

Annotated bibliography of research on marijuana and health

Assembled by the Colorado School of Public Health,
intended as background for the Marijuana and Public Health Symposium on March 7, 2014.

This is a selective bibliography intended as a primer on the scientific evidence relating marijuana and health. This is a selective listing of the most recent research, favoring evidence-based reviews over individual studies. The annotated summaries were written by Tim Byers. This bibliography can also be found online at <http://publichealthpractice.org>.

General reviews of marijuana and health

1. *Marijuana: current concepts.* Greydanus A. et al. *Frontiers in Public Health* 2013; 1:1-17.

This is really a more general overview paper about cannabis but it emphasizes mental health issues more than other issues, so it is best regarded as a cannabis and mental health review.

2. *The pharmacologic and clinical effects of medical cannabis.* Borgelt L et al. *Pharmacotherapy* 2013; 33:195-209.

This is an excellent non-systematic review written by Dr. Laura Borgelt from the Skaggs School of Pharmacy at the Anschutz Medical Campus. Although this review focuses on medical marijuana, it is an excellent summary of cannabis pharmacology and toxicology, including a summary of evidence on potential adverse health effects.

3. *The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: Results from the GBD 2010 Study.* Degenhardt L et al. *PLOS ONE* 2013. 8:e76635

This is only one aspect of a much larger study, the Global Burden of Disease Study, funded by the Gates Foundation. This aspect reviewed the literature on health effects of cannabis use and concluded there were only two meaningful hazards: dependence per se as an adverse outcome, and contribution to schizophrenia risk. The size of the impact on schizophrenia was tiny (only .04% of all schizophrenia being caused by cannabis), but the size of the impact on dependence was larger (about 0.2% of the North American population).

4. *Does cannabis use increase the risk of death? Systematic review of epidemiologic evidence on adverse effects of cannabis use.* Calabria B et al. *Drug and Alcohol Review* 2010; 29:318-30.

This systematic review of all studies linking mortality to cannabis use was based on 19 studies. The data presentation and discussion are not particularly enlightened. They concluded mostly that evidence was inconclusive except for death from traffic crashes, and that better long-term cohort studies are needed.

5. *Medical marijuana. Clearing away the smoke.* Grant I et al. *The Open Neurology Journal* 2012; 6:18-25.

Although this review is principally focused on medical marijuana, it presents a thoughtful summary of the challenges in interpreting research on marijuana, so is good background reading.

6. *The adverse health effects of chronic cannabis use.* Hall W et al. *Drug Testing and Analysis* 2013. 6:39-45.

This is a general review of adverse health effects associated with chronic use. Although this paper is not very systematically written and is inferior to the other general reviews in terms of its scientific quality, it is included here because it is succinct and recent.

Marijuana and cancer

1. *The intersection between cannabis and cancer in the United States. Bowles D. et al. Critical Reviews in Oncology Hematology 2012; 83:1-10.*

This is an excellent review written by Dr. Daniel Bowles from the University of Colorado School of Medicine at the Anschutz Medical Campus. Although much of this review deals with the efficacy of medical marijuana on symptoms in the cancer patient, it also nicely summarizes the evidence of connections between marijuana use and risk of getting cancer. Cannabinoids are not carcinogenic, but marijuana smoke contains many hundreds of combustion products that could increase cancer risk. Some epidemiologic studies have suggested increased risk for lung cancer, while others have not. Although it is hard to separate-out effects of tobacco from those of marijuana, research to date suggests that marijuana smoke is substantially less carcinogenic than tobacco.

2. *The association between marijuana smoking and lung cancer. A systematic review. Mehra R. et al. Archives of Internal Medicine 2006; 166:1359-67.*

From this review of 19 studies on this question, there is not a pattern suggesting marijuana causes lung cancer, but studies do show increased inflammation of bronchial mucosa, so there is a biologic basis for concern.

3. *Marijuana use and risk of lung cancer: a 40-year cohort study. Callaghan R et al. Cancer Causes and Control 2013; 24:1811-1820.*

This is a single study, included here because it is both recent and large, though an earlier study of about this same size was null. This is a follow-up of about 50,000 military recruits in Sweden. Heavy marijuana use at the time of recruitment (1.7% of the cohort) was found to be associated with a 2.1-fold increased risk of lung cancer after 40 years, after adjusting for baseline tobacco use. Lower levels of marijuana use were not associated with increased risk. It is important to note that there was no assessment of tobacco cessation over time, so any association between heavy marijuana use and persistent tobacco use would confound the marijuana association.

4. *Association of marijuana smoking with oropharyngeal and oral tongue cancers: Pooled analysis from the INHANCE Consortium. Marks M et al. Cancer Epidemiology, Biomarkers, and Prevention 2013; 23:160-71.*

The pooled analysis of 1,921 oropharyngeal cancer cases, 356 tongue cancer cases, and 7,639 controls found a 24% higher risk for oropharyngeal cancer, but no increased risk (actually 53% lower risk) for tongue cancer. After adjusting for potential human papilloma virus infection (a major risk factor for oropharyngeal cancer) the association with marijuana disappeared. Although this is interpreted by the authors as evidence that cannabinoids may be both pro-carcinogenic and anti-carcinogenic, it is probably best regarded as evidence that any association between cannabis use and increased risk of cancers in the mouth would be quite small.

Marijuana and heart diseases

1. *At the heart of the matter: the endocannabinoid system in cardiovascular function and dysfunction. Montecucco F et al. Trends in pharmacological sciences 2012; 33:331-40.*

This is a very technical and dense article that explains the functioning of the endocannabinoid system, which has complex regulatory functions in various parts of the body, including the brain and circulatory system. Although this is a very technical review, it does help in understanding the various neurologic and physiologic effects of cannabis as reviewed in other papers.

2. *Cannabinoids and atherosclerotic coronary heart disease. Singla S et al. Clinical Cardiology 2012; 35:329-35.*

This is also a technical review, including many details of molecular biology. It nicely covers the questions of effects of cannabinoids on various conditions, such as blood pressure, insulin resistance, and circulating lipid levels. The acute increases in heart rate and blood pressure are correlated with increased myocardial infarction risk in the first hour after use among those with pre-existing coronary artery disease. The authors also discuss the apparent paradox observed in from animal studies of adverse acute effects but beneficial long-term effects on cardiovascular disease risk.

3. *Effect of blockage of the endocannabinoid system by CB1 antagonism on cardiovascular risk. Mach F et al. Pharmacological Reports 2009; 61:13-21.*

This is other review of the physiology of the endocannabinoid system, explaining its effects on blood pressure, glucose metabolism, lipid metabolism, and immune function from the perspective of the documented effects from randomized controlled trials using rimonabant, a cannabinoid receptor antagonist. This drug has multiple beneficial effects, including on weight loss, blood pressure, insulin sensitivity, and lipids, but it has not been approved for use because of a high rate of neurologic side effects (nausea and dizziness).

4. *Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: What cardiologists need to know. Am J Cardiology 2014; 113:187-190.*

This is only an average-quality review, not very systematic in approach, but included here as a general review since it is recent.

5. *Marijuana and long-term mortality among survivors of acute myocardial infarction. Frost L. et al. Am Heart J 2013;165:170-5.*

This is a single cohort study of about 3900 survivors of an MI who were followed for 18 years for mortality. There were 22 deaths among the 109 who reported using marijuana at some time during the year before their MI. This was a rate of death that was 29% higher than among who did not report marijuana use, though it was not a statistically significant increase.

Marijuana and stroke

1. *Cannabis-related stroke. Myth or reality? Wolff V. et al. Stroke 2013; 44:558-63.*

This review addresses the question of co-occurrence of strokes and marijuana use, whether this is a causal connection or only coincidental. This paper reviews 59 case reports in the medical literature in which strokes occurred following marijuana use. As cases are reported only when they are unusual, it is important to note that this series is young, with an average age of 33. There is some evidence that a condition similar to Reversible Cerebral Vasoconstriction Syndrome (RCVS) may be induced by cannabis and may account for some of these strokes. The author concludes that the co-occurrence of strokes and cannabis use reflects a causal connection between the two caused by reversible cerebral narrowing, but the scientific evidence supporting causality is not clear-cut. See also their subsequent response to a critical letter in *Stroke*, 44:e57.

2. *Cannabis, ischemic stroke, and transient ischemic attack: A case-control study. Barber P. et al. Stroke 2013; 44:2327-29.*

Among 218 consecutive patients ages 18-55 who were admitted to a single New Zealand hospital for ischemic stroke or TIA, 15% tested positive for cannabis in their urine, compared to 8% of people admitted for other reasons. Risk for stroke or TIA was increased 2.3-fold, but marijuana smokers were also more likely to smoke tobacco, so after adjustment for tobacco use risk was only 59% higher (and not a statistically significant increase). This study provides weak evidence in support of the idea that cannabis increases stroke risk.

Marijuana and lung diseases

1. *Marijuana and lung diseases. Joshi M et al. Current Opinions in Pulmonary Medicine. 2014; 20: online publication.*

This is a good review. They conclude that despite short-term benefits of cannabis smoking for bronchial dilation, there are potential long-term adverse effects tied to increased inflammation. Chronic marijuana smokers have about a 2-fold increased risk for chronic cough, and bronchial biopsies show clear evidence for increased inflammation. To date no convincing adverse effects have been seen for chronic obstructive pulmonary disease (COPD) or lung cancer, but there are biologic bases for concern for those conditions.

2. *Effects of smoking cannabis on lung function. Lee M. et al. Expert Rev. Resp. Med. 2011; 5:537-47.*

There are short-term benefits of cannabis smoking for bronchial dilation, but potential long-term adverse effects from increased inflammation. It is hard to separate the effects of cannabinoids from the many other constituents of inhaled smoke. There does not seem to be a link between marijuana use and risk for COPD. The review concludes by stating that harm to the lungs is substantially greater from tobacco than from marijuana.

3. *Association between marijuana exposure and pulmonary function over 20 years. Pletcher M et al. JAMA 2012; 307:173-181.*

This is a single cohort study, but one that was very well done and quite recent. They measured pulmonary function in the CARDIA cohort of about 5000 men over 20 years. There was no association between marijuana smoking and declines in lung function, though the expected declines were clearly seen with tobacco smoking.

4. *Effects of Marijuana Smoking on the Lung. Tashkin. Annals of the American Thoracic Society, 2013, 10: 239–247.*

This is the most recent narrative review of research on the effects of marijuana smoking on the lung. It makes the same points covered by Lee et al.

Marijuana and mental health

1. *Pathways from cannabis to psychosis: a review of the evidence. Burns J. Frontiers in Psychiatry. 2013; 4:128-xxx.*
This is a review of the co-existence of many different types of mental health issues and marijuana. Separating cause from effect in these relationships is hard, as early symptoms of mental illness can lead to use of drugs. Marijuana use is higher among adolescents who are later diagnosed with schizophrenia. Marijuana seems to shorten the time to psychosis. The authors provide a speculative model for cannabis effects on psychosis.
2. *Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. Battalla A et al. PLOS ONE 2013; 8:e55821.*
This analysis reviews 43 studies, including 8 in adolescents. This very complex article shows several studies have found structural brain changes related to chronic cannabis use, especially in areas of the brain that are rich in cannabinoid receptor like the hippocampus.
3. *Cannabis use during adolescent development: susceptibility to psychiatric illness. Chadwick B. et al. Frontiers of Psychiatry 2013; 4:xx-xx.*
This review is not particularly systematic in style, but it does cover the question of brain development. Although it is quite technical on the endocannabinoid system, it documents the reasons for concern that because the adolescent brain is still in active development, drugs such as cannabinoids that alter development of brain signaling pathways and structures, and could thereby have adverse effects on brain development.
4. *Persistent cannabis users show neuropsychological decline from childhood to midlife. Meier M et al. PNAS 2012; e2657-64.*
This is a cohort study of about 1000 New Zealanders followed from birth to age 38. Neurocognitive functioning was measured at age 13 then again at age 38. Although an association was found between marijuana use and cognitive decline, that decline was due to higher IQ scores at age 13 among those who would subsequently use marijuana (IQ scores at age 38 did not differ). Adolescent use had more effect on cognitive decline than did adult use. An accompanying editorial by Raul Gonzalez in that same issue reviews evidence to the contrary, but acknowledges that adolescence may be a particularly sensitive time for adverse effects on brain development.
5. *Cannabis and psychosis: Have we found the missing links? Parakh P et al. Asian J Psychiatry 2013;6:281-7.*
This reviews the literature linking adolescent marijuana use to psychosis onset. This is a thoughtful, but speculative, discussion of the mechanisms of increased risk. They conclude that although marijuana itself is not causal, it might accelerate the processes leading to psychosis among those who are otherwise susceptible.
6. *The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Lev-Ran S et al. Psychological Medicine 2014; 44:797-810.*
This is a systematic review based on 14 cohort studies relating marijuana use to the onset of depression. There was a 17% increased risk for depression onset among all users. Among heavy users (defined as a cannabis use disorder or use at least weekly) risk was increased by 62%. There were no differences noted by age.
7. *Changes in cannabis use among young people: impact on mental health. Copeland J et al. Curr Opin Psychiatry 2013;26:325-9.*
This is a general review summarizing the associations between cannabis use in adolescence and various mental health disorders.

8. *An overview of systematic reviews on cannabis and psychosis: Discussing apparently conflicting results. Monozzi S et al. Drug and Alcohol Review 2010; 29:304–317*

This is a summarization of findings of systematic reviews on the association between cannabis use and psychosis. The authors carefully assessed the reasons for discordant results across five systematic reviews. The reviews that performed a meta-analysis all showed an association between marijuana use and psychosis. This overview shows a consistent association between cannabis use and psychotic symptoms, though they also conclude that reverse causality and residual confounding cannot be excluded.

Marijuana and drug dependency

1. *Cannabis use disorder: epidemiology and management. Copeland J et al. International Review of Psychiatry. 2009;21:96-103.*

Although cannabis is not addictive it induce a dependency. This is a review of the definition and treatment of cannabis use disorder. Estimates are that about 1% of US adults meet the definition of cannabis dependence in the previous year. There are not any medications shown to be helpful for treatment, but brief cognitive behavioral therapy seems to help.

2. *Actions of delta-9-tetrahydrocannabinol in cannabis: relation to use, abuse, dependence. Cooper Z et al. International Reviews Psychiatry. 2009; 21:104-112.*

This is a very technical review that largely covers animal model systems and brain neurochemistry. Although this evidence is not easily applicable to human clinical behavior, it is a good basic science summary of the neurologic effects of cannabinoids that are relevant to dependency and withdrawal.

3. *Primary prevention of cannabis use: A systematic review of randomized controlled trials. Norberg M et al. PLOS ONE 2013; 8:e53187.*

This review included 49 studies. Overall, effects of interventions for preventing marijuana use were characterized as “trivial to small”. Programs that were more universal and more multi-modal were superior to more focused programs. The review criticized much of the research as difficult to evaluate, but concluded that there is not yet any compelling evidence that marijuana prevention programs have any substantial effects.

Marijuana and pregnancy, breast feeding

Cannabis, the pregnant woman, and her child: weeding out the myths. Jaques S et al. J. of Perinatology 2014; 1-8.

This is a non-systematic review of various issues tied to cannabis exposures in utero or during lactation. There is no compelling evidence suggesting cannabis causes birth defects or that it is associated with poor birth outcomes. However, cannabis does easily cross the placental barrier and is excreted in milk, so there is reason to believe that cannabis may interfere with normal brain development of the fetus (from exposures during pregnancy) or infant (from exposures for lactation), though there are as yet no empirical data on neurocognitive outcomes following early life exposures.

Marijuana and traffic safety

There have been three recent systematic reviews of cannabis and motor vehicle crashes:

1. *Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis.* Asbridge M et al. *British Medical Journal* 2012; 344:e536.
This metaanalysis is based on 9 studies, showing a 1.9-fold increased risk for all crashes, and a 2.1-fold increased risk for fatal crashes.
2. *Marijuana use and motor vehicle crashes.* Mu-Chen L. et al. *Epidemiologic Reviews* 2012; 34:65-72.
This metaanalysis of 9 studies produced an overall estimate of a 2.7-fold increased risk for car crashes with cannabis use, and a dose-response relationship of higher risk with higher levels of cannabis in the blood.
3. *Cannabis effects on driving skills.* Hartman R. et al. *Clinical Chemistry* 2013; 59:478-92.
This metaanalysis is based on 10 studies, concluding a 2-fold increased risk for motor vehicle accidents after marijuana use.
4. *Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies.* Elvik, R. *Accident Analysis and Prevention* 2013; 60:254-67.
This systematic review and meta-analysis including 66 studies that have assessed the risk of accident associated with the use of different types of drugs when driving. For fatal crashes, adjusting for publication biases, there was a 31% increased risk from cannabis, compared to 3-fold increase from cocaine, and 2-fold increased risk from benzodiazepine tranquilizers.

Avoiding unintentional marijuana exposures

1. *Pediatric marijuana exposures in a medical marijuana state.* Wang GS. *JAMA Pediatrics* 2013; 167:630-33.
This is a timely report by George Sam Wang about increases noted in unintentional marijuana poisonings showing up in the emergency department of Childrens' Hospital in Denver subsequent to the legalization of medical marijuana in Colorado in 2009. See also accompanying editorials in this same issue of *JAMA Pediatrics* by Sharon Levy from Harvard (pp 60-61) and William Hurley from Seattle (pp 602-603) commenting on the potentially large impact on children of more widely available cannabis products in homes.
2. *Association of unintentional pediatric exposures with decriminalization of marijuana in the United States.* Wang GS et al. *Annals of Emergency Medicine* 2014; 63:1450-55.
This is an analysis of national data from poison control centers, showing that although unintentional marijuana ingestion is uncommon, it has increased more in states that have legalized medical marijuana than in states that have not over time.