Articles

Effects of the Multiple Risk Factor Intervention Trial Smoking Cessation Program on Pulmonary Function
A Randomized Controlled Trial

WARREN S. BROWNER, MD, MPH, *San Francisco, California;* ALAIN G. DU CHENE, *Minneapolis, Minnesota;* *and* STEPHEN B. HULLEY, MD, MPH, *San Francisco, California*

To determine whether the decline in pulmonary function in smokers is modified by stop-smoking intervention, a randomized controlled study (the Multiple Risk Factor Intervention Trial) was done comparing participants in a special intervention group that included an intensive smoking cessation program with those assigned to usual care. The subjects were 6,347 middle-aged male smokers who had serial measurements of pulmonary function—principally the forced expiratory volume in 1 second (FEV_1)—during 6 to 7 years of follow-up. No overall differences were detected in the rate of loss of FEV_1 in the two groups. The use of β-blockers, which had detrimental effects on FEV_1, was significantly more common in the intervention group. Among nonusers of β-blockers, heavy smokers lost FEV_1 at a rate about 11 ml per year slower in the intervention group than in the control group ($2P=.09$) and ended the trial with an FEV_1 about 90 ml higher ($2P=.05$). These results support the inference from observational studies that smoking cessation has a beneficial effect on pulmonary function in heavy smokers.

(Browner WS, DuChene AG, Hulley SB: Effects of the Multiple Risk Factor Intervention Trial smoking cessation program on pulmonary function—A randomized controlled trial. West J Med 1992 Nov; 157:534-538)

A man who smokes is about ten times more likely than a nonsmoker to die of chronic obstructive pulmonary disease (COPD). In the United States, mortality from COPD due to cigarette smoking is about 14,000 annually and costs about $500 million a year in lost productivity.[1] Although it seems clear that COPD can be largely prevented by a lifelong avoidance of smoking, whether programs that encourage current smokers to quit will have a similar benefit is unknown.

Smokers lose pulmonary function more rapidly than nonsmokers: on the average, the gradual age-related loss of pulmonary function (expressed as the forced expiratory volume in one second [FEV_1]) occurs about 25% to 50% faster in smokers than in nonsmokers.[2-5] Many studies have also shown that cigarette smokers who quit have a slower rate of loss of the FEV_1 than continuing smokers,[2,5-11] especially if quitting takes place before the start of pulmonary dysfunction.[12]

But quitters may differ in several ways from nonquitters; they smoke fewer cigarettes, for example,[13,14] and are less likely to inhale.[13] Confounding factors of this sort, if they are known and have been measured, can be adjusted for when assessing the effects of smoking cessation in an observational study. Only a randomized trial, however, can definitively demonstrate that quitting smoking per se, rather than some unknown or unmeasured characteristic of the quitter, is beneficial in preventing smoking-induced loss of pulmonary function. Randomized trials are not easy to design for this research question: smokers cannot be randomly assigned to quit (or not to quit) smoking, they can only be randomly assigned to receive (or not to receive) an intervention designed to encourage them to quit.

A previous randomized trial of a quit-smoking program reported a statistically significant benefit on pulmonary function in the first year of the study but not in subsequent years.[13] That study assigned 1,445 middle-aged male smokers to either an intervention group that received a series of stop-smoking visits with a study physician or a "normal care" control group. Smokers randomly assigned to the intervention lost an average of 75 ml of FEV_1 in the first year of the study, compared with an average loss of 115 ml in those assigned to the control group. In the next two years of the study, however, the loss of the FEV_1 was actually slightly greater (an additional 56 ml) in the intervention group than in the control group (37 ml). Although the net effect at three years was still reported to be in favor of the intervention, only 61% of those originally randomly assigned to one of the groups had their pulmonary function measured at that time; no further measurements of pulmonary function were made during the remaining seven years of the study.

The Multiple Risk Factor Intervention Trial (MRFIT), though primarily a study of the prevention of coronary heart disease, provided another opportunity to address this question in a randomized trial.[14] About two thirds of the men who volunteered for the MRFIT were cigarette smokers at baseline, and serial measurements of pulmonary function were made during the trial. Technically acceptable pulmonary function measurements were available for 6,347 smokers and were analyzed to determine whether random assignment to

From the Division of Clinical Epidemiology, Department of Epidemiology and Biostatistics (Drs Browner and Hulley), University of California, San Francisco, School of Medicine; the General Internal Medicine Section, Department of Medicine, Department of Veterans Affairs Medical Center, San Francisco (Dr Browner); and the Multiple Risk Factor Intervention Trial Coordinating Center, Minneapolis, Minnesota (Mr DuChene).

Reprint requests to Warren S. Browner, MD, MPH, General Internal Medicine, VA Medical Center 111A1, San Francisco, CA 94121.

ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in 1 second
MRFIT = Multiple Risk Factor Intervention Trial

the MRFIT smoking-cessation intervention modified the rate of change in pulmonary function.

Subjects and Methods

Subjects and Design

The MRFIT enrolled 12,866 men aged 35 to 57 who were at high risk for coronary heart disease because of elevated blood pressures, serum cholesterol levels, or cigarette smoking.[14] All expressed interest in modifying their cardiovascular risk factors. Men with chronic obstructive pulmonary disease (as diagnosed by the MRFIT examining physician) were excluded.

Half of the men (6,428) were randomly assigned to a special intervention group; the others (6,438) were assigned to usual care and served as the comparison group. The special intervention group participated in an intensive integrated program to lower the three major cardiovascular risk factors (smoking, hypertension, and hypercholesterolemia), and the usual care group received no specific therapy. The smoking cessation intervention has been described elsewhere.[15] The program began with a series of weekly group discussions and continued throughout the trial with counseling and various behavior modification techniques. Subjects were examined annually for six to eight years.

At the start of the trial (screen 3), 3,786 men in the special intervention group (59%) and 3,772 men in the usual care group (59%) were cigarette smokers. Baseline smoking and technically acceptable (described later) pulmonary function data over the period of follow-up were available for 6,347 (84%) of these smokers (3,189 in special intervention and 3,158 in usual care); they comprise the sample for this study. There were no substantial differences in baseline characteristics between those men for whom data were available and the remainder of the study participants.[5]

Measurements

Data were collected by questionnaire for age, race, age at start of cigarette smoking, current number of cigarettes smoked per day (at first screening visit), and medication use throughout the trial, including the use of β-blockers (primarily for the treatment of hypertension). Subjects who reported smoking cigarettes at screening visits 1 and 3 were classified as smokers. Smoking cessation was ascertained by questionnaire and verified by serum thiocyanate levels, an objective measurement of recent smoking.[16]

Pulmonary function, measured by the FEV_1, was determined annually using 10-liter Stead Wells water-filled spirometers. All spirograms were reviewed and rated for several indices of technical quality.[17] Because the measurement of pulmonary function during the first few years of the trial was poorly standardized and of uncertain validity, this report is limited to smokers who had at least three acceptable annual FEV_1 measurements, or two FEV_1 measurements at least two years apart, made after the MRFIT pulmonary function testing was standardized during the third annual visit cycle. A final FEV_1 was defined as an acceptable measurement recorded at the sixth annual visit and was available for 5,634 participants. We were unable to determine directly the effect of the intervention during the early years of the trial. Random assignment, however, of the large number of smokers in MRFIT makes it highly probable that the missing initial FEV_1 values in the special intervention and usual care groups were nearly identical. Any unmeasured benefit of the intervention in preserving pulmonary function in the early years of the trial should be reflected in higher final FEV_1 values in the special intervention group; we were able to measure these last values.

Analysis

The change in the FEV_1 over time was assessed for each participant by calculating the slope of the least-squares regression line of FEV_1 versus time, using three to five measurements of FEV_1 over two to four years of follow-up. Each participant's "slope" was treated statistically as a single observation. Using the method of Fletcher and co-workers, each subject's FEV_1 values were checked for outliers before a slope was calculated.[3(pp179-180)] The FEV_1 at the midpoint of follow-up was estimated by the mean value of all FEV_1s measured. Expected FEV_1 values before and after that time were estimated by assuming an annual decline in the FEV_1 of 50 ml per year, approximately that observed for the entire MRFIT cohort; values that differed by more than 500 ml from the expected value were labeled as outliers. The few subjects with outliers (46 in special intervention, 54 in usual care) were excluded from this report; other analyses that included them produced nearly identical results.

All statistical analyses were done comparing the special intervention and usual care groups using an intention-to-treat analysis without regard to an individual subject's success at stopping smoking. Continuous data are reported as the mean plus or minus one standard deviation. Mean slopes and final FEV_1 values were compared with the t test, and proportions were compared with the z statistic.[18] Nominal two-sided P values are reported, unadjusted for multiple hypothesis testing. Because of the overwhelming prior probability, based on observational studies, that quitting smoking would reduce rather than increase the rate of loss of pulmonary function, two-sided P values of less than .10 favoring special intervention (equivalent to one-sided values of less than .05) were taken as evidence for the inference that the effect observed in our sample is present in the population.[19] Standard techniques were used to determine 90% confidence intervals.[20]

To check the adequacy of randomization, given that some pulmonary function data were missing, we compared baseline characteristics that might be related to pulmonary function—including age, race (percentage of nonwhite), height, and smoking history (cigarettes per day, total pack-years)—in the special intervention and usual care analysis groups. There were no between-group differences in these characteristics among the subjects in the main analysis group, among the nonusers of β-blockers within that group, or among the heavy smokers within that subgroup (all $P > .17$).

Results

At the sixth annual visit, thiocyanate-adjusted quit rates were higher among smokers in the special intervention group (33%) than in the usual care group (20%) ($P < .0001$). In addition, 13% of the smokers in special intervention but only 3% of those in usual care refrained from smoking throughout

the trial ($P < .0001$). There were no significant differences, however, between the special intervention and the usual care smokers in either the rate of loss of the FEV_1 over the final half of the trial or the final FEV_1 value (Table 1). Both groups lost about 60 ml in their FEV_1 per year.

During the trial, study physicians caring for subjects in the special intervention group prescribed β-blockers for the treatment of hypertension more commonly than did the community physicians caring for the subjects receiving usual care. Thus, slightly more smokers in the special intervention group reported the use of β-blockers than did those in the usual care group (22.5% versus 19.8%, $P < .01$). The mean rate of loss of the FEV_1 was about a third higher and the mean final FEV_1 about 100 ml lower in users of β-blockers compared with nonusers (75 ± 114 ml per year versus 56 ± 102 ml per year, $P < .0001$; $2,950 \pm 673$ ml versus $3,055 \pm 685$ ml, $P < .0001$). Thus, β-blocker use confounded the effect of the smoking cessation intervention. Stratifying by the use of β-blockers, however, did not reveal any overall differences in pulmonary function between the special intervention and the usual care groups (Table 2).

Further stratification of nonusers by age, total pack-years, and baseline smoking (Tables 3 and 4) shows that the rates of loss of the FEV_1 were higher and the final FEV_1 lower with increasing age, baseline smoking, and total pack-years consumed (Tables 3 and 4). These effects are best

TABLE 1.—*Change in Forced Expiratory Volume in 1 Second (FEV_1) and Final FEV_1 in Smokers in Special Intervention and Usual Care Groups in the Multiple Risk Factor Intervention Trial*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Change in FEV_1, ml/yr	3,189	−60.9	107.0	3,158	−59.6	102.8	−1.3	.62	−5.6, 3.0
Final FEV_1, ml	2,812	3,043	677	2,822	3,022	688	22	.24	−8, 52

TABLE 2.—*Change in Forced Expiratory Volume in 1 Second (FEV_1) and Final FEV_1 in Smokers in Special Intervention and Usual Care Groups in the Multiple Risk Factor Intervention Trial, Stratified by Use of β-Blockers*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Users of β-Blocker									
Change in FEV_1, ml/yr	717	−76.7	115.3	625	−73.4	114.3	−3.3	.60	−13.6, 7.1
Final FEV_1, ml	644	2,950	664	556	2,949	684	1	.99	−63, 65
Nonusers of β-Blocker									
Change in FEV_1, ml/yr	2,472	−56.3	104.0	2,533	−56.2	99.5	−0.1	.97	−4.9, 4.6
Final FEV_1, ml	2,168	3,071	680	2,266	3,039	688	32	.12	−2, 65

TABLE 3.—*Change in Forced Expiratory Volume in 1 Second (FEV_1) (ml/yr) in Smokers in Special Intervention and Usual Care Groups Who Did Not Use β-Blockers, by Age at Entry, Pack-years of Cigarette Smoking, and Baseline Number of Cigarettes Smoked per Day*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Age, years									
35-39	452	−49.0	96.3	494	−50.4	112.6	1.4	.84	−9.9, 12.6
40-44	603	−58.8	114.5	610	−53.1	93.7	−5.8	.34	−15.6, 4.1
45-49	719	−55.5	97.8	690	−59.4	97.7	3.8	.46	−4.7, 12.4
50-54	515	−56.9	105.7	545	−57.6	91.8	0.6	.92	−9.3, 10.6
55+	183	−66.9	105.2	194	−65.0	109.2	−1.9	.87	−20.1, 16.3
Cigarette Smoking, pack-years (Approximate Quartiles)									
0-32	639	−50.9	104.4	615	−49.6	114.6	−1.3	.83	−11.5, 8.8
33-47	608	−56.5	102.2	621	−52.1	95.4	−4.4	.44	−13.6, 4.9
48-64	597	−62.8	99.2	629	−55.8	87.0	−7.0	.19	−15.7, 1.8
65+	628	−55.4	109.7	668	−66.3	99.0	10.9	.06*	1.4, 20.5
Cigarettes/Day (Screen 1)									
1-20	644	−51.8	102.5	628	−49.2	104.2	−2.6	.66	−12.1, 7.0
21-30	599	−62.1	105.0	623	−56.4	88.7	−5.7	.31	−14.8, 3.5
31-40	689	−59.1	99.8	732	−57.3	103.6	−1.8	.74	−10.7, 7.1
41+	540	−51.6	109.7	550	−62.3	100.0	10.7	.09*	0.2, 21.1
Total	2,472	−56.3	104.0	2,533	−56.2	99.6	−0.1	.97	−4.9, 4.6

*Significant at 2-sided $P < .10$ favoring special intervention.

TABLE 4.—*Final Forced Expiratory Volume in 1 Second (FEV_1) (ml) in Smokers in Special Intervention and Usual Care Groups Who Did Not Use β-Blockers, by Age at Entry, Pack-years of Cigarette Smoking, and Baseline Number of Cigarettes Smoked per Day*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Age, years									
35-39	389	3,522	613	428	3,421	628	101	.02*	29, 172
40-44	523	3,209	636	540	3,211	643	−2	.96	−66, 62
45-49	640	2,995	616	625	3,001	637	−6	.86	−64, 51
50-54	465	2,785	628	493	2,751	603	34	.39	−30, 100
55+	151	2,621	612	180	2,530	687	91	.21	−27, 210
Cigarette Smoking, pack-years (Approximate Quartiles)									
0-32	557	3,268	692	545	3,300	628	−31	.42	−97, 33
33-47	530	3,133	652	556	3,099	642	34	.39	−30, 98
48-64	536	3,003	658	557	2,984	698	18	.66	−49, 85
65+	545	2,873	651	608	2,799	686	74	.06*	9, 139
Cigarettes/Day (Screen 1)									
1-20	566	3,104	681	556	3,122	658	−18	.64	−84, 47
21-30	529	3,081	713	563	3,058	669	23	.58	−45, 92
31-40	605	3,047	654	656	3,011	698	35	.35	−27, 98
41+	468	3,048	671	491	2,959	724	89	.05*	14, 163
Total	2,168	3,070	679	2,266	3,039	689	31	.13	−2, 65

*Significant at 2-sided $P<.10$ favoring special intervention.

seen in the usual care group: smokers with at least a 65 pack-year history, for example, lost FEV_1 at a rate that was 19% faster than in all other smokers (66.3 ± 99.0 ml per year versus 55.5 ± 99.6 ml per year, $P < .02$) and had a final FEV_1 that was 327 ml lower ($2,799 \pm 686$ versus $3,127 \pm 657$, $P < .0001$).

This stratification also demonstrates statistically significant benefits from the intervention among heavy smokers, whether heavy smoking is defined as at least 65 pack-years of smoking history or as smoking more than two packs of cigarettes per day at baseline. Heavy smokers assigned to the special intervention group lost FEV_1 at a mean rate that was about 16% slower than those in the usual care group. The estimated difference between the special intervention and the usual care groups in the mean FEV_1 slope of 11 ml per year was consistent with the observation that the mean FEV_1 was about 70 to 90 ml greater in the special intervention group at the six-year point in the trial.

The number of users of β-blockers was small; thus, the power to detect any intergroup differences among them was limited. Stratification by age, pack-years, and baseline cigarette consumption showed no intergroup differences for either the FEV_1 slope (all $P > .17$) or the final FEV_1 (all $P > .23$) in those subgroups.

Discussion

Our results suggest that the intervention in the MRFIT—the largest randomized trial of a smoking cessation program ever undertaken—had a beneficial effect on pulmonary function. Among heavy smokers who did not use β-blockers, those who were randomly assigned to the special intervention group had a 16% slower rate of loss of FEV_1 over the latter half of the trial than the controls receiving usual care. They also had a significantly greater FEV_1 at the end of the trial. Because many smokers in the special intervention group continued to smoke (and some smokers in the control group quit), our results actually underestimate the beneficial effect on pulmonary function of quitting.

These findings are consistent with the overwhelming evidence from nonrandomized studies showing that smokers have a more rapid loss of the FEV_1 than nonsmokers and that quitting smoking slows that decline. We observed this within the MRFIT itself, at least during the latter half of the trial when pulmonary function data were available. Continuing smokers lost FEV_1 at a rate of 60.4 ml per year, compared with 51.9 ml per year in those who quit.[5] These results are consistent with recent estimates by Tager and associates that middle-aged male smokers lose FEV_1 at a rate about 10 ml per year faster than nonsmokers.[21] Other investigators have shown the harmful effects of smoking and the beneficial effects of quitting on other measures of pulmonary function, including expiratory flow rates,[8,11,12,22,23] the ratio of the closing volume to vital capacity,[6,12,22] and the slope of phase III of the single-breath nitrogen washout.[6,7,10] We cannot determine whether using one of these more sophisticated tests would have enabled us to detect an overall intervention effect.

There was no effect of the intervention on pulmonary function among the entire MRFIT cohort of smokers, among those who used β-blockers, or among light smokers. Likely explanations for these results are that most smokers in the special intervention group continued to smoke, whereas some smokers in the usual care group quit; compared with the effect of β-blocker use, the effect of quitting smoking on pulmonary function is small[24-26]; compared with the intrinsic variability in measurements of FEV_1 and the age-related declines in pulmonary function, the effect of quitting in light smokers is modest; and the overall effect was dominated by the light smokers, who made up the majority of our sample. Only after excluding users of β-blockers and then only among heavy smokers, who had a substantially greater loss of pulmonary function, were the effects of the intervention

manifest. In light smokers, for example, the standard deviation of the annual change in FEV_1 of about 100 ml per year was 13 times greater than the projected benefit of 8 ml per year (assuming the same 16% reduction in FEV_1 slope that was observed among heavy smokers). As the confidence intervals in Tables 3 and 4 indicate, our study did not have adequate power to exclude the possibility of a small benefit in these lighter smokers.

This study is subject to several potential biases. The MRFIT was not primarily designed to study pulmonary function: acceptable data were available for only 84% of the subjects, raising the possibility of selection bias. This seems unlikely, however. There were no substantial intergroup differences either in the baseline characteristics known to affect pulmonary function—including age, race, height, and smoking history—or in the frequency of technically unacceptable measurements of FEV_1.

As to co-intervention bias, it is possible that some other aspect of the multifactorial intervention used in the trial was responsible for the observed differences in pulmonary function. There is no reason to think that dietary counseling to reduce elevated serum cholesterol levels would have such an effect, but β-blockers (which reduce the FEV_1) were used to treat hypertension more often in men in special intervention than in those in usual care. This has been dealt with in the analysis by stratification—looking just at the nonusers of β-blockers in both groups—but adjusting for a postrandomization factor in this way does not entirely eliminate the possibility of confounding. It remains possible, for example, that physicians providing special interventions were more likely than those providing usual care to prescribe β-blockers in heavy smokers who were destined for other reasons to be rapid losers of pulmonary function. The remaining heavy smokers in special intervention who did not use β-blockers would then have slower rates of loss of pulmonary function than those receiving usual care, which would falsely appear to be an effect of the intervention. Given that the detrimental effects of β-blockers on pulmonary function were well known to clinicians years before the start of the trial[24] and that the baseline characteristics of heavy smoking nonusers of β-blockers were similar in both groups, confounding of this sort seems unlikely.

The results in the heavy smokers might represent a type I error—finding an effect by chance in the MRFIT sample, or in a subgroup of that sample, that would not be present in the population. We think, for example, that chance is the most likely explanation for the apparent benefit of the intervention on the final FEV_1 but not on the rate of loss of FEV_1 in 35- to 39-year-old men. Our results in heavy smokers have internal consistency, however. We found a substantial positive effect on two separate albeit not entirely independent measures of pulmonary function (change in FEV_1 and the final FEV_1) and using two definitions of heavy smoking—baseline consumption of more than two packs per day and the highest quartile of pack-years of smoking history. Although we tested several hypotheses, we did not dredge the data for significant P values: both outcome variables (annual change in FEV_1 and final FEV_1) and all five predictor variables (special intervention versus usual care, use of β-blockers, age, pack-years, and baseline cigarette consumption) were selected a priori; these were the only variables examined. Similarly, the decision to use a two-sided α of .10 for pulmonary function comparisons favoring the special intervention group was made before we analyzed the data. When the P values we report are viewed in the context of the prior probabilities of the tested hypotheses[19]—in this case the wealth of observational evidence that has shown quitting smoking to be associated with a slower rate of loss of pulmonary function—it seems unlikely that the results in heavy smokers are due to chance. Still, subgroup analyses must be viewed with caution; a conservative interpretation is that our results suggest, but do not establish, that there is a benefit in heavy smokers.

In conclusion, we have found that randomly assigning heavy smokers to a smoking cessation program slows the rate of loss of pulmonary function by about 16%—a beneficial effect of more than 10 ml per year in the FEV_1. We think that this benefit is real and that it can be indirectly generalized to lighter smokers and probably to women. It will be difficult, however, to demonstrate such a benefit using a randomized design. Most important, our results suggest that even among heavy and long-term smokers, it is not too late to quit.

Acknowledgment

Mary Townsend, DrPH, contributed substantially to this work in the acquisition and analysis of the MRFIT pulmonary function data and in comments on previous drafts of the manuscript.

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