₁ (% pred)*	89 (50-128)	91 (60-122)	96 (61-131)†‡
Histamine PC ₁₀ of ≤ 16 mg/ml; no. (%)	25 (53)	196 (56)	116 (42)†§
Histamine PC ₁₀ (mg/ml)	5.2 (0.6-40.4)	6.9 (0.8-54.0)	5.7 (0.3-94.6)†

*Mean (95% confidence interval).

†Adulthood: $n = 285$.‡ $p < 0.05$; childhood and adulthood data, paired Student's *t* test.§ $p < 0.05$; childhood and adulthood data, McNemar's chi-square test.

||Geometric mean (95% CI).

$p = 0.05$). Because otherwise no significant differences were found between subjects who fully participated in the second survey and those who only replied to the questionnaire in the second survey, in Table I childhood data for these two groups are not presented separately.

Outcome in adulthood

In this study 348 of the initial 406 patients (86%; mean age, 24.7 years; range 21 to 29 years) were reinvestigated, and 285 subjects (70%) participated fully in the second survey. The interval between the two surveys varied from 11 to 19 years, with a mean interval of 14.8 years. In adulthood 266 (76%) of the participants still had respiratory symptoms.

In cross-sectional analyses, the relationship between histamine PC₁₀ and percent predicted FEV₁ was significant in both surveys; in childhood, however, this correlation was weak ($r = 0.17$, $p = 0.001$), whereas in adulthood it was stronger ($r = 0.41$, $p = 0.001$). Data are presented in Fig. 1, A and B.

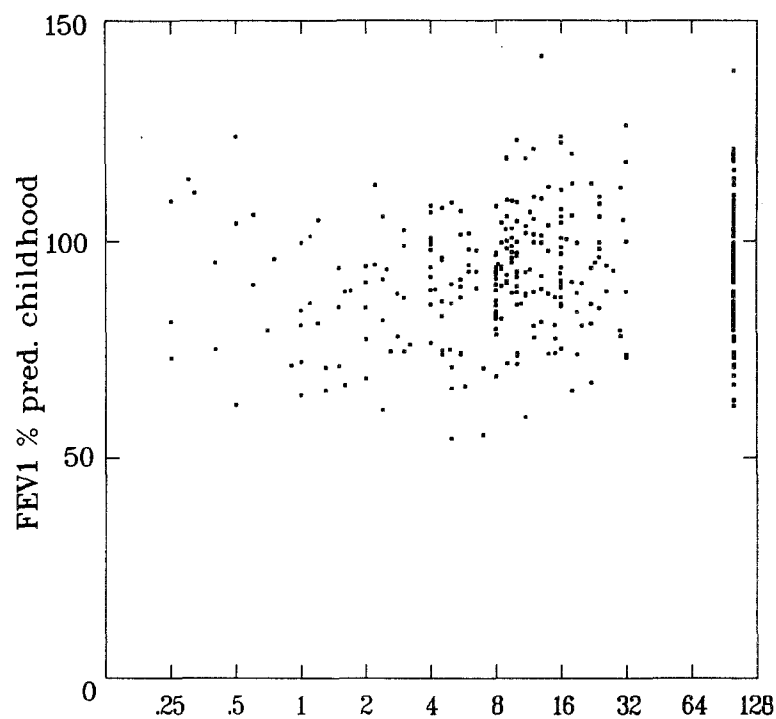
In the subjects who were reexamined in adulthood, a significant increase in mean percent predicted FEV₁ from childhood to adulthood ($p < 0.01$) as well as in mean percent predicted IVC ($p < 0.01$) was found (Table I). The proportion of subjects with a histamine PC₁₀ of 16 mg/ml or less significantly decreased from childhood to adulthood ($p < 0.01$). In the subjects who re-

mained hyperresponsive to histamine, geometric mean histamine PC₁₀ had increased slightly but not significantly.

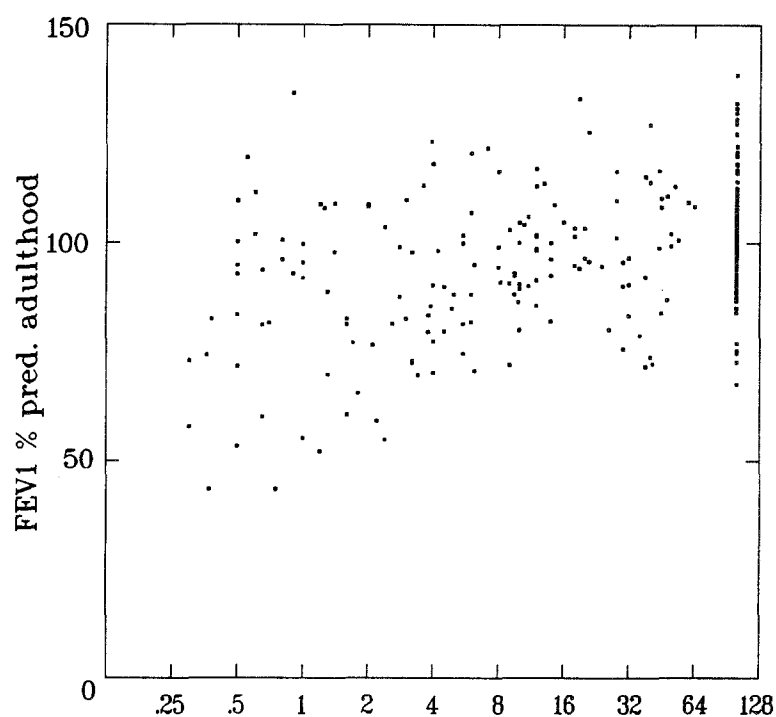
Mean percent predicted IVC was lower in female subjects than in male subjects in both surveys (childhood: 93 [95% CI, 62 to 124] vs 99 [95% CI, 77 to 121], $p < 0.01$; adulthood: 100 [95% CI, 77 to 123] vs 106 [95% CI, 82 to 130], $p < 0.01$). No significant differences were found in mean percent predicted FEV₁ between the sexes, either in childhood or in adulthood (childhood: 89 [95% CI, 54 to 131] vs 92 [95% CI, 61 to 123], $p = 0.19$; adulthood: 94 [95% CI, 57 to 131] vs 97 [95% CI, 64 to 130], $p = 0.23$).

The proportion of female subjects with a histamine PC₁₀ of 16 mg/ml or less in adulthood was unchanged since childhood (49%) ($p = 0.93$). Female subjects were slightly (but not significantly) more responsive in adulthood (geometric mean histamine PC₁₀ [in milligrams per milliliter] in childhood 5.9 [95% CI, 0.7 to 47.9] vs 4.2 [95% CI, 0.2 to 92.7] in adulthood, $p = 0.42$). In male subjects the percentage with a histamine PC₁₀ of 16 mg/ml or less had significantly decreased since childhood (children: 62%; adults: 39%, $p < 0.01$). In men the level of bronchial responsiveness was comparable in the two surveys (geometric mean histamine PC₁₀ [in milligrams per milliliter] in childhood: 7.0 [95% CI, 1.0 to 49.4]; in adulthood: 6.7 [95% CI, 0.5 to 99.5]; $p = 0.45$).

In Table II data are presented for subjects with



A PC₁₀ histamine childhood



B PC₁₀ histamine adulthood

FIG. 1. **A**, Relationship between degree of bronchial responsiveness in childhood (PC₁₀ histamine, x axis) and pulmonary function in childhood (FEV₁ % pred., y axis). **B**, Relationship between degree of bronchial responsiveness in adulthood (PC₁₀ histamine, x axis) and pulmonary function in adulthood (FEV₁ % pred. y axis).

TABLE II. Comparison of data for adults with and without current respiratory symptoms who fully participated in the first (childhood) and the second survey (adulthood)

Characteristic	Respiratory symptoms in adulthood			
	Childhood data		Adulthood data	
	Yes (<i>n</i> = 221)	No (<i>n</i> = 64)	Yes (<i>n</i> = 221)	No (<i>n</i> = 64)
IVC (% pred)*	97 (70-124)	98 (77-119)	103 (78-128)†	106 (83-129)†
FEV ₁ (% pred)*	90 (57-123)	93 (66-120)	94 (59-129)†	103 (78-128)†‡
Histamine PC ₁₀ of ≤ 16 mg/ml n/N (%)	139/219 (63)	36/63 (57)	104/215 (48)	12/64 (19)§
PC ₁₀ histamine, (mg/ml)¶	7.0 (0.9-55.7)	6.0 (0.7-47.9)	5.3 (0.3-99.5)	9.7 (1.2-77.5)‡

*Mean (95% CI).

†*p* < 0.05; childhood and adulthood data, paired Student's *t* test.‡*p* < 0.05; subjects with and without symptoms in adulthood, unpaired Student's *t* test.§*p* < 0.05; subjects with and without symptoms in adulthood, chi-square test.||*p* < 0.05; childhood and adulthood data, McNemar's chi-square test.

¶Geometric mean (95% CI).

and without current symptoms in adulthood. Although mean percent predicted FEV₁ in childhood was slightly lower in subjects who still had symptoms in adulthood compared with childhood data of adults without symptoms, this difference was not significant (*p* = 0.11). No difference in mean childhood percent predicted IVC was seen between the adults with symptoms and those without symptoms (*p* = 0.58). The number of subjects with a histamine PC₁₀ of 16 mg/ml or less in childhood was slightly but not significantly higher (*p* = 0.47) in subjects who had symptoms in adulthood, compared with childhood data of adults without symptoms. The degree of bronchial responsiveness was comparable for the two groups in childhood (*p* = 0.33). For both subjects with and those without current symptoms in adulthood, the level of pulmonary function in adulthood had improved since childhood. Adults with current symptoms had a significantly lower percent predicted FEV₁ than subjects without symptoms (*p* < 0.01). Mean percent predicted IVC was only 3% lower (*p* = 0.09). The number of subjects with a histamine PC₁₀ of 16 mg/ml or less had decreased from childhood to adulthood in both subjects with and those without respiratory symptoms in adulthood (*p* < 0.01). Adults without respiratory symptoms were less hyperresponsive in adulthood than in childhood (*p* = 0.047). In subjects with current respiratory symptoms in adulthood, the degree of bronchial responsiveness had increased slightly since childhood (*p* = 0.87).

The percentage of active smokers was higher in

adults without symptoms. This difference failed to reach the level of significance (*p* = 0.44). The age of onset of smoking and cigarette pack-years in adulthood did not differ significantly between the groups.

Predictive value of childhood measurements for prognosis in young adulthood

In Table III the outcome of adult histamine PC₁₀ of 16 mg/ml or less in logistic analysis is presented. A significant influence of childhood histamine PC₁₀ was found (*p* = 0.02). A trend toward a significant predictive value of female gender (*p* = 0.07), age of onset of respiratory symptoms (*p* = 0.08), and childhood respiratory symptom score (*p* = 0.06) was demonstrated. Moreover, a significant relationship was found between adult histamine PC₁₀ with the need for medication in adulthood (*p* < 0.01).

The influence of the same childhood variables on continuous outcome variables (the level of FEV₁ [absolute volume in milliliters] in adulthood and the degree of bronchial responsiveness in adulthood) was assessed with multiple regression techniques. In Table IV it is shown that FEV₁ in adulthood is significantly predicted by the level of percent predicted FEV₁ in childhood (*p* < 0.01). Although the adult FEV₁ (absolute volume) was highly significantly influenced by gender, no significant influence of gender on the outcome of percent predicted FEV₁ was found. The mean level of percent predicted FEV₁ was 94 (95% CI, 57 to 131) in female subjects and 97 (95% CI, 64 to 130) in male subjects. The degree of bronchial

TABLE III. Odds ratios and 95% CIs of variables in relation to outcome of current bronchial responsiveness (histamine PC₁₀ of ≤ 16 mg/ml) in adulthood

Variable	Histamine PC ₁₀ of ≤ 16 mg/ml (adults)		
	OR	95% CI	p Value
Sex*	0.49	0.22-1.05	0.067
Age at onset of respiratory symptoms (yr)	1.35	0.96-1.90	0.084
Duration of respiratory symptoms (yr)	1.23	0.88-1.73	0.243
Symptom score in childhood	1.41	0.99-2.02	0.061
IVC in childhood (% pred)	1.01	0.97-1.05	0.621
FEV ₁ in childhood (% pred)	0.98	0.96-1.03	0.899
Ln histamine PC ₁₀ in childhood, (mg/ml)	0.75	0.58-0.96	0.022
Passive smoking in childhood	0.98	0.43-2.28	0.983
Age in adulthood	0.80	0.64-1.03	0.085
Active smoking in adulthood (pack-yr)	0.98	0.92-1.05	0.565
Use of medication in adulthood	5.46	2.65-11.17	<0.001

OR, Odds ratio.

*Male = 0; female = 1.

responsiveness in adults was significantly predicted by gender ($p = 0.047$): female subjects were more responsive in adulthood than male subjects. No significant predictive effect of the childhood degree of bronchial responsiveness on the adult degree of bronchial responsiveness was found ($p = 0.19$). A significant relationship was found between the adult level of FEV₁ and the degree of bronchial responsiveness with the need for medication in adulthood ($p < 0.01$).

When the interaction of childhood level of percent predicted FEV₁ and childhood degree of bronchial responsiveness was included as an independent variable in the analyses, it was not significantly predictive of either pulmonary function or bronchial responsiveness in adulthood.

We also studied the predictive value of the log dose-response slope included as an independent variable in the analysis instead of the Ln histamine PC₁₀. Again, results remained roughly the same.

DISCUSSION

In this study of children with asthma diagnosed on the basis of clinical symptoms, we have examined the outcome of level of FEV₁ and degree of histamine PC₁₀ in adulthood. The cohort of children that was studied is likely to be representative of children with asthma who are treated in our outpatient department. We do realize that chil-

dren who are referred to a pediatrician or pediatric pulmonologist may in some way be a "negative" sample of the general population of children with asthma. The prognosis of children with merely mild asthma, who are not referred to a specialist and who are treated by general practitioners, is probably slightly better.

Pulmonary function level (FEV₁)

Pulmonary function becomes closer to normal the longer a subject with asthma has been free of wheezing.^{9, 25, 26} In adults without symptoms who had childhood asthma, pulmonary function seems to be related to severity of asthma in childhood. Subjects with only minor wheezing in childhood who had been free of wheezing for at least 3 years had a mean FEV₁ that was indistinguishable from that of healthy control subjects.²⁵ In subjects with more severe asthmatic symptoms in childhood, the adult level of FEV₁ was abnormal, despite the absence of current symptoms.^{10, 13, 25}

In our study in the subjects who were free of symptoms in adulthood, the adult mean level of percent predicted FEV₁ was in the normal range and the childhood level of FEV₁ was only mildly reduced. The only childhood factor predictive of the adult level of FEV₁ was the childhood level of pulmonary function. The fairly normal level of percent predicted FEV₁ in childhood may explain the normal values of the same parameter in adult-

TABLE IV. Coefficients of multiple linear regression and *p* values of various variables in relation to the outcome of childhood asthma (FEV₁ in adulthood histamine PC₁₀ in adulthood)

Variable	FEV ₁ (ml)			Ln Histamine PC ₁₀ (mg/ml)		
	Coefficient	SE	<i>p</i> Value	Coefficient	SE	<i>p</i> Value
Sex*	524.3	118.6	<0.001	0.48	0.24	0.047
Age at onset of respiratory symptoms†	-29.6	35.1	0.400	-0.14	0.10	0.159
Duration of respiratory symptoms at referral‡	-11.4	35.7	0.749	-0.08	0.10	0.395
Symptom score in childhood§	-55.1	37.9	0.147	-0.15	0.11	0.190
IVC in childhood (% pred)§	-0.6	4.5	0.902	-0.01	0.01	0.583
FEV ₁ in childhood (% pred)§	15.2	3.9	<0.001	0.00	0.01	0.679
Ln histamine PC ₁₀ in childhood	-25.1	27.5	0.363	0.10	0.08	0.194
Passive smoking in childhood¶	77.8	86.8	0.371	-0.03	0.25	0.890
Active smoking in adulthood*	-7.4	6.8	0.281	0.02	0.02	0.431
Use of medication in adulthood¶	-370.5	82.2	<0.001	-1.23	0.24	<0.001

FEV₁ is corrected for age and height.

*Male = 0; female = 1.

¶No = 0; Yes = 1.

Unit changes of variables in the analysis:

†1 year.

‡1 (unit).

§1%.

||1 mg/ml.

#1 pack-year.

hood. In a previous study by Gerritsen et al.¹³ adult pulmonary function level was mainly determined by childhood percent predicted FEV₁, histamine PC₁₀, and childhood symptom score. Subjects in that study probably had more severe asthma, because mean percent predicted FEV₁ in childhood was lower.

An inverse relationship between symptom severity and level of FEV₁ has been found in a follow-up study in Australia.^{4, 6, 9} Subjects were resurveyed every 7 years and stratified at the time of each survey according to symptom severity. Mean percent predicted FEV₁ was lowest in subjects with most severe asthma.^{4, 6, 9} FEV₁ below the fifth percentile at age 10 or 14 was associated with more troublesome asthma at age 21. Percent predicted FEV₁ remained significantly lower in these subjects with severe asthma. We found a predictive effect of childhood percent predicted

FEV₁ on the outcome of adult level of FEV₁, which is in agreement with the results of the Australian study.

It has been found that smoking leads to a decrease in the rate of growth of FEV₁.²⁷ In our study smoking was related to a lower level of FEV₁ in male subjects. In female subjects no effect of cigarette smoking on level of FEV₁ was demonstrated. It appeared that smokers were predominantly subjects with less severe asthma, and the lack of negative effects on disease severity in our study was supposed to be due to this so-called "healthy smoker effect." Moreover, the number of pack-years was limited.

Bronchial hyperresponsiveness (histamine PC₁₀)

In univariate analyses a clear difference existed between subjects with and those without current

symptoms in adulthood. In subjects who had symptoms, nearly half (48%) still had a histamine PC₁₀ of 16 mg/ml or less. In subjects without symptoms, only 19% were still hyperresponsive. In adults with symptoms the degree of bronchial responsiveness had increased, whereas it had decreased in subjects who were free of symptoms. The presence but not the degree of bronchial responsiveness in adulthood was predicted by the childhood histamine PC₁₀ level. The childhood log dose-response slope had no predictive effect on the outcome of the adult degree of bronchial responsiveness either.

The degree of bronchial responsiveness was measured only at two time points; the results of our study might have been different if more data were available.

In a recent study in children with asthma aged 1 to 17 years, no dependency of bronchial responsiveness on age was found.²⁸ In epidemiologic surveys, conflicting results were obtained. In a study in the Netherlands of subjects aged 14 to 64 years, the prevalence of airway responsiveness increased with age.²⁹ In a survey in America, the prevalence of airway responsiveness decreased from 28% in subjects aged 5 to 24 years to 8% in subjects aged 25 to 44 years.³⁰

The increase in degree of bronchial responsiveness in adults with symptoms does not seem to correspond to a slight decrease in mean symptom score since childhood. In regression analysis the childhood level of bronchial responsiveness did predict a high score of respiratory symptoms in adulthood. A relationship between asthma severity and bronchial responsiveness (to metacholine) was also found in a survey of adult subjects with asthma, who were studied at 7-year intervals since childhood.⁹ In that investigation, however, no childhood measurements of bronchial responsiveness were available.

No strong effect of either passive smoking in childhood or active smoking in adulthood on outcome of bronchial responsiveness in adulthood was demonstrated in this investigation. For active smoking, this might be explained by the healthy smoker effect in combination with a limited number of pack-years in young adulthood. Our findings are consistent with results from one other study in young adults.³¹

Although bronchial responsiveness is one of the principal characteristics of asthma, it cannot be equated with severity of disease. Because a significantly higher proportion of subjects with current

respiratory symptoms also had bronchial hyperresponsiveness, it is clear that some relationship does exist. A correlation between the degree of bronchial responsiveness and respiratory symptoms, as well as the treatment to control symptoms, has previously been found.²¹ We also found a strong association between the presence and degree of bronchial responsiveness and the need for medication in adulthood in our study.

There is sufficient evidence that inflammation of the airways plays an important role in the pathogenesis of bronchial responsiveness.^{32, 33} In adult subjects with asthma, a more rapid decline in pulmonary function (FEV₁) was found in subjects with marked bronchial responsiveness than in subjects with only mild or moderate bronchial responsiveness.³⁴

It is now generally assumed that treatment of airway inflammation, reflected by bronchial responsiveness, is probably the most fundamental method of asthma therapy.³⁵ However, it is not known whether treatment of bronchial inflammation and hyperresponsiveness may also have a positive effect on the long-term prognosis of patients with asthma from childhood to adulthood.

Conclusion

In this study the level of pulmonary function (FEV₁) in adults with asthma was significantly predicted only by childhood level of FEV₁. The presence of bronchial responsiveness in adulthood was significantly predicted by female gender and the degree of bronchial responsiveness in childhood. The degree of bronchial responsiveness in adulthood was only weakly related to the initial degree of responsiveness in childhood and was significantly predicted by female gender. Both surveys showed a weak but significant relationship between percent predicted FEV₁ and histamine PC₁₀.

Because in univariate analyses the proportion of subjects who remained hyperresponsive was significantly higher in adults with current respiratory symptoms and because a more severe hyperresponsiveness was found in adults with symptoms, a relationship between presence of respiratory symptoms in adulthood and concurrent bronchial responsiveness was established. Therefore efforts to reduce the degree of bronchial responsiveness by allergen avoidance or by anti-inflammatory treatment may also be important in reducing respiratory symptoms and altering the natural course of the disease.

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