Fetal Origins of Obesity: The Role of Nutrition and The Environment

Brianna Moore, PhD
Assistant Professor of Epidemiology
The University of Texas School of Public Health
Michael and Susan Dell Center for Healthy Living
Introduction

• I am an epidemiologist.

  • PhD in Environmental Health, Epidemiology

  • Postdoctoral trainee in Epidemiology

• My research examines how early-life exposures influence childhood growth and neurodevelopment.

  • Exposures: tobacco, cannabis, air pollution, and nutrition.
Outline

• Fetal origins hypothesis
• Fetal origins of obesity: The role of nutrition
• Fetal origins of obesity: The role of the environment
• Intersection of nutrition and the environment
• Translation of findings
• Future directions
Fetal origins hypothesis
Obesity is a growing public health concern

- Obesity has been increasingly steadily since the 1960’s
- Diabetes, metabolic syndrome, and other cardiometabolic disturbances are also on the rise

Source: Ogden et al. 2012; National Center for Health Statistics
Fetal origins hypothesis

- Growing interest in Developmental Origins of Health and Disease (DOHaD) or the fetal origins hypothesis

Source: Heindel et al 2017; Reproductive Toxicology
Fetal origins hypothesis

- Sensitive windows in which environmental stressors can lead to increased susceptibility to adverse health outcomes.

- Fetal life represents a critical period when an exposure may have lifelong effects.

- Investigated in both nutrition (David Barker) and environmental health fields, beginning in 1990’s.
Field of Nutrition: David Barker

- Low birthweight is associated with coronary heart disease in adults.

- Why?
  - Undernutrition in utero permanently changes the body's structure, function and metabolism (example: Dutch famine).
  - Overnutrition (increased maternal fuels) also associated with increased risk of obesity.

Figure adapted from Handbook of Famine, Starvation, and Nutrient Deprivation.
Working in Parallel: Field of Environmental Health

- Early example:
  - Daughters of mothers who took diethylstilbestrol (DES, a synthetic form of estrogen) had a greater risk of clear cell adenocarcinoma (a rare vaginal cancer) (Herbst et al.; 1972).
Programming of obesity may be evident at birth

• Birth weight has long been associated with childhood obesity.

• Pregnancy may be an ideal time for obesity prevention.

  • Some evidence that neonatal adiposity, but not birth weight, is influenced by mother’s nutrition (Crume et al. 2016; *Am J Obstet Gynecol*)

• Does neonatal adiposity predict childhood BMI?
Neonatal adiposity and childhood obesity

- Air displacement plethysmography
- Neonatal adiposity is the proportion of fat mass divided by total mass (% fat mass)
Predicted BMI levels according to neonatal adiposity, girls

Moore et al. 2020; Pediatrics
Predicted BMI levels according to neonatal adiposity

Moore et al. 2020; Pediatrics
Leveraging a well-characterized cohort: The Healthy Start Study
The Healthy Start Study

- Pre-birth cohort of 1,410 ethnically diverse pregnant women and their offspring
Examples of exposures and outcomes collected

• Pregnancy:
  • Maternal BMI, gestational weight gain, lipids, glucose, diet
  • Environmental exposures:
    • Perfluoroalkyl substances (PFAS), ambient air pollution, tobacco use/exposure (cotinine)
• Offspring
  • Body composition (PEA POD)
  • Heights/weights from medical records (trajectories)
Fetal origins of obesity: The role of nutrition
Overnutrition in pregnancy

- Fetal origins hypothesis suggests that obesity may be “transferred” from mother to offspring.

- Pre-pregnancy BMI and gestational weight gain increases neonatal adiposity (Starling et al. 2015; *Am J Clin Nutr*).

- Effects may be trimester-specific.

Adapted from Dabelea and Crume 2011, *Diabetes*
Diet quality in pregnancy

• Healthy Eating Index (HEI-2010)
  • 13 dietary component
  • Scores range from 0-100
• Poor diet quality during pregnancy increases neonatal adiposity but not birth weight, independent of maternal BMI (Shapiro et al. 2017; Int J Obes).
  • Nutrition may be just as clinically important as BMI/gestational weight gain.

<table>
<thead>
<tr>
<th>Mean difference for HEI-2010 score (≤57 vs. &gt;57)</th>
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<td>Birth weight (g)</td>
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<td>Neonatal adiposity (%)</td>
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Fetal origins of obesity: The role of the environment
Smoking

• Smoking consistently linked to low birth weight (Butler et al. 1972; *BMJ*).

• Smoking is also associated with rapid “catch up growth” and obesity.
Offspring born to active smoking mothers experience...

- Lower birth weight (-341g; 95% CI: -472, -211) and neonatal fat mass (-79g; 95% CI: -131, -27).

  - (Moore et al. 2018; *Int J Obes*)
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Rapid “catch-up” growth that is similar to the offspring of secondhand smokers. (0.27 kg/m² per year; p<0.01)

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Air pollution

- High levels of exposure to traffic-related and ambient air pollution (PM$_{2.5}$, ozone) have been linked to low birth weight.
Air pollution

- Limited evidence that ozone and PM$_{2.5}$ exposures in pregnancy were associated with birth weight or neonatal adiposity in Healthy Start (Starling et al. 2019; *Environmental Research*).
  - Inconsistent with previous studies.
  - Lower concentrations or low variability across Denver metro.
  - Third factor may influence these associations.
    - Social factors (Martenies et al. 2019; *Environmental Epidemiology*)
    - Smoking (preliminary data)
Offspring of mothers with high exposure to PM$_{2.5}$ during the third trimester experience...

No difference in birth weight or neonatal adiposity.

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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).

(preliminary data)
Intersection between nutrition and the environment
Do nutrition and the environment interact?

- The association between secondhand smoke and infant adiposity differed by the duration of exclusive breastfeeding (Moore et al. 2017; *Ped Obes*)
  - If infants who were breastfed, there was no change in adiposity.
  - If infants who were NOT breastfed, secondhand smoke was associated with increased adiposity.

Exposure: Secondhand smoke

Modifier: Breastfeeding

Outcome: Infant adiposity (fat mass %)
Does overnutrition mediate environmental links?

- The association between perfluoroalkyl substances (PFAS) and neonatal adiposity mediated by maternal fasting glucose (Starling et al. 2017; *Environmental Health Perspectives*).
Translation of findings
Opportunities for intervention

• Nutrition:
  • Treatment or prevention of gestational diabetes (Ritchie et al. 2019 *Clinical Diabetes*; Gillman et al. 2010 *Diabetes*)

• Environmental Health:
  • Smoking cessation efforts

• Community interventions:
  • Examples: Pest management, organically grown food, “natural” beauty/cleaning products (Brenner and Galvez, in *Endocrine Disrupting Chemicals*)
Opportunities for policy: Environmental health

- Air pollution:
  - EPA Air Quality Standards (Ozone, PM$_{2.5}$, NO$_2$, CO, Pb)
  - Reducing indoor exposures (cooking, carpeting, pets)

- Smoking:
  - Smoke-free policies
  - Tobacco taxes
  - Stronger warning labels
Opportunities for policy: Environmental health

- Perfluoroalkyl Substances (PFAS):
  - Voluntary phase out in 2006
  - Persistent in the environment (water) and human bodies
    - Half-life is 2-5 years (5 half-lives for complete removal)
  - “GenX” chemicals – less environmentally persistent
Future directions
Lifecourse approach

- Exposures during pregnancy, infancy, childhood, etc.
  - Windows of susceptibility
  - Accumulation of risks over one’s life
- Effect modification, mediation, and multi-pollutant/mixture models
The exposome

Adapted from Vrijheid 2014, Thorax
The exposome

Lifestyle

Physical/chemical environment

Social environment

Internal environment

Transcriptomics
Proteomics
Metabolomics

Neurodevelopment

Obesity and other cardiometabolic outcomes

Respiratory outcomes

- Cancers
- Infectious diseases
- Reproductive health

Adapted from Vrijheid 2014, *Thorax*
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