

# Cannabinoids and Health

## Module 10

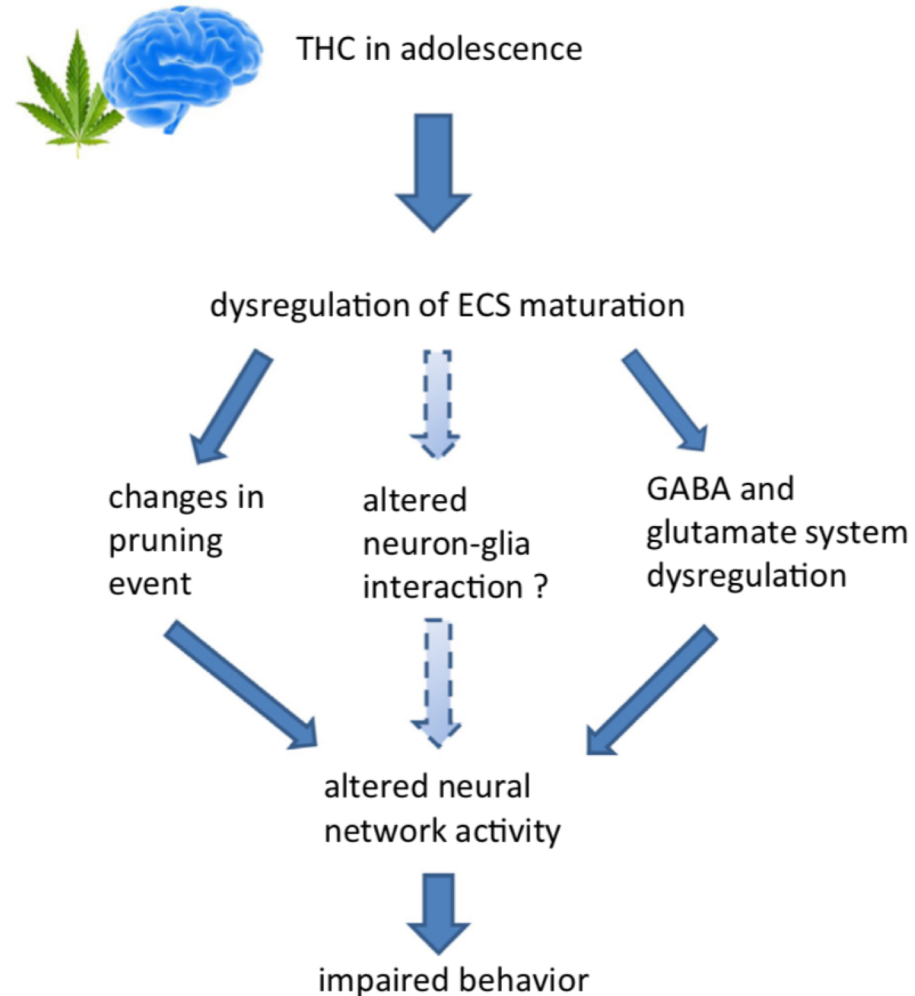
### Lecture 5: Cannabis and Mood Disorders and Psychosis – Chicken or the Egg Conundrum

# Testing Causality: Cannabis & Mental Health

- Does cannabis lead to mood disorders and psychosis (this lecture)?
- Or are people attempting to self-medicate with cannabis (next lecture)?

# Cannabis and Mood Disorders: Concern for Causality

- Adolescent brain is dense in cannabinoid receptors
- And may be vulnerable to alterations in activity precipitated by cannabis use



## Review

**The Impact of Exposure to Cannabinoids in Adolescence: Insights From Animal Models**

Tiziana Rubino and Daniela Parolaro

Biological  
Psychiatry

# Testing Causality: Cannabis & Depression

- Some studies have linked adolescent use with development of disorders
- Earlier cannabis use is associated with increased odds of depression



Research report

Are early-onset cannabis smokers at an increased risk of depression spells?

Brian J. Fairman\*, James C. Anthony

**Table 3**

Exploratory adjusted logistic regression analysis of association between depression spell and fine-grained cannabis onset exposure.

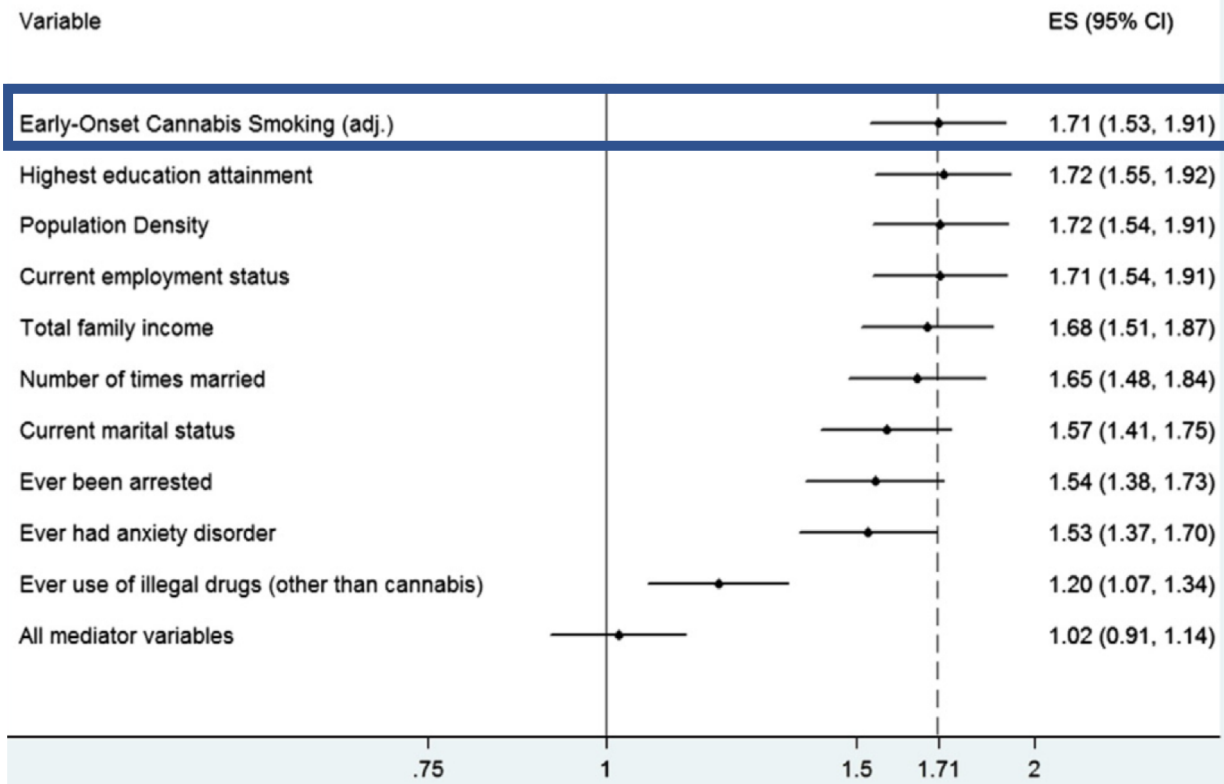
	Model 3 <sup>a</sup> – adjusted logistic regression (fine grained onset)		
	OR	(95% CI)	p-value
Cannabis onset			
Never	1.0		
≤ 15 years	1.9	(1.6, 2.1)	<0.001
15 years	1.7	(1.5, 2.0)	<0.001
16 years	1.6	(1.4, 1.8)	<0.001
17 years	1.6	(1.4, 1.9)	<0.001
≥ 18 years	1.7	(1.6, 1.9)	<0.001

OR, odds ratio.

<sup>a</sup> Model adjusted for elapsed time of cannabis involvement, tobacco cigarette onset, alcohol onset, sex, age, race/ethnicity, and survey year.

# Testing Causality: Cannabis & Depression

- Adolescent cannabis use is linked to mental health
- Cannabis use is associated with greater odds for depression
- But, the effect is not stronger than other factors



# Cannabis and Mood Disorders: Twin Studies

- Discordant twin designs suggest that cannabis use is associated with depression but **DOES NOT** have a causal role (Lynskey et al, 2004)
- Some studies find no association (Blanco et al., 2016, *JAMA Psychiatry*)
- Yet recent meta-analysis of longitudinal studies suggests a modest association with an OR=1.7 (Gobbi et al., 2019, *JAMA Psychiatry*)
- While overall evidence suggests an association between cannabis use and depression, causality is difficult to determine (e.g., is cannabis use a cause or an attempt to self-medicate)

# Cannabis and the Etiology of Psychosis

- There is a clear statistical association between cannabis use and psychosis
  - However, the association could arise for many reasons.
  - To establish a causal relationship, Ksir and Hart (2016, *Curr Psychiatry Rep*) used the “Hill Criteria” – a set of nine criteria used to examine causal links
- Criterion 1: Is the association strong enough to warrant attention?
  - Cannabis users have a 2:1 risk for psychosis (vs. abstainers)
  - Heavy users have a 6:1 risk for psychosis (vs. abstainers)
  - Unclear if the link is due to causality or shared vulnerability

# Cannabis and the Etiology of Psychosis

- Criterion 2: Are findings consistent?
  - There is a consistent link over many studies, but findings don't support a specific hypothesis (e.g., causality)
- Criterion 3: Is cannabis use specific to psychosis risk?
  - Schizophrenia is associated with heavy tobacco smoking
  - Patterns of use are similar for tobacco/cannabis in psychosis
  - Cannabis is linked to a variety of other psychiatric disorders
- Criterion 4: Does cannabis use precede psychosis?
  - Cannabis may be a cause, or a self-medicating, for psychosis
  - Cannabis use (adolescence) typically occurs before the first episode of psychosis (25-27)
  - Cannot draw conclusions based on timing.



# Cannabis and the Etiology of Psychosis

- Criterion 5: Is there a biological gradient?
  - Heavier users, with greater exposure, are at greater risk
  - This dose-response relationship provides powerful evidence
  - However, this comes with other confounds
- Criterion 6: Is there a plausible biological pathway?
  - The dopamine and endocannabinoid systems have been proposed pathways
  - There are no consistent findings of a biological mechanism.
  - The shared vulnerability hypothesis doesn't require a shared mechanism.

# Cannabis and the Etiology of Psychosis

- Criterion 7: Does either hypothesis provide a better fit?
  - Ksir & Hart conclude that, given the lack of evidence for a causal pathway, a shared vulnerability pathway is more plausible.
- Criterion 8: Is there (quasi-)experimental evidence?
  - Cannot conduct experiments, but natural experiments...
  - There's been a 10-fold increase in cannabis use in the UK since the 1970s, but there have been no increases in psychosis
- Criterion 9: Is there another, similar agent that cause psychosis? None that are known.

## **GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia**

We also found a significant genetic correlation between cannabis use and schizophrenia ( $r_g=0.24$ ), which is in line with previous findings, indicating that genetic risk factors for cannabis use and schizophrenia are positively correlated. As for the causal direction of this correlation, we found weak evidence for a causal link from cannabis use to schizophrenia and much stronger evidence for a causal link from schizophrenia to cannabis use. This suggests that individuals with schizophrenia have a higher risk to start using cannabis. These results are in contrast with results from a MR study by Vaucher et al., who found strong evidence for a causal effect from cannabis use to schizophrenia (causality in the other direction was not tested). However, our findings are in line with a MR study by Gage et al. who used genetic instruments similar to ours and also found weak evidence for a causal effect of cannabis use to schizophrenia and much stronger evidence for a causal effect in the other direction. Our findings may indicate that individuals at risk for developing schizophrenia experience prodromal symptoms or negative affect that make them more likely to start using cannabis to cope or self-medicate.

# Conclusions

- Studies have reported an association between cannabis use early in life and future depression and schizophrenia
- Difficult to know which precedes the other (chicken or the egg problem)
- Some genetic studies have suggested this association may be due to common, underlying genetic factors
- Bottom line is that everybody agrees that adolescents should not be using cannabis, especially if there is a family history of psychosis (because we simply do not fully understand the causality at this point)