Long-term Cannabis Use and Cognitive Reserves and Hippocampal Volume in Midlife

MADELINE H. MEIER, PHD

ARIZONA STATE UNIVERSITY

What We Know

Meta-analyses have shown that heavy cannabis users exhibit mild cognitive deficits and smaller hippocampal volume compared with non-users

But most studies are based on adolescent and young adult cannabis users

Journal of the International Neuropsychological Society (2003), **9**, 679–689.

DOI: 10.1017/S1355617703950016

Association
/a0029117

Research

er

JAMA Psychiatry | Original Investigation

Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults
A Systematic Review and Meta-analysis

J. Cobb Scott, PhD; Samantha T. Slomiak, MD; Jason D. Jones, PhD; Adon F. G. Rosen, BS; Tyler M. Moore, PhD; Ruben C. Gur, PhD

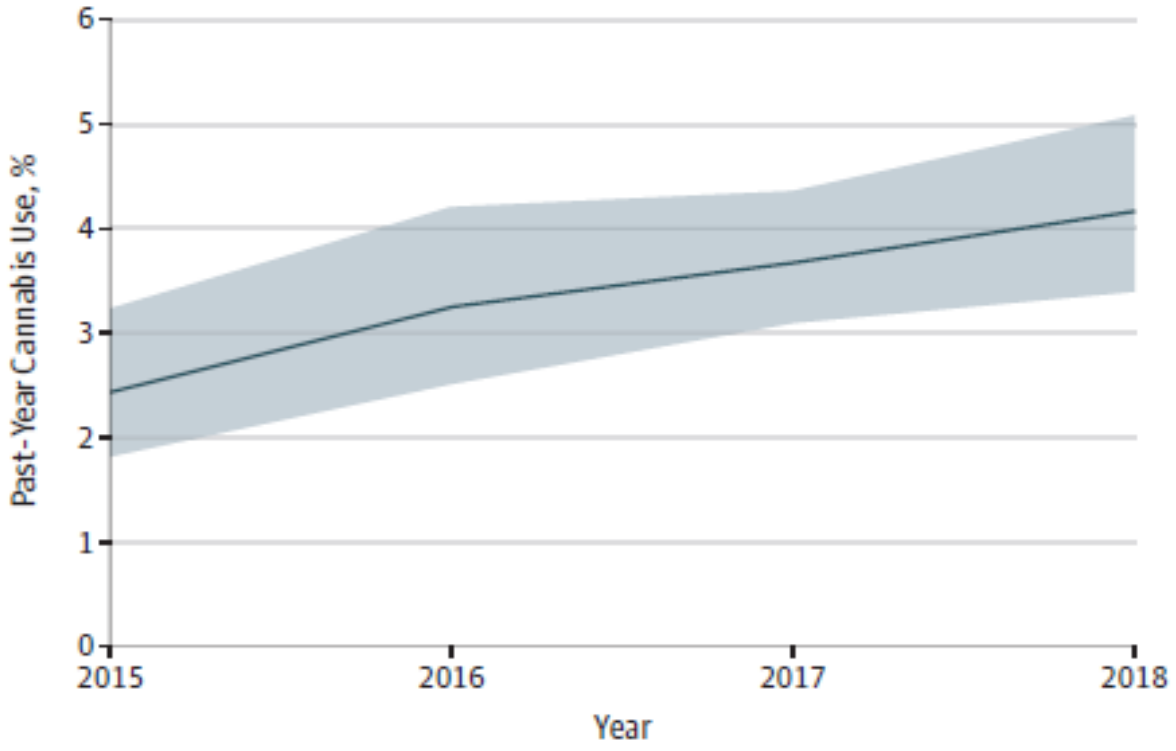
What We Don’t Know

Will the subtle cognitive deficits and brain differences observed in young cannabis users be larger in midlife and older adult cannabis users with longer histories of use?

Timely

Midlife and older adults are using cannabis at historically high rates

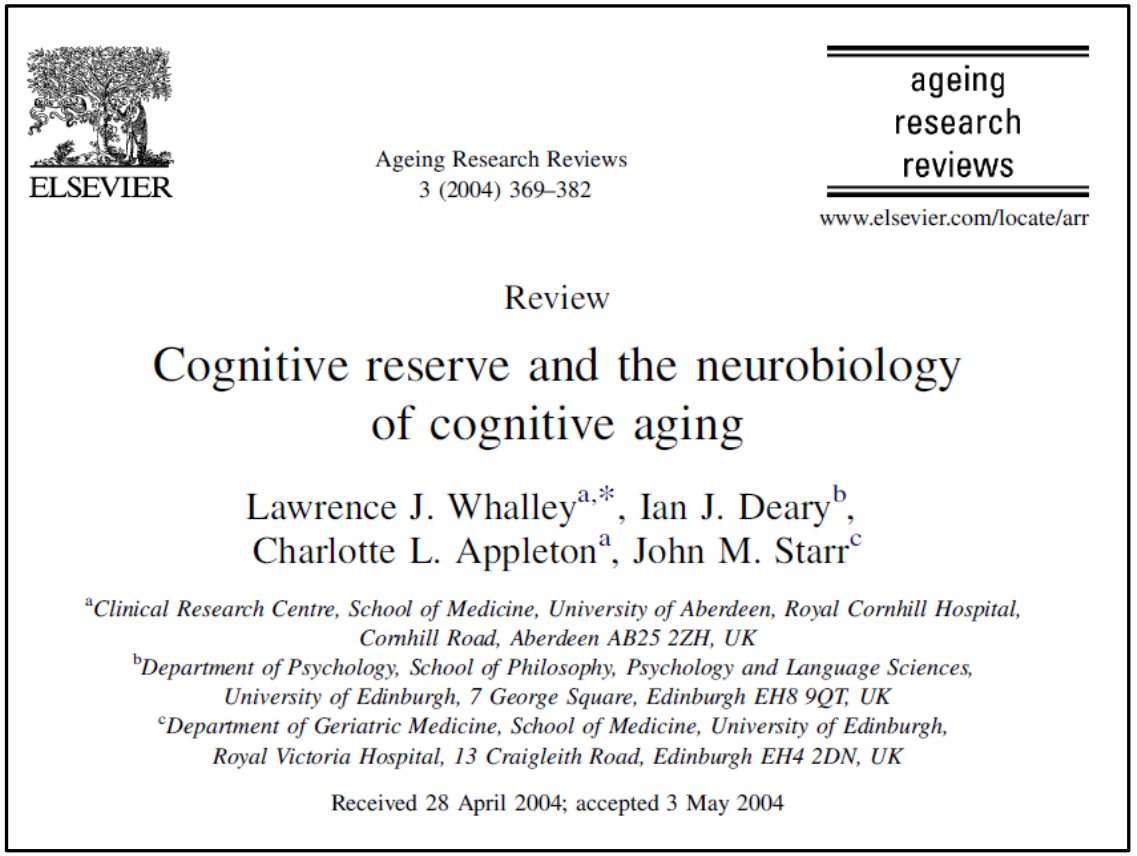
Figure. Trend in Prevalence of Past-Year Cannabis Use Among Adults 65 Years and Older in the United States, 2015 to 2018



The shading indicates 95% CIs.

Figure from Han & Palomar, JAMA Internal Medicine, 2020

Important



ELSEVIER

Ageing Research Reviews
3 (2004) 369–382

ageing research reviews

www.elsevier.com/locate/arr

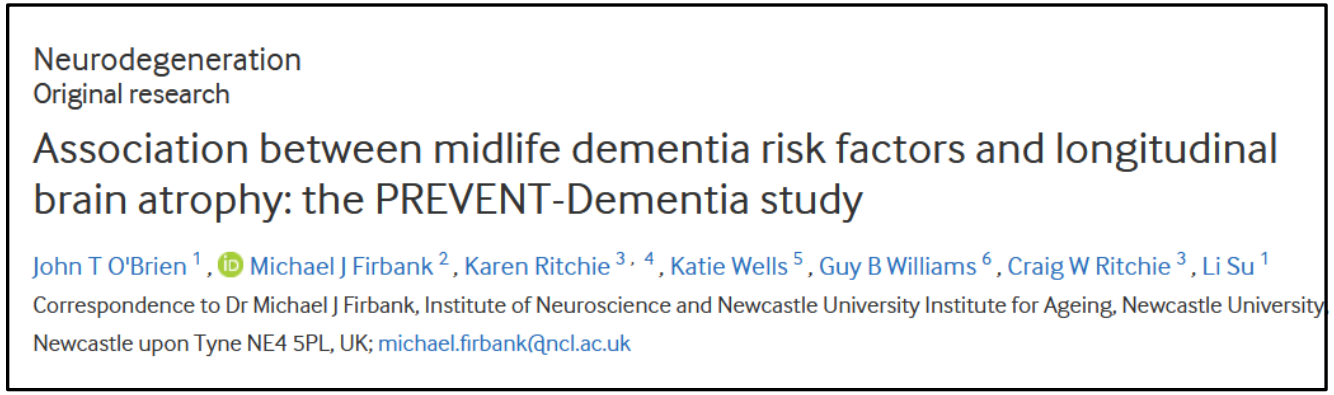
Review

Cognitive reserve and the neurobiology of cognitive aging

Lawrence J. Whalley[a,*], Ian J. Deary[b], Charlotte L. Appleton[a], John M. Starr[c]

[a]*Clinical Research Centre, School of Medicine, University of Aberdeen, Royal Cornhill Hospital, Cornhill Road, Aberdeen AB25 2ZH, UK*
[b]*Department of Psychology, School of Philosophy, Psychology and Language Sciences, University of Edinburgh, 7 George Square, Edinburgh EH8 9QT, UK*
[c]*Department of Geriatric Medicine, School of Medicine, University of Edinburgh, Royal Victoria Hospital, 13 Craigleith Road, Edinburgh EH4 2DN, UK*

Received 28 April 2004; accepted 3 May 2004



Neurodegeneration
Original research

Association between midlife dementia risk factors and longitudinal brain atrophy: the PREVENT-Dementia study

John T O'Brien [1], Michael J Firbank [2], Karen Ritchie [3, 4], Katie Wells [5], Guy B Williams [6], Craig W Ritchie [3], Li Su [1]

Correspondence to Dr Michael J Firbank, Institute of Neuroscience and Newcastle University Institute for Ageing, Newcastle University, Newcastle upon Tyne NE4 5PL, UK; michael.firbank@ncl.ac.uk

Extant Studies of Midlife and Older Adults

Fewer than a dozen

Rely on retrospective reports of cannabis use

Lack neuroimaging data

Four Questions of Policy Significance

1. Are all midlife cannabis users at risk?

2. Are cannabis-related cognitive and hippocampal volume differences minor compared with alcohol-related and tobacco-related deficits?

3. Do cognitive deficits among long-term cannabis users persist after cessation?

4. Do hippocampal volume differences among long-term cannabis users underlie cognitive deficits

Two Approaches

(1) Compare long-term cannabis users with:

- **Lifelong cannabis nonusers**
- **Midlife recreational cannabis users**
- **Long-term tobacco users and long-term alcohol users**
- **Cannabis quitters**

Two Approaches

(2) Dose-response associations using continuously measured persistence of cannabis use

- Rigorously adjusted for numerous confounders derived from multiple longitudinal waves and data sources.
- Robust dose-response associations would be expected if associations were causal.

Hippocampus focus

European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-019-00979-1

ORIGINAL PAPER

Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies

Valentina Lorenzetti[1] · Yann Chye[2] · Pedro Silva[3] · Nadia Solowij[4] · Carl A. Roberts[3]

Received: 25 September 2018 / Accepted: 3 January 2019

Hippocampus focus

Received: 10 June 2020 | Revised: 6 October 2020 | Accepted: 14 October 2020

DOI: 10.1111/adb.12984

ORIGINAL ARTICLE

Addiction Biology SSA WILEY

Cannabis use-related working memory deficit mediated by lower left hippocampal volume

Subhadip Paul[1] | Sagnik Bhattacharyya[1,2]

Dunedin Longitudinal Study

Age	Year	Number	Percent
Birth	1972-73		
3	1975-76	1,037	100%
5	1977-78	991	96%
7	1979-80	954	92%
9	1980-82	955	92%
11	1983-84	925	90%
13	1985-86	850	82%
15	1987-88	976	95%
18	1990-91	993	97%
21	1993-94	992	97%
26	1998-99	980	96%
32	2004-05	972	96%
38	2010-12	957	95%
45	2018-19	938	94%

“Before and After” IQ Testing

IQ Testing

Ages 7-13

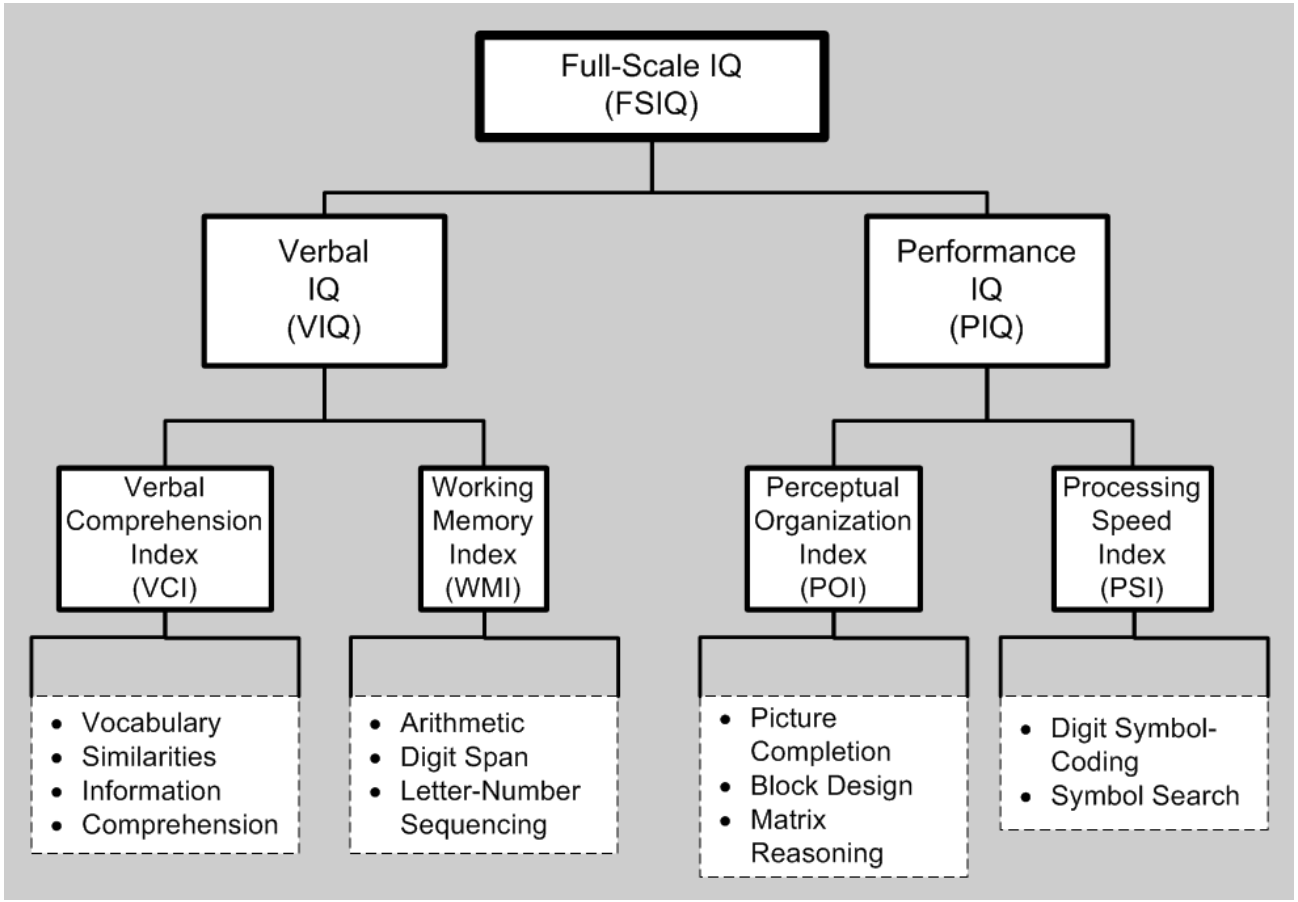
Cannabis Assessments

Ages 18-45

IQ Testing

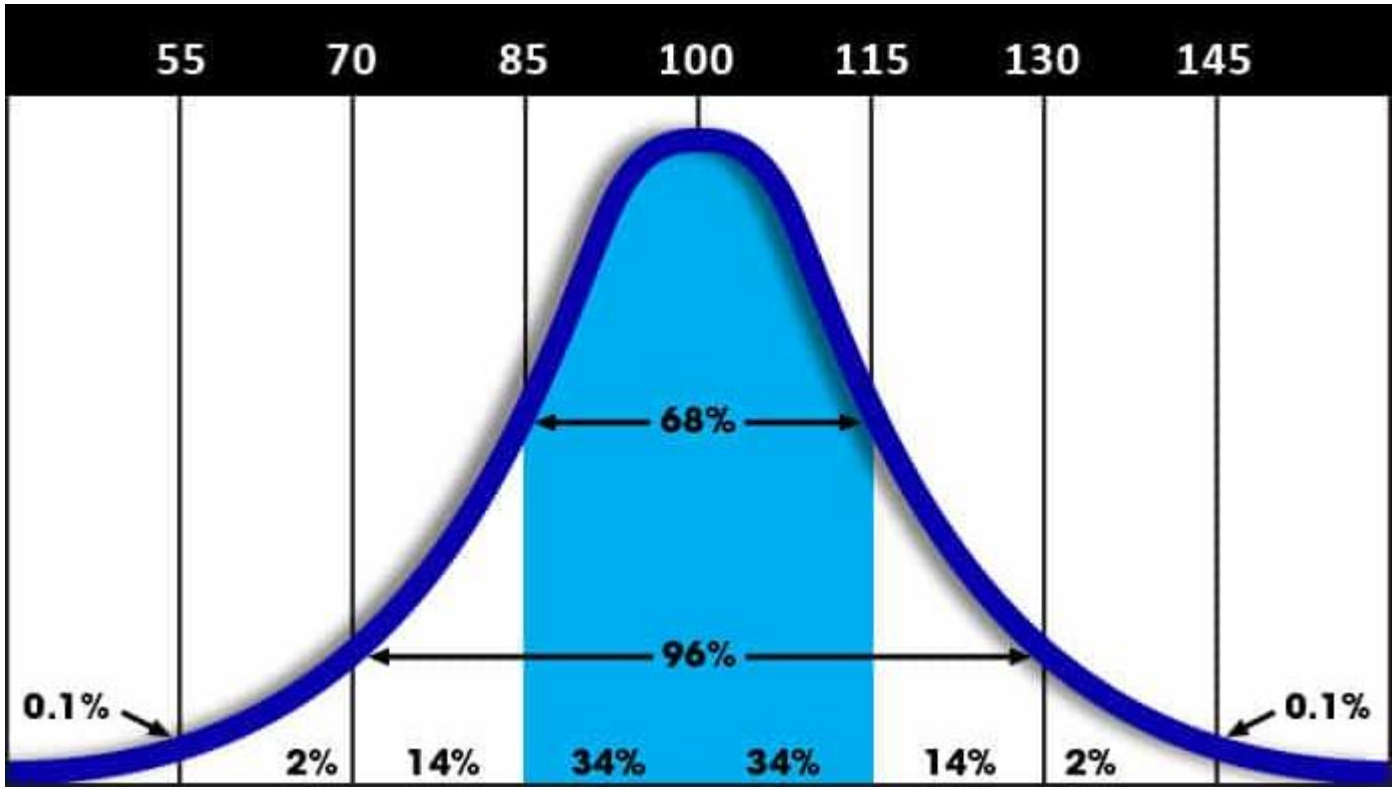
Age 45

IQ

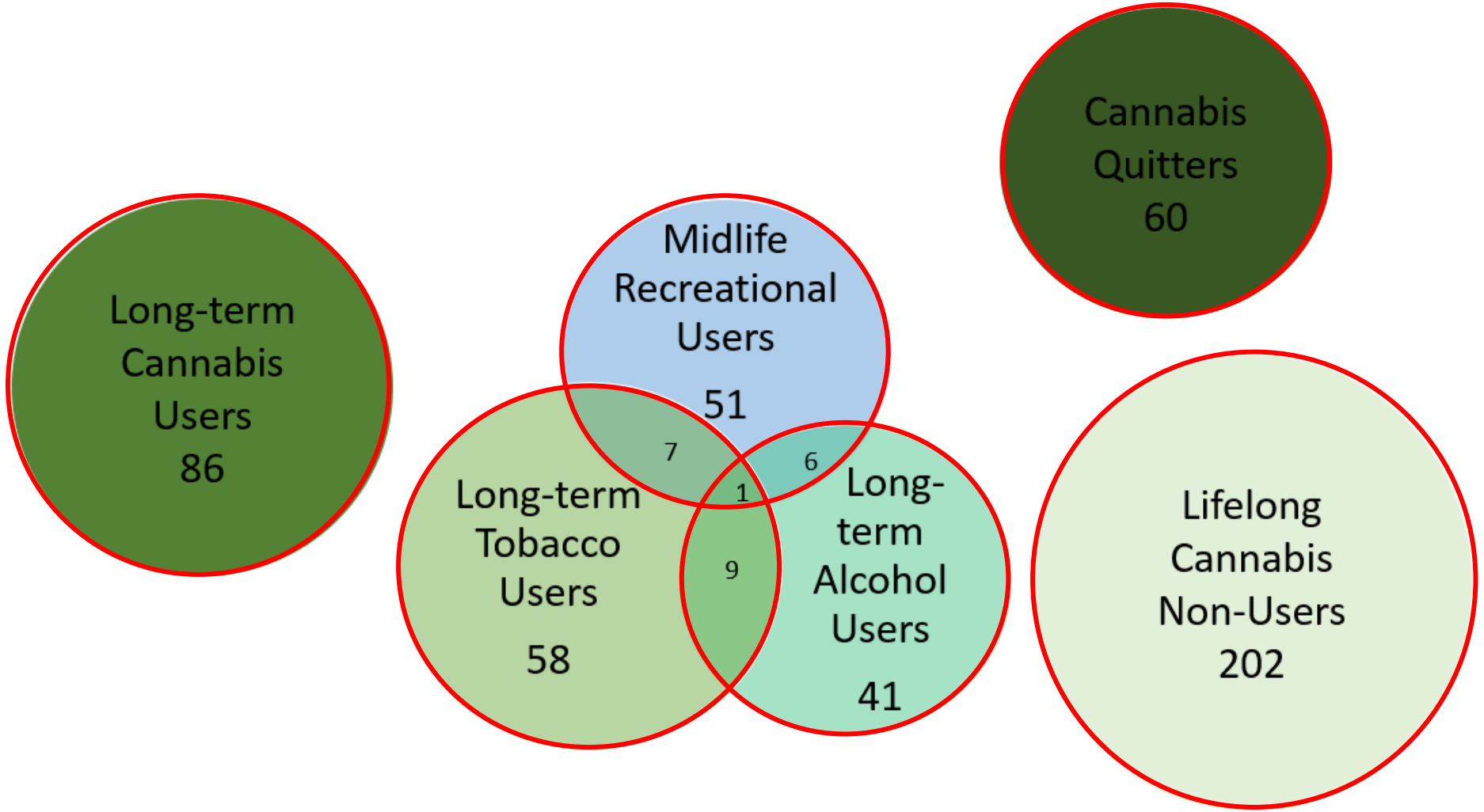

Full-Scale IQ
(FSIQ)
Verbal
IQ
(VIQ)
Performance
IQ
(PIQ)
Verbal
Comprehension
Index
(VCI)
Working
Memory
Index
(WMI)
Perceptual
Organization
Index
(POI)
Processing
Speed
Index
(PSI)
• Vocabulary
• Similarities
• Information
• Comprehension
• Arithmetic
• Digit Span
• Letter-Number
Sequencing
• Picture
Completion
• Block Design
• Matrix
Reasoning
• Digit Symbol-
Coding
• Symbol Search

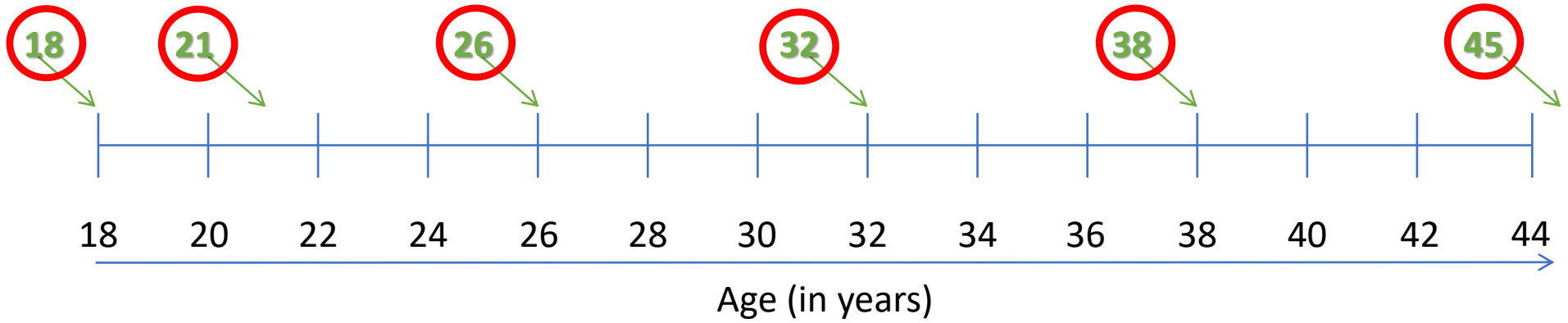
IQ

Average IQ = Score of 100



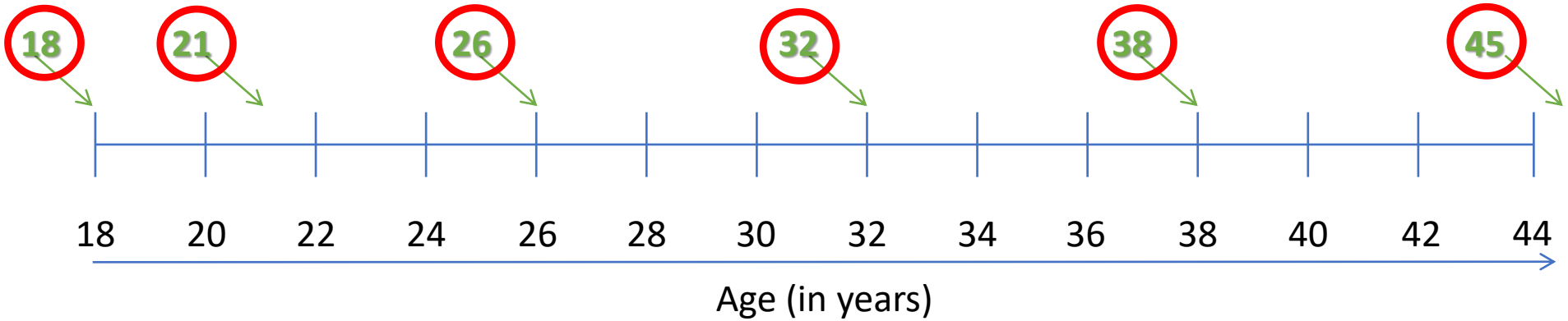
Long-Term Cannabis Users and 5 Comparison Groups

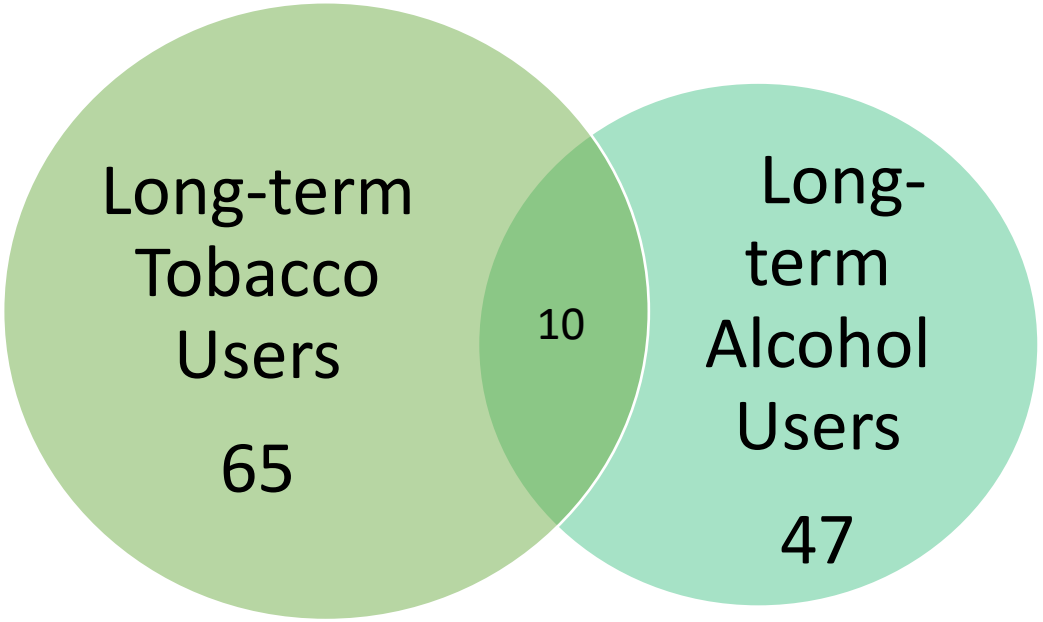




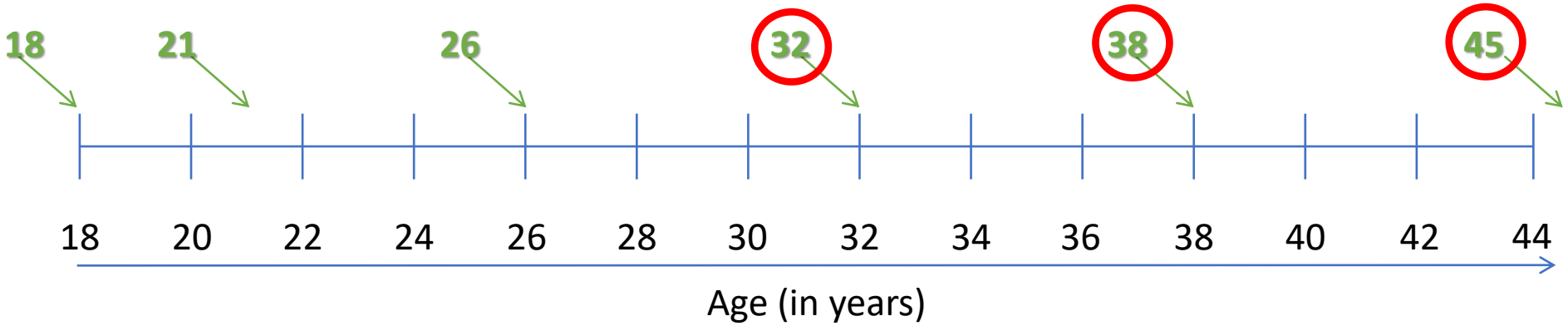
Long-term Cannabis Users
86

- Used weekly+ at age 45
- Used weekly+ at 1 or more previous assessment waves
- On average, this group used 4+ days per week for 3.4 of 6 waves (SD=1.4)





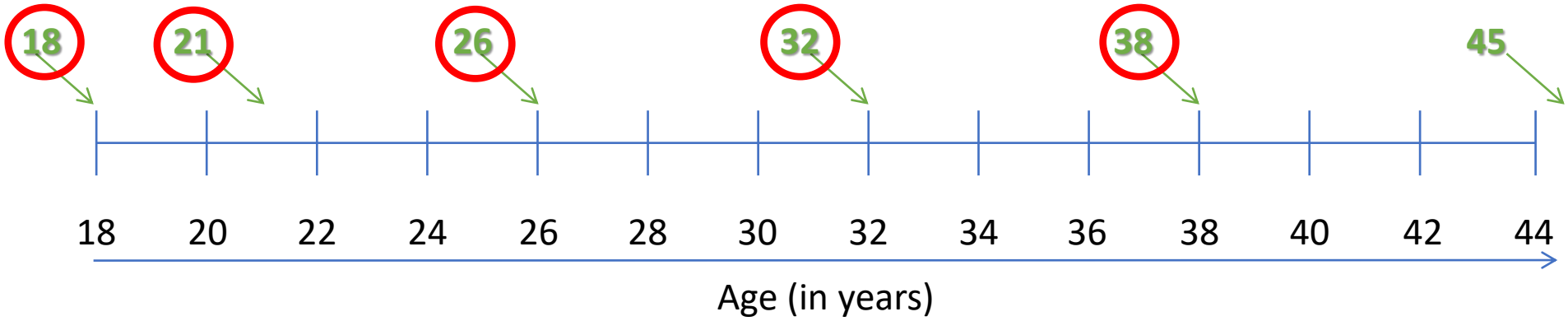
- Used frequently at age 45
- Used frequently at 1 or more previous assessment waves
- No cannabis use at age 45
- No history of weekly cannabis use or cannabis dependence



Midlife Recreational Users

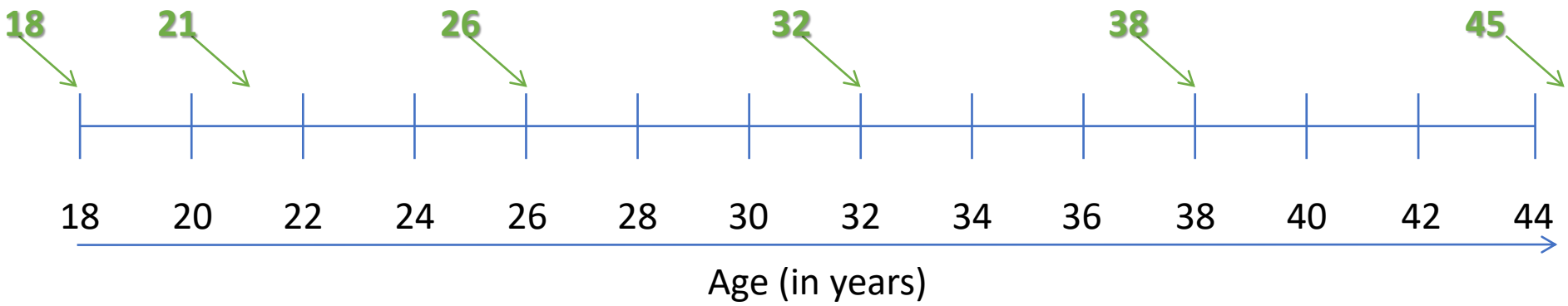
65

- Used cannabis infrequently (less than once a week) in midlife



Cannabis Quitters 60

- No cannabis use at age 45
- Used cannabis 4+ days a week *or* cannabis dependent at a previous assessment wave



Lifelong Cannabis Non-Users
202

- Never used cannabis at any assessment wave

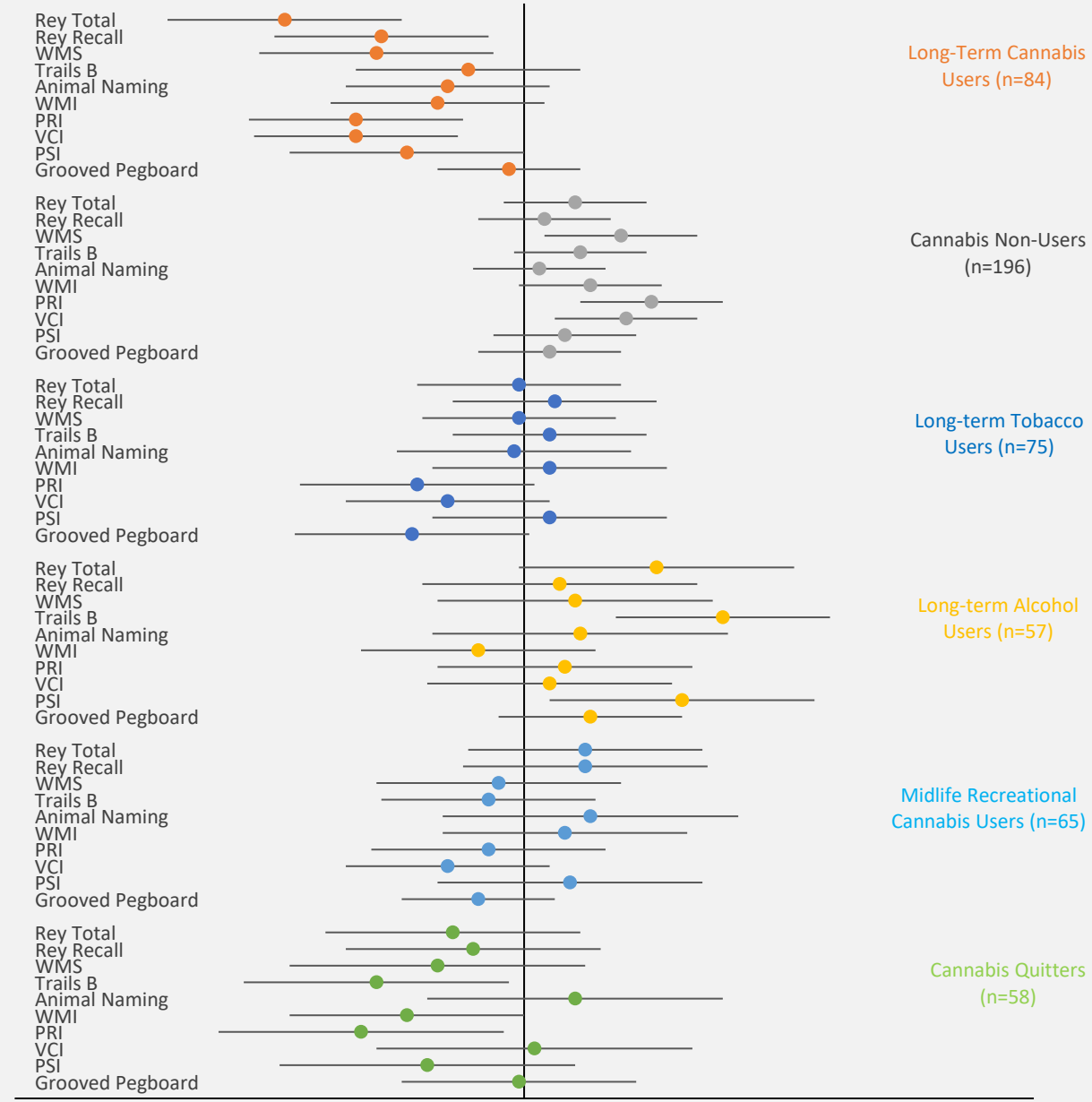
Do Long-Term Cannabis Users Show Larger IQ Decline Than 5 Informative Comparison Groups?

IQ in Childhood and Adulthood

Groups	N	Age 7-11 Full-Scale IQ	Age 45 Full-Scale IQ	Δ in IQ
Long-Term Cannabis Users	84	99.3	93.8	-5.5
Cannabis Non-Users	196	101.4	102.1	0.70
Long-term Tobacco Users	75	93.0	91.5	-1.5
Long-Term Alcohol Users	57	99.3	98.8	-0.50
Midlife Recreational Users	65	105.1	101.6	-3.5
Cannabis Quitters	59	97.6	94.3	-3.3

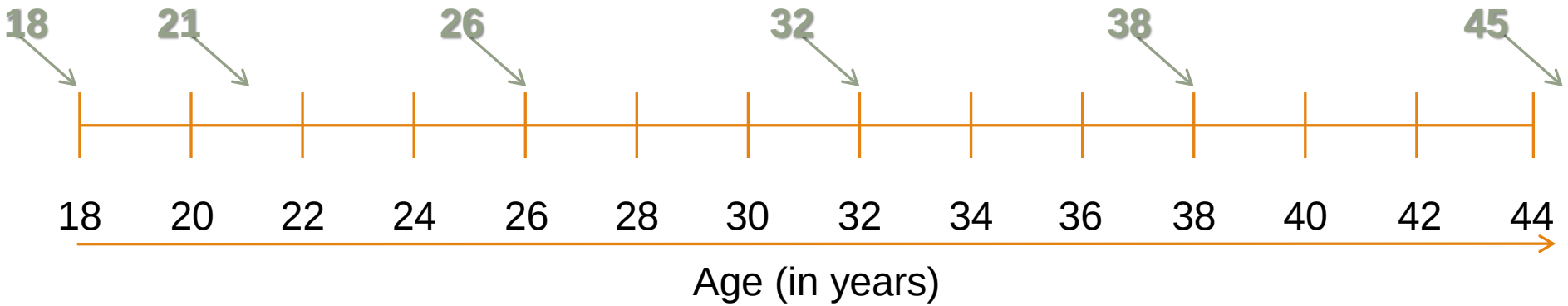
Do Long-term Cannabis Users Show Deficits in Other Cognitive Domains?

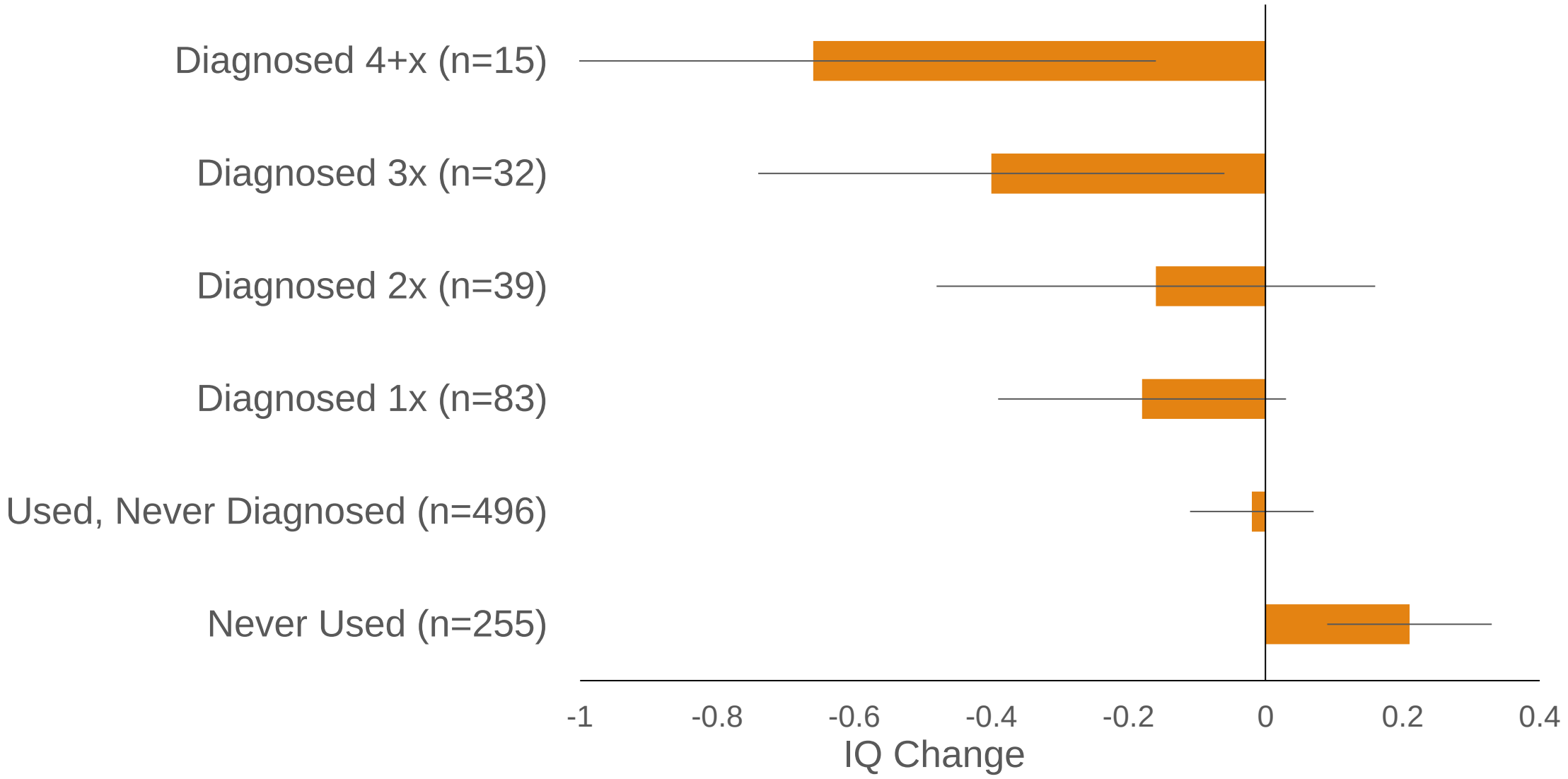
Learning
Memory
Working Memory
Executive Function
Verbal Fluency
Working Memory Index
Perceptual Reasoning Index
Verbal Comprehension Index
Processing Speed Index
Motor Function



Dose-Response Associations?

Do people who use cannabis more persistently show greater IQ decline than people who use less persistently?

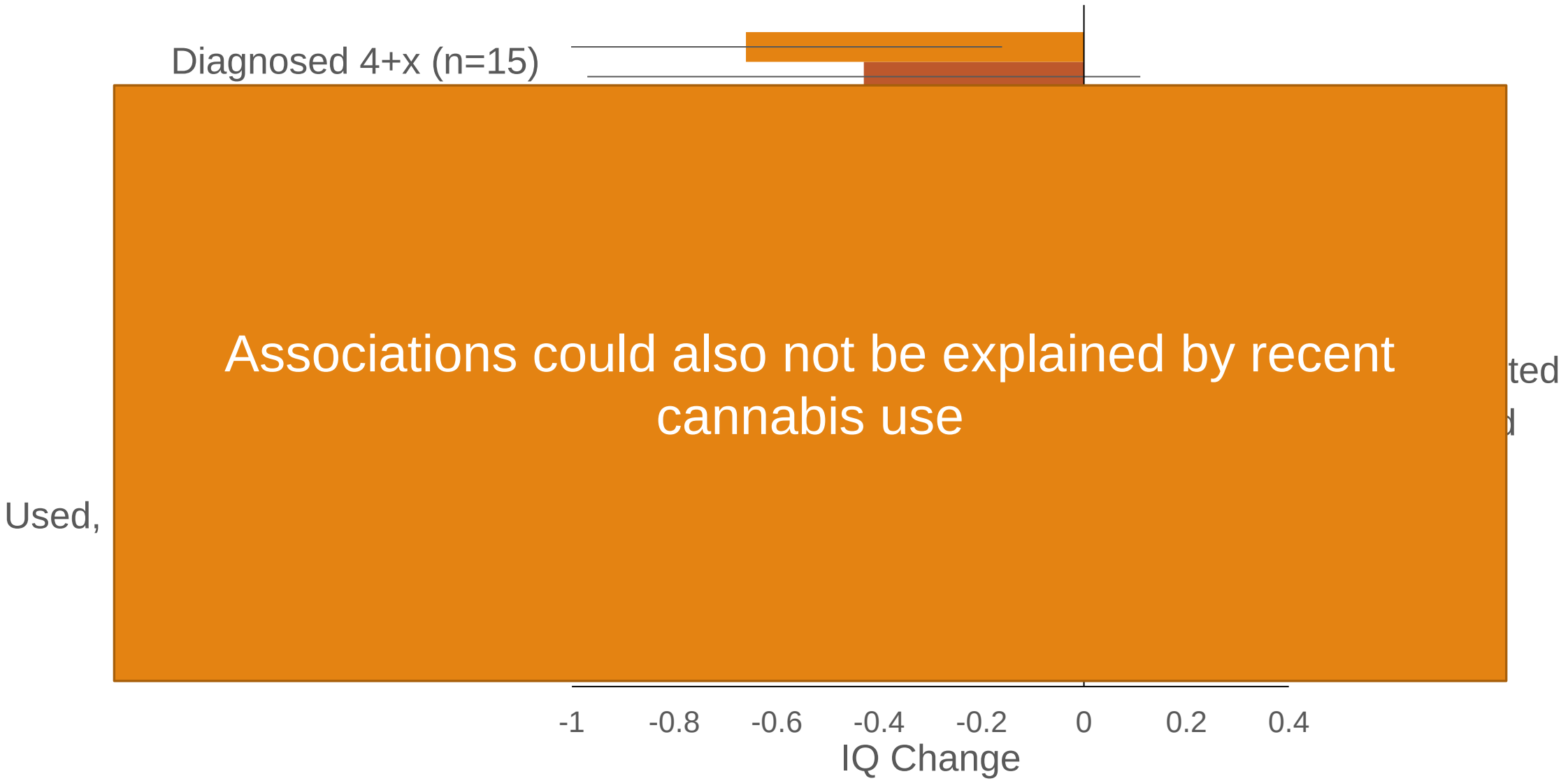



Diagnosed 4+x (n=15)
Diagnosed 3x (n=32)
Diagnosed 2x (n=39)
Diagnosed 1x (n=83)
Used, Never Diagnosed (n=496)
Never Used (n=255)
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
IQ Change

Alternative Explanations?

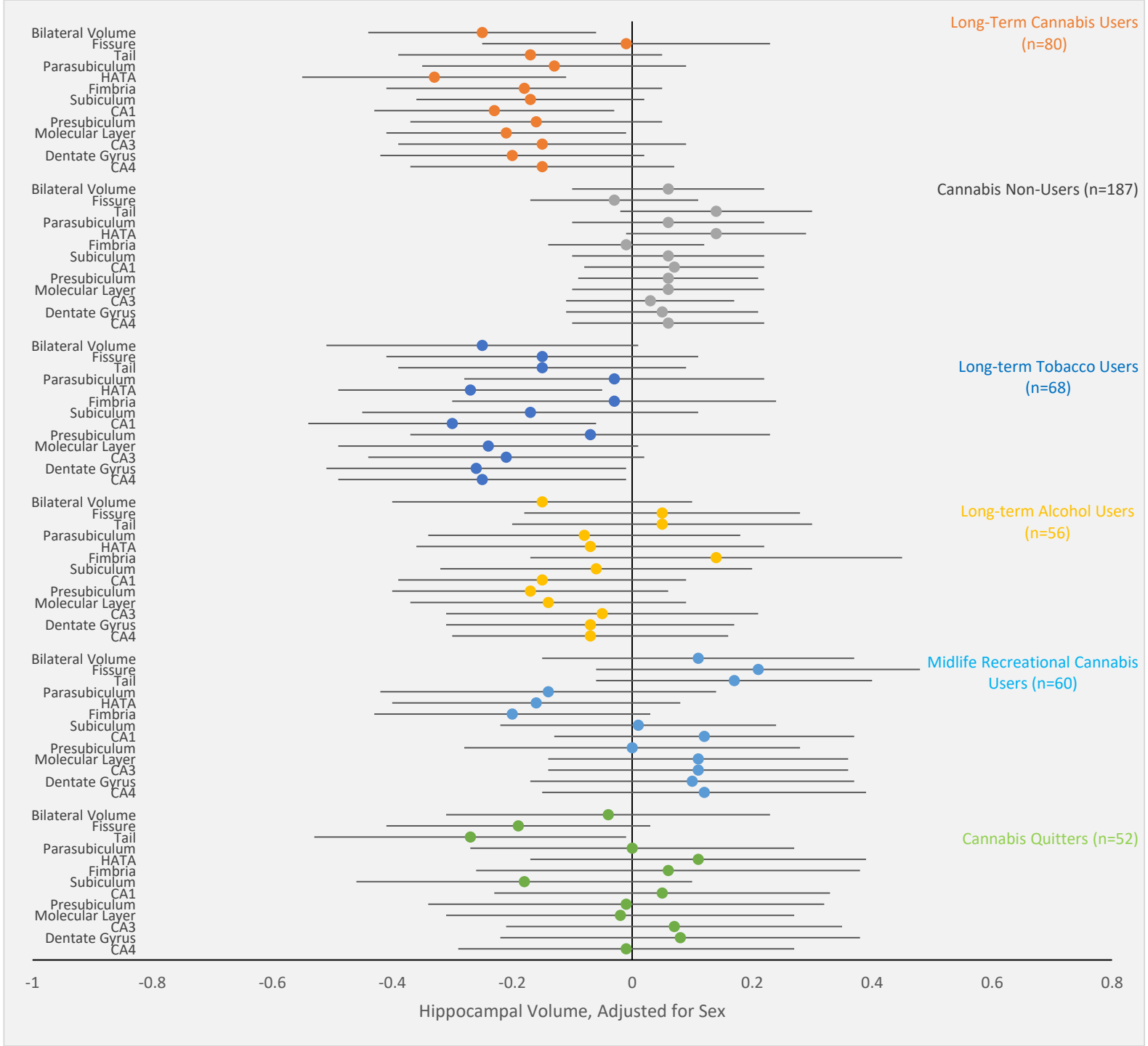
Can the dose-response association be explained by….

- Persistent tobacco dependence?
- Persistent alcohol dependence?
- Persistent other illicit drug dependence?
- Childhood socioeconomic status?
- Childhood low self-control?
- Family history of substance use problems?

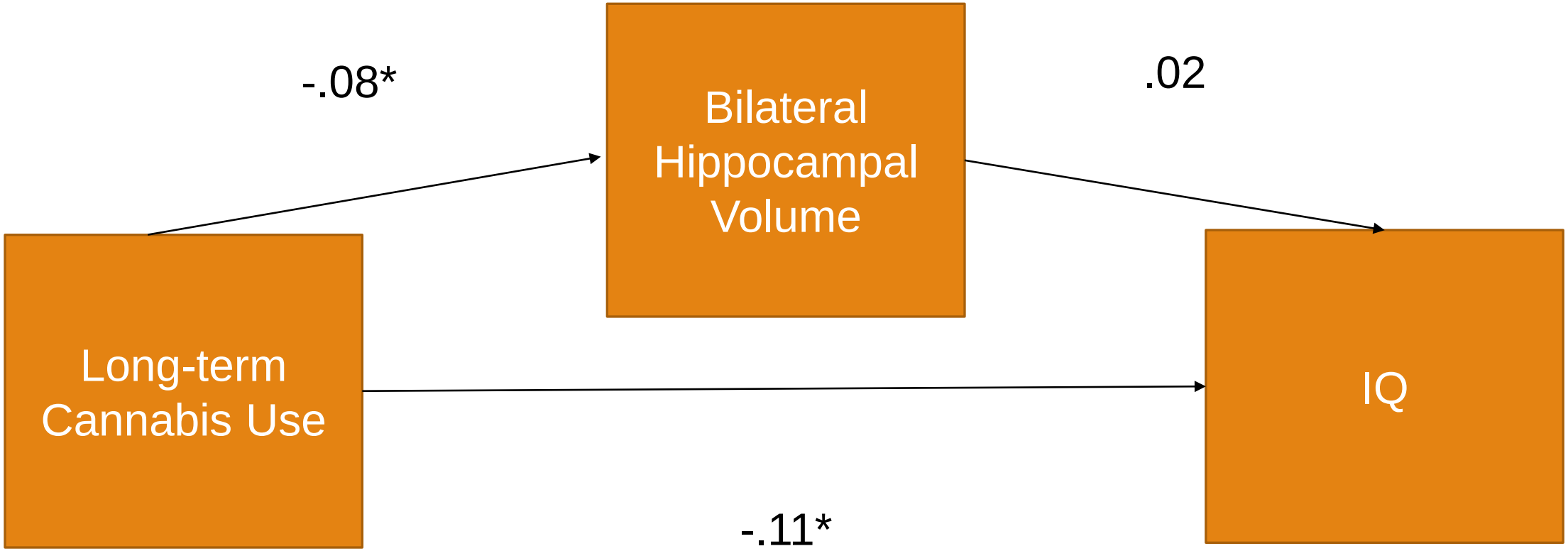

Diagnosed 4+x (n=15)
Associations could also not be explained by recent cannabis use
Used,
ted
d
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
IQ Change

Do Long-term Cannabis Users Show Smaller Hippocampal Volume?

Bilateral Volume
Fissure
Tail
Parasubiculum
HATA
Fimbria
Subiculum
CA1
Presubiculum
Molecular Layer
CA3
Dentate Gyrus
CA4



Does smaller hippocampal volume among long-term cannabis users underlie cognitive deficits?



Indirect = -.001, p=.58

Summary: 6 Key Take-Home Points

1. Long-term cannabis users showed IQ decline and poorer learning and processing speed in midlife relative to their childhood IQ

   People who knew them well described them as having memory and attention problems

   Associations were not explained by other factors

Summary

2. Long-term cannabis users showed significantly larger IQ decline, poorer learning and memory, and poorer processing speed than long-term tobacco or alcohol users
3. Midlife recreational cannabis users did not show cognitive deficits and should not be conflated with long-term users in future research

Summary

4. Cannabis quitters showed subtle cognitive deficits that may explain inconsistent findings on the benefits of cessation

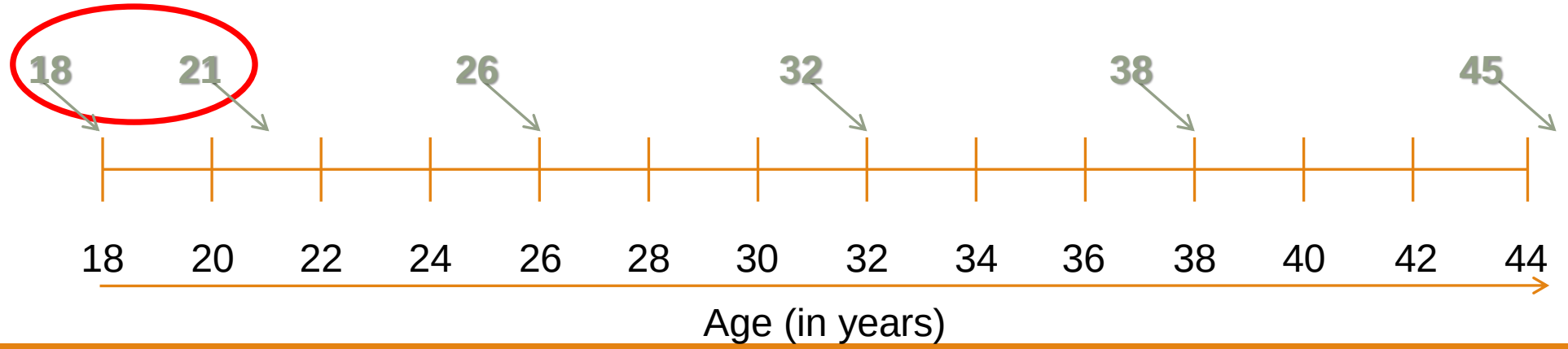
Summary

5. Long-term cannabis users showed smaller hippocampal volume, consistent with case-control studies
6. But, hippocampal volume could not explain cannabis-related cognitive deficits
   - Too reductionistic
   - Other mechanisms of cannabis-related IQ decline?

How Do Findings Compare?

A number of studies have shown limited evidence of cannabis-related cognitive deficits

But these studies are of adolescents with a far less serious level of cannabis use



Implications

Midlife cognitive deficits among long-term cannabis users may be consequential

- Effect sizes for midlife cognitive deficits among long-term cannabis users are comparable to midlife cognitive deficits observed among people who go on to develop dementia

Table 1
Demographic characteristics of participants who attended ARIC visit 1 by visit 5 status

Total N = 15,680	Deceased before V5	Alive, did not attend V5	Normal	MCI	Dementia
N	5030	4194	4743	1371	342
Median follow-up (yrs)	14.55	24.04	23.65	23.71	23.79
Female (%)	45	61	61	53	57
African-American (%)	33	26	23	21	42
Age at visit 1 (mean, SD)	56.9 (5.45)	54.1 (5.69)	51.4 (4.92)	53.4 (5.26)	55.9 (5.36)
Education					
<HS	34	25	14	14	38
HS grad	38	43	41	44	34
>HS	28	32	45	41	28
V2 DWRT Z-score (mean, SD)	−0.29 (1.04)	0.02 (0.97)	0.26 (0.93)	−0.01 (0.91)	−0.32 (1.13)
V2 DSST Z-score (mean, SD)	−0.38 (1.01)	−0.00 (0.94)	0.38 (0.93)	0.01 (0.84)	−0.53 (1.07)
V2 WFT Z-score (mean, SD)	−0.19 (1.03)	−0.04 (0.97)	0.25 (0.97)	−0.08 (0.91)	−0.34 (1.05)

Table taken from Knopman et al., 2018, Alzheimer's and Dementia

Implications

Will long-term cannabis users show elevated rates of dementia in later life?

- Important given the huge burden of dementia
- Timely given the confluence of two trends: the growth of the aging population, and the record high rates of cannabis use among today's older adults.

What should we do?

Encourage cessation

Increase awareness among older adults of risks of cannabis-related cognitive deficits

Midlife interventions

Disclosures

National Institute on Aging

National Institute on Mental Health

UK Medical Research Council

NZ Health Research Council

Jacobs Foundation

New Zealand Ministry of Business, Innovation and Employment

Thank you

Terrie Moffitt

Avshalom Caspi

Ahmad Hariri

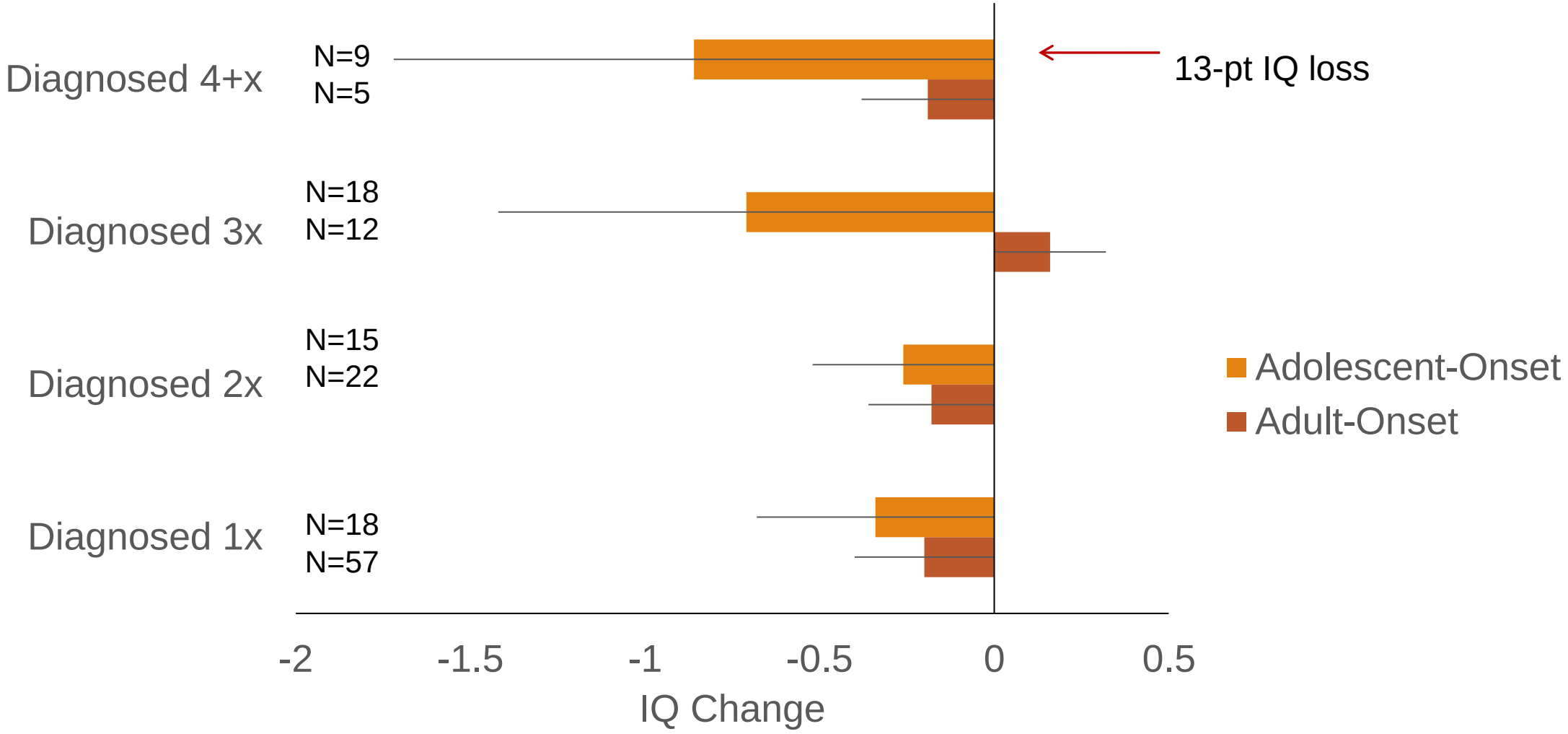
Annchen Knodt

Dunedin Study Team

Contact Information

Madeline.Meier@asu.edu

Are Adolescent-Onset Cannabis More Vulnerable?


Diagnosed 4+x
N=9
N=5
Diagnosed 3x
N=18
N=12
Diagnosed 2x
N=15
N=22
Diagnosed 1x
N=18
N=57
13-pt IQ loss
Adolescent-Onset
Adult-Onset
-2
-1.5
-1
-0.5
0
0.5
IQ Change