

Marijuana: Clearing the Smoke on Clinical and Policy Issues

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Learning objectives

- Define the key components of marijuana as a substance and review relevant epidemiology and terminology
- Explore US policy regarding MJ decriminalization to legalization
- Summarize adverse health effects and other potential risks of marijuana use
- Examine the tension between health risks of marijuana vs. marijuana as medicine

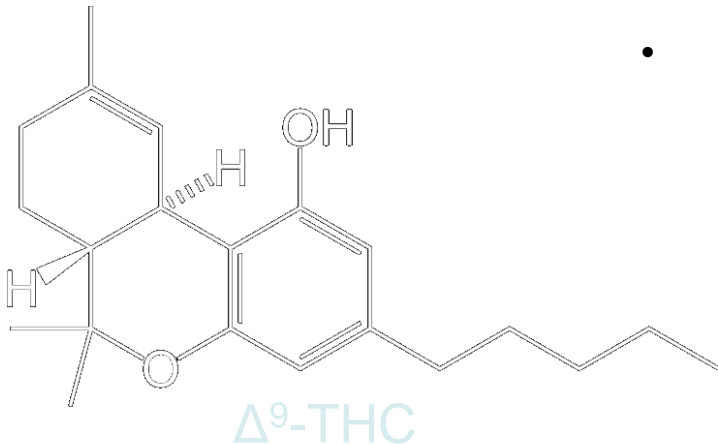


What is marijuana?

- Dried flowers, leaves, stems and seeds of the *Cannabis sativa* plant
- Usually smoked as a cigarette or in a pipe; can be orally ingested
- Potency related to concentration of Δ^9 -tetrahydrocannabinol (THC) and route of administration



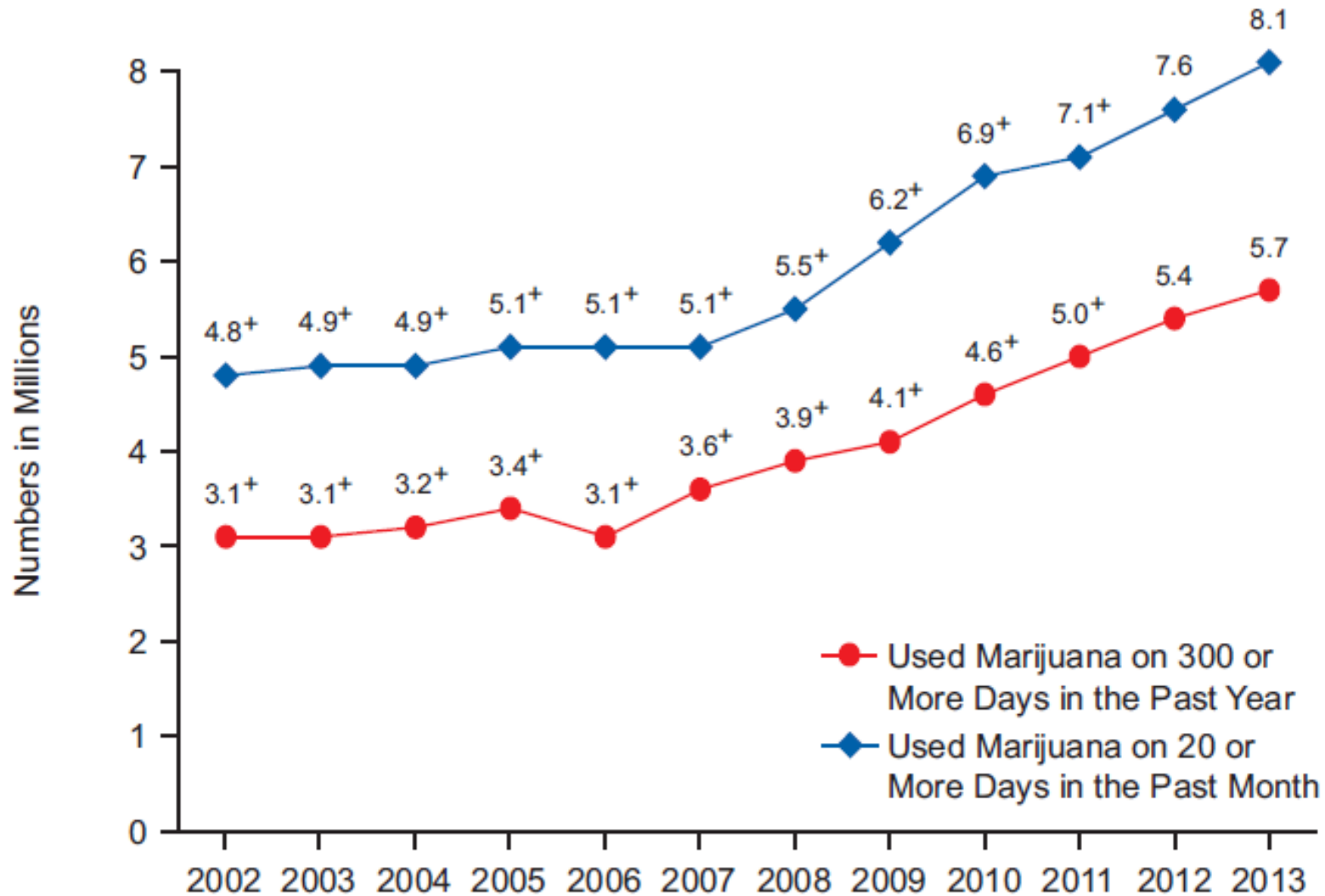
Δ^9 -TETRAHYDROCANNABINOL (THC)



- Psychoactive ingredient in *Cannabis sativa*
- Synthetic form is active ingredient of dronabinol (Marinol), approved in 1985 for intractable nausea
- 70+ other cannabinoids, many of which are present to varying degrees in a single *C. sativa* plant; **some non-THC cannabinoids *may* have medical use**



Marijuana use among individuals age 17 or older

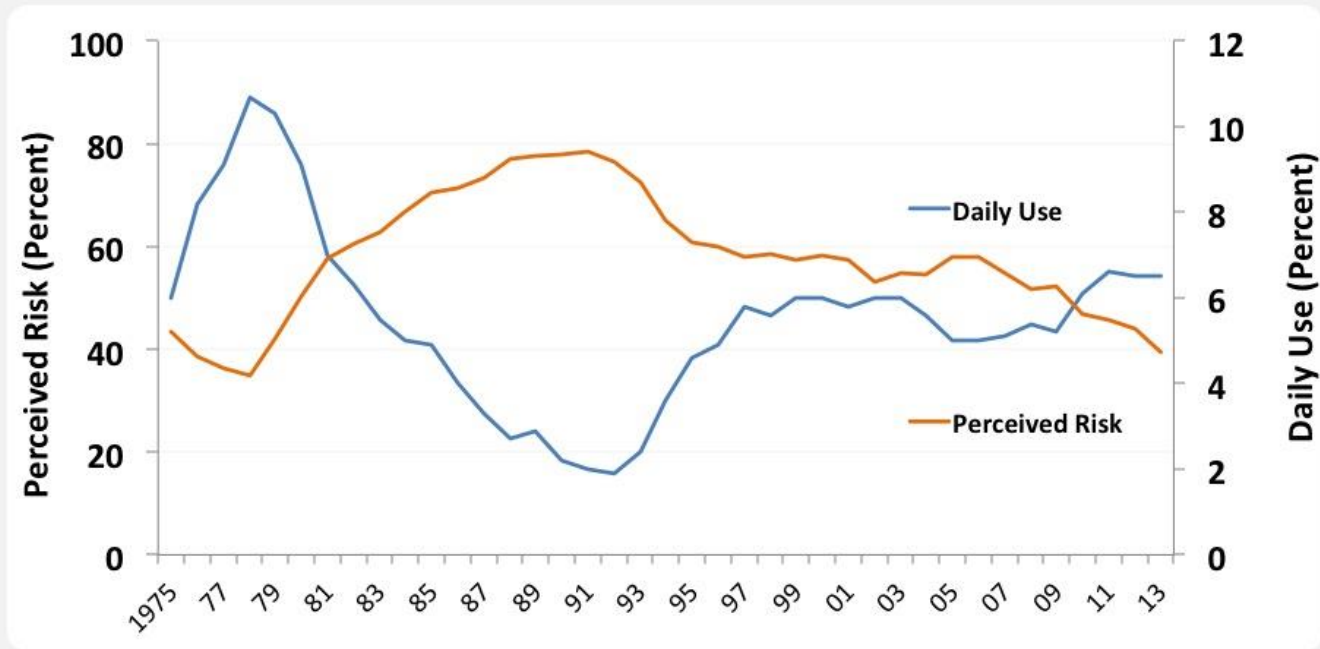


NSDUH 2013



Why the increase?

Daily Marijuana Use vs. Perceived Risk of Regular Marijuana Use among 12th Graders, 1975-2013



Source: University of Michigan, 2013 Monitoring the Future Study



Cannabis Use Disorder DSM 5

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by two or more of the following within a 12-month period:

- Cannabis is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control cannabis use
- A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects
- Craving, or a strong desire or urge to use cannabis



Cannabis Use Disorder, Cont'd

- Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis
- Important social, occupational, or recreational activities are given up or reduced because of cannabis use
- Recurrent cannabis use in situations in which it is physically hazardous
- Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by use
- Tolerance
- Withdrawal



Cannabis withdrawal: New to DSM 5

- Cessation of cannabis use that has been heavy and prolonged
- Three or more of the following signs and symptoms develop within approximately one week after the cannabis cessation:
 - Irritability, anger, or aggression
 - Nervousness or anxiety
 - Sleep difficulty (eg, insomnia, disturbing dreams)
 - Decreased appetite or weight loss
 - Restlessness
 - Depressed mood
 - At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
- Cause distress or impairment
- No other explanation for symptoms

Of note, symptoms generally resolve in 7-14 days but may persist for weeks



US *Love-Hate* Relationship



Reefer Madness, 1936
“A cautionary tale about the ill effects of marijuana ... a trio of drug dealers try to corrupt innocent teenagers with wild parties and jazz music.”



Fast Times at Ridgemont High, 1982...
Jeff Spicoli



US *Love-Hate* Relationship



Reefer Madness, 1936
“A cautionary tale about the ill effects of marijuana ... a trio of drug dealers try to corrupt innocent teenagers with wild parties and jazz music.”



Harold and Kumar Go To White Castle
2004



Policy timeline

- 1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I drug
- 1985: dronabinol (synthetic THC) approved in the US for treatment of intractable nausea
- 1996-2018: 29 states + PR, Guam medical marijuana, 9 states & D.C. legalize recreational use
- 2005: Supreme Court decision (Gonzales v. Raich)
 - Federal law enforcement has the authority to arrest and prosecute MDs or patients
- 2009, 2014: Department of Justice Memorandum
 - Federal resources should not be used to prosecute those who comply with states laws
- 2008-2010: IOM, ACP, AMA
 - Petitioned DEA/FDA to reschedule marijuana to schedule II ...it remains schedule I to this day
- 2018: AG Sessions rescinds Obama-era memoranda
- 4/20/18: Schumer (D, NY)- Introduces bill to decriminalize marijuana



Moderate acute effects

- Acute marijuana intoxication
 - agitation, psychosis, and anxiety
 - tachycardia and hypertension
- Cannabinoid Hyperemesis Syndrome
- Pediatric Exposures

Kim & Monte Annals of Em Med 2016

Yale School of Medicine, Section of General Internal Medicine

Cannabinoid Hyperemesis Syndrome



Symptoms:

- Cyclic Vomiting (Can last for hours or days)
- Abdominal Pain
- Excessive thirst
- Nausea
- Gastric Pain
- Compulsive bathing (to ease the pain)

THE PARADOX?

Marijuana can help with nausea and appetite

But not when it is consumed in

EXCESS



GREEN RUSH DAILY

<https://www.greenrushdaily.com/2016/08/17/cannabinoid-hyperemesis-syndrome-cannabis/>

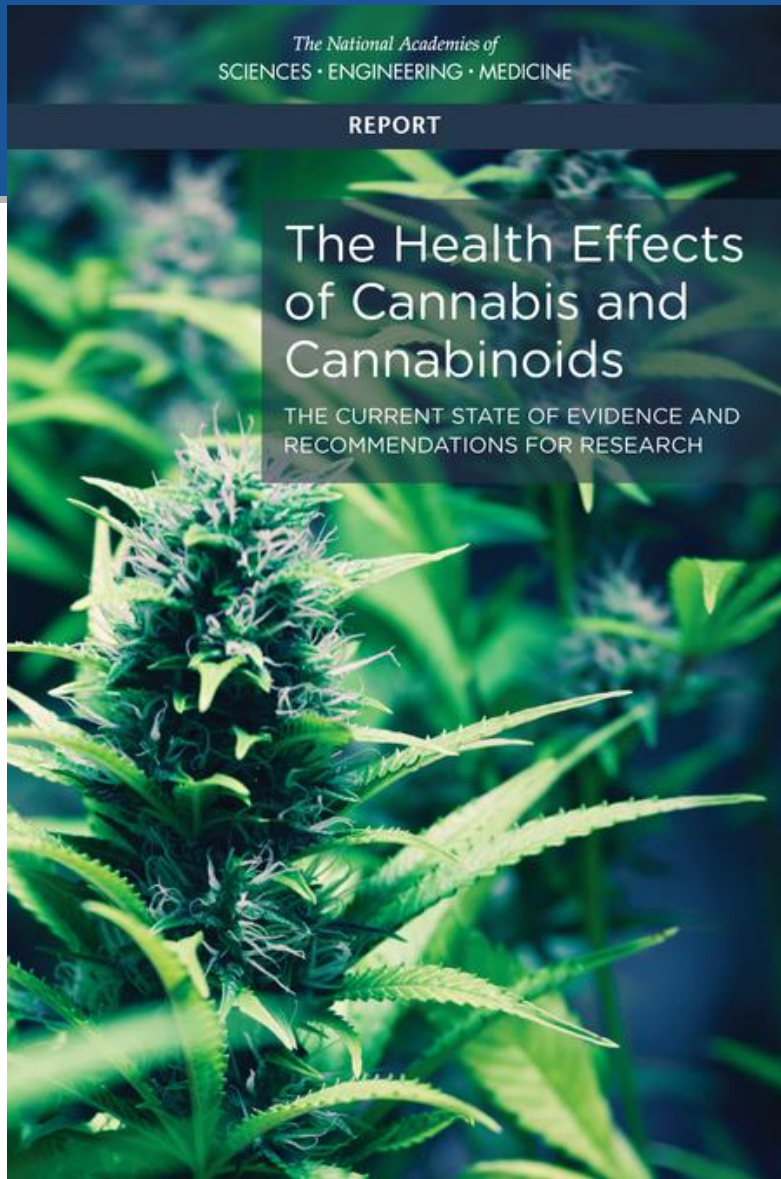


Adverse effects of marijuana use

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low



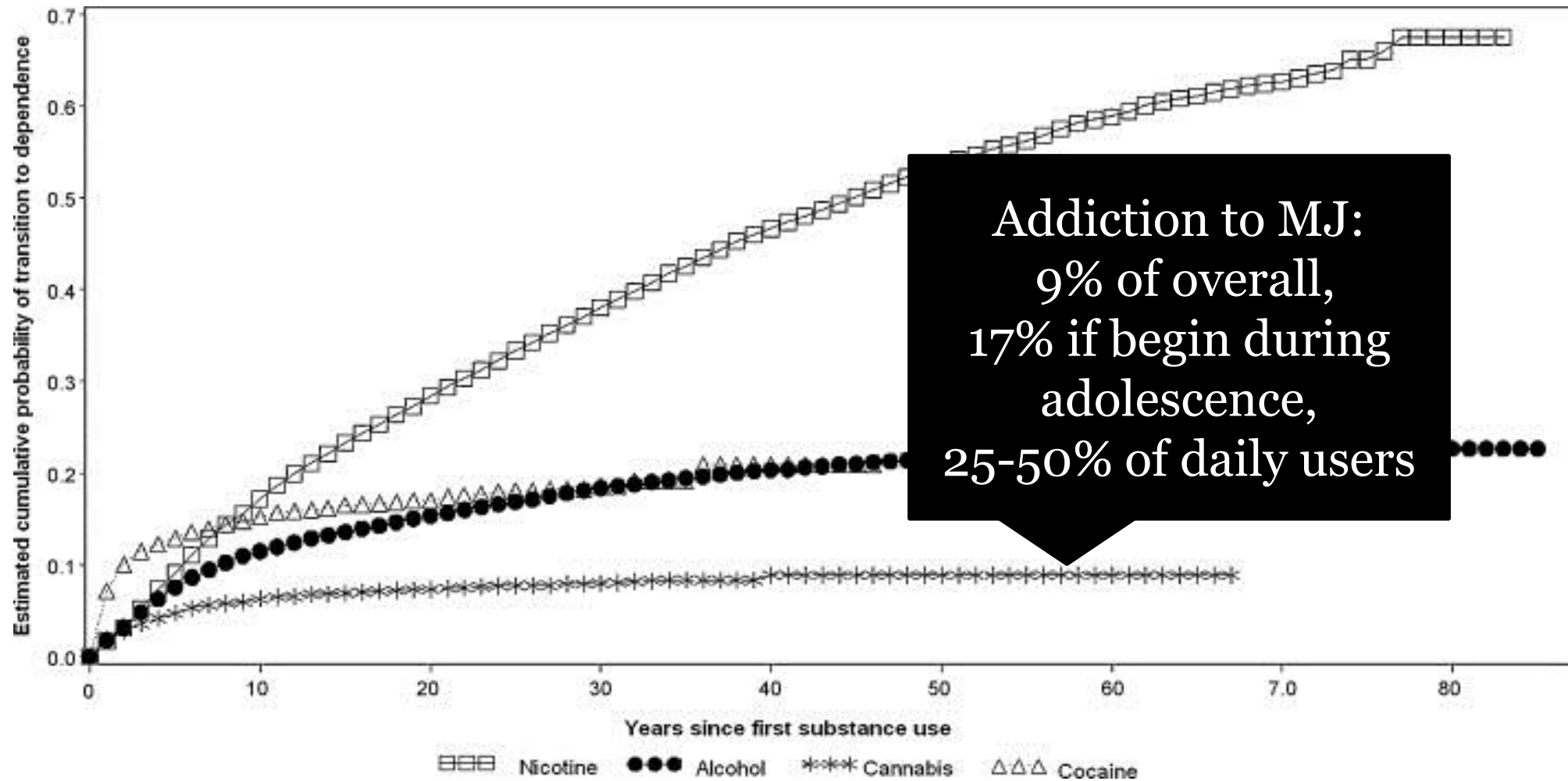


- 16 person committee reviewed > 10,000 abstracts published since 1999
- Focused on recently published systematic reviews and high quality primary research for 11 groups of health effects including both harms and therapeutic effects

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Health Effects of Cannabis and Cannabinoids. 2017



Cumulative Probability of Transitioning to Substance Use Disorder for Nicotine, Alcohol, Marijuana and Cocaine



Lopez-Quintero, C. et al. *Drug & Alcohol Dependence* 2011



Health effects of cannabis and cannabinoids: SUD

There is substantial evidence that:

- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use

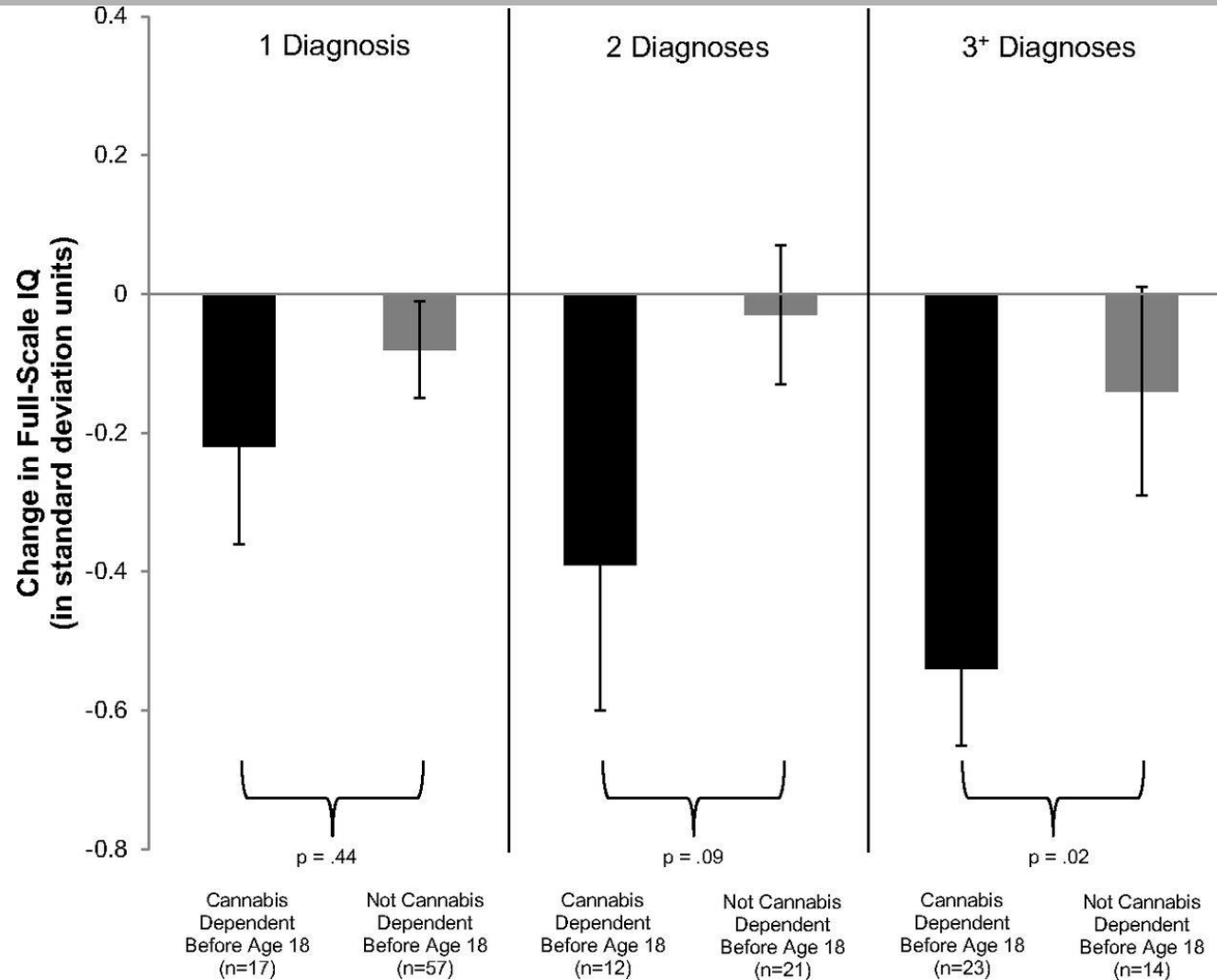
There is moderate evidence of a statistical association between cannabis use and:

- The development of substance use disorder for substances, including alcohol, tobacco, and other illicit drugs

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Adolescent vulnerability in IQ decline



Meier M H et al. PNAS 2012



Health effects of cannabis and cannabinoids: Psychosocial domains

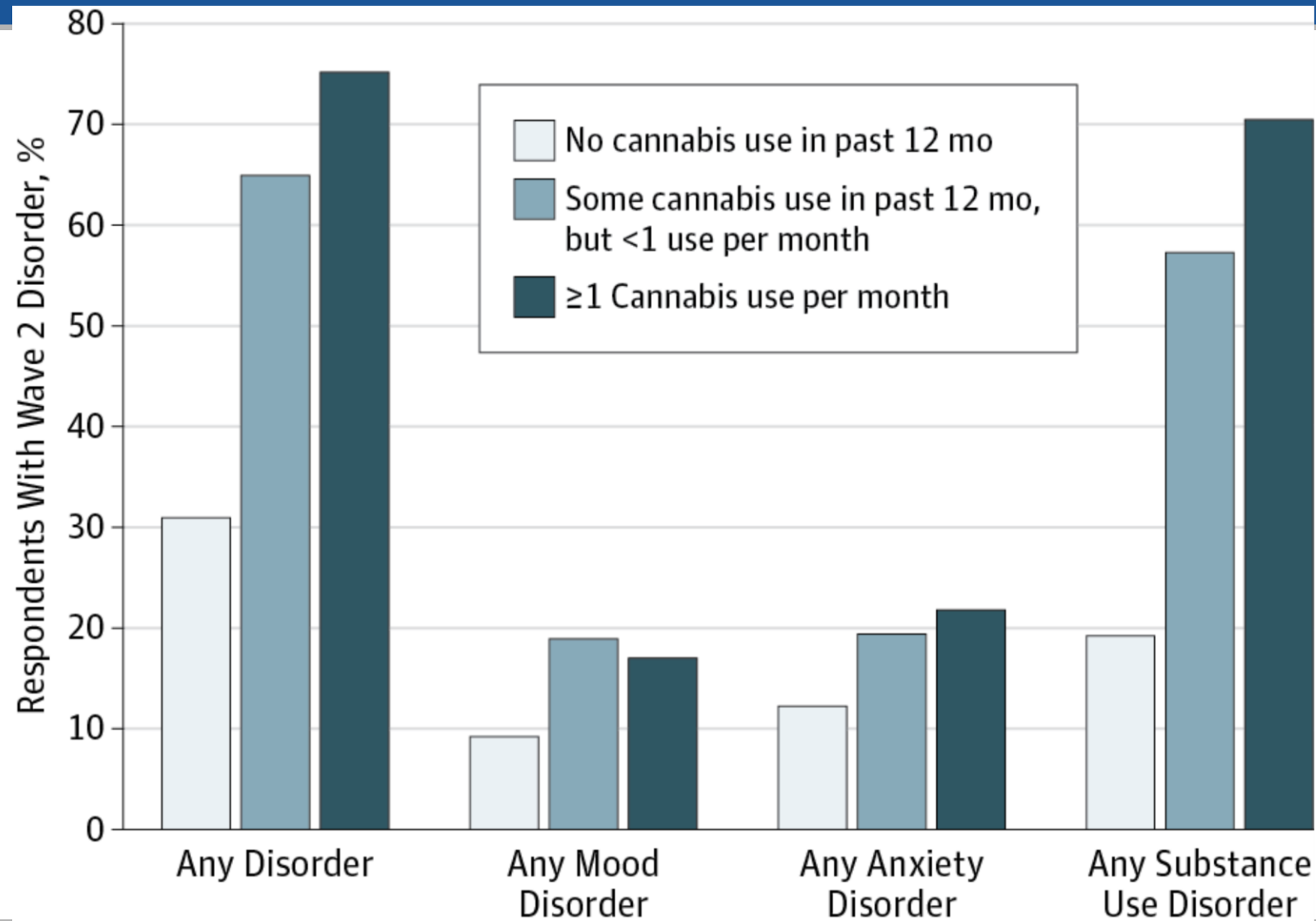
There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention

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Association between mental health conditions and MJ use



Health effects of cannabis and cannabinoids: Mental Health

There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users

There is moderate evidence of a statistical association between cannabis use and:

- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use)
- A small increased risk for the development of depressive disorders
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users
- Increased incidence of suicide completion
- Increased incidence of social anxiety disorder (regular cannabis use)
- Major depressive disorder is a risk factor for the development of problem cannabis use

Pulmonary effects of smoked marijuana

- Acute → bronchodilation (FEV₁ increase ~ 0.15-0.25L)
- Long-term → cough (OR 2.0, 95% CI 1.32-3.01), phlegm, wheeze; however data were inconclusive regarding an association between long-term marijuana smoking and airflow obstruction(1)
- At low levels of exposure, FEV₁ increased by 13 mL/joint-year and FVC by 20 mL/joint-year, but at higher levels of exposure, airflow obstruction was observed(2)

1. Tetrault JM et al. Archives IM 2007

2. Pletcher MJ et al. JAMA 2012



Health effects of cannabis and cannabinoids: Respiratory disease

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use
- Higher forced vital capacity (FVC)

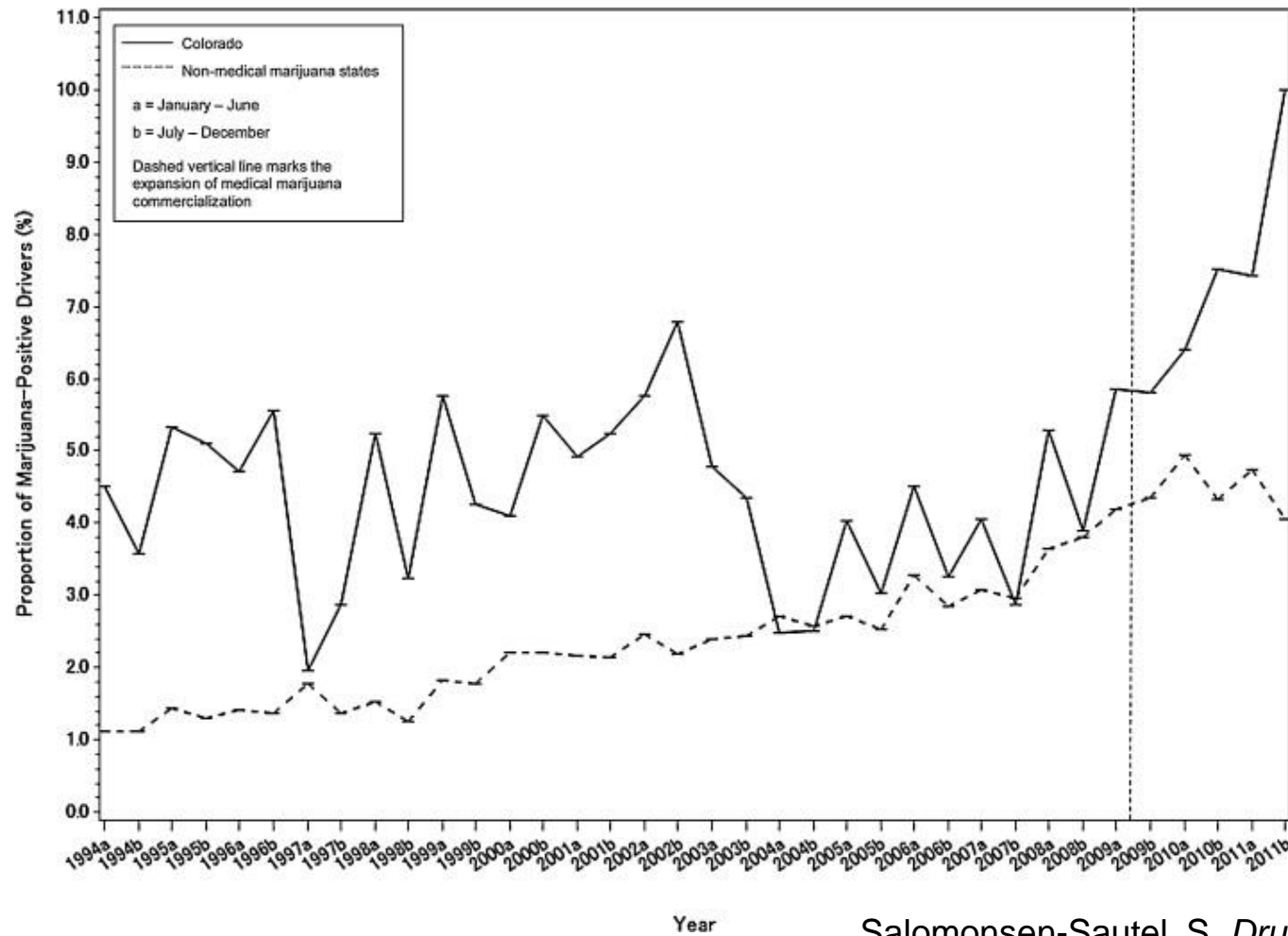
There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms

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Trends in fatal motor vehicle crashes before and after marijuana commercialization in CO



Salomonsen-Sautel, S. *Drug & Alcohol Dependence*, 2014



Health effects of cannabis and cannabinoids: Injury and death

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

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Treatment Options

- Pharmacotherapy
 - No currently approved medication
 - cannabinoid antagonist
 - oral THC for withdrawal, maintenance or short-term treatment?
 - cannabinoid agonist—Levin FR DAD 2011
 - N-Acetylcysteine
- Behavioral
 - Substance use treatment setting
 - cognitive-behavioral therapy, contingency management, motivational enhancement, therapeutic living
 - General medical settings
 - Brief interventions



Synthetic marijuana: K2, Spice, etc.



- General Information:
 - Marketed as safe legal alternative to marijuana; generally smoked; very common among adolescents
- Effects:
 - Mild euphoria and relaxation
 - The ‘giggles’
 - Increased sensitivity to external stimuli
 - Frank, vivid hallucinations
- Adverse effects:
 - Dry mouth, palpitations, rapid HR, vomiting, agitation
 - **Not detected in urine**
 - May be adulterated with heavy metal residues or other fillers including rat poison-→ severe bleeding (Apr 2018)

Fundamental tension

- Intoxication and withdrawal of marijuana are not fatal
- Overdose is unlikely
- Long-term, moderate use seems to be relatively frequent (compared to other drugs)
- Risk of end-organ damage appears to be lower than several other legal and illegal substances
- Ratio of medical benefit to harm *may be* equal or better than some controlled substances



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PHARMACOPŒIA
OF THE
LANE LIBRARY
UNITED STATES OF AMERICA.

BY AUTHORITY OF THE
NATIONAL MEDICAL CONVENTION,
HELD AT
WASHINGTON,
A. D. 1850.



PHILADELPHIA:
LIPPINCOTT, GRAMBO, & CO.
SUCCESSORS TO GRIGG, ELLIOT, & CO.
1851.

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Health effects of cannabis and cannabinoids: Therapeutic effects

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

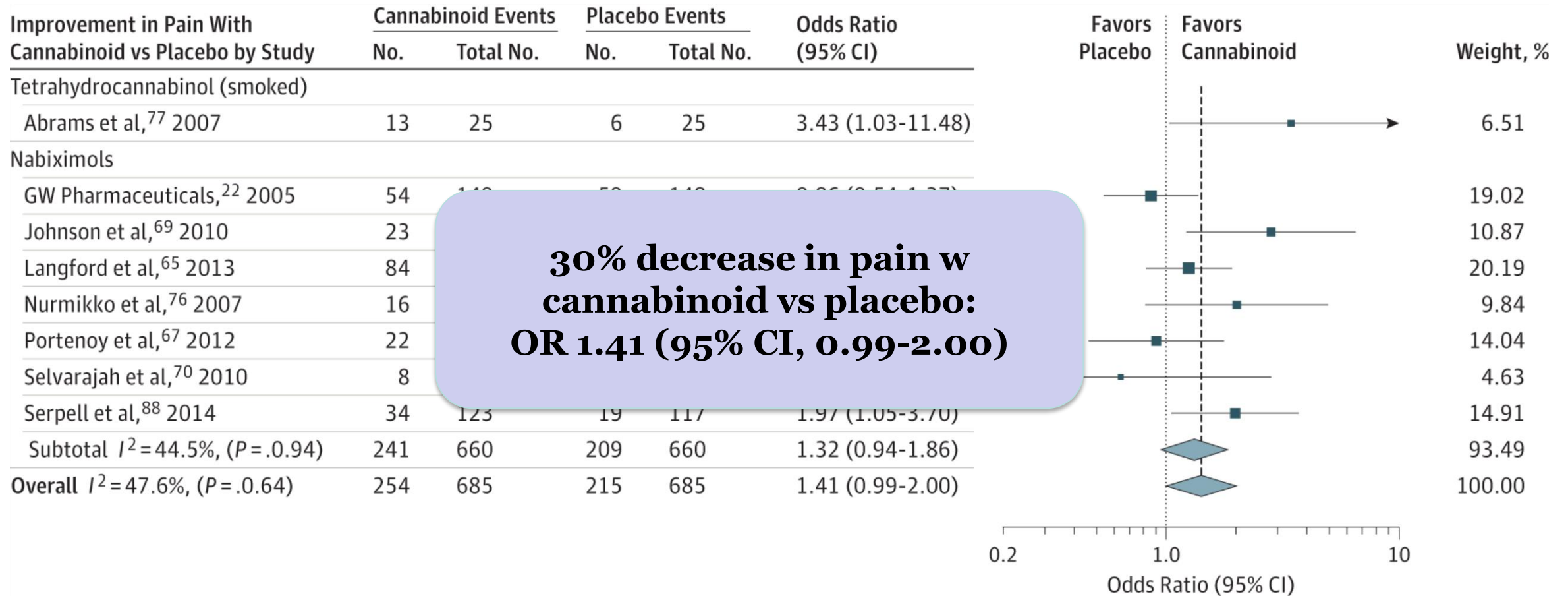
There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols)

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Cannabinoids for medical use: Pain



Medical Marijuana and OD risk

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

Independent Variable ^a	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
	Estimate (95% CI) ^b	Estimate (95% CI) ^c	Estimate (95% CI) ^d
Medical cannabis law	-24.8 (-37.5 to -9.5) ^e	-31.0 (-42.2 to -17.6) ^f	-23.1 (-37.1 to -5.9) ^e
Prescription drug monitoring program	3.7 (-12.7 to 23.3)	3.5 (-13.4 to 23.7)	7.7 (-11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (-10.4 to 23.1)	4.1 (-11.4 to 22.5)	2.3 (-15.4 to 23.7)
Increased state oversight of pain management clinics	-7.6 (-19.1 to 5.6)	-11.7 (-20.7 to -1.7) ^e	-3.9 (-21.7 to 18.0)
Annual state unemployment rate ^g	4.4 (-0.3 to 9.3)	5.2 (0.1 to 10.6) ^e	2.5 (-2.3 to 7.5)

^a All models adjusted for state and year (fixed effects).

^b $R^2 = 0.876$.

^c All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; $R^2 = 0.873$.

^d Findings include all heroin overdose deaths, even if no opioid analgesic was

involved. All covariates were the same as in the primary analysis. $R^2 = 0.842$.

^e $P \leq .05$.

^f $P \leq .001$.

^g An association was calculated for a 1-percentage-point increase in the state unemployment rate.

Bachhuber MA et al. JAMA 2014



Marijuana legislation and prescription opioids

- Between 2011-2016, among Medicaid enrollees, medical marijuana laws associated with **5.88% lower opioid prescribing rates**
 - Adult-use marijuana laws associated with 6.38% lower opioid prescribing rates
- Between 2010-2015, among Medicare part D recipients, **prescriptions filled for all opioids decreased by 2 million daily doses** per year from an average of 23 million daily doses per year when a state instituted any medical cannabis law.
 - Prescriptions for all opioids decreased by 3.742 million daily doses per year when medical cannabis dispensaries opened.
- Cannabis use associated with **increase in nonmedical use of prescription opioids** (OR 5.78, 95% CI 4.23-7.9)
 - Cannabis use associated with OUD (OR 7.76, 95% CI 4.95-12.2)

Wen, H et al, JAMA Internal Medicine Apr 2018
Bradford AC et al. JAMA Internal Medicine Apr 2018
Hill KP et al, JAMA Internal Medicine Apr 2018
Olfson M et al. Am J Psychiatry 2018



State Level Variation

- Physician certification for patients with certain qualifying diagnoses
- Patient may possess only a one month supply (varies)
 - CT=2.5 oz; WA=12 oz
- Growers are certified by Department of Consumer Protection to cultivate MJ
 - Application fee often prohibitive
- Pharmacists able to obtain a dispensing license from DCP
 - State regulates amount of licenses



Challenges in conducting research on adverse health effects or therapeutic effects of cannabis

- Regulatory barriers, including the classification of cannabis as a Schedule I substance, impede the advancement of cannabis research
- Difficult for researchers to gain access to the quantity, quality, and type of product necessary to address research questions on health effects
- A diverse network of funders is needed to support cannabis research
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed

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Thank you

Questions?

Acknowledgements: several slides adapted from Dr. William Becker (Yale), Dr. Hilary Kunins (NY DPH), Dr. Jeffrey Hunt (Brown), Dr. Zoe Weinstein (BU)

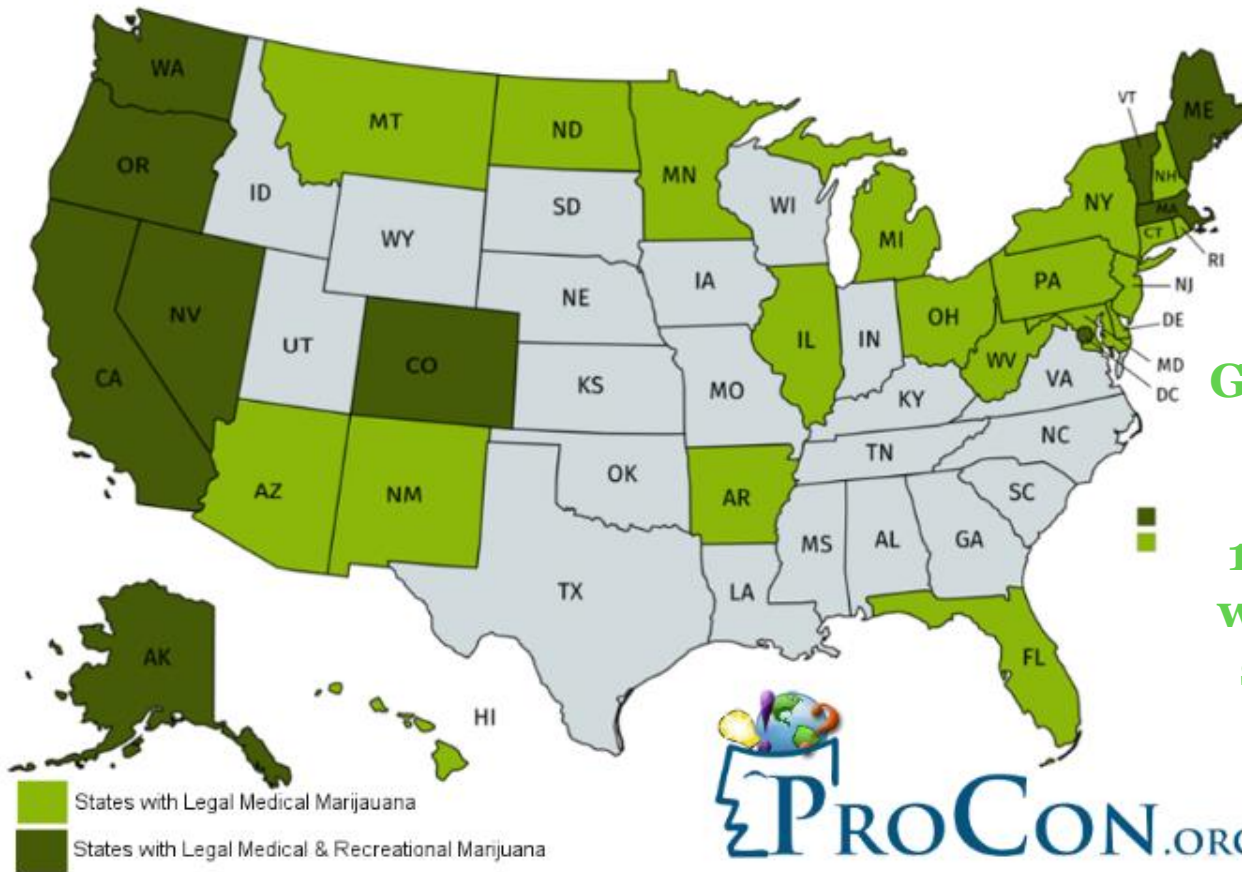


Extra Slides



Current State of the Union

29 Legal Medical Marijuana States & DC
9 Legal Recreational Marijuana States & DC



Guam, PR

17 States
with CBD
specific
laws

States with Recreational Laws:

Washington
Oregon
California
Nevada
Alaska
Colorado
Massachusetts
Maine
Vermont
+ Washington D.C.



Interactive teaching scenario: Morning report/role play

- Set up a “spicy,” public health debate regarding legalization of recreational marijuana using the following citation as a spring board for discussion:

Kilmer B. Recreational Cannabis — Minimizing the Health Risks from Legalization. Perspective. NEJM. February 23, 2017
- Assign report participants to one of two groups:
 - Recreational marijuana SHOULD be legalized in all states nationwide
 - Citing adverse effects of criminalization and potential for increasing state budgets through taxation, potential impact on opioid epidemic
 - Recreational marijuana SHOULD NOT be legalized in all states nationwide
 - Citing current research on adverse health effects and natural experiment data from states that have already legalized recreational marijuana
- All arguments need to be evidence-based and factual



Other cognitive effects of marijuana

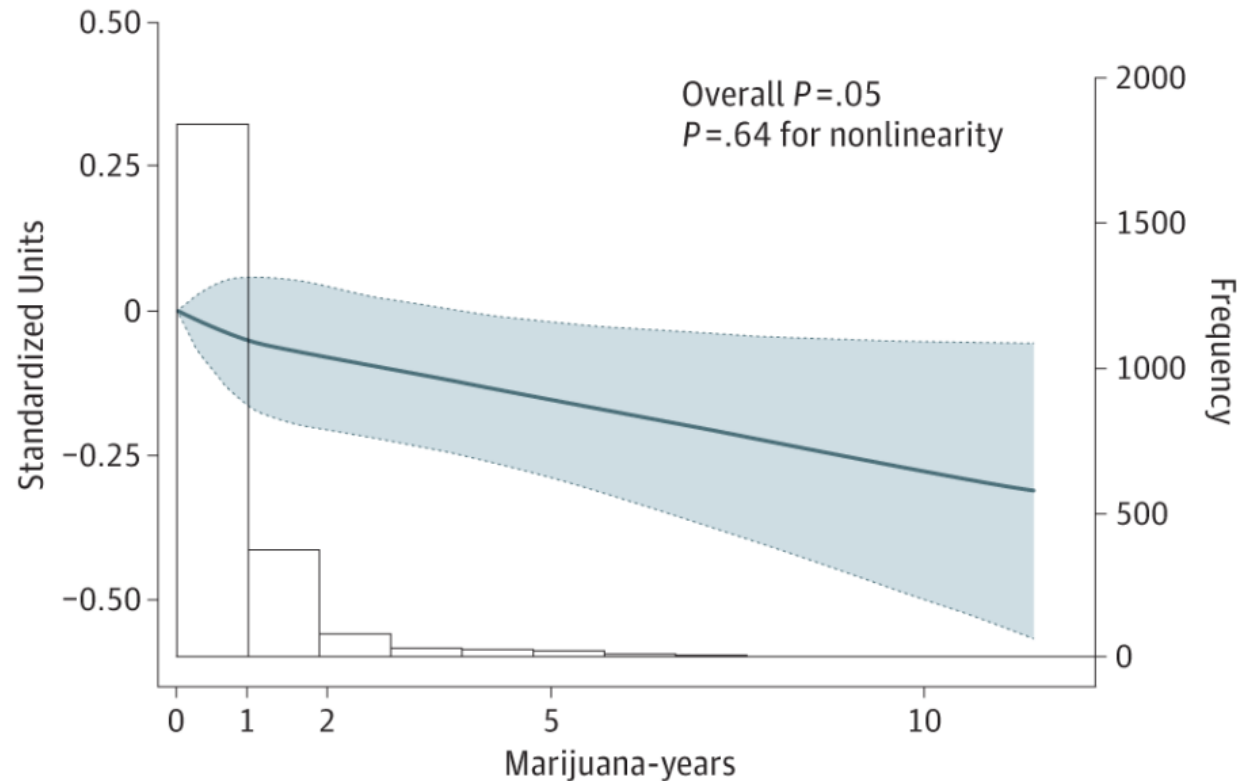
- In a large study of 5115 adults at 18-30yo at baseline followed up for 25 years
- Current use of marijuana associated with worse verbal memory and processing speed
- Cumulative lifetime exposure was associated with worse performance in verbal memory, processing speed and executive function
- For each 5 years of past exposure, verbal memory was 0.13 standardized units lower (95% CI, -0.24 to -0.02; $P = .02$)
 - corresponds to **remembering 1 word less from a list of 15, for every 5 years of use.**

Auer R et al. JAMA Intern Med. 2016;176(3):352-361

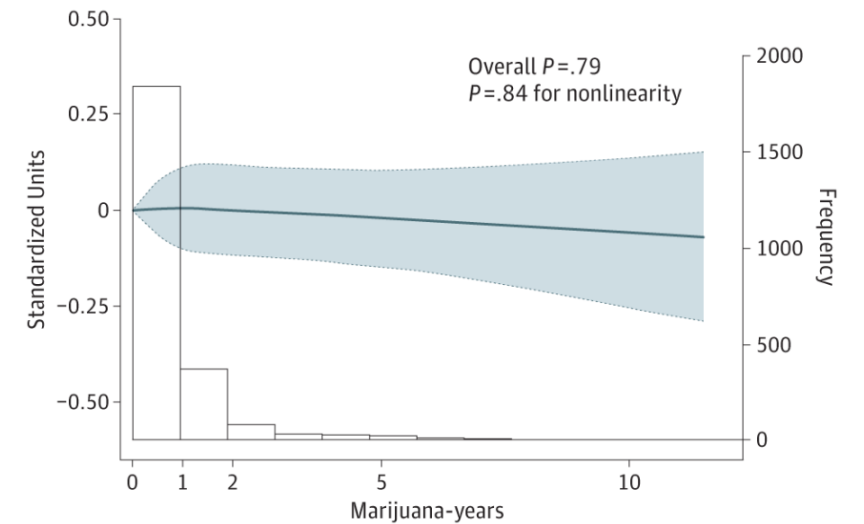


Association between lifetime marijuana use and cognitive function in middle age: The CARDIA Study

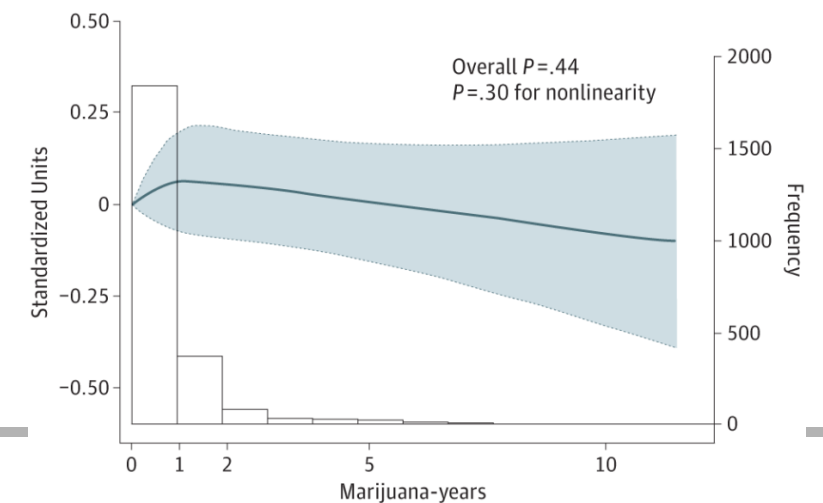
A Rey auditory verbal test



B Digital symbol substitution test

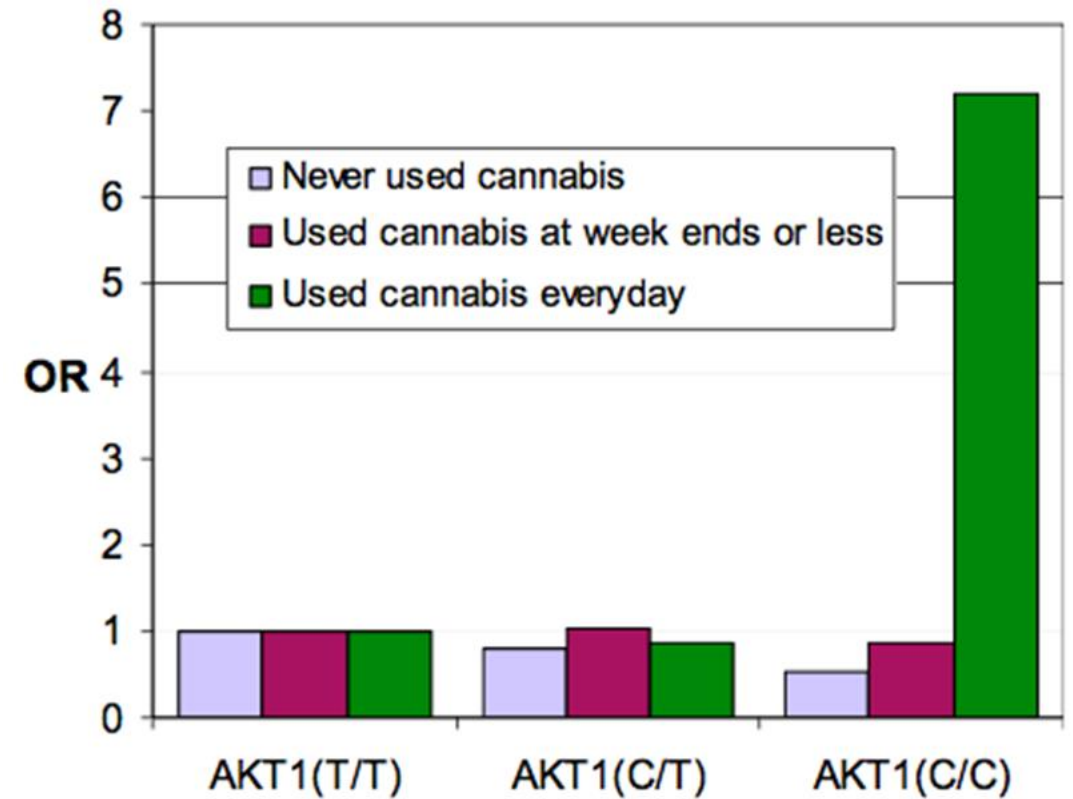
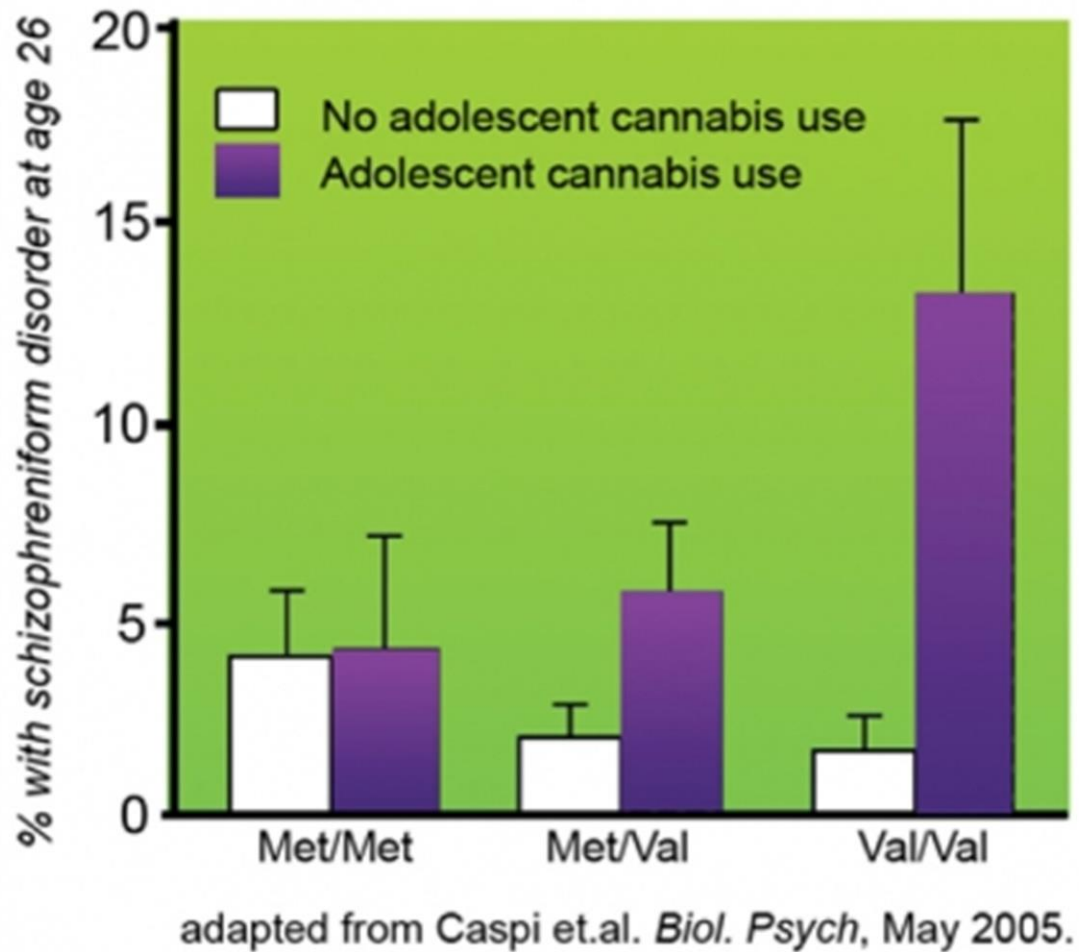


C Stroop test



Auer R et al. JAMA Intern Med. 2016;176(3):352-361

Genetic variation influences harmful effects of marijuana



BIOL PSYCHIATRY 2012;72:811-816



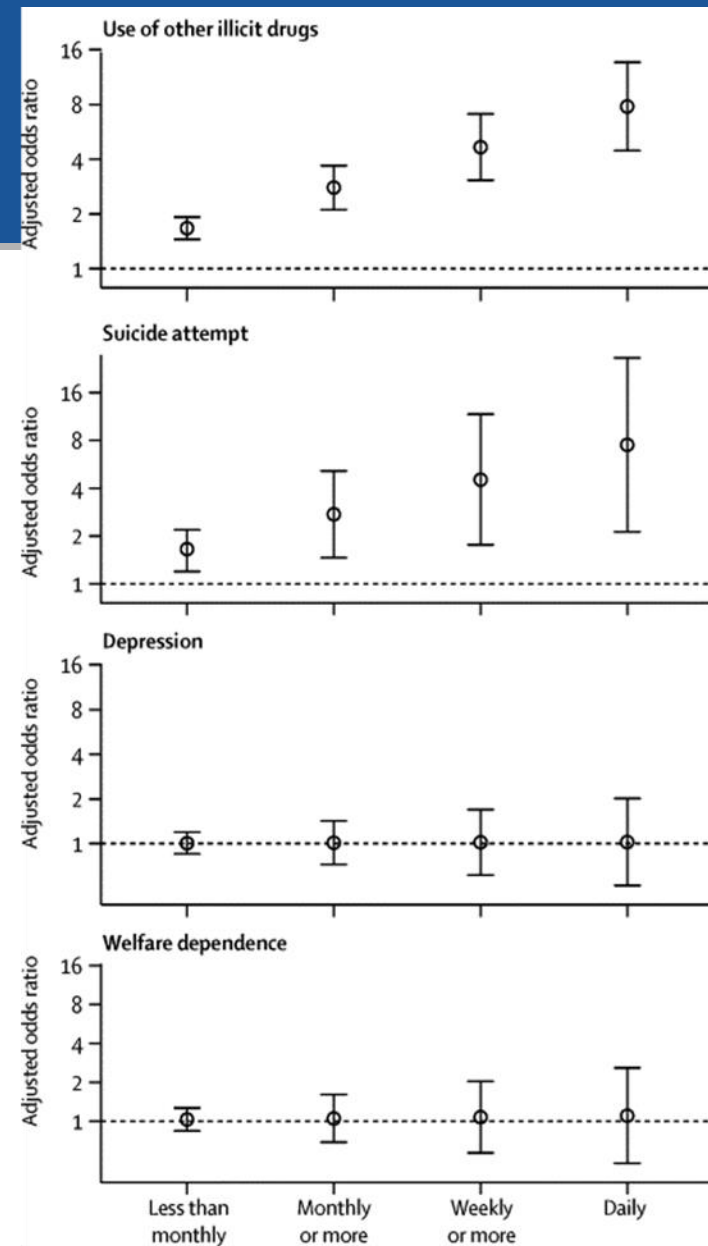
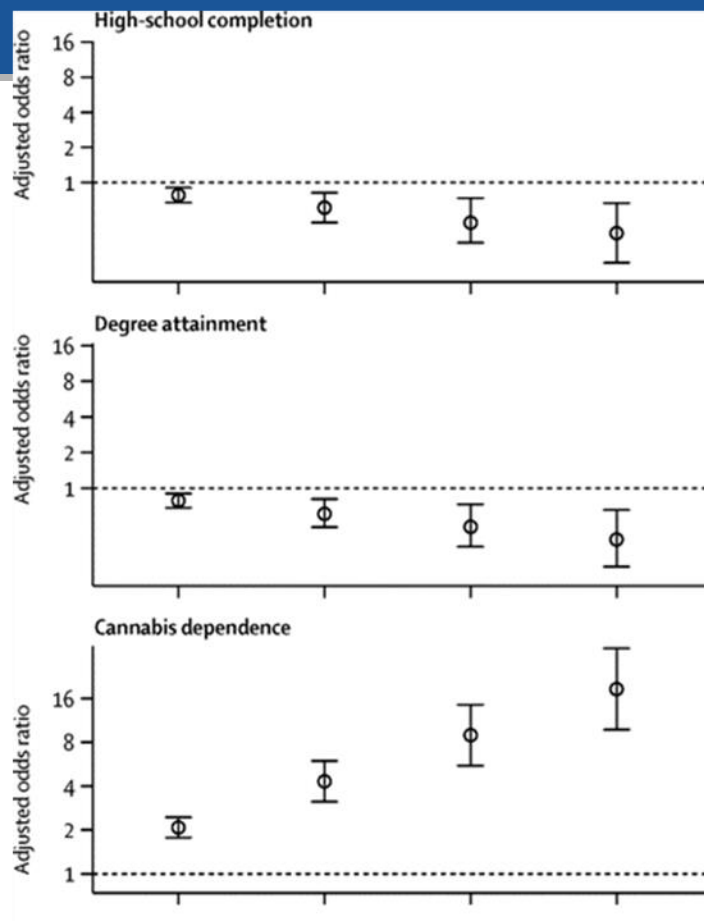
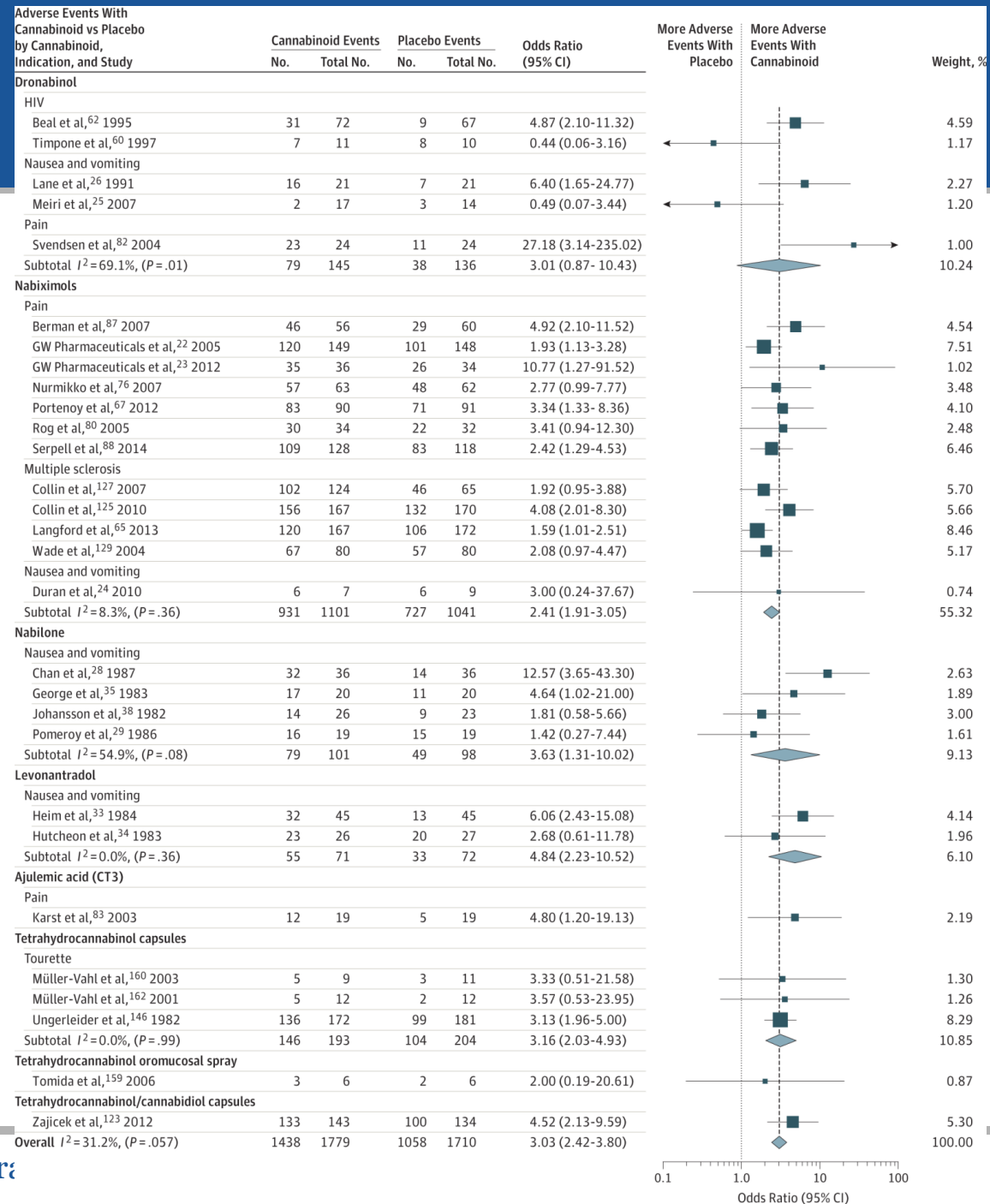


Figure 2. Adjusted odds ratios (log scale) between maximum frequency of cannabis use before age 17 years and young adult outcomes in combined data, compared with individuals who have never used cannabis. Error bars show 95% CIs.



Odds of Adverse Events

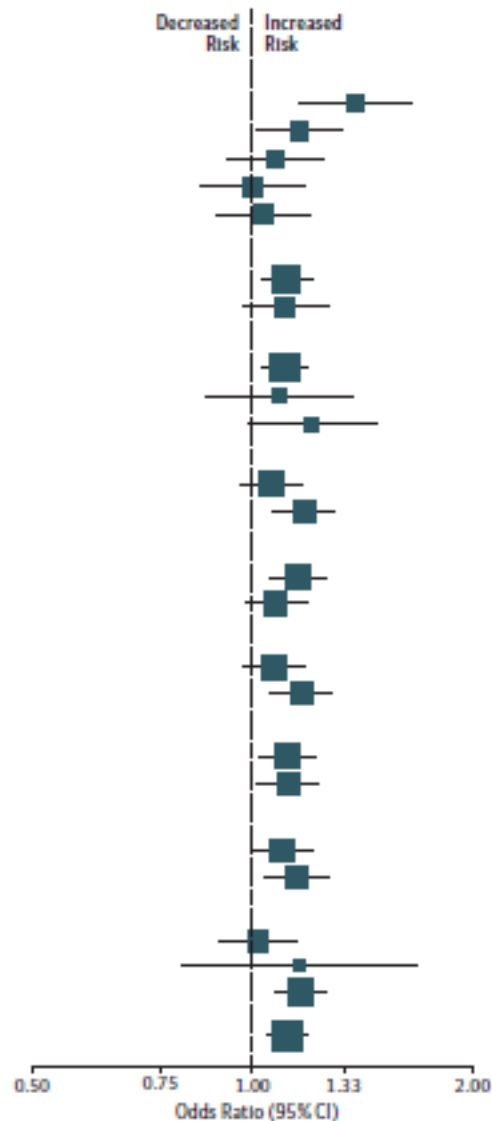


Whiting PF et al. JAMA. 2015;313(24):2456-2473



Figure 1. Relative Risk of Traffic Crash on April 20

Subgroup	Drivers in crashes on April 20	Drivers in crashes on control days
Age, y		
≤20	207	300
21-30	353	610
31-40	265	494
41-50	223	446
≥50	287	554
Sex		
Male	998	1792
Female	342	617
Vehicle type		
Passenger	1101	1988
Other	114	210
Motorcycle	154	255
Era		
Remote (1992-2003)	673	1266
Recent (2004-2016)	696	1187
Crash day		
Monday-Thursday	737	1279
Weekend (Friday-Sunday)	632	1174
Time of crash		
4:20 PM to 7:59 PM	681	1272
8:00 PM to midnight	688	1181
State-level cannabis use		
Less high	757	1375
Higher	612	1096
Road type		
Rural	672	1222
Urban	609	1060
Drug police report		
Negative	403	793
Positive	44	76
Not tested or not reported	922	1584
Entire cohort, No.	1369	2453



Forest plot showing relative increase in risk of a traffic crash on April 20 compared with control days exactly 1 week earlier and later. Solid squares indicate point estimate; relative dimensions, sample size, and horizontal lines, 95% CIs. Vertical columns show total counts between 4:20 PM and 11:59 PM on April 20 and control days. Main findings show an increase in relative risk on April 20, no significant contrary findings, and an accentuated effect for younger individuals. State-level estimates of the prevalence of marijuana use among adults from the 2002-2003 National Surveys on Drug Use and Health (near the midpoint of our study) were used to categorize states as "Higher use" (median and above) and "Less high use" (below the median).



Health effects of cannabis and cannabinoids: Other effects

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother
- Admission of the infant to the neonatal intensive care unit (NICU)

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking)
- Incidence of head and neck cancers

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