Developmental Origins of Health and Disease

(Theory to) Evidence to Policy

Matthew W. Gillman, MD, SM

Harvard Catalyst Child Health Symposium
7 October 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* b, Vincent W.V. Jaddoe c
Developmental Origins of Health and Disease

• DOHaD emphasizes prenatal period and early childhood as important periods for development of chronic disease throughout life
Theory…

Godfrey et al., Trends Endocrinol Metab 2010; 21:199-205
Now comes a new paradigm: the precursors of adult chronic diseases, and thus the potential for prevention, are determined in utero.

In the grip of an enthusiast...one must be wary. ...What exactly is poor nutrition or undernutrition? ...One wonders about biases, especially loss to follow up. Barker makes an attempt to deal with potential confounding factors, but his efforts are not persuasive...
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

DOHaD Interdisciplinary Approach

Thanks to Sue Ozanne
5 Years Later…

Commentary

The fetal origins of adult disease: from sceptic to convert

Matthew W. Gillman and Janet W. Rich-Edwards
Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, USA

We approached the field of fetal origins of adult disease as sceptics. As one of us has said, ‘Some of us were rooting for the null hypothesis for the first time in our lives’. But, with the recent publication of epidemiological studies that have started to overcome the flaws of the initial work, we have become reluctant converts.
At first glance, it may seem implausible that your mother’s exposure to stress or toxins while she was pregnant with you, how she fed you when you were an infant, or how fast you grew during childhood can determine your risk for chronic disease as an adult. Mounting evidence, however, indicates that events occurring in the earliest stages of human development have long-lasting impact on health outcomes decades later. Researchers have found consistent inverse associations between birth weight and a central distribution of body fat, insulin resistance, the metabolic syndrome, type 2 diabetes mellitus, and ischemic cardiovascular disease. Moreover, the phenotype of lower birth weight coupled with a higher body-mass index in
A = normal development and decline; B = exposure in early life reducing lung function potential; C = exposure acting in mid to later life accelerating age-related decline.
In 2015

Why so little impact on practice and health policy?
Bark(er)ing up the wrong tree

“I keep barking up the wrong tree.”
If we have the wrong evidence

“Hey, I’m over here”
How can we get to here?

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

- Etiology
- Prediction
- Risk/benefit analyses
- Implementation of interventions
- Long-term effects
- Policy evaluation
Equal opportunity stone thrower

“People who live in glass houses should not throw stones”
Improving DOHaD Evidence for Policy Translation

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

• Prediction

• Risk/benefit analyses

• Interventions

• Long-term effects

• Policy Evaluation
Animal Experiments
Could be more helpful
Why do animal experiments
Developmental Origins Research

• In animal models, perinatal programming of adult health outcomes well known

• Programming
  – Perturbation at a critical period of development causes alterations with lifelong, sometimes irreversible consequences
Couch Potato Syndrome

Gluckman, Vickers, Breier, et al., 2003
or

The Thrifty Phenotype

Hales & Barker 1992
Same Genotype → Different Phenotype?

Thanks to Rob Waterland
Same Genotype, Different Epigenotype → Different Phenotype
Animal Experiments

- Exposures, timing, mechanisms, effects on outcomes
- Proved the programming principle
- Showed untoward consequences of combination of prenatal restriction and postnatal surfeit
- 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
Animal Experiments

• Exposures, timing, mechanisms, effects on outcomes

• “Translating up”

• Systematic reviews, meta-analyses
  – Harmonizing interventions, measures across studies

• Importance of publishing null results
# Human Population Studies

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

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

Socio/cultural

Obesity

Breastfeeding

Fast-growing babies wean (reverse causality)

Decision to breastfeed Socio/cultural

Obesity Prevention Program
Risk of Obesity in Adolescence By *Duration* of Breastfeeding in Infancy

Gillman et al, JAMA 2001; GUTS cohort
<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>A few studies suggest this phenomenon, but could be in opposite direction to hypothesis</td>
</tr>
<tr>
<td>Biological effects of formula</td>
<td>Conflicting data on adipokines</td>
</tr>
<tr>
<td>Behavioural effects of nursing</td>
<td>RCTs of high vs low protein (+/- energy) result in more adiposity and related outcomes</td>
</tr>
<tr>
<td>Ecological analysis</td>
<td>Short-term studies suggest less self-regulation in bottle- vs breast-fed infants</td>
</tr>
<tr>
<td></td>
<td>Breastfeeding rates have gone up along with emergence of the obesity epidemic, but that does not rule out inverse individual-level effects</td>
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</tbody>
</table>

Summarizing evidence for and against the hypothesis that having been breastfed reduces the risk of obesity.
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<tr>
<td>No</td>
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<tr>
<td>Anthropometric 6.5 or 11.5 years observational data or cohort studies show no</td>
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<tr>
<td>positive association</td>
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<td>-level of mean BMI after control, but limited studies with ta</td>
</tr>
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<td>but in some setting of exposure</td>
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</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

Followup at 11.5 y, N = 13,879 (~80%)
Breastfeeding did not reduce adiposity at 11.5 y ITT, adjusted for cluster and covariates

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

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

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

Prenatal exposures

↑ Maternal BMI, gestational weight gain, glycemia
↓ Dietary PUFA, vitamin D

Birth

Cord blood DNA-Me

Follow up: Repeated visits up to 12 years

Adiposity

Child blood DNA-Me

Insulin resistance, blood pressure, lipids

Discovery in Project Viva (n=500)

Pyrosequencing for Technical Validation of the Results

Replication: confirm results in Generation R (n=500)
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
Role of Epigenetics in Policy-Relevant Evidence

- Intermediate between pre-/peri-natal exposures and obesity-related outcomes
  - Surrogate outcome
  - Provide signatures for prediction?
    - 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??
Is this an effective message??

Epigenetics Warning:
What You Eat Today Could Harm
The Health of Your Children
and Grandchildren

DNA

AncestralChef.com
Society: Don't blame the mothers

Sarah S. Richardson, Cynthia R. Daniels, Matthew W. Gillman, Janet Golden, Rebecca Kukla, Christopher Kuzawa & Janet Rich-Edwards

Nature 2014;512(7513):131-2
So I blame you for everything
- whose fault is that?
Role of Epigenetics in Policy-Relevant Evidence

- Intermediate between pre-/peri-natal exposures and obesity-related outcomes
  - Surrogate outcome
  - Provide signatures for *prediction*?
  - 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].”

Hertzman and Boyce 2010
Role of Epigenetics in Policy-Relevant Evidence

• Epigenetics at the right “archeological” level to motivate how pre and perinatal factors cause obesity and chronic disease
  – Relatively easy to communicate from science to policy
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.
# Developmental Origins of Obesity

## How Important Can It Be?

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

Adjusted for maternal BMI, education; HH income; child race/ethnicity
Risk of obesity at age 7-10 y according to combinations of 4 pre/post-natal risk factors

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

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</tbody>
</table>

PAR% ~ 20-50%
Implication

- Multiple risk factor interventions in early developmental periods hold promise for preventing obesity and its consequences
  - Now testing 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

Rapid Weight Gain in Infancy
Rapid Weight Gain in Infancy

- Associated with later obesity/CVD risk factors
- But....
  - Multiple exposures
    - Linear growth, gain in adiposity
  - Multiple outcomes
    - Neurocognition, obesity/CVD
  - Multiple scenarios
    - Full term, preterm
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>
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<tr>
<td>Neurodevelopment</td>
<td>↔</td>
<td>↔</td>
<td>+</td>
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</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.

Risk/Benefit

• Take account of multiple exposures, outcomes, scenarios
• To help with establishing guidelines
Improving DOHaD Evidence for Policy Translation

• Etiology
• Prediction
• Risk/benefit analyses
• Interventions
  – Move beyond efficacy
  – Implementation for effectiveness, sustainability, dissemination
• Long-term effects
• Policy Evaluation
Whole-of-community Approach to Obesity Prevention
Focus on environment & policy

Social Ecological Model – Influencers of Obesity


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

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  – Effectiveness
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• 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, FRCP, 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
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
Evidence-based Policy

- While good (valid, actionable) evidence is not sufficient to make sound policy, it sure is helpful.

Evidence to the rescue:
- Synthesis
- Policy briefs
- Influencing
- Advocacy
- Knowledge-sharing portals
- Publications
- Engagement with end users
- Press releases
- Communication capacity