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

- Fetal hypoxia (Reiter & Walsh, 2016)
- Tobacco
  - Low birth weight
  - Rapid catch-up
  - Childhood obesity (Moore et al. 2018; Int J Obes)
- Epigenetic modifications/inheritance (Joubert et al. 2014 Cancer Epidemiol Biomarkers Prev)
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*)
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)
Leveraging a well-characterized cohort: The Healthy Start Study
Healthy Start

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

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Cotinine (major metabolite of nicotine)
Healthy Start

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- Seven repeated measures of secondhand smoke

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).
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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• 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.)
Conclusions

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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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  - 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*
Offspring of mothers with high exposure to PM$_{2.5}$ during the third trimester experience…

No difference in birth weight or neonatal adiposity.

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.

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.
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).
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

Source: Alamy

Source: Dreamstime
Potential mechanisms – And a link with low birth weight?

Nicotine exposure during pregnancy

Loss of gray or white brain matter

Impaired fine motor skills

Low birth weight or smaller head circumference as proxy?

(Source: Alamy

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

Source: Dreamstime)
Next steps (student-led)

- Impact of tobacco on childhood behavior
- Critical windows
- Joint effects with nutrition (e.g. maternal intakes of folate during pregnancy)
3. Future directions
Cannabis use during pregnancy and childhood growth and neurodevelopment
Cannabis use among pregnant women

Self-reported cannabis use during pregnancy (PRAMS)

Prevalence (%)
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?

Source: Getty
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

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- 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.
Policy – Pregnancy Warning Signs

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

Keep your baby as healthy as possible by avoiding cannabis while pregnant and breastfeeding.

The American Medical Association, American Academy of Pediatrics, and the Academy of Breastfeeding Medicine all advise against cannabis use while pregnant or breastfeeding.

Learn more at KnowThisAboutCannabis.org.
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Citations


Citations


Citations


Citations


- 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


Citations


• 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
