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Lung Function in Young Adults Predicts Airflow Obstruction 20 Years Later

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Abstract

Rationale—The burden of obstructive lung disease is increasing, yet there are limited data on its natural history in young adults.

Objectives—To determine in a prospective cohort of generally healthy young adults the influence of early adult lung function on the presence of airflow obstruction in middle age.

Methods—Longitudinal study of 2,496 adults who were 18-30 years of age at entry, did not report having asthma, and returned at Year 20. Airflow obstruction was defined as an FEV_1/FVC ratio less than the lower limit of normal.

Measurements and Main Results—Airflow obstruction was present in 6.9% and 7.8% of participants at Years 0 and 20. Less than 10% of participants with airflow obstruction self-reported COPD. In cross sectional analyses airflow obstruction was associated with less education, smoking, and self-reported COPD. Low FEV_1 and FEV_1/FVC and airflow obstruction in young adults were associated with low lung function and airflow obstruction 20 years later. Of those with airflow obstruction at Year 0, 52% had airflow obstruction 20 years later. The FEV_1/FVC at Year 0 was highly predictive of airflow obstruction 20 years later (c-statistic 0.91; 95% CI 0.89-0.93). The effect of cigarette smoking on lung function decline with age was most evident in young adults with pre-existing airflow obstruction.

Conclusions—Airflow obstruction is mostly unrecognized in young and middle age adults. A low FEV_1, low FEV_1/FVC and airflow obstruction in young adults, in addition to smoking, are highly predictive of low lung function and airflow obstruction in middle age.

Keywords

Airflow obstruction; CARDIA; chronic obstructive pulmonary disease; COPD; natural history

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death in the world and is projected to be the fourth by the year 2030 [1]. COPD prevalence increases with age and is typically diagnosed after age 50, but symptoms and airflow obstruction precede the diagnosis by 10 or more years [2,3]. Several studies have reported the prevalence of airflow obstruction in population samples, but most were cross-sectional [3-6] or had follow-up periods of only a few years [7]. A recent international survey identified airflow obstruction ($FEV_1/FVC \leq 0.70$) [8,9] in almost 4% of young adults ages 20-44 years [4]. In addition, chronic cough and sputum were associated with an increased risk for developing airflow obstruction over a 10 year period [10]. However, these studies are limited by lack of stratification by age, short follow-up, and use of a fixed cut-point to define airflow obstruction, which under-diagnoses it in younger subjects and over-diagnoses it in older individuals [11-13].

Recently, Martinez and colleagues made the observation that reduced airway function shortly after birth is a risk factor for airflow obstruction in young adults [14]. Other studies have reported that lung function in school aged children tracks over time such that those with low lung function at the initial examination had low lung function throughout childhood [15,16]. The Busselton Health Study provided similar findings in adults, but the data were derived from a mix of cross-sectional and longitudinal observations [17]. No study has reported the influence of early adult lung function on the presence of airflow obstruction in middle age in a young adult population followed for a prolonged time.

The Coronary Artery Risk Development in Young Adults (CARDIA) study was initiated in 1985-6 and has followed randomly selected, generally healthy individuals who were ages 18-30 years at study entry [18,19]. Lung function was measured and information obtained on pulmonary signs, symptoms and diagnoses at entry, Year 20, and several times in between. At Year 20 participants were 38-50 years of age, an age when symptoms and airflow obstruction are usually present in those who are subsequently diagnosed with airflow obstruction [2,3].

In the present study we determined the prevalence of airflow obstruction and the association between lung function at study entry and airflow obstruction at Year 20. Our hypotheses were that airflow obstruction is mostly undiagnosed in otherwise healthy young and middle age adults and that low lung function in young adults predicts low lung function and airflow obstruction 20 years later.

Methods

Participants and Measurements

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a multi-center cohort study. Participants were recruited from the general population, by telephone from populations in Birmingham, AL, Chicago, IL, and Minneapolis, MN, and randomly sampled from a prepaid health plan in Oakland, CA. The detailed methods, instruments and quality control procedures are described in previous reports [18,19]. In 1985-86 (Year 0), 5,115 individuals were recruited for the initial exam. They included approximately equal numbers of participants who were black and white, men and women, aged 18-24 and 25-30, and had more than or less than or equal to a high school education.

At Year 20, 3549 (69%) of the original cohort returned for the Year 20 exam. We included all participants who returned for this exam, had lung function measured, and were not pregnant (N=3253). Participants with a diagnosis of asthma at any visit were excluded

(N=660) as we were interested in those with undiagnosed airflow obstruction and it was shown that asthmatics with low lung function as young adults continue to have low lung function in middle age [20]. Asthma diagnosis was made if the participant had a physician diagnosis of asthma or was taking asthma medication [21]. Participants with a current or previous diagnosis of asthma were included, however, if they reported a diagnosis of COPD, emphysema or chronic bronchitis at Year 20 (N=28). We also excluded participants who were missing data on baseline BMI, smoking status, or second hand smoke exposure (N=31), had poor quality lung function tests at Year 20 (N=65), or were transgender (N=1). This left a sample size of 2,496.

Demographic characteristics, lifestyle habits (e.g., smoking history), second-hand smoke exposure, and medical history were collected by questionnaire.

Lung function at Years 0 to 10 was measured using a Collins Survey 8-liter water sealed spirometer and Eagle II Microprocessor (Warren E. Collins, Inc., Braintree, MA). At Year 20, lung function was measured using a dry rolling-seal OMI spirometer (Viasys Corp, Loma Linda, CA). Spirometer accuracy was validated using the Pulmonary Waveform Generator (MH Custom Design and Manufacturing, Midvale, UT), a computer driven simulator that is accurate to within 0.5%. The results obtained on the OMI spirometers exceeded American Thoracic Society (ATS) criteria for accuracy and precision [22], as did the four Collins spirometers that were used at the earlier visits and were still functional. A comparability study performed on 25 volunteers at the LDS Hospital (Salt Lake City, UT) demonstrated an average difference between the Collins and OMI spirometers of 6 ml for FVC and 21 ml for FEV_1. Standard quality control and testing procedures are detailed in the manual of operations [8,23,24].

Lung function was analyzed using the the largest FVC and FEV_1 from five satisfactory maneuvers. Airflow obstruction was diagnosed using the lower limit of normal for the FEV_1/FVC ratio [25]. We chose this definition rather than an $FEV_1/FVC < 0.7$ [26] to reflect airflow obstruction across different ages [11-13]. Bronchodilator testing was not performed.

Participants were categorized based on the presence or absence of airflow obstruction and the presence or absence of a self-diagnosis of chronic bronchitis, emphysema or COPD. Those who answered positively to one or more of these diagnoses were labeled as having COPD. Self-reported chronic bronchitis was validated by analyzing responses to questions about chronic cough and sputum production. Participants were further characterized based on sex, race, education level, body mass index (BMI), smoking history, second hand smoke exposure, and Year 0 and 20 pulmonary function.

Statistical Methods

Body mass index (BMI) was computed as weight (kg) divided by height squared (m^2). Age, race, education, and number of cigarettes smoked were self-reported. Second-hand tobacco smoke exposure was defined as any exposure in the home, a small space other than the home (e.g., office, car), or a large indoor area (e.g., restaurant). Smoking status was categorized as never, former and current smoker.

Associations of risk factors with airflow obstruction or self-reported COPD were assessed in univariate analysis using Chi-square tests for categorical variables and t-tests or ANOVA for continuous variables. Logistic regression was used to assess multivariable associations. Generalized estimating equations (GEE) were used to examine the association of airflow obstruction at Year 0 with age trends in FEV_1. In one model, designed to provide a visual assessment of goodness of fit to linear slope over age, age was categorized into 2-year age

groups and adjusted mean FEV_1 values were computed for each of seventeen two-year groups and plotted. In a second model in which ages less than 25 were truncated, age was treated as a continuous variable and interactions between Year 0 airflow obstruction and age were included to assess whether age trends differed for those with compared to those without baseline obstructive airways disease. The GEE model adjusted for race-sex group, center, exam year, time-dependent height, height squared, time-dependent BMI, and cumulative pack-years of cigarette exposure. Analyses were conducted using SAS for Windows, release 9.2 (Cary, NC).

To assess the accuracy of predicting airflow obstruction at Year 20 using Year 0 risk factors including lung function, we computed the c statistic, which is equivalent to the area under the receiver operating characteristic curve [27]. A nonparametric statistical test was performed [28] to determine whether the area under the curve from different models was significantly different. IRB approval was obtained at each study site.

Results

Participant Characteristics at Years 0 and 20

Participant characteristics are provided in table 1. The mean FEV_1, FVC and FEV_1/FVC were normal at Years 0 and 20, reflecting the generally healthy study population. Nonetheless, 6.9% of the participants had airflow obstruction at Year 0 and 7.8% at Year 20. The FEV_1, FVC and FEV_1/FVC in those with and those without airflow obstruction at Years 0 and 20 are presented in table 2. Only 5.2% and 7.2% of participants with airflow obstruction at Years 0 and 20 self-reported COPD. Participant characteristics at Year 0 that differentiated those with airflow obstruction from those without were male sex, less education, current smoking, and self-reporting COPD. At Year 20 the differentiating features were similar although not identical – less education, being a past or current smoker, secondhand smoke exposure, self-reporting COPD, and a lower BMI. In multivariable analysis, these characteristics remained significant except for second hand smoke exposure. Those who were excluded from the analysis were younger, more likely to be black, less likely to have more than a high school education, more likely to smoke, and had slightly lower FEV_1.

Self-Reported COPD

About 2% of participants self-reported COPD at Years 0 and 20 (table 1). At Year 20 they had a mean FEV_1/FVC of 0.73, yet only 28% met the criteria for airflow obstruction. The sensitivity and specificity of self-reported COPD in identifying airflow obstruction at Year 20 were 7.2% (14/195) and 98.4% (2265/2301), respectively (table 2).

Characteristics at Year 0 Associated with Airflow Obstruction at Year 20

Younger age, female sex, lower BMI, current smoking, less education, lower FEV_1, lower FEV_1/FVC, and higher FVC at Year 0 were positively associated with having airflow obstruction 20 years later (table 3). Of those with airflow obstruction at Year 0, 52.0% (90/173) had airflow obstruction at Year 20. In contrast, only 4.5% (105/2323) of participants without airflow obstruction at Year 0 had airflow obstruction 20 years later ($p<0.0001$).

Young Adult Lung Function Predicts Lung Function and Airflow Obstruction in Middle Age

The association between lung function at Year 0 and subsequent years was further explored by dividing participants into those with and without airflow obstruction at Year 0 and plotting the change in FEV_1 with increasing age. The starting age for analysis was 25 years to avoid the effect of lung growth between ages 18 and 24. Individuals without airflow

obstruction at Year 0 had a slightly, but significantly greater loss of FEV_1 than those with airflow obstruction (-18 ml/yr vs. -14 ml/yr; p=0.005). However, the two groups maintained their relative positions over time (fig. 1A). When participants with and without airflow obstruction at Year 0 were subdivided into never smokers and ever smokers, smoking had little effect on the decline in FEV_1 with age in those without airflow obstruction (-19 ml/yr vs. -20 ml/yr; p=0.18), but it had a significant effect in those with airflow obstruction (-12 ml/yr vs. -19 ml/yr; p=0.01) (fig. 1B).

How well Year 0 lung function predicted airflow obstruction 20 years later was examined by calculating the c-statistic. Participants at Year 0 with airflow obstruction were included because pulmonary function testing is not ordinarily conducted in asymptomatic, young adults and they would have been undiagnosed at that time. The c-statistics (95% CI) for FEV_1, FVC, and FEV_1/FVC were 0.70 (0.66-0.74), 0.57 (0.52-0.61), and 0.87 (0.84-0.90), respectively. All were significant with the FEV_1/FVC at Year 0 best predicting airflow obstruction at Year 20. When age, sex, BMI, smoking history, and education were added to the model, the c-statistic for FEV_1/FVC increased to 0.91 (0.89-0.93). Figure 2 shows the receiver operating curve for FEV_1/FVC.

Discussion

This report provides new insight into the characteristics of generally healthy young adults that predict low lung function and airflow obstruction in middle age. Lower values for FEV_1 and FEV_1/FVC and the presence of airflow obstruction in young adults strongly predicted low lung function and airflow obstruction two decades later, and the effect of smoking on age-related lung function decline was greatest in young adults with airflow obstruction. In addition, 7-8% of these young and middle age adults had airflow obstruction, which was cross-sectionally associated with smoking, less education, and self-reported COPD. Yet, COPD was self-reported in less than 10% of those with airflow obstruction.

Previous studies have reported that airflow obstruction is largely undiagnosed in adults. Estimates of the prevalence of undiagnosed airflow obstruction (including COPD and asthma) range from 3-12% [3,29]. Results from 3 National Health and Nutrition Examination Surveys (NHANES I and II, HHANES) identified COPD in 3-5% of never smokers 40-49 years of age [30]. However, COPD was defined as physician diagnosed chronic bronchitis or emphysema and not confirmed by pulmonary function tests. In a study from Spain, COPD was diagnosed by spirometry in 9% of individuals ages 40-69 years, 78% of whom had not been previously diagnosed [31]. In an international survey of young adults (ages 20-44), 3.6% had airflow obstruction [4]. In high risk groups COPD prevalence is higher. In one study 19% of current and former smokers seen in general practices in the United States and Scotland had COPD; nearly half of them had moderate or severe disease [32]. In another study 30% of current smokers in Belgium who were 40-70 years of age had undiagnosed COPD [33]. The cross-sectional data from the CARDIA study are consistent with these earlier studies.

Results from this longitudinal study of young adults support the hypothesis that the earliest step in airflow obstruction may involve suboptimal lung growth during childhood and adolescence [34], as those with low lung function and airflow obstruction as young adults were most likely to have low lung function and airflow obstruction 20 years later. The results also extend the data obtained in infants and children by Martinez and colleagues, which indicate that lung function in infancy and early childhood is an important determinant of young adult lung function [14]. Their study included participants up to 22 years old. The CARDIA study began with individuals 18-30 years of age at entry (mean age 25), who were then followed for 20 years. That the CARDIA data are consistent with what was observed in

children [14-16] strengthens the concept of early life and genetic determinants of lung function and airflow obstruction in the general population. Our results also suggest that lung function values obtained in early adulthood, combined with smoking history, can be used to identify those at greatest risk for developing airflow obstruction and having more severe disease. However, this requires population-based spirometry screening of asymptomatic individuals, something that is not generally accepted [35].

This study also confirms the limited predictive value of self-reported COPD for the presence of airflow obstruction [35]. Only 28% of participants self-reporting COPD had airflow obstruction. This is not surprising as chronic bronchitis, the major contributor to self-reported COPD in this study, may not be associated with airflow obstruction. This was the case even though 62% of those with chronic bronchitis said they had asthma. Had we removed chronic bronchitis from the definition of COPD, fewer than 10% of those who self-reported COPD would have remained in this category and the results regarding undiagnosed COPD would be more striking.

There is increasing interest in the role of gender in the development and progression of COPD [36]. Previous studies have reported that physicians are more likely to diagnose COPD in men than in women [37], while women are more likely to report symptoms consistent with COPD and have a poorer self-evaluation of health [38]. Although more females than males self-reported COPD, we found the prevalence of airflow obstruction in middle age to be the same in both groups. Contrary to that reported by Coultas et al [29], undiagnosed airflow obstruction was not more common in males than in females. Why our data differ is unclear, but it may reflect the unbiased population sampling in CARDIA, the relatively young age of the study population, or true population differences.

Our study differs from most previous studies that explored the prevalence of and factors associated with airflow obstruction in young adults in the high response rate to the initial recruitment strategy (approximately 50%), the large sample size and excellent retention, the generally good health of the subjects at study entry, and the availability of lung function data over 20 years. Limitations are inclusion of only those participants who had acceptable lung function tests at both Years 0 and 20, exclusion of participants with asthma (except those with co-existing chronic bronchitis, emphysema or COPD), the epidemiologic diagnosis of asthma, the possibility that some of those with airflow obstruction may have had undiagnosed asthma, and use of pre-bronchodilator lung function.

In conclusion, low lung function and airflow obstruction in young adults, in addition to smoking, predicts low lung function and airflow obstruction 20 years later. Airflow obstruction not due to recognized asthma in young and middle age adults in the United States is relatively common and mostly unrecognized. Because of the increasing societal burden of airflow obstruction, whether due to asthma or COPD, these results support using strategies to detect low lung function and airflow obstruction in asymptomatic young adults. An early, accurate diagnosis of airflow obstruction enables implementation of new smoking cessation strategies and other treatment modalities sooner, which may slow disease development and progression, thereby reducing the morbidity, mortality and costs associated with airflow obstruction.

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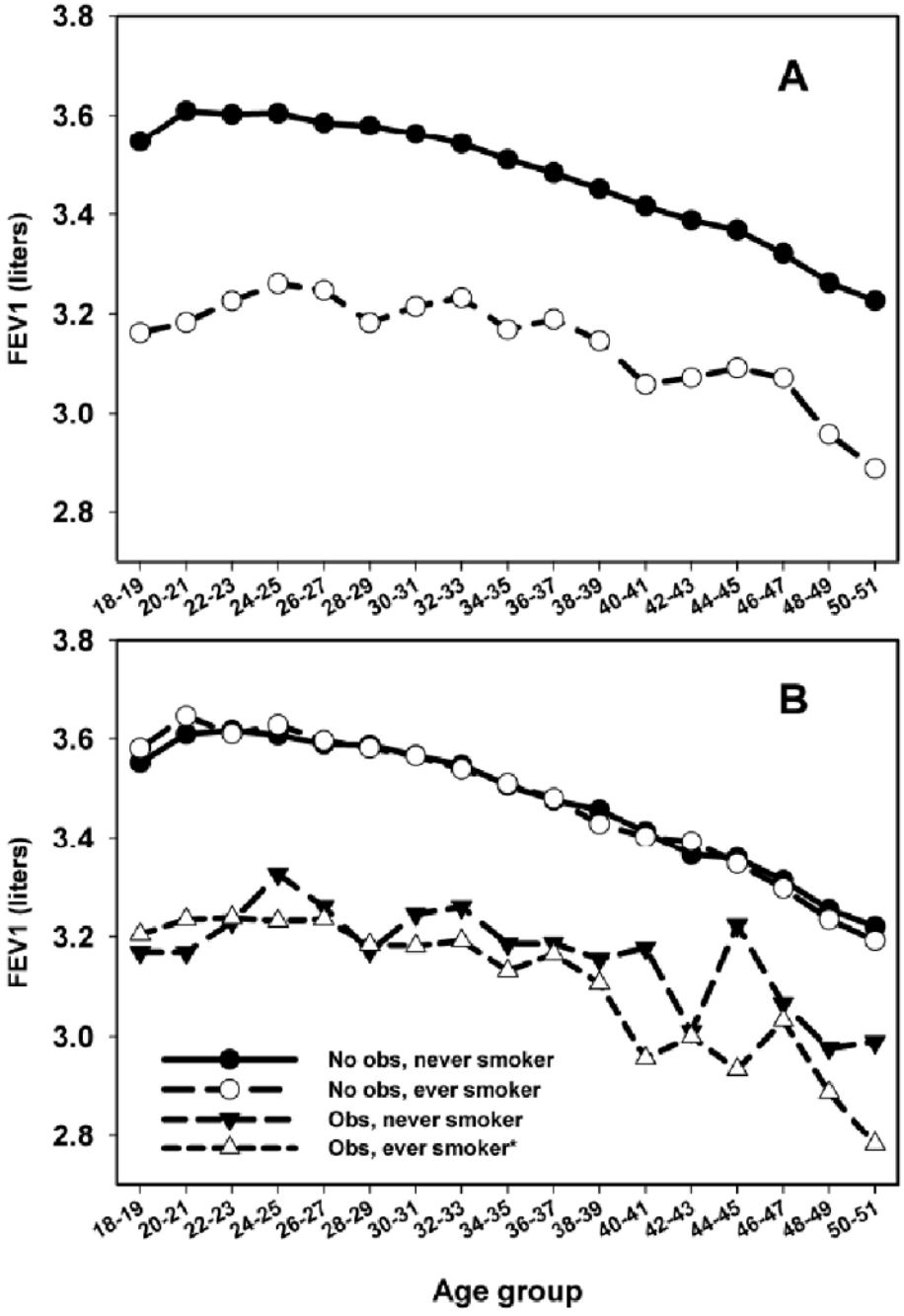

Figure 1.

A. FEV_1 change with age in participants with (open circles) and without (solid circles) airflow obstruction at study entry (Year 0). The decline in FEV_1 was 18 ml/yr in the participants without airflow obstruction and 14 ml/yr in those with airflow obstruction at study entry (P=0.005). B. FEV_1 change with age in participants with and without airflow obstruction at study entry and subdivided by never or ever smoking. Rates of change in FEV_1 were computed with ages 24 and lower truncated from the GEE model. *p=0.01 compared to the participants with airflow obstruction who were never smokers.

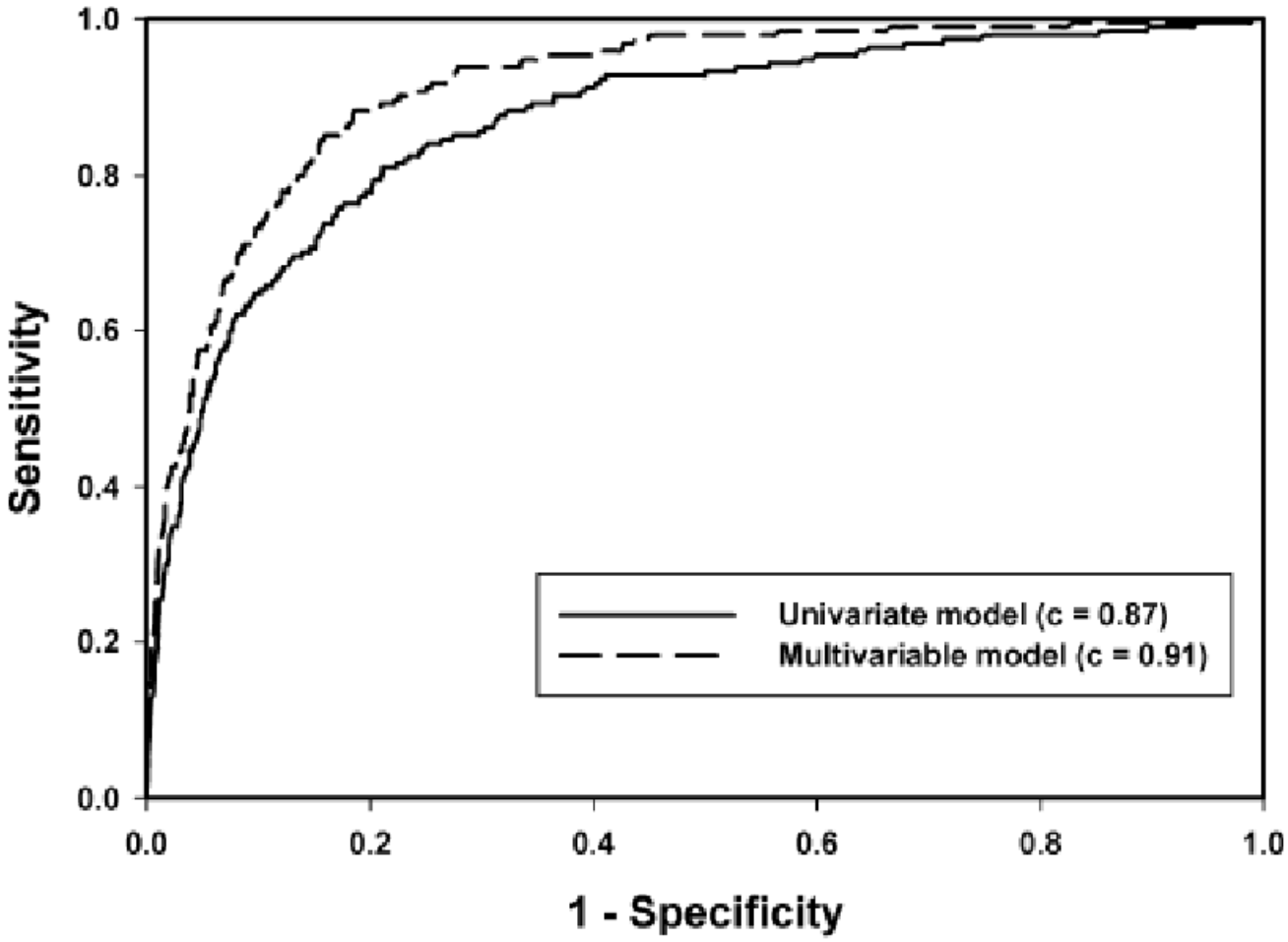

Figure 2.

The FEV_1/FVC at Year 0 is highly predictive of airflow obstruction at Year 20 as indicated by the receiver operating curve (ROC). The c-statistics for univariate and multivariable models are provided. A higher value indicates better predictive ability.

Table 1
Participant Characteristics at Years 0 and 20

	Year 0	Year 20
Number	2,496	
Age – years	25.1 (3.6)	45.3 (3.6)
Male (%)	45.4	
White (vs. black) (%)	56.9	
Education > high school (%)	67.2	77.4
BMI – kg/m^2	24.4 (4.7)	29.1 (6.6)
Smoking – current / previous / never (%)	25.0/14.4/60.6	18.0/19.5/62.4
Exposure to second hand smoke (%)	95.5	47.8
FEV_1 % predicted	98.9 (11.2)	95.2 (13.8)
FVC % predicted	100.7 (11.3)	96.6 (13.4)
FEV_1/FVC	0.84 (0.06)	0.79 (0.06)
FEV_1/FVC < LLN (%)	6.9	7.8
Self reported doctor or nurse diagnosis of COPD (%)	54 (2.2%)	50 (2.0%)*
- Chronic bronchitis	48	45
- Emphysema	6	6
- COPD	N.A.	3

The results are mean (SD) unless otherwise noted.

*The total number of COPD diagnoses (chronic bronchitis, emphysema, COPD) adds up to more than 50 since some participants reported more than one diagnosis.

N.A. – Not applicable as COPD was not a choice in the Year 0 questionnaires.

Table 2
Airflow Obstruction at Years 0 and 20

Airflow Obstruction	Present	Absent	Present	Absent
	Year 0		Year 20	
Number (%)	173 (6.9%)	2323 (93.1%)	195 (7.8%)	2301 (92.2%)
Age – years	25.5 (0.3)	25.0 (0.1)	45.0 (0.3)	45.3 (0.1)
Male – number (%)	95 (54.9%)	1039 (44.7%)†	89 (45.6%)	1045 (45.4%)
White – number (%)	103 (59.5%)	1316 (56.7%)	121 (62.1%)	1298 (56.4%)
Education > high school - number (%)	102 (59.0%)	1575 (67.8%)*	140 (71.8%)	1793 (77.9%)*
BMI[1]- kg/m^2	24.3 (0.3)	24.4 (0.1)	26.9 (0.4)	29.3 (0.1)§
Smoking – current / previous / never (%)[2]	39.9/ 13.3 / 46.8	23.9 / 14.5 / 61.6§	34.6 / 23.0 / 42.4	16.7 / 19.2 / 64.1§
Exposure to second hand smoke (%)[3]	166 (96.0%)	2118 (95.5%)	107 (54.9%)	1082 (47.2%)*
FEV_1 % predicted	88.7 (0.9)	99.6 (0.2)§	82.5 (1.1)	96.3 (0.3)§
FVC % predicted	106.1 (1.0)	100.3 (0.2)§	100.0 (1.1)	96.3 (0.3)†
FEV_1/FVC	0.71 (0.00)	0.85 (0.00)§	0.66 (0.00)	0.80 (0.01)§
COPD self-reported – number (%)	9 (5.2%)	45 (1.9%)*	14 (7.2%)	36 (1.6%)§

The results are mean (SE) unless otherwise noted. There are 2,496 participants.

Airflow obstruction is defined as FEV_1/FVC < age, race, sex specific lower limit of normal [24]; specifics in text.

Comparisons made between airflow obstruction present and absent groups using chi-square tests for categorical variables and t-tests for continuous variables.

* $p < 0.05$

† $p < 0.01$

‡ $p < 0.001$

§ $p < 0.0001$

Table 3

Adjusted Odds Ratios (95% CI) of Having Airflow Obstruction at Year 20 Based on Participant Characteristics Measured at Year 0

	Year 0
Age	0.90 (0.85-0.94)‡
Gender – male (vs. female)	0.39 (0.27-0.58)‡
Race – white (vs. Black)	0.99 (0.67-1.47)
BMI	0.84 (0.79-0.89)‡
Exposure to second hand smoke (vs. no exposure)	0.92 (0.38-2.23)
Past smoker (vs. never smoker)	1.12 (0.65-1.93)
Current smoker (vs. never smoker)	1.89 (1.27-2.81)*
Education > high school (vs. ≤ high school)	0.59 (0.40-0.86)*
FEV_1 % predicted (Y0)	0.93 (0.92-0.95)‡ *a*
FVC % predicted (Y0)	1.03 (1.01-1.04)† *a*
FEV_1/FVC (Y0)	0.74 (0.71-0.77)‡

Number of participants studied = 2496

All results from logistic regression analysis

ORs are adjusted for age, gender, race, BMI, exposure to second hand smoke, smoking status, education and FEV_1/FVC

a Adjusted for all variables listed above except FEV_1/FVC

* $p < 0.01$

† $p < 0.001$

‡ $p < 0.0001$