The Effects of Cannabis on the Developing Brain: From Prenatal Development Through Early Adulthood

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Disclosure Statement

- I have no actual or potential conflict of interest in relation to this presentation

Learning Objectives

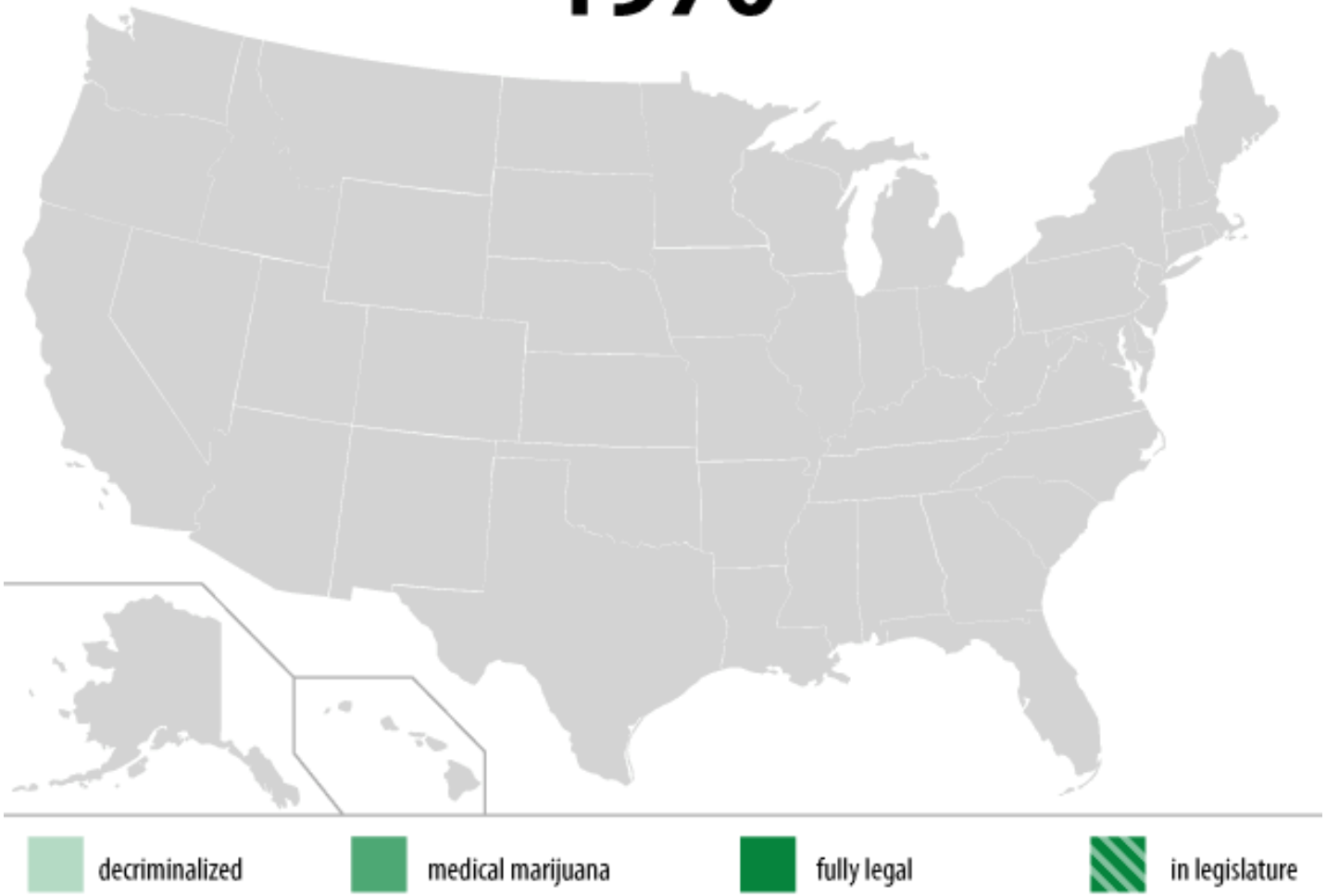
- After the conclusion of this presentation, participants will be able to:
  - Describe how THC moves through the body
  - Discuss acute effects of THC on the brain and on other parts of the body (e.g., heart and lungs)
  - Describe the potential long-term risks of prenatal cannabis exposure
  - Discuss the short-term and potential long-term risks of cannabis use in adolescents

DEA's position on marijuana

Marijuana is properly categorized under Schedule I of the Controlled Substances Act (CSA), 21 U.S.C. § 801, et seq. The clear weight of the currently available evidence supports this classification, including evidence that smoked marijuana has a high potential for abuse, has no accepted medicinal value in treatment in the United States, and evidence that there is a general lack of accepted safety for its use even under medical supervision.

Other Schedule I Substances: Heroin, lysergic acid diethylamide (LSD),3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote

1970



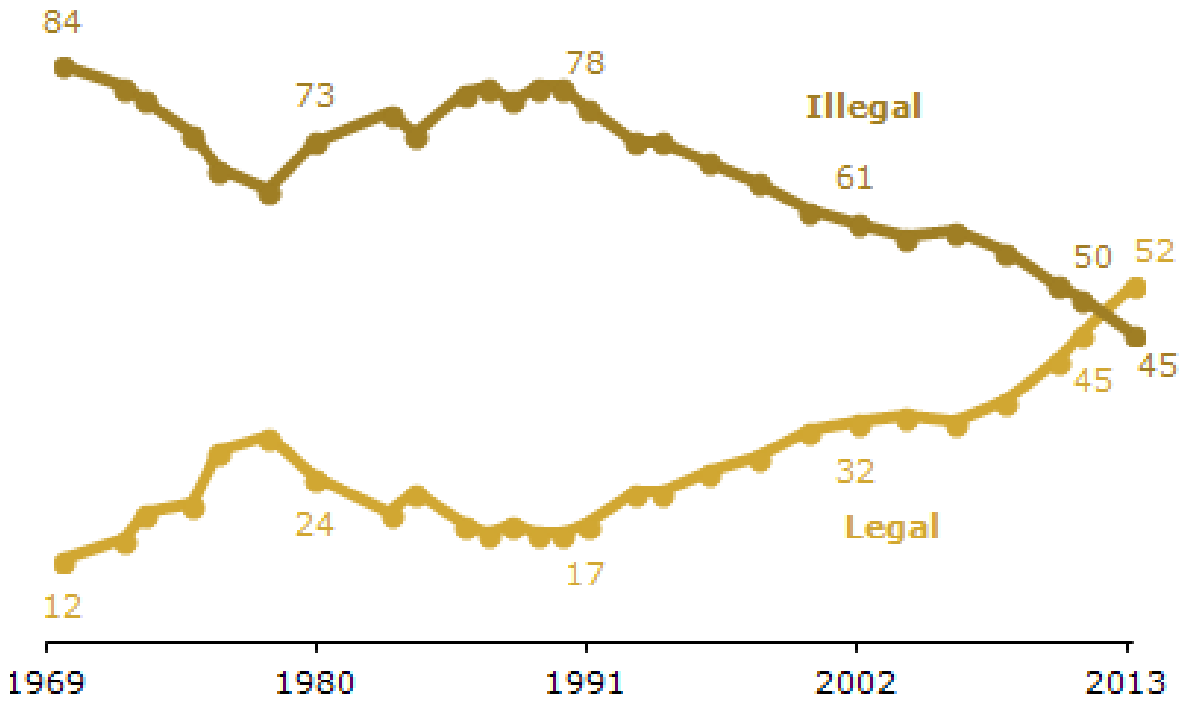
SOURCE: Wire Magazine (accessed 2014)

Initiative-502

- Adults **over 21 years old** can possess up to **1 ounce of marijuana** (or 16 ounces of solid marijuana-infused product, like cookies, or 72 ounces of infused liquid, like oil) for personal use

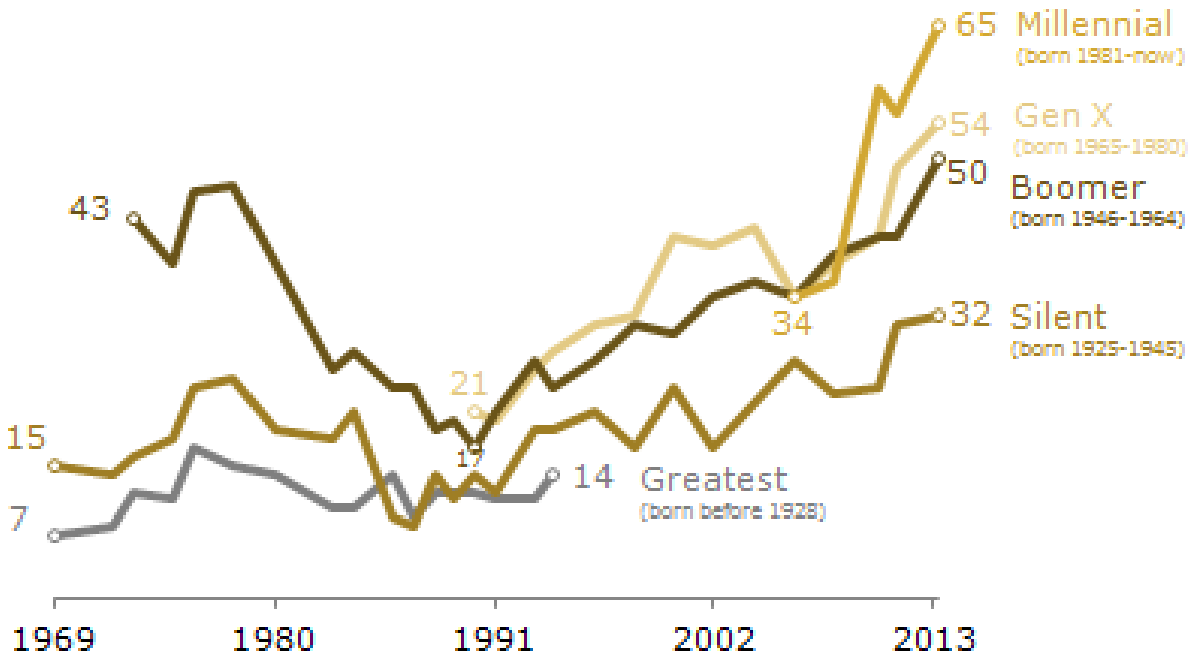
Views of Legalizing Marijuana: 1969-2013

% saying marijuana should be ...



PEW RESEARCH CENTER March 13-17, 2013.
1973-2008 data from General Social Survey; 1969 and 1972 data from Gallup.

Boomers' Support for Legalization Rebounds to 1970s Levels

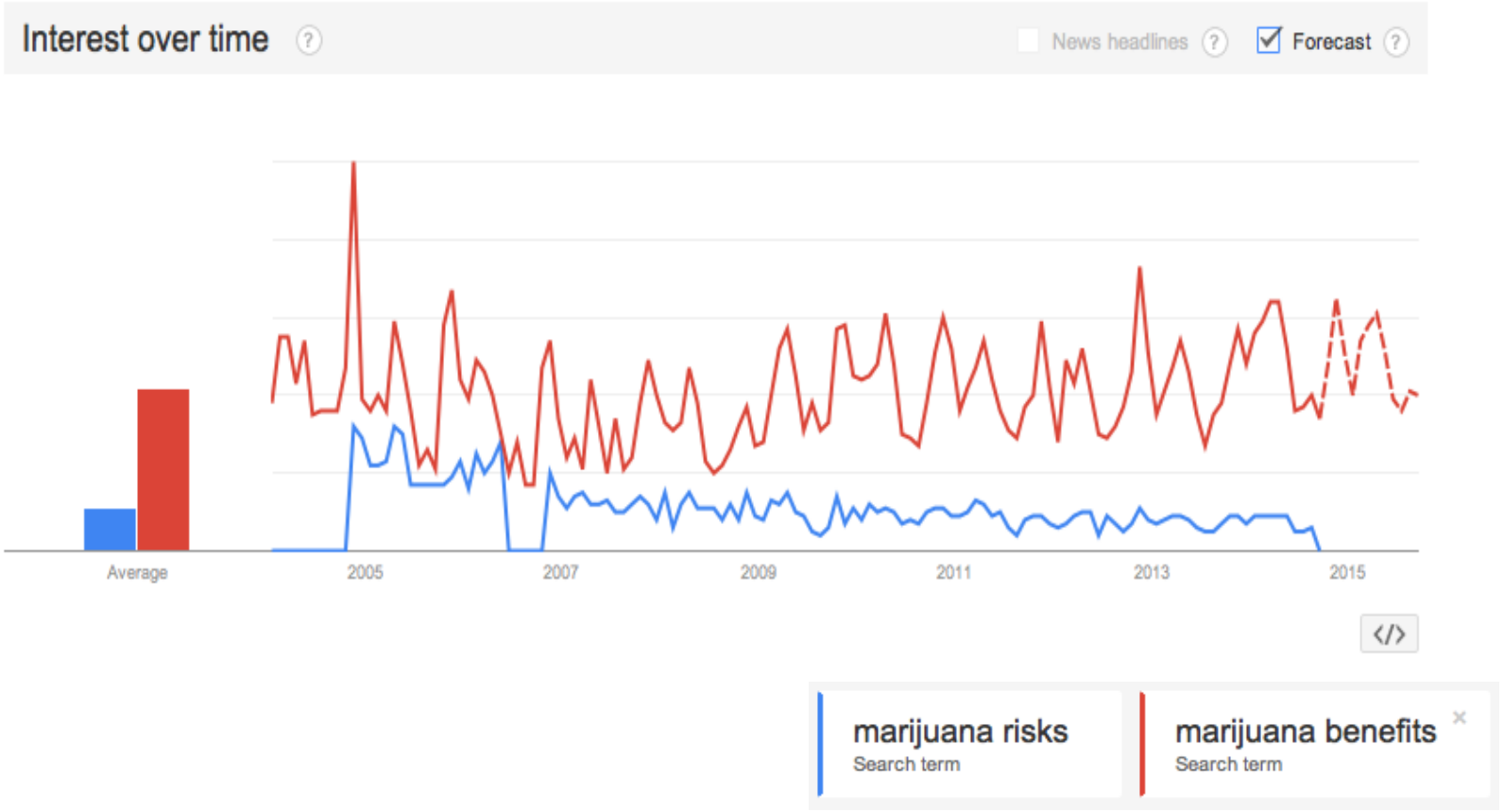


Younger

Older

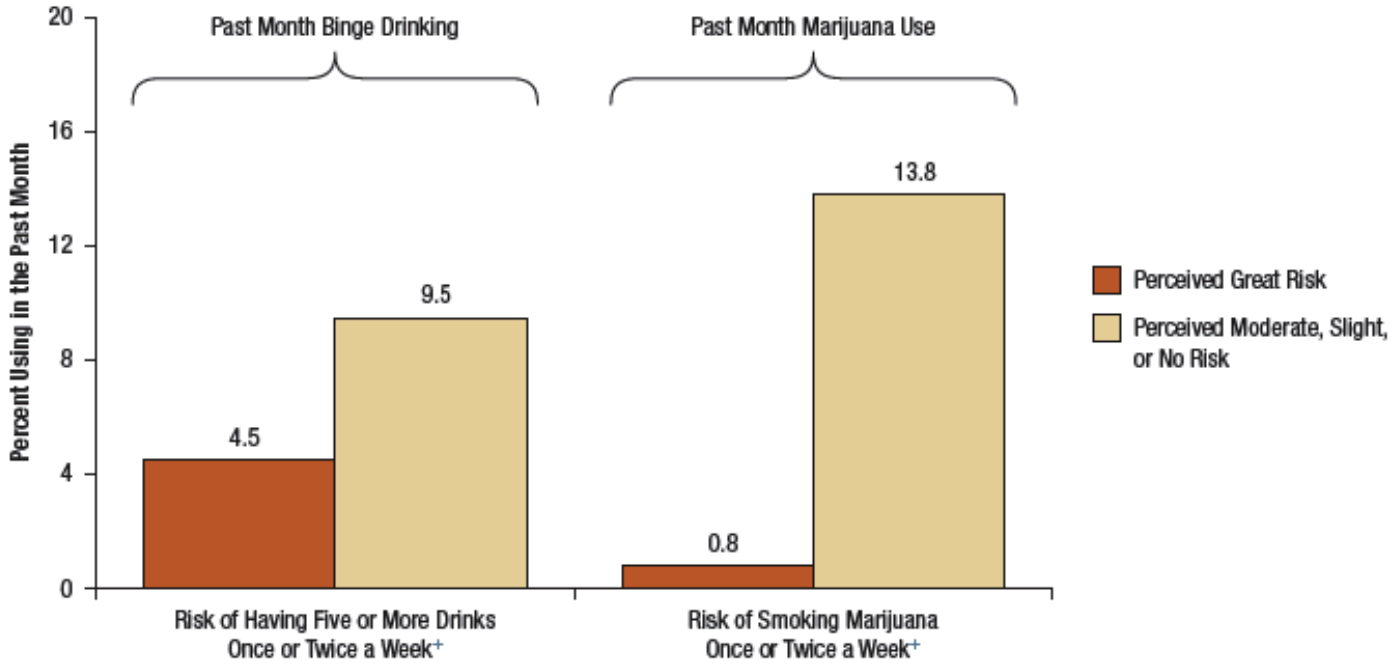
PEW RESEARCH CENTER March 13-17, 2013. 1973-2008 data from General Social Survey; 1969 and 1972 data from Gallup. Generational lines shown when significant sample is available.

Attitudes towards cannabis



Source: Google Trends

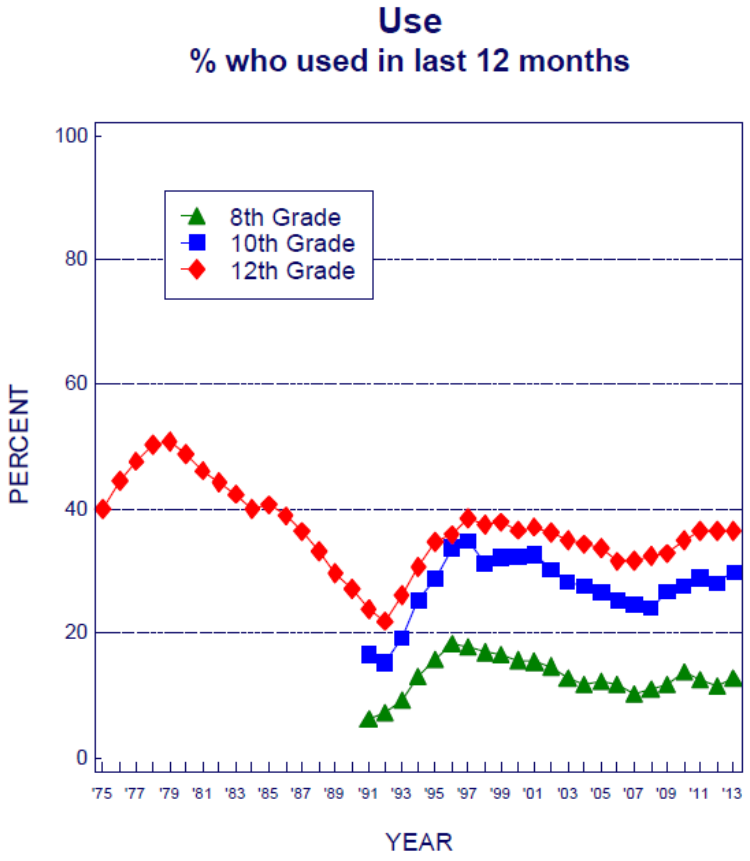
Past month binge drinking and marijuana use among adolescents aged 12 to 17, by perceptions of risk: 2011

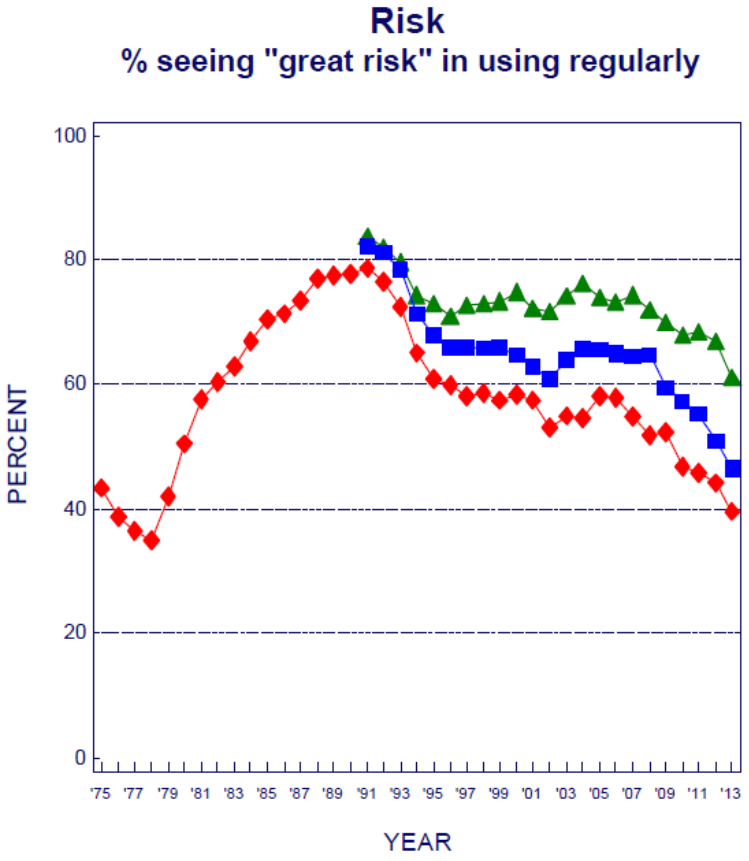


+ Difference between those perceiving great risk and those perceiving moderate, slight, or no risk is statistically significant at the .05 level.

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Surveys on Drug Use and Health (NSDUHs), 2002 to 2011 (revised March 2012).

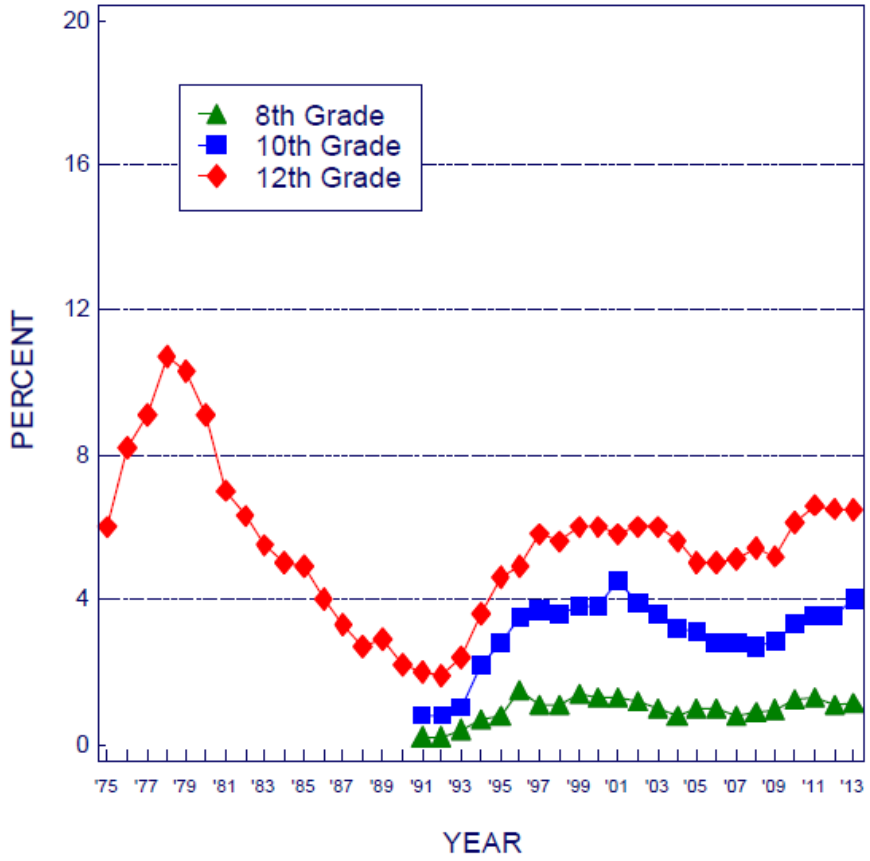
Marijuana: Trends in annual use, risk, disapproval, and availability Grades 8, 10, and 12





Source: The Monitoring The Future (2012).

Percentage of young people who report daily marijuana use



Source: Monitoring the Future (2012)

RESEARCH REPORT

doi:10.1111/j.1360-0443.2005.01322.x

Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis

David M. Fergusson, Joseph M. Boden & L. John Horwood

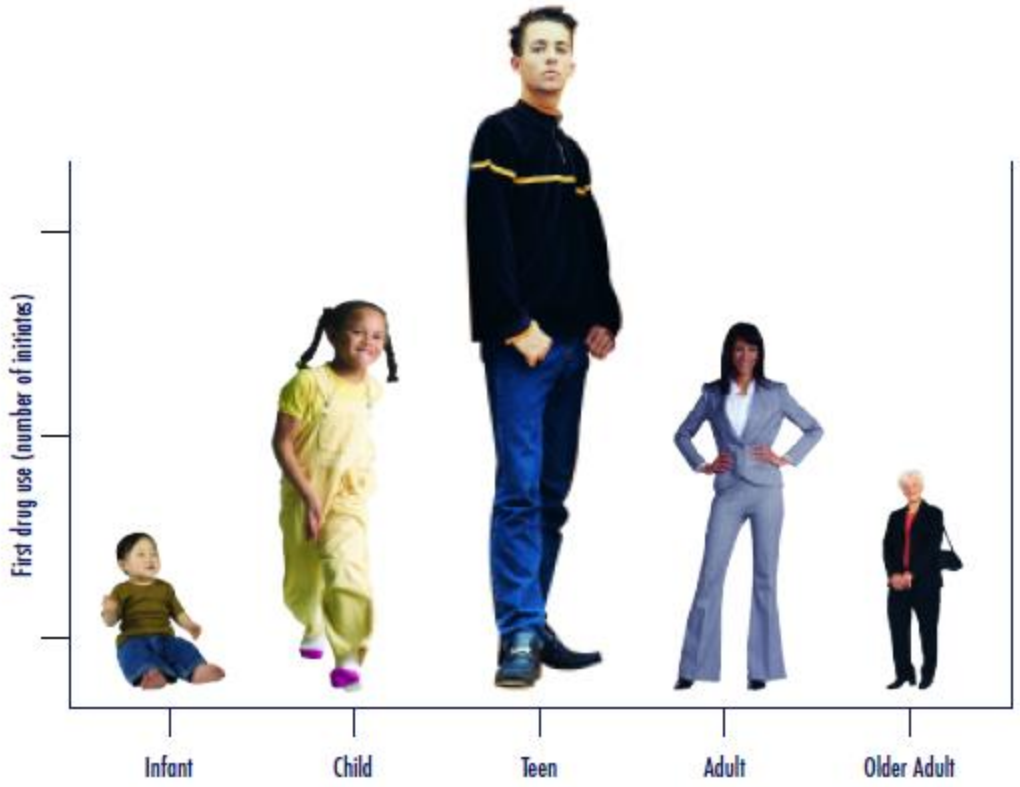
Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand

ABSTRACT

Aim To examine the associations between the frequency of cannabis use and the use of other illicit drugs. **Design** A 25-year longitudinal study of the health, development and adjustment of a birth cohort of 1265 New Zealand children. **Measurements** Annual assessments of the frequency of cannabis use were obtained for the period 14–25 years, together with measures of the use of other illicit drugs from the same time period. **Findings** The frequency of cannabis use was associated significantly with the use of other illicit drugs, other illicit drug abuse/dependence and the use of a diversity of other drugs. This association was found to be particularly strong during adolescence but declined rapidly as age increased. Statistical control for confounding by both fixed and time dynamic factors using random- and fixed-effects regression models reduced the strength of association between frequency of cannabis use and other illicit drug use, but a strong association between frequency of cannabis use and other illicit drug use remained even after control for non-observed and time-dynamic sources of confounding. **Conclusions** Regular or heavy cannabis use was associated with an increased risk of using other illicit drugs, abusing or becoming dependent upon other illicit drugs, and using a wider variety of other illicit drugs. The risks of use, abuse/dependence, and use of a diversity of other drugs declined with increasing age. The findings may support a general causal model such as the cannabis gateway hypothesis, but the actual causal mechanisms underlying such a gateway, and the extent to which these causal mechanisms are direct or indirect, remain unclear.

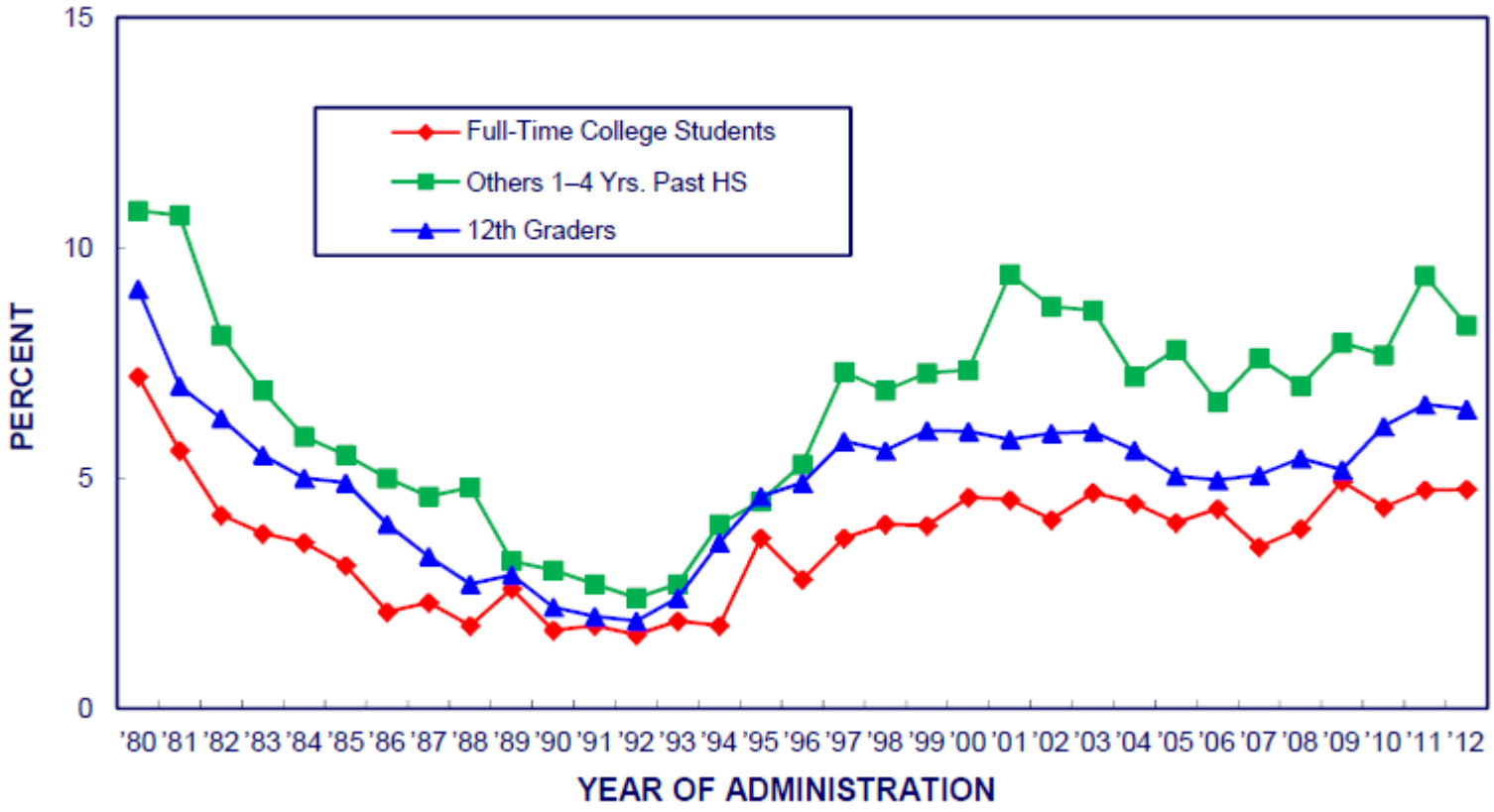
Keywords Cannabis, fixed-effects models, gateway, illicit drug use, longitudinal study.

Drug abuse starts early and peaks in teen years



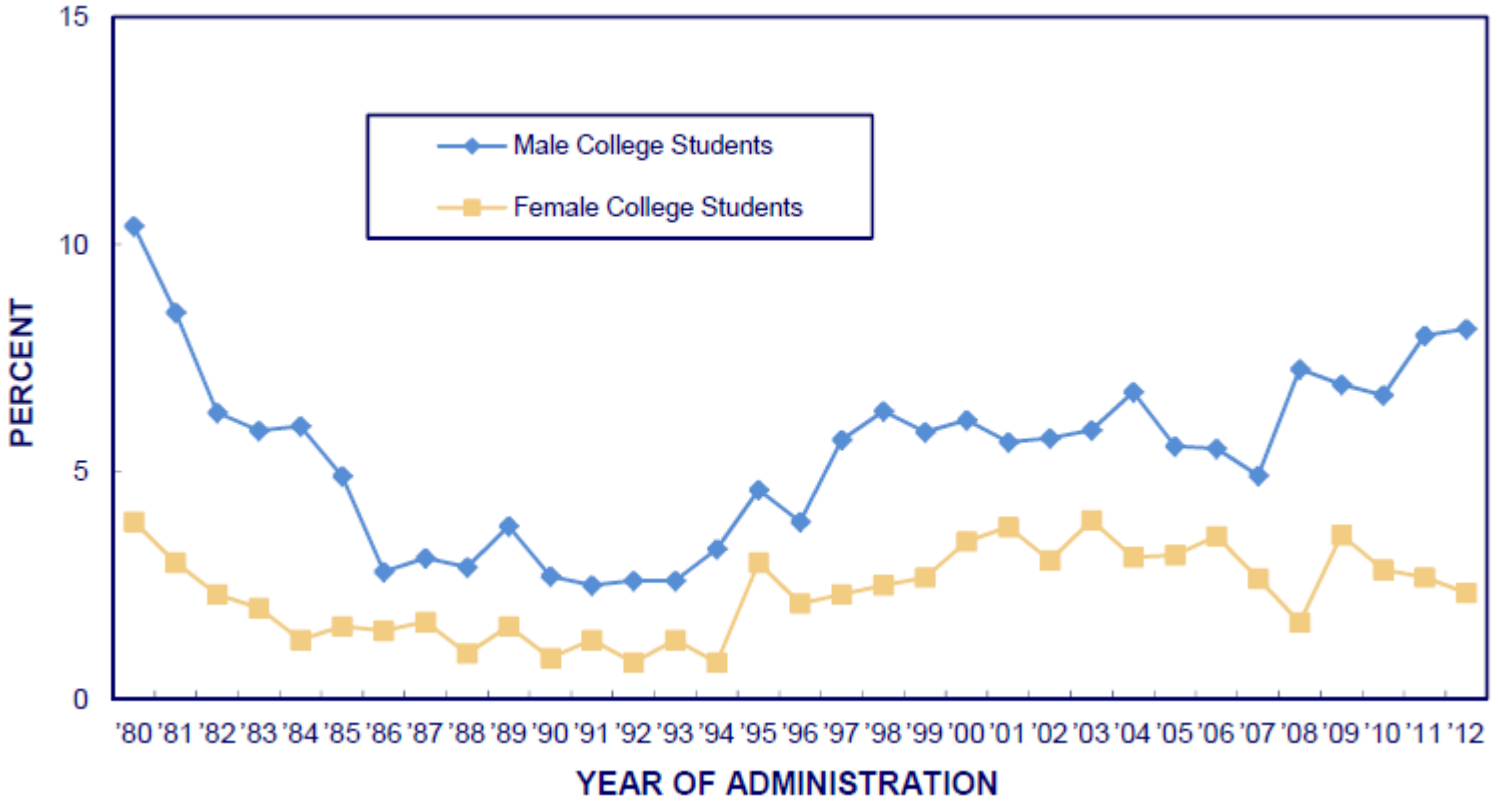
Source: NIDA (2010)

Trends in 30-day prevalence of daily use among college students vs. others 1 to 4 years beyond high school



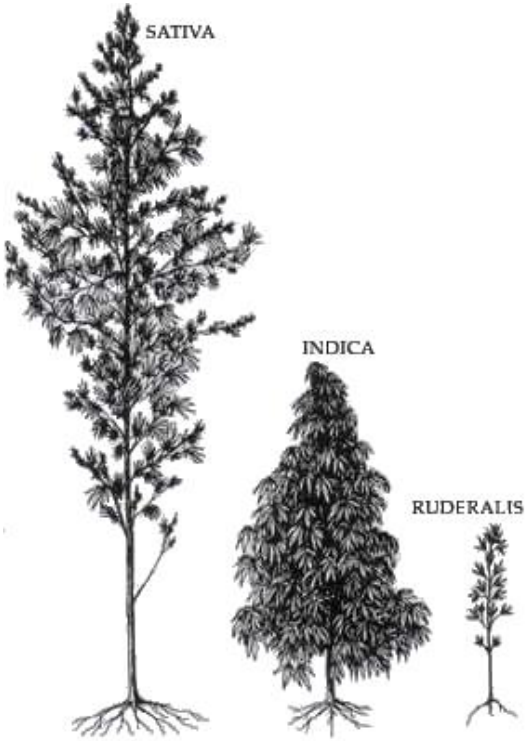
Source: Monitoring the Future (2012)

Trends in 30-day prevalence of daily use among male vs. female college students

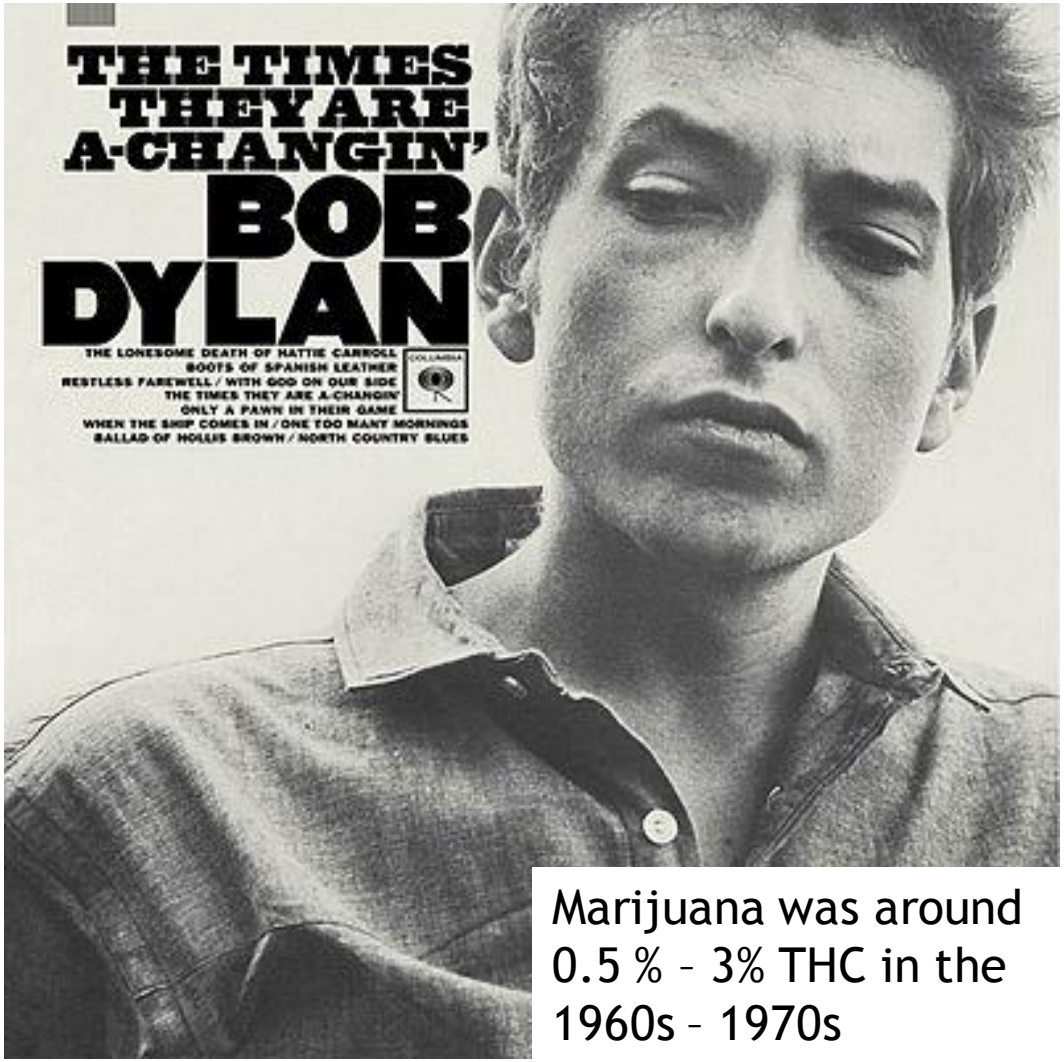


Source: Monitoring the Future (2012)

Types of cannabis



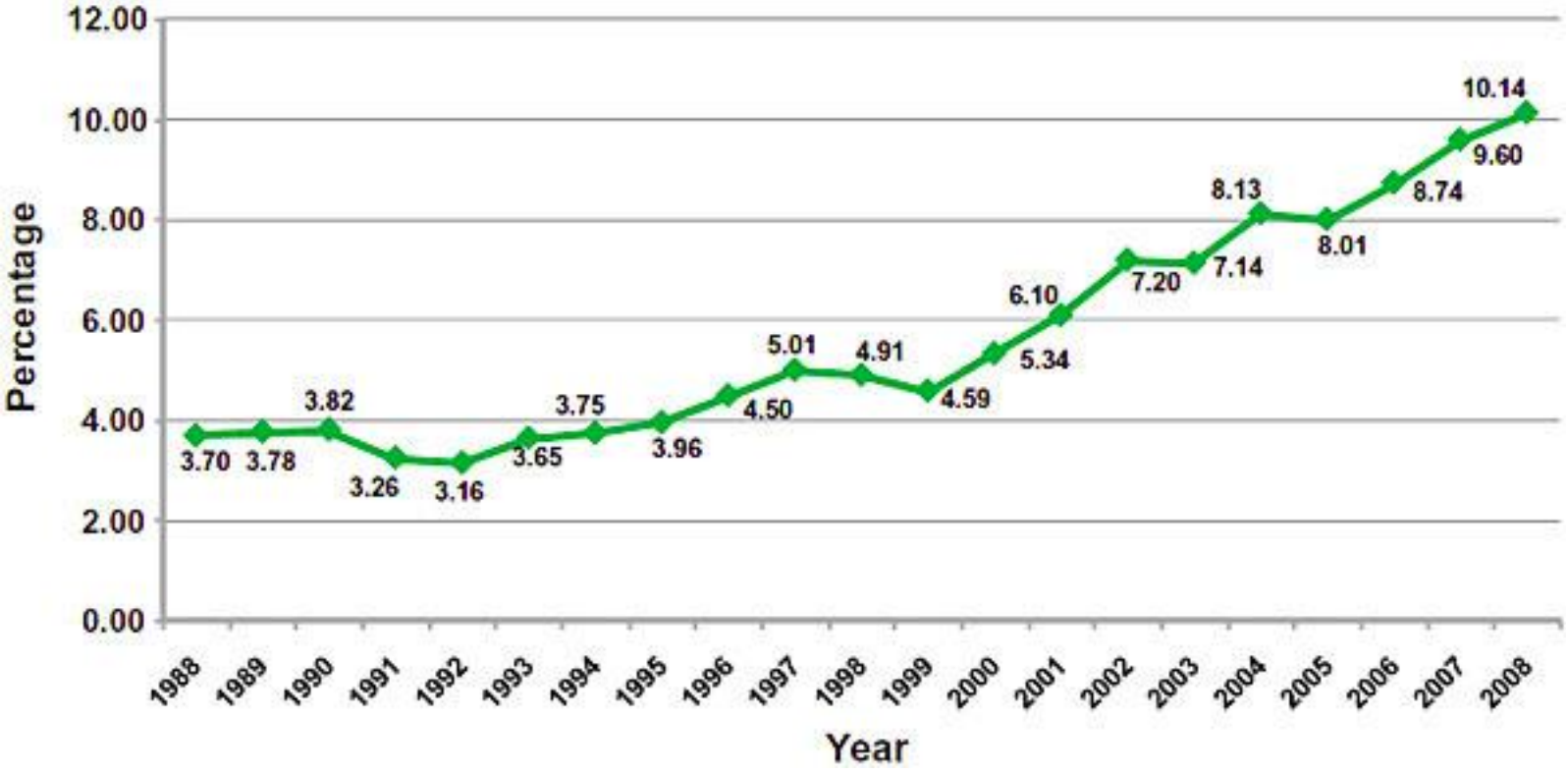
- Constituents of cannabis
  - **Tetrahydrocannabinol (THC)** – psychoactive
  - **Cannabidiol (CBD)** - not psychoactive, may block affective THC



Marijuana was around 0.5 % – 3% THC in the 1960s – 1970s

*THC, incidentally, had been isolated and identified in 1964

Rising potency of marijuana



Source: National Drug Prevention Alliance (accessed 2014)

Potency

Hash Oil

Hashish (resin)

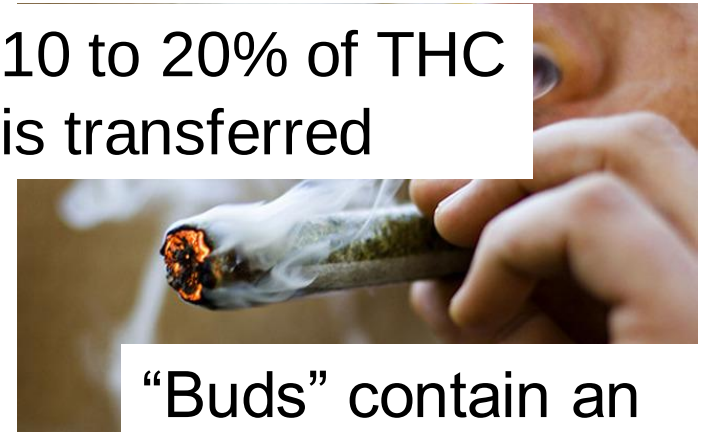
Marijuana (dried leaves/flowers)

80%
THC

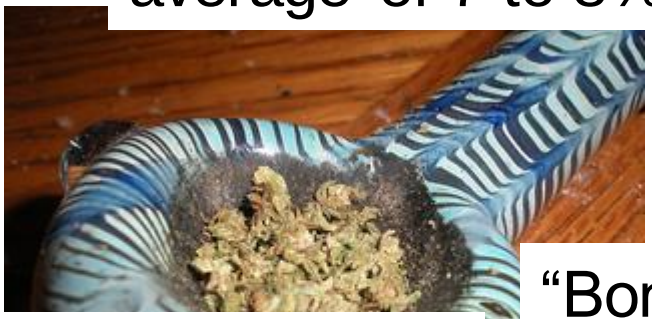
“BHO”

Traditional methods of ingestion

10 to 20% of THC is transferred



“Buds” contain an average of 7 to 8% THC

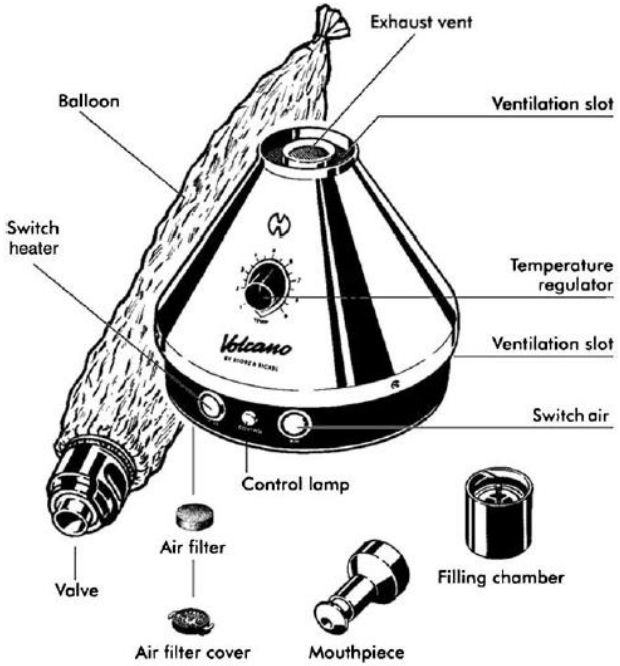


40 to 50% of THC is transferred

“Bongs” are even more efficient because the water traps the smoke until it is inhaled

Vaping


STOP
Arresting
Patients
FOR MEDICAL
MARIJUANA


Exhaust vent
Balloon
Ventilation slot
Switch
heater
Temperature
regulator
Volcano
Ventilation slot
Switch air
Control lamp
Air filter
Filling chamber
Valve
Air filter cover
Mouthpiece

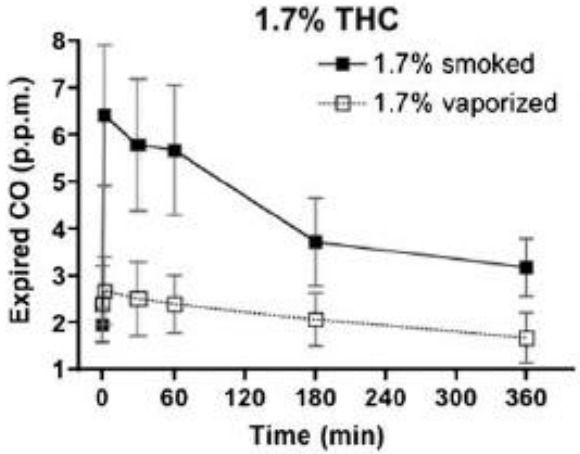
Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study

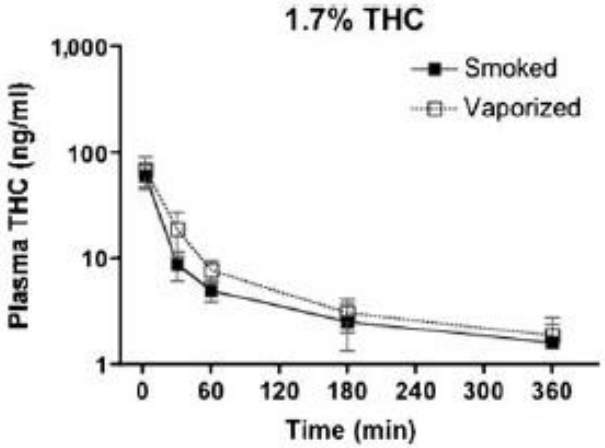
DI Abrams[1,2,3], HP Vizoso[1,3], SB Shade[1,3], C Jay[4,5], ME Kelly[1,2,3] and NL Benowitz[3,6]

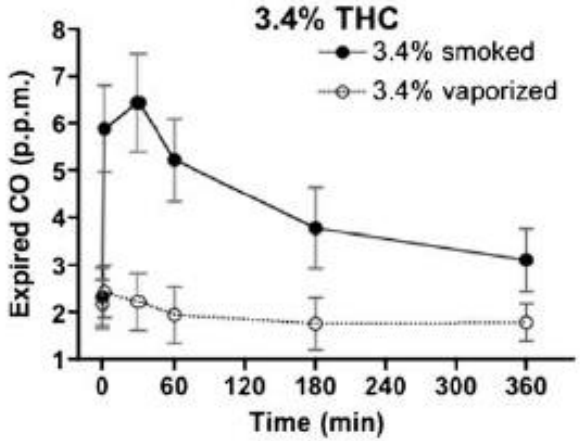
Although cannabis may have potential therapeutic value, inhalation of a combustion product is an undesirable delivery system. The aim of the study was to investigate vaporization using the Volcano® device as an alternative means of delivery of inhaled *Cannabis sativa*. Eighteen healthy inpatient subjects enrolled to compare the delivery of cannabinoids by vaporization to marijuana smoked in a standard cigarette. One strength (1.7, 3.4, or 6.8% tetrahydrocannabinol (THC)) and delivery system was randomly assigned for each of the 6 study days. Plasma concentrations of Δ-9-THC, expired carbon monoxide (CO), physiologic and neuropsychologic effects were the main outcome measures. Peak plasma concentrations and 6-h area under the plasma concentration–time curve of THC were similar. CO levels were reduced with vaporization. No adverse events occurred. Vaporization of cannabis is a safe and effective mode of delivery of THC. Further trials of clinical effectiveness of cannabis could utilize vaporization as a smokeless delivery system.

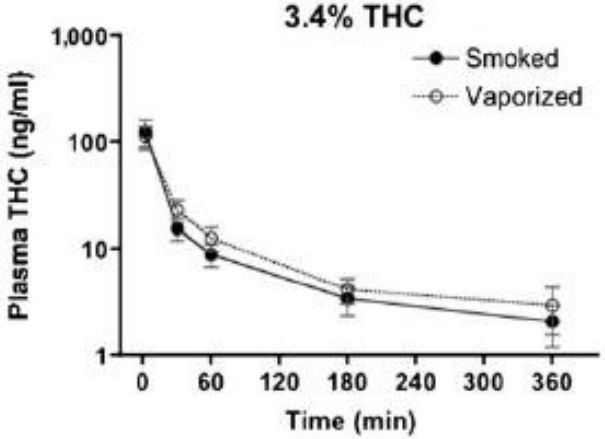
The Institute of Medicine (10m) report on Marijuana as Medicine published in 1999 concluded that "scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, appetite stimulation; smoked marijuana, however is a crude THC delivery system that also delivers harmful substances".[1] The report recommended that clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid onset, reliable, and safe delivery systems. While acknowledging therapeutic

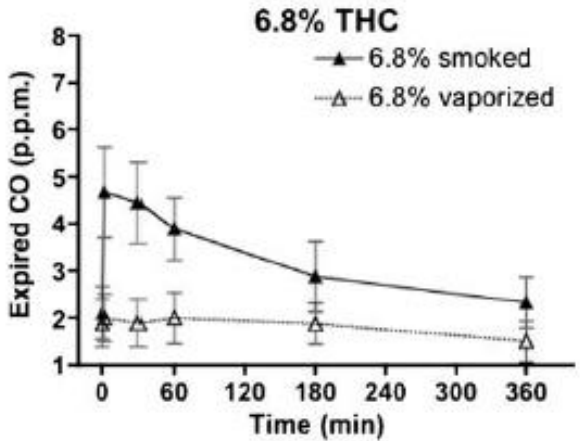
Cannabis vaporization is a technology for delivering inhaled tetrahydrocannabinol (THC) and other cannabinoids while reducing toxic byproducts of smoked cannabis primarily caused by combustion.[2,3] By heating cannabis to a temperature between 180 and 200°C, it is possible to vaporize the cannabinoids that reside on the trichomes on the surface of cannabis flowers and leaves, while avoiding combustion (which occurs at 230°C and above) and attendant smoke toxins. Vaporization is a relatively new technology. Various vaporizer designs are currently under development. The

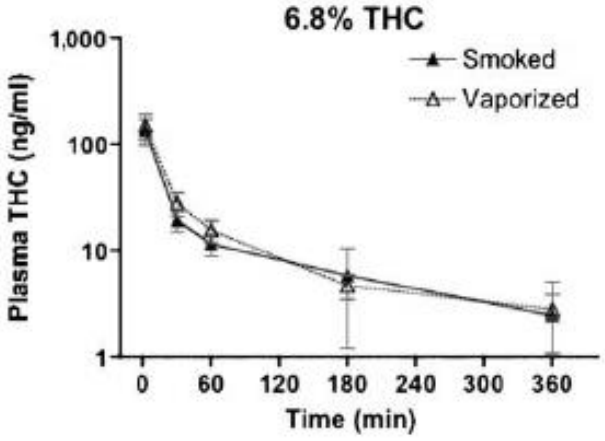

1.7% THC
1.7% smoked
1.7% vaporized
Expired CO (p.p.m.)
Time (min)


1.7% THC
Smoked
Vaporized
Plasma THC (ng/ml)
Time (min)

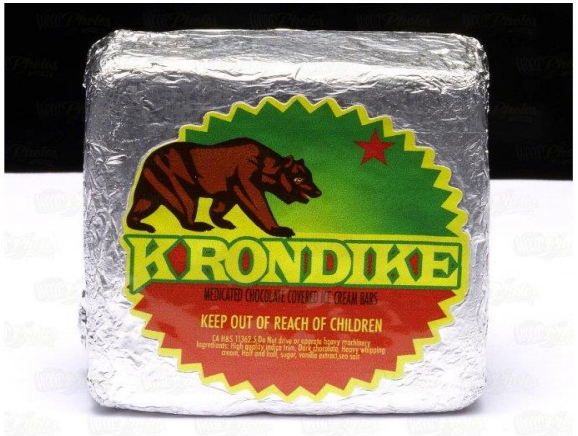

3.4% THC
3.4% smoked
3.4% vaporized
Expired CO (p.p.m.)
Time (min)


3.4% THC
Smoked
Vaporized
Plasma THC (ng/ml)
Time (min)


6.8% THC
6.8% smoked
6.8% vaporized
Expired CO (p.p.m.)
Time (min)

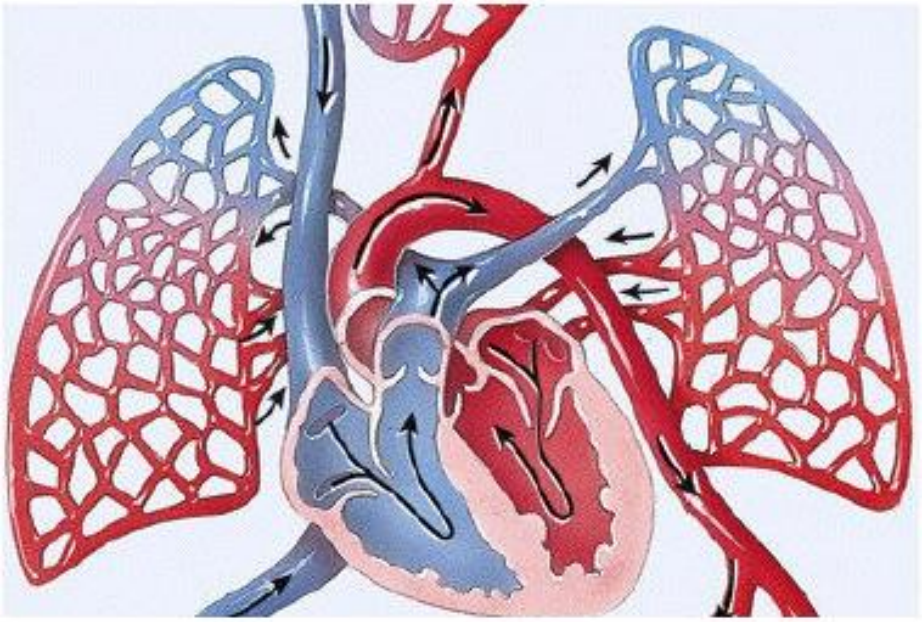

6.8% THC
Smoked
Vaporized
Plasma THC (ng/ml)
Time (min)

Oral administration



Oral administration

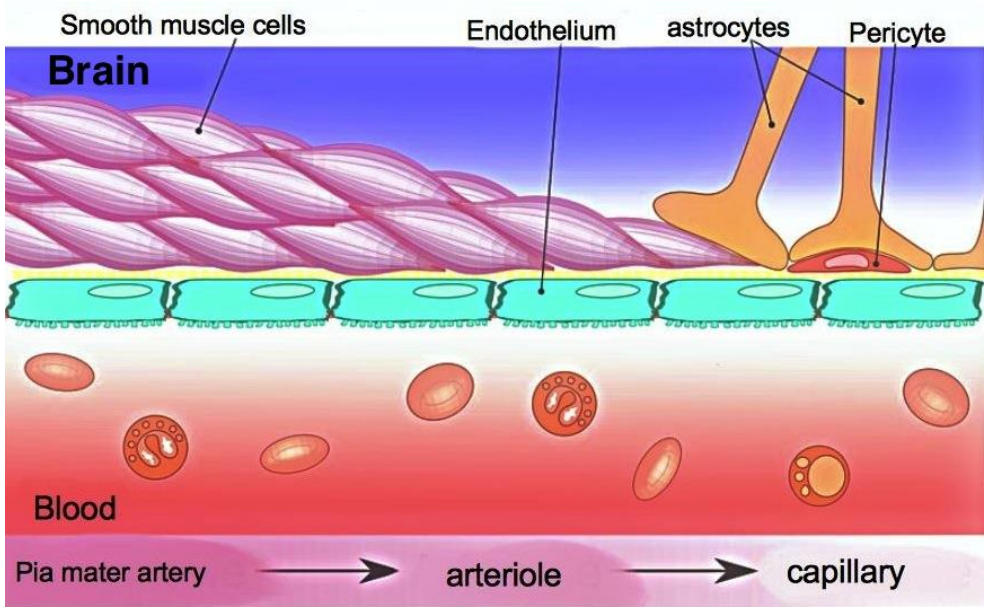
Smoked or “vaped”



Inhaled cannabis passes easily through the membrane lining of the lungs

Source: Iverson, 2008

Cannabis readily crosses the blood-brain barrier



Within seconds, active THC is present on cannabis receptors in the brain

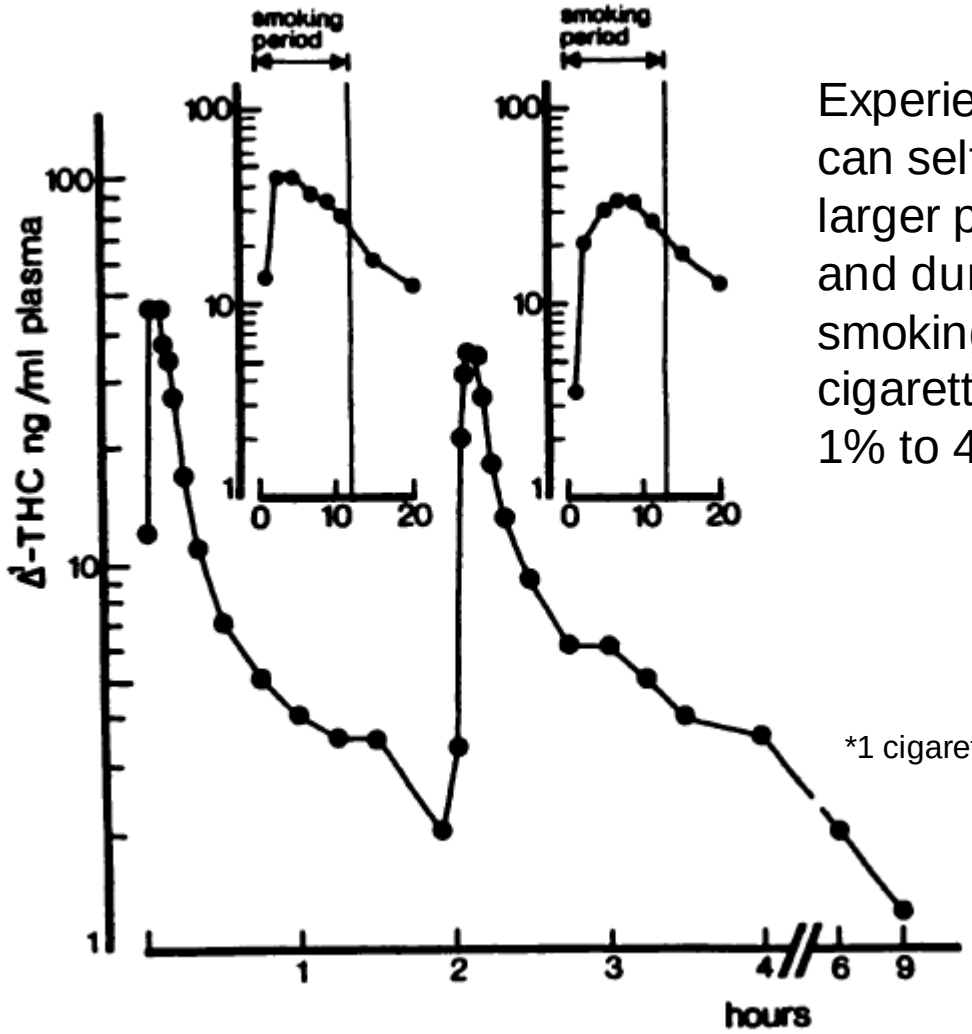
Source: Wikipedia, accessed October 19, 2014

Absorption of THC

- Absorption is influenced by rate of inhalation, depth of puffs, duration of puffs, volume inhaled, the length of cigarettes smoked, etc.
  - **10-25%** of the THC content of the cannabis cigarette enters the circulation

Source: Ranganathan and D'Souza (2006)

Average plasma THC concentrations after smoking 2 cigarettes*, 2 hours apart

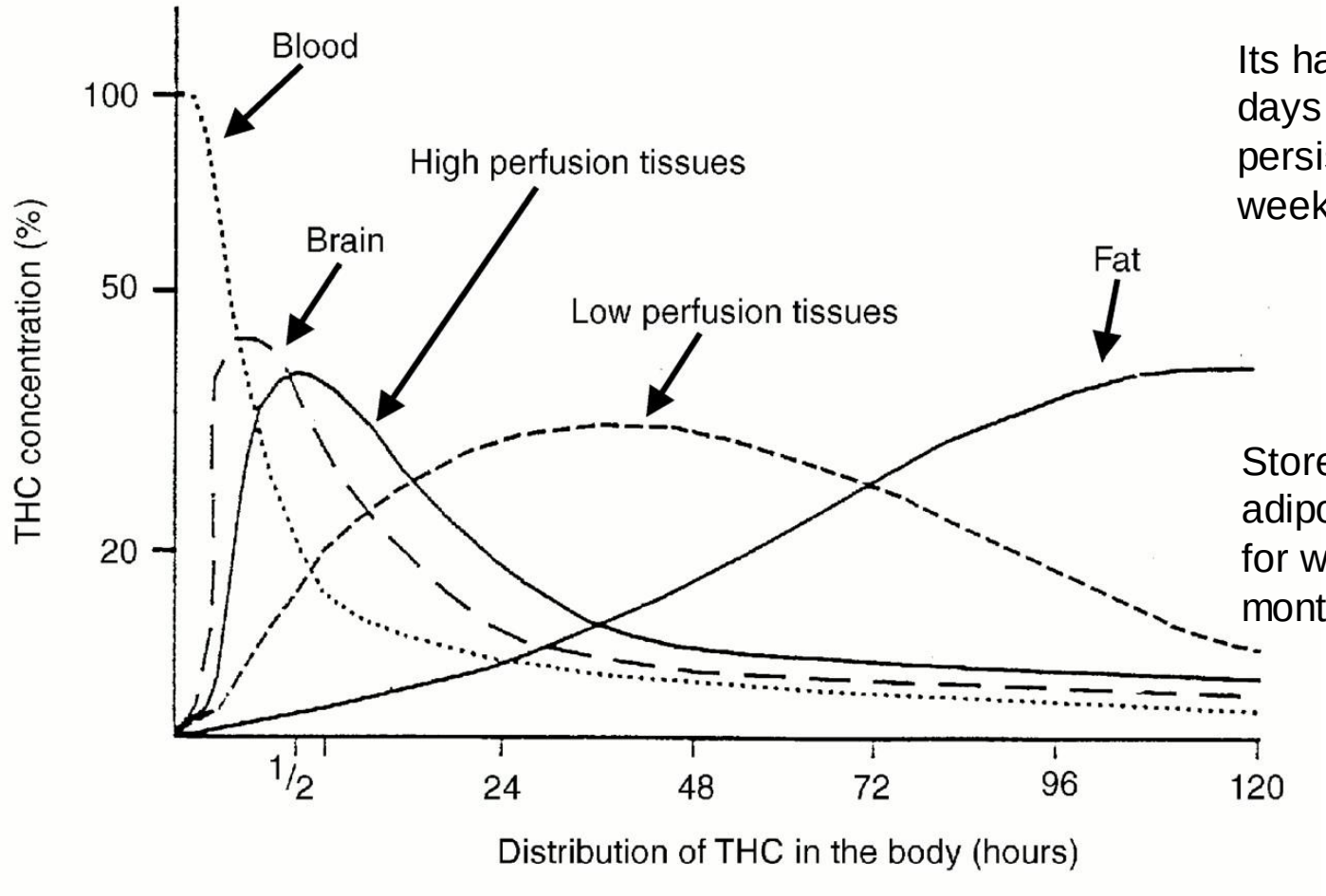


Experienced smokers can self-titrate with larger puff volumes and duration when smoking less potent cigarettes (e.g., from 1% to 4%)

*1 cigarette = 9 mg of THC

Source: Agurell et al., 1986; ; Heishman et al., 1989; Herning et al., 1986

Distribution of THC in the body after smoking

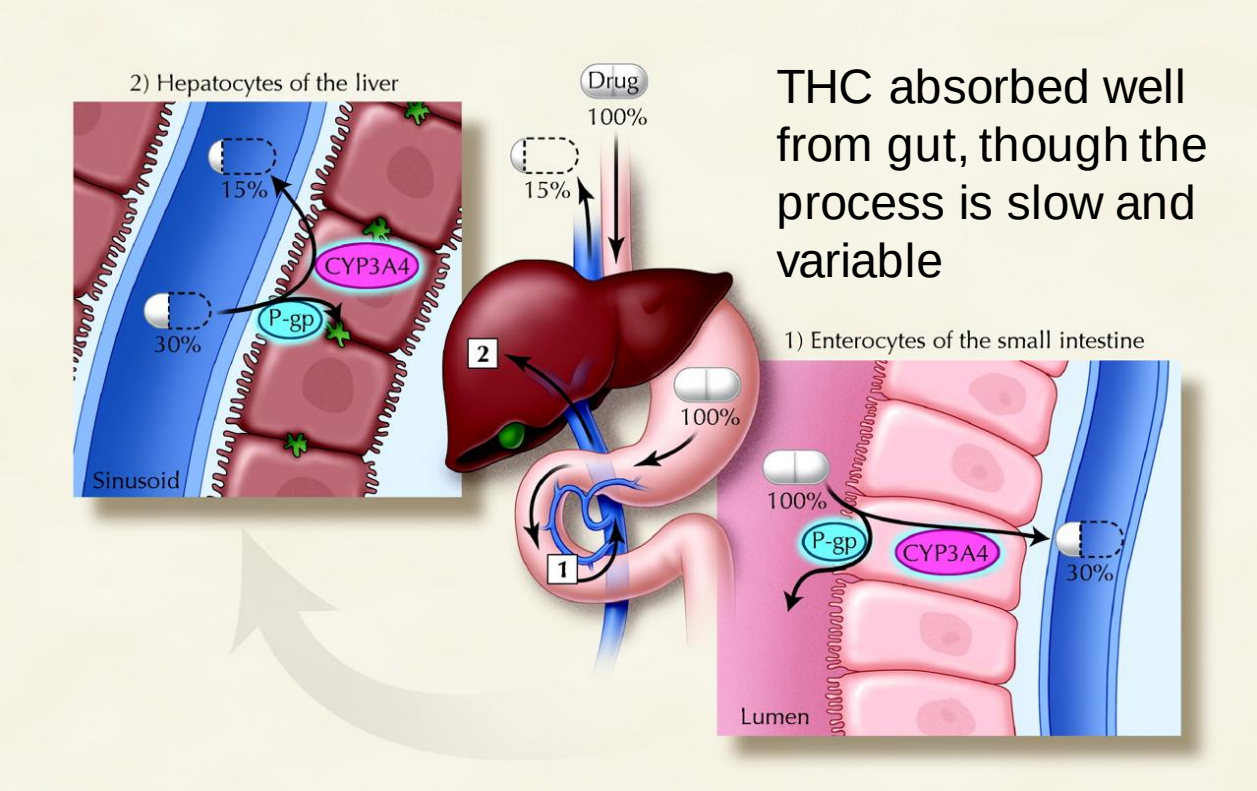


Its half-life is 1 to 2.3 days (traces can persist up to 4-6 weeks)

Stored in adipose tissues for weeks to months

Source: Ashton, C. .H. BJP 2001;178:101-106; Hale (2006)

Oral administration

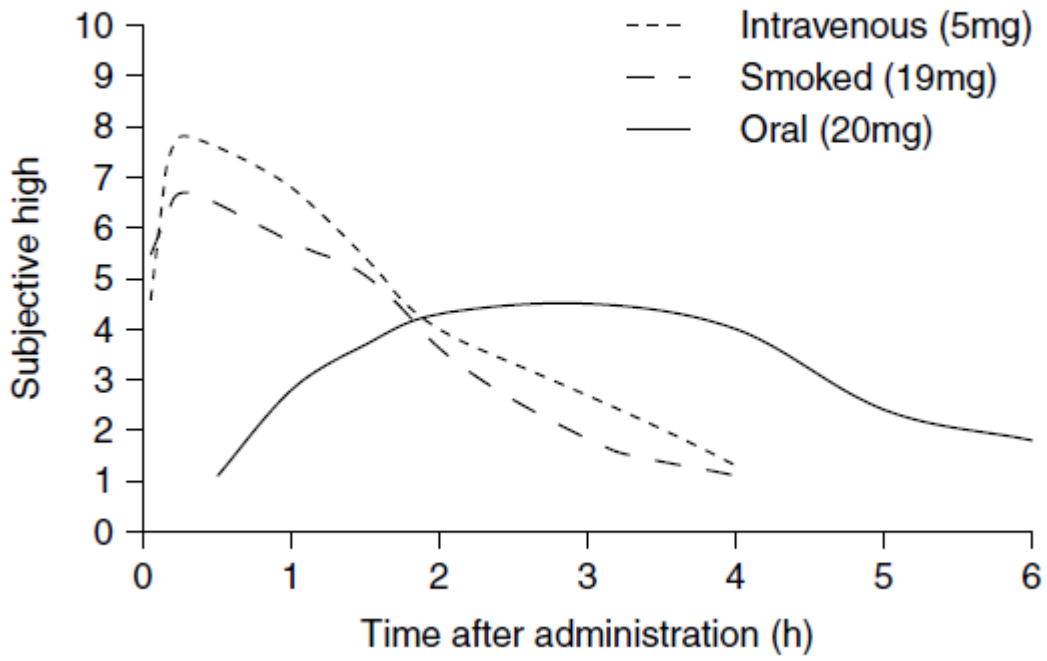


THC absorbed well from gut, though the process is slow and variable

Bioavailability is lower with oral consumption **(<10% THC**; cf. 10-25% from inhalation)

Source: Canadian Medical Association, accessed 9/8/2014

Subjective high after intravenous, smoked, and oral ingestion



Source: Grotenhermen (2003)

Drug Testing

- A single use of cannabis may be detected by a typical* **urine drug test** for **1-6 days**
- Cutoff levels used by the test: 15 ng/ml, 20 ng/ml, 50 ng/ml, 100 ng/ml
- Frequent or daily use may be detected by a **urine drug test** for **7-30 days**
- SAMHSA/NIDA recommend an immunoassay test of **50 ng/ml** for a “positive” result

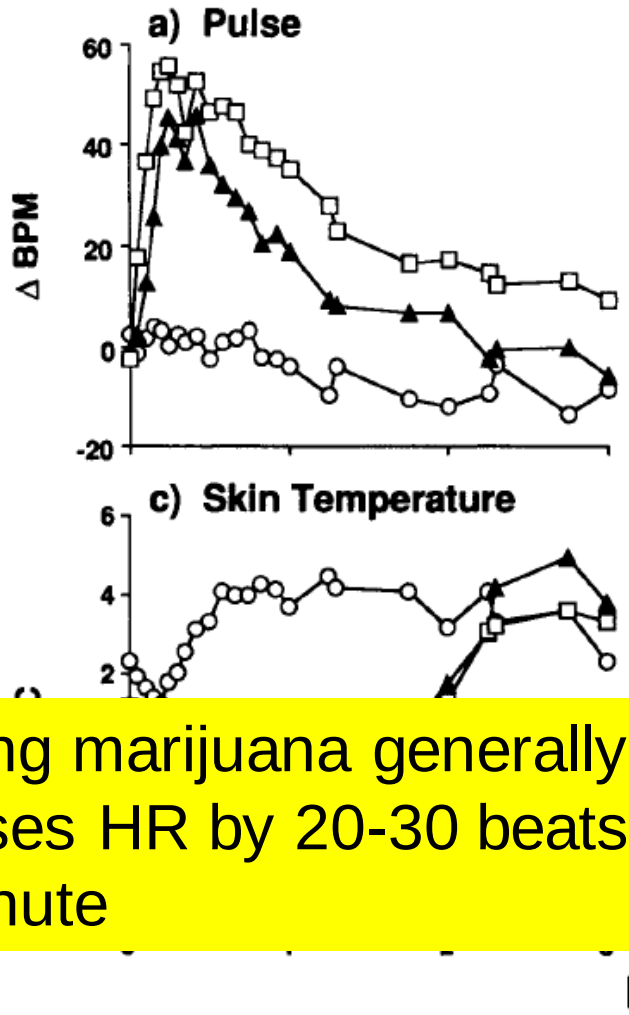
Source: Erowid, Accessed 9/8/2014; *NIDA-Approved

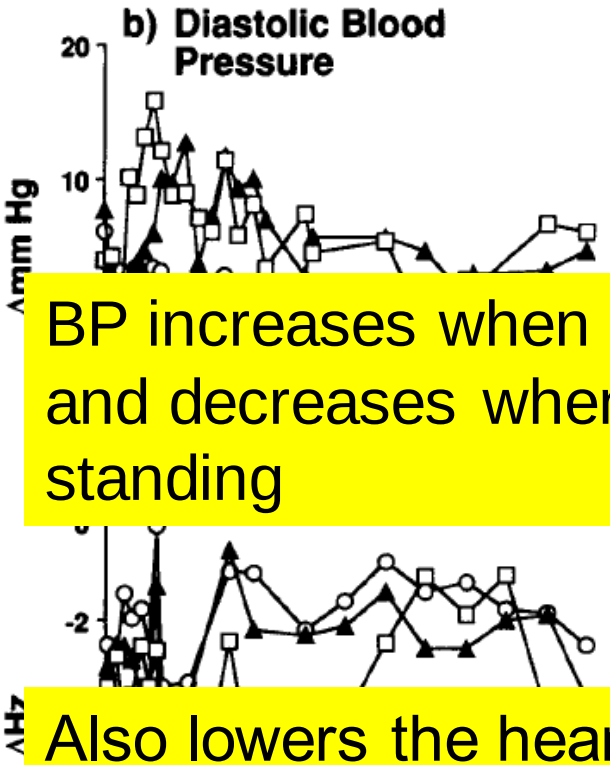
Drug Testing

- **Hair tests** usually take the most recent 1.5 inches of growth
  - These tests provide a detection period of approximately **90 days**
- Cannabis is detectable in the **blood** for approximately **2-3 days**
- Frequent use can be detected in the **blood** for approximately **2 weeks**.

Source: Erowid, Accessed 9/8/2014;

Changes in Pulse, Diastolic BP, Skin Temperature, and Critical Flicker Fusion Threshold After Smoking of a Single MJ Cigarette





BP increases when seated and decreases when standing

Smoking marijuana generally increases HR by 20-30 beats per minute

Also lowers the heart's pumping efficiency during exercise, increasing the workload on the heart

Source: Huestis et al., 1992; Kuhn et al., 2014

Triggering Myocardial Infarction by Marijuana

Murray A. Mittleman, MD, DrPH; Rebecca A. Lewis; Malcolm Maclure, ScD;
Jane B. Sherwood, RN; James E. Muller, MD

Background—Marijuana use in the age group prone to coronary artery disease is higher than it was in the past. Smoking marijuana is known to have hemodynamic consequences, including a dose-dependent increase in heart rate, supine hypertension, and postural hypotension; however, whether it can trigger the onset of myocardial infarction is unknown.

Methods and Results—In the Determinants of Myocardial Infarction Onset Study, we interviewed 3882 patients (1258 women) with acute myocardial infarction an average of 4 days after infarction onset. We used the case-crossover study design to compare the reported use of marijuana in the hour preceding symptoms of myocardial infarction onset to its expected frequency using self-matched control data. Of the 3882 patients, 124 (3.2%) reported smoking marijuana in the prior year, 37 within 24 hours and 9 within 1 hour of myocardial infarction symptoms. Compared with nonusers, marijuana users were more likely to be men (94% versus 67%, $P<0.001$), current cigarette smokers (68% versus 32%, $P<0.001$), and obese (43% versus 32%, $P=0.008$). They were less likely to have a history of angina (12% versus 25%, $P<0.001$) or hypertension (30% versus 44%, $P=0.002$). The risk of myocardial infarction onset was elevated 4.8 times over baseline (95% confidence interval, 2.4 to 9.5) in the 60 minutes after marijuana use. The elevated risk rapidly decreased thereafter.

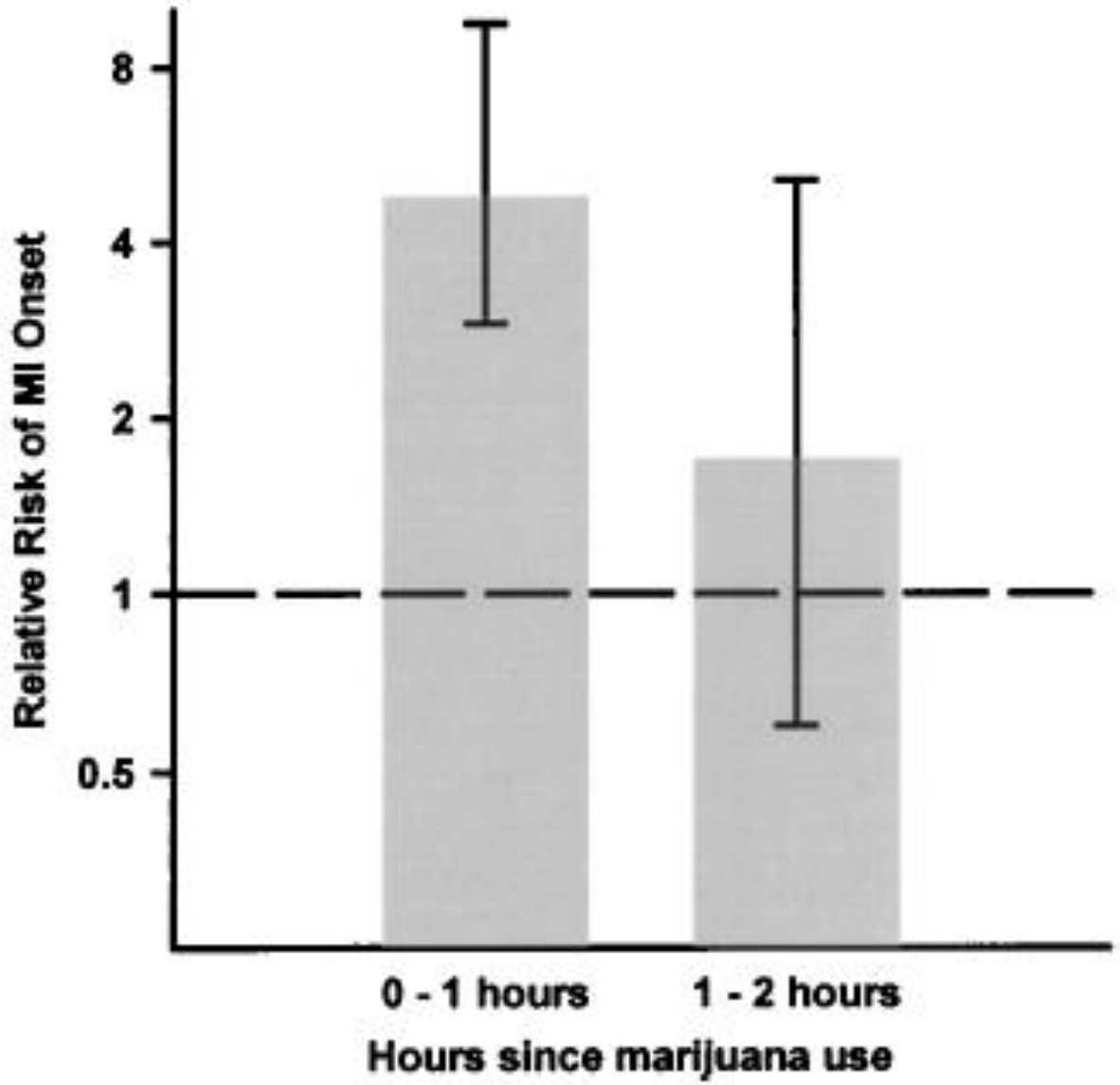
Conclusions—Smoking marijuana is a rare trigger of acute myocardial infarction. Understanding the mechanism through which marijuana causes infarction may provide insight into the triggering of myocardial infarction by this and other, more common stressors. (*Circulation*. 2001;103:2805-2809.)

Key Words: cannabis ■ myocardial infarction ■ epidemiology ■ cross-over studies

Marijuana is the most widely used illicit drug in the United States. In 1998, >72 million Americans, accounting for 33% of the population older than 12 years, had used marijuana or hashish at least once in their lifetime, with 8.6% reporting using the drug in the past year and 5.0% reporting use in the past month.[1] Self-reported use of marijuana is greatest among adults between 18 and 25 years of age.[1] Historically, the prevalence of smoking marijuana was very low among older adults. However, as the generation born in the 20 years after the end of the Second World War ages, the prevalence of marijuana use in the age group prone to coronary artery disease has increased.

in patients with chronic stable angina.[3,11] Furthermore, there are several reports of myocardial infarction occurring in close proximity to marijuana use in otherwise low-risk individuals.[12–14]

An Institute of Medicine report on marijuana and medicine released in 1999 noted that although the cardiovascular effects of marijuana do not seem to pose a health problem for healthy young users, they may present a serious problem for older subjects.[15] The report also noted that any effect of marijuana use on cardiovascular disease could have a substantial impact on public health. The magnitude of the impact remains to be determined: long-term marijuana users from the


Relative Risk of MI Onset
8
4
2
1
0.5
0 - 1 hours
1 - 2 hours
Hours since marijuana use

Cardiovascular Effects

- Studies show that smoking cannabis produces angina in patients with heart disease
- A French study showed that 9.5% of 200 cannabis-related hospitalizations between January 2004 and December 2007 involved cardiovascular disorders

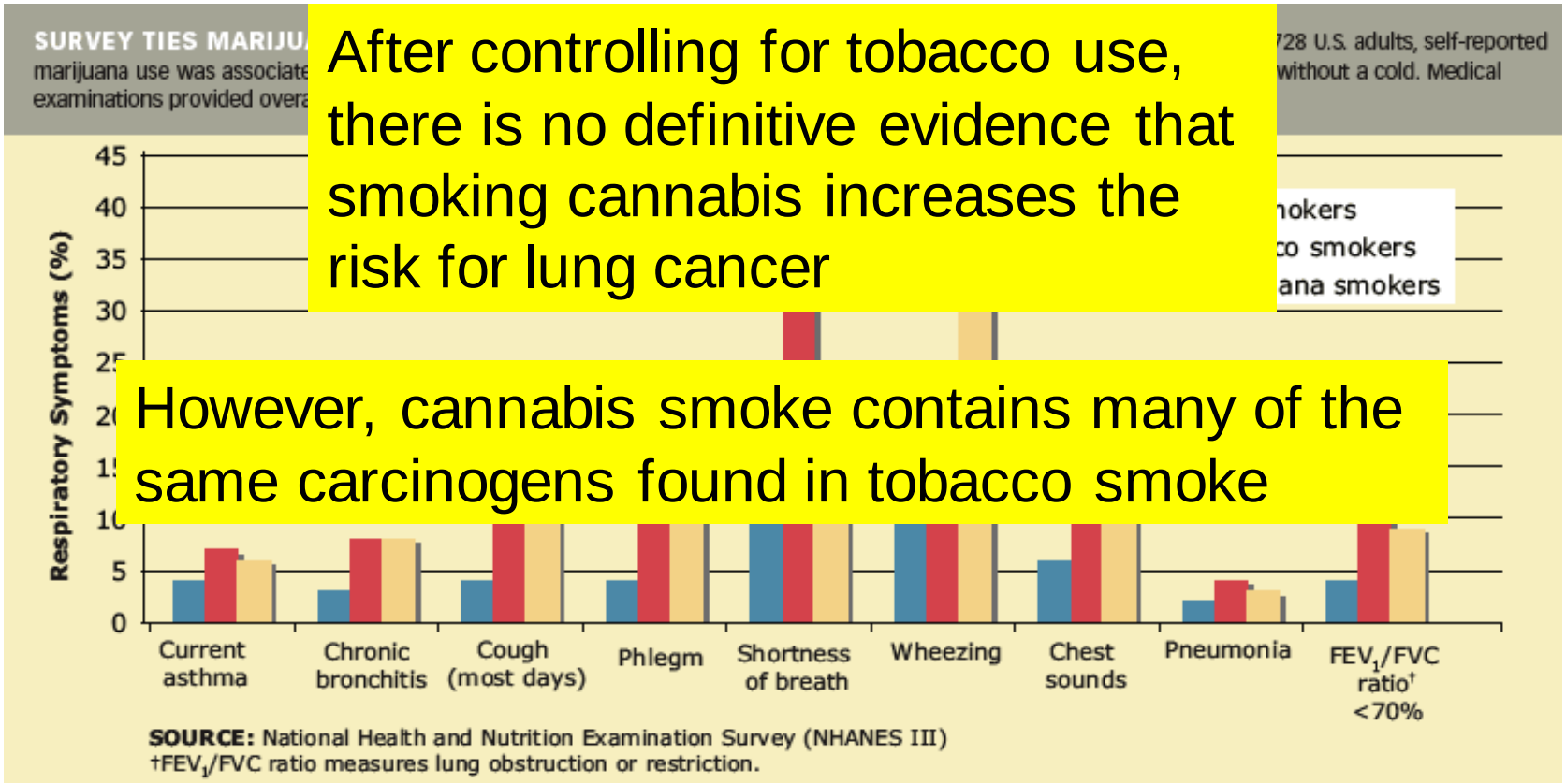
Sources: Gottschalk et al., 1977; Jouanjus et al., 2011

Respiratory Risks of Cannabis Smoking

- One marijuana cigarette causes more harm than one tobacco cigarette in altering lung tissue and causing bronchial irritation and inflammation
- The immunological effectiveness of the respiratory system in cannabis-only smokers is associated with increased respiratory infections

Sources: Doweicko, 2012; Grilly and Salamone, 2012; Tashkin et al., 2002

Respiratory Risks of Cannabis Smoking



Source: Advokat, Comaty, & Julien, 2014; Tashkin, 2005

Cannabis and the Brain

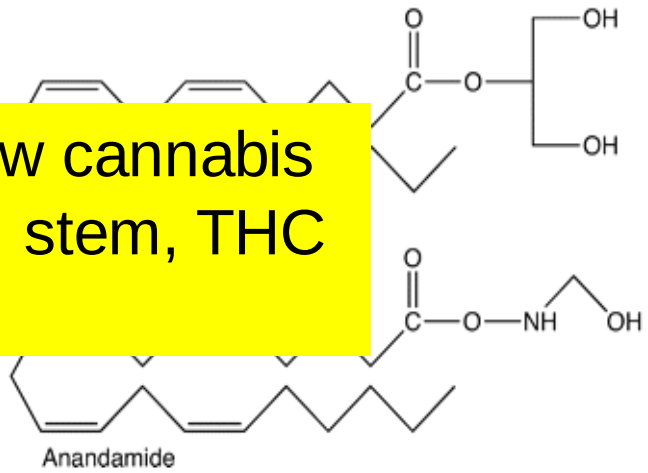
The endocannabinoid system

- **CB1** (brain) and **CB2** (mainly, immune system) **receptors**
- Anandamide
- 2-AG

Distribution

- **Hippocamp**
  amygdala (r
  behavior); **b**
  cerebellum (coordination and selective attention); **nucleus accumbens** (reward mechanisms); **cortex** and **frontal lobe** (executive function, judgment, synthesis, evaluation)

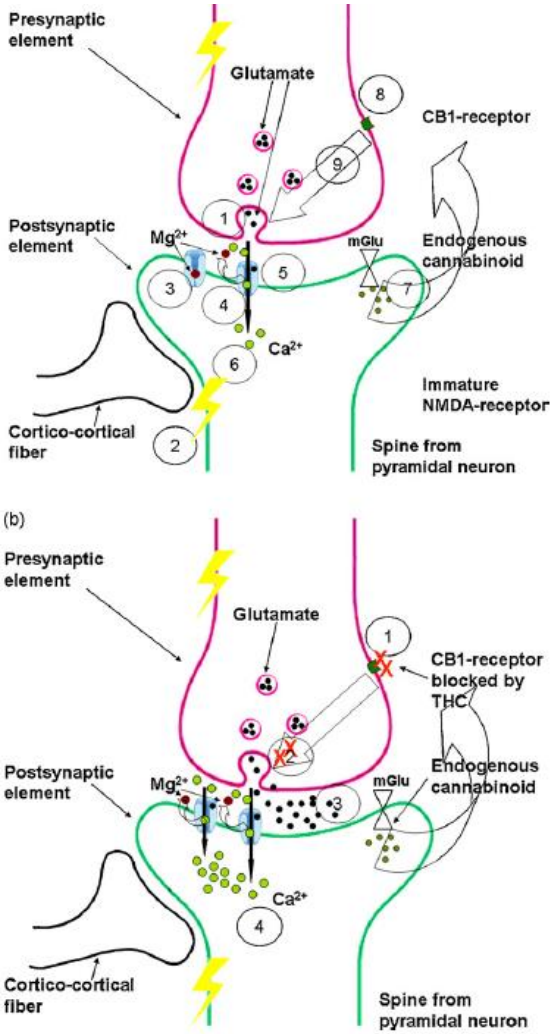
Because there are few cannabis receptors in the brain stem, THC has very low toxicity

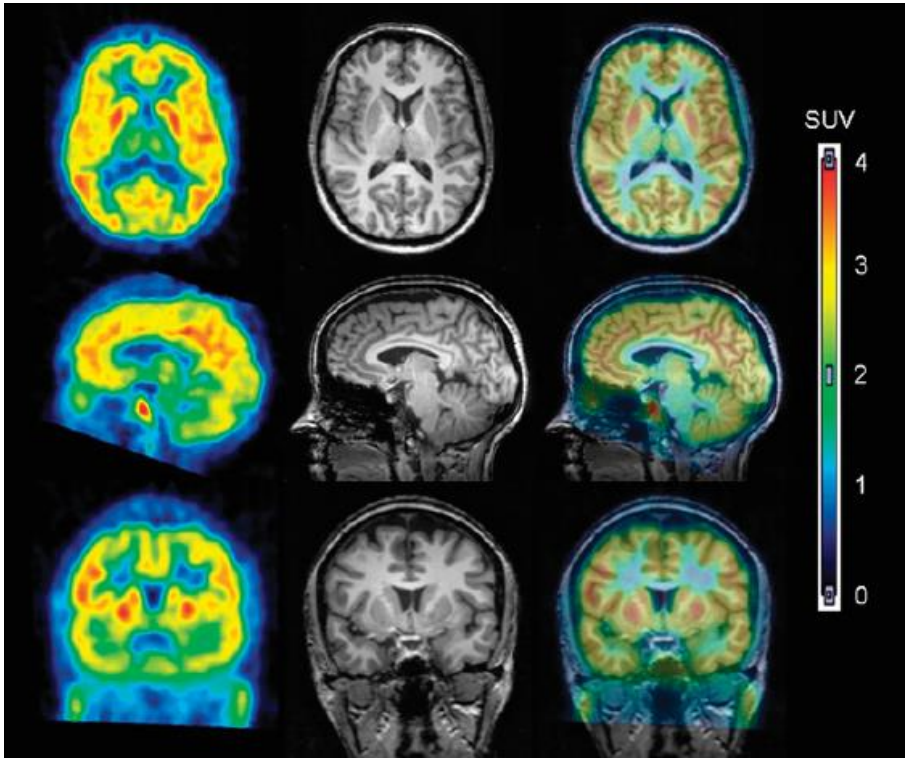


Anandamide

Source: Devane et al. (1992), *Science*; Marcotte (2014); Advocat, Comaty, and Julien (2014)

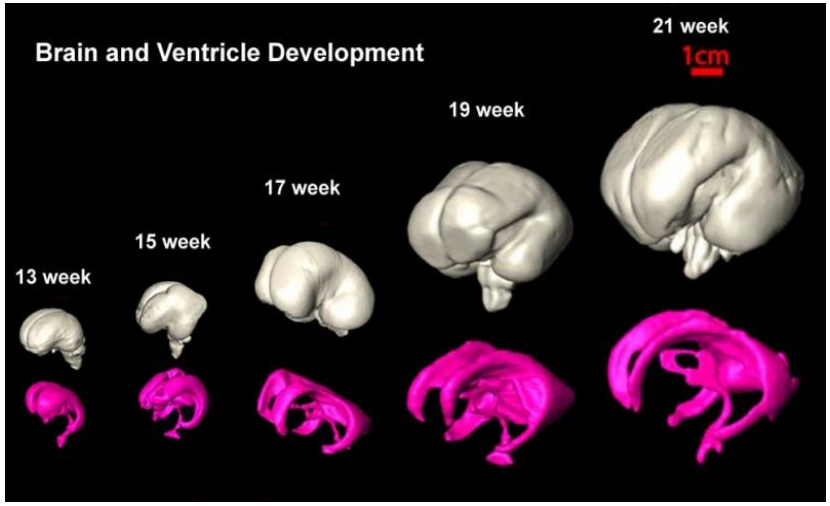
Cannabinoid CB1 receptors in the human brain

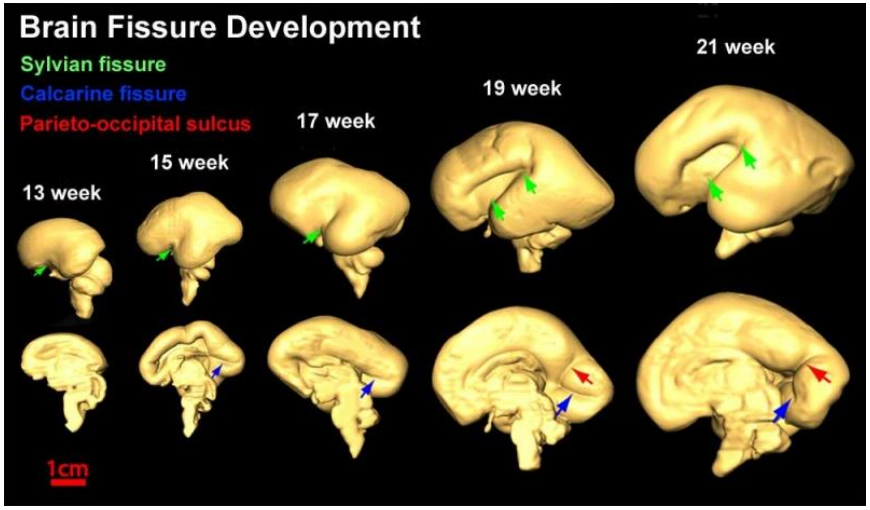




Source: Terry et al. (2010); Bossong and Niesink, 2010

Prenatal brain development





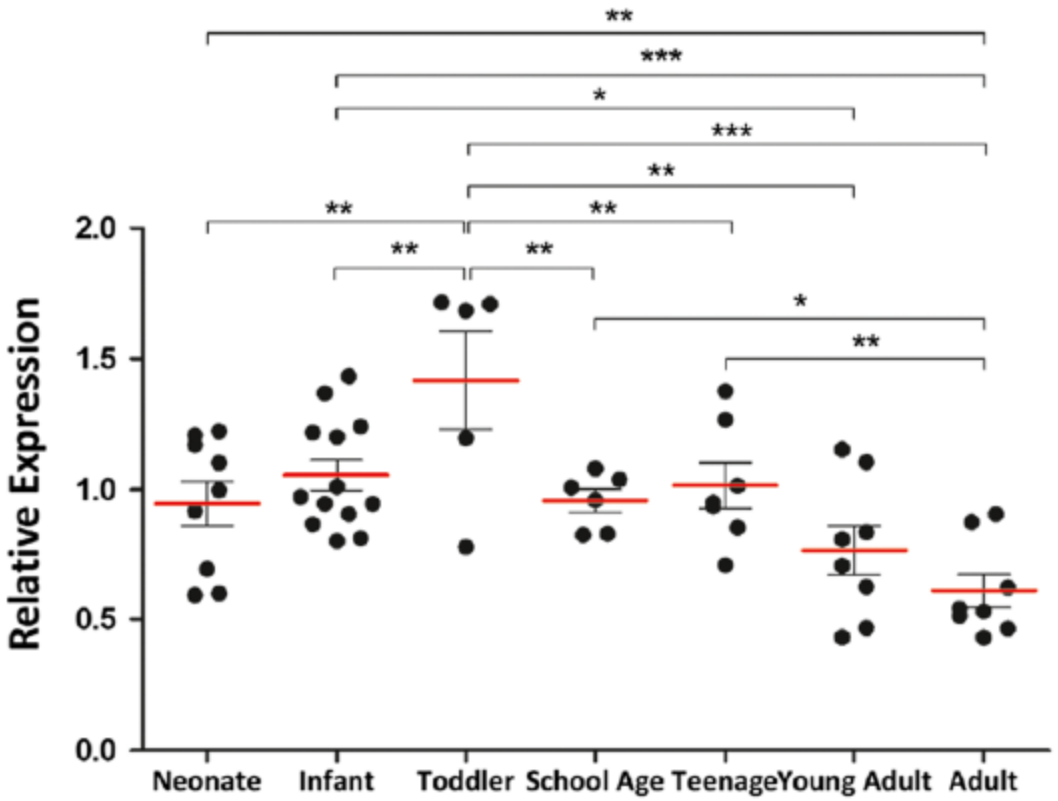
Endogenous cannabinoids and cannabinoid receptors are expressed early in the fetal brain

CB1 receptors are involved in neuronal proliferation, migration, and synaptogenesis

Source: Huppi etal., (1998), *Ann Neurol 43(2)*: 224-235; Jaques et al. (2013), Journal of Perinatology, 1-8

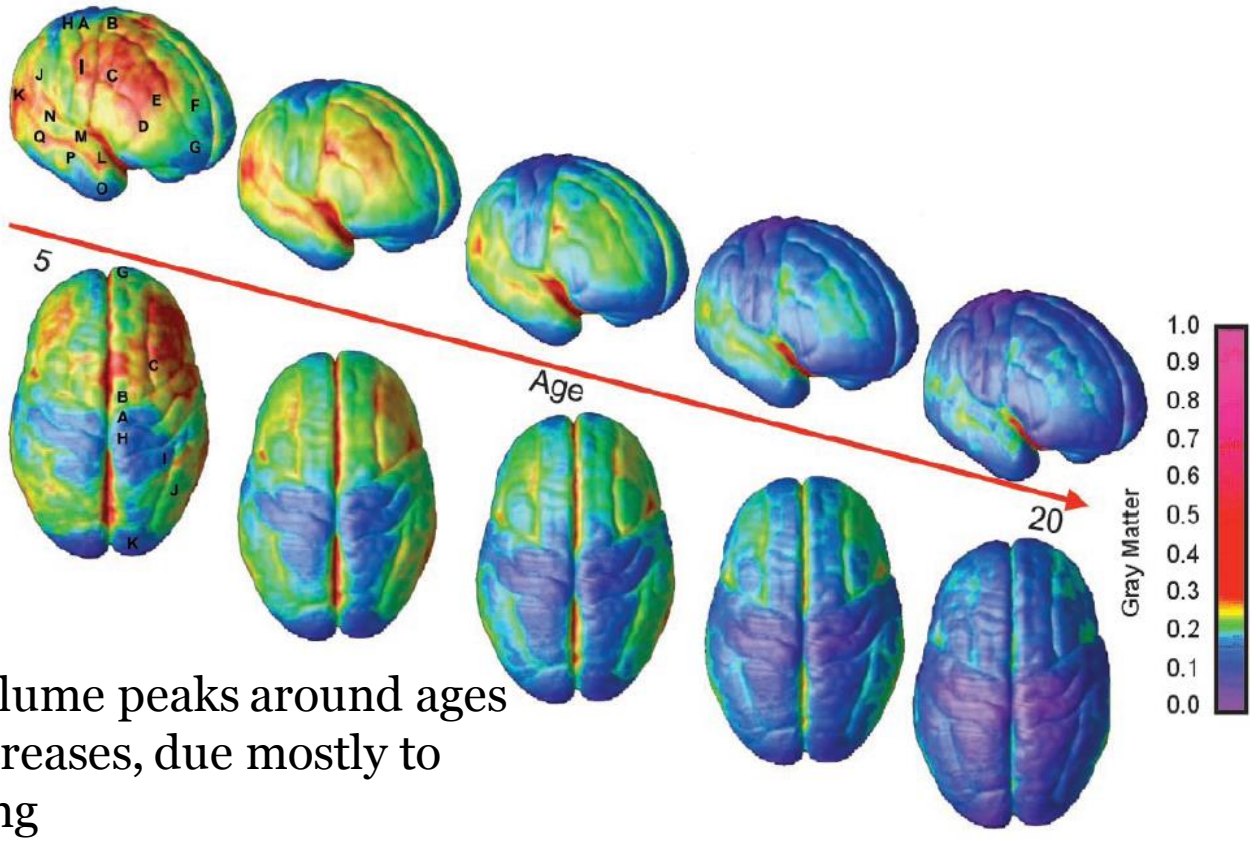
Expression of CB_1R mRNA in the endocannabinoid system (DLPFC) changes with maturation

CB1 cannabinoid receptor levels peak in early adolescence



Source: Belue et al. (1995); Long et al. (2012)

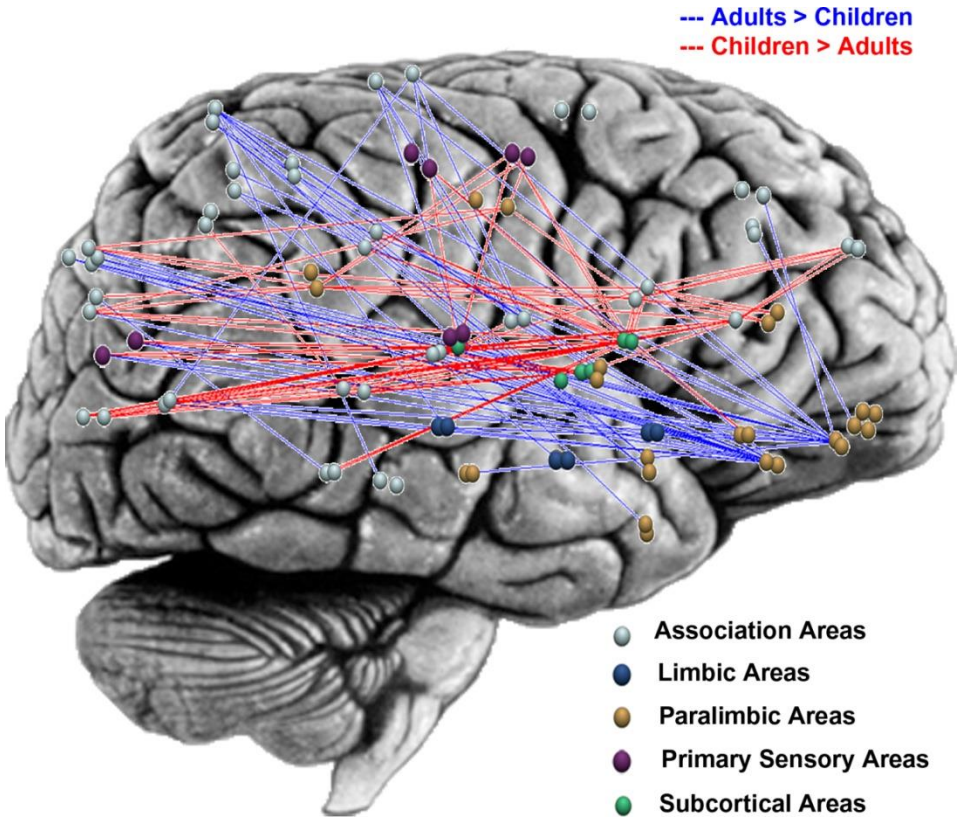
Human cortical development during childhood through early adulthood



Gray matter volume peaks around ages 12–14 then decreases, due mostly to synaptic pruning

Source: Gogtay et al. (2004); Huttenlocher (1990); Toga et al. (2006)

Functional organization of the human brain



Source: Supekar, Musen, and Menon (2009)

Cognitive effects of THC

- Subtly worse **memory**, **attention**, and **processing speed** performances
- Users vs. nonusers decreases (show decreases in performance)
- **Limited impairment** after prolonged abstinence in adults
- **Improvements after just 1 week**

- Ongoing neurodevelopment developmental processes in adolescents
  - School and stimulation

Source: Hart et al. (2001)

BMJ

BMJ 2012;344:e536 doi: 10.1136/bmj.e536 (Published 9 February 2012)

RESEARCH

Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis

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Abstract

Objective To determine whether the acute consumption of cannabis (cannabinoids) by drivers increases the risk of a motor vehicle collision.

Design Systematic review of observational studies, with meta-analysis.

Data sources We did electronic searches in 19 databases, unrestricted by year or language of publication. We also did manual searches of reference lists, conducted a search for unpublished studies, and reviewed the personal libraries of the research team.

Review methods We included observational epidemiology studies of motor vehicle collisions with an appropriate control group, and selected studies that measured recent cannabis use in drivers by toxicological analysis of whole blood or self report. We excluded experimental or simulator studies. Two independent reviewers assessed risk of bias in each selected study, with consensus, using the Newcastle-Ottawa scale. Risk estimates were combined using random effects models.

Results We selected nine studies in the review and meta-analysis. Driving under the influence of cannabis was associated with a significantly increased risk of motor vehicle collisions compared with unimpaired driving (odds ratio 1.92 (95% confidence interval 1.35 to 2.73); P=0.0003); we noted heterogeneity among the individual study effects (I^2=81). Collision risk estimates were higher in case-control studies (2.79 (1.23 to 6.33); P=0.01) and studies of fatal collisions (2.10 (1.31 to 3.36); P=0.002) than in culpability studies (1.65 (1.11 to 2.46); P=0.07) and studies of non-fatal collisions (1.74 (0.88 to 3.46); P=0.11)

those aged 15-24 years used cannabis at least once in the previous year.[1] Rates of driving under the influence of cannabis have also risen in recent years; national data collected in 2004 indicate that 4% of Canadian adults reported driving within one hour of consuming cannabis, up from 1.9% recorded in 1996-7.[2] These results are reflected in other jurisdictions across the world. A roadside survey of 537 drivers in Scotland reported that 15% of respondents aged 17-39 years admitted to having consumed cannabis within 12 hours of driving a vehicle,[3] and the European Monitoring Centre for Drugs and Drug Addiction found that between 0.3% and 7.4% of drivers tested positive for cannabis from roadside surveys in the United Kingdom, Denmark, the Netherlands, Norway, the United States, and Australia.[4]

Much of the early research assessing the effects of cannabis on driving performance was done by laboratory and driving simulator studies. The results of these studies are generally consistent: at increased doses, cannabis impairs the psychomotor skills necessary for safe driving.[5-12] However, although laboratory studies have high internal validity with regard to the dose related effects of cannabis on performance, the dose-response association is unclear in relation to driving ability and collision risk outside the laboratory.[7 8 13 14] As a result, these studies do not always translate well to driving scenarios in the real world, and generally focus on experienced cannabis users consuming the drug in unorthodox surroundings and undertaking

Odds ratios for MJ intoxication on driving sorted by type of study

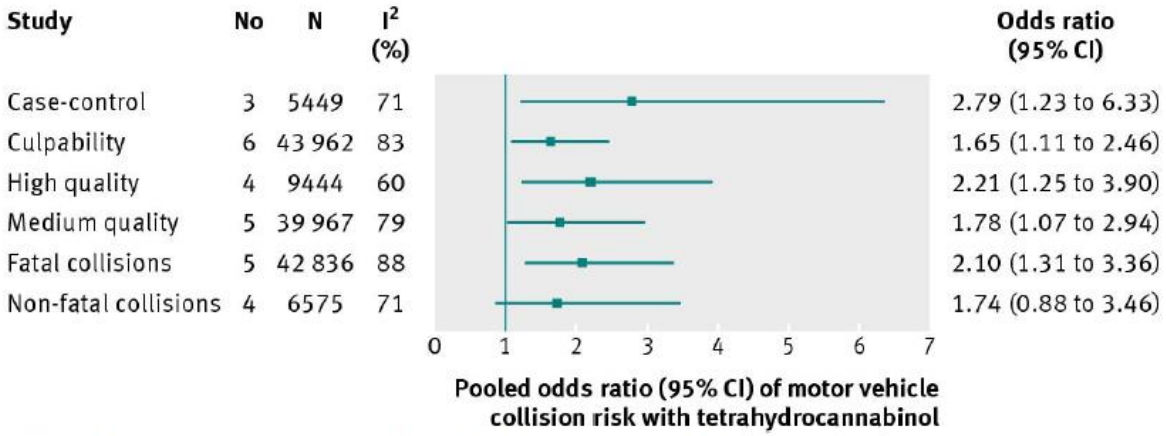
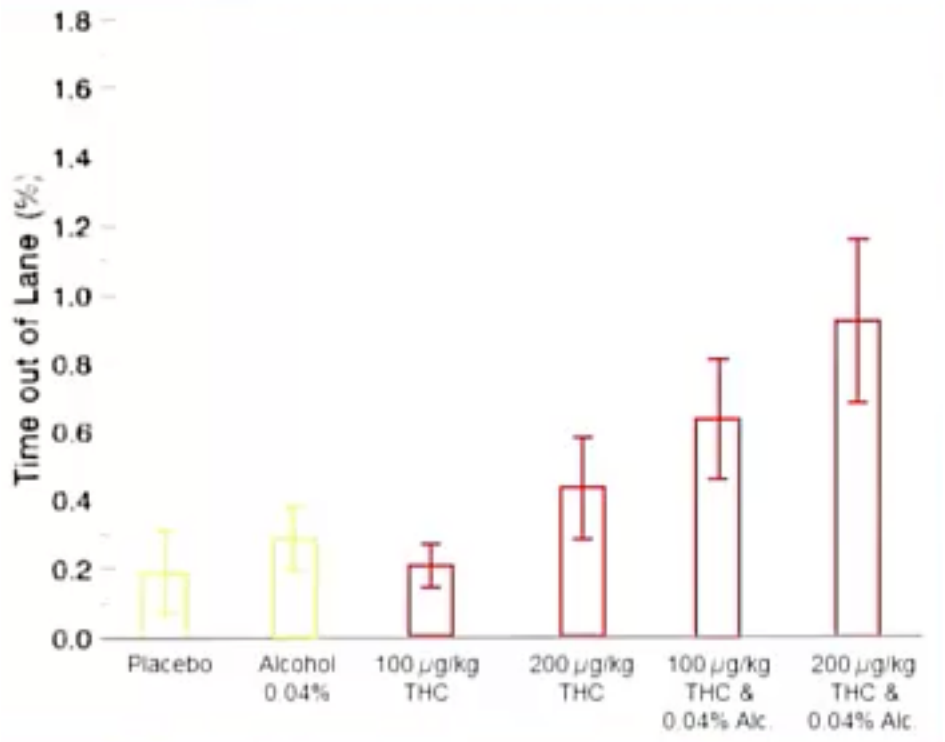


Fig 3 Pooled odds ratio (95% CI) of motor vehicle collision risk with tetrahydracannabinol for subgroups of studies

Source: Asbridge et al. (2012)

Driving and cannabis



Source: Ramaekers et al. (2000); Grant (2014)

Drug and Alcohol Dependence 106 (2010) 133–141

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Cannabis withdrawal severity and short-term course among cannabis-dependent adolescent and young adult inpatients

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ABSTRACT

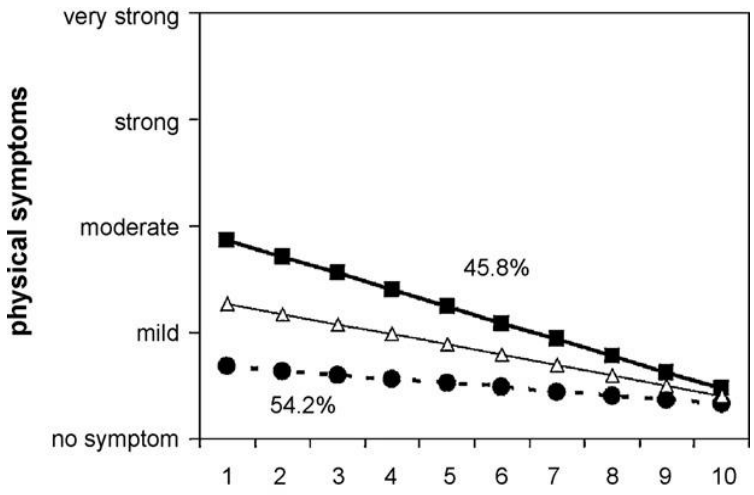
Objective: While previous studies questioned the existence of a cannabis withdrawal syndrome (CWS), recent research provided increasing evidence of a number of clinical symptoms after cessation of frequent cannabis consumption. The aim of this study is to prospectively assess the course of CWS in a sample of cannabis-dependent inpatients and to provide an estimate of the proportion of subjects experiencing CWS.

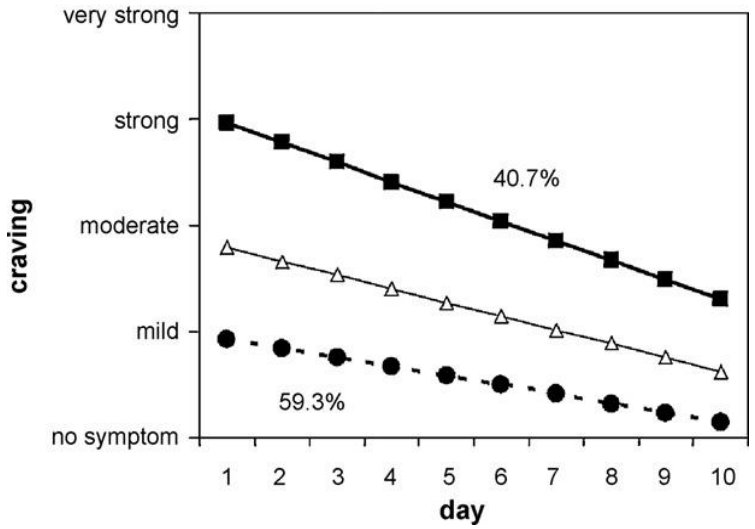
Methods: 118 subjects, aged 16–36 years, diagnosed with a cannabis dependence (DSM-IV, assessed by SCID I) were enrolled in the study. CWS was assessed prospectively over 10 days using a modified version of the Marijuana Withdrawal Checklist. Personality dimensions were assessed with the NEO-FFI.

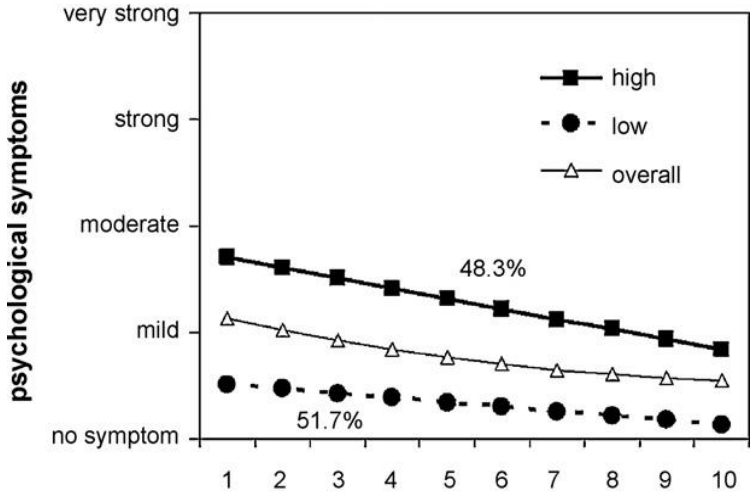
Results: 73 subjects (61.3%) completed all assessments over the observation period. Most symptoms peaked on day 1. Model-based analyses revealed a high and low intensity CWS group. Less than half of the patients belonged to the high intensity craving, psychological, or physical withdrawal symptoms group. Symptom intensity decreased almost linearly over time. Indicators of cannabis consumption intensity as well as personality dimensions, but not recalled withdrawal were related to membership in the high intensity CWS group.

Discussion: A clinically relevant CWS may only be expected in a subgroup of cannabis-dependent patients. Most subjects with an elevated CWS experience physical and psychological symptoms. The small to negligible associations between recalled and prospectively assessed symptoms raise questions about the validity of the former approach.

Course of withdrawal symptoms

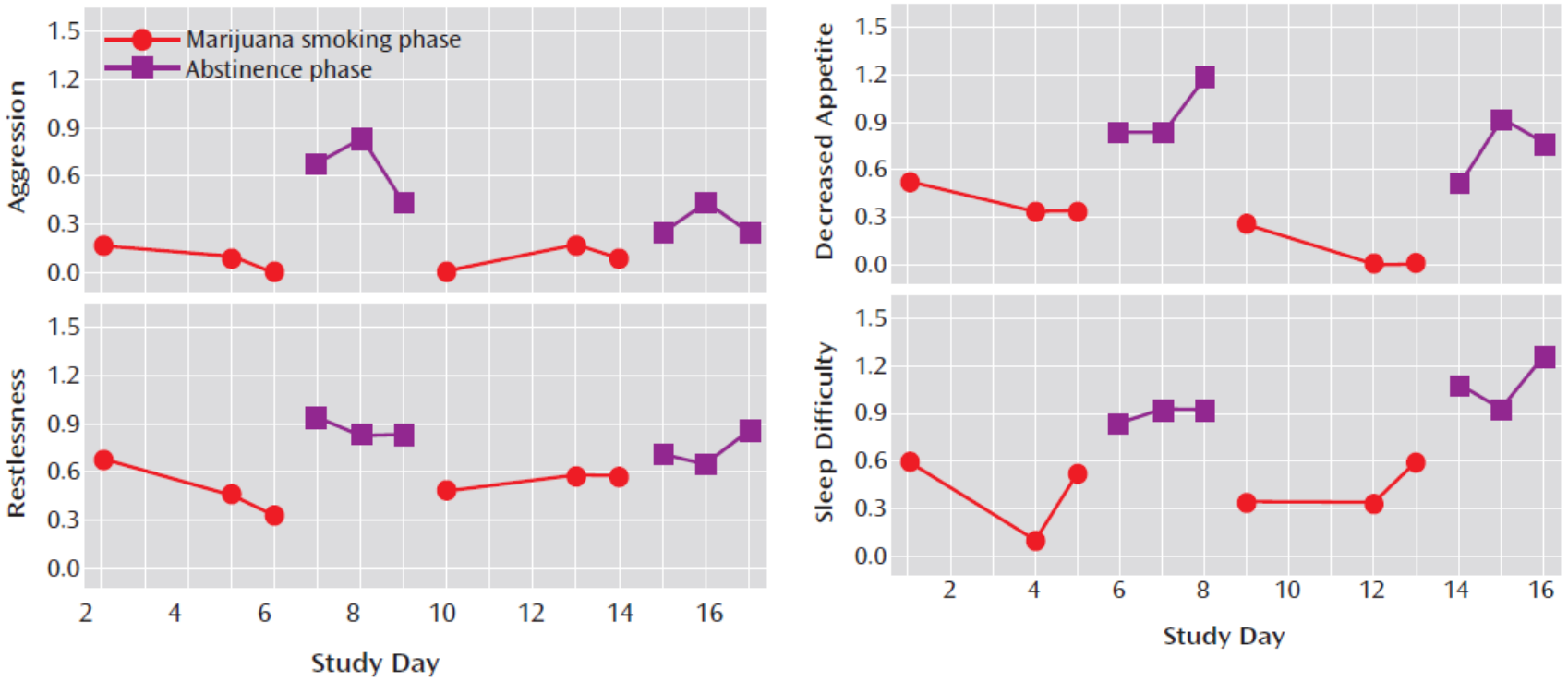






Source: Preuss et al., 2010

Mean scores for four withdrawal checklist items across time in a 16-day study of effects of abstinence from cannabis



Source: Budney et al. (2004)

Published in final edited form as:
J Int Neuropsychol Soc. 2012 July ; 18(4): 678–688. doi:10.1017/S1355617712000276.

Increased Marijuana Use and Gender Predict Poorer Cognitive Functioning in Adolescents and Emerging Adults

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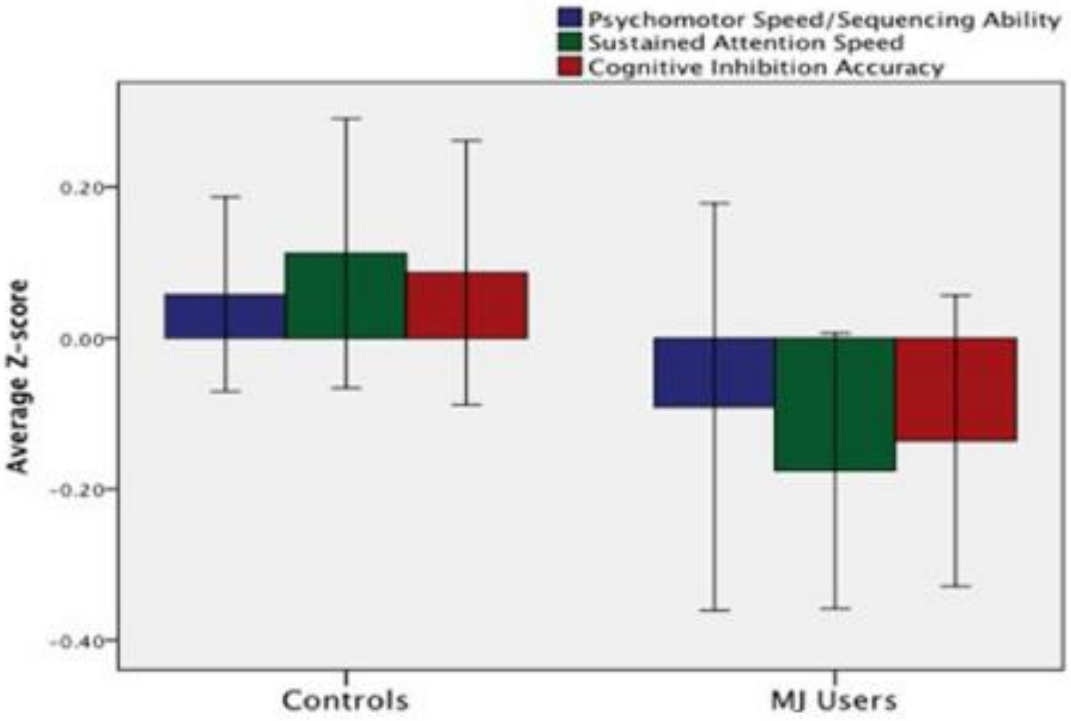
Abstract

This study sought to characterize neuropsychological functioning in MJ-using adolescents and emerging adults (ages 18–26) and to investigate whether gender moderated these effects. Data were collected from 59 teens and emerging adults including MJ users (n = 23, 56% female) and controls (n = 35, 50% female) aged 18–26 (M = 21 years). Exclusionary criteria included independent Axis I disorders (besides SUD), and medical and neurologic disorders. After controlling for reading ability, gender, subclinical depressive symptoms, body mass index, and alcohol and other drug use, increased MJ use was associated with slower psychomotor speed/sequencing ability (p< .01), less efficient sustained attention (p< .05), and increased cognitive inhibition errors (p< .03). Gender significantly moderated the effects of MJ on psychomotor speed/sequencing ability (p< .003) in that males had a more robust negative relationship. The current study demonstrated that MJ exposure was associated with poorer psychomotor speed, sustained attention and cognitive inhibition in a dose-dependent manner in young adults, findings that are consistent with other samples of adolescent MJ users. Male MJ users demonstrated greater cognitive slowing than females. Future studies need to examine the neural substrates underlying with these cognitive deficits and whether cognitive rehabilitation or exercise interventions may serve as a viable treatments of cognitive deficits in emerging adult MJ users.

Cognition following 1 week minimum of abstinence



Source: Lisdahl and Price (2012)

Addictive Behaviors 35 (2010) 970–976

Contents lists available at ScienceDirect

Addictive Behaviors

Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence

Karen L. Hanson [a,b,*], Jennifer L. Winward [c], Alecia D. Schweinsburg [d], Krista Lisdahl Medina [e], Sandra A. Brown [a,b,c], Susan F. Tapert [a,b]

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Adolescence
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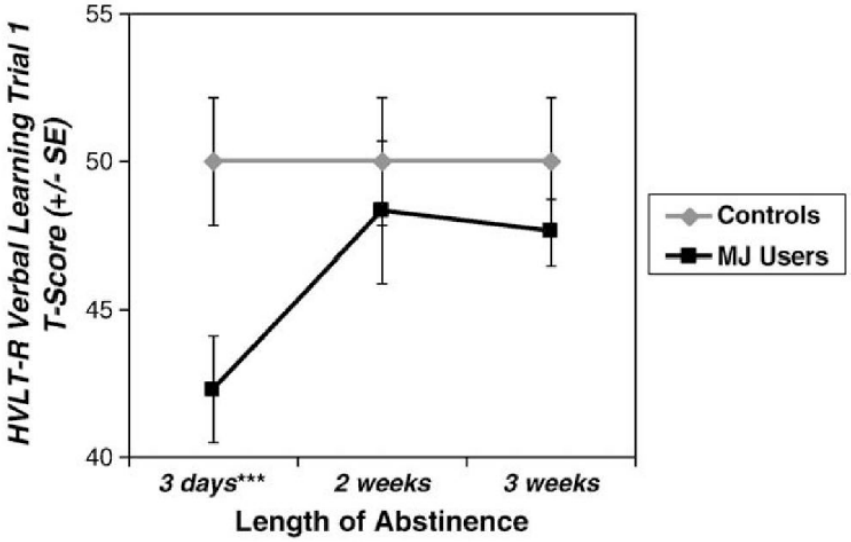
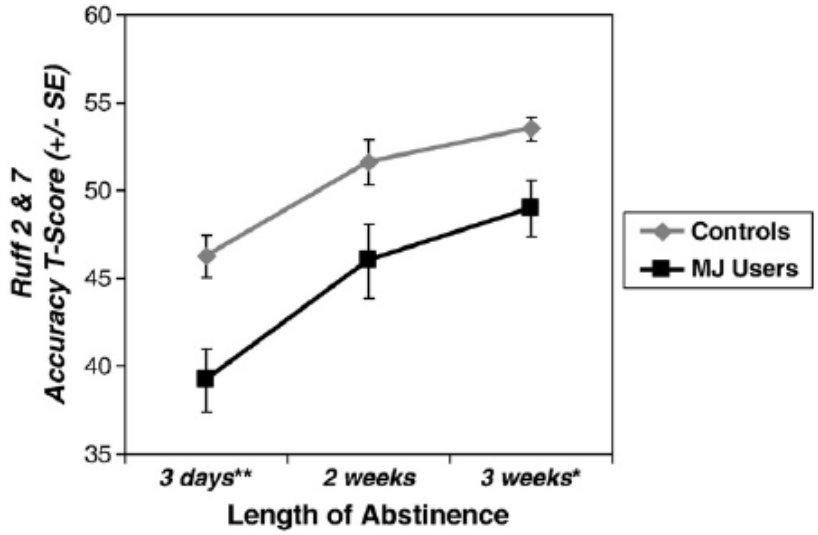
Cannabis
Drug effects
Recovery

ABSTRACT

Background: Cognitive deficits that persist up to a month have been detected among adult marijuana users, but decrements and their pattern of recovery are less known in adolescent users. Previously, we reported cognitive deficits among adolescent marijuana users after one month of abstinence (Medina, Hanson, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007). In this longitudinal study, we characterized neurocognitive changes among marijuana-using adolescents across the first three weeks of abstinence.
Method: Participants were adolescent marijuana users with limited alcohol and other drug use ($n=19$) and demographically similar non-using controls ($n=21$) ages 15–19. Participants completed a brief neuropsychological battery on three occasions, after 3 days, 2 weeks, and 3 weeks of stopping substance use. Abstinence was ascertained by decreasing tetrahydrocannabinol metabolite values on serial urine drug screens. Verbal learning, verbal working memory, attention and vigilance, and time estimation were evaluated.
Results: Marijuana users demonstrated poorer verbal learning ($p<.01$), verbal working memory ($p<.05$), and attention accuracy ($p<.01$) compared to controls. Improvements in users were seen on word list learning after 2 weeks of abstinence and on verbal working memory after 3 weeks. While attention processing speed was similar between groups, attention accuracy remained deficient in users throughout the 3-week abstinence period.
Conclusions: This preliminary study detected poorer verbal learning and verbal working memory among adolescent marijuana users that improved during three weeks of abstinence, while attention deficits persisted. These results implicate possible hippocampal, subcortical, and prefrontal cortex abnormalities.

Memory performance at 3 weeks abstinence





Source: Hanson et al.(2010)

CME

Dose-related neurocognitive effects of marijuana use

K.I. Bolla, PhD; K. Brown, MPH; D. Eldreth, BA; K. Tate, BA; and J.L. Cadet, MD

Abstract—*Background:* Although about 7 million people in the US population use marijuana at least weekly, there is a paucity of scientific data on persistent neurocognitive effects of marijuana use. *Objective:* To determine if neurocognitive deficits persist in 28-day abstinent heavy marijuana users and if these deficits are dose-related to the number of marijuana joints smoked per week. *Methods:* A battery of neurocognitive tests was given to 28-day abstinent heavy marijuana abusers. *Results:* As joints smoked per week increased, performance decreased on tests measuring memory, executive functioning, psychomotor speed, and manual dexterity. When dividing the group into light, middle, and heavy user groups, the heavy group performed significantly below the light group on 5 of 35 measures and the size of the effect ranged from 3.00 to 4.20 SD units. Duration of use had little effect on neurocognitive performance. *Conclusions:* Very heavy use of marijuana is associated with persistent decrements in neurocognitive performance even after 28 days of abstinence. It is unclear if these decrements will resolve with continued abstinence or become progressively worse with continued heavy marijuana use.

NEUROLOGY 2002;59:1337–1343

Marijuana is the most widely used illicit drug in the United States and the western hemisphere. In 2000, an estimated 76% of America's 14.8 million illicit drug users used marijuana alone (59%) or in conjunction with other illicit drugs (17%).[1] About 7 million people in the US population use marijuana at least weekly.[1] Because of debate about medicinal uses and legalization of marijuana, knowing whether marijuana has persistent effects on the brain is of interest.

Studies of residual cognitive effects of marijuana following a brief period of abstinence show that heavy marijuana use is associated with deficits in executive cognitive functioning, sustained attention, and memory.[2-8] These studies have some methodologic limitations. First, marijuana users were only monitored for abstinence for 17 to 72 hours before testing. Because marijuana has an apparent half-life of 4.1 ± 1.1 days,[6] it is difficult to determine if the these observations[2-8] were due to drug residues in the body or to withdrawal symptoms such as anxiety or irritability.[7] Second, the quantification of heavy versus light users may be problematic. Marijuana users have been grouped by frequency of use[3] and education (a cohort effect). Third, no structured psychiatric interview was used to exclude disorders like depression,[3] which is associated with poor cognitive performance.[8]

Until 2001, there were no published reports of the residual effects of marijuana use on cognitive functioning after a period of abstinence longer than 12 to 72 hours. In a carefully designed study, marijuana users were grouped by frequency of use and neurocognitive testing was repeated over 28 days of abstinence (0, 1, 7, and 28 days).[9] Decrements in memory for word lists were found at 7 days of abstinence but not after 28 days of abstinence. The authors thus concluded that cognitive deficits are reversible after 7 days of abstinence and are related to recent, not cumulative, cannabis use. Knowledge about the cognitive effects of marijuana could also provide a basis for determining the relative contribution of marijuana when used in combination with other drugs such as methylenedioxymethamphetamine (MDMA).[10,11]

The current study was conducted to determine whether neurocognitive deficits persist in 28-day abstinent heavy marijuana users and if these deficits

Dose-related effect in 28-day abstinent heavy cannabis users

Dependent variable	Independent variable*	Exposure variable	p Value	Total R^2
RAVLT—delayed recall		Joints/wk	0.01	0.27
Symbol–digit paired associate learning	Joints/wk^2 × Shipley IQ ($p = 0.01$)	Joints/wk^2	0.02	0.45
Stroop	Joints/wk × Shipley IQ ($p = 0.01$)	Joints/wk	0.01	0.45
WCST—categories completed		Joints/wk	0.02	0.28
Rey complex figure—copy		Duration	0.05	0.19
RT—simple		Joints/wk^2	0.01	0.52
RT—repetition of numbers, number correct	Joints/wk^2 × Shipley IQ ($p = 0.03$)	Joints/wk^2	0.01	0.57
RT—numbers in sequence, false positives†	Shipley IQ ($p = 0.01$)	Joints/wk	0.04	0.32
Grooved Pegboard—nondominant hand	Joints/wk^2 × Shipley IQ ($p = 0.01$)	Joints/wk^2	0.02	0.44

Source: Bolla et al. (2006)

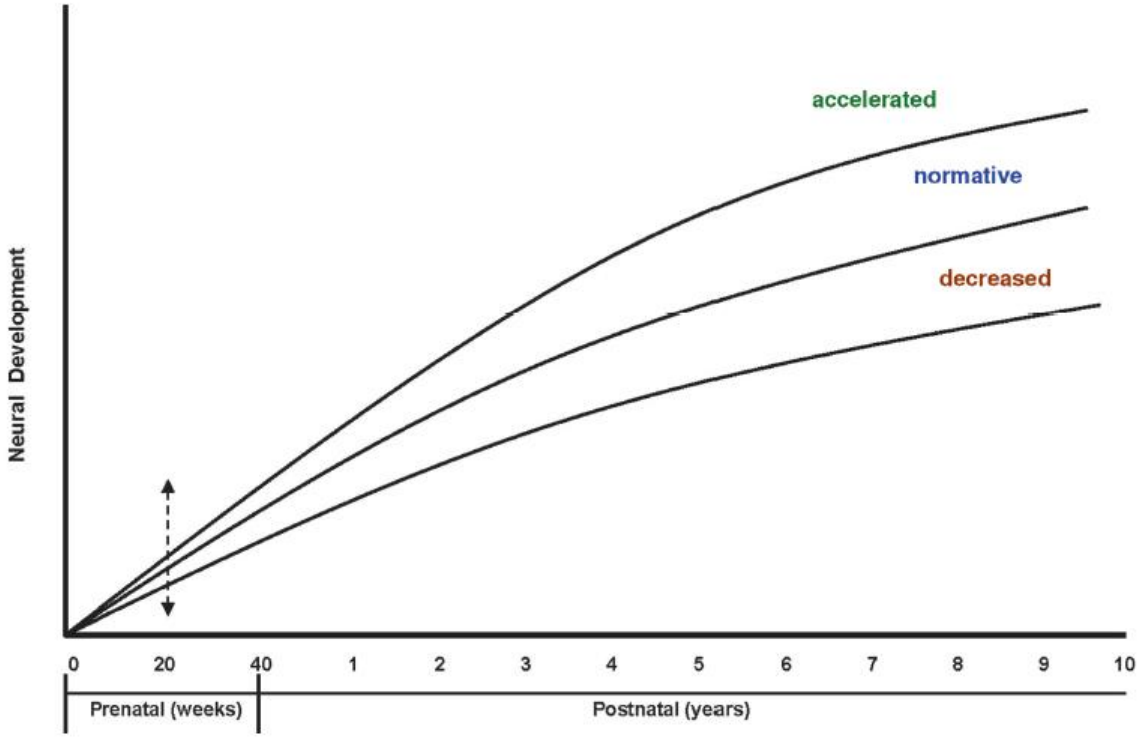
Source: Hutchings, et al. (1989)

Prevalence of cannabis use during pregnancy

- 2.8% of pregnant women report past-month use
- Prospective, longitudinal studies examining cannabis use during pregnancy report rates ranging from
  - 10-16% in middle-class samples
  - to 23-30% in inner-city samples

Source: Fried (2002); SAMHSA (2006)

Developmental trajectories from fetus into childhood



Source: DiPietro (2010). *Maternal influence on fetal development* (pp. 9-17).

nature publishing group

Clinical Investigation | **Articles**

Birth outcomes associated with cannabis use before and during pregnancy

Mohammad R. Hayatbakhsh[1,2], Vicki J. Flenady[2], Kristen S. Gibbons[2], Ann M. Kingsbury[2], Elizabeth Hurrion[2], Abdullah A. Mamun[1] and Jake M. Najman[1]

INTRODUCTION: This study aimed to examine the association between cannabis use before and during pregnancy and birth outcomes.

RESULTS: Overall, 26.3% of women reported previous use of cannabis and 2.6% reported current use. Multivariate analysis, controlling for potential confounders, including tobacco smoking, alcohol consumption, and use of other illicit drugs, showed that cannabis use in pregnancy was associated with low birth weight (odds ratio (OR) = 1.7; 95% confidence interval (CI): 1.3–2.2), preterm labor (OR = 1.5; 95% CI: 1.1–1.9), small for gestational age (OR = 2.2; 95% CI: 1.8–2.7), and admission to the neonatal intensive care unit (OR = 2.0; 95% CI: 1.7–2.4).

DISCUSSION: The results of this study show that the use of cannabis in pregnancy is associated with increased risk of adverse birth outcomes. Prevention programs that address cannabis use during pregnancy are needed.

METHODS: Data were from women birthing at the Mater Mothers' Hospital in Brisbane, Australia, over a 7-y period (2000–2006). Women were interviewed in the initial antenatal visit about their use of cannabis and other substances. Records for 24,874 women who provided information about cannabis use, and for whom birth outcomes data were available, were included in the analysis.

age (SGA) (7), and small birth length (11,12). However, other studies have disputed these findings (10,12–18).

Although the volume of literature on the association between cannabis use in pregnancy and birth outcomes has been growing, there remains concern about the limitations of previous research. Limitations include small or highly selected samples (8,12); lack of prospectively collected measures of cannabis use; and lack of control for potential confounders, e.g., socioeconomic status and maternal health, and also use of other substances (cigarettes, alcohol, and other drugs) (7). Cannabis users differ from nonusers in a range of ways and any observed association with ever using cannabis may be indicative of residual or uncontrolled confounding. Distinguishing between ever cannabis use and use in pregnancy and birth outcomes is of particular importance. As most cannabis users also use other substances, such as tobacco and alcohol, it is difficult to identify the specific effects of cannabis on the fetus (4). This study aims to examine the association between birth outcomes and use of cannabis prior to and during pregnancy, independent of potential confounding factors.

RESULTS

Between 2000 and 2006, 25,073 women presented to Mater Mothers' Hospital (MMH) for antenatal care. Of those, 24,874,

Adjusted association of cannabis use during pregnancy with birth outcome, Mater Mother's Hospital, 2000-2006

	Cannabis use during pregnancy		
	Unadjusted	Adjusted[a]	Adjusted[b]
Birth outcome	OR (95% CI)[c]	OR (95% CI)[c]	OR (95% CI)[c]
Birth weight			
<2,500 g	2.4 (2.0–2.9)**	2.3 (1.9–2.9)**	1.7 (1.3–2.2)**
2,500–4,000 g	Ref	Ref	Ref
>4,000 g	0.3 (0.2, 0.5)**	0.3 (0.2–0.5)**	0.5 (0.3–0.8)*
Preterm birth			
No	Ref	Ref	Ref
Yes	1.7 (1.4–2.1)**	1.7 (1.3–2.1)**	1.5 (1.1–1.9)*
SGA			
No	Ref	Ref	Ref
Yes	3.1 (2.5–3.7)**	3.1 (2.5–3.7)**	2.2 (1.8–2.7)**
NICU admission			
No	Ref	Ref	Ref
Yes	2.3 (1.9–2.7)**	2.3 (1.9–2.8)**	2.0 (1.7–2.4)**

Different from reference category at *P value < 0.01, **P value < 0.001.

CI, confidence interval; NICU, neonatal intensive care unit; OR, odds ratio; Ref, reference category; SGA, small for gestational age.

[a]Adjusted for mother's age, parity, ethnicity, and weight. [b]Adjusted for mother's age, parity, ethnicity, weight, cigarette smoking, alcohol consumption, and use of other illicit drugs during pregnancy. [c]No use of cannabis considered reference category.

Intrauterine Cannabis Exposure Affects Fetal Growth Trajectories: The Generation R Study

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ABSTRACT

Objective: Cannabis is the most commonly consumed illicit drug among pregnant women. Intrauterine exposure to cannabis may result in risks for the developing fetus. The importance of intrauterine growth on subsequent psychological and behavioral child development has been demonstrated. This study examined the relation between maternal cannabis use and fetal growth until birth in a population-based sample. **Method:** Approximately 7,452 mothers enrolled during pregnancy and provided information on substance use and fetal growth. Fetal growth was determined using ultrasound measures in early, mid-, and late pregnancy. Additionally, birth weight was assessed. **Results:** Maternal cannabis use during pregnancy was associated with growth restriction in mid- and late pregnancy and with lower birth weight. This growth reduction was most pronounced for fetuses exposed to continued maternal cannabis use during pregnancy. Fetal weight in cannabis-exposed fetuses showed a growth reduction of −14.44 g/week (95% confidence interval −22.94 to −5.94, $p = .001$) and head circumference (−0.21 mm/week, 95% confidence interval −0.42 to 0.02, $p = .07$), compared with nonexposed fetuses. Maternal cannabis use during pregnancy resulted in more pronounced growth restriction than maternal tobacco use. Paternal cannabis use was not associated with fetal growth restriction. **Conclusions:** Maternal cannabis use, even for a short period, may be associated with several adverse fetal growth trajectories. *J. Am. Acad. Child Adolesc. Psychiatry,* 2009;48(12):1173–1181. **Key Words:** intrauterine cannabis exposure, fetal growth, ultrasound measurements, longitudinal population cohort.

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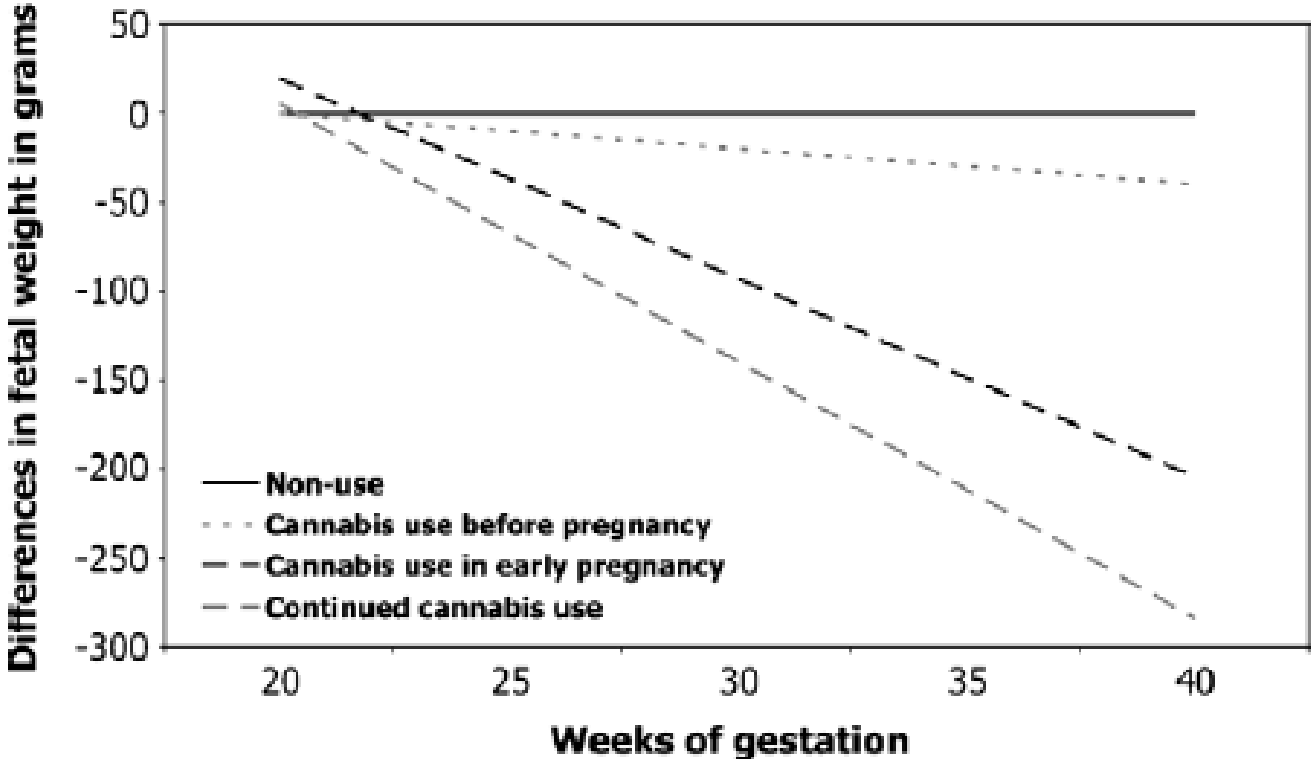
Mrs. El Marroun and Dr. Jaddoe are with the Generation R Study Group; Mrs. El Marroun and Drs. Huizink, Tiemeier, Verhulst, Jaddoe, Hofman, and Steegers are with the Erasmus MC: University Medical Center Rotterdam. Dr. van den Brink is with the Academic Medical Center University of Amsterdam.

Cannabis is the most commonly consumed illicit drug among pregnant women.[1] Because of improved breeding and greenhouse technology, particularly of Dutch cannabis, concentration in marijuana and hashish of Δ-9-



Estimated growth curve and difference in fetal weight due to maternal cannabis use in pregnancy contrasted with fetuses of mothers who did not use cannabis or tobacco during pregnancy

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0892-0362/99 $–see front matter

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Growth from Birth to Early Adolescence in Offspring Prenatally Exposed to Cigarettes and Marijuana

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FRIED, P. A., B. WATKINSON AND R. GRAY. *Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana.* NEUROTOXICOL TERATOL **21**(5) 513–525, 1999.—Weight, height, and head circumference were examined in children from birth to early adolescence for whom prenatal exposure to marijuana and cigarettes had been ascertained. The subjects were from a low-risk, predominantly middle-class sample participating in an ongoing longitudinal study. The negative association between growth measures at birth and prenatal cigarette exposure was overcome, sooner in males than females, within the first few years, and by the age of six, the children of heavy smokers were heavier than control subjects. Pre and postnatal environmental tobacco smoke did not have a negative effect upon the growth parameters; however, the choice of bottle-feeding or shorter duration of breast-feeding by women who smoked during pregnancy appeared to play an important positive role in the catch-up observed among the infants of smokers. Prenatal exposure to marijuana was not significantly related to any growth measures at birth, although a smaller head circumference observed at all ages reached statistical significance among the early adolescents born to the heavy marijuana users.

Cigarettes Marijuana Pregnancy Growth Birthweight

SINCE its recognition in 1957 (70), the most consistently reported effect of cigarette smoking on pregnancy has been the lowered birth weight of the offspring. It is generally accepted that smoking during pregnancy reduces fetal growth (birth weight, birth length, and head circumference) in a dose-response fashion (1,14,28,56,72,76). The average reduction in birth weight associated with smoking a pack of cigarettes a day is approximately 200 g, and is not due to a shortened gestation period (21). Some earlier investigators speculated that this reduction in birth weight was attributable to reduced appropriational reduction in weight and length (6,14,46,51,72), while others (28) note a lower PI (weight was more affected than length) in the offspring of women who averaged more than a pack a day, either during their entire pregnancy or during the third trimester, and in a recent paper, Zarén et al. (76) reported a similar lower PI in both light and heavy smokers.

Maternal exposure to passive smoke during pregnancy has been reported by most (37,49,50,63,77) but not all (48) to be associated with a slight decrement (frequently nonsignificant) in birth weight. The degree of effect varies considerably from

GROWTH MEASUREMENTS FOR MARIJUANA GROUPS: MEANS OF RAW AND ADJUSTED STANDARD SCORES

	Raw						Adjusted		
	Joints/week*						Joints/week*		
	0		> 0 & < 6		⩾ 6		0	> 0 & < 6	⩾ 6
	Z-score (SD)	*n*	Z-score (SD)	*n*	Z-score (SD)	*n*	Z-score (SE)	Z-score (SE)	Z-score (SE)
Weight									
Birth	0.70 (1.2)	564	0.55 (1.1)	79	0.22 (1.2)†	36	0.67 (0.04)	0.53 (0.12)	0.53 (0.18)
12 Months	−0.06 (1.0)	148	−0.32 (1.1)	37	0.35 (0.9)‡	16	−0.07 (0.08)	−0.28 (0.17)	0.33 (0.26)
24 Months	0.02 (1.2)	90	−0.15 (1.2)	31	0.46 (1.3)	16			
36 Months	−0.10 (0.8)	89	−0.19 (1.0)	26	0.28 (1.1)	20			
48 Months	−0.03 (0.8)	80	−0.13 (0.9)	21	0.46 (1.3)‡	16	−0.05 (0.09)	−0.05 (0.18)	0.48 (0.21)‡
72 Months	0.40 (0.8)	87	0.40 (1.0)	25	0.38 (1.3)	19			
9–12 Years	0.48 (1.0)	93	0.70 (1.0)	23	0.18 (0.9)	19			
Height									
Birth	0.69 (1.2)	550	0.64 (0.9)	77	0.34 (1.8)	34			
12 Months	0.03 (1.0)	150	0.03 (1.1)	37	0.04 (1.1)	16			
24 Months	0.02 (0.9)	90	0.13 (1.1)	30	0.21 (1.1)	16			
36 Months	0.35 (0.9)	89	0.37 (1.1)	26	0.74 (1.0)	20			
48 Months	0.24 (0.9)	80	0.28 (1.3)	21	0.56 (1.0)	16			
72 Months	0.63 (1.0)	87	0.68 (1.2)	25	0.53 (1.0)	19			
9–12 Years	0.76 (1.0)	93	1.06 (1.1)	23	0.62 (1.1)	19			
Head circumference									
Birth	0.15 (1.3)	520	0.00 (1.5)	74	−0.36 (1.4)	25			
12 Months	0.61 (1.1)	150	0.49 (1.1)	37	0.38 (1.1)	16			
24 Months	0.80 (1.0)	90	0.55 (1.1)	30	0.51 (0.9)	16			
36 Months	1.15 (1.1)	89	1.00 (1.1)	26	0.67 (1.0)	20			
48 Months	0.86 (1.0)	80	0.65 (1.1)	21	0.43 (1.2)	16			
72 Months	1.20 (1.2)	87	1.07 (1.2)	25	0.51 (1.4)‡	19	0.94 (0.13)	1.06 (0.24)	0.49 (0.28)‡
9–12 Years	1.41 (1.2)	93	1.94 (1.4)	23	0.82 (1.1)†	19	1.41 (0.13)	1.93 (0.26)	0.83 (0.28)†

Statistical tests were one-way between-subjects analyses of variance. No significant intergroup differences were revealed with post-hoc comparisons (Scheffé test (61) using alpha = 0.05). SD = standard deviation; SE = standard error.

*Marijuana use averaged across pregnancy.

†$p \leqslant 0.05$.

‡$p \leqslant 0.10$.

Prenatal Marijuana Exposure and Intelligence Test Performance at Age 6

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JENNIFER WILLFORD, PH.D., AND NANCY L. DAY, PH.D.

ABSTRACT

Objective: This is a prospective study of the effects of prenatal marijuana exposure on the intelligence test performance of 648 children at a 6-year follow-up. **Method:** Women were interviewed about the amount and frequency of their marijuana use at 4 and 7 months of pregnancy and at delivery. Participants were light to moderate users of marijuana and represented a lower income population. Children were assessed with the Stanford-Binet Intelligence Scale by examiners blind to exposure status. Multiple regression was applied to examine the effects of prenatal marijuana exposure on children's intelligence after partialing out the effects of other significant predictors. **Results:** There was a significant nonlinear relationship between marijuana exposure and child intelligence. Heavy marijuana use (one or more cigarettes per day) during the first trimester was associated with lower verbal reasoning scores on the Stanford-Binet Intelligence Scale. Heavy use during the second trimester predicted deficits in the composite, short-term memory, and quantitative scores. Third-trimester heavy use was negatively associated with the quantitative score. Other significant predictors of intelligence included maternal IQ, home environment, and social support. **Conclusions:** These findings indicate that prenatal marijuana exposure has a significant effect on school-age intellectual development. *J. Am. Acad. Child Adolesc. Psychiatry*, 2008;47(3):254–263. **Key Words:** cognitive ability, Stanford-Binet Intelligence Scale.

This study examines the effects of prenatal marijuana exposure (PME) on the children's intellectual develop-

on intelligence at age 3 continued to be evident at age 6 years.

Mean Stanford-Binet Scores by Levels of Prenatal Marijuana Exposure

	Group 1: Abstain (n = 380)	Group 2: Light/Moderate (n = 175)	Group 3: Heavy (n = 93)	p^a
First-trimester use				
Composite score[b,c]	92	93	87	.001
Verbal reasoning[b,c]	101	102	96	.000
Quantitative reasoning[c]	94	95	90	.03
Abstract/visual reasoning	85	86	82	.06
Short-term memory[c]	92	95	89	.009
	Group 1:	Group 2:	Group 3:	
Second-trimester use	Abstain (n = 455)	Light/Moderate (n = 103)	Heavy (n = 30)	p^a
Composite score[b,c]	92	92	84	.007
Verbal reasoning[b,c]	101	101	94	.01
Quantitative reasoning[b,c]	94	94	84	.008
Abstract/visual reasoning	85	85	81	.22
Short-term memory[c]	93	94	86	.05
	Group 1:	Group 2:	Group 3:	
Third-trimester use	Abstain (n = 528)	Light/Moderate (n = 88)	Heavy (n = 32)	p^a
Composite score[b,c]	92	93	86	.03
Verbal reasoning	101	101	96	.12
Quantitative reasoning[b,c]	94	96	85	.02
Abstract/visual reasoning	85	86	82	.45
Short-term memory	92	95	88	.07

Note: Abstainer = no use; Light/Moderate = more than 0 and less than 1 marijuana cigarette per day; Heavy = 1 or more marijuana cigarettes per day.

[a] Overall significance using F test.

[b] Group 1 differed significantly from group 3 based on Tukey multiple comparison test.

[c] Group 2 differed significantly from group 3 based on Tukey multiple comparison test.

13-16 year olds

- Data from both OPPS and MHPCD cohorts demonstrated that problems with executive functions persist well into adolescence
- In the OPPS cohort , 13-16 year olds who were heavily exposed to cannabis (>.86 joints/day) evidenced deficits in visual memory, visual perceptual abilities, and sustained attention

Source: Fried et al. (2003); Fried and Watkinson (2001)

Cannabis and Breastfeeding

- Moderate amounts of THC are excreted into human breast milk
- The infant would ingest the equivalence of 0.8% of 1 joint in 1 feeding
- Infants can excrete THC in their urine for up to 2 to 3 weeks

Source: Bennett (1997); Liston (1998); Perez-Reyes and Wall (1982)

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Review Article

Cannabis and Breastfeeding

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Cannabis is a drug derived from hemp plant, *Cannabis sativa*, used both as a recreational drug or as medicine. It is a widespread illegal substance, generally smoked for its hallucinogenic properties. Little is known about the adverse effects of postnatal cannabis exposure throw breastfeeding because of a lack of studies in lactating women. The active substance of cannabis is the delta 9 TetraHydroCannabinol (THC). Some studies conclude that it could decrease motor development of the child at one year of age. Therefore, cannabis use and abuse of other drugs like alcohol, tobacco, or cocaine must be contraindicated during breastfeeding. Mothers who use cannabis must stop breastfeeding, or ask for medical assistance to stop cannabis use in order to provide her baby with all the benefits of human milk.

	Motor Development PDI
Days of infant Cannabis exposure	Mean
Lactation month one	
0	**102** ($n = 81$)
1 to 44	106 ($n = 38$)
45 to 90	**90** ($n = 17$)
Lactation month three	
0	102 ($n = 84$)
1 to 44	103 ($n = 28$)
45 to 90	97 ($n = 13$)

*Motor developmental scores (Psychomotor Development Index, PDI) were from Bayley Scales of Infant Development. During the first trimester, PDI decreased with increasing cannabis exposure (test for linear trend, $P = .005$). During the first lactation month, mean PDI for the higher exposure group was lower than the PDI for the no or low exposure groups (one-way ANOVA $P = .008$).

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Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study

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(RECEIVED September 12, 2002; REVISED December 4, 2002; ACCEPTED December 23, 2002)

Abstract

The possible medicinal use of cannabinoids for chronic diseases emphasizes the need to understand the long-term effects of these compounds on the central nervous system. We provide a quantitative synthesis of empirical research pertaining to the non-acute (residual) effects of cannabis on the neurocognitive performance of adult human subjects. Out of 1,014 studies retrieved using a thorough search strategy, only 11 studies met essential *a priori* inclusion criteria, providing data for a total of 623 cannabis users and 409 non- or minimal users. Neuropsychological results were grouped into 8 ability domains, and effect sizes were calculated by domain for each study individually, and combined for the full set of studies. Using slightly liberalized criteria, an additional four studies were included in a second analysis, bringing the total number of subjects to 1,188 (i.e., 704 cannabis users and 484 non-users). With the exception of both the learning and forgetting domains, effect size confidence intervals for the remaining 6 domains included zero, suggesting a lack of effect. Few studies on the non-acute neurocognitive effects of cannabis meet current research standards; nevertheless, our results indicate that there might be decrements in the ability to learn and remember new information in chronic users, whereas other cognitive abilities are unaffected. However, from a neurocognitive standpoint, the small magnitude of these effect sizes suggests that if cannabis compounds are found to have therapeutic value, they may have an acceptable margin of safety under the more limited conditions of exposure that would likely obtain in a medical setting.

Domain	Effect size (99% CI)
Attention	−.11 (−.34, .12) −.083 (−.32, .15)
Abstraction/Executive	−.15 (−.34, .032) −.13 (−.32, .052)
Forgetting/Retrieval*	−.27 (−.49, −.044)
Learning*	−.24 (−.41, −.064) −.21 (−.39, −.040)
Motor	−.26 (−.96, .43)
Perceptual–Motor	−.065 (−.28, .15) −.026 (−.25, .20)
Simple Reaction Time	.0086 (−.25, .26)
Verbal/Language	−.28 (−.62, .060)

Note. * denotes a significant effect size; Rows with two sets of numbers contain the values obtained before and after the removal of an outlier study (i.e., Wig & Varma), in the respective order; *df* = degrees of freedom.

OPEN

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Long-Term Effects of Cannabis on Brain Structure

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The dose-dependent toxicity of the main psychoactive component of cannabis in brain regions rich in cannabinoid CB1 receptors is well known in animal studies. However, research in humans does not show common findings across studies regarding the brain regions that are affected after long-term exposure to cannabis. In the present study, we investigate (using Voxel-based Morphometry) gray matter changes in a group of regular cannabis smokers in comparison with a group of occasional smokers matched by the years of cannabis use. We provide evidence that regular cannabis use is associated with gray matter volume reduction in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex; these regions are rich in cannabinoid CB1 receptors and functionally associated with motivational, emotional, and affective processing. Furthermore, these changes correlate with the frequency of cannabis use in the 3 months before inclusion in the study. The age of onset of drug use also influences the magnitude of these changes. Significant gray matter volume reduction could result either from heavy consumption unrelated to the age of onset or instead from recreational cannabis use initiated at an adolescent age. In contrast, the larger gray matter volume detected in the cerebellum of regular smokers without any correlation with the monthly consumption of cannabis may be related to developmental (ontogenic) processes that occur in adolescence.
Neuropsychopharmacology (2014) **39,** 2041–2048; doi:10.1038/npp.2014.67; published online 16 April 2014

INTRODUCTION

Cannabis is one of the most widely used recreational drugs, taking third place among drugs of concern in addiction treatment services (Degenhardt *et al*, 2008). Despite these statistics pointing to the potential harms associated with long-

different locations in frontal and parietal lobes without overlapping findings across studies (Churchwell *et al*, 2010; Gruber *et al*, 2011; Matochik *et al*, 2005). The discrepancy in the results might be due to heterogeneity in sample characteristics, inter-individual differences linked to past

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Why So Impulsive? White Matter Alterations Are Associated With Impulsivity in Chronic Marijuana Smokers

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Abstract

Difficulty monitoring and inhibiting impulsive behaviors has been reported in marijuana (MJ) smokers; neuroimaging studies, which examined frontal systems in chronic MJ smokers, have reported alterations during inhibitory tasks. Diffusion tensor imaging (DTI) provides a quantitative estimate of white matter integrity at the microstructural level. We applied DTI, clinical ratings, and impulsivity measures to explore the hypotheses that chronic, heavy MJ smokers would demonstrate alterations in white matter microstructure and a different association between white matter measures and impulsivity relative to nonsmoking control subjects (NS). Fractional anisotropy (FA), a measure of directional coherence, and trace, a measure of overall diffusivity, were calculated for 6 locations including bilateral frontal regions in 15 chronic MJ smokers and 15 NS. Subjects completed clinical rating scales, including the Barratt Impulsivity Scale (BIS). Analyses revealed significant reductions in left frontal FA in MJ smokers relative to NS and significantly higher levels of trace in the right genu. MJ smokers also had significantly higher BIS

PNAS PLUS

SEE COMMENTARY

Persistent cannabis users show neuropsychological decline from childhood to midlife

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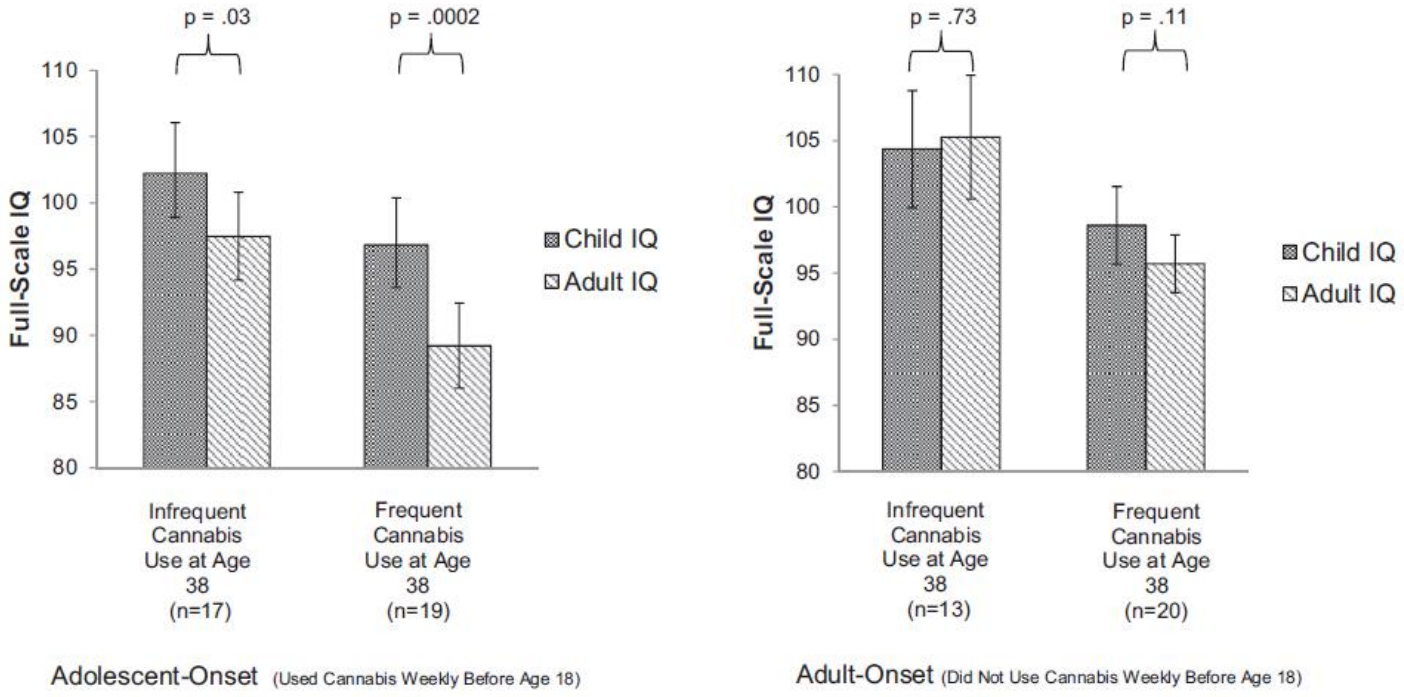
Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological function-

nence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is reliance on retrospectively reported quantity, frequency, duration, and age-of-onset of cannabis use, often inquired about years after initiation of heavy use.

A prospective, longitudinal investigation of the association between cannabis use and neuropsychological impairment could redress these limitations and strengthen the existing evidence base by assessing neuropsychological functioning in a sample of youngsters before the onset of cannabis use, obtaining prospective data on cannabis use as the sample is followed over a number of years, and readministering neuropsychological tests after some members of the sample have developed a pattern of long-term cannabis use. To our knowledge, only one prospective, longitudinal study of the effects of cannabis on neuropsychological functioning has been conducted (21), and in this study

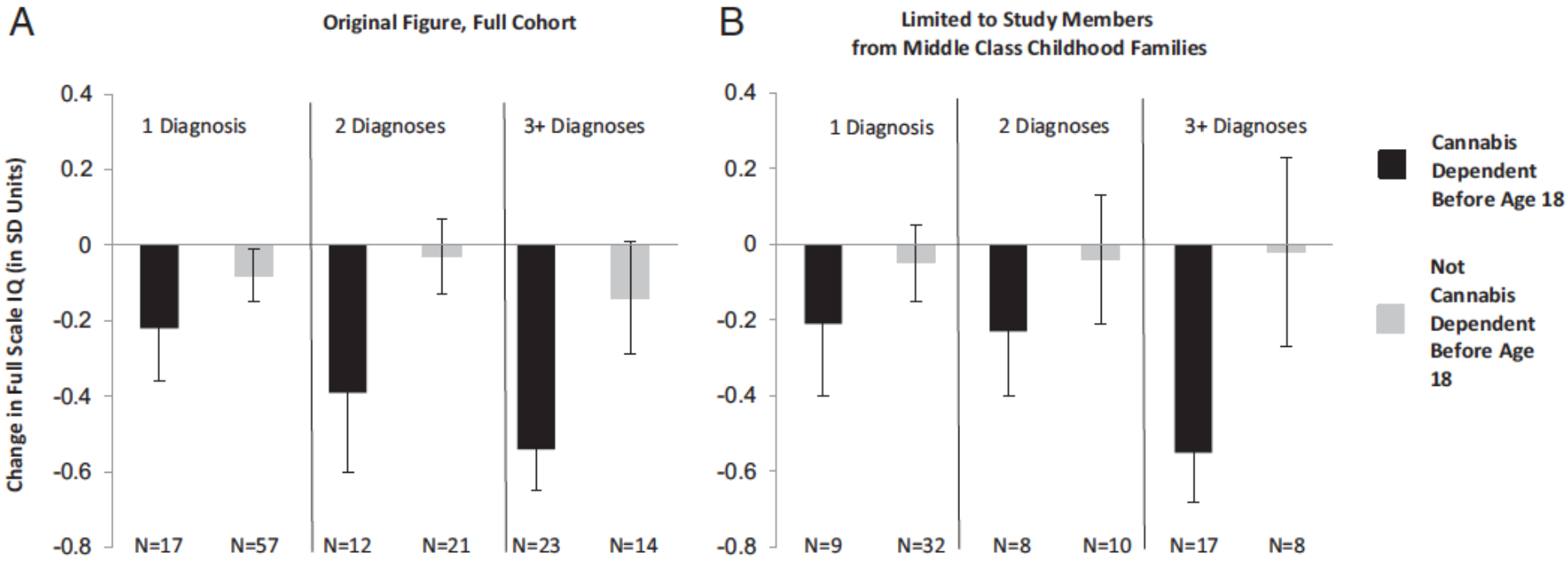
LOGICAL AND IVE SCIENCES

Persistent cannabis users show cognitive decline from childhood to midlife



Source: Meier et al. (2012)

Adolescent MJ use and IQ



Source: Moffitt (2013)

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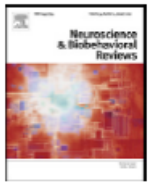

Review

Cannabis use in young people: The risk for schizophrenia

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ABSTRACT

Cannabis is one of the most commonly used illicit drugs, and despite the widely held belief that it is a safe drug, its long-term use has potentially harmful consequences. To date, the research on the impact of its use has largely been epidemiological in nature and has consistently found that cannabis use is associated with schizophrenia outcomes later in life, even after controlling for several confounding factors. While the majority of users can continue their use without adverse effects, it is clear from studies of psychosis that some individuals are more vulnerable to its effects than others. In addiction, evidence from both epidemiological and animal studies indicates that cannabis use during adolescence carries particular risk. Further studies are warranted given the increase in the concentration of the main active ingredient (Δ^9-tetrahydrocannabinol) in street preparations of cannabis and a decreasing age of first-time exposure to cannabis.

Contents

Association between cannabis use and psychosis

Country in which the study was conducted	Study design	Number of participants	Follow up	Odd ratio (95% CI) (adjusted risk)
United States (Tien and Anthony, 1990)	Population based	4494	NA	2.4 (1.2–7.1)
Sweden (Andreasson et al., 1987; Zammit et al., 2002)	Conscript cohort	50,053	15 years	2.3 (1.0–5.3)
			27 years	3.1 (1.7–5.5)
The Netherlands (NEMESIS) (Van Os et al., 2002)	Population based	4045	3 years	2.8 (1.2–6.5)
Israel (Weiser et al., 2002)	Population based	9724	4–15 years	2.0 (1.3–3.1)
New Zealand (Christchurch) (Fergusson et al., 2003)	Birth cohort	1265	3 years	1.8 (1.2–2.6)
New Zealand (Dunedin) (Arseneault et al., 2002)	Birth cohort	1034	15 years	3.1 (0.7–13.3)
The Netherlands (Ferdinand et al., 2005)	Population based	1580	14 years	2.8 (1.79–4.43)
Germany (EDSP) (Henquet et al., 2005a)	Population based	2437	4 years	1.7 (1.1–1.5)
United Kingdom (Wiles et al., 2006)	Population based	8580	18 months	1.5 (0.55–3.94)
Greece (Stefanis et al., 2004)	Birth cohort	3500	NA	4.3 (1.0–17.9)

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Age at Initiation of Cannabis Use Predicts Age at Onset of Psychosis: The 7- to 8-Year Trend

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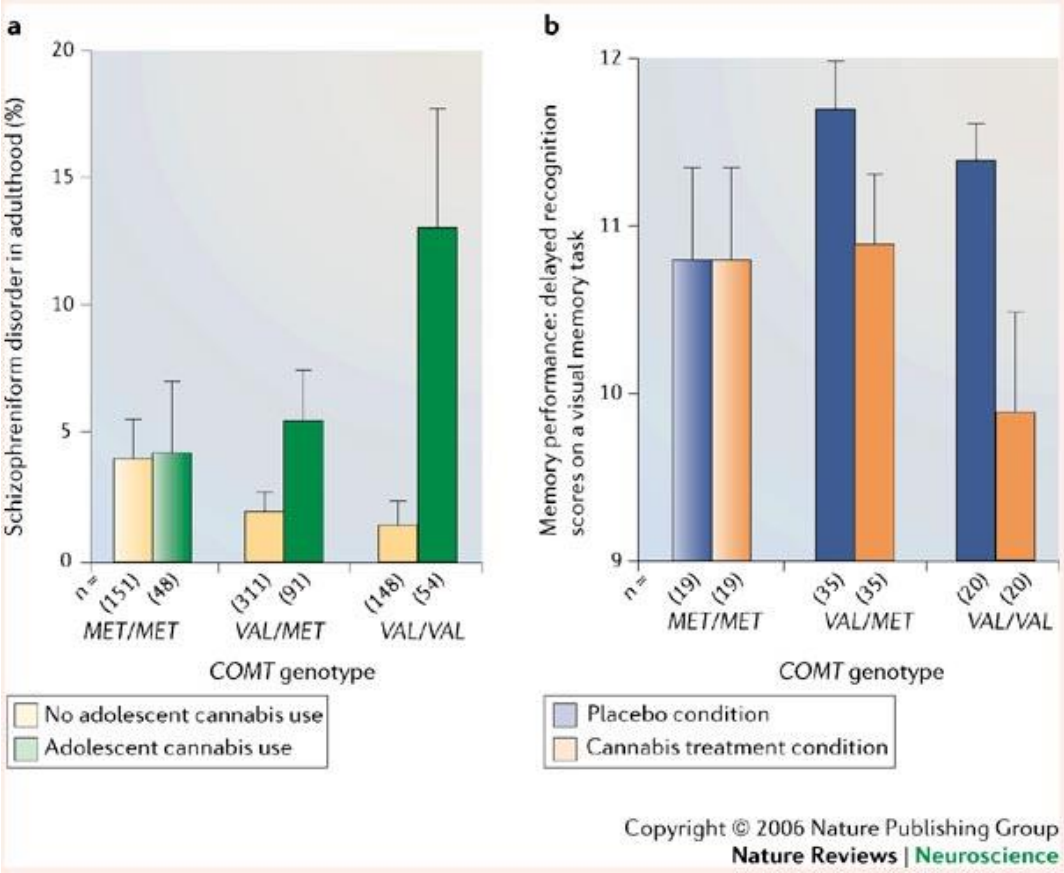
We investigated the existence of a temporal association between age at initiation of cannabis use and age at onset of psychotic illness in 997 participants from the 2010 Survey of High Impact Psychosis (SHIP) in Australia. We tested for group differences in age at onset of psychotic illness and in the duration of premorbid exposure to cannabis (DPEC). Analyses were repeated in subgroups of participants with a schizophrenia-spectrum disorder (SSD), a diagnosis of lifetime cannabis dependence (LCD), and a comorbid SSD/ LCD diagnosis. The association between age at initiation of cannabis use and age at onset of psychotic illness was linear and significant, $F(11, 984) = 13.77$, $P < .001$, even after adjusting for confounders. The effect of age at initiation of cannabis use on DPEC was not significant (mean duration of 7.8 years), and this effect was similar in participants with a SSD, LCD, and comorbid SSD/ LCD diagnosis although a shift toward shorter premorbid exposure to cannabis was noted in the SSD/LCD subgroup (mean duration of 7.19 years for SSD/LCD). A temporal direct relationship

A recent meta-analysis by Large et al. (2011)[1] reported an earlier mean AOP in samples with cannabis use and made a strong argument for causality, although increased use of cannabis by those approaching the onset of psychosis, ie, "self-medication" was considered a reasonable interpretation of the association. If cannabis use brings forward the AOP, then one may anticipate that a temporal relationship between age at initiation of cannabis use (AIC) and AOP might be observed after adjustment for confounder effects. However, few studies have specifically addressed this question within sufficiently large samples of participants with psychosis.

Several small studies have demonstrated that AIC is significantly associated with AOP.[2–5] In 123 consecutive referrals with first-episode psychosis to an early intervention service, Barnett et al. (2007)[2] reported that AIC, cocaine, ecstasy, and amphetamine use was significantly associated with age at first-psychotic symptoms. In a sample of 99 participants with a first-

Cannabis and schizophrenia



* catechol-O-methyltransferase (COMT) gene – a valine allele at codon 158

Source: Caspi and Moffitt (2006)

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Cannabis and depression: An integrative data analysis of four Australasian cohorts☆

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ABSTRACT

Background: This study presents an integrative data analysis of the association between frequency of cannabis use and severity of depressive symptoms using data from four Australasian cohort studies. The integrated data comprised observations on over 6900 individuals studied on up to seven occasions between adolescence and mature adulthood.

Methods: Repeated measures data on frequency of cannabis use (not used/<monthly/≥monthly/≥weekly) and concurrently assessed depression scores were pooled over the four cohorts. Regression models were fitted to estimate the strength of association between cannabis use and depression. Fixed effects regression methods were used to control for confounding by non-observed fixed factors.

Results: Increasing frequency of cannabis use was associated with increasing depressive symptoms ($p < 0.001$). In the pooled data weekly users of cannabis had depression scores that were 0.32 (95%CI 0.27–0.37) SD higher than non-users. The association was reduced but remained significant ($p < 0.001$) upon adjustment for confounding. After adjustment depression scores for weekly users were 0.24 (95%CI 0.18–0.30) SD higher than non-users. The adjusted associations were similar across cohorts. There was a weak age × cannabis use interaction ($p < 0.05$) suggesting that the association was strongest in adolescence. Attempts to further test the direction of causality using SEM methods proved equivocal.

Conclusions: More frequent cannabis use was associated with modest increases in rates of depressive symptoms. This association was stronger in adolescence and declined thereafter. However, it was not possible from the available data to draw a definitive conclusion as to the likely direction of causality

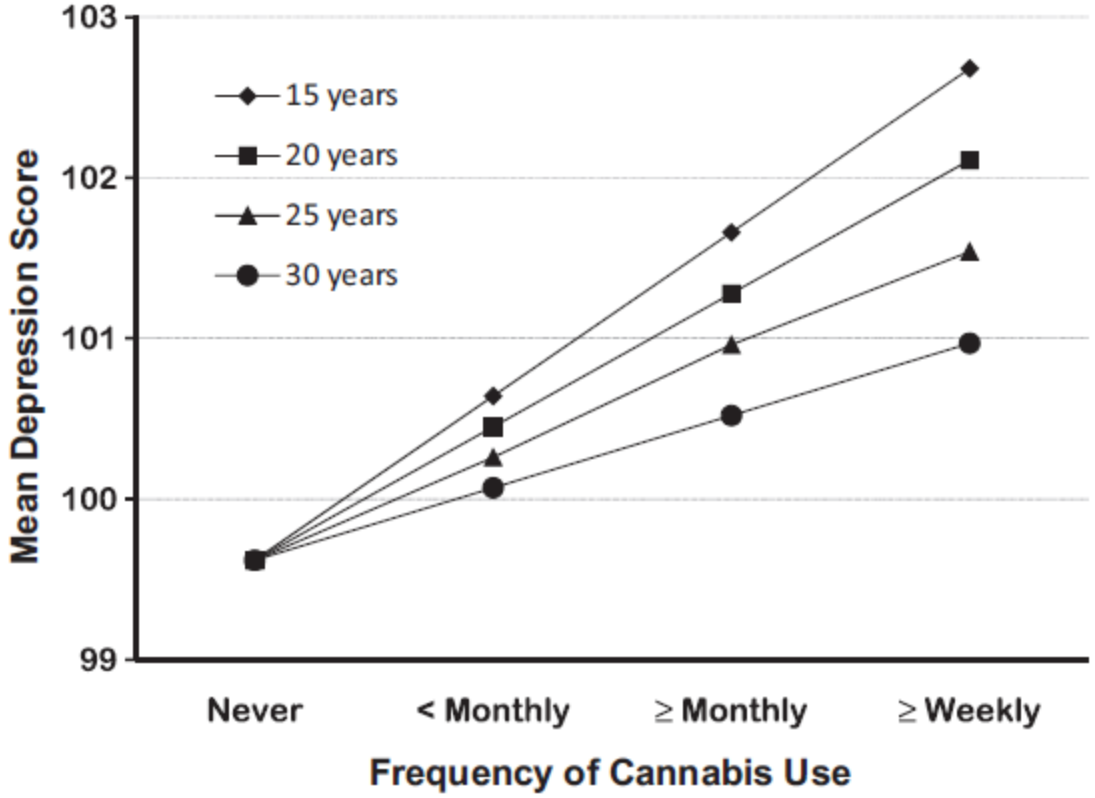

Fig. 1. Estimated associations between frequency of cannabis use and mean depression scores at selected ages (15, 20, 25, 30 years) after adjustment for fixed sources of confounding.

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ORIGINAL ARTICLE

The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies

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Background. Longitudinal studies reporting the association between cannabis use and developing depression provide mixed results. The objective of this study was to establish the extent to which different patterns of use of cannabis are associated with the development of depression using meta-analysis of longitudinal studies.

Method. Peer-reviewed publications reporting the risk of developing depression in cannabis users were located using searches of EMBASE, Medline, PsychINFO and ISI Web of Science. Only longitudinal studies that controlled for depression at baseline were included. Data on several study characteristics, including measures of cannabis use, measures of depression and control variables, were extracted. Odds ratios (ORs) were extracted by age and length of follow-up.

Results. After screening for 4764 articles, 57 articles were selected for full-text review, of which 14 were included in the quantitative analysis (total number of subjects=76058). The OR for cannabis users developing depression compared with controls was 1.17 [95% confidence interval (CI) 1.05–1.30]. The OR for heavy cannabis users developing depression was 1.62 (95% CI 1.21–2.16), compared with non-users or light users. Meta-regression revealed no significant differences in effect based on age of subjects and marginal difference in effect based on length of follow-up in the individual studies. There was large heterogeneity in the number and type of control variables in the different studies.

Conclusions. Cannabis use, and particularly heavy cannabis use, may be associated with an increased risk for developing depressive disorders. There is need for further longitudinal exploration of the association between cannabis use and

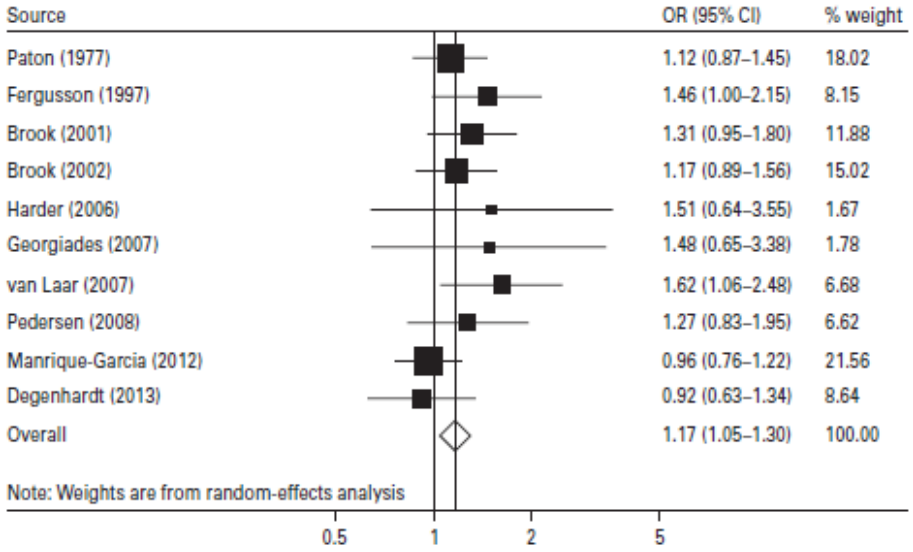

Fig. 2. Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for any depressive outcome according to cannabis use in individual studies (random effects).

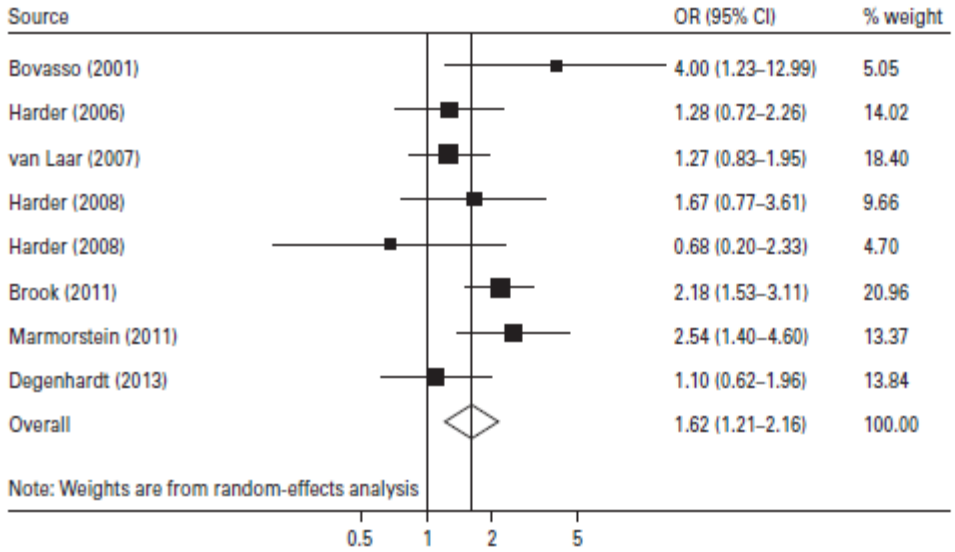

Fig. 3. Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for any depressive outcome according to heavy cannabis use (defined as a cannabis use disorder or at-least weekly use) in individual studies (random effects).

Cannabis and mental health

- Depressed teens are 2x as likely as non-depressed teens to use marijuana
- Teens who use cannabis at least once a month are 3x more likely to have suicidal thoughts than non-users
- Depressed teens are >2x as likely as their peers to abuse or become dependent on marijuana
- Of those who try MJ before 17, 17% become dependent (compared to 9% if they try it after 18 years of age)

Source: Office of National Drug Control Policy Executive Office of the President (2008); TEDS(2012)

Thank You!