The Adolescent Brain Cognitive Development (ABCD) Study: Overview and Contributions to our Understanding of Adolescent Mental Health

Monica Luciana, Ph.D. and William Iacono, Ph.D.

Department of Psychology and Minnesota Center for Twin and Family Research, University of Minnesota,

Minneapolis MN 55455

Adolescent Brain Cognitive Development®

Teen Brains. Today's Science. Brighter Future.

Goals of this presentation

- Overview of The Adolescent Brain Cognitive Development (ABCD) study
- ABCD's Assessment Scheme
- Findings to date
- Genes vs. Environment: How the ABCD study is poised to address important questions regarding vulnerabilities and cause/effect associations

About Us

- We are professors in the Dept of Psychology at the University of Minnesota and co-directors of the UMN’s ABCD data collection site
- We both have Ph.D.s in clinical psychology with interests in adolescent mental health, adolescent brain development, and vulnerabilities to substance use disorders.
- Luciana is an expert on the development and neural underpinnings of executive functions and emotional systems that continue to develop through adolescence.
- Iacono is the founder and director of the Minnesota Center for Twin and Family Research. He is a behavior geneticist who has used twin and adoption study methods to dissociate genetic vs. environmental influences over mental health outcomes.

Overview of the Adolescent Brain Cognitive Development (ABCD) Study:
Study Design, Objectives, and Sample

ABCD Initiated by NIH Collaborative Research on Addiction (CRAN)

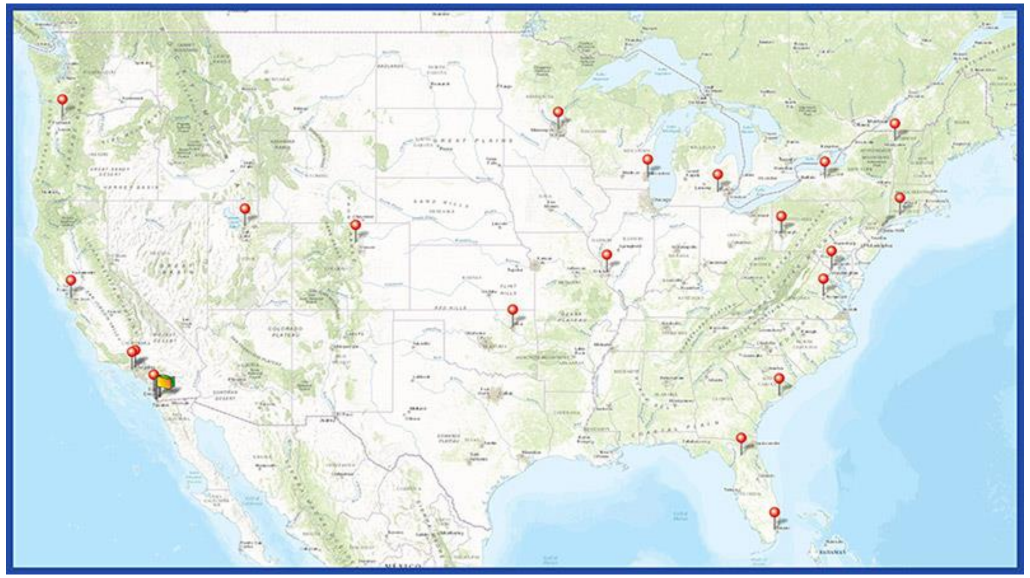
- NIDA, NIAAA, National Cancer Institute
- Many other federal collaborators are now participating

Federal Partners: ***Teen Brains. Today's Science. Brighter Future.***

- National Institute on Drug Abuse
- National Institute on Alcohol Abuse and Alcoholism
- National Cancer Institute
- National Institute of Mental Health
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- National Heart, Lung, and Blood Institute
- National Institute of Neurological Disorders and Stroke
- National Institute on Minority Health and Health Disparities
- NIH Office of Behavioral and Social Sciences Research
- NIH Office of Research on Women's Health
- Centers for Disease Control and Prevention - Division of Adolescent and School Health
- National Institute of Justice
- Centers for Disease Control and Prevention - Division of Violence Prevention
- National Science Foundation
- National Endowment for the Arts

Design Overview

- **The largest adolescent-focused study of brain and behavioral development world-wide**
- **11,875 youth ages 9-10 have been enrolled nationwide; goal is to follow them for a period of at least 10 years**
  - Singletons and twins are part of the study sample
  - School-based recruitment, epidemiologically ascertained sample (singletons)
  - Recruitment from birth registries (twins; 4 sites within the Consortium)
  - Multimodal neuroimaging
  - Extensive health and behavioral assessment
  - Activities and environments monitored; novel technologies
  - Biosamples: hormones, substance use
  - Open science framework



Study Objectives

- Develop national standards for normal brain development in youth.
- Identify individual developmental trajectories (e.g., of cognitive, and emotional development), and the factors that can impact them (risk and protection).
- Examine the roles of genetic vs. environmental factors on development, as well as interactions (e.g., by analysis of data from over 800 twin pairs).
- Study the effects of health, physical activity, sleep, as well as sports and other injuries on brain development and other outcomes.
- Study the onset and progression of mental disorders, factors that influence course or severity; and the relationship between mental disorders and substance use.
- Determine how exposure to substances such as alcohol, nicotine, & cannabis, affects developmental outcomes and vice versa.

Why now?

Maturing Technology

- Multisite, multiple modality neuroimaging, affordable genotyping
- Novel assessment technologies (i.e., web, mobile, wearables).

Maturing Scientific Workforce

- Experience in long-term multi-site studies with families and youth.
- Increasing acceptance of open science
- Advanced computational expertise

Rapid Changes in the Culture

- Changing policies and laws with respect to substances available to youth
- Changes in substances, modes of use
- Increasing screen time, social media engagement, etc.

Children's Hospital Los Angeles

Florida International University

Laureate Institute for Brain Research

Oregon Health & Science University

Medical University of South Carolina

SRI International

University of California, Los Angeles

University of California, San Diego

Coordinating Center
University of California, San Diego
Program Co-Directors
Associate Directors

University of Colorado

University of Florida

Data Analysis & Informatics Center
University of California, San Diego
Project Director

University of Maryland

University of Michigan

Federal Collaborators
NIDA, NIAAA, NCI, NICHD, NIMH, NIMHD, NINDS, OBSSR, ORWH, CDC-DASH, NIJ, NHLBI, NEA

University of Minnesota

University of Pittsburgh

University of Rochester

University of Utah

University of Vermont

University of Wisconsin-Milwaukee

Virginia Commonwealth University

Washington University

Yale University

ABCD Assessment Schedule

Adolescent Brain Cognitive Development

- Comprehensive assessments at baseline and biennial follow up visits (including multimodal imaging)
- Briefer assessments at face-to-face interim year visits
- More frequent phone/web assessments (every 6 months)
- Both parents and youth provide information
- Goal was to select measures that are brief, automated, and harmonized with other large-scale studies

ABCD Youth Protocol Summary: Baseline

Physical Health
- PhenX Anthropometrics (height/ weight/waist measurements)
- Snellen Vision Screener
- Edinburgh Handedness Inventory
- Youth Risk Behavior Survey: Exercise
- Pubertal Development Scale
- Menstrual Cycle Survey (pubescent girls)
- Screen Time Survey

Brain Imaging
Structural MRI
- 3D T1 - Weighted
- 3D T2 - Weighted
- Diffusion Tensor Imaging

Functional MRI (fMRI)
- Resting State
- Monetary Incentive Delay Task
- Stop Signal Task
- Emotional N-Back Task

Biospecimens
- Breathalyzer and Oral Fluids (subset)
- Saliva Samples for DNA, Puberty
- Blood Samples (subset)
- Hair Sample
- Baby Teeth

Mental Health
Kiddie Schedule for Affective Disorders and Schizophrenia
- Background Items Survey
- Diagnostic Interview for DSM-5 (5 modules)

PhenX UPPS-P for Children Survey

PhenX Behavioral Inhibition/ Behavioral Approach System (BIS/BAS) Scales

Prodromal Psychosis Scale

Youth Resilience Scale

Neurocognition
NIH Toolbox Tasks:
- Picture Vocabulary
- Flanker Inhibitory Control & Attention
- List Sorting Working Memory
- Dimensional Change Card Sort
- Pattern Comparison Processing Speed
- Picture Sequence Memory
- Oral Reading Recognition

Rey Auditory Verbal Learning Task

Cash Choice Task

Little Man Task

Matrix Reasoning Task

RAVLT Delayed Recall

Culture & Environment
- Prosocial Tendencies Survey
- PhenX Acculturation Survey
- Parental Monitoring Survey
- Acceptance Subscale from Children's Report of Parental Behavior Inventory (CRPBI) - Short
- PhenX Family Environment Scale - Family Conflict
- PhenX Neighborhood Safety/ Crime Survey
- PhenX School Risk & Protective Factors Survey

Substance Use
For most participants*:
- Timeline Follow-Back Survey
- PhenX Peer Group Deviance Survey
- PATH Intention to Use Tobacco Survey
- Caffeine Intake Survey
- Participant Last Use Survey (PLUS) for substance use within the last 24 hrs

Other Data Sources
- Geocoding from Residential History
- School Records
- FitBit® (subset)
- Brief Problem Monitor - Teacher Form

Adolescent Brain Cognitive Development

Teen Brains. Today's Science. Brighter Future.

*For participants with differing levels of substance use (low, moderate, heavy), follow-up items include: iSay II Q2 Sipping items; Tobacco Low-Level Use Measure; MJ Low-Level Use Measure; PhenX Acute Subjective Response to Alcohol, Tobacco, or MJ; Hangover Symptom Scale; Rutgers Alcohol Problem Index (RAPI); Nicotine Dependence (PATH); Drug Problem Index (MAPI); MJ Problem Index (MAPI)

ABCD Parent Protocol Summary: Baseline

Physical Health

PhenX Demographics Survey

Medical History Questionnaire

Developmental History Questionnaire

PhenX Medications Survey

Menstrual Cycle Survey

Sleep Disturbances Scale for Children

Sports and Activities Involvement Questionnaire

Screen Time Survey

Ohio State TBI Screen - Short

Mental Health

Kiddie Schedule for Affective Disorders and Schizophrenia

- Background Items Survey
- Diagnostic Interview for DSM-5

Child Behavior Checklist

General Behavior Inventory - Mania

Adult Self Report Survey

Family History Assessment Survey

Substance Use

Parent Rules Survey

PhenX Community Risk and Protective Factors

Participant Last Use Survey (PLUS) for substance use within the last 24 hrs.

Culture & Environment

Vancouver Index of Acculturation - Short Survey

Multi-Group Ethnic Identity Measure-R Survey

Prosocial Tendencies Survey

Mexican American Cultural Values Scale

PhenX Acculturation Survey

PhenX Family Environment Scale - Family Conflict

PhenX Neighborhood Safety/ Crime Survey

Native American Acculturation Scale

Adolescent Brain Cognitive Development

Teen Brains. Today's Science. Brighter Future.

ABCDStudy.org

*For participants with differing levels of substance use (low, moderate, heavy), follow-up items include: iSay II Q2 Sipping items; Tobacco Low-Level Use Measure; MJ Low-Level Use Measure; PhenX Acute Subjective Response to Alcohol, Tobacco, or MJ; Hangover Symptom Scale; Rutgers Alcohol Problem Index (RAPI); Nicotine Dependence (PATH); Drug Problem Index (MAPI); MJ Problem Index (MAPI)

ABCD Mid-year Follow-up Protocol Summary

ABCD Follow-up Measure	What it measures:	Youth (min)	Parent (min)
Introduction			4
Brief Problem Monitor Scale	Dimensional psychopathology, adaptive functioning in past week	3	
Yes/No Substance Use Questions	Past 6-month heard-of or use of substances	3-7	
NIH Toolbox Positive Affect Short Form	Positive emotions and affective well-being in past week	1	
Mid Year Phone Interview Closing Questions		2	
	Total Minutes	9-13	4

Adolescent Brain Cognitive Development®

Teen Brains. Today's Science. Brighter Future.

Mid-year follow-ups (every six months) in the form of phone calls

Youth = the source of information

Emphasis is on substance use behaviors, adaptive function/psychopathology, and affective well-being

ABCD Youth Protocol Summary: One-year Follow-up

Physical Health

PhenX Anthropometrics (height/weight/waist measurements)

Pubertal Development Scale and Menstrual Cycle Survey

Screen Time Survey

Gender Identity Questionnaire

Mental Health

Kiddie Schedule for Affective Disorders and Schizophrenia

- Background Items Survey
- Diagnostic Interview for DSM-5 (Suicide module and Alcohol Use Disorder/Drug Use Disorder modules, if applicable)

Prodromal Psychosis Scale

7-Up Mania Items

Abbreviated Self-Reported Delinquency Scale

NIH Toolbox Positive Affect Items

Brief Problem Monitor Scale

Life Events Scale

Substance Use

Participant Last Use Survey (PLUS) for substance use within the last 24 hrs

For most participants*:

PhenX Peer Group Deviance Survey

PATH Intention to Use Tobacco Survey

PhenX Perceived Harm of Substance Use

PhenX Peer Tolerance of Use

Alcohol Expectancies Questionnaire

Adolescent Smoking Consequences (Expectancies)

Marijuana Effect Expectancy Questionnaire

Timeline Follow-back Survey

ISay II Q2 Sipping Items (sip)

Low Level Tobacco Use (puff)

Low Level Marijuana Use (puff/taste)

Caffeine Intake Survey

Neurocognition

Delay Discounting Task

Emotional Faces Stroop Task

Culture & Environment

Prosocial Behavior Survey

PhenX Acculturation Survey

Parental Monitoring Survey

Acceptance Subscale from Children's Report of Parental Behavior Inventory - Short

PhenX Family Environment Scale - Family Conflict

PhenX Neighborhood Safety/Crime Survey

PhenX School Risk & Protective Factors Survey

Perceived Discrimination Scale

Wills Problem Solving Scale

Biospecimens

Subset of participants:
Breathalyzer (alcohol screen)
Oral Fluids (drug screen)
Urine (NicAlert)

Oral Fluids (pubertal hormones)

Hair (substance use metabolites)

Baby Teeth (substance and environmental toxin exposure)

The one-year assessment does not include neuroimaging and is more limited in scope.

Data Access and Findings

- The Consortium maintains rigorous processes for data quality control
- ABCD encourages an open science model
- Anyone can access the data via the NIH National Data Archive (NDA): https://nda.nih.gov/
- Curated data releases occur annually; to date, there have been two such releases
- Fast track imaging data can be accessed more frequently

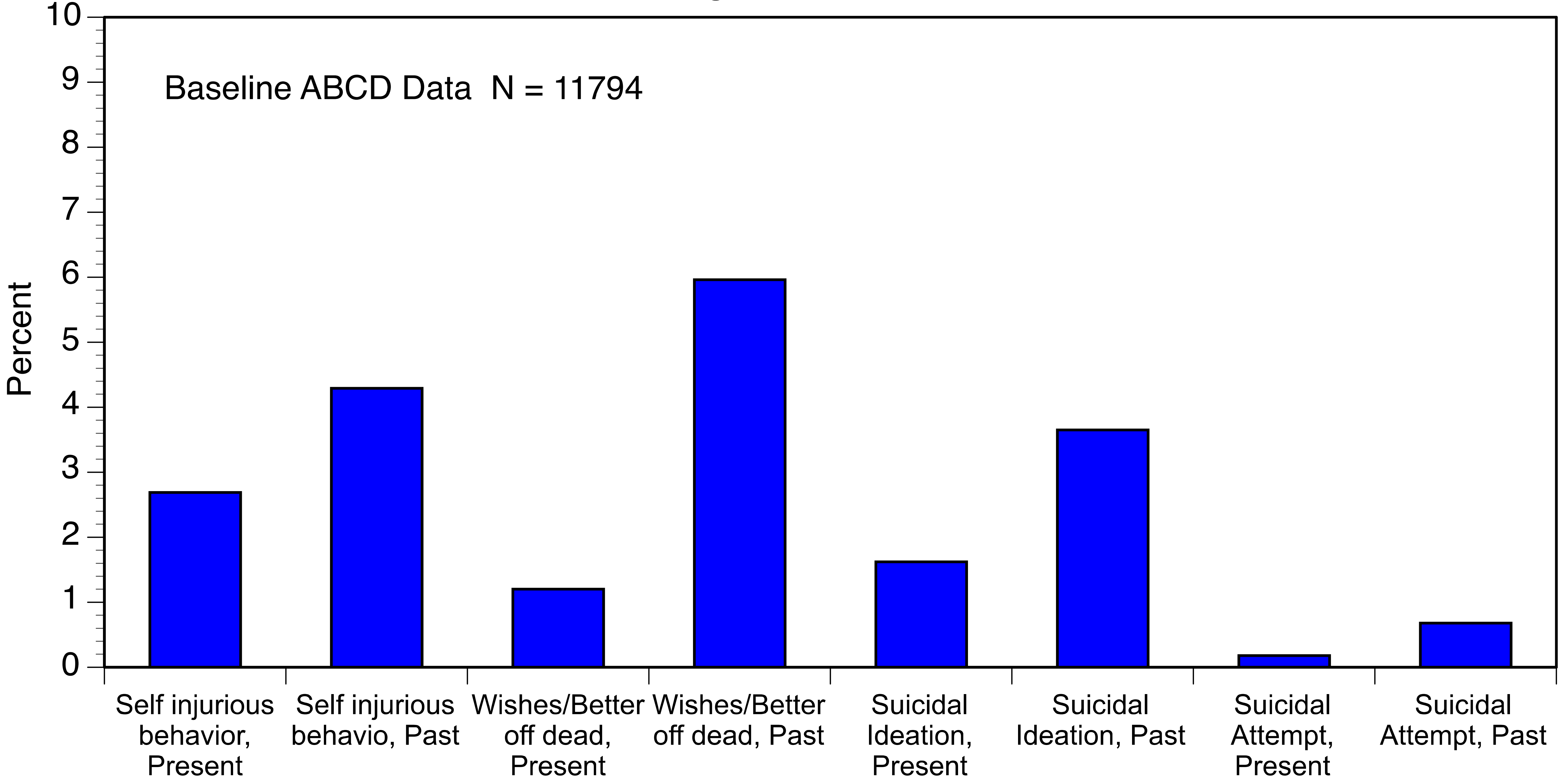
Findings to date have emphasized

- Methods development
- Understanding of risk and protective factors for adolescent mental health*
- Brain-behavior associations*
- Substance misuse: Neurotoxic consequences vs. premorbid effects*

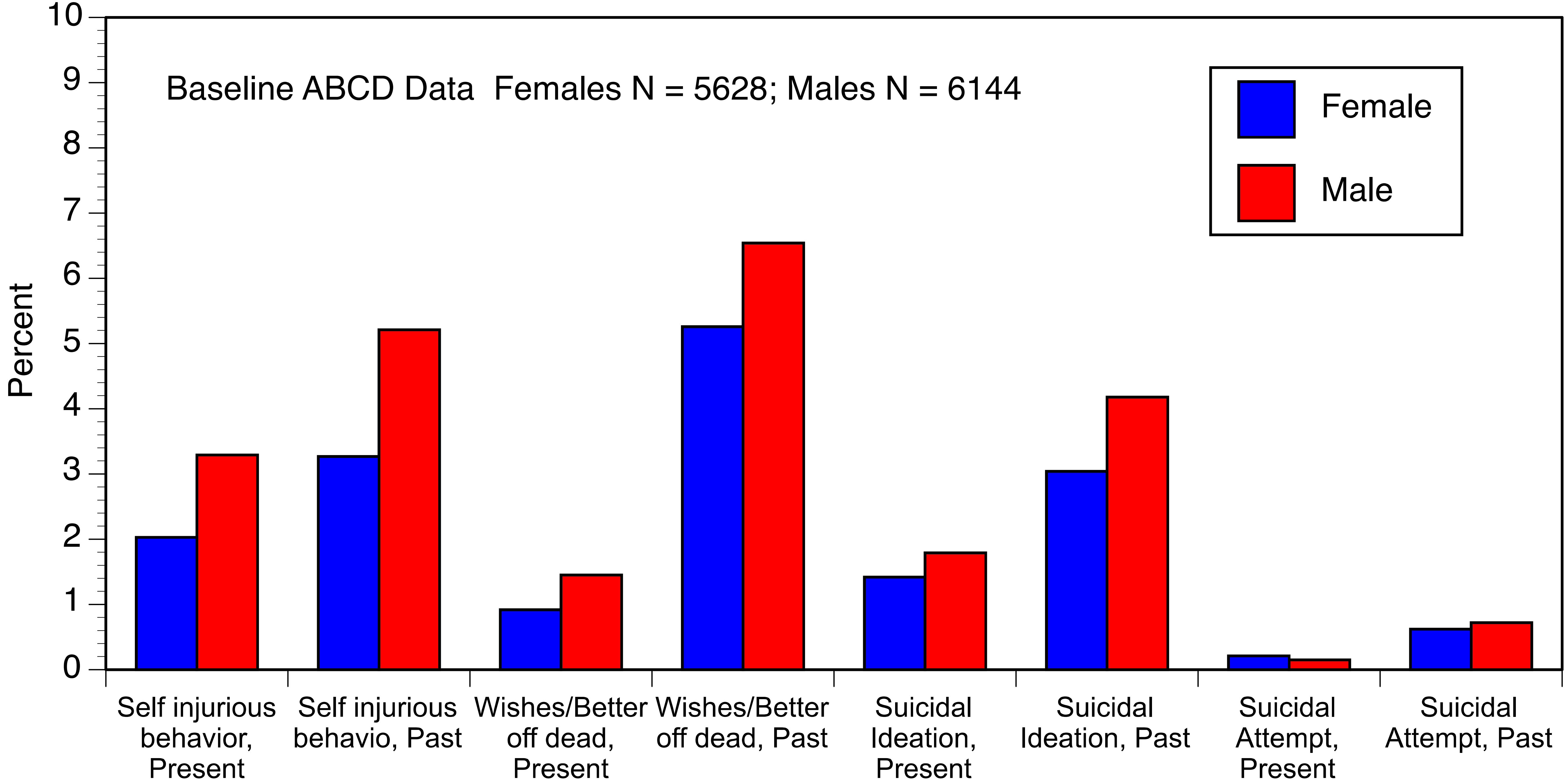
Adolescent Brain Cognitive Development

Understanding of risk and protective factors for adolescent mental health: Suicidal ideation and behavior and non suicidal self-injury in the ABCD baseline cohort

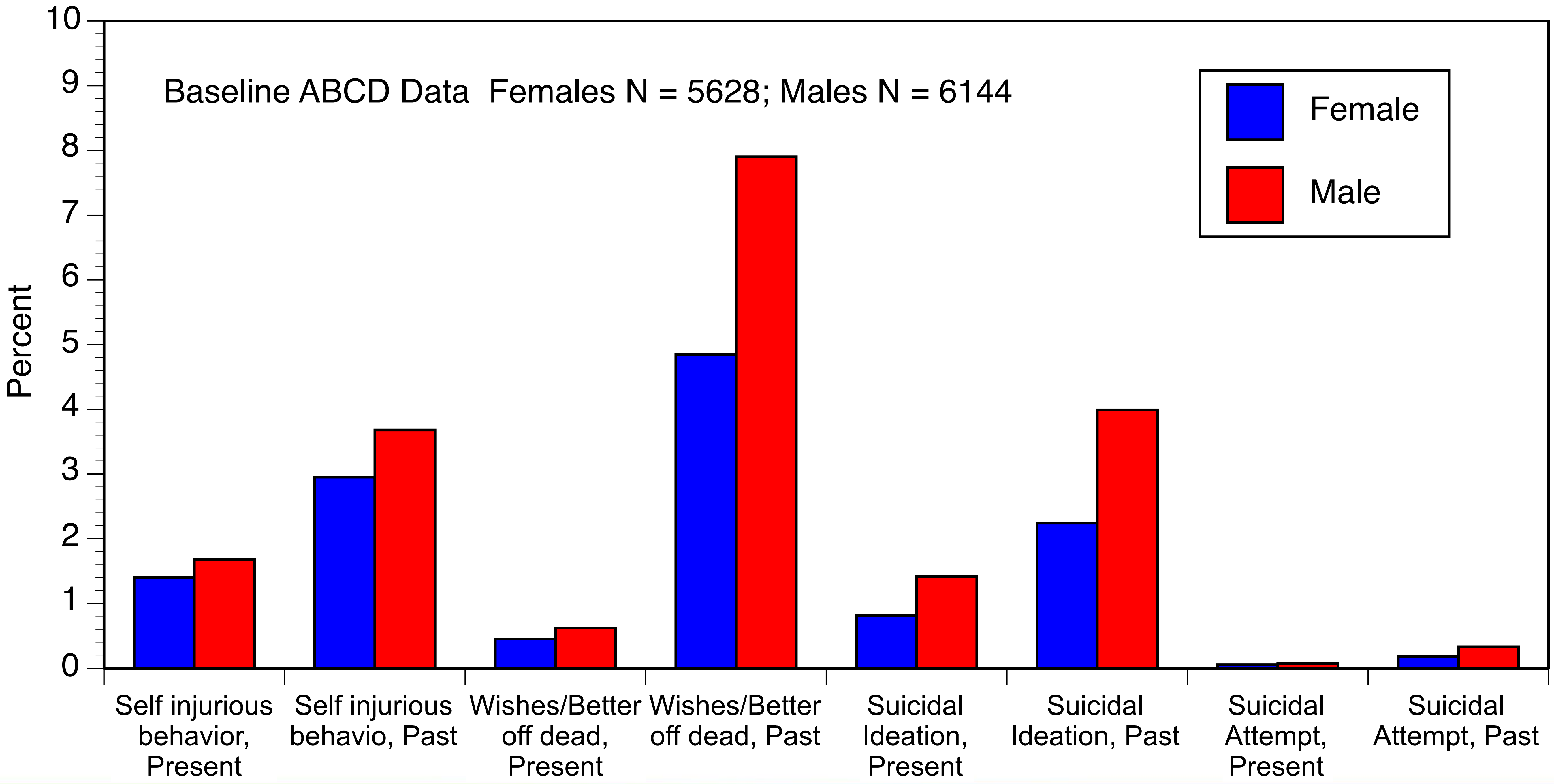
Child Self Report – Both Sexes



Child Self Report – By Sex



Parent Report-By Sex



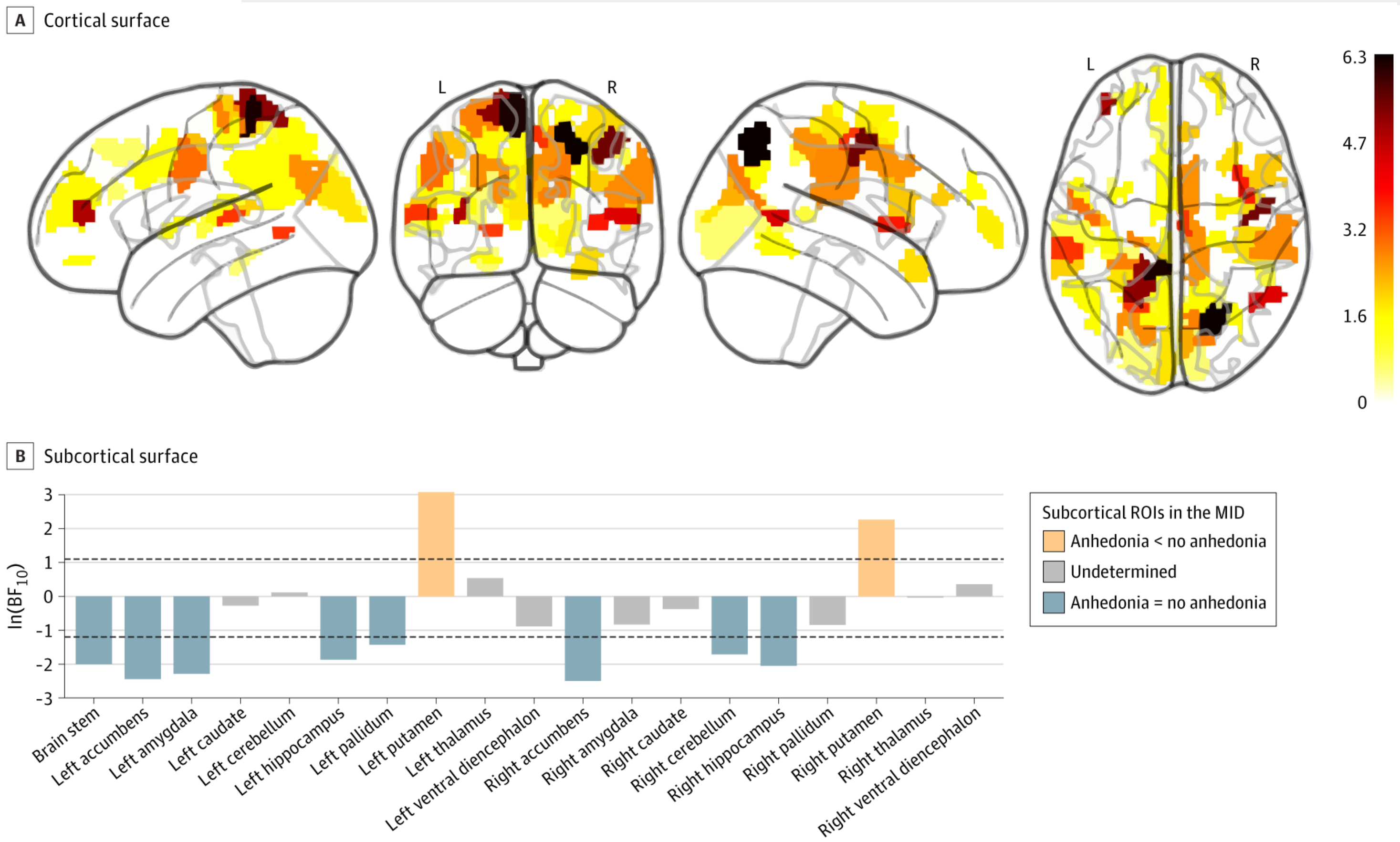
Rates of suicidal ideation

- General agreement between parent and child reports
- Intriguing that rates are higher in males vs. females
- Will be important to follow the sample through the pubertal transition to see how these findings change over time and to assess behavioral correlates
- There have been some attempts, using the baseline data, to explore correlates of depressive symptomatology.

Brain-Behavior Associations

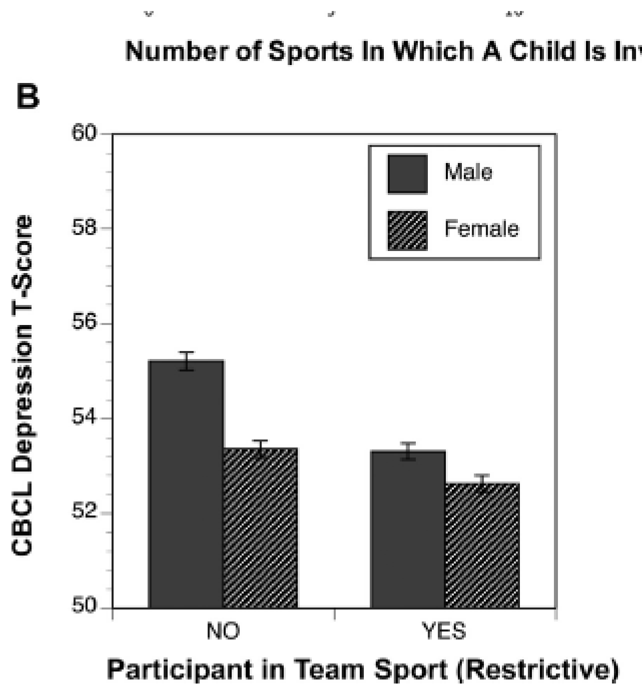
From: **Association Between Childhood Anhedonia and Alterations in Large-scale Resting-State Networks and Task-Evoked Activation**

JAMA Psychiatry. 2019;76(6):624-633. doi:10.1001/jamapsychiatry.2019.0020



Group differences between children with and Without anhedonia in task-evoked functional MRI activation during reward anticipation (Monetary Incentive Delay Task: large reward neutral cue). Figure shows regions of weaker activation in children with anhedonia

Sports involvement as a protective factor?



Involvement in sports is associated with fewer depressive symptoms in boys; this association was partially mediated by hippocampal volume. Longitudinal data will allow causal mechanisms to be investigated.

Biological Psychiatry: CNNI

Archival Report

Involvement in Sports, Hippocampal Volume, and Depressive Symptoms in Children

Lisa S. Gorham, Terry Jernigan, Jim Hudziak, and Deanna M. Barch

ABSTRACT

BACKGROUND: Recent studies have found that higher levels of exercise are associated with fewer symptoms of depression among young people. In addition, research suggests that exercise may modify hippocampal volume, a brain region that has been found to show reduced volume in depression. However, it is not clear whether this relationship emerges as early as preadolescence.

METHODS: We examined data from a nationwide sample of 4191 children 9 to 11 years of age from the Adolescent Brain and Cognitive Development Study. The parents of the children completed the Child Behavior Checklist, providing data about the child's depressive symptoms, and the Sports and Activities Questionnaire, which provided data about the child's participation in 23 sports. Children also took part in a structural magnetic resonance imaging scan, providing us with measures of bilateral hippocampal volume.

RESULTS: Sports involvement interacted with sex to predict depressive symptoms, with a negative relationship found in boys only ($t = -5.257$, $\beta = -.115$, $p < .001$). Sports involvement was positively correlated with hippocampal volume in both boys and girls ($t = 2.810$, $\beta = .035$, $p = .007$). Hippocampal volume also interacted with sex to predict depressive symptoms, with a negative relationship in boys ($t = -2.562$, $\beta = -.070$, $p = .010$), and served as a partial mediator for the relationship between involvement in sports and depressive symptoms in boys.

CONCLUSIONS: These findings help illuminate a potential neural mechanism for the impact of exercise on the developing brain, and the differential effects in boys versus girls mirror findings in the animal literature. More research is needed to understand the causal relationships between these constructs.

Keywords: Children, Depression, Exercise, Hippocampus, Neuroimaging, Structural

https://doi.org/10.1016/j.bpsc.2019.01.011

Table 2. Relationship Between Involvement in Sports and Depressive Symptoms

	Overall		Sex Interaction FDR	Male		Female	
Independent Variable	β	*t* Score	*p* Value	β	*t* Score	β	*t* Score
No. of Activities	−.072	−4.481[c]	.023[a]	−.097	−4.391[c]	−.021	−0.850
No. of Sports	−.089	−5.590[c]	.023[a]	−.115	−5.257[c]	−.041	−1.655
No. of Nonsport Activities	−.007	−0.428	.350	—	—	—	—
Team Sport (Broad)	−.093	−5.816[c]	.0035[b]	−.129	−5.888[c]	−.031	−1.248
Team Sport (Restrictive)	−.112	−6.909[c]	.0035[b]	−.139	−6.401[c]	−.059	−2.540
Individual Sport	−.076	−4.897[c]	.023[a]	−.103	−4.789[c]	−.037	−1.601
Structured Sport	−.097	−6.092[c]	.0047[b]	−.133	−6.070[c]	−.038	−1.525

All analyses use covariates of age (in months), race, ethnicity, parental education, and family income.
FDR, false discovery rate.
[a] $p < .05$.
[b] $p < .01$.
[c] $p < .001$.

"Sports involvement interacted with sex to predict depressive symptoms, with a negative relationship found in boys only ($t = -5.257$, $\beta = -.115$, $p < .001$). Sports involvement was positively correlated with hippocampal volume in both boys and girls ($t = 2.810$, $\beta = .035$, $p = .007$). Hippocampal volume also interacted with sex to predict depressive symptoms, with a negative relationship in boys ($t = -2.562$, $\beta = -.070$, $p = .010$), and served as a partial mediator for the relationship between involvement in sports and depressive symptoms in boys."

Substance misuse: Neurotoxic consequences vs. premorbid effects

Substance Use in the ABCD Baseline Cohort

- ABCD Release 2.0
- Baseline Data: Age 9-10 years

Substance	N	% of total N
Full Drink Alcohol	21	0.18%
More than Puff – Cigarette	9	0.08%
More than Puff – E-cig/Vape	11	0.10%
More than Puff - Marijuana	5	0.04%

Because substance use is so minimal at baseline, ABCD is well-positioned to be able to differentiate premorbid vulnerabilities from exposure effects over time.

Genes vs. Environment: How the ABCD study is poised to address important questions regarding vulnerabilities and cause/effect associations

Does Adolescent Marijuana Use Cause Cognitive Decline?

What is currently known?

Overview of Literature

- Findings have been inconsistent, with some studies reporting IQ effects and others no effect
- Not clear if any reported effects are causal or due to confounding factors (e.g., genetic influence, low SES, comorbidity, school underparticipation, etc.)
- Not always clear to what degree effects attributable to current use vs. chronic use
- Not clear if effects are permanent
- Largely cross sectional and correlational
- Largely small N, case-control
- Largely retrospective reporting of use
  - Few prospective studies with 1st assessment preceding initiation

Two Key Studies that Have Extended this Literature

- Meier et al. (2012) *PNAS* prospective singleton study showing that adolescent marijuana use is associated with decline in IQ
- Jackson et al. (2016) *PNAS* prospective twin study showing that adolescent marijuana use is associated with decline in IQ, but marijuana is not causal
- These two studies highlight the value of the ABCD research design which is both prospective and includes twins

PNAS PLUS

SEE COMMENTARY

PSYCHOLOGICAL AND COGNITIVE SCIENCES

Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

[a]Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, [b]Department of Psychology and Neuroscience, and [c]Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; [d]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; [e]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and [f]Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

marijuana | longitudinal | cognition

Cannabis, the most widely used illicit drug in the world, is increasingly being recognized for both its toxic and its therapeutic properties (1). Research on the harmful and beneficial effects of cannabis use is important because it can inform decisions regarding the medicinal use and legalization of cannabis, and the results of these decisions will have major public-health consequences. As debate surrounding these issues continues in the United States and abroad, new findings concerning the harmful effects of cannabis on neuropsychological functioning are emerging.

Accumulating evidence suggests that long-term, heavy cannabis ... nence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is reliance on retrospectively reported quantity, frequency, duration, and age-of-onset of cannabis use, often inquired about years after initiation of heavy use.

A prospective, longitudinal investigation of the association between cannabis use and neuropsychological impairment could redress these limitations and strengthen the existing evidence base by assessing neuropsychological functioning in a sample of youngsters before the onset of cannabis use, obtaining prospective data on cannabis use as the sample is followed over a number of years, and readministering neuropsychological tests after some members of the sample have developed a pattern of long-term cannabis use. To our knowledge, only one prospective, longitudinal study of the effects of cannabis on neuropsychological functioning has been conducted (21), and, in this study, the sample was small and the average duration of regular cannabis use was only 2 y.

In the present study, we investigated the association between persistent cannabis use—prospectively assessed over 20 y—and neuropsychological functioning in a birth cohort of 1,037 individuals. Study members underwent neuropsychological testing in 1985 and 1986 before the onset of cannabis use and again in 2010–2012, after some had developed a persistent pattern of cannabis use. We tested six hypotheses. First, we tested the "cognitive decline" hypothesis that persistent cannabis users evidence greater decline in test performance from childhood to adulthood than nonusers. By examining within-person change in neuropsychological functioning, any effect of premorbid deficits on later (postcannabis-initiation) test performance was nullified. Second, we tested the "specificity" hypothesis to address whether impairment is confined to specific neuropsychological domains or whether it is more global. To test this hypothesis, we admin-

Meier et al. 2012

- Dunedin NZ community birth cohort (N=874)
- IQ assessed at ages 7-13 and age 38 with Wechsler individually administered IQ tests (WISC-R & WAIS-IV)
- 18% of sample met criteria for cannabis dependence, and 18% met criteria for regular use (used 4 days/week for a year)

Persistence of Dependence & Regular Use

Table 1. IQ before and after cannabis use

	N	% male	Age 7–13 full-scale IQ	Age 38 full-scale IQ	Δ IQ effect size*
Persistence of cannabis dependence					
Never used, never diagnosed	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never diagnosed	479	49.48	102.32 (13.34)	101.25 (14.70)	–0.07
1 diagnosis	80	70.00	96.40 (14.31)	94.78 (14.54)	–0.11
2 diagnoses	35	62.86	102.14 (17.08)	99.67 (16.11)	–0.17
3+ diagnoses	38	81.58	99.68 (13.53)	93.93 (13.32)	–0.38
Persistence of regular cannabis use					
Never used	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never regularly	508	50.59	102.27 (13.59)	101.24 (14.81)	–0.07
Used regularly at 1 wave	47	72.34	101.42 (14.41)	98.45 (14.89)	–0.20
Used regularly at 2 waves	36	63.89	95.28 (10.74)	93.26 (11.44)	–0.13
Used regularly at 3+ waves	41	78.05	96.00 (16.06)	90.77 (13.88)	–0.35

Means (SDs) are presented for child and adult full-scale IQ as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence or reported using cannabis on a regular basis (at least 4 d/wk). The last column shows that study members with more persistent cannabis use showed greater IQ decline from childhood to adulthood.
*This coefficient indicates change in IQ from childhood to adulthood, with negative values indicating decreases in IQ. These change scores are in SD units, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large changes, respectively.

Persistence of Dependence

Table 1. IQ before and after cannabis use

	N	% male	Age 7–13 full-scale IQ	Age 38 full-scale IQ	Δ IQ effect size*
Persistence of cannabis dependence					
Never used, never diagnosed	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never diagnosed	479	49.48	102.32 (13.34)	101.25 (14.70)	−0.07
1 diagnosis	80	70.00	96.40 (14.31)	94.78 (14.54)	−0.11
2 diagnoses	35	62.86	102.14 (17.08)	99.67 (16.11)	−0.17
3+ diagnoses	38	81.58	99.68 (13.53)	93.93 (13.32)	−0.38
Persistence of regular cannabis use					
Never used	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never regularly	508	50.59	102.27 (13.59)	101.24 (14.81)	−0.07
Used regularly at 1 wave	47	72.34	101.42 (14.41)	98.45 (14.89)	−0.20
Used regularly at 2 waves	36	63.89	95.28 (10.74)	93.26 (11.44)	−0.13
Used regularly at 3+ waves	41	78.05	96.00 (16.06)	90.77 (13.88)	−0.35

Means (SDs) are presented for child and adult full-scale IQ as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence or reported using cannabis on a regular basis (at least 4 d/wk). The last column shows that study members with more persistent cannabis use showed greater IQ decline from childhood to adulthood.
*This coefficient indicates change in IQ from childhood to adulthood, with negative values indicating decreases in IQ. These change scores are in SD units, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large changes, respectively.

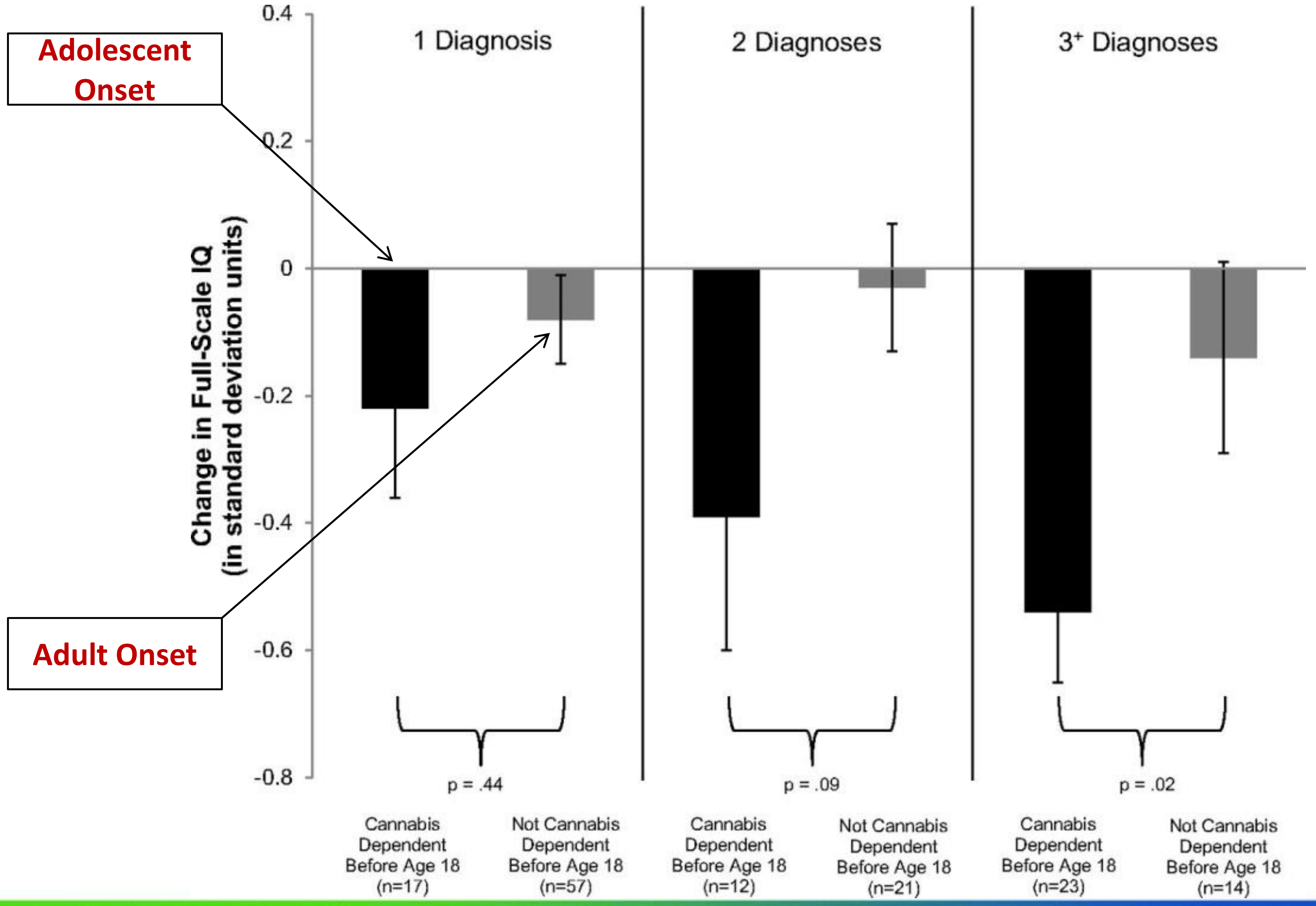
Persistence of Regular Use

Table 1. IQ before and after cannabis use

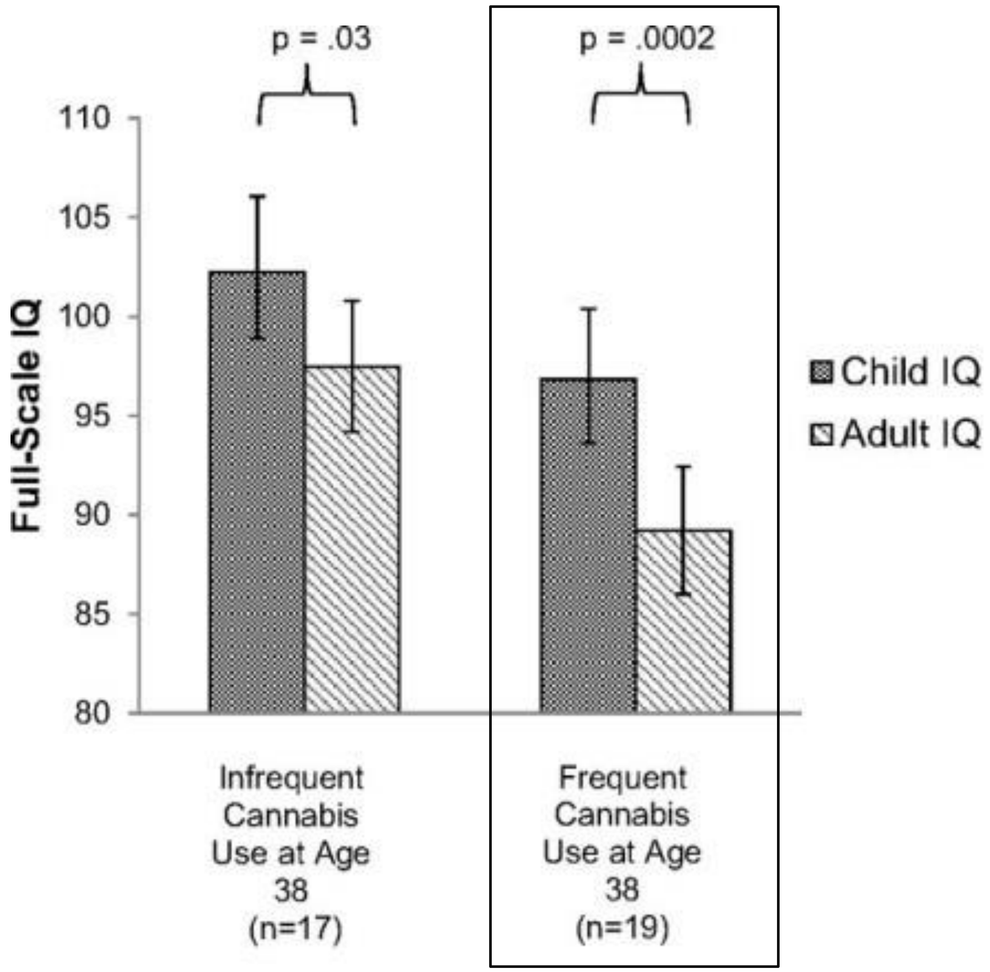
	N	% male	Age 7–13 full-scale IQ	Age 38 full-scale IQ	Δ IQ effect size*
Persistence of cannabis dependence					
Never used, never diagnosed	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never diagnosed	479	49.48	102.32 (13.34)	101.25 (14.70)	−0.07
1 diagnosis	80	70.00	96.40 (14.31)	94.78 (14.54)	−0.11
2 diagnoses	35	62.86	102.14 (17.08)	99.67 (16.11)	−0.17
3+ diagnoses	38	81.58	99.68 (13.53)	93.93 (13.32)	−0.38
Persistence of regular cannabis use					
Never used	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never regularly	508	50.59	102.27 (13.59)	101.24 (14.81)	−0.07
Used regularly at 1 wave	47	72.34	101.42 (14.41)	98.45 (14.89)	−0.20
Used regularly at 2 waves	36	63.89	95.28 (10.74)	93.26 (11.44)	−0.13
Used regularly at 3+ waves	41	78.05	96.00 (16.06)	90.77 (13.88)	−0.35

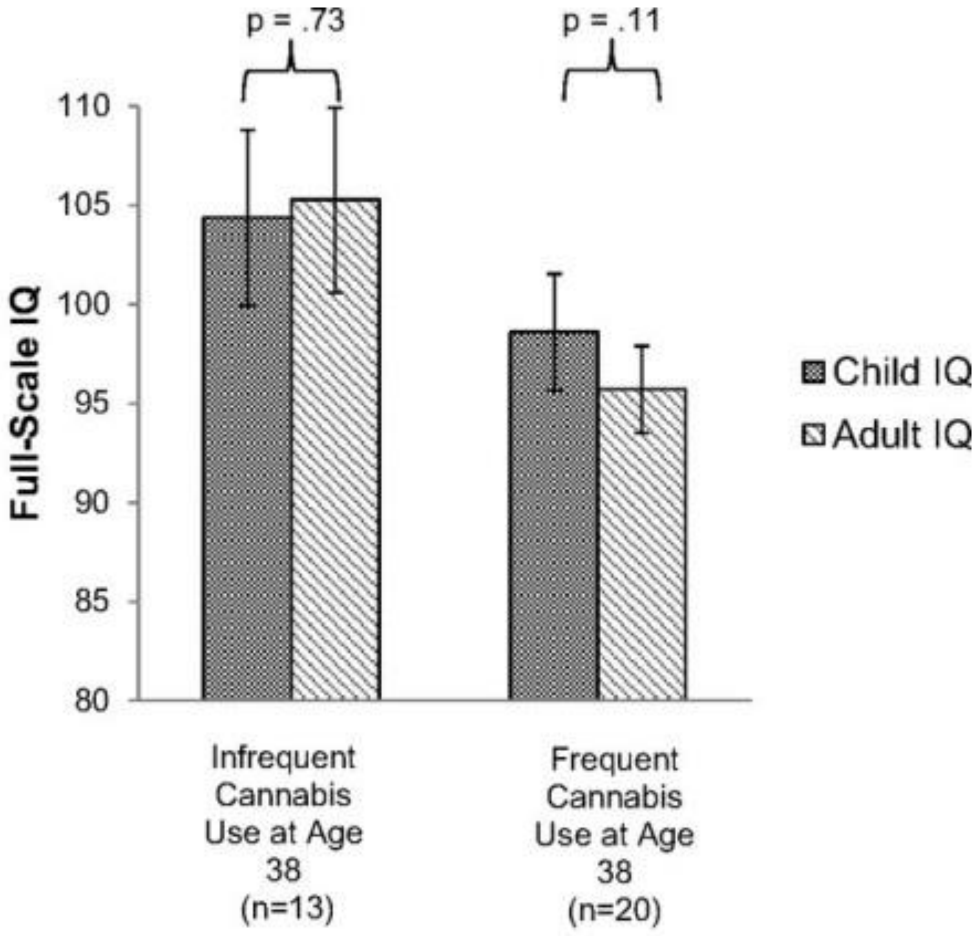
Means (SDs) are presented for child and adult full-scale IQ as a function of the number of study waves between ages 18 y and 38 y for which study members met criteria for cannabis dependence or reported using cannabis on a regular basis (at least 4 d/wk). The last column shows that study members with more persistent cannabis use showed greater IQ decline from childhood to adulthood.
*This coefficient indicates change in IQ from childhood to adulthood, with negative values indicating decreases in IQ. These change scores are in SD units, with values of 0.20, 0.50, and 0.80 reflecting small, medium, and large changes, respectively.

Adolescent Vulnerability & Persistence of Dependence



Is there recovery from adolescent heavy use?

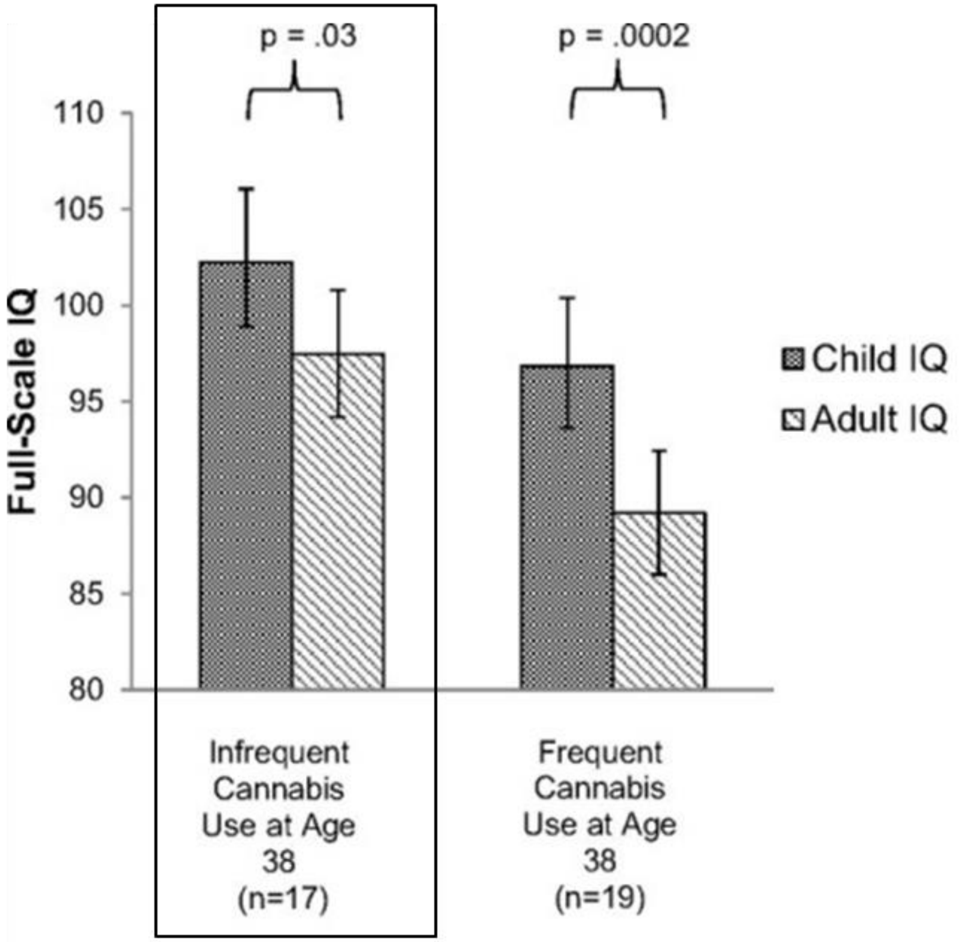




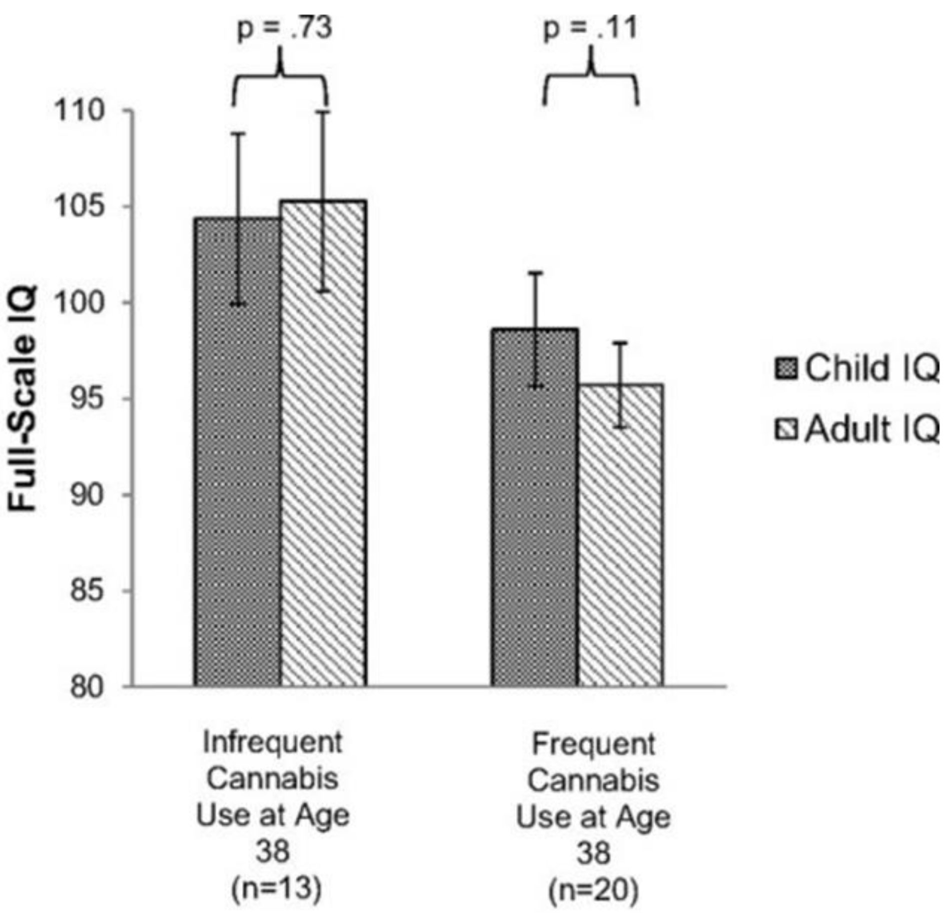
Adolescent Onset (weekly use before age 18)

Adult Onset (no weekly use before age 18)

Is there recovery from adolescent heavy use?

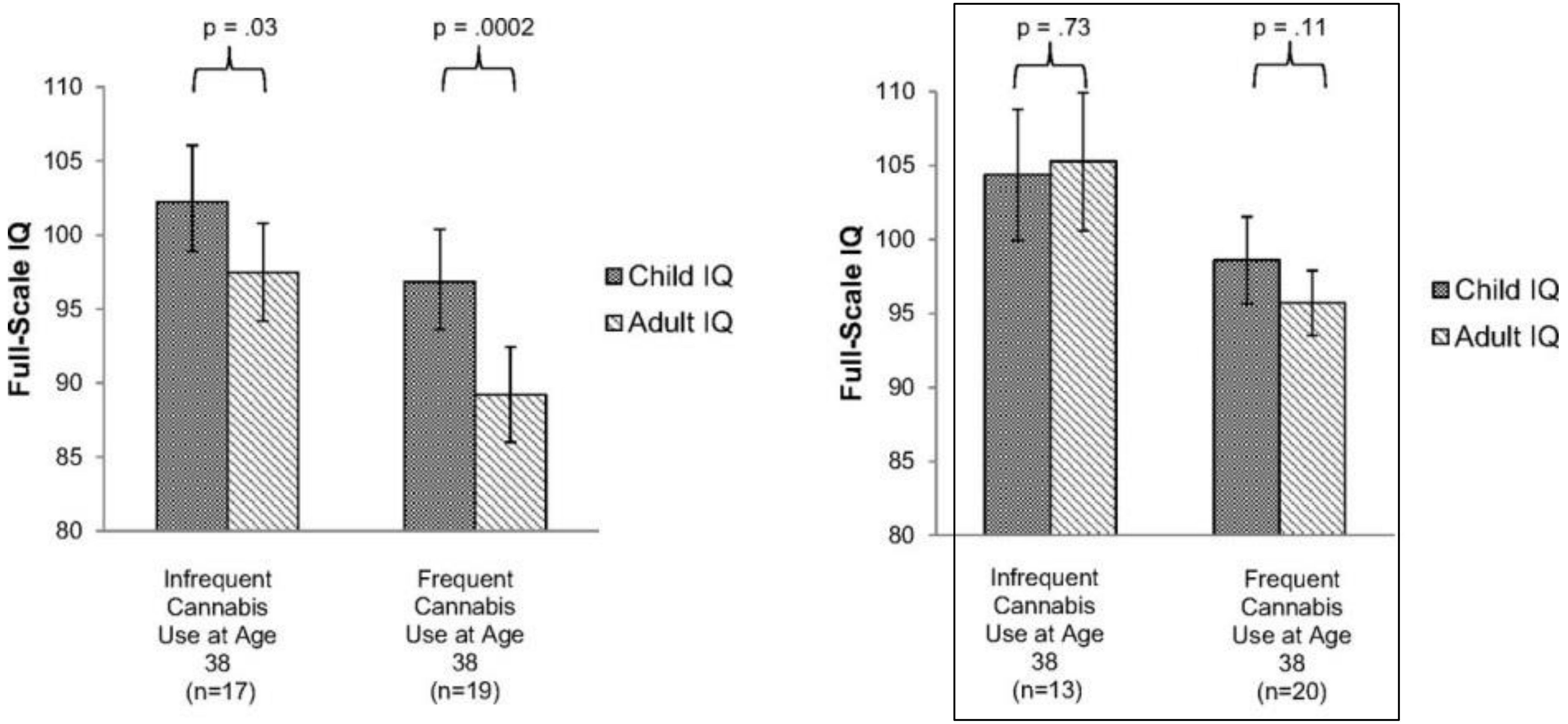


Adolescent Onset (weekly use before age 18)



Adult Onset (no weekly use before age 18)

Is there recovery from adolescent heavy use?



Adolescent Onset (weekly use before age 18)

Adult Onset (no weekly use before age 18)

Take Away Message from Meier et al. 2012

- Adolescent use was associated with poor cognitive functioning and decline in IQ
- Effects stronger for persistent use
- Effects appeared specific to adolescent onset and did not vary with frequency of use during the year preceding age 38 assessment
- Findings consistent with possible neurotoxic effect of cannabis use

Limitations of Longitudinal Studies

- Such findings can be interpreted as evidence of marijuana’s deleterious effects on adolescent brain development
- But adolescents who are disposed to use cannabis differ from those who do not even if they don’t use cannabis
  - They are at high genetic & environmental risk – IQ decline may occur in the absence of use
  - Poor academic performance predicts initiation (Hawkins et al., 1992) - low IQ may precede marijuana initiation

Why Does It Matter Whether Marijuana is Causal?

- Regardless of the reason for the cognitive decline associated with marijuana use, adolescents should not use marijuana
- But the reason does matter: Optimal prevention strategy depends on answer
  - If the problem is the liability - target resources to the high risk individual
  - If the problem is the consequences of use - target resources to limit marijuana access
    - Especially important if legalization trends continue

An MCTFR Project

PNAS PNAS PNAS

Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies

Nicholas J. Jackson[a,b,1], Joshua D. Isen[c,1,2], Rubin Khoddam[a], Daniel Irons[c], Catherine Tuvblad[a,d], William G. Iacono[c], Matt McGue[c], Adrian Raine[e,f,g], and Laura A. Baker[a]

[a]Department of Psychology, University of Southern California, Los Angeles, CA 90089; [b]Department of Medicine Statistics Core, University of California, Los Angeles, CA 90024; [c]Department of Psychology, University of Minnesota, Minneapolis, MN 55455; [d]School of Law, Psychology and Social Work, Örebro University, 702 81 Örebro, Sweden; [e]Department of Criminology, University of Pennsylvania, Philadelphia, PA 19104; [f]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104; and [g]Department of Psychology, University of Pennsylvania, Philadelphia, PA 19104

Edited by Valerie F. Reyna, Cornell University, Ithaca, NY, and accepted by the Editorial Board December 14, 2015 (received for review August 20, 2015)

Marijuana is one of the most commonly used drugs in the United States, and use during adolescence—when the brain is still developing—has been proposed as a cause of poorer neurocognitive outcome. Nonetheless, research on this topic is scarce and often shows conflicting results, with some studies showing detrimental effects of marijuana use on cognitive functioning and others showing no significant long-term effects. The purpose of the present study was to examine the associations of marijuana use with changes in intellectual performance in two longitudinal studies of adolescent twins (*n* = 789 and *n* = 2,277). We used a quasiexperimental approach to adjust for participants' family background characteristics and genetic propensities, helping us to assess the causal nature of any potential associations. Standardized measures of intelligence were administered at ages 9–12 y, before marijuana involvement, and again at ages 17–20 y. Marijuana use was self-reported at the time of each cognitive assessment as well as during the intervening period. Marijuana users had lower test scores relative to nonusers and showed a significant decline in crystallized intelligence between preadolescence and late adolescence. However, there was no evidence of a dose–response relationship between frequency of use and intelligence quotient (IQ) change. Furthermore, marijuana-using twins failed to show significantly greater IQ decline relative to their abstinent siblings. Evidence from these two samples suggests that observed declines in measured IQ may not be a direct result of

and Gray (22) showed significant intelligence quotient (IQ) test declines among current heavy users of marijuana relative to nonusers but no decline in former heavy users of marijuana. Meier et al. (23) focused on marijuana use and cognitive decline, where participants were examined over a three-decade period from childhood to adulthood. In this seminal paper, the authors demonstrated a dramatic drop in intelligence for those with persistent cannabis dependence. Although Meier et al.'s study has been the largest and most complete longitudinal examination of IQ decline and marijuana use, there is disagreement as to whether this decline is a direct consequence of marijuana involvement or perhaps attributable to confounding variables (19, 24).

Although studies have demonstrated that heavy marijuana use may impact IQ test performance even a month after cessation (16, 25), deficits seem to be more related to recent use rather than reflecting a permanent insult to cognition (22, 26, 27). Indeed, some studies find no long-term association of marijuana use and IQ (22, 28) or, if so, only on measures of verbal ability (19). Part of this disagreement in the literature speaks to the complexity of trying to infer causal mechanisms from correlational data. The associations between marijuana use and IQ could simply be a matter of confounding, by which other variables that are causal to both low IQ and marijuana use have not been accounted for. As such, one must consider the totality of evidence that would

Questions posed by Jackson et al. 2016

- Is adolescent marijuana use associated with poor cognitive functioning?
- Is adolescent marijuana use associated with decline in IQ?
- Is greater use associated with greater decline in IQ?
- Are observed effects more likely to reflect consequences of use or familial confounding factors associated with both low IQ and use that might reflect the liability to use?
- Does poor cognitive functioning precede marijuana use?

Jackson et al. (2016)

- Replication across two geographically and ethnically distinct community samples (USC RFAB N=789; MTFS N=2277)
  - Largest sample to date N=3,066
- Twin IQ assessed at ages 9-12 and 17-20 using Wechsler scale subtests prorated to yield IQ
  - USC RFAB –WASI at both intake and follow-up
    - Vocabulary, similarities, block design, matrix reasoning
  - MTFS – WISC-R and WAIS-R
    - Vocabulary, information, block design, picture arrangement

Co-Twin Control Design

- Co-twin control (CTC) analysis carried out on pairs discordant for use and discordant for heavy use (MTFS)
- CTC logic as applied to discordant MZ twins
  - IQ of nonusing twin provides indication of what the cognitive ability of the using twin should be had the using twin not used
  - If the using twin shows more IQ decline than the nonusing twin => low IQ is a consequence of use
  - If the IQ of the twins is the same => genetic/familial liability accounts for the IQ decline

Sample Characteristics (N=3,066)

	RFAB (USC)			MTFS (UMN)		
	Non Users N=314	Users N=475 (60%)	P-value	Non Users N=1455	Users N=822 (36%)	P-Value
Age at Baseline	9.6	9.6		11.8	11.8	
Age at Follow-up	19.5	20.0	<.05	18.0	18.2	<.05
MJ Use>30x		49%			37%	
Daily MJ Use		21%			23%	
White	27%	33%	<.05	95%	89%	<.05

Marijuana User Group IQ Results Overview

	RFAB, IQ				MTFS, IQ			
	Baseline (age 9–10 y)		Follow-up (age 19–20 y)		Baseline (age 11–12 y)		Follow-up (age 17–19 y)	
IQ subtest	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vocabulary								
Nonusers	100.2	15.0	102.0	14.8	100.7	15.3	102.0	15.1
Users	99.9	15.0	98.1	15.0	98.8	14.3	96.3	14.1
Information								
Nonusers					101.2	15.0	102.3	15.0
Users					97.9	14.7	96.4	14.2
Similarities								
Nonusers	100.8	14.9	100.6	14.9				
Users	99.5	15.0	99.4	15.1				
Block Design								
Nonusers	100.7	14.9	100.7	14.8	100.7	15.0	100.9	15.3
Users	99.5	15.1	99.3	15.2	98.7	14.9	98.3	14.3
Matrix Reasoning								
Nonusers	101.2	15.1	100.2	15.2				
Users	99.2	14.9	99.9	14.9				
Picture Arrangement								
Nonusers					100.3	15.2	100.2	15.3
Users					99.5	14.6	99.8	14.6

Verbal IQ in Marijuana User Groups: RFAB

IQ subtest	RFAB, IQ Baseline (age 9–10 y) Mean	SD	RFAB, IQ Follow-up (age 19–20 y) Mean	SD	MTFS, IQ Baseline (age 11–12 y) Mean	SD	MTFS, IQ Follow-up (age 17–19 y) Mean	SD
Vocabulary								
Nonusers	100.2	15.0	102.0	14.8	100.7	15.3	102.0	15.1
Users	99.9	15.0	98.1	15.0	98.8	14.3	96.3	14.1
Information								
Nonusers					101.2	15.0	102.3	15.0
Users					97.9	14.7	96.4	14.2

Baseline: No IQ difference

Verbal IQ in Marijuana User Groups: RFAB

	RFAB, IQ				MTFS, IQ			
	Baseline (age 9–10 y)		Follow-up (age 19–20 y)		Baseline (age 11–12 y)		Follow-up (age 17–19 y)	
IQ subtest	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vocabulary								
Nonusers	100.2	15.0	102.0	14.8	100.7	15.3	102.0	15.1
Users	99.9	15.0	98.1	15.0	98.8	14.3	96.3	14.1
Information								
Nonusers					101.2	15.0	102.3	15.0
Users					[illegible]	14.7	96.4	14.2

Follow-up: User deficit ~4 points

Verbal IQ in Marijuana User Groups: MTFS

	RFAB, IQ				MTFS, IQ			
	Baseline (age 9–10 y)		Follow-up (age 19–20 y)		Baseline (age 11–12 y)		Follow-up (age 17–19 y)	
IQ subtest	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vocabulary								
Nonusers	100.2	15.0	102.0	14.8	100.7	15.3	102.0	15.1
Users	99.9	15.0	98.1	15.0	98.8	14.3	96.3	14.1
Information								
Nonusers					101.2	15.0	102.3	15.0
Users					97.9	14.7	96.4	14.2

Baseline:
User deficit
~2 points

Verbal IQ in Marijuana User Groups: MTFS

	RFAB, IQ				MTFS, IQ			
	Baseline (age 9–10 y)		Follow-up (age 19–20 y)		Baseline (age 11–12 y)		Follow-up (age 17–19 y)	
IQ subtest	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vocabulary								
Nonusers	100.2	15.0	102.0	14.8	100.7	15.3	102.0	15.1
Users	99.9	15.0	98.1	15.0	98.8	14.3	96.3	14.1
Information								
Nonusers					101.2	15.0	102.3	15.0
Users					97.9	14.7	96.4	14.2

Follow-up:
User deficit
~6 points

Meier et al. 2012: IQ deficit in early adolescence as a function of age 38 outcome

Age 38 Outcome	N	Age 7-13 IQ	*p*-value	Effect Size
No Diagnosis	721	101.5		
Dependence	153	98.5		
IQ difference		-3.0	P<.01	-.22
No Regular Use	750	101.5		
Regular Use	124	97.9		
IQ Difference		-3.6	P<.025	-.26

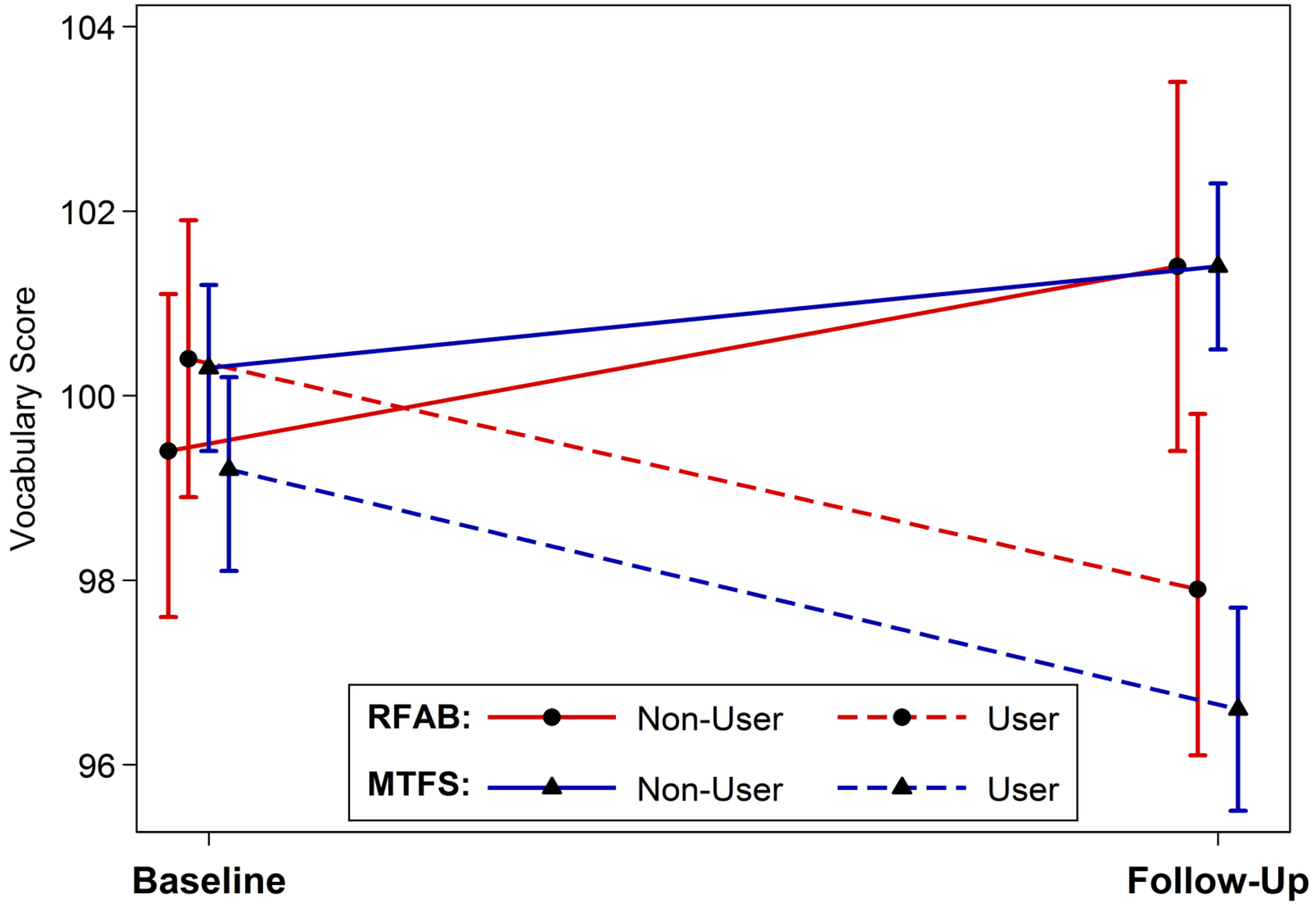
Similarities Subtest IQ in Marijuana User Groups: RFAB

	RFAB, IQ				MTFS, IQ			
	Baseline (age 9–10 y)		Follow-up (age 19–20 y)		Baseline (age 11–12 y)		Follow-up (age 17–19 y)	
IQ subtest	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vocabulary								
Nonusers	100.2	15.0	102.0	14.8	100.7	15.3	102.0	15.1
Users	99.9	15.0	98.1	15.0	98.8	14.3	96.3	14.1
Information								
Nonusers					101.2	15.0	102.3	15.0
Users					97.9	14.7	96.4	14.2
Similarities								
Nonusers	100.8	14.9	100.6	14.9				
Users	99.5	15.0	99.4	15.1				

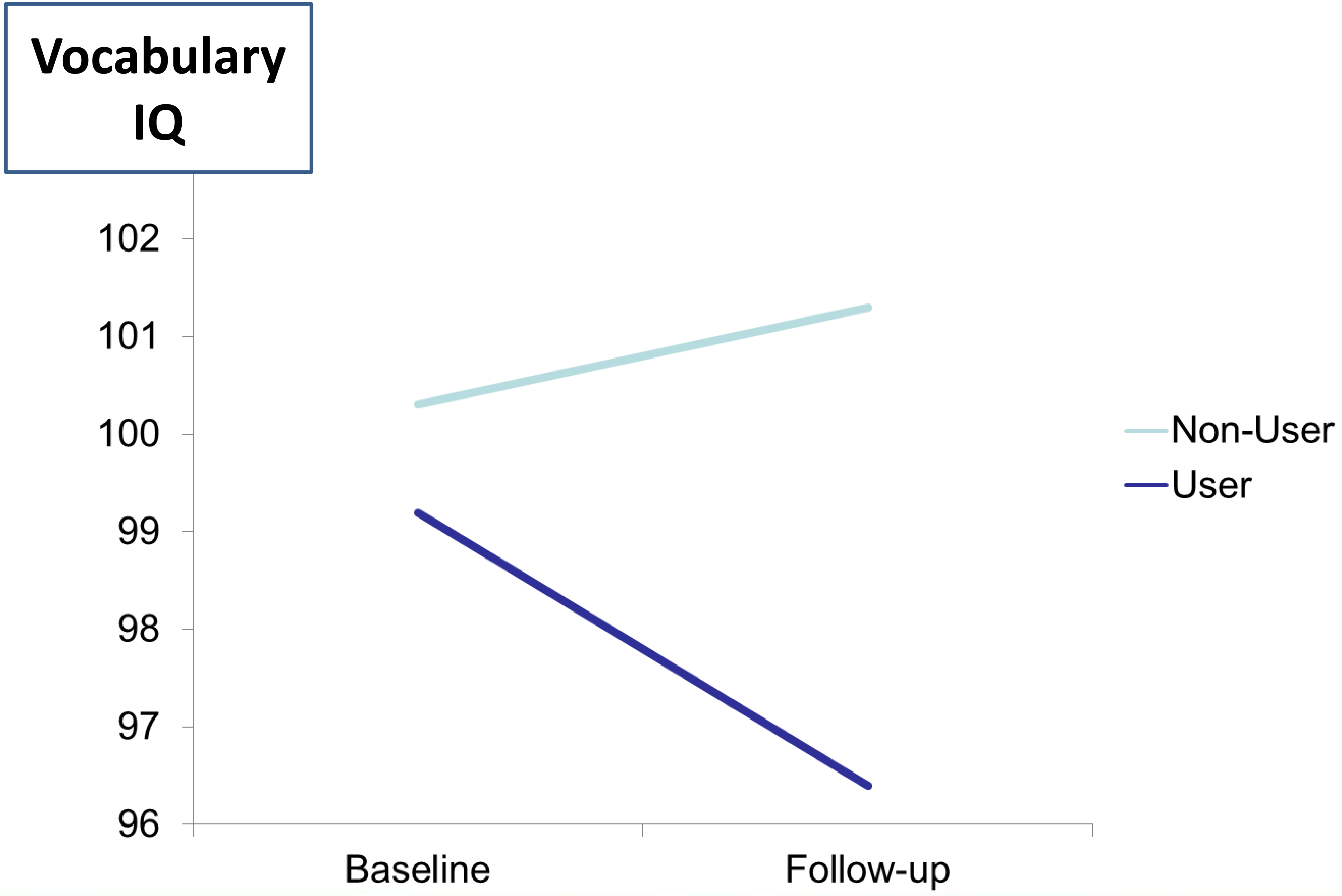
Performance IQ in Marijuana User Groups

	RFAB, IQ				MTFS, IQ			
	Baseline (age 9–10 y)		Follow-up (age 19–20 y)		Baseline (age 11–12 y)		Follow-up (age 17–19 y)	
IQ subtest	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vocabulary								
Nonusers	100.2	15.0	102.0	14.8	100.7	15.3	102.0	15.1
Users	99.9	15.0	98.1	15.0	98.8	14.3	96.3	14.1
Information								
Nonusers					101.2	15.0	102.3	15.0
Users					97.9	14.7	96.4	14.2
Similarities								
Nonusers	100.8	14.9	100.6	14.9				
Users	99.5	15.0	99.4	15.1				
Block Design								
Nonusers	100.7	14.9	100.7	14.8	100.7	15.0	100.9	15.3
Users	99.5	15.1	99.3	15.2	98.7	14.9	98.3	14.3
Matrix Reasoning								
Nonusers	101.2	15.1	100.2	15.2				
Users	99.2	14.9	99.9	14.9				
Picture Arrangement								
Nonusers					100.3	15.2	100.2	15.3
Users					99.5	14.6	99.8	14.6

Vocabulary Score Results



Change in IQ from Age 11 to age 18 for MCTFR Marijuana Users and Non-Users (N=2,277)



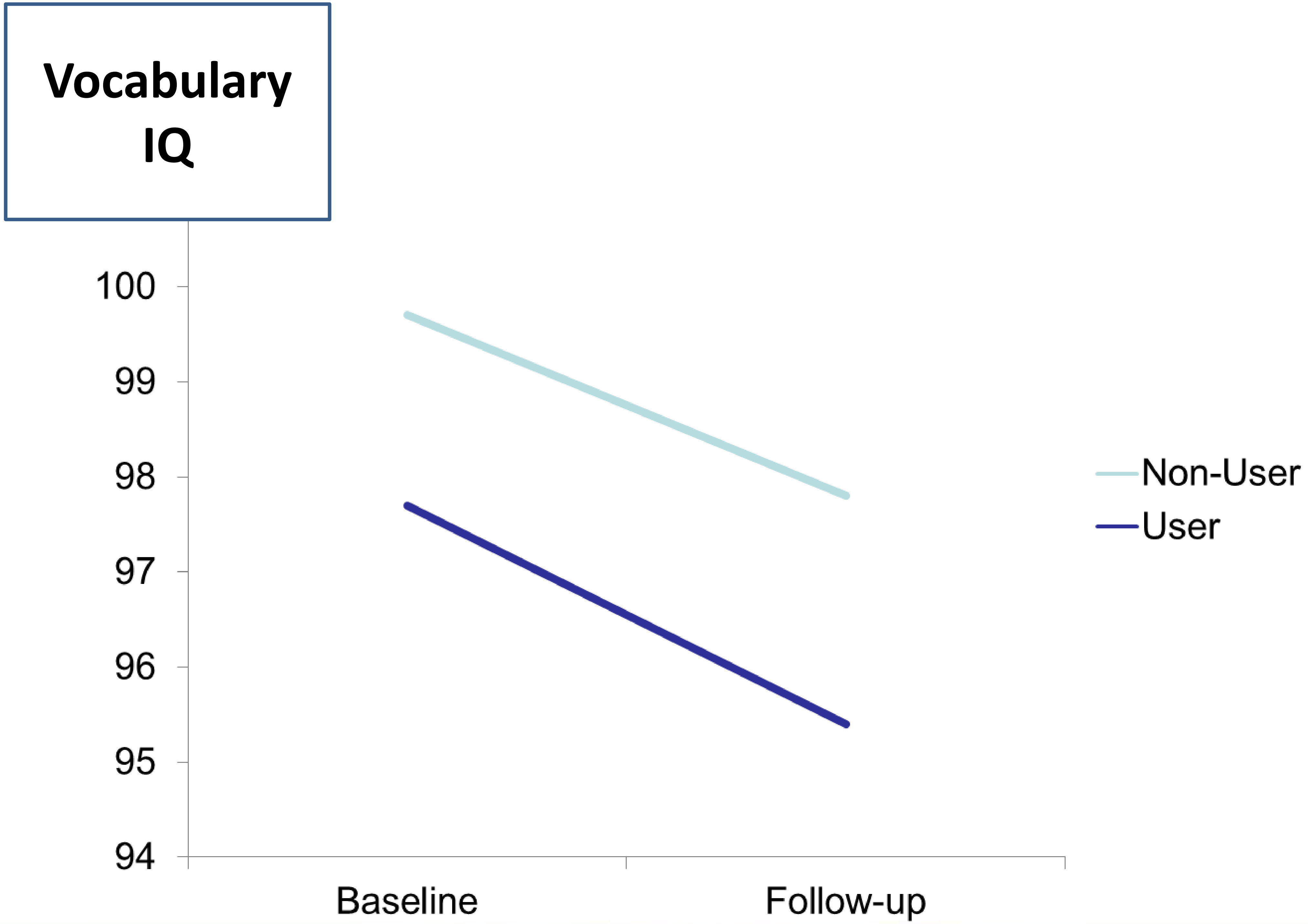
Age 11-18 Change in IQ: Abstinent vs. Heavy Using Discordant MTFS Twin Pairs

Table S6. Cotwin control analysis of discordant heavy users in the MTFS on change in IQ

	Discordant Heavy Users		
IQ subtest	*N*	β (95% CI)	*P*
Vocabulary			
MZ and DZ	47	−1.5 (−5.5 to 2.6)	0.481
Information			
MZ and DZ	47	0.2 (−5.1 to 5.6)	0.931
Block Design			
MZ and DZ	47	−1.6 (−7.3 to 4.1)	0.584
Picture Arrangement			
MZ and DZ	47	5.2 (−4.1 to 14.6)	0.276

N represents the no. of discordant twin pairs in MZ and DZ groups. CI, confidence interval.

MTFS MZ Twins Discordant for Marijuana Use
Change in IQ from Age 11 to age 18 (N=112 discordant pairs)



Heavy & Daily Users Not More Likely to Have IQ Deficit

Table 4. Interactions of marijuana use frequency (>30 times and daily use) with change in IQ among marijuana users

	RFAB			MTFS		
IQ subtest	*N*	β (95% CI)	*P*	*N*	β (95% CI)	*P*
Vocabulary						
Use >30 times	372	−0.8 (−4.2 to 2.6)	0.657	813	−0.6 (−2.4 to 1.2)	0.530
Daily use	375	−0.4 (−4.5 to 3.7)	0.841	783	−0.7 (−2.7 to 1.4)	0.537
Information						
Use >30 times				815	0.7 (−1.4 to 2.8)	0.523
Daily use				785	−1.5 (−4.0 to 1.0)	0.241
Similarities						
Use >30 times	372	1.7 (−2.1 to 5.5)	0.383			
Daily use	375	0.5 (−4.1 to 5.1)	0.833			
Block Design						
Use >30 times	372	0.4 (−2.9 to 3.8)	0.794	815	−0.8 (−3.0 to 1.4)	0.465
Daily use	375	1.5 (−2.5 to 5.5)	0.468	785	0.2 (−2.3 to 2.7)	0.846
Matrix Reasoning						
Use >30 times	372	−1.6 (−5.2 to 2.1)	0.399			
Daily use	375	1.9 (−2.5 to 6.3)	0.393			
Picture Arrangement						
Use >30 times				815	−0.1 (−3.5 to 3.3)	0.959
Daily use				785	0.3 (−3.7 to 4.2)	0.894

Models were adjusted for age, sex, race, zygosity, SES, and MTFS cohort. CI, confidence interval.

Jackson et al. 2016

- **Key results:**
  - Use was associated with lower IQ at follow-up, but only for vocabulary and information (crystalized) subtests
    - Results held after adjusting for age, sex, race, zygosity, SES
    - Meier et al. 2012 subtest analysis showed significant results for vocabulary and information, but not for block design and picture arrangement
  - Use was associated with IQ deficit at follow-up (~4-6 points) for these subtests
  - Heavier use was *not* associated with a greater drop in IQ
  - Low crystallized IQ (~2 points) preceded use in MTFS sample (similar effect seen for block design)
  - CTC interaction effects were nonsignificant, thus failing to confirm that the using twin showed a steeper rate of IQ decline than the nonusing twin

Take Away Message from Jackson et al. 2016

Novel Features

- Largest prospective sample study to date
- First prospective twin study providing opportunity to evaluate causal effects
- Included replication sample & ethnic diversity

Conclusions

- Like Meier et al. 2012, found adolescent use associated with low IQ and decline in IQ
- Familial liability, not marijuana use, accounts for IQ decline
- Specific mechanisms not identified, but derive from risk factors the twins had in common that would be expected to lower the IQs of both, e.g., low educational opportunity, increased truancy, decreased parental monitoring

Overall Conclusions

- Adolescents who misuse marijuana have diminished cognitive ability
- Low IQ of adolescent marijuana users precedes use
- Adolescent marijuana use does not appear to cause IQ decline during adolescence
- Unidentified familial factors are likely responsible for the association between marijuana use and low IQ
- Possible causal effects of continued, long-term use, and effects on different brain measures remain to be evaluated
- ABCD project, with its twin sample embedded in its longitudinal design, is uniquely poised to further our understanding of causes and consequences of adolescent marijuana use

Thank You MCTFR Staff!

MCTFR funding provided by NIDA, NIAAA, NIMH, & NCI

Thanks for your attention!

ABCD Council of Investigators

Questions?

- Monica Luciana (lucia003@umn.edu)
- Bill Iacono (wiacono@umn.edu)