Heavy Habitual Marijuana Smoking Does Not Cause an Accelerated Decline in FEV_1 With Age

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To assess the possible role of daily smoking of marijuana in the development of chronic obstructive pulmonary disease (COPD), we evaluated the effect of habitual use of marijuana with or without tobacco on the age-related change in lung function (measured as FEV_1) in comparison with the effect of nonsmoking and regular tobacco smoking. A convenience sample of 394 healthy young Caucasian adults (68% men; age: 33 ± 6 yr; mean ± SD) including, at study entry, 131 heavy, habitual smokers of marijuana alone, 112 smokers of marijuana plus tobacco, 65 regular smokers of tobacco alone, and 86 nonsmokers of either substance were recruited from the greater Los Angeles community. FEV_1 was measured in all 394 participants at study entry and in 255 subjects (65 %) on up to six additional occasions at intervals of ⩾ 1 yr (1.7 ± 1.1 yr) over a period of 8 yr. Random-effects models were used to estimate mean rates of decline in FEV_1 and to compare these rates between smoking groups. Although men showed a significant effect of tobacco on FEV_1 decline ($p < 0.05$), in neither men nor women was marijuana smoking associated with greater declines in FEV_1 than was nonsmoking, nor was an additive effect of marijuana and tobacco noted, or a significant relationship found between the number of marijuana cigarettes smoked per day and the rate of decline in FEV_1. We conclude that regular tobacco, but not marijuana, smoking is associated with greater annual rates of decline in lung function than is nonsmoking. These findings do not support an association between regular marijuana smoking and chronic COPD but do not exclude the possibility of other adverse respiratory effects. **Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV_1 with age.** AM J RESPIR CRIT CARE MED 1997;155:141–148.

Marijuana remains the most commonly smoked illicit substance in American society (1, 2). After more than a decade of declining prevalence of marijuana use in the United States, an upswing in its use has recently been demonstrated, especially among young individuals (1, 2). Because the constituents of marijuana smoke are similar in many respects to those of tobacco (3, 4), it is possible that habitual smoking of marijuana may lead to some of the same respiratory effects that derive from regular tobacco use. This possibility is supported by several animal and cellular studies, which have shown that chronic exposure to marijuana smoke can injure respiratory tissue (5–9). Although earlier studies in humans yielded conflicting data about the association between heavy marijuana smoking and clinical evidence of respiratory illness (10–14), more recent clinical studies have demonstrated a relationship between habitual marijuana use and symptoms of chronic bronchitis (15, 16). Moreover, histopathologic studies have revealed epithelial alterations in biopsies from proximal bronchi of marijuana smokers (goblet-cell metaplasia, reserve-cell hyperplasia, squamous metaplasia) (17, 18) that are consistent with symptoms of mucus hypersecretion.

In contrast to the concordance of findings in recent studies with respect to the impact of regular marijuana smoking on chronic respiratory symptoms, cross-sectional studies of marijuana users in Los Angeles (15) and of smokers of nontobacco (presumably and hereafter referred to as marijuana) in Tucson (16) have revealed conflicting effects on lung function. The Los Angeles study (15) failed to demonstrate any relationship between marijuana use and impairment in tests of lung function, including sensitive indices of small airways dysfunction, whereas the Tucson study (16) demonstrated obstructive ventilatory defects additive to those attributable to regular tobacco use. Recent analysis of longitudinal data from the Tucson study (19) estimated significant decrements in FEV_1 in continuing male (but not female) marijuana smokers ⩾ 1 yr after marijuana smoking was first reported. Moreover, these decrements were twice as large as the estimated decrements in continuing tobacco smokers, and the effects of both habits were additive. The latter data suggest that marijuana smoking might be a significant risk factor for progressive airflow obstruction.

To further evaluate the possibility that continuing marijuana smoking might lead to progressive declines in lung function not consistently apparent in cross-sectional studies, we invited nonsmokers and smokers of marijuana and/or tobacco who were participants in a cohort study of the pulmonary effects of habitual

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marijuana use (15) to undergo repeat lung function testing on up to six additional occasions at intervals of at least 1 yr. The present report presents the results of the analysis of this longitudinal study of lung function.

METHODS

The initial sample consisted of healthy volunteers 25 to 49 yr of age, including 144 heavy, habitual smokers of marijuana alone (MS), 135 regular smokers of both marijuana and tobacco (MTS), 70 smokers of tobacco only (TS), and 97 nonsmokers (NS) of any substance (15). Subjects were initially recruited from the general Los Angeles area through newspaper and radio announcements from 1983 through 1985. Criteria for study entry have been previously reported (15). Specifically excluded were persons who reported current or previous intravenous drug use or smoking of other illicit substances (e.g., crack cocaine, phencyclidine, methamphetamine, heroin, and opium) more than 12 times in their lives or within the previous 6 mo. Persons with significant occupational exposures to substances potentially hazardous to respiratory health, or with a history of chronic respiratory illness, were also excluded.

Eligible subjects completed a detailed respiratory and drug use questionnaire adapted from the American Thoracic Society/National Heart, Lung and Blood Institute (ATS/NHLBI) questionnaire (20) and the National Institute on Drug Abuse (NIDA) nationwide survey on drug abuse (21). An extensive battery of pulmonary function tests was also performed. Details of the testing procedures, methods of calculation, and comparison with expected reference values used in the study have been described previously (15). A subset of these participants (36 MS, 42 MTS, 26 TS, and 40 NS) also underwent fiberoptic bronchoscopy, bronchoalveolar lavage (BAL), and bronchial mucosal biopsies at variable times following pulmonary function testing. Results of the bronchoscopic studies have been reported previously (17, 18, 22, 23).

Since 1985, extensive efforts have been made to recontact at least annually, by mail and telephone, all 446 participants who had undergone initial testing in 1983 through 1985. Mail was sent under a U.S. Postal Service arrangement that provided the sender with identification of the address to which the mail was delivered. Participants who were lost to follow-up (e.g., undelivered mail with no forwarding address) were traced through work telephone numbers, contacts with individuals identified by the subject as likely to know his or her whereabouts, State department of motor vehicle rosters, voter registration files, the U.S. Social Security forwarding system, and commercial credit searches. A field visit to the last known residence of a participant was utilized if necessary. The National Death Index (NDI) was used to identify deaths in the study group. NDI searches were run each year for individuals not known to be alive at the end of that year. For deaths of study subjects identified by the NDI, death certificates and hospital and pathology records were requested to determine the cause of death.

Recontacted participants were invited to undergo subsequent rounds of examinations at periods of $\geq$ 1 yr, including an interval respiratory and drug use interview and at least forced expiratory spirometry. Two experienced technicians who were cross-trained in the study procedures performed the initial and follow-up pulmonary function tests. The same pulmonary function equipment and testing procedures were used throughout the study (15). Questionnaires were administered by trained interviewers.

Data Analysis

For FEV_1, random-effects modeling was used to estimate the rate of decline in lung function with age in relation to smoking status for marijuana or tobacco at any point in time, with smoking status as a time-dependent covariable (24, 25). Other potential covariables were height (constant) and intensity of use of marijuana (joints/day) and tobacco (cigarettes/day), the tobacco–marijuana interaction, and former smoking of each substance, which were all assessed at each survey (time-dependent). The model also included data from subjects with only one measurement. These single observations contribute to the estimate of the intercept but do not affect the slope estimate. The advantage of this model is that it allows for one or more changes in smoking status over time. Analyses were performed for men and women separately.

We also fitted a second random-effects model in which tobacco and marijuana status were constant covariables, rather than time-dependent. For this analysis, each subject was classified as a never or continuing smoker of each substance separately, based on whether the subject was either a nonsmoker or a smoker of that substance at each and every time, respectively. Otherwise, subjects were classified as intermittent smokers for that substance.

RESULTS

Of the 446 eligible subjects initially enrolled in the study, 394 underwent measurements of lung function. Demographic characteristics, smoking status, and FEV_1 of the 394 study participants with evaluable lung function are shown in Table 1 by smoking category at the time of study entry (Visit 1). The tobacco-only smokers were slightly older than subjects in the other smoking categories ($p < 0.05$). The marijuana smokers were heavy daily smokers (mean of more than 3.5 joints/d), whereas the tobacco smokers smoked an average of nearly 1 to 1.5 packs of cigarettes per day. The combined smokers of marijuana plus tobacco smoked less tobacco than did the tobacco-only smokers ($p < 0.03$), whereas the current intensity and lifetime amount of marijuana smoking was not significantly different between the dual and marijuana-only smokers. The mean age and tobacco consumption of the female subjects in each smoking category were similar to those of the male subjects in the same category. Baseline % predicted FEV_1 did not differ across smoking categories.

Table 2 shows the number of longitudinal assessments by gender. The mean interval between consecutive visits was 1.7 $\pm$ 1.1 (SD) yr, with minimum and maximum intervals of approximately 1 and 8 yr, respectively. The mean interval between the first and last visit for each subject was 4.9 $\pm$ 2.0 yr. Nearly two-thirds of the cohort (255/394) were tested on two or more occasions. Nearly all of those not retested had moved out of the area or were otherwise lost to follow-up. The proportion of male and female subjects who underwent more than one set of lung function tests was similar, and the proportion of subjects who were tested more than once (MS 66.7%; MTS 56.3%; TS 64.6%; NS 73.3%) did not differ significantly from those who did not undergo follow-up testing by baseline smoking category ($p > 0.09$; chi-square analysis). Moreover, within each smoking category, no significant differences were found in the age, baseline smoking characteristics, or baseline FEV_1 of the subjects who were studied only once and those with multiple tests, except that MTS in the follow-up group were slightly lighter tobacco smokers (16.0 cigarettes/d) than MTS who were studied only once (21.7 cigarettes/d) ($p < 0.05$).

Fourteen participants were known to have died during the follow-up period, including 8 MTS, 2 MS, 3 TS, and 1 NS. Known causes of death included acquired immune deficiency syndrome (AIDS) (1 MS, 1 MTS, and 2 TS); violence (3 MTS); suicide (1 MTS); drug overdose (1 MTS); breast cancer (1 MTS and 1 NS); and asphyxiation from aspirated food (1 TS).

The number of subjects in each smoking category who remained "continuing smokers" of each substance or temporarily quit (or started) smoking a particular substance during the follow-up period ("intermittent smokers") is shown in Table 3. More than 80% of smokers of marijuana with or without tobacco continued to smoke marijuana throughout the follow-up period, and approximately 90% of tobacco-only smokers continued to smoke, whereas 75% of dual smokers of tobacco and marijuana continued to smoke tobacco. Relatively few subjects in any smoking category began smoking either tobacco or marijuana during follow-up. Although most smokers of marijuana initially (58% of MS and 67% of MTS), including those who quit smoking

TABLE 1

DEMOGRAPHIC AND SMOKING CHARACTERISTICS OF SUBJECTS AT VISIT 1

Subjects	N (M/F)	Mean Age (yr)	Tobacco (cigarettes/d)	Tobacco (pack-yr)	Marijuana (joints/d)	Marijuana (joint-yr)	FEV_1 (% pred)
MS	101/30	31.8 ± 0.5*	0.0 ± 0.0	3.4 ± 0.8	4.1 ± 0.6	56.2 ± 11.9	108 ± 1.4
MTS	81/31	33.8 ± 0.6	18.4 ± 1.3†	16.0 ± 1.3†	3.6 ± 0.5	45.1 ± 3.9	108 ± 1.1
TS	33/32	36.7 ± 0.9‡	27.5 ± 1.7	21.0 ± 1.9	0.0 ± 0.0	0.0 ± 0.0	106 ± 1.9
NS	53/33	32.0 ± 0.6	0.1 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	109 ± 1.4

Definition of abbreviations: M = male; F = female; MS = marijuana smokers; MTS = marijuana plus tobacco smokers; TS = tobacco smokers; NS = nonsmokers; joints/d = number of joints (or joint-equivalents) per day; joint-yr = number of joints (or joint-equivalents) per day × number of years smoked.

* SEM.

† Significantly lower than TS ($p < 0.05$).

‡ Significantly higher than other smoking categories ($p < 0.05$).

marijuana, reduced their daily amount of marijuana use, others (31% of MS and 26% of MTS) increased their use; the resultant average reduction in use was relatively small (0.7 and 1 joint among MS and MTS, respectively). Among initial tobacco smokers, including those who subsequently quit smoking tobacco, 49% of TS and 36% of MTS reduced their daily number of cigarettes, whereas 19% of TS and 34% of MTS increased their daily use of tobacco; the mean changes in TS and MTS were reductions of 4.8 and 0.8 cigarettes/d, respectively.

Figure 1 shows the estimated decline in FEV_1 with age by smoking status derived from the random-effects model for men (Figure 1A) and women (Figure 1B), with smoking status for tobacco and marijuana, and the tobacco–marijuana interaction entered as a time-dependent covariable. In men, tobacco smoking, but not marijuana smoking, was associated with a significantly steeper decline in FEV_1 compared with nonsmoking, indicating an accelerated decline in lung function with increasing age for tobacco smoking but not for marijuana smoking compared with nonsmoking. Similar findings were observed in women, although the slope difference for tobacco did not achieve statistical significance. A negative interaction was found between marijuana and tobacco smoking in men but not in women (Figure 1A; Table 4).

When the intensity of marijuana smoking on FEV_1 decline with age was examined in men, no differences were noted between even quite heavy marijuana smoking (i.e., 3 joints/d) and nonsmoking of marijuana (Figure 2A). Similar findings were noted in women. In contrast, the amount of tobacco smoked was significantly correlated with decline in FEV_1 with age (Figure 2B), although a dose-response relationship for tobacco was not demonstrated in women.

Figure 3 shows the effect of the continuity of marijuana smoking among men who were nonsmokers of tobacco (Figure 3A) or continuing tobacco smokers (Figure 3B), with marijuana smoking status (never, continuing, intermittent) as a constant covariable. Neither the continuing nor the intermittent marijuana smokers exhibited any significantly different rates of decline in FEV_1 as compared with never smokers of marijuana. This lack of a marijuana effect was independent of the effect of tobacco, as indicated by the similarity of the findings for the different categories of marijuana smokers (never, continuing, intermittent) when the analyses were confined to either never tobacco smokers (Figure 3A) or continuing tobacco smokers (Figure 3B). Similar observations were noted in women. The slopes for all categories of marijuana smokers are steeper among the continuing tobacco smokers than among the never tobacco smokers, as a consequence of the effect of tobacco (not marijuana) on the rate of decline in FEV_1.

In contrast to marijuana, the continuity of tobacco smoking did affect the rate of decline in lung function, with a consistent gradient of increasing decline from never through intermittent to continuing tobacco smoking, as shown for men in Figure 4.

Table 4 shows the results of random-effects models, which are plotted in Figures 1 through 4; *t* tests were used to determine whether the slope coefficients differed from zero. The listed coefficients represent the decline in FEV_1 with age for each of the reference groups, and for the nonreference groups they represent the rate of decline relative to each reference group. For example, the results for Figure 1A indicate that the reference group (nonsmokers) had a 25.3 ml/yr rate of decline, whereas marijuana smokers had a 30.8 ml/yr rate of decline, or a difference of 5.5 ml/yr (as shown in Table 4) from the reference group. MTS had a decline 10.5 ml/yr greater than did NS, which is the sum of the marijuana and tobacco terms and their interaction (which is zero for all groups except MTS). Slight differences from the figures are due to round-off error. According to the model for Figure 2A, FEV_1 in marijuana smokers declined only 0.036 ml/yr faster than in nonsmokers of marijuana for each joint per day regularly smoked. In Figure 3A (never smokers of tobacco only), FEV_1 in intermittent and continuing smokers of marijuana declined 0.97 and 1.94 ml/yr faster than in never smokers of marijuana, respectively.

TABLE 2

NUMBER OF SUBJECTS WITH ONE OR MORE VISITS

Visit No.	1	2	3	4	5	6	7	Total
Male	98	49	38	25	23	21	14	268
Female	41	24	17	16	13	9	6	126
Total	139	73	55	41	36	30	20	394

TABLE 3

CONTINUITY OF SMOKING STATUS

Initial Status	n	Number of Subjects in Each Category: Marijuana Continuing	Marijuana Intermittent	Tobacco Continuing	Tobacco Intermittent
MS	87	71	16	–	8
MTS	63	46	17	40	23
TS	42	–	1	37	5
NS	63	–	1	–	2

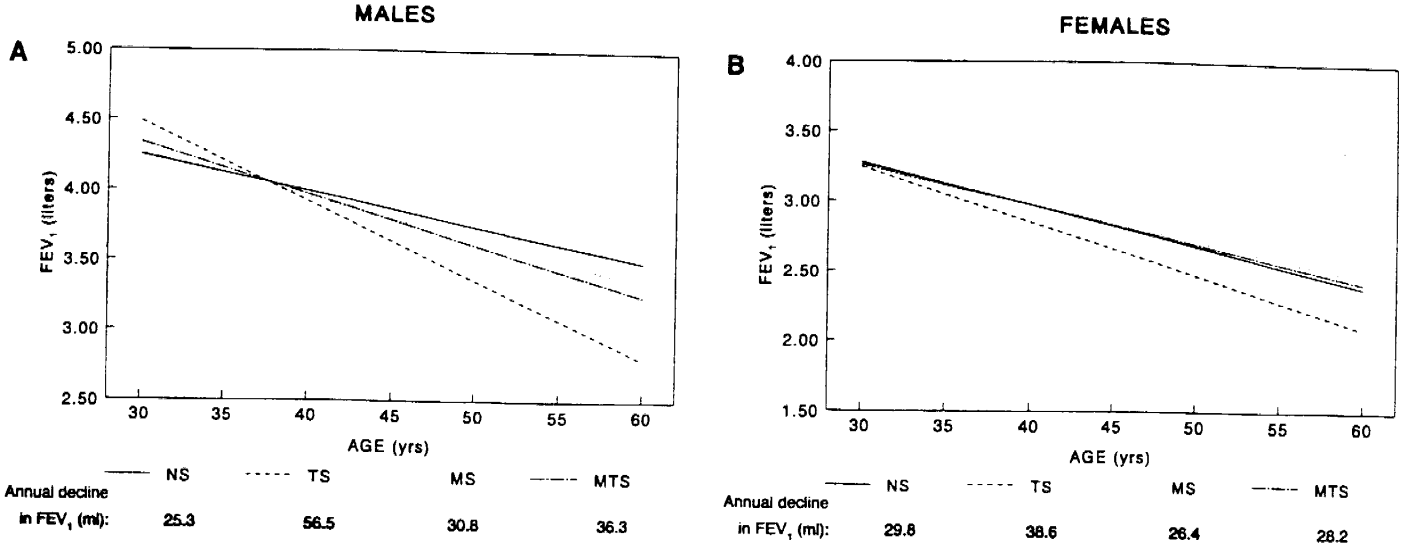

Figure 1. Declines in FEV_1 (in liters) with age (in years) by smoking status at any measurement time, estimated from linear random-effects model in men (*A*) and women (*B*). Slope coefficients for annual decline in FEV_1 (in milliliters) for each smoking status are shown at *bottom* of each panel. The model includes terms for tobacco and marijuana smoking status and tobacco–marijuana interaction.

DISCUSSION

Data from the present prospective study of 255 nonsmokers and smokers of marijuana and/or tobacco (including approximately 150 heavy habitual smokers of marijuana with or without tobacco smoking at study initiation) who were tested on 2 to 7 separate occasions over a maximum span of 8 yr extend the results of an earlier cross-sectional survey of lung function in 394 smoking and nonsmoking young adults, which failed to show any impact of heavy, habitual marijuana smoking (average of > 3 joints, or joint-equivalents, per day) on lung function. Longitudinal findings from this follow-up study fail to demonstrate that habitual daily smoking of marijuana in amounts as much as 3 joints (or joint-equivalents) per day is associated with greater age-related rates of decline in FEV_1 than is nonsmoking (Figures 1, 2A and 3). These results are in contrast to the accelerated annual rate of decline in lung function that occurs in regular tobacco smokers of comparable age (Figures 1, 2B, and 4). Moreover, no additive effects of marijuana and tobacco on the age-related decline in lung function were noted. A negative interaction between marijuana and tobacco, however, was noted (Table 4), as suggested by

TABLE 4

RANDOM EFFECTS MODELS
SLOPE COEFFICIENTS FOR VARIABLES BY AGE

Figure	Variable	Slope Coefficient (SE)†	*t*	p Value
1A	Nonsmokers*	−25.3		
	Marijuana	−5.5 (5.6)	0.98	0.33
	Tobacco	−31.0 (8.5)	3.68	0.00025
	Marijuana–tobacco interaction	−26.0 (10.0)	2.56	0.011
1B	Nonsmokers*	−29.8		
	Marijuana	3.3 (7.3)	0.46	0.65
	Tobacco	−8.8 (7.3)	1.20	0.23
	Marijuana–tobacco interaction	7.1 (9.8)	0.72	0.47
2A	Nonsmokers of marijuana*	−3.36		
	Marijuana amount	−0.036 (0.37)	0.099	0.92
2B	Nonsmokers of tobacco*	−2.85		
	Tobacco amount	−0.66 (0.19)	3.43	0.00063
3A and B	Nonsmokers*	−2.45		
	Tobacco	−13.0 (3.7)	3.50	0.00049
	Marijuana	−0.97 (3.6)	0.27	0.78
4	Nonsmokers*	−23.5		
	Tobacco	−13.0 (3.7)	3.56	0.00039

* Reference group. Slope coefficient indicates difference from reference group.
† Slope coefficients are ml per year of change in FEV_1.
All models include a term for height (not shown).
Units of current smoking amount: marijuana = number of joints (or joint-equivalents) per day, tobacco = number of cigarettes per day. Time-dependent smoking status terms for marijuana and tobacco (Figure 1A and B): 0 = not currently smoking, 1 = currently smoking. Marijuana-tobacco interaction term is 1 for MTS, 0 for all others.
Constant smoking status terms (Figures 3 and 4): 1 = never smoked, 2 = intermittent smoking, 3 = continuous smoking. See text for further explanation.

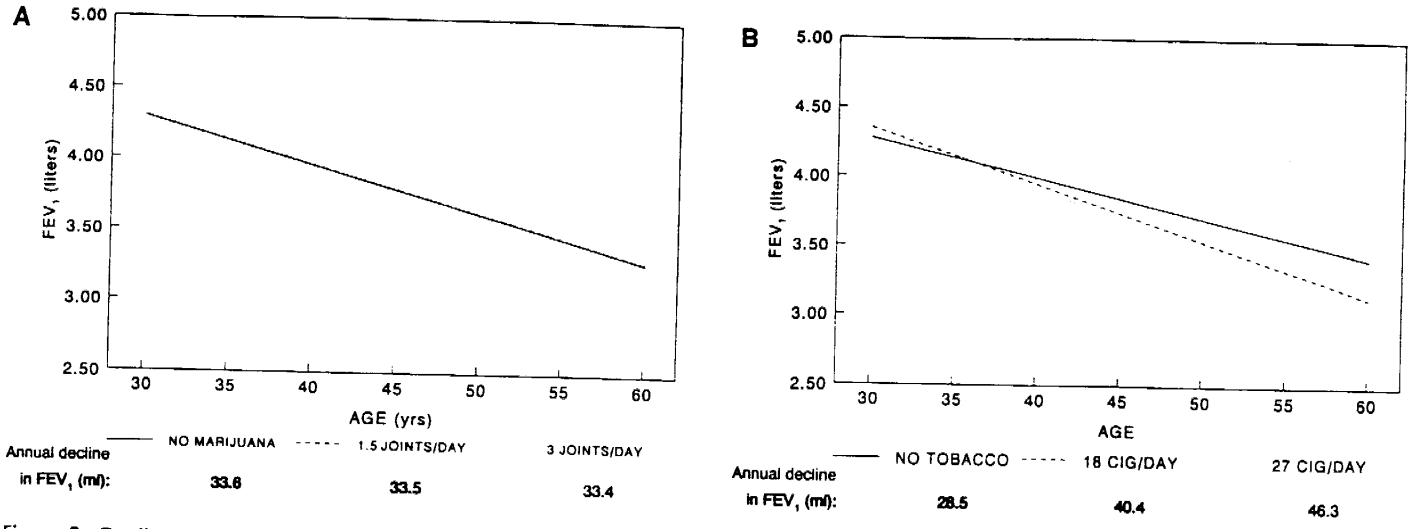

Figure 2. Declines in FEV_1 (in liters) with age (in years) by intensity of smoking marijuana (*A*) or tobacco (*B*), estimated from random-effects model in men. Slope coefficients for annual decline in FEV_1 (in milliliters) for smokers of 0, 1.5, 3.0 joints/d (*A*) or 0, 18, and 27 tobacco cigarettes/d (*B*) are shown at the *bottom* of the figure.

the similarity of the annual rate of decline in FEV_1 in the combined smokers of marijuana and tobacco and in the nonsmoking control subjects, in contrast to the accelerated rate of decline found among the tobacco-only smokers (Figure 1A). Although the dynamics of recruiting the different smoking groups were similar, we cannot exclude the possibility that the results in the dual smokers of marijuana and tobacco might have been influenced by an inadvertent sampling bias. Nonetheless, overall, the findings in the present study do not support an association between even heavy, regular marijuana smoking and the development of chronic obstructive pulmonary disease (COPD).

These findings are at variance with the results of a previous longitudinal study in which data were analyzed from a stratified random sample (n = 856) of young adult residents (age ⩽ 40 yr) of Tucson, Arizona (19). The latter sample, which included less than 100 self-reported smokers of nontobacco (marijuana) either alone or with tobacco at study entry, had lung function measured in 2 to 4 surveys conducted every 2 yr over a maximum span of 8 yr. In the latter study, the estimated annual decline in FEV_1 attributed to marijuana smoking reported at least during the initial survey was 142 ml/yr, which was equivalent to approximately 5% of the predicted FEV_1, in contrast to an expected rate of decline of approximately 1% of predicted FEV_1 in nonsmokers. In the same study, moreover, the annual decrement in FEV_1 among the marijuana smokers was twice as large as the estimated annual decline due to current tobacco cigarette smoking (68 ml), and the effects of smoking both types of substances were additive (19).

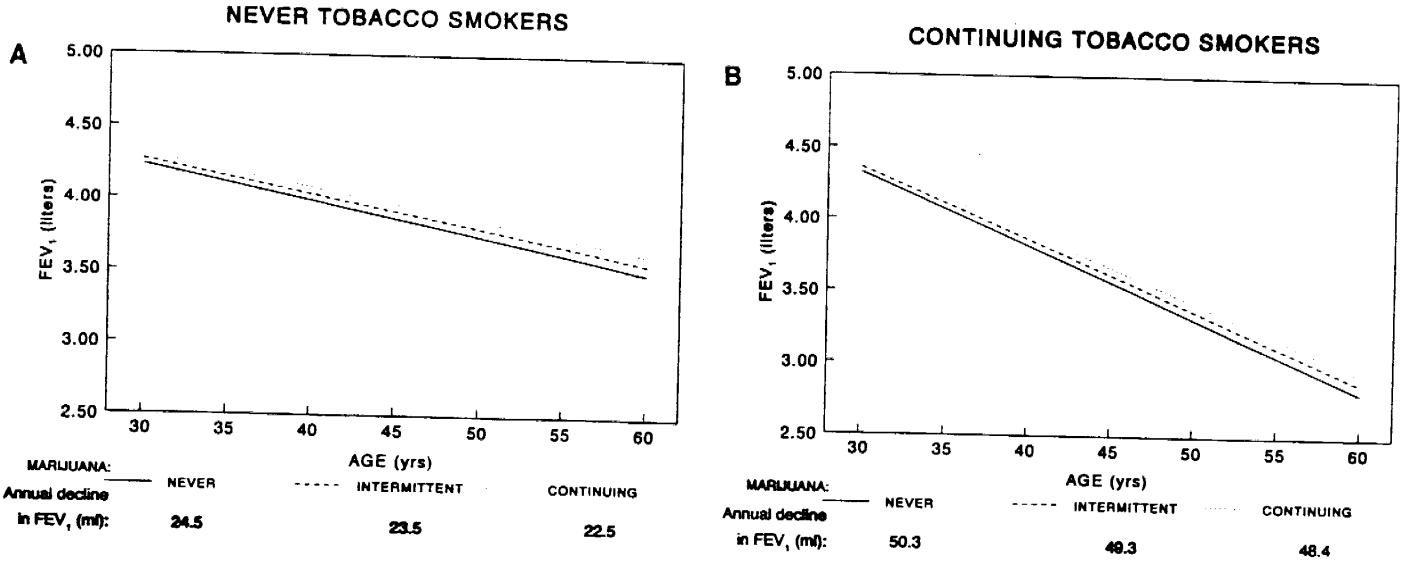

Figure 3. Declines in FEV_1 (in liters) with age (in years) by continuity of marijuana smoking (never, intermittent, and continuing), estimated from linear random-effects model among male never tobacco smokers (*A*) and continuing tobacco smokers (*B*). Slope coefficients for annual decline in FEV_1 (in milliliters) in never, intermittent, and continuing marijuana smokers are shown at *bottom* of each panel.

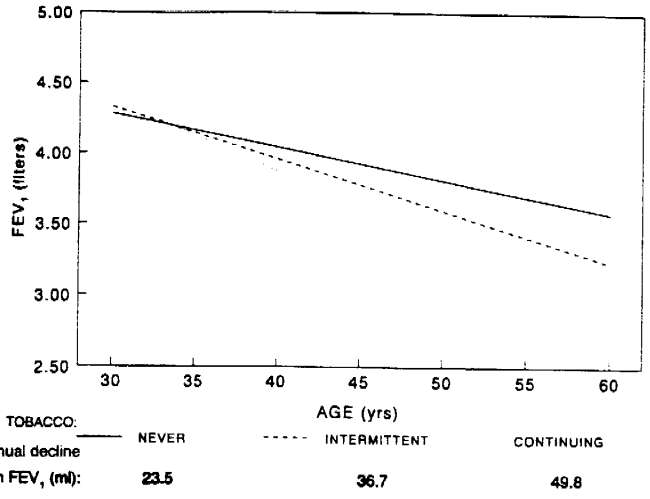

Figure 4. Declines in FEV_1 (in liters) with age (in years) by continuity of tobacco smoking (never, intermittent, and continuing), estimated from random effects model in men. Slope coefficients for annual decline in FEV_1 (in milliliters) for never, intermittent, and continuing tobacco smokers are shown at the *bottom* of the figure.

The reason for the discrepancy between the results of these two longitudinal studies is unclear. One possible reason might be due to population sampling differences, since the randomly selected Tucson sample was more likely to be representative of the marijuana smoking population as a whole than was the Los Angeles convenience sample, which may have selectively underrecruited "sicker" smokers. Other possible reasons for these discrepant results include differences in environmental or occupational exposures, concomitant substance abuse (aside from tobacco, such as crack cocaine, phencyclidine, or heroin), intensity and continuity of marijuana smoking, and other host characteristics, such as allergy and concomitant illness. With regard to possible confounding by differences in intensity and/or continuity of marijuana use, it is noteworthy that the marijuana smokers in the present study were particularly heavy current users (mean of over 3 joints/d) and reported heavy lifetime use (mean of 45 to 56 joint-yr, defined as the number of joints per day times the number of years smoked), and most (82% of MTS and 73% of MS) continued to smoke marijuana during the entire follow-up period. In contrast, the marijuana smokers in the Tucson cohort were much lighter smokers (< 1 joint/d, on average), and reported a much lower lifetime intensity of use (mean of 8.3 marijuana joint-yr, when calculated as the number of joints per day times the number of years smoked) (19). Although the authors do not specify the continuity of marijuana use in their cohort of ever marijuana users, continuing or quitting marijuana smoking did not influence the decrements in lung function estimated from their model. Thus, differences in current and lifetime amount of marijuana use, or in continuity of use during the course of follow-up, do not appear to account for the discrepant results of the two studies, since one would not expect the more intense and prolonged use among the Los Angeles marijuana smokers to have resulted in the much lower rate of decline in FEV_1 relative to nonsmoking (and even tobacco smoking) than that which was observed in the Tucson study.

Specifically excluded from the present study were individuals with preexisting chronic chest disease, including asthma or a history of intravenous drug abuse or of smoking substances other than tobacco and/or marijuana. Moreover, only a small minority of the follow-up sample from this cohort (12.6%) initiated crack cocaine smoking during the follow-up period, and none initiated intravenous drug abuse. Asthma or other chest illness was not listed as an exclusionary criterion for participation in the Tucson study (16, 19). It is unlikely, however, that the presence of these illnesses would have accounted for the differentially greater rate of loss of lung function in the marijuana smokers compared with the nonsmoking or tobacco smoking participants in the Tucson study (19). Although a higher rate of initiation of smoking of other illicit substances (e.g., crack cocaine, which would be included as a nontobacco substance) by the nontobacco smokers in the Tucson follow-up sample might have contributed to the observed excessive rates of decline among these smokers, it is of interest that habitual crack smoking has generally not been associated with impairment in spirometric indices, at least in cross-sectional studies (26, 27).

Although a "healthy smoker" effect might have accounted for the absence of an abnormally rapid decline in lung function in the marijuana smoking volunteers for the Los Angeles study, this possibility seems unlikely, since tobacco-smoking participants in the same study did exhibit accelerated declines in FEV_1, and one would not expect that a "healthy smoker" effect would be confined only to the marijuana smokers. Additional evidence against a "healthy smoker" effect in the Los Angeles marijuana smokers is their relatively high prevalence of symptoms of chronic and acute bronchitis at Visit 1, which was comparable with the prevalence of these same symptoms in the tobacco smokers in the same study (15), as well as in the nontobacco (marijuana) smokers in the Tucson study (16).

A weakness of the present study is the relatively low follow-up rate (65%), raising the possibility of a differential loss to follow-up of the sicker participants, who might have exhibited greater rates of decline in lung function over time. Although the latter possibility cannot be excluded, the fact that nearly all participants who could be contacted and did not move out of the area returned for retesting, that follow-up rates were comparable across smoking categories, and that baseline lung function was similar in those who did and those who did not undergo follow-up testing diminishes the likelihood of this explanation for the lack of a demonstrable impact of continuing marijuana smoking on lung-function decline, particularly since an accelerated decline in FEV_1 was detected in the tobacco-smoking participants.

Other potential confounding influences that might have affected the results of this longitudinal study of lung function change include systematic differences in technician or equipment performance. However, the same equipment was used throughout the entire study, and all tests were performed by two highly experienced technicians who adhered to a rigorous daily calibration and quality control protocol (28), and were cross-trained in spirometry using the same instrument. Moreover, any instrument drift or intertechnician variability in test performance would not be expected to differentially influence the results only in the marijuana smokers, since subjects in all smoking categories were tested at similar times throughout the follow-up period.

Our failure to find evidence of progressive lung dysfunction in the continuing marijuana smokers who we followed contrasts with our own observations that the proportion of these smokers who reported symptoms of chronic bronchitis was comparable with that of the tobacco smokers in the same cohort (15), and that many of the continuing marijuana smokers have shown as extensive histopathologic alterations on bronchial mucosal biopsies as the tobacco-only smokers (17, 18). However, these similarities between the effects of habitual smoking of marijuana and tobacco on chronic respiratory symptoms and proximal bronchial histopathology do not necessarily imply similar consequences with respect to bronchiolar and alveolar injury that might lead to smoking-related obstructive small airways disease

and/or emphysema. Although symptoms of chronic bronchitis are believed to be related histopathologically to hypertrophy of submucosal bronchial mucous glands, alterations in ciliated bronchial epithelial cells, and hyperplasia of mucus-secreting goblet cells (29), these symptoms of mucus hypersecretion are not thought to be necessarily linked to the progressive damage to and narrowing of peripheral airways that accompany the evolution of smoking-related chronic obstructive airways disease (30).

It is possible that the contrasting effects of marijuana and tobacco smoking in the present study on progressive changes in lung function might be due to the marked disparity in the quantity of the two substances that were smoked: an average of 4.1 joints/d in the marijuana-only smokers versus 27.5 cigarettes/d in the tobacco-only smokers. Although the precise amount of marijuana smoked cannot be accurately determined because of the uncertain reliability of self-reported usage and the common practice of sharing joints, it is highly likely that the amount of actual usage of marijuana was far less than that of tobacco. On the other hand, differences in filtration of smoke through the more densely packed tobacco cigarettes (in which cellulose filters were generally incorporated) and the more loosely packed, filterless marijuana joints, which are usually smoked to a smaller butt length, approximately double the tar yield of the marijuana joint (18). Moreover, differences in smoking topography (larger cumulative puff volumes and inhaled volumes of marijuana smoke and a $\geq$ fourfold longer smoke retention time for marijuana than for tobacco), added to the differences in smoke filtration, may result in a fourfold greater retention of tar in the lungs of marijuana smokers compared with smokers of a comparable quantity of whole tobacco (31). This amplification of the exposure of the lungs to the smoke of marijuana narrows the gap between a $\geq$ sixfold greater quantity of reported usage of tobacco to perhaps an only approximately twofold greater exposure of the lungs to the smoke from tobacco compared with marijuana. Thus, quantitative differences alone may not entirely explain the disparity in longitudinal rates of decline in lung function between the two types of smokers. Evidence that qualitative differences between the two types of smoke may be more important than quantitative differences with respect to the development of COPD derives from animal studies in which morphologic and physiologic evidence of emphysema was found in rats exposed for 6 mo to tobacco smoke, but not in rats exposed for the same period to smoke from a comparable quantity of marijuana (32).

Peripheral deposition of inhaled particles in the lung depends largely on particle size. If particulates in marijuana smoke were substantially larger than those in tobacco smoke, it could be argued that these particulates do not reach the small airways and alveoli as efficiently as the submicronic particles in tobacco smoke, and are therefore less likely to cause tissue injury at those sites primarily affected in COPD. On the other hand, aerodynamic measurements of particles in marijuana and tobacco smoke, made with laser Doppler velocimetry techniques, have confirmed that the mass median aerodynamic diameter of the particles from the two types of smoke are comparable (approximately 0.5 μm) (33), thus refuting this argument.

The results of the present 8-yr study also contrast with findings from a short-term prospective study (34) that demonstrated an accelerated decline in FEV_1 (approximately 3% of baseline) in 28 healthy male marijuana smokers over only 8 to 9 wk of much heavier than usual exposure (mean of 5 joints/d, compared with their customary use of an average of 1 joint/d). One month after cessation of this unusually heavy use, the latter subjects exhibited a return of their FEV_1 to baseline. Although it is difficult to explain the discrepancy between these two prospective studies, it is possible that the participants in the short-term study (34) experienced a temporarily steep step-decline in their lung function, after daily exposure of their airways to much more marijuana smoke than they were accustomed to, which would not have progressed at the same rate with much more prolonged exposure in the face of emerging adaptive mechanisms.

In conclusion, findings from the present long-term, follow-up study of heavy, habitual marijuana smokers argue against the concept that continuing heavy use of marijuana is a significant risk factor for the development of COPD. These negative findings, however, do not imply that regular marijuana smoking is free of harmful pulmonary effects. Habitual marijuana smoking is associated with a higher than expected prevalence of symptoms of chronic bronchitis (15, 16), as well as a higher incidence of acute bronchitis (15). Moreover, other evidence suggests that marijuana may be an important risk factor for the development of respiratory infection (9, 35), and possibly respiratory malignancy (36). Further studies are required to document the real respiratory risks of this commonly smoked substance.

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