Cannabis Use and Association with Risk for Mental Illness

Ken Winters, Ph.D.
Senior Scientist
Oregon Research Institute (MN location)

&

Consultant, National American Indian & Alaska Native Technology Transfer Center

winte001@umn.edu

for

Center for Practice Transformation
December 10, 2021

Professional Disclosure

- I am a member of Smart Approaches to Marijuana Minnesota (www.SAMMn.org).

- SAMMn's Mission: To educate Minnesotans on the science of cannabis use relevant to health and social issues.

  The public health position is that the current science does not support the commercialization and normalization of recreational cannabis use.

Personal Disclosure: Favorite Hobby

Favorite Band

Guilty Pleasure

1. Extent and Nature of Association

2. Why THC Impacts Mental Health

3. Youth Vulnerability

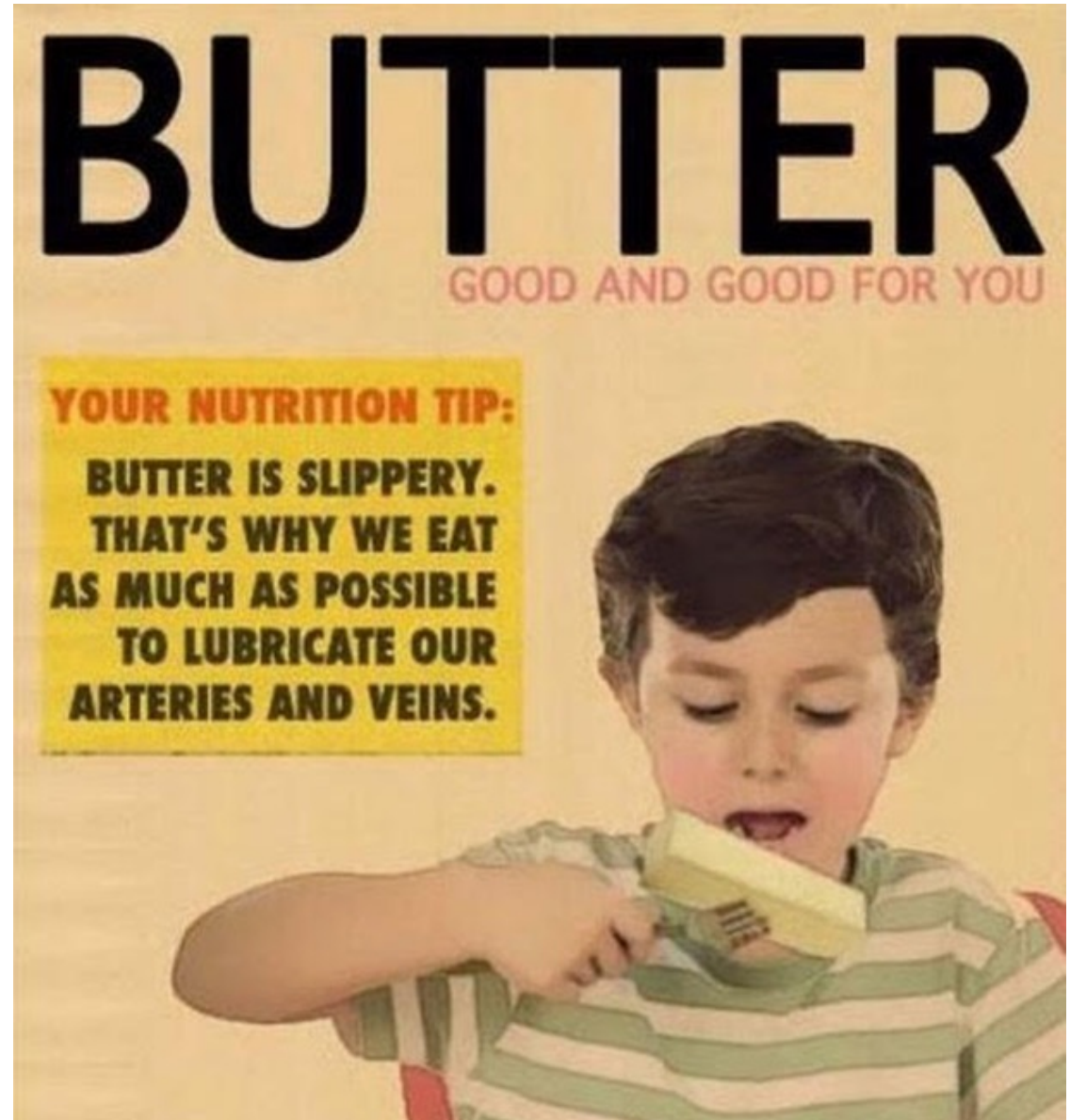
4. Is Cannabis Medicine For Mental Illness?

5. Summary

1. Introductory Comments

- **How to approach the question of *Does cannabis use cause mental illness*?**
  - **demonstrating that THC may or may not cause mental illness is a complicated topic**
    - **partially cause?**
    - **contributor only when risk is present?**
    - **contributor if "no risk"?**
    - **if yes to any above...in what ways? what are the moderators?**
  - **no perfect study is possible**
    - **researching complex public health questions is the process of looking for convergence or non-convergence of findings from animal, laboratory, epidemiological surveys, community- and individual-level cross-sectional studies, and longitudinal studies**
    - **context: our understanding that 'smoking causes cancer' was based on the convergence of numerous lines of evidence that took decades to occur; the general public did not think smoking was harmful for an extended period**

The Public Can be Misled When Other Interests Advance Self-Interested Messages

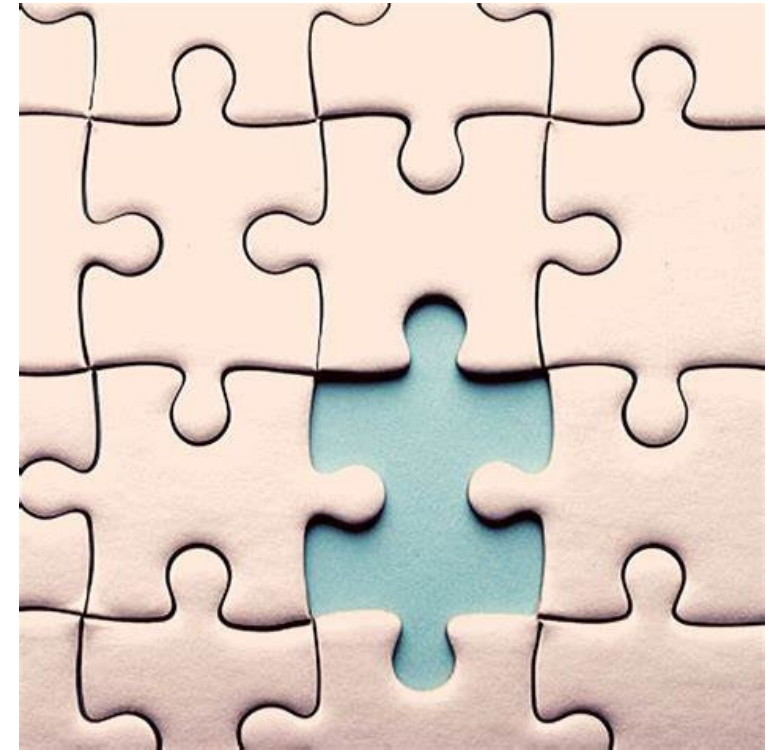


2. Introductory Comments

- **Most of the research cited refers to mental illness defined by diagnostic categories**
  - **strengths**
    - **helps communication**
    - **some research support for the validity of this approach**
  - **weaknesses**
    - **overlap between symptoms can make diagnosis tricky**
    - **the “presence” vs “absence” perspective belies the continuum of symptom severity**
    - **can lead to labeling and stigma, which can be a barrier to seeking services**

3. Introductory Comments

- **Also, most of the research cited is based on white samples; stay tuned for how findings may differ or not among racial/ethnic samples**



4. Introductory Comments

Clinical Review & Education

Review

Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review

Nora D. Volkow, MD; James M. Swanson, PhD; A. Eden Evins, MD; Lynn E. DeLisi, MD; Madeline H. Meier, PhD; Raul Gonzalez, PhD; Michael A. P. Bloomfield, MRCPsych; H. Valerie Curran, PhD; Ruben Baler, PhD

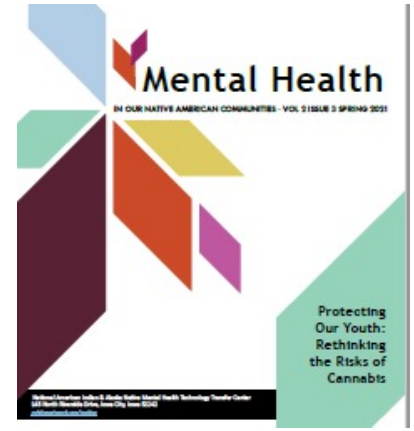
"The changing landscape of cannabis (e.g., strains with THC potency; new routes of administration; novel drug combinations), and a culture of rapidly changing norms and perceptions, raise the possibility that our current, limited knowledge may only apply to the ways the drug was used in the past."

5. Introductory Comments

- **Free resources**

i. https://www.drugabuse.gov/publications/research-reports/marijuana/there-link-between-marijuana-use-psychiatric-disorders

ii. https://www.nativecenter.org/



Introductory Comments

- **Free resources**

iii. https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-06-01-001.pdf

1. Extent and Nature of Association

2. Why THC Impacts Mental Health

3. Youth Vulnerability

4. Is Cannabis Medicine For Mental Illness?

5. Summary

Five Recent Literature Summaries of the Health Effects of Cannabis Use That Included Behavioral and Mental Disorders

Eight Adverse Health Effects of Chronic Cannabis Use (Volkow et al., 2014)

2014

The NEW ENGLAND JOURNAL of MEDICINE

- "Low Level of Confidence"
  - Lung cancer
- "Medium Level of Confidence"
  - Increased risk of schizophrenia, depression and anxiety disorders (in persons with a predisposition to such disorders)
  - Altered brain development
  - Progression to use of other drugs
- "High Level of Confidence"
  - Addiction
  - Motor vehicle accidents
  - Diminished life achievement (including cognitive impairment and poor educational outcome)
  - Symptoms of chronic bronchitis

National Academies of Sciences, Engineering, and Medicine.
The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.

2017

Substantial/moderate evidence that cannabis is associated with these adverse health effects:

- development of schizophrenia or other psychoses; highest risk among heavy users
- increased risk of motor vehicle crashes
- increased risk for lung cancer
- lower birth weight of the offspring (maternal cannabis smoking)
- cognitive impairments (acute effects)
- development of problem cannabis use when early onset of use

2018

Miller's Review of the Cannabis and Mental Health Connection

Disorder	Cross-Sectional Data	Longitudinal Data
Schizophrenia	++	++
Bipolar	+	
Anxiety Disorders	+	+
Depressive Disorders	+	+
Risk of Suicide	+	

Key: ++ = several studies; + = a few studies

Miller, C. L. (2018). The impact of marijuana on mental health. In K. Sabet & K.C. Winters, *Contemporary health issues on marijuana.* NY: Oxford University Press.

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
CLINICAL ISSUES: SUBSTANCE USE DISORDERS AND THE BODY
doi:10.1111/add.14776

Heavy cannabis use, dependence and the brain: a clinical perspective

Emese Kroon[1,2], Lauren Kuhns[1,2], Eva Hoch[3,4] & Janna Cousijn[1,2]

Neuroscience of Addiction Lab, Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands,[1] The Amsterdam Brain and Cognition Center (ABC), University of Amsterdam, Amsterdam, the Netherlands,[2] Cannabinoid Research and Treatment Group, Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilan University, Munich, Germany[3] and Division of Clinical Psychology and Psychological Treatment, Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany[4]

2020

- **Although causality is unclear, heavy and dependent cannabis use is consistently associated with a high prevalence of psychiatric disorders**

- **Potential moderators of the impact of cannabis:**
  - **age of onset**
  - **THC potency used**

Lower-Risk Cannabis Use Guidelines (Fischer et al., 2021)


International Journal of Drug Policy xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Drug Policy

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

Review

Lower-Risk Cannabis Use Guidelines (LRCUG) for reducing health harms from non-medical cannabis use: A comprehensive evidence and recommendations update

Benedikt Fischer[a,b,c,*], Tessa Robinson[b,d], Chris Bullen[b,e], Valerie Curran[f,g], Didier Jutras-Aswad[b,h], María Elena Medina-Mora[i,k], Rosalie Liccardo Pacula[l], Jürgen Rehm[m,n], Robin Room[o,p], Wim van den Brink[q,r], Wayne Hall[s,t]

2021

General Precaution A: People who use cannabis (PWUC) need to know that there is no universally safe level of cannabis use; thus, the only reliable way to avoid any risk for harm from using cannabis is to abstain from its use.
Evidence Grade: Conclusive

Recommendation #1: The initiation of cannabis use should be delayed until after late adolescence, or the completion of puberty, to reduce development-related vulnerabilities for harm.
Evidence Grade: Moderate

Recommendation #11: Some specific groups of people are at elevated risk for cannabis use-related health problems because of biological pre-dispositions or co-morbidities. They should accordingly (and possibly on medical advice as required) avoid or adjust their cannabis use.
Evidence Grade: Moderate to Limited

Affective Disorders

JAMA Psychiatry | Original Investigation

Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood

A Systematic Review and Meta-analysis

Gabriella Gobbi, MD, PhD; Tobias Atkin, BA; Tomasz Zytynski, MD; Shouao Wang, MSc; Sorayya Askari, PhD; Jill Boruff, MLIS; Mark Ware, MD, MSc; Naomi Marmorstein, PhD; Andrea Cipriani, MD, PhD; Nandini Dendukuri, PhD; Nancy Mayo, PhD

- **Based on review of 11 longitudinal studies comprising 23,371 adolescents**
- **Compared youth cannabis users vs non-users and subsequent (young adulthood) mental health problems….**
  1. **Findings: no greater risk among cannabis users for later anxiety disorders**
  2. **Findings: greater risk among cannabis users for later...**
     - **depressive disorders: 1.3 times more likely**
     - **suicidal ideation: 1.5 times more likely**
     - **suicidal attempts: 3.5 times more likely**

Journal of Affective Disorders
Volume 281, 15 February 2021, Pages 467-475

Review article

Comorbid Cannabis Use Disorder with Major Depression and Generalized Anxiety Disorder: A Systematic Review with Meta-analysis of Nationally Representative Epidemiological Surveys

Vivian N. Onaemo [a, b], Timothy O. Fawehinmi [c], Carl D'Arcy [b, d]

- **A meta-analysis of 8 nationally representative epidemiological surveys of adults (U.S. and Australia)**
- **Separate analysis of...**
  - **co-occurring Cannabis Use Disorder (CUD) and Generalized Anxiety Disorder (GAD)**
  - **co-occurring Cannabis Use Disorder (CUD) and Major Depression (MD)**
- **Results: a three-fold increase in the risk of comorbid CUD with GAD (pooled odds ratio=2.99) and comorbid CUD with MD (pooled odds ratio= 3.22)**
- **"comorbidity of CUD with GAD and CUD with MD is pervasive in the general population"**

Suicidality and Young Adults

JAMA Network Open

Original Investigation | Psychiatry

Associations of Suicidality Trends With Cannabis Use as a Function of Sex and Depression Status

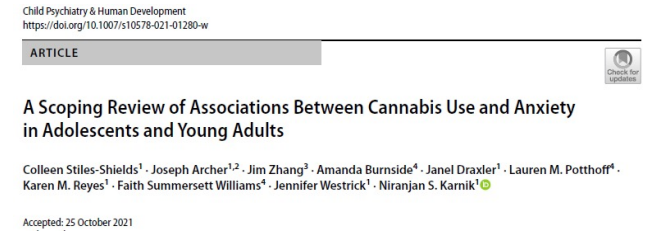
Beth Han, MD, PhD, MPH; Wilson M. Compton, MD, MPE; Emily B. Einstein, PhD; Nora D. Volkow, MD

- **The authors analyzed survey data from more than 280,000 young adults (age 18-35) and found a strong association between cannabis use and increased risks of thoughts of suicide (suicidal ideation), suicide planning, and suicide attempts.**

- **These associations remained regardless of whether someone was also experiencing depression, and the risks were greater for women than for men.**

- **"While we cannot establish that cannabis use caused the increased suicidality that we observed in this study, these associations warrant further research, especially given the great burden of suicide on young adults," said NIDA Director Nora Volkow, M.D., one of the authors of this study.**

Anxiety in Adolescents and Young Adults


Child Psychiatry & Human Development
https://doi.org/10.1007/s10578-021-01280-w

ARTICLE

A Scoping Review of Associations Between Cannabis Use and Anxiety in Adolescents and Young Adults

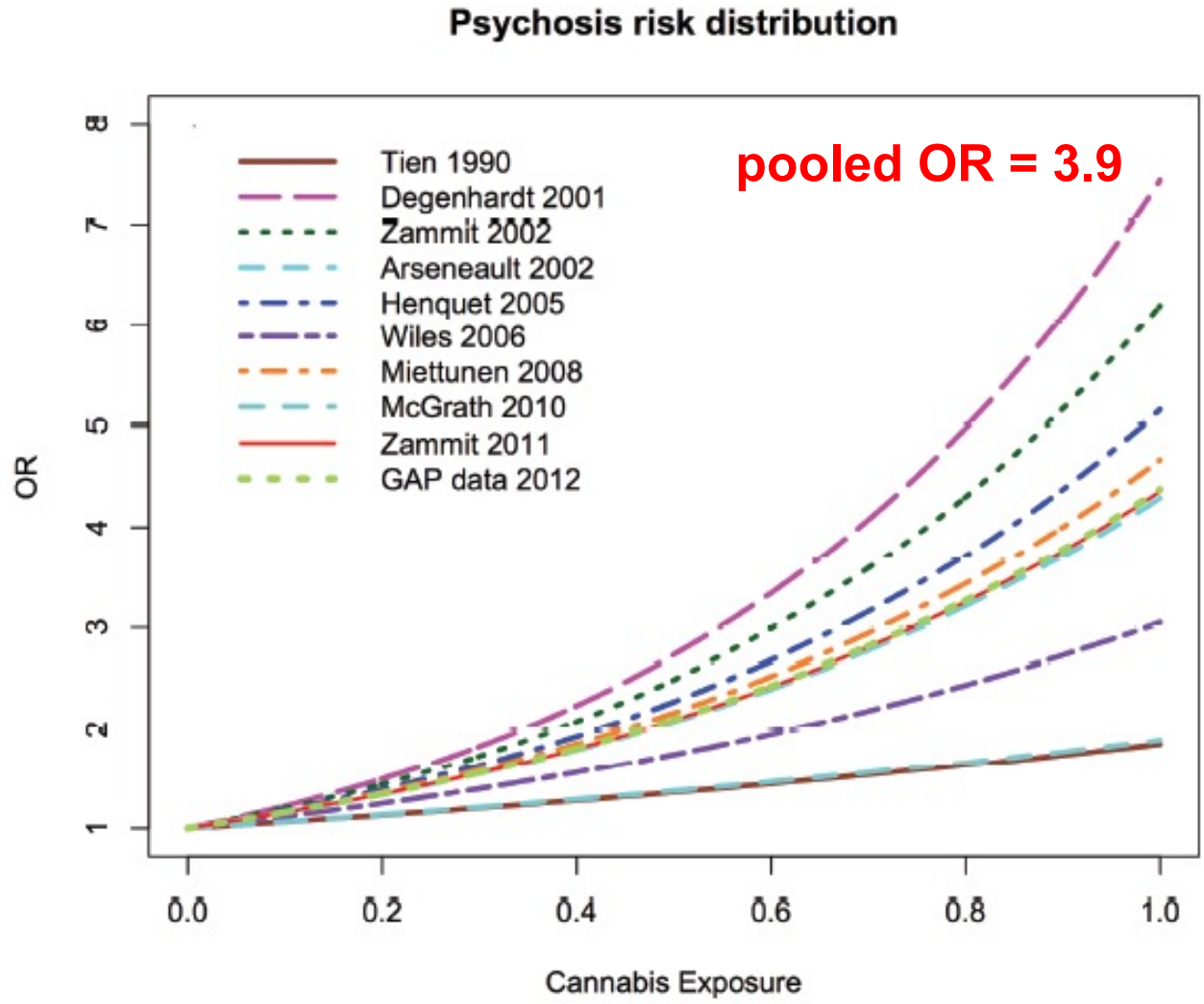
Colleen Stiles-Shields[1] · Joseph Archer[1,2] · Jim Zhang[3] · Amanda Burnside[4] · Janel Draxler[1] · Lauren M. Potthoff[4] · Karen M. Reyes[1] · Faith Summersett Williams[4] · Jennifer Westrick[1] · Niranjan S. Karnik[1]

Accepted: 25 October 2021

- **In this scoping review of the literature by Stiles-Shields and colleagues..**
  - **47 studies were identified that examined the relationship between anxiety and cannabis use among adolescents & young adults.**
  - **of these studies, 23 of them (49%) found a positive association that greater anxiety among youth was associated with greater cannabis use.**
  - **among the remaining studies, ether a negative or no association was found between anxiety and cannabis use.**
  - **“In aggregate, these findings present a mixed picture with unclear outcomes.”**

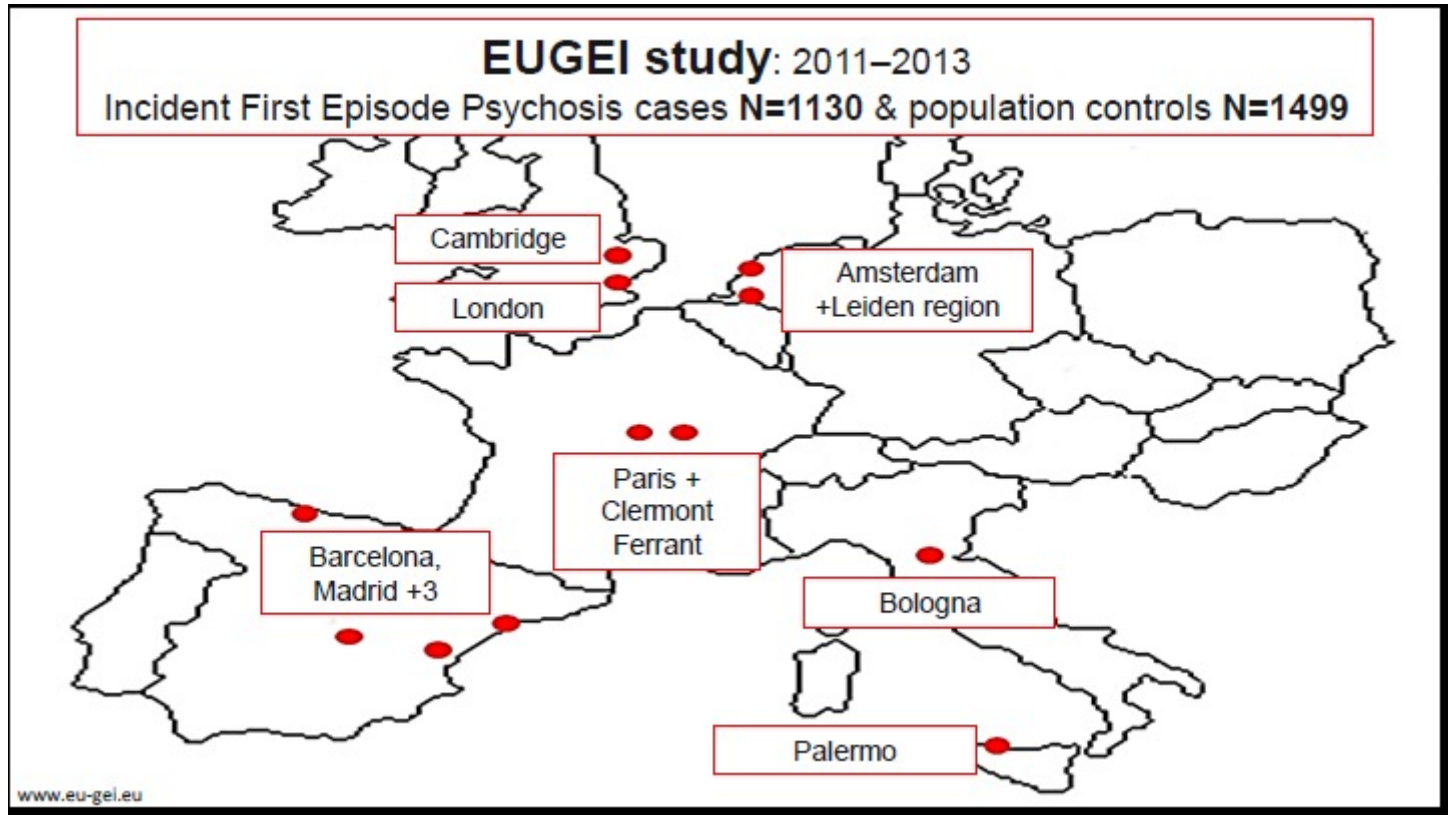
Psychotic Disorders

Meta-analysis: Estimated risk ratio of psychosis by level of cannabis use in original studies (Marconi et al., 2016)



Is there a relationship between prevalence of cannabis use in the population and the incidence rates of psychosis?

source: Di Forti



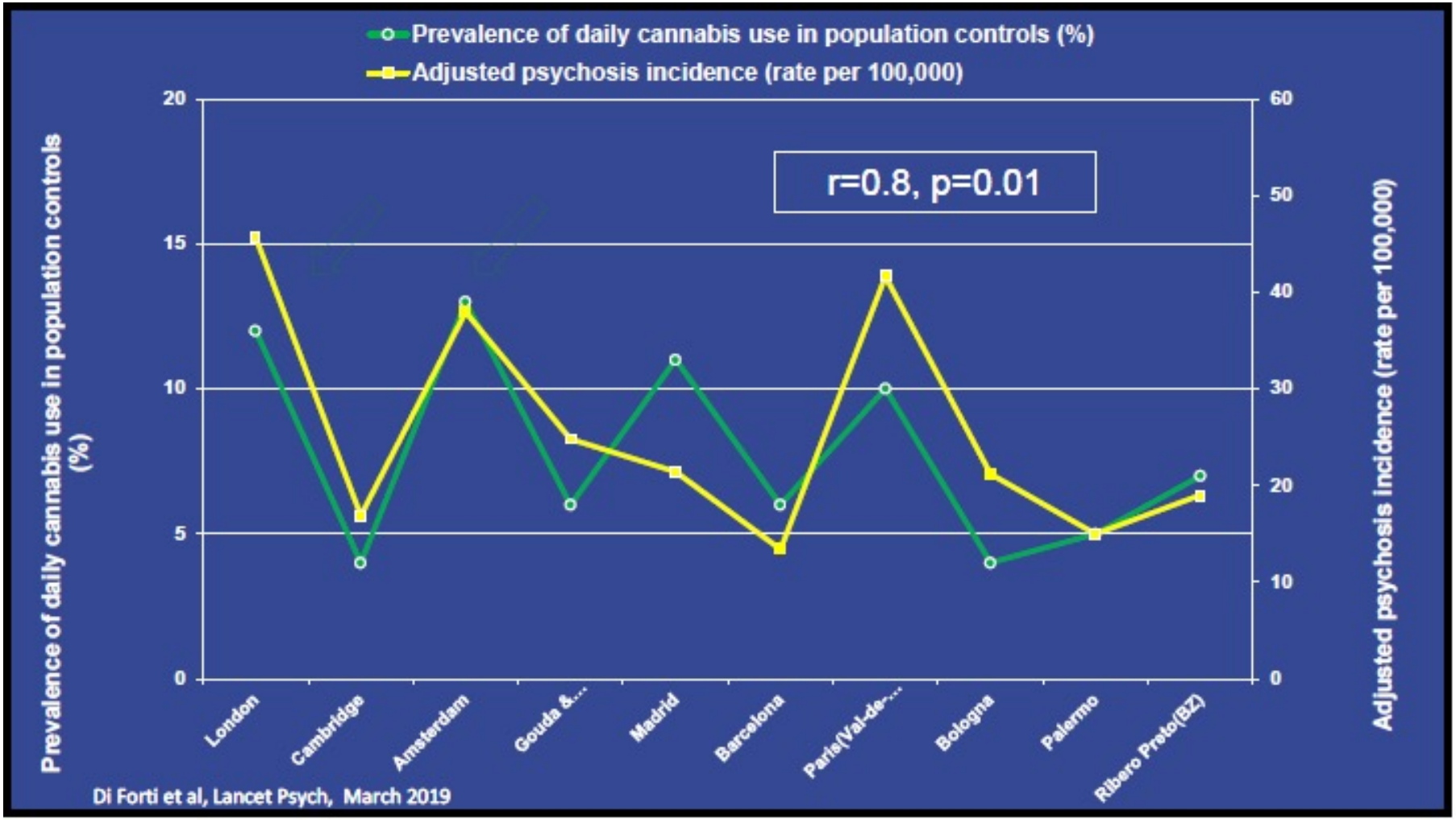
- **Compared two data sets in 12 European sites:**
  - **incidence (new cases) of psychosis**
  - **cannabis use among population controls**

source: DiForte et al., 2019

The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study

Marta Di Forti, PhD • Diego Quattrone, MD • Tom P Freeman, PhD • Giada Tripoli, MSc • Charlotte Gayer-Anderson, PhD • Harriet Quigley, MD • et al. Show all authors •

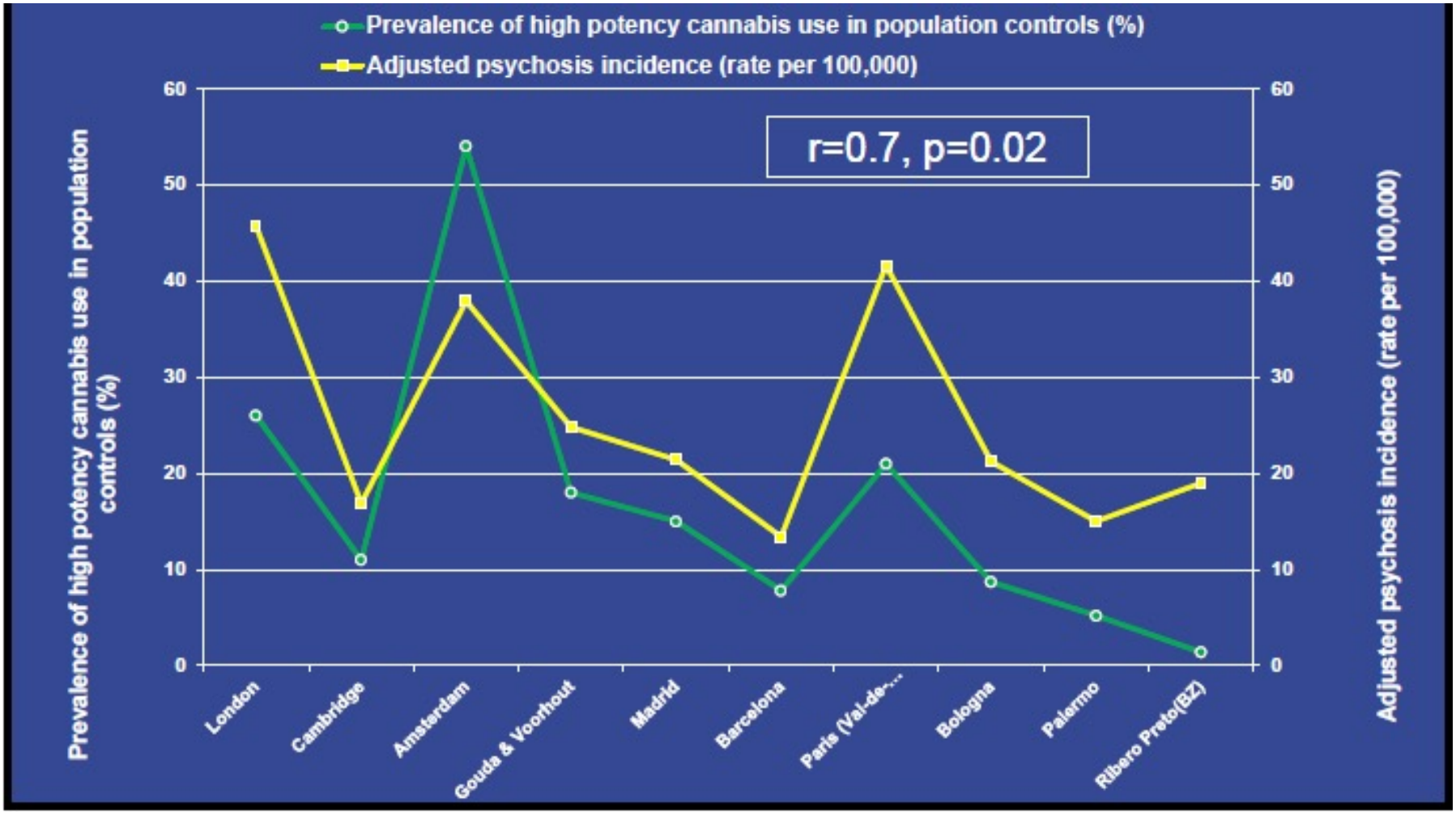
Psychosis and Incidence of First Episode Psychosis as a Function of Daily Cannabis Use



The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study

Marta Di Forti, PhD • Diego Quattrone, MD • Tom P Freeman, PhD • Giada Tripoli, MSc • Charlotte Gayer-Anderson, PhD • Harriet Quigley, MD • et al. Show all authors •

Psychosis and Incidence of First Episode Psychosis as a Function of High Potency (THC > 10%) Cannabis Use



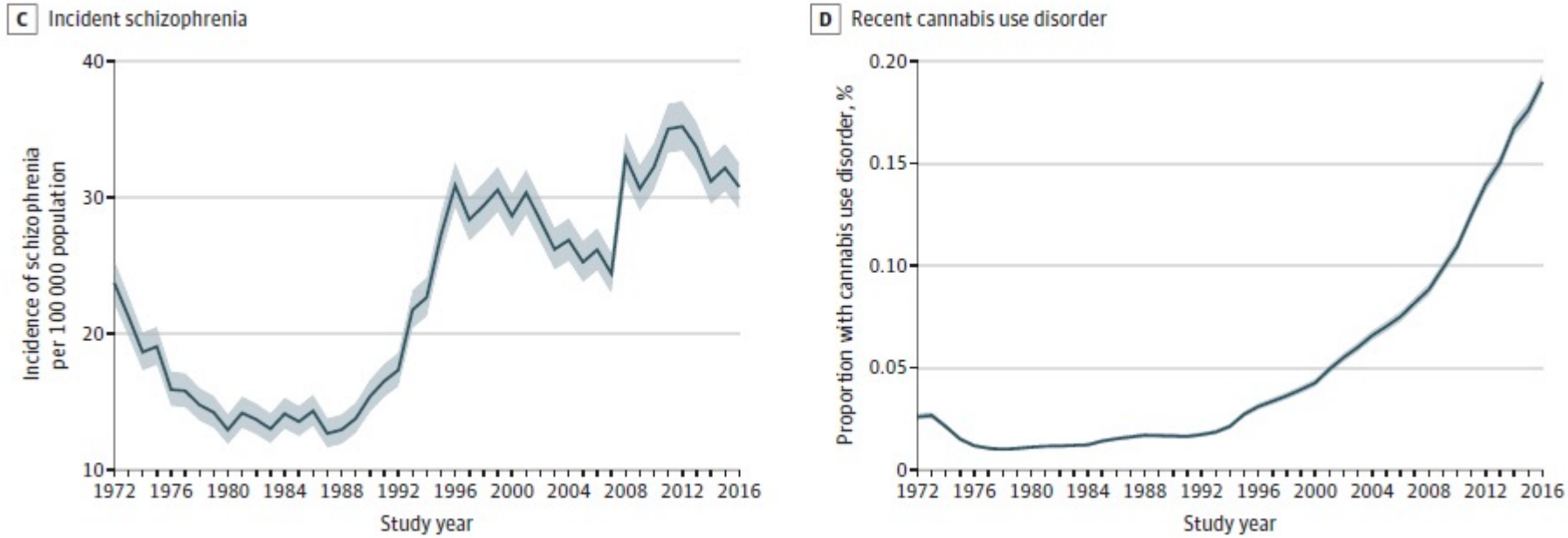
Danish National Study (1972-2016)

Research

JAMA Psychiatry | Original Investigation

Development Over Time of the Population-Attributable Risk Fraction for Cannabis Use Disorder in Schizophrenia in Denmark

Carsten Hjorthøj, PhD; Christine Merrild Posselt, MSc; Merete Nordentoft, DrMedSc

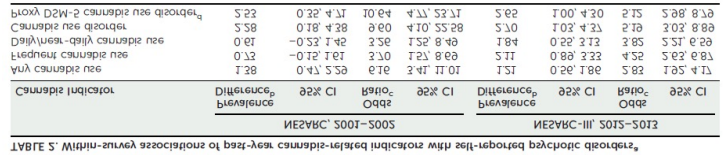


- **The health system in Denmark consists of nationwide, register-based historical health database of its citizens.**
- **The authors of this conducted a cohort study of all people in Denmark who were (1) born before December 31, 2000, and (2) alive and 16 years or older at some point from January 1, 1972, to December 31, 2016.**
- **Research question: whether there was an increase in the proportion of cases of schizophrenia that can be attributable to cannabis use.**
- **The results from these analyses "show the proportion of cases of schizophrenia associated with cannabis use disorder has increased 3- to 4-fold during the past 2 decades, which is expected given previously described increases in the use and potency of cannabis."**

Association of Cannabis Use and Psychotic Disorders

Association of Cannabis Use–Related Predictor Variables and Self-Reported Psychotic Disorders: U.S. Adults, 2001–2002 and 2012–2013

Ofir Livne, M.D., Dvora Shmulewitz, Ph.D., Aaron L. Sarvet, M.P.H., Melanie M. Wall, Ph.D., Deborah S. Hasin, Ph.D.



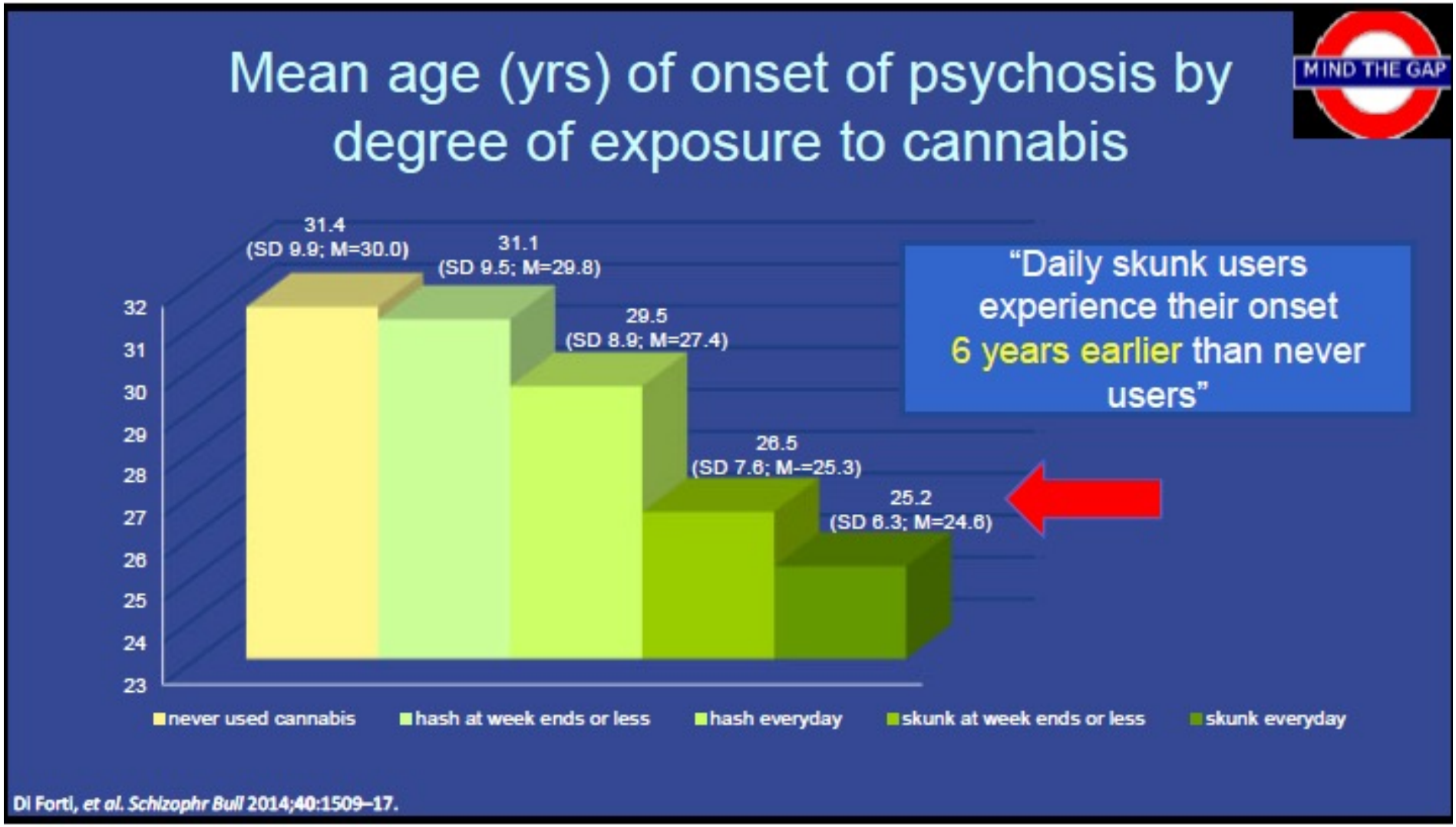
- **Data from the U.S. general population collected between 2001-2002 and 2012-2013 were compared with respect to self-reported psychotic disorder and cannabis use**

- **Prevalence of past-year self-reported psychosis:**
  - **increased significantly between 2001–2002 and 2012–2013**
  - **first reported change in prevalence of self reported psychotic disorders based on large-scale, nationally representative samples of U.S. adults.**

- **Association of self-reported psychosis and cannabis use:**
  - **2001–2002: self-reported psychotic disorders <u>were unrelated</u> to use of nonmedical cannabis**

  - **2012–2013: self-reported psychotic disorders <u>were significantly more common</u> among respondents who reported nonmedical cannabis use; largest association with daily users and those with a cannabis use disorder**

Sidebar Issue: Age of Psychosis Onset and Cannabis Exposure



Cannabis Use Disorder

Cannabis Use Disorder

- Cannabis Use Disorder (CUD) is recognized in the DSM-5
  - tolerance and withdrawal symptoms may be less salient for CUD than for other substance use disorders
- THC can be addictive; between 9% to 30% may develop a cannabis use disorder in their lifetime
- Numerous individual risk factors and use patterns moderate one's likelihood of developing a CUD
  - one risk factor: age of initiation (more on this soon)

1. Extent and Nature of Association

5. Summary

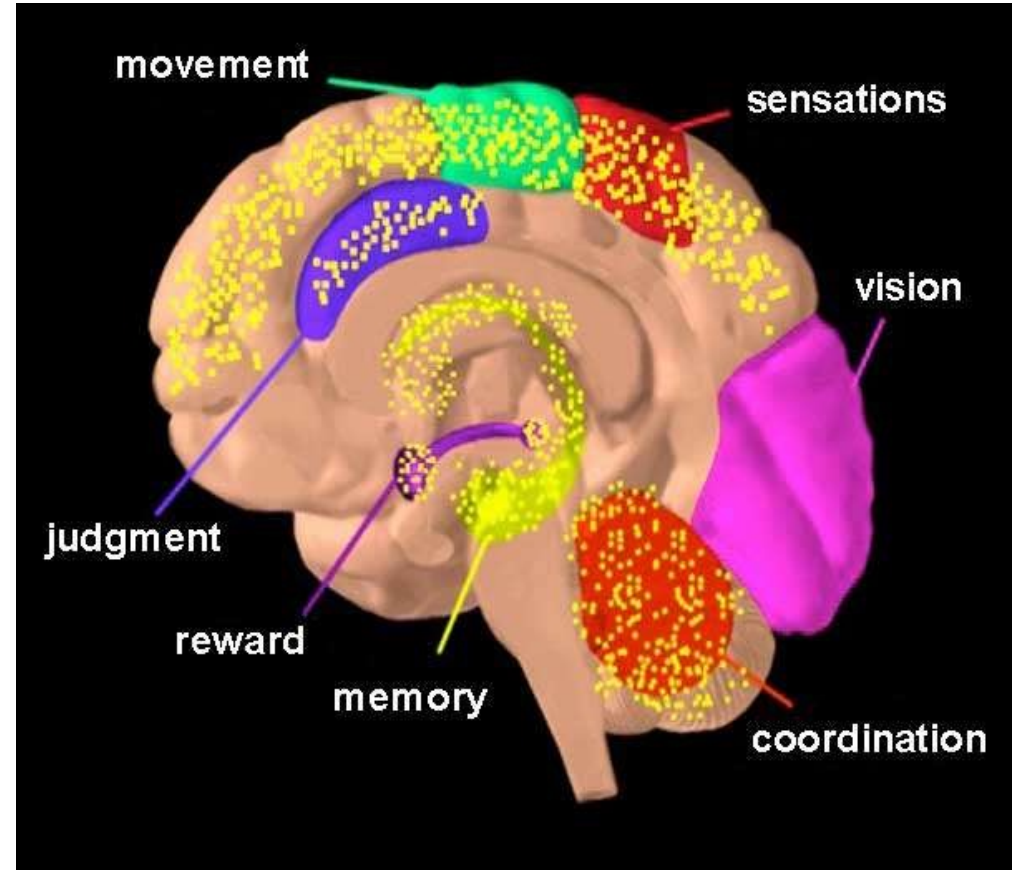
2. Why THC Impacts Mental Health

4. Is Cannabis Medicine For Mental Illness?

3. Youth Vulnerability

The Endocannabinoid System is Ubiquitous Across Several Brain Regions

- Multiple regions of the brain are rich with cannabinoid receptors
  - Nucleus accumbens
  - Hippocampus
  - Amygdala
  - Hypothalamus
  - Medulla
  - Cerebellum
  - Brain stem and spinal cord



source: Hayden Center, Ph.D. & NIDA

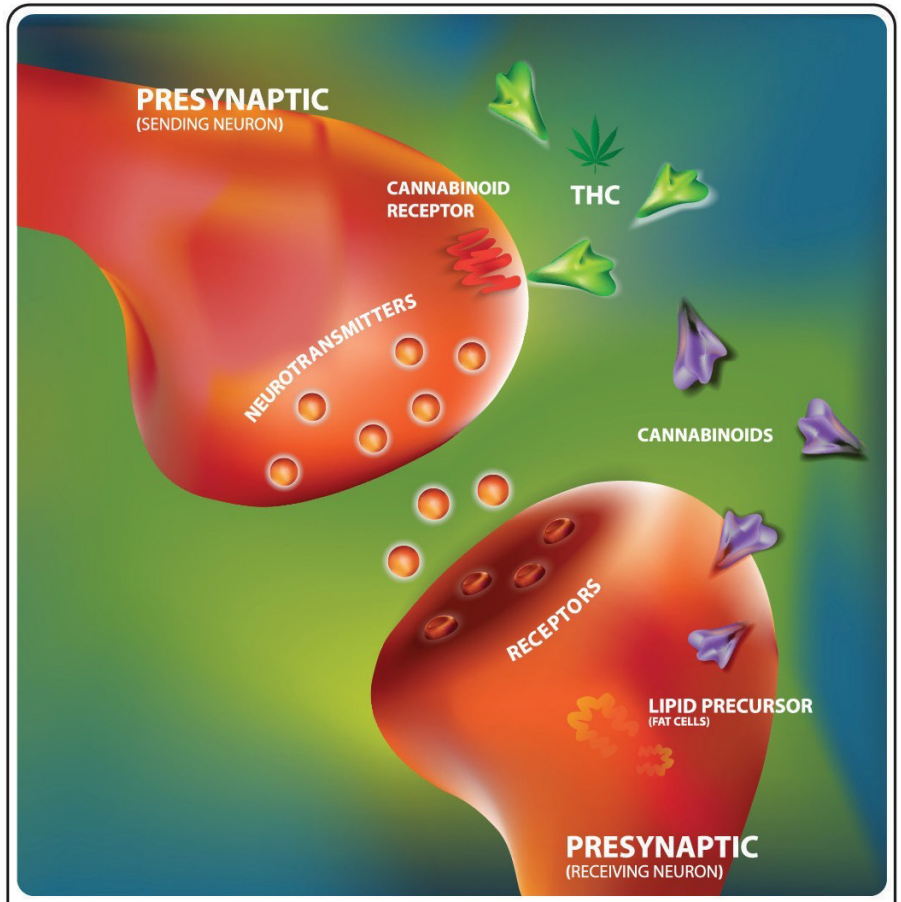
Two Metaphors for the Importance of the Endocannabinoid System

- **The endocannabinoid system serves as a "volume control" for numerous functions of pleasure, mood, pain, appetite, motivation & memory; additionally the system also serves as a "safety helmet" by virtue of protecting the normal function of these volume controls during brain development and beyond.**

slide courtesy of Sion Kim & Marta Di Forti

THC Disrupts the Normal Functioning of the Endocannabinoid System

- Primarily based on animal studies:
  - THC and other cannabinoids in the cannabis plant bind to the brain's own endocannabinoid system, disrupting the body's normal levels of naturally occurring cannabinoids



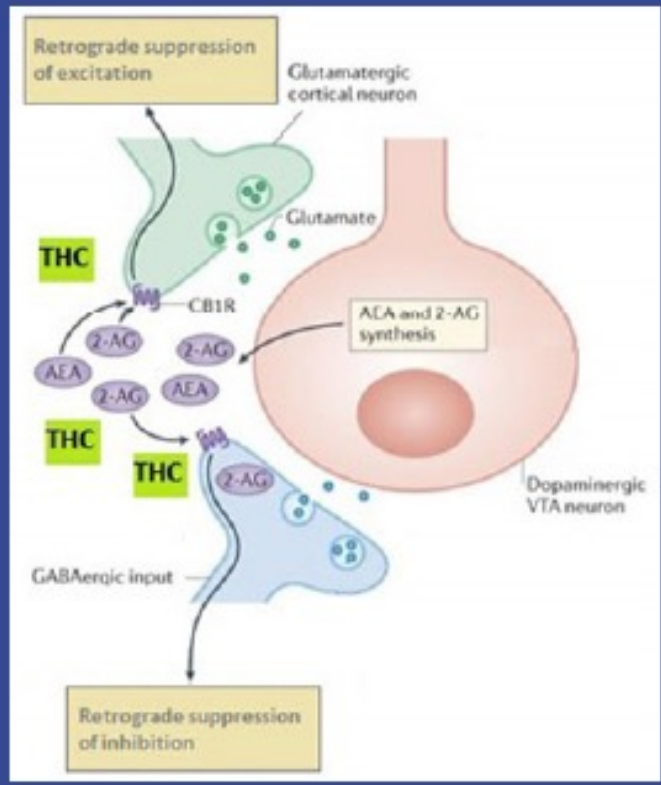
Source: Jacobus, J., & F Tapert, S. (2014) Effects of cannabis on the adolescent brain. *Current Pharmaceutical Design, 20*(13), 2186-2193.

source: Jacobus & Tapert, 2014; SAMHSA, 2021, *Preventing Marijuana Use Among Youth*

How Might THC Exposure Be Linked to Mental Illness?

Dopamine

The Endocannabinoid (eC)system and Psychosis: what is the link?



1.Dopamine. The eC system modulates this key neurotransmitter

- Dopamine transmission impacts mood, decision making and other cognitive functions
- **THC induces an over-production of dopamine and disrupts cognitive functioning**

source: Marta Di Forti

How Might THC Exposure Be Linked to Mental Illness?

Other Neurotransmitters

2.Glutamate

- Glutamate, as leading neurotransmitter in the brain, is especially important in the networks of the cerebral cortex important for processing complex perceptions and cognitions
- **One of the major actions of THC is that it inhibits glutamate release throughout the brain**

3.Anandamide

- Anandamide is an anti-inflammatory agent in the brain and is neuroprotective
- **THC contributes to lower levels of anandamide**

4.Serotonin

- Serotonin is a mood regulator
- **Regular exposure to THC makes the brain hypersensitive to serotonin**

source: Marta Di Forti

1. Extent and Nature of Association

2. Why THC Impacts Mental Health

3. Youth Vulnerability

4. Is Cannabis Medicine For Mental Illness?

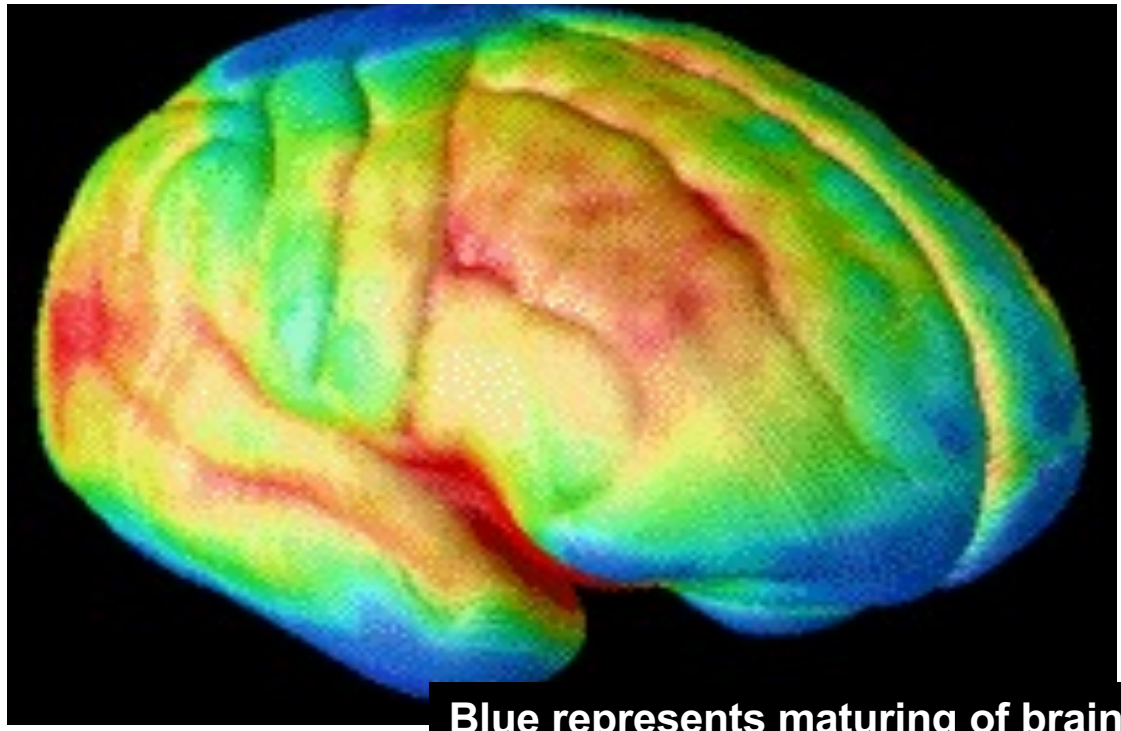
5. Summary

Maturation Occurs from Back to Front of the Brain and Inside to Outside

Images of Brain Development in Healthy Youth (Ages 5 – 20)

Earlier: Limbic
- **Motor Coordination**
- **Emotion**
- **Motivation**

Later: Frontal
- **Judgment**

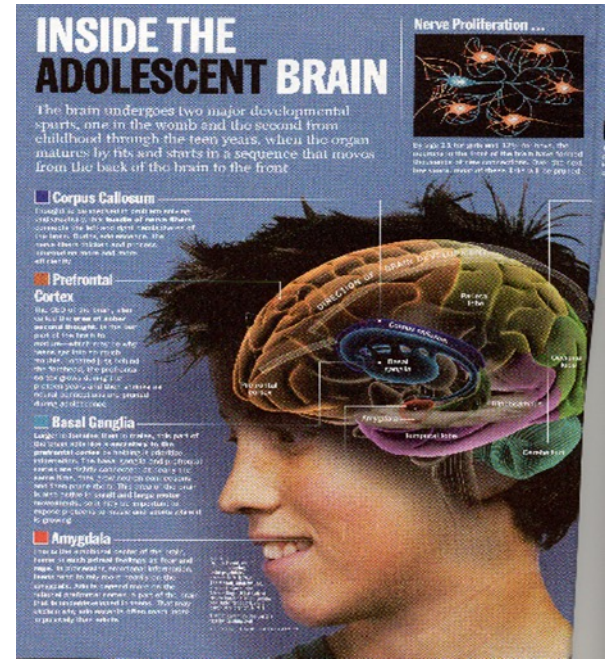


Blue represents maturing of brain areas

Source: PHAS USA 2004 May 25; 101(21): 8174-8179. Epub 2004 May 17.

Developing Brain's Vulnerability to Cannabis Exposure

- **"When the active ingredient of cannabis, THC, is consumed, the numerus cannabinoid receptors that are <u>important to brain development</u> are over-activated and their normal neurodevelopment can be disrupted" (Volkow et al., 2016).**



source: Volkow et al., 2016

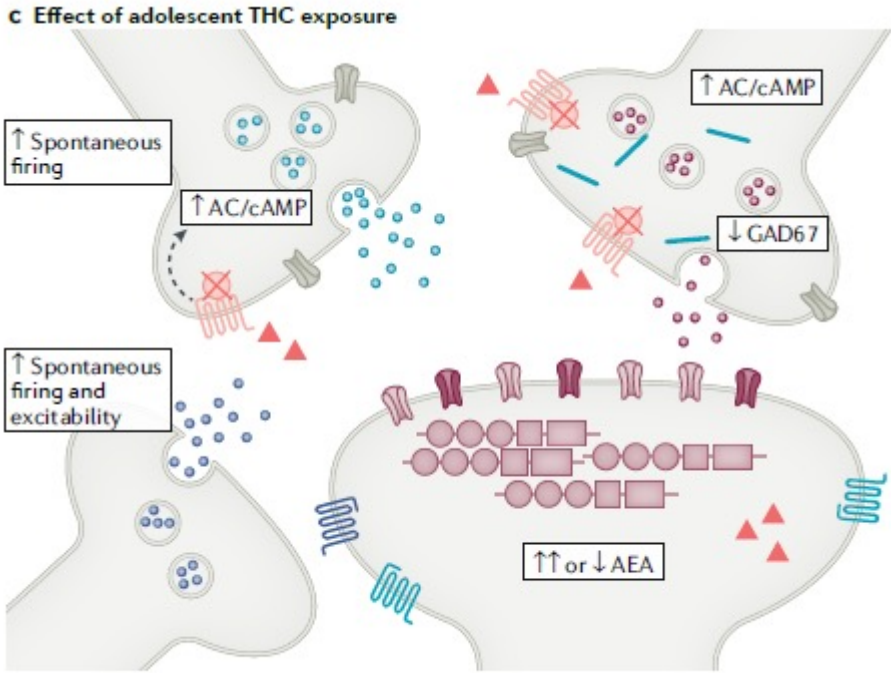
Developing Brain's Vulnerability to Cannabis Exposure

REVIEWS

Check for updates

Cannabis and synaptic reprogramming of the developing brain

Anissa Bara[1,2,3,4], Jacqueline-Marie N. Ferland[1,2,3,4], Gregory Rompala[1,2,3,4], Henrietta Szutorisz[1,2,3,4] and Yasmin L. Hurd[1,2,3,4]



- **Bara and colleagues: "…accumulating evidence from various lines of research demonstrates that there is potential for exposure (to THC) during prenatal and adolescent periods to change the trajectory of various neurobiological systems."**

- **"Importantly, the causal disturbances of neural processes in adulthood by early cannabinoid exposure are linked to behavioural phenotypes predictive of psychiatric and addiction risk."**

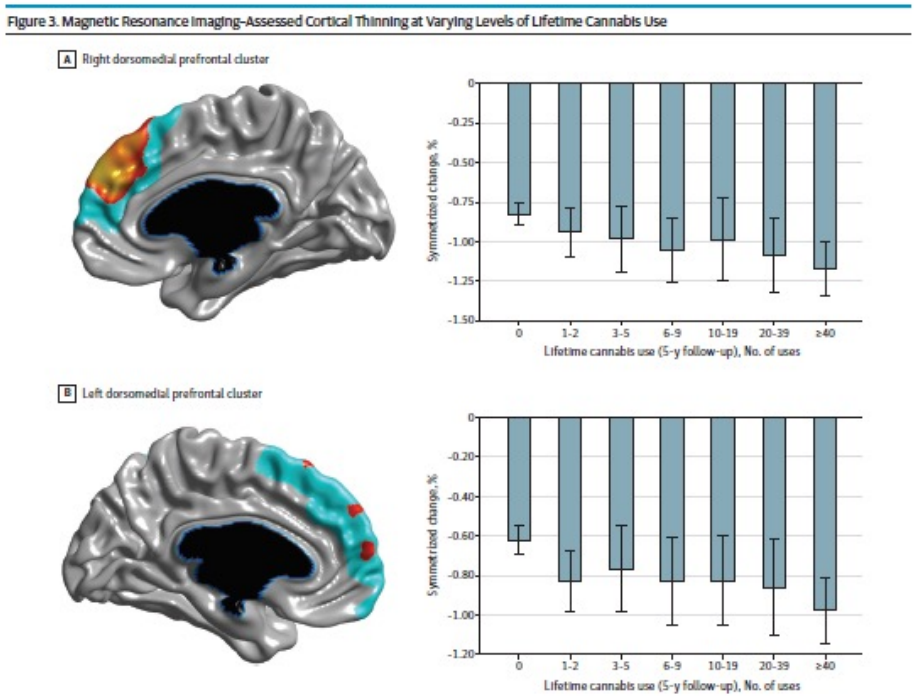
Developing Brain's Vulnerability to Cannabis Exposure

Research

JAMA Psychiatry | Original Investigation

Association of Cannabis Use During Adolescence With Neurodevelopment

Matthew D. Albaugh, PhD; Jonatan Ottino-Gonzalez, PhD; Amanda Sidwell, BS; Claude Lepage, PhD; Anthony Juliano, PsyD; Max M. Owens, PhD; Bader Chaarani, PhD; Philip Spechler, PhD; Nicholas Fontaine, BS; Pierre Rioux, MSc; Lindsay Lewis, PhD; Seun Jeon, PhD; Alan Evans, PhD; Deepak D'Souza, MD; Rajiv Radhakrishnan, MD; Tobias Banaschewski, MD, PhD; Arun L. W. Bokde, PhD; Erin Burke Quinlan, PhD; Patricia Conrod, PhD; Sylvane Desrivières, PhD; Herta Flor, PhD; Antoine Grigis, PhD; Penny Gowland, PhD; Andreas Heinz, MD, PhD; Bernd Ittermann, PhD; Jean-Luc Martinot, MD, PhD; Marie-Laure Paillère Martinot, MD, PhD; Frauke Nees, PhD; Dimitri Papadopoulos Orfanos, PhD; Tomáš Paus, MD, PhD; Luise Poustka, MD; Sabina Millenet, PhD; Juliane H. Fröhner, MSc; Michael N. Smolka, MD; Henrik Walter, MD, PhD; Robert Whelan, PhD; Gunter Schumann, MD; Alexandra Potter, PhD; Hugh Garavan, PhD; for the IMAGEN Consortium



- **longitudinal brain imaging data on 799 teens at two time points: baseline (no use yet) and 5 years later (many had initiated use)**
- **cannabis use during adolescence was associated with altered neuro-development, particularly in the regions of the brain that are rich with cannabinoid receptors**
- **a dose-dependent relationship: the heavier the cannabis use, the greater the altered neurodevelopment**

Eight Adverse Health Effects of Chronic Cannabis Use (Volkow et al., 2014)

2014

The NEW ENGLAND JOURNAL of MEDICINE

- "Low Level of Confidence"
  - Lung cancer
- "Medium Level of Confidence"
  - Increased risk of schizophrenia, depression and anxiety disorders (in persons with a predisposition to such disorders)
  - Altered brain development
  - Progression to use of other drugs
- "High Level of Confidence"
  - Addiction
  - Motor vehicle accidents
  - Diminished life achievement (including cognitive impairment and poor educational outcome)
  - Symptoms of chronic bronchitis

additional increased risk if teen initiation of cannabis use

National Academies of Sciences, Engineering, and Medicine.
The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.

2017

Substantial/moderate evidence that cannabis is associated with these adverse health effects:

- development of schizophrenia or other psychoses; highest risk among heavy users
- increased risk of motor vehicle crashes
- increased risk for lung cancer
- lower birth weight of the offspring (maternal cannabis smoking)
- cognitive impairments (acute effects)
- development of problem cannabis use when early onset of use

2018

Miller's Review of the Cannabis and Mental Health Connection

Disorder	Cross-Sectional Data	Longitudinal Data
Schizophrenia	++	++
Bipolar	+	
Anxiety Disorders	+	+
Depressive Disorders	+	+
Risk of Suicide	+	

Key: ++ = several studies; +a few studies
Yellow box = risk greater when cannabis use onset during youth.

Miller, C. L. (2018). The impact of marijuana on mental health. In K. Sabet & K.C. Winters, *Contemporary health issues on marijuana.* NY: Oxford University Press.

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
CLINICAL ISSUES: SUBSTANCE USE DISORDERS AND THE BODY
doi:10.1111/add.14776

Heavy cannabis use, dependence and the brain: a clinical perspective

Emese Kroon[1,2], Lauren Kuhns[1,2], Eva Hoch[3,4] & Janna Cousijn[1,2]

Neuroscience of Addiction Lab, Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands,[1] The Amsterdam Brain and Cognition Center (ABC), University of Amsterdam, Amsterdam, the Netherlands,[2] Cannabinoid Research and Treatment Group, Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilan University, Munich, Germany[3] and Division of Clinical Psychology and Psychological Treatment, Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany[4]

2020

- **Although causality is unclear, heavy and dependent cannabis use is consistently associated with a high prevalence of psychiatric disorders**

- **Additional potential moderators of the impact of cannabis:**
  - **age of onset**
  - **THC potency used**

Lower-Risk Cannabis Use Guidelines (Fischer et al., 2021)


International Journal of Drug Policy xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Drug Policy

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

Review

Lower-Risk Cannabis Use Guidelines (LRCUG) for reducing health harms from non-medical cannabis use: A comprehensive evidence and recommendations update

Benedikt Fischer, Tessa Robinson, Chris Bullen, Valerie Curran, Didier Jutras-Aswad, María Elena Medina-Mora, Rosalie Liccardo Pacula, Jürgen Rehm, Robin Room, Wim van den Brink, Wayne Hall

2021

General Precaution A: People who use cannabis (PWUC) need to know that there is no universally safe level of cannabis use; thus, the only reliable way to avoid any risk for harm from using cannabis is to abstain from its use.
Evidence Grade: Conclusive

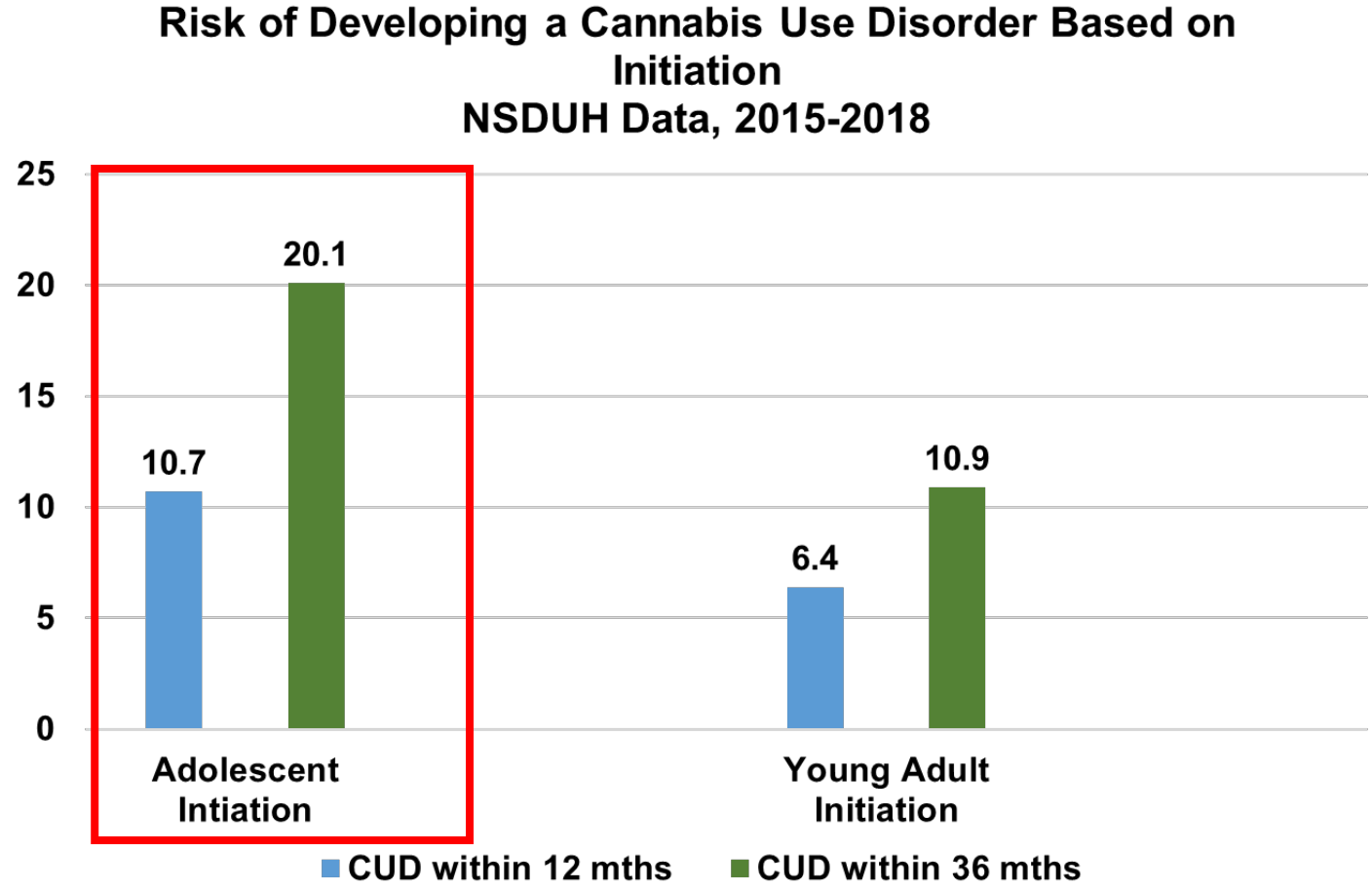
Recommendation #1: The initiation of cannabis use should be delayed until after late adolescence, or the completion of puberty, to reduce development-related vulnerabilities for harm.
Evidence Grade: Moderate

Recommendation #11: Some specific groups of people are at elevated risk for cannabis use-related health problems because of biological pre-dispositions or co-morbidities. They should accordingly (and possibly on medical advice as required) avoid or adjust their cannabis use.
Evidence Grade: Moderate to Limited

Cannabis Use Disorder Focus:
Later Age of Initiation of Cannabis = Less Risk of Developing a Cannabis Use Disorder

Cannabis Use Disorder during adolescence (Volkow et al., 2021)

- Among teens who initiated use of cannabis during their teenage years, within 12 months of initiation, 11% had developed a CUD; and within 36 months, 20% had met criteria for a CUD.
- In comparison: Among young adults who initiated cannabis use during ages 18-25, the CUD rate was about half that of the teenagers.
- **These results support the principle that there is a slower transition to a cannabis use problem the older the age of initiation of use.**



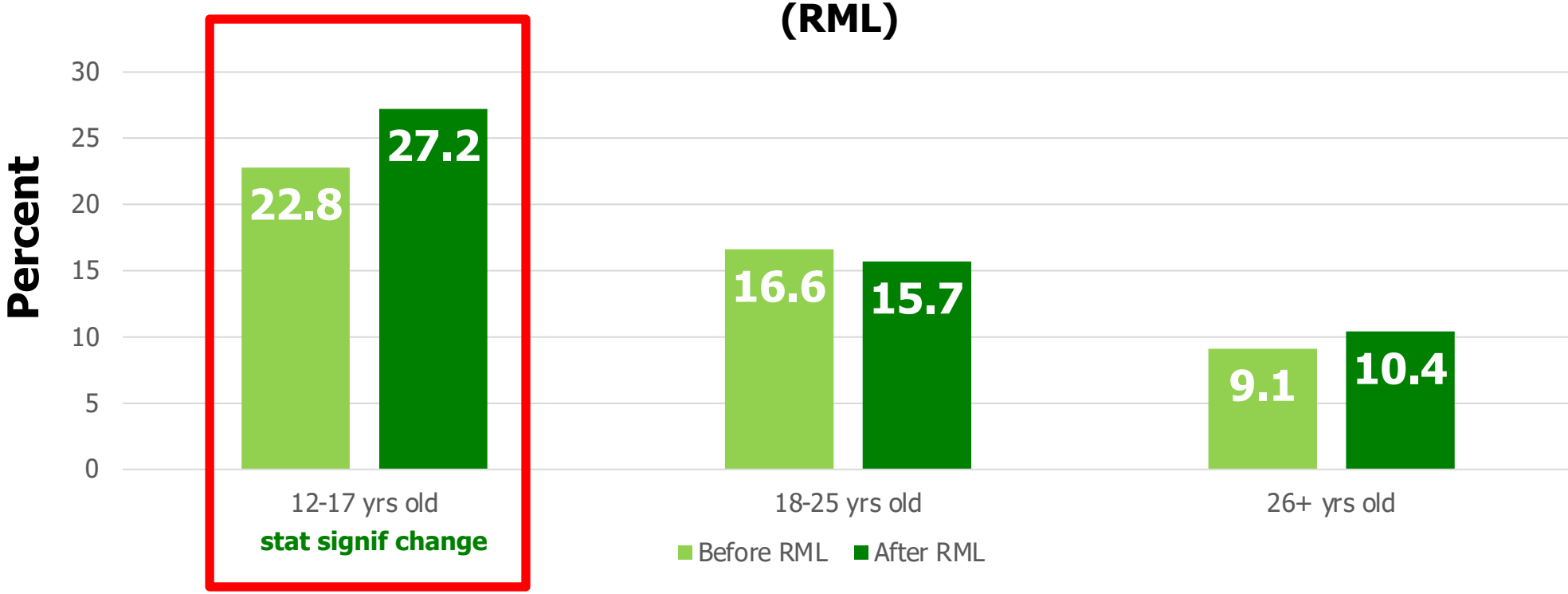
Sidebar: Cannabis Use Disorder Focus and Legalization

JAMA Psychiatry | Original Investigation

Association Between Recreational Marijuana Legalization in the United States and Changes in Marijuana Use and Cannabis Use Disorder From 2008 to 2016

Magdalena Cerdá, DrPH; Christine Mauro, PhD; Ava Hamilton, BA; Natalie S. Levy, MPH; Julián Santaella-Tenorio, DrPH; Deborah Hasin, PhD; Melanie M. Wall, PhD; Katherine M. Keyes, PhD; Silvia S. Martins, MD, PhD

Prevalence of Cannabis Use Disorder Among Past Yr. Cannabis Users, Before and After Recreational Marijuana Legalization (RML)



Why Youth Vulnerability?

1. **Behaviors and decision making impacted by brain development may promote the initiation of use and reduce the likelihood of desisting use**

2. **Early exposure sets in motion early learn and increases habit strength**

2. **THC deleteriously alters brain developm**

Why Youth Vulnerability?

1. Behaviors and decision making impacted by brain development may promote use

2. **Early exposure sets in motion early learning and increases habit strength**

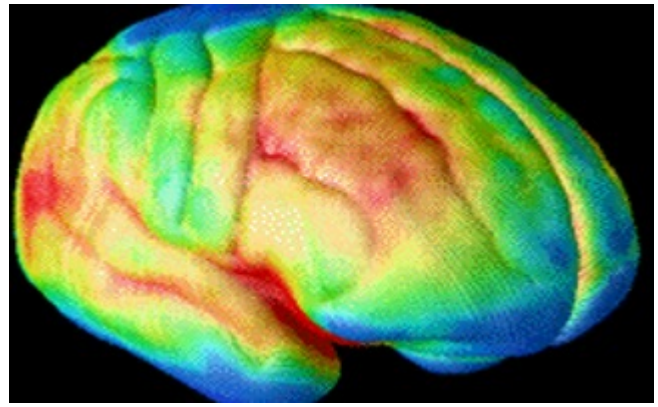
3. THC deleteriously alters brain developm

Why Youth Vulnerability

1. Developing neurological reward pathways are hyper-sensitive to dopamine activation

2. Behaviors and decision making impacted by brain development may promote use

3. **THC may deleteriously alter brain development**
   (Albaugh et al., Bara et al., Volkow et al.)



1. Extent and Nature of Association

2. Why THC Impacts Mental Health

3. Youth Vulnerability

4. Is Cannabis Medicine for Mental Illness?

5. Summary

Review in *The Lancet* (2019)

- There is scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis.
- There is very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions.
- There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework.

Why Do So Many States, Including Minnesota, Permit Medicinal Cannabis for Some Mental Disorders?

- My 2-cents on possibilities:
  1. the science is not always followed
  2. over-persuaded by anecdotal reports when not enough science available
  3. political pressures

Does Desistance of Cannabis Positively Affect Mental Illness?

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
CLINICAL ISSUES: SUBSTANCE USE DISORDERS AND THE BODY
doi:10.1111/add.14776

Heavy cannabis use, dependence and the brain: a clinical perspective

Emese Kroon[1,2], Lauren Kuhns[1,2], Eva Hoch[3,4] & Janna Cousijn[1,2]

Neuroscience of Addiction Lab, Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands,[1] The Amsterdam Brain and Cognition Center (ABC), University of Amsterdam, Amsterdam, the Netherlands,[2] Cannabinoid Research and Treatment Group, Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilian University, Munich, Germany[3] and Division of Clinical Psychology and Psychological Treatment, Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany[4]

- **"Whereas heavy and dependent cannabis use is consistently associated with a high prevalence of learning and memory impairments, these deficits may recover after a period of abstinence.**
- **For those with mental disorders, abstinence from cannabis use may improve treatment because of improved cognitive functioning."**

CBD as Medicine for Schizophrenia?

Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial

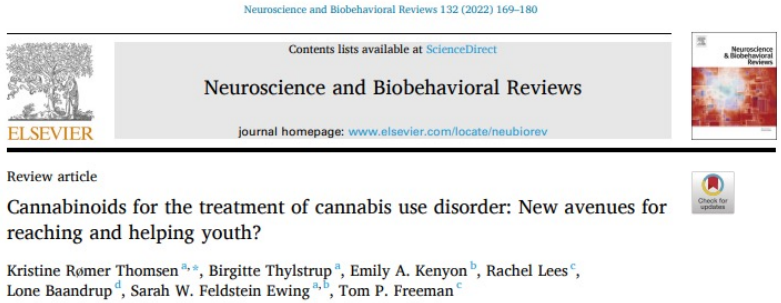
Philip McGuire, F.R.C.Psych., F.Med.Sci., Philip Robson, M.R.C.P., F.R.C.Psych., Wieslaw Jerzy Cubala, M.D., Ph.D., Daniel Vasile, M.D., Ph.D., Paul Dugald Morrison, Ph.D., M.R.C.Psych., Rachel Barron, B.Vet.Med., M.R.C.V.S., Adam Taylor, Ph.D., Stephen Wright, F.R.C.P.(Edin), F.F.P.M.

Source: *American Journal of Psychiatry, 2018*

- **Small samples in an exploratory double-blind parallel-group trial**
- **After 6 weeks of treatment, compared with the placebo group, the CBD group had significantly lower levels of positive psychotic symptoms**
- **No CBD effect on negative symptoms**
- **CBD well tolerated**

CBD and THC as Medicine to Treat Cannabis Use Disorder? Stay Tuned!!

1. **Preliminary findings that pharmaceutical THC can be effective for CUD withdrawal symptoms**



Neuroscience and Biobehavioral Reviews 132 (2022) 169–180

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

ELSEVIER

Review article

Cannabinoids for the treatment of cannabis use disorder: New avenues for reaching and helping youth?

Kristine Rømer Thomsen[a,*], Birgitte Thylstrup[a], Emily A. Kenyon[b], Rachel Lees[c], Lone Baandrup[d], Sarah W. Feldstein Ewing[a,b], Tom P. Freeman[c]

2. **Marta Di Forte, MD, PhD (leading UK researcher on addictions):**
   - **"Some promising early indications that CBD may be effective. We are starting a controlled trial."**

1. Extent and Nature of Association

2. Why THC Impacts Mental Health

3. Youth Vulnerability

4. Is Cannabis Medicine For Mental Illnesses?

5. Summary

Summary

1. Several lines of evidence support the claim that THC is implicated as a contributor to mental illness, particularly psychosis

2. Cannabinoid receptors in the brain are disrupted by exposure to THC

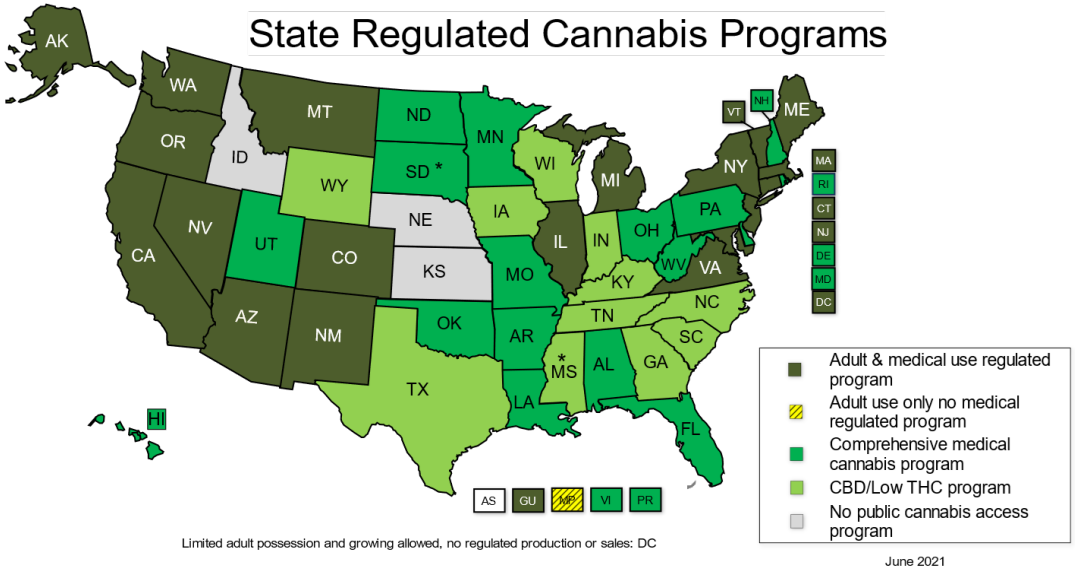
3. Several factors are associated with elevating one's vulnerability to mental health issues if THC is used, including....
   - pre-existing genetic risk
   - frequent and long-term use of high potency THC
   - initiation during adolescence

Summary: What Do the Experts Say about THC's Role with Mental Illness?

4. How might THC impact risk for and recovery from mental illness?
   i. elicit the mental disorder when it may have remained in a latent state if THC were not used
   ii. contribute to earlier onset than if no exposure to THC
   iii. aggravate symptoms in a person who is already suffering from a mental illness
   iv. contribute to treatment barriers by the negative impact of THC on a person's judgement, or contribute to the illusory belief that THC is helpful

Summary

5. Proactive preventive approaches are important



THANK YOU

winte001@umn.edu

Questions and Discussion