

# Cannabis Use During Pregnancy and While Breastfeeding: Sorting Through Hazy Evidence



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# Disclosures

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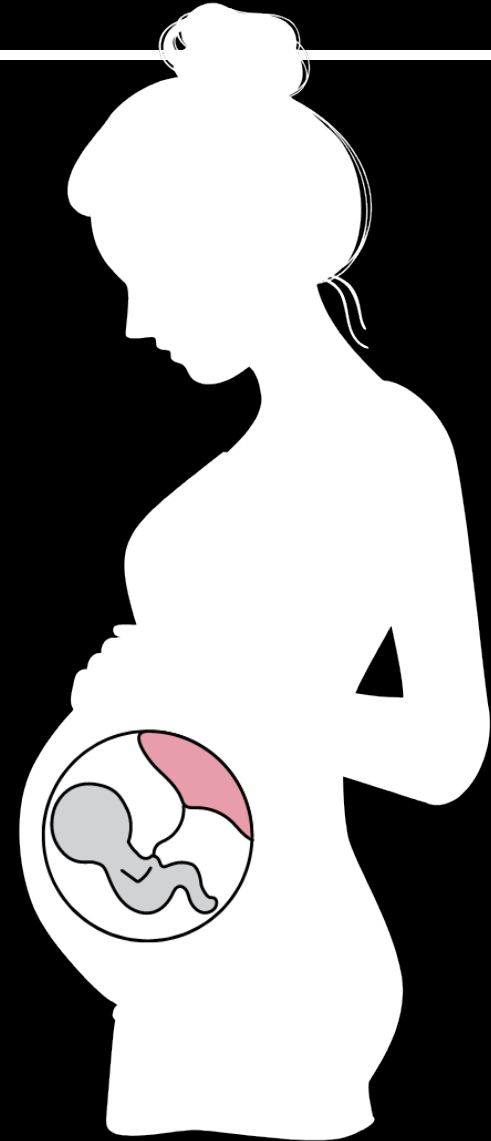
- No conflicts of interest related to the content of this presentation

# Learning Objectives

- Define prevalence of cannabis use in pregnancy and reported reasons for use.
- Counsel patients regarding the risks of cannabis use during pregnancy and while breastfeeding based on current evidence.
- Recommend and utilize available resources when counseling individuals regarding cannabis use in pregnancy and breastfeeding.

# Background

- Cannabis most common illicit drug used in pregnancy
- Crosses the placenta
- Increasing use with increasing legalization of recreational cannabis



# Prevalence of Cannabis Use

- Reported prevalence 3-30%
- Data from NSDUH
  - Cross sectional, nationally representative
  - 2.4% past-month use among pregnant patients in 2002
  - 3.9% in 2014
  - 4.9% in 2016

*Brown et al JAMA 2016 ; <https://www.samhsa.gov/data/report/results-2016-national-survey-drug-use-and-health-detailed-tables>*

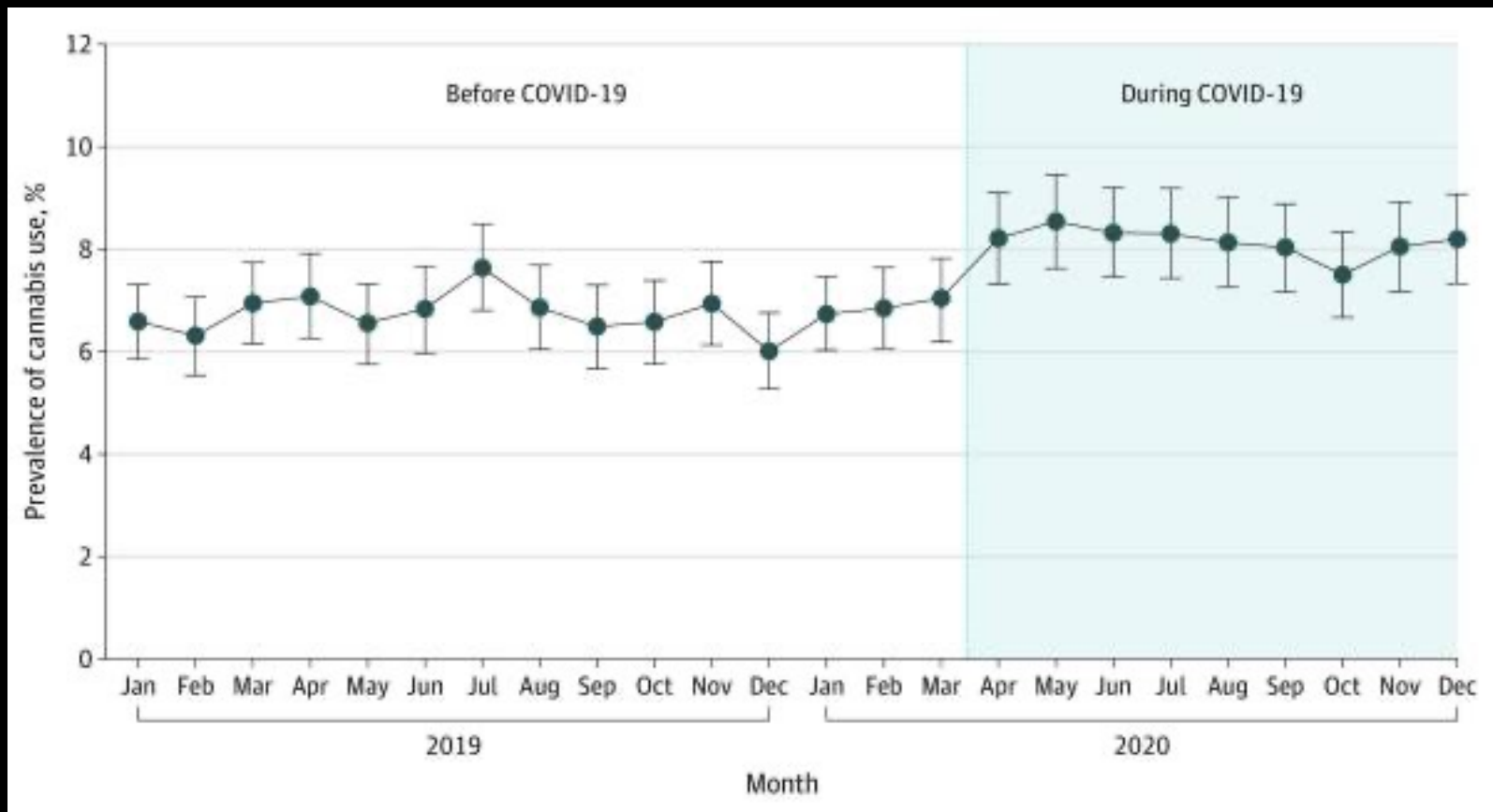
# Prevalence

- Retrospective cohort (2009-17)
- Kaiser Permanente Northern California
- N=281,025
- Urine toxicology 4.9%
- Self-report 2.5%
- Being older, of Hispanic ethnicity and lower household income were associated with misclassification of not using cannabis by self-report

# CCTSI Cross-Sectional Pilot Results

- N=116 paired samples (cord & survey)
- 2.6% reported to healthcare provider
- 6.0% reported use in last 30 days on anonymous survey
- 10.3% THC-A above LOQ (200 pg/g) in the umbilical cord homogenate
- 22.4% THC-A above LOD (100 pg/g)

# What happened during pandemic?





# Cannabis Use Disorder

- 2012-13 National Epidemiologic Survey on Alcohol and Related Conditions-III
- 414 pregnant and 902 postpartum individuals
- Prevalence past-year cannabis use 9.8%
- Prevalence cannabis use disorder 3.2%
- Odds of use higher with co-existing mental health disorders

# What are the reasons for use?

- Tricounty Health Department in CO surveyed clients participating in Special Supplemental Nutrition Program for Women Infant and Children (WIC)
- Monthly caseload of 25,000 clients
- Convenience sample of approx. 1700 individuals

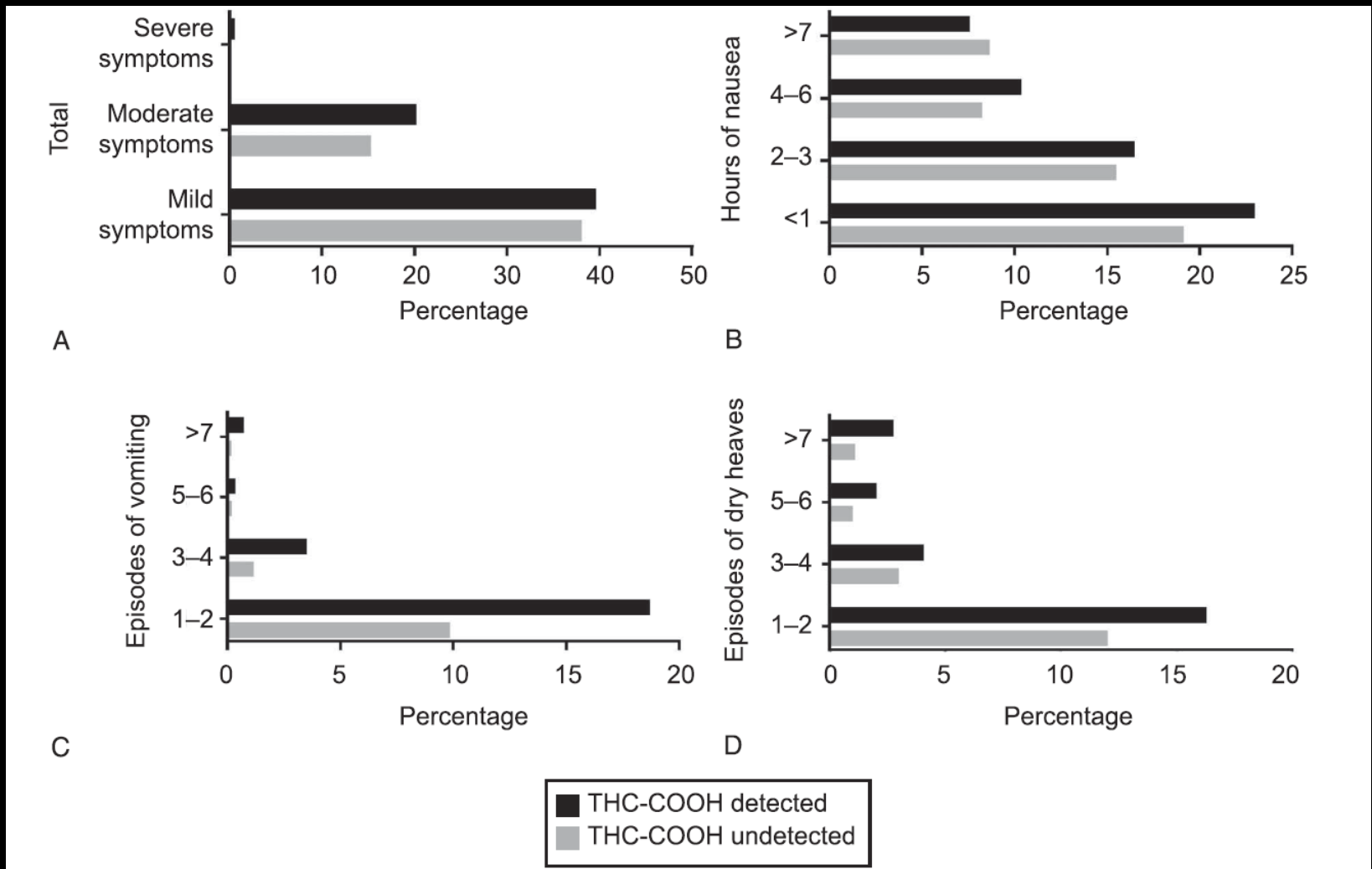
# Perceived Benefits WIC Survey

Reasons for Use	Use Ever (%, n)	Current Use (%, n)	Past Use (%, n)
Help with depression/anxiety/stress	35% (164)	63% (60)	28% (103)
Help with pain	29% (135)	60% (57)	21% (78)
Help with nausea/vomiting	23% (108)	48% (46)	17% (62)
For fun/recreation	59% (277)	39% (37)	65% (240)
Other reason	16% (75)	14% (13)	16% (58)

# Nausea and Vomiting

- Retrospective cohort (N=279,457)
- Kaiser Northern California
- Universal screening with utox and questionnaire
- ICD diagnoses for N/V of pregnancy
- Severe nausea (2.4%), mild nausea (15.2%)
- Individuals with severe NVP (aOR 3.80, 95%CI 3.19-4.52) and mild NVP (aOR 2.37, 95% CI 2.17-2.59) had increased odds of cannabis use

# Nausea and Vomiting



# Increasing Perceived Safety

- National Survey on Drug Use and Health data

	No past 30 day use, pregnant	No past 30 day use, non-pregnant	Past 30 day use, pregnant	Past 30 day use, non-pregnant
2005	3.5%	3.1%	25.8%	23.7%
2015	16.5%	14.8%	65.4%	62.6

# Problems with Existing Studies

- Lack of quantification/timing of exposure
- Difficulty adjusting for tobacco, other drugs, sociodemographic factors
- Reliance on self-report
  - Shiono et al (1995) completed a prospective cohort study with structured interviews and maternal serum toxicology screens
  - 70% of individuals with positive THC on serum tox screen denied use in structured interview



Top 10 Action Movies of the 1980s

PLAY ▶





# Perinatal Outcomes Meta-Analysis

- Gunn et al conducted a systematic review and meta-analysis
  - Primary Outcomes: maternal, fetal or neonatal up to 6 weeks postpartum after cannabis exposure
  - Conducted meta-analyses when 3 or more studies available with same outcome (anemia, LBW, BW, neonatal length, NICU admission, GA at del, head circumference, PTB)
- Increased odds anemia, LBW, NICU admit
- More studies needed

# Neonatal Outcomes: Meta-Analysis

- Conner et al performed systematic review and meta-analysis
- Aim: estimate if marijuana use increases risk of adverse neonatal outcomes
  - Primary outcomes: LBW (<2500gm), PTB (<37 wk)
  - Secondary outcomes: BW, GA at delivery, SGA, level II nursery or greater, stillbirth, SAB, low Apgar, abruption, perinatal death

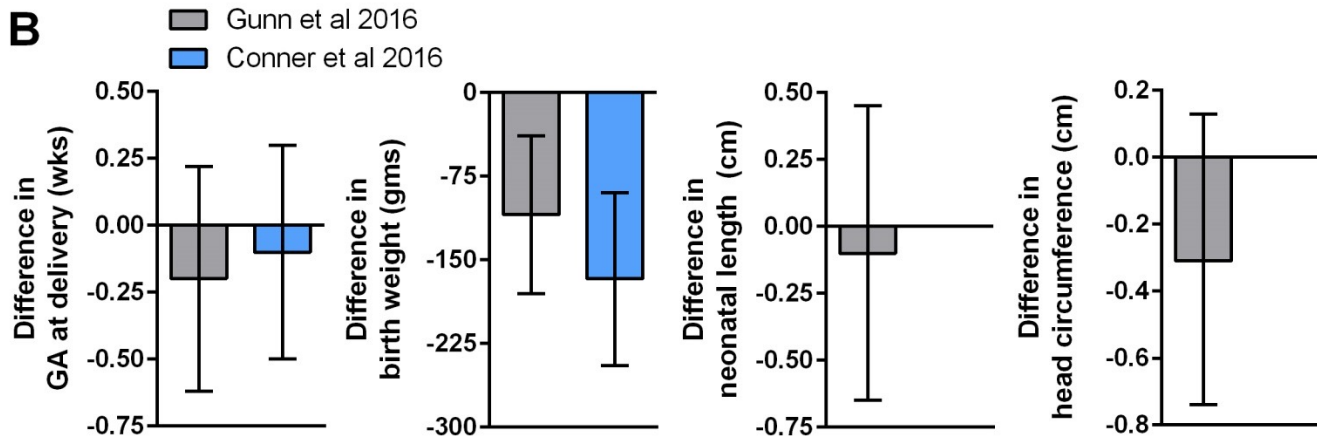
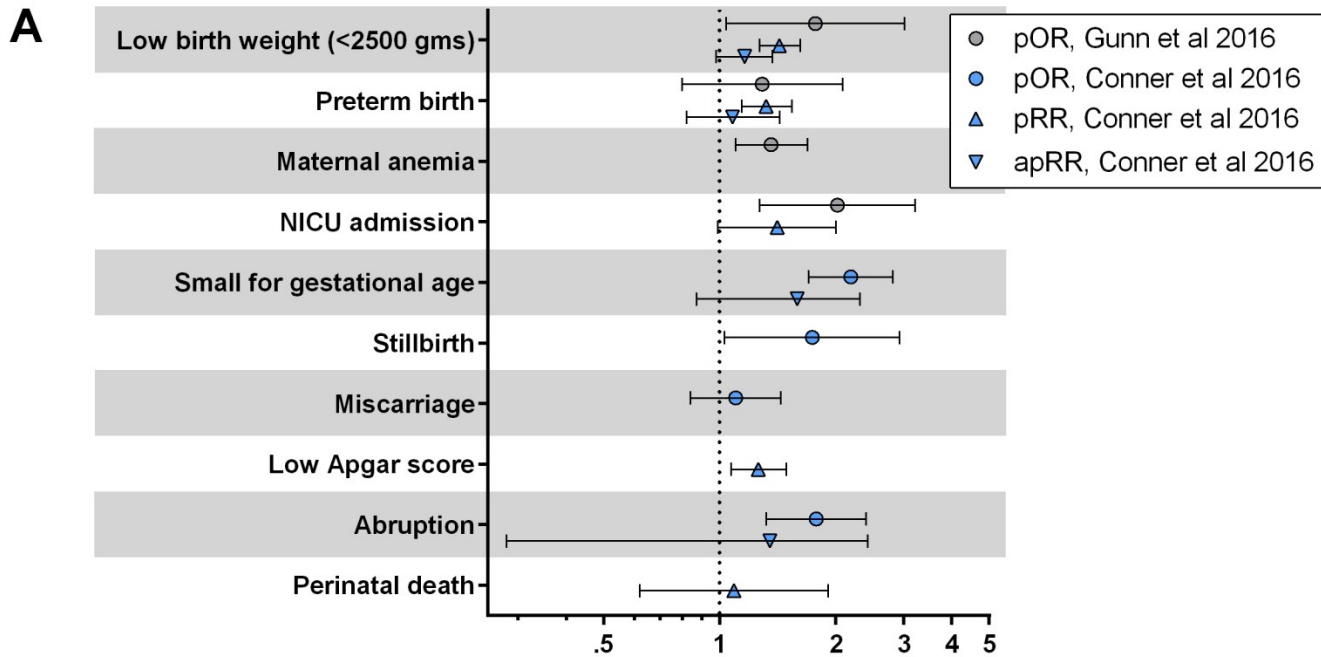
# Neonatal Outcomes: Meta-Analysis

- 31 studies total (12 LBW, 14 PTB)
- Pooled unadjusted data demonstrated an association between THC and LBW/PTB
  - LBW (15.4% vs 10.4%, RR 1.43, 95% CI 1.27-1.62)
  - PTB (15.3% vs 9.6%, RR 1.32, 95% CI 1.14-1.54)
- After adjustment for tobacco and other confounders no longer an association
  - LBW (pooled RR 1.16, 95% CI 0.98-1.37)
  - PTB (pooled RR 1.08, 95% CI 0.82-1.43)

# Neonatal Outcomes: Meta-Analysis

- Planned subanalysis of moderate to heavy use (defined as at least once per week)
- Cannabis use associated with low birth weight (RR 1.90, 95% CI 1.44-2.45)
- Cannabis use associated with preterm birth (RR 2.04, 95% CI 1.32-3.17)

# Summary Meta-Analyses



# Marchand Meta-Analysis

- Increased risk of LBW, 8 studies, pooled RR 2.06 (1.25-3.42)
- Increased risk of SGA, 6 studies, pooled RR 1.61 (1.44-1.79)
- Increased risk of preterm delivery, 12 studies, pooled RR 1.28 (1.16-1.42)
- Increased risk of NICU admission, 6 studies, pooled RR 1.38 (1.18-1.62)

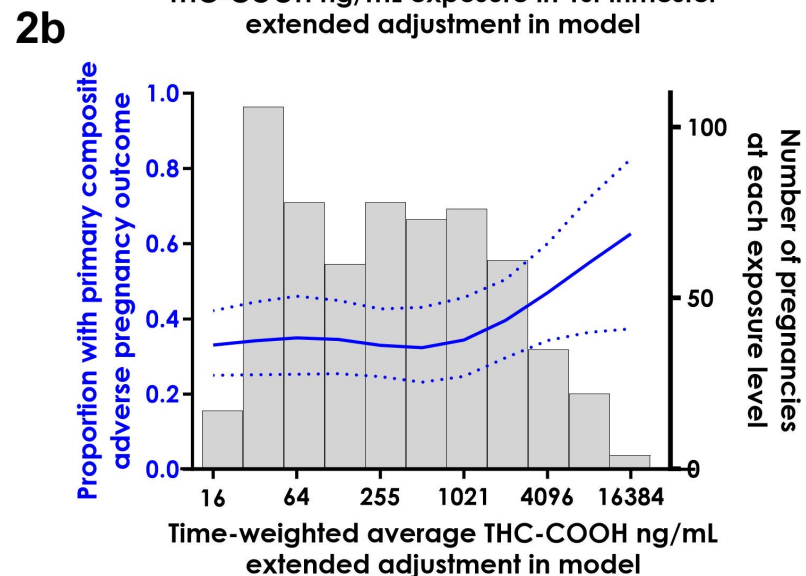
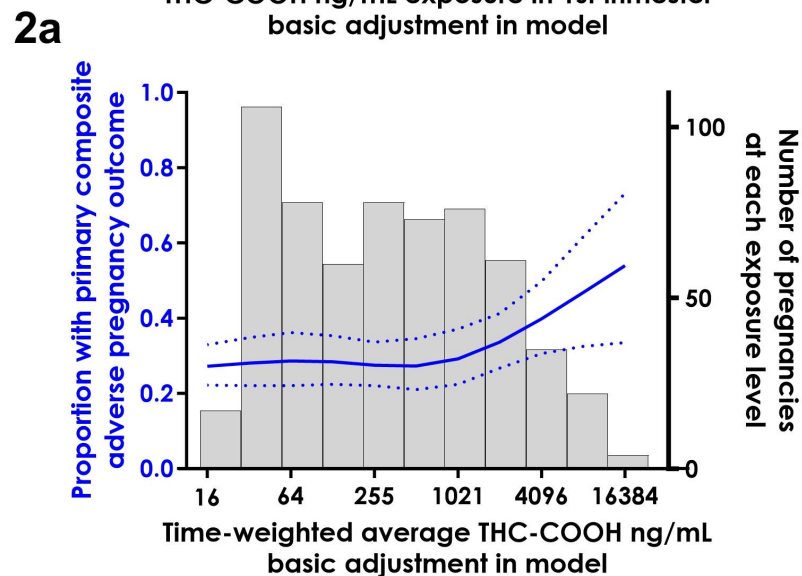
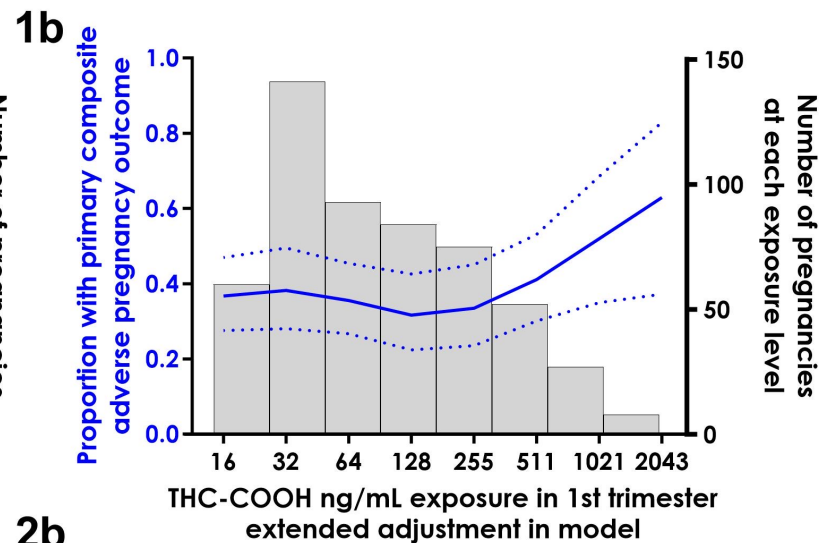
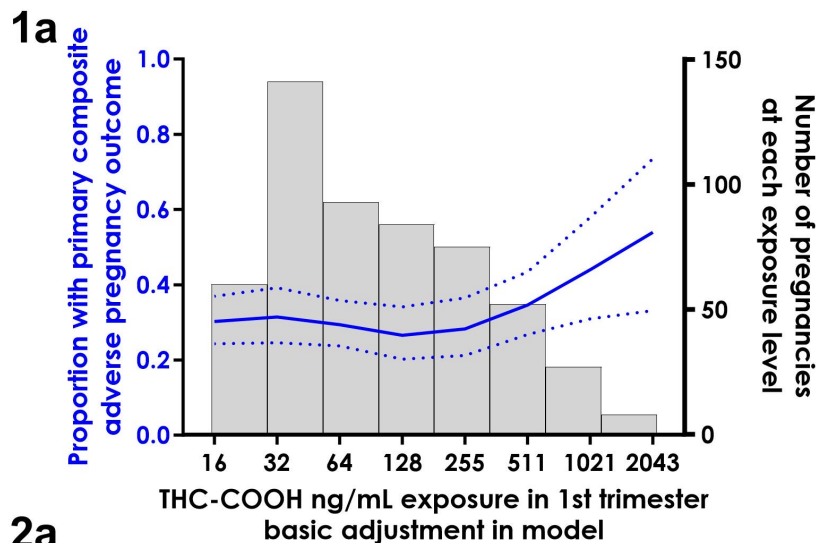
# Cannabis Use and APOs

- Ancillary study of NICHD nuMoM2b cohort (2010-13)
- Urine samples from three timepoints in pregnancy assayed for THC-COOH, cotinine and other drugs
- 9,257 participants; 610 (6.6%) exposed to cannabis

# Cannabis Use and APOs

- Cannabis use associated with composite outcome related to placental dysfunction (SGA, HDP, stillbirth, MIPTB)
  - 26% exposed vs 17% unexposed, aRR 1.27, 95% CI 1.07-1.49)
- Not significant when use stopped in first trimester





Bar indicating instances of zero exposure (1a, 1b n=8717, and 2a, 2b n=8647) omitted from figure.

<sup>a</sup> Basic adjusted model includes tobacco use as detected by urine cotinine  $\geq 300$  ng/mL at 1st study visit, age  $\geq 30$  years, body mass index ( $<20$  kg/m<sup>2</sup>, 20-29.9 kg/m<sup>2</sup>,  $\geq 30$  kg/m<sup>2</sup>), marital status (married, yes/no), public insurance, maternal medical comorbidities (preexisting diabetes or chronic hypertension, yes/no), study site (8 categories).

<sup>b</sup> Extended adjusted model includes all covariates in the basic adjusted model plus Edinburgh Postnatal Depression screen score ( $\geq 11$ , yes/no), stress from the Perceived Stress Scale (tertile: low, moderate, high), anxiety from the State-Trait Anxiety Inventory (tertile: none/low, moderate, high), other illicit drug use by urine assay at study visit 1.

# Stillbirth

- DATA ARE LIMITED
- Case-control study by Stillbirth Collaborative Research Network
  - Association between stillbirth and cannabis use as demonstrated by cord homogenate positive for THC (OR 2.34, 95% CI 1.13-4.81)
  - Adjusting for cotinine in the maternal serum to account for tobacco use reduced the stillbirth OR for cannabis by approximately 10%

# Congenital Anomalies

- DATA ARE LIMITED AND MIXED
- Linn (1983) found no association with major malformation (OR 1.36, 95% CI 0.97-1.91)
- Large retrospective cohort studies based on birth defects registries
  - Incomplete ascertainment of confounders
  - Potential for recall bias

# Congenital Anomalies

- Atlanta Birth Defects Registry
- 122 cases VSD and 3,029 controls
- Adjusted for maternal age, race, overt diabetes, vitamin use
- Periconceptual cannabis associated with VSD (OR 1.90, 95% CI 1.29-2.81)
- More data are needed
- Not adequate evidence of association with any specific congenital birth defect

# Anomalies: Systematic Review

- 11 studies
- Pooled aOR 1.22 (95% CI 1.00-1.50)
- 2 anomalies associated with cannabis use
  - Ebstein anomaly, two studies, aOR 2.19 (95% CI 1.25-3.82)
  - Gastroschisis, five studies, aOR 2.50 (95% CI 1.09-5.74)
- Heterogeneous studies, high risk of bias, inconsistent evidence

# Paternal Cannabis Use

- Preconception paternal cannabis use associated with lower birth weight, SAB and SIDS
- Altered sperm DNA methylation in genes involved in neurodevelopment and autism spectrum disorder

# Neurodevelopment

- Alterations in neurotransmitters in rat models
  - Especially dopaminergic pathways
- Postmortem human fetal brains (elective terminations 17-22 weeks)
  - Dopamine receptors reduced in marijuana-exposed fetuses
  - Most prominent effect in males
  - Directly correlated with amount of cannabis used during pregnancy

# Prospective Longitudinal Studies

STUDY AND INVESTIGATOR	INITIATION DATE AND LOCATION	STUDY SIZE (N)	POPULATION
Ottawa Prenatal Prospective Study (OPPS), Fried et al	1978 Ottawa, Canada	180	Low-risk, European-American, middle-class; Exposure to marijuana and cigarettes
Maternal Health Practices and Child Development Study (MHPCD), Day et al	1982 Pittsburgh, Pennsylvania	636	High-risk, mixed ethnicity (57% African American), single (71%), low socioeconomic status; Exposure to marijuana and alcohol
Generation R Study, Hoffman et al	2002 Rotterdam, Netherlands	9778	Multi-ethnic, higher socio-economic status

Drug Alcohol Depend 1980;5:415-24. Neurotoxicol Teratol 1998;20:293-306.

Clin Perinatol 1991;18:77-91. Neurotoxicol 13:329-34. Paediatr Perinat Epidemiol 2004;18:61-

72. Prog Neuropsychopharmacol Biol Psychiatry. 2014;52:45-52.



# Neurodevelopment

- DATA ARE LIMITED BY CONFOUNDING
- OPPS
  - No differences between groups below age 4 years
  - At age 4 years, increased behavioral problems, worse language comprehension, decreased sustained attention and memory difficulties
- MHPCD
  - Decreased verbal reasoning at age 6 years
  - Worse academic performance at age 10 years
  - Increased substance use at age 14 years

# Neurodevelopment

- Generation R Study
- Higher aggression scores in cannabis-exposed girls, but not boys at 18 months
- No differences in behavior at 3 years of age
- Ongoing follow-up into adulthood for children born from 2002-2006

# Neurodevelopment

- Cross-sectional study (N=11,489 children)
- Adolescent Brain and Cognitive Development Study
- 5.7% exposed to cannabis prenatally
- Mean age at follow-up 9.9 years
- Cannabis exposure after maternal knowledge of pregnancy associated with greater psychotic-like experiences and externalizing, attention, thought and social problems

# Neurodevelopment

- Secondary analysis of two MFMU parallel RCTs related to maternal thyroid function
- 1,197 pregnant individuals; 8.3% positive for cotinine and 3.9% positive for THC-COOH
- No difference in childhood IQ at 60 months of age between exposed to THC and unexposed
- Exposed children worse attention scores at 48 months of age

# National Academy of Sciences

- Consistent association between prenatal cannabis use and lower birth weight
- Limited evidence of an association between cannabis use and NICU admission
- Insufficient evidence of an association between cannabis use and neurocognitive outcomes
  - Cannot adjust for subtle environmental differences

# Breastfeeding

- THC passes to the neonate in breastmilk
- Letter to the editor NEJM of **two patients**
  - Chronic heavy use can result in levels up to 8x plasma

# Breastfeeding

- Observational study of 8 women
  - Purchased product with known concentration of THC
  - Abstained from use for 24 hrs prior
  - Inhaled cannabis then collected breast milk at 20 minutes, 1, 2 and 4 hours
  - Exclusively breastfed infant ingests mean of 2.5% of maternal dose

# Breastfeeding

- 54 samples from milk donors
- Delta-9-THC detectable 63% samples up to 6 days after last reported use
- Median concentration 9.47 ng/mL
- Number of daily uses and time from sample collection to analysis were predictors of THC concentration in breastmilk



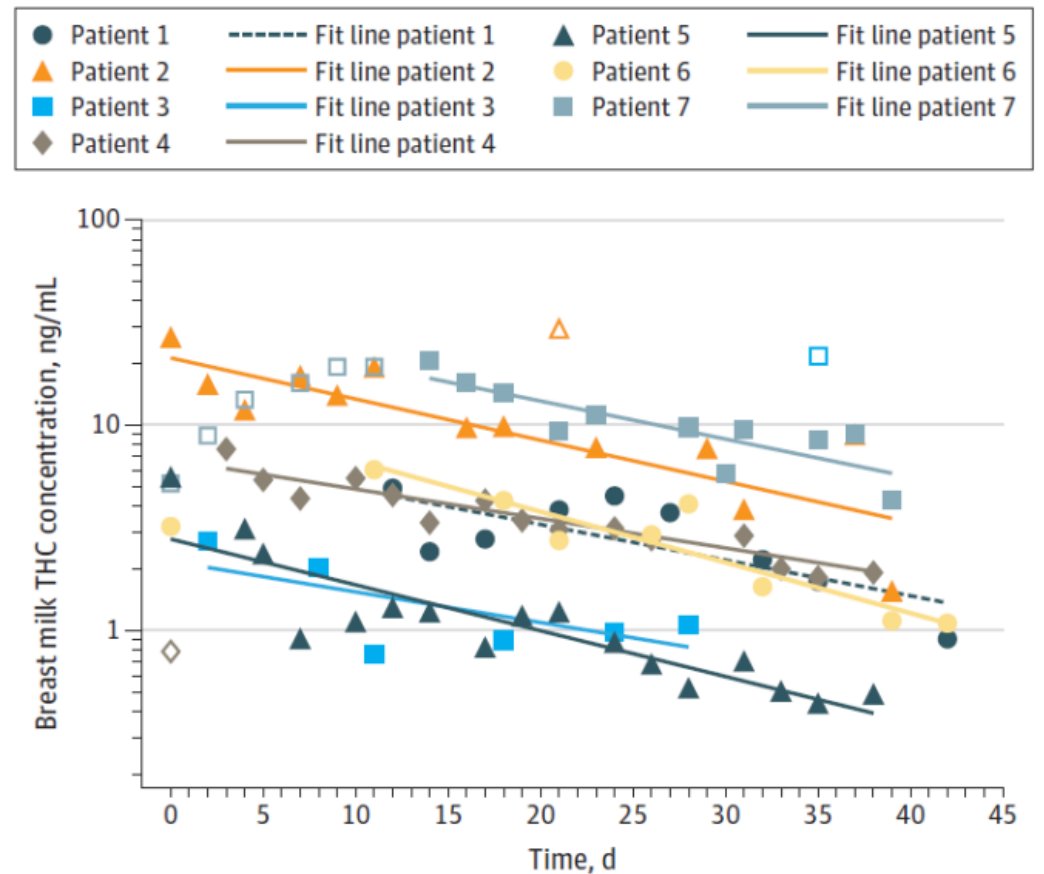
# Breastfeeding

- Prospective cohort study to estimate time to elimination of marijuana metabolite from breastmilk (N=25)
- Inclusion criterion of plan for abstinence
  - 12/25 abstinent by plasma sampling
- Primarily inhalation consumption during pregnancy (more than 2 times weekly)
- Detectable THC in breastmilk in all participants during 6- week study period

# Breastfeeding

- 402 serial samples obtained and analyzed
- Half-life 17 days
- Projected elimination > 6 weeks
- Cannot “pump and dump”

Figure. Pharmacokinetic Modeling for the Estimated Time to Elimination of  $\Delta$ -9-Tetrahydrocannabinol (THC) in Breast Milk Following Delivery



# ACOG Committee Opinion

- People should not use marijuana during pregnancy or while lactating
  - Ob-gyns should not prescribe for medicinal purposes to pregnant or lactating individuals
  - Insufficient evidence for effects on nursing infant

# How are we doing now?

- Holland et al recorded patient encounters and evaluated obstetric provider response to disclosure of cannabis use
- 90/460 (19%) reported use at OB intake
- 47 different health care providers
- 48% of the time provider did not respond to cannabis disclosure
- When discussed, response non-specific and focused on tox screens and social services

# Dispensary Project

- Mystery shopper study (400 randomly selected dispensaries)
- Caller was 8 weeks pregnant with nausea
- Nearly 70% had product recommendations
  - Predominantly recommended edibles
  - 65% based recommendation on personal opinion
  - Only 32% recommended discussion with healthcare provider without prompting

# How are we doing now?

- Cross-sectional study 2017-2019 PRAMS
- Prenatal care visits 8 states
  - 2 with legal cannabis
- N=10,696
- 37.2% not asked about cannabis use
- 62.7% not advised against cannabis use
- Of those reporting cannabis use, 49.8% advised not to use in pregnancy
- 7.7% advised to use cannabis at PNV

# What do we tell patients?

- No known benefits of cannabis use in pregnancy
- Possible risks of cannabis use in pregnancy
- Advise patients not to use cannabis during pregnancy
- No known “safe” amount of cannabis in pregnancy and while breastfeeding

# Grant Support

- University of Colorado CCTSI Child-Maternal Health Junior Pilot Program
- Women's Reproductive Health Research Scholar K12HD001271
- NIDA R01DA049832



# Thank you!



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# References

- Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. *Neurotoxicol. Teratol.* 1990;12(2):161-168.
- Brar BK, Patil PS, Jackson DN, Gardner MO, Alexander JM, Doyle NM. Effect of intrauterine marijuana exposure on fetal growth patterns and placental vascular resistance. *J Matern Fetal Neonatal Med* 2019; Nov 11; 1-5.
- Burns L, Mattick RP, Cooke M. The use of record linkage to examine illicit drug use in pregnancy. *Addiction (Abingdon, England)*. 2006;101(6):873-882.
- Chasnoff IJ. Medical marijuana laws and pregnancy: implications for public health policy. *Am J Obstet Gynecol* 2016; epub ahead of print.
- Conner SN, Bedell V, Lipsey K, et al. Maternal marijuana use and adverse neonatal outcomes. *Obstet Gynecol* 2016; 128(4): 713-23.
- Corsi DJ, Walsh L, Weiss D, et al. Association between self-reported prenatal cannabis use and maternal, perinatal and neonatal outcomes. *JAMA* 2019; 322(2):145-52.
- Day NL, Richardson GA, Goldschmidt L, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. *Neurotoxicol. Teratol.* 1994;16(2):169-175.
- Dekker GA, Lee SY, North RA, McCowan LM, Simpson NA, Roberts CT. Risk factors for preterm birth in an international prospective cohort of nulliparous women. *PloS one*. 2012;7(7):e39154.
- El Marroun H, Tiemeier H, Steegers EA, et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(12):1173-1181.

# References

- English DR, Hulse GK, Milne E, Holman CD, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. *Addiction (Abingdon, England)*. 1997;92(11):1553-1560.
- Fergusson DM, Horwood LJ, Northstone K, Pregnancy ASTALSo, Childhood. Maternal use of cannabis and pregnancy outcome. *BJOG*. 2002;109(1):21-27.
- Fried PA. The Ottawa Prenatal Prospective Study (OPPS): methodological issues and findings-- it's easy to throw the baby out with the bath water. *Life Sci*. 1995;56(23-24):2159-2168.
- Gibson GT, Baghurst PA, Colley DP. Maternal alcohol, tobacco and cannabis consumption and the outcome of pregnancy. *Aust. N. Z. J. Obstet. Gynaecol*. 1983;23(1):15-19.
- Gunn JKL, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcome: a systematic review and meta-analysis. *BMJ Open* 2016; 6:e009986.
- Hayatbakhsh MR, Flenady VJ, Gibbons KS, et al. Birth outcomes associated with cannabis use before and during pregnancy. *Pediatr Res*. 2012;71(2):215-219.
- Holland CL, Rubio D, Rodriguez KL, et al. Obstetric healthcare providers' counseling responses to pregnant patient disclosures of prenatal marijuana use. *Obstet Gynecol* 2016; 127(4):681-7.
- Ko JY, Farr SL, Tong VT, Creanga AA, Callaghan WM. Prevalence and patterns of marijuana use among pregnant and nonpregnant women of reproductive age. *Am J Obstet Gynecol* 2015; 213(2): 201.e1-201.e10.
- Linn S, Schoenbaum SC, Monson RR, Rosner R, Stubblefield PC, Ryan KJ. The association of marijuana use with outcome of pregnancy. *Am. J. Public Health*. 1983;73(10):1161-1164.
- Metz TD and Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. *Am J Obstet Gynecol* 2015; 213(6):761-78.

# References

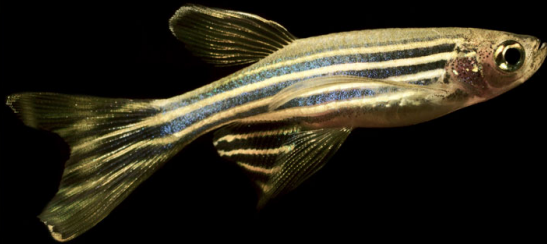
- Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med*. 1982;307(13):819-820.
- Roberson EK, Patrick WK, Hurwitz EL. Marijuana use and maternal experiences of severe nausea during pregnancy in Hawai'i. *Hawaii J Med Public Health*. 2014;73(9):283-287.
- Saurel -Cubizolles MJ, Prunet C, Blondel B. Cannabis use during pregnancy in France in 2010. *BJOG*. 2014;121(8):971-977.
- Shiono PH, Klebanoff MA, Nugent RP, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. *Am J Obstet Gynecol*. 1995;172(1 Pt 1):19-27.
- Varner MW, Silver RM, Rowland Hogue CJ, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstet. Gynecol*. 2014;123(1):113-125.
- Warshak CR, Regan J, Moore B, et al. Association between marijuana use and adverse obstetrical and neonatal outcomes. *J Perinatol* 2015; 35:991-5.
- Westfall RE, Janssen PA, Lucas P, Capler R. Survey of medicinal cannabis use among childbearing women: patterns of its use in pregnancy and retroactive self-assessment of its efficacy against 'morning sickness'. [Reprint in *Complement Ther Clin Pract*. 2009 Nov;15(4):242-6; PMID: 19880090]. *Complement Ther Clin Pract*. 2006;12(1):27-33.
- Young-Wolff KC, Sarovar V, Tucker LY, et al. Association of nausea and vomiting in pregnancy with prenatal marijuana use. *JAMA Intern Med* 2018; 178(10):1423-4.
- Young- Wolff KC, Sarovar V, Tucker LY, et al. Validity of self-reported cannabis use among pregnant females in Northern California. *J Addict Med* 2020; 14(4):287-92.

# Cannabidiol

- Cannabidiol (CBD) component of *Cannabis sativa* plant
- Not psychoactive, sedative, ? therapeutic
- Little known about CBD in isolation in pregnancy
- In vitro models demonstrate adverse effects on trophoblasts and placental remodeling

# Cannabidiol

- Zebra fish embryos
- Neural activity decreased more by CBD than THC
- Both decreased neural activity
- Possible synergistic effect with more pronounced effect of CBD in presence of THC



# Cannabidiol

- Biologically plausible effect on placentation and trophoblast invasion
- Endocannabinoid system active in early pregnancy with placentation
- Active in late pregnancy during fetal neurodevelopment
- Essentially no data specific to CBD in humans