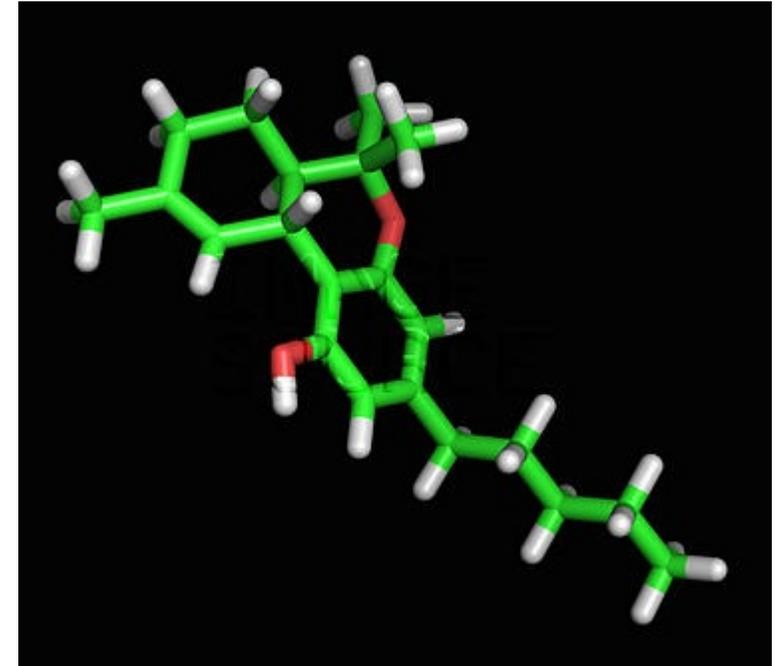


# Update on Cannabis Science and Impacts of COVID-19 Pandemic on U.S. Overdose Crisis

Wilson M. Compton, M.D., MPE  
Deputy Director, NIDA

# Cannabis: most commonly used federally illicit drug in the U.S.

- Almost 33 million Americans 12 and older report past month cannabis use.
- Almost 50 million Americans 12 and older report past year cannabis use.
- An estimated 2.8 million Americans used cannabis for the first time; 1.0 million were between the ages of 12-17.



Tetrahydrocannabinol (THC)  
Psychoactive Ingredient in cannabis

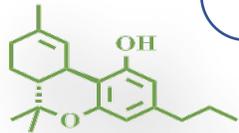
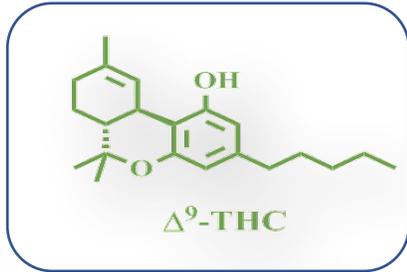
# MARIJUANA'S Acute Effects

(Intoxication phase)



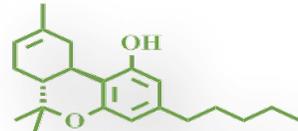
- Euphoria
- Calmness
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impairs coordination and balance
- Increased heart rate: 20 - 100%
- Orthostatic (postural) hypotension
- Increased risk of accidents (~2 fold), higher when combined with alcohol
- Impaired short-term memory
  - Difficulty with complex tasks
  - Difficulty learning
- Executive Function
  - Impaired decision-making
  - Increased risky behavior – STDs, HIV?
- Mood (especially after high doses or Edibles)
  - Anxiety – panic attacks
  - Psychosis – paranoia

# Cannabis contains >120 cannabinoids plus, other chemicals in varying concentrations



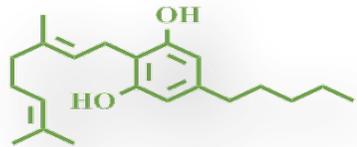
**Δ<sup>9</sup>-THCV**

**delta-9-tetrahydrocannabivarin**



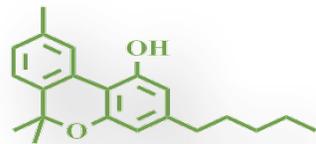
**Δ<sup>8</sup>-THC**

**delta-8-tetrahydrocannabinol**

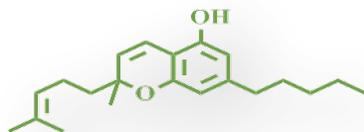


**CBG**

**cannabigerol**

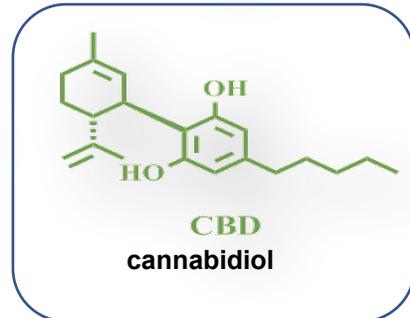


**CBN**



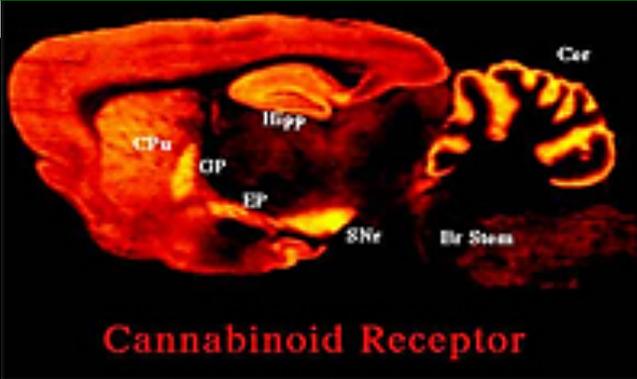
**CBC**

**cannabichromene**



- Plant with long history of use worldwide
- Illegal under US Federal law (Schedule I substance)
  - Legal for medical use in 36 States + D.C.
  - Legal for adult use in 15 States + D.C.
  - Low THC (High CBD) legal in 11 states for medical use
  - CBD from Hemp (defined as cannabis sativa <0.3% THC) no longer in the Controlled Substances Act (CSA)
- Versions of active ingredients approved (or in clinical trials) for medical indications in U.S. and other countries
  - Synthetic - Marinol, Syndros, Cesamet
  - Plant Derived –Sativex (THC/CBD)
  - Plant Derived – Epidiolex (CBD: FDA approved: No longer scheduled)

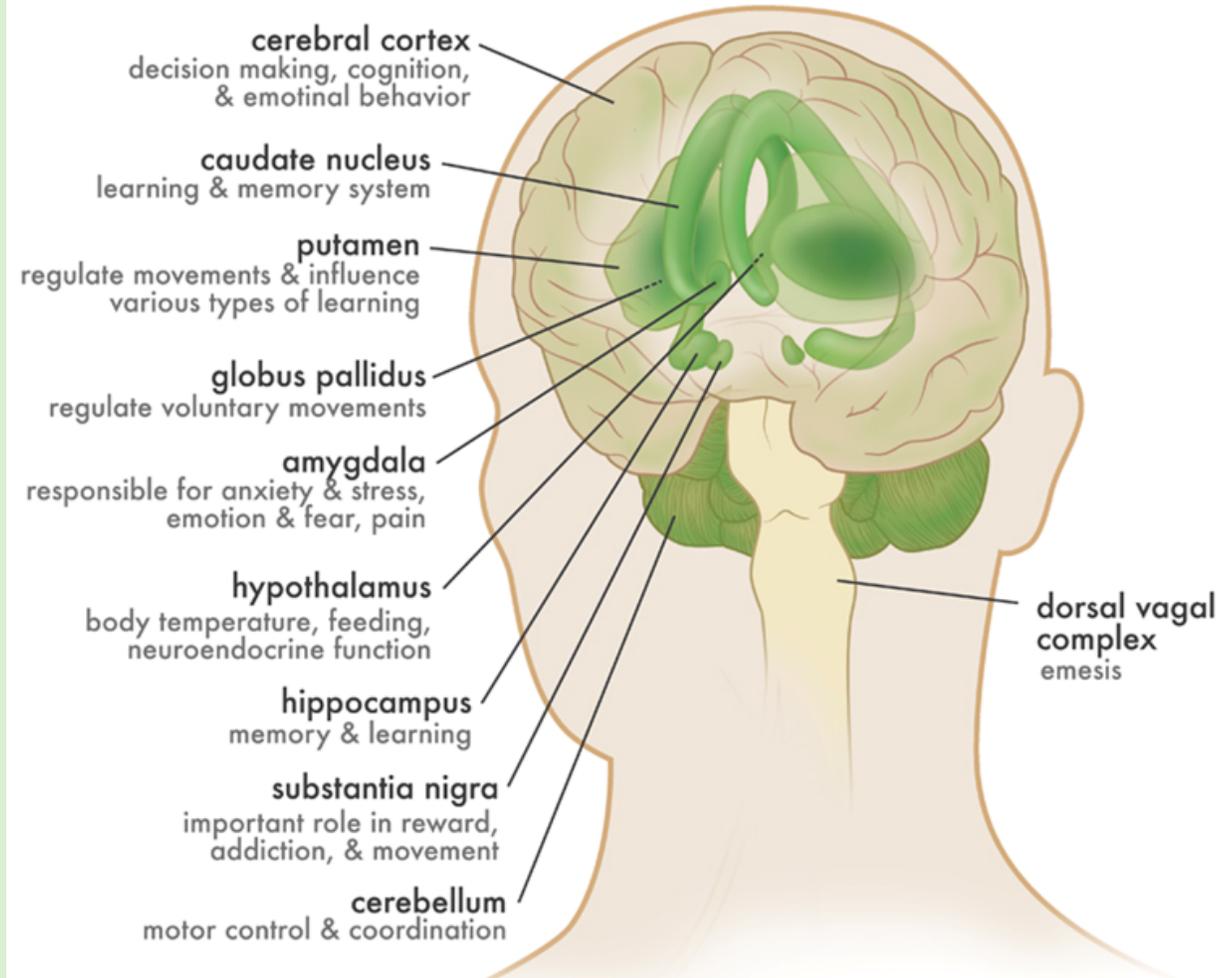
# Cannabinoid Receptors Are Located Throughout the Brain



**Cannabinoid Receptor**

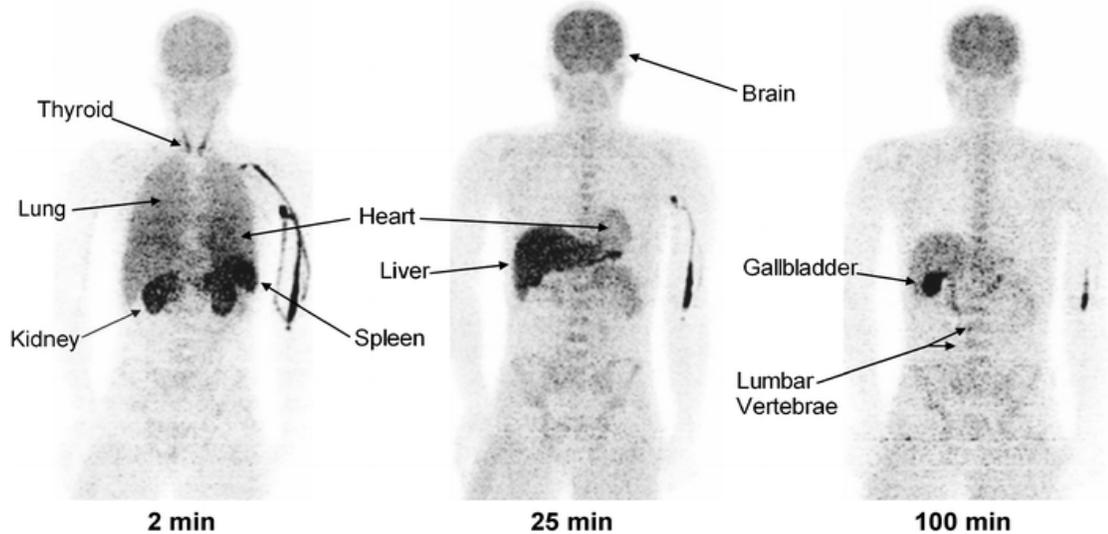
## Regulation of:

- Brain Development
- Memory and Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immunological Function
- Appetite
- Motivational Systems & Reward



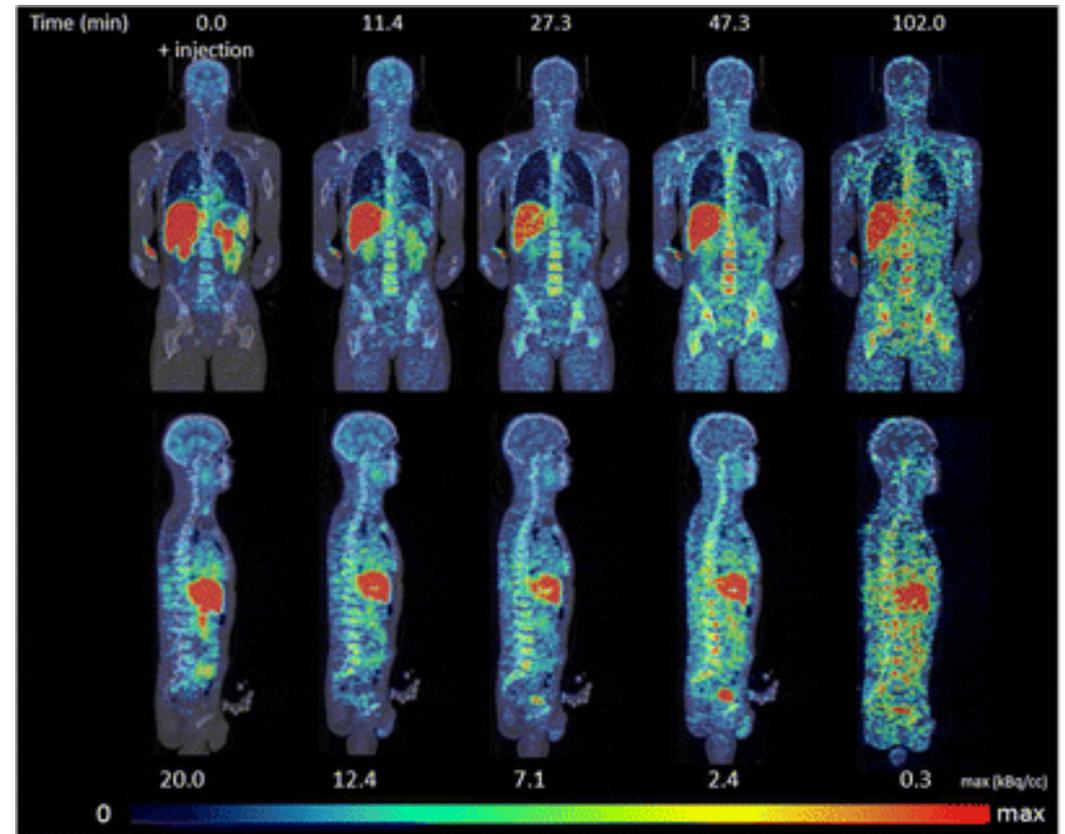
# Cannabinoid *Receptors* Are Also Located Throughout the Body

Whole Body Distribution of CBI Receptors (2, 25, and 100 min after injection of  $^{111}\text{C}$ -MePPEP)



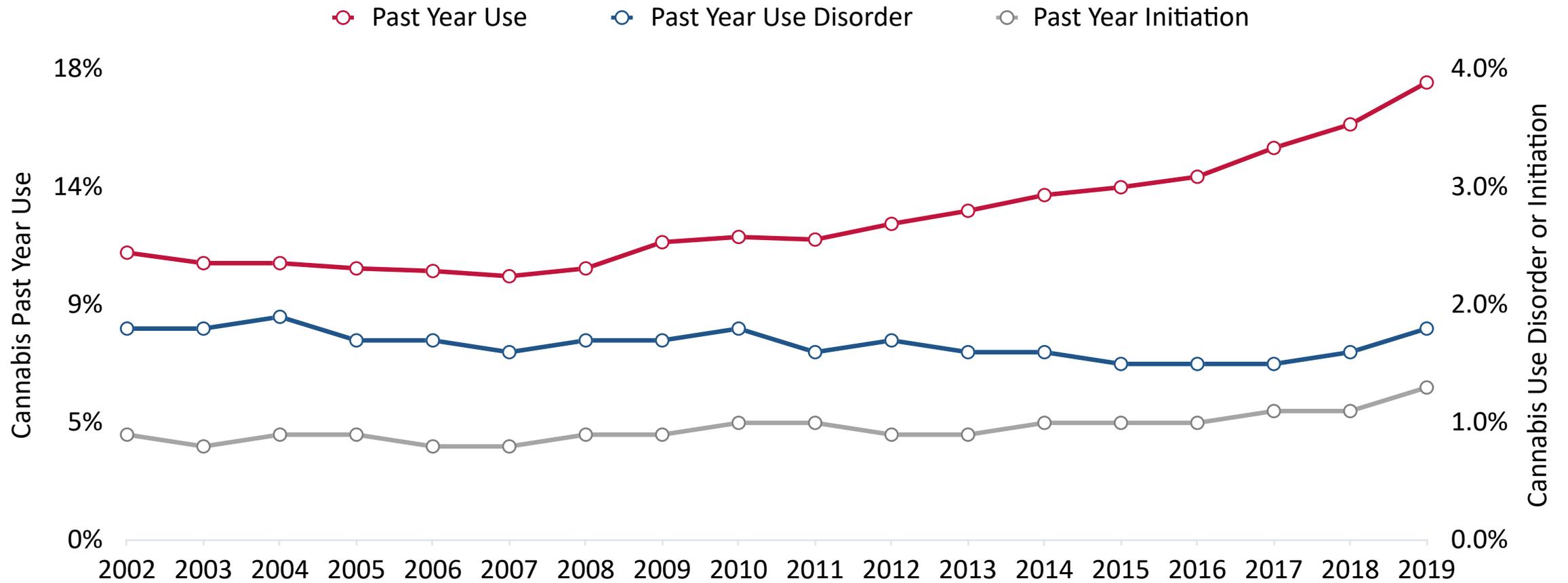
Terry et al., *Eur J Nucl Med Mol Imaging*. 2010

PET images of  $^{11}\text{C}$ -NE40 (CB2R radioligand)



Ahmad et al., *Mol Imaging Biol*. 2013 A

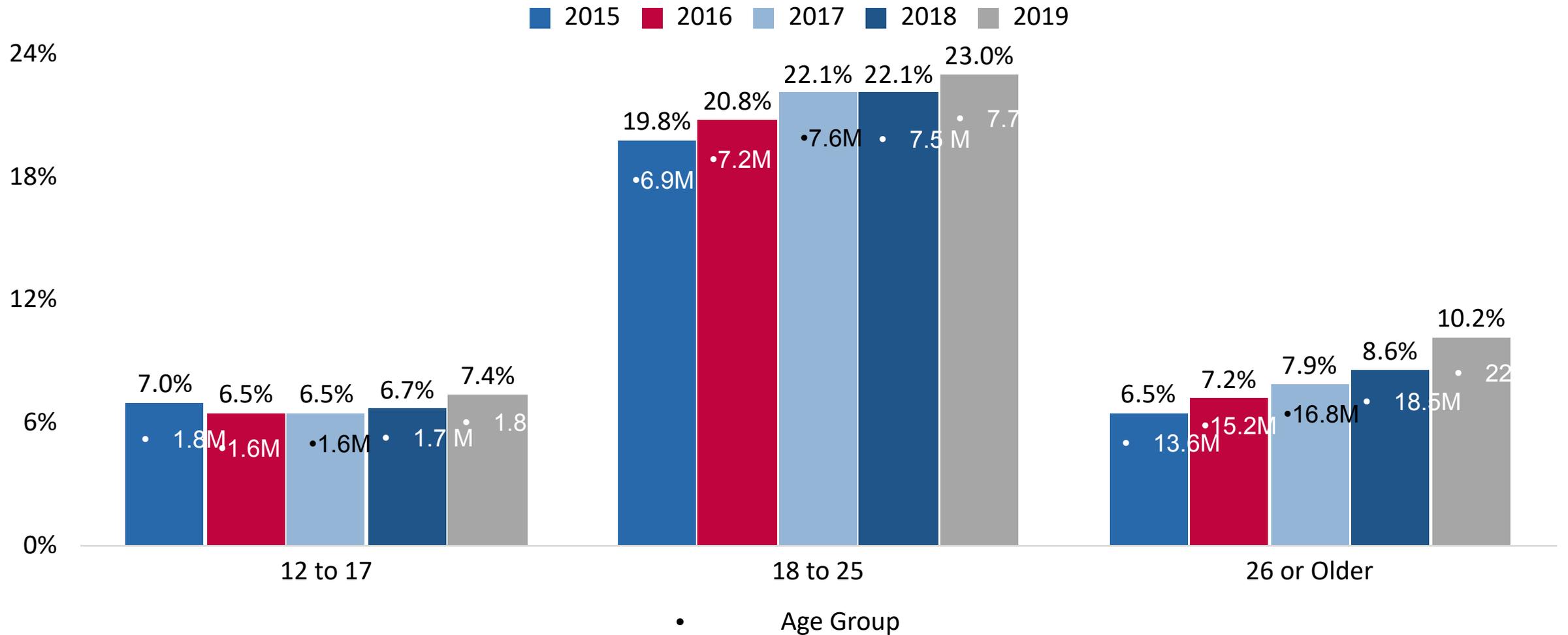
# Cannabis past year use, use disorder or initiation, among persons aged 12 or older



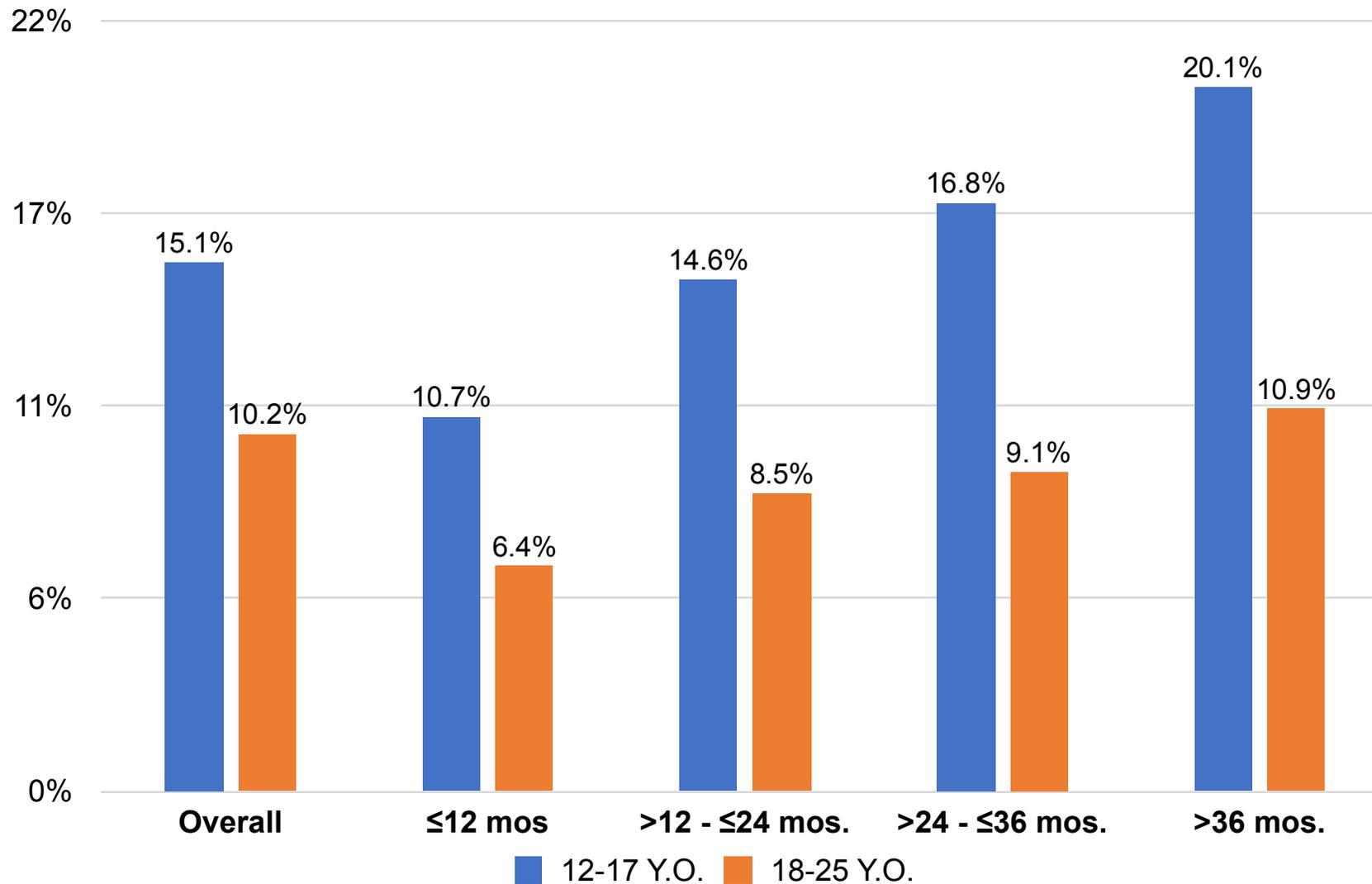
Source: 2019 National Survey on Drug Use and Health, SAMHSA

○ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.

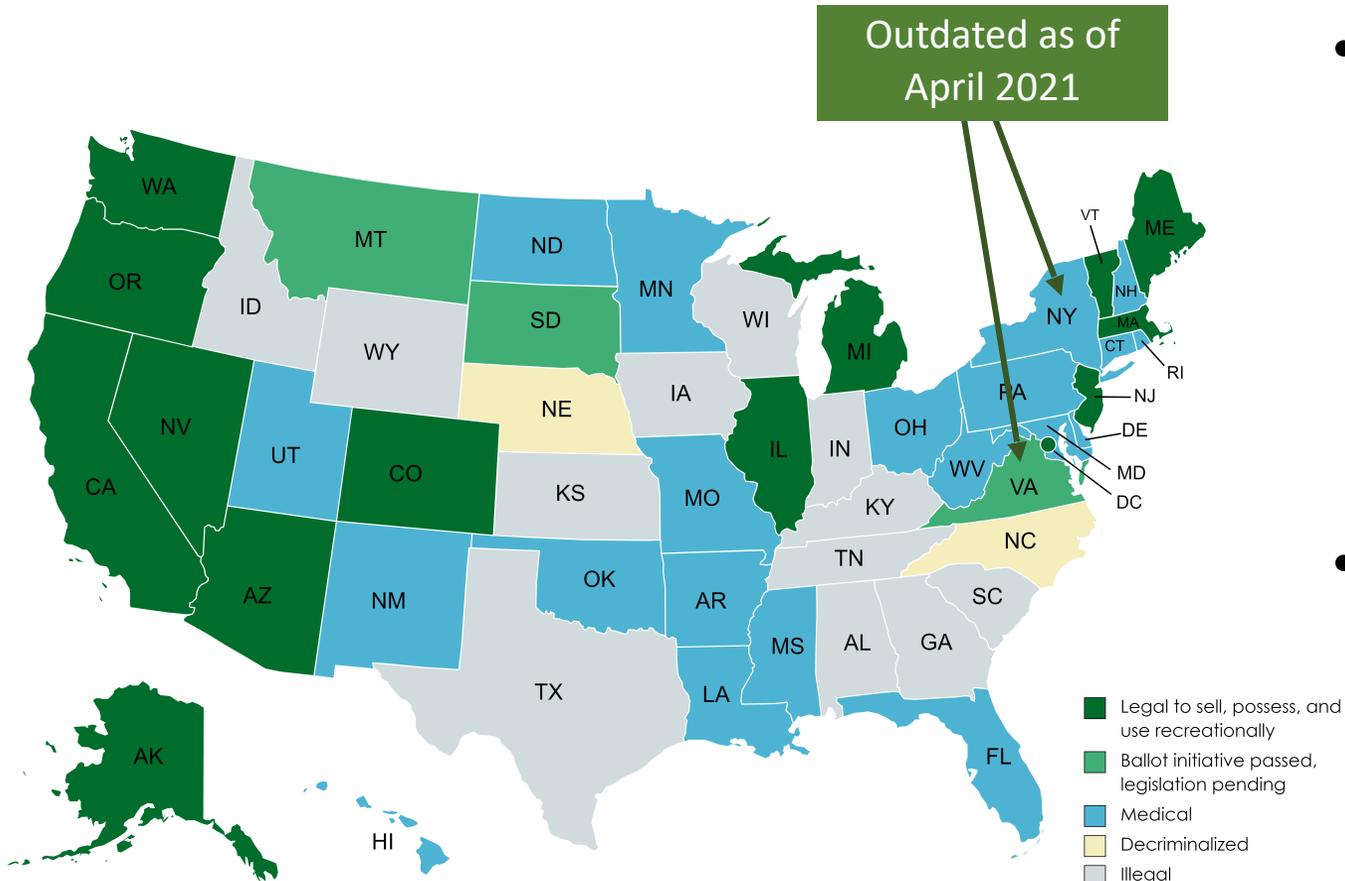
# Past month cannabis use increasing in adults



# Prevalence of Onset of Cannabis Use Disorders in Youth (age 12-17) and Young Adults (age 18-25), According to Time Since First Use



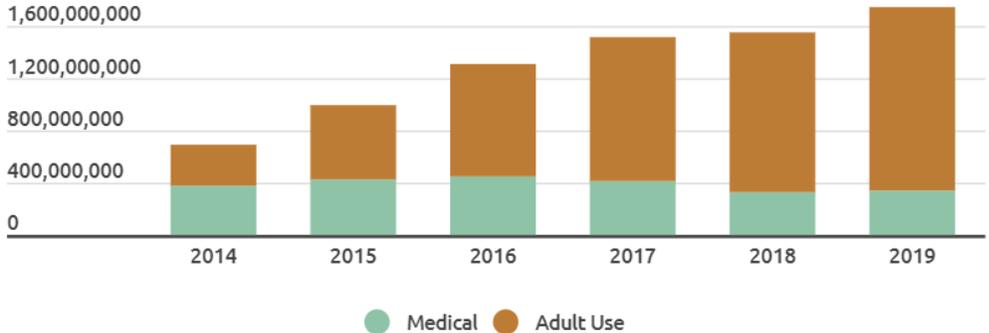
# U.S. state cannabis laws



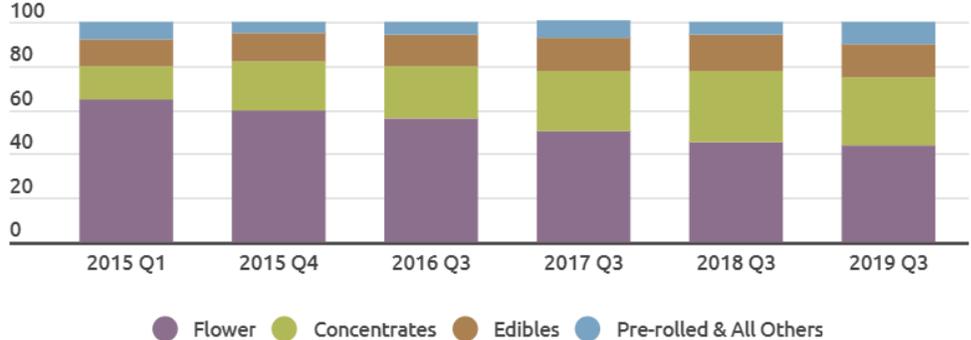
- States with MML vary on:
  - Allowable conditions and routes of administration
  - Dispensaries/home growth and registries
  - Testing, regulatory requirements
- States with Adult Use Laws vary on:
  - Marketing, product labeling, distribution (home growth, delivery)
  - Public consumption
  - Taxation
  - Licensing
  - Expungement and Equity

# Colorado: Market share is shifting away from flower towards concentrates

## Medical and Recreational Sales

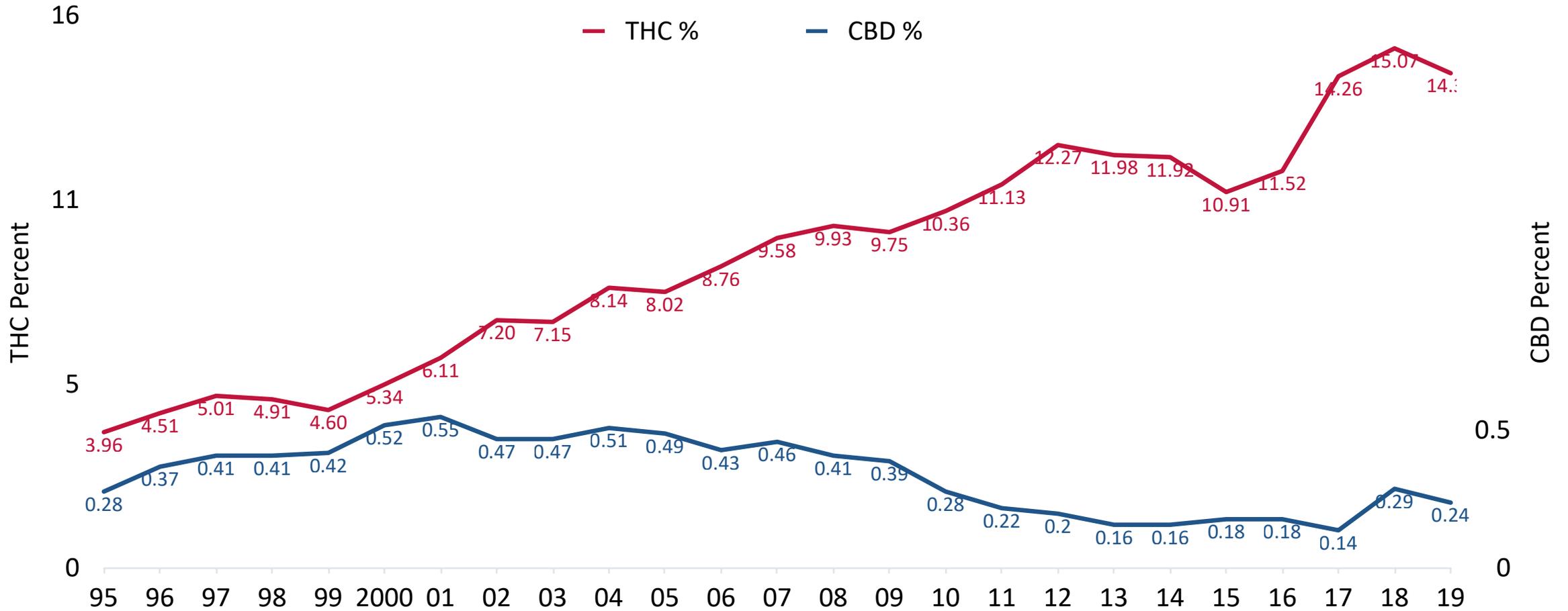


## Cannabis Products Sales

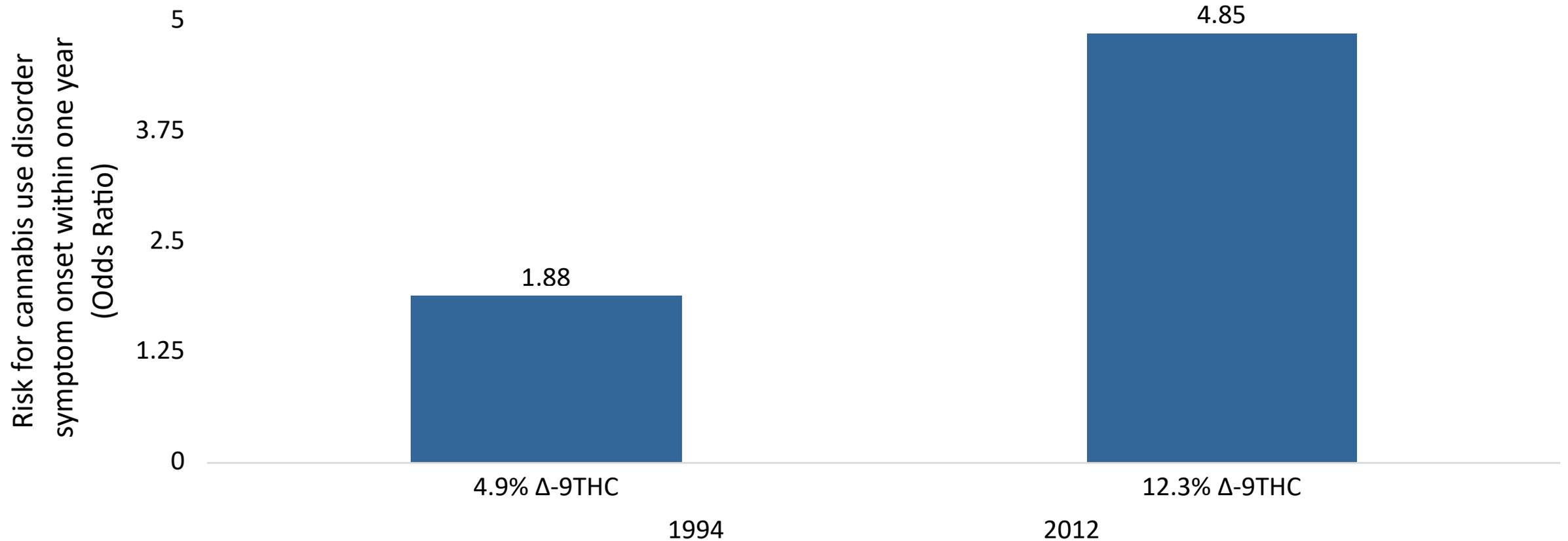


- Colorado’s retail sales in adult-use and medical dispensaries combined grew from \$675 million in 2014 to about \$1.75 billion in 2019, including \$338 million medical and \$1,407 million recreational cannabis sales.
- In 2019, cannabis sales averaged \$.45 million per retail location in Colorado’s adult-use market and \$0.77 million per location in the medical channel.
- Cannabis consumers spent \$1,205 million from January to July in 2020, including \$250 million medical and \$955 million recreational cannabis sales.

# Changing landscape: Increasing THC (potency) and decreasing CBD



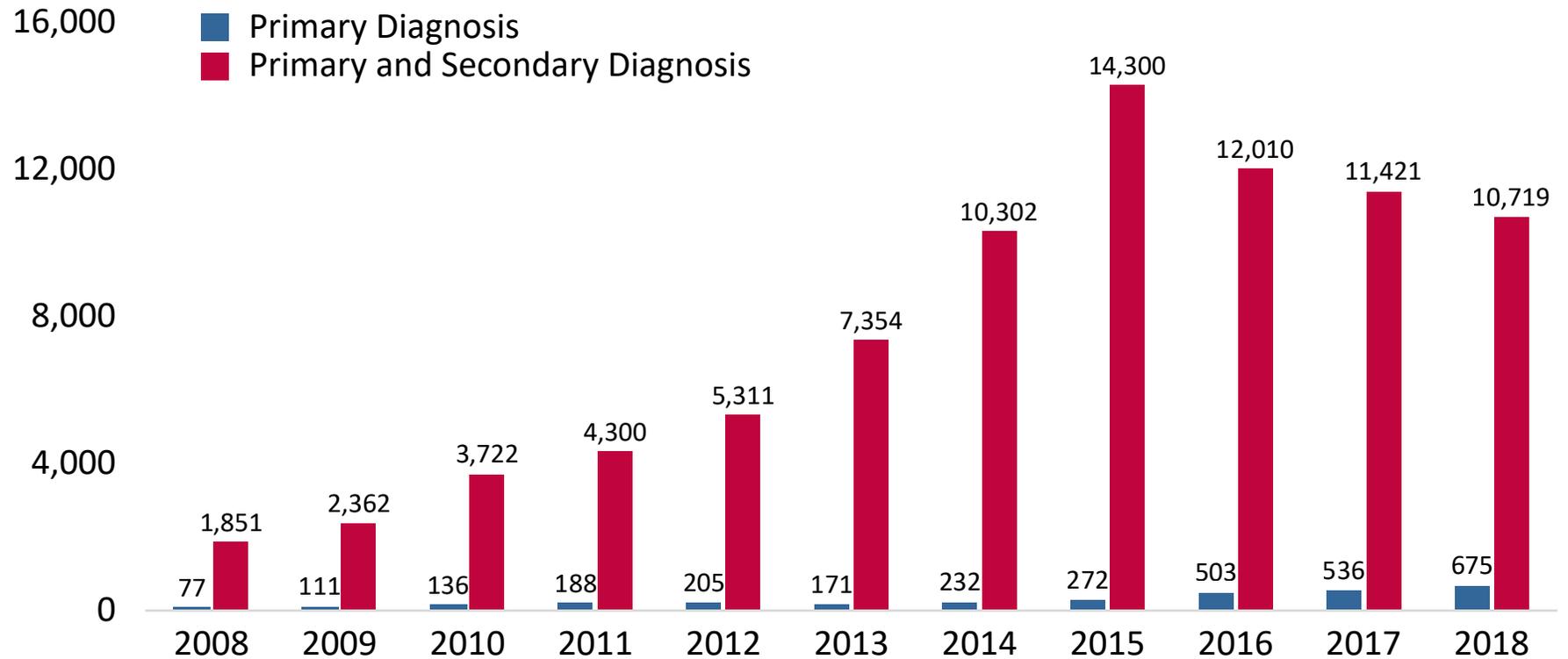
# Higher potency cannabis, on average, increases the risk for Cannabis Use Disorder onset within 1 year



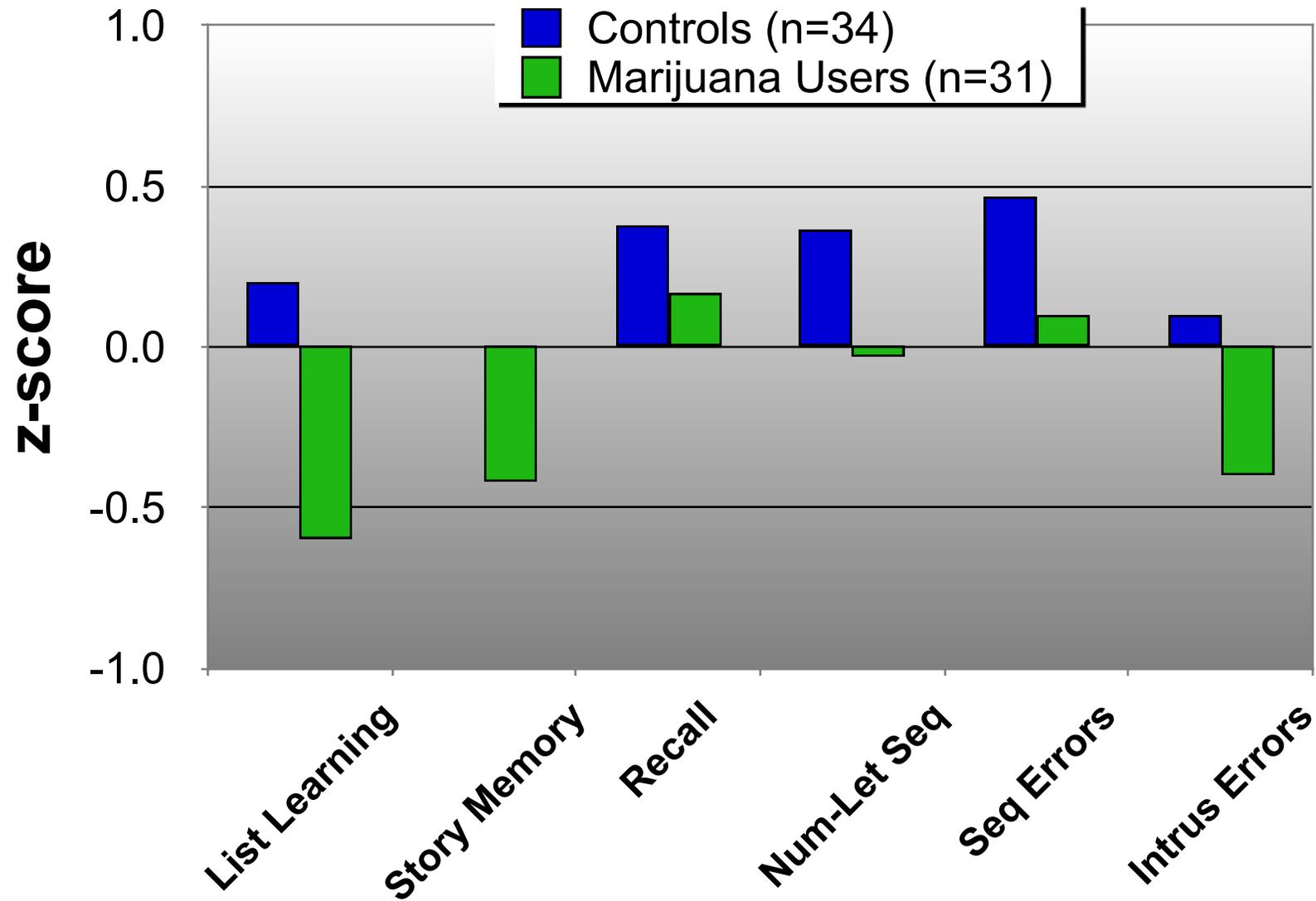
# ED visits with cannabis related diagnoses in San Diego county, 2006-2018



Typical Emergency Department (ED) Diagnoses: Accidents, Psychosis, Panic Attacks, Hyperemesis, CVD/Stroke

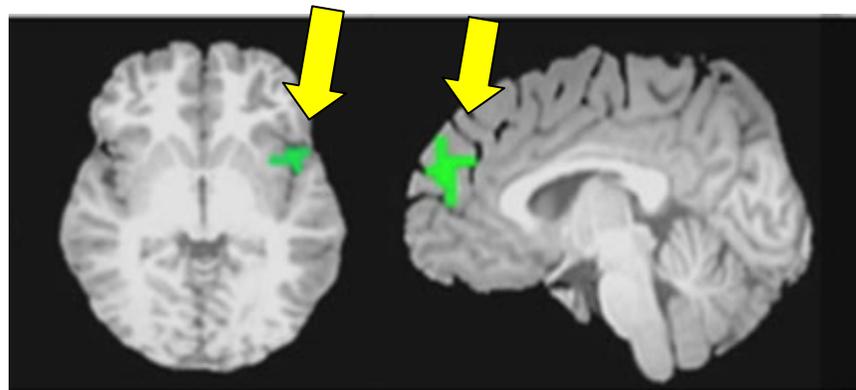
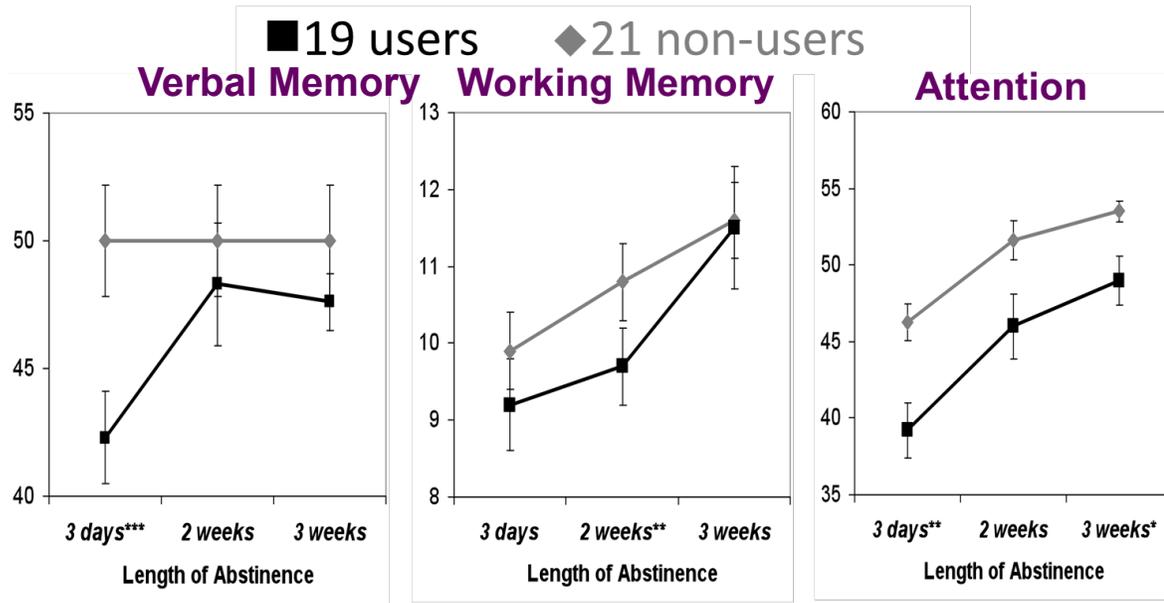


# Cannabis Worsens Memory



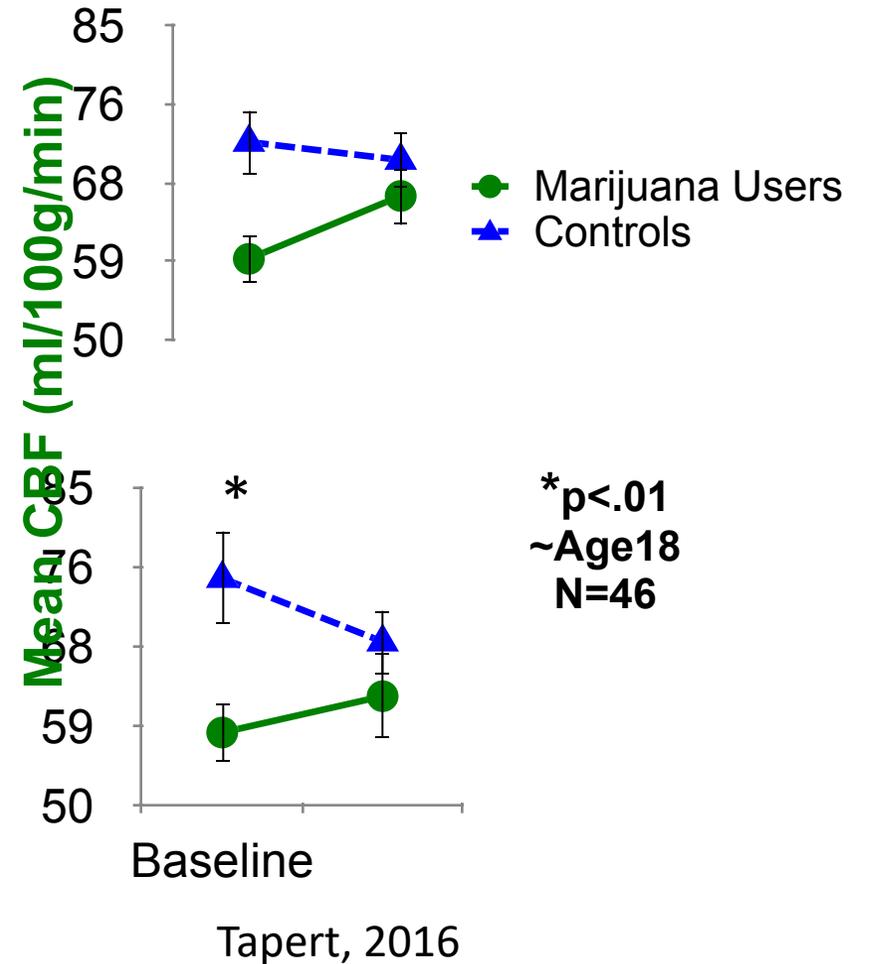
Medina, Hanson, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007

# Memory Impairments Improve with Abstinence

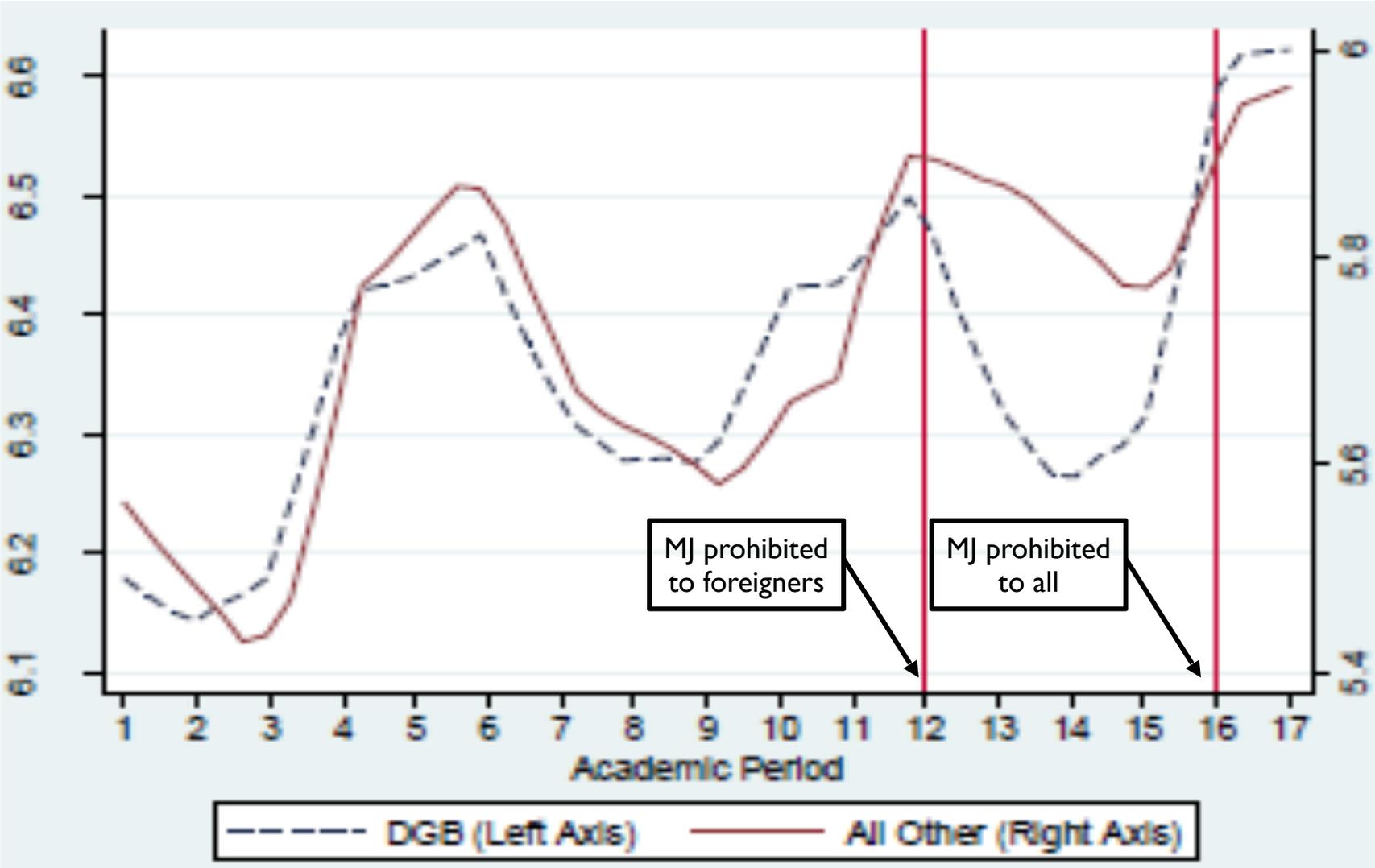


Left Insula      Medial Frontal Gyrus

## Brain blood flow after 28 days monitored abstinence

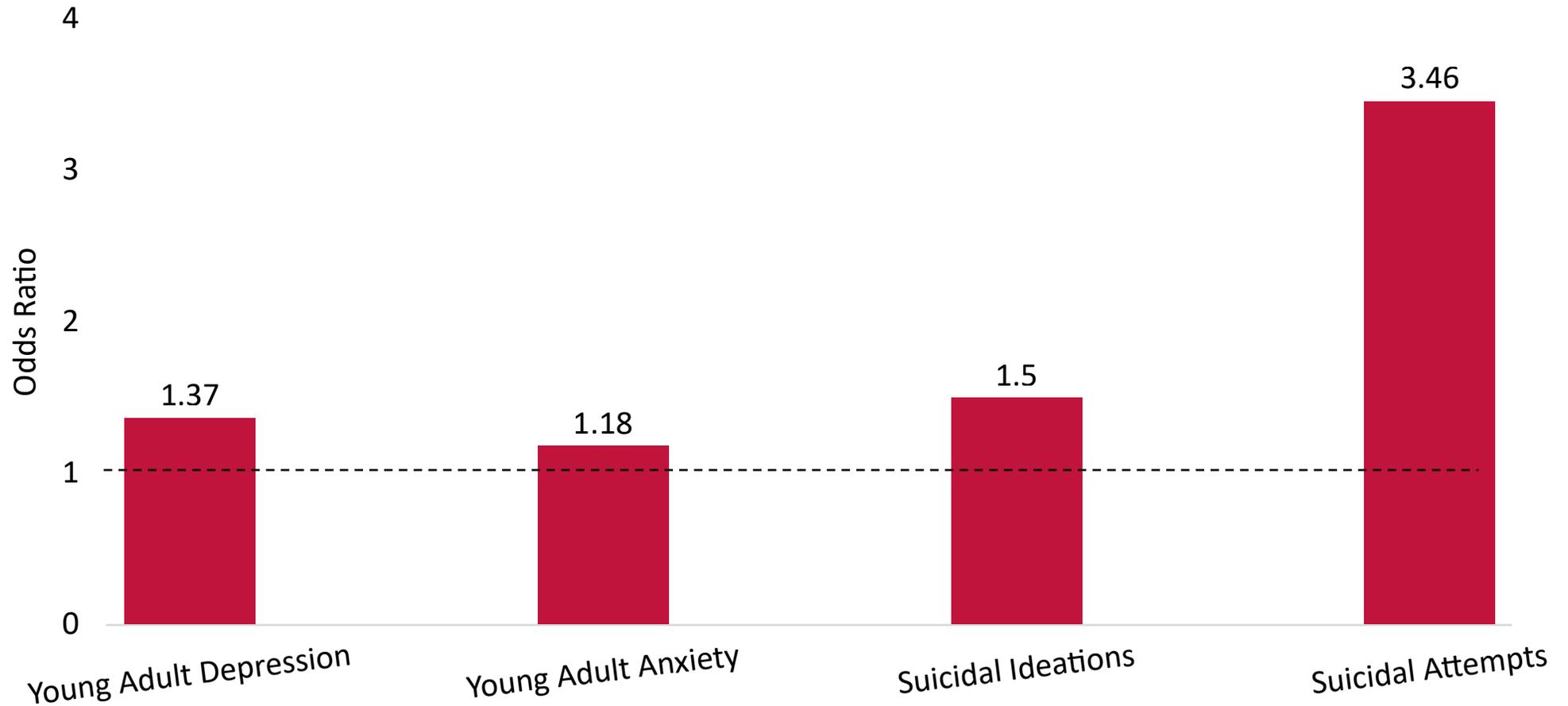


# When Marijuana Sales Were Restricted in The Netherlands, University Grades Improved



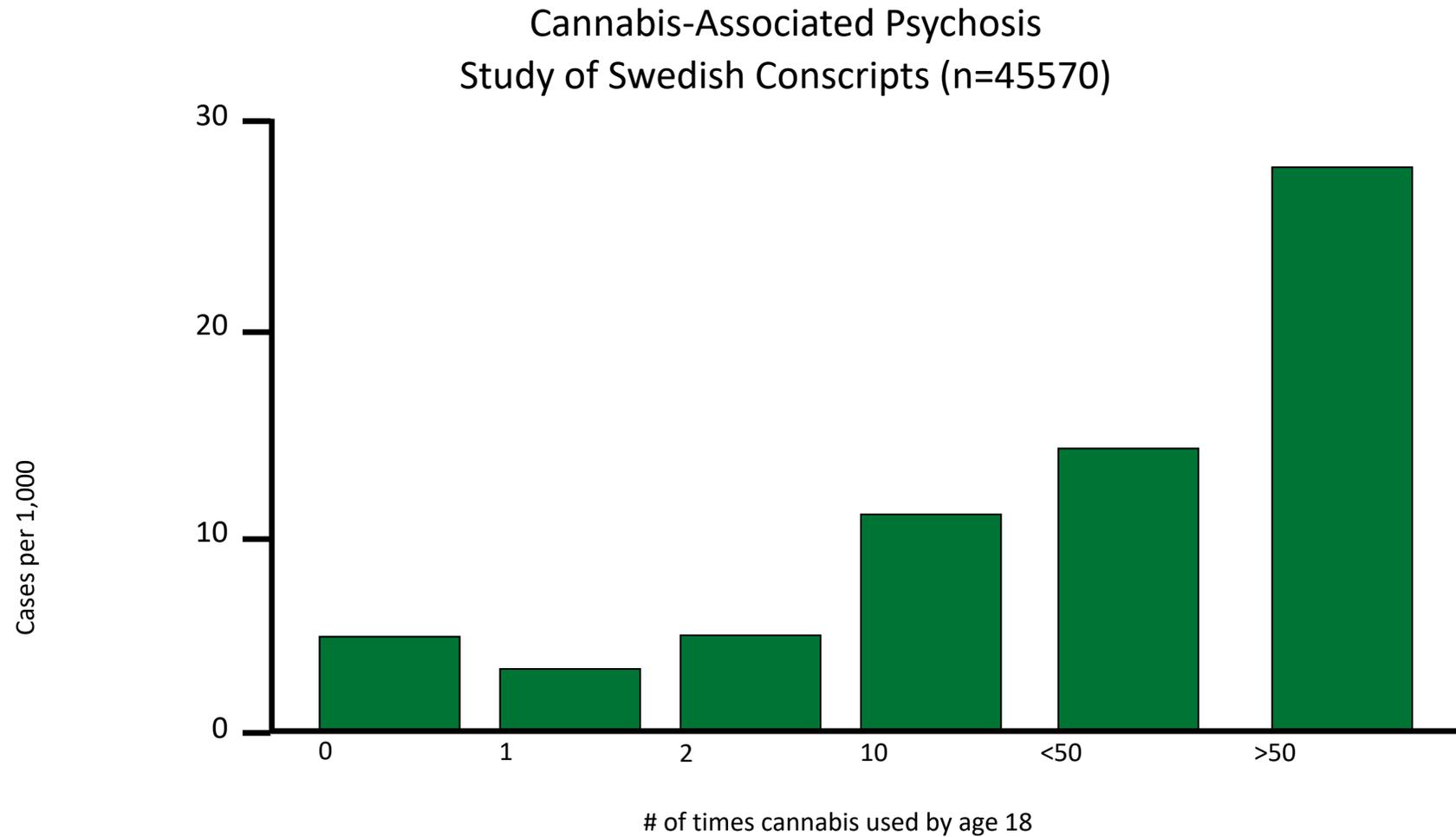
Marie O, Zollitz U. Review of Economic Studies 2017;84:1210-123

# Longer-term Outcomes: Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood—Systematic Review and Meta-analysis



Source: Gobbi G et al., JAMA Psychiatry (2019)

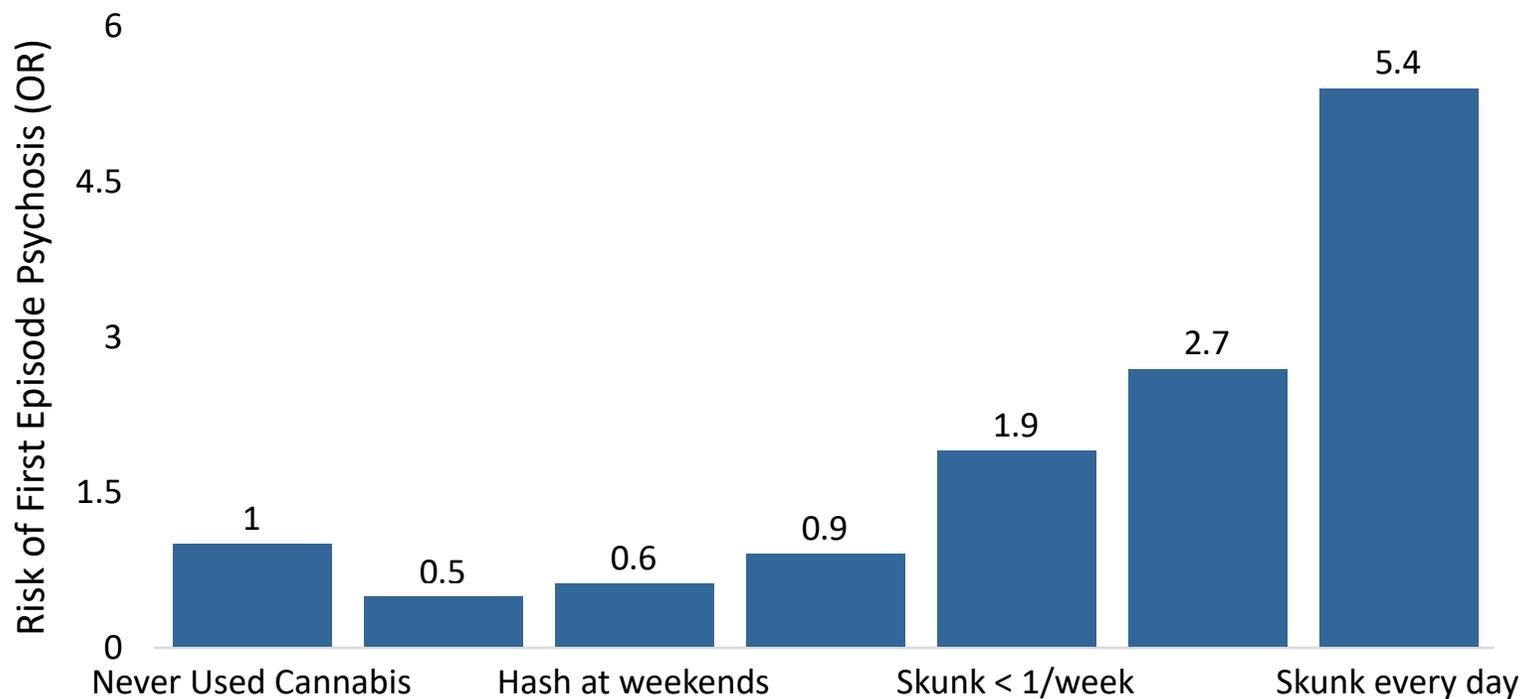
# Cannabis and Psychosis: Emerging Evidence



Source: Andréasson et al., Lancet (1987)

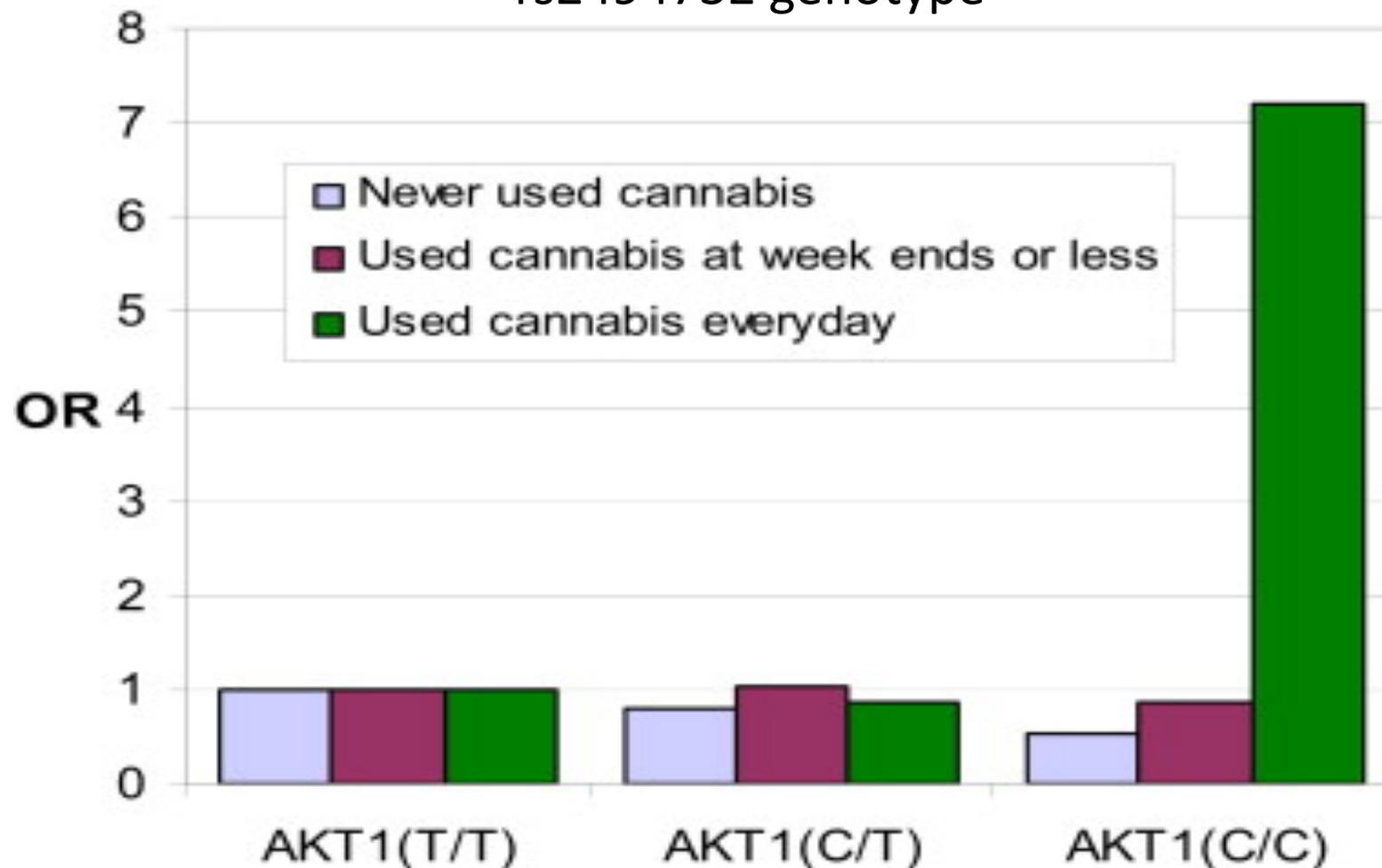
# Cannabis and Psychosis: Emerging Evidence

## Effect of High Potency Cannabis on Risk of Psychosis



# Cannabis and Psychosis: Emerging Evidence

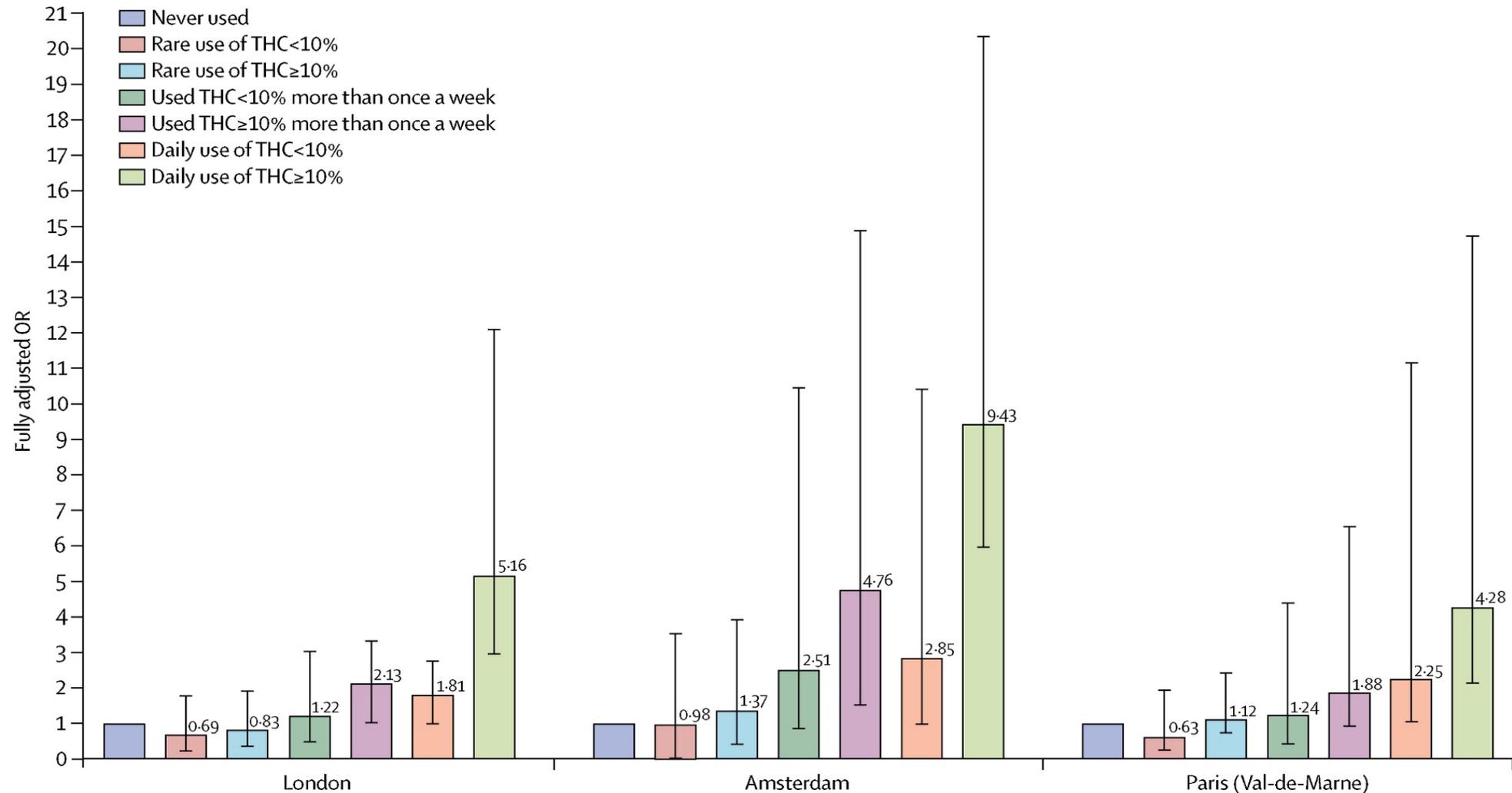
Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype



Source: Di Forti M et al., Biological Psychiatry (2012)

# Cannabis and Psychosis: Emerging Evidence

Odds ratios of psychotic disorders for the combined measure of frequency plus type of cannabis used in London, Amsterdam, Paris



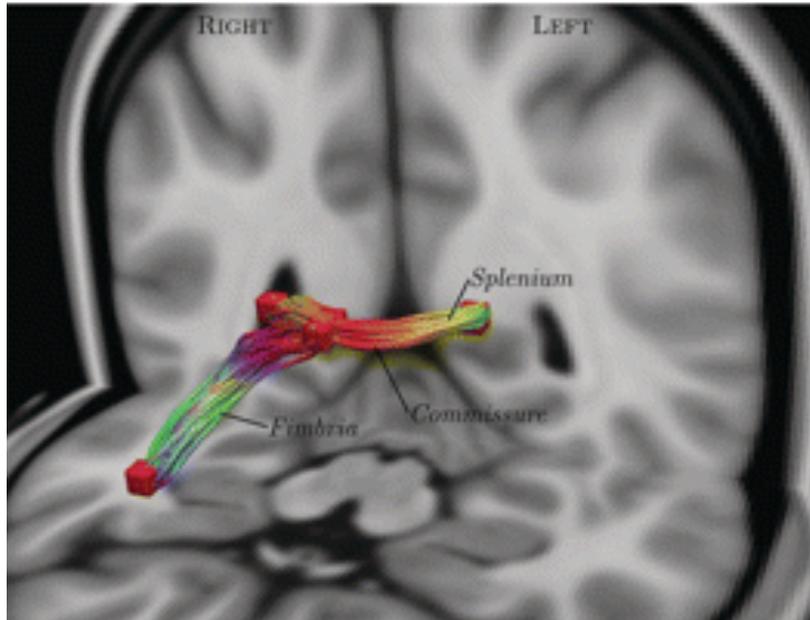
London (201 cases, 230 controls), Amsterdam (96 cases, 101 controls), and Paris (54 cases, 100 controls)

Error bars represent 95% CIs. OR=odds ratio. Source: DiForti M et al., The Lancet Psychiatry (2019)

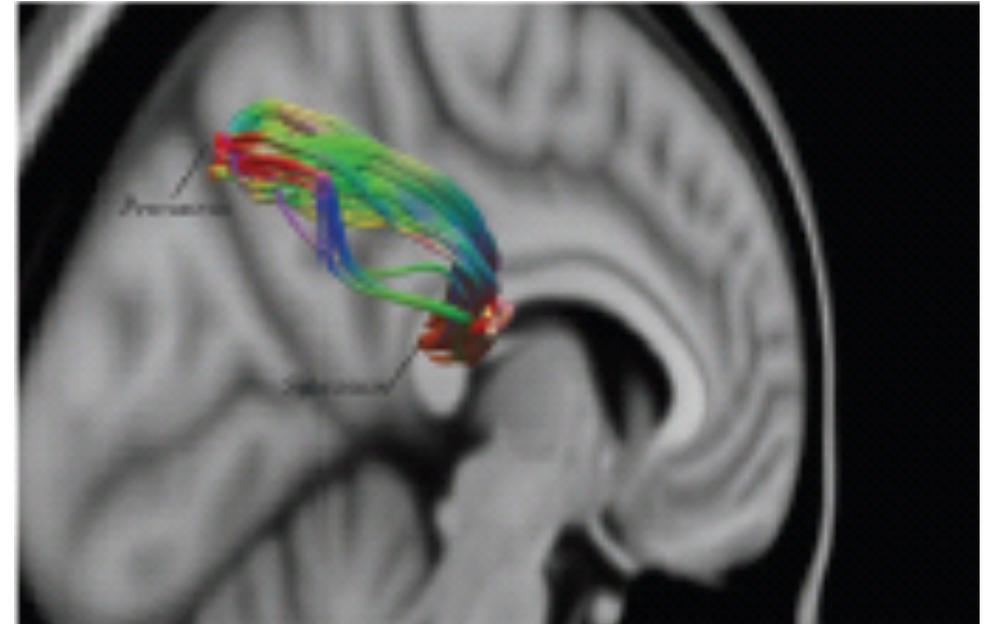
# Multiple studies show altered brain structure and function in youth who regularly use cannabis

## Early (<18y) Cannabis Use Decreases Axonal Fiber Connectivity

Precuneus  
to splenium



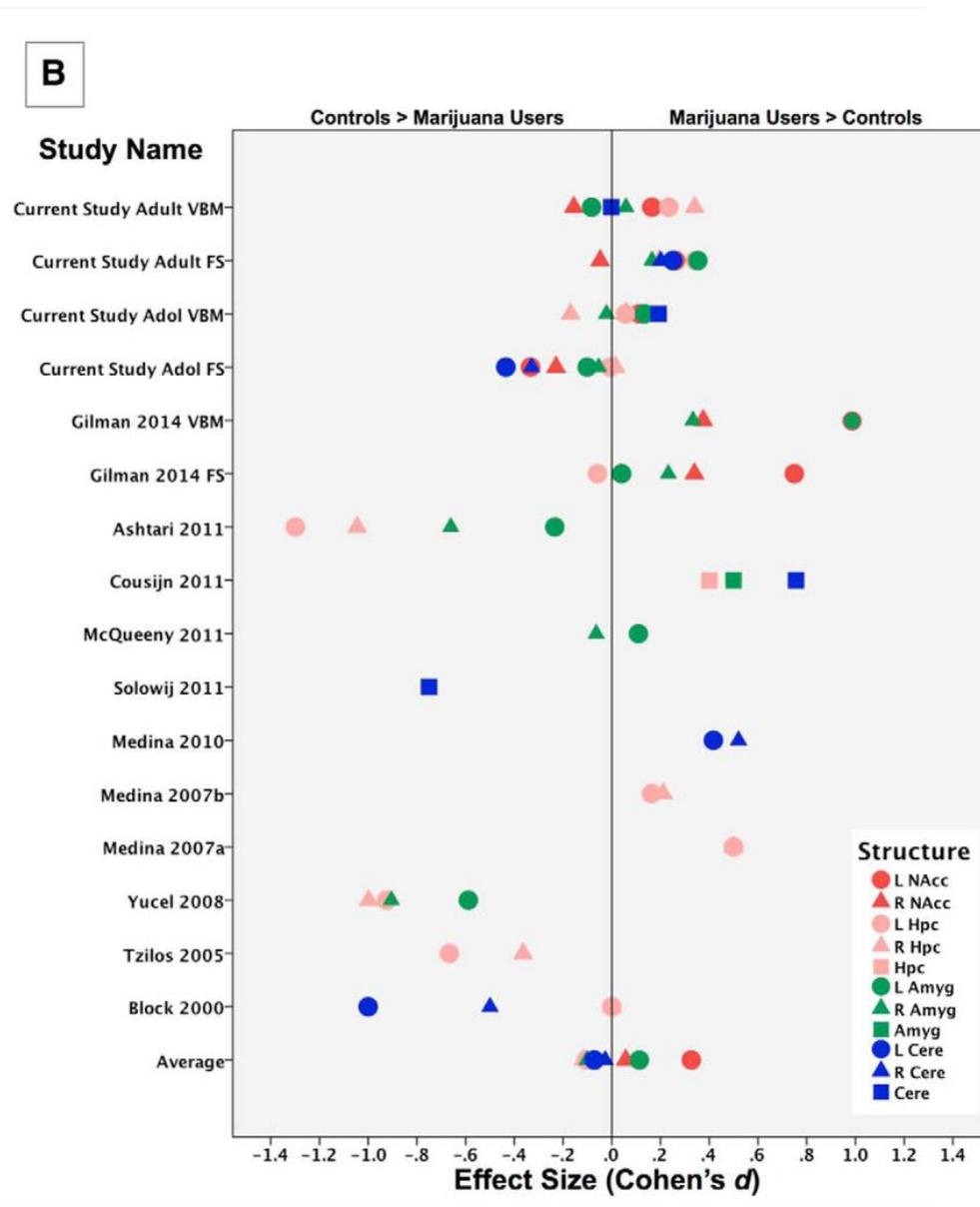
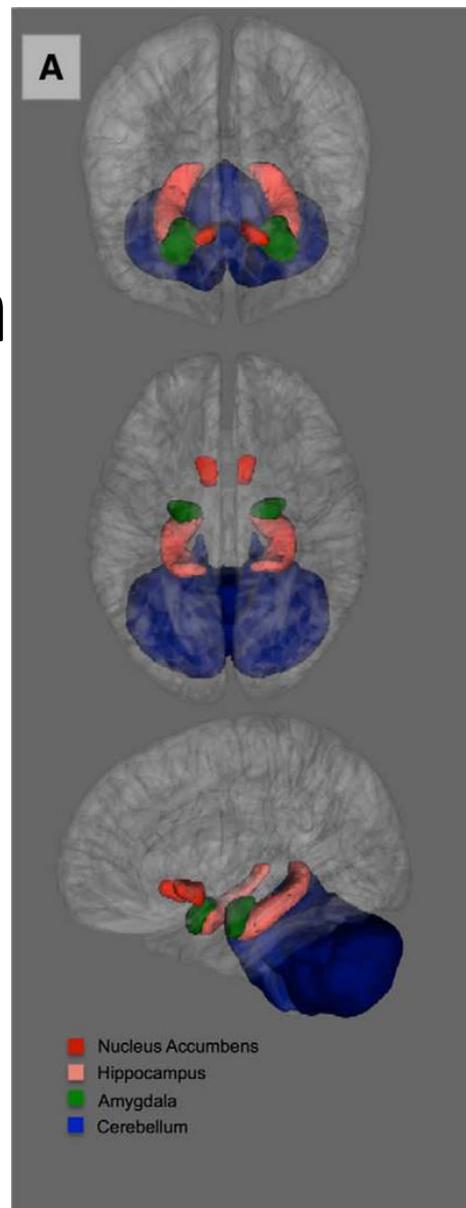
Fimbria of  
hippocampus,  
hippocampal  
Commissure,  
and  
splenium



Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

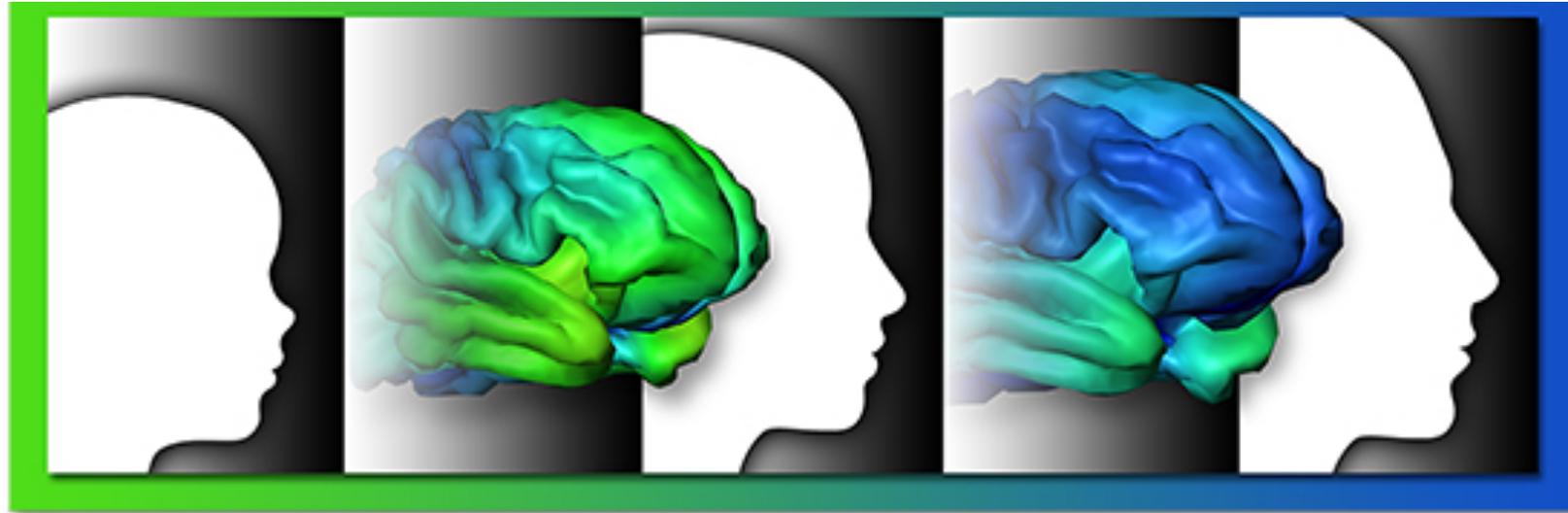
# Not all studies find differences: Subcortical structures

No differences between regular cannabis users and nonusers when participants were matched on alcohol use



# Adolescent Brain Cognitive Development (ABCD) Study

A Federal Collaboration: NIDA, NIAAA, NCI, NIMH, NIMHD, NICHD, NINDS, OBSSR, ORWH, CDC-DASH, CDC-DVP, DOJ, NEA



**Adolescent Brain Cognitive Development**<sup>®</sup>

*Teen Brains. Today's Science. Brighter Future.*

Ten-year longitudinal study of ~12,000 children from age 10 to 20 years to assess effects of childhood experiences, including use of cannabis and other substances on individual brain development trajectories

# What do we know?

- Acute effects of cannabis/THC exposure can include acute psychiatric symptoms and memory impairments
- Possible role for reduced CBD in higher potency cannabis risks
- Association of adolescent cannabis use with higher rates of cannabis use disorder, worse social outcomes and onset of psychosis

# Take Home Messages

- Cannabis is increasing in prevalence among young adults and older adults and is the most commonly used illicit drug in U.S.
- Marijuana use generally begins in adolescence.
- Use of marijuana can have a wide range of effects on an individual's brain, body and behavior including:
  - Brain development
  - Memory and cognition
  - Motivational systems and reward
  - Addiction
  - Lung health
- Prevention can be effective—when successfully implemented.

# Intersection of the SARS-CoV-2 Pandemic and Addiction

## 'Opioid overdoses are skyrocketing': as Covid-19 sweeps across US an old epidemic returns

The pandemic is creating the social conditions - no jobs, isolation, despair - that helped enable the opioid crisis to emerge in the first place. Now it's back



## 'There was nothing to help me': how the pandemic has worsened opioid addiction

US treatment centers have shut down or turned away patients amid as they struggle to adhere to Covid-19 safety protocols



I-TEAM

## Drug overdose deaths spike amid COVID-19 pandemic

By Chuck Goudie and Barb Markoff, Christine Tressel, Ross Weidner, Jonathan Fagg  
Wednesday, February 10, 2021

THE OTHER EMERGENCY

## Covid-19 is undoing a decade of progress on the opioid epidemic



## THE WALL STREET JOURNAL.

## Opioid Use Hits Construction Industry as Overdoses Soar

Physically challenging work often leads laborers to turn to addictive painkillers, and Covid-19 makes treatment more difficult

U.S.

## The Opioid Crisis, Already Serious, Has Intensified During Coronavirus Pandemic

Overdose deaths rise as job losses and stress from Covid-19 destabilize people struggling with addiction

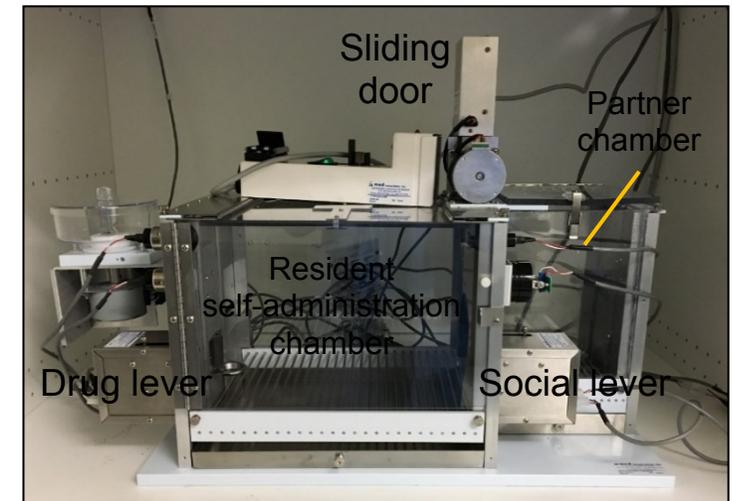
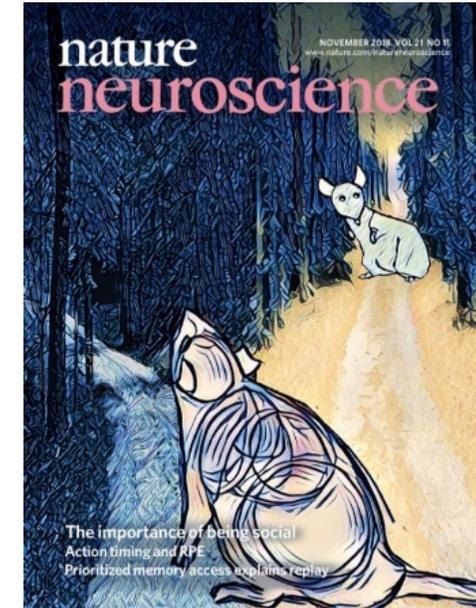
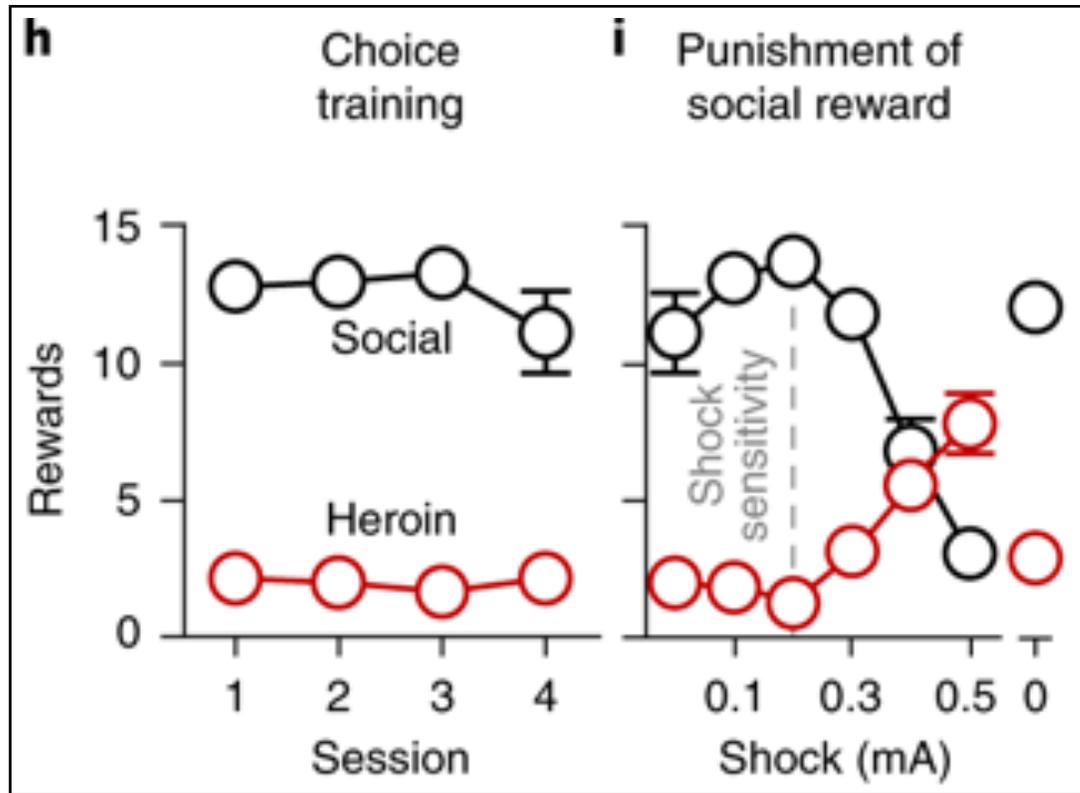
# Structural and Social Challenges for SUD During COVID-19

- Stress and Stigma
- Limited medication access and limited peer-support groups/social connection
- Social distancing increases likelihood of opioid overdoses happening with no observers who can administer naloxone
- Job losses
- Housing instability/homelessness
- Incarceration (>50% of U.S prisoners have SUD) and prison populations are at greatest risk SARS-CoV-2 transmission



# Social Interaction Preferred Over Drug

Drug preference increases when social reward is punished

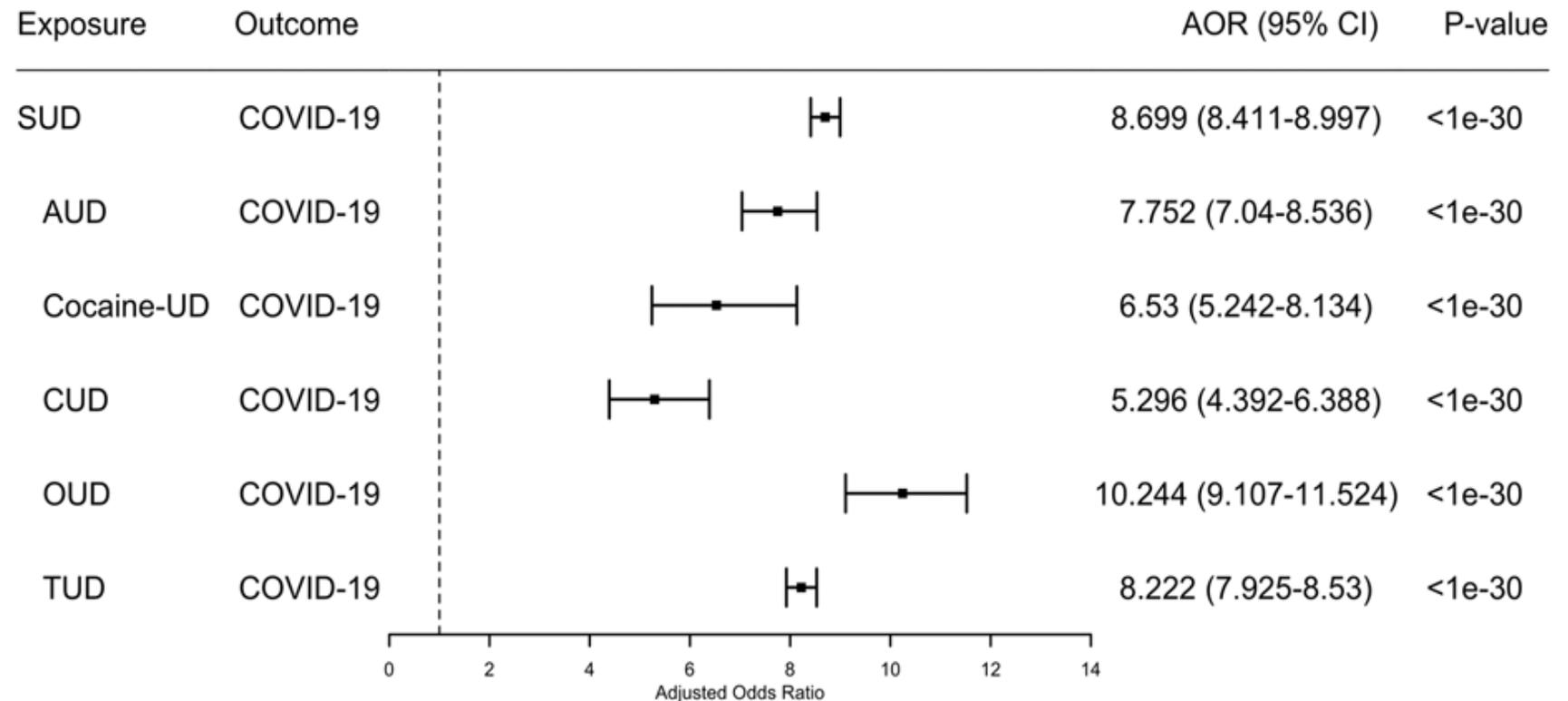


# Higher COVID-19 Susceptibility and Worse COVID-19 Outcomes for Those with Substance Use Disorders (SUD)

## Methods

- Analysis of non-identifiable electronic health records of 73 million patients in the United States.
- Individuals with an SUD constituted 10.3% of the total study population, and 15.6% of the COVID-19 cases.

Risk Associated with Recent SUD Diagnosis and COVID-19



# Increased Overdose Death Rates During COVID-19 Pandemic

12-months ending June 2019 compared to 12-months ending May 2020

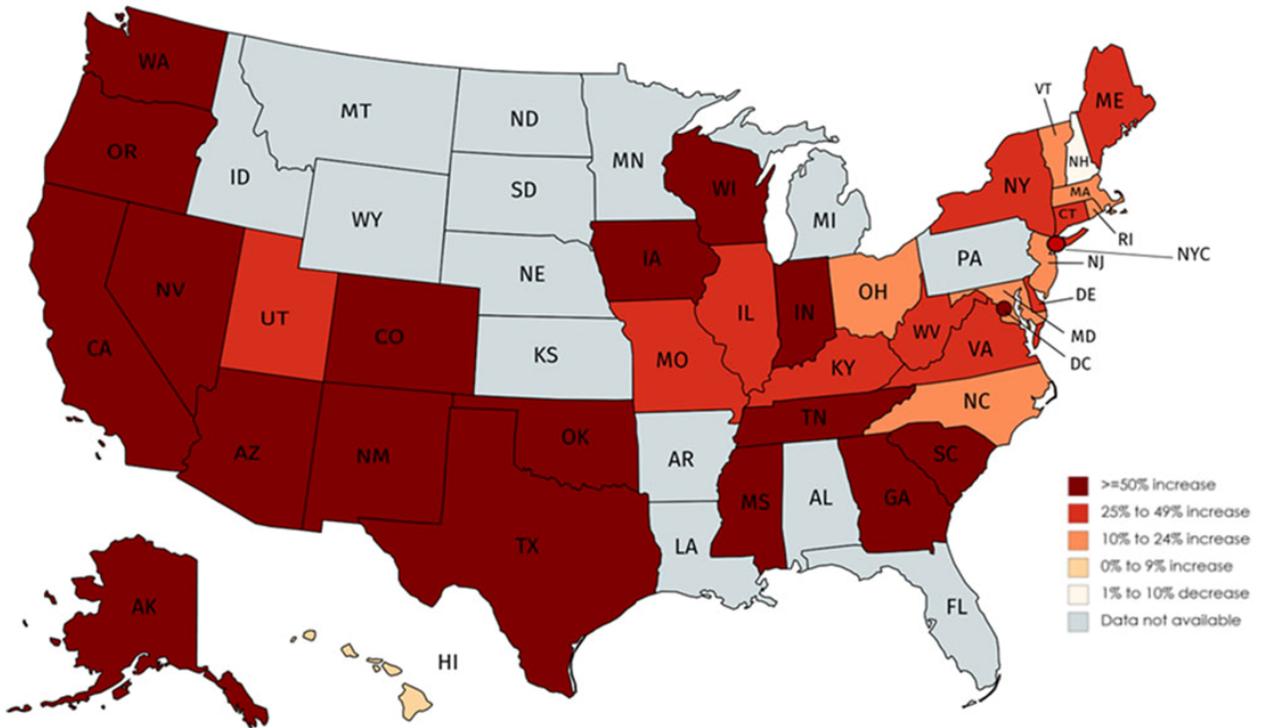
April 15, 2021 THE WALL STREET JOURNAL.

U.S.

## Fentanyl Has Spread West and Overdoses Are Surging

More than twice as many people died from drug overdoses as from Covid-19 in San Francisco last year

- ↑ 98.0% - 10 western states
- ↑ 35.4% - 12 southern states & DC
- ↑ 32.1% - 6 midwestern states
- ↑ 21.1% - 8 northeastern states & NYC



# Drug-involved Overdose Deaths\* Continue to Increase

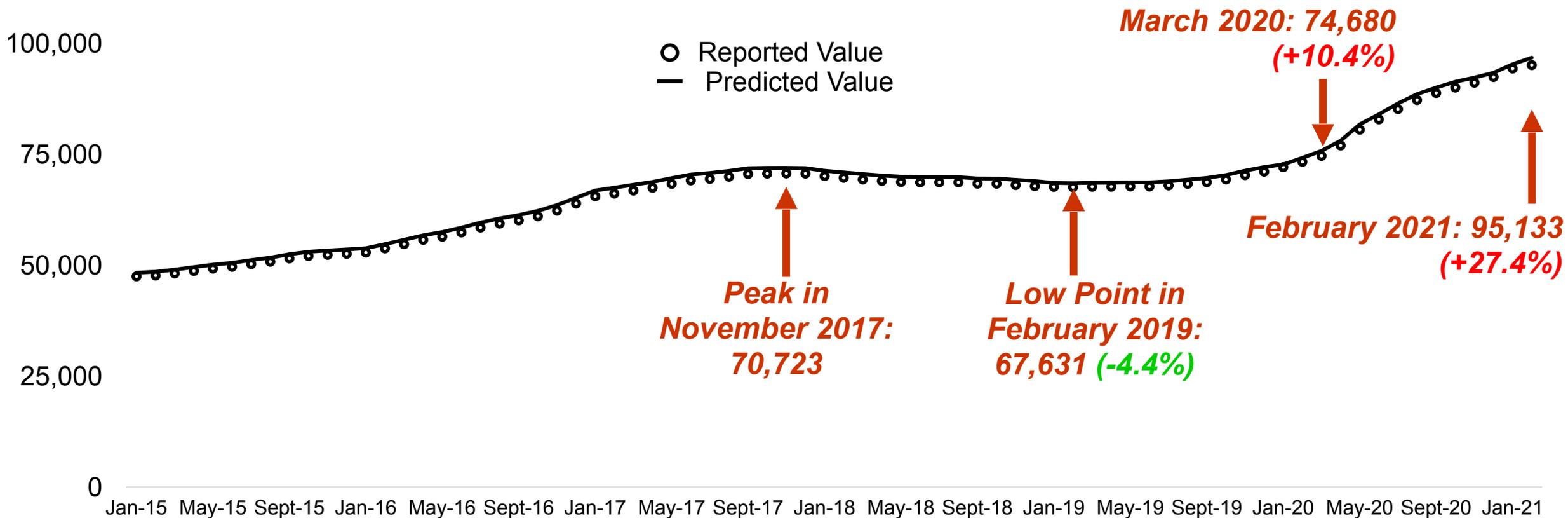
	ALL DRUGS	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
2/2020*	74,234	14,172	12,288	2,791	39,361	17,000	17,434
8/2020*	88,598	14,495	13,451	3,436	52,561	19,868	22,287
2/2021*	96,801	12,859	13,806	3,770	60,857	20,231	26,128
Percent Change 2/20-2/21	<b>30.3%</b>	<b>-9.3%</b>	<b>12.4%</b>	<b>35.1%</b>	<b>54.6%</b>	<b>19.0%</b>	<b>49.9%</b>

\*NCHS Provisional drug-involved overdose death counts are PREDICTED VALUES, 12 months ending in select months.

<https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

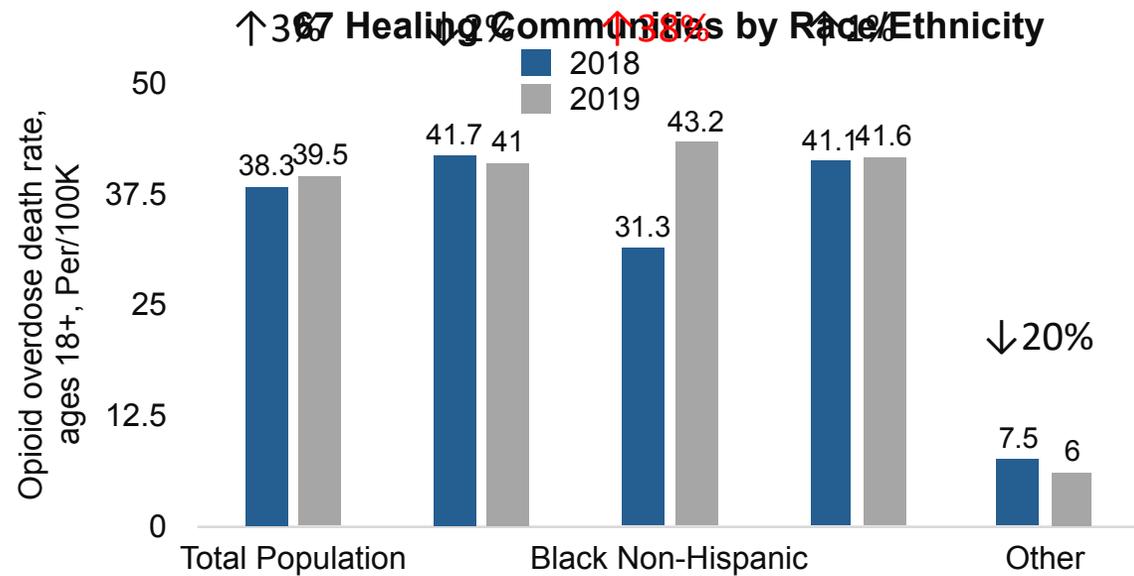
# Recent Increases in Overdose Deaths

12 month ending provisional counts (*reported values*) of drug-involved overdose deaths in the U.S.



NCHS Provisional Drug Overdose Death Counts: <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>, September 19, 2021

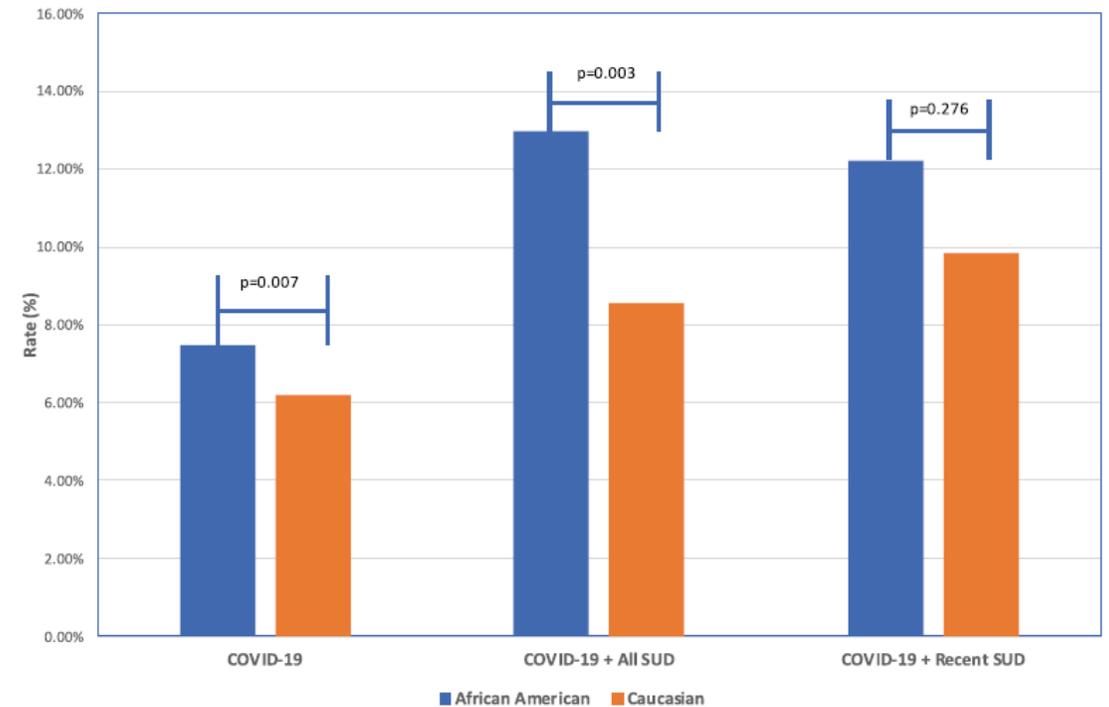
# Mortality from Opioid Involved Overdoses Healing Community Study



MR Larochelle, S Slavova, ED Root, et al., AJPH. 2021. published online

# Mortality from COVID Electronic Health Records

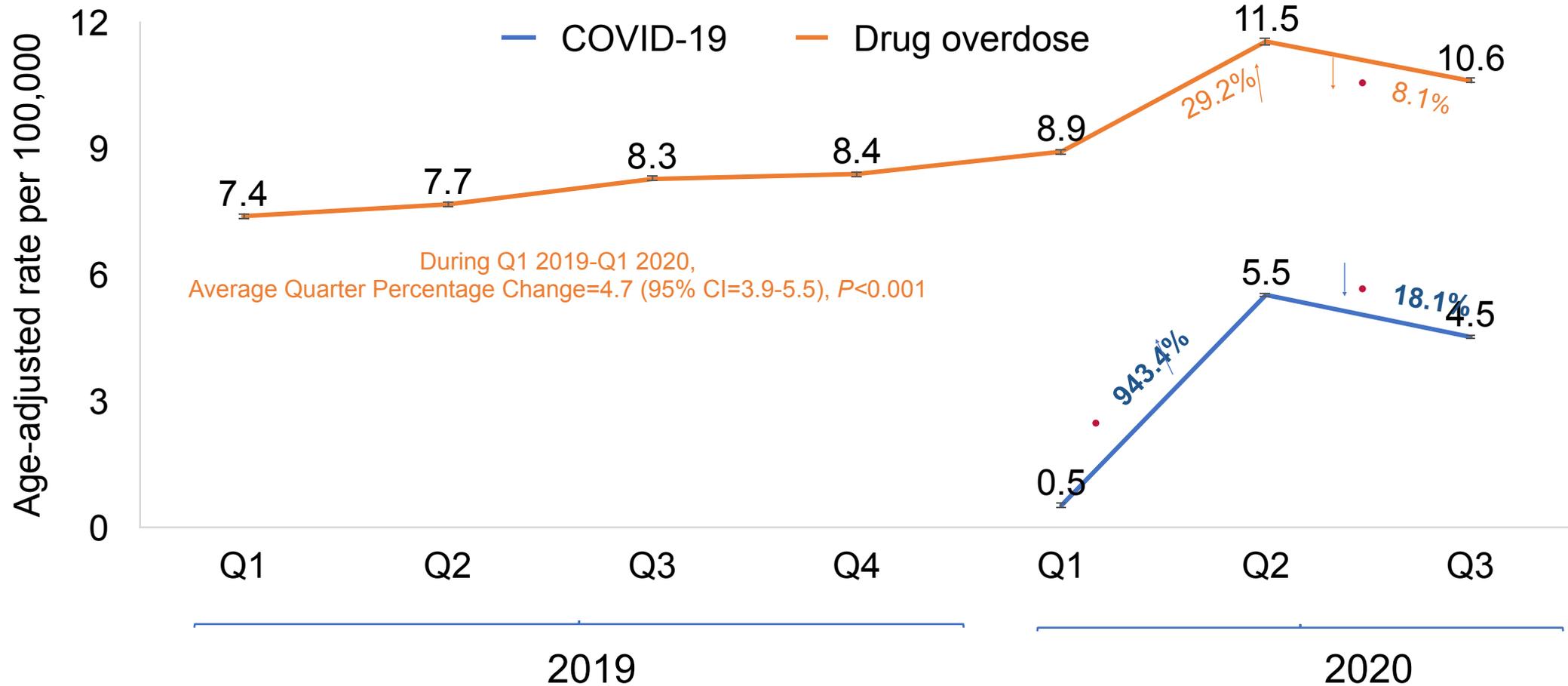
A Death rates among COVID-19 patients with SUD



Mortality from COVID is higher in Individuals with SUD but these disparities are markedly exacerbated among African Americans

QQ Wang, DC Kaelber, R Xu, et al., Mol Psychiatry. 2020;26:30-39

# Age-adjusted Rates Of COVID-19 Or Drug-overdose Deaths For People Aged 15-54 In USA For 2019-2020



# SUD Services Have Shifted During the Pandemic

- Increased use of telemedicine
- Establishment of mental health hot lines
- Deployment of virtual support meetings
- Expansion of take-home medicines for MOUD
- Buprenorphine prescribing via Telehealth
- Release of non-violent offenders with SUD from jails and prisons(might improve their outcomes)
- Development of web-based educational material that can be used to help in rehabilitation

# Take Home Messages

- The U.S. Overdose Epidemic has **ACCELERATED** during the COVID-19 public health emergency.
- Fentanyl-related overdoses have been an increasing concern.
- Polydrug use is common (especially stimulants).
- Science offers tests of solutions—both shorter term and longer.

