

# An Exploratory Prospective Study of Marijuana Use and Mortality Following Acute Myocardial Infarction

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Authors and Disclosures

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## Abstract

**Background:** The relationship of marijuana use with coronary heart disease, including prognosis among patients with coronary heart disease, is uncertain.

**Methods:** We conducted an inception cohort study of 1913 adults hospitalized with myocardial infarction (heart attacks) at 45 US hospitals between 1989 and 1994, with a median follow-up of 3.8 years. We ascertained total mortality according to self-reported marijuana use in the preceding year.

**Results:** A total of 52 patients reported marijuana use during the prior year, and 317 patients died during follow-up. Compared with nonuse, marijuana use less than weekly was associated with a hazard ratio of 2.5 (95% CI, 0.9-7.3). The corresponding hazard ratio for weekly use or more was 4.2 (95% CI, 1.2-14.3). The age and sex adjusted hazard ratios associated with any use were 1.9 (95% CI, 0.6-6.3) for cardiovascular mortality and 4.9 (95% CI, 1.6-14.7) for non-cardiovascular mortality. In a comparison of 42 marijuana users and 42 other patients matched on propensity scores, there were 6 deaths among marijuana users and one among non-users (log-rank P = .06).

**Conclusions:** These preliminary results suggest possible hazards of marijuana for patients who survive acute myocardial infarction (heart attacks). Although marijuana use has not been associated with mortality in other populations, it may pose particular risk for susceptible individuals with coronary heart disease.

## Introduction

Marijuana use is not uncommon in the United States. A 2001-2002 national survey found that 4.1% of the adult population of the United States had used marijuana within the last year.<sup>[1]</sup> Although younger adults were most likely to report marijuana use, such use among adults aged 45 to 64 years was almost 3-fold higher than it had been a decade earlier.

Few studies have documented the long-term outcomes of marijuana users. In one previous study of marijuana use and mortality in the general population,<sup>[2]</sup> Sidney et al<sup>[2]</sup> found no increased risk of mortality associated with marijuana use among Kaiser Permanente enrollees less than 50 years old, very similar to earlier findings among Swedish conscripts.<sup>[3]</sup> However, marijuana use has cardiovascular effects that could pose particular risk for older adults and those with coronary heart disease, including a sizable increase in resting heart rate.<sup>[4]</sup> Moreover, in a previous analysis of the Onset Study, the risk of triggering a myocardial infarction (MI - heart attacks) was elevated almost 5-fold within 1 hour after smoking marijuana, compared with periods of nonuse,<sup>[5]</sup> consistent with case reports describing this phenomenon.<sup>[6-10]</sup> However, Steffens et al<sup>[11]</sup> recently found that orally administered delta9-tetrahydrocannabinol, a cannabinoid derivative, inhibits atherosclerosis progression in a mouse model, apparently through effects on lymphoid and myeloid cells. Marijuana use also has a wide variety of non-cardiovascular effects, including potentially adverse respiratory, neurologic, and immunologic effects.<sup>[12-14]</sup> The net balance of these apparently disparate effects of marijuana use on the most clinically vulnerable patients, such as those with established coronary heart disease, has not been studied.

An impediment to understanding the clinical consequences of marijuana use has been the stark dearth of studies that have collected information on exposure.<sup>[2,3,15]</sup> To address this paucity of information, we explored the association of marijuana use assessed at the time of acute MI (AMI) with subsequent

mortality among participants of the Onset Study. This multicenter, prospective cohort study included chart reviews and in-depth personal interviews with hospitalized patients with confirmed AMI.<sup>[16,17]</sup>

## Discussion

In this preliminary prospective cohort study of early survivors of AMI (heart attacks), marijuana use, as measured at the time of hospitalization, was associated with 3-fold higher mortality after infarction. There was a gradient in risk, with the highest risk of death among individuals who used marijuana most frequently, and the risk was entirely unchanged by multivariate adjustment.

Marijuana use has important cardiovascular effects that could pose risk for patients with coronary heart disease. Among the best-defined of these is an increase in resting heart rate that can be selectively blocked by pretreatment with a cannabinoid receptor antagonist.<sup>[26]</sup> This effect may be related to the prolonged catecholamine release that marijuana can induce.<sup>[27]</sup>

Marijuana use can also increase supine blood pressure, although it leads to orthostatic hypotension, postural dizziness, and even syncope (loss of consciousness) in some cases.<sup>[28,29]</sup>

At the same time that marijuana increases heart rate and, therefore, myocardial oxygen demand, it may also limit oxygen uptake. Marijuana smoking leads to a dose-dependent increase in carbon monoxide exposure<sup>[30]</sup> and even higher blood levels of carboxyhemoglobin than does cigarette smoking.<sup>[12]</sup> These effects have a demonstrably detrimental impact on patients with known coronary heart disease, in whom marijuana use decreases exercise time to the onset of angina by 50%, twice as great an effect as use of a standard cigarette.<sup>[31]</sup>

Marijuana use could also lead to higher risk of death among patients by interfering with adherence to standard therapies. Although the relationship of marijuana use and adherence to therapy among patients with coronary heart disease has not been evaluated, it may interfere with adherence to other life-saving medication, such as antiretroviral therapy for human immunodeficiency virus infection.<sup>[32]</sup> The effects of marijuana use on cognitive function could conceivably exacerbate this further.<sup>[33]</sup>

Over half of deaths among Onset Study participants who reported marijuana use were noncardiovascular, a substantially higher proportion than in nonusers. Despite the lack of specificity inherent in use of death certificates to assign accurate causes of death,<sup>[34]</sup> our results suggest that patients with coronary heart disease who use marijuana may be at particular for risk for all causes of death, and not recurrent cardiovascular disease alone. In this regard, the possible effects of marijuana use on unintentional injury and upper airway malignancy may be particularly important.<sup>[35,36]</sup> Marijuana use also directly increases risk-taking behavior in some settings,<sup>[37,38]</sup> but our findings were not altered by adjustment for other markers of risky behavior that were available, including binge drinking and cocaine use, perhaps because marijuana use was less strongly related to risk-taking in this relatively older aged cohort.

Similar to our findings, Sidney et al<sup>[2]</sup> also found that marijuana use was associated with AIDS-related death in men. It seems likely that this, at least in part, reflects confounding by indication, in which marijuana is used for nausea or appetite stimulation. However, cannabinoids may also have direct immunosuppressive effects that could accelerate disease progression among susceptible individuals.<sup>[14]</sup> Further studies to understand the degree to which marijuana use could influence post-infarct mortality (heart attack within 5-6 days after the first) via direct cardiovascular effects, cognitive changes that reduce adherence, noncardiovascular effects of marijuana, or simply other confounding factors related to marijuana use are clearly needed.

The Onset Study has both strengths and limitations. An important and perhaps unique strength is its assessment of marijuana use in a population of early survivors of MI; to our knowledge, no comparable cohort studies exist. All participants were interviewed in a standardized manner during hospitalization

for enzymatically confirmed infarcts, and a relatively large body of information on clinical and sociodemographic variables was obtained.

As with any observational study, we cannot prove cause-and-effect relationships, although it is unclear how a randomized trial to test our findings could be performed. Our results were also consistently unchanged by adjustment for a wide variety of clinical characteristics, including alcohol intake and smoking. Nonetheless, there are apt to be unmeasured confounding clinical or lifestyle factors that may be responsible for our findings.

We asked participants to report their usual marijuana use over the year prior to the infarction that resulted in their hospitalization and did not have information on post-MI use, which is likely to have differed from that measured here. Assuming that some marijuana users cease use after hospitalization, we may have underestimated the true effect of post infarction marijuana use on survival. On the other hand, by assessing marijuana exposure before infarction and before follow-up, we minimized the potential bias that could affect assessment of post infarction marijuana use alone if sicker patients give up marijuana use more often than healthier patients after hospitalization. Future studies should also include repeated assessments of marijuana use to address this possibility.

**In conclusion,** marijuana use was associated with 3-fold greater mortality after AMI in this exploratory study, with a graded increase in risk with more frequent use. Because marijuana use appears to be increasing among middle-aged and older adults, this finding may have growing importance in the future. Although marijuana use does not appear to be associated with mortality among the general population, our results suggest that it may carry particular risks for vulnerable populations with established cardiovascular disease.

## References

1. Compton WM, Grant BF, Colliver JD, et al. Prevalence of marijuana use disorders in the United States: 1991-1992 and 2001-2002. *JAMA*. 2004;291:2114-2121.
2. Sidney S, Beck JE, Tekawa IS, et al. Marijuana use and mortality. *Am J Public Health*. 1997;87:585-590.
3. Andreasson S, Allebeck P. Cannabis and mortality among young men: a longitudinal study of Swedish conscripts. *Scand J Soc Med*. 1990;18:9-15.
4. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol*. 2002;42(11 Suppl):64S-70S.
5. Mittleman MA, Lewis RA, Maclure M, et al. Triggering myocardial infarction by marijuana. *Circulation*. 2001;103:2805-2809.
6. Kotsalou I, Georgoulas P, Karydas I, et al. A rare case of myocardial infarction and ischemia in a cannabis-addicted patient. *Clin Nucl Med*. 2007;32:130-131.
7. Tatli E, Yilmaztepe M, Altun G, et al. Cannabis-induced coronary artery thrombosis and acute anterior myocardial infarction in a young man. *Int J Cardiol*. 2007;120:420-422.
8. Caldicott DG, Holmes J, Roberts-Thomson KC, et al. Keep off the grass: marijuana use and acute cardiovascular events. *Eur J Emerg Med*. 2005;12:236-244.
9. Lindsay AC, Foale RA, Warren O, et al. Cannabis as a precipitant of cardiovascular emergencies. *Int J Cardiol*. 2005;104:230-232.
10. Collins JS, Higginson JD, Boyle DM, et al. Myocardial infarction during marijuana smoking in a young female. *Eur Heart J*. 1985;6:637-638.
11. Steffens S, Veillard NR, Arnaud C, et al. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature*. 2005;434:782-786.
12. Wu TC, Tashkin DP, Djahed B, et al. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med*. 1988;318:347-351.
13. Harrison GP, Gruber AJ, Hudson JI, et al. Cognitive measures in long-term cannabis users. *J Clin Pharmacol*. 2002;42(11 Suppl):41S-47S.
14. Friedman H, Newton C, Klein TW. Microbial infections, immunomodulation, and drugs of abuse. *Clin Microbiol Rev*. 2003;16:209-219.
15. Braun BL, Hannan P, Wolfson M, et al. Occupational attainment, smoking, alcohol intake, and marijuana use: ethnic-gender differences in the CARDIA study. *Addict Behav*. 2000;25:399-414.
16. Mittleman MA, Maclure M, Tofler GH, et al. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med*. 1993;329:1677-1683.
17. Mukamal KJ, Maclure M, Muller JE, et al. Prior alcohol consumption and mortality following acute myocardial infarction. *JAMA*. 2001;285:1965-1970.
18. Mukamal KJ, Maclure M, Muller JE, et al. Tea consumption and mortality after acute myocardial infarction. *Circulation*. 2002;105:2476-2481.

19. Mukamal KJ, Maclure M, Muller JE, et al. Caffeinated coffee consumption and mortality after acute myocardial infarction. *Am Heart J*. 2004;147:999-1004.
20. Mittleman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. *Circulation*. 1995;92:1720-1725.
21. Mukamal KJ, Maclure M, Muller JE, et al. Binge drinking and mortality after acute myocardial infarction. *Circulation*. 2005;112:3839-3845.
22. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol*. 1984;119:837-839.
23. Mukamal KJ, Muller JE, Maclure M, et al. Evaluation of sex-related differences in survival after hospitalization for acute myocardial infarction. *Am J Cardiol*. 2001;88:768-771.
24. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol*. 1999;150:327-333.
25. Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. In: *Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference*; 2001. Cary (NC): SAS Institute, Inc; 2001;p. 214-226.
26. Huestis MA, Gorelick DA, Heishman SJ, et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Arch Gen Psychiatry*. 2001;58:322-328.
27. Gash A, Karliner JS, Janowsky D, et al. Effects of smoking marihuana on left ventricular performance and plasma norepinephrine: studies in normal men. *Ann Intern Med*. 1978;89:448-452.
28. Mathew RJ, Wilson WH, Davis R. Postural syncope after marijuana: a transcranial Doppler study of the hemodynamics. *Pharmacol Biochem Behav*. 2003;75:309-318.
29. Mathew RJ, Wilson WH, Humphreys D, et al. Middle cerebral artery velocity during upright posture after marijuana smoking. *Acta Psychiatr Scand*. 1992;86:173-178.
30. Azorlosa JL, Greenwald MK, Stitzer ML. Marijuana smoking: effects of varying puff volume and breathhold duration. *J Pharmacol Exp Ther*. 1995;272:560-569.
31. Aronow WS, Cassidy J. Effect of smoking marihuana and of a high-nicotine cigarette on angina pectoris. *Clin Pharmacol Ther*. 1975;17:549-554.
32. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med*. 2003;114:573-580.
33. Kalant H. Adverse effects of cannabis on health: an update of the literature since 1996. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:849-863.
34. Lloyd-Jones DM, Martin DO, Larson MG, et al. Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med*. 1998;129:1020-1026.
35. Gerberich SG, Sidney S, Braun BL, et al. Marijuana use and injury events resulting in hospitalization. *Ann Epidemiol*. 2003;13:230-237.
36. Mao L, Oh Y. Does marijuana or crack cocaine cause cancer?. *J Natl Cancer Inst*. 1998;90:1182-1184.
37. Lane SD, Yechiam E, Busemeyer JR. Application of a computational decision model to examine acute drug effects on human risk taking. *Exp Clin Psychopharmacol*. 2006;14:254-264.
38. Lane SD, Cherek DR, Tcheremissine OV, et al. Acute marijuana effects on human risk taking. *Neuropsychopharmacology*. 2005;30:800-809.