

A 15-YEAR FOLLOW-UP STUDY OF VENTILATORY FUNCTION IN ADULTS WITH ASTHMA

PETER LANGE, M.D., PH.D., JAN PARNER, JØRGEN VESTBO, M.D., PH.D., PETER SCHNOHR, M.D.,
AND GORM JENSEN, M.D., PH.D.

ABSTRACT

Background Although the prevalence of asthma and morbidity related to asthma are increasing, little is known about the natural history of lung function in adults with this disease.

Methods We used data from a longitudinal epidemiologic study of the general population in a Danish city, the Copenhagen City Heart Study, to analyze changes over time in the forced expiratory volume in one second (FEV₁) in adults with self-reported asthma and adults without asthma. The study was conducted between 1976 and 1994; for each patient, three measurements of lung function were obtained over a 15-year period. The final data set consisted of measurements from 17,506 subjects (8136 men and 9370 women), of whom 1095 had asthma.

Results Among subjects who participated in all three evaluations, the unadjusted decline in FEV₁ among subjects with asthma was 38 ml per year, as compared with 22 ml per year in those without asthma. The decline in FEV₁ normalized for height (FEV₁ divided by the square of the height in meters) was greater among the subjects with asthma than among those without the disease (P<0.001). Among both men and women, and among both smokers and non-smokers, subjects with asthma had greater declines in FEV₁ over time than those without asthma (P<0.001). At the age of 60 years, a 175-cm-tall non-smoking man without asthma had an average FEV₁ of 3.05 liters, as compared with 1.99 liters for a man of similar age and height who smoked and had asthma.

Conclusions In a sample of the general population, people who identified themselves as having asthma had substantially greater declines in FEV₁ over time than those who did not. (N Engl J Med 1998;339:1194-200.)

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ALTHOUGH asthma is a very common condition with increasing prevalence, its natural history has not been well described.¹ Recent studies of patients with asthma selected from the general population have shown increased mortality in subjects with reduced ventilatory function and have thus underlined the importance of preservation of normal lung function.²⁻⁴ Although a few previous studies have reported the development of persistent airway obstruction in some patients with asthma, the data are limited.^{5,6} A few studies have focused on the decline of lung function in adults with asthma, but the results are conflicting with regard both to the magnitude of the

effect of asthma and to the effect of smoking on lung function and decline in lung function.⁷⁻¹¹

We analyzed changes in forced expiratory volume in one second (FEV₁) among subjects with self-reported asthma and those without asthma in the general population. The analyses are based on the 15-year follow-up of the participants in the Copenhagen City Heart Study, an ongoing epidemiologic study of people who live in the city of Copenhagen, Denmark.

METHODS

Study Population

The subjects participated in the Copenhagen City Heart Study, a prospective epidemiologic study initiated in 1976. Details of the selection procedure, a description of the eligible nonparticipants and the complete examination program, and information on the subjects have been presented elsewhere.¹²⁻¹⁴ We previously reported that mortality among the subjects with asthma in this cohort was approximately 1.6 times as high as that among the subjects without asthma.⁵ Data from the first five years of follow-up also showed a trend toward a greater decline in FEV₁ among subjects with asthma.¹¹ We now analyze data on FEV₁ values from the 15-year follow-up evaluation of each patient.

The study sample, consisting of 19,698 persons, was selected in January 1976 from a population of approximately 90,000 residents of Copenhagen who were 20 years of age or older and who were listed in the Copenhagen Population Register. The first examination round lasted 25 months, from February 27, 1976, to March 31, 1978. A total of 14,223 subjects were examined, 74 percent of those who were invited and were still alive. The response rates were highest among subjects between 40 and 70 years of age (68 to 80 percent) and lowest among subjects 80 years old or older (28 to 41 percent).

At the end of the first examination, we planned to visit a random sample of 223 subjects selected from among the nonparticipants in order to determine whether they differed significantly from the participants. However, only 67 of these people (30 percent) could be contacted, despite several attempts. The prevalence of asthma and chronic mucus hypersecretion among the nonparticipants who were visited in their homes was slightly higher than among the participants. Between 1981 and 1983, the whole population sample (both participants and nonparticipants), together with a new sample of 500 subjects 20 to 25 years of age, was invited to undergo a second examination. A total of 12,698 of the 18,089 subjects who were still alive were examined (response rate, 70 percent). Finally, a third examination of the cohort, together with an additional sample of 3000 subjects 20 to 39 years of age, was performed between 1991 and 1994. A total of 10,127 subjects participated in this examination (response rate, 61 percent). After subjects with insufficient data for the analyses

From the Copenhagen City Heart Study, Epidemiologic Research Unit, Bispebjerg University Hospital (P.L., J.P., J.V., P.S., G.J.); the Department of Respiratory Medicine 129, Hvidovre Hospital and University of Copenhagen (P.L., J.V.); and the Department of Biostatistics, University of Copenhagen (J.P.)—all in Copenhagen, Denmark. Address reprint requests to Dr. Lange at the Department of Respiratory Medicine 129, Hvidovre Hospital, DK-2650 Hvidovre, Denmark.

TABLE 1. NUMBER OF EXAMINATIONS UNDERGONE BY THE 17,506 STUDY SUBJECTS.

NO. OF EXAMINATIONS AND YEARS	WOMEN	MEN	TOTAL
One			
1976–1978	1161	1291	2452
1981–1983	473	497	970
1991–1994	1099	1075	2174
Two			
1976–1978 and 1981–1983	2815	2398	5213
1981–1983 and 1991–1994	349	321	670
1976–1978 and 1991–1994	242	207	449
Three			
1976–1978, 1981–1983, and 1991–1994	3231	2347	5578

of FEV₁ were excluded, the final data base consisted of 17,506 subjects (8136 men and 9370 women) who were examined at least once during the study (Table 1). The study was approved by the ethics committee for the city of Copenhagen, and all participants provided oral informed consent.

Procedures

In the first and second examinations of the survey, FEV₁ and forced vital capacity (FVC) were measured with an electronic spirometer (model N 403, Monaghan, Littleton, Colo.), which was calibrated daily with a 1-liter syringe and weekly against a water-sealed Godard spirometer. In the third round of examinations, a dry wedge spirometer (Vitalograph, Maidenhead, United Kingdom), which was calibrated weekly with a 1-liter syringe, was used. Unfortunately, at the time of the third survey, the electronic spirometer used in the two previous examinations was no longer functioning, precluding a direct comparison between the results obtained with the two spirometers. After at least one trial blow, three values were obtained. As a criterion for correct performance of the procedure, at least two measurements of FEV₁ and FVC differing by less than 5 percent had to be produced. The highest FEV₁ was used in the analyses. Data on FEV₁ are reported both as absolute values and as percentages of predicted values.¹¹

A self-administered questionnaire concerning symptoms, somatic diseases, socioeconomic status, smoking status, and drinking habits was completed by participants and reviewed by one of the investigators. Chronic hypersecretion of mucus was defined as bringing up phlegm during at least three months per year for at least two consecutive years. The subjects described themselves as current smokers, as exsmokers, or as having never smoked. Exsmokers and those who had never smoked were classified as non-smokers.

The subjects were categorized in terms of the presence or absence of asthma. Like other epidemiologic studies, our study relied on the subjects' perception of whether they had the disease.^{15,16} Thus, the presence of asthma was defined by an affirmative response to the question, "Do you have asthma?"

Statistical Analysis

After adjustment for height, we compared the mean FEV₁ and the mean decline in FEV₁ with age within subgroups of subjects classified according to the presence or absence of asthma, smoking status, and the presence or absence of chronic hypersecretion of mucus. Separate comparisons were performed for men and women. The subgroups were generated in the following way. Subjects who reported having asthma during at least one examination were considered to have had asthma throughout the 15-year observation period. This conclusion is consistent with previous observations that the lung function of people in whom asthma

develops is often reduced before the disease becomes clinically apparent, probably reflecting the subclinical course of the disease. It is also in line with the view of asthma as a disease that seldom disappears in adults and that, even in remission, may result in reduced lung function.^{1,11,17} Since chronic hypersecretion of mucus, like self-reported asthma, tended to be reported repeatedly by the same subjects throughout the examinations ("tracking"), subjects who reported having chronic mucus hypersecretion at least once during the observation period were classified as having had hypersecretion during the whole study period. On the other hand, because changes in smoking habits influence the decline in FEV₁ within a short time, and our analyses were mainly longitudinal and thus focused on changes in FEV₁, we decided to relate lung-function measurements to smoking status at the time of examination.¹⁸ The height-adjusted values for FEV₁ (the FEV₁ divided by the square of the height in meters) and declines in FEV₁ in different subgroups of subjects were compared with use of both the Wilcoxon test and nonparametric analysis of variance. All reported P values are based on two-sided tests of significance.

RESULTS

Table 2 shows the age, smoking status, presence or absence of mucus hypersecretion, and results of spirometric tests of lung function among participants with and without asthma at the initial examination. Participants with asthma had significantly lower FEV₁ values than those without asthma at the initial examination and at subsequent examinations. During the follow-up period, the prevalence of asthma increased from 2.3 percent at the first examination to 3.3 percent at the second and to 6.3 percent at the third. Thus, 364 subjects who did not report having asthma at either their first or their second examination did so at a later examination. In contrast, 79 subjects who reported having asthma at either their first or their second examination did not report having asthma at a later examination.

Among subjects who participated in all three surveys, the average decline in FEV₁ was 22 ml per year in those without asthma and 38 ml per year in those with asthma. Table 3 shows the observed decline in FEV₁ in subjects who participated in at least two examinations, according to sex, age, smoking status, and the presence or absence of asthma. In most subgroups, subjects with asthma and smokers had a greater decline in FEV₁ than those without asthma and nonsmokers, respectively. Adjustment for height did not change these findings.

Figure 1 shows changes with age in height-adjusted FEV₁ according to sex, smoking status, and the presence or absence of asthma. The data are for 9370 women and 8136 men with at least one measurement of lung function. For both sexes, the levels of FEV₁ were higher and the declines in FEV₁ were less steep among subjects without asthma than among those with asthma. The average difference between subjects with asthma and those without asthma increased with age. The difference in the average value for FEV₁ between the two most extreme groups, non-smokers without asthma and smokers with asthma, was substantial. At 60 years of age, a 175-cm-tall

TABLE 2. CHARACTERISTICS OF THE SUBJECTS ACCORDING TO THE PRESENCE OR ABSENCE OF ASTHMA AT THE FIRST EXAMINATION IN 1976–1978.*

CHARACTERISTIC	WOMEN			MEN		
	NO ASTHMA (N=7023)	ASTHMA (N=423)	P VALUE	NO ASTHMA (N=5888)	ASTHMA (N=355)	P VALUE
Age (yr)	52.3±11.7	52.0±10.4	0.55	52.5±12.4	53.3±10.9	0.29
FEV ₁						
Liters	2.24±0.58	1.90±0.66	<0.001	3.04±0.87	2.35±0.97	<0.001
% of predicted	94.0±18.9	78.9±23.3	<0.001	93.7±19.9	73.3±25.3	<0.001
Current smoking (%)	57	68	<0.001	69	74	<0.001
Chronic mucus hypersecretion (%)	15	54	<0.001	22	63	0.06

*Plus–minus values are means ±SD. FEV₁ denotes the forced expiratory volume in one second.

TABLE 3. ANNUAL CHANGE IN FEV₁ IN SUBJECTS WHO PARTICIPATED IN AT LEAST TWO EXAMINATIONS.*

AGE AND VARIABLE	WOMEN				MEN			
	NO ASTHMA		ASTHMA		NO ASTHMA		ASTHMA	
	nonsmokers	smokers	nonsmokers	smokers	nonsmokers	smokers	nonsmokers	smokers
20–39 yr								
Change in FEV ₁ (ml)	+5.0±2.7	-5.8±2.5	-1.5±12.0	-5.0±11.4	-4.6±4.2	-15.9±2.9	-32.4±15.6	-54.0±8.0
No. of subjects	433	621	21	42	357	600	16	29
40–59 yr								
Change in FEV ₁ (ml)	-17.7±1.4	-27.3±1.2	-31.1±5.0	-38.2±3.2	-24.2±2.6	-39.7±1.7	-32.8±9.1	-57.6±5.8
No. of subjects	1471	2230	70	201	780	1979	36	150
60–79 yr								
Change in FEV ₁ (ml)	-31.7±2.1	-39.6±2.4	-26.3±12.6	-47.2±6.8	-37.1±3.7	-46.8±3.1	-25.9±8.7	-48.9±9.1
No. of subjects	809	638	34	52	455	769	29	57

*Values are means ±SD. FEV₁ denotes the forced expiratory volume in one second. Negative numbers indicate declines in the FEV₁, and positive numbers increases. P<0.001 for all comparisons between smokers and nonsmokers, people with asthma and those without asthma, and women and men by both the Wilcoxon test and nonparametric analysis of variance.

nonsmoking man had an average FEV₁ of 3.05 liters, as compared with 1.99 liters for a man of similar age and height who smoked and had asthma. The curves relating FEV₁ to age were compared between subjects with and without asthma. Among both men and women and among both smokers and nonsmokers, the curves differed significantly between subjects with asthma and those without asthma (P<0.001).

To evaluate the effect of mucus hypersecretion, we performed additional analyses of data on subjects with asthma. Figure 2 shows changes with age in height-adjusted FEV₁ according to sex, smoking status, and the presence or absence of chronic mucus hypersecretion among subjects with asthma. There were 1187 measurements of FEV₁ for women and 944 measurements for men. In both sexes, the presence of mucus hypersecretion and smoking was associated with a significantly greater decline in FEV₁; smokers with asthma had the lowest values (P<0.01).

DISCUSSION

In this large, community-based study, people who identified themselves as having asthma had substan-

tially greater declines in FEV₁ over time than those who did not. Stratification according to smoking status showed that smoking significantly accelerated the decline in lung function in both subjects with asthma and those without asthma. In addition, chronic mucus hypersecretion was a significant marker of a greater decline in FEV₁ in people with asthma, regardless of their smoking status. This observation suggests that the response to this rather simple and old-fashioned question regarding sputum production still has important clinical implications. Our findings are in keeping with previous results from this cohort, which showed increased mortality among people who reported themselves as having asthma; this increase was mediated mainly through the reduced level of ventilatory function.³

The greater decline in FEV₁ among subjects with asthma was apparent from both the raw data on the subgroup of subjects who participated in at least two examinations (Table 3) and from our analysis of FEV₁ in all subjects (Fig. 1). A conclusion drawn solely on the basis of the decline in lung function among those who underwent several examinations may be subject

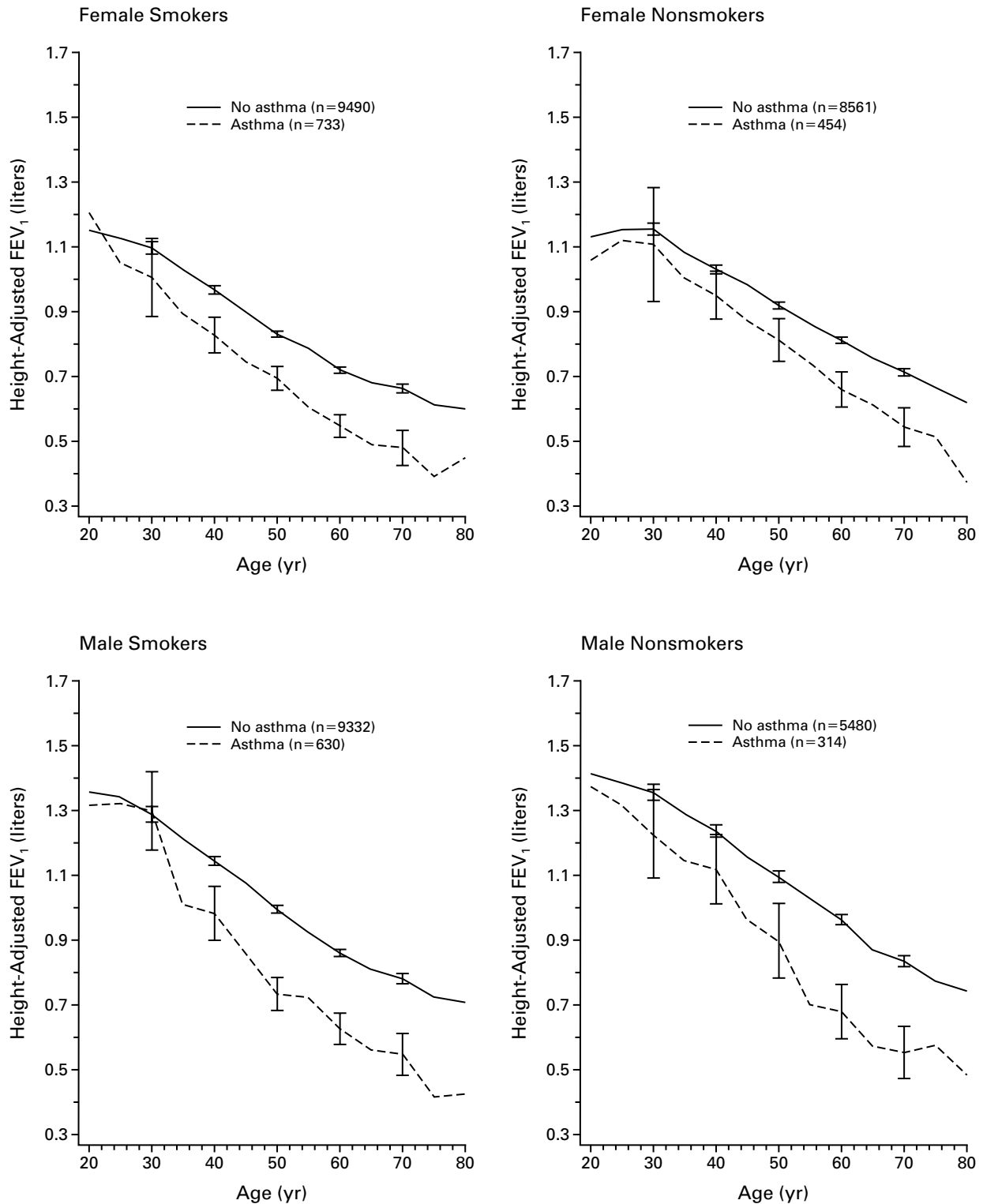


Figure 1. Changes with Age in the Height-Adjusted Forced Expiratory Volume in One Second (FEV₁) According to Sex, Smoking Status, and the Presence or Absence of Asthma.

Values are means \pm SE, based on 5-year age groups (bars are shown for each 10 years). The numbers of measurements in the various subgroups are shown in parentheses. The curves in each panel differ significantly from each other ($P < 0.001$), indicating that among both men and women and among both smokers and nonsmokers, subjects with asthma had a significantly greater decline in FEV₁ than those without asthma.

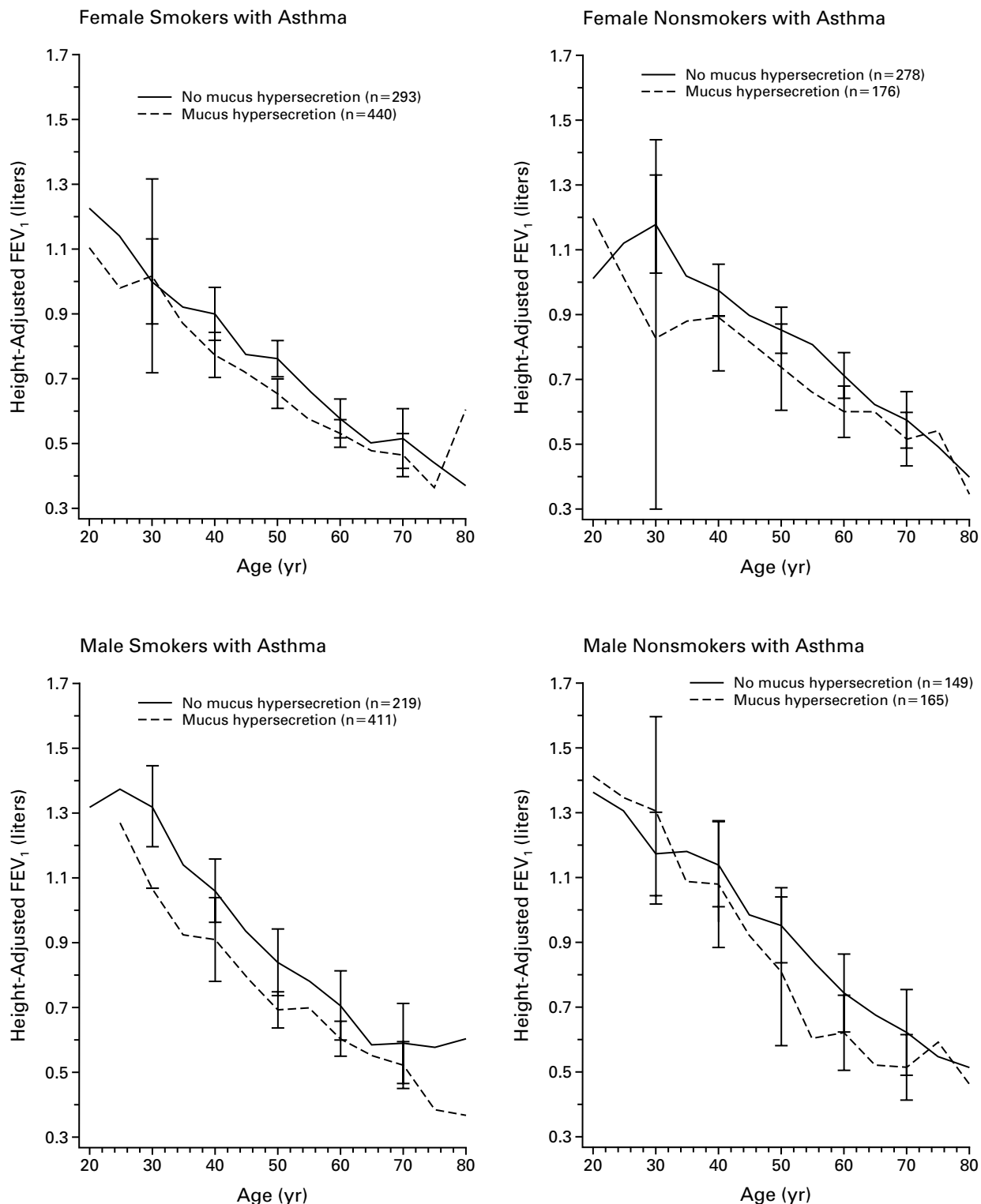


Figure 2. Changes with Age in the Height-Adjusted Forced Expiratory Volume in One Second (FEV₁) According to Sex, Smoking Status, and the Presence or Absence of Chronic Mucus Hypersecretion among Subjects with Asthma.

Values are means \pm SE, based on 5-year age groups (bars are shown for each 10 years). The numbers of measurements in the various subgroups are shown in parentheses. The curves in each panel differ significantly from each other ($P < 0.01$), indicating that among both men and women with asthma and among both smokers and nonsmokers with asthma, subjects with chronic mucus hypersecretion had a significantly greater decline in FEV₁ than those without chronic mucus hypersecretion.

to bias, since the decline in FEV₁ in this survivor population is likely to have been less steep than that in the whole sample.

In order to account for the longitudinal nature of the data and for the correlation of repeated measurements in individual subjects, we also performed a more detailed analysis, in which we modeled FEV₁ using a specific method for covariate-dependent random effects.¹⁹ A nonlinear mixed-effects model with asthma, age, and smoking status as covariates was developed to incorporate FEV₁ measurements from all subjects who underwent at least one examination.²⁰ Since the results of these analyses were consistent with those of our simpler analyses, only the results of the simpler analyses are presented.

Our findings suggest that every effort should be made to keep the lung function of people with asthma at the highest achievable level. Although not smoking is clearly desirable, even people with asthma who did not smoke had, on average, a significantly greater decline in FEV₁ than other nonsmokers in our study. A study of early and continuous treatment of mild asthma with inhaled steroids for up to three years found beneficial effects, not only in terms of symptoms of asthma but also in terms of lung function.^{21,22} However, there is at present no definite evidence that long-term treatment with any asthma medication can prevent the decline in lung function. Unfortunately, since our only detailed information on medications used comes from the last examination, between 1991 and 1994, we were unable to evaluate prospectively the effect of treatment on the decline in FEV₁.

The results of previous studies of the decline in FEV₁ in people with asthma are generally consistent with our findings, but there are exceptions. In the study by Fletcher and coworkers,²³ the mean unadjusted decline in FEV₁ was 22 ml per year greater in men with asthma than in men without asthma, a value similar to the 16 ml per year found in our study. In the studies of Peat and coworkers and in our report of the five-year follow-up, a similar pattern was observed, but the results were not always statistically significant.^{8,11} These studies and earlier Danish studies of patients in chest clinics used less sophisticated statistical models, mainly simple linear regression models.^{9,10} However, in the Tucson lung study,⁷ declines in FEV₁ of less than 5 ml per year were observed in adults with asthma. Clinical reports based on small numbers of patients with long-standing asthma have shown that persistent airway obstruction developed in many such patients, but it is not known whether this is an exception or a common finding in asthma.^{5,6,24} In a recent report of 25-year follow-up data on adults from a Dutch asthma clinic, more than 75 percent of the patients had FEV₁ values below 90 percent of the predicted values at the final examination.²⁵ Our findings and most previous

reports are thus in line with the perception that asthma is a chronic inflammatory disease in which ongoing tissue injury and repair may result in irreversible fibrotic changes in the airways.^{26,27} In addition, since bronchial hyperreactivity is considered a central feature of asthma, our observation of an increased decline in FEV₁ with age among people with asthma is also conceptually in line with the hypothesis that increased airway responsiveness is a risk factor for an accelerated decline in lung function.^{28,29}

The finding that chronic mucus hypersecretion was a significant marker of an accelerated decline in FEV₁ is also in accordance with our previous findings of changes in lung function in subjects without asthma during the first five years of our survey.³⁰ Mucus hypersecretion is quite prevalent in people with asthma and could be regarded as an indicator of poor control of asthma and severe disease.^{31,32} Although we are unaware of pathoanatomical studies linking airway inflammation in asthma with sputum production, such correlations have been reported in patients with chronic bronchitis.³³

The most important potential bias in our study concerns the classification of asthma.³ The use of a patient's report of the diagnosis invariably leads to some degree of misclassification, because the condition will remain undiagnosed in some subjects with mild asthma, whereas some subjects with chronic obstructive pulmonary disease will probably report that they have asthma. However, since the prevalence of self-reported asthma in our cohort was only around 6 percent and showed no increase with age, we do not think that many subjects who reported having asthma in fact had smoking-induced chronic obstructive pulmonary disease. Finally, because asthma had a consistent negative influence on the FEV₁, regardless of smoking status, misclassification of asthma and chronic obstructive pulmonary disease is unlikely to have biased our results severely.

In conclusion, we found that adults with self-reported asthma had a greater decline in FEV₁ over time than those without asthma and that smoking adversely influenced this course. Special efforts should be made to motivate people with asthma not to smoke, and long-term studies should evaluate treatments to postpone the accelerated decline of lung function that occurs in people with asthma.

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