



Impact of Cannabis Use on Male and Female Fertility

54th Annual Primary Care Review

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Disclosures

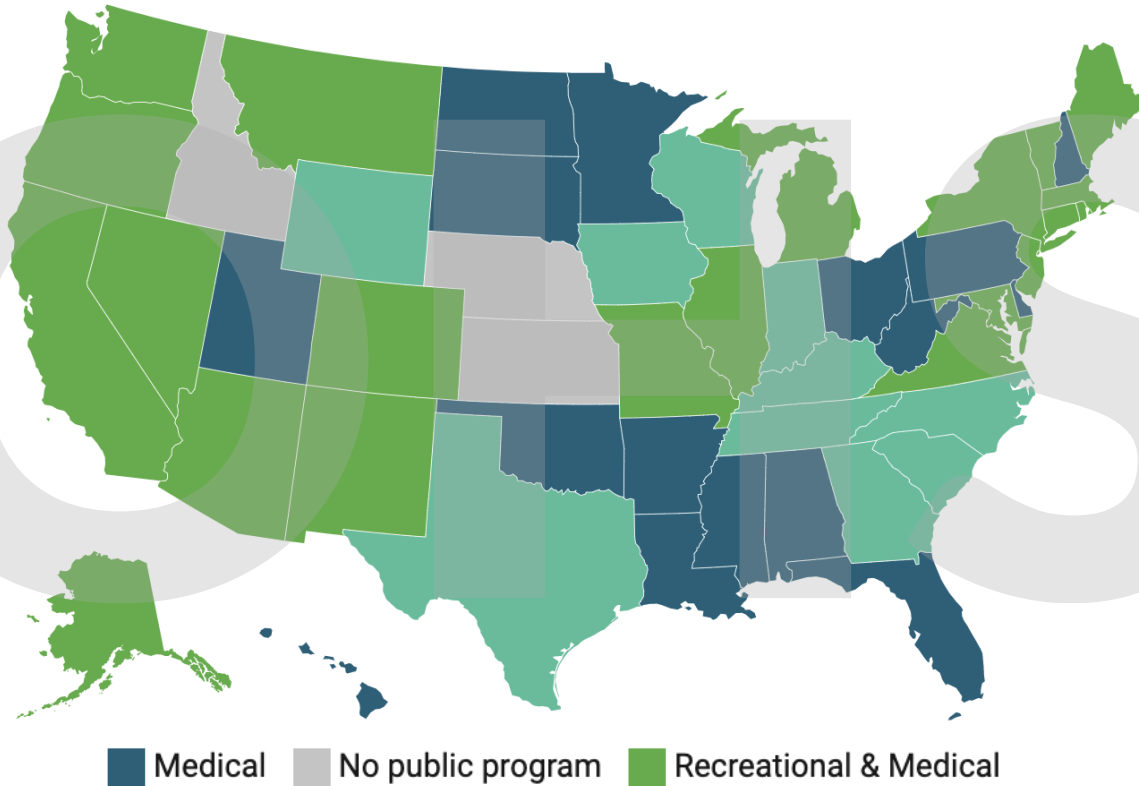
No financial disclosures

OHSU

Objectives

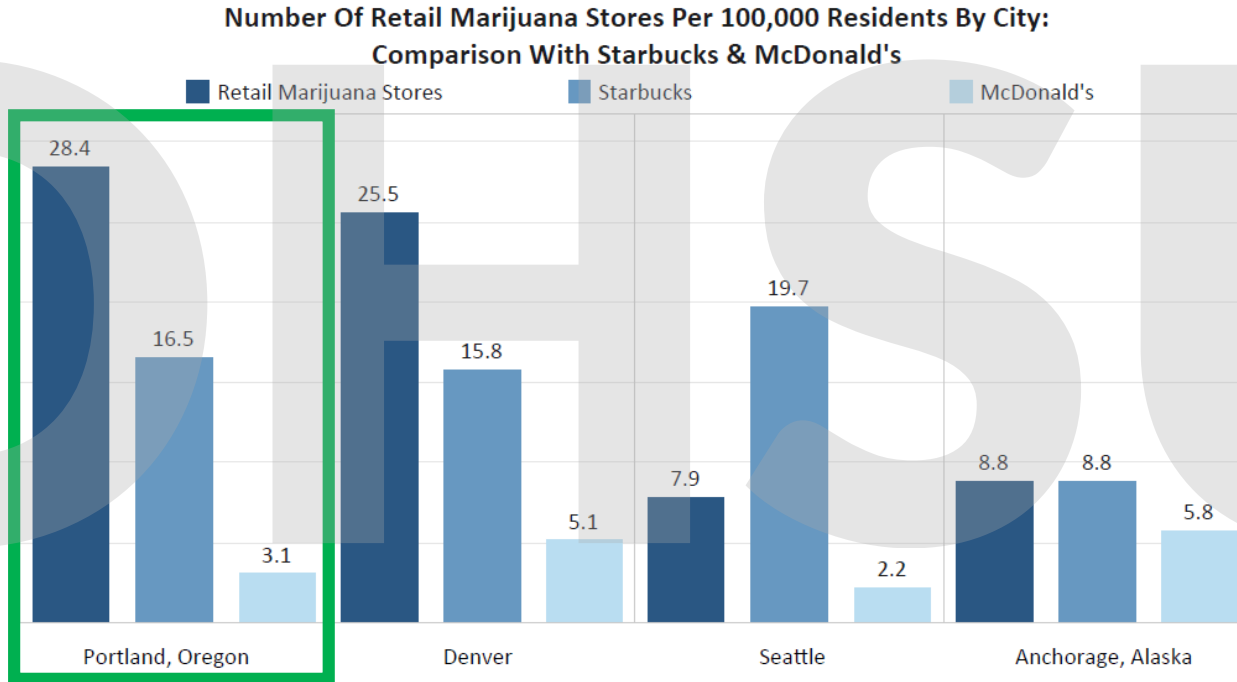
- Review current trends of cannabis composition and patterns of use
- Discuss the risks of cannabis use relating to male and female fertility
- Discuss the benefits of cessation of use when attempting to conceive
- Provide tools and data for counselling patients regarding the potential impacts of paternal or maternal cannabis use preconception and offspring outcomes

Current Legalization Landscape



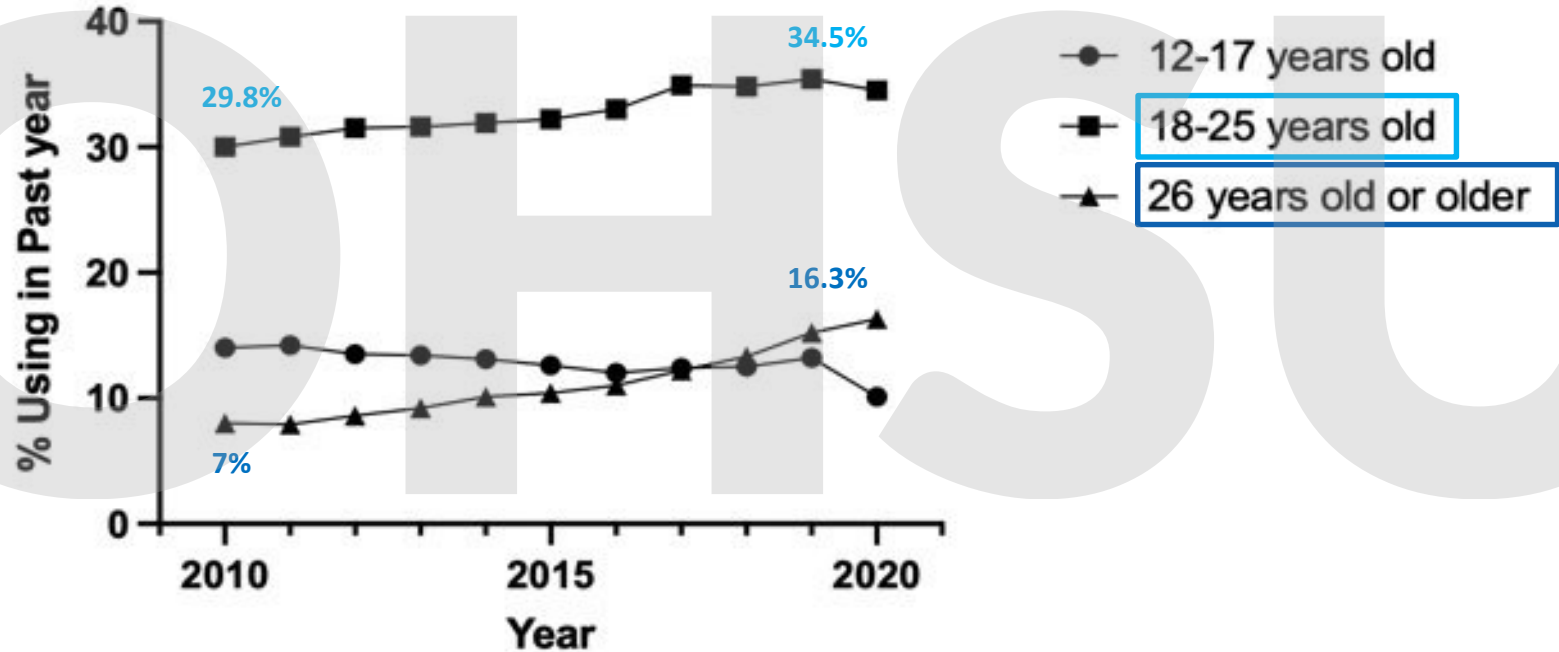
- Cannabis is the most commonly used illicit drug in the US and world
- 39 states and Washington DC have legalized medical cannabis
- 21 states and Washington DC have legalized recreational cannabis

Cannabis availability

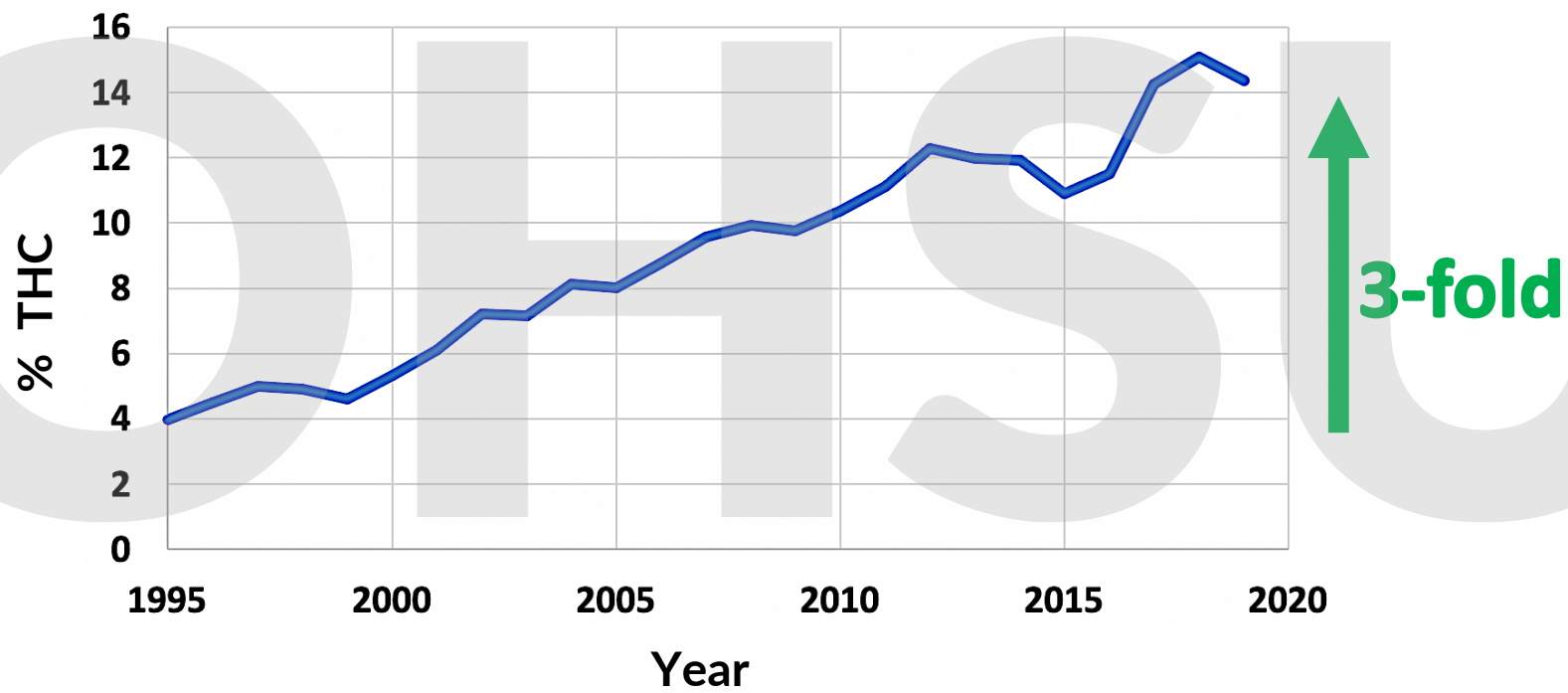


Reference: Oregon Liquor Control Commission, Colorado Department of Revenue, Washington Liquor and Cannabis Board, Alaska Alcohol and Marijuana control office. 2019 Marijuana Business Daily.

Prevalence of cannabis use is rising



Increased potency of cannabis



Reference: Potency Monitoring Program, Quarterly Report #146, drugabuse.gov

Cannabis - More than just a weed



- Contains over 600 chemicals
- **Delta-9-tetrahydrocannabinol (THC):**
 - Main psychoactive component
 - Small and highly lipophilic
 - Rapidly distributed to the brain and fat
 - Metabolized by the liver
 - Half-life is 20-36hrs to 4-6 days

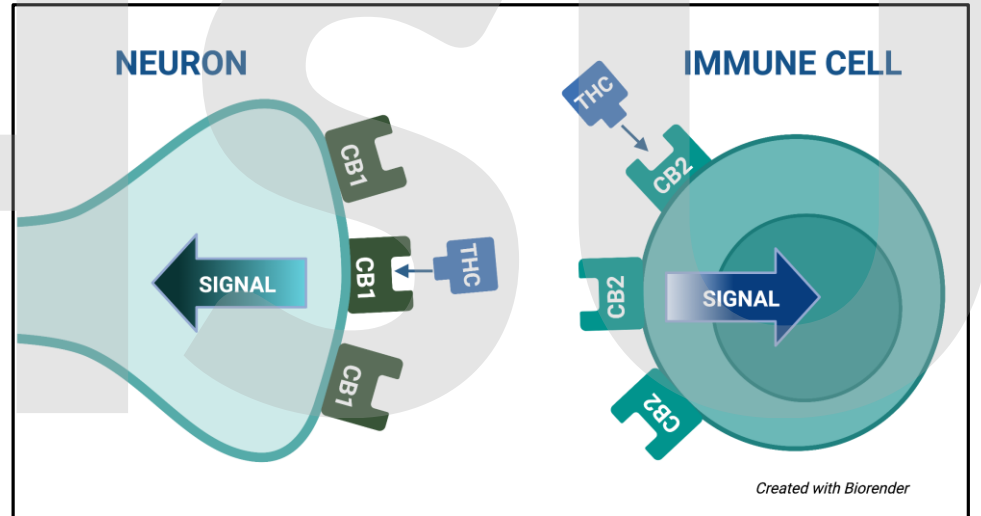
Endocannabinoid system and fertility

- **Cannabinoid receptors (CB1/CB2)**

- Brain (anterior pituitary)
- Testes/Ovaries
- Sperm

- **Cannabis as an aphrodisiac**

- India
- China
- Germany
- Angola



Limitations of existing studies

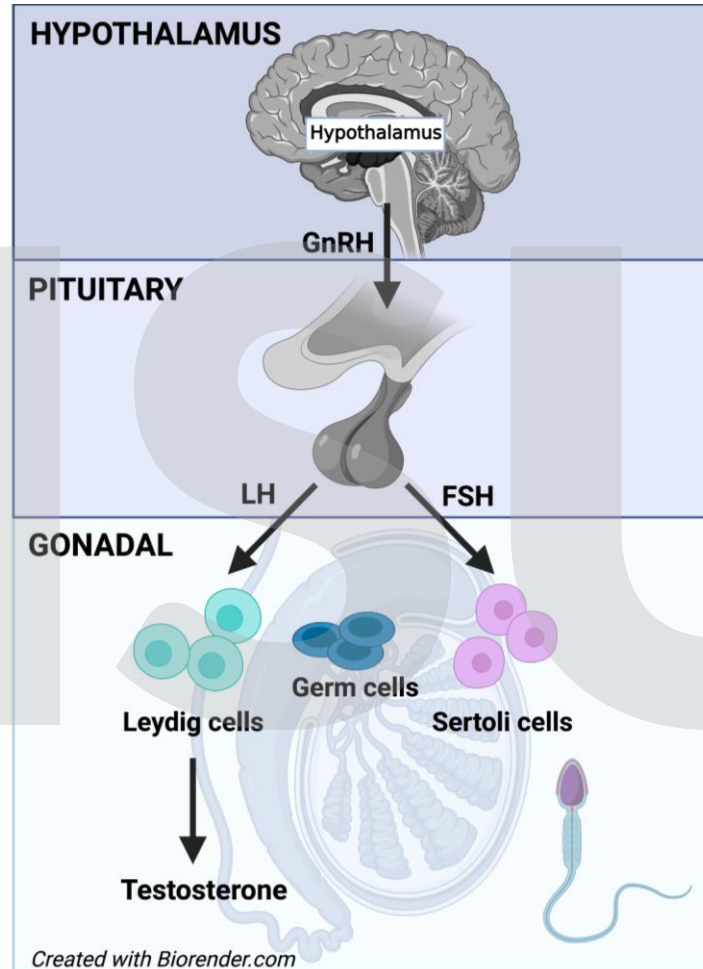
- Recruitment bias
- Retrospective or observational design
- Patient self-report
- Confounded by tobacco, polysubstance use, small sample size, inaccurate dosing information
- Lack of quantification/timing of exposure
- Most studies reflect cannabis exposure through smoking
- Existing literature is largely from the 1980s when cannabis products were less potent



Cannabis and male reproductive health



Male Hypothalamus- Pituitary-Gonadal (HPG) Axis



Male Infertility Workup

- Semen Analysis (x2)
- Hormones:
 - Follicle stimulating hormone
 - Luteinizing hormone
 - Testosterone
- Testicular Volume
- Sexual Function
- DNA Fragmentation (?)

Semen Parameter	WHO 2021
Semen volume (mL)	1.4 (1.3–1.5)
Total sperm number (10^6 per ejaculate)	39 (35–40)
Total motility (%)	42 (40–43)
Progressive motility (%)	30 (29–31)
Non progressive motility (%)	1 (1–1)
Immotile sperm (%)	20 (19–20)
Vitality (%)	54 (50–56)
Normal forms (%)	4 (3.9–4)

Worsened semen parameters

- Strongest evidence of an adverse impact of cannabis on male fertility
- Reduction in:
 - Sperm count
 - Concentration
 - Motility
 - Viability
- Abnormal morphology
- Inhibition of capacitation and fertilization



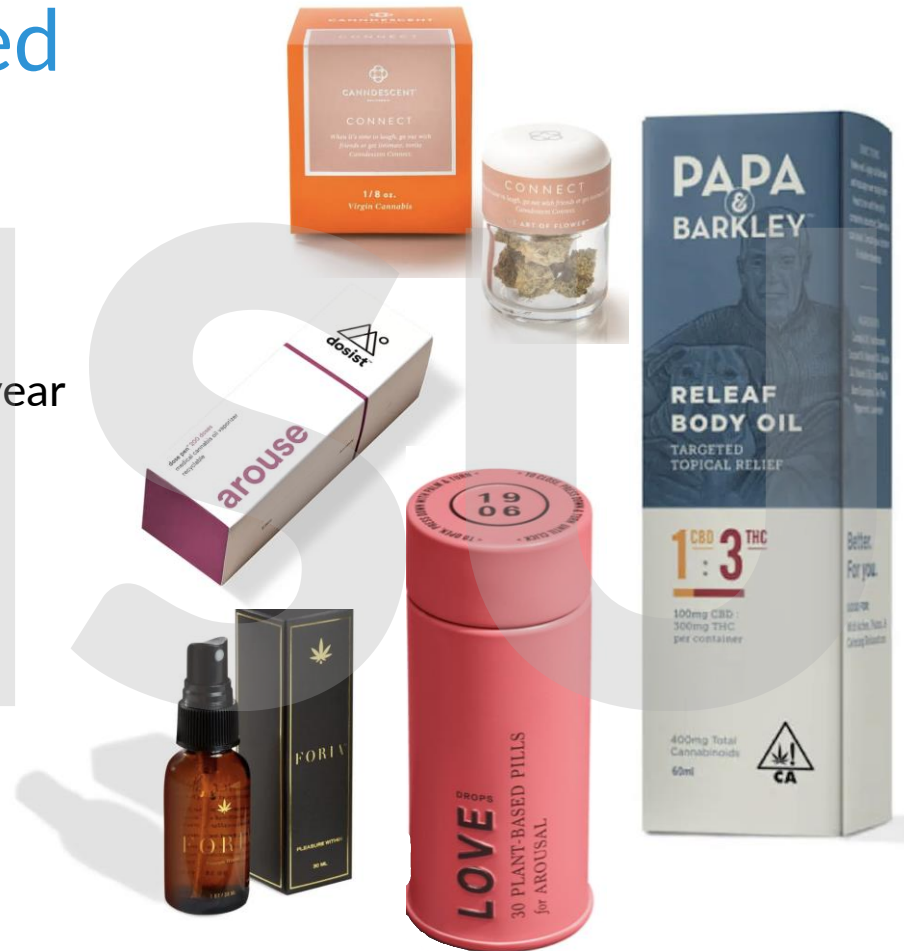
Variable affect on hormones

- Follicle stimulating hormone (FSH)
 - no change
- Luteinizing hormone (LH)
 - Lower
 - Less response to GnRH
- Testosterone
 - Variable
 - Effect may be acute and transient



Sexual Desire is Increased

- **Any use:** increased coital frequency
 - 8.8 vs 7.8 events/month, $p < 0.05$
- **Daily use:** 2 or more partners in previous year
 - OR 2.08 for men, 2.58 for women
- **Survey in Dispensary**
 - Increased orgasmic function
 - Improved erectile function
 - Higher sexual satisfaction



Erectile Function is Compromised

- Erectile dysfunction prevalence is doubled
- Orgasmic function
 - too quickly (OR 2.68)
 - too slowly (OR 2.05)
 - inability to reach (OR 3.94)



Testicular Volume is Decreased



HHS Public Access

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Chronic delta-9-tetrahydrocannabinol exposure impacts testicular volume and male reproductive health in rhesus macaques

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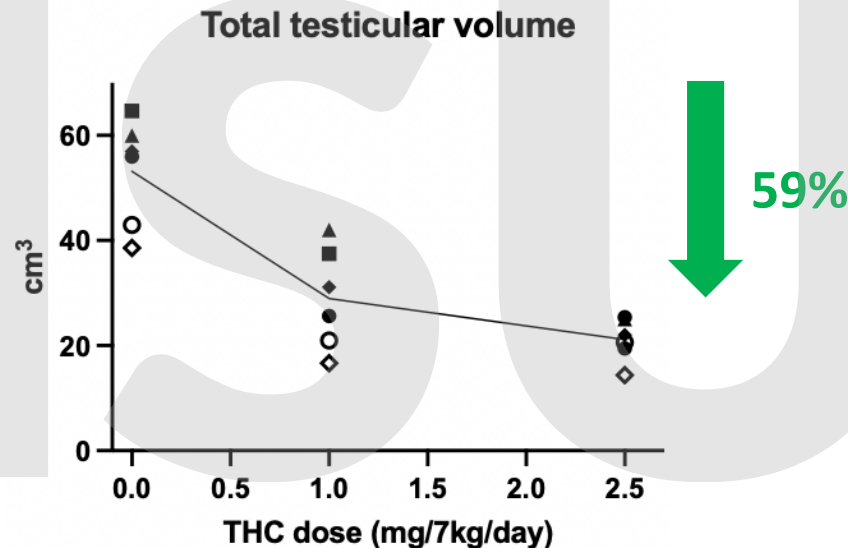
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Gundersen – The Danish Study (2015)



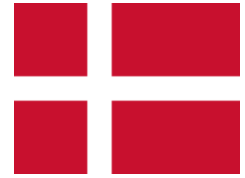
- 1,215 men (18-28 yo) undergoing military service screening from 2008-2012
- Cannabis use categories
 - No use
 - Use once per week or less
 - Use more than once per week

Gundersen – The Danish Study



- 45% smoked cannabis within the prior 3 months
- Cannabis more than once per week
 - 28% lower sperm concentration (95% CI: -48, -1)
 - 29% lower total sperm count (95% CI: -46, -1)
- Cannabis more than once per week and other recreational drugs
 - 52% lower sperm concentration (95% CI: -68, -27)
 - 55% lower total sperm count (95% CI: -71, -31)

Gundersen – The Danish Study



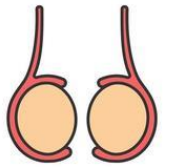
- Cannabis smokers had higher levels of testosterone
 - Similar to cigarette smokers
- Men who had used cannabis during the last 3 months had higher:
 - Alcohol and caffeine intake
 - Prevalence of smoking tobacco
 - Intrauterine tobacco exposure
 - Stress and sleep score
 - Prevalence of sexually transmitted diseases
 - Use of recreational drugs

Thistle – The NHANES Study (2017)



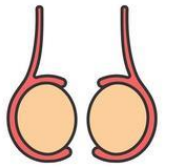
- US National Health and Nutrition Examination Survey (NHANES)
- 1,577 men from 2011-2012
- Cannabis use:
 - Ever-users: 66.2%
 - Current users: 26.6%
- Testosterone
 - No difference between ever-users and never-users
 - Inversely associated with time since last regular use (p-value for trend = 0.02)
 - Trend stronger in younger men (age 18-29, $p < 0.01$)
 - Recency of use stronger than duration or frequency

Nassan – The Markers Study (2019)

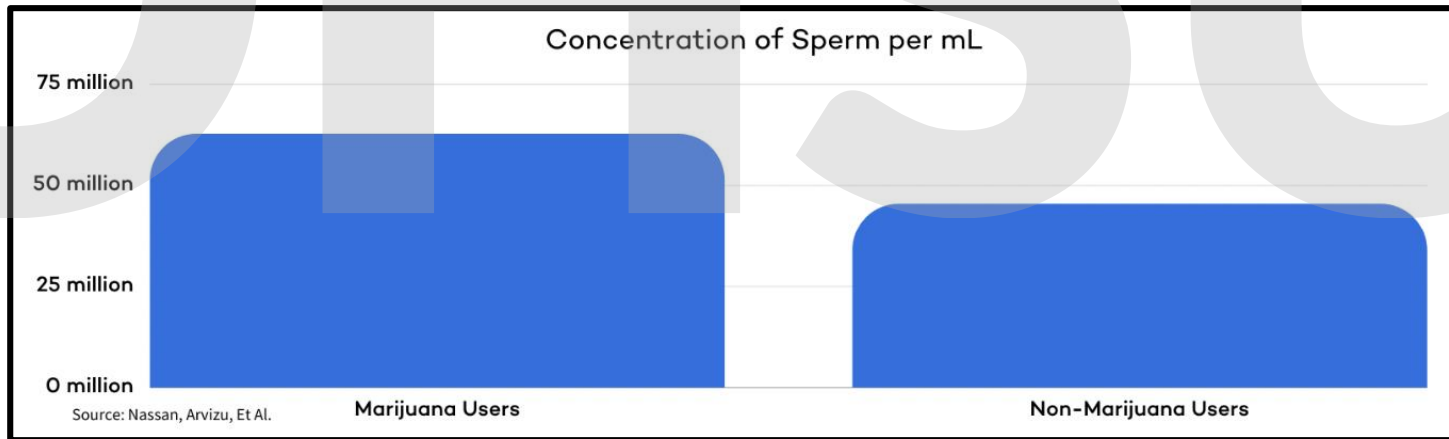


- 662 subfertile men enrolled at the Massachusetts General Hospital Fertility Center between 2000-2017
- Semen and blood samples were obtained and analyzed
- FSH is 16% lower in smokers than never smokers
- No difference in sperm DNA fragmentation, LH, testosterone, or estradiol

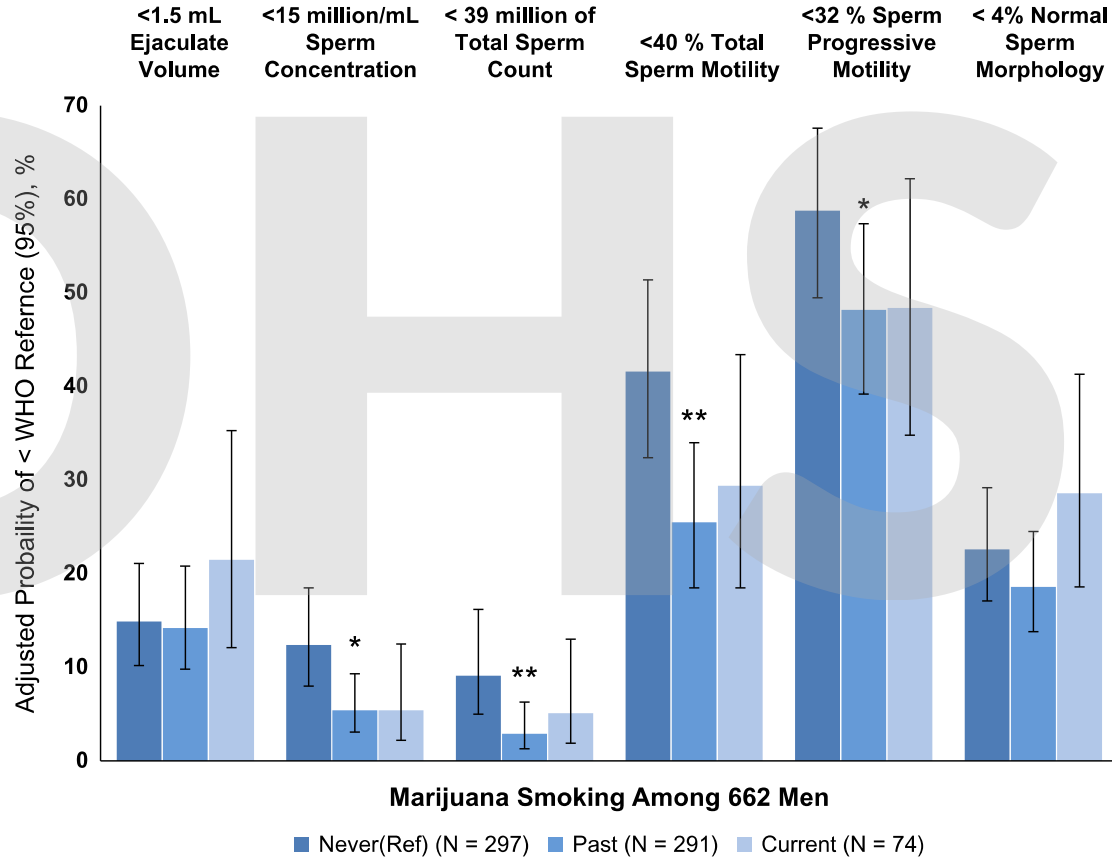
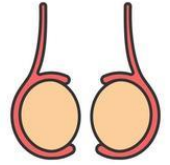
Nassan – The Markers Study (2019)



- Sperm concentration
 - Ever THC smoker 62.7 mill/ml (95% confidence interval: 56.0, 70.3)
 - Never smoker 45.4 mill/ml (38.6, 53.3) (P = 0.0003)
 - Current vs prior smoker: no difference

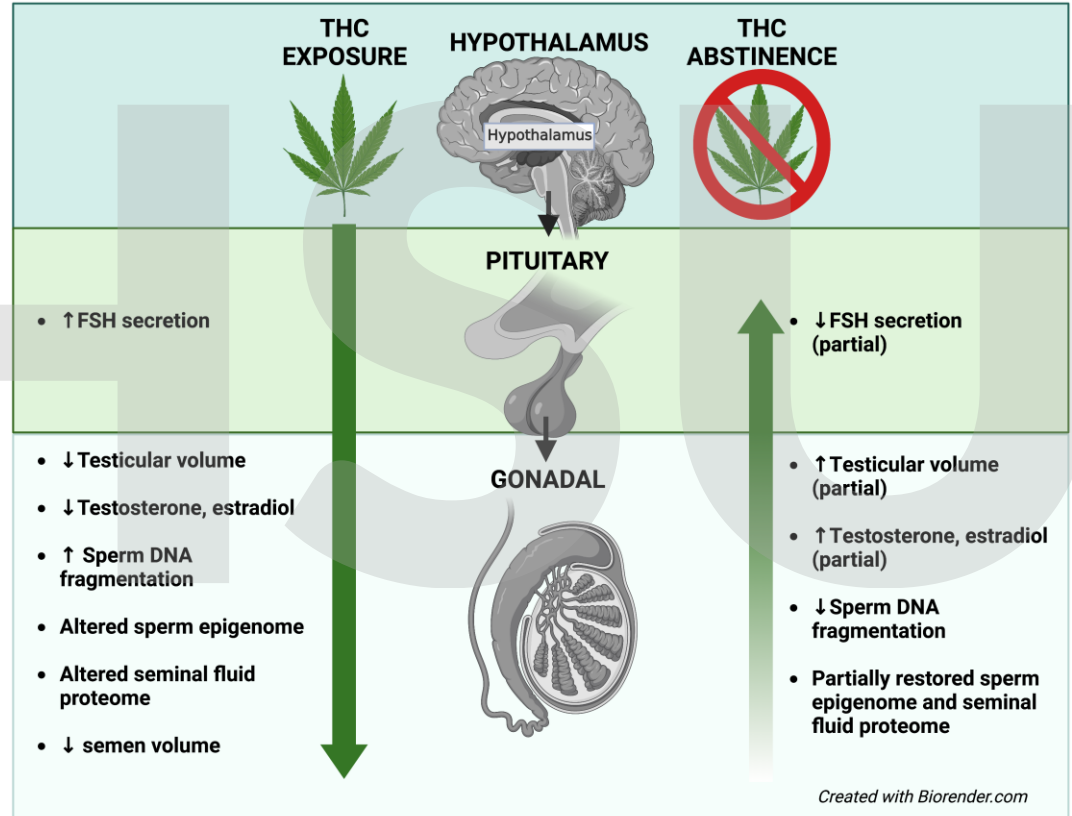


Nassan – The Markers Study



Possibility for recovery?

- Rhesus macaques (n=6) with THC exposure for ~7 months
- THC discontinued for 4 months
- Partial recovery noted



Harlow – PRESTO Study (2021)



- 1,535 North American couples from 2013-2019
- Preconception cannabis use:
 - <1 time/week: 9%
 - ≥ 1 time/week: 8%
- Couples with male partners who used cannabis ≥ 1 time/week preconception had a higher risk of spontaneous abortion
 - HR 2.0 (CI 1.2-3.1)
 - Even with non-using female partner

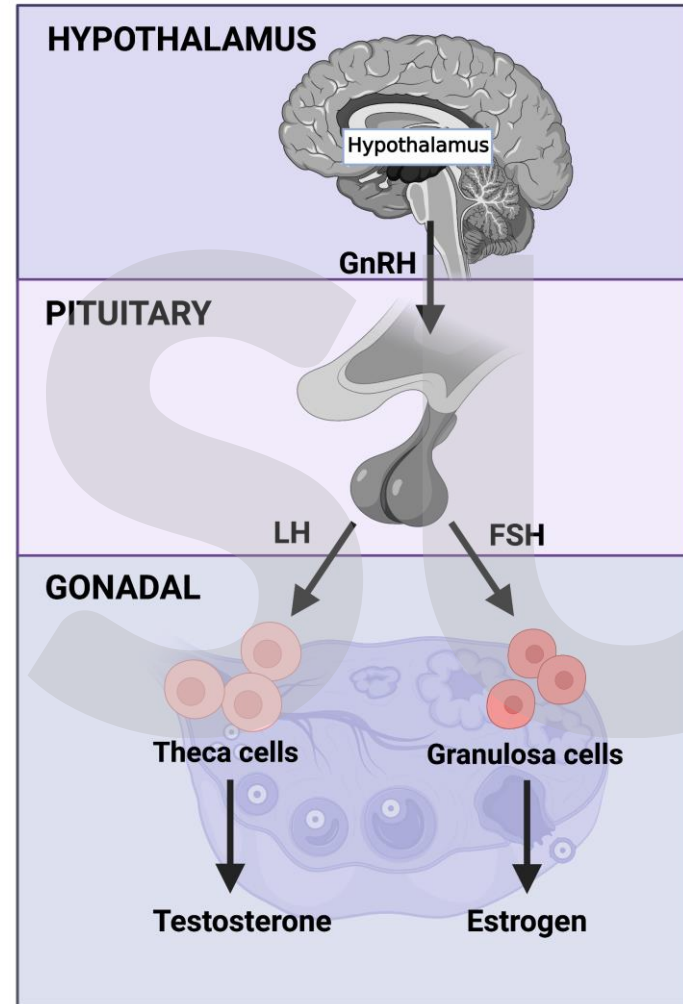
Take-Home Points

- Cannabis use is increasing among men of reproductive age
- Its effects on fertility are not fully elucidated
- The current literature supports a negative impact on fertility and sexual health, with likely dose-dependent and reversible effects
- Men interested in fertility should be counselled towards cessation.
- Those using cannabis medically should weigh the benefits of use against potential detriment to their fertility with their provider, and attempt reduced consumption

Cannabis and female reproductive health



Female Hypothalamus- Pituitary-Gonadal (HPG) Axis



Perceptions of cannabis and fertility

- Cannabis is commonly used among infertility patients
- Disruption of GnRH production and secretion
- Inhibition of FSH and LH production and secretion
- Jordan et al. (2020) cross-sectional study of 270 infertility patients
 - 13% reported cannabis use and 72% would or have disclosed use to provider
 - 9.4% reported their healthcare provider recommended cessation of use
 - Those recently using were less likely to think cannabis can negatively affect fertility
 - Perception of harm from cannabis varied with form of use, edibles were most popular and perceived safe

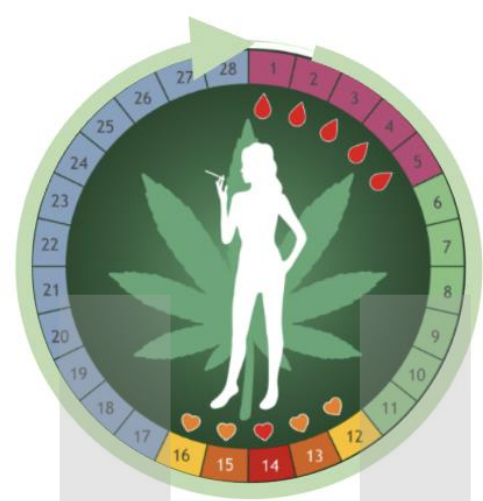
Decreased *in-vitro* fertilization success

- Poorer oocyte quality and disruption to oocyte maturation that can result in poorer embryo development
- Klonoff-Cohen et al. (2006), prospective study of 221 couples
 - Women smoked 1 cannabis within 1 year prior to IVF
 - 25% fewer oocytes retrieved and 28% fewer oocytes fertilized



Effect on menstrual cycles

- Irregular menstrual cycles
- Cannabis use can delay or inhibit ovulation
- Jukic et al. (2007) studied 201 women who smoked cannabis at least once in the prior 3 months
 - Ovulation was delayed 1.7-3.5 days ($p=0.04$) compared to controls and increased anovulatory cycles in cannabis smokers



Cannabis impacts menstrual cyclicity and time to conception in rhesus macaques



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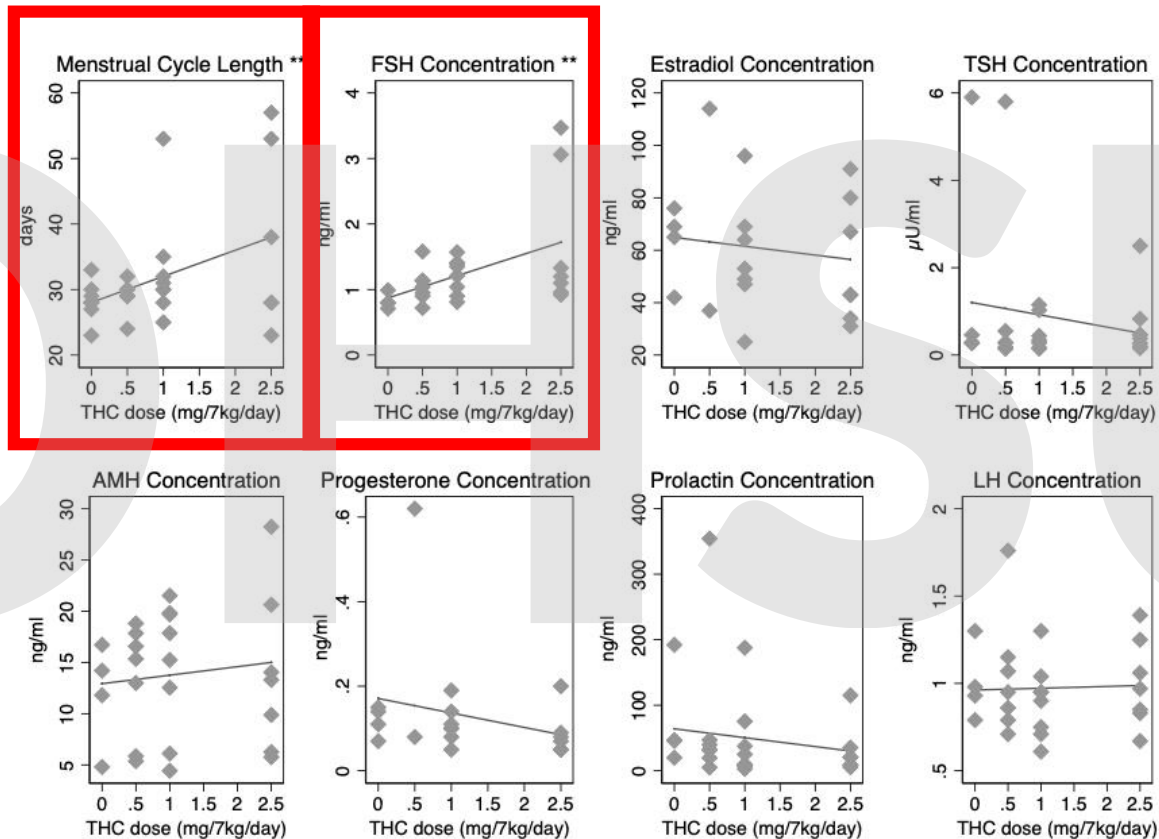
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The effects of delta-9-tetrahydrocannabinol exposure on female menstrual cyclicity and reproductive health in rhesus macaques

Kimberly S. Ryan, M.D.^a, Shruthi Mahalingaiah, M.D.^{b,c}, Lily R. Campbell, B.A.^d, Victoria H. J. Roberts, Ph.D.^e, Juanito Jose D. Terrobias, B.S.^e, Chelsey S. Naito, B.S.^e, Emily R. Boniface, Ph.D.^a, Laura M. Borgelt, Ph.D.^f, Jason C. Hedges, M.D., Ph.D.^g, Carol B. Hanna, Ph.D.^e, Jon D. Hennebold, Ph.D.^{a,e}, Jamie O. Lo, M.D.^{a,e}

THC results in ovulatory dysfunction (n=8)



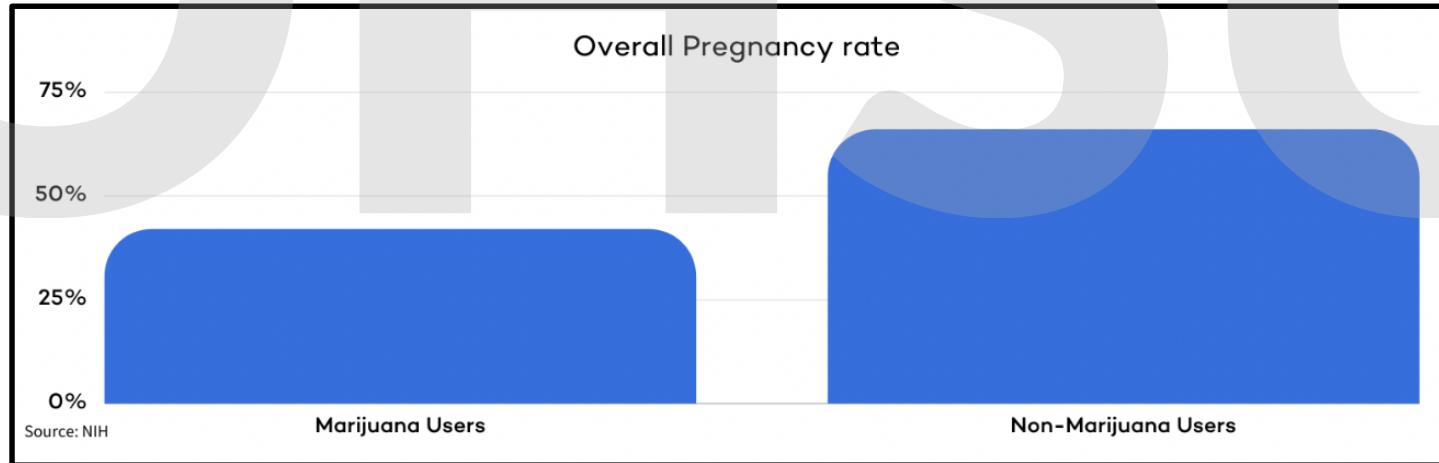
**p=0.01

THC exposure increases time to conception

Animal #	# Offspring	Prior # of Matings until Conception	# of Matings in this study	Pregnancy
1	5	1-2	2	Yes
2	4	1	3	Yes
3	1	1	1	Yes
4	3	1-2	6	Yes
5	1	1	1	Yes
6	1	1	1	Yes
7	1	1	6	Yes
8	5	1	7	Yes

Cannabis use decreases fecundability

- Mumford (2021) prospective cohort study of 1,228 women from aged 18-40yo with a history of pregnancy loss from 2006-2012
- Preconception use was associated with reduced fecundability (FOR 0.59; 95% CI 0.38-0.92)



Cannabis use decreases fecundability

- Preconception use was also associated with:
 - Increased frequency of intercourse per cycle
 - Anovulation
 - Decreased live births
- No association with pregnancy loss

Kasman – National Survey of Family Growth (2018)



- Population-based study of 121 geographic areas in the US of 758 male and 1,076 female participants trying to actively conceive
- 16.5% of men vs. 11.5% of women used cannabis while trying to conceive
- Time ratio to pregnancy for never smokers versus daily users of cannabis in men was 1.08 (95% CI 0.79-1.47) and in women 0.92 (95% CI 0.43-1.95)
- Neither cannabis use or frequency was associated with time to pregnancy for men and women

Wise – The Fecundability Study (2018)



- 4,194 women large prospective population-based cohort study using online preconception monthly surveys
- **Fecundability:**
 - The average per-cycle probability of conception in a given menstrual cycle of regular unprotected intercourse
 - Fecundity ratio for female cannabis use vs. non-use
 - <1 time/week: 0.99 (95% CI 0.85 to 1.16)
 - ≥ 1 time/week 0.98 (95% CI 0.80 to 1.20)
 - Fecundity ratio for male cannabis use vs. non-use
 - <1 time/week: 0.87 (95% CI 0.66 to 1.15)
 - ≥ 1 time/ week: 1.24 (95% CI 0.90 to 1.70)

Wise – The Fecundability Study



Frequent cannabis use was positively associated with:

- BMI
- Intake of alcohol and caffeine
- Perceived stress
- Depressive symptoms
- History of STIs
- Intercourse frequency
- Active and passive smoking
- Having a partner who uses cannabis

Chronic cannabis use was inversely associated with:

- Education
- Income
- Daily multivitamin use

Take-Home Points

- For most couples, cannabis use likely will not affect their ability to conceive but for couples with subfertility or infertility, it could be a contributing factor
- Impact the body's natural hormone cycles
- Increase the risk for miscarriage
- Exacerbate existing infertility factors



Preconception cannabis use and impact on offspring

- Paternal cannabis use
 - Impacted sperm DNA methylome that can persist despite discontinuation of cannabis
 - Select sperm DNA methylation changes and genes affected are associated with developmental processes especially early in life
 - Limited findings suggest influence on short- and longer-term offspring health
- Maternal cannabis use
 - Increased anxiety behavior and perturbation of the brain epigenome in offspring
 - Increased offspring addiction vulnerability later in life

Provider Resources

- SAMHSA – Substance Use and Mental Health Services Administration
- STEM (Systematically Testing the Evidence on Marijuana)
www.cannabisevidence.org
- Colorado Cannabis – www.cannabis.Colorado.gov
- Canada Cannabis -
www.canada.ca/en/services/health/campaigns/cannabis/health-effects.html
- American Society of Reproductive Medicine -
<https://www.asrm.org/topics/topics-index/alcohol-and-drug-use/>

Thank You



- The National Survey on Drug Use and Health 2019, Substance Abuse and Mental Health Services Administration
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