

Adolescent Cannabis Use

Wilson M. Compton, M.D., M.P.E.

Deputy Director

National Institute on Drug Abuse

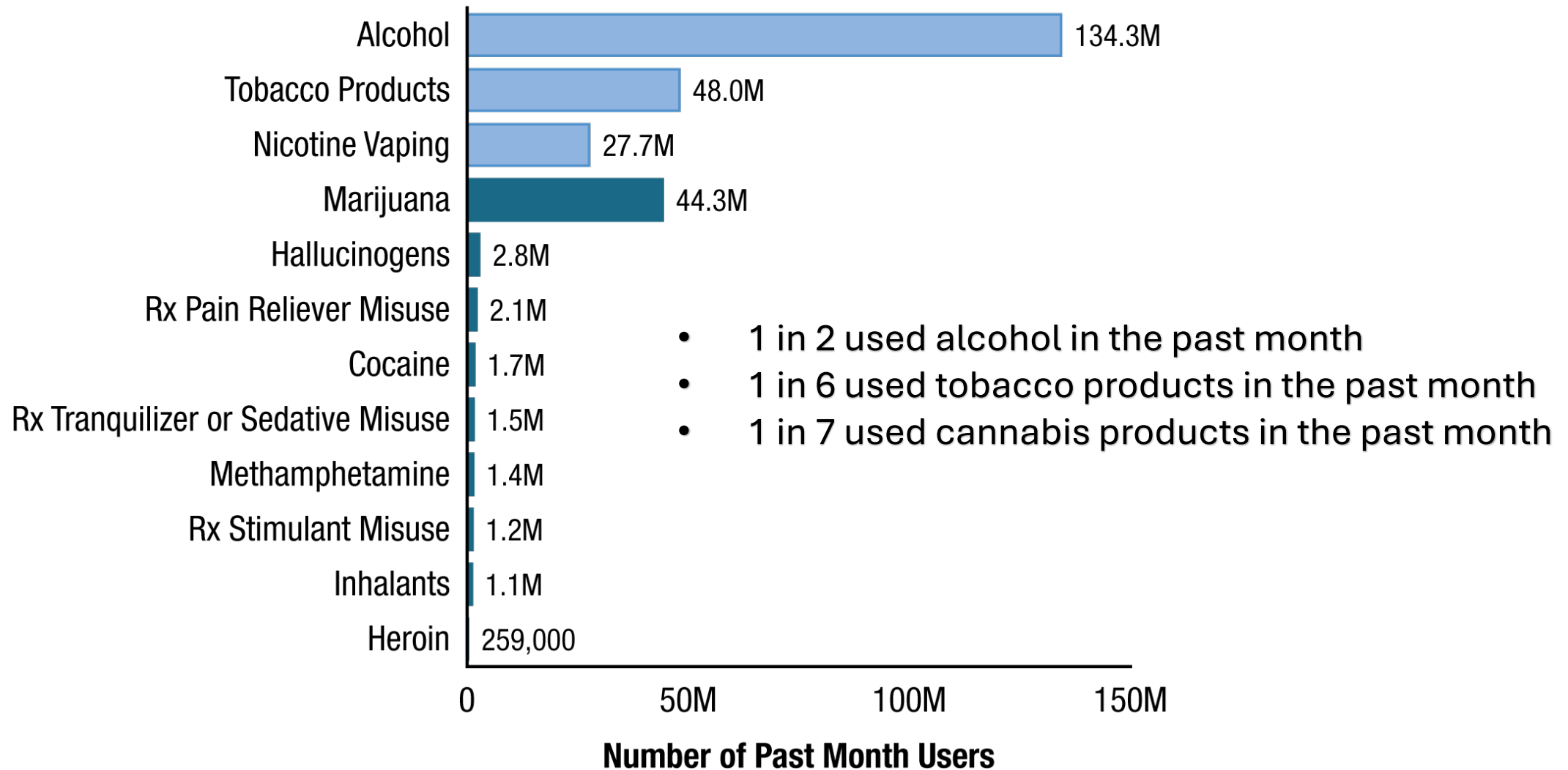
email: wcompton@nida.nih.gov



Disclosures of Interests: Wilson M. Compton, MD, MPE

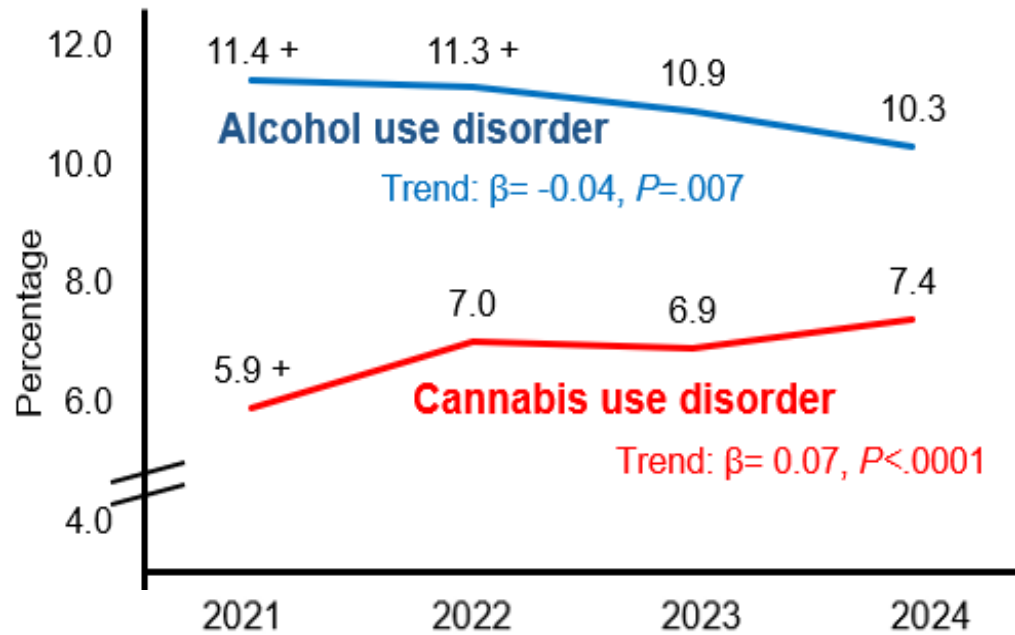
- **Stock Equity:**
 - 3M Company (under \$5,000)
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- **Consulting Relationships:** None
- **Current Positions:**
 - Deputy Director, National Institute on Drug Abuse, NIH
 - Professor (adjunct), Georgetown University

Alcohol, Nicotine, and Cannabis are the Most Commonly Used Substances in the U.S.

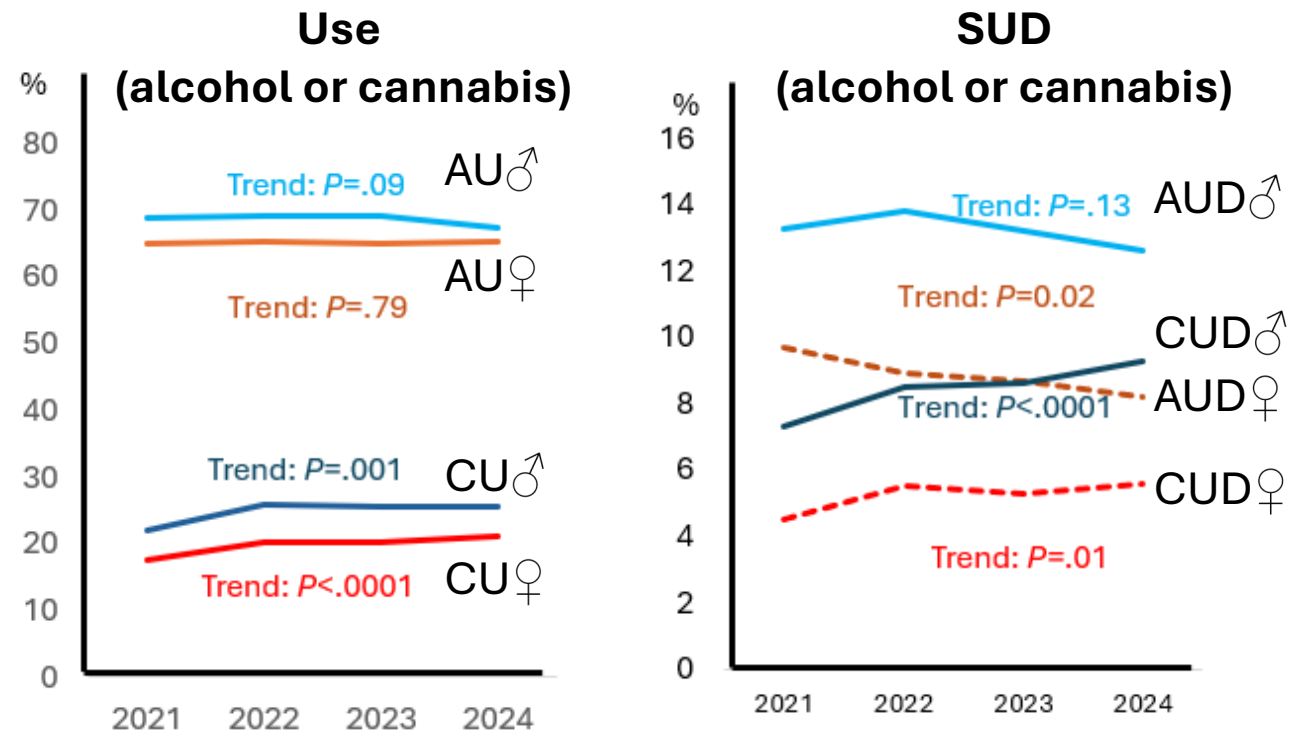


Trends in Past-Year Cannabis and Alcohol Use and Substance Use Disorders Among Adults

Past-Year Cannabis and Alcohol Use Disorders Among Adults



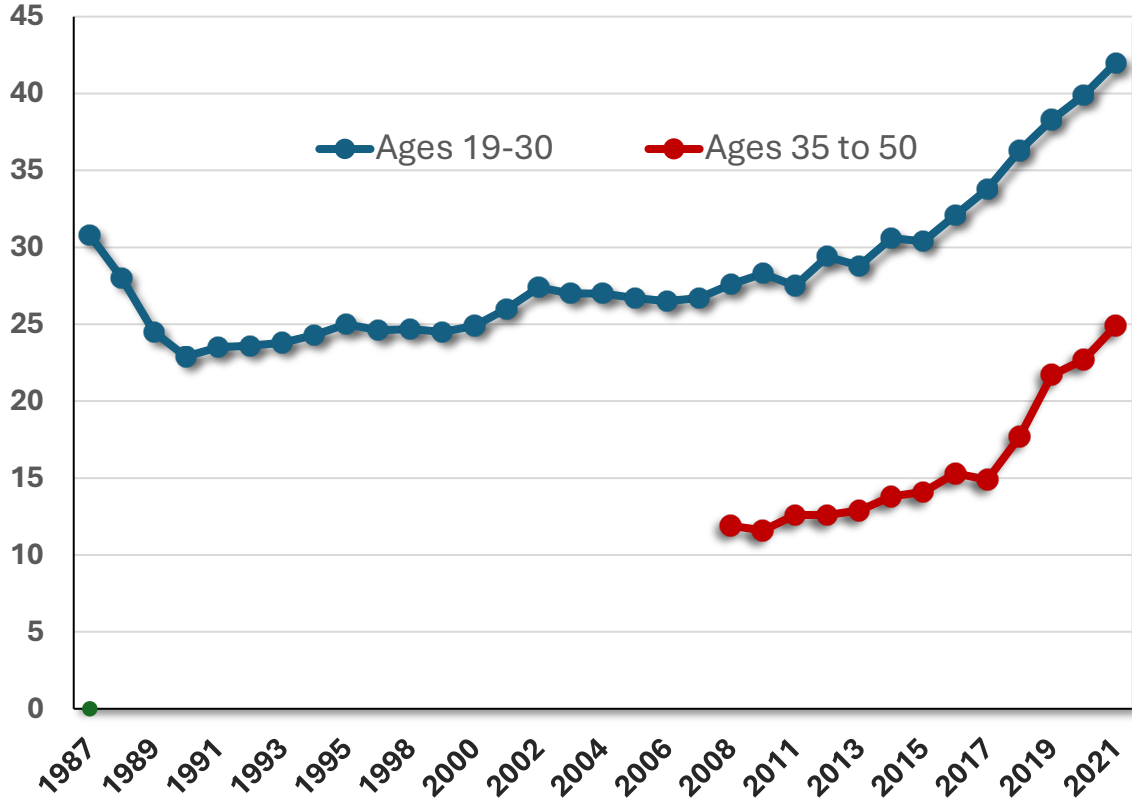
Past-Year Cannabis and Alcohol Use and Use Disorders Among Male and Female Adults



Cannabis Use Increasing Among Adults Age 19-59: MTF Survey

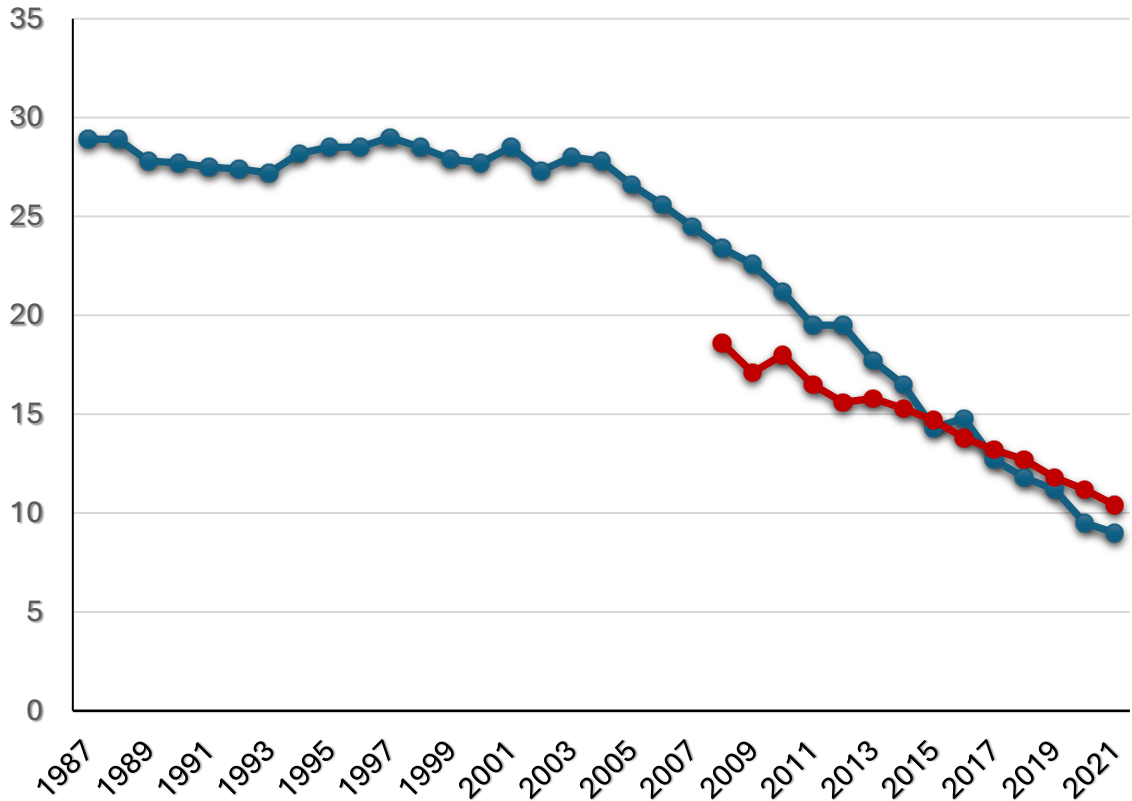
MARIJUANA

Trends in 12 Month Prevalence
Among Respondents of Modal Ages 19 through 59



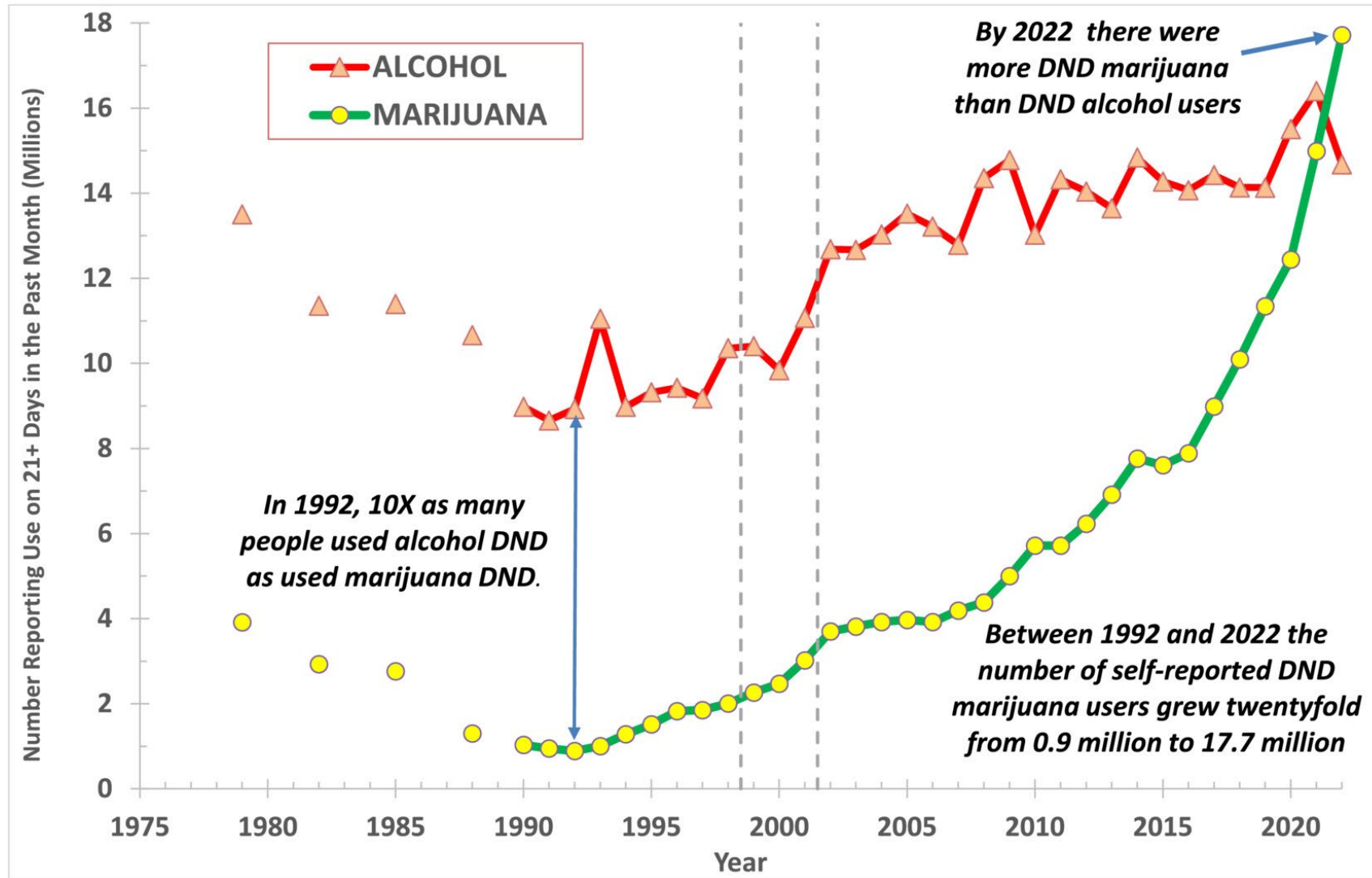
CIGARETTES

Trends in 12 Month Prevalence
Among Respondents of Modal Ages 19 through 59



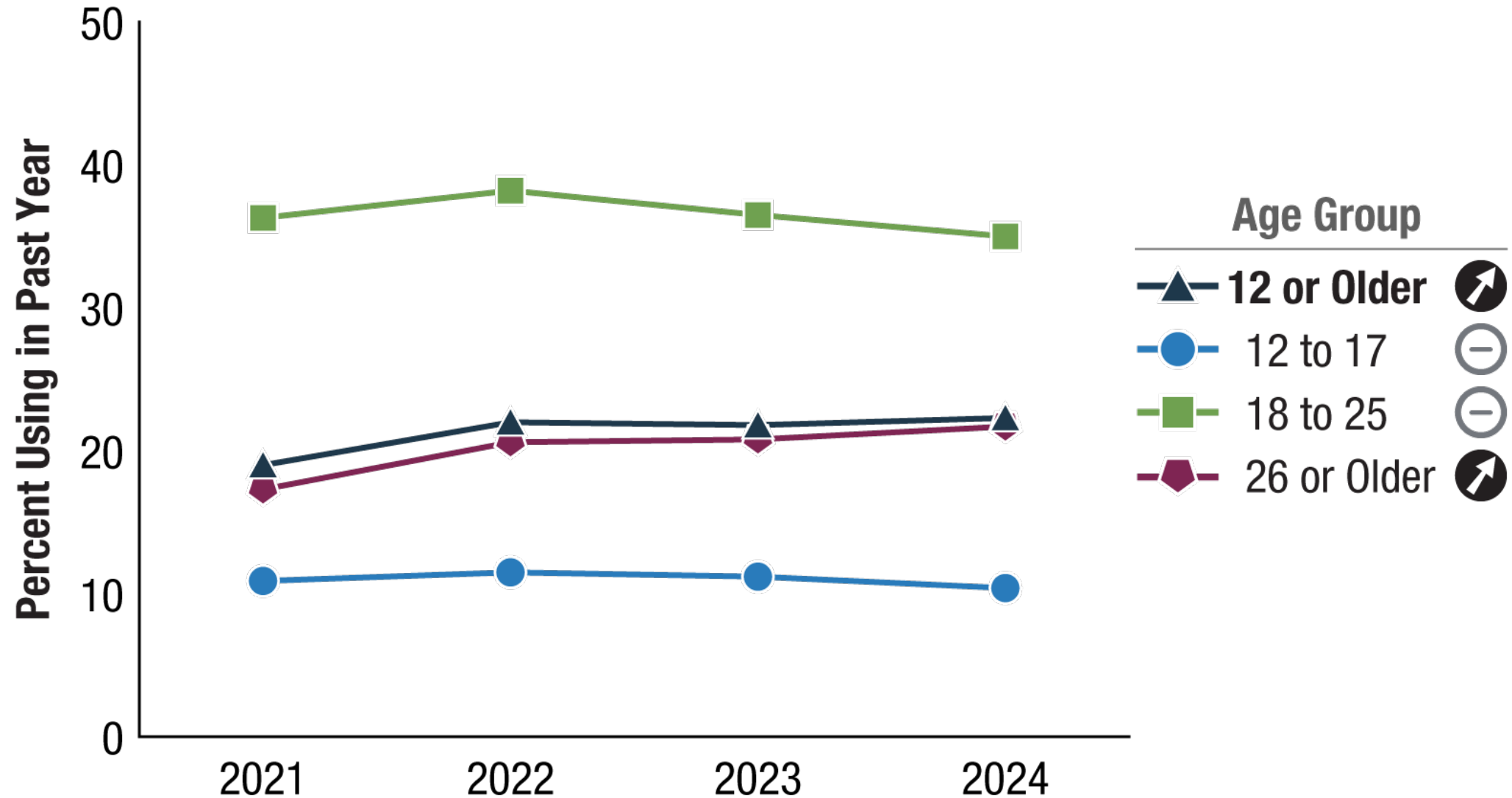
Source: Patrick ME et al (2022). Monitoring the Future Monograph Series. : doi:10.7826/ISR-UM.06.585140.002.07.0001.2022

Changes in Self-Reported Daily or Near-Daily Cannabis Use Among U.S. Adults from 1979-2022

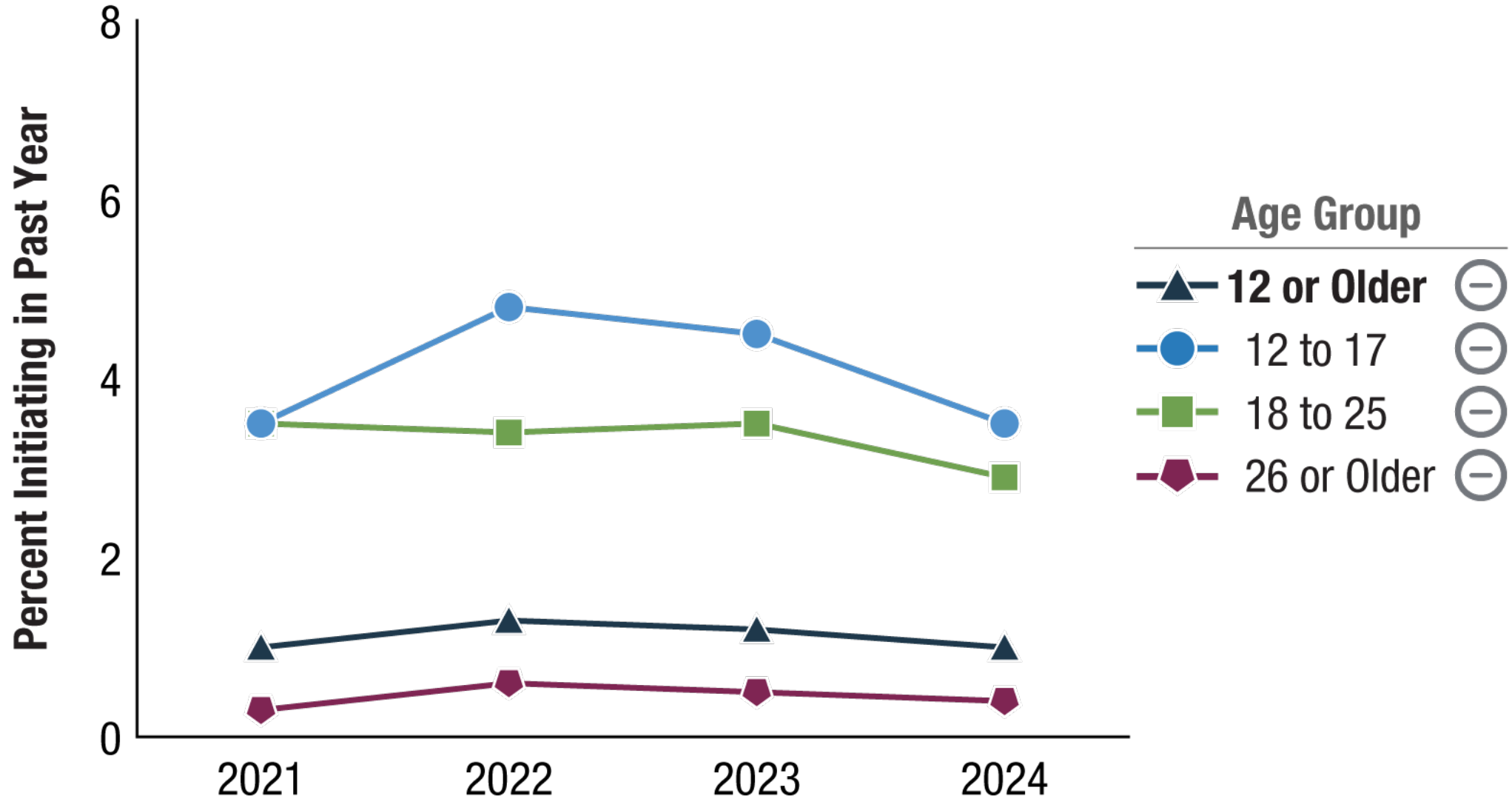


Epidemiology of Adolescent Substance Use

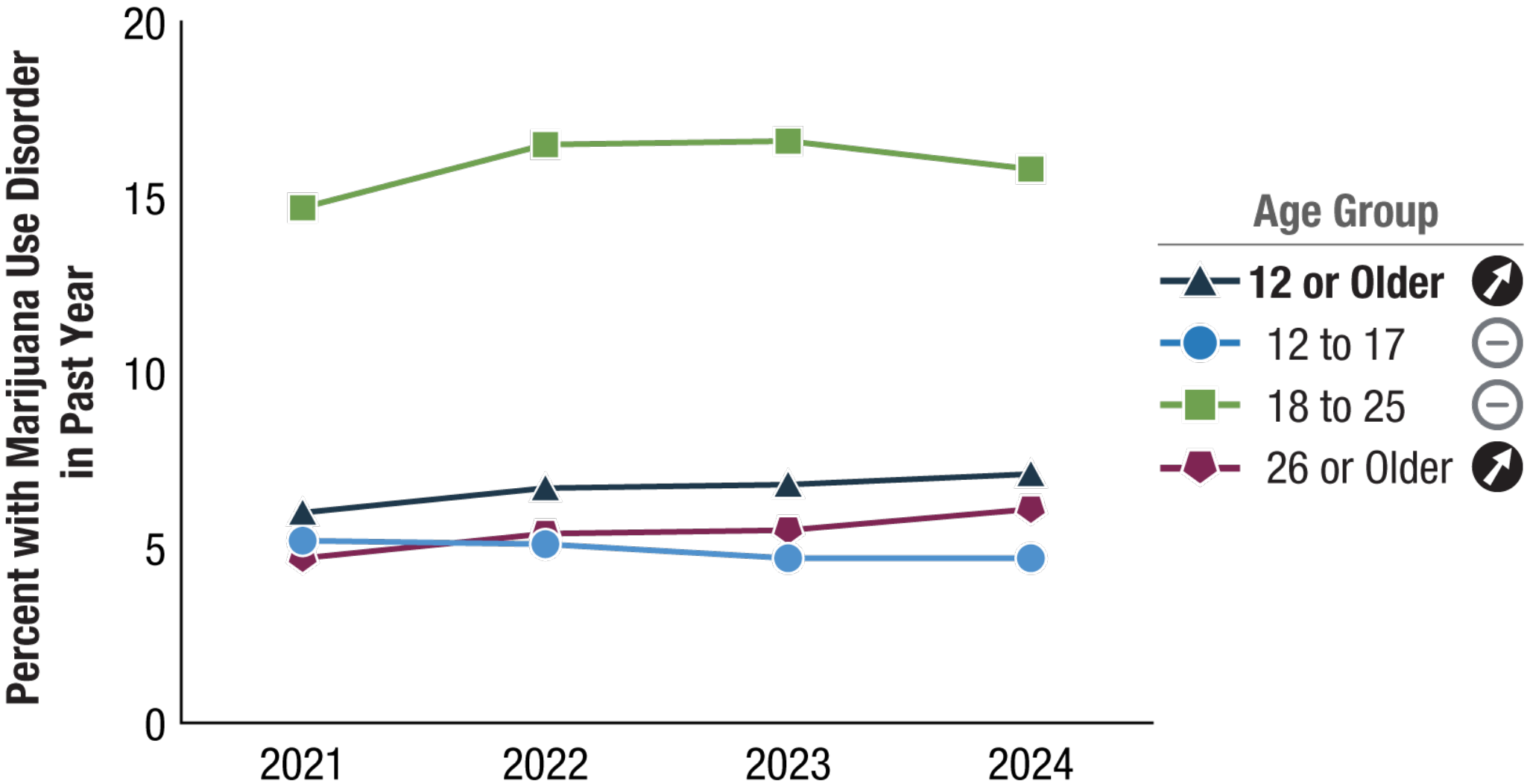
Young Adults have the Highest Rates of Past-Year Cannabis Use



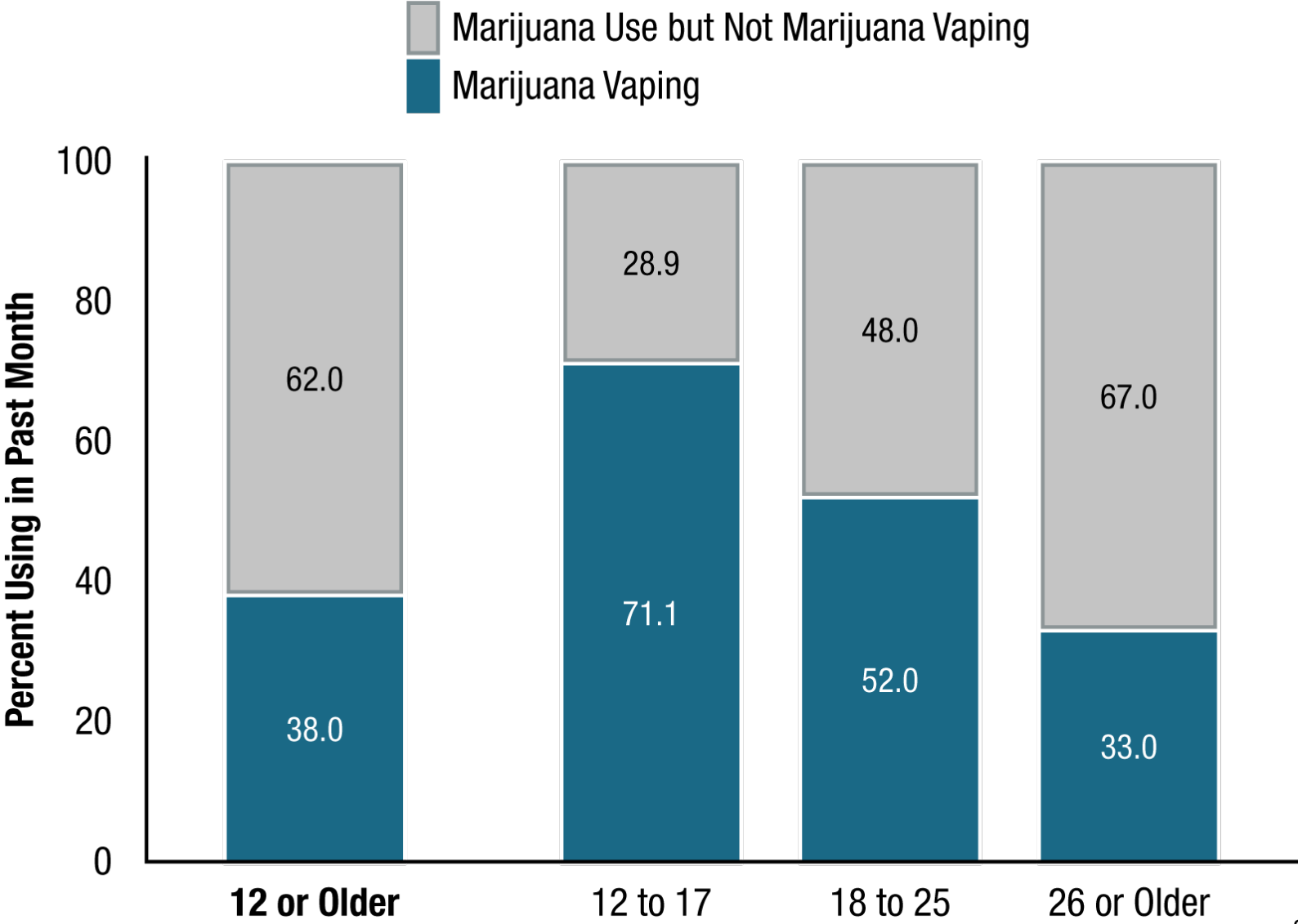
Youth and Young Adults Have the Highest Rates of Cannabis Use Initiation



Young Adults have the Highest Rates of Cannabis Use disorder

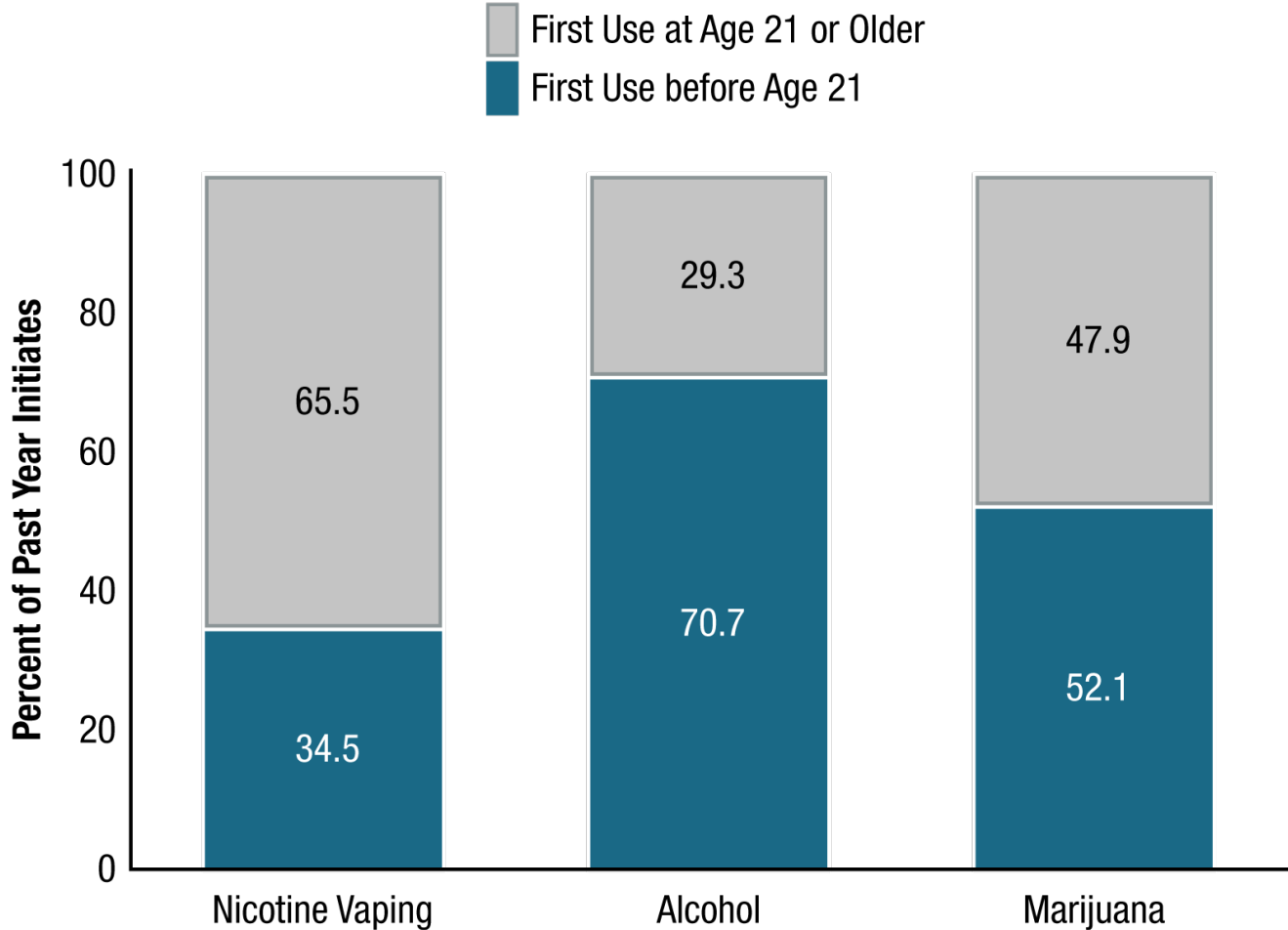
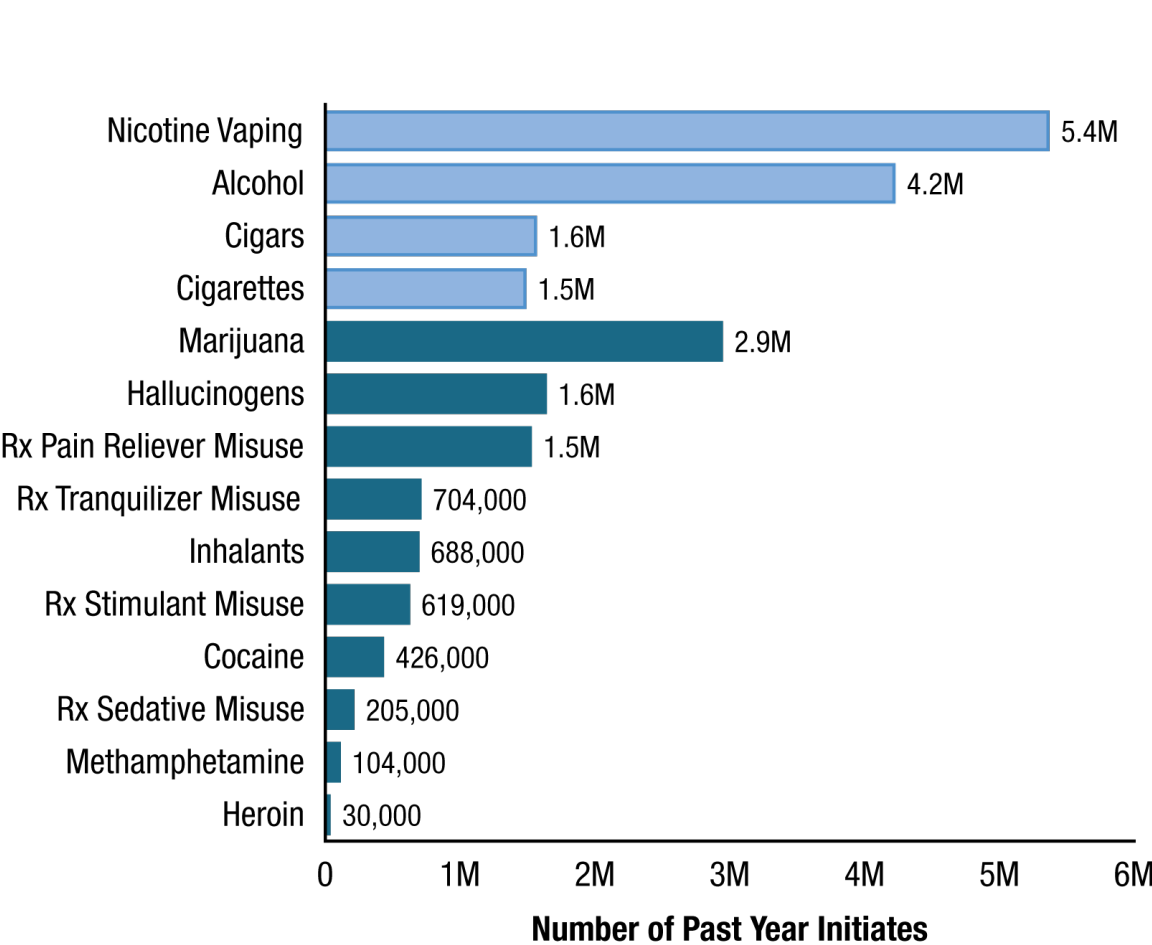


Cannabis Vaping is More Common Among Youth and Young Adults



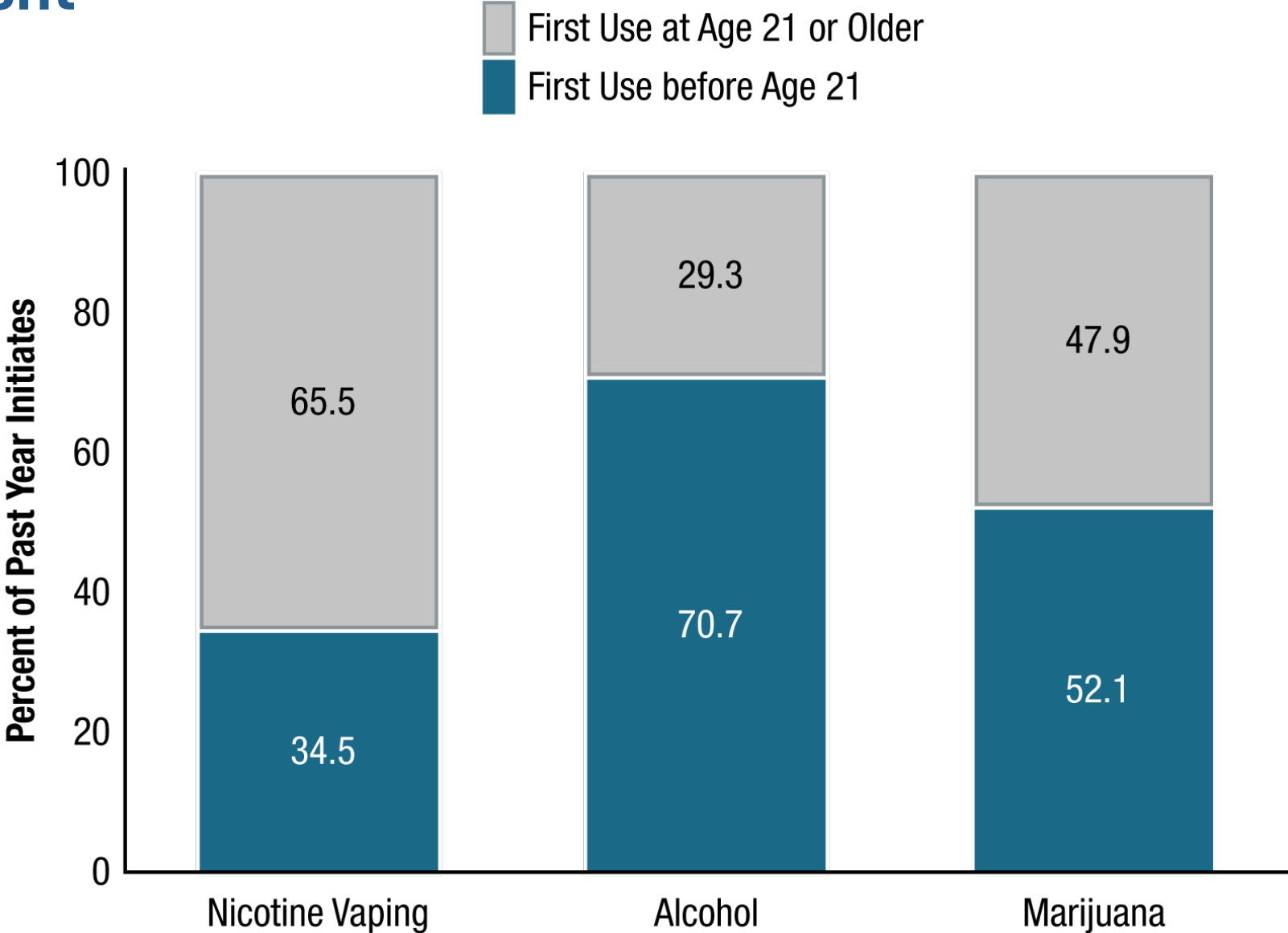
Source: SAMHSA NSDUH, 2024

Substance Use Initiation Prior to Age 21



Source: SAMHSA NSDUH, 2024

Substance Use Initiation Varies by Age, with Early Initiation Prominent



Source: SAMHSA NSDUH, 2024

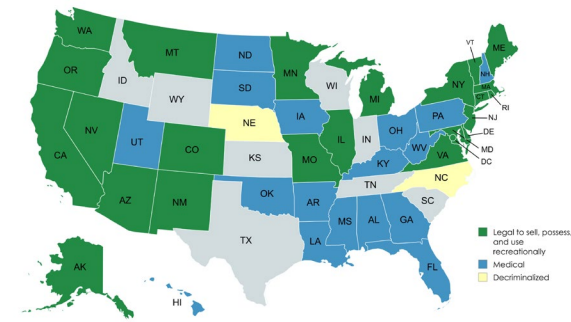
Cannabis Use Among Youth Aged 12-17 is Associated with Broader Substance Use Risk

Among those reporting cannabis use in the past year,

- **12.5%** reported daily or near daily cannabis use
- Many reported other past-year substance use
 - **69.5%** reported past-year alcohol use
 - **69.1%** reported past-year nicotine use
 - **22.9%** reported past-year other Illicit drug use
- **2.0M** had a substance use disorder
 - **1.2M** had cannabis use disorder
 - **775K** had alcohol use disorder
 - **267K** had opioid use disorder

Changing Landscape of Cannabis Products in the U.S.

Federal and State Policies Differ Dramatically



Federal Policies

Controlled Substances Act

- Cannabis (>0.3% delta-9 THC dry weight) is controlled under Schedule I; high abuse potential; no currently accepted medical use
 - *Per a 2025 Executive Order, cannabis may be moved to Schedule III to facilitate research*

Agriculture Improvement Act of 2018 (“Farm Bill”)

- Hemp ($\leq 0.3\%$ delta-9 THC dry weight) is not controlled
 - Intoxicating hemp-derived cannabinoid products (e.g., delta-8 THC) emerged and are widely available
 - *The FY26 Agriculture Appropriations Act places these products in Schedule I by November 2026; Industrial hemp and CBD set to remain uncontrolled*

State Policies

40 States & DC with Medicinal Cannabis Laws

Laws vary on:

- Allowable conditions and routes of administration
- Dispensaries/home growth and registries
- Testing, regulatory requirements

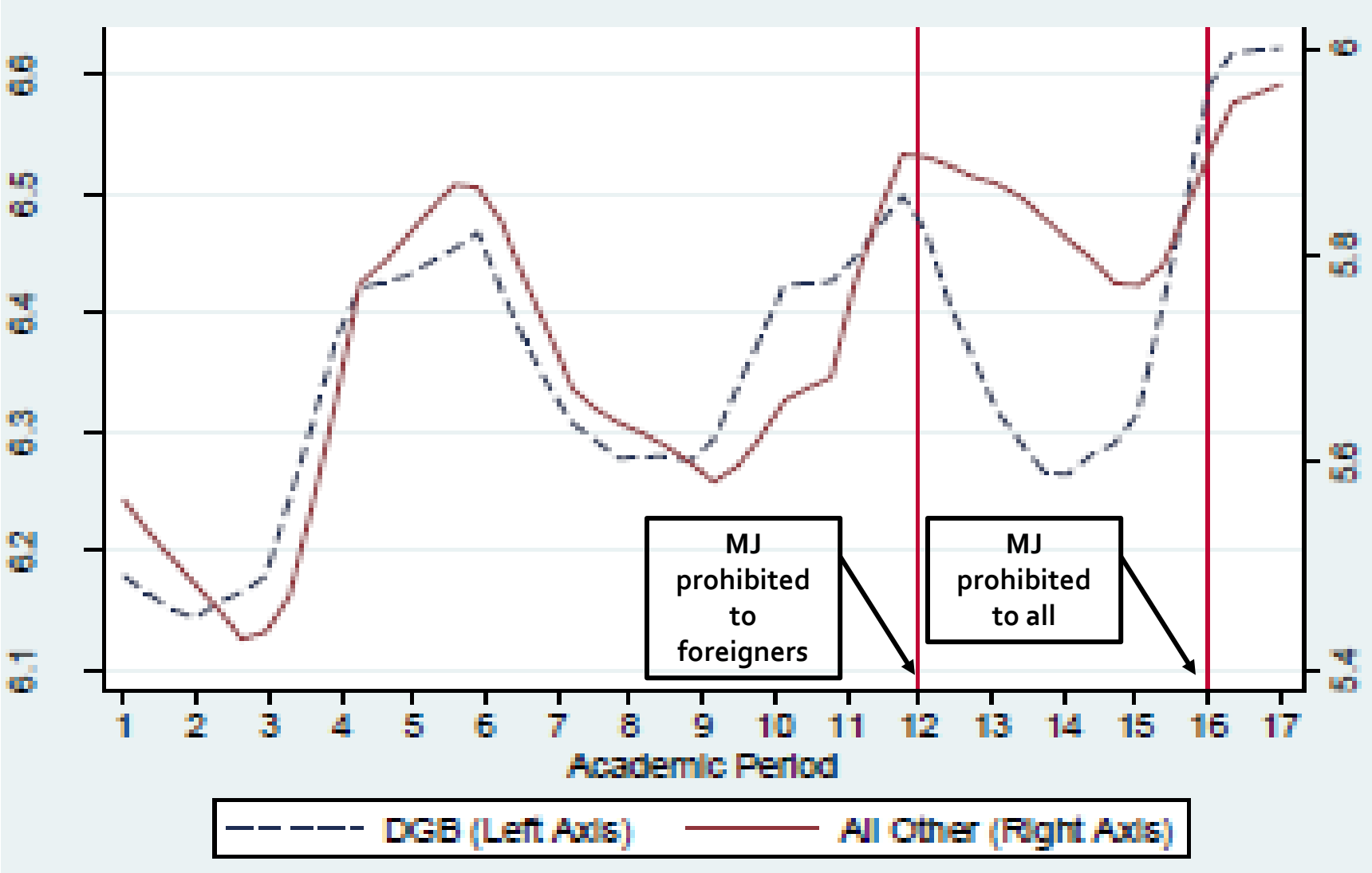
24 States & DC with Non-Medicinal Use Laws

Laws vary on:

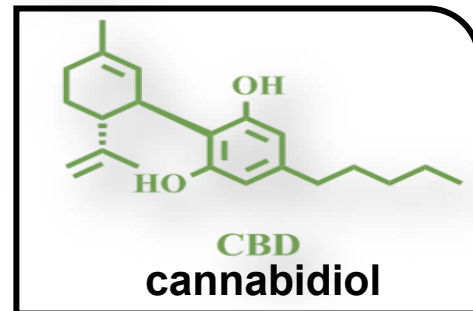
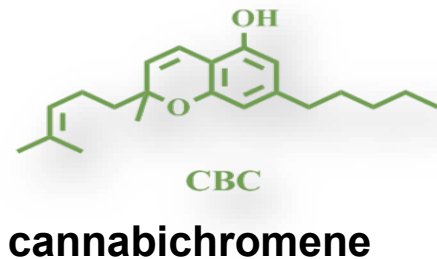
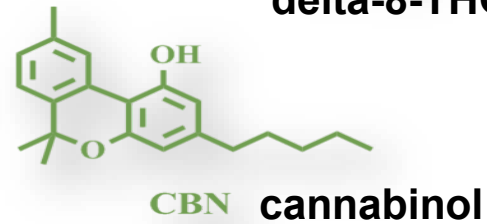
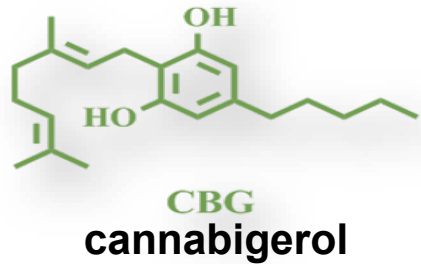
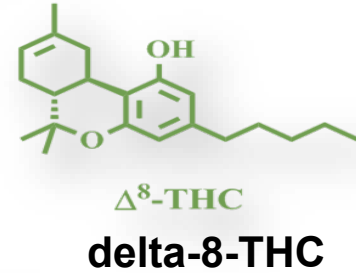
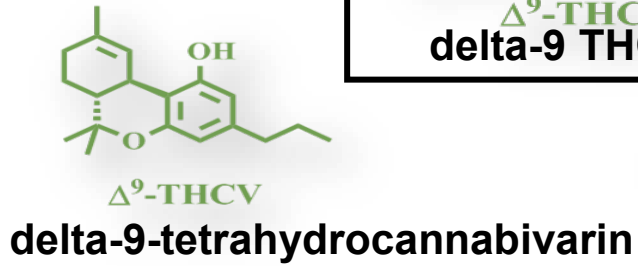
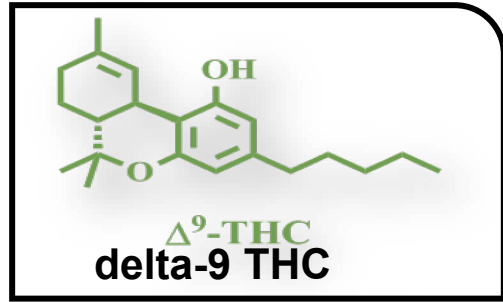
- Marketing, product labeling, distribution (home growth, delivery), public consumption, taxation, licensing, expungement and equity

Most cannabis in the U.S. comes from black and gray markets

Policy Impacts: When Cannabis Sales were Restricted in the Netherlands, University Grades Improved



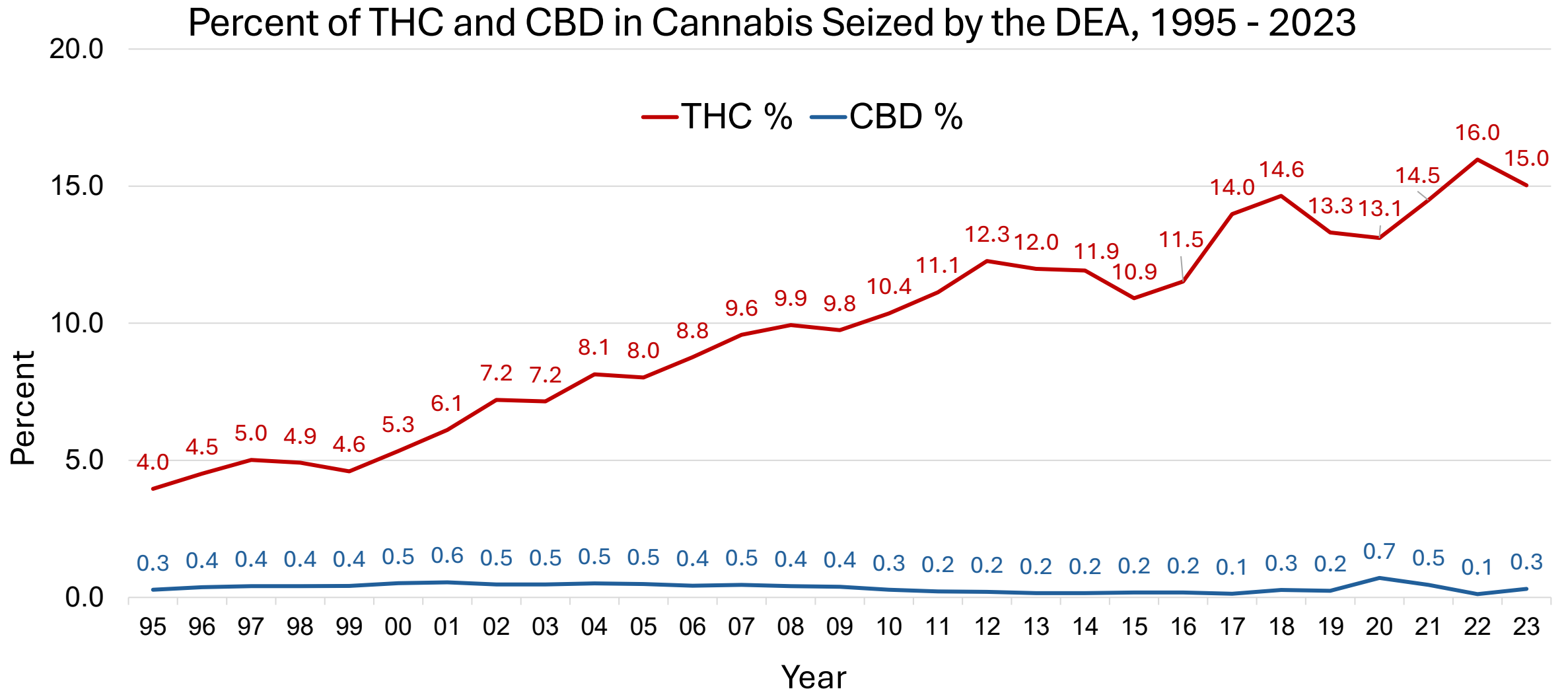
Cannabis is a Highly Complex Plant



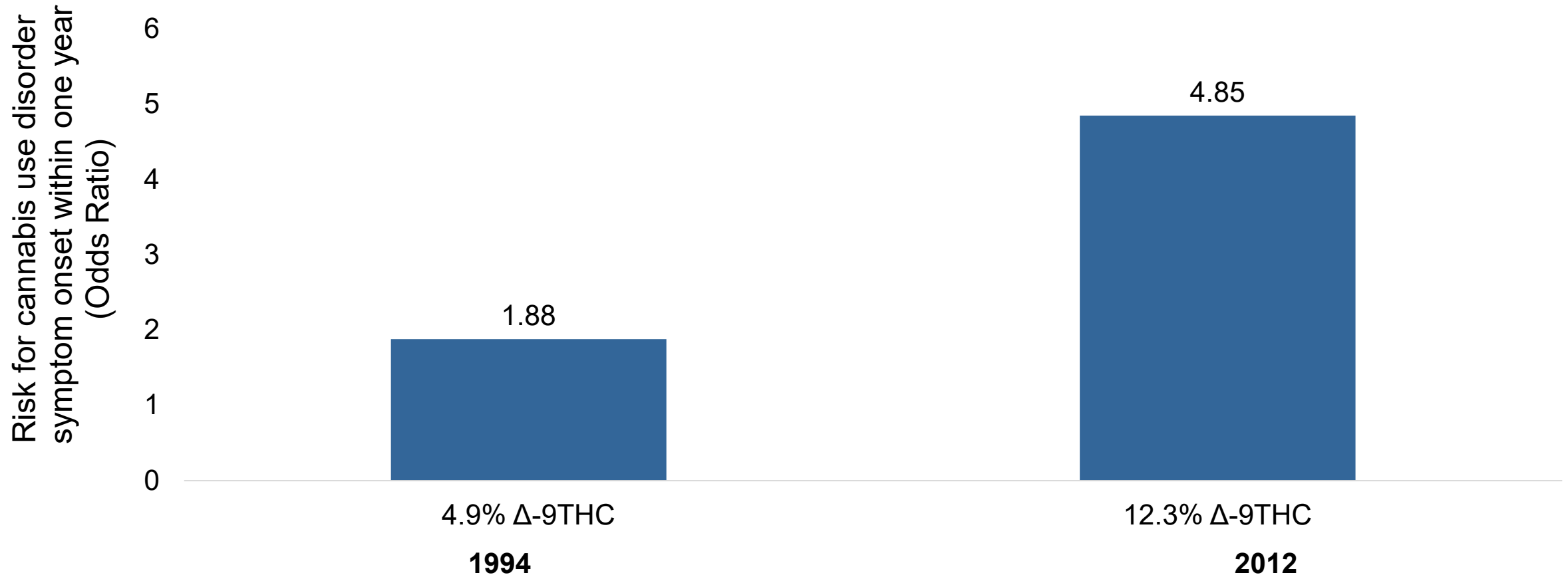
- The *Cannabis sativa* L plant contains >500 chemicals, including >120 cannabinoids
- Primary cannabinoids are delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD).
- THC is intoxicating; CBD is not.
- Different routes of administration have various onset times, duration, and effects.



The Potency (THC Concentration) of Cannabis has Drastically Increased

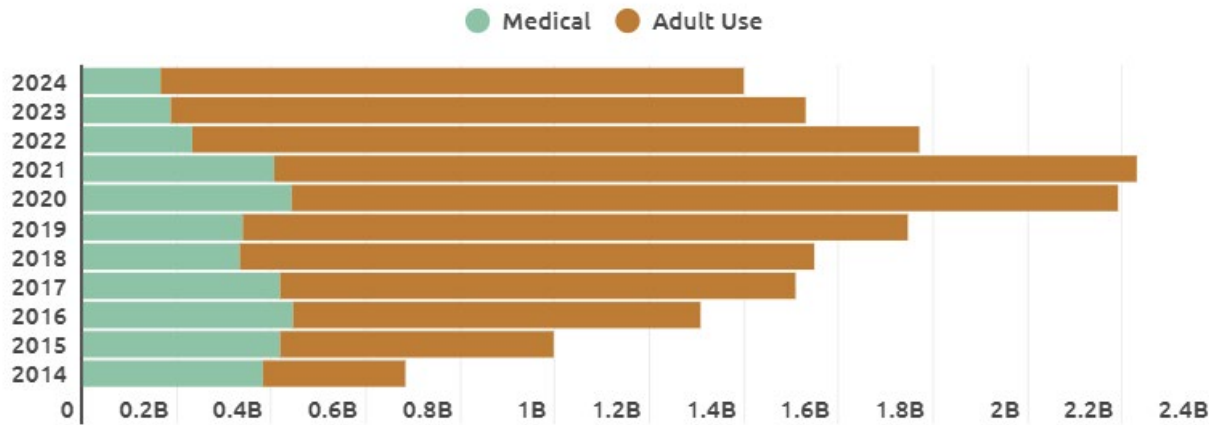


Higher Potency Cannabis, on Average, Increases Risk for Cannabis Use Disorder Onset Within 1 Year

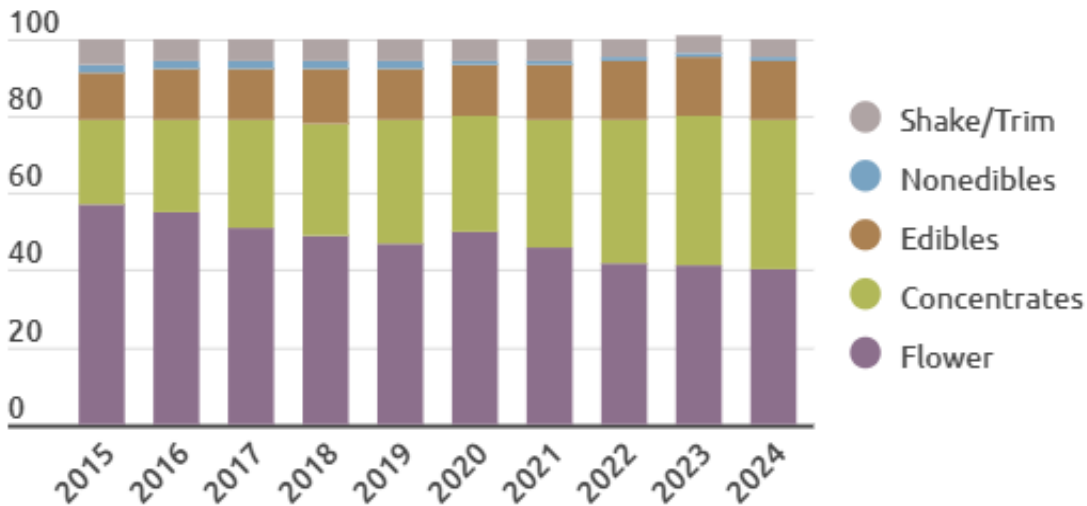


Colorado Market is Shifting Away From Flower Toward Concentrates

Medical and Recreational Sales



Cannabis Product Sales

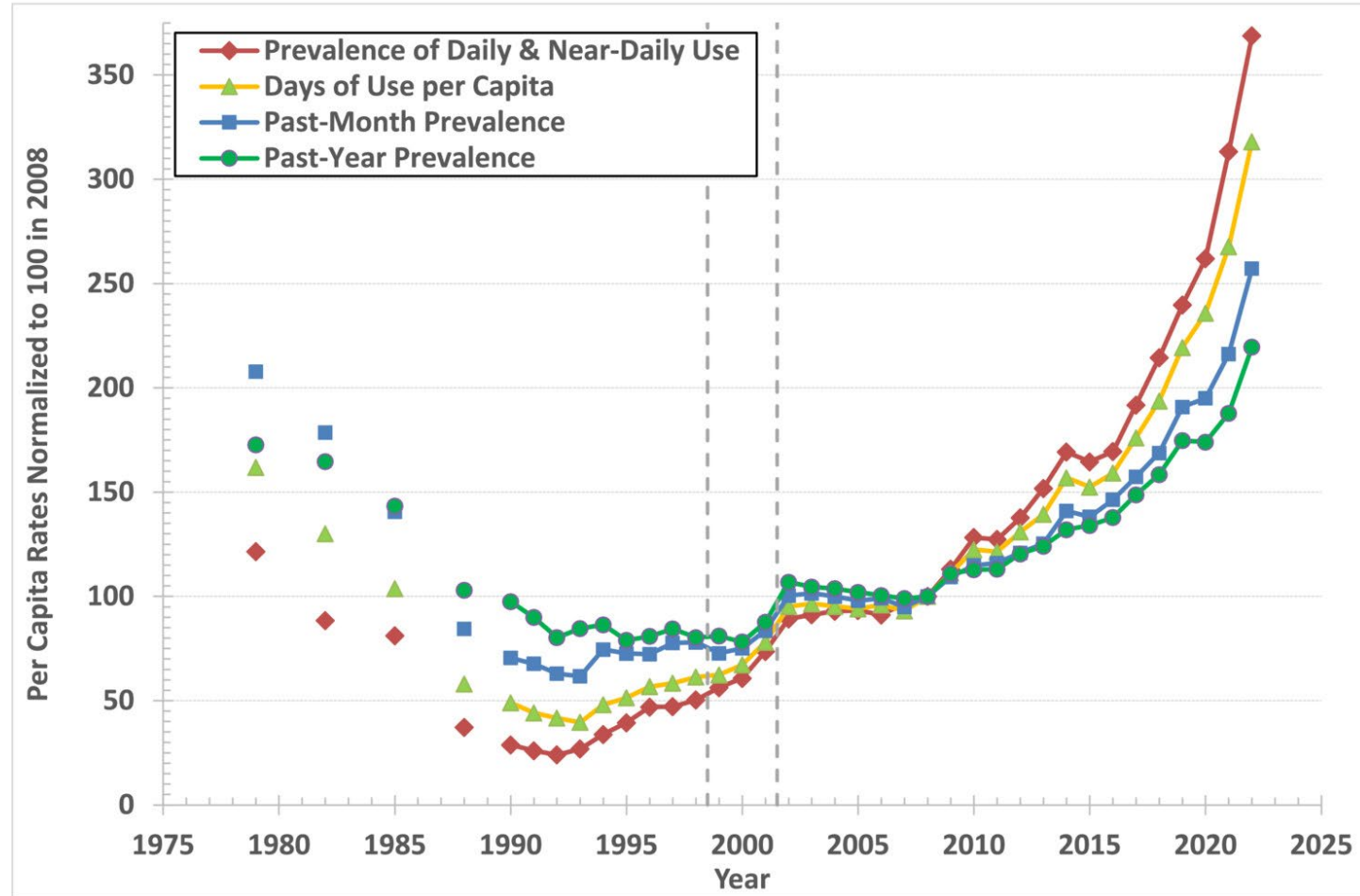


- Colorado’s retail sales in adult-use and medical dispensaries combined grew from \$675 million in 2014 to about \$1.77 billion in 2022, including \$231 million medical and \$1,538 million recreational cannabis sales.
- In 2023, cannabis consumers spent \$1,529 million, including \$185 million medical and \$1,344 million recreational cannabis sales.
- In 2024, cannabis sales averaged \$1.87 million per retail location in Colorado’s adult-use market and \$0.53 million per location in the medical channel.

As Cannabis Products have Diversified, Use has Increased

- The diversity of products has expanded dramatically; new routes of administration (edibles, concentrates, vapes, tinctures...)
- Patterns of use have changed, including far more daily/near daily use
- Measurement of exposure is difficult: Products are not labeled consistently or in ways that consumers understand; population studies do not provide sufficient granularity

(All indexed to be 100 in 2008; Dashed lines indicate two major survey redesigns)



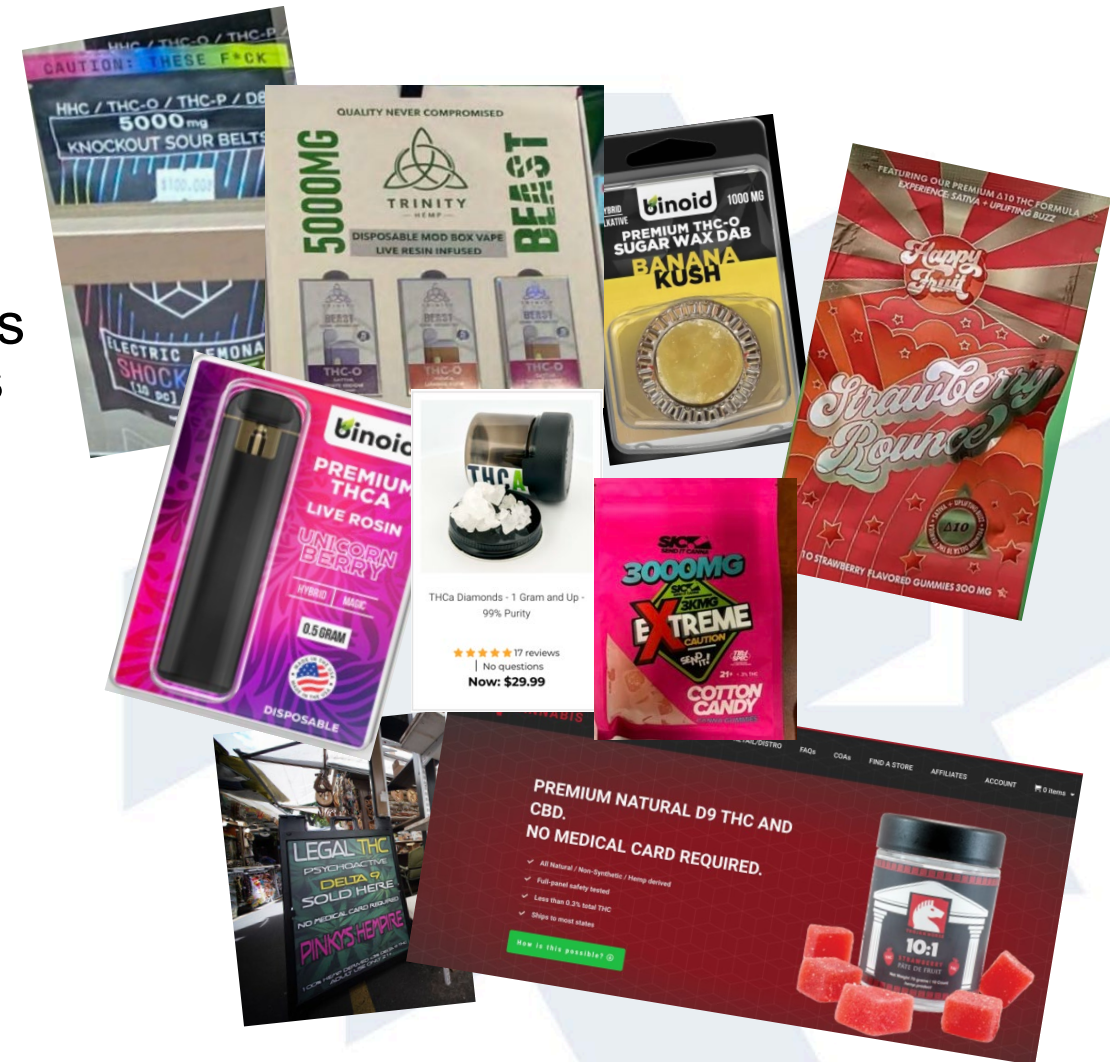
Intoxicating Hemp Products have Emerged from Loopholes in the Agriculture Improvement Act of 2018 (Farm Bill)

Derivatives - Chemically derived impairing cannabinoids (Delta-8, Delta-10, HHC, THCO, etc.)

THCA – Products being marketed with high levels of THCA that are indistinguishable from cannabis products.

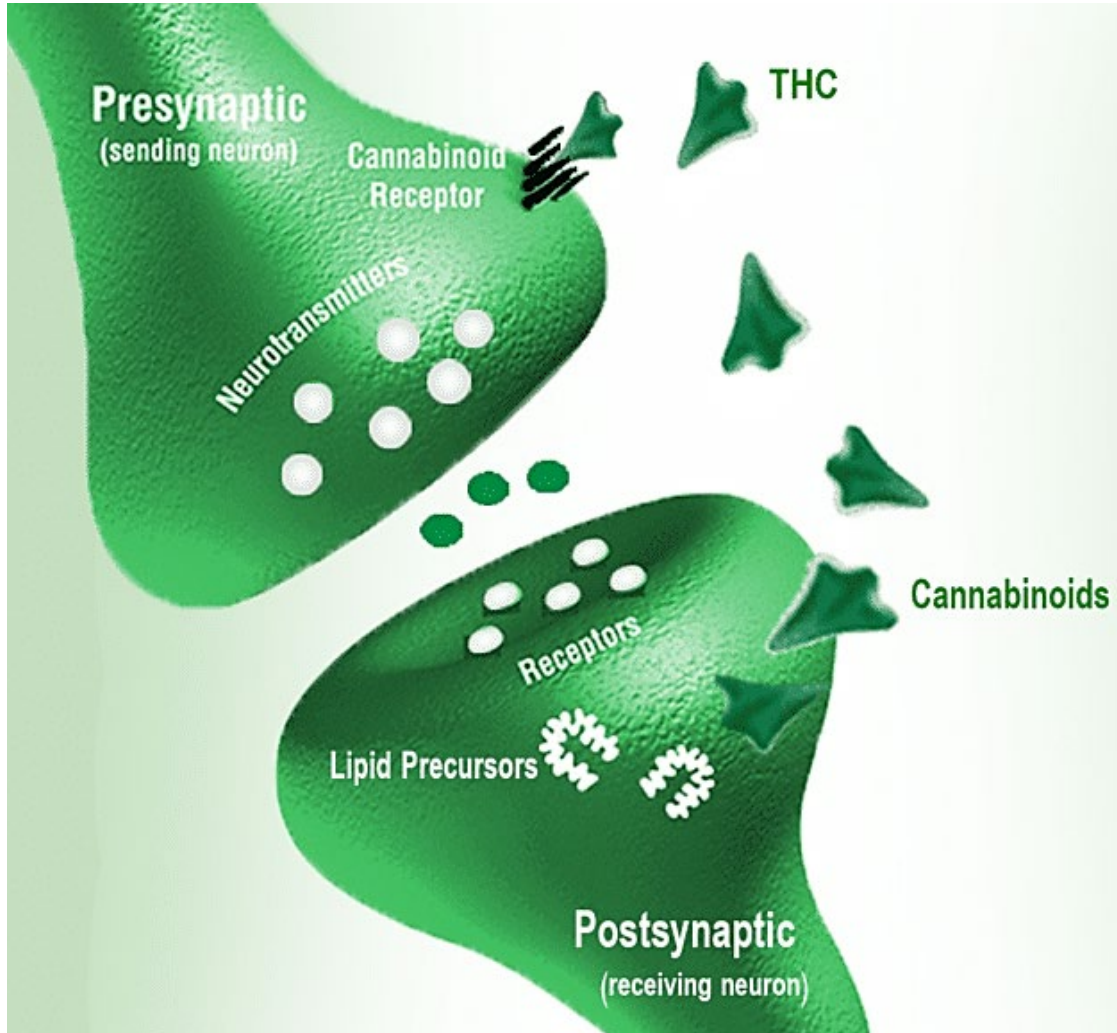
0.3% loophole - Impairing amounts of Delta-9 THC in products that meet the legal definition of “hemp” per the 2018 farm bill.

These products are widely available in gas stations, convenience stores, dispensaries, and online



Endocannabinoid System

Endocannabinoid System Plays Key Role in Regulating Homeostasis



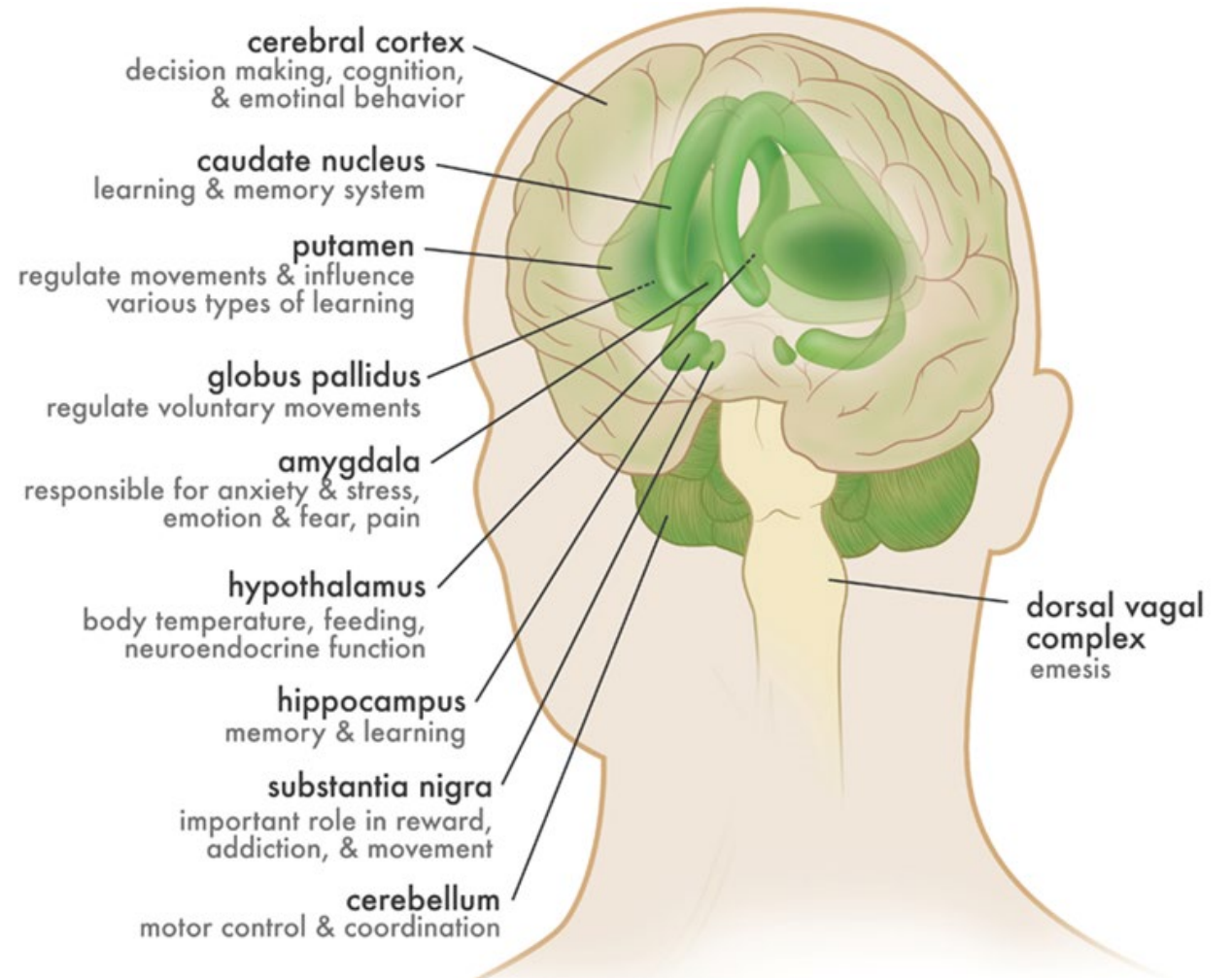
Endogenous cannabinoids play a central role in regulating physiological processes to maintain homeostasis.

Endocannabinoids are produced *on demand*. They travel back to the transmitting neuron to dampen further activity.

Two cannabinoid receptors:
Cannabinoid Receptor 1 (CB1)
Cannabinoid Receptor 2 (CB2)

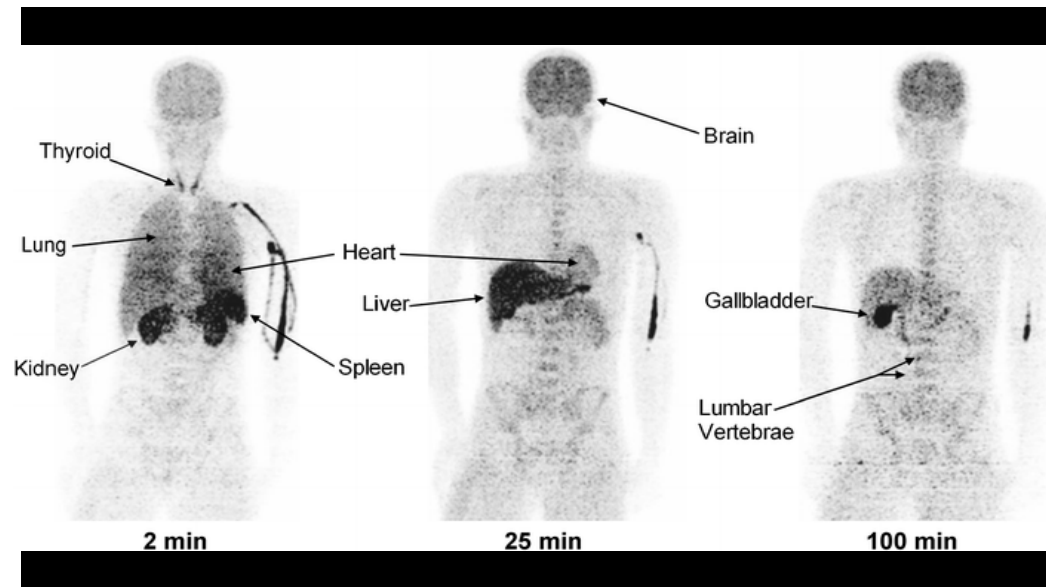
Cannabinoid Receptors are Located Throughout the Brain

- Brain Development
- Memory & Cognition
- Coordination & Balance
- Pain Regulation & Analgesia
- Immune Function
- Appetite
- Motivational Systems & Reward



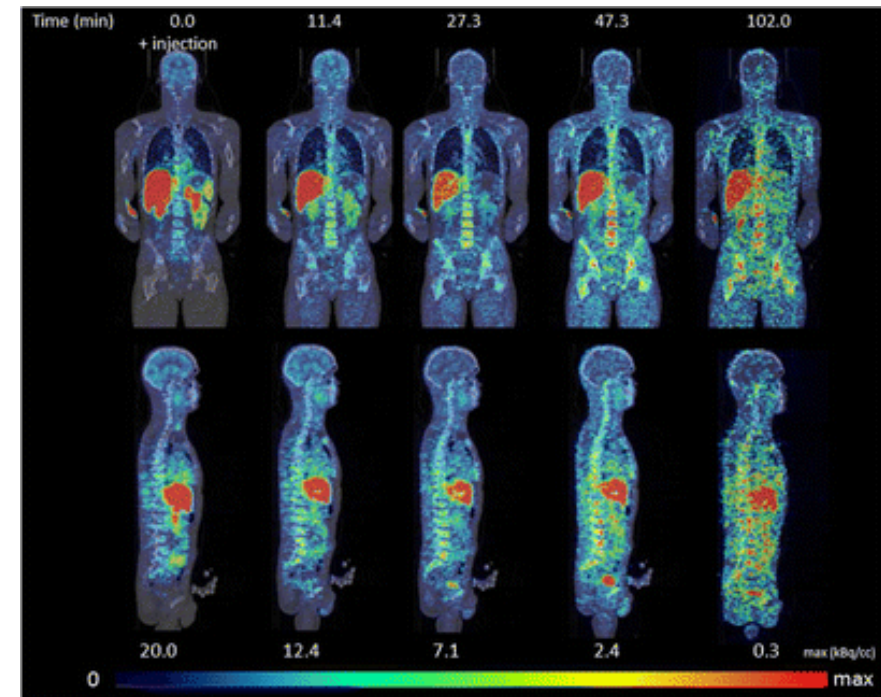
Cannabinoid Receptors are Distributed Throughout the Body

Whole Body Distribution of CB1 Receptors



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

PET Images



Source: Ahmad et al., Mol Imaging Biol. 2013

Exogenous Cannabinoids Modulate the Endocannabinoid System

Δ 9-tetrahydrocannabinol (Δ 9-THC)

Partial agonist at cannabinoid receptors
More potent than Δ 8-tetrahydrocannabinol (Δ 8-THC)

Receptors: CB1 receptor, CB2 receptor

Effects: euphoria and psychosis

Δ 8-THC

Partial agonist at cannabinoid receptors
Less potent than Δ 9-THC

Receptors: CB1 receptor, CB2 receptor

Effects: euphoria and psychosis

Cannabidiol (CBD)

Negative allosteric modulator of CB1 with low affinity to cannabinoid receptors
May modulate receptor signaling indirectly and interact with other receptors
Not known to cause acute intoxication or euphoria

Receptors: 5-HT1A (serotonin 1A receptor), TRPV1 (transient receptor vanilloid 1), GPR55 (G protein-coupled receptor 55), NaV 1.8 (sodium channel subtype), CB1 receptor, CB2 receptor

Effects: Anxiolysis, antidepressant, antiseizure, anti-inflammation, decreased appetite, and analgesia

Acute Cannabis Use Impairs Cognition, Memory, Mood, and Psychomotor skills



Euphoria

Appetite Stimulation

Heightened Sensation

Increased Heartrate

Altered Perception of Time

Anxiety/Panic

Impaired Cognition/Memory

Impaired Decision-Making

Psychomotor Impairment

Increased Risk-Taking

Reduced Inhibition

Increased Risk of Accidents

Chronic Cannabis Use and Substance Co-Use Raise Risks of Health Harms



Cannabis Use Disorder

Poorer School/Career Outcomes

Mental Illnesses

Cannabis hyperemesis

Heart and lung problems

Head and neck cancers

- Co-Use of Other Substances

- Enhances reinforcing effects, increasing addiction risk
- Elevates risk for mental illnesses

- Tobacco Co-Use

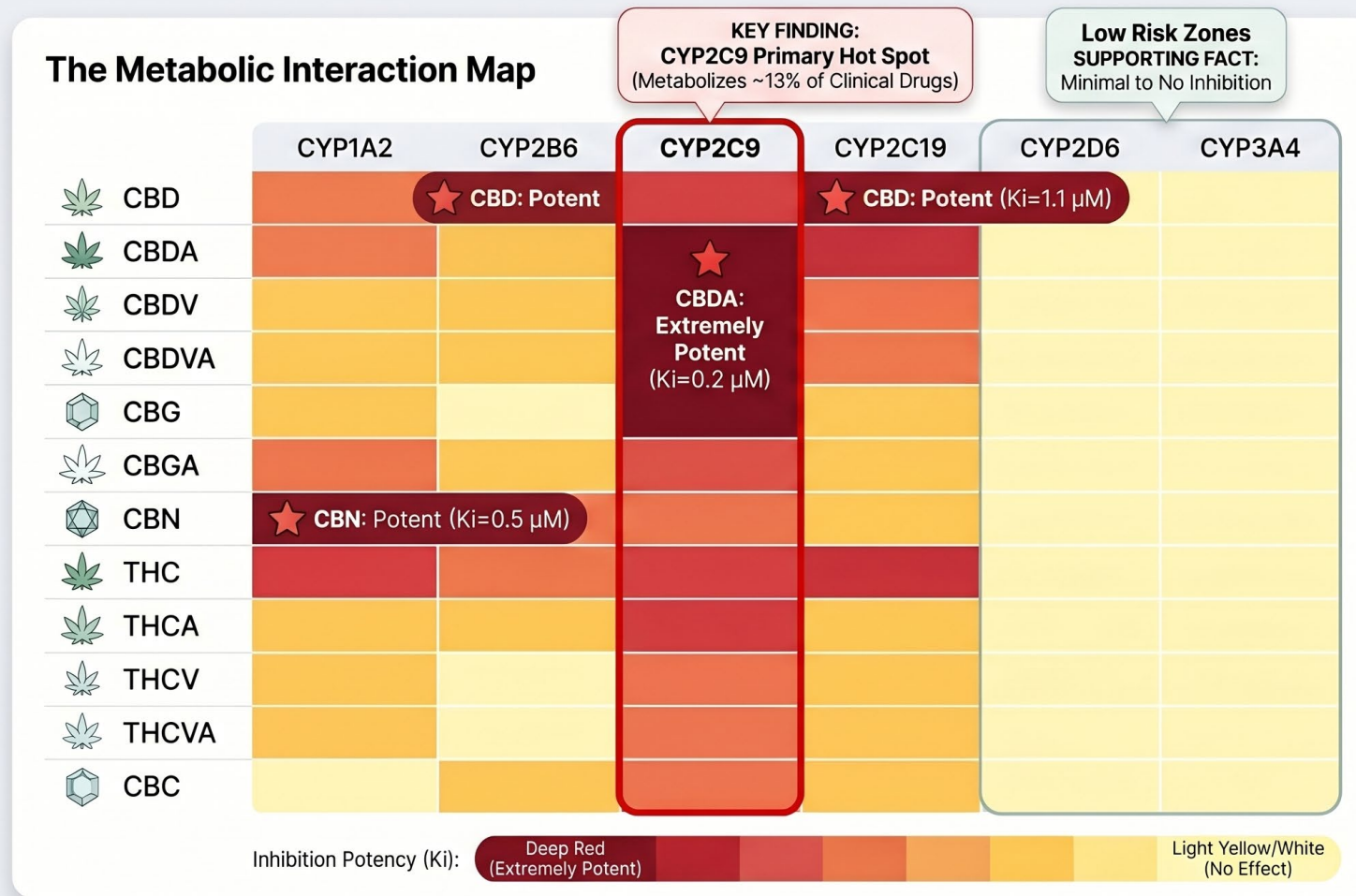
- Heightens respiratory and cardiovascular risks
- Increases exposure to toxins and carcinogens

- Alcohol Co-Use

- Amplifies intoxication and impairment
- Exacerbates risk taking

Cannabinoids Can Alter the Metabolism, Levels, and Effects of Co-Administered Medications

Cannabinoid-CYP450 Drug Interaction Map



Clinical Implications & Patient Safety



Narrow Therapeutic Index (NTI) Risk

Inhibition is most dangerous for NTI drugs, where tiny changes in blood concentration can cause toxicity or treatment failure.

Critical Risks for Warfarin (Blood Thinner)

This clinical risk is linked to CYP2C9, CYP2C19 inhibition

Critical Risks for Phenytoin (Anti-Seizure)

This specific risk is associated with the inhibition of CYP2C8 and CYP2C19

KEY FINDING: Clinically Relevant Concentrations

Inhibitors like CBDA and CBD reach high enough levels in the blood during typical use to trigger significant real-world drug interactions.

Cannabinoid Exposure and the Developing Brain

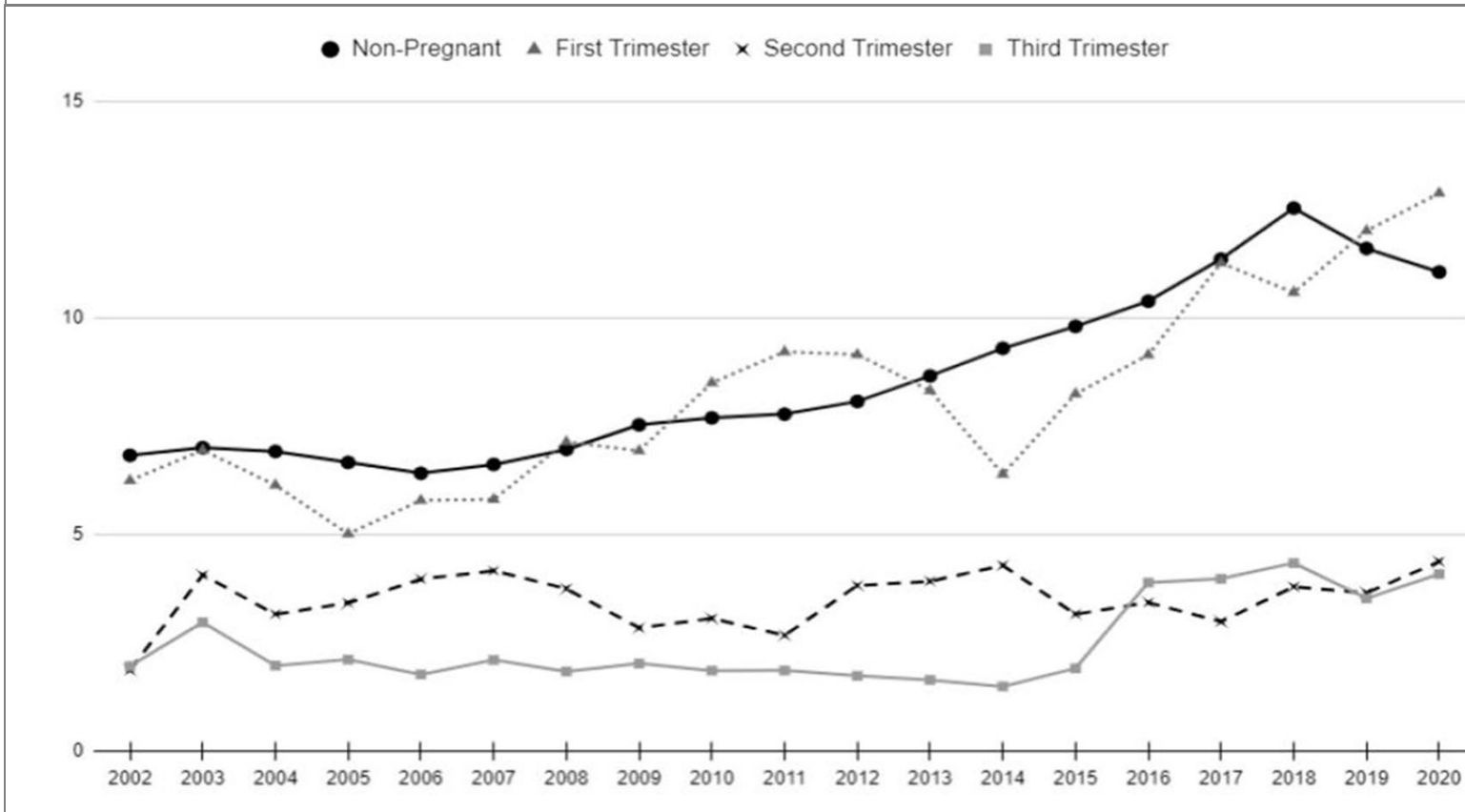
Cannabinoids and Fetal Development: ECS Function and Exposure Risks



- Endocannabinoid system (ECS) is involved in implantation; placentation; fetal organ development; and neural development
- Exogenous cannabinoids cross the placenta and accumulate in fetal tissues, especially brain.
- Human fetal imaging studies find changes in dopamine D2 receptors; may be sex-dependent.
- Prenatal exposure is linked to fetal growth restriction and low birth weight.
- Longitudinal human studies report subtle to modest impact on later cognition and neuropsychiatric outcomes (with multiple caveats).
- Preclinical studies show changes in synapse formation and function; and lasting effects of THC exposure on adult drug seeking, stress responses, and brain reward systems.

Cannabis Use is Increasing Among Pregnant Women

Percentage of Women Reporting Past-Month Cannabis use
By Pregnancy Status (NSDUH, 2002-2020)



- Past-month use in the first trimester increased more than 2.5-fold, from 6.3% to 16%, with the largest increase occurring in first month.
- Past-month use in the second trimester increased about 2.2-fold, from 1.9% to 4.2%
- Past-month use in the third trimester increased 2.3-fold, from 2% to 4.6%

Adolescent Cannabis Use is Associated with Serious Risks

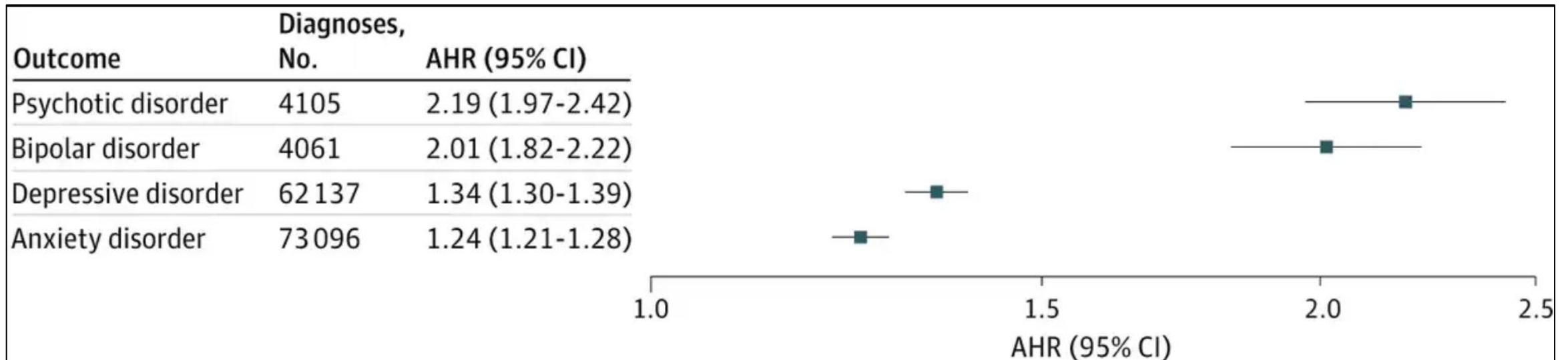
- Impaired learning and measures of IQ
- Lower motivation
- Worse long term academic and career outcomes
- Greater risk for cannabis use disorder and other SUDs
- Higher risk of mental disorders



Adolescent Cannabis Use is Linked with Increased Incidence of Mental Disorders



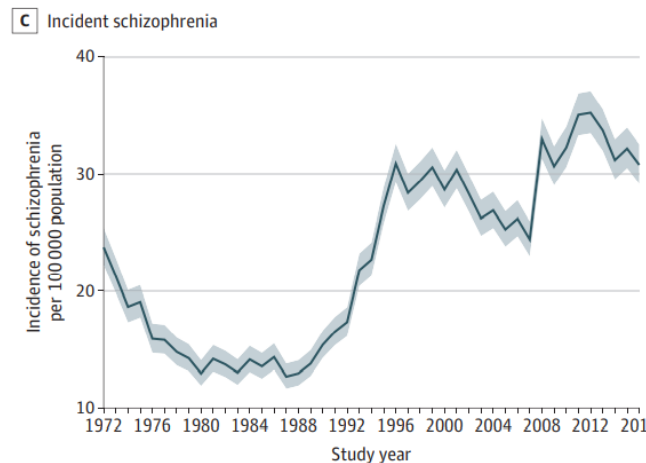
- Late adolescence and young adulthood is the most vulnerable window for the onset of mental illness.
- A retrospective analysis of a longitudinal cohort study found that past-year cannabis use at ages 13-17 was linked with an increase in new cases of mental disorders by age 26.



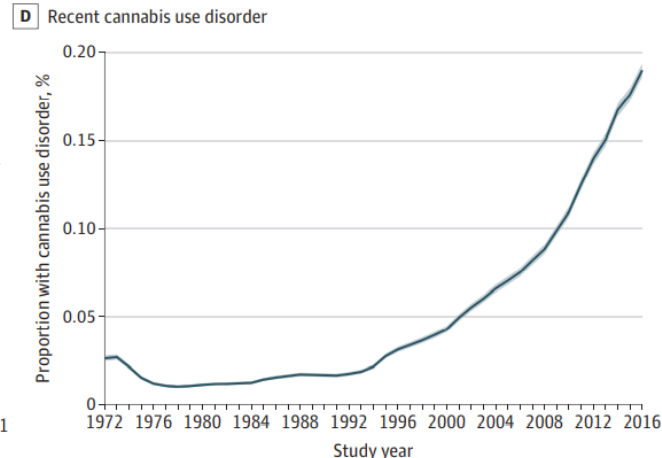
Population-attributable risk fraction (PARF) for schizophrenia increased during the last 20 years.

Danish nationwide prospective cohort study of all people aged 16-49 at some point during 1972-2021.

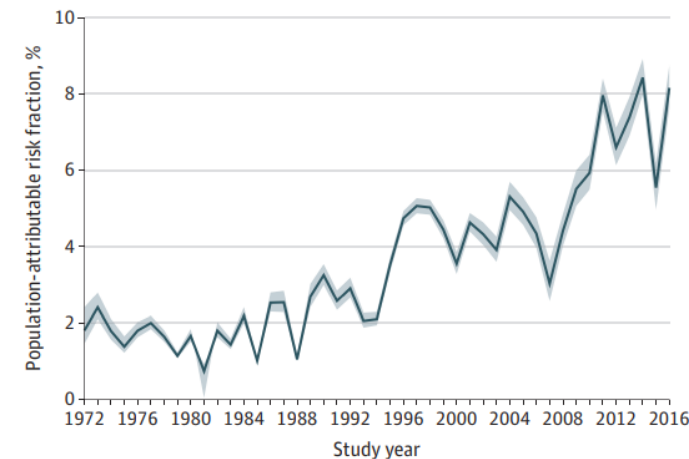
Incidence of Schizophrenia



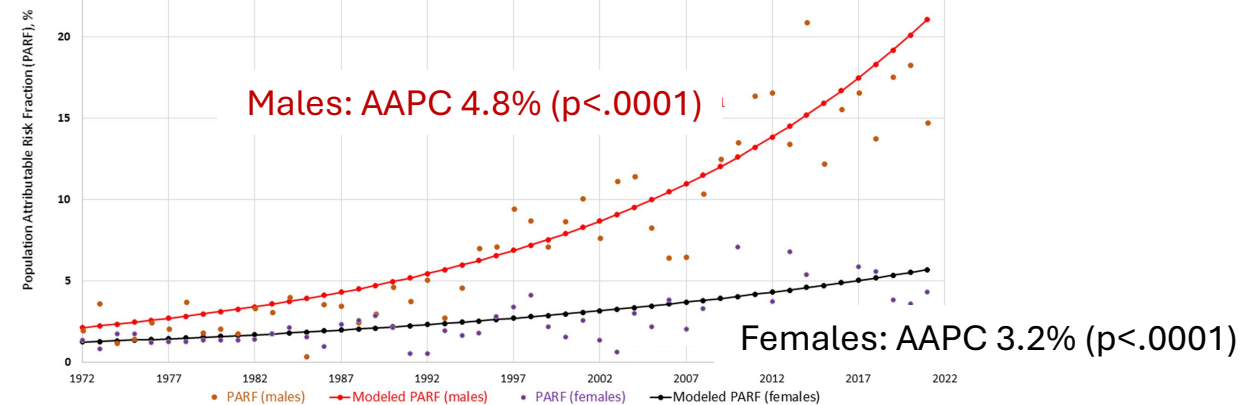
Recent Cannabis Use Disorder



(PARF) of CUA in Schizophrenia



(PARF) of CUA in Schizophrenia for Males and Females

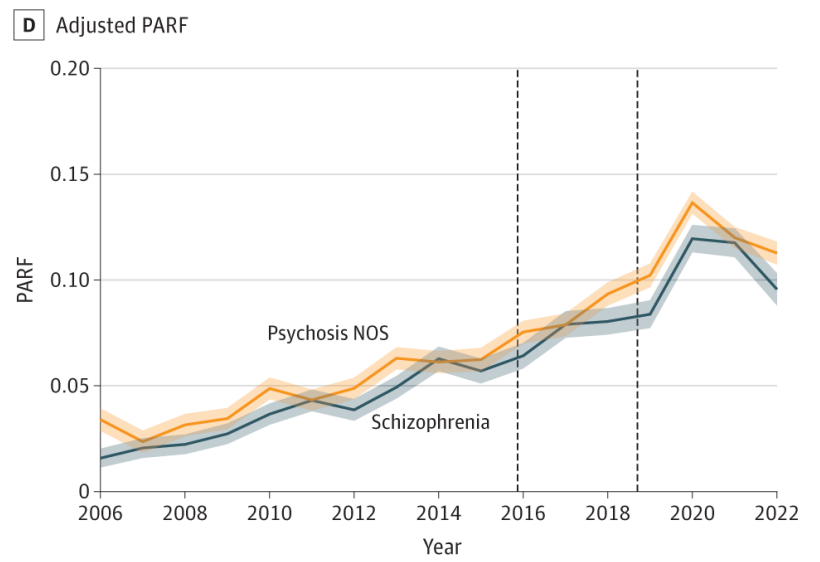
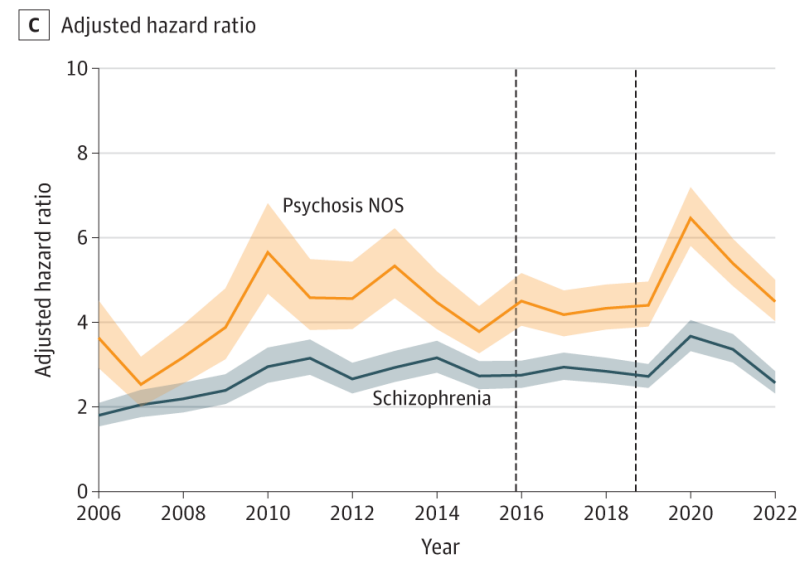
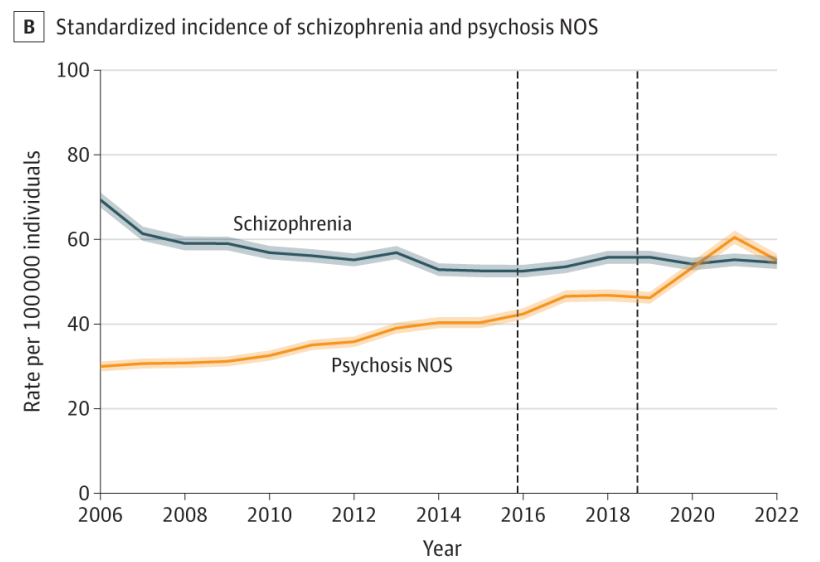
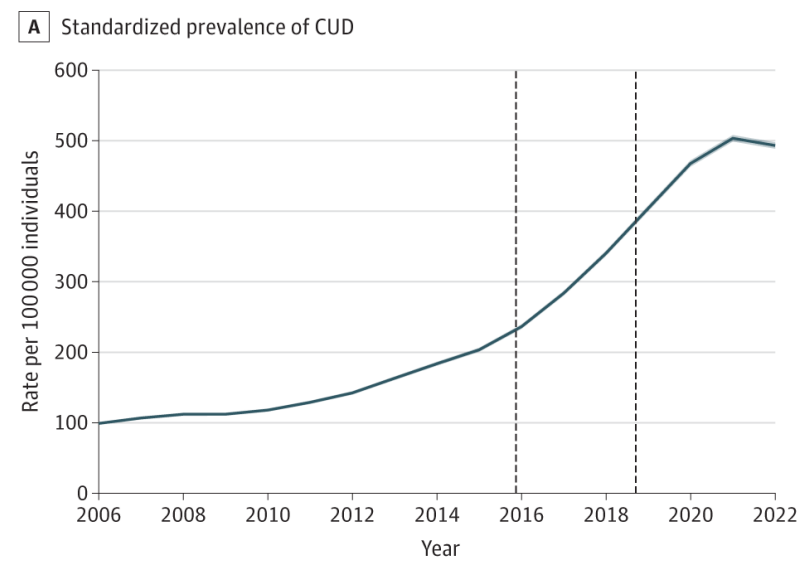


PARF=Population attributable risk fraction. Modeled PARF= PARF results from the selected joinpoint regression model. APC=annual percentage change. AAPC=average APC during 1972-2021. APC=AAPC. Indicate that no joinpoints were identified using Bayesian Information Criterion.

- Schizophrenia associated with CUD increased 3- to 4-fold during the past 2 decades (*alongside increases in cannabis use and potency*)
- Supports hypothesis that cannabis may be involved in the etiology of a growing number of schizophrenia cases, especially for males.
- What are the mechanisms?

Incident Schizophrenia Diagnoses Associated with Cannabis Use Disorder after Cannabis Legalization in Ontario (Canada)

Myran et al. *JAMA Network Open*. 2025 Feb 4;8(2):e2457868.

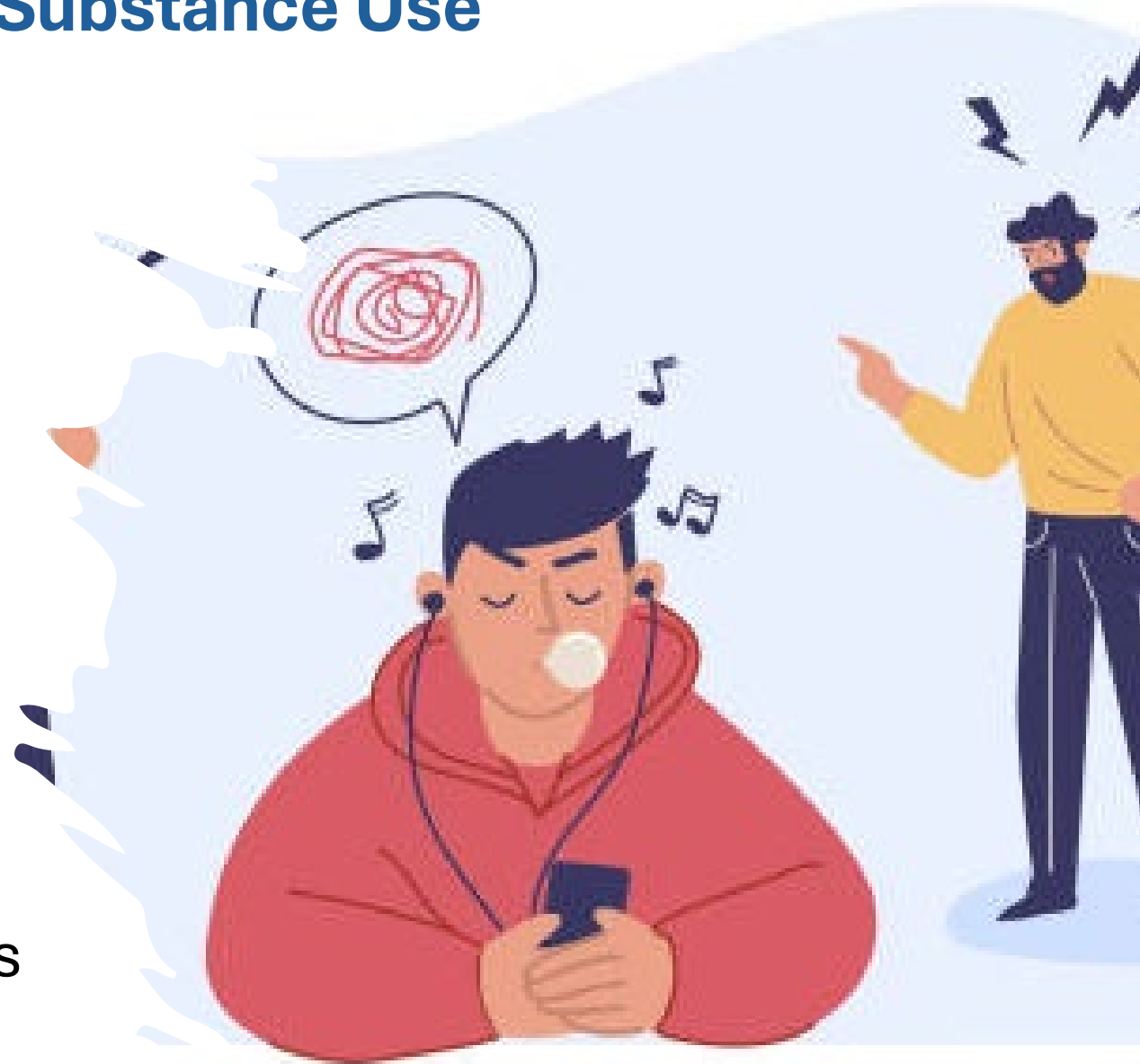


Changes in the Past 3-Year Prevalence of Cannabis Use Disorder (CUD), Incidence of Schizophrenia and Psychosis NOS, and the Population-Attributable Risk Fraction (PARF) Over Time. Rates standardized for age and sex using the 2022 population. Shaded regions indicate 95% CIs. The dashed vertical lines indicate, from left to right, the liberalization of medical and nonmedical cannabis and the legalization of nonmedical cannabis, respectively.

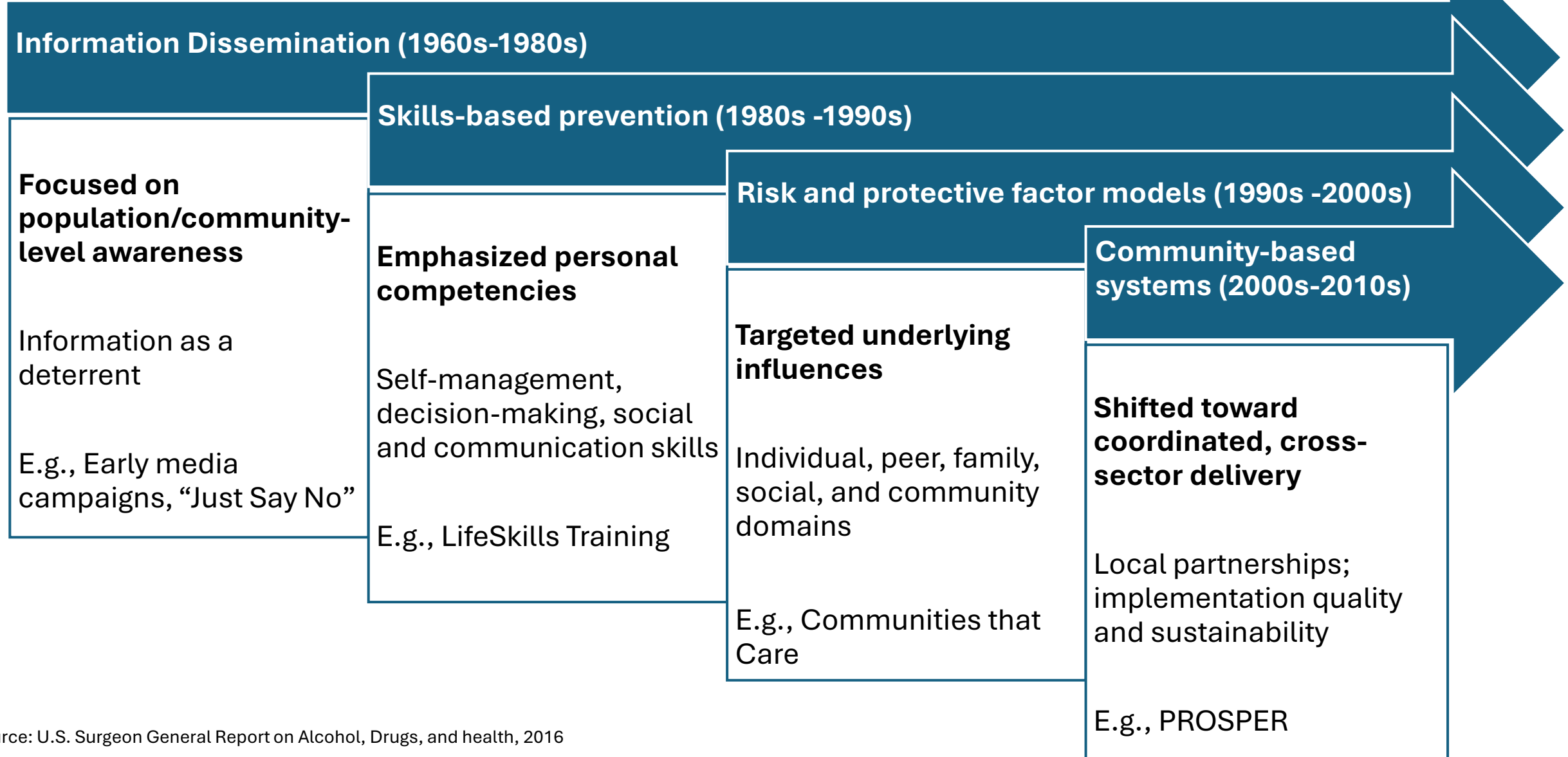
Preventing Substance Use and Substance Use Disorders Among Adolescents

Predictive Factors for Adolescent Substance Use

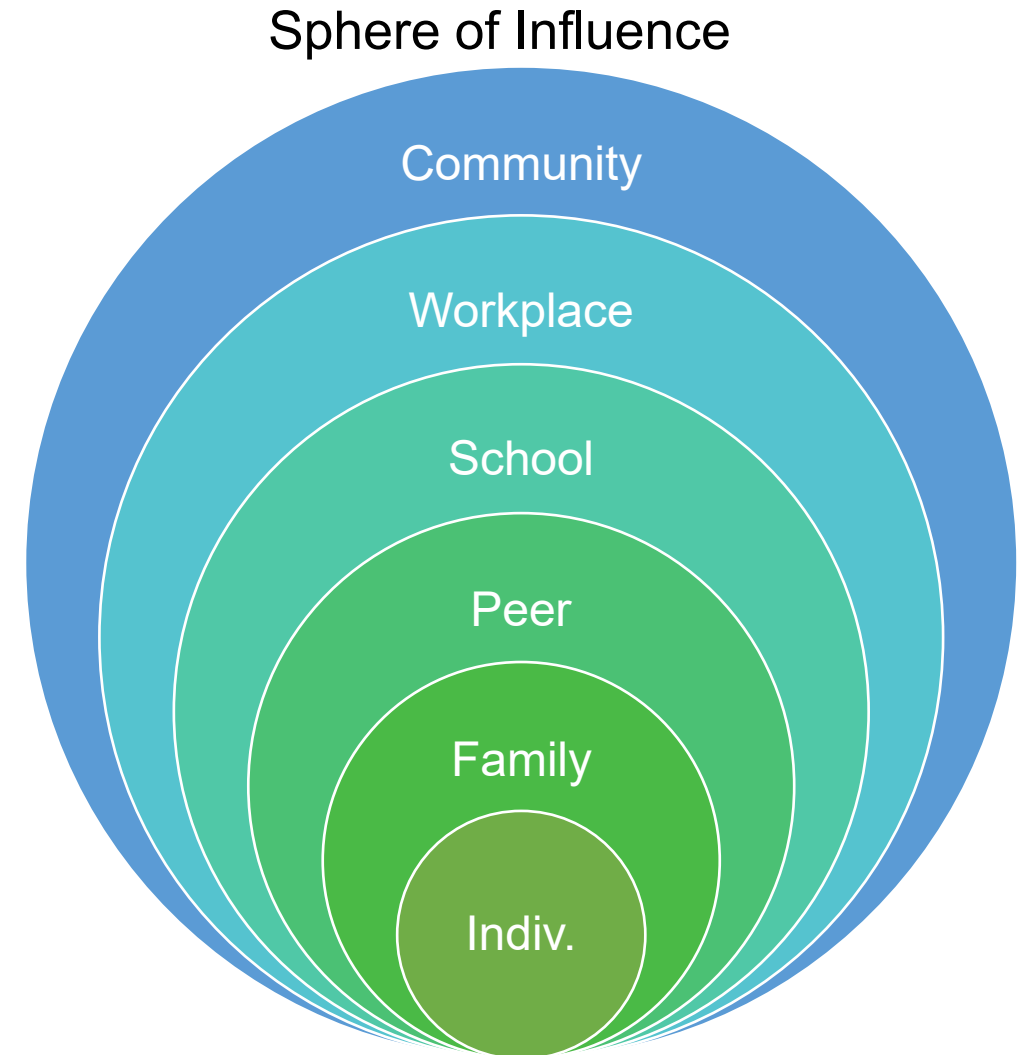
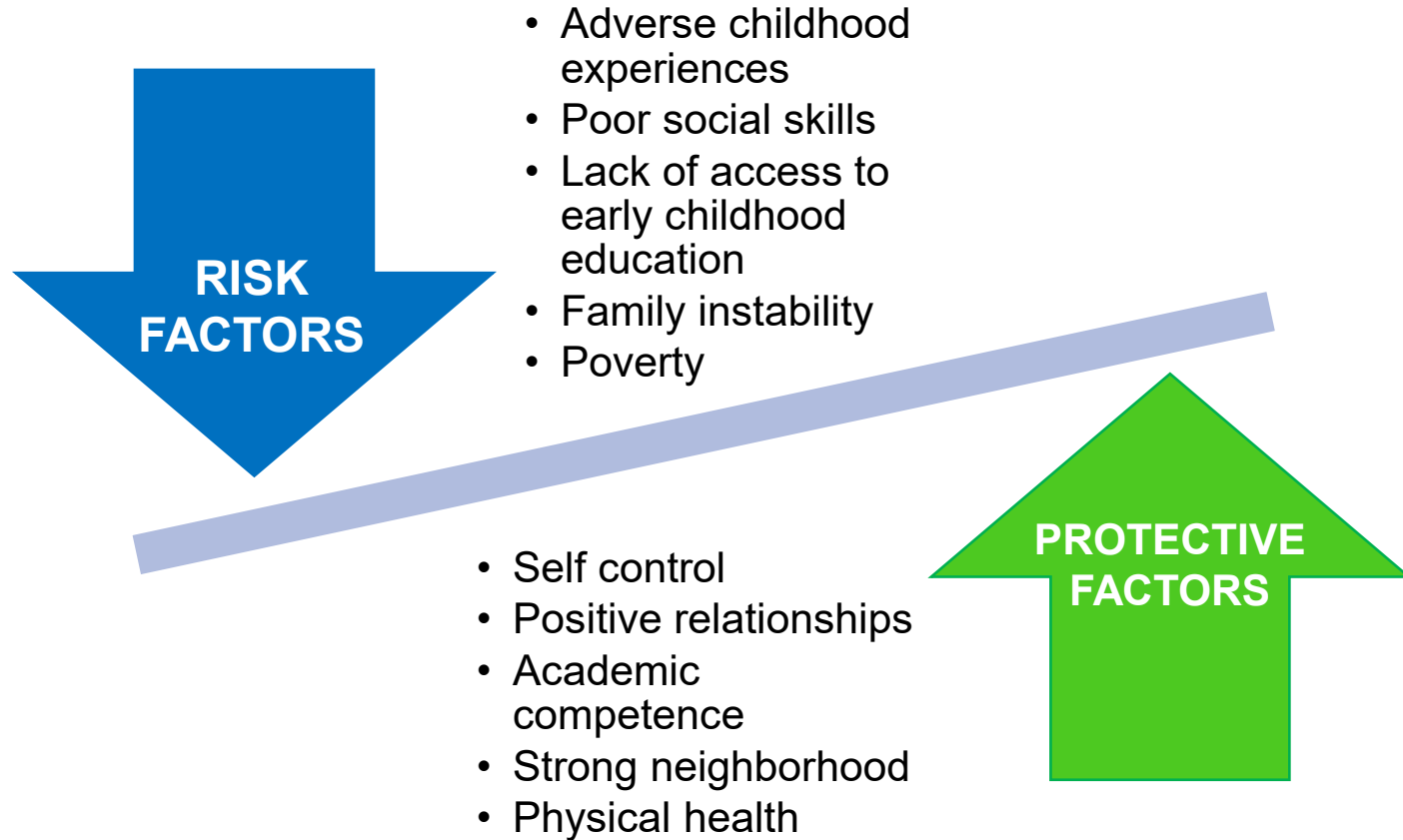
- Adverse childhood experiences
- Family and environmental stress
- Peer use, approval, bullying
- Positive expectations about the effects of substances
- Neurocognitive factors, impulsivity, externalizing problems



Evolution of Substance Use Prevention: Adding Strategies, Targets, and Levels of Impact

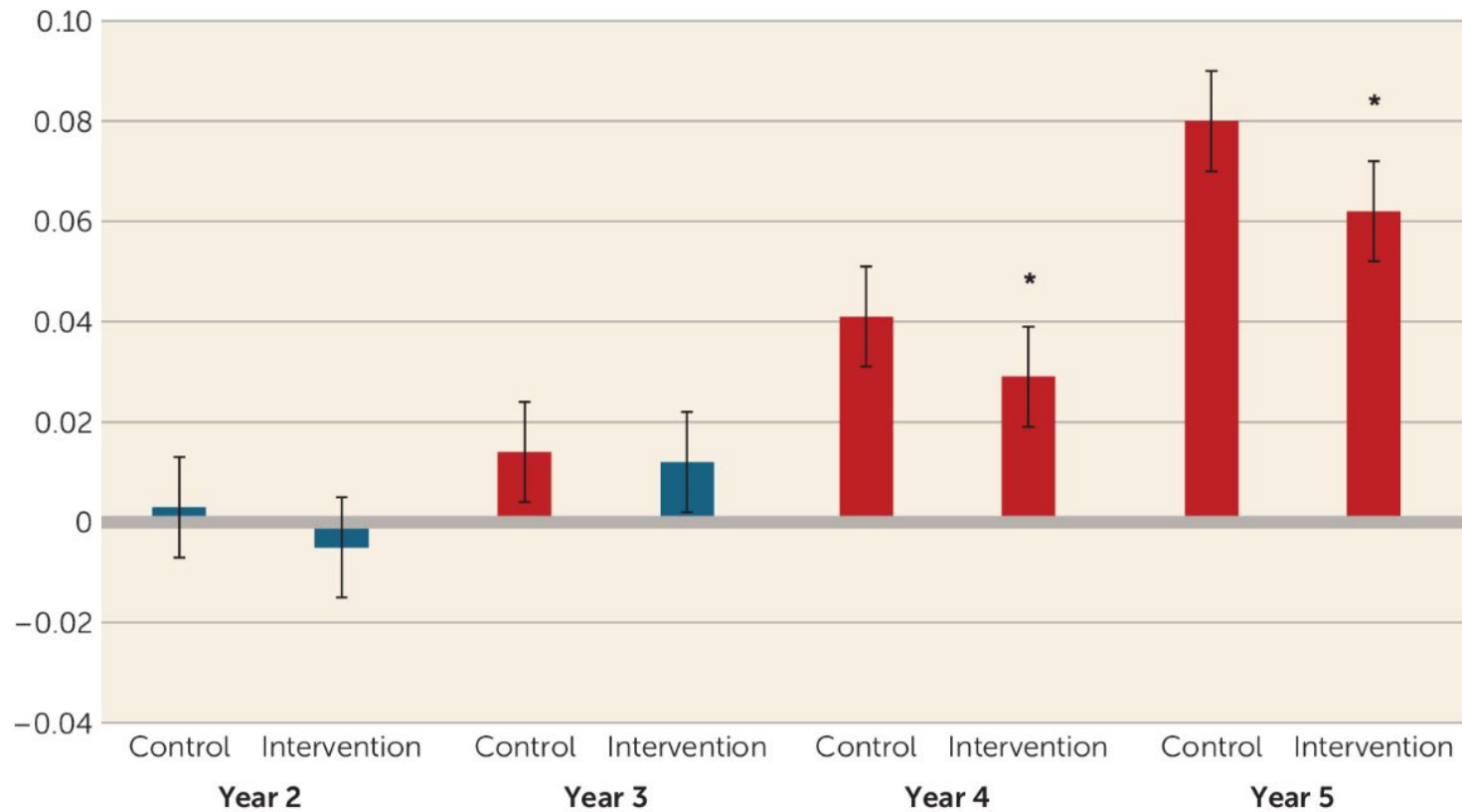


Modern Prevention: Integrating Decades of Evidence



Personality-Focused Intervention Decreased Odds of Substance Use Disorders Among Adolescents

Simple Contrast Estimates Comparing Probability of SUD at Each Year Relative to Baseline

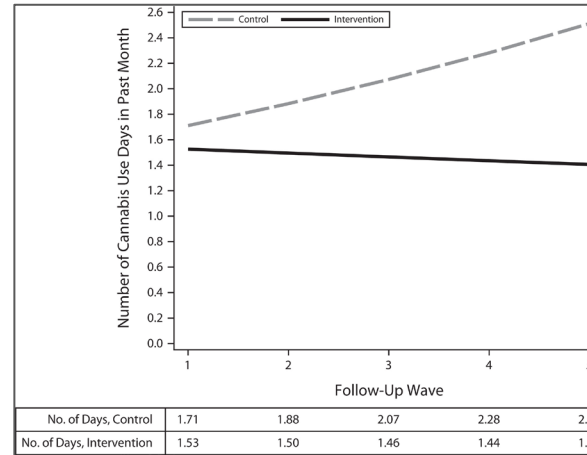


- 7th grade students participated in two 90-min small-group CBT sessions led by a school counselor.
- Focused on personality-specific skills and self-efficacy to strengthen coping strategies.
- Intervention group showed significantly lower increases in odds of SUD vs. control.

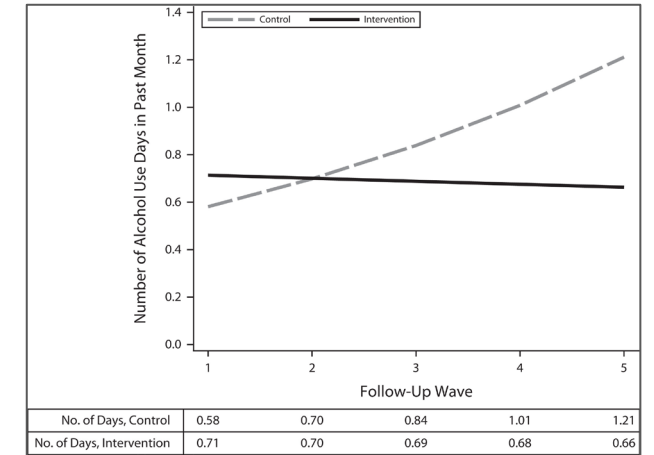
Combined School and Family Intervention Lowered Expected Increases in Adolescent Substance Use

- Rural/tribal students received 15-minute computerized motivational interviewing (MI) + family intervention to strengthen relationships, health, and wellbeing.
- Delivered up to 4 times over 2 years via an animated narrator assessing risk, providing info, and initiating MI; higher-risk students got coach follow-up.
- Family component promoted time together, guidance on substance use and mental health, and media literacy and advocacy skills.
- The combined intervention significantly reduced typical substance use escalation at ages 16-18.

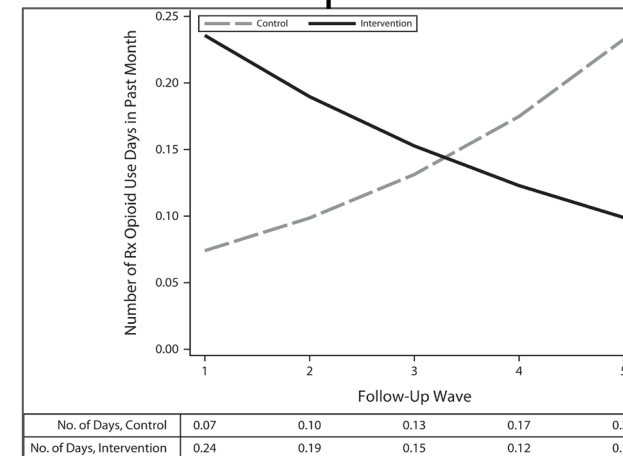
Cannabis



Alcohol



Rx Opioids



Key Takeaways

- The cannabis product landscape is rapidly evolving with higher THC potency, hemp-derived cannabinoids, and diverse routes of administration.
- Early initiation is associated with increased risk of addiction and mental disorders, including lasting psychosis.
- Cannabis use during adolescence is linked to other adverse outcomes like impaired cognition, lower motivation, and school/work problems.
- Prevention works: Targeted school- and family-based interventions can reduce adolescent substance use and SUD.