

Cannabis Involvement Across the First Three Decades of Life: Predictors, Pathways and Outcomes

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The University of Vermont
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A few questions

1. Is cannabis use safe/low risk?
2. Is cannabis use safe/low risk *for teens*?
3. How does the risk compare to other substances?



What is Cannabis (Marijuana)?

Contains over 100 compounds?!?

CBGA (Cannabigerolic acid)

THCA (Δ^9 -tetrahydrocannabinolic acid)

CBDA (Cannabidiolic acid)

CBCA (Cannabichromenonic acid)

CBGVA (Cannabigerovarinic acid)

THCVA (Tetrahydrocannabivarinic acid)

CBDVA (Cannabidivarinic acid)

CBCVA (Cannabichromevarinic acid)

THCA (Δ^8 -tetrahydrocannabinolic acid)

Terpenes: essential oils, smells, flavor



What is Cannabis/Marijuana?

- Smoking
- Vaping
- Dabbing
- Edibles
- Lotions/Cremes



What is Cannabis (Marijuana)?

Potency (%THC) Plant Material / Flowers

THC: 0.6% - 30.6%

CBD: 0.04% - 14.6%

Potency (%THC) Concentrates (Oils, Tinctures, Wax)

THC: 35.3% - 87.5%

CBD: 0.01% - 40.3%

Potency (%THC) Edibles

THC: 20mg – 100mg

CBD: 20mg

Potency (%THC) Capsules or Drops

THC: 5-50mg

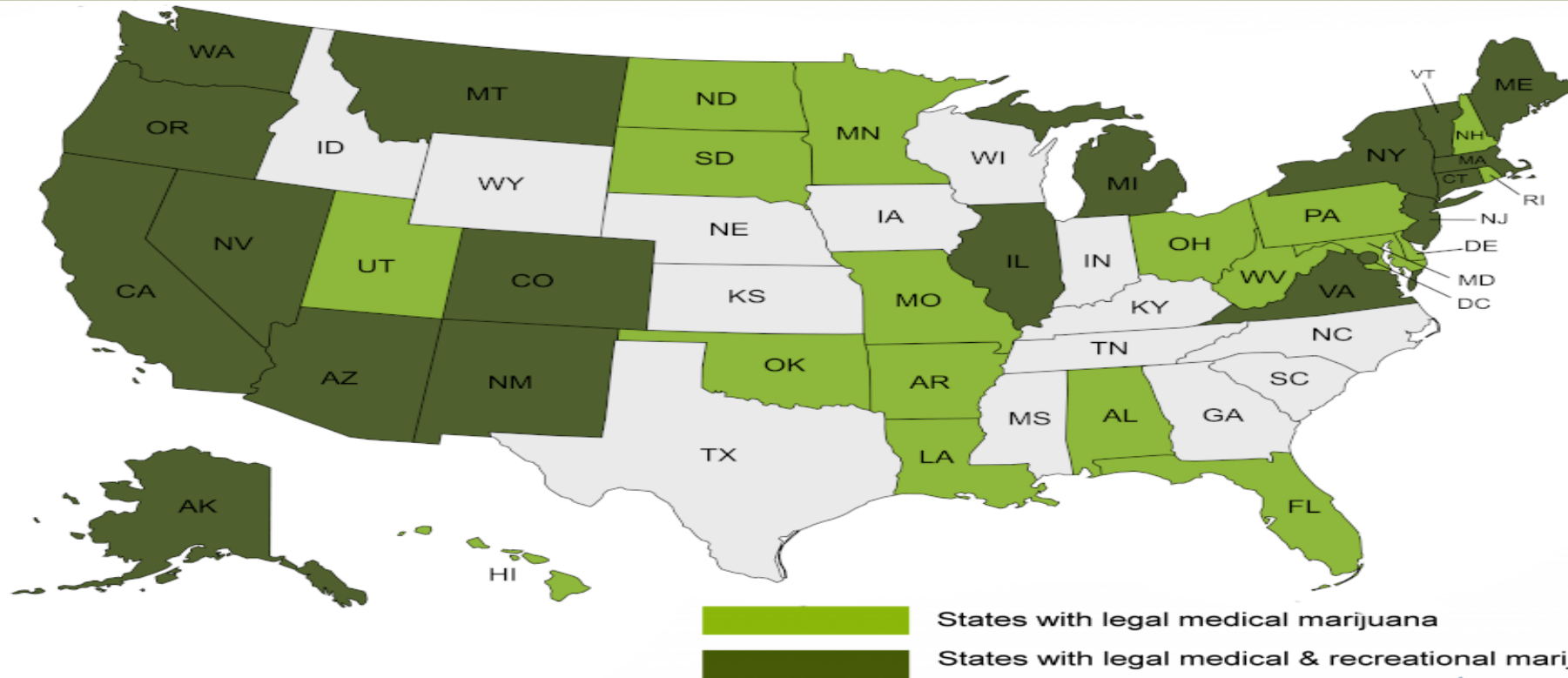
CBD: 5-25mg



19 RCL States

37 MCL States

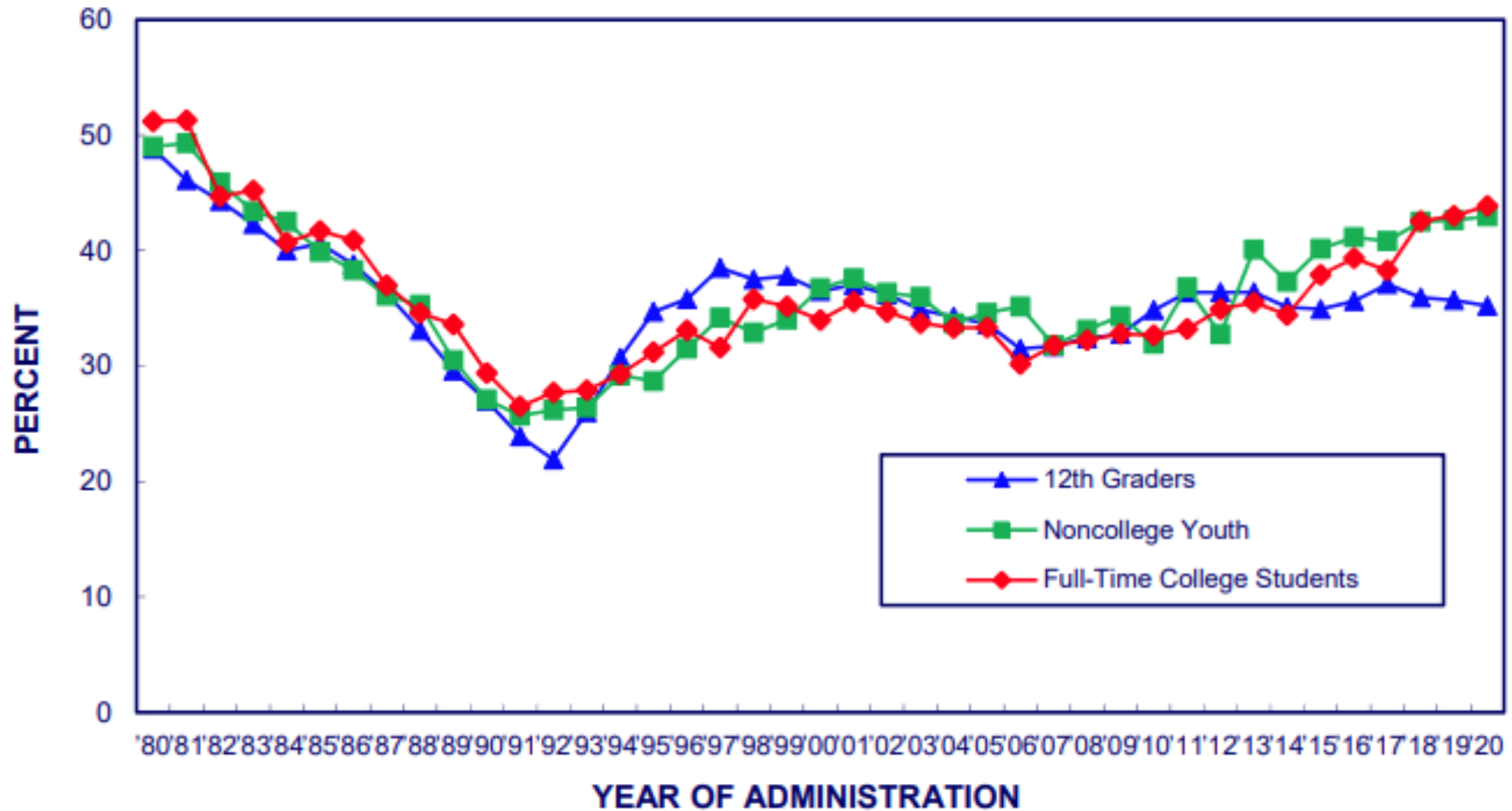
Legal Medical & Recreational Marijuana States



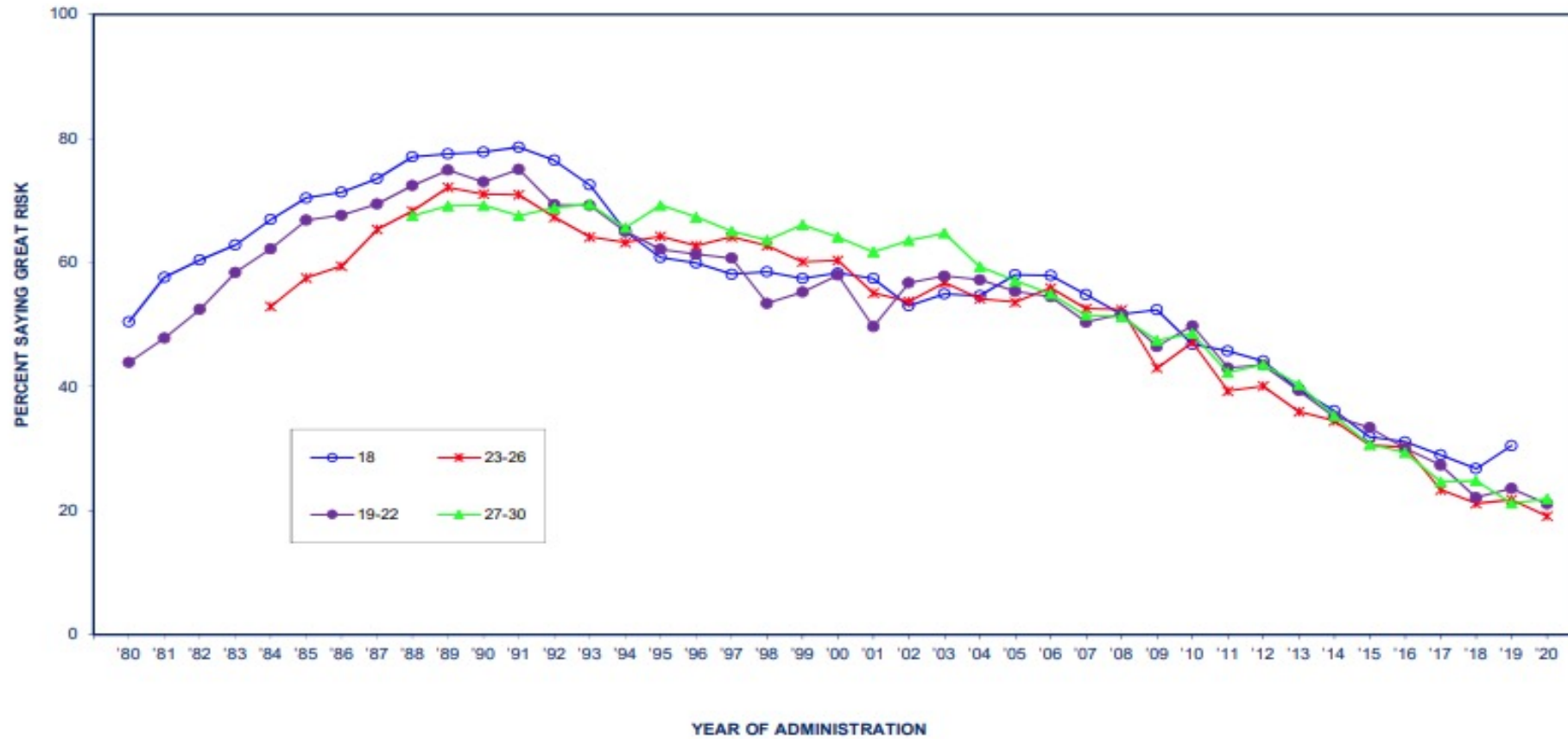
Created with mapchart.net

BRITANNICA
PROCON.ORG | RELIABLE.
NONPARTISAN.
EMPOWERING.

Annual prevalence



Perceived risk of regular use



AGENDA

- How common is cannabis use (and problematic use) in the first 3 decades of life?
- What is the best way to define problematic cannabis use?
- What are risk factors for early cannabis use?
- What are the outcomes of early cannabis use?

- Brief Overview of Great Smoky Mountain Study



Great Smoky Mountain Study

A community-representative study of 1420 children in Western NC followed into adulthood and interviewed up to 12 times over 25+ years, about their psychosocial functioning.



Great Smoky Mountain Study

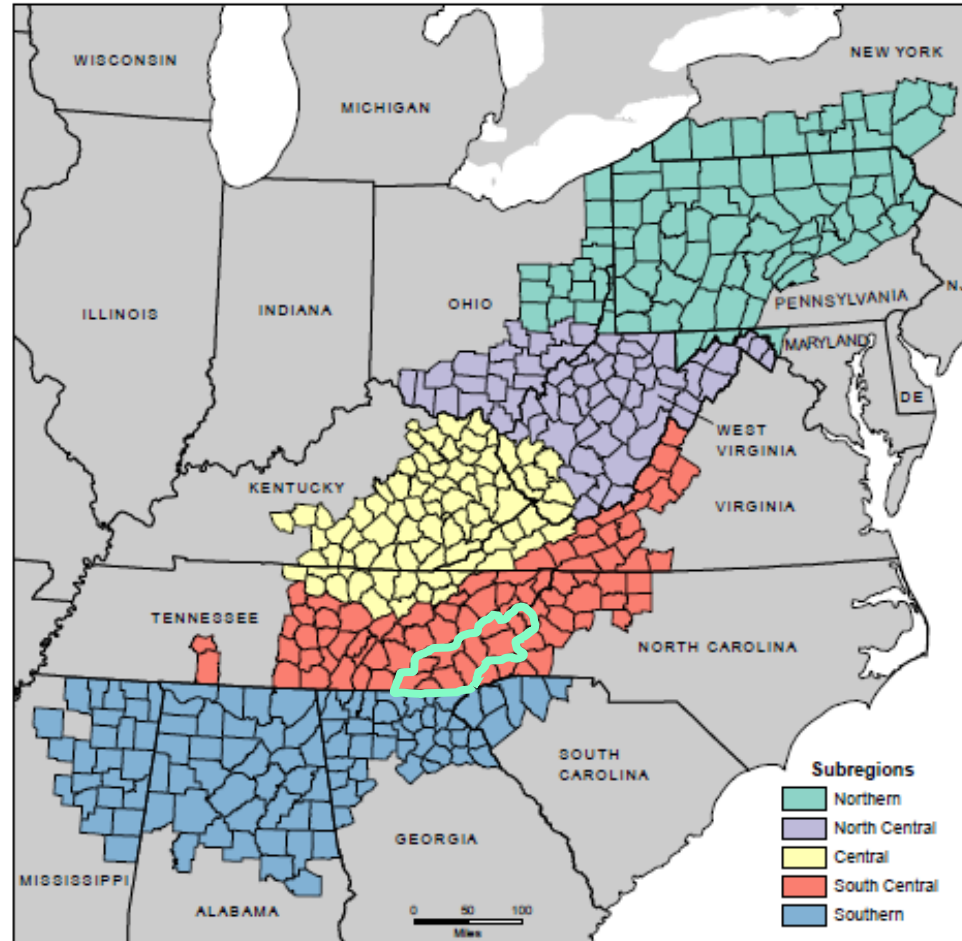








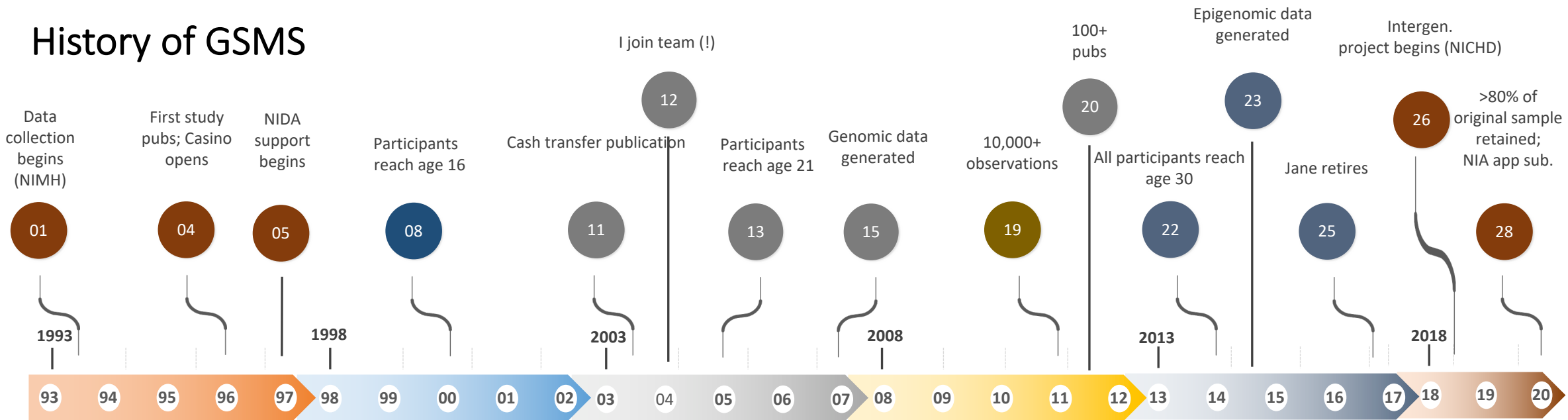




Data source: Appalachian Regional Commission, Created November 2009

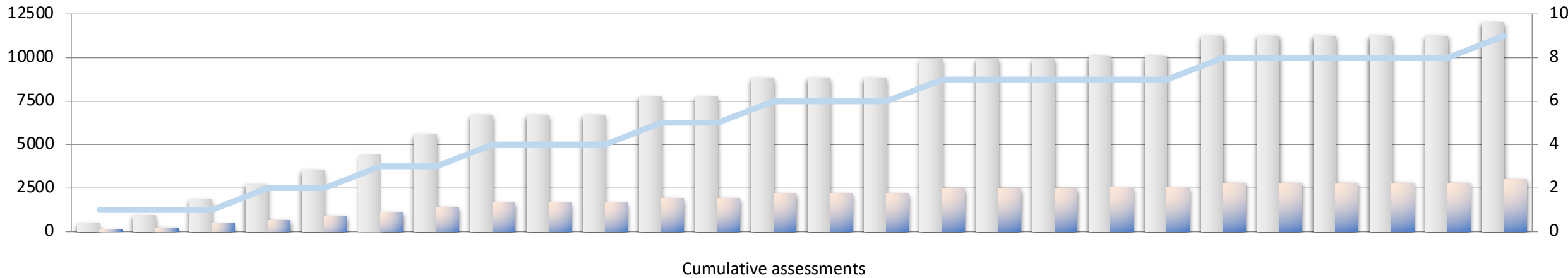
Meit, M., Hefferman, M., Tanenbaum, E., & Hoffmann, T. (2017). *Final report: Appalachian diseases of despair.*

History of GSMS



Cohort ages

9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40



25+ year GSMS history - Assessment

- Structured diagnostic interview of participants
 - Child and Adolescent: CAPA (ages 9-16)
 - Young Adult: YAPA (ages 19+)
- Structure diagnostic interview of parent's MH
- Biomeasures at each assessment
 - Height, weight, pulmonary function
 - Blood spot collection of 10 spots (7000+ banked dried bloodspots)
- Bloodspots have been assayed for the following:
 - Pubertal hormones
 - Stress biomarkers (Cortisol)
 - Inflammatory markers (CRP and EBV antibodies)
 - 800k DNA genotyping complete + imputation of additional 2M+ markers
 - Whole genome methylation sequencing
- Linkage to education, criminal, juvenile justice, voting, and health records
- Geospatial coding and census data linkage

THE CHILD AND ADOLESCENT PSYCHIATRIC ASSESSMENT

(CAPA)

Child Interview Version 5.0

ADRIAN ANGOLD, MRCPsych

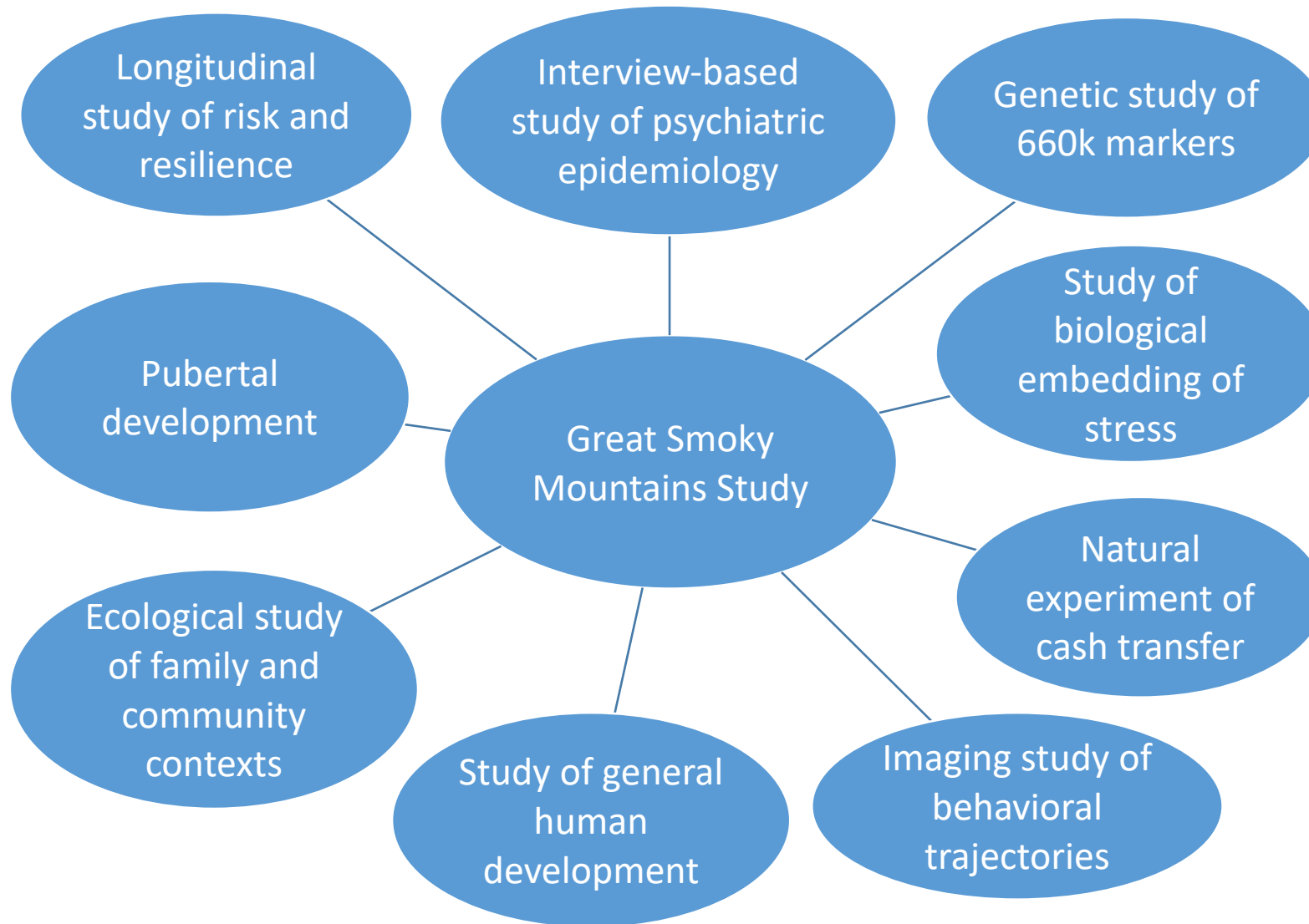
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A Angold, A Cox, M Prendergast, M Rutter, E Simonoff
Copyright (1987,1990,1992,1994,1996,1998)

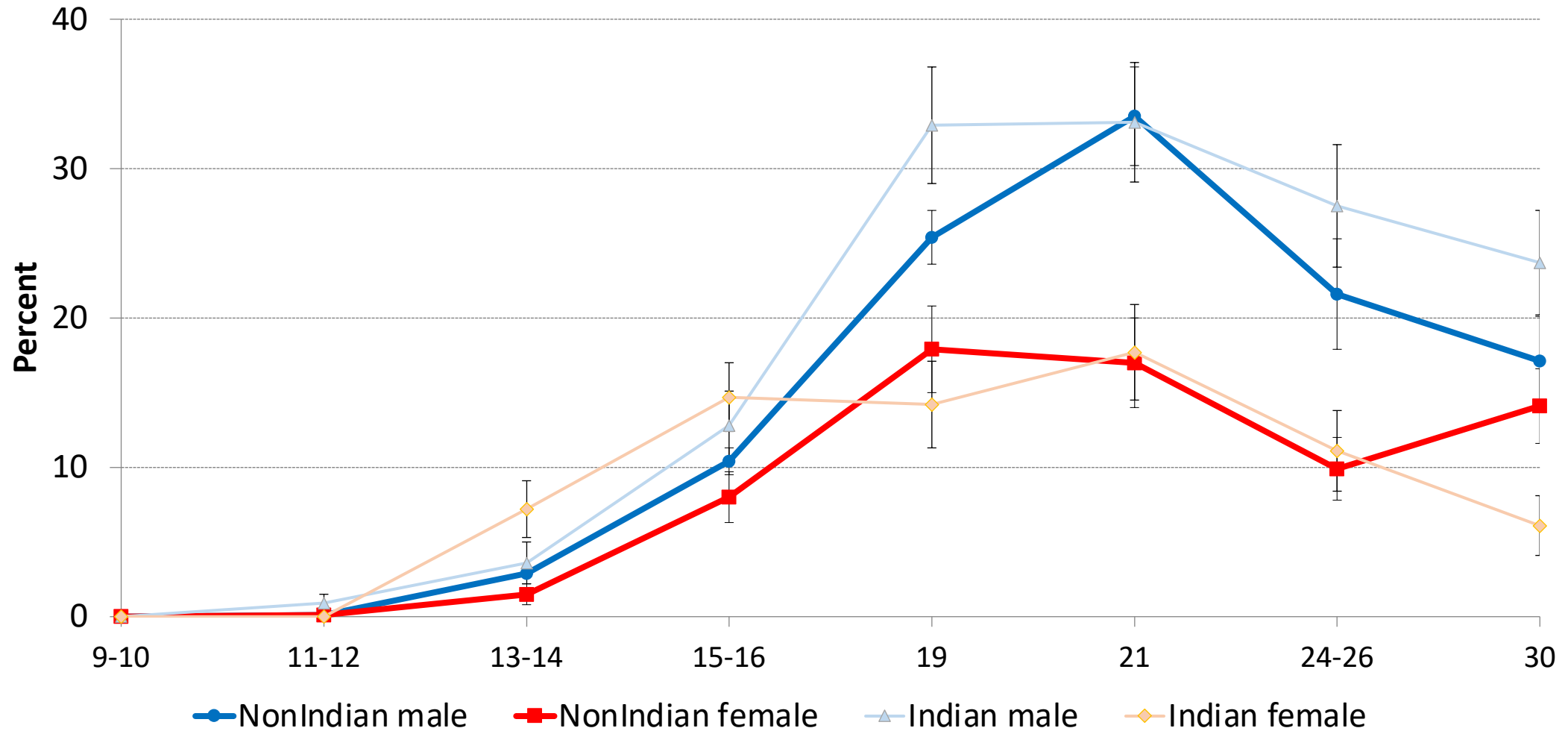


GSMS has informed developmental psychopathology from molecular and biological determinants to population-level outcomes and policies.

How common is cannabis use across development from birth to age 30?

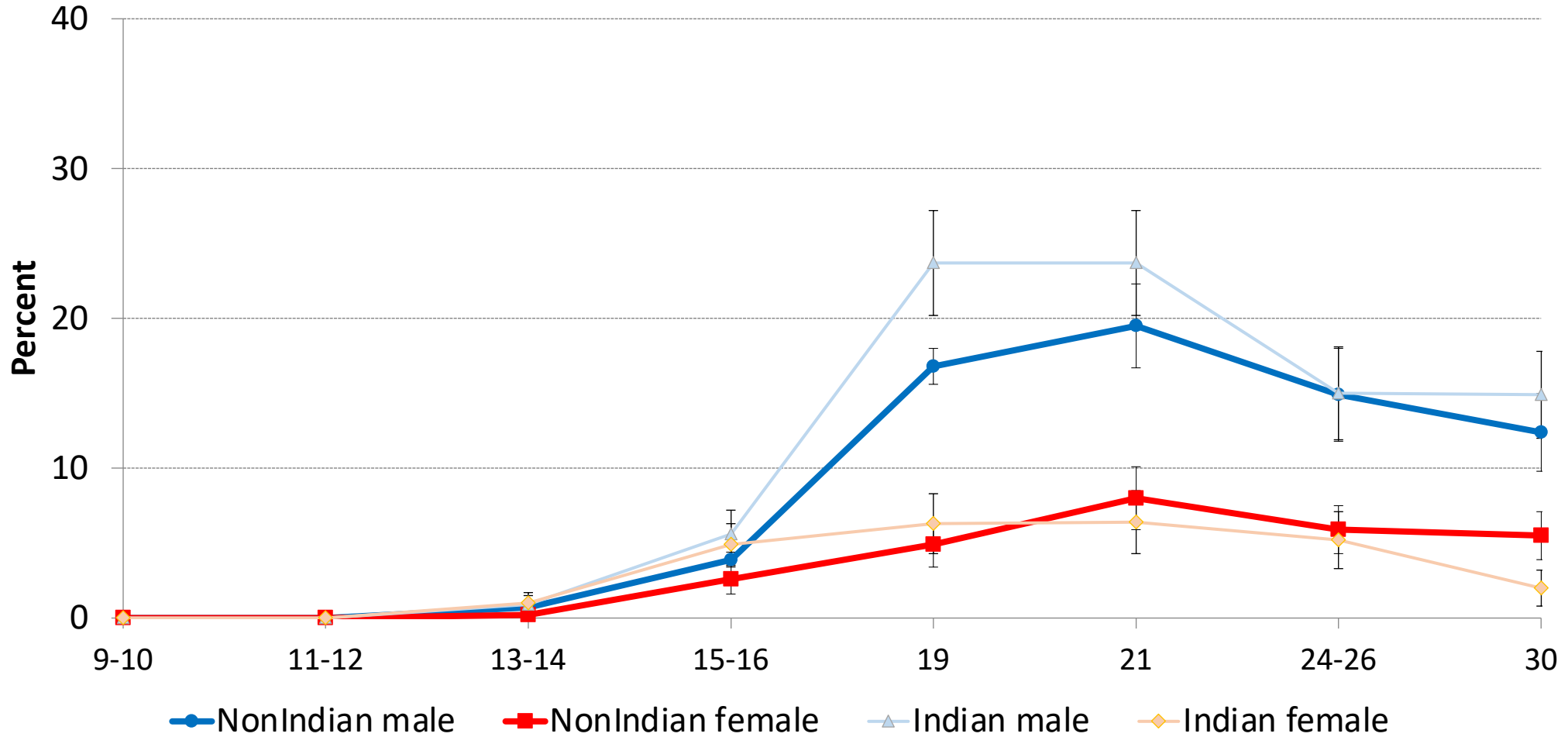


Any Cannabis use in last 3 months

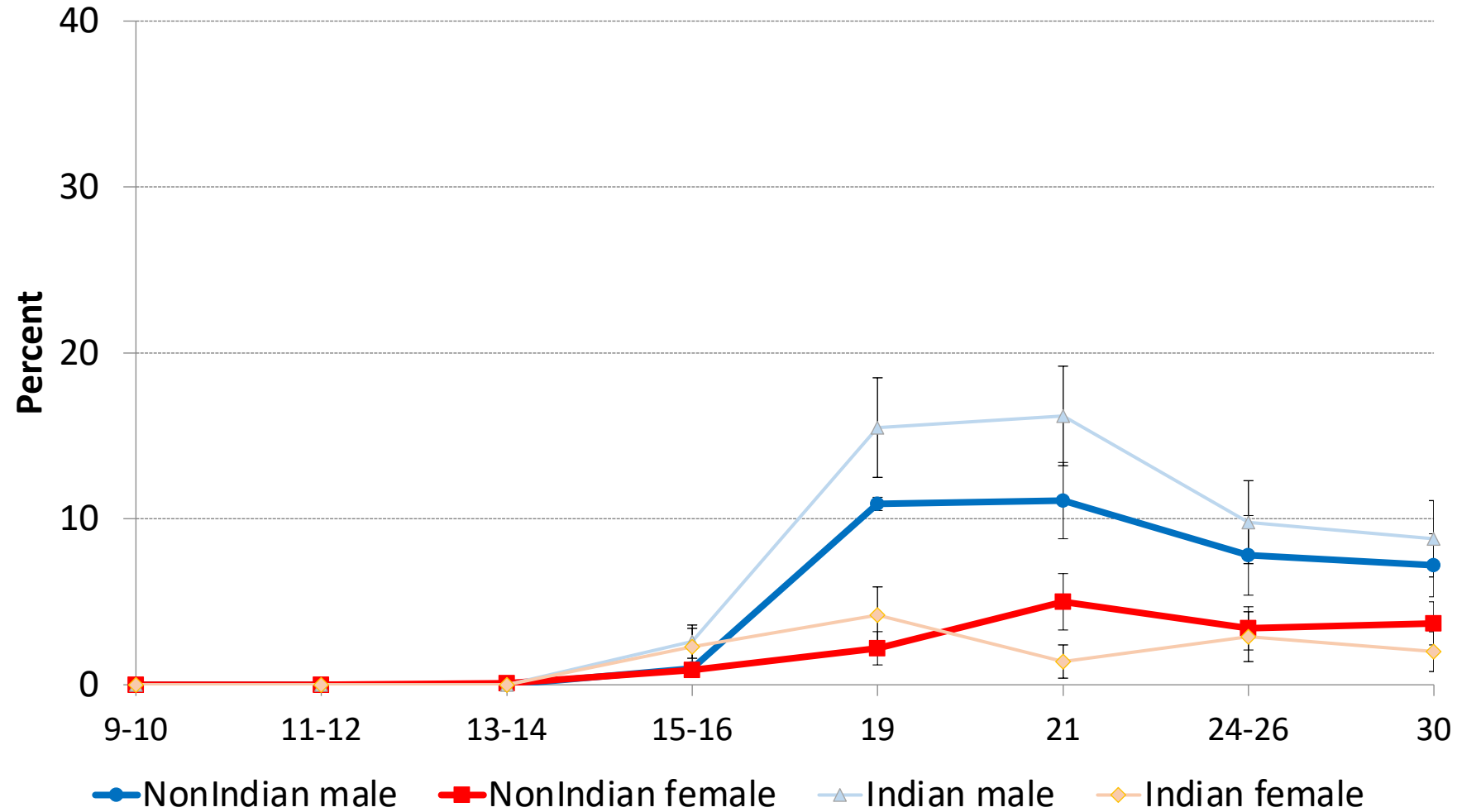


Common developmental pattern for risky behaviors

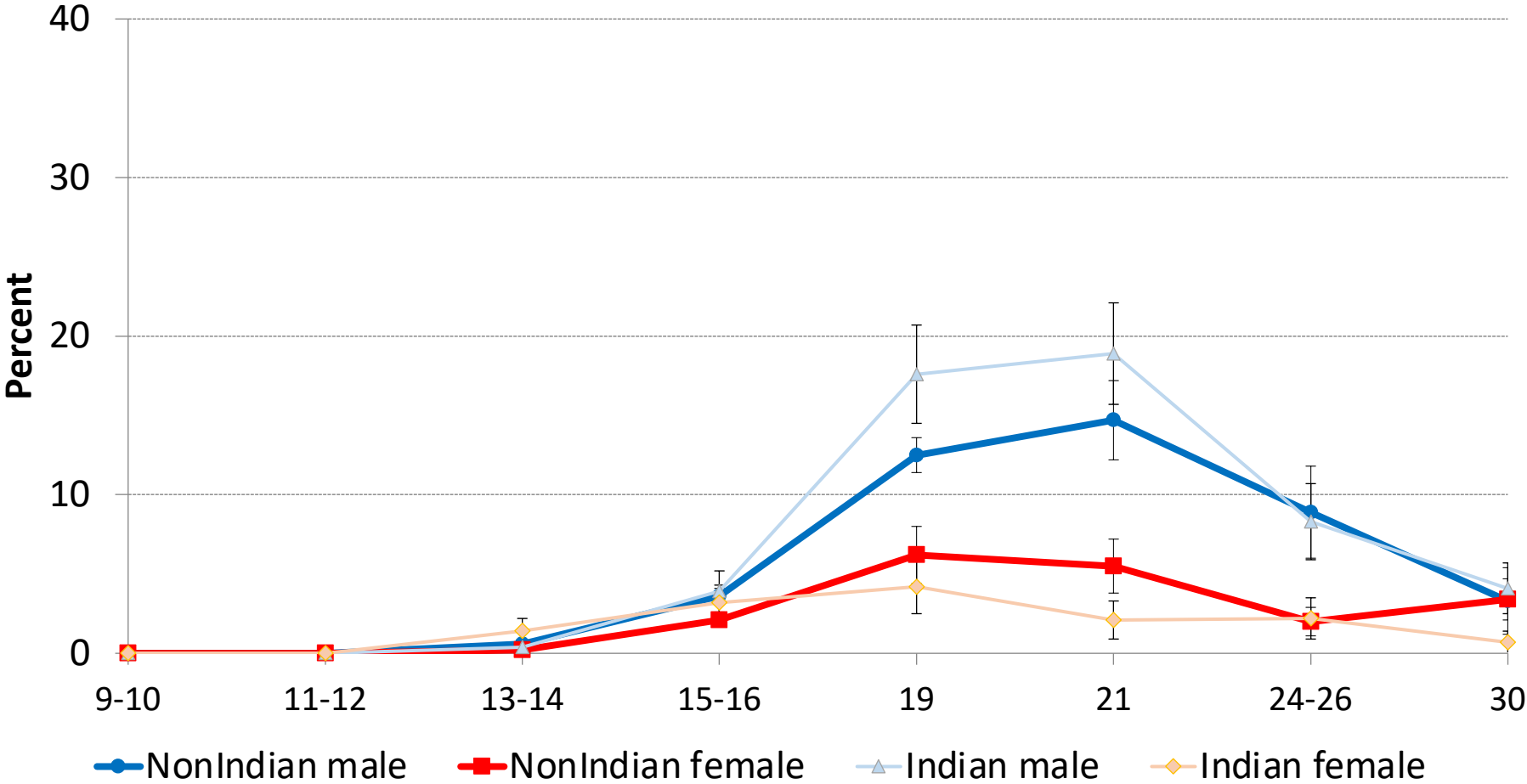
Weekly Use in last 3 month



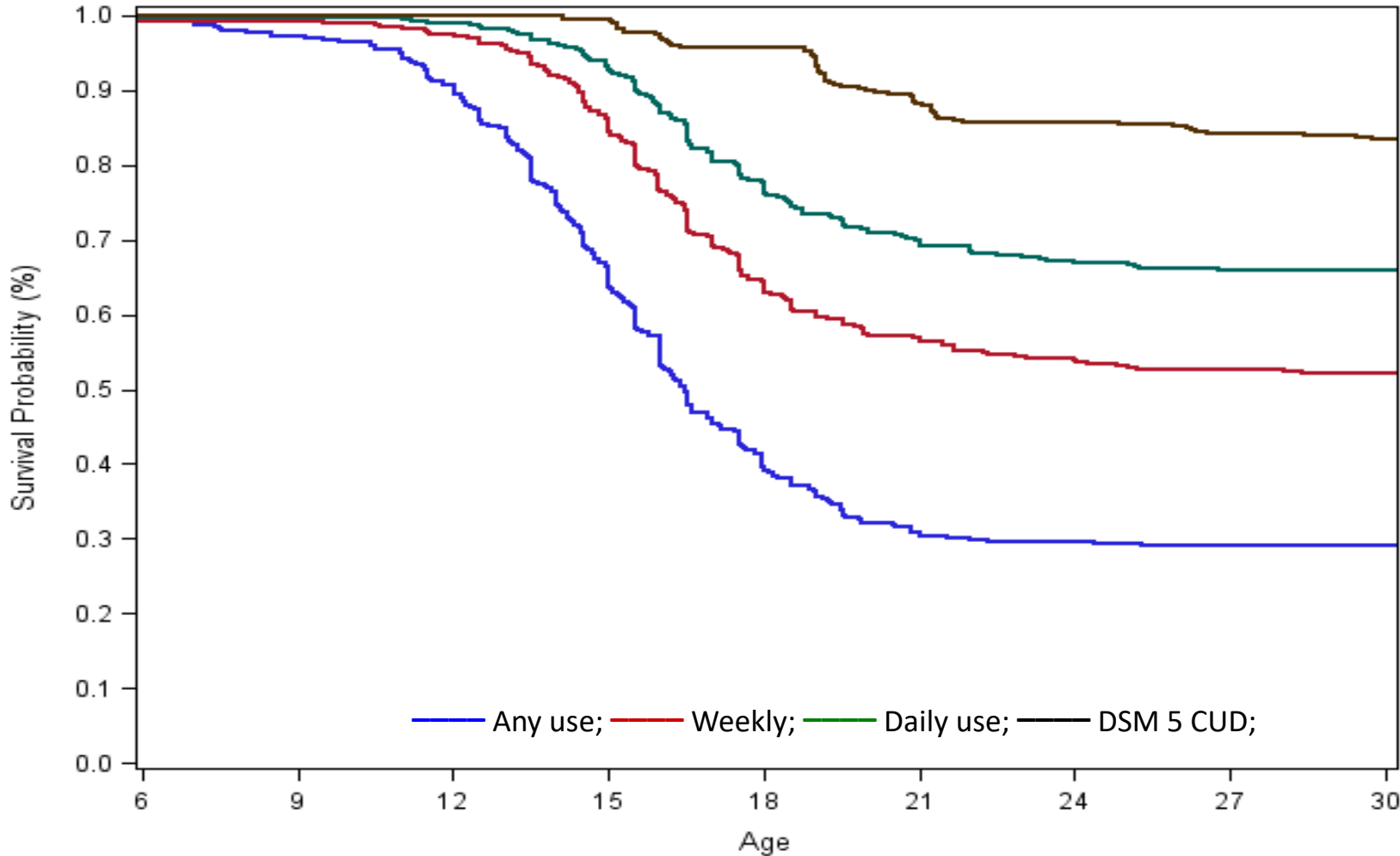
Daily Use in last 3 month



3-month DSM-5 CUD Prevalence Rates

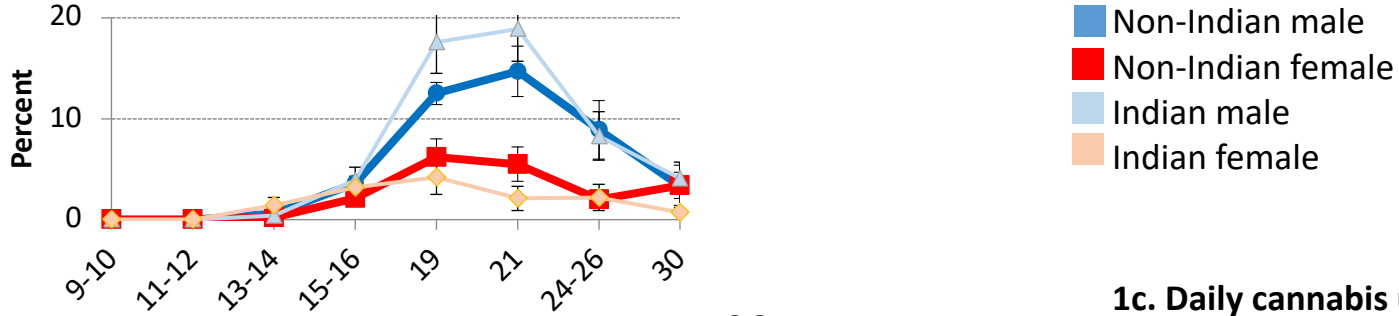


Age of onset survival curves

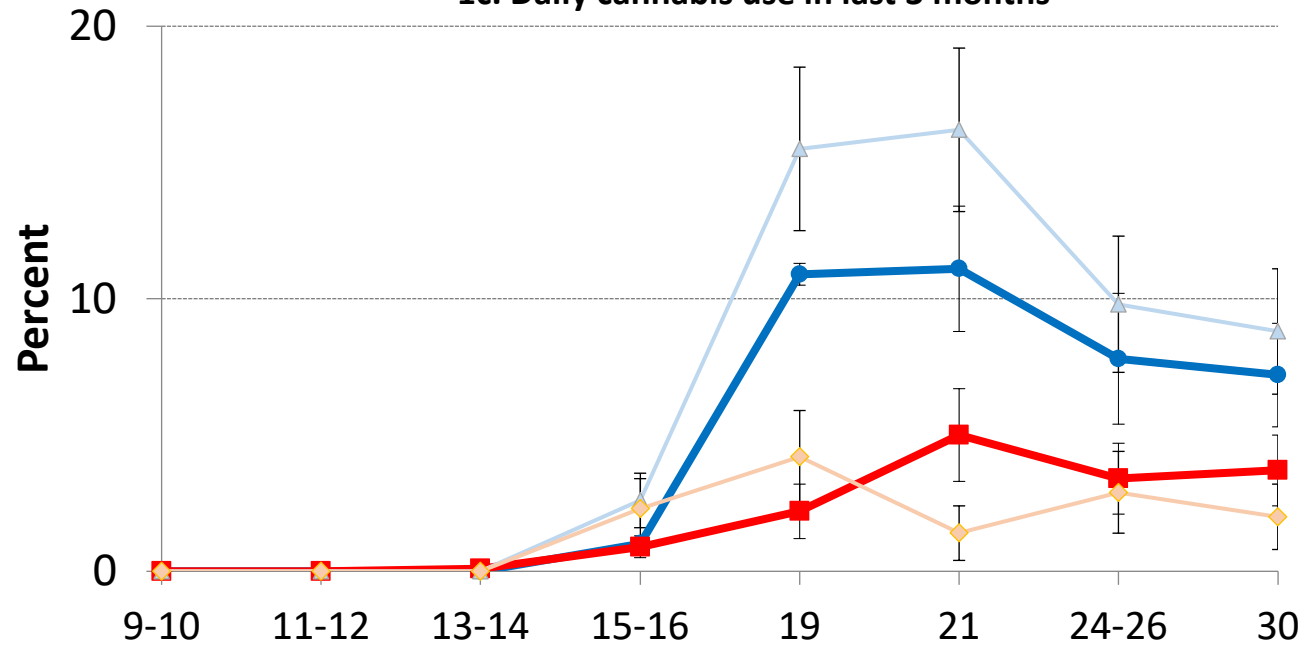


Daily Use Prevalence Rates

1a. DSM-5 Cannabis Use Disorder in last 3 months



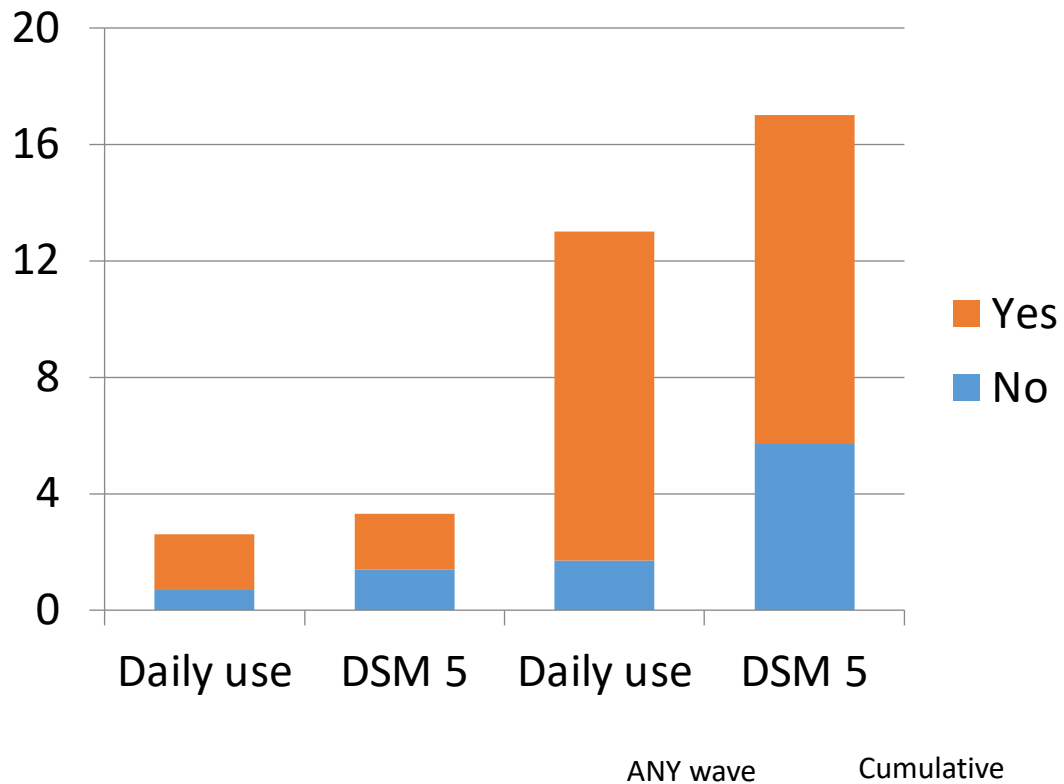
1c. Daily cannabis use in last 3 months



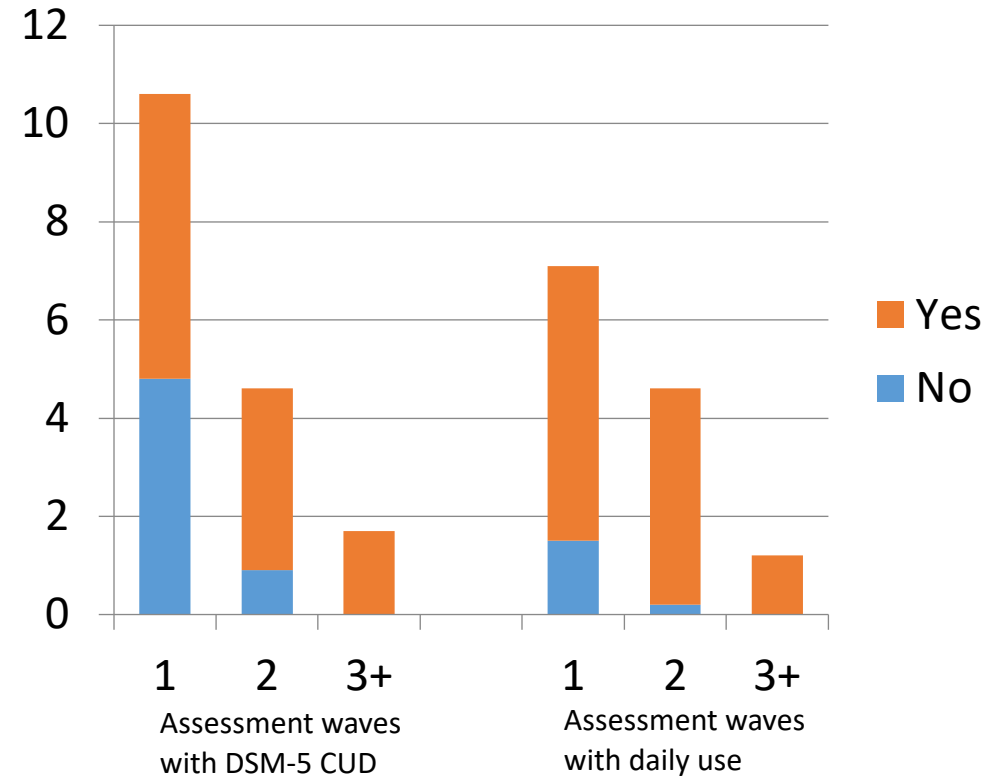
DSM-5 patterns are slightly higher than cannabis daily use.

Co-occurrence of DSM-5 and Daily use

By ANY Wave and Cumulatively



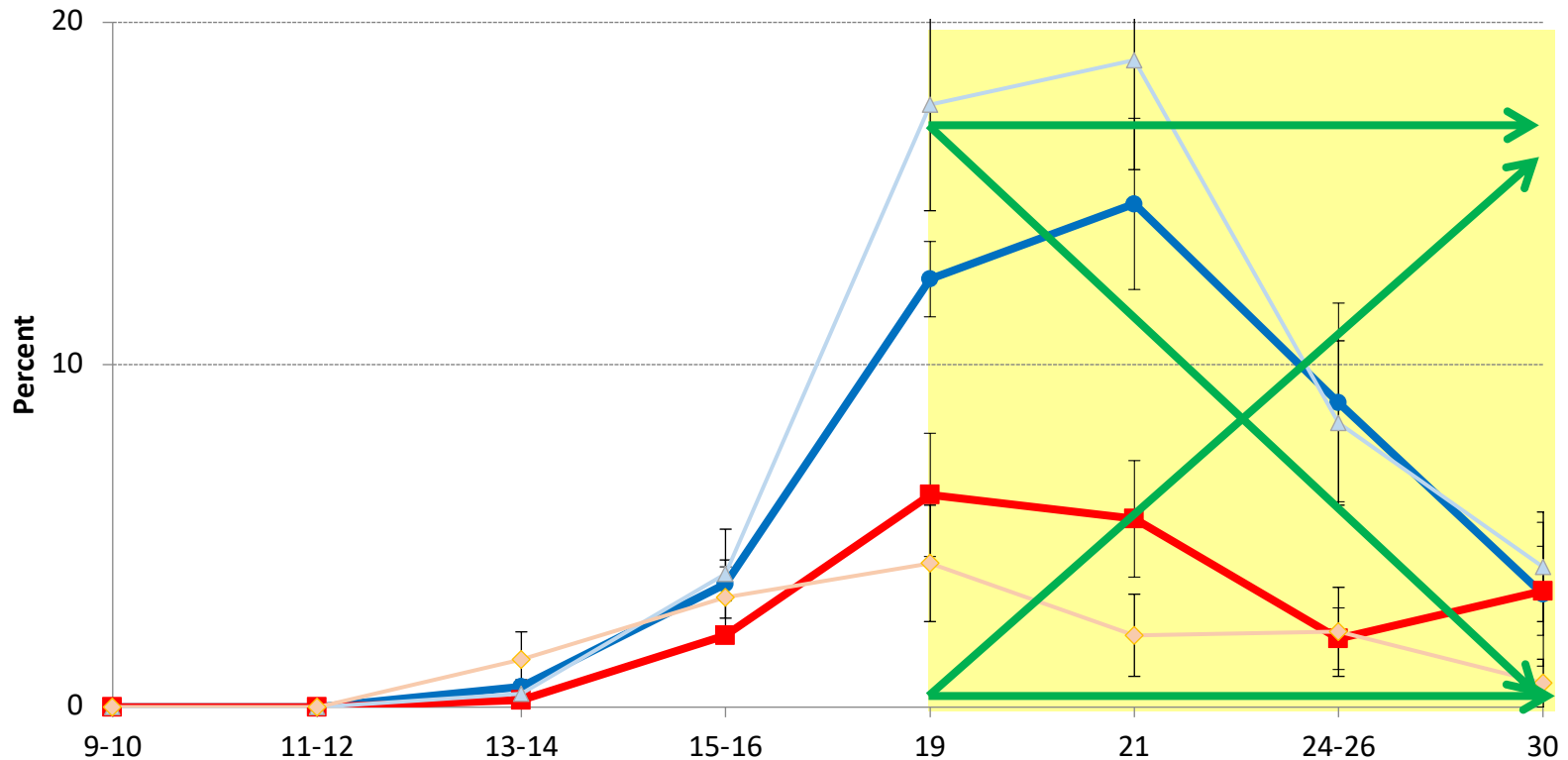
By Number of Assessments



What are risk factors for early problematic cannabis use?



Patterns of Problematic Cannabis Use



Groups:

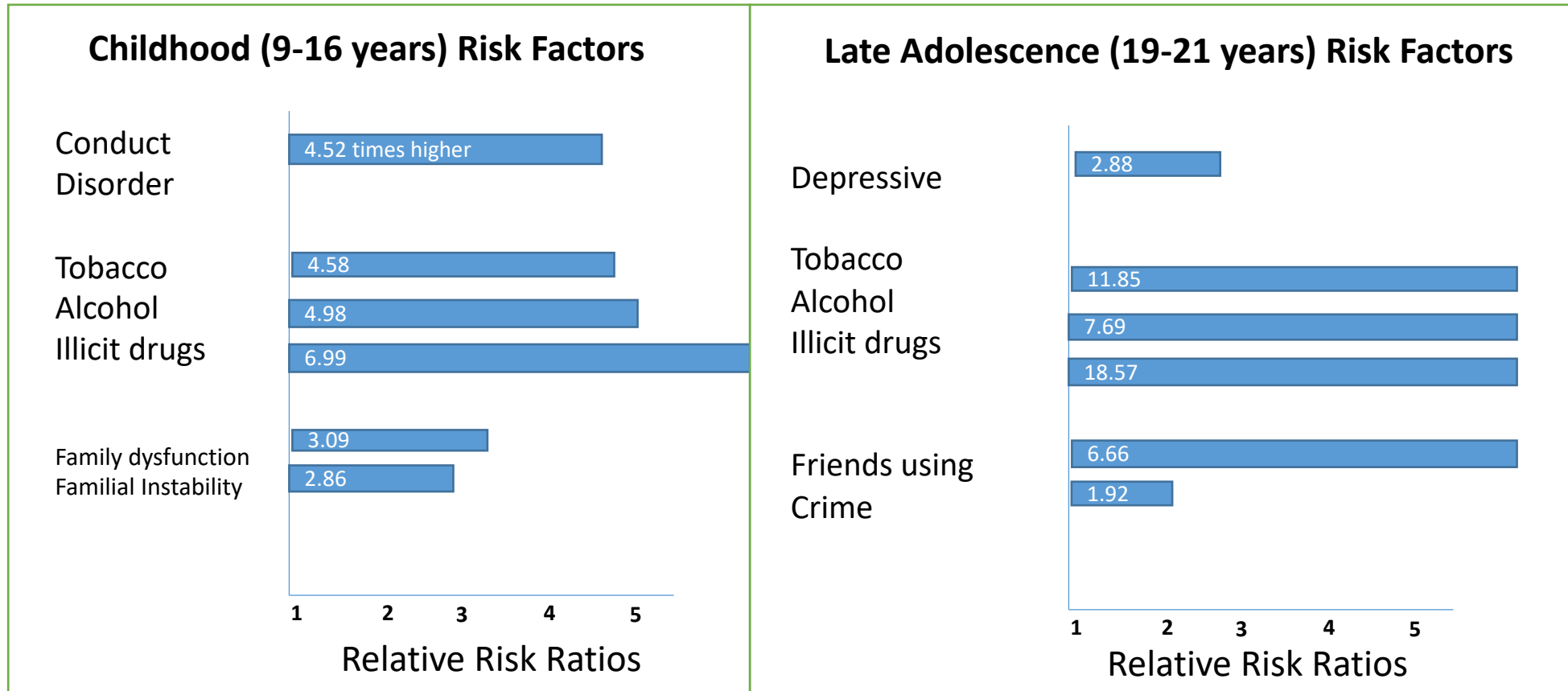
- Low/no use = 76%
- Adolescent-Limited use = 13%
- Persistent use = 7%
- Adult onset (delayed) use = 4%

- Males have higher levels of all use groups

We assessed 4 developmental pathways of cannabis use in early adulthood .

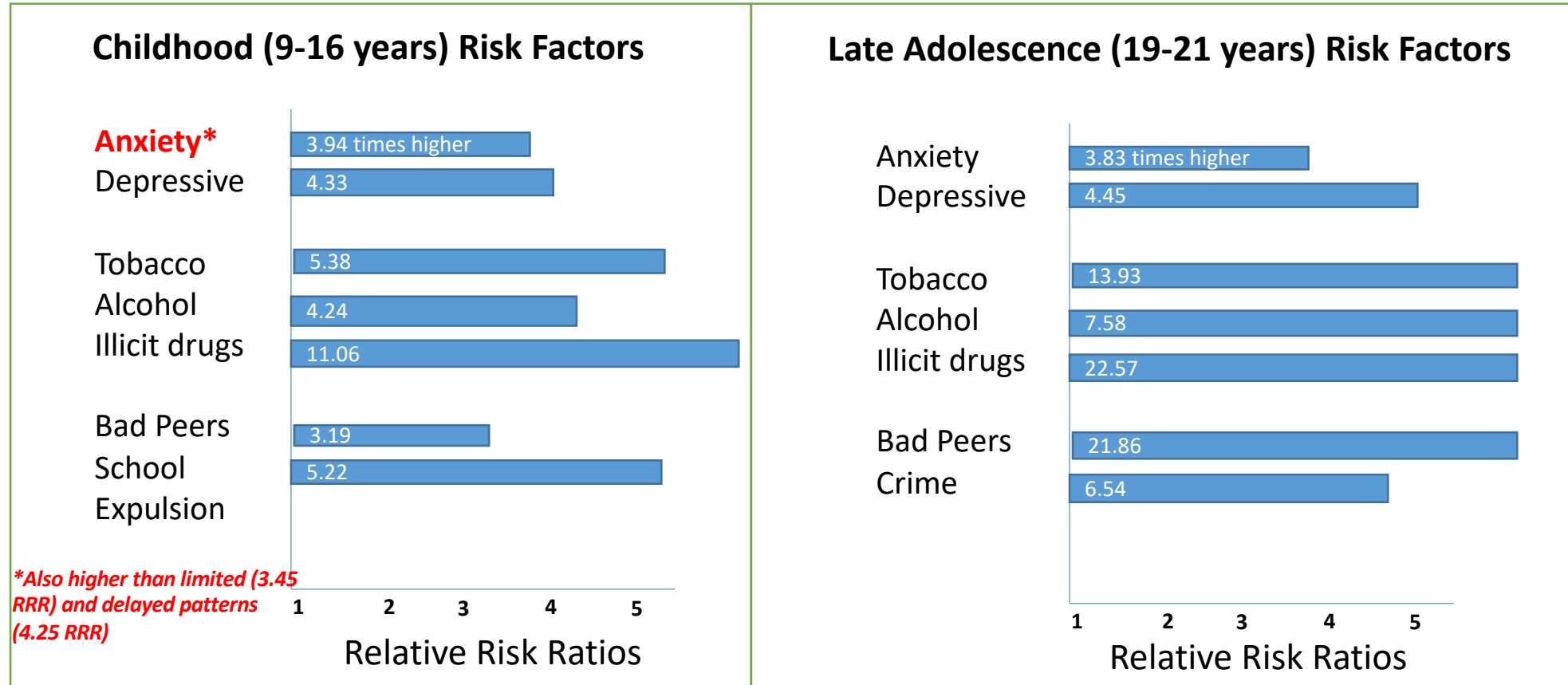


Limited Patterns vs Non-problematic



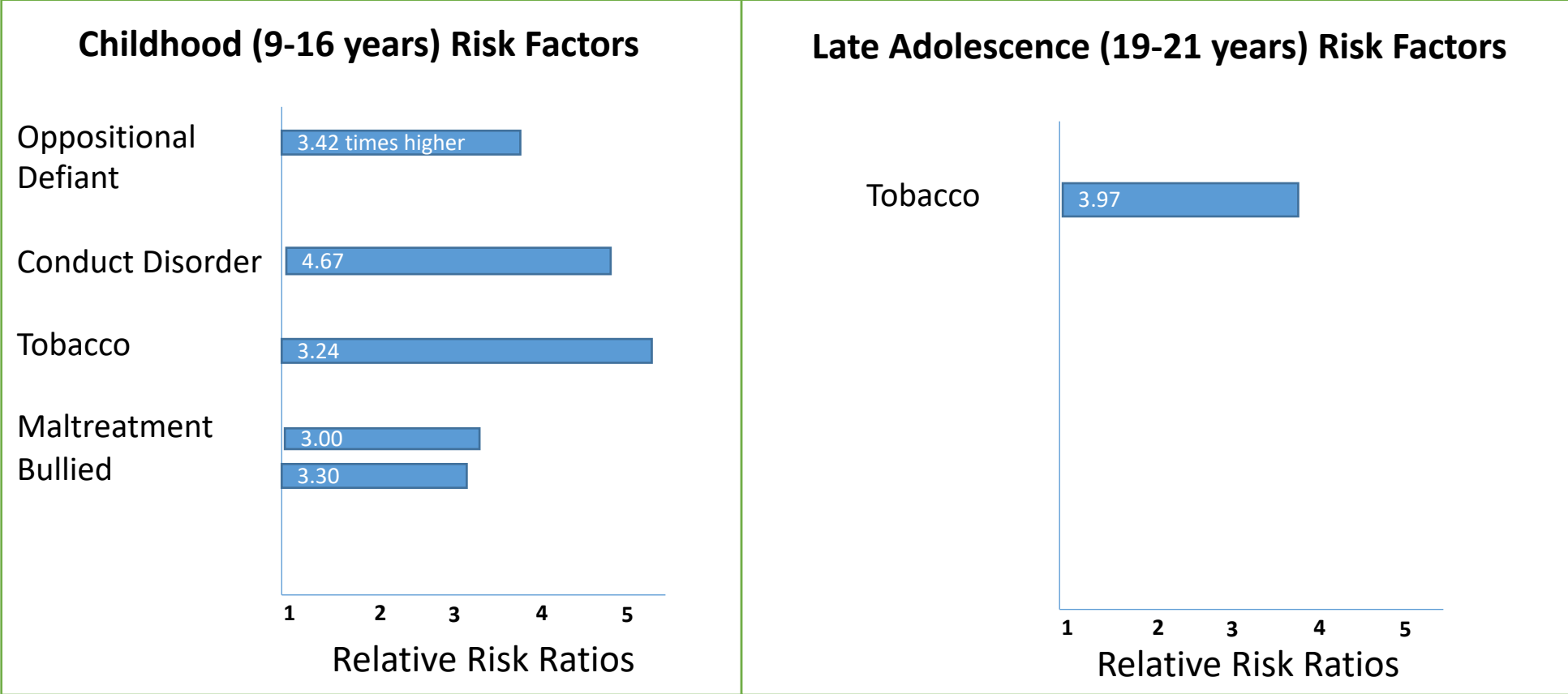
Limited users had higher rates of family dysfunction in childhood.

Persistent vs Non-problematic Patterns



Persistent users had higher rates of anx/dep in childhood and late-adolescence.

Delayed Patterns vs Non-problematic



Delayed users had more externalizing disorders and victimization in childhood.

Lesson Objective

- There were distinctive risk profiles for problematic cannabis use patterns.
 - All groups had elevated levels of early substance use
 - Limited pattern had more family dysfunction/instability in childhood (plus externalizing problems)
 - Delayed pattern had more victimization in childhood (plus externalizing problems)
 - Persistent problematic cannabis-use pattern was characterized by more anxiety/depressive disorders across development (plus externalizing problems)



What are the Adult Outcomes of Early Cannabis Use?

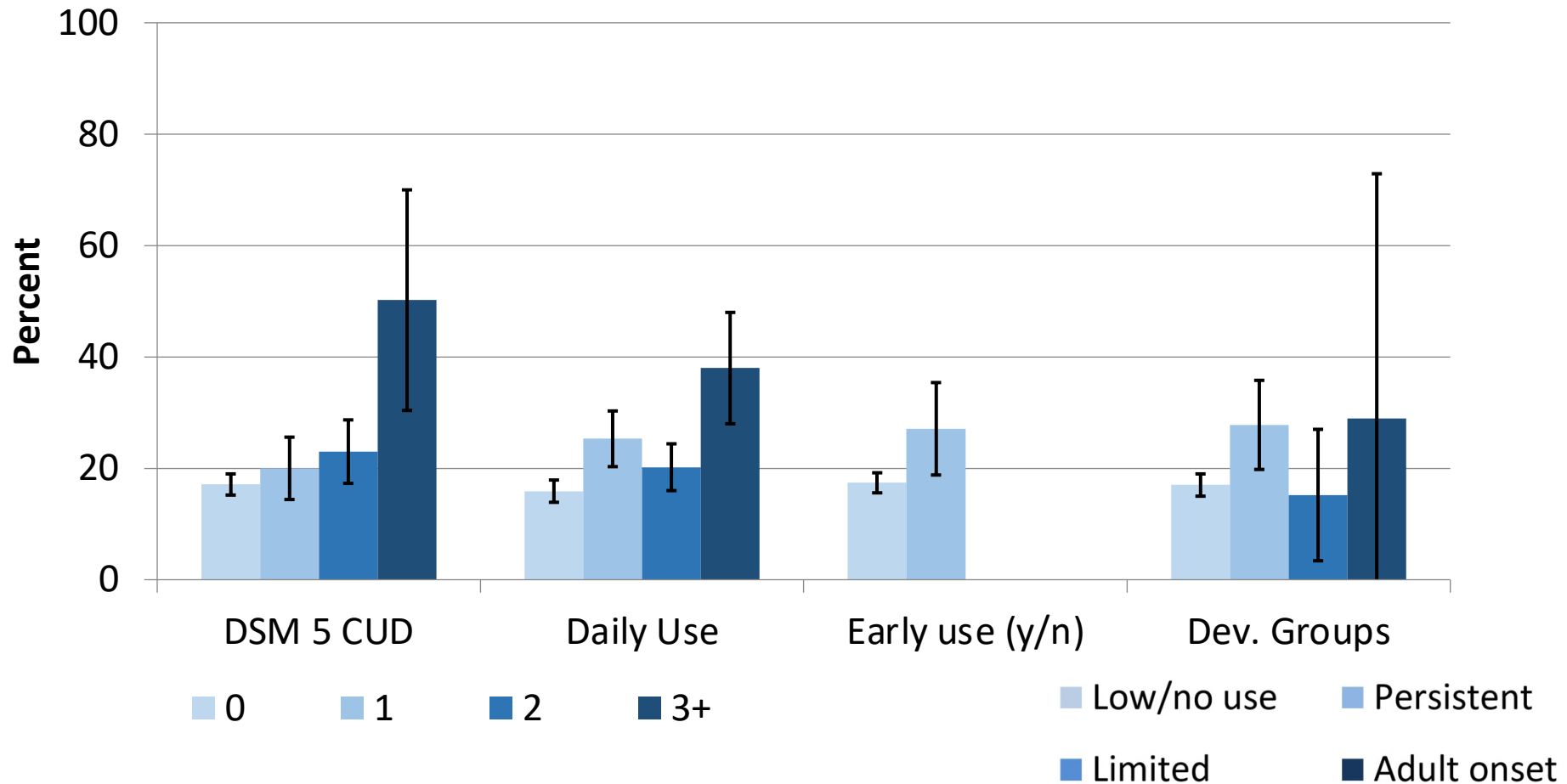


How do you define early cannabis use

1. Cumulative Cannabis Use Disorder
2. Cumulative Daily Use
3. Developmental Problematic Use Patterns
 - Non-problematic
 - Limited
 - Delayed/Adult-Onset
 - Persistent/Chronic
4. Really early problematic use (prior to age 16)

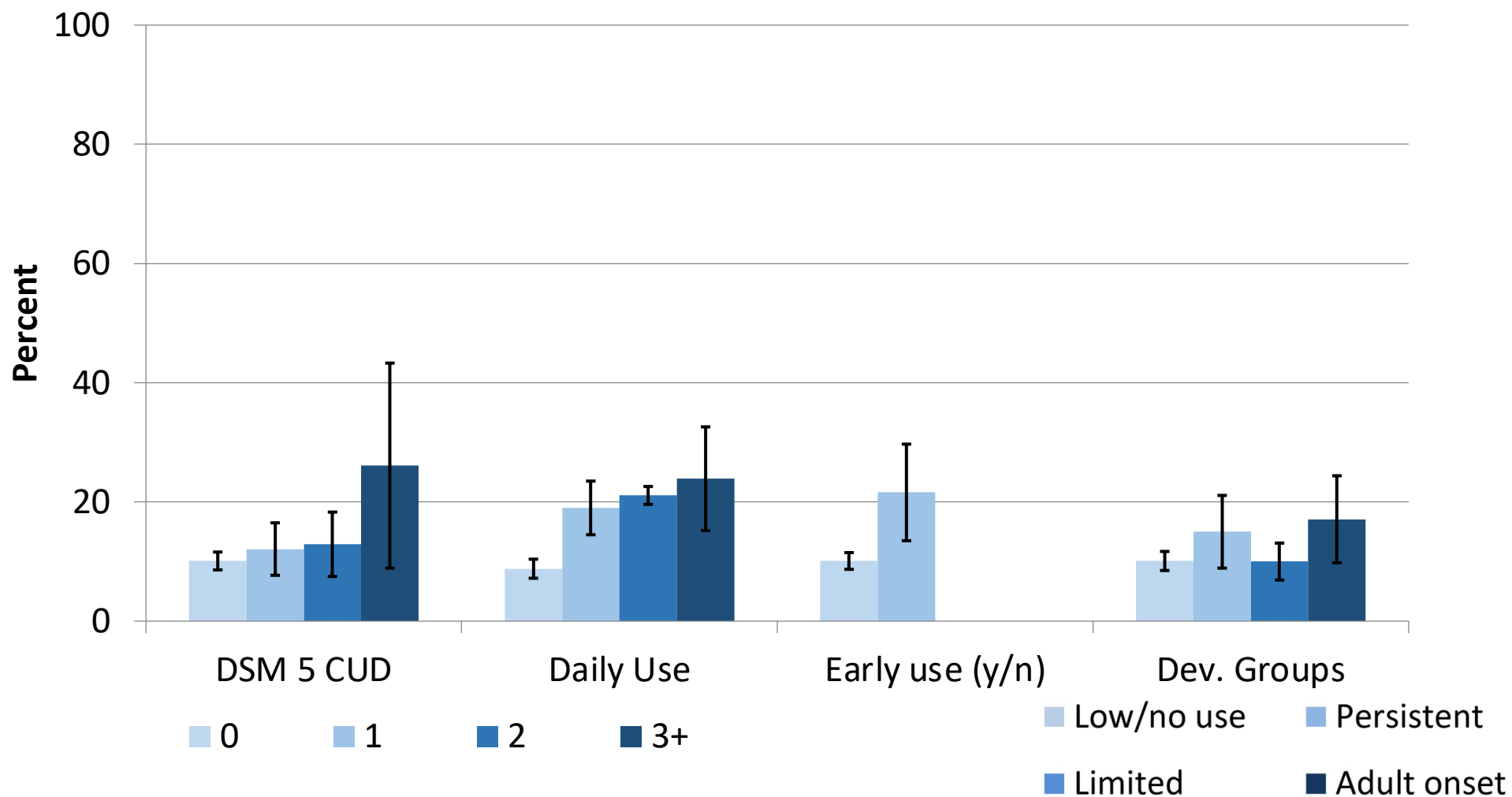


Any psychiatric disorder



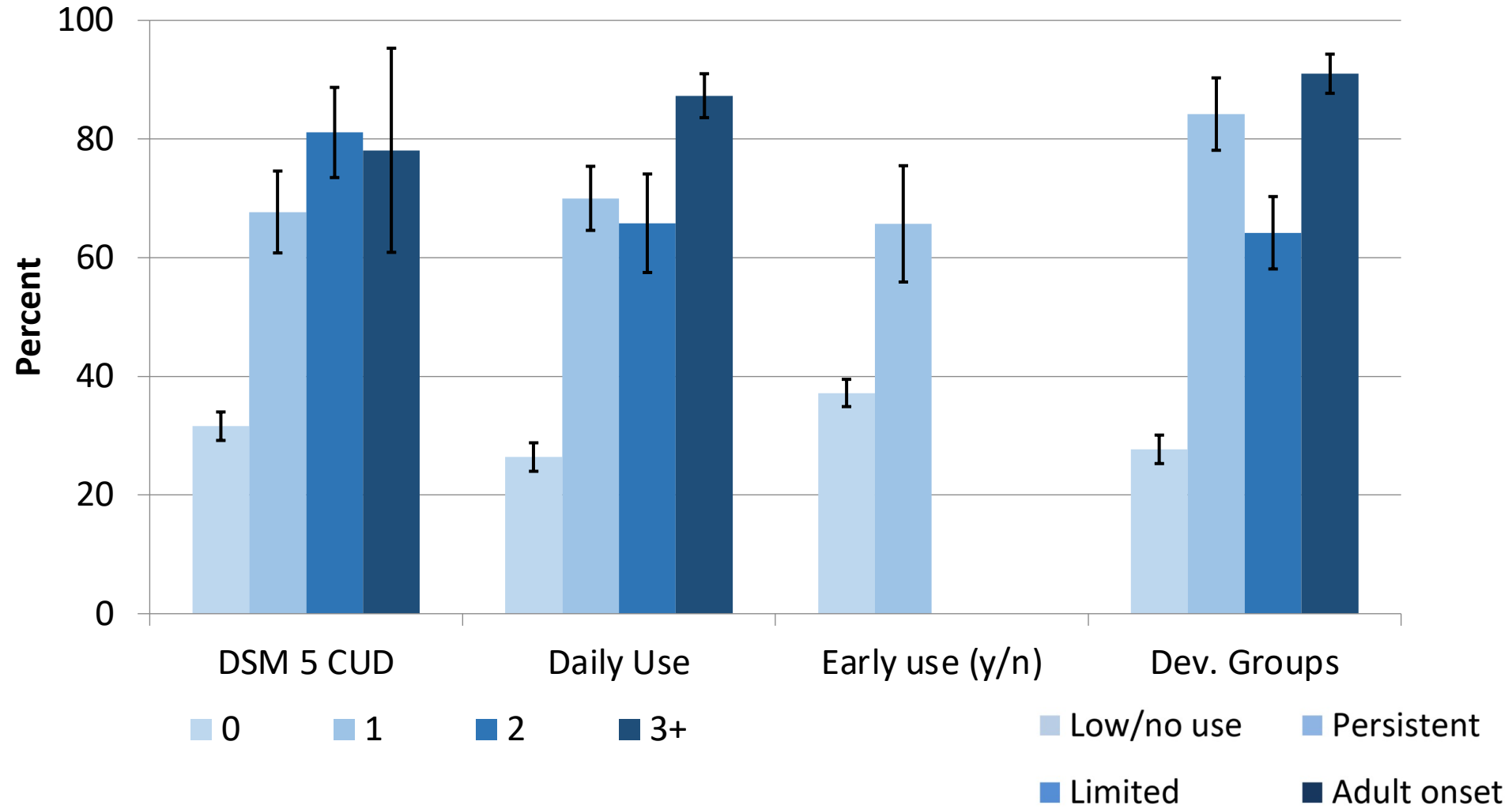
All definitions associated with some increased risk, but . . .

Any anxiety disorder



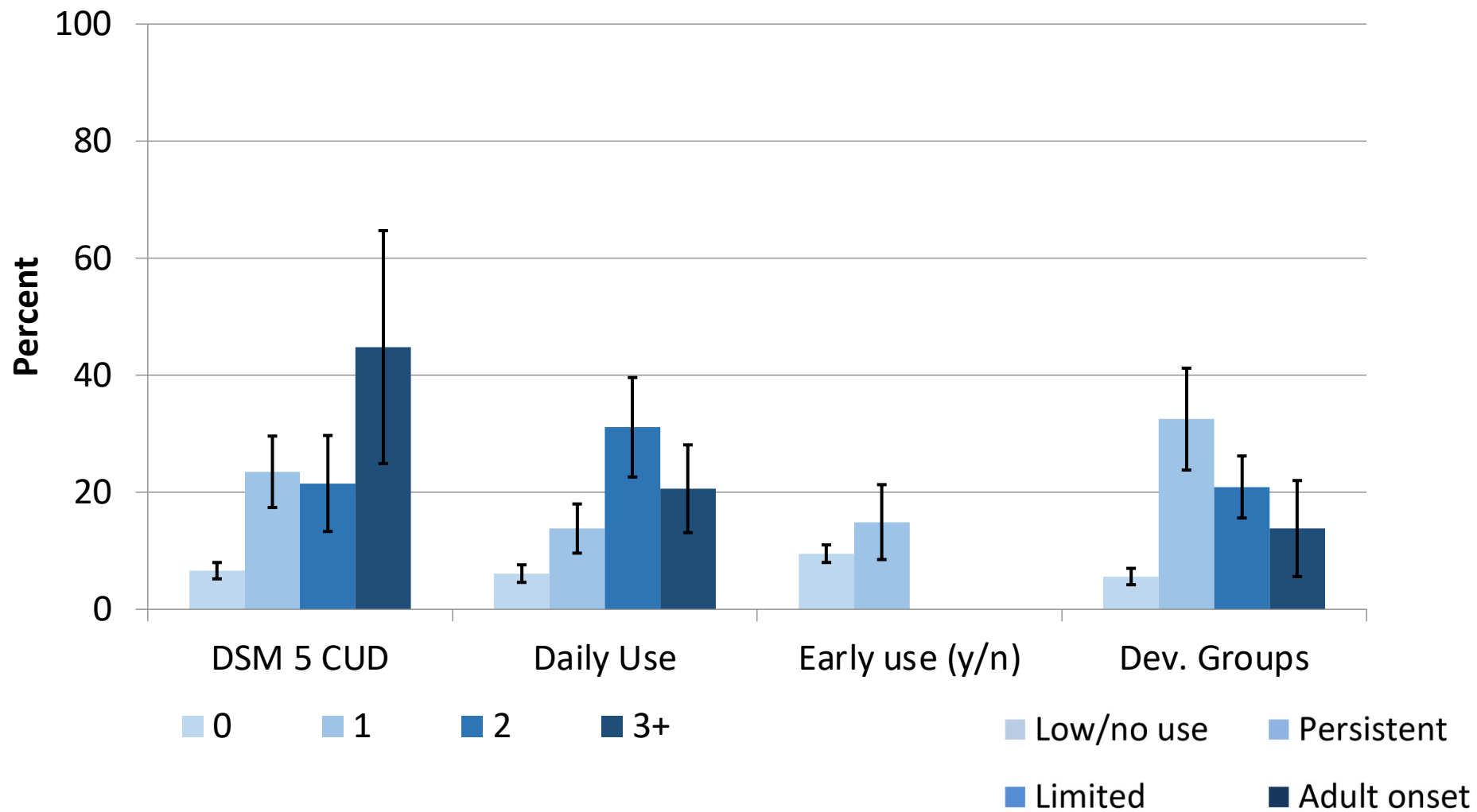
Associations with CUD and Daily use accounted for by early risk

Regular nicotine use



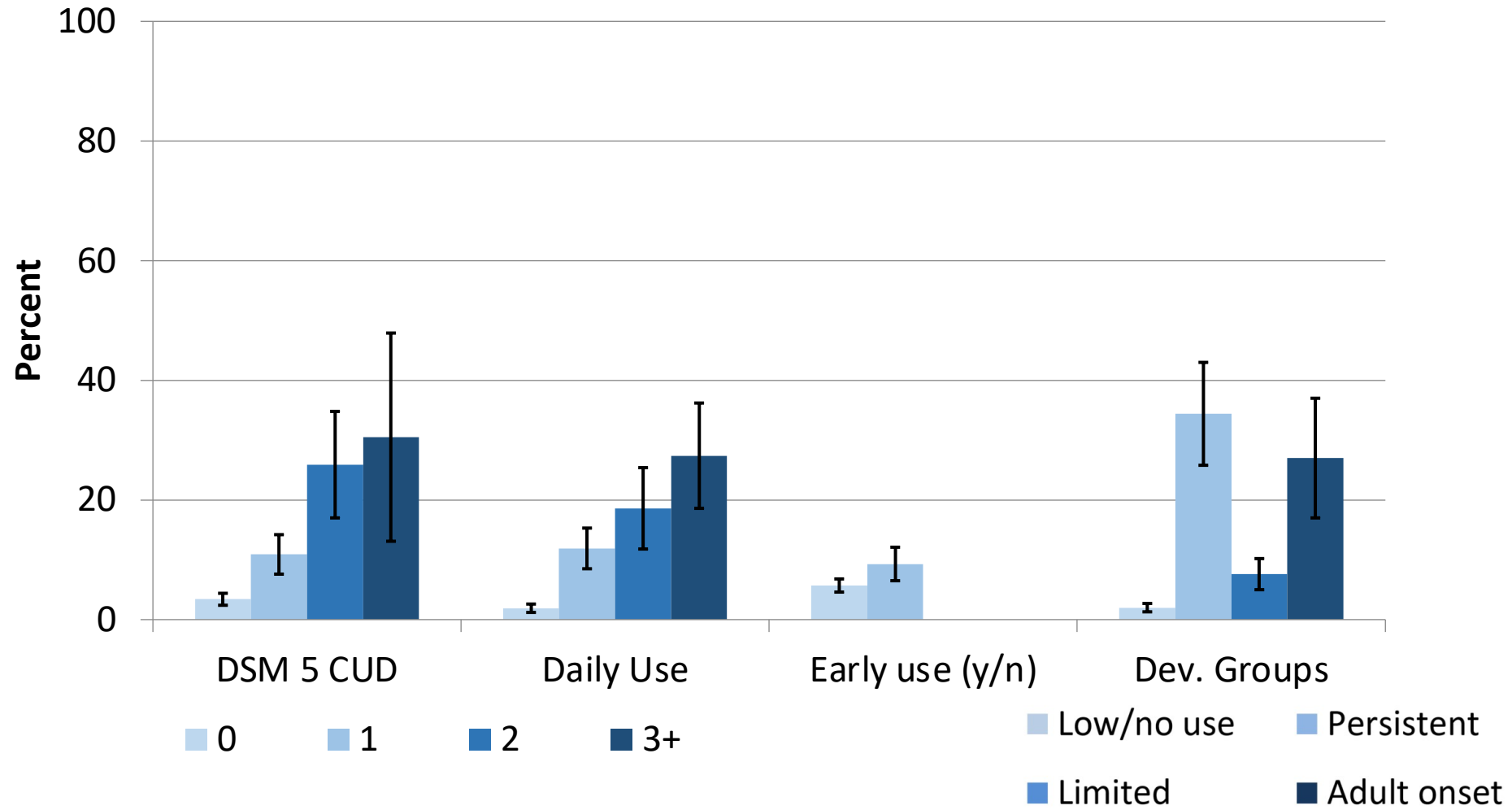
Daily use, CUD, persistent use, and adult onset associated with later nicotine use

Alcohol dx



Daily use, CUD, and persistent use associated with later alcohol dx

Illicit drug use (including heroin, cocaine, meth)

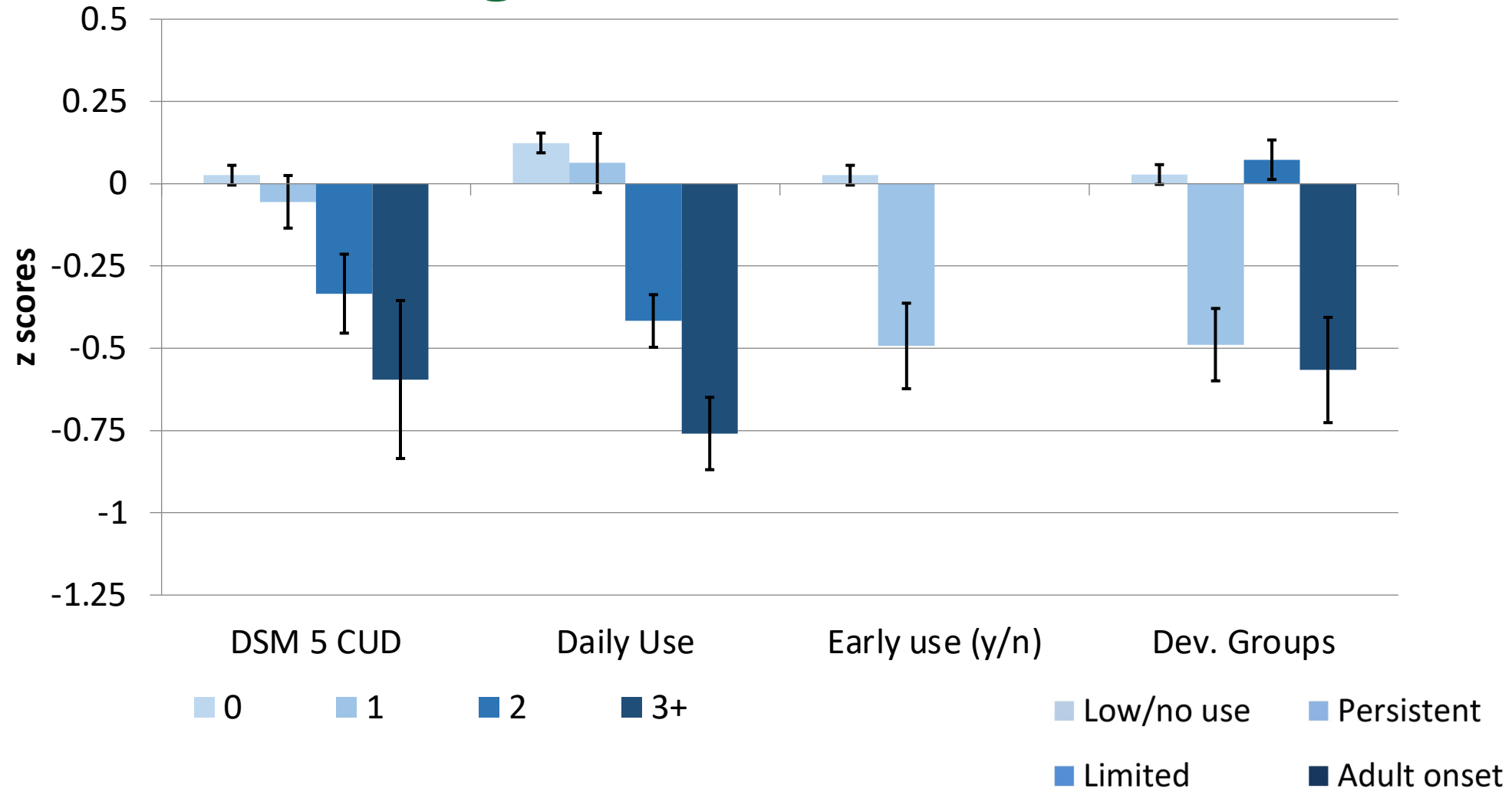


Strong associations with illicit drug use (except early use)

Adulthood Functional Outcomes Scales

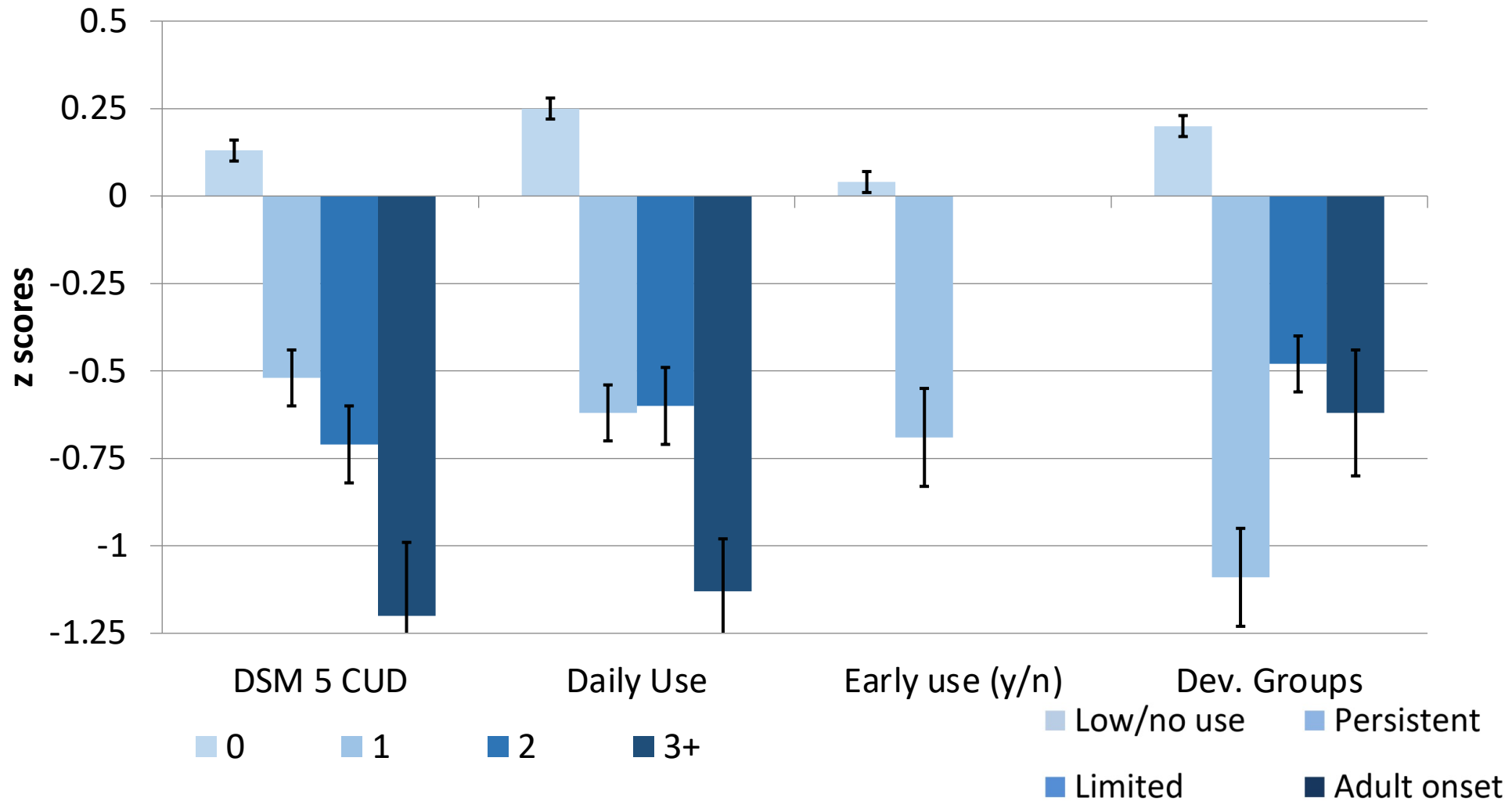
Construct	Factors measured
Health Functioning (US PHS Problems Survey)	Serious Physical Condition, Serious Accident Ever, Sexually Transmitted Disease Ever, Obesity, Daily Smoker, Perceived Poor Health, Frequent Illnesses, Slow Illness Recovery
Risky/Illegal Behaviors	Felony Charges, Police Contact, Often Lying, Frequent Physical Fights, Breaking into Properties, Frequent Drunkenness, Recent Use of Illegal Substances, Sex with Strangers
Financial/ Educational Attainment	Impoverished, High School Dropout, Fired or Quitting Job, Failing to Honor Debts/Financial Obligations, Poor Financial Management
Social Functioning	Marital Status, Parenthood, Conflicts in Interpersonal Relationships

Health functioning



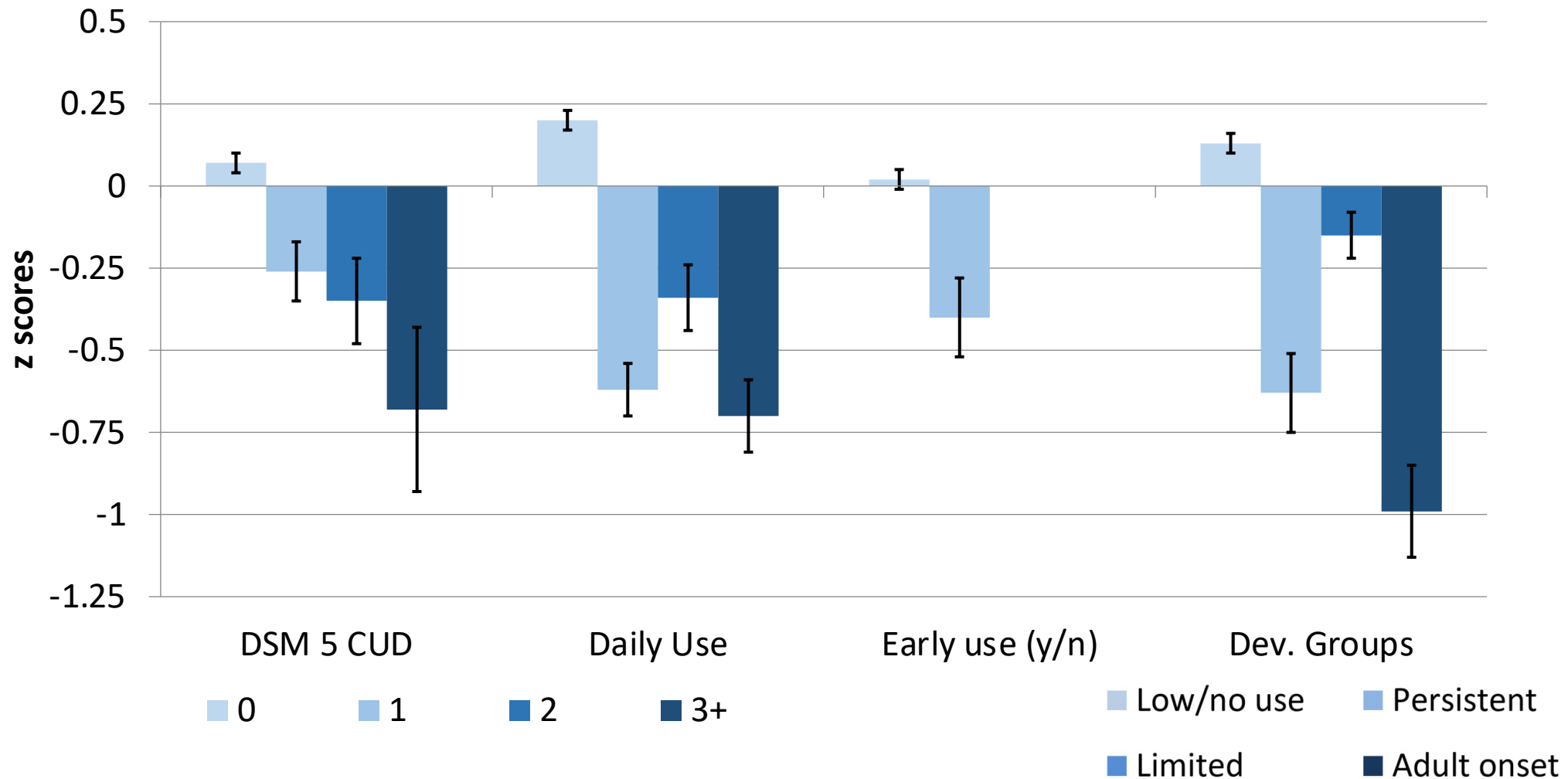
Poor health associated with chronic and recent use

Illegal/criminal behavior



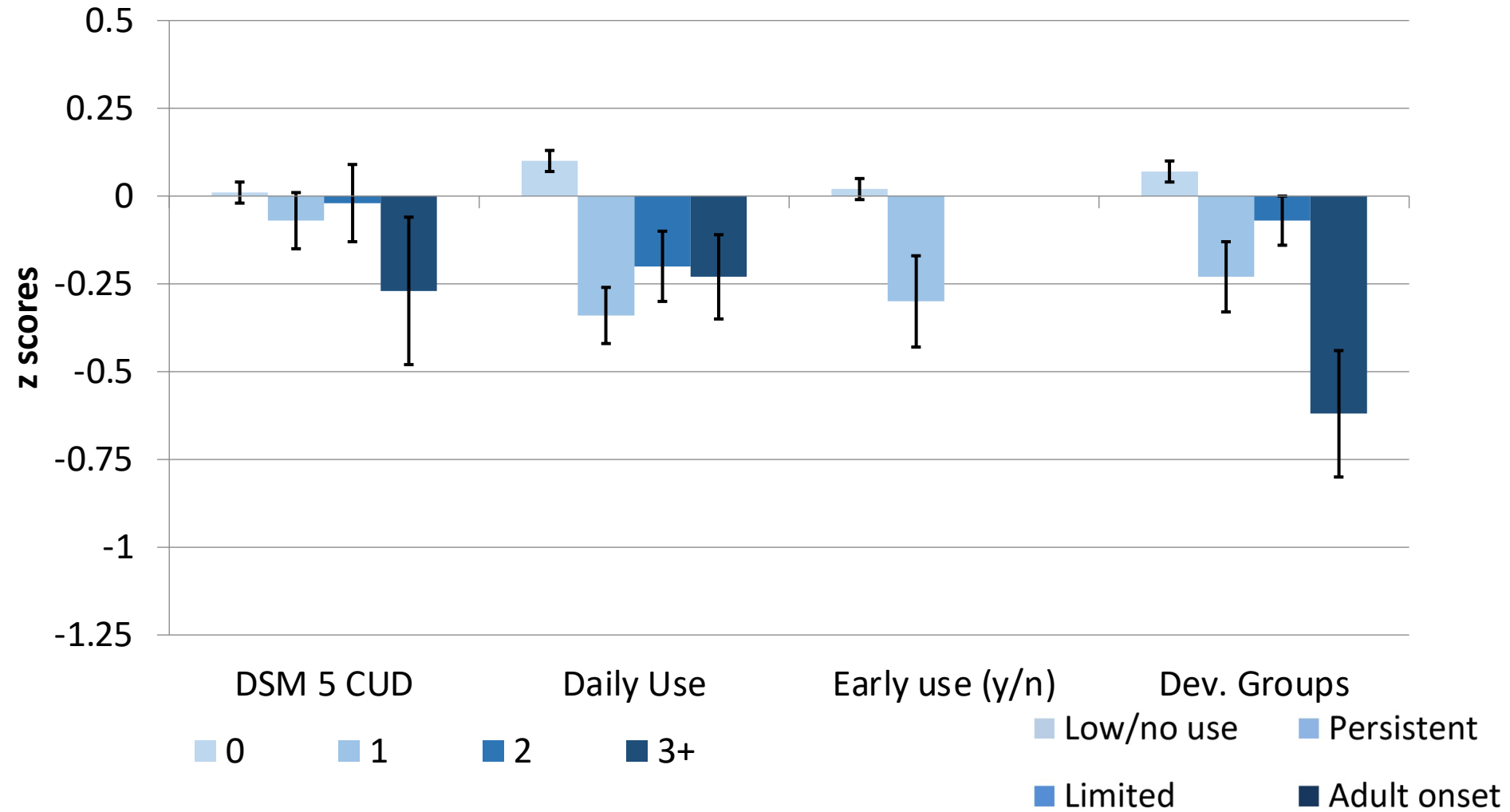
Criminality associated with chronic and recent use

Financial/educational behavior



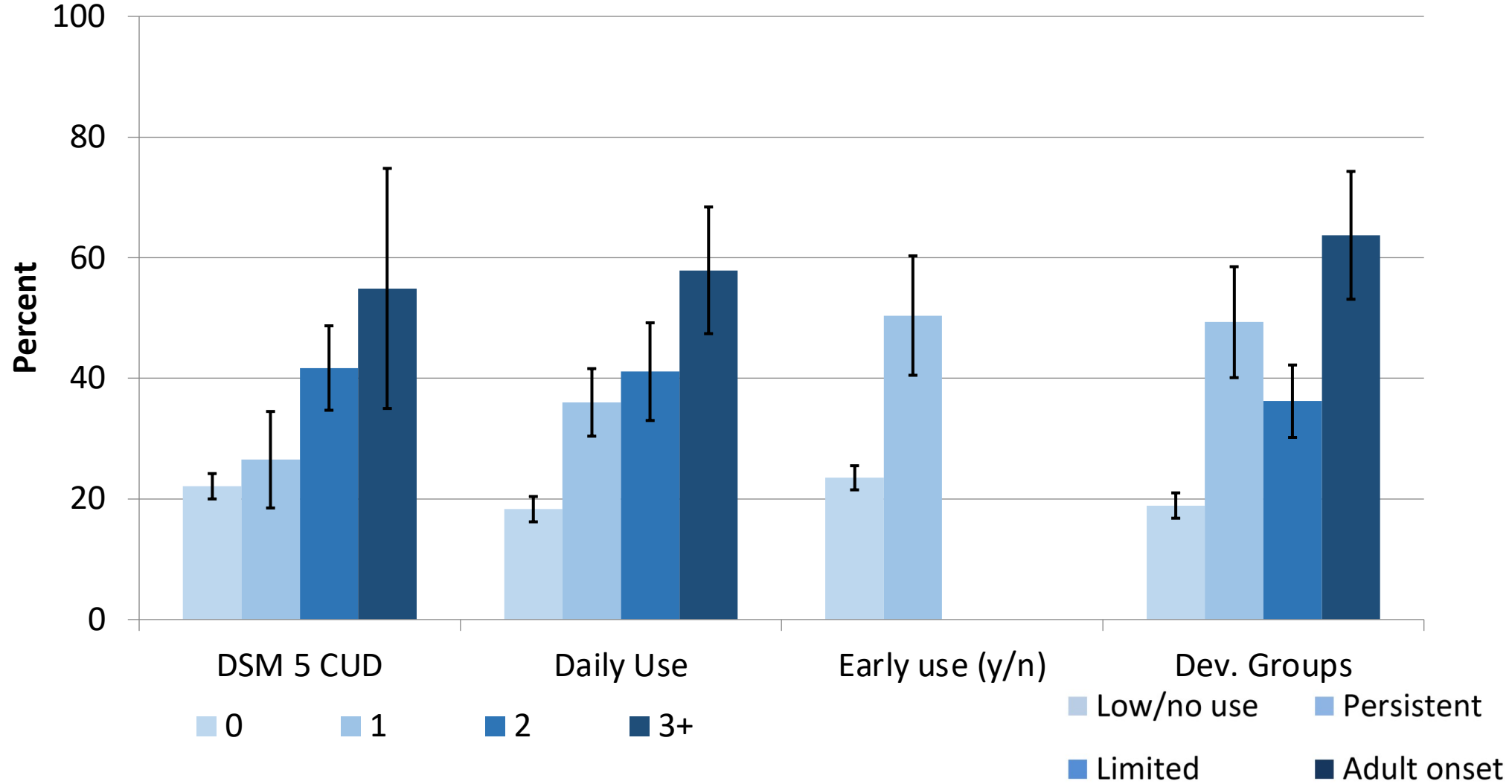
Financial health associated with chronic and recent use

Social behavior



Not much doing

Derailments



Chronic and recent use associated with disrupted transition to adulthood

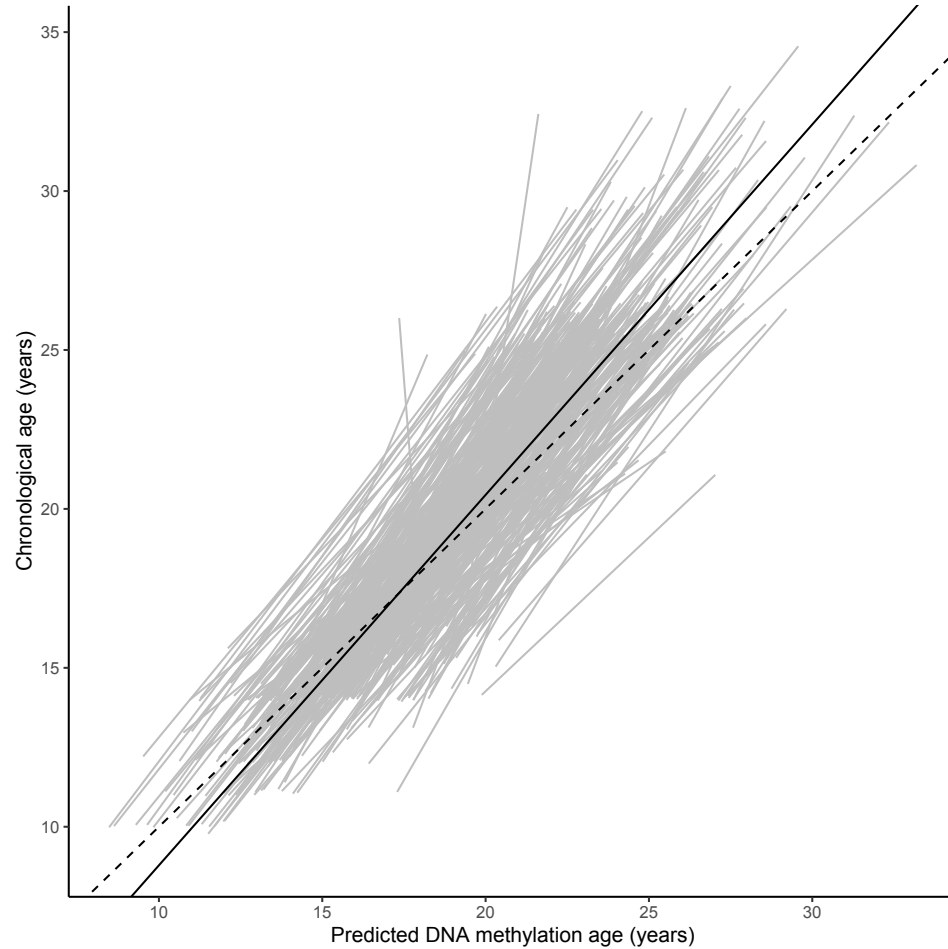
Summary of outcome models

- Early use was not associated with emotional disorders in adulthood, but was strongly associated with adult substance use
- *Really* early use not associated with any long-term outcomes
- Daily, continued-over-time cannabis use beginning on adolescence was problematic for a range of adult outcomes.
- Cessation of early use did not fully eliminate later risks; but was associated with fewer negative outcomes, with weaker effect sizes



Does such repetitive early use of cannabis use affect aging?





DNA methylation age predictions
Correlation between predicted DNA methylation age and chronological age ($r=0.90$, $P<0.0001$). Diagonal dashed line reflects the line of identity ($x=y$). Each gray line represents one individual.

Early substance use and accelerated epigenetic aging

	Difference Score		
	B	S.E.	P-value
Alcohol			
Years used up to 18	0.077	0.143	0.020
Cumulative Alcohol Quantity - log	0.078	0.187	0.024
Smoking			
Years used before 18	0.057	0.120	0.065
Cumulative Cigarette Quantity - log	0.053	0.031	0.090
Cannabis			
Years used up to 18	0.066	0.162	0.042
Years of weekly use up to 18	0.098	0.276	0.004

The difference score models were adjusted for adult chronological age, the difference between the participant's age at the time of the adolescent and adult timepoint, sex, race/ethnicity.

Caveats

Study has important strengths:

- Community- representative
- Prospective
- Rigorous assessment
- Long-term follow-up

Also, some limitations:

- Not population-representative
- Cannabis use was illegal in NC during study
- Potential for unmeasured confounding
- Causal claims not warranted



A few questions

1. Is cannabis use safe/low risk?
2. Is cannabis use safe/low risk *for teens*?
3. How does it compare to other substances?



A few thoughts

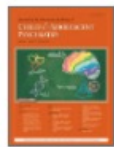
1. Pay more attention to LATE adolescence
2. Early risk factors can discriminate long-term patterns
3. Cannabis does has consequences, it varies, but there are some clues

Want to know more?



Journal of the American Academy of Child & Adolescent Psychiatry

Volume 56, Issue 2, February 2017, Pages 124-132.e2



New research

Cannabis Use and Disorder From Childhood to Adulthood in a Longitudinal Community Sample With American Indians

William E. Copeland PhD ^a, Sherika Hill PhD ^a, E. Jane Costello PhD ^a, Lilly Shanahan PhD ^b



Journal of the American Academy of Child & Adolescent Psychiatry

Available online 17 August 2021

In Press, Corrected Proof



New research

Adult Psychiatric, Substance, and Functional Outcomes of Different Definitions of Early Cannabis Use

William E. Copeland PhD ^a, Sherika N. Hill PhD, MHA ^b, Lilly Shanahan PhD ^c



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Journal of the American Academy of Child & Adolescent Psychiatry

Volume 56, Issue 11, November 2017, Pages 966-974.e4



New research

Predicting Persistent, Limited, and Delayed Problematic Cannabis Use in Early Adulthood: Findings From a Longitudinal Study

Sherika Hill PhD ^a, Lilly Shanahan PhD ^b, E. Jane Costello PhD ^a, William Copeland PhD ^a



Journal of the American Academy of Child & Adolescent Psychiatry

Volume 60, Issue 12, December 2021, Pages 1524-1532



New research

Methylomic Investigation of Problematic Adolescent Cannabis Use and Its Negative Mental Health Consequences

Shaunna L. Clark PhD ^a, Robin Chan PhD ^b, Min Zhao DDS ^b, Lin Y. Xie MS ^b, William E. Copeland PhD ^c, Karolina A. Aberg PhD ^b, Edwin J.C.G. van den Oord PhD ^b

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GSMS collaborators: Jane, Adrian, Lilly Shanahan, Sherika Hill

GSMS select funding for this work: R01MH117559, R01DA03652, R03MH094605, R01DA011301, R01DA016977, R01MH063970, R01HD29409, R01HD32336

GSMS participants, their parents, GSMS field staff





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Medicinal Marijuana?

- **Scarce / weak data** to suggest that cannabinoids improve depressive disorders, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis.
- **Very low-quality data** that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions
- Remains **insufficient evidence** to provide guidance on the use of any cannabinoids for treating mental disorders within a regulatory framework
- Data exist to support further research on the potential of cannabinoids on varying types of mental illness

IMAGEN: Age 14 Predictors of Cannabis Use at 16

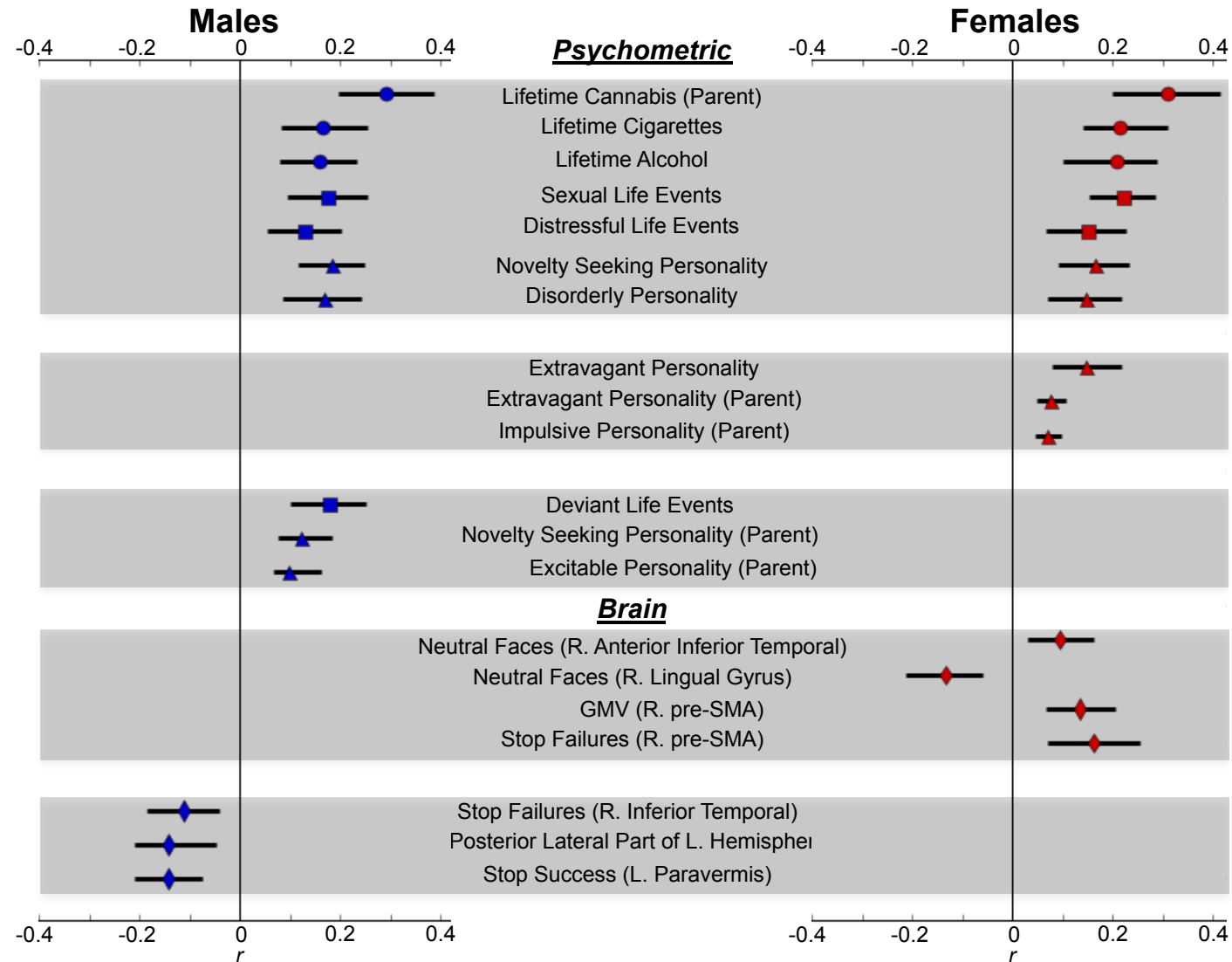
**All subjects were cannabis-naïve at age 14;
173 went on to use cannabis by age 16 (>6 uses);
1,203 reported no use by age 16.**

Variables Assessed

Modality	Measures	Data points
<i>Psychometric</i>	<ul style="list-style-type: none">• Demographics• Cognitive assessments• Personality assessment• Life-events questionnaires• Baseline smoking & alcohol use• Parent personality and substance abuse	<ul style="list-style-type: none">• 80 measures
<i>SNP</i>	<ul style="list-style-type: none">• A-priori SNPs	<ul style="list-style-type: none">• 108 SNPs
<i>Structural Neuroimaging</i>	<ul style="list-style-type: none">• Total GMV• Gray-Matter Volume ROIs	<ul style="list-style-type: none">• 1 total GMV• 278 GMV ROIs
<i>Functional Neuroimaging</i>	<ul style="list-style-type: none">• Reward Processing Task (2 Contrasts)• Stop Signal Task (2 Contrasts)• Social Processing Task (3 Contrasts)	<ul style="list-style-type: none">• 1946 ROIs (278 per contrast)
Predictors per subject		2413



IMAGEN: Age 14 Predictors of Cannabis Use at 16



Great Smoky Mountain Study

