

ABSTRACT

Objectives. The purpose of this study was to examine the relationship of marijuana use to mortality.

Methods. The study population comprised 65 171 Kaiser Permanente Medical Care Program enrollees, aged 15 through 49 years, who completed questionnaires about smoking habits, including marijuana use, between 1979 and 1985. Mortality follow-up was conducted through 1991.

Results. Compared with nonuse or experimentation (lifetime use six or fewer times), current marijuana use was not associated with a significantly increased risk of non-acquired immunodeficiency syndrome (AIDS) mortality in men (relative risk [RR] = 1.12, 95% confidence interval [CI] = 0.89, 1.39) or of total mortality in women (RR = 1.09, 95% CI = 0.80, 1.48). Current marijuana use was associated with increased risk of AIDS mortality in men (RR = 1.90, 95% CI = 1.33, 2.73), an association that probably was not causal but most likely represented uncontrolled confounding by male homosexual behavior. This interpretation was supported by the lack of association of marijuana use with AIDS mortality in men from a Kaiser Permanente AIDS database. Relative risks for ever use of marijuana were similar.

Conclusions. Marijuana use in a prepaid health care-based study cohort had little effect on non-AIDS mortality in men and on total mortality in women. (*Am J Public Health*. 1997;87:585-590)

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Introduction

Marijuana is the most commonly used illegal drug in the United States. Over 65 million Americans (31% of the US population aged 12 and older) are estimated to have used marijuana¹; its mean retail sales value in the United States is approximately \$10 billion.² Despite its longstanding popularity and increasing use among youth in recent years,^{1,3} we still know little about long-term health risks associated with marijuana use. Harvard policy analyst Mark Kleiman recently concluded that "aside from the almost self-evident proposition that smoking anything is probably bad for the lungs, the quarter century since large numbers of Americans began to use marijuana has produced remarkably little laboratory or epidemiological evidence of serious health damage done by the drug."^{4(p253)} Similar appraisals of the health effects of cannabis were offered in the two most comprehensive reviews from the 1980s.^{5,6} More currently, Hall and coauthors concluded that while there are no well-established health or psychological effects of chronic cannabis use, the following were considered to be probable major adverse effects: respiratory diseases associated with smoking as the method of administration, including chronic bronchitis and premalignant histopathological changes in the lung; development of a cannabis dependence syndrome; and subtle forms of cognitive impairment.^{7(p16)}

The only other large-scale study of marijuana use and mortality was performed in a cohort of 45 540 male Swedish conscripts, aged 18 through 20 years at baseline and followed for 15 years.⁸ In this study, the relative risk (RR) for mortality associated with marijuana use (more than 50 times) was 1.2 (95%

confidence interval [CI] = 0.8, 1.9) after adjustment for social background.

We report here the findings of a study of the relationship of marijuana use to mortality in a cohort of over 65 000 members of a large prepaid health plan. Data on marijuana use in this cohort were collected before the "war on drugs" escalated in the latter half of the 1980s, which may have resulted in underreporting of illegal drug use.⁹ Mortality is one of several health outcomes being studied; other endpoints include cancer incidence and outpatient utilization for respiratory illnesses and injuries. We hypothesized that marijuana use would be associated with increased risk of respiratory disease and injury.

Methods

Study Population

A cohort of 65 171 men and women aged 15 through 49 years (mean age, 33 years) completed detailed self-administered research questionnaires on tobacco, marijuana, and alcohol use from mid-1979 through 1985. The subjects were undergoing multiphasic health checkups in the San Francisco (until 1980) and Oakland Kaiser Permanente facilities. Mortality was followed through December 31, 1991, for a mean length of 10.0 years.

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TABLE 1—Sociodemographic Characteristics of a Cohort of Kaiser Permanente Medical Care Program Members (n = 65 171), by Sex and Marijuana Use Status: Oakland and San Francisco, June 1979 through December 1985

	No.	Marijuana Use, %			
		Never	Experimental	Former	Current
Men					
		(n = 9103)	(n = 5304)	(n = 6114)	(n = 7560)
Age at entry, y					
15-19	968	32.1	17.5	17.1	33.4
20-29	7 802	21.6	16.3	25.2	36.9
30-39	11 619	27.9	18.6	25.1	28.4
40-49	7 692	50.3	22.1	13.8	13.7
Race					
White	16 175	26.4	19.1	24.7	29.8
Black	6 622	30.4	19.0	19.9	30.8
Asian	3 075	65.3	16.7	11.4	6.6
Hispanic	1 353	37.3	21.3	19.2	22.2
Other/unknown	856	36.6	18.6	21.3	23.6
Education					
High school or less	4 788	35.7	18.1	18.1	28.2
Technical or business school	1 113	37.9	18.9	18.2	25.1
Some college	8 406	28.8	18.6	22.2	30.4
College graduate	6 424	34.8	18.3	21.9	25.0
Postgraduate	6 793	31.5	20.3	23.9	24.3
Unknown	557	31.4	19.4	26.6	22.6
Marital status					
Never married	9 159	22.0	16.7	24.3	37.1
Married	12 949	43.9	19.6	18.7	17.9
Remarried	1 777	27.2	24.0	24.3	24.5
Separated	951	21.0	18.2	22.7	38.1
Divorced	2 660	20.6	19.8	24.9	34.6
Widowed	71	42.3	29.6	14.1	14.1
Unknown	514	28.4	17.7	29.2	24.7
Total	28 081	32.4	18.9	21.8	26.9
Women					
		(n = 15 952)	(n = 7913)	(n = 6657)	(n = 6568)
Age at entry, y					
15-19	1 773	33.6	22.1	19.4	24.9
20-29	12 414	30.9	21.1	22.6	25.3
30-39	14 240	40.1	22.3	20.1	17.5
40-49	8 663	67.0	19.8	7.5	5.7
Race					
White	18 323	30.9	23.3	24.1	21.8
Black	11 689	48.5	21.6	13.1	16.8
Asian	4 154	74.7	13.3	7.2	4.8
Hispanic	1 807	56.8	18.3	12.1	12.8
Other/unknown	1 117	44.9	21.3	16.9	16.9
Education					
High school or less	7 927	52.4	19.8	13.0	14.9
Technical or business school	1 945	48.4	22.3	13.0	16.3
Some college	12 019	41.2	21.5	18.0	19.4
College graduate	7 918	43.3	20.3	19.1	17.3
Postgraduate	6 524	33.3	23.9	23.4	19.5
Unknown	757	41.0	21.9	23.3	13.9
Marital status					
Never married	11 559	29.9	21.1	22.9	26.2
Married	15 550	56.4	19.4	13.6	10.7
Remarried	2 009	38.6	26.8	20.2	14.3
Separated	1 521	36.4	23.9	16.4	23.3
Divorced	5 340	35.4	24.9	19.3	20.4
Widowed	416	64.2	17.6	9.4	8.9
Unknown	695	36.1	23.3	24.3	16.3
Total	37 090	43.0	21.3	17.8	17.7

Definitions of Use

Current marijuana smoking was defined by admission to smoking currently and more than six times ever. Former marijuana smoking was defined by denial of current smoking but admission to having smoked more than six times ever. Nonsmoking was defined as never having smoked. Experimenters were defined as those admitting to having ever smoked from one through six times. Ever users included current and former users but excluded experimenters. Smoking duration was expressed as total years of use. Smoking frequency was expressed as less than once per month, once or twice per month, once or twice per week, and daily or almost daily.

Persons were classified as current, former, or never smokers and users of alcoholic beverages on the basis of their questionnaire responses.^{10,11} Current and former smokers were categorized by frequency (number of cigarettes per day) and duration (years) of smoking. Current alcohol users were categorized by usual numbers of drinks consumed per day.

Mortality Follow-Up

Mortality was ascertained through 1991 by computer-matching study cohort members with the Kaiser Permanente Medical Care Program membership file as of 1992 and extracting a list of subjects who were no longer members. From this list we accepted as confirmed deaths those ascertained in previous research studies. The mortality status of the remaining study subjects who were no longer members was ascertained by computer-matching names and other demographic data with the California death file, using the California Automated Mortality Linkage and Information System (CAM-LIS).¹² Death certificate-specified underlying causes of death (International Classification of Diseases, 9th rev.—ICD-9) were used for coding. Centers for Disease Control and Prevention criteria were used to code acquired immunodeficiency syndrome (AIDS) prior to the introduction of specific disease codes associated with the human immunodeficiency virus (HIV) in 1987.¹³

Deaths of subjects who left California were investigated by linking pertinent Social Security numbers to a Pension Benefits Information (Tiburon, Calif) database that included mortality data from the state of California Center for Health Statistics, the Social Security Administration, the Department of Defense, the Civil

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TABLE 2—Relative Risk of Death for Ever Users and Current Users of Marijuana, by Sex and Cause of Death: Kaiser Permanente Medical Care Program Members (n = 65 171), Oakland and San Francisco, June 1979 through December 1985

Cause of Death	Ever Users			Current Users			No. Deaths in Reference Group (Nonusers/Experimenters)
	No. Deaths	Full Model ^a RR (95% CI)	Nonsmokers/ Occasional Drinkers ^b RR (95% CI)	No. Deaths ^d	Full Model ^a RR (95% CI)	Nonsmokers/ Occasional Drinkers ^b RR (95% CI)	
Men							
AIDS	152	1.80 (1.29, 2.52)	2.34 (1.32, 4.14)	104	1.90 (1.33, 2.73)	1.91 (1.02, 3.55)	55
Non-AIDS	266	1.11 (0.92, 1.34)	1.25 (0.82, 1.89)	153	1.12 (0.89, 1.39)	1.15 (0.67, 1.97)	315
Neoplasms	45	0.78 (0.52, 1.18)	0.46 (0.15, 1.41)	30	0.97 (0.61, 1.55)	0.75 (0.21, 2.69)	90
Circulatory disease	60	1.08 (0.75, 1.55)	1.36 (0.58, 3.19)	37	1.22 (0.80, 1.87)	1.80 (0.68, 4.73)	102
Injury/poisoning	92	1.24 (0.87, 1.75)	1.65 (0.84, 3.23)	47	0.99 (0.65, 1.50)	1.23 (0.51, 2.95)	72
Other causes	69	1.47 (0.98, 2.22)	1.71 (0.62, 4.68)	39	1.39 (0.86, 2.24)	0.68 (0.14, 3.45)	51
Unknown	12	8	7
Total	430	1.28 (1.09, 1.50)	1.58 (1.14, 2.18)	265	1.33 (1.11, 1.59)	1.50 (1.01, 2.22)	377
Women							
Neoplasms	36	0.82 (0.54, 1.22)	0.70 (0.31, 1.58)	19	0.86 (0.51, 1.45)	0.56 (0.17, 1.90)	155
Circulatory disease	13	0.68 (0.35, 1.33)	0.34 (0.04, 2.90)	10	0.96 (0.46, 2.02)	0.70 (0.08, 5.95)	64
Injury/poisoning	28	1.39 (0.79, 2.44)	1.40 (0.65, 3.04)	19	1.86 (0.99, 3.51)	2.04 (0.85, 4.91)	38
Other causes ^c	16	0.76 (0.39, 1.46)	0.40 (0.05, 3.35)	10	0.95 (0.45, 2.04)	0.84 (0.10, 7.23)	50
Unknown	4	3	4
Total	97	0.90 (0.69, 1.16)	0.81 (0.49, 1.34)	61	1.09 (0.80, 1.48)	1.03 (0.55, 1.90)	311

Note. RR = relative risk, CI = confidence interval.

^aAdjusted for age, race, education, marital status, obesity, cigarette smoking, and alcohol use.

^bAdjusted for age, race, education, marital status, and obesity.

^cIncludes 3 AIDS deaths.

^dNo. deaths in current users is included in no. deaths in ever users.

Service Commission, and the Railroad Retirement Board. While Social Security numbers were available for about two thirds of the study cohort, only 27 of 1215 deaths (2.2%) were ascertained by out-of-state search. Since causes of death were unavailable for out-of-state deaths, these deaths were included in analyses of total mortality but excluded in subcategory mortality analyses.

The overall age-specific mortality rates of this group were about three quarters as large as the corresponding 1987 United States rates,¹⁴ a discrepancy we attribute to the probable better health and predominantly employed status of our insured population and to our inability to ascertain mortality in subjects without Social Security numbers who had left California.

Analysis

SAS programs were used for statistical analyses.¹⁵ Cox proportional hazards models were used to examine the joint effect of sociodemographic characteristics and use of marijuana, tobacco, and alcohol on mortality risk; estimates of relative risks and associated 95% confi-

dence intervals were obtained from these models.¹⁶ Age-squared terms were entered into Cox proportional hazards models to determine whether there was a nonlinear relationship between age and mortality and were included when significant. Interactions between marijuana and tobacco use and between marijuana and alcohol use were tested in the selected models (total mortality, AIDS mortality [men only], non-AIDS mortality [men only], and mortality from injuries/poisonings) by including cross-product terms in our proportional hazards models. None of the interactions were statistically significant ($P < .05$).

Results

Sociodemographic characteristics of the sample are shown in Table 1. The cohort consisted of 38% nonusers, 20% experimenters, 20% former users, and 22% current users. The percentage of ever users was highest in the 20- through 29-year-old age group. Ever use of marijuana was more common among men than among women and was highest among Whites. Never-married men and women

were about twice as likely to be ever users as their married counterparts. Sociodemographic patterns were generally similar for current marijuana use.

Current marijuana users were twice as likely as never users to be current tobacco cigarette smokers and nearly 2.5 times as likely to be alcohol drinkers. The percentage of current smokers was 21% for never marijuana users, 31% for experimenters, 32% for former users, and 42% for current users. The corresponding percentages of those consuming one or more drink per day were 16%, 27%, 31%, and 39%. While few marijuana users were nonusers of alcohol, a substantial proportion of ever marijuana users (25% of men, 30% of women) and current marijuana users (22% of men, 28% of women) were nonsmokers of tobacco cigarettes and occasional (less than once per month) drinkers.

We compared risks of mortality associated with ever and current use relative to never or experimental use of marijuana. There were 807 deaths among men and 408 deaths among women in this cohort. We performed analyses for total mortality, AIDS (men only), neoplasms, circula-

TABLE 3—Risk of Mortality Associated with Current Cigarette, Alcohol, and Marijuana Use: Kaiser Permanente Medical Care Program Members (n = 65 171), Oakland and San Francisco, June 1979 through December 1985

	Current Cigarette Smoking ^a	Consumption of Three or More Alcoholic Drinks per Day ^b	Current Marijuana Use ^c	
	RR (95% CI)	RR (95% CI)	At Least Once a Week RR (95% CI)	Daily RR (95% CI)
Men				
AIDS	1.64 (1.15, 2.34)	0.94 (0.60, 1.47)	2.09 (1.42, 3.06)	1.65 (0.97, 2.82)
Non-AIDS	1.76 (1.40, 2.20)	1.21 (0.94, 1.56)	1.17 (0.91, 1.51)	1.31 (0.93, 1.84)
Total mortality	1.75 (1.45, 2.11)	1.13 (0.91, 1.40)	1.46 (1.19, 1.79)	1.43 (1.08, 1.90)
Women: Total mortality	1.58 (1.25, 2.01)	1.90 (1.31, 2.76)	1.23 (0.84, 1.80)	1.44 (0.80, 2.56)

Note. The model was adjusted for age, race, education, marital status, obesity, cigarette smoking, and alcohol use. RR = relative risk; CI = confidence interval.

^aRelative to nonsmoking.

^bRelative to occasional alcohol use.

^cRelative to nonuser/experimental user status.

tory disease, injury or poisoning, "other causes" of mortality, and total non-AIDS mortality (men only) (Table 2).

Marijuana Use in Relation to Mortality

For men, ever use of marijuana was associated with a significantly increased risk of total mortality (28%) and AIDS mortality (80%) and a nonsignificant ($P > .05$) increase (11%) in risk of non-AIDS mortality. Relative risks associated with ever marijuana use for these mortality categories were similar or higher in nonsmokers/occasional drinkers (a group in which marijuana use could be evaluated without uncontrolled confounding by cigarette and substantial alcohol use). Of note was the nearly significant 47% increase in "other causes" of mortality, examination of which revealed higher proportions of deaths from infectious diseases and from alcohol and drug abuse in ever users than in never users/experimenters. Current marijuana use was also associated with a significantly increased risk in men of total mortality (33%) and AIDS mortality (90%).

In women, there were no significant increases or decreases in mortality risk associated with ever or current marijuana use. Current use was associated with a nearly significant 86% increase in mortality from injury or poisoning, which could not be attributed to any specific category of injury.

Relative risks associated with marijuana use among nonsmokers/occasional drinkers were generally similar to those for the complete cohort, suggesting that increased risks in the complete cohort

were not an artifact resulting from incomplete control of the effects of cigarette smoking or alcohol use. The results of an analysis of mortality excluding subjects who died within the first 5 years of follow-up (data not shown) were similar to the overall results shown in Table 2, suggesting that the overall results were uncompromised by the possibility that serious illness occurring before the multiphasic health checkup affected subjects' decision to use marijuana.

Duration of use in current marijuana users was not consistently related to the risk of AIDS mortality in men or to total mortality in women, and had an inverse tendency in relationship to total and non-AIDS mortality in men (data not shown). A continuous duration-of-use variable was not significant when added to the full models for each mortality outcome.

Marijuana use at least once a week was associated with slightly higher relative risks of mortality than less frequent use. The addition of frequency of use improved the fit of the model ($P < .05$) only for total mortality in men (RR = 1.25, 95% CI = 0.97, 1.62, for total mortality among those who used less than once a week and RR = 1.46, 95% CI = 1.19, 1.79, among those who used at least once a week, relative to nonusers/experimenters).

AIDS Mortality

The vast majority of AIDS deaths (172/207 = 83%) occurred among never married men. Current marijuana use was nearly twice as high in never married as in married men (Table 1), raising the ques-

tion of whether analytic control for marital status was insufficient to adjust for confounding lifestyle factors, particularly male homosexual behavior.

To address this question, the study cohort was linked to the Northern California Kaiser Permanente Medical Care Program AIDS Database, which revealed 214 men with a diagnosis of AIDS after determination of their marijuana use status. The prevalence of current marijuana use at the time of the checkup (56%) in these AIDS patients was substantially higher than the prevalence in unmarried men in the total study cohort (38%).

For these 214 AIDS patients, current marijuana use was associated with a nonsignificant decrease in relative risk for total mortality (RR = 0.78, 95% CI = 0.47, 1.30) and for AIDS mortality (RR = 0.71, 95% CI = 0.41, 1.23). Assuming that most of the unmarried men who developed AIDS were homosexual or bisexual, these findings supported the hypothesis that the prevalence of marijuana use was higher in homosexual and bisexual men in the cohort, a group at high risk for AIDS mortality. Therefore, male homosexual behavior, a critical confounding variable, could not be controlled for in complete cohort mortality analyses.

Comparative Risks of Tobacco, Alcohol, and Marijuana Use

The relative risks of total mortality in men and women, and of AIDS and non-AIDS mortality in men, associated with current cigarette smoking, consumption of three or more drinks per day, and current marijuana use are shown in Table 3. Except for AIDS mortality, the risks

associated with marijuana use were lower than those for tobacco cigarette smoking. Compared with consumption of three or more drinks per day, marijuana use was associated with a higher risk of total mortality and AIDS mortality in men and a lower risk of total mortality in women.

Discussion

The main overall findings were an increased risk of total mortality associated with marijuana use in men but not in women. The increased risk of total mortality in men was explained by the strong relationship between marijuana use and AIDS mortality. Marijuana use was unassociated with non-AIDS mortality in men.

The question of the effect of marijuana use on AIDS mortality is an important one. Marijuana use has been advocated as a therapeutic adjunct to ameliorate the nausea and loss of appetite commonly associated with the wasting syndrome in AIDS.¹⁷ We have provided substantial evidence that the increased risk of AIDS mortality in the total study cohort probably resulted from uncontrolled confounding by homosexual behavior. Other studies have reported a substantially higher prevalence of marijuana use in homosexual and bisexual men, supporting the hypothesis that marijuana use is a marker for homosexuality or bisexuality.¹⁸⁻²⁰

There are several other potential explanations for the increased risk of AIDS in marijuana users. Marijuana smoking might theoretically place AIDS patients at increased risk of infection because of its irritative effects on the respiratory system or because of infectious contaminants (e.g., fungi) in marijuana. Other potential explanations include marijuana as a marker of high-risk sexual behavior or intravenous drug use; initiation of marijuana use as a result of having HIV or AIDS, rather than preceding the disease; and possible immunosuppressive properties of marijuana.

The use of alcohol and nonmedical psychoactive drugs, including marijuana, is associated with risky sexual behavior such as unprotected intercourse,²⁰ but methodological limitations have made it impossible to determine causality.²¹ Marijuana use may serve to a certain extent as a marker of intravenous drug use. However, the relative risk of AIDS mortality associated with marijuana use did not diminish when the analysis was limited to men who were nonsmokers of tobacco

and occasional alcohol drinkers, a subgroup unlikely to contain many parenteral drug users. Additional evidence against marijuana as a marker for parenteral drug use was the finding of only one case of infective endocarditis in Kaiser Permanente hospitalization records of the AIDS decedents.

The lack of increased mortality during the first 5 years of follow-up suggests that therapeutic use of marijuana at baseline for AIDS-related symptoms has little, if any, explanatory effect on the association between marijuana use and AIDS. Furthermore, the majority of AIDS patients initiated marijuana use long before the onset of clinical disease; nearly two thirds (65%) of AIDS patients reported initiation before 1976, when HIV infection in the San Francisco Bay area was either nonexistent or negligible.²²

While marijuana and its psychoactive cannabinoids possess known immunosuppressive qualities, there is no consensus as to whether typical doses result in clinical immunosuppression in humans.²³ Marijuana use has been associated with a higher prevalence of seropositivity for HIV in some cross-sectional studies of homosexual and bisexual men,^{20,24} but it has not been shown to be an independent predictor of seroconversion,²⁵ nor does it increase the risk of AIDS in seropositive men.²⁴

The nearly significant increase in mortality risk from injury or poisoning for female current marijuana users was consistent with our hypothesis that marijuana use is a risk factor for death due to injury. Marijuana is known to decrease psychomotor performance; some studies have implicated its use in motor vehicle crashes.^{7(pp43-50)} Marijuana use is also strongly associated with alcohol use, another major risk for accidental death. There were too few deaths to meaningfully study the other main hypothesis, that marijuana use would be associated with increased respiratory disease mortality. Another study performed on a subgroup of this cohort showed that daily or near-daily marijuana users who were not tobacco cigarette smokers had a 19% higher risk of outpatient visits for respiratory disorders than nonusers of both substances.²⁶

The major limitations of this study include its reliance on self-report for ascertainment of marijuana use status; the inability to study changes in marijuana use status during follow-up; a lack of lengthy follow-up into the geriatric age range (maximum follow-up, 12.5 years;

maximum age reached, 63 years); a lack of information regarding other illegal drug use; and potential underascertainment of mortality (noted earlier). Estimates of marijuana use were similar to those obtained during this period by the National Household Survey on Drug Abuse, the most authoritative source of illegal drug use information for US adults.²⁷ The lack of longitudinal data regarding use status is common to many cohort studies. It seems unlikely that "ever" marijuana use status would have changed substantially over time, because relatively few adults in this cohort are likely to have initiated marijuana use during follow-up in a period (the 1980s) when there was a marked secular decline in self-reported marijuana use in the United States.¹ It is possible that relationships between marijuana use and mortality might be found with longer-term follow-up or later in life. It is likely that if information on subjects' use of other illegal drugs had been available, adjustment for other drug use would have lowered the relative risk estimates for marijuana use.

As noted earlier, relatively few adverse clinical health effects from the chronic use of marijuana have been documented in humans.^{7(p16)} The criminalization of marijuana use may itself be a health hazard, since it may expose the consumer to violence and criminal activity.²⁸ While reducing the prevalence of drug abuse is a laudable goal, we must recognize that marijuana use is widespread despite the long-term, multibillion dollar War on Drugs. Therefore, medical guidelines regarding its prudent use should be established, akin to the commonsense guidelines that apply to alcohol use. Unfortunately, clinical research on potential therapeutic uses for marijuana has been difficult to accomplish in the United States, despite reasonable evidence for the efficacy of tetrahydrocannabinol (THC) and marijuana as antiemetic and antiglaucoma agents and the suggestive evidence for their efficacy in the treatment of other medical conditions, including AIDS.^{7(pp185-262)}

In summary, this study showed little, if any, effect of marijuana use on non-AIDS mortality in men and on total mortality in women. The increased risk of AIDS mortality in male marijuana users probably did not reflect a causal relationship, but most likely represented uncontrolled confounding by male homosexual behavior. The risk of mortality associated with marijuana use was lower than that

associated with tobacco cigarette smoking. □

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