Developmental Origins of Health and Disease
Roles of Maternal Nutrition

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Thanks to...

Faculty, Trainees, & Staff

Obesity Prevention Program
Department of Population Medicine
Harvard Medical School/Harvard Pilgrim Health Care Institute
Today

• DOHaD concepts
• What is fetal nutrition?
  • Maternal diet is 1 element
• Does maternal diet predict offspring health?
  • Focus on fish and Hg
• What we can do about it
Developmental Origins of Health and Disease

• DOHaD emphasizes prenatal period and early childhood as important periods for development of chronic disease throughout life
Developmental Origins Research

• In animal models, perinatal nutritional programming of adult obesity-related outcomes goes back decades

• Programming
  – Perturbation at a critical period of development causes alterations with lifelong, sometimes irreversible consequences
Animal studies showed early energy intake can permanently program body size.

21 days: Weights 14g, 60g

Widdowson and McCance, 1960

75 days: Weights 86g, 230g
Animal studies showed early energy intake permanently programs body size.

Food restriction just during weeks 0-3 results in sustained lower body weight.

21 day period of food restriction

Widdowson & McCance, 1960
Timing is important

Later food restriction (weeks 9-12) – rats quickly regain and perhaps overshoot body weight

21 day period of food restriction
Why Early Intervention Makes Sense

Godfrey et al., Trends Endocrinol Metab 2010; 21:199-205
Time Scales of Adaptive Processes

<table>
<thead>
<tr>
<th>Ecological cycle duration</th>
<th>Adaptation</th>
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<tbody>
<tr>
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<td>Process</td>
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<tr>
<td>0.000000001 years</td>
<td>seconds</td>
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<tr>
<td>0.0001</td>
<td>hours</td>
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<tr>
<td>0.001</td>
<td>days</td>
</tr>
<tr>
<td>0.1</td>
<td>months</td>
</tr>
<tr>
<td>1</td>
<td>years</td>
</tr>
<tr>
<td>10</td>
<td>decades</td>
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<tr>
<td>100</td>
<td>centuries</td>
</tr>
<tr>
<td>1000</td>
<td>millennia</td>
</tr>
<tr>
<td>10000000</td>
<td>millions</td>
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</tbody>
</table>

- **Mode**: Physiologic
- **Process**: Homeostasis & Allostasis
- **Mode**: Developmental
- **Process**: Plasticity
- **Mode**: Intergenerational
- **Process**: Inertia
- **Mode**: Genetic
- **Process**: Natural selection

Hanson M A, and Gluckman P D Physiol Rev 2014;94:1027-1076
DOI: 10.1159/000356448

Appreciating David Barker (1938–2013)

Matthew W. Gillman\textsuperscript{a, b} Vincent W.V. Jaddoe\textsuperscript{c}
Birthweight and CVD Outcomes
Nurses’ Health Study

Curhan et al., Rich-Edwards et al.
Animal studies of energy and macronutrient restriction and supplementation

+ Human studies of birth weight

→ Focus on fetal nutrition (under-, then over-)
Reminders

Fetal Nutrition $\neq$ Birth Weight

$\Delta$ birth weight is a byproduct of some pathways
Maternal Nutrition ≠ Fetal Nutrition
The entire supply line

Mom’s own intrauterine and childhood experiences
Mom’s peri-conceptional health
Diet during pregnancy
Utero-placental blood flow, placental function
Fetal metabolism
Reminders

Maternal Diet ≠ Maternal Nutrition

- Weight status
  - Pre-pregnancy BMI
  - Gestational weight gain
- Body composition
- Biomarkers
  - Nutrient (or toxicant) levels in
    - Blood
    - Urine, fat, nails, hair, …
PATHOPHYSIOLOGICAL NON-ADAPTIVE PROCESSES IN DEVELOPMENTAL DISRUPTION

Evolutionarily novel or severe challenges:
- Maternal overnutrition
- Parental obesity
- High gestational weight gain
- GDM
- Pre-eclampsia
- Preterm birth
- IUGR
- Type 1 or 2 diabetes
- Cardiovascular disease
- Smoking
- Exposure to toxins, EDCs
- Severe stress
- Infant overfeeding

Teratogenesis

or

Congenital defects, perinatal death

Immediately adaptive response

Reduced organ growth
Reduced physiological function

PATHOPHYSIOLOGICAL PROCESSES (EPIGENETIC & NON-EPIGENETIC)

Trade-offs/ coping response
Challenged survival to reproduce, health, longevity, transgenerational effects

Hanson and Gluckman. Physiol Rev 2014;94:1027-1076
What is Maternal Diet?

• What mothers ingest
  – Food
  – Supplements?
  – Toxins?
What is Maternal Diet?

• What mothers ingest
• When they eat
  – Long before pregnancy
  – Around conception
  – Early, mid, late pregnancy
What is Maternal Diet?

• What mothers ingest
• When they eat
• How we assess diet

• Features of diet
  – Energy, e.g., famine
  – Macronutrients—protein, carbohydrate, fat (fatty acids)
  – Micronutrients, e.g., vitamin D
  – Single foods, e.g., milk
  – Food groups, e.g., fish
  – Dietary patterns, e.g., Mediterranean diet
What is Maternal Diet?

• Features of diet
  – Energy
  – Macronutrients
  – Micronutrients
  – Single foods
  – Food groups
  – Dietary patterns
  – Supplements, e.g., DHA
  – Food-borne toxins, e.g., Hg
  – Additives, e.g., aspartame
What is Maternal Diet?

• Features of diet

• Determinants of intake
  – Social ecological model
    • Individual, family, community, ..., policy
  – Pregnancy-specific
    • Nausea/vomiting
    • Cravings/aversions
  – Environmental
    • Flour folate fortification
    • Policies, e.g., fish warnings
Mothers' postnatal diet

Fetal metabolic and endocrine status
Nutrients in fetal blood stream
Fetal body size and composition
Placental transfer/function
Nutrients in maternal blood stream
Mobilisation of tissue stores and physiological adaptation
Mother's metabolic and endocrine status
Mother's body size and composition
Change in infant metabolic capacity (development)
Change in infant body size and body composition (growth)

Infants' diet
Environmental Stressors (e.g., passive smoking, psychological or social stresses etc)
Genetic influences

Mothers' diet
Environmental Stressors (e.g., smoking, psychological or social stresses etc)
Genetic influences

DISEASE RISK
Example

Fish intake during pregnancy
Fish intake during pregnancy

• What is the balance of nutritional benefit and toxic harm from eating fish during pregnancy on offspring outcomes?
  – Cognition
  – Obesity and cardiovascular risk

• Can we avoid the harms with fatty acid supplements?

• How could women choose the right fish to eat?

• Could we intervene to increase intake of those fish?
Associations of maternal 2\textsuperscript{nd} trimester fish intake and erythrocyte mercury levels with child cognitive test results at age 3 years

Effect estimates adjusted for each other plus parent and child characteristics

Oken et al., Am J Epidemiol 2008;167:1171-81
Prenatal long-chain n-3 fatty acid status inversely associated with early childhood adiposity

Donahue et al, Am J Clin Nutr 2011
No association of maternal blood Hg, or intake of n-3 fatty acids or fish, with child BP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Childhood (n=1031)</td>
</tr>
<tr>
<td>Mothers</td>
<td></td>
</tr>
<tr>
<td>2nd trimester erythrocyte mercury, ng/g</td>
<td></td>
</tr>
<tr>
<td>First quartile</td>
<td>0.0 (ref)</td>
</tr>
<tr>
<td>Second quartile</td>
<td>1.1 (−0.9 to 3.0)</td>
</tr>
<tr>
<td>Third quartile</td>
<td>1.5 (−0.4 to 3.5)</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>1.3 (−0.5 to 3.2)</td>
</tr>
<tr>
<td>2nd trimester DHA+EPA intake, gm/day</td>
<td>1.8 (−2.4 to 6.0)</td>
</tr>
<tr>
<td>2nd trimester fish intake, servings/week</td>
<td>0.00 (−0.5 to 0.5)</td>
</tr>
</tbody>
</table>
Omega-3 Fatty Acids and Offspring Adiposity
How good is the evidence from human RCTs?

• 3 studies fit selection criteria
  – Wide variation in study design, dose of n-3 LCPUFA and timing and duration of intervention
  – Issues with study quality
    • high attrition
    • concealment of allocation unclear
  – Disparate results
    • increase, decrease no, change

Muhlhausler et al, AJCN, 2010
Fish oil RCT in late pregnancy  
No effect on adiposity or cardio-metabolic outcomes at 19 y

### TABLE 4
Differences in BMI and waist circumference in the fish-oil (FO) and no-oil (NO) groups relative to the olive oil group

<table>
<thead>
<tr>
<th></th>
<th>Crude(^1) (n = 243)</th>
<th>Adjusted(^2) (n = 219)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FO (n = 243)</td>
<td>NO (n = 219)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>(-0.15 (-1.24, 0.93))</td>
<td>(-0.24 (-1.35, 0.87))</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>(-0.3 (-3.2, 2.6))</td>
<td>(0.3 (-2.6, 3.1))</td>
</tr>
<tr>
<td></td>
<td>(0.13 (-0.92, 1.17))</td>
<td>(0.02 (-1.15, 1.19))</td>
</tr>
<tr>
<td></td>
<td>(0.7 (-2.1, 3.4))</td>
<td>(1.6 (-1.5, 4.7))</td>
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### TABLE 5
Relative differences in concentrations of biochemical variables in the fish-oil (FO) and no-oil (NO) groups relative to the olive oil group

<table>
<thead>
<tr>
<th></th>
<th>Crude(^3) (n = 243)</th>
<th>Adjusted(^4) (n = 219)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>FO (n = 243)</td>
<td>NO (n = 219)</td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>(4 (-10, 20))</td>
<td>(6 (-10, 24))</td>
</tr>
<tr>
<td>Blood glucose (%)</td>
<td>(1 (-2, 4))</td>
<td>(2 (-1, 5))</td>
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<tr>
<td>Hb A(_1c) (%)</td>
<td>(-1 (-3, 0))</td>
<td>(-2 (-3, 0))</td>
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<tr>
<td>HOMA-IR (%)(^5)</td>
<td>(5 (-10, 21))</td>
<td>(8 (-9, 27))</td>
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<tr>
<td>Leptin (%)</td>
<td>(23 (-13, 75))</td>
<td>(36 (-8, 102))</td>
</tr>
<tr>
<td>Adiponectin (%)</td>
<td>(8 (-3, 20))</td>
<td>(3 (-9, 16))</td>
</tr>
<tr>
<td>IGF-I (%)</td>
<td>(-4 (-10, 3))</td>
<td>(-1 (-8, 8))</td>
</tr>
<tr>
<td>hs-CRP (%)</td>
<td>(43 (-4, 112))</td>
<td>(23 (-21, 94))</td>
</tr>
</tbody>
</table>

Conclusion: The evidence does not conclusively support or refute that omega-3 LCPUFA supplementation in pregnancy improves cognitive or visual development. Am J Clin Nutr 2013;97:531–44.

The effect of maternal omega-3 (n−3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials1−3

Jacqueline F Gould, Lisa G Smithers, and Maria Makrides
Interventions
Maternal Diet During Pregnancy

• Nutrient supplements—often default
  – Analogy to drug trials
  – Single nutrient trials in adults disappointing

• Back to Foods
  – Fish has multiple potential beneficial nutrients
  – Allows for multiple behavior change approaches
  – But...
    • Feasible?
Behavior Change Interventions

• Behavior is not easy to change
…especially if this is your environment…
Behavior Change Interventions
In Pregnancy

• Some advantages
  – Women may be willing to change behavior
Fish Intake in Pregnancy Before and After National Hg Warnings

Oken et al., Obstet Gynecol 2003
For shame! pregnant + eating fish?! Think of the baby!
A Randomized Trial of Fish Consumption During Pregnancy

Oken et al, Nutr J 2013;12:33
A Randomized Trial of Fish Consumption During Pregnancy

Nuanced advice to promote consumption of low-Hg, high-DHA fish

Oken et al, Nutr J 2013;12:33
Food for Thought

• Study Population
  – Women living in greater Boston, MA area
  – 12-22 weeks gestation, singleton pregnancy
  – Consuming <=2 monthly servings of fish
  – Willing to eat fish (e.g. not allergic, not vegetarian)

• Study Design
  – Random allocation:
    Arm 1: \textbf{(Education, n=20)} Health benefits of DHA and information on low-mercury, high DHA fish
    Arm 2: \textbf{(Education + GC, n=20)} Education plus $10/week Whole Foods Gift Cards (GC) to purchase fish
    Arm 3: \textbf{(Control, n=21)} General healthful habits and diet (not fish)
  – Women blinded to study’s focus on fish
  – Survey 31 types of fish/shellfish at baseline & follow-up (12 wk)
### Eat Fish

**for a healthy pregnancy and a healthy baby**

While you are pregnant and nursing, **avoid eating these fish, because they have high levels of mercury and other contaminants:**
- king mackerel
- swordfish
- shark
- tilefish (from the Gulf of Mexico)
- raw or uncooked fish
- raw or uncooked shellfish
- tuna steak

- freshwater fish caught in streams, rivers, lakes, and ponds in Massachusetts
- lobster caught in New Bedford Harbor
- bluefish caught off the Massachusetts coast
- lobsters, flounder, soft-shelled clams, and bivalves from Boston Harbor

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### These Fish

**all have DHA and are low in mercury**

- salmon (farm raised, wild caught, or canned)
- whitefish/walleye
- herring
- anchovies (canned)
- trout (farm raised)

**ONE 6-ounce serving** of these fish each week will give you the recommended weekly amount of DHA:

- atlantic mackerel
- sardines (canned)
- trout (wild caught)
- mussels
- pollock
- salt cod/bacalao

**TWO 6-ounce servings** (12 ounces total) of these fish each week will give you the recommended weekly amount of DHA:

- squid/calamari
- ocean perch
- flatfish
- flounder
- sole

**THREE 6-ounce servings** (18 ounces total) of these fish each week will give you the recommended weekly amount of DHA:

- whiting
- scallops
- octopus
- haddock
- cod
- clams
- shrimp
- tilapia
- catfish
- eel
- crayfish
- crab (includes imitation crab)

These fish have less DHA, but they are still a good source of protein and other nutrients:

If you eat tuna, choose chunk light tuna.

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For more information, please contact us:

Email: FoodForThought@harvardpilgrim.org
Phone: (617) 509-9903
Results

Increased fish and DHA intake

No change in Hg intake

(No changes in blood DHA or Hg)

Oken et al, Nutr J 2013;12:33
Food for Thought

• Pilot RCT
• Intake:
  – Increased fish
  – Increased DHA
  – Did not increase Hg
→ favorable nutritional/toxicant balance
Should we advise pregnant women to eat fish?

• If so,
  – How much?
  – Which types?
  – How strong is the evidence?
• If not fish, what?
Why is this question so complex?

• 4 major perspectives have influenced fish consumption advice:
  – Nutritional benefits, toxicant risks, ecologic concerns, economic influences

• Complexities include:
  – Within each one, uncertainty exists
  – Different perspectives often in conflict
  – Previous advice (often from 1 perspective) has had unintended, adverse consequences
<table>
<thead>
<tr>
<th>Source</th>
<th>Target population</th>
<th>Contaminant exposure</th>
<th>Fatty acid/nutrient intake</th>
<th>Ecological impact</th>
<th>Economic influences</th>
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<tr>
<td>2004 FDA/EPA</td>
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<td>Monterey Bay</td>
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<td>Dietary Guidelines</td>
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<td>Fish for your health</td>
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<td>Blue Ocean Institute</td>
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<td>Kidsafe</td>
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<td>Fishwise</td>
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<td>Washington State DOH</td>
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<td>Food and Water Watch</td>
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<td>Mercury Policy Project</td>
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<td>National Geographic</td>
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<td>Greenpeace International</td>
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<td>NOAA</td>
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<td>Shedd Aquarium</td>
<td></td>
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</table>

Oken et al., Environ Health Perspect 2012; 120:790–798
What You Need to Know About Mercury in Fish and Shellfish

“Eat up to 12 ounces (2 average meals) a week of a variety of fish and shellfish that are lower in mercury.”

Maternal Nutrition Group
Recommendations for Fish Consumption During Pregnancy

“Consume a minimum of 12 ounces of seafood per week.”
Maternal Diet, Toxins, & DOHaD
The Future

• Etiology
  – Animal experiments
    • Attention to study design principles
    • Testing interventions suggested by human cohorts
  – Human cohorts
    • Testing exposures/pathways suggested by animal studies
    • Large sample sizes/pooling
    • Combining primary & secondary data
    • Exposure assessment
      – Biomarkers
      – Dietary toxins
Toxins in Maternal Diet

- Dietary assessment (e.g., FFQ)
- Foods or food groups
  - Database of toxin concentration in each food or food group
    - Sum of (intake X concentration) over all foods eaten for each individual
  - Regression (e.g., reduced rank regression) with blood levels of toxin
    - Sum of (intake X factor loading) over all foods eaten for each individual
Toxins in Maternal Diet

• Dietary assessment (e.g., FFQ)
• Foods or food groups
  – Database of toxin concentration in each food or food group
    • Sum of (intake X concentration) over all foods eaten for each individual
  – Regression (e.g., reduced rank regression) with blood levels of toxin
    • Sum of (intake X factor loading) over all foods eaten for each individual
    • Example: 604 pregnant women with both diet and dioxin blood levels
    • 13 food groups known to contain dioxin-like compounds
    • Dioxin-like activity via DR-CALUX®
    • RRR for factor loadings
    • Dioxin-diet score for each individual
Toxins in Maternal Diet

Higher dioxin-diet score associated with lower birth weight

Table 2

<table>
<thead>
<tr>
<th>Food groups</th>
<th>Dioxin-dietary pattern factor loadings</th>
</tr>
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<tbody>
<tr>
<td>Red meat</td>
<td>0.27</td>
</tr>
<tr>
<td>White meat</td>
<td>0.27</td>
</tr>
<tr>
<td>Processed meat</td>
<td>-0.14</td>
</tr>
<tr>
<td>Fatty-fish</td>
<td>0.27</td>
</tr>
<tr>
<td>Lean fish</td>
<td>0.35</td>
</tr>
<tr>
<td>Mix fish dishes</td>
<td>0.24</td>
</tr>
<tr>
<td>High-fat milk/yoghurt</td>
<td>-0.15</td>
</tr>
<tr>
<td>High-fat cheese</td>
<td>-0.54</td>
</tr>
<tr>
<td>Low-fat dairy</td>
<td>0.30</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.14</td>
</tr>
<tr>
<td>Butter</td>
<td>-0.10</td>
</tr>
<tr>
<td>Salty snacks</td>
<td>-0.25</td>
</tr>
<tr>
<td>Fast-food</td>
<td>0.16</td>
</tr>
<tr>
<td>Explained variation of dioxin-like activity in maternal blood (%)</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Table 4

Association between dioxin-diet score with gestational age and birth weight for pregnant women and their children in the NewGeneris project.
Maternal Diet, Toxins, & DOHaD
The Future

• Tradeoffs of benefit and risk
  – Simulation modeling

• Intervention
  – The “what” – for etiology, biology, and efficacy
  – The “how” – for effectiveness and implementation
  – Large/long enough for clinical outcomes

• Policy
  – Integration of etiology, tradeoffs, intervention

• Interdisciplinary