Smoking Cessation and Lung Function in Mild-to-Moderate Chronic Obstructive Pulmonary Disease

The Lung Health Study

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Previous studies of lung function in relation to smoking cessation have not adequately quantified the long-term benefit of smoking cessation, nor established the predictive value of characteristics such as airway hyperresponsiveness. In a prospective randomized clinical trial at 10 North American medical centers, we studied 3,926 smokers with mild-to-moderate airway obstruction (3,818 with analyzable results; mean age at entry, 48.5 yr; 36% women) randomized to one of two smoking cessation groups or to a nonintervention group. We measured lung function annually for 5 yr. Participants who stopped smoking experienced an improvement in FEV_1 in the year after quitting (an average of 47 ml or 2%). The subsequent rate of decline in FEV_1 among sustained quitters was half the rate among continuing smokers, 31 $\pm$ 48 versus 62 $\pm$ 55 ml (mean $\pm$ SD), comparable to that of never-smokers. Predictors of change in lung function included responsiveness to β-agonist, baseline FEV_1, methacholine reactivity, age, sex, race, and baseline smoking rate. Respiratory symptoms were not predictive of changes in lung function. Smokers with airflow obstruction benefit from quitting despite previous heavy smoking, advanced age, poor baseline lung function, or airway hyperresponsiveness. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, Tashkin DP, for the Lung Health Study Research Group. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: The Lung Health Study. AM J RESPIR CRIT CARE MED 2000;161:381–390.

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In 1996, 106,146 Americans died from chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in the United States (1). Ten to 15% of all smokers (2) and up to 26% of heavy smokers (3) develop COPD. As the prevalence of smoking has risen among women and decreased slightly among men, the sexual distribution of COPD deaths has shifted from 19% female in 1970 to 38.5% in 1993 (4).

Factors that contribute to the development of COPD include tobacco smoking, particularly heavy smoking, long duration of smoking, and smoking of high-tar cigarettes. Other factors associated with the development of COPD include poor initial lung function, advanced age, male sex, childhood respiratory illness, occupational respiratory exposures, air pollution, low educational attainment or socioeconomic status, blood type A or AB, α_1 protease deficiency, and other familial factors (5). With the exception of α_1 protease deficiency, these factors contribute to, but do not by themselves cause, COPD. In general, we cannot explain why some smokers are more likely than others to develop impaired lung function, but it seems likely that differences in susceptibility are related to as-yet-unknown genetic factors.

The Dutch hypothesis (6) states that the risks of COPD and asthma are related to environmental exposures in combination with the genetic makeup of the individual. Bronchial hyperresponsiveness is one endogenous factor that may contribute to the development of COPD (7). Genetic factors that contribute to this risk are still poorly understood. We have no way of modifying endogenous predisposition to asthma or COPD. In contrast, the principal environmental factor in COPD is well known—exposure to cigarette smoke—and it can be modified. Hence, the most direct approach to reduce the risk of COPD is to reduce cigarette smoking.

A low FEV_1 predicts not only an increased rate of decline in FEV_1 (3, 8), but also morbidity and mortality from smoking-related illnesses (COPD, lung cancer, and cardiovascular disease) (9–11). Since lung function declines with time, the best time to prevent morbidity and mortality from smoking-related illness should be early in the life. Unfortunately, most smoking cessation intervention programs have had high relapse rates (12).

In the Lung Health Study (LHS), smokers with mild-to-moderate COPD were recruited to determine the effectiveness of an intensive smoking cessation program plus maintenance bronchodilator therapy in reducing the rate of decline in lung function as well as morbidity and mortality. The intent-to-treat analysis showed that participants randomized to the smoking intervention program with or without maintenance bronchodilator treatment had an improvement in pulmonary function during the first year of the study, compared with control subjects, but in subsequent years the decline in lung function was parallel in all groups. Those who quit smoking had a greater benefit compared with those who continued smoking (13). This article reports further analysis of the effects of *successful* smoking cessation on the lung function of participants in the LHS.

METHODS

Study Design and Recruitment

Recruitment was carried out from November 1986 to January 1989. We sought current smokers, 35 to 60 yr of age, with mild-to-moderate airflow obstruction who were otherwise healthy and who expressed a willingness to participate in a 5-yr research program (14, 15). A total of 5,887 participants was recruited at 10 centers in North America (16).

Participants were randomized, on a 2:1 basis, to engage in an intensive, long-term smoking cessation program (special intervention, or SI) or to receive usual care (UC). Participants in the SI group were further randomized on a 1:1 basis to use either inhaled ipratropium bromide (Atrovent [Boehringer Ingelheim, Ridgefield, CT], 18 μg/puff; SI-A group) or an identical-appearing placebo administered by metered-dose inhaler (2 puffs three times daily; SI-P group) for the duration of the study. Participants in both groups completed annual health questionnaires and lung function measurements. The UC group did not participate in the intervention program. Each participant was monitored for 5 yr (14, 15). The smoking cessation program was designed to achieve a maximal sustained smoking cessation rate. Details and results of the program have been reported previously (17).

Pulmonary Function Measurement

Spirometry was performed with a dry rolling-seal spirometer. A standardized spirometry protocol, which exceeded the American Thoracic Society (ATS) testing standards, and a strict quality control program were used to obtain acceptable and reproducible data (18). The quality control program and results of baseline pulmonary function studies have been reported (19).

Screening spirometry was performed to identify smokers with an FEV_1/FVC ratio ≤ 0.75 and an FEV_1 percent predicted (FEV_1% pred) between 50 and 90% of the value predicted for their age, height, sex, and race (20). A second screening (Screen 2) visit confirmed eligibility if prebronchodilator FEV_1%pred was between 55 and 90% and $FEV_1/FVC \leq 0.70$. Randomization was performed at the third screening visit. A modified ATS-DLD-78 Respiratory Symptoms Questionnaire (21) was administered, and measurement of methacholine reactivity was performed at the third screening visit (22). Methacholine reactivity was calculated from the dose–response curve, using the logarithm of the percent decline in FEV_1 between the postdiluent control value and the value after the highest concentration of methacholine administered (*see* Table 1 footnote) (23).

Follow-up Visits

Clinic visits were scheduled every 4 mo for SI participants. At these visits, smoking status was monitored by questionnaire and measurement of exhaled carbon monoxide (CO) with either a MiniCO model 1000 (Catalyst Research, Owings Mills, MD) or Vitalograph EC50 (Vitalograph, Buckingham, UK) (17). Inhaler canisters were exchanged and weighed (24), and inhaler technique checked. Additional smoking cessation intervention and counseling were provided as needed to prevent relapse (17).

Annual clinic visits for all SI and UC participants included administration of respiratory questionnaires, spirometry, and a request for permission to obtain records of reported hospitalizations. Smoking status was determined by self-report ($<$ 1 cigarette per week was considered a nonsmoker), and validated with salivary cotinine assay and exhaled CO measurement (25, 26).

Statistical Methods

We defined "sustained quitters" (Q) as those participants who were validated by salivary cotinine or exhaled CO as abstinent at every annual visit. "Continuing smokers" (S) were individuals who reported smoking at each annual visit. We assume in this analysis that participants who did not attend annual visits had continued smoking or relapsed. Those who were not sustained quitters or continuing smokers were called "intermittent quitters" (I). For the present analysis, all comparisons are between sustained quitters and continuing smokers from the SI-P and the UC groups. Members of the SI-A group (randomized to ipratropium) were not included in this analysis to avoid the confounding effect of bronchodilator therapy on the rate of decline in FEV_1.

Statistical analyses were based on counts (for categorical data) or means and standard deviations (for quantitative variables such as age, cotinine levels, or FEV_1%pred). Univariate comparisons between the various smoking categories were assessed by χ^2 statistics (for categorical variables) or unpaired *t* tests (for quantitative variables). Comparisons of outcome variables, when controlling for other factors, were done by analysis of covariance. For univariate analyses, no adjustment was made for multiple comparisons; nominal p values are displayed. For analyses of the relationships between change in FEV_1%pred and possible predictors, the SI-P and UC groups were pooled. Rates of decline in lung function within groups were calculated as the mean of individual slopes.

Multivariate linear regression analysis of the changes in postbronchodilator FEV_1%pred was performed using PROC GLM in the SAS

TABLE 1

BASELINE CHARACTERISTICS BY FINAL SMOKING STATUS: SI-P AND UC PARTICIPANTS

Baseline Characteristics	Q (Sustained Quitters)* (*n* = 559)	I (Intermittent Quitters)* (*n* = 991)	S (Continuing Smokers)* (*n* = 2,268)	Significantly Different Pairs ($p < 0.05$)
Age, yr	49.1 (6.8)	48.6 (6.9)	48.3 (6.8)	Q,S
Sex, % female	32.9	38.1	36.1	NS
Married, %	74.1	72.6	69.6	NS
Years of education	13.8 (2.9)	13.9 (2.9)	13.5 (2.8)	Q, S; I, S
Nonwhite, %	3.3	4.2	4.6	NS
Cigarettes per day	30.1 (12.6)	29.8 (12.3)	32.0 (12.8)	Q, S; I, S
Salivary cotinine, ng/ml	332.4 (199.8)	334.8 (187.0)	389.0 (207.5)	Q, S; I, S
Age started smoking, yr	17.6 (3.6)	17.8 (3.9)	17.3 (3.8)	I, S
Pack-years	40.1 (18.8)	39.4 (18.2)	40.8 (19.0)	NS
Smoke pipes, cigars, %	5.4	4.3	7.5	I, S
Use alcohol, %	70.8	71.1	70.2	NS
Drinks per week among alcohol users	6.4 (5.7)	6.0 (5.3)	6.2 (5.7)	NS
Body mass index, kg/m^2	26.0 (3.9)	25.9 (3.9)	25.4 (3.9)	Q, S; I, S
FEV_1 (post-BD), L	2.82 (0.64)	2.74 (0.64)	2.75 (0.61)	NS
FEV_1%pred (post-BD)	79.4 (9.1)	78.4 (9.2)	78.1 (8.9)	Q, S
FEV_1/FVC (post-BD), %	63.1 (5.6)	62.9 (5.5)	63.0 (5.4)	NS
Bronchodilator response, %	4.5 (4.9)	4.6 (4.8)	4.1 (5.1)	I, S
Log methacholine reactivity (LMCR), %/mg/ml†	0.442 (0.388)	0.478 (0.406)	0.444 (0.373)	Q, I
Men	0.344 (0.349)	0.376 (0.382)	0.353 (0.350)	
Women	0.613 (0.382)	0.615 (0.370)	0.595 (0.379)	
Respiratory symptoms‡				
Chronic cough, %§	39.7	40.6	44.3	NS
Chronic phlegm, %‖	32.2	35.8	37.7	Q, S
Chronic bronchitis, %#	26.1	26.5	30.3	NS
Wheezing grade 1 or higher, %**	74.4	76.8	76.9	NS
Dyspnea grade 1 or higher, %††	39.0	41.3	44.1	NS

Definition of abbreviations: BD = bronchodilator; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; I = intermittent quitters; Q = sustained quitters; S = continuing smokers; SI-P = smoking intervention and placebo; UC = usual care. Respiratory symptoms are defined by ATS-DLD-78 respiratory questionnaire (21).

* *See* METHODS for a description of smoking status categories.

† Methacholine reactivity (LMCR) is defined as $\log_{10}(0.681 - P/C)$, where P is the percent change in FEV_1 from diluent to maximal concentration, and C is the maximal concentration of methacholine administered.

‡ From the ATS-DLD-78 questionnaire (21), question numbers; chronic cough (questions 7A, 7E, and 7F); chronic phlegm (questions 8A, 8E, and 8F); chronic bronchitis (both chronic cough and chronic phlegm); wheezing (any wheezing).

§ Questions 7A, 7E, and 7F.

‖ Questions 8A, 8E, and 8F.

Both chronic cough and chronic phlegm.

** Questions 10A to 10A-3.

†† Questions 13A to 13E.

package (SAS, Cary, NC) (27). Separate analyses were performed for changes from baseline to Year 1 and from Year 1 to Year 5. Variables were entered stepwise, and were included in the final model if they contributed significantly to the predictive power of the model. In addition to smoking status, we considered baseline characteristics, including treatment group (SI-P or UC), age, sex, FEV_1%pred, bronchodilator responsiveness, methacholine reactivity, smoking rate (cigarettes per day), race, and respiratory symptoms. We analyzed these individually, and looked for nonlinear effects and interaction with smoking status. The results are summarized in terms of changes in FEV_1% pred associated with specified increments in the predictors or the interaction terms in the models.

RESULTS

Baseline Characteristics

The SI-P and UC groups were similar at the time of entry into the study (16). Table 1 shows baseline characteristics of 3,818 SI-P and UC participants with analyzable results, classified by smoking status at the end of the study. Compared with continuing smokers, sustained quitters were older at baseline, smoked fewer cigarettes per day, had greater educational attainment, lower salivary cotinine, higher body mass index, higher FEV_1%pred, and lower prevalence of chronic sputum production.

Follow-up Rates

At Year 1, questionnaires were completed for more than 94% of participants and spirometry was completed for more than 89% of participants. At Year 5, both questionnaires and spirometry were completed for more than 94% of participants (13).

Smoking Cessation Rates

Using biochemically validated smoking cessation rates, 34.4% of SI-P participants were abstinent (quitters) at Year 1, 37.4% were abstinent at Year 5 (cross-sectional quit rate), and 22.3% remained abstinent without relapse from Year 1 through Year 5 (sustained quitters). Among UC participants, 9.0% were abstinent at Year 1, increasing to 21.4% at Year 5; 5.3% were sustained quitters at Year 5 (13).

Effects of Smoking Cessation on Changes in Lung Function

Study participants in the SI-P and UC groups who stopped smoking in Year 1 had an average increase in FEV_1 of 47 ml

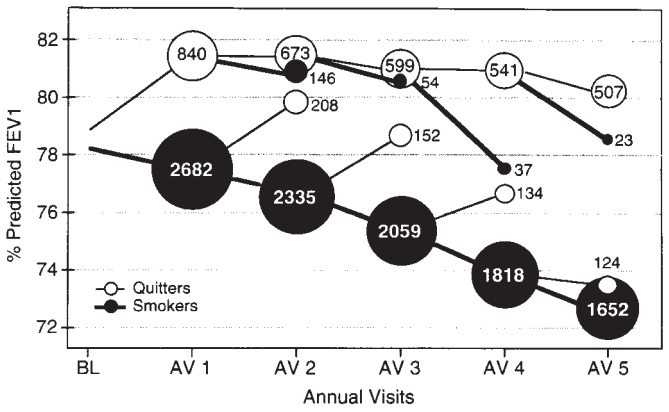


Figure 1. Lung function improved during Year 1 among quitters, but declined among continuing smokers. The subsequent rate of decline is twice as great among continuing smokers as among sustained quitters. Those who relapsed lost function and those who delayed quitting benefited regardless of when they quit.

TABLE 2

MEAN ANNUAL CHANGE IN FEV_1 FROM YEAR 1 TO YEAR 5, BY YEAR 5 SMOKING STATUS*

	Sustained Quitters	Intermittent Quitters	Continuing Smokers	All Smoking Groups
SI-P	−32 (46)	−47 (57)	−62 (55)	−50 (55)
UC	−30 (54)	−39 (57)	−62 (55)	−55 (57)
Total	−31 (48)	−43 (57)	−62 (55)	−52 (56)

Definition of abbreviations: FEV_1 = forced expiratory volume in 1 s; SI-P = special intervention and placebo; UC = usual care.

* Data presented are means (SD); change in FEV_1 is presented as milliliters per year. The rate of decline in lung function is normal in sustained quitters, but twice as great in continuing smokers. Intermittent quitters have a rate intermediate between those of continuing smokers and sustained quitters.

or 1.98%pred at the Year 1 visit (Figure 1; *see also* Figure 5 in Reference 13). Between Year 1 and Year 5, the sustained quitters had a rate of decline in FEV_1 of 31 ± 48 ml/yr or 0.27% pred/yr.

In contrast, continuing smokers showed a more rapid rate of decline in FEV_1, both during the first year and between Year 1 and Year 5. At the Year 1 visit, FEV_1 had decreased by 49 ml or 0.74% pred. Between Year 1 and Year 5, FEV_1 decreased by 62 ± 55 ml/yr, twice the rate observed in sustained quitters ($p < 0.001$, Table 2).

Participants who quit during the first year and then relapsed after Year 1 showed a 1.59 ± 5.04% decline in FEV_1% pred after relapsing ($p < 0.001$). Those participants who quit smoking after the first year showed a 1.61 ± 5.62% improvement in FEV_1%pred after quitting ($p < 0.001$), which was also comparable to the benefit observed in SI-P quitters at Year 1 (Figure 1).

Effects of Baseline Lung Function

Continuing smokers with the lowest baseline FEV_1 had larger declines in the first year (−0.9 ± 5.7%pred or −49 ± 195 ml for the lowest quintile) compared with those with the highest baseline lung function (−0.03 ± 4.91%pred or −29 ± 172 ml for the highest quintile, $p = 0.024$). However, among quitters, baseline lung function was not predictive of the degree of improvement at Year 1 ($p > 0.10$, results not shown).

Between Year 1 and Year 5, continuing smokers with the lowest baseline FEV_1%pred had the most rapid annual declines in FEV_1%pred: −1.6 ± 2.1% pred/yr for the lowest quintile versus −1.0 ± 1.6%pred/yr for those in the highest quintile ($p < 0.001$; Figure 2). This trend did not hold for FEV_1 itself: the annual rates of decline were −63 ± 56 ml/yr for the continuing smokers in the lowest quintile of baseline FEV_1, and −61 ± 63 ml/yr for those in the highest quintile (NS). For sustained and intermittent quitters, baseline FEV_1 was not predictive of Year 1 to Year 5 changes in FEV_1 (ml/yr), and baseline FEV_1%pred was not as strongly related to changes in FEV_1%pred in quitters as in continuing smokers ($p = 0.184$ for a test for interaction of FEV_1%pred with smoking status).

Effect of Methacholine Reactivity

The role of methacholine reactivity in predicting changes in lung function has been reported in detail elsewhere (23). Methacholine reactivity was a strong determinant of the initial benefit of smoking cessation: quitters with the greatest degree of methacholine reactivity had the largest improvement in FEV_1%pred at Year 1. Lung function declined throughout the study in continuing smokers and after Year 1 in sustained quitters. In both groups, the rate of decline was strongly related to degree of methacholine reactivity (greatest among the most responsive).

Effect of Bronchodilator Responsiveness

Among LHS participants, the mean increase in FEV_1 after isoproterenol at baseline was 4.3 ± 5.1%, or 111 ± 130 ml. Despite this modest degree of bronchodilator responsiveness, there was a strong relationship between the degree of bronchodilator responsiveness and change in FEV_1%pred from baseline to Year 1 both for continuing smokers and for sustained quitters ($p < 0.001$; Figure 3). Bronchodilator responsiveness was not predictive of change in FEV_1%pred from Year 1 to Year 5 except in the intermittent quitter group (results not shown).

Effect of Age

Among quitters, the Year 1 improvement in FEV_1%pred and FEV_1 were greater in the youngest quintile compared with the oldest quintile (+2.53 ± 5.07 versus +1.32 ± 5.77%pred; or +70.4 ± 189 versus +18 ± 190 ml, $p < 0.02$ for either comparison; Figure 4A). Among continuing smokers, the decline in lung function during the first year was not related to age.

From Year 1 to Year 5, older subjects who were either smokers or intermittent smokers had a slightly more rapid annual decline in lung function than did younger subjects in either group ($p = 0.002$ for smokers; $p = 0.032$ for intermittent smokers). This was not true among quitters ($p = 0.670$; Figure 4B).

Effect of Sex

The role of sex in predicting changes in lung function will be reported separately (Owens, G. R., A. S. Buist, J. E. Connett, R. A. Wise, W. C. Bailey, and P. A. Lindgren, for the Lung Health Study Research Group. 1999. Changes in smoking status affect women more than men: results of the Lung Health Study. In preparation.) Women who became sustained quitters had an average improvement in Year 1 in FEV_1%pred that was 2.5 times as great as the improvement in men. In contrast, women who continued to smoke had a proportionately greater annual decline in lung function than men with comparable smoking rates (−1.08% pred for women versus −0.77% pred for men). These effects were closely related to the greater degree of methacholine reactivity observed in women and may be related to airway geometry and baseline lung function.

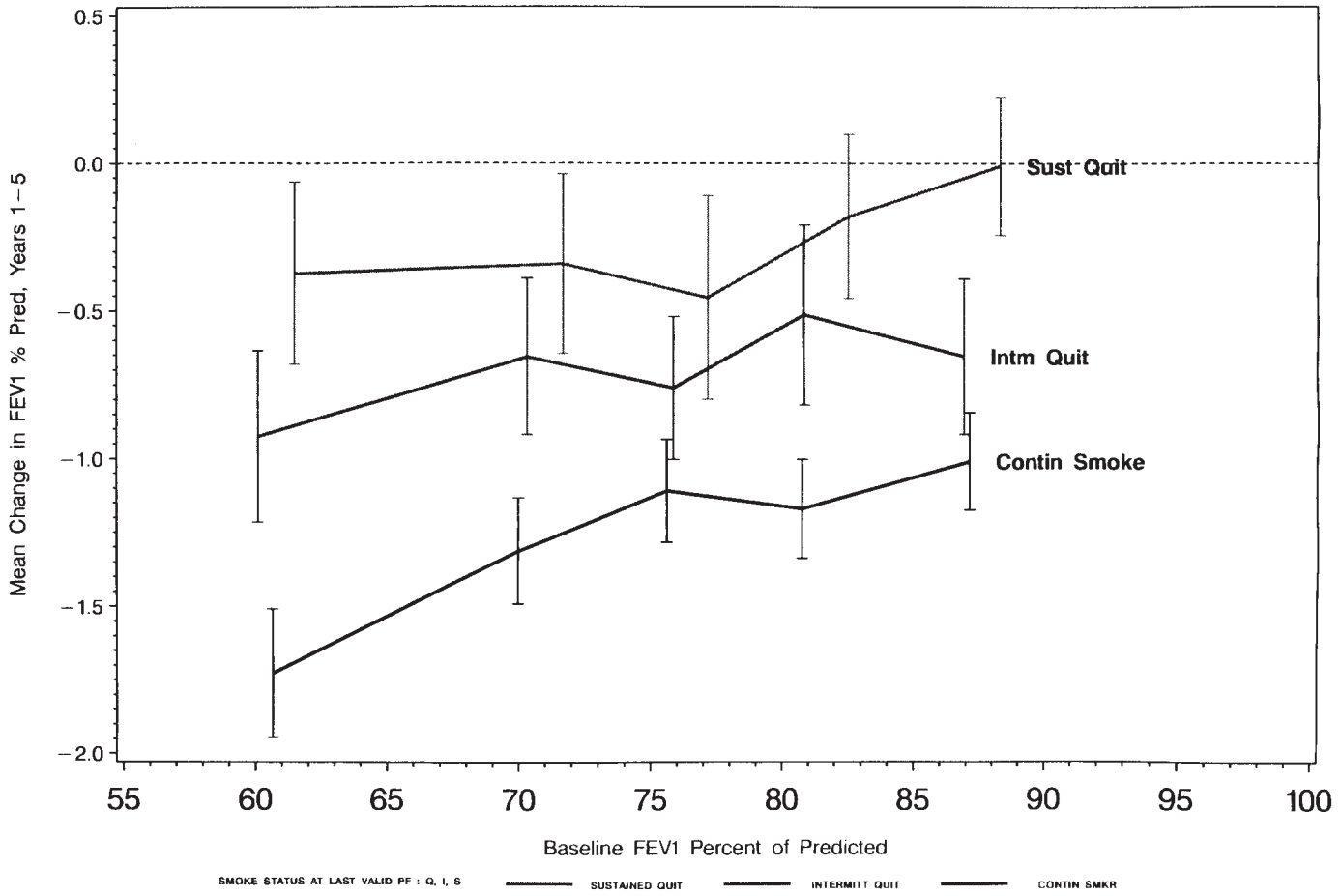


Figure 2. Continuing smokers with the lowest baseline lung function had more rapid declines in FEV_1% pred than those with the best lung function at baseline ($p < 0.001$).

Effect of Race

In the multivariate analysis, nonwhite subjects (4.2% of the total cohort) had a greater decline in FEV_1%pred during Year 1 than did white subjects ($p = 0.024$; Table 3A). There was no difference in the rate of change in FEV_1%pred between Year 1 and Year 5 ($p = 0.64$).

Effect of Baseline Smoking Rate

Among sustained quitters, in both SI-P and UC groups, lung function improved more in the first year for formerly heavy smokers ($+3.33 \pm 6.22$% pred or $+96 \pm 227$ ml for the heaviest smoking quintile) than for light smokers ($+0.51 \pm 4.54$% pred or -16 ± 148 ml for the lightest smoking quintile, $p = 0.001$; Figure 5). Among continuing smokers the heaviest smokers had a greater decline than light smokers (-1.23 ± 5.15% pred or -67 ± 191 ml versus -0.54 ± 5.49% pred or -39 ± 178 ml, $p = 0.028$; Figure 5). Smoking mentholated cigarettes did not affect the rate of decline in lung function in Year 1 or between Year 1 and Year 5 ($p = 0.229$ and 0.64, respectively, data not shown).

From Year 1 to Year 5, the predictive value of baseline smoking rate persisted only among continuing smokers: heavier smokers at baseline had a more rapid rate of decline in lung function than did lighter smokers ($p = 0.016$). This was not true among sustained quitters and intermittent quitters (data not shown).

Lack of Predictive Value of Baseline Respiratory Symptoms

Respiratory symptoms at baseline (cough, phlegm, wheezing of any degree, dyspnea; Table 1) were not predictive of changes in lung function, either alone or in combination with smoking cessation, when adjusted for age, sex, baseline lung function, methacholine reactivity, and baseline smoking rate.

Multivariate Analysis

The results of the multivariate analysis of the changes in FEV_1%pred from baseline to Year 1 are shown in Table 3A. The strongest predictor of lung function at Year 1 is change in smoking status. Other significant predictors include baseline FEV_1%pred, bronchodilator responsiveness, race, methacholine reactivity, randomization group, and age. There are nonlinear effects of baseline FEV_1%pred and bronchodilator response; these are represented in the model by quadratic terms for these two variables. There are also interaction effects of both sex and methacholine reactivity with change in smoking status.

The results of the multivariate analysis from Year 1 to Year 5 are shown in Table 3B. The greatest predictor of Year 1 to Year 5 change is final smoking status, followed by methacholine reactivity, age, baseline FEV_1%pred, and baseline smoking rate (Table 3B). Randomization group, bronchodilator responsiveness, race, and sex are not significant independent predictors. There were no nonlinear effects or interactive ef-

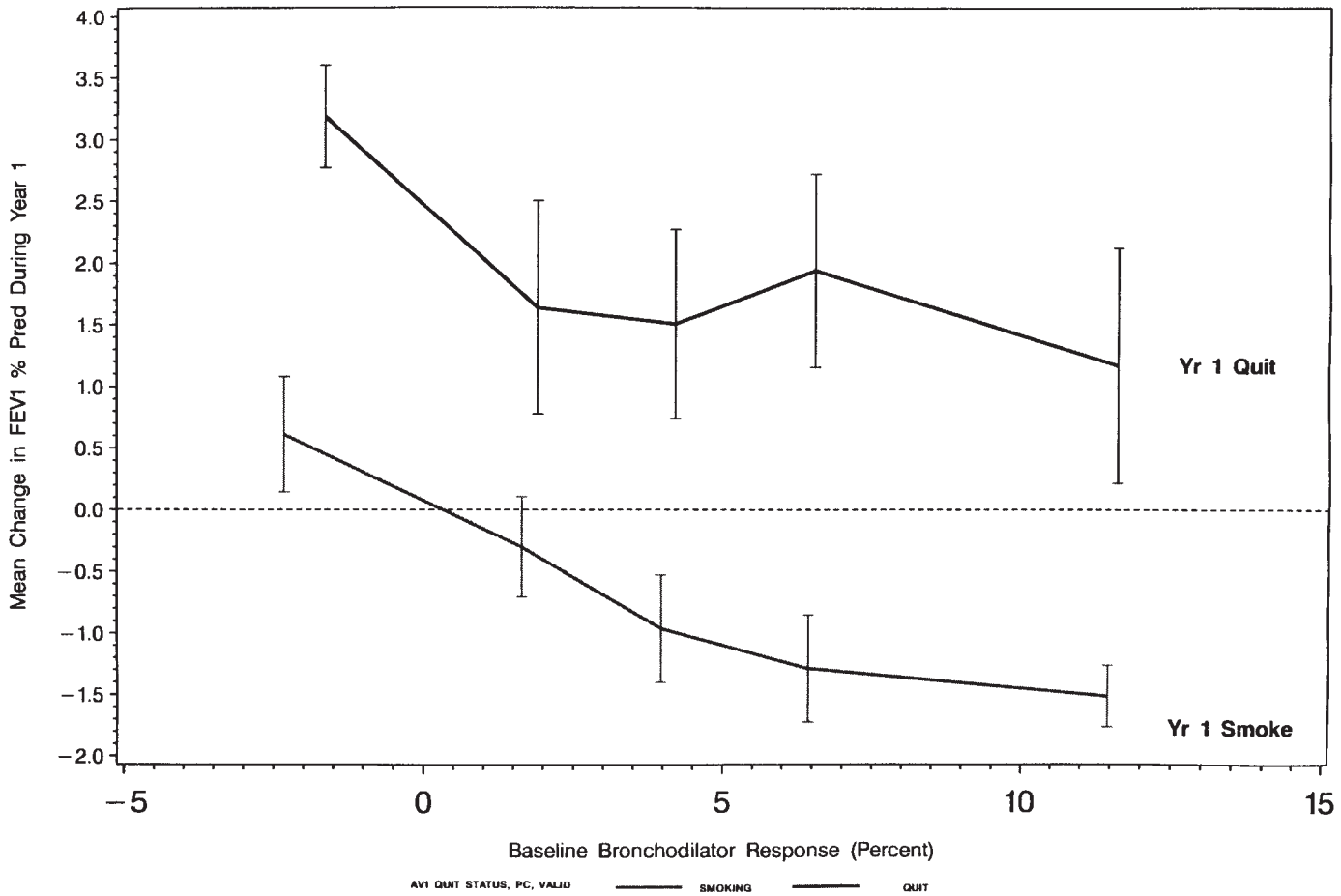


Figure 3. Subjects with the greatest bronchodilator response ranked by quintiles showed the greatest decline or least improvement at Year 1 ($p < 0.001$ for both quitters and continuing smokers).

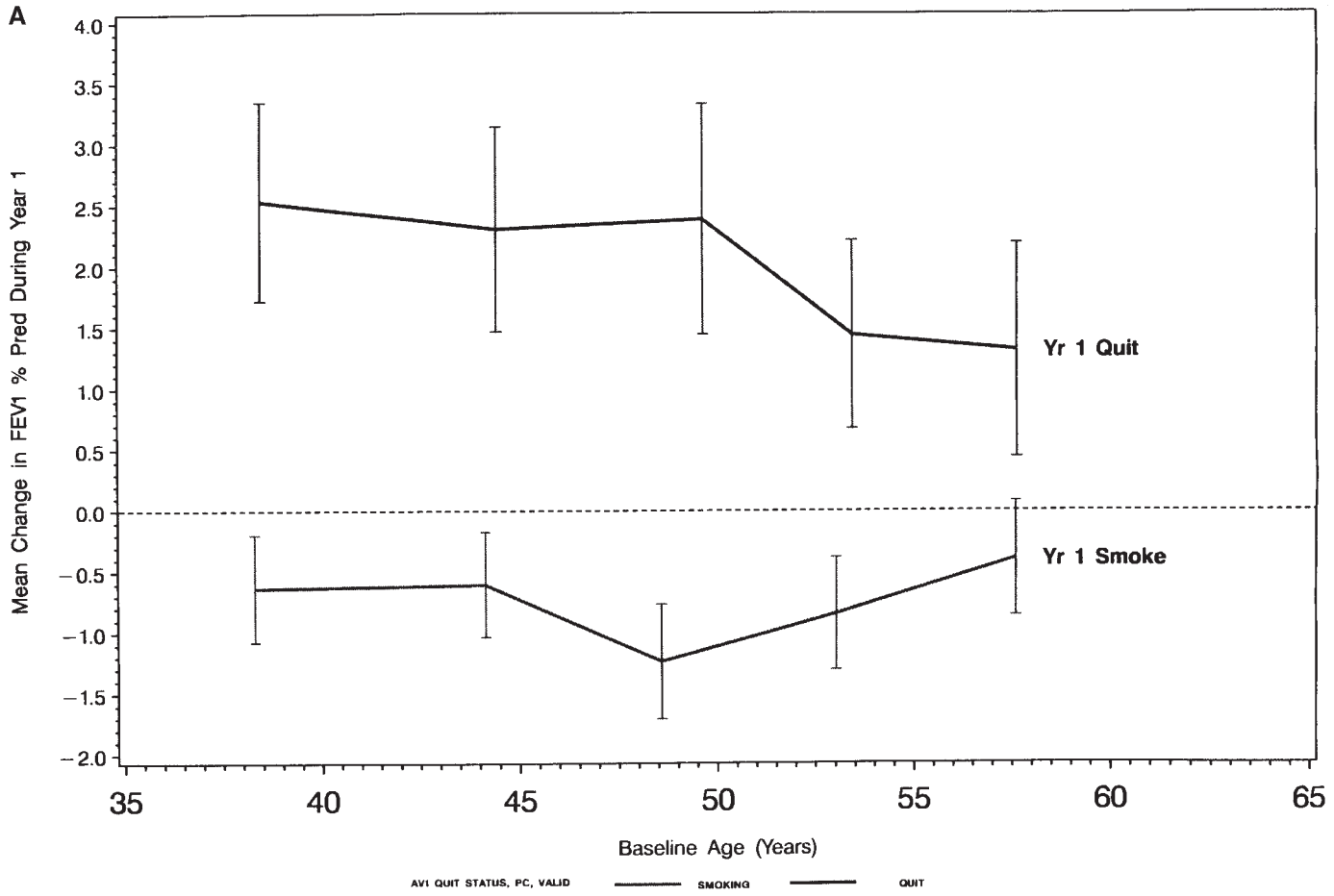
fects identified. The variables included in the multivariate equation account for 9.9% (i.e., $R^2 = 0.099$) of the variability in decline in FEV_1%pred between Year 1 and Year 5.

DISCUSSION

The major findings of this analysis of the effects of smoking cessation in smokers with mild-to-moderate COPD include the following: (*1*) among those who quit smoking, the annual rate of decline in FEV_1 over 4 yr was half that observed among those who continued smoking (31 versus 62 ml/yr). This rate among quitters was comparable to published rates for decline in FEV_1 in healthy never-smokers (28); (*2*) in addition to change in smoking status, the determinants of the degree of improvement in, or stabilization of, FEV_1 included baseline lung function, baseline bronchodilator responsiveness, race, methacholine reactivity, randomization group, and age; (*3*) there was a small improvement in lung function for smokers who quit after smoking intervention; among quitters in the SI-P group, the increase in FEV_1 in the first year was 47 ± 191 ml, or 2.0 ± 5.5%pred. This represents a 96-ml or 2.74% improvement compared with continuing smokers; (*4*) participants with greater airway responsiveness improved more in the first year after smoking cessation than did those who were less responsive. Methacholine reactivity and bronchodilator responsiveness were both independently predictive of change in the first year. In subsequent years, the rate of decline in lung function was related to methacholine reactivity, but not to bronchodilator responsiveness; (*5*) lower initial lung function was predictive of greater benefit from quitting during the first year and, to a lesser degree, during subsequent years; (*6*) younger quitters benefited more than older quitters, but the effect of age was small (i.e., the benefit of quitting was large, regardless of age); (*7*) women had a proportionately larger improvement in the first year after quitting than did men; and women who continued to smoke had a greater loss of function in subsequent years than did men with comparable smoking rates; (*8*) heavy smokers benefited from smoking cessation more than did light smokers. In the multivariate analysis, this effect was strongly related to airway hyperresponsiveness; and (*9*) baseline respiratory symptoms did not predict change in lung function in either quitters or continuing smokers.

The primary objectives of the LHS were to determine the effect of smoking cessation intervention and bronchodilator

Figure 4. (*A*) Baseline to Year 1; (*B*) Year 1 to Year 5. The youngest quitters ranked by quintiles had the greatest initial improvement ($p = 0.014$). The oldest continuing smokers had the greatest functional loss ($p = 0.0021$). The benefit of smoking cessation was large for all ages.


A
Mean Change in FEV1 % Pred During Year 1
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−2.0
Yr 1 Quit
Yr 1 Smoke
35
40
45
50
55
60
65
Baseline Age (Years)
AV1 QUIT STATUS, PC, VALID
SMOKING
QUIT

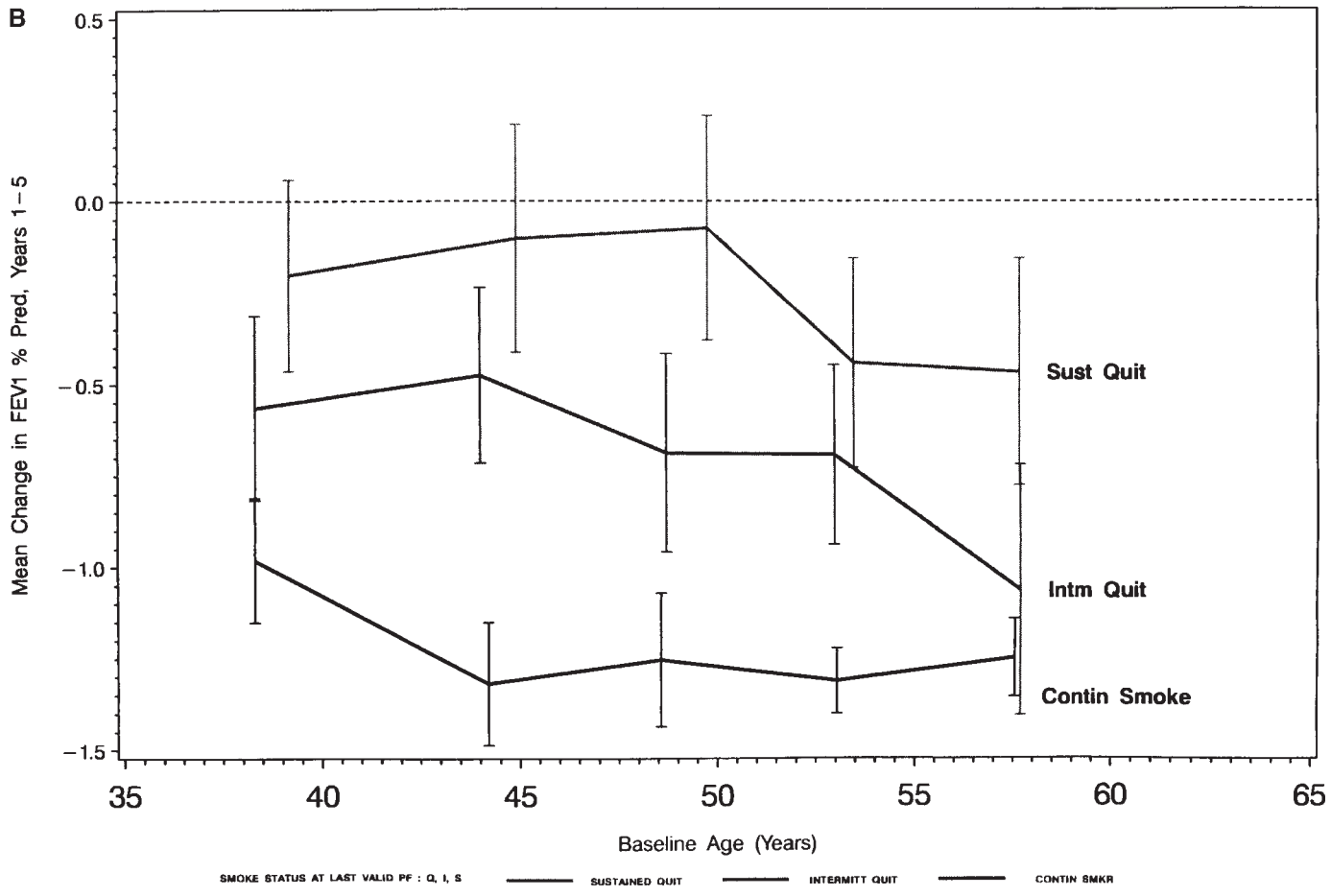

B
Mean Change in FEV1 % Pred, Years 1 – 5
0.5
0.0
−0.5
−1.0
−1.5
Sust Quit
Intm Quit
Contin Smoke
35
40
45
50
55
60
65
Baseline Age (Years)
SMOKE STATUS AT LAST VALID PF : Q, I, S
SUSTAINED QUIT
INTERMITT QUIT
CONTIN SMKR

TABLE 3

ESTIMATED EFFECTS OF SPECIFIED INCREMENTS IN COVARIATES AND INTERACTIONS: CHANGES IN FEV_1 PERCENT PREDICTED*

Covariate or Interaction	Increment or Comparison	Estimated Effect (*% pred*)	Standard Error of Estimate	p Value
	A. Baseline to Year 1			
Treatment group	UC versus SI-P	−0.74	0.19	< 0.001
Year 1 smoking status	Quit versus Smoking	+2.45	0.51	< 0.001
FEV_1%pred	+10	−4.75	1.29	< 0.001
FEV_1%pred squared	+10	+0.33	0.09	< 0.001
Bronchodilator response, %	+5	−1.38	0.14	< 0.001
Bronchodilator response, % squared	+5	+0.23	0.05	< 0.001
Log methacholine reacitvity, %/mg/ml	+0.5	−0.36	0.14	0.019
Nonwhite race	Nonwhite versus white	−1.19	0.47	0.012
Age, yr	+10	−0.32	0.14	0.021
Sex	Female versus male	+0.18	0.23	0.442
Baseline cigarettes per day	+10	−0.01	0.07	0.943
Interaction terms				
Meth reactivity × quit smoking	+0.5, quit versus 0, smoking	+0.94	0.30	0.002
Male sex × quit smoking	Female, quit versus male, smoking	+1.22	0.47	0.012
	B. Mean Annual Changes, Year 1 to Year 5			
Treatment group	UC versus SI-P	−0.05	0.06	0.390
Year 5 smoking status	Sust quit versus contin smoking	+0.99	0.08	< 0.001
	Sust quit versus interm smoking	+0.36	0.09	< 0.001
Log methacholine reactivity, %/mg/ml	+0.5	−0.35	0.04	< 0.001
Age, yr	+10	−0.20	0.04	< 0.001
Baseline cigarettes per day	+10	−0.05	0.02	0.020
FEV_1%pred	+10	+0.07	0.03	0.031
Bronchodilator response, %	+5	−0.04	0.03	0.176
Sex	Female versus male	+0.03	0.06	0.584

Definition of abbreviations: FEV_1 = forced expiratory volume in 1 s; meth = methacholine; SI-P = smoking intervention and placebo; UC = usual care.

* Overall R^2 value = 0.095. Multivariate analysis, predictors of lung function. Log methacholine reactivity is defined in Table 1.

therapy on the rate of decline in lung function, and on smoking-related morbidity and mortality. The current analysis was performed to determine the effect of smoking cessation per se on lung function. Randomization into the LHS was according to intervention group, not smoking status, and so conclusions regarding pulmonary function in relation to smoking status should be considered with caution. The small differences in the baseline characteristics between the continuing smokers and the sustained quitters must be noted, but do not appear to have had an impact on the outcomes reported. The effect of randomization group on the Year 1 improvement in lung function is partly explained by differences in timing of smoking cessation and amount smoked at baseline. A quitting effect of comparable magnitude was observed among delayed quitters, reinforcing the impression that it is likely a real phenomenon.

The effects of smoking and smoking cessation on lung function have been addressed by many studies. Cross-sectional data indicate lower levels of lung function in smokers, and prospective studies have demonstrated more rapid rates of decline among current cigarette smokers than among never-smokers. The annual decline in FEV_1 in prospective studies ranges from 19 to 52 ml/yr among nonsmokers; and from 34 to 79 ml/yr among heavy smokers (29). Smoking cessation results in a reduced rate of decline in lung function, which may approach that of never-smokers. An *improvement* in lung function after smoking cessation, such as that experienced by LHS participants, has been reported by only a few studies (30, 31).

Strengths of the LHS include the prospective, interventional design, the large number of participants, the large proportion of women, the high rate of follow-up, the high rates of smoking cessation, the high quality of pulmonary function data, and the methacholine reactivity data. Because of these strengths, the data from the LHS can better define the effects of smoking cessation on lung function and predictors of those effects. The results of the Lung Health Study may be applicable to other populations of smokers, especially those with mild-to-moderate airflow obstruction. Among smokers without airflow obstruction, the effect of smoking cessation on lung function would likely be smaller. The LHS intervention program is unlikely to be reproduced in the current practice of smoking intervention because of cost constraints; nonetheless, the effects of actual smoking cessation, as evaluated by the current study, should be relevant to other smoking cessation interventions.

Baseline lung function is a predictor of changes in lung function. FEV_1%pred is strongly associated with methacholine reactivity and may serve as a partial surrogate for airway responsiveness. Since measurement of airway responsiveness is expensive and is often thought (wrongly) to be hazardous in persons with compromised lung function, it is rarely performed in patients with COPD. The LHS has shown that lung function can predict the benefit of smoking cessation or the harm of continued smoking for smokers with airflow obstruction. This reinforces the utility of spirometry for identifying smokers at risk of developing severe COPD.

Significance for Smoking Intervention

In the LHS, smoking status was the most powerful predictor of decline in lung function in smokers with COPD. When smokers are counseled to quit smoking, they may rationalize their unwillingness or inability to quit by claiming that they are too old to benefit from quitting, that they smoke too heavily and cannot quit, or that they have already damaged their lungs irreparably. Similarly, in public policy, insurance payment criteria, and health care guidelines or programs, a nihilistic attitude exists that suggests that smoking cessation intervention is

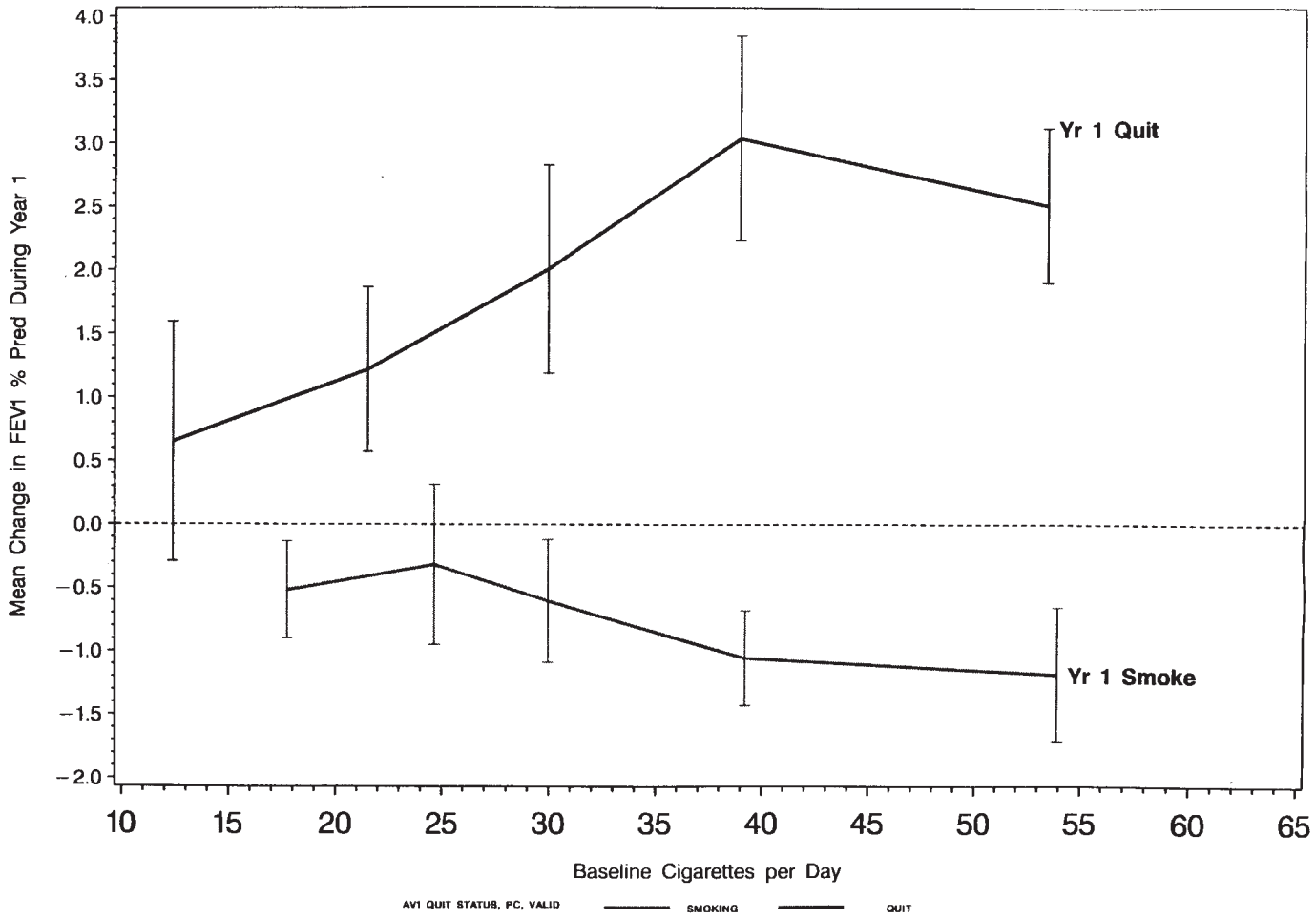


Figure 5. The heaviest smokers ranked by quintiles had the largest improvement in the first year after quitting ($p = 0.001$ compared with the lightest smoking quintile), and the largest functional loss during the first year if they continued smoking ($p = 0.028$).

not worthwhile for older smokers or those with established smoking-related disease (32). The results of the LHS provide a strong counterargument to such attitudes. Heavy smokers stand to benefit the most if they quit and to lose the most if they continue smoking. Older smokers benefit nearly as much, in terms of improved rates of decline in function, as younger smokers. Smokers with the worst lung function deteriorate most rapidly if they continue smoking; therefore they benefit the most from smoking cessation.

The LHS intervention program resulted in a high rate of sustained smoking cessation among heavy smokers. This is probably because of the intensity and duration of the program, along with the extended use of nicotine replacement therapy. Such intensive programs may be necessary for heavy smokers with compromised lung function. Analyses of the costs and benefits of such interventions are needed.

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