Perinatal Nutrition and Environmental Exposures: Effects on Metabolic Homeostasis and the Epigenome

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University of Michigan School of Public Health

PEPH Webinar
Diet, Nutrition, and Environmental Public Health
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Overview

- **Brief Introduction:** Environmental & Nutritional Epigenetics & the Developmental Origins of Health and Disease

- **Conceptual Framework of U-M Children’s Environmental Health Center:** Focus on Nutrient-Toxicant Interactions & Combines Animal Model and Human Population Approaches

- **Perinatal Exposures and Epigenetic Effects:**
  - **(A) Diet matters** (mitigate and exacerbate toxicant effects)
  - **(B) Lifecourse matters** (epigenetic drift with age)
  - **(C) Future generations matter** (Somatic vs germline vs transgenerational)
A Tail of Two Mice
- or -
Why DNA is Not (Necessarily) Your Destiny
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

J. D. Watson
F. H. C. Crick

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.
April 2.
The Epigenome

Reading the chart
The outer ring represents 35 million base pairs in Chromosome 22. Orange marks highlight areas of the chromosome that were tested for CpG methylation in a pilot study by the Human Epigenome Project.

Measuring CpG methylation
Bar charts indicate the average amount of CpG methylation found within the tested areas. Each chart covers 100,000 base pairs. Some charts have been shifted, shown with connecting lines.

AMOUNT OF METHYLATION
- 0 to 20%
- 20 to 80%
- 80 to 100% of CpG sites
The Agouti Sisters
Epigenetic Switches

The two main components of the epigenetic code:

**DNA methylation**
Methyl marks added to certain DNA bases repress gene activity.

**Histone modification**
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
Bisphenol A (BPA)

courtesy of NIH
From Mice to People
A\textsuperscript{vy} Mouse Model

Population-based Birth Cohorts and prospectively collected samples

Perinatal Bisphenol A (BPA) Exposure, Epigenetics, and Metabolic Homeostasis

Perinatal Lead (Pb) Exposure, Epigenetics, Metabolic Homeostasis, and Adult Neuropathology

Perinatal Exposures & Life Course Follow-up
Dietary Assessment
Epigenetic Drift with Age
Tissue and Cell Specific Epigenetic Alterations
(A) Diet Matters: Maternal Supplementation Counteracts BPA

Dolinoy et al PNAS 2007
Bernal and Jirle Birth Def Res 2010
<table>
<thead>
<tr>
<th>Chow Ingredients</th>
<th>Control</th>
<th>Mediterranean</th>
<th>Western</th>
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<tbody>
<tr>
<td>Kcal/g Diet</td>
<td>3.98</td>
<td>4.53</td>
<td>4.72</td>
</tr>
<tr>
<td>% Calories from Fat</td>
<td>16%</td>
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<td>40%</td>
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<td>PUFA:SFA:MUFA</td>
<td>1 : 0.2 : 0.5</td>
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Lipid composition and type of carbohydrate were altered and protein kept constant.

Vitamins and minerals were altered to mimic human HFDs

Med diet based on human Cretan diet (Kafatos et all 2000 *JADA*) and Western chow was based on US. Junk food diet (USDA 2012)
(A) Diet Matters: Maternal Diet and Epigenetics in Humans


Waterland RA. et al *PLoS Genetics* 2010

Dominguez-Salas P. et al *Nature Communications* 2014
Gametogenesis

Pre-implantation stage of embryogenesis

Fetal/neonatal development

Puberty

Old age

Jirtle and Skinner *Nature Reviews Genetics* 2007
(B) Lifecourse Matters: Perinatal Lead (Pb) Exposure and Coat Color

Coat Color Distribution by Treatment

- **Avy Pups**
  - Pseudo Agouti
  - Heavily Mottled
  - Mottled
  - Slightly Mottled
  - Yellow

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>0 ppm</th>
<th>3.7 ppm</th>
<th>27 ppm</th>
<th>55 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avy Pups</td>
<td>39</td>
<td>43</td>
<td>48</td>
<td>42</td>
</tr>
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</table>

n= 39 43 48 42
Body weight was higher at weaning and persisted across lifespan in the males exposed to Pb perinatally.
(B) Lifecourse Matters: Perinatal BPA and Physical Activity

**Horizontal Activity**
- **Female:**
  - Control: Blue square (p=0.04)
  - ng: Red square (p=0.05)
  - ug: Green triangle (p=0.02)
  - mg: Purple x (p=0.001)
- **Male:**
  - Control: Blue square (p=0.05)
  - ng: Red square (p=0.007)
  - ug: Green triangle (p=0.01)
  - mg: Purple x (p=0.001)

**Vertical Activity**
- **Female:**
  - Control: Blue square (p=0.06)
  - ng: Red square (p=0.05)
  - ug: Green triangle (p=0.06)
  - mg: Purple x (p=0.01)
- **Male:**
  - Control: Blue square (p=0.01)
  - ng: Red square (p=0.01)
  - ug: Green triangle (p=0.001)
  - mg: Purple x (p=0.004)

Anderson et al. FASEB 2013
(B) Lifecourse Matters: Perinatal BPA and Liver Tumors

Percentage of animals with neoplastic and pre-neoplastic lesions

* p<0.05 on exact test and test of trend

Low dose incidence of multinucleated hepatocytes

(non-significant)
(B) Life Course Matters
Early Life Pb Exposure and Epigenetic Drift in the ELEMENT Cohort

Cord Blood DNA
N=76

Venous Blood DNA
N=246

Pb Biomarkers*

* M=maternal (blood during pregnancy, tibia and patella Pb at 1 month PP)
C=children (cord blood at birth, venous blood for the rest)
Adjusted for gestational age, gender, maternal folate intake in linear regression model:

Beta = -0.02 (p = 0.04)

LINE-1 methylation decreases by 0.02% per each µg/g maternal patella Pb
(C) Future Generations Matter:

Inter- or Multi-generational (F1, F2)

Transgenerational (F3 or beyond)

http://www.germlineexposures.org

http://www.germlineexposures.org


PLoS ONE 2010; Anway et al 2005
Science; Anway et al 2006
Endocrinology
Perinatal Exposures
- Metal mixtures
- Endocrine disruptors
- Diet

Child Exposures
- Metal mixtures
- Endocrine disruptors

Adolescent Exposures
- Metal mixtures
- Endocrine disruptors
- Diet

Epigenetic Regulation
- Target versus bioavailable tissues
- Longitudinal change

Infant Health Outcomes
- Metabolic Abnormalities
- Insulin/glucose ratio
- Lipid levels, inflammation
- Body weight

Child Health Outcomes
- Metabolic Abnormalities
- Insulin resistance
- Lipid levels, inflammation
- Body weight & composition
- Hyperadrenergia

Adolescent Health Outcomes
- Metabolic syndrome
- Insulin resistance
- Lipid levels, inflammation
- Blood pressure
- Body weight & composition
- Hyperadrenergia
- Sexual maturation

University of Michigan Children’s Environmental Health Center
Conceptual Framework – Obesity and Metabolic Syndrome Risk
P01 Children’s Environmental Health & Disease Prevention Center

University of Michigan

- Karen E. Peterson (contact PI, Project 2 Co-PI), Vasantha Padmanabhan (co-PI, Project 2 Co-PI), Dana Dolinoy (Project 3 PI), John Meeker (Project 1 PI), Peter Song, Howard Hu, Joyce Lee, Subramaniam Pennathur, Brisa Sanchez, Maureen Sartor, Almudena Veiga Lopez

- Post Doctoral Fellows: Christopher Faulk, Jaclyn Goodrich, Deborah Watkins

- Doctoral and Masters Students (previous and current): Olivia Anderson, PhD, Lauren Johns, Kelly Ferguson, PhD, Joseph Kochmanski, Ryan Lewis, Yun (Jamie) Liu, Lisa Marchlewicz, Carly McCabe, Meghan Moynihan, Kari Neier, Matthew Savidge, Monica Silver, Lu Tang, Zhenzhen Zhang, Tiffany Yang, PhD

- Tamara Jones, Lead Technician and Program Manager, Dolinoy Lab

- Samantha Milewski, Clinical Research Coordinator, Padmanabhan Lab

- Seema Jolly, Environment and Nutrition Research Manager

- Undergraduate Students: Amanda Barks, Maxwell Scherer, John Francis

Mexico

- Instituto Nacional de Salud Pública (INSP): Martha Maria Tellez Rojo (Subaward PI), INSP Field Staff

- Instituto Nacional de Perinatología (INP): Lourdes Schnaas (Co-Investigator)

Yale Schools of Medicine and Public Health: Adrienne Ettinger (Subaward PI)

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(A) Diet Matters:
BPA + High Fat Diets: Humanized Diets

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<tr>
<td><strong>MACRONUTRIENTS</strong></td>
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<td>Kcal/g Diet</td>
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<td><strong>VITAMINS &amp; MINERALS</strong></td>
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</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>4000</td>
<td>8000</td>
<td>4000</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>0</td>
<td>500</td>
<td>0</td>
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<tr>
<td>Vitamin D (IU)</td>
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<td>400</td>
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<tr>
<td>Vitamin E (IU)</td>
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<td>25</td>
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<tr>
<td>Folic Acid (mg)</td>
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<td>4</td>
<td>1</td>
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<tr>
<td>Sodium (mg)</td>
<td>1039</td>
<td>1039</td>
<td>7000</td>
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<tr>
<td>Potassium (mg)</td>
<td>3600</td>
<td>8000</td>
<td>3600</td>
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<tr>
<td>Magnesium (mg)</td>
<td>513</td>
<td>850</td>
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- Lipid composition and type of carbohydrate were altered; protein was kept constant. Vitamins & minerals were altered to mimic the human HFDs.

- Mediterranean HFD chow was based on the human Cretan diet [Kafatos et al. 2000. *JADA*. 100:1487-1493].

- Western HFD chow was based on the US junk food diet [USDA 2012].