

Prenatal and Postnatal Marijuana Exposure: **It's A Bad Thing. Seriously.**

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Outline

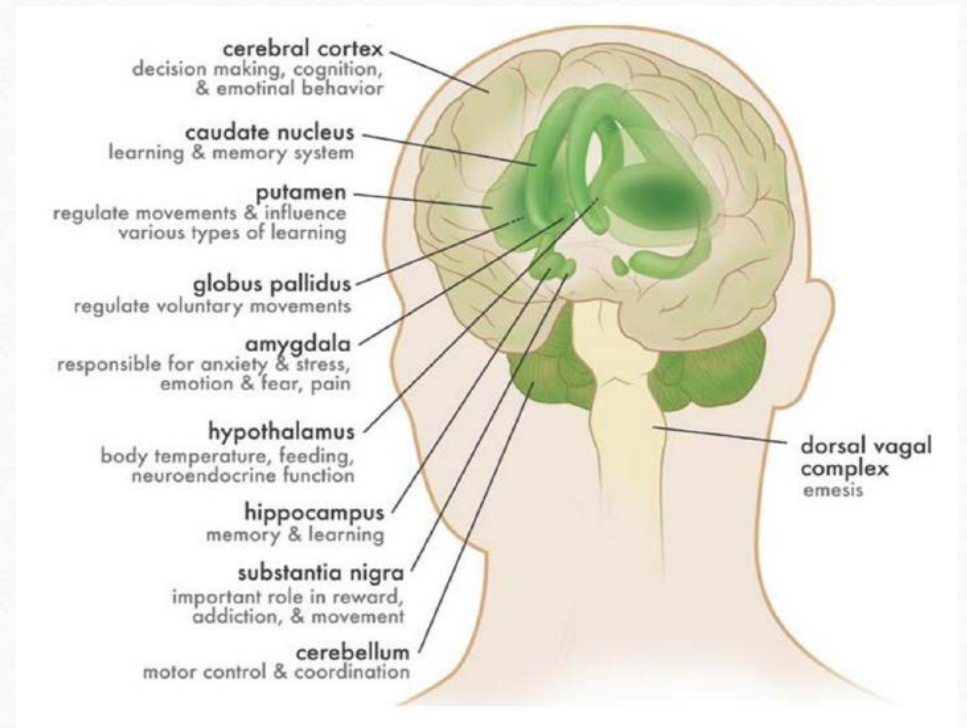
- Epidemiology/Physiology/History
- Adult Users: Short term/**high dose/long term effects**
- Trends in potency and the law
- Neonatal effects
- Childhood effects
- Observational data - systemically making sense of observations
- Implications for practice

Marijuana Use - Epidemiology

- #1 used illicit substance in the world
 - Estimated 182 million users worldwide
- 19.6% of 18-25 year old's in US report use in the past month
- 9% of individuals that ever use will become dependent
- Among US 12th graders, marijuana use (21%) > cigarette use (11%)

Marijuana Physiology

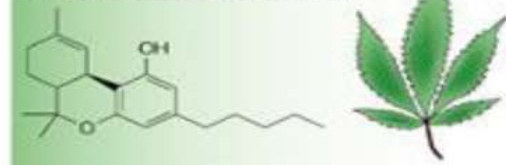
- Active components
 - THC (tetrahydrocannabinol)
 - CBD (cannabidiol)
- **Marijuana Receptors: CB1 and CB2**
 - **CNS (memory/emotion/cognition)**
 - Hematopoietic Cells
 - Reproductive Tissues
 - Gastrointestinal Tract
 - Skeletal Muscle



Endocannabinoid System (ECS)

Plant-derived cannabinoid

Δ^9 -Tetrahydrocannabinol (THC)

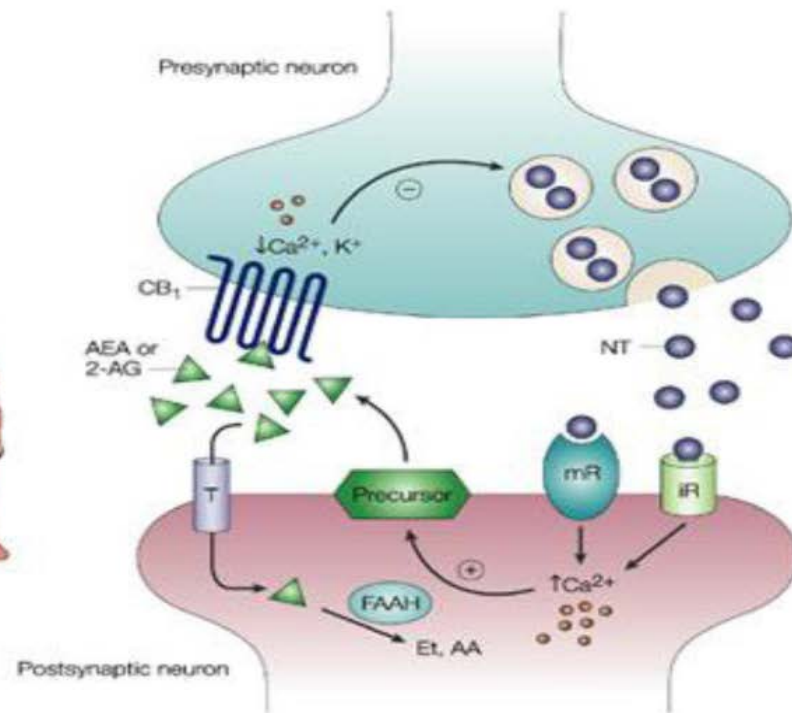


Endogenous cannabinoids

Anandamide (AEA)



2-Arachidonoylglycerol (2-AG)



History of Marijuana in US

- 1851: included in 3rd edition of Pharmacopeia of the United States (USP)
 - Indications: tetanus, mental disorders, analgesic, anticonvulsant
- Early 1900s: concerns of health effects → outlawed in several states
- 1937: Federal prohibition

Recreational Marijuana

Intoxication

- Enhanced sociability and sensitivity to stimuli (colors, music, etc.)
- Impaired short-term memory
- Altered perception of time
- Impaired coordination
- Heightened appetite
- Feeling of relaxation/“buzz” /pleasurable “rush”

Recreational Marijuana

High Dose/Withdrawal

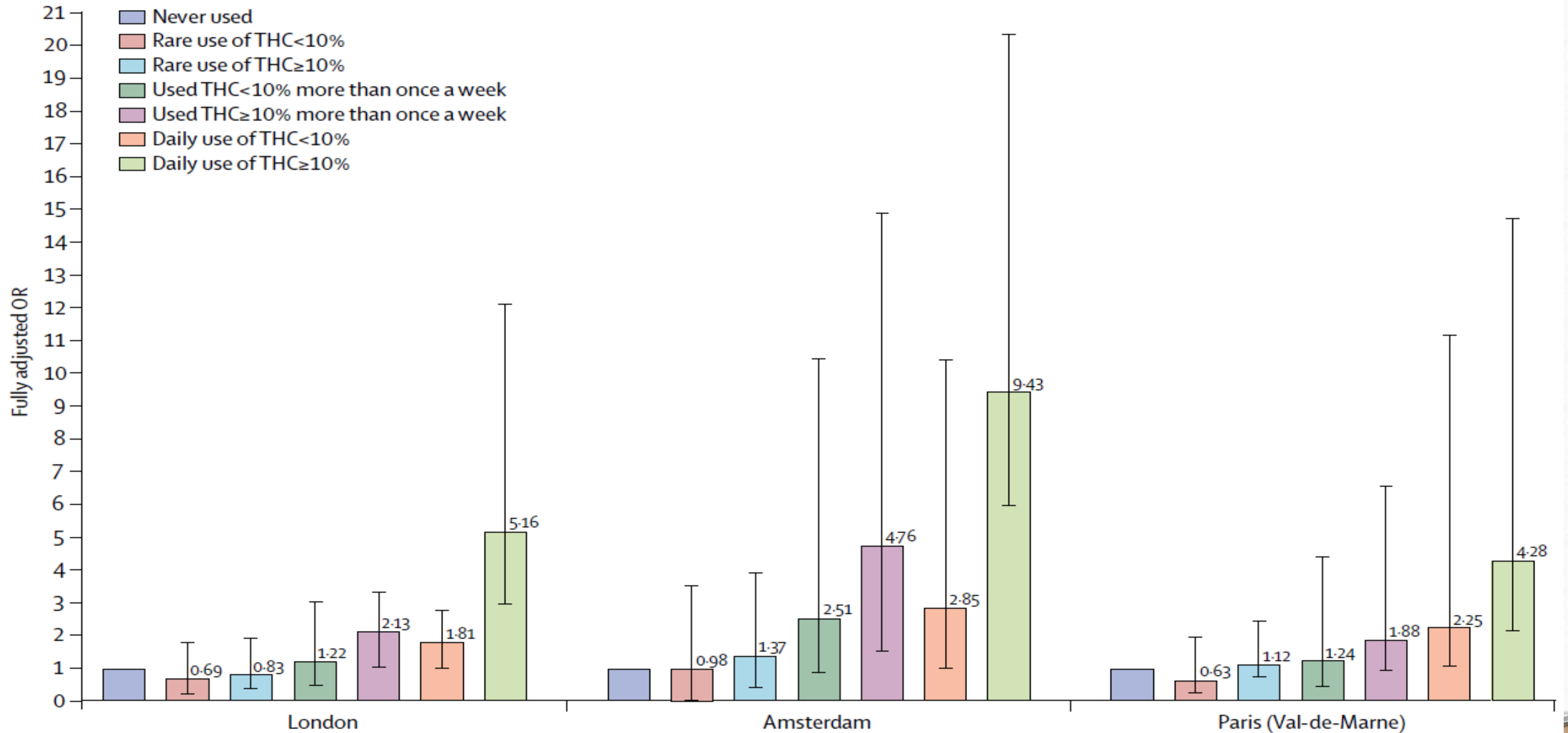
- Higher/Recurrent THC load
 - Panic attacks/Hallucinations/Paranoia
 - Coma
 - Seizures
 - Hyperemesis
- **Withdrawal** → irritability, insomnia, anxiety
 - Infants → high pitched cry, decreased sleep

Recreational Marijuana

Chronic Effects

- Chronic **bronchitis**
- Associations with **psychosis**, anxiety, depression
- **Altered brain structure**
 - Impaired neural connectivity (fewer fibers) especially w/early use
 - Brain regions: **memory, alertness, and cognition**/learning
- **Amotivational syndrome** (decreased self efficacy?/blunted reward CNS?)
- **IQ decline** from childhood to adulthood

Adjusted Odds Ratios – Marijuana (by type and frequency) and Psychosis

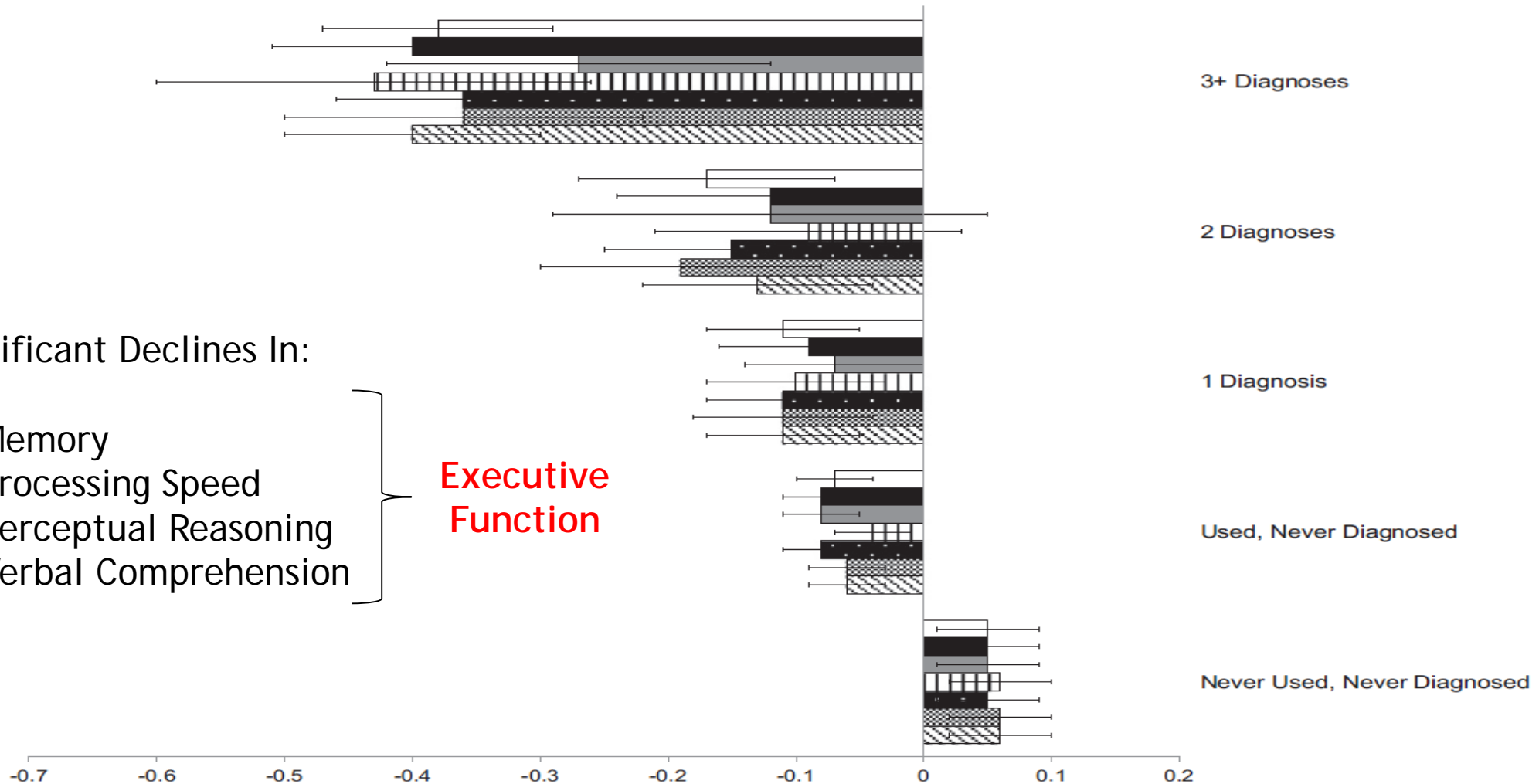


Standard Deviation IQ Changes 7-13yo → Adults

Significant Declines In:

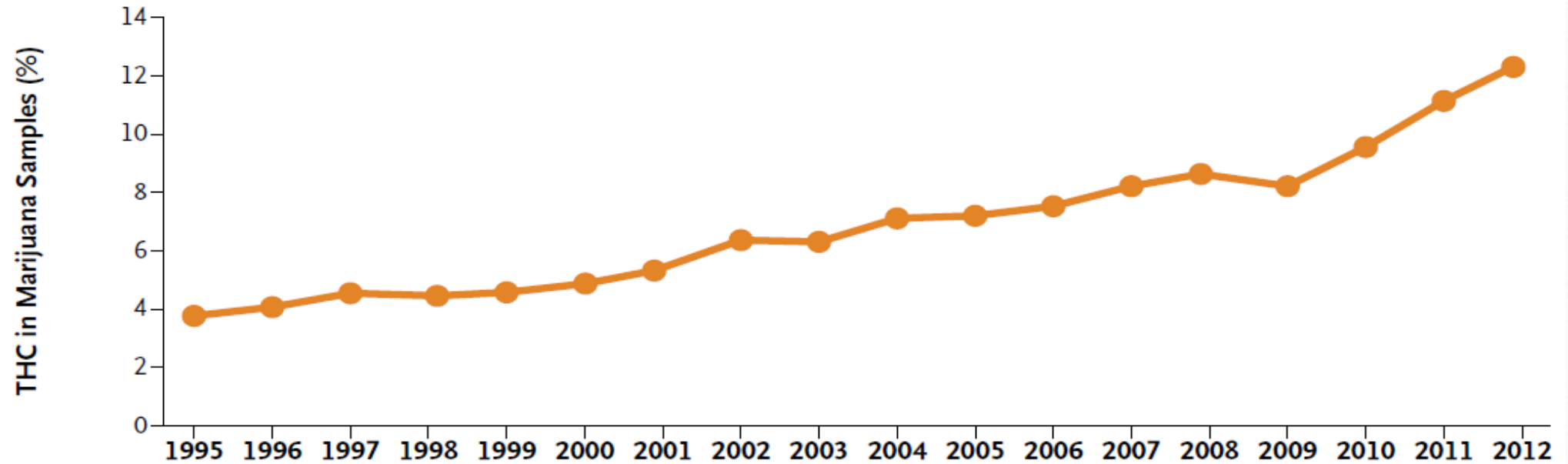
- Memory
- Processing Speed
- Perceptual Reasoning
- Verbal Comprehension

Executive Function

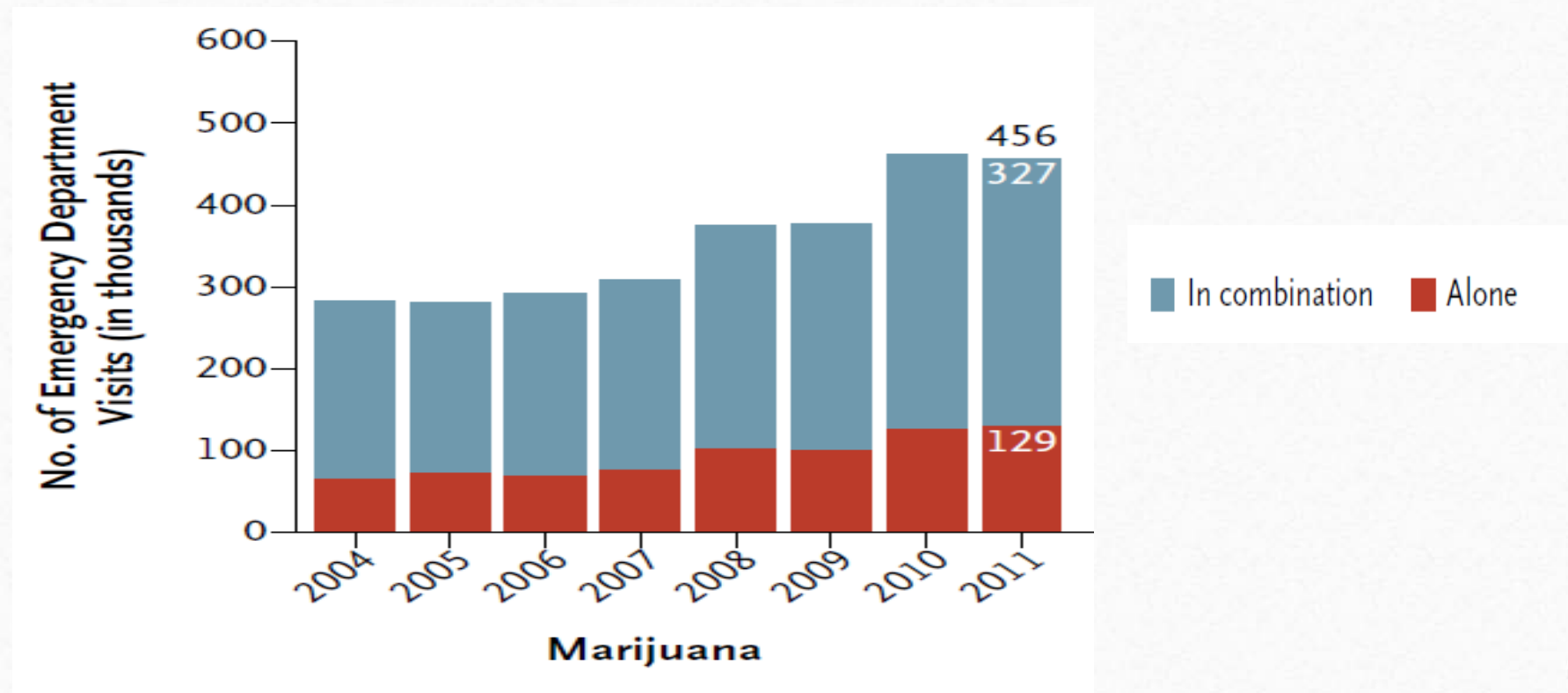


Marijuana Potency Over Time

A Potency of THC

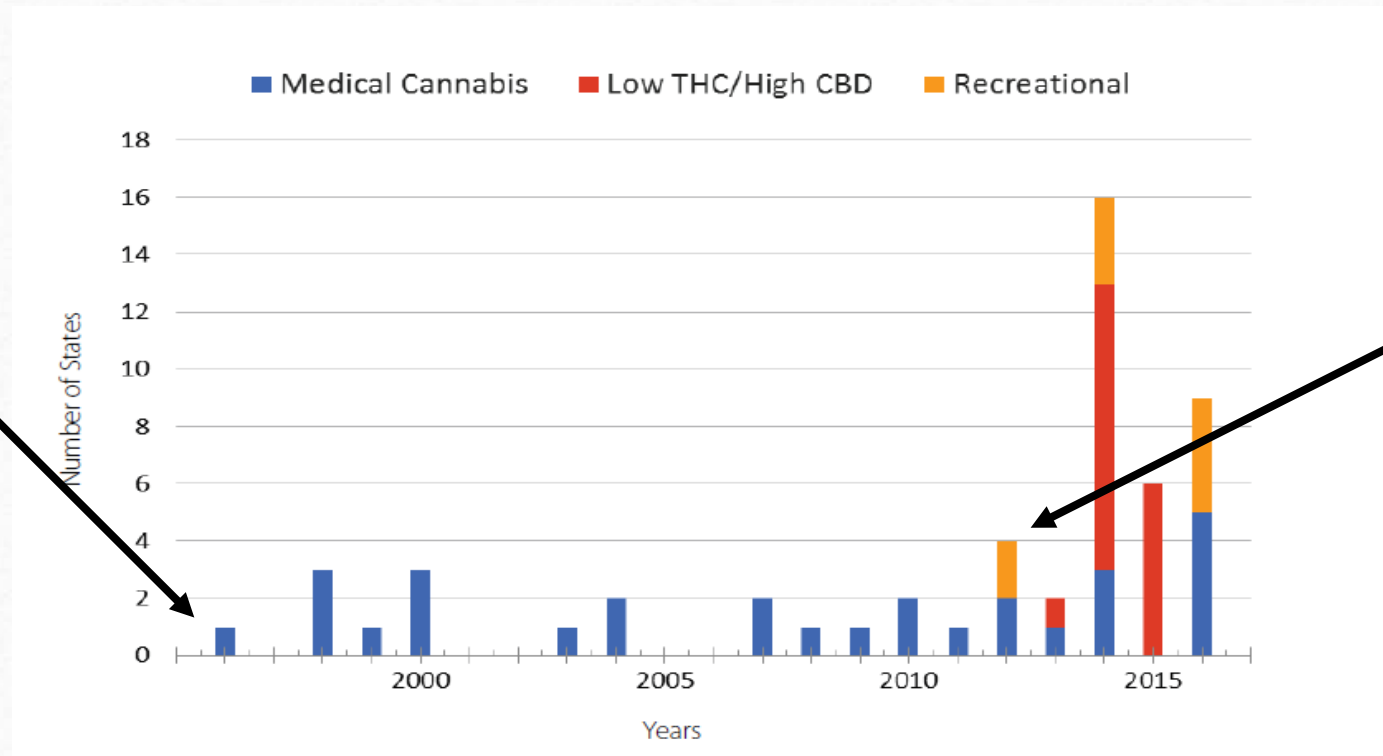


Marijuana-Related ED Visits Over Time



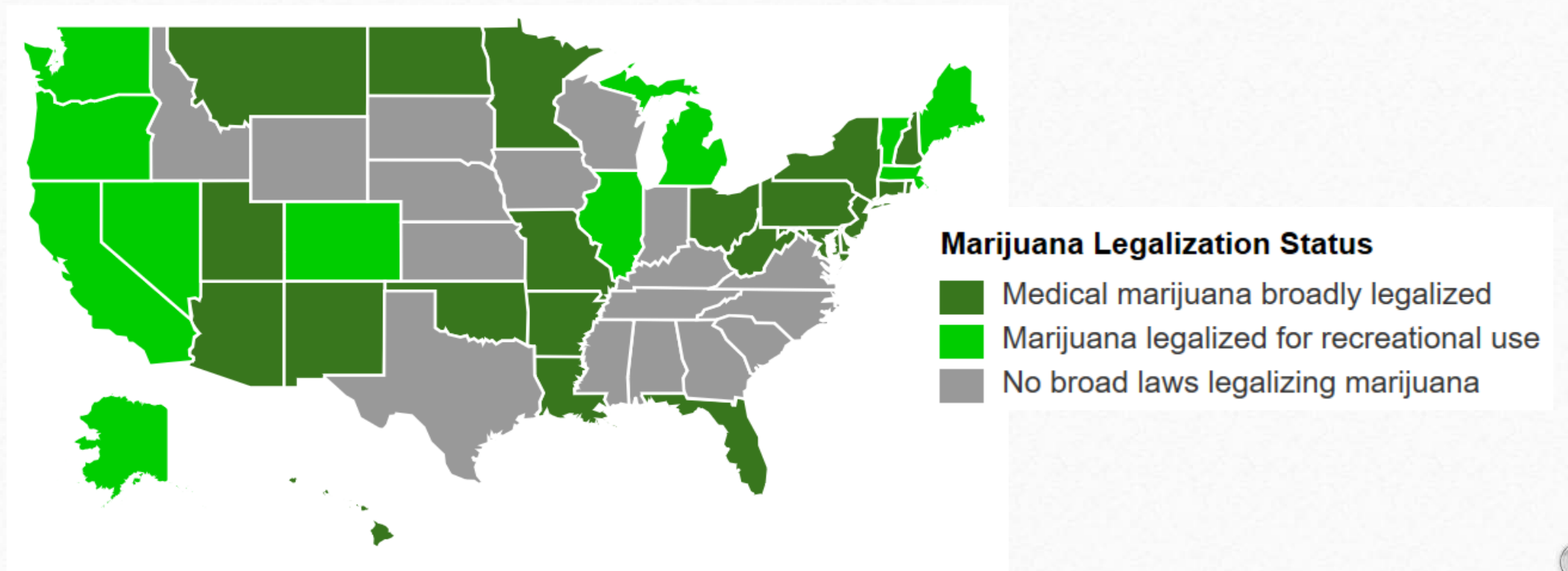
Passage Of State Laws

Medicinal
California 1996

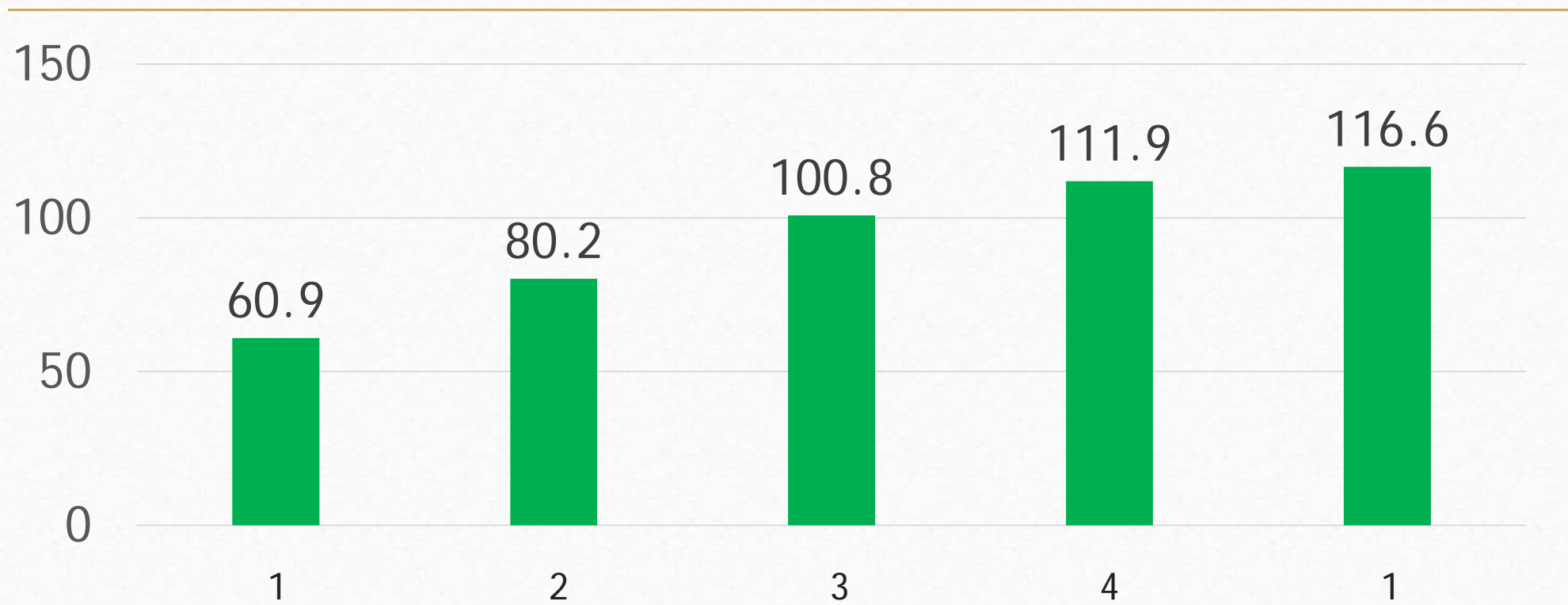


Recreational
Colorado 2012

Marijuana Laws By State



California Marijuana Tax Revenue (Millions) Per Quarter 2018 and Q1 2019



“Prescribing” Marijuana

- **It is illegal for physicians to *prescribe* marijuana**
- Doctors can write a *recommendation* if a patient suffers from a condition that the state’s law deems to warrant medicinal marijuana
- The patient must register with the state’s database to obtain a marijuana patient ID card, after which he or she can pick up medicinal marijuana from a dispensary

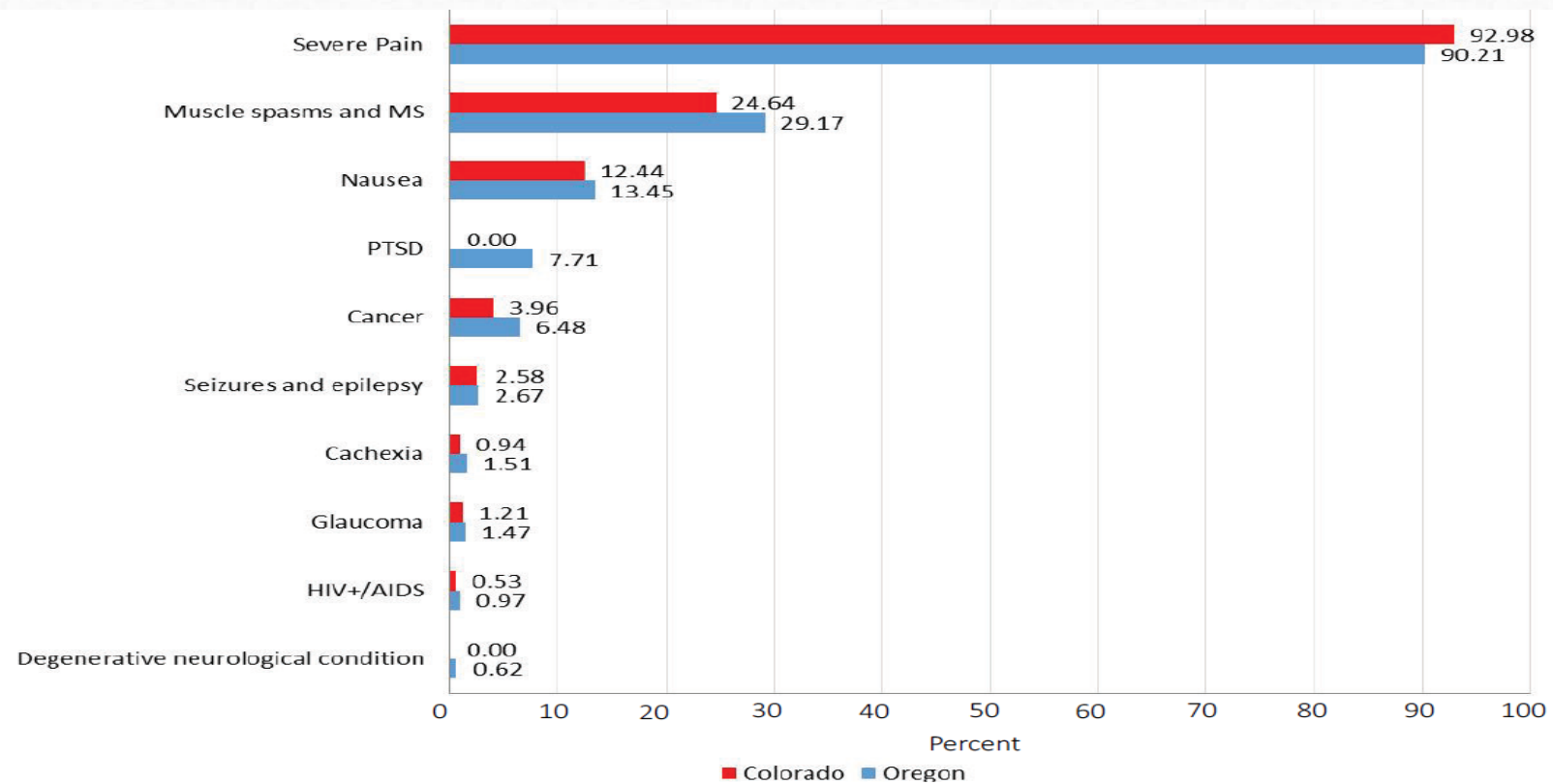
Potential Medical Uses for Marijuana

- Epilepsy*
- Nausea w/chemo*
- AIDS associated anorexia*
- Chronic Pain
- Inflammation (RA, Crohns, UC)
- Multiple Sclerosis*
- PTSD
- Glaucoma

FDA Approval

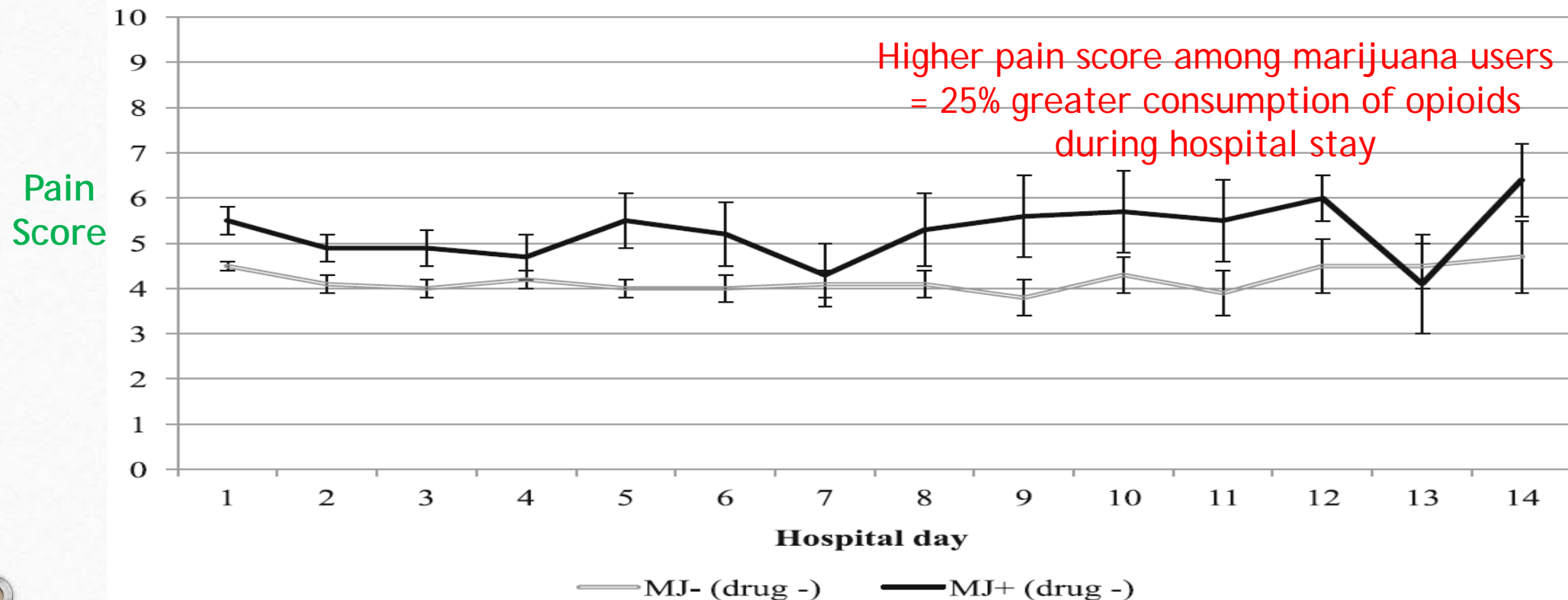
- “The FDA has not approved marijuana as a safe and effective drug for any indication” -FDA.GOV
- The FDA has approved Epidiolex (concentrated CBD) for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome
- Other drugs approved by FDA that contain *synthetic THC*:
 - Drobinol/Marinol - nausea w/chemo, appetite stimulated for AIDS
 - Nabilone/Cesamet - nausea w/chemo, appetite stimulated for AIDS

Reported “Medical” Uses of Cannabis Colorado/Oregon 2016



Pain Scores/Opioid Use after MVA

Marijuana vs Non-Marijuana Users

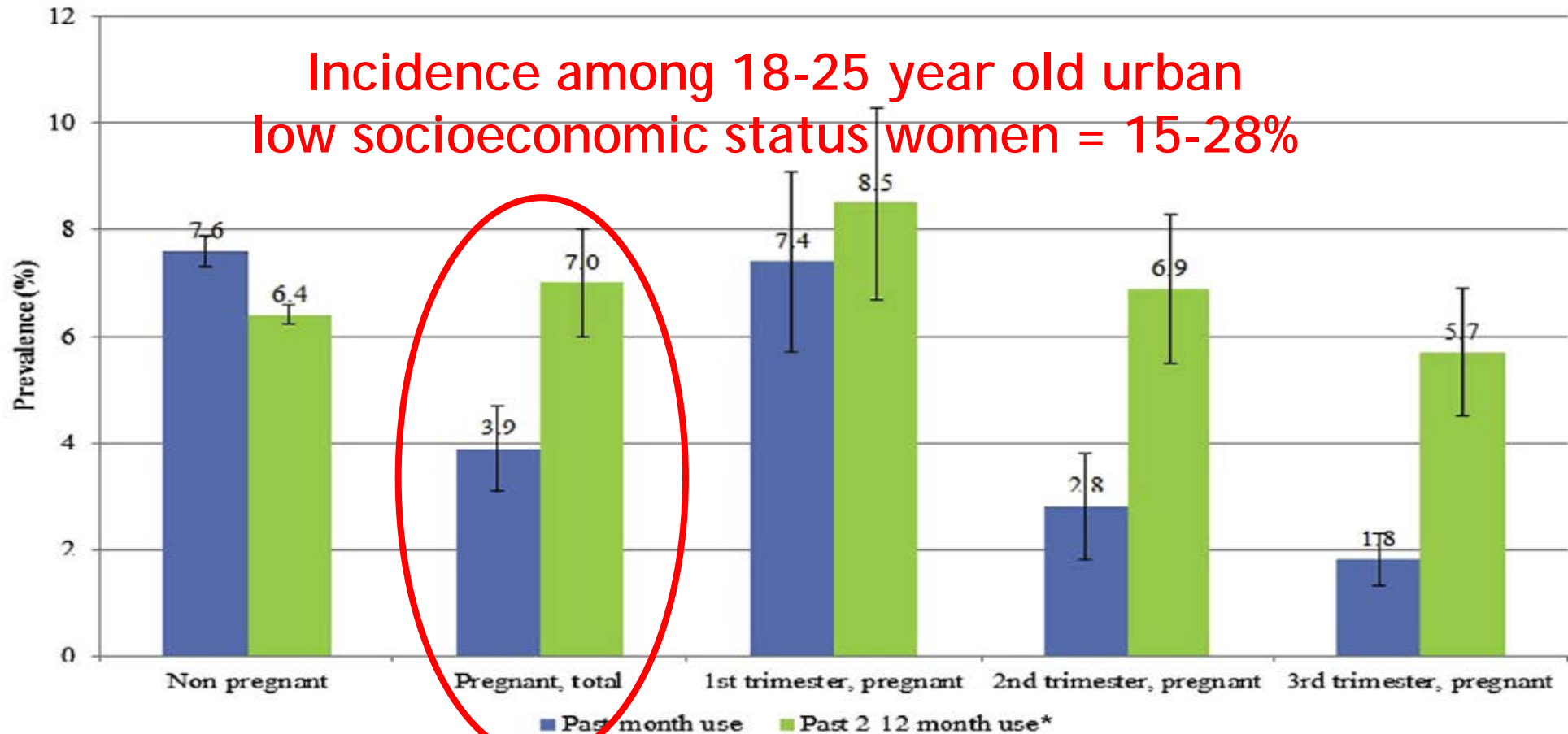


Sedation Requirement Endoscopic Procedures Marijuana vs Non-Marijuana Users

Sedative	Amount of Sedation Required			P Value	
	Cannabis Nonusers (n=225)	Cannabis Users (n=25)	Greater Requirement, %	t Test	Mann-Whitney U Test
Fentanyl, µg	109.91	125.93	14	.029	.003
Midazolam, mg	7.61	9.15	19.6	<.001	<.001
Propofol, mg	13.83	44.81	220.5	.026	.001

FIGURE

Prevalence of marijuana use among women of reproductive age



Characteristics of Marijuana Users Among Pregnant Women

- More likely to be:
 - Single
 - Younger (<25)
 - Primigravida
 - African American/Hispanic
 - Enrolled in WIC
 - 12th grade or less education

Why Pregnant Women Use

- Vancouver Canada Survey of Pregnant Women:
 - Nausea/Lack of appetite (77%)
 - Pain
 - Insomnia
 - Anxiety/Depression

Dispensary Advise to Pregnant Women (Colorado)

931 Recommendations from cannabis dispensaries on first trimester marijuana use



Betsy Dickson¹, Chanel Mansfield², Maryam Guiahi¹,
Amanda A. Allshouse³, Laura Borgelt¹, Jeanelle Sheeder¹,
Robert M. Silver⁴, Torri D. Metz^{1,5}

¹University of Colorado School of Medicine, Aurora, CO, ²University of Colorado, Denver, CO, ³Colorado School of Public Health, Aurora, CO, ⁴University of Utah Health, Salt Lake City, UT, ⁵Denver Health and Hospital Authority, Denver, CO

OBJECTIVE: To characterize recommendations given to pregnant women by Colorado marijuana dispensaries regarding use of cannabis products for nausea during the first trimester.

- 400 Dispensaries contacted
- 70% recommended marijuana as a treatment for nausea in the first trimester

Placental Transfer of Marijuana

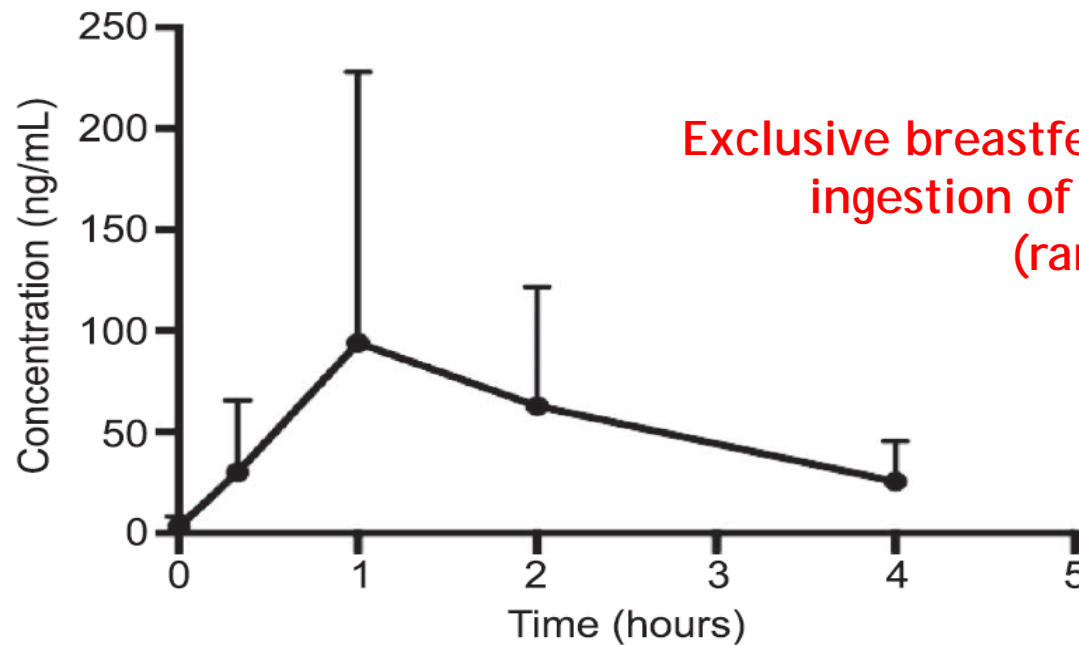
- Marijuana DOES readily cross the placenta
- Rat model:
 - Fetal blood levels 10% to 33% of maternal levels
- Spanish study of pregnancy terminations 2012
 - THC in maternal hair = THC in placenta/fetal tissue

Marijuana and the Fetus

- CB receptors present in embryo by 5 weeks
- **CB receptors concentrated** in areas responsible for:
 - **Memory**
 - **Emotional regulation**
 - **Cognition/processing speed**

Marijuana in Breastmilk

Concentration of Marijuana in Breastmilk after inhalation of 23mg of THC



Exclusive breastfeeding would result in infant ingestion of 2.5% of maternal dose (range 0.4-8.7%)

Maternal and Neonatal Outcomes In Prenatal Marijuana Use

- Washington University, St. Louis 2004-2008 - 8,138 women
 - “**Marijuana use is common in pregnancy but may not be an independent risk factor for poor neonatal outcomes in term pregnancies.**”

Maternal and Neonatal Outcomes

Prenatal Marijuana Use

- Baylor College of Medicine 2011-2015 - 12,069 women
 - “**Marijuana exposure was NOT associated with significant perinatal adverse outcomes**”

Marijuana Exposure and Preterm Infants

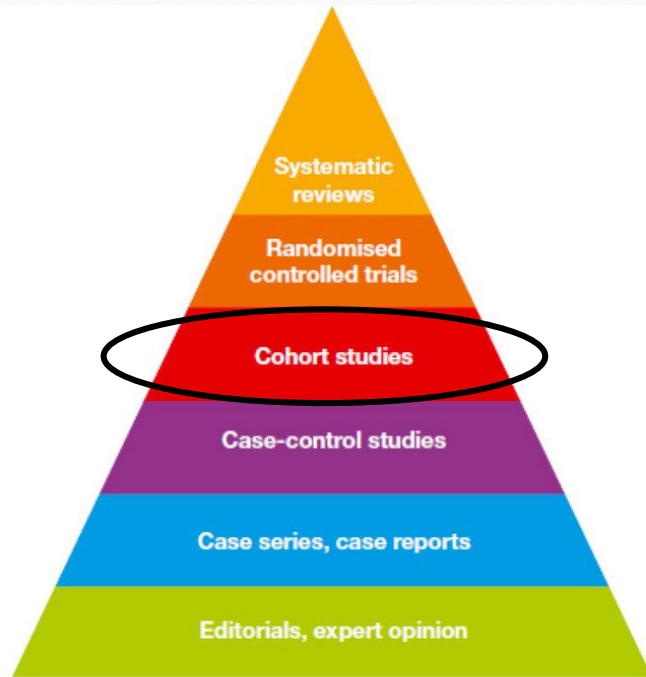
- 23 5/7 to 31 6/7 infants from 20 centers between 1997 and 2004

Results: 1867 infants met inclusion criteria; 135(7.2%) were MJ-exposed. There were no differences in neonatal (20% vs. 26%, $p=0.14$) or childhood (26% vs. 21%, $p=0.21$) outcomes in MJ-exposed infants compared to MJ-unexposed infants. In adjusted models, MJ-exposure was not associated with adverse neonatal outcomes (aOR 0.83 95% CI 0.47,1.44) or early childhood outcomes (aOR 1.47, 95% CI 0.97,2.23).

Conclusions: Among infants born <35 weeks of gestation, MJ-exposure was not associated with adverse neonatal or childhood outcomes. Long-term follow-up studies are needed to assess later childhood neurodevelopmental outcomes following MJ-exposure.

Scientific Evidence vs ... Suboptimal “Evidence”

Hierarchy of Scientific Evidence



Suboptimal “Evidence” AKA Not Science

- Random websites (circleofmoms.com)
- YouTube
- Personal Anecdotes
- Personal Feelings

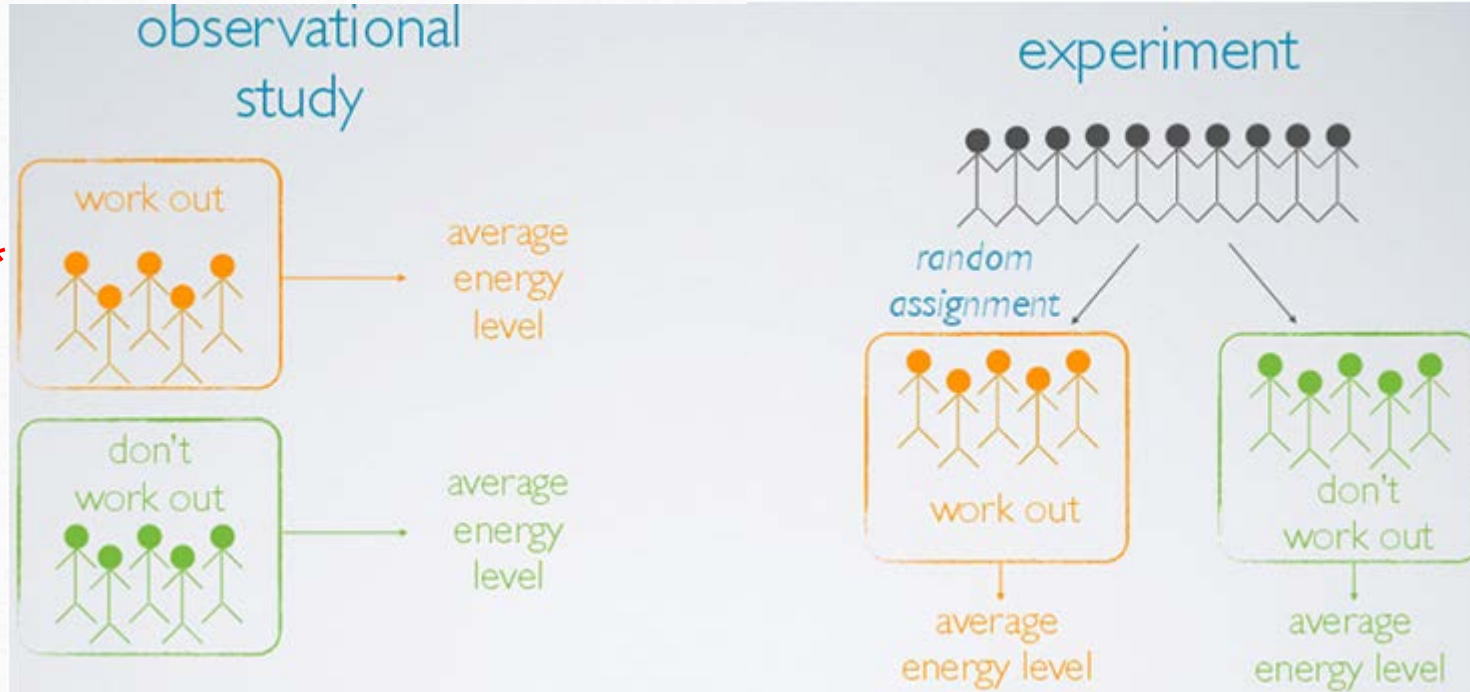
Observational v Randomized Study

Potential Problems

Confounding

Bias

Chance



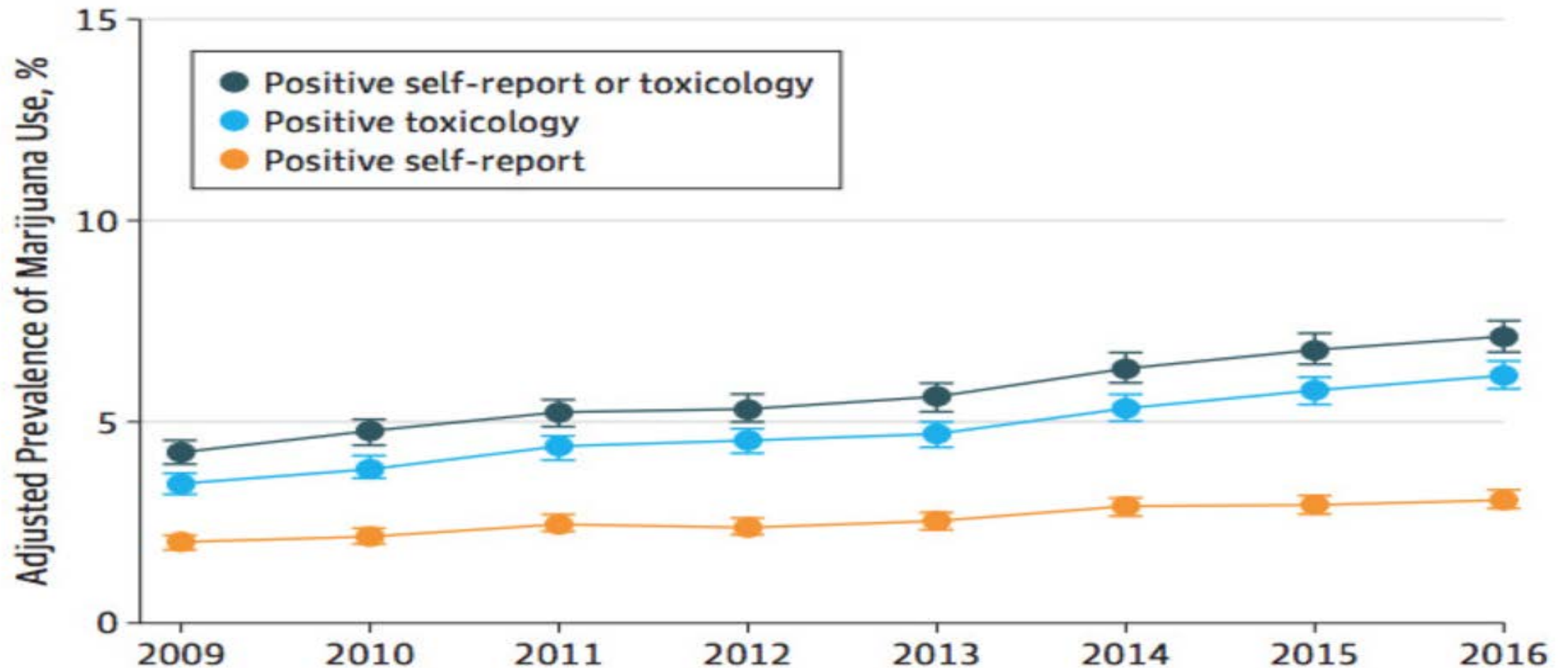
Potential Problems

Recruitment

Cost

Time

Figure 1. Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Screening Type, 2009-2016



Bias – THC and Pregnancy

- St. Louis study -> 8% marijuana use, BUT mostly low SES population
 - CDC marijuana use in low SES = 15-28%
- Baylor College of Medicine = 0.88% marijuana use
- **Under reporting of THC use → BIAS toward NO effect of THC use**

Marijuana Exposure and Preterm Infants

Characteristics associated with childhood morbidity	Odds Ratio	95% CI	p value
Marijuana use	1.47	0.97, 2.23	0.073
Race (African-American = referent)	-	-	-
Caucasian	0.90	0.69, 1.17	0.42
Other	1.27	0.94, 1.72	0.12
No prenatal care	0.73	0.47, 1.15	0.17
Received magnesium sulfate	0.96	0.76, 1.21	0.75
High school education or less	1.23	0.94, 1.60	0.13
Male infant	1.50	1.19, 1.88	<0.01

Marijuana Exposure and Preterm Infants

	No MJ (n =1732)	MJ use	p value
Adverse early childhood outcome ^b	369 (21.3)	35 (25.9)	0.21
Death prior to age 2	28 (1.6)	3 (2.2)	0.60
Moderate or severe cerebral palsy	38 (2.2)	0 (0)	0.08
Missing	77 (4.5)	3 (2.2)	
MDI <70	235 (13.6)	25 (18.5)	0.12
Missing	339 (19.6)	25 (18.5)	
PDI <70	209 (12.1)	20 (14.8)	0.35
MDI <85	610 (35.2)	60 (44.4)	0.03

Marijuana Exposure and Preterm Infants

- 23 5/7 to 31 6/7 infants from 20 centers between 1997 and 2004

Results: 1867 infants met inclusion criteria; 135(7.2%) were MJ-exposed. There were no differences in neonatal (20% vs. 26%, $p=0.14$) or childhood (26% vs. 21%, $p=0.21$) outcomes in MJ-exposed infants compared to MJ-unexposed infants. In adjusted models, MJ-exposure was not associated with adverse neonatal outcomes (aOR 0.83 95% CI 0.47,1.44) or early childhood outcomes (aOR 1.47, 95% CI 0.97,2.23).

Conclusions: Among infants born <35 weeks of gestation, MJ-exposure was not associated with adverse neonatal or childhood outcomes. Long-term follow-up studies are needed to assess later childhood neurodevelopmental outcomes following MJ-exposure.

National Academy of Sciences 2017

“There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and outcomes in the offspring.”

Validating Observational Studies

Hill Criteria – What supports *causation*?

- Consistency
- Strength of Association
- Dose Response
- Biologic Plausibility

THE Observational Study

Framingham Heart Study

- 1948: 5,209 men/women 30-62 recruited from Framingham, MA
- Goal: To identify risk factors for CVD
- By 1961 six risk factors for CVD:
 - Diabetes, High BP, Cholesterol,
 - Smoking, Family Hx, Male Gender
- Study is ongoing to this day

Dr. Thomas Royle (Roy) Dawber



Ann N Y Acad Sci 1963, 107:539-556

AN APPROACH TO LONGITUDINAL STUDIES IN A COMMUNITY: THE FRAMINGHAM STUDY

Thomas R. Dawber, William B. Kannel, Lorna P. Lyell
*Heart Disease Epidemiology Study, Framingham, Mass. and the National Heart
Institute, National Institutes of Health, Public Health Service, U. S. Department
of Health, Education, and Welfare, Washington, D. C.*

Those concerned with community health have a legitimate interest in all matters related to promoting the health of the community. These interests may vary depending on the purposes for which the health agency was organized, its location, the skills and resources available to it, and many other factors. In general, the major objective of community health activities is to prevent, or improve the medical care of, existing disease.

In the past, research engaged in by health agencies has usually been initiated because of some real or suspected problem affecting the health of their community. Because of inability to answer certain crucial questions pertaining to the problem, an investigation is undertaken to attempt to provide the desired information. Studies might be undertaken to assist in administrative planning concerning the number of beds required for some major emergency or to meet changing patterns of disease incidence, or of ways to convert existing facilities for such purposes. e.g., conversion of tuberculosis sanatoria to chronic disease hospitals. Research may be required to discover ways of improving medical care for particular diseases by determining methods required to bring persons with given diseases under medical care early in the course of the illness, in order to minimize disability. This type of research has usually been done with specific uses in mind and can be considered under the category of applied research.

In addition to research aimed directly at solving immediate local problems, it is now increasingly common for health agencies to ask how the facilities and resources available to them can best be used for purposes of research to increase general knowledge without necessarily being motivated by the immediate needs of the particular health agency. Studies may

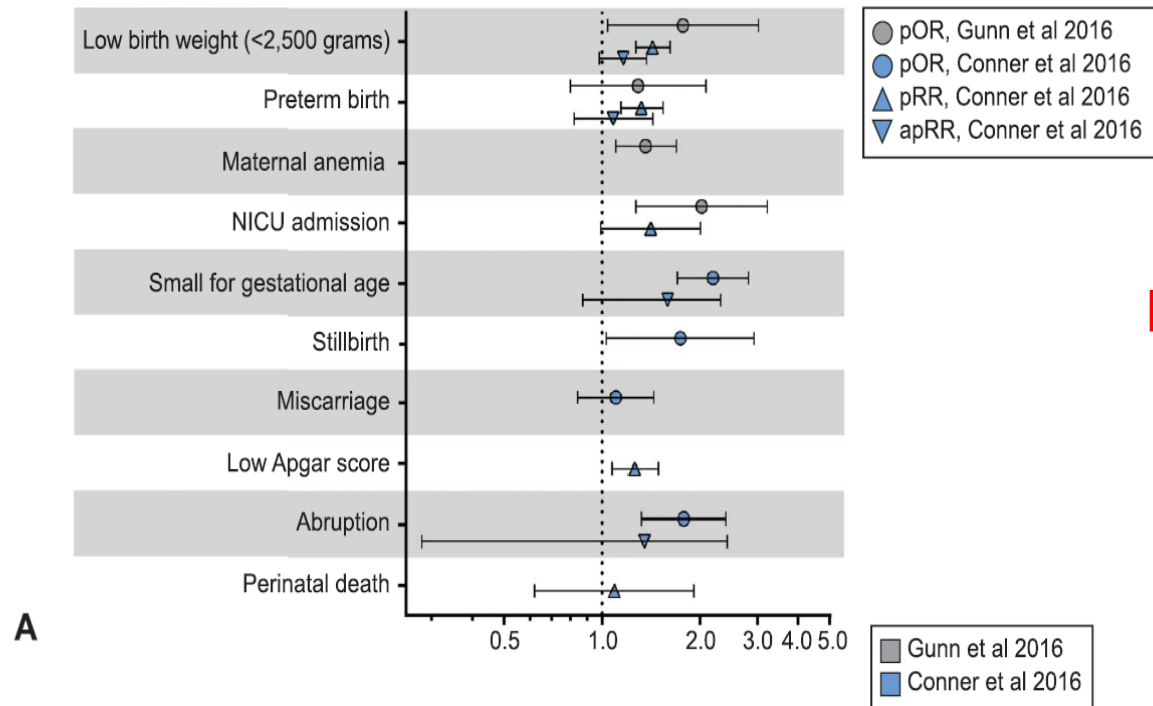
Dawber TR, Meadors GF, Moore FEJ: Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health* 1951, **41**:279-286. _

Dawber TR, Kannel WB, Bevilacqua N, Stokes JJ, Kagan A, Gordon T: Some factors associated with the development of coronary heart disease: six years' follow-up experience in the Framingham Study. *Am J Public Health* 1959, **49**:1349-1356. _

Maternal and Neonatal Outcomes

Systematic Review (55 studies combined results)

Maternal Anemia



Still Birth

Low birth weight

NICU Admission

Systematic Review (Australia, 10 studies)

Dose Response and Birth Weight

- Low birth weight (<2500 grams) by frequency of marijuana use
 - No use = 6.7% low birth weight
 - Less than weekly use = 8.8% low birth weight
 - At least weekly use = 11.2% low birth weight

Long-Term Effects of Prenatal Marijuana

Ottawa Prenatal Prospective Study (N=698) Ottawa, Canada, 1978
(mostly middle income Caucasian)

- 3 yo - no difference in intelligence testing
- 4-8 yo - impaired **memory**, attention, language comprehension
- 9-12 yo - IQ same, more likely to have diagnosis of **ADHD**
- 13-16 yo - impaired **problem solving** and sustained **attention**
- 18-22 yo - **MRI → decreased neural activity** in memory tasks

Long Term Effects of Prenatal Marijuana

Maternal Health Practices and Child Development Study (N=564)

Pittsburgh, Pennsylvania 1982

(mostly low income African American)

- 3-6 yo - impaired verbal reasoning, **memory, attention,** language comprehension
- 6-10 yo - increased **ADHD**
- 9-12 yo - impaired **problem solving** and increased **ADHD**
- 14 yo - **lower math/reading/composite scores** with heavy prenatal exposure

Prenatal Marijuana Exposure

6 yo testing – By Trimester Exposure and Dose Response

	Group 1: Abstain (<i>n</i> = 380)	Group 2: Light/Moderate (<i>n</i> = 175)	Group 3: Heavy (<i>n</i> = 93)	<i>p</i> ^a
First-trimester use				
Composite score ^{b,c}	92	93	87	.001
Verbal reasoning ^{b,c}	101	102	96	.000
Quantitative reasoning ^c	94	95	90	.03
Abstract/visual reasoning	85	86	82	.06
Short-term memory ^c	92	95	89	.009
Second-trimester use				
	Group 1: Abstain (<i>n</i> = 455)	Group 2: Light/Moderate (<i>n</i> = 103)	Group 3: Heavy (<i>n</i> = 30)	<i>p</i> ^a
Composite score ^{b,c}	92	92	84	.007
Verbal reasoning ^{b,c}	101	101	94	.01
Quantitative reasoning ^{b,c}	94	94	84	.008
Abstract/visual reasoning	85	85	81	.22
Short-term memory ^c	93	94	86	.05
Third-trimester use				
	Group 1: Abstain (<i>n</i> = 528)	Group 2: Light/Moderate (<i>n</i> = 88)	Group 3: Heavy (<i>n</i> = 32)	<i>p</i> ^a
Composite score ^{b,c}	92	93	86	.03
Verbal reasoning	101	101	96	.12
Quantitative reasoning ^{b,c}	94	96	85	.02
Abstract/visual reasoning	85	86	82	.45
Short-term memory	92	95	88	.07

1st Tri exposure →
4/5 Intel Categories Stat Sig

2nd Trimester exposure →
4/5 Intel Categories Stat Sig

3rd Trimester exposure →
3/5 Intel Categories Stat Sig

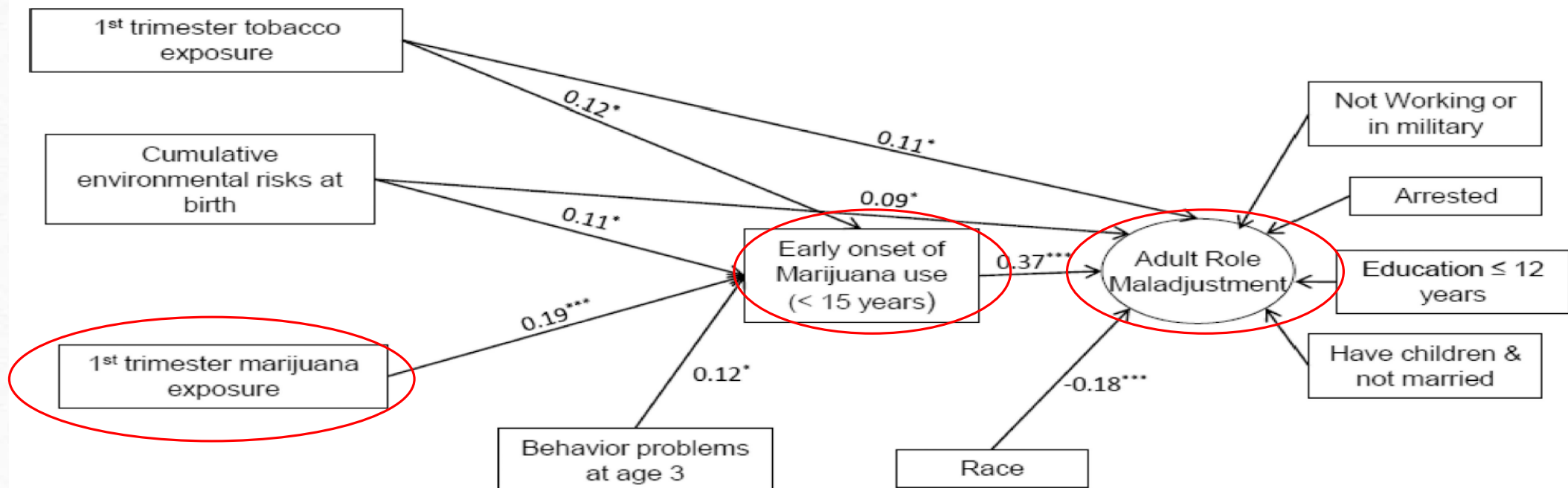
Prenatal Marijuana Exposure 14 yo testing – Dose Response

	Non-exposed N = 306	Light/ Moderate ^a N = 139	Heavy exposure ^b N = 79	p ^c
WIAT Screener at 14				
Composite	89.9	89.8	83.9	0.003
Basic Reading	93.8	93.1	87.8	0.001
Mathematics	90.7	90.7	86.0	0.02
Spelling	93.8	94.4	90.1	N.S.

Long-Term Effects of Prenatal Marijuana

Maternal Health Practices and Child Development Study (N=564)
Pittsburgh, Penn 1982
(mostly low income African American)

Correlates of Adult (age 22yo) Role Maladjustment



Long-Term Effects of Prenatal Marijuana

Generation R Study (N=9778) Rotterdam, Netherlands

- 18 mo - higher aggression (girls), decreased attention

STATE POLICIES ON SUBSTANCE USE DURING PREGNANCY

STATE	SUBSTANCE USE DURING PREGNANCY CONSIDERED:		WHEN DRUG USE DIAGNOSED OR SUSPECTED, STATE REQUIRES:		DRUG TREATMENT FOR PREGNANT WOMEN		
	Child Abuse	Grounds for Civil Commitment	Reporting	Testing	Targeted Program Created	Pregnant Women Given Priority Access in General Programs	Pregnant Women Protected from Discrimination in Publicly Funded Programs
Alabama	X*					X	X
Alaska			X				
Arizona	X		X			X	
Arkansas	X		X		X	X	
California			X		X		
Colorado	X				X [§]		
Connecticut					X		

Prenatal Marijuana Exposure and the Law

- Citation: Penal Code § 11165.13 **A positive toxicology screen at the time of the delivery of an infant is not in and of itself a sufficient basis for reporting child abuse or neglect.** However, any indication of maternal substance abuse shall lead to an assessment of the needs of the mother and child pursuant to the law.

Marijuana Secondhand Smoke Childhood Health

Frequency of past-year adverse health outcomes by indoor cannabis smoking behavior among study participants in San Diego County, CA (N = 192).

Outcome	No indoor cannabis smoking	Any indoor cannabis smoking	p-value ^a
	n (%)	n (%)	
Cumulative health outcomes ^b			0.04
	0	86 (52.8)	9 (31.0)
	1	40 (24.5)	13 (44.8)
	≥ 2	37 (22.7)	7 (24.1)

Validating Observational Studies

- Consistency
- Strength of Association
- Dose Response
- Biologic plausibility

Marijuana Dose Response Summary

Variable	Light use	Heavy use
Low Birthweight	8.8%	11.2%
IQ (6 yo)	93 (average score)	87 (average score)
IQ (14 yo)	89 (average score)	84 (average score)
IQ child to adult	-0.1 (standard dev)	-0.4 (standard dev)
Psychosis	0.98 (odds ratio)	4.3-9.4 (odds ratio)

Validating Observational Studies

- Consistency
- Strength of Association
- Dose Response
- Biologic plausibility
 - THC transfer in utero/via breastmilk
 - CB receptors in fetus (memory, emotion, cognition)
 - Animal models - in utero exposure and adolescent/adult effects
 - Reversibility of CB receptor downregulation

Postnatal Effects of Maternal Marijuana

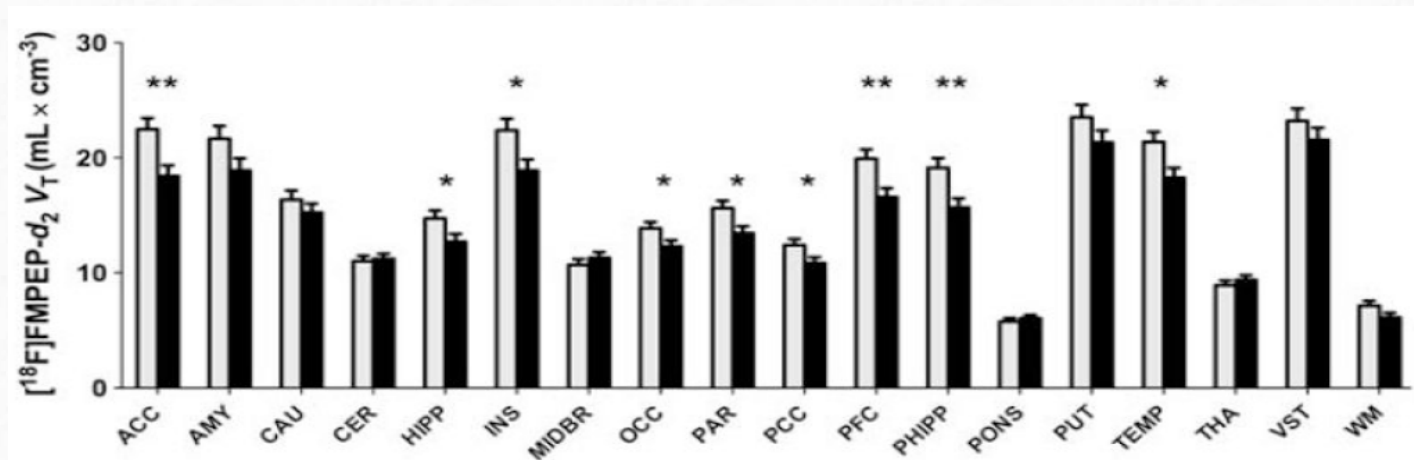
Biologic Plausibility – Animal Models

- Rat model marijuana exposure during pregnancy
 - Inattention and hyperactivity in adolescence
 - **Blunted emotional reactivity/social interaction**
 - Decreased adult performance:
 - spatial learning
 - short olfactory memory
 - long term memory

Biologic Plausibility

Reversibility of CB1 Downregulation

Adult Control v THC user CB1 receptor radioligand densities by brain regions
(* = statistically significant difference)

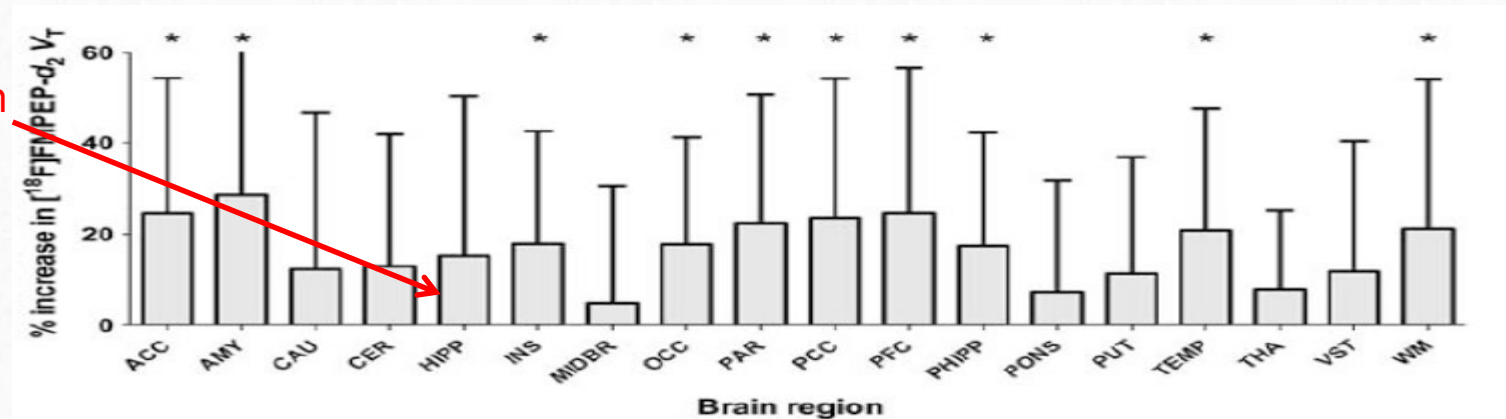


Biologic Plausibility

Reversibility of CB1 Downregulation

Percent increase in CB1 receptor radioligand densities by brain regions after 4 weeks of THC abstinence
(* = statistically significant difference)

Nonsignificant increase in CB1 receptor density in hippocampus (memory)



Take Home Points

- Marijuana use is associated with both short/longer term adverse effects
- Marijuana potency is increasing AND access is increasing
- Prenatal/Perinatal marijuana exposure is associated with:
 - Neonatal: stillbirth, NICU admission, low birth weight
 - Childhood: inattention/hyperactivity, impaired memory/processing
 - Adult: decreased IQ, maladjustment (arrest, out of work, poor education, unmarried)
- Associations limited by observational nature of data
- Available observational data is consistent, significant, +dose response, biologically credible

Counseling Mothers on Marijuana Use

- ACOG 2017 (Committee on Obstetric Practice):
 - “Women reporting marijuana use should be counseled about concerns regarding potential adverse health consequences of continued use during pregnancy”
 - “Women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use”
 - “Breastfeeding women should be informed that the potential risks of exposure to marijuana metabolites are unknown and should be encouraged to discontinue marijuana use”



MARIJUANA PREGNANCY & BREASTFEEDING GUIDANCE

FOR COLORADO HEALTH CARE PROVIDERS PRENATAL VISITS



Tips for using this guidance: all information in italics is scripted talking points to share with parents.

Marijuana Questions – Scripted Answers

Q: Since it is legal, is it safe?

Using marijuana during pregnancy can harm your baby, just like alcohol or tobacco. Being legal does not make it safe.

Q: Can marijuana be good for your baby?

Some researchers found that marijuana may be bad for children whose moms used marijuana during pregnancy. Some children did not do well in school when they were older. It may also make it hard for your child to pay attention and learn.

Q: Is marijuana a safe treatment for nausea during pregnancy?

THC in marijuana may harm your baby. Talk to your doctor about safer choices that do not risk harming your baby.

Questions?

“While laboratory animals are an expensive way of understanding the risk of cannabis use, Americans come free.”

- *The Economist* (March 22 2019)

Marijuana Detection

Biological sample	Duration of positive result	Test limitations
Maternal urine	2-3 d in occasional users; several weeks in chronic users	Chronicity of use determines duration of positive result
Maternal serum	2-3 d in occasional users; several weeks in chronic users	Chronicity of use determines duration of positive result Invasive sample Shorter half-life than urine
Maternal hair	Several weeks	Less accurate for marijuana than for other drugs False-positives from passive exposure Not clinically used because of cost and inaccuracy
Meconium	Positive result indicates second- and third-trimester exposure	Small amount of detectable THC in the samples High false-positive rate (up to 43%) Send out to reference laboratory Costly and impractical at many sites
Neonatal hair	Positive result indicates third-trimester exposure	Costly and impractical at many sites Less sensitive than meconium

Breastfeeding Survey

- Survey of 74 lactation professionals in New England
 - 44% would recommend breastfeeding despite marijuana use
 - 41% recommendation would depend on amount of use
 - 15% would recommend not breastfeeding with marijuana use