

Is Adolescent Cannabis Use a Causal Factor for Schizophrenia?

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**I have no relevant financial
relationship with a commercial
interest to disclose.**

Adolescent Cannabis Use Increases Risk for Psychosis

- Multiple, prospective epidemiologic studies
- Consistent association when cannabis use precedes psychosis, independent of confounding and intoxication
- Association of cannabis exposure with psychosis stronger:
 - Psychotic disorder vs. psychotic sx.
 - Earlier age of cannabis exposure
 - Higher potency (THC concentration) exposure
 - Frequent/daily exposure
- Association between cannabis use & psychosis significant after controlling for familial risk, SES, other drug use, urbanicity, prior psychiatric sx

Strong Dose Effect of Cannabis Exposure, Despite Extensive Control for Familial Factors in Case Control Studies

Study	Number of cases	Odds ratio	Design
DiForti 2009 / UK	280 cases first episode psychosis 174 controls (age, gender, ethnicity, education, employment)	No difference in ever use 2.1 (0.9, 8.4) > 5 yrs. use 6.4 (3.2, 28.6) Daily use 6.8 (2.6, 25.4) High THC use	Case-control Population Control
DiForti 2015 / UK	410 cases first episode psychosis 370 controls	No difference in ever use or duration of use 3.0 (1.9, 7.8) Daily use 2.9 (1.5, 3.6) High THC use 5.4 (2.8, 11.3) Daily High THC use	Case-control Population Control
Giordano 2014 / Sweden*	5456 with Schizophrenia, each matched with 5 schizophrenia free controls	10.4 (9.0, 12.1) vs. gen. pop. 5.1 (4.2, 6.2) vs. full siblings 1.98 (1.6, 2.5) vs. full siblings with 7 years between MJ use and	Co-relative case-control with full sibling, half sibling, and 1 st cousin comparisons

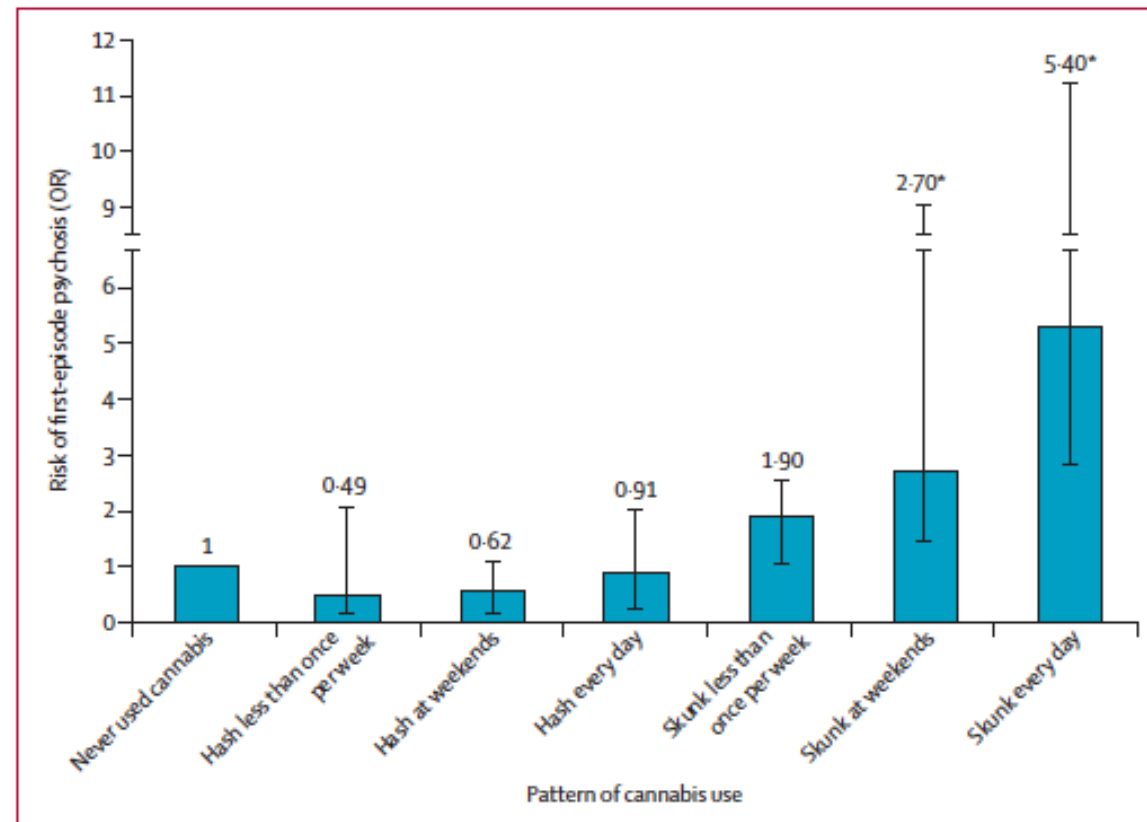
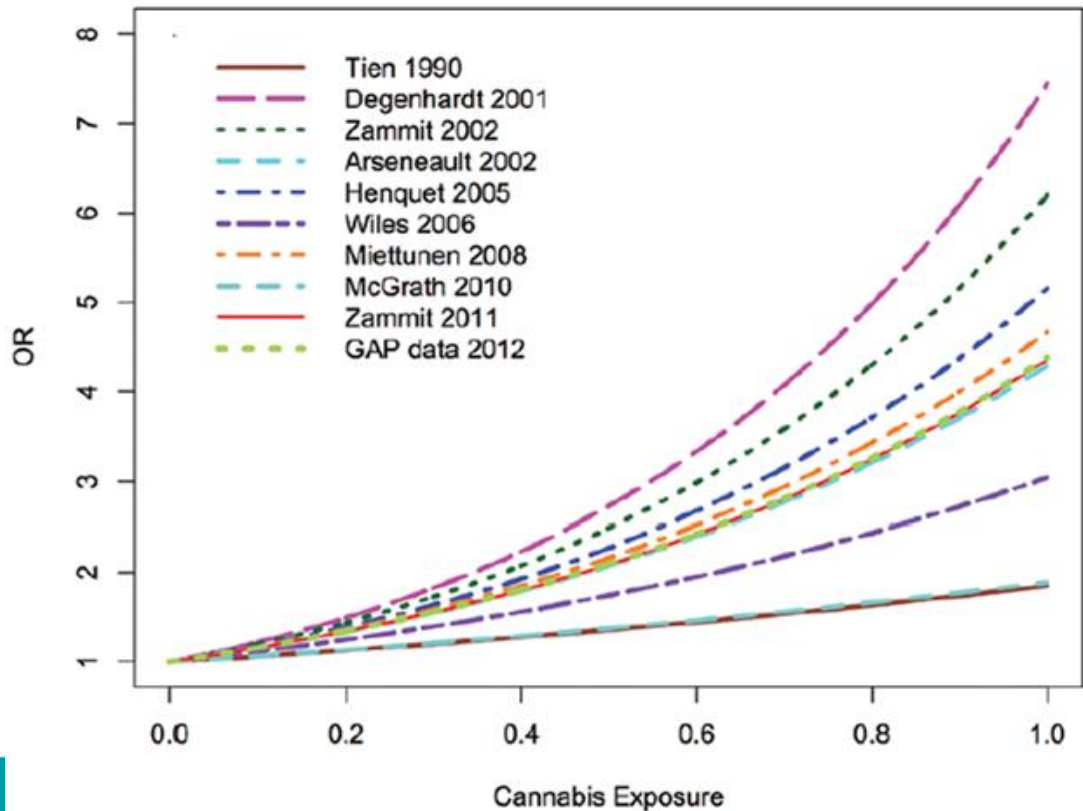
Author / Country	Subjects	Follow up	Adjusted Odds Ratio	Design
Andreasson 1987,*# Zammit 2002* / Sweden	50,053	15, 25 years	2.5 (1.2, 5) > 5 yrs bet use & dx 3.1 (1.7, 5.5) > 50x use	Conscript cohort * Schizophrenia diagnosis, dose response relationship
van Os 2002 *# / The Netherlands / NEMESIS	4,045	3 years	2.8 (1.2, 6.5) use; 1.9 (1.3-2.9) linear trend dose	Population based * ORs higher for diagnosis vs sx # dose response relationship
Weiser 2002 * / Israel	9,724	4-15 years	2.0 (1.3, 3.1)	Population based
Fergusson 2005 #@/ New Zealand Christchurch	1,055	7 years	IRR = 1.8 (1.3, 2.4) in daily users	Birth cohort , earlier exposure: increased odds psychosis
Arseneault 2002 * @ / New Zealand Dunedin	1,253	15 years	3.1 (0.7, 13.3) OR > 11 use >15	Birth cohort , * schizophreniform dx age 26
Miettunen 2008 # / Finland	6,330	14 years	2.2 (1.7, 2.9) ever vs never	Population based, outcome is 3+ prodromal sx
Henquet 2005 # / Germany	2,437	4 years	1.7 (1.1, 1.5)	Population based, adjusted for predisposition for psychosis
Wiles 2006 / United Kingdom	8,580	1.5 years	1.5 (0.55, 3.94)	Population based
Moore 2007 # / Meta Analysis 11 cohorts		Adjusted ORs	2.1 (1.5, 2.8) in regular users	Henquet 2005 # Meta Analysis pooled OR = 2.1 (1.7, 2.5)
Marconi 2016 # / Meta Analysis 10 studies	66,816	Un-adjusted ORs:	2.0 (1.7, 2.3) use, 3.9 (2.8, 5.3) heavy use	OR: 5.1 (2.8, 5.3) for ICD or DSM Dx of schizophrenia, schizophreniform disorder

Dose Effect

Odds of developing psychotic disorder
by cannabis exposure across a
standardized 'dose' score.

DiForti, 2015

Psychosis risk distribution



Estimated odds of psychosis by ranked
level of cannabis exposure vs those with
no exposure, across 10 studies. Marconi, 2016

Time Effect:

- Swedish Conscripts: Significant association despite ≥ 5 years between cannabis use onset and schizophrenia
- Christchurch: Cannabis use $\leq$ age 18 predicted psychosis at 21 & 25. Psychosis at 18 reduced odds of cannabis use at ages 21 & 25
- Swedish National Registry Co-relative Control: ORs of 3.3 and 1.6 with 3 and 7 year delays between cannabis use and schizophrenia

Cannabis use consistently predates psychotic disorder.

But schizophrenia is a neurodevelopmental disorder, with prodrome characterized by non-specific symptoms that can present long before psychotic symptoms present or diagnostic criteria are met.

Does Genetic Risk for Psychosis Confer Risk for MJ Use?

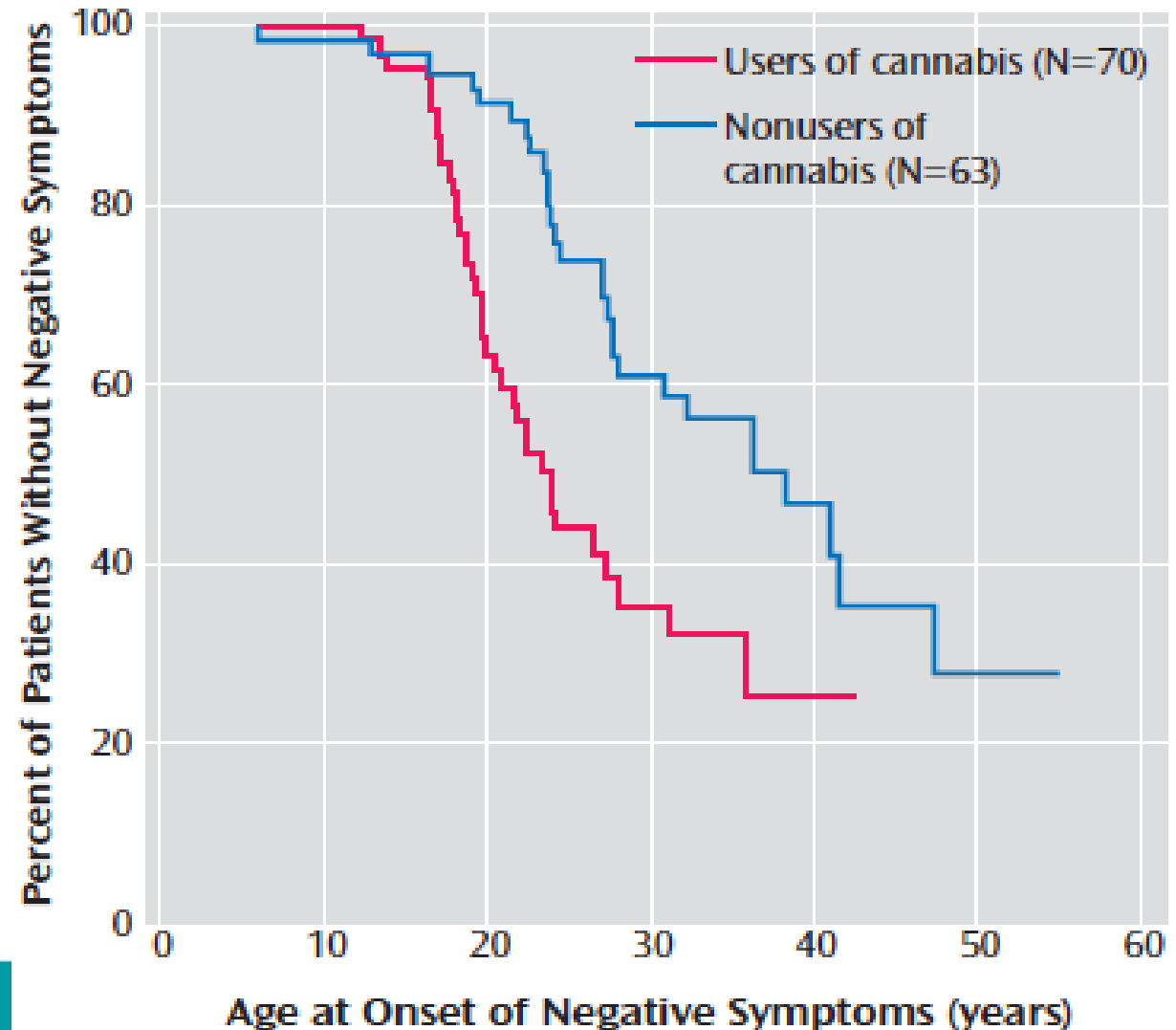
- PRS for psychosis calculated from the Psychiatric Genomics Consortium GWAS divided the sample (410 FEP cases, 370 controls) by genetic risk for schizophrenia
 - No difference in genetic load for schizophrenia between cannabis users and non-users or high vs lower THC potency cannabis use.
- Association between schizophrenia PRS and cannabis, ever use and by dose, tested in 2082 healthy individuals.
 - Schizophrenia PRS predicted a fraction of the variance in cannabis use.
 - Concluded part of the association between schizophrenia and MJ due to shared genetic etiology - a gene environment correlation.

DiForti et al., *Lancet* 2015; Power et al., *Mol Psych.* 2014

Association with Earlier Onset

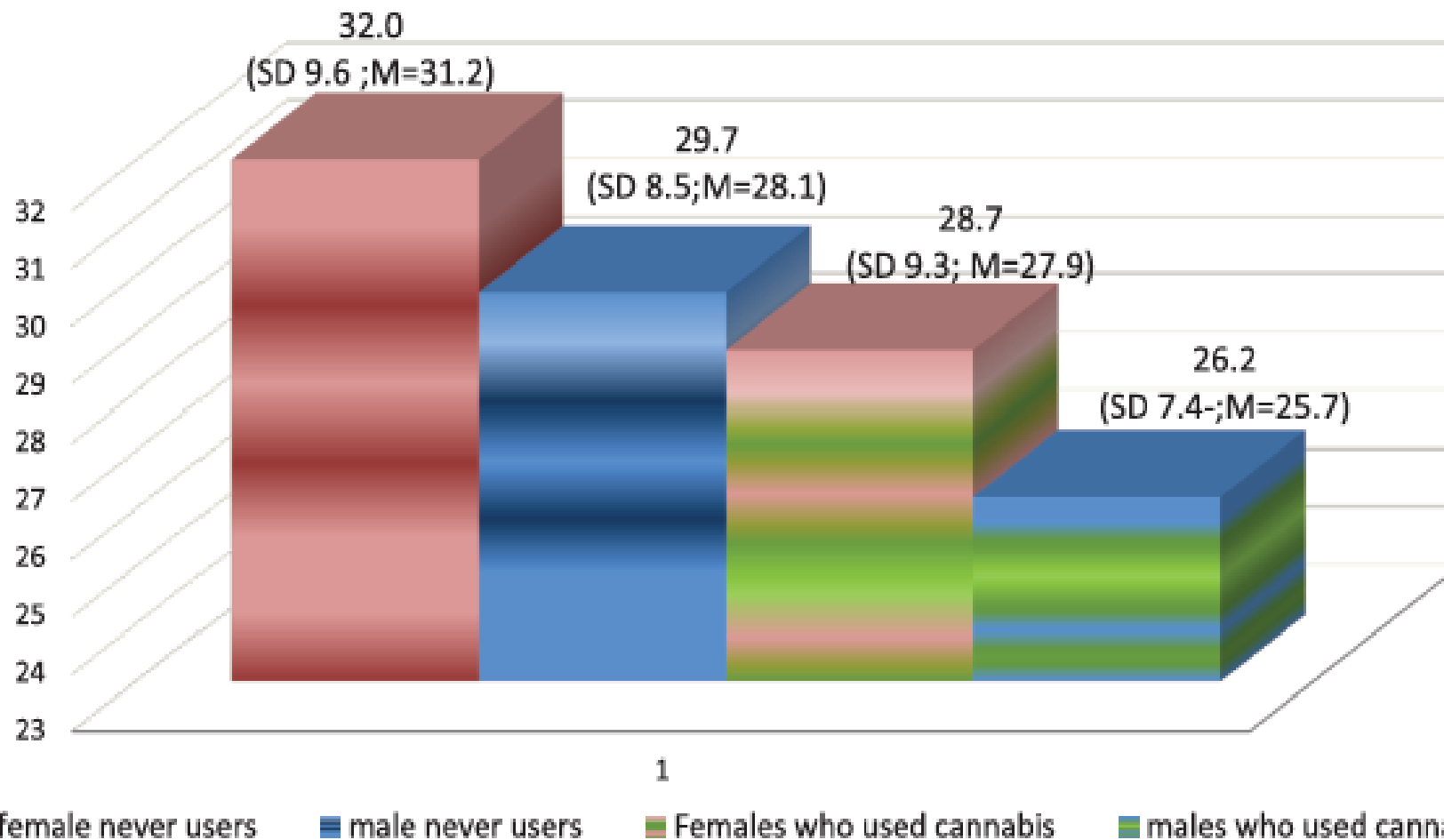
Negative Symptoms of Schizophrenia

Cannabis use associated
with earlier onset of
prodrome,
psychotic sx,
negative sx
and
1st episode
schizophrenia Dx.

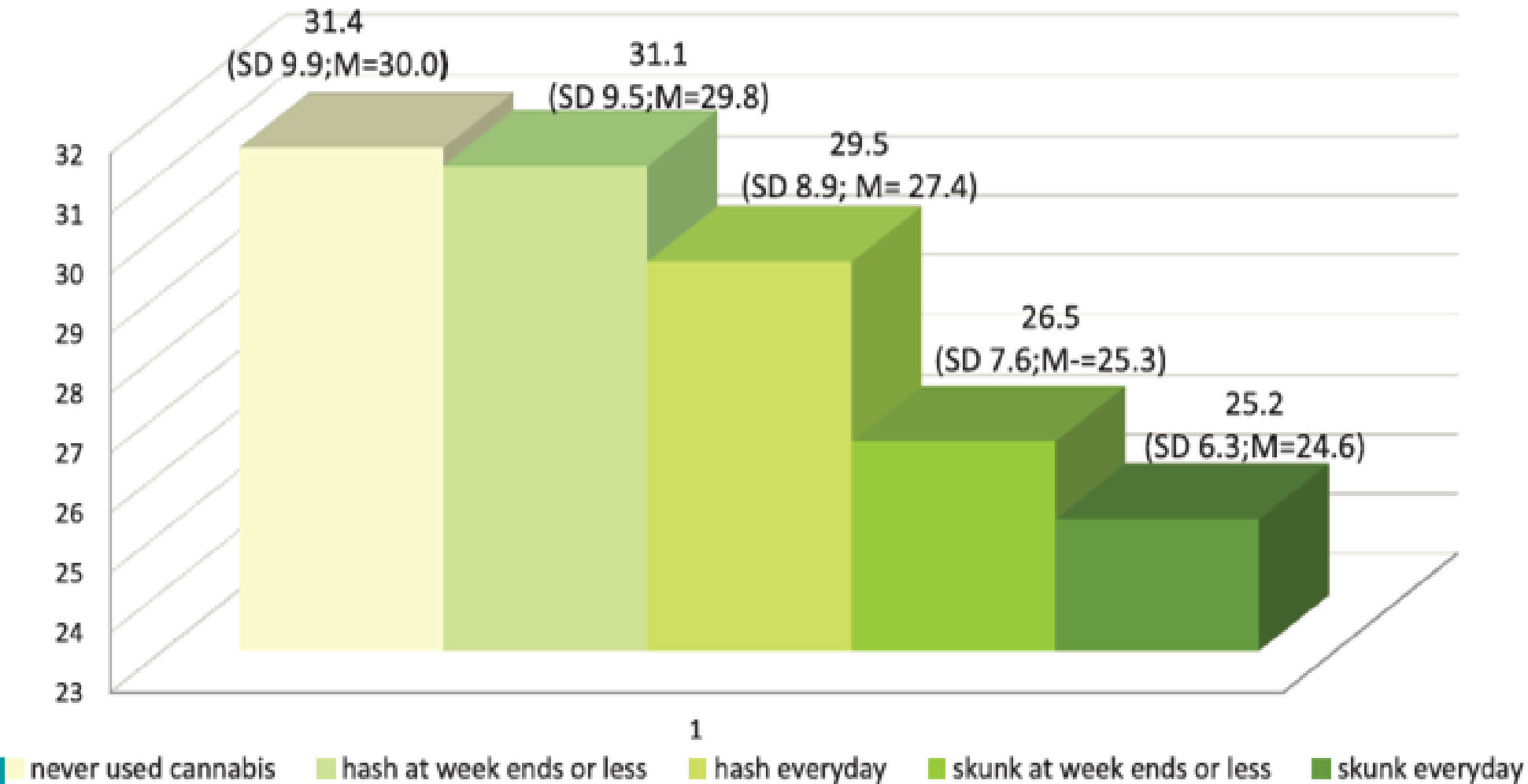


Cannabis Use Associated with Earlier Onset First Episode Schizophrenia

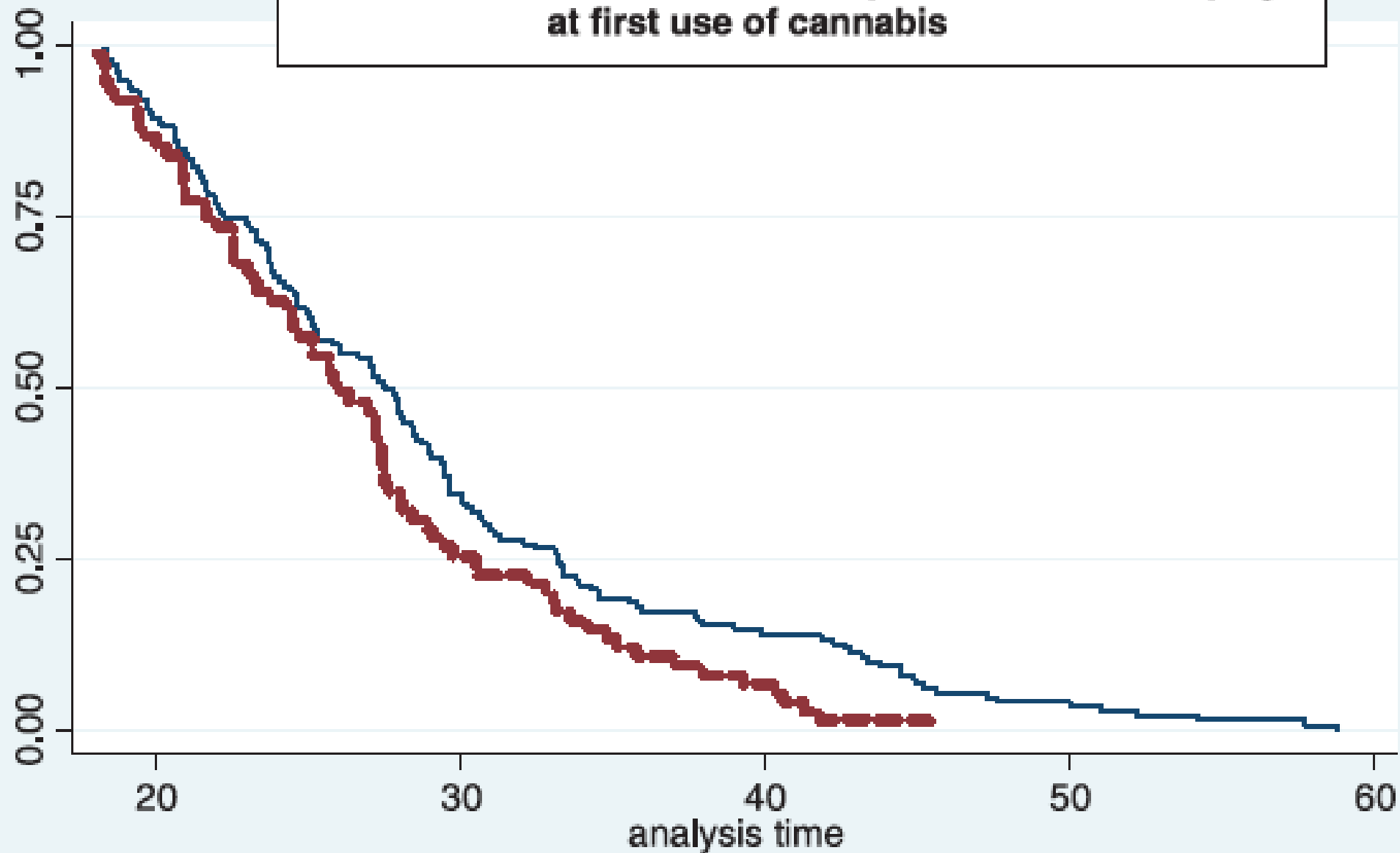
Mean age (yrs) of onset of psychosis by
history of cannabis and gender



Mean Age of Psychosis Onset by Cannabis Exposure Frequency and Potency



Differences Rates of onset of Psychotic disorders by age at first use of cannabis



— age at 1st use >15 yrs - - - - - age at 1st use <= 15yrs

Premorbid Cannabis Use:

Males with schizophrenia
with vs. without cannabis use before age 18-20
followed for 21 years had:

- Median duration first hospitalization: (59 vs. 30 days)
- Median number of hospitalizations: (10 vs. 4)
- Total hospital days: (547 vs. 184)
- Odds of >20 hospitalizations: OR=3.1 (1.3–7.3)
- Odds of hospital stay >2 years: OR=2.4 (1.1–7.4)

Controlling for personality disorder, family SES, IQ, marital status, urban residence,
risky alcohol and other drug use

Implications for Clinical Practice

- Cannabis use likely **component cause** that interacts with other factors to cause psychotic disorders.
 - As such, it is a preventable risk factor for schizophrenia.
- Prevention, early identification, and treatment of cannabis use could potentially delay onset of psychotic illness in those at high-risk
 - Age of onset of psychosis is a key prognostic factor in schizophrenia.
- First Episode Programs in U.S. actively advise siblings of those with first episode schizophrenia against cannabis use.

Schizophrenia Commission 2012; Compton et al., Am J Psych 2009; Personal communication, Yale First Episode Program

Schizophrenia Etiology is Multifactorial

Development Period	Contextual Risks		
		Family	Neighborhood
Preconception/prenatal	Genetic predisposition Second-generation immigrant Problems during pregnancy (diabetes and bleeding) Problems with fetal growth and development Maternal stress during pregnancy (such as spousal death) Maternal infection or flu exposure during pregnancy Hypoxia-related delivery complications Male gender	Parental diagnosis of schizophrenia	Urban setting Low socioeconomic status
Infancy	Head injury		Urban setting Social adversity
Early childhood	Head injury Motor, language, and cognitive impairments	Family dysfunction	Urban setting Social adversity
Middle childhood	Head injury Self-reported psychotic symptoms	Family dysfunction	Urban setting Social adversity
Adolescence	Head injury Cannabis use	Family dysfunction	Urban setting Social adversity
Young adulthood	Head injury	Family dysfunction	Social adversity

Gene-environment interactions may account for inter-individual variability in effects of cannabis exposure. Most who use cannabis do not develop schizophrenia. Cannabis increases risk of schizophrenia approx 2-fold, accounting for 8-14% of cases/ 24% for high THC content cannabis in areas where its use is common.

What We Know:

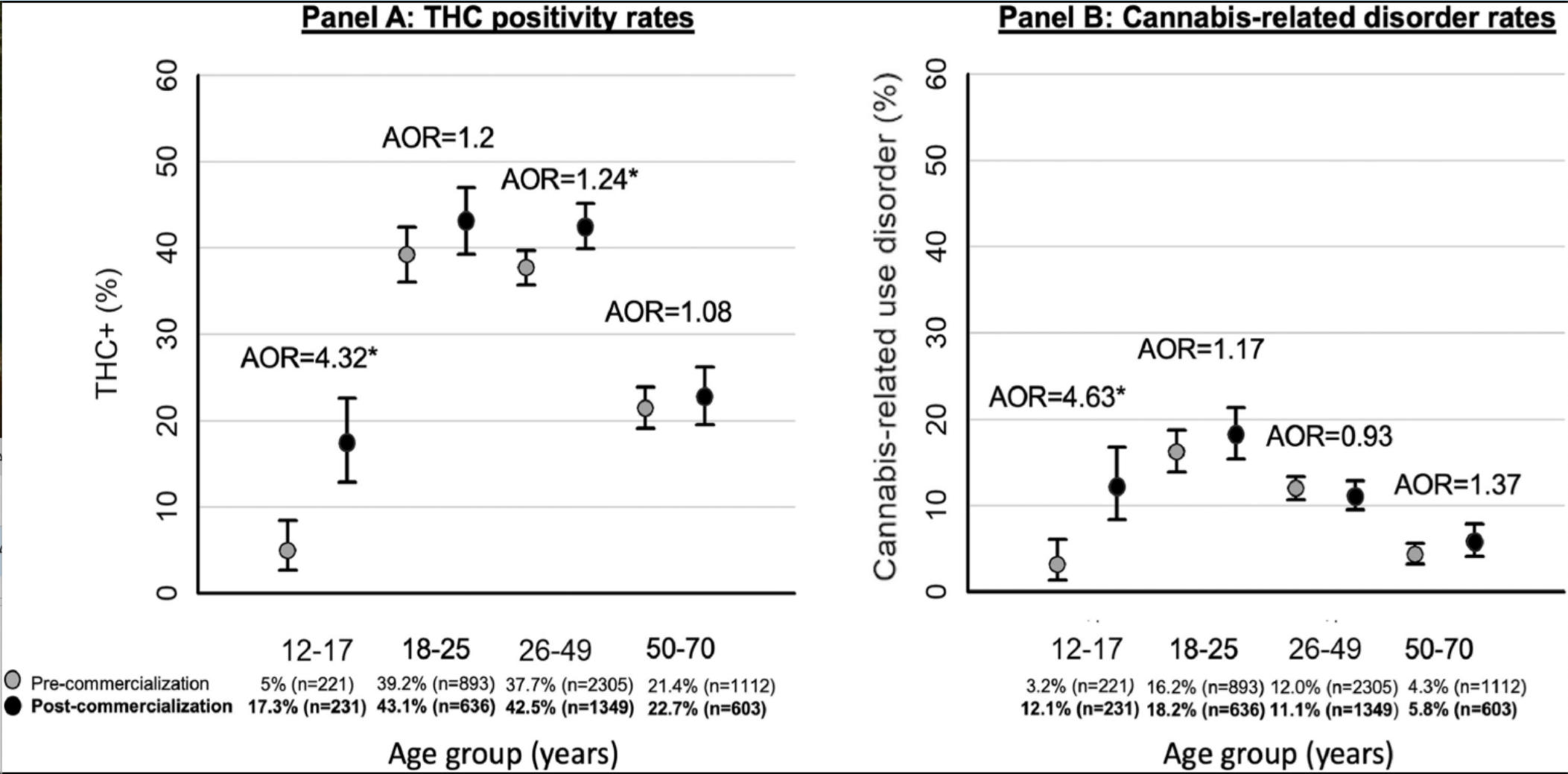
There is an association between cannabinoid exposure and psychotic outcomes, including development of schizophrenia.

- Association between cannabis exposure and psychotic outcomes in epi, experimental, and animal studies has major dose and developmental stage of exposure effects.
- Inter-individual variability in this effect.
- Gene exposure interactions may moderate risk for cannabis induced psychosis.
- Reducing exposure at critical periods may reduce incidence and severity, and/or delay onset of psychotic outcomes.

The nature of the association between cannabis use and the development of schizophrenia - including who is at risk - is not known.

- Factors that moderate the impact of cannabinoid exposure on risk for psychosis. Need longitudinal studies.
- Molecular / neurophysiologic mechanisms underlying cannabinoid effects on adolescent brain.
- Clarify effect of cannabinoids on neurodevelopmental processes and brain structures relevant to psychotic disorders.
- In those at risk, are there identifiable protective factors that make those exposed to cannabis less likely to develop psychosis / schizophrenia?
- Is there a physiologic basis for the observation that many with schizophrenia regularly use cannabis?

Increased THC Positivity and CUD Dx in Youth Presenting to Psychiatric ED After Cannabis Commercialization in MA



Disproportionate Impact on Adolescents

Foo, et al., 2025 *Am J Prev Med*

Cannabis Use Among Individuals With Psychosis After State-Level Commercial Cannabis Legalization

Andrew S. Hyatt, MD; Michael William Flores, PhD, MPH; Julie Johnson, PhD; Danta Bien-Aime, BA; A. Eden Evins, MD, MPH; Dost Öngür, MD, PhD; Benjamin Lê Cook, PhD, MPH

- 1856 US adults ≥ 18 years with lifetime psychosis, PATH 2014-2022, 7465 responses
- People with lifetime psychosis in states with commercial cannabis increased current cannabis use by 9.5 percentage points; $P = 0.004$
- Sensitivity analyses: significant effect after retail outlets opened, not before
- Biggest effect 5 years post legalization, coinciding with market maturity

Regulatory Landscape of Cannabis Warning Labels in US States with Legal Retail Nonmedical Cannabis, 2024

 Caroline J. Meek, MPH, Leah M. Ranney, PhD, MA, Sonia A. Clark, MHA, Kristen L. Jarman, MSPH, Rachel Callanan, JD, MNM,
and Sarah D. Kowitt, PhD, MPH

- Cannabis commercialization increased exposure to advertising with cannabis-related mental health claims.
- Few states require warnings about mental health harms.
 - Only 2 states require warnings about the link between cannabis and psychosis.
- Mitigation strategies for public health impacts of cannabis commercialization,
 - Health warnings for those with family or personal history of psychosis on cannabis packaging
 - Require evidence for mental health–related claims for cannabis product advertising.
 - THC potency caps
 - Taxation by potency rather than weight

- **Warning:** Frequent and prolonged use of cannabis can contribute to mental health problems over time, including anxiety, depression, stunted brain development and impaired memory. **2 states - 10%**

Regulatory Landscape of Cannabis Warning Labels in US States with Legal Retail Nonmedical Cannabis, 2024

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- Warning: This is a high potency product and may increase your risk for psychosis. **2 states - 10%**
- Text must be no smaller than size 6 font, bolded, legible, unobscured, and visible to the customer. **13 states - 65%**
- Use by pregnant or breastfeeding women or by women planning to become pregnant or breastfeeding may result in fetal injury, preterm birth, low birth weight, or developmental problems for the child. **13 states - 65%**
- Marijuana impairs concentration, coordination, and judgment. Do not operate a vehicle or machinery under its influence. **17 states - 85%**