Tobacco exposure and children's health: Identifying critical windows and joint effects

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Introduction

- I am an environmental epidemiologist.
  - PhD in Environmental Health, Epidemiology
  - Postdoctoral trainee in Epidemiology
  - Assistant professor of Epidemiology
- My research examines how early-life exposures influence childhood growth and neurodevelopment.
  - Exposures: tobacco, cannabis, air pollution, and nutrition.

Outline

1. Tobacco exposure and childhood obesity
2. Tobacco exposure and childhood neurocognitive development
3. Future directions
4. Implications

1. Tobacco exposure and childhood obesity

Tobacco is a member of the nightshade family

- Other nightshades are tomatoes, potatoes, peppers, and eggplants.
- These foods also have nicotine but in much lower amounts (0.003 mg in a medium potato versus ~12 mg in one cigarette)

Source: Cottercrunch

Tobacco use among U.S. women

- 1920s: "Mild as May" marketing to women
- 1965: Prevalence peaked at 34% (Giovino et al. 1994; *MMWR*).
- 2016: 7.1% of pregnant women report smoking (Kondracki 2016; *Reprod Health*)

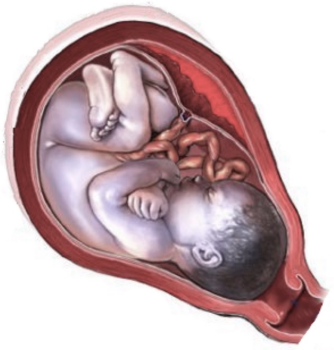
Maternal smoking during pregnancy

- Smoking consistently linked to low birth weight (Butler et al. 1972; *BMJ*).
- Smoking is also associated with rapid “catch up growth” and obesity in childhood.

Source: Alamy

Mechanisms

Tobacco



Fetal hypoxia

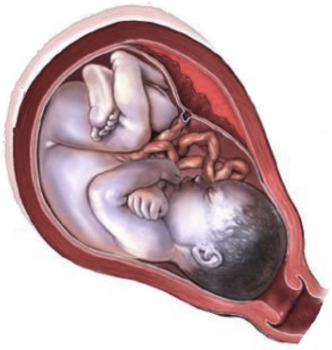
Reiter & Walsh, 2016

Epigenetic modifications/ inheritance

(Joubert et al. 2014 *Cancer Epidemiol Biomarkers Prev*)

Mechanisms

Tobacco



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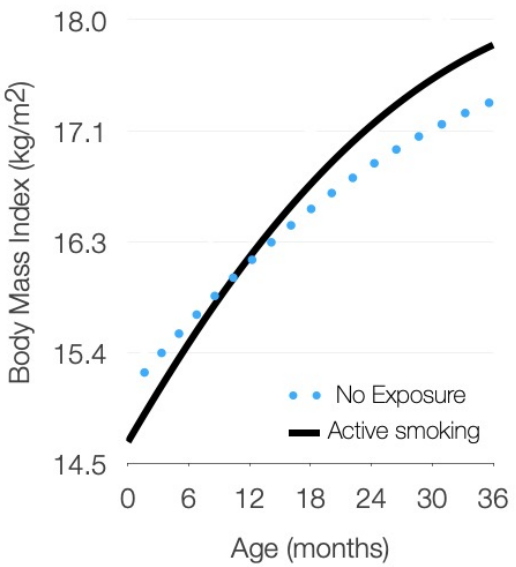

- Low birth weight
- Rapid catch-up
- Childhood obesity

(Moore et al. 2018; *Int J Obes*)

Postnatal exposure to tobacco smoke is experienced by 40% of children.

- Induces inflammation (Pope and Dockery 2006; J Air Waste Man Assoc) and oxidative stress (Church and Pryor 1985; *Environ Health Perspect)*).
- Postnatal exposure increases risk by at least 30% (Moore et al. 2016; *Environ Health Perspect)*

Source: Custom Medical Stock Images

Gaps in knowledge – Critical windows

- Few studies have examined both prenatal and postnatal exposures within the same study.
- Most susceptible developmental periods are unknown.
- There is a need to apply a life course approach.

Gaps in knowledge – Joint effects

- Concurrent exposure to air pollution may augment risk.
- Similar mechanisms such as altering metabolic profile of adipose tissue (Blumberg et al. 2011; *J Biochem Mol Biol)*

Source: Getty images

Gaps in knowledge – Joint effects

- Concurrent exposure to air pollution may augment risk.
- Similar mechanisms such as altering metabolic profile of adipose tissue (Blumberg et al. 2011; *J Biochem Mol Biol)*
- Early-life nutrition may minimize the effects of secondhand smoke.
- Example: Breast milk provides infants with anti-inflammatory and antioxidant protection (Bartok et al. 2009; *Int J Pediatr Obes*)


Source: Getty images


Source: Getty images

Leveraging a well-characterized cohort: The Healthy Start Study

Healthy Start

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

Healthy Start

- 1,410 mother-child pairs
- Seven repeated measures of secondhand smoke

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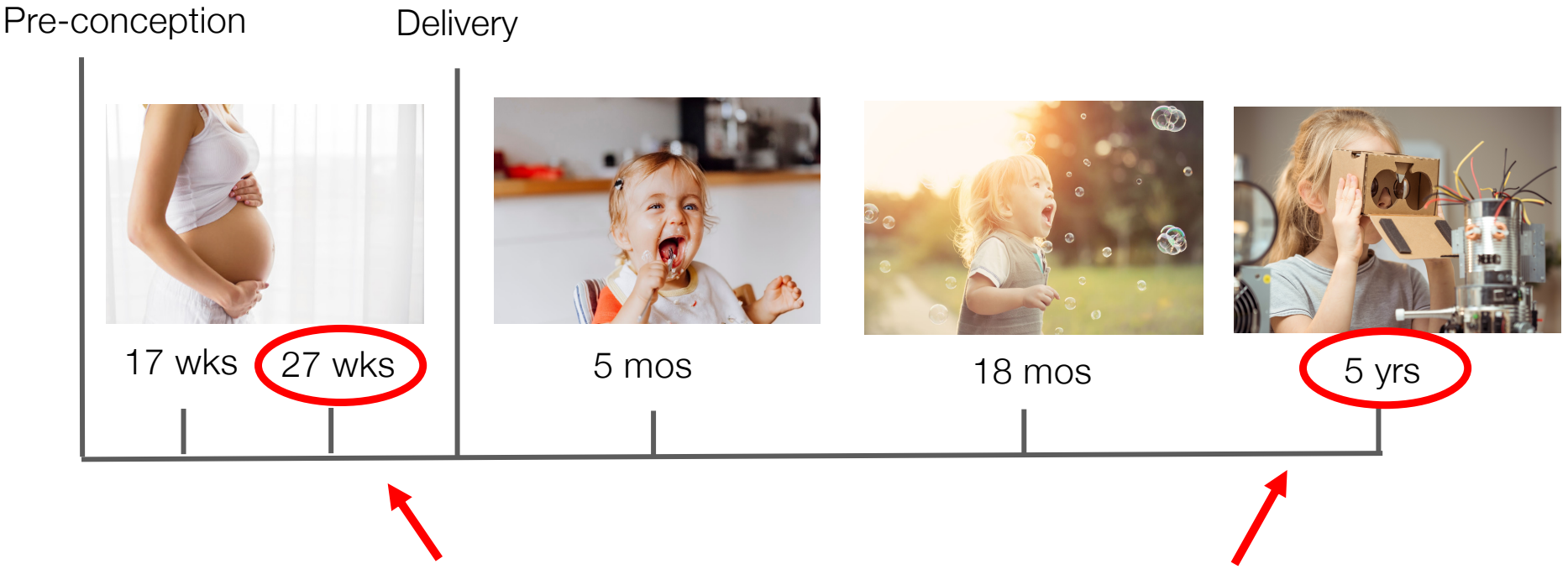

Cotinine (major metabolite of nicotine)

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Healthy Start

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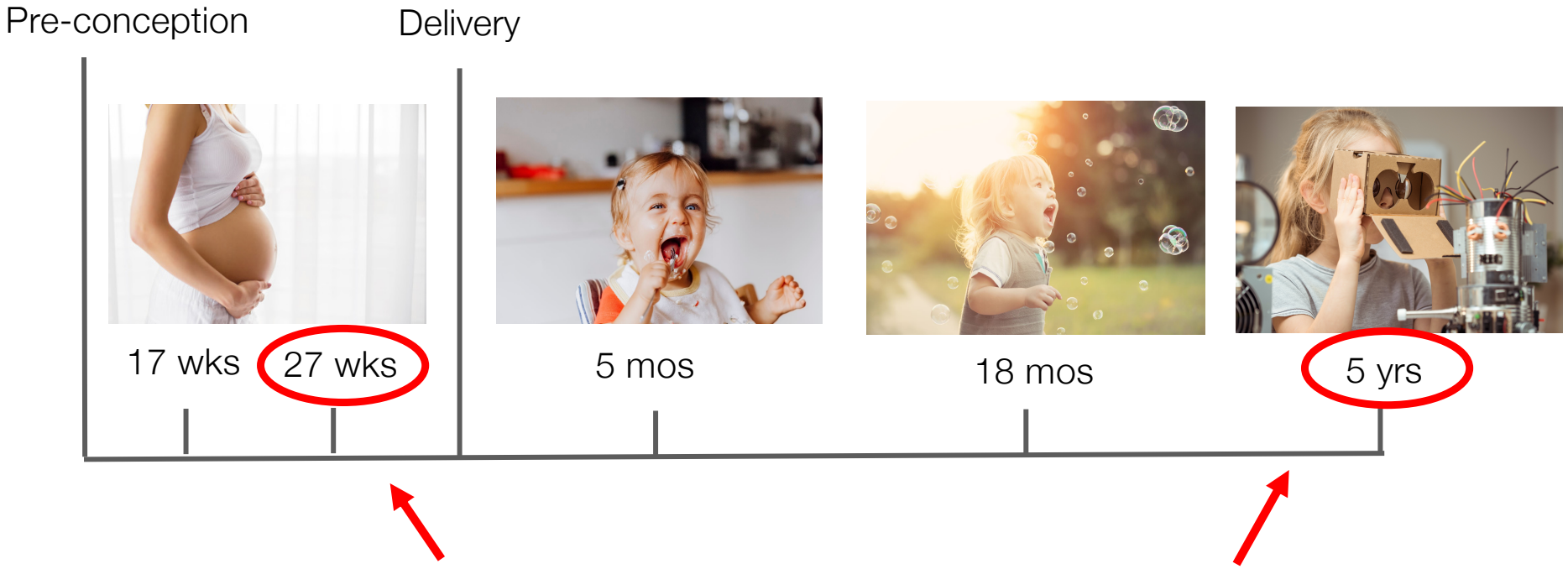


Cotinine (major metabolite of nicotine)

Self-report at all time points

Gap in knowledge – Critical windows

Research question:

Does the association between exposure to tobacco on childhood adiposity depend on the timing of exposure?

Neonatal and childhood adiposity

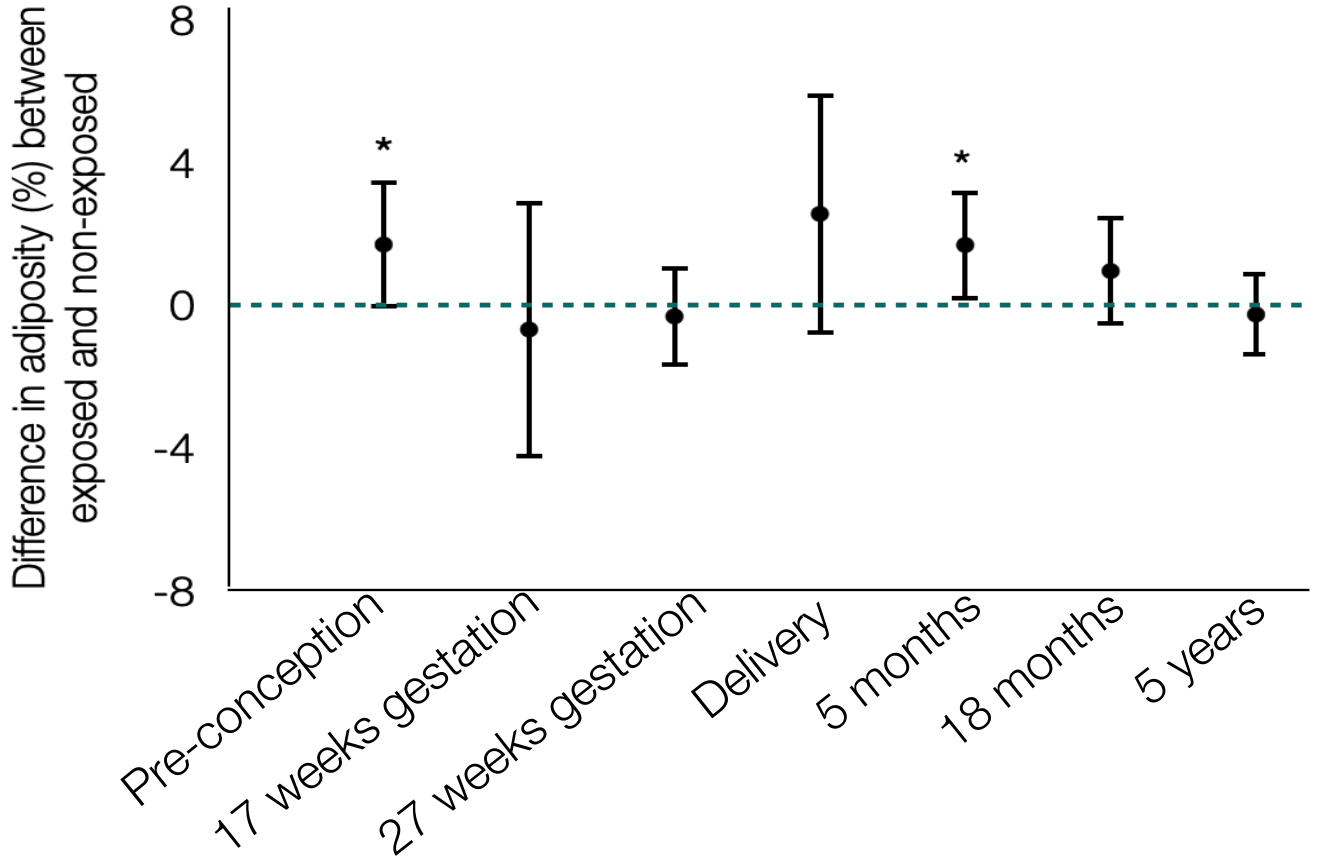
- Air displacement plethysmography (PEA POD/BOD POD)
- Neonatal/childhood adiposity is the proportion of fat mass divided by total mass (% fat mass)

Source: Cosmed USA

Statistical analysis

- Outcomes:
  - Adiposity at age 5 *years*
  - Changes in adiposity from birth to age 5 years
- Multiple informant approach within GEEs estimated the associations between secondhand smoke with outcomes (Sanchez et al. 2011; *Environ Health Perspect*).
- A product term between tobacco exposure and timing of the exposure was included in all models to determine whether the associations depend on timing.

Children experienced increased adiposity at 5 years of age if…



Mother smoked pre-conception (1.7%; [95% CI: 0.1, 3.2]) or at 5 months of age (1.7% [95% CI: 0.1, 3.6]).

Moore et al. 2021; under review with *Int J Obes*

Children experienced increased adiposity accretion from birth to age 5 years if mother smoked pre-conception (3.1%; 95% CI: 1.0, 5.1) or until delivery (4.0%; 95% CI: 0.4, 7.6).

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Children experienced increased adiposity accretion from birth to age 5 years if mother smoked pre-conception (3.1%; 95% CI: 1.0, 5.1) or until delivery (4.0%; 95% CI: 0.4, 7.6).

Strong evidence that this association depended on timing of the exposure (p for interaction: 0.01)

Moore et al. 2021; under review with *Int J Obes*

Conclusions

- Fetal/childhood exposure to tobacco immediately before pregnancy, during late gestation, and in early infancy may have the greatest impact on childhood adiposity.

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  - provide novel insights about the underlying mechanisms (epigenetic inheritance/modifications, structural and functional changes to the placenta, and postnatal physiological and behavioral changes.)

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- Our results:
  - provide novel insights about the underlying mechanisms (epigenetic inheritance/modifications, structural and functional changes to the placenta, and postnatal physiological and behavioral changes.)
  - emphasize the need for smoking cessation efforts to be tailored for pre-conception through the early postpartum period when smoking relapse is common.

Joint effects with air pollution

Air pollution

- High levels of exposure to traffic-related and ambient air pollution ($PM_{2.5}$, ozone) have been linked to low birth weight (Salam et al. 2005; *Environ Health Perspect*).

Air pollution

- In Healthy Start, there is limited evidence that ozone and $PM_{2.5}$ exposures in pregnancy were associated with birth weight or neonatal adiposity (Starling et al. 2019; *Environmental Research*).
  - Inconsistent with previous studies.
  - Lower concentrations or low variability across Denver metro.

Air pollution

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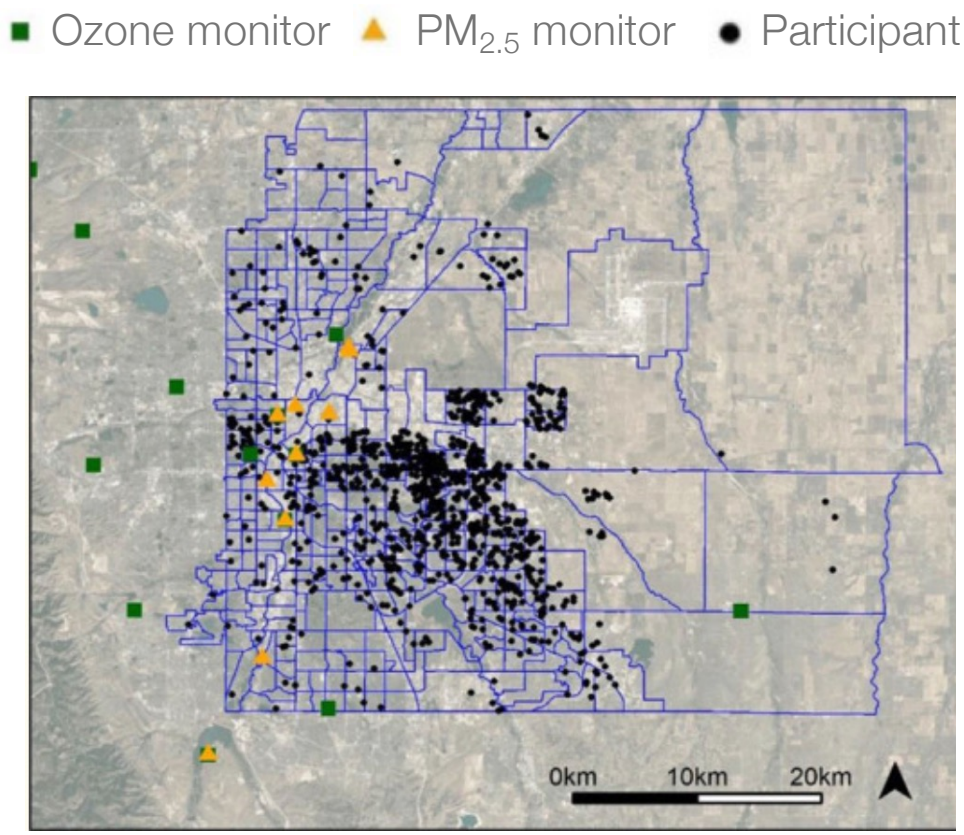
  - Inconsistent with previous studies.
  - Lower concentrations or low variability across Denver metro.
- Other factors may alter risk.
  - Social factors (Martenies et al. 2019; *Environmental Epidemiology*)
  - Tobacco (Moore et al. 2021; *Environmental Epidemiology*)

Research question:

Is the joint effect of fetal exposure to tobacco and ambient air pollution on childhood growth trajectories greater than would be expected due to the individual exposures alone?

Joint effects of fetal exposure to tobacco and ambient air pollution

- Exposures:
  - Ozone
  - $PM_{2.5}$
- Estimated via inverse-distance weighted interpolation from EPA monitors.
- Whole pregnancy and trimester-specific exposure
- Categorized as low vs. high



Martenies et al. 2019; *Environ Epidemiol*

Joint effects of fetal exposure to tobacco and ambient air pollution

Statistical methods:

- Linear regression models for the outcome of neonatal adiposity
- Mixed-effects models for the outcome of BMI trajectories.
- A product term between cotinine categories and O_3/$PM_{2.5}$ categories was included in all models to assess whether the effect estimate for both was greater than would be expected due to the individual exposures alone.

Offspring of mothers with high exposure to $PM_{2.5}$ during the third trimester experience…

No difference in birth weight or neonatal adiposity.

Moore et al. 2021; *Environmental Epidemiology*

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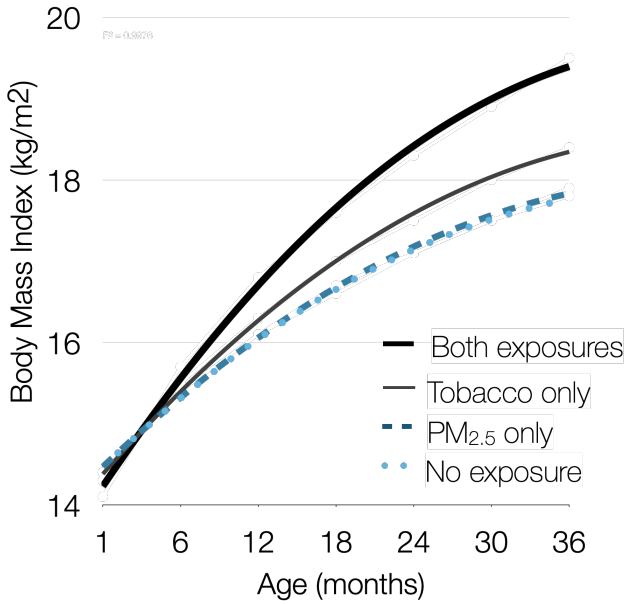


BMI growth that was more rapid than would be expected due to individual exposures

(0.6 kg/m^2 per year; 95% CI: 0.1, 2.3; p for interaction=0.03).

Moore et al. 2021; *Environmental Epidemiology*

Conclusions

- In the Denver metro, $PM_{2.5}$ was generally below the EPA air quality standards.
- Yet higher exposure during the third trimester may influence BMI trajectories when combined with maternal smoking.
- Childhood obesity prevention strategies may need to target both exposures to achieve the maximum public health benefit.

Air Quality Index (AQI)	PM 2.5
Good	0 - 12.0 µg/m^3
Moderate	12.1 - 35.4 µg/m^3/td>
Unhealthy for Sensitive Groups	35.5 - 55.4 µg/m^3
Unhealthy	55.5 - 150.4 µg/m^3
Very Unhealthy	150.5 - 210.4 µg/m^3
Hazardous	Above 210.5 µg/m^3

Source: EPA

Joint effects with breastfeeding

Breastfeeding

- Breast milk provides infants with anti-inflammatory and antioxidant protection
  (Bartok et al. 2009; Int J Pediatr Obes)
- Lactational exposure to nicotine and other chemicals.

Source: Getty

Research question:

Does the association between postnatal exposure to secondhand smoke on infant adiposity depend on the duration of exclusive breastfeeding?

Exposure to secondhand smoke and exclusive breastfeeding

- At the 5 month visit:
  - Women reported infant feeding
    - Formula fed (~6%)
    - Mixed formula (49%)
    - Exclusively breastfed (45%)
  - Women reported household smokers
  - Infant adiposity was via PEA POD

The association between secondhand smoke and infant adiposity differed by the infant feeding.

Among infants who were NOT breastfed, secondhand smoke was associated with a 1-kg increase in fat mass.

No difference in adiposity among breastfed infants.

Moore et al. 2021; *Environmental Epidemiology*

Conclusions

- Breastfeeding may be a critical window and an opportunity for intervention
  - Smoking relapse during the early postpartum period is common (Colman and Joyce 2003; Am J Prev Med).
  - Breastfeeding initiation may be a key strategy for preventing relapse (Kendzor et al. 2010; Nicotine Tob Res).
  - Longer duration of breastfeeding associated with reduced risk of relapse (Logan et al. 2017; Nicotine Tob Res).


Source: Getty

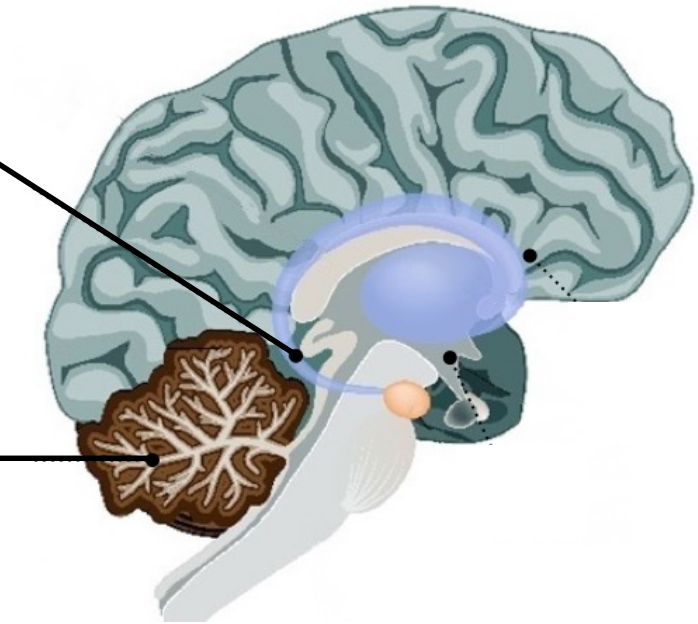
2. Early-life exposure to tobacco and childhood neurocognitive development

Tobacco is toxic to the fetal brain

- Fetal exposure to tobacco may overstimulate nicotinic acetylcholine receptors.
- These receptors are abundant in:

Hippocampus
(responsible for memory and learning)

Cerebellum
(responsible for motor control)



Research question:

Does fetal exposure to tobacco impact childhood neurocognitive development, independent of low birth weight and pre-term birth?

Methods

- Explored the association between fetal exposure to active/secondhand maternal smoking with:

Developmental milestones

Cognitive skills (e.g. inhibitory control)

- Restricted our analyses to offspring born ≥37 weeks and with a birth weight ≥2,500g

  - Confounders or mediators (along the causal pathway)

Offspring with fetal exposure to tobacco experience...

Delayed fine motor development
(OR: 3.5; 95% CI: 1.5, 8.6).

(Moore et al. 2018; *J Peds*)

Offspring with fetal exposure to tobacco experience...

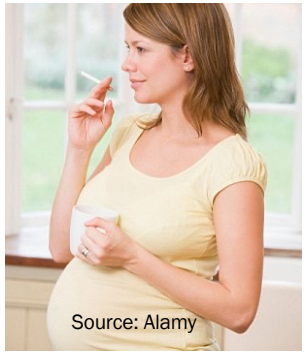
Delayed fine motor development (OR: 3.5; 95% CI: 1.5, 8.6).

Reduced inhibitory control (mean difference: -3.5, 95% CI: -6.5, -0.5).

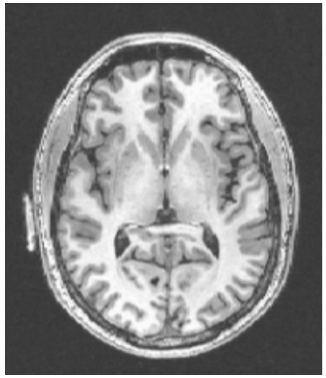
(Moore et al. 2018; *J Peds*)

Potential mechanisms –
And a link with low birth weight?

Nicotine exposure during pregnancy



Loss of gray or white brain matter



Impaired fine motor skills

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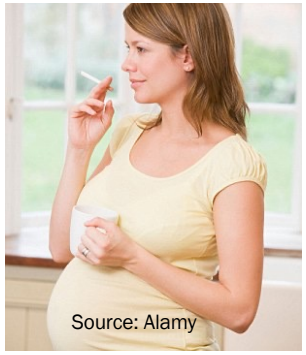

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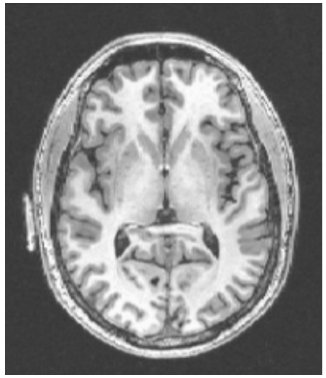


Impaired fine motor skills

Low birth weight or smaller head circumference as proxy?

(Parker et al. 2016: *J. Dev. Orig. Health Dis*.)

Next steps (student-led)

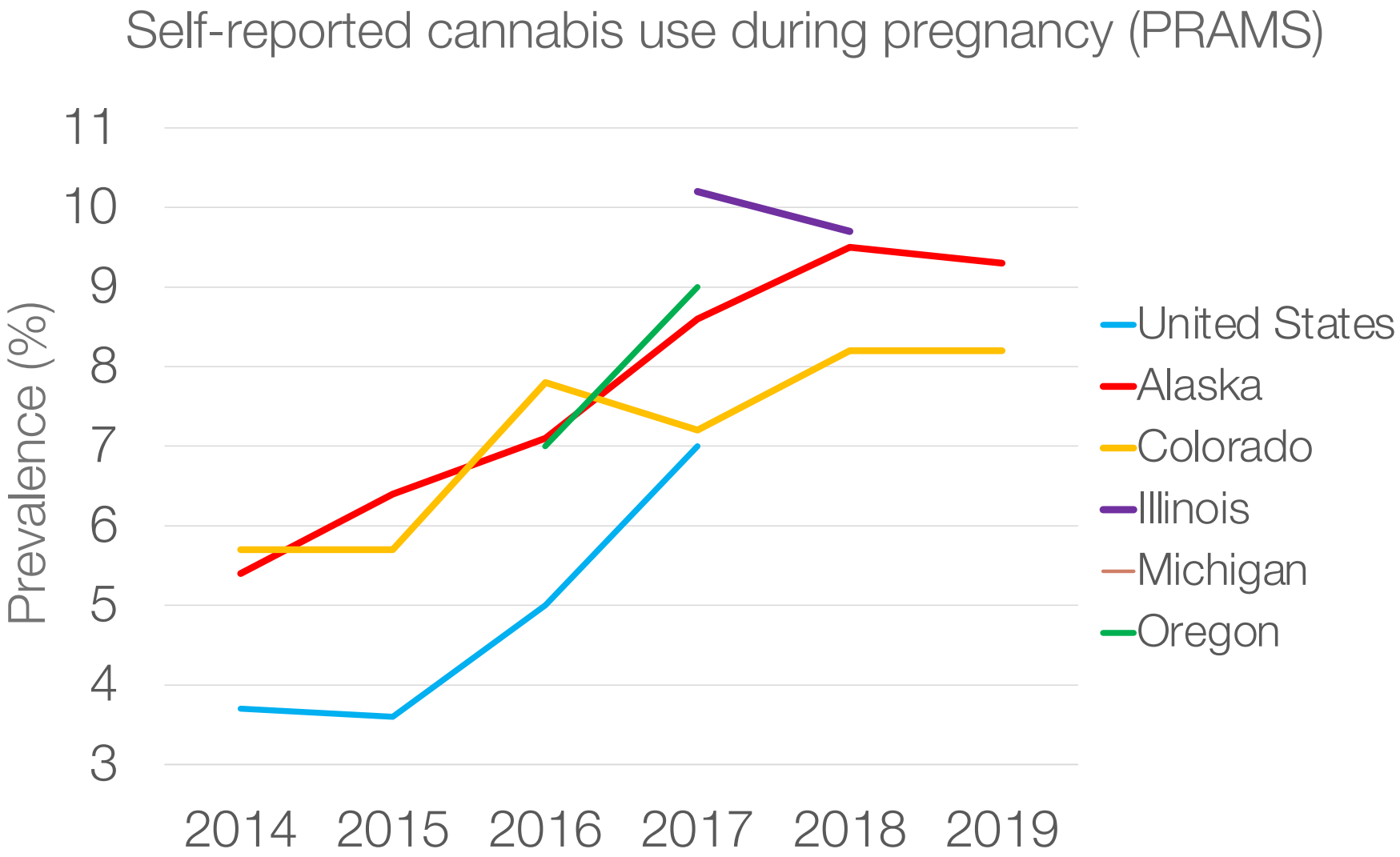
- Impact of tobacco on childhood behavior
- Critical windows
- Joint effects with nutrition
  (e.g. maternal intakes of folate during pregnancy)

Source: Premier Health

3. Future directions

Cannabis use during pregnancy and childhood growth and neurodevelopment

Cannabis use among pregnant women



Cannabis use in pregnancy

- Cannabis use linked to impaired neurodevelopment (Fried et al. 1992; *Neurotoxicol Teratol*) and low birth weight (Crume et al. 2018; *J Peds*).
- Effects could be stronger than previously reported since THC potency is 6-7 times higher than 1970s (ElSohly et al. 2016; *Biol Psychiatr*).
- THC and CBD have opposing effects on the brain
  - CBD has neuroprotective properties (Niesink et al. 2013).

Gaps in literature

- Does exposure to cannabis in pregnancy contribute to low birth weight and rapid catch up growth?

Gaps in literature

- Does exposure to cannabis in pregnancy contribute to low birth weight and rapid catch up growth?

- Does exposure to cannabis in pregnancy contribute to impaired cognitive function or behavioral problems?

Gaps in literature

- Does exposure to cannabis in pregnancy contribute to low birth weight and rapid catch up growth?

- Does exposure to cannabis in pregnancy contribute to impaired cognitive function or behavioral problems?

- Do cannabinoids (THC, CBD, etc.) have opposing effects?

Ongoing research

- THC, CBD, and nine other cannabinoids are being measured in stored urine and umbilical cord tissue samples.
- The proposed study will be the first to attempt to disentangle the effects of THC and CBD use during pregnancy on offspring growth and development.

Ongoing research

- THC, CBD, and nine other cannabinoids are being measured in stored urine and umbilical cord tissue samples.
- The proposed study will be the first to attempt to disentangle the effects of THC and CBD use during pregnancy on offspring growth and development.
- Preliminary data for future NIDA grants:

Avenir Award Program for Genetics or Epigenetics of Substance Use Disorders (DP1 Clinical Trial Optional)

Funding Opportunity Announcement (FOA) Number

PAR-19-223

Notice of Special Interest (NOSI): Effects of Cannabis Use and Cannabinoids on the Developing Brain

Notice Number:

NOT-DA-20-039

4. Implications

Interventions – Smoking Cessation

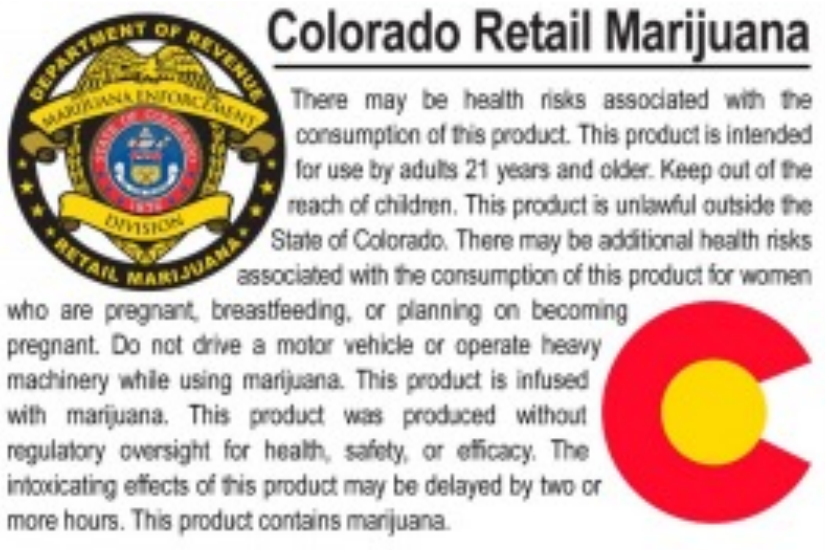
- Smoking cessation campaigns may need to be extended in include all of the critical windows.
  - Pre-conception is the earliest critical window. However, it may be more difficult to reach this population.
  - During pregnancy, women may be more motivated to change their behavior.
  - Postpartum, well-child visits may be an opportunity for interventions.


Source: Deposit Photos


Source: Deposit Photos

Policy – Pregnancy Warning Signs

- There is a need for new policies, such as requiring Pregnancy Warning Signs to be displayed in dispensaries.



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Citations

- Bartok CJ, Ventura AK. Mechanisms underlying the as- sociation between breastfeeding and obesity. Int J Pediatr Obey 2009; 4: 196–204.
- Blumberg B, Iguchi T, Odermatt A. Endocrine disrupting chemicals. J Steroid Biochem Mol Biol. 2011;127(1-2):1-3.
- Butler NR, Goldstein H, Ross EM. Cigarette smoking in pregnancy: its influence on birth weight and perinatal mortality. British medical journal. 1972;2(5806):127-130.
- Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. *Environmental health perspectives.* 1985;64:111-126.
- Colman GJ, Joyce T. Trends in smoking before, during, and after pregnancy in ten states. American Journal of Preventive Medicine. 2003;24:29–35.
- Crume TL, Juhl AL, Brooks-Russell A, Hall KE, Wymore E, Borgelt LM. Cannabis Use During the Perinatal Period in a State With Legalized Recreational and Medical Marijuana: The Association Between Maternal Characteristics, Breastfeeding Patterns, and Neonatal Outcomes. The Journal of pediatrics. 2018;197:90-96.

Citations

- ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. Biol Psychiatry. 2016 Apr 1;79(7):613-9.
- Fried PA, Watkinson B, Gray R. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes, and alcohol. Neurotoxicology and teratology. 1992;14(5):299-311.)
- Giovino GA, Schooley MW, Zhu B-P, Chrismon JH, Tomar SL, Peddicord JP, Merritt RK, Husten CG, Eriksen MP. Surveillance for selected tobacco-use behaviors-United States, 1900-1994. Morbidity and Mortality Weekly Report . 1994;43(SS-3):1–43.
- Joubert BR, Håberg SE, Bell DA, et al. Maternal smoking and DNA methylation in newborns: in utero effect or epigenetic inheritance? Cancer Epidemiol Biomarkers Prev. 2014;23(6):1007-1017.

Citations

- Kendzor DE, Businelle MS, Costello TJ, et al. Breast feeding is associated with postpartum smoking abstinence among women who quit smoking due to pregnancy. Nicotine Tob Res 2010; 12: 983–988.
- Kondracki AJ. Prevalence and patterns of cigarette smoking before and during early and late pregnancy according to maternal characteristics: the first national data based on the 2003 birth certificate revision, United States, 2016. Reprod Health. 2019 Sep 13;16(1):142.
- Logan CA, Rothenbacher D, Genuneit J. Postpartum Smoking Relapse and Breast Feeding: Defining the Window of Opportunity for Intervention. Nicotine Tob Res. 2017 Mar 1;19(3):367-372.
- Martenies SE, Allshouse WB, Starling AP, et al. Combined environmental and social exposures during pregnancy and associations with neonatal size and body composition: The Healthy Start study. Environmental Epidemiology. 2019;3(2).

Citations

- Moore BF, Starling AP, Magzamen S, et al. Fetal exposure to maternal active and secondhand smoking with offspring early-life growth in the Healthy Start study. International journal of obesity (2005). 2019;43(4):652-662.
- Moore BF, Sauder KA, Starling AP, Ringham BM, Glueck DH, Dabelea D. Exposure to secondhand smoke, exclusive breastfeeding and infant adiposity at age 5 months in the Healthy Start study. Pediatric Obesity. 2017;12:111-119.a
- Moore BF, Shapiro AL, Wilkening G, Magzamen S, Starling AP, Allshouse WB, Adgate JL, Dabelea D. Fetal exposure to tobacco and offspring neurodevelopment in the Healthy Start study. Journal of Pediatrics. 2019 Nov 20. pii: S0022-3476(19)31467-2.
- Moore BF, Clark ML, Bachand A, Reynolds SJ, Nelson TL, Peel JL. Interactions of diet and secondhand smoke on the prevalence of obesity among children — Results from NHANES, 2007-2010. Environmental Health Perspectives. 2016 Aug;124(8):1316-22.

Citations

- Niesink RJM, van Laar MW. Does Cannabidiol Protect Against Adverse Psychological Effects of THC? Frontiers in psychiatry. 2013;4:130-130.
- Parker SE, Collett BR, Speltz ML, Werler MM. Prenatal smoking and childhood behavior problems: is the association mediated by birth weight? Journal of developmental origins of health and disease. 2016:1-9.
- Pope CA, 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *Journal of the Air & Waste Management Association (1995).* 2006;56(6):709-742.
- Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, Gilliland FD. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. Environ Health Perspect. 2005 Nov;113(11):1638-44. doi: 10.1289/ehp.8111. PMID: 16263524; PMCID: PMC1310931.

Citations

- Sánchez BN, Hu H, Litman HJ, Téllez-Rojo MM. Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. Environmental health perspectives. 2011;119(3):409-415.
- Starling AP, Moore BF, Thomas DSK, et al. Prenatal exposure to traffic and ambient air pollution and infant weight and adiposity: The Healthy Start study. Environ Res. 2020;182:109130.