Fetal Programming of Childhood Obesity and Metabolic Dysfunction: Role of Prenatal Stress and Maternal-Placental-Fetal Stress Biology

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University of California, Irvine, School of Medicine.

6th Biennial Childhood Obesity Conference
San Diego, CA, June 28-30, 2011.
6th Biennial Childhood Obesity Conference

- very comprehensive in scope – 8 tracks – 40 sessions -- covers diet, physical activity, built environment, community, marketing, health care, public policy, etc.

- 2 sessions on preconceptional care, perinatal influences and early childhood development.....

- main theme of this presentation: **primary prevention** of obesity should begin during the fetal/ intrauterine period of life.

- it is not as much a question of our genetic makeup, but it is largely developmental processes in prenatal and early postnatal life that define an individual’s **susceptibility** for obesity and metabolic dysfunction.
Outline

- Origins of obesity: rationale for study of fetal/developmental origins...
- Fetal programming of childhood obesity and metabolic dysfunction: rationale for study of prenatal stress and stress biology...
- Overview of maternal-placental-fetal biological pathways
  - Maternal-placental-fetal (MPF) neuroendocrine processes...
  - Infection and immune processes...
  - Maternal-fetal gene-environment interactions...
- Prenatal stress and long-term health outcomes...
  - Metabolic outcomes
  - Immune outcomes
  - Endocrine outcomes
  - Cognitive outcomes
  - Cellular aging
- Prenatal stress biology and fetal programming of newborn and infant body composition, metabolic function and obesity risk: on-going studies and future directions...
The University of California Irvine Development, Health and Disease Research Program

Interdisciplinary study of the interplay between biological, psychosocial and behavioral processes in fetal, neonatal and infant life.

- dynamic processes with multiple, bi-directional feedback loops (both - and +)
- time, place and context dependency
Outline

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- **Overview of maternal-placental-fetal biological pathways**
  
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  - Metabolic outcomes
  - Immune outcomes
  - Endocrine outcomes
  - Cognitive outcomes
  - Cellular aging

- **Prenatal stress biology and fetal programming of newborn and infant body composition, metabolic function and obesity: on-going studies and future directions**
GLOBAL THREAT WAITING AREA

OBESITY

BIRD FLU

GLOBAL WARMING
Fat for Life?
Six Million Kids Are Seriously Overweight. What Families Can Do.
By Geoffrey Cowley & Sharon Begley
ONE APPROACH TO CHILDHOOD OBESITY THAT WOULD NEVER OCCUR TO SELF-APPOINTED "FOOD POLICE!"

IT SAYS ON THE CAN: "WARNING: BEFORE EATING OR DRINKING OUR PRODUCTS, GET YOUR LAZY BUTT OUT FROM IN FRONT OF THE TV AND GO OUTSIDE AND PLAY HOCKEY OR BASEBALL OR KICK-THE-CAN OR TAG OR HOPSCOTCH....."

Yeah, like that'll happen.
The dynamics of obesity

Kevin D Hall
Carson C Chow
Laboratory of Biological Modeling, NIDDK, NIH
Genesis of obesity

Energy Intake (EI) > Energy Expenditure (EI)

+ at comparable level excess energy intake, inter-individual variation in propensity to gain weight/accrue fat mass

(i.e., for same amount of energy intake ➞ amount of energy spent vs. stored)
DEVELOPMENTAL (FETAL) ORIGINS OF ADULT HEALTH AND DISEASE

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### Burden of disease in “developed” nations and societies in rapid transition

#### In adult life
- cardiovascular
- type 2 diabetes
- cancers
- neurodegenerative diseases
- depression

#### In early life
- premature birth
- obesity
- asthma and atopic disorders
- neurodevelopmental problems (cognitive, affective, behavioral)

*(fetal life, at birth, during infancy and childhood)*
Determinants of Health and Disease

for any given individual,

\[ p \text{ (complex common disease)} = f \text{ [exposure to risk factors } \times \text{ predisposition]} \]

Traditional Paradigm: predisposition = genetic makeup \((DNA \text{ basepair sequence})\)

Fetal Programming Paradigm: predisposition = \(f\) [integrity of structure + efficiency of function]

Structural + functional robustness = \(f[\text{genes} \times \text{early environment}]\)

DEVELOPMENTAL PROGRAMMING: The developing embryo/fetus responds to, or is acted upon by, conditions in the internal or external environment during sensitive periods of cellular proliferation, differentiation, and maturation, resulting in structural and functional changes in cells, tissues, and organ systems. These changes may, in turn, either independently or through interactions with subsequent developmental processes and environments, have short-term and/or long-term consequences for health and disease susceptibility.

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IN HUMANS

birth phenotype/prenatal environment

birth weight

developmental risk factor for later diseases

- hypertension
- coronary artery disease
- diabetes
  [dyslipidemia, impaired glucose tolerance, vascular endothelial dysfunction]
- endocrine cancers
- ↓ pulmonary function

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Obesity: rationale for study of fetal origins

- EI > EE
- Inter-individual variation
- Childhood obesity – strong predictor of adult obesity
- High heritability (maternal > paternal)
- Genetic factors (DNA base pair variability) account for relatively small proportion of variance
- Importance of primary prevention (because of efficiency of energy balance homeostatic mechanisms that maintain body weight and protect against weight loss)
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  - metabolic outcomes
  - immune outcomes
  - endocrine outcomes
  - cognitive outcomes
  - cellular aging

- Prenatal stress biology and fetal programming of newborn and infant body composition, metabolic function and obesity risk: on-going studies and future directions
Processes underlying the genesis of childhood obesity

1) Increased adipose mass
   - Hyperplasia of adipocytes
   - Hypertrophy of adipocytes
   - Location - subcutaneous vs. visceral
   - Type – brown vs. white

2) Brain circuits that regulate energy balance
   
   **Energy intake**
   - *appetite* (hypothalamus, peripheral signals, e.g., glucose, ghrelin)
   - *satiety* (hypothalamus, peripheral signals, e.g. leptin, insulin)
   - limbic system, prefrontal cortex

   **Energy expenditure**
   - sympathetic nervous system, vagus (PVN)
   - thyroid axis

   ➔ Proliferation, differentiation of neurons, synaptogenesis, connectivity between regions

3) Metabolic function
   - # of insulin producing cells
   - capacity to produce insulin
   - sensitivity of insulin receptors
   - liver function
   - muscle energetics

Systems develop very early in life

Potential for intrauterine conditions to influence structure and function
### Early life factors associated with childhood obesity

1. **Epidemiological**
   - birth weight
   - fetal growth velocity
   - catch-up growth
   - maternal pre-pregnancy BMI
   - maternal weight gain during pregnancy

2. **Nutrition**
   - Diet (maternal, infant), breast feeding

3. **Clinical**
   - GDM, hyperglycemia
   - Hypertension
   - Preeclampsia
   - Inflammation/ infection
   - Fetal hypoxia

4. **Behavioral**
   - Smoking, Sleep, Psychosocial stress

5. **Biomarkers**
   - Leptin
   - CRH
   - glucose, insulin, IGF-1

6. **Animal studies (experimental)**
   - Maternal under-nutrition
   - Maternal over-nutrition
   - Content of maternal diet (e.g., high protein)
   - Maternal stress
   - LPS/ poly:IC stimulation
   - GC administration

---

**Common underlying factor?**

**MPF stress biology**
Intrauterine perturbations

Maternal-placental-fetal stress biology
[CRH, cortisol, IL-6, CRP]

Fetal brain and peripheral targets implicated in energy balance regulation

Increased risk of childhood obesity and associated conditions
Early life risk factors associated with childhood obesity

### Epidemiological
- birth weight
- fetal growth velocity
- catch-up growth
- Maternal pre-pregnancy BMI
- Maternal weight gain during pregnancy

### Clinical / Behavioral / Psychosocial
- GDM, hyperglycemia
- Hypertension
- Preeclampsia
- Inflammation / infection
- Fetal hypoxia
- Smoking
- Maternal diet

### Biomarkers
- Leptin
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### MPF stress biology

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<thead>
<tr>
<th>CRH</th>
<th>cortisol</th>
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   - Subcutaneous vs. visceral fat
   - [Kind of fat (brown vs. white)]

2) Brain circuits that regulate energy balance
   
   **Energy intake**
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   - sympathetic nervous system, vagus (PVN)
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3) Metabolic function
   - # of insulin producing cells
   - Capacity to produce insulin
   - Sensitivity of insulin receptors
   - Liver function
# Adipose Tissue as a Target of Programming by Stress Biology

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Adipose tissue</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal stress</td>
<td>adipose mass, ↑body weight, ↑fat mass, ↑leptin levels, ↑adipocyte differentiation, ↑PPARγ activity, adipocyte function, ↑11βHSD-1 expression in adipocytes</td>
<td>• Tamashiro et al., Diabetes, 2009&lt;br&gt;• Mueller et al., Physiol &amp; Behav, 2006&lt;br&gt;• Kaufmann et al., Diabetes, 2007&lt;br&gt;• Entringer et al., AJOG, 2008&lt;br&gt;• Li et al., PLoS, 2010</td>
</tr>
<tr>
<td>Glucocorticoids (endogenous, exogenous or in vitro)</td>
<td></td>
<td>• Harris &amp; Seckl, Horm &amp; Behav, 2011&lt;br&gt;• Dahlgren et al., Am Journ Physiol Endocrin Metab, 2001&lt;br&gt;• Hauner et al., JCEM, 1987&lt;br&gt;• Hauner et al., J Clin Invest, 1989&lt;br&gt;• Campbell et al., Am J Physiol Cell Physiol, 2011&lt;br&gt;• Vidal-Puig et al., J Clin Invest, 1997</td>
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<tr>
<td>CRH</td>
<td></td>
<td>• Gillman et al., Obesity, 2006</td>
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<tr>
<td>Proinflammatory cytokines</td>
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<td>• Dahlgren et al., Am Journ Physiol Endocrin Metab, 2001&lt;br&gt;• Radaelli et al., Journ Soc Gynec Invest, 2006</td>
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</table>
# Exposure

**Brain circuits involved in energy balance regulation**

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<tr>
<th>Exposure</th>
<th>Brain circuits involved in energy balance regulation</th>
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</tr>
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<tbody>
<tr>
<td>Prenatal stress</td>
<td>Hypothalamus, limbic structures, prefrontal cortex</td>
<td>• Murmu et al., <em>Eur J Neurosc</em>, 2006</td>
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<td></td>
<td>Structural changes</td>
<td>• Coe et al., <em>Biolog Psychiatry</em>, 2003</td>
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<td></td>
<td>neurogenesis</td>
<td>• Salm et al., <em>Brain Research Dev Brain Res</em>, 2004</td>
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<td></td>
<td>synaptogenesis</td>
<td>• Yaka et al., <em>Brain Res</em>, 2007</td>
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<td>dentritic growth</td>
<td>• Fumagalli et al., <em>Eur J Neurosc</em>, 2004</td>
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<td>myelination</td>
<td>• Pankevich et al., <em>Physiol Behav</em>, 2009</td>
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<td>Glucocorticoids</td>
<td>Functional changes</td>
<td>• Uno et al., <em>Brain Research Dev Brain Res</em>, 1990</td>
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<tr>
<td></td>
<td>neurotransmitter availability</td>
<td>• Tauber et al, <em>Brain Pathol</em>, 2006</td>
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<td></td>
<td>Behavioral changes</td>
<td>• Nakayama et al., <em>Endocr J</em>, 2011</td>
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<td></td>
<td>e.g., hyperphagia</td>
<td>• Huang et al., <em>Int J Dev Neurosci</em>, 2001</td>
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<td>CRH</td>
<td></td>
<td>• Baram et al., <em>Brain Res</em>, 1997</td>
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<td>• Brunson et al., <em>PNAS</em>, 2001</td>
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<td>Proinflammatory cytokines</td>
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<td>• Baerwald et al., <em>J Neurosci Res</em>, 1998</td>
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<td>• Golan et al., <em>Neuropharmacology</em>, 2005</td>
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<td>• Jarskog et al., <em>Int J Dev Neurosci</em>, 1997</td>
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<td>• Marx et al., <em>Biol Psychiatry</em>, 2001</td>
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## METABOLIC FUNCTION AS A TARGET OF PROGRAMMING BY STRESS BIOLOGY

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Glucose regulation, pancreas liver</th>
<th>Reference</th>
</tr>
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</table>
| Prenatal stress               | Glucose regulation
↑ Insulin resistance | • Entringer et al., AJOG, 2008
• Kaufman et al., Diabetes, 2009 |
| Glucocorticoids               | Pancreas
↓ number of islet cells         | • Nyrienda et al., J Clin Inv, 1998
• De Vries et al., J Clin Invest, 2007
• Dalziel et al., Lancet, 2005
• Tamashiro et al., Diabetes, 2009 |
| Proinflammatory cytokines     | Liver
↑ PEPCK  
↑ Glucocorticoid receptors     | • Dahlgren et al., Am Journ Physiol Endocrin Metab, 2001                   |

**Glucose regulation**
- Insulin resistance

**Pancreas**
- Number of islet cells

**Liver**
- PEPCK
- Glucocorticoid receptors
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  - Endocrine outcomes
  - Cognitive outcomes
  - Cellular aging

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Research Question

Does maternal stress during pregnancy influence fetal development and subsequent birth, infant, child and adult health outcomes?

- which aspects of maternal stress?
- which fetal (and subsequent child/adult) outcomes?
- independent effect or epiphenomenon?
- magnitude and nature of effect?
- when in gestation? (critical periods of susceptibility)
- mechanisms? – biological/behavioral
- which biological system(s)?
- how are “stress” signals transduced between the maternal and fetal compartments?
maternal stress

nature, timing, duration

immune

endocrine

vascular

utero-placental function

placental CRH

intrauterine environment

fetal environment

fetal development, birth and child outcomes


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Primate (Human) Maternal-Placental-Fetal Unit

Mechanisms:
- Effects of placental CRH
- Transplacental passage of cortisol

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Infection and inflammation in human pregnancy
Gene-environment interactions in human pregnancy

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Modeling maternal-fetal gene-environment interactions

Premature birth

ENVIRONMENT A

ENVIRONMENT B
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Is there a direct association between measures of the prenatal environment (psychosocial stress) and measures of physiology in adult life *that is independent of birth phenotype*?
First step: 
*retrospective case-control, quasi-experimental design*

Selection of stressor: 
*major stressful event in index pregnancy*

Selection of outcomes: 
*metabolic (obesity/diabetes), immune (asthma/atopy), endocrine (HPA axis), cognitive (prefrontal cortex), telomere length (ageing)*

Age of study population: 
*young adults – focus on pre-disease markers of physiological dysregulation*

Strategy:  
*employment of appropriate challenge tests*

Consideration of co-variates: 
*effects of established obstetric, birth and childhood risk factors controlled by study design*
<table>
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<th>OUTCOMES</th>
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<tbody>
<tr>
<td><strong>Endocrine system</strong></td>
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<tr>
<td>- Basal HPA axis function</td>
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<td>- ACTH stimulation test</td>
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<td>- Psychosocial stress test (TSST)</td>
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<tr>
<td>- Dexamethasone Suppression test</td>
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<tr>
<td><strong>Immune system</strong></td>
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<tr>
<td>- Lymphocyte subtype trafficking</td>
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<tr>
<td>- Cytokine production (PHA, LPS)</td>
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<tr>
<td>- Antibody production against latent Epstein Barr</td>
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<tr>
<td><strong>Metabolic function</strong></td>
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<tr>
<td>- Glucose Tolerance Test</td>
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<tr>
<td>- Insulin, leptin, adiponectin, IGF-2</td>
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<td>- Lipid profile</td>
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<td><strong>Cognitive</strong></td>
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<td>- Memory tests (before and after cortisol administration)</td>
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<td><strong>Genetics</strong></td>
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<td>- GR/MR Genotype</td>
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<tr>
<td>- Telomere length</td>
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I. Metabolic Outcomes

- Oral Glucose Tolerance Test
- Insulin, C-Peptide, HOMA-IR index
- Lipid Profile
- BMI
- Leptin/adiponectin
- Inflammatory cytokines (IL-1, IL-6, TNF-α)
Oral Glucose Tolerance Test

**Glucose (mg/dL)**
- Main effect PS: n.s.
- Time x PS: n.s.

**Insulin (pmol/mL)**
- Main effect PS: p = .04
- Time x PS: p = .08

**C-peptide (pmol/L)**
- Main effect PS: n.s.
- Time x PS: p = .10

**Leptin (ng/mL)**
- Main effect PS: p = .05
- Time x PS: n.s.

$p = .065$

Entringer et al., 2008, *AJOG*

**HOMA-IR**

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BMI and Body Fat

main effect PS: $p = .04$
(corrected for BMI: $p = .03$)

Entringer et al., 2008, *AJOG*

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Lipid panel

- no differences in total cholesterol (in normal range)

Entringer et al., 2008, *AJOG*
PS subjects exhibited ↑ insulin resistance

Primary insulin resistance

Not secondary to
- body composition / BMI
- Pro-inflammatory state (cytokines, other inflammatory diseases)
- Behavioral factors: smoking, diet and physical activity

Also not related to maternal/paternal history of T2DM, gestational diabetes, or to size at birth.

Entringer et al., 2008, AJOG
II. Immune outcomes

1) Trafficking of immune cells
   Count of immune cells before and after stress

2) Activation of cells
   Production of cytokines after stimulation

3) Functional capacity
   Functional assays
Cytokine production findings

- Prenatally-stressed subjects: bias for a Th2 cytokine pattern (over-production of IL-4 relative to INF-γ)

- Th2 responses: increased susceptibility for allergic reactions, asthma, autoimmune diseases

- Th2 bias also impairs Th1 responses (counter-regulation): susceptibility for infection, the defense against which is primarily through cellular immune mechanism

Entringer et al., 2008, *Developmental Psychobiology*
III. Endocrine findings

- Prenatally-stressed subjects:
  - Altered ACTH and cortisol responses to acute social and pharmacological challenge
  - Altered HPA-axis feedback sensitivity
  - Effects moderated by gender/sex
  - PS-associated endocrine profile similar to profile produced by early life trauma/abuse.

Entringer et al., 2009, *Hormones and Behavior*
1. Developmental Origins of Health and Disease Risk
   - Conditions in fetal life → child and adult health and disease risk
   - **Prenatal psychosocial stress exposure** → metabolic, immune, endocrine and cognitive dysregulation in young adults.

2. Behavioral Medicine and Biological Psychiatry
   - Psychosocial stress exposure → onset and progression of disease
   - Role of **telomere biology** as a mediator

---

**Prenatal stress**
- **Comparison group**

\[ \beta = -0.090; p<.01; d = 0.41 \text{ SD units} \]

- Adjusted for: age, BMI, sex, birth weight, posnatal adversity, current stress

---

295 base pairs ~ 4.5 years
SOME CONSIDERATIONS…

- PS group: prenatal stress occurred 25 years ago (in fetal life)

- Study included only healthy young women and men with normal birth phenotypes.

- **No** association between measures of birth phenotype and the immune, endocrine, metabolic and cognitive outcomes of interest.

- Prenatal stress was significantly associated with altered endocrine, immune, metabolic and cognitive function, and with cellular aging.
On-going studies and future directions

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Among pregnant women exposed to “high” levels of “stress,”

- WHICH WOMEN/ FETUSES
- UNDER WHAT CONDITIONS (CONTEXT)
- AT WHICH STAGE(S) OF GESTATION

are especially vulnerable to the potentially detrimental effects of prenatal stress?

\[ p (\text{stress-related adverse health outcome}) = f[(\text{exposure to stress}) \times (\text{individual differences in biological responsivity to stress})] \]

- No assessment of the role of individual differences in biological stress responsivity.

- Rely exclusively on summary, self-report measures of psychosocial stress - prone to several biases/ measurement error.

- No assessment of context (diet/nutrition, sleep, physical activity, time of day, etc.)
Ecological Momentary Assessment in Human Pregnancy

Real-time assessment of mental state, dietary intake, physical activity, and physiological function (cardiovascular, respiratory, endocrine) in human pregnancy.

Electrocardiogram
Respiration
Physical activity and posture
Sleep
Electronic diary

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Ecological Momentary Assessment of Maternal Stress in Human Pregnancy

- **Ecological momentary assessment (EMA):** Repeated measures in participants’ natural environments aim to obtain assessments in nearly real time to minimize or eliminate recall.

- **REAL-TIME ASSESSMENT OF PSYCHOSOCIAL, BEHAVIORAL AND PHYSIOLOGICAL PARAMETERS**
  - context (where, doing what?)
  - psychological state
  - social interactions
  - behaviors: dietary intake
  - physiological: maternal HR, BP, salivary cortisol
  - physical activity/sleep

- 4 days/assessment x 3 assessments over the course of gestation
Stress-Nutrition Interactions in Human Pregnancy

Bi-directional interactions between the nutrition and stress

- Nutritional manipulations alter stress (endocrine, immune) physiology
- Stress alters dietary intake (amount and constituents) and metabolic fate
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AIM 1: MPF biology and body composition

Body composition: DXA scans (total and regional fat and lean mass)

Does MPF biology over pregnancy predict
Body composition at birth, at 6 months and change in body composition from 0-6 months?
Birth weight, gestational age at birth, and newborn body composition
AIM 2: MPF biology and energy balance homeostasis set points

- Longitudinal assessment of total energy expenditure (TEE) with doubly-labeled water (DLW) at birth and at 6 months age

- At any given time point: TEE=EI=EE

- TEE increases with increasing body mass

- TEE/kg declines as an individual grows and accumulates greater mass

*rate of decline* over time in TEE/kg
  
  a) will predict change in the fat to fat-free mass ratio, such that a steeper decline will be associated with more fat mass relative to fat-free mass
  
  b) will mediate the effect of intrauterine stress on change in body composition from birth till 6 months age.
Birth Weight and Total Energy Expenditure
[assessed by doubly-labeled water]
AIM 3: MPF biology and insulin sensitivity

- Fasting insulin/glucose levels from heel-stick

- Does MPF biology
  - predict insulin sensitivity at birth and at 6 months age?
  - predict the strength of the association between insulin sensitivity and body composition?
Future Directions

1) Brain circuits involved in energy balance
   - Morphology (MRI)
   - Connectivity (DTI)
   - Activation in presence of food cues (fMRI)
   - Imaging of white vs. brown adipose tissue

2) Gene × prenatal stress exposure interactions for common variants in genes related to stress and obesity, including mtDNA

3) Human mesenchymal stem cell (MSC) tissue culture system studies

4) Gut microbiome

5) Adenovirus 36
FETAL PROGRAMMING OF NEWBORN AND INFANT BRAIN DEVELOPMENT

Determinants
Sociodemographic
Obstetric Risk
Behavioral
Psychosocial
Nutritional
Sleep

Biological Processes
Maternal-Placental-Fetal endocrine
Immune/Inflammatory

Neonatal Brain morphology (structural MRI, Diffusion Tensor Imaging)

Infant Brain morphology (structural MRI, Diffusion Tensor Imaging)

Neonatal cognitive, motor and emotional behavior (Bayley Performance)

Infant cognitive, motor and emotional behavior (Bayley Performance)

Follow-Up (Future Directions)

Trajectories

Pregnancy
Birth
12 months

Postnatal Environment

THE UNIVERSITY OF CALIFORNIA IRVINE DEVELOPMENT, HEALTH AND DISEASE RESEARCH PROGRAM
The Hispanic Acculturation Paradox:
Role of Biobehavioral Processes in Pregnancy and Fetal Development

- Collaboration with Orange County Health Care Agency, Division of Family Health (former Director Dr. Eric Walsh and current Director Dr. David Nunez).

- WIC Program (Program Manager Maridet Ibanez).
The U.S. National Children’s Study

- Largest and most comprehensive study in the world of genetic and environmental influences on development and health.
- Longitudinal cohort study, beginning prior to birth and continuing through age 21 years.
- Size: representative sample of 1,200,000 women of child-bearing age, with approximately 120,000 live births and 100,000 subjects at 21 years age.
- Genetic influences broadly defined (child, mother, father, grandparents, genetic makeup of microorganisms in maternal reproductive tract), nuclear and mtDNA, epigenetic processes.
- Environmental influences broadly defined (physical, chemical, social, biological).
- Priority health outcomes – pregnancy and fetal development; growth/body composition/obesity/diabetes; asthma; neurodevelopment; injuries.
- National in scope; 7 Vanguard Centers + 100 Centers
- Scheduled to begin subject recruitment in 2012.
Development of interventions

- What kind of interventions? Target interplay between stress and nutrition.
- On whom? Adolescent girls and women of child-bearing age, pregnant women, and mothers and infants.
- When? Pre and periconceptional periods.
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