Examining a Developmental Approach to Childhood Obesity: The Fetal and Early Childhood Years

Theory to Policy

Matthew W. Gillman

IOM
26-27 February 2015
Thanks to...

Faculty and Trainees
Obesity Prevention Program

Department of Population Medicine
Harvard Medical School/Harvard Pilgrim Health Care Institute
Appreciating David Barker (1938–2013)

Matthew W. Gillman\textsuperscript{a, b}  Vincent W.V. Jaddoe\textsuperscript{c}
Theory…

Chronic disease risk vs. Life course

- No/late intervention
- With early intervention

Timely intervention

Plasticity

Inadequate response to new challenges

TRENDS in Endocrinology & Metabolism

Godfrey et al., Trends Endocrinol Metab 2010; 21:199-205
…to Health Policy

• To improve public health via government actions
  – National, state, local
  – Legislative, regulatory

• To improve individuals’ health via organization, financing and delivery of medical care services
  – “Health care policy”
Health policy
in DOHaD

• Health care policy a key piece of overall health policy
  – Pregnant women and infants see medical providers for routine care more often than in any other period of life course
Health policy in DOHaD—Examples

• Government policy
  – Cigarette tax, to reduce smoking in pregnancy
  – 60 min/d physical activity in child care centers

• Health care policy
  – Baby Friendly Hospital Initiative to promote breastfeeding initiation, duration, exclusivity
  – GDM screen & treat recommendations

• Mixture
  • IOM guidelines for gestational weight gain
Health policy
Role of Evidence

• To develop policies
• To evaluate policies
Health policy
Role of Evidence

• To develop policies
• To evaluate policies
If we have the wrong evidence

“Hey, I’m over here”
That’s more like it

- Pragmatics & Contingencies
- Experience & Expertise
- Judgement
- Lobbyists & Pressure Groups
- Evidence
- Habits & Tradition
- Resources
- Values and Policy Context

www.gsr.gov.uk
Steps in Developing Policy
Example from RWJF

- Identify the problem and promising solutions
- Design and conduct research and demonstration projects to fill gaps in evidence
- Evaluate demonstration projects
- Translate and synthesize information for policy-makers
  - Use strategic communications
- Engage strategic partners
- Build the capacity of individuals and institutions

Improving DOHaD Evidence for Policy Translation

- Etiology
- Prediction
- Risk/benefit analyses
- Interventions
- Long-term effects
- Policy Evaluation
Improving DOHaD Evidence for Policy Translation

• Etiology
  – Animal experiments could be more helpful
  – Better causal methods for observational studies
    • Role of epigenetics
  – Followup of RCTs

• Prediction

• Risk/benefit analyses

• Interventions

• Long-term effects

• Policy Evaluation
Animal Experiments
Could be more helpful
Animal Experiments
Could be more helpful

“People who live in glass houses should not throw stones”
Animal Experiments

- Exposures, timing, mechanisms, effects on outcomes
- Proved the programming principle
- So…
Whole Animal Experiments Should Be More Like Human Randomized Controlled Trials

Beverly S. Muhlhausler¹*, Frank H. Bloomfield²,³,⁴, Matthew W. Gillman⁵,⁶

• Often missing
  – Source population
  – Sampling frame, eligibility criteria
  – Recruitment/retention rates
  – Blinding
  – Intention to treat analyses
  – Attention to missing data
  – Cluster methods for litter size >1
Example

Maternal high-fat diet in Rodents
Animal models of maternal high fat feeding and offspring glycaemic control
(An effort at) a systematic review

- Few (11 of 1483) studies met criteria
- Among the 11, quality scores low (mean 57, 0-100 scale)
- Large variability
  - Maternal diet
    - Some hypocaloric, others hypercaloric, others not stated, none isocaloric
    - Wide range of fat and carbohydrate content
  - Different postnatal feeding regimens, age at outcome, outcome assessment
- Cannot summarize or meta-analyze results

Ainge et al., Int J Obes 2011; 5:325
Animal Experiments
How they could be more helpful

• Follow (as well as lead) the epidemiology
  – Pre-pregnancy obesity
  – Gestational weight gain
  – Low carbohydrate/high protein
  – Glycemic index/load
  – Vitamin D
  – Smoking
DOHaD Interdisciplinary Approach

Population-based Studies
- Cohort studies
- Randomized trials
- Biomarkers

Clinical Studies
- Tissue biopsies
- Molecular markers
- Small trials

Animal Models
- Physiology
- Metabolism
- Genetic Susceptibility
- Epigenetic mechanisms

In Vitro Studies
- Isolated tissue studies
- Molecular markers
- Epigenetic mechanisms

Thanks to Sue Ozanne
Animal Experiments

- Exposures, timing, mechanisms, effects on outcomes
- Systematic reviews, meta-analyses
  - Harmonizing interventions, measures across studies
  - Importance of publishing null results
- “Translating up”
# Human Population Studies

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Observational Studies (Cohort)</th>
<th>RCTs</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Many exposures</td>
<td>• Many exposures</td>
<td>• Minimize confounding</td>
<td>• Humans</td>
</tr>
<tr>
<td>• Dose, duration, timing</td>
<td>• Dose, duration, timing</td>
<td>• Most direct way to assess programming</td>
<td>• Many outcomes</td>
</tr>
<tr>
<td>• Can assess harm</td>
<td>• Can assess harm</td>
<td>• Can assess practice (effectiveness) as well as etiology (efficacy)</td>
<td></td>
</tr>
<tr>
<td>• Often more generalizable</td>
<td>• Often more generalizable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Observational Studies (Cohort)</th>
<th>RCTs</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Confounding</td>
<td>• Confounding</td>
<td>• ~Single dose, duration, timing</td>
<td>• Inadequate sample size, esp for interaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lack of generalizability (efficacy trials)</td>
<td>• Loss to followup</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Need for equipoise</td>
<td>• Information biases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cannot assess harm</td>
<td>• Shallow dive into mechanisms*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Expensive</td>
</tr>
</tbody>
</table>
Observational Cohort Studies
Tricks of the trade to overcome confounding

- Innovative study designs/analyses
  - Judicious multivariable analysis
  - Sib-pair design
  - Cohorts with different confounding structures
  - Comparing mother v. father effects
  - Long-term followup of RCTs
  - Mendelian randomization
  - Biomarkers—exposure/pathway/outcome
  - Quasi-experimental (interrupted time series)
Observational Cohort Studies
Tricks of the trade to overcome confounding

• Innovative study designs/analyses
  – Each has strengths and weaknesses
  – Together they form a basis for judging evidence
Example

Breastfeeding and child obesity
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Supports protective effect of breastfeeding?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster randomized controlled trial of breastfeeding promotion</td>
<td>Yes</td>
</tr>
<tr>
<td>Cohort studies, mostly White European descent</td>
<td>Three pooled meta-analyses of (dichotomous) obesity show modest associations, but limited confounder control</td>
</tr>
<tr>
<td>Cohort studies in developing countries and racial/ethnic minorities</td>
<td>No effects on anthropometric outcomes at 6.5 or 11.5 years of age, but observational data within the cohort show no (or slightly +) association</td>
</tr>
<tr>
<td>Sib-pair analyses in cohort studies</td>
<td>One individual-level meta-analysis of mean BMI shows no effect after confounding control, but limited number of studies with sufficient data</td>
</tr>
<tr>
<td>Comparison of cohorts with different confounding structure</td>
<td>Many are null, but in some misclassification of exposure may exist</td>
</tr>
<tr>
<td>‘Reverse causality?’</td>
<td>Three studies suggest effect, but low power</td>
</tr>
<tr>
<td>Biological effects of breast milk</td>
<td>One study suggests that confounding explains observed associations</td>
</tr>
<tr>
<td>Biological effects of formula</td>
<td>A few studies suggest this phenomenon, but could be in opposite direction to hypothesis</td>
</tr>
<tr>
<td>Behavioural effects of nursing</td>
<td>Conflicting data on adipokines</td>
</tr>
<tr>
<td>Ecological analysis</td>
<td>Breasftfeeding rates have gone up along with emergence of the obesity epidemic, but that does not rule out inverse individual-level effects</td>
</tr>
</tbody>
</table>

Summarizing evidence for and against the hypothesis that having been breastfed reduces the risk of obesity.
Table 1 The ‘2011 Scorecard’

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Supports protective effect of breastfeeding?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster randomized trial of breastfeeding promotion</td>
<td>No</td>
</tr>
<tr>
<td>Cohort studies, mostly European descent</td>
<td></td>
</tr>
<tr>
<td>Cohort studies in different countries and racial minorities</td>
<td></td>
</tr>
<tr>
<td>Sib-pair analyses in studies</td>
<td></td>
</tr>
<tr>
<td>Comparison of cohorts with different confounders</td>
<td></td>
</tr>
<tr>
<td>‘Reverse causality?’</td>
<td></td>
</tr>
<tr>
<td>Biological effects of breastfed infants</td>
<td></td>
</tr>
<tr>
<td>Ecological analysis</td>
<td></td>
</tr>
</tbody>
</table>

Summarizing evidence for and against the hypothesis that having been breastfed reduces the risk of obesity.
PROBIT

PROmotion of Breastfeeding Intervention Trial

A Cluster-Randomized Trial in the Republic of Belarus

Baby Friendly Hospital Initiative v. Usual Care

31 Maternity Hospitals and Affiliated Pediatric Practices
Breastfeeding Promotion Did Not Reduce Adiposity at 11.5 y

ITT analysis
31 clusters, 13,879 participants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Groups</th>
<th>Intervention (n = 7405)</th>
<th>Control (n = 6474)</th>
<th>Intraclass Correlation Coefficient</th>
<th>Difference, Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg(^b)</td>
<td>No. 7402 mean (95% CI)</td>
<td>7402 18.32 (18.25 to 18.39)</td>
<td>6464 18.05 (17.97 to 18.12)</td>
<td>0.01</td>
<td>0.19 (-0.09 to 0.46)</td>
</tr>
<tr>
<td>FMI, kg(^b)</td>
<td>No. 7342 mean (95% CI)</td>
<td>7342 3.40 (3.35 to 3.45)</td>
<td>6427 3.24 (3.19 to 3.29)</td>
<td>0.01</td>
<td>0.12 (-0.03 to 0.28)</td>
</tr>
<tr>
<td>FFMI, kg(^b)</td>
<td>No. 7348 mean (95% CI)</td>
<td>7348 14.92 (14.89 to 14.95)</td>
<td>6426 14.83 (14.80 to 14.87)</td>
<td>0.02</td>
<td>0.04 (-0.11 to 0.18)</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>No. 7345 mean (95% CI)</td>
<td>7345 17.38 (17.20 to 17.56)</td>
<td>6433 16.78 (16.59 to 16.97)</td>
<td>0.01</td>
<td>0.47 (-0.11 to 1.05)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>No. 7402 mean (95% CI)</td>
<td>7402 64.68 (64.50 to 64.87)</td>
<td>6471 64.77 (64.58 to 64.97)</td>
<td>0.09</td>
<td>0.30 (-1.41 to 2.01)</td>
</tr>
<tr>
<td>Triceps skinfold thickness, mm</td>
<td>No. 7399 mean (95% CI)</td>
<td>7399 13.62 (13.47 to 13.76)</td>
<td>6470 14.20 (14.05 to 14.36)</td>
<td>0.13</td>
<td>-0.07 (-1.71 to 1.57)</td>
</tr>
<tr>
<td>Subscapular skinfold thickness, mm</td>
<td>No. 7399 mean (95% CI)</td>
<td>7399 9.07 (8.95 to 9.19)</td>
<td>6470 9.16 (9.02 to 9.30)</td>
<td>0.03</td>
<td>-0.02 (-0.79 to 0.75)</td>
</tr>
<tr>
<td>IGF-I (z-score)(^c)</td>
<td>No. 6668 mean (95% CI)</td>
<td>6668 0.01 (-0.02 to 0.03)</td>
<td>5712 -0.01 (-0.03 to 0.02)</td>
<td>0.02</td>
<td>-0.02 (-0.12 to 0.08)</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>No. 7402 mean (95% CI)</td>
<td>7402 78.38 (78.20 to 78.56)</td>
<td>6471 77.38 (77.18 to 77.57)</td>
<td>0.03</td>
<td>0.82 (-0.20 to 1.84)</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>No. 7402 mean (95% CI)</td>
<td>7402 82.56 (82.42 to 82.70)</td>
<td>6471 83.73 (83.59 to 83.88)</td>
<td>0.25</td>
<td>-0.44 (-2.63 to 1.75)</td>
</tr>
<tr>
<td>Standing height, cm</td>
<td>No. 7403 mean (95% CI)</td>
<td>7403 150.39 (150.2 to 150.6)</td>
<td>6471 149.16 (149.0 to 149.4)</td>
<td>0.05</td>
<td>0.52 (-0.78 to 1.82)</td>
</tr>
<tr>
<td>Leg length, cm</td>
<td>No. 7395 mean (95% CI)</td>
<td>7395 72.01 (71.90 to 72.13)</td>
<td>6460 71.28 (71.17 to 71.40)</td>
<td>0.05</td>
<td>0.59 (-0.22 to 1.40)</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>No. 7402 mean (95% CI)</td>
<td>7402 53.61 (53.57 to 53.65)</td>
<td>6471 53.50 (53.46 to 53.54)</td>
<td>0.10</td>
<td>0.20 (-0.18 to 0.58)</td>
</tr>
<tr>
<td>Mid-upper arm circumference, cm</td>
<td>No. 7399 mean (95% CI)</td>
<td>7399 22.12 (22.05 to 22.18)</td>
<td>6467 21.95 (21.88 to 22.02)</td>
<td>0.03</td>
<td>0.19 (-0.19 to 0.57)</td>
</tr>
</tbody>
</table>

BMI ≥85th percentile\(^d\)                   |
- No. 1192 mean (95% CI)                     | 1192 16.1 (16.1)\(^e\)          | 910 (14.1)\(^e\)          | NA 1.18 (1.01 to 1.39)\(^f\)     |

BMI ≥95th percentile\(^d\)                   |
- No. 397 mean (95% CI)                      | 397 5.4 (5.4)\(^e\)            | 304 (4.7)\(^e\)           | NA 1.17 (0.97 to 1.41)\(^f\)     |

Martin et al., JAMA. 2013;309(10):1005-1013
Breastfeeding-Child Obesity

• Earlier studies suggested considerable protection
• More recent studies cast doubt
• PROBIT
  – Cluster RCT of BFHI policy
    • Examines effect of policy
    • Also good test of causality
Example

Epigenetics as a pathway biomarker
Novel Epigenomic Biomarkers of Prenatal Risk Factors and Childhood Obesity
Funded by NINR (PI: Baccarelli)
Prenatal Risk Factors, Epigenetics, and Childhood Obesity
Simplified

Exposures → Intermediate (surrogate) → Health Outcomes

Prenatal factors → DNA-Me → Adiposity, etc
Role of Epigenetics in Policy-Relevant Evidence

• Intermediate between pre-/peri-natal exposures and obesity-related outcomes
  – Surrogate outcome
    • Makes studies feasible
  – Elucidates mechanism
    • Biological plausibility for causation (AB Hill)
    • Rationale for primordial prevention
• Optimize socio-behavioral milieu starting at conception, or before
• Avoid maternal obesity, excess GWG, GDM, smoking, ….in the 1st place
• Not primarily a medical model
Role of Epigenetics in Policy-Relevant Evidence

• “Experiences get under the skin early in life in ways that affect the course of human development.”
  – “Epigenetic regulation is the best example of operating principles relevant to biological embedding [of societal influences].”
So I blame you for everything
- whose fault is that?
Role of Epigenetics in Policy-Relevant Evidence

• Epigenetics at the right “archeological” level to motivate how pre and perinatal factors cause obesity
  – Relatively easy to communicate from science to policy
Role of Epigenetics in Policy-Relevant Evidence

• Intermediate between pre-/peri-natal exposures and obesity-related outcomes
  – Surrogate outcome
  – Elucidates mechanism
  – *May* provide signatures for *prediction*
    • Risk stratification for “precision prevention”
    • But high bar for proof
      – Needs to have high Se/Sp, or improve AUC
      – Not just mildly elevated RR
    • A medical model
    • Drugs for pregnant women and infants??
Improving DOHaD Evidence for Policy Translation

- Etiology
- Prediction
- Risk/benefit analyses
- Interventions
- Long-term effects
- Policy Evaluation
Perspective

How Early Should Obesity Prevention Start?

Matthew W. Gillman, M.D., and David S. Ludwig, M.D., Ph.D.

Risk of obesity at age 7-10 y according to combinations of 4 pre/post-natal risk factors

Risk of obesity at age 7-10 y according to combinations of 4 pre/post-natal risk factors

Smoking + – – – – + + + – + + – + + +
Gest. weight gain – + – + – – + + + + – – + + + – +
Breastfeeding – – + – – + – – + + – – + + + – +
Sleep – – – – – – + – – – + – + + + – +
Prob. obesity 0.04 0.06 0.07 0.07 0.08 0.10 0.10 0.11 0.11 0.13 0.13 0.16 0.18 0.18 0.20 0.28
Pred. BMI-z 0.07 0.24 0.22 0.23 0.31 0.39 0.40 0.48 0.38 0.46 0.47 0.55 0.63 0.64 0.62 0.79
Pred. DXA % fat 23.2 23.0 24.5 24.1 24.4 24.0 24.2 25.4 25.7 25.3 25.3 25.5 25.2 26.6 26.5
Prevalence in this cohort 6.9% 10.4% 20.3% 0.2% 5.2% 26.6% 0.2% 5.6% 1.1% 7.2% 0.1% 3.5% 9.2% 0.3% 1.5% 1.9%

PAR% ~ 20-50%
Implication

• Multiple risk factor interventions in early developmental periods hold promise for preventing obesity and its consequences
  – Need to test with actual interventions
Prediction

• Can quantify overall potential benefit of intervening early

• Can distinguish most important determinants
  – May vary by population or subgroup
Improving DOHaD Evidence for Policy Translation

• Etiology
• Prediction
• Risk/benefit analyses
  – Multiple outcomes and/or multiple determinants
• Interventions
• Long-term effects
• Policy Evaluation
Example

Gestational weight gain
Gestational Weight Gain

• What is the optimal amount in the era of epidemic obesity?
• Important for updating guidelines
What is optimal GWG?
Short & long-term outcomes for both mother & child
Associations with different outcomes differ

<table>
<thead>
<tr>
<th></th>
<th>Shape of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>U-shape</td>
</tr>
<tr>
<td>SGA</td>
<td>Inverse</td>
</tr>
<tr>
<td>LGA</td>
<td>Direct</td>
</tr>
<tr>
<td>PPWR</td>
<td>Direct</td>
</tr>
<tr>
<td>Child obesity</td>
<td>Direct</td>
</tr>
</tbody>
</table>
Optimal GWG = Nadir of Each Curve

- **Obese:**
  - Average weight gain: \(-0.19\) kg/wk
  - Total weight gain over 40 weeks: \(-7.6\) kg

- **Normal weight:**
  - Average weight gain: \(0.28\) kg/wk
  - Total weight gain over 40 weeks: \(11.2\) kg

- **Overweight:**
  - Average weight gain: \(-0.03\) kg/wk
  - Total weight gain over 40 weeks: \(-1.2\) kg

**Oken et al., Am J Epidemiol 2009**
Example

Rapid Weight Gain in Infancy
Rapid weight gain & linear growth in infancy
Differing effects on obesity & neurodevelopment depending on gestational age

<table>
<thead>
<tr>
<th></th>
<th>Healthy AGA full term</th>
<th>Preterm</th>
<th>Full term SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear growth</td>
<td>Gain in WFL</td>
<td>Linear growth</td>
</tr>
<tr>
<td>Obesity/cardiometabolic risk</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Neurodevelopment</td>
<td>↔</td>
<td>↔</td>
<td>+</td>
</tr>
</tbody>
</table>

WFL = weight-for-length
↔ = no association
+ = positive association
? = insufficient evidence

*Gain in weight-for-length during NICU hospitalization associated with better neurodevelopment; weight-for-length gain after NICU discharge appears less important

Improving DOHaD Evidence for Policy Translation

• Etiology
• Prediction
• Risk/benefit analyses

• Interventions
  – Focus on implementation for effectiveness, sustainability, dissemination
  – Cluster RCTs

• Long-term effects
• Policy Evaluation
### Prevention Interventions
#### Cluster RCTs

<table>
<thead>
<tr>
<th>Name</th>
<th>Funder</th>
<th>Age</th>
<th>Setting</th>
<th>N</th>
<th>Status</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC Eat &amp; Run</td>
<td>NHLBI..</td>
<td>25 y +</td>
<td>HVMA</td>
<td>298</td>
<td>Completed</td>
<td>Interactive phone calls</td>
</tr>
<tr>
<td>Step Up, Trim Down</td>
<td>Industry</td>
<td>25-65 y</td>
<td>HVMA</td>
<td>100</td>
<td>Completed</td>
<td>Interactive website</td>
</tr>
<tr>
<td>EatSmart</td>
<td>RWJF..</td>
<td>18 y +</td>
<td>HVMA</td>
<td>501</td>
<td>Completed</td>
<td>Tailored diet</td>
</tr>
<tr>
<td>Healthy Directions-2</td>
<td>NCI</td>
<td>18 y +</td>
<td>HVMA</td>
<td>2400</td>
<td>Completed</td>
<td>Effectiveness &amp; sustainability</td>
</tr>
<tr>
<td>STAR</td>
<td>DHHS</td>
<td>6-12 y</td>
<td>HVMA</td>
<td>1400</td>
<td>Analysis</td>
<td>Health information technology</td>
</tr>
<tr>
<td>CORD</td>
<td>CDC</td>
<td>2-18 y</td>
<td>MA cities</td>
<td>2 cities</td>
<td>Recruiting</td>
<td>Whole-of-community</td>
</tr>
<tr>
<td>Obesity &amp; HIT</td>
<td>ADA</td>
<td>2-18 y</td>
<td>HVMA</td>
<td>~60K</td>
<td>Completed</td>
<td>Guideline adherence</td>
</tr>
<tr>
<td>High Five for Kids</td>
<td>NICHD</td>
<td>2-6 y</td>
<td>HVMA</td>
<td>500</td>
<td>Completed</td>
<td>Chronic Care Model</td>
</tr>
<tr>
<td>Parents &amp; Tots Together</td>
<td>HPHCF, AHA</td>
<td>2-5 y</td>
<td>CHCs</td>
<td>50</td>
<td>Follow-up</td>
<td>Parenting groups</td>
</tr>
<tr>
<td>Happy Homes</td>
<td>CDC</td>
<td>2-5 y</td>
<td>CHCs</td>
<td>120</td>
<td>Follow-up</td>
<td>TV, sleep, eating behaviors</td>
</tr>
<tr>
<td>Creciendo Sanos</td>
<td>NIH (Fogarty)</td>
<td>2-6 y</td>
<td>Mexico</td>
<td>500</td>
<td>Completed</td>
<td>Integrated clinical/child care sys</td>
</tr>
<tr>
<td>Baby NAP</td>
<td>NIDDK</td>
<td>0-2 y</td>
<td>MA child care</td>
<td>30 centers</td>
<td>Completed</td>
<td>Changes child care environment and (provider) behavior</td>
</tr>
<tr>
<td>1st Steps for Mommy/Me</td>
<td>RWJF, HPHCF</td>
<td>0-6 m</td>
<td>HVMA</td>
<td>84</td>
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<td>Dual focus moms &amp; infants</td>
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<td>LIMIT</td>
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<td>Follow-up</td>
<td>Limit GWG in ow/obese</td>
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<td>Kaiser NW</td>
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<td>Pregnancy &amp; postpartum</td>
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<td>HVMA</td>
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<td>Analysis</td>
<td>Prevent T2DM after GDM</td>
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Whole-of-community Approach to Obesity Prevention
Focus on environment & policy

Social Ecological Model – Influencers of Obesity

- Policy
  - Advocacy
  - Media

- Social Norms and Values

- Sectors of Influence
  - Food Systems
  - Built Environment
  - Transportation
  - Park & Recreation
  - Health Systems
  - Research & Education
  - Industry/Marketing

- Behavior Settings
  - Home
  - Early Childcare
  - School
  - Worksite
  - Community
  - Faith-Based Settings

- Families and Individuals

- Nutrition & Physical Activity
  - Attitudes, Beliefs and Behaviors


Courtesy Christina Economos
COMPACT
Childhood Obesity Models for Prevention and Community Transformation

Funded by NIH (NHLBI, OBSSR)
MPI: Gillman, Hammond
COMPACT

• “What works, for whom, and under what circumstances?”
  – For 0-5-year-olds

• Apply computational systems science modeling to whole-of-community interventions
  – 2 completed intervention studies, US and AU
  – 1 ongoing cluster RCT, AU
  – Design new intervention for under-5’s, US
Improving DOHaD Evidence for Policy Translation

• Etiology
• Prediction
• Risk/benefit analyses
• Interventions
• Long-term effects
  – Simulation modeling
• Policy Evaluation
Long-term effects

• What we want to know
  – Effectiveness
  – Safety
  – Costs
  – Cost-effectiveness

• How to integrate data from multiple sources?
Long-term effects

• What we want to know
  – Effectiveness
  – Safety
  – Costs
  – Cost-effectiveness

• How to integrate data from multiple sources?
  – Simulation modeling
Effectiveness and Cost-Effectiveness of Blood Pressure Screening in Adolescents in the United States

Y. Claire Wang, MD, ScD, Angela M. Cheung, MD, PhD, FRCPC, Kirsten Bibbins-Domingo, PhD, MD, Lisa A. Prosser, MS, PhD, Nancy R. Cook, PhD, Lee Goldman, MD, MPH, and Matthew W. Gillman, MD, SM
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Two-Stage Model Structure

Childhood to AGE 35 y
BP Tracking, Screening/Treatment

AGE 35 to death
CHD Policy Model
Apply to US Population

Baseline Cohort: 15 year-old U.S. Adolescents in 2000

Stage 1
AGE 15-35
BP Distribution/Tracking, Screening/Treatment

Stage 2
AGE 35-death
CHD Policy Model

Compare several screen-and-treat and population-wide strategies
Population-wide policy approaches are both more effective and less costly than screen & treat strategies.
Improving DOHaD Evidence for Policy Translation

- Etiology
- Prediction
- Risk/benefit analyses
- Interventions
- Long-term effects
- Policy Evaluation
  - Natural experiments
Fish Intake in Pregnancy Before and After National Hg Warnings

Oken et al., Obstet Gynecol 2003
Associations of Tobacco Control Policies With Birth Outcomes

Summer Sherburne Hawkins, PhD; Christopher F. Baum, PhD; Emily Oken, MD; Matthew W. Gillman, MD

**DESIGN, SETTING, AND PARTICIPANTS** Using a quasi-experimental approach, we analyzed repeated cross sections of US natality files with 16,198,654 singleton births from 28 states and Washington, DC, between 2000 and 2010.

**CONCLUSIONS AND RELEVANCE** Increases in the cigarette tax are associated with improved health outcomes related to smoking among the highest-risk mothers and infants. Considering that US states increase cigarette taxes for reasons other than to improve birth outcomes, these findings are welcome by-products of state policies.

Reducing Racial/Ethnic Disparities in Childhood Obesity
The Role of Early Life Risk Factors

CONCLUSIONS AND RELEVANCE  Racial/ethnic disparities in childhood adiposity and obesity are determined by factors operating in infancy and early childhood. Efforts to reduce obesity disparities should focus on preventing early life risk factors.

To achieve evidence-based policies (and their implementation)

• Animal studies
  – Consistent methods
  – Harmonization of designs/measures

• Human studies of etiology
  – Observational and intervention
  – Innovative designs/analyses
  – Compare/combine across studies
  – Can help with science-policy communication
    • Epigenetics
To achieve evidence-based policies (and their implementation):

• Prediction models
  – Potential intervention targets
  – [Risk stratification]

• Risk/benefit estimates
  – To inform guidelines

• Intervention
  – Beyond efficacy
  – Implementation

• Long-term simulation models
  – Including cost-effectiveness

• Evaluation of current policies
  – For impact
'Congratulations! It's an obesity-time bomb...'
Different Types of Evidence for Policy

- Experimental
  - Quasi-Experimental
  - Counterfactual

- Social Ethics
  - Public Consultation

- Cost-Benefit
  - Cost-Effectiveness
  - Cost-Utility
  - Econometrics

- Ethical Evidence

- Descriptive
  - Analytical Evidence

- Impact Evidence

- Attitudinal Evidence

- Statistical Modelling

- Implementation Evidence

- Multivariate Analysis

- Surveys
  - Admin Data
  - Comparative Qualitative

- Surveys Qualitative

www.gsr.gov.uk
A systematic review on animal models of maternal high fat feeding and offspring glycaemic control

Ainge et al., Int J Obes 2011; 5:325

<table>
<thead>
<tr>
<th>Inclusion</th>
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<tbody>
<tr>
<td>Maternal high fat diet (Fat content &gt; 30% of total energy content) intervention during gestation or gestation and lactation.</td>
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<tr>
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Eligibility criteria used to assess all articles throughout systematic search.

**Table 1** Eligibility criteria

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<tr>
<th>Search set</th>
<th>Results by database</th>
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<td>‘High fat-fed OR high fat diet OR dietary fats’</td>
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<tr>
<td>‘Fetal programming OR fetal development OR offspring’</td>
<td>58 430</td>
</tr>
<tr>
<td>‘Pregnancy OR gestation OR offspring’</td>
<td>656 188</td>
</tr>
<tr>
<td>‘Insulin resistance OR impaired glucose tolerance OR Type 2 diabetes’</td>
<td>61 539</td>
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<tr>
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</tr>
<tr>
<td>Electronic search result (including duplicates)</td>
<td>1483</td>
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</table>

Numerical results yielded for respective search engines.
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<tr>
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Numerical results yielded for respective search engines.

International Journal of Obesity
### Childhood BP Screening C-E Analysis

#### Summary of Analytic Approach

<table>
<thead>
<tr>
<th>Overall Approach</th>
<th>Model Phase 1</th>
<th>Model Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No Screening/Treatment</td>
<td>No Intervention, Individual-based Programs&lt;br&gt;- Weight loss&lt;br&gt;- Exercise&lt;br&gt;- Salt-reduction&lt;br&gt;- Treatment if secondary causes/LVH</td>
<td>CHD Outcome (35 y to death, CHDPM)&lt;br&gt;CHD events&lt;br&gt;Deaths (CHD &amp; non-CHD)&lt;br&gt;Costs&lt;br&gt;Quality-adjusted Life Years (QALYs)</td>
</tr>
<tr>
<td>2. Screen-and-Treat&lt;br&gt;Universal Screening (2a-2f)&lt;br&gt;Selective Screening (Overweight only, 2g-2i)</td>
<td>Policies&lt;br&gt;- Increase PE classes&lt;br&gt;- Salt reduction campaign</td>
<td>After 35 y</td>
</tr>
<tr>
<td>3. Population-wide&lt;br&gt;Treat all overweight (3a-3c)&lt;br&gt;Treat all (3d, 3e)&lt;br&gt;Population-wide policy (3f, 3g)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adolescence (15y) to Young Adulthood (35y)**

- BP Outcome (15 y to 35y): No effect on BP (Natural History), Reduced mean diastolic BP at age 35
Wide range of both fat and carbohydrate

Table 6  Study and maternal diet summary

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Species</th>
<th>n</th>
<th>Diet Ref</th>
<th>P</th>
<th>C</th>
<th>F</th>
<th>Fat Type</th>
<th>E (kJ/g)</th>
<th>Diet Ref</th>
<th>P</th>
<th>C</th>
<th>F</th>
<th>E (kJ/g)</th>
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<td>Saturated Animal fat - Oleic acid (n-9 fatty acid)</td>
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<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>23</td>
<td>2009</td>
<td>SD</td>
<td>42</td>
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<td>20</td>
<td>20</td>
<td>60</td>
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<td>17</td>
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<tr>
<td>24</td>
<td>2008</td>
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<td>14</td>
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<td>Saturated animal</td>
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<td>16% protein rodent diet: Harlan Teklad, Madison, WI Details Storlien, L.H (1991)</td>
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<td>26</td>
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<td>Product no. F3282 Bioserve, French Town, NJ Details Storlien, L.H (1991)</td>
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<td>24</td>
<td>60</td>
<td>Saturated fat (palm oil)</td>
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<td>omega 6 PUFA — safflower oil</td>
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<td>1995</td>
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<td>Modified AIN—76 Diet</td>
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<td>Purina Lab. Chow no. 5002 Ralston Purina, St Louis, MO.</td>
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Abbreviations: C, % carbohydrate; E, total dietary energy (kJ/g); F, % fat; HFD, high-fat fed; n, number of pregnancies; P, % protein; SD, Sprague-Dawley; WS, Wistar; (---), not recorded. Summary of study design protocols and maternal experimental HFD and control diets. The bolded column represents % fat.
Some hypocaloric, others hypercaloric, others not stated, none isocaloric

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<th>Reference</th>
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Different postnatal feeding regimens, age at outcome, outcome assessment → Disparate results, cannot summarize

Table 8  Offspring outcomes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cr</th>
<th>D</th>
<th>BWt</th>
<th>WWt</th>
<th>CWt</th>
<th>Cull Age</th>
<th>BC</th>
<th>FPL</th>
<th>FBG</th>
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<th>Method</th>
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<tr>
<td>22</td>
<td>1 F</td>
<td>↓6</td>
<td>↑14</td>
<td>NS</td>
<td>PND 175</td>
<td>↑†</td>
<td>↑†</td>
<td>NS</td>
<td>↑†</td>
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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>23</td>
<td>1 F</td>
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<td>↑</td>
<td>↑↑</td>
<td>PND 21</td>
<td>↑*</td>
<td>↑↑</td>
<td>↑</td>
<td>▲</td>
<td>▲</td>
<td>▲</td>
<td>OGTT</td>
<td>↑, Glucose response</td>
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<tr>
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<td>NS</td>
<td>↑43</td>
<td>↑43</td>
<td>PND 20</td>
<td>↑*</td>
<td>↑501</td>
<td>NS</td>
<td>↑132</td>
<td>IPGTT</td>
<td>↑, Glucose response</td>
<td>PND 20</td>
<td></td>
</tr>
<tr>
<td>25</td>
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<td>NS</td>
<td>↓27</td>
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<td>11</td>
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<td>NS</td>
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<td>NS</td>
<td>PND 90</td>
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<td>↑</td>
<td>↑14</td>
<td>↑74</td>
<td>—</td>
<td>↑33</td>
<td>PND 120</td>
<td>↑, Glucose response</td>
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<tr>
<td>12</td>
<td>1 NA</td>
<td>NS</td>
<td>NA</td>
<td>NS</td>
<td>PND 1</td>
<td>↑40</td>
<td>↑40</td>
<td>NS</td>
<td>↑40</td>
<td>NS</td>
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<td>Clamp</td>
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<td>NS</td>
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<td>HbA1c</td>
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<td>NS</td>
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<td>NS</td>
<td>NA</td>
<td>NS</td>
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<td>↓30</td>
<td>NS</td>
<td>↑40</td>
<td>I:G</td>
<td>NS</td>
<td>PND 1</td>
</tr>
<tr>
<td>2</td>
<td>2 F</td>
<td>NS</td>
<td>↑15</td>
<td>↑15</td>
<td>PND 22</td>
<td>↑102+</td>
<td>↑19</td>
<td>NS</td>
<td>I:G</td>
<td>—</td>
<td>—</td>
<td>NS</td>
<td>PND 22</td>
</tr>
</tbody>
</table>
Duration & exclusivity substantially higher in experimental group
Example

Fish intake during pregnancy
Capt. Bob's Fish Sticks

For shame! pregnant & eating fish?!
Think of the baby!

Great talk! Thanks! Jack.
Donahue et al, Am J Clin Nutr 2011
Which Fish Should I Eat?
Prenatal fish consumption and the health of mothers, babies, and the planet

Emily Oken et al.
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>
</tr>
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<tbody>
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<td>2004 FDA/EPA</td>
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<td>Monterey Bay</td>
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<td>EDF</td>
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<td>Dietary Guidelines</td>
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<td>Fish for your health</td>
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<tr>
<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>Connecticut State DPH</td>
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<td>NRDC</td>
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<td>Turtle Island</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>Star Chefs</td>
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<td>Greenpeace International</td>
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<tr>
<td>NOAA</td>
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<td>Shedd Aquarium</td>
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</table>
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

Recommendations for Pregnant Women Regarding Fish Consumption

“I. Pregnant, breastfeeding and postpartum women are recommended to consume a variety of fish and shellfish that are lower in mercury (e.g., cod, pollock, lobsters, shrimp, scallops, sole, flounder, canner tuna, and albacore tuna).”

“Consume a minimum of 12 ounces of seafood per week.”
Risk/Benefit

• To help with establishing guidelines

• Outcomes in addition to obesity/CVD
  – Neurocognition

• Larger sample sizes
  – Compare or combine studies
Implementation
Intervention Studies

• Efficacy
  – Etiology > implementation

• Effectiveness
  – Implementation > etiology

• Sustainability

• Disseminability
Interventions
Maternal Diet During Pregnancy

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

Interventions
Maternal Diet During Pregnancy

• Nutrient supplements—often default
  – Analogy to drug trials

• Foods, dietary patterns
  – Single nutrient trials in adults disappointing
  – More effective for offspring outcomes?
  – Allows for multiple behavior change approaches
  – People have to eat
  – 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
Example

Fish intake during pregnancy
A randomized trial of fish consumption during pregnancy

food for thought

Emily Oken PI
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: *(Education, n=20)* Health benefits of DHA and information on low-mercury, high DHA fish
    Arm 2: *(Education + GC, n=20)* Education plus $10/week Whole Foods Gift Cards (GC) to purchase fish
    Arm 3: *(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)
**Wallet card**

---

**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-shell clams, and bivalves from Boston Harbor

---

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

**ONE 6-ounce serving**

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

**TWO 6-ounce servings**

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

**THREE 6-ounce servings**

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

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

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

If you eat tuna, choose chunk light tuna.

---

For more information, please contact us:

Email: FoodforThought@harvardpilgrim.org
Phone: (617) 509-9903
Change in fish intake

Intervention arm

Control  Education  Education + Gift card

Fish intake oz/week

0.1  3.8  5.5

p=0.047

Oken et al., preliminary data
Risk/Benefit
## Gestational Weight Gain

### 1990 IOM Recommendations

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>BMI (kg/m²)</th>
<th>Recommended total gain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lb</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;19.8</td>
<td>28-40</td>
</tr>
<tr>
<td>Normal</td>
<td>19.8-26</td>
<td>25-35</td>
</tr>
<tr>
<td>Overweight</td>
<td>&gt;26-29</td>
<td>15-25</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt;29</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>
# Gestational Weight Gain

**2009 IOM Recommendations**

<table>
<thead>
<tr>
<th>BMI Category</th>
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<th>Recommended total gain</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lb</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;18.5</td>
<td>28-40</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td>25-35</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
<td>15-25</td>
</tr>
<tr>
<td>Obese</td>
<td>30+</td>
<td>11-20</td>
</tr>
</tbody>
</table>
More gestational weight gain associated with higher BMI at 3 y

Oken et al., Am J Obstet Gynecol 2007; 196:322e1
...and at age 9-14 years

Oken et al., Am J Ob Gyn 2008
Change in DHA intake

-15 mg/day to 68 mg/day

p = 0.0002

Control
Education
Education + Gift card

Intervention arm

DHA intake mg/day
Change in mercury intake

Mercury intake mcg/kg/day

Control
Education
Education + Gift card

Intervention arm

p=0.50

Change in mercury intake

0.003
-0.004
0.013

Food for Thought
Food for Thought

• Pilot RCT
• Increased fish intake
• Increased DHA
• Did not increase Hg
→ favorable nutritional/toxicant balance
Behavior Change Interventions
In Pregnancy

• Some advantages
  – Women may be willing to change behavior
  – They are in clinical care frequently
  – Few months long
  – Potential to lead to postpartum interventions for mother and child
    • Also pre-conceptional for next pregnancy
Example

Using EMR capabilities to reduce excess GWG
An EMR-based system for Gestational Weight Gain Counseling and Tracking (ENCOUNTER)

GWG “Growth charts”
Patient handouts
Clinician reminders
Postpartum follow-up

Emily Oken, MD, MPH
Funded by the CDC 200-2010-M-33818
NHLBI Pilot Grant (P30 HL101312)
and Harvard Pilgrim Health Care Institute
An EMR-based system for Gestational Weight Gain Counseling and Tracking (ENCOUNTER)

Recommended range of weight gain during pregnancy for women with pre-pregnancy body mass index (BMI) 18.5-24.9

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An EMR-based system for Gestational Weight Gain Counseling and Tracking (ENCOUNTER)

Patient has gained weight outside of recommended range!
Would you like to:
- Print patient education handout
- Order Nutrition Referral
- Read guidelines
- Get more information

GWG “Growth charts”
Patient handouts
Clinician reminders
Postpartum follow-up
An EMR-based system for Gestational Weight Gain Counseling and Tracking (ENCOUNTER)

Pregnancy and Weight Gain

Based on your pre-pregnancy height and weight, your recommended total weight gain is 28-40 pounds.

Gaining in the recommended weight range will help keep you and your baby healthy, both during pregnancy and after the baby is born. Excess weight gained during pregnancy can be a challenge to lose and can increase your health risks over time.

In the first trimester you should gain about 1-4 pounds, and then about 5 pounds each month after that. Here are some tips to help you gain the recommended amount of weight:

**HEALTHY EATING**
Healthy, nutrient-rich choices will give you and your growing baby the nutrients and energy you both need. Two extra snacks a day can give you the extra calories you need. Try low-fat yogurt with fruit or granola, crackers with hummus, or a handful of nuts.

**EXERCISE**
Prenatal Risk Factors, Epigenetics, and Childhood Obesity

Simplified

Concept: epigenetics as surrogate outcome
Prenatal Risk Factors, Epigenetics, and Childhood Obesity

Simplified Concept: epigenetics as surrogate outcome
Prenatal Risk Factors, Epigenetics, and Childhood Obesity

Simplified

Exposures → Intermediate (surrogate) → Health Outcomes

1st → DNA-Me → 2nd

Prenatal factors → Adiposity, etc

Usual Reality
# Developmental Origins of Obesity

How Important Can It Be?

<table>
<thead>
<tr>
<th>Prenatal</th>
<th>Infancy</th>
<th>( P \ (Ob) ) at 7 y</th>
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</thead>
<tbody>
<tr>
<td><strong>Maternal smoking</strong></td>
<td><strong>GWG (IOM cat.)</strong></td>
<td><strong>Breastfeeding duration</strong></td>
</tr>
<tr>
<td>N</td>
<td>Inadequate/ Adequate</td>
<td>12+ m</td>
</tr>
<tr>
<td>Y</td>
<td>Excessive</td>
<td>&lt;12 m</td>
</tr>
</tbody>
</table>

Adjusted for maternal BMI, education; HH income; child race/ethnicity
Etiology—Human Studies

• Observational
  – Innovative study designs/analyses
  – Harmonizing across studies
    • Combined analyses
    • Meta-analyses

• Intervention
  – Following children of completed RCTs
  – New intervention studies
    • Animal and observational studies for hypotheses
Feasibility and impact of Creciendo Sanos, a clinic-based pilot intervention to prevent obesity among preschool children in Mexico City

Gloria Oliva Martínez-Andrade, Elizabeth M Cespedes, Sheryl L Rifas-Shiman, Guillermina Romero-Quechol, Marco Aurelio González-Unzaga, Maria Amalia Benítez-Irejo, Samuel Hores-Huerta, Chrissy Horan, Jess Haines, Elsie M Taveras, Ricardo Pérez-Cuevas and Matthew W Gillman