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The Effects of a Smoking Cessation Intervention on 14.5-Year Mortality

A Randomized Clinical Trial

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Background: **Randomized clinical trials have not yet demonstrated the mortality benefit of smoking cessation.**

Objective: **To assess the long-term effect on mortality of a randomly applied smoking cessation program.**

Design: **The Lung Health Study was a randomized clinical trial of smoking cessation. Special intervention participants received the smoking intervention program and were compared with usual care participants. Vital status was followed up to 14.5 years.**

Setting: **10 clinical centers in the United States and Canada.**

Patients: **5887 middle-aged volunteers with asymptomatic airway obstruction.**

Measurements: **All-cause mortality and mortality due to cardiovascular disease, lung cancer, and other respiratory disease.**

Intervention: **The intervention was a 10-week smoking cessation program that included a strong physician message and 12 group sessions using behavior modification and nicotine gum, plus either ipratropium or a placebo inhaler.**

Results: **At 5 years, 21.7% of special intervention participants had stopped smoking since study entry compared with 5.4% of usual care participants. After up to 14.5 years of follow-up, 731 patients died: 33% of lung cancer, 22% of cardiovascular disease, 7.8% of respiratory disease other than cancer, and 2.3% of unknown causes. All-cause mortality was significantly lower in the special intervention group than in the usual care group (8.83 per 1000 person-years vs. 10.38 per 1000 person-years; $P = 0.03$). The hazard ratio for mortality in the usual care group compared with the special intervention group was 1.18 (95% CI, 1.02 to 1.37). Differences in death rates for both lung cancer and cardiovascular disease were greater when death rates were analyzed by smoking habit.**

Limitations: **Results apply only to individuals with airway obstruction.**

Conclusion: **Smoking cessation intervention programs can have a substantial effect on subsequent mortality, even when successful in a minority of participants.**

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Smoking cessation almost certainly has beneficial effects on subsequent mortality (1). However, the strongest support for this assertion comes from cohort studies, where smokers and quitters were self-selected. Results from randomized trials, which avoid the selection issue, have largely been disappointing because mortality benefits have not been clear or have not been clearly attributable to smoking cessation (1).

The Lung Health Study (LHS) was a randomized clinical trial of smoking cessation and inhaled bronchodilator (ipratropium) therapy in smokers 35 to 60 years of age who did not consider themselves ill but had evidence of mild to moderate airway obstruction (2). Individuals with serious disease, hypertension, obesity, or excessive alcohol intake were excluded. The primary research questions were whether a smoking cessation program and use of inhaled ipratropium would decrease the rate of decline of lung function and would affect mortality and morbidity over 5 years. These results have been reported elsewhere (3, 4). The smoking cessation program was associated with cumulative reduced decline in lung function (FEV_1) that was largest in participants who stopped smoking early in the study; inhaled ipratropium produced a small noncumulative increase in FEV_1 that disappeared when the drug was withdrawn (3). Intention-to-treat analysis after 5 years did not reveal differences in morbidity or mortality among treatment groups (4), although subgroup analysis showed that smoking cessation was associated with significant reductions in fatal or nonfatal cardiovascular disease and coronary heart disease. This paper reports the effects of the study intervention on mortality in LHS participants 14.5 years after randomization.

METHODS

The design of the LHS has been described in detail elsewhere (2). The participants, all volunteers, were smokers who did not consider themselves ill but had evidence of airway obstruction and little evidence of other disease. Researchers recruited participants from the community using

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Context

Although there are many health benefits for smokers who stop smoking, we still lack evidence from randomized, controlled trials that smoking cessation programs reduce mortality.

Contribution

In this randomized, controlled trial of a 10-week-long smoking cessation intervention in 5887 smokers with asymptomatic airway obstruction, 14-year mortality rates were higher in the usual care group than in the smoking cessation group (hazard ratio, 1.18 [95% CI, 1.02 to 1.37]). The mortality benefit was greatest among the 21.7% of the intervention group who actually managed to quit smoking.

Implications

Smoking cessation programs substantially reduce mortality even when only a minority of patients stop smoking.

–The Editors

a wide variety of techniques (5). In 10 clinical centers, 5887 participants were randomly assigned to 3 groups. Two special intervention groups received an intensive 10-week smoking cessation program. Briefly, the cessation intervention consisted of a strong physician message and 12 two-hour group sessions, using behavior modification and nicotine gum. Quitters entered a maintenance program that stressed coping skills. One special intervention group also received ipratropium, while the other received a placebo inhaler. A third group received usual care. About 75% of the original participants were followed continuously for the subsequent 10 years by biannual telephone contacts and 1 clinic visit at approximately 11 to 12 years after randomization (6). Telephone contacts served to check smoking status, morbidity, and mortality and were not part of the intervention.

All study participants provided written informed consent for the original LHS before beginning the study. The consent documents stated that smoking increases the risk for chronic obstructive pulmonary disease, respiratory tract cancer, and cardiovascular disease and that smoking cessation would decrease such risks. Additional written informed consent was obtained from persons who participated in the biannual telephone calls. Institutional review boards at each of the 10 clinical centers and the coordinating center approved the study design and consent documents.

When biannual phone calls revealed a participant death, staff attempted to collect death certificates, autopsy reports, relevant medical records, and interviews with attending physicians or eyewitnesses. An independent mortality and morbidity review board examined these data and classified causes of death. In addition, a National Death Index review provided date and cause of death for all U.S. study participants through the end of 2001. Vital status at 31 December 2001 or 14.5 years, whichever was earlier, was successfully determined for 98.3% of all participants; missing individuals were Canadians who had been lost to follow-up and were not accessible through the National Death Index. Mortality end points were classified in 7 categories: coronary heart disease, cardiovascular disease including coronary heart disease, lung cancer, other cancer, respiratory disease excluding lung cancer, other, and unknown. The "other" category included but was not limited to liver disease, kidney disease, sepsis, accidents, suicide, and AIDS.

Analyses were performed on an intention-to-treat basis, comparing the special intervention group with the usual care group. The special intervention group was a combination of the groups originally assigned to receive inhaled ipratropium or placebo therapy. Both of these groups, which were very similar at baseline, received the smoking cessation program and exhibited similar rates of smoking cessation (3). Participants were also divided into 3 groups according to smoking history during the initial 5 years of the trial. *Sustained quitters* were participants who stopped smoking in the first year after randomization and maintained biochemically validated abstinence (3) throughout follow-up. *Continuing smokers* were participants who reported smoking at all follow-up visits. *Intermittent quitters* were participants who reported smoking at some but not all of their follow-up visits or during the time between visits.

Statistical Analysis

Baseline differences between the special intervention and usual care groups were tested by using *t*-tests for continuous variables and chi-square statistics for categorical variables. Cause-specific death rates and times to events were analyzed by using the Kaplan–Meier product-limit method (7). Survival was compared among groups by using the log-rank test. Hazard ratios and adjusted analyses were obtained by using the Cox proportional hazards model. Interactions were assessed by comparing hierarchically related proportional hazards models. All *P* values result from 2-sided tests; no adjustments were made for multiple comparisons.

Role of the Funding Source

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RESULTS

Baseline characteristics of LHS participants are shown in **Table 1**. Most were middle-aged; smoked heavily; and had substantial smoking histories, airway obstruction (FEV_1–FVC ratio $\leq$ 70%), and borderline low FEV_1 val-

Table 1. **Baseline Characteristics of Lung Health Study Participants***

Baseline Variable	Mean Value in the Special Intervention Group (n = 3923) ± SD	Mean Value in the Usual Care Group (n = 1964) ± SD
Age, *y*	48.48 ± 6.84	48.44 ± 6.80
Men, %	62.40 ± 48.44	63.85 ± 48.06
Cigarettes per day, *n*	31.36 ± 12.88	31.10 ± 12.80
Length of smoking, *pack-years*	40.40 ± 19.25	40.54 ± 18.88
Body mass index, kg/m^2	25.57 ± 3.93	25.56 ± 3.92
Systolic blood pressure, *mm Hg*	120.4 ± 14.00	120.6 ± 13.83
Diastolic blood pressure, *mm Hg*	77.06 ± 9.33	77.17 ± 9.28
Married, %†	71.99 ± 44.91	69.45 ± 46.07
Education, *y*	13.57 ± 2.84	13.68 ± 2.80
Nonwhite ethnicity, %	4.15 ± 19.96	4.38 ± 20.47
Drinks alcohol, %	70.30 ± 45.70	70.06 ± 45.81
Drinks per week, *n*	6.19 ± 5.73	6.22 ± 5.58
Post-BD FEV_1, *L*	2.74 ± 0.63	2.76 ± 0.62
Post-BD FEV_1, *% predicted*	78.27 ± 9.09	78.22 ± 9.05
Post-BD FVC, *L*	4.23 ± 0.95	4.26 ± 0.94
Post-BD FVC, *% predicted*	98.04 ± 10.57	98.00 ± 10.44
FEV_1–FVC ratio, %	64.96 ± 6.11	64.91 ± 6.08

* BD= bronchodilator.
† $P = 0.04$.

ues. On average, participants were normotensive and had normal body mass indices. Most participants were of white ethnicity; 37% were women. The average participant had some postsecondary education and did not drink heavily. The special intervention and usual care groups did not significantly differ at baseline, except in percentage of participants who were married, which was higher in the special intervention group ($P = 0.04$). Smoking status after the first 5 years differed significantly between treatment groups ($P \leq 0.001$). Among special intervention participants and usual care participants, respectively, 21.7% and 5.4% were sustained quitters, 29.3% and 23.3% were intermittent quitters, and 49.0% and 71.3% were continuing smokers.

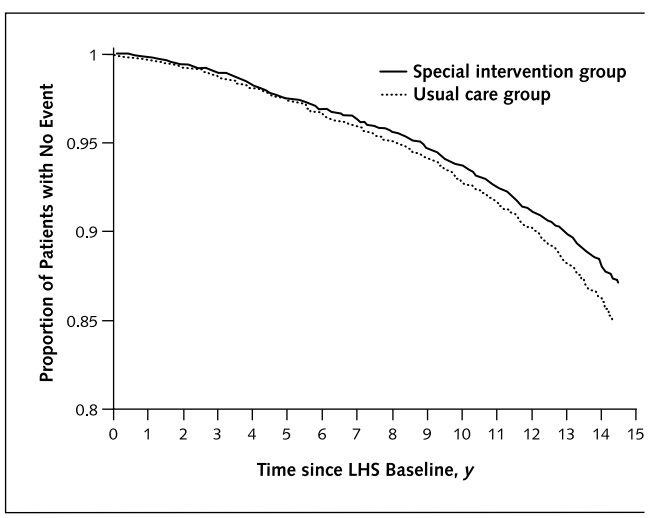
There were 731 known deaths among LHS participants, as shown in **Table 2**. Lung cancer was the most common cause of death (n = 240 [33%]). Coronary heart disease accounted for 77 deaths (10.5%), and cardiovascular disease including coronary heart disease accounted for 163 deaths (22%). One hundred fifty-four participants (21%) died of cancer of organs other than the lung. Deaths due to respiratory disease other than cancer were relatively uncommon (n = 57 [7.8%]). The cause of death was unknown in only 17 participants (2.3%). Mortality did not significantly differ between the special intervention groups originally assigned to ipratropium or placebo (**Table 2**).

Figure 1 shows all-cause survival rates in the 2 treatment groups. Death rates were significantly higher in the usual care group than in the special intervention group (10.38 per 1000 person-years vs. 8.83 per 1000 person-years; $P = 0.03$). The hazard ratio for mortality in the usual care group was 1.18 (95% CI, 1.02 to 1.37) compared with the special intervention group. **Figure 2** shows categorical causes of death in the 2 treatment groups. In all categories except "other," death rates were higher in the usual care group than in the special intervention group, but the difference was significant only for deaths from respiratory diseases not related to lung cancer (1.08 per 1000 person-years vs. 0.56 per 1000 person-years; $P = 0.01$).

When survival was analyzed according to smoking habit, it differed significantly between groups ($P < 0.001$), even after adjustment for baseline differences (data not shown). Mortality was 6.04 per 1000 person-years in sustained quitters, 7.77 per 1000 person-years in intermittent quitters, and 11.09 per 1000 person-years in continuing smokers. No significant differences in death rates were seen between special intervention and usual care participants in any of the 3 smoking categories. **Figure 3** shows categorical causes of death among the 3 smoking groups. Death rates were significantly related to smoking habit for coronary heart disease ($P = 0.02$), cardiovascular disease ($P \leq 0.001$), lung cancer ($P = 0.001$), and other causes ($P = 0.03$). Death rates were not significantly related to smoking habit for cancer other than lung cancer and for respiratory deaths not related to lung cancer. Baseline FEV_1, expressed as a percentage of the predicted normal value, was inversely related to all-cause mortality ($P \leq 0.001$) and to deaths from coronary heart disease ($P = 0.003$), cardiovascular disease ($P = 0.002$), lung cancer ($P = 0.02$), other cancer ($P = 0.03$), and respiratory disease other than cancer ($P \leq 0.001$).

Differences between the special intervention group and the usual care group in all-cause mortality were examined in relation to subgroups identified at baseline (**Table 3**). There was a significant mortality difference between the special intervention and usual care groups in the youngest tertile of participants, those younger than 45 years of age

Figure 1. **All-cause 14.5-year survival.**



461 of 3923 patients died in the special intervention group vs. 270 of 1964 patients in the usual care group ($P = 0.031$, log-rank test). LHS = Lung Health Study.

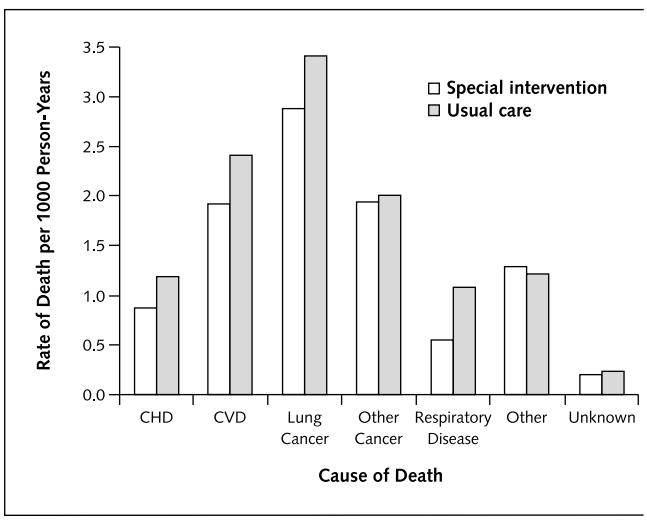
Table 2. **Causes of Death by Treatment Group***

Cause of Death	Treatment Group, *n* (%)		
	Special Intervention with Ipratropium (*n* = 1961)	Special Intervention with Placebo Inhaler (*n* = 1962)	Usual Care (*n* = 1964)
CHD	24 (10.6)	22 (9.4)	31 (11.5)
Cardiovascular disease including CHD	54 (23.9)	46 (19.6)	63 (23.3)
Lung cancer	74 (32.7)	77 (32.8)	89 (33.0)
Other cancer	50 (22.1)	52 (22.1)	52 (19.3)
Respiratory disease other than cancer	15 (6.6)	14 (6.0)	28 (10.4)
Other	26 (11.5)	42 (17.9)	32 (11.9)
Unknown	7 (3.1)	4 (1.7)	6 (2.2)
Total	226	235	270

* CHD= coronary heart disease. Numbers of deaths in each column do not sum to the totals because deaths in the CHD category are listed separately and are also included in the cardiovascular disease category.

(hazard ratio, 1.88; $P = 0.001$), but not in the middle tertile (45 to 52 years of age) or oldest tertile (53 to 60 years of age). Interaction between treatment group and age was significant ($P = 0.04$). Mortality did not differ significantly between groups by sex, and no significant interaction between treatment group and sex was observed. There was a significant mortality difference between the usual care and special intervention groups among participants smoking at least 40 cigarettes per day (hazard ratio, 1.30; $P = 0.03$), but not among those smoking 25 to 39 cigarettes per day or fewer than 25 cigarettes per day. In addition, no significant interactive effect on mortality was observed between smoking intensity and treatment group. There was a significant difference in mortality between the special intervention and usual care groups for participants in the middle tertile of baseline FEV_1 (75% to 83% predicted) (hazard ratio, 1.39; $P = 0.01$), but not in tertiles with higher or lower values of FEV_1. No significant interactive effect on mortality was observed between treatment group and FEV_1.

Figure 2. **Mortality rates at 14.5 years by cause.**



The only significant difference was in respiratory disease other than lung cancer (log-rank test). CHD = coronary heart disease; CVD = cardiovascular disease.

DISCUSSION

The striking feature of our findings is the statistically significant difference in all-cause mortality in the intention-to-treat analysis. Mortality was higher in the usual care group than in the special intervention group even though the intervention—smoking cessation—was successful in only a minority of special intervention participants. Since death rates between special intervention and usual care participants with similar smoking habits did not differ, the differences observed in the groups as a whole were almost certainly due to differential cessation rates. It must be emphasized that this finding applied to a special group of heavy smokers who had preexisting airway obstruction.

From its inception, the LHS was characterized by very high follow-up rates. Of the original cohort, only 75 participants (1.27%), all of whom were Canadian, were censored because of loss to follow-up at less than 12.5 years. Cause of death was adjudicated by a mortality and morbidity review board, which had access to data in 653 of the 731 deaths. In the remaining cases, cause of death was derived from the National Death Index. The 17 deaths due to unknown causes showed trends similar to the remainder of deaths in terms of treatment group and smoking status (**Figures 2** and **3**) and therefore were probably not a source of bias. Smoking status was ascertained at the fifth year following entry into the LHS, that is, 5 years after randomization. We have shown that smoking status established at 5 years changed relatively little in the next 6 years, especially among sustained quitters (6).

To our knowledge, no directly comparable studies have examined the long-term effects of a randomly applied smoking intervention. Many intervention trials aimed at cardiovascular disease have used smoking cessation along with other interventions. Of these, the most directly comparable to the LHS was the Multiple Risk Factor Intervention Trial (MRFIT), which was conducted in North Amer-

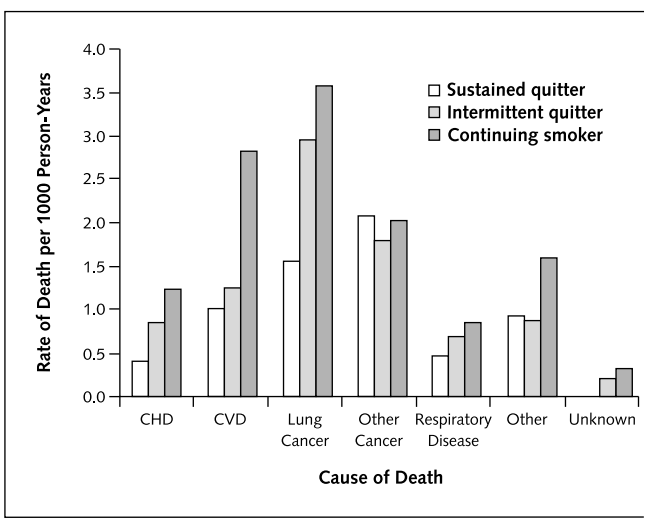
ica, enrolled participants of similar age, and had similar follow-up periods (8). At 16 years after randomization, MRFIT had slightly lower all-cause mortality than the LHS at 14.5 years (10.5% vs. 12.4%). More than 50% of MRFIT deaths were attributed to cardiovascular disease, reflecting the fact that MRFIT participants were selected for cardiovascular risk factors while the LHS attempted to avoid them. However, LHS participants had substantially higher death rates for lung cancer and respiratory disease than did MRFIT participants, reflecting their heavier tobacco use and abnormal lung function. All-cause mortality did not differ significantly between treatment groups in MRFIT at 10.5 years (9) or at 16 years, perhaps in part because smoking habits did not differ greatly between the intervention and control groups after the initial 6-year follow-up (10). Similar convergence in smoking habits was observed in long-term follow-up of 2 European cardiovascular trials (11, 12), both of which initially reported significant decreases in cardiac events in the intervention groups but did not observe significant differences in all-cause mortality at 8.5 and 10 years, respectively. All-cause mortality probably differed between the special intervention and usual care groups in our study because smoking cessation has a powerful effect on mortality in heavy smokers with airway obstruction and because more than 90% of LHS participants who quit smoking during the first 5 years of the study were able to maintain cessation thereafter (6, 13).

We did not measure the cost of the LHS smoking cessation program, and researchers who worked with the intervention group had other roles in the study, such as obtaining follow-up data. However, a unit price of $2000 would probably cover the LHS smoking intervention, including intensive initial counseling, nicotine replacement therapy, and the long-term maintenance program. This seems a modest price for a life-saving intervention. An inexpensive intervention with a relatively low success rate can make an important difference if it has great potential and is applied early in the course of the diseases of interest. Indeed, the most prominent difference between the special intervention and usual care groups was observed in the youngest participants. It could be argued, therefore, that smoking cessation was most effective in preventing truly premature death.

Table 3. **Hazard Ratios for Death for Usual Care Compared with the Special Intervention, by Subgroup**

Subgroup	Hazard Ratio (95% CI)	*P* Value for Special Intervention vs. Usual Care	*P* Value for Subgroup–Treatment Interaction
Age			0.04
35–44 y	1.88 (1.28–2.77)	0.001	
45–52 y	1.07 (0.82–1.41)	>0.2	
53–60 y	1.09 (0.89–1.34)	>0.2	
Sex			>0.2
Male	1.17 (0.97–1.40)	0.10	
Female	1.19 (0.92–1.56)	0.19	
FEV_1 at baseline			0.19
<75%	1.11 (0.88–1.40)	>0.2	
75%–83%	1.39 (1.08–1.81)	0.01	
>83%	1.04 (0.76–1.40)	>0.2	
Cigarettes per day			>0.2
<25	1.14 (0.86–1.52)	0.2	
25–39	1.07 (0.82–1.40)	>0.2	
≥40	1.30 (1.03–1.65)	0.03	

Figure 3. **Mortality rates at 14.5 years by cause and smoking status.**



Rates were significantly different for coronary heart disease (*CHD*), cardiovascular disease (*CVD*), lung cancer, and other causes of death (log-rank test).

The leading causes of death in the LHS were lung cancer and coronary heart disease, and smoking cessation was of benefit in both (**Figure 3**). These results are not unprecedented. In MRFIT, smoking cessation in conjunction with other risk modification strategies was shown to decrease morbidity and mortality from coronary heart disease (14), and we observed such an effect within the first 5 years of LHS follow-up (4). These results are compatible with those of many cohort and case–control studies that have shown a decline in death from coronary heart disease within 2 years of smoking cessation (15). In MRFIT, risk for myocardial infarction in participants who still smoked was roughly 3 times that in participants who had stopped smoking more than 5 years previously (15); this finding was similar to our data on death from coronary heart disease (**Figure 3**).

The mechanisms by which smoking induces coronary events are apparently reversible to some extent in the short term. To our knowledge, our data are the first to show an effect of smoking cessation on the rate of death from lung cancer in the context of a clinical trial. Our data are consistent with those of previous cohort and case–control stud-

ies showing that measurable effects of cessation on lung cancer are usually not evident in the first 5 years and that lung cancer risk is probably still elevated 15 years after smoking cessation (16). In our study, death from lung cancer was roughly 2.2 times more common in current smokers than in sustained quitters (**Figure 3**), a finding similar to data from cohorts observed for similar lengths of time (16). Smoking is thought to cause potentially irreversible genetic changes in epithelial cells. Therefore, the effects of cessation are probably due to the absence of further insult rather than to reversal of existing disease.

To some extent, the LHS was a study about the FEV_1, and our results again demonstrate the prognostic value of this test. It is obvious and axiomatic that death from lung disease other than cancer should be related to FEV_1. However, it is not yet clear why FEV_1, independent of smoking habits, predicts death from cardiovascular disease (17) and lung cancer (18, 19). The mechanisms involved are likely to be different because FEV_1 predicts coronary artery disease in both smokers and nonsmokers (20) but apparently predicts lung cancer only in smokers and former smokers (21). Of interest, our data showed that death from other types of cancer was related to FEV_1 but not to smoking habits. These results differ from those of the larger Renfrew and Paisley population study (22), which found that death due to nonrespiratory cancer was not related to FEV_1 after smoking had been considered. In addition, good data link smoking to many types of nonpulmonary cancer.

The LHS was one of the few studies that examined a substantial cohort of smoking women (**Table 1**). Of interest, lung cancer mortality was very similar between sexes: 3.02 per 1000 person-years in men and 3.14 per 1000 person-years in women. This is in agreement with most of the other studies that have examined this issue (22, 23) but is at variance with a case–control study suggesting that women are more likely to develop lung cancer than men given the same smoking exposure (24). In the LHS, female continuing smokers smoked an average of approximately 3 fewer cigarettes per day than did male continuing smokers (5). However, it is difficult to argue that our results support the hypothesis that women are more sensitive to cigarette smoke than men.

In summary, we demonstrated that an intensive smoking cessation program followed by 5 years of reinforcement leads to a substantial and significant reduction in all-cause mortality in people with mild to moderate airway obstruction.

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Appendix

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