Developmental Programming and Metabolic Health: Obesity and Diabetes

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Knight Cardiovascular Institute,
Division of Endocrinology, Diabetes, and Clinical Nutrition,
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Current and Projected Obesity Prevalence Rates from 1960 to 2025

Prevalence of Overweight, Obesity, and Severe Obesity in US Adults: 1960-2018


Prevalence of Obesity Among Non-Hispanic White Adults, by State and Territory, BRFSS, 2017-2019
Prevalence of Obesity Among Non-Hispanic Black Adults, by State and Territory, BRFSS, 2017-2019
Trends in Obesity in US Children: 1963-2018

https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm
Relationship of Obesity to Co-Morbid Diseases
Willet, et al. NEJM. 341:427-34, 1999

Women

Men

- Type 2 diabetes
- Cholelithiasis
- Hypertension
- Coronary heart disease

(a) Relative risk vs. Body-mass index for women
(b) Relative risk vs. Body-mass index for men
Worldwide Diabetes Prevalence: 2013

Epidemiology: Summary

• Trends for obesity, diabetes continue to rise
• Communities of color are disproportionately affected
• Number of “healthy weight” Americans is now < 30%
Causes of Obesity

Primary:
• Genetics: 40 - 70%
• Environment

Secondary:
• Hypercortisolemia
• Drugs
Danish Adoptees Study
Twins Studies

Monozygous (Identical) Twins

Dizygous (Fraternal) Twins
Genetic Mutations Associated With BMI and Obesity Measures

\[ n = 250,000. \text{ 165 Loci associated with BMI or waist circumference.} \]

All alleles accounted for 6-11% of genetic variation in BMI.
Up to 1,100 undetected loci...
Genetic Mutations Associated With BMI

n = 250,000
BMI-associated Genetic Loci: Tissue Specificity
Hypothalamic control of energy homeostasis by adiposity signals: The Set Point

[Diagram showing the hypothalamic control of energy homeostasis with labeled neurons and factors such as Leptin, Insulin, POMC, MC4R, LHA, and PVN.]
Causes of Obesity – Environmental Factors

Primary:
• Genetics: 40 - 70%
• Environment
  • Low activity
  • Calorie dense foods (high fat, refined sugar)
  • Microbiome
  • Environmental toxins
  • In-utero

Secondary:
• Hypercortisolemia
• Drugs
Causes of Obesity – In-Utero Environment

Primary:
• Genetics: 40 - 70%
• **Environment**
  • Low activity
  • Calorie dense foods (high fat, refined sugar)
  • Microbiome
  • Environmental toxins
  • **In-utero**

Secondary:
• Hypercortisolemia
• Drugs
Early Life Programming of Diabetes and Obesity: Undernutrition
Dutch Famine ("Hongerwinter") Study

- Glucose Intolerance
  - Microalbuminuria
  - Obstructive airway disease
- Glucose Intolerance
- Obesity
- Dyslipidemia
- Hypercoagulable state
- CVD
- Breast CA
# Fetal Undernutrition & Later Obesity

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>TIMING</th>
<th>TYPE</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human: Dutch Famine</td>
<td>Early-mid gestation</td>
<td>Decrease Global Calories</td>
<td>Increase Obesity</td>
</tr>
<tr>
<td>Human: Birth-to-10 (S Afr)</td>
<td>Throughout gestation</td>
<td>Decrease Global Calories</td>
<td>Increase Visceral fat IF increase postnatal</td>
</tr>
<tr>
<td>Sheep</td>
<td>Early-mid gestation</td>
<td>Decrease Global Calories</td>
<td>Increase Visceral fat</td>
</tr>
<tr>
<td>Rats</td>
<td>Throughout gestation</td>
<td>Decrease Global Calories</td>
<td>Increase Visceral fat</td>
</tr>
</tbody>
</table>
Adult Offspring Impaired Glucose Tolerance (IGT) Risk by Birthweight
Early Life Programming of Diabetes and Obesity: 

Over (mal) nutrition
Progeny Wt Gain of Wistar Rat Moms Fed a High Fat Diet
Increased Prevalence of Offspring Overweight at Age 16 From Overweight Women and GDM
Maternal Glycemia and Offspring Obesity At Age 5 – 7 Years

<table>
<thead>
<tr>
<th>Maternal glucose scale with screening for GDM by GCT and OGTT</th>
<th>n</th>
<th>Child’s weight &gt;95th percentile*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prevalence (%)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)‡§</td>
</tr>
<tr>
<td>Women with normal GCT (quartiles)</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>43–94 mg/dl</td>
<td>1,987</td>
<td>10.3</td>
</tr>
<tr>
<td>95–108 mg/dl</td>
<td>1,953</td>
<td>12.0</td>
</tr>
<tr>
<td>109–121 mg/dl</td>
<td>1,801</td>
<td>13.4</td>
</tr>
<tr>
<td>122–140 mg/dl</td>
<td>1,868</td>
<td>13.2</td>
</tr>
<tr>
<td>Women with GCT/OGTT</td>
<td>9,439</td>
<td></td>
</tr>
</tbody>
</table>

Reference

1.15 (0.92–1.44)
1.20 (0.96–1.50)
1.28 (1.02–1.60)
Birth Size and Obesity in Adult Life: Trouble at Both Ends of the Birth Weight Spectrum
Early Life Programming of Diabetes and Obesity: Mechanisms
Effect of In Utero and Early-Life Conditions on Adult Health and Disease: Epigenetics
Epigenetic inheritance at the agouti locus in mice.
Transgenerational Obesity Phenotype of Agouti Mouse is Modified by Methyl Supplemented Diet
Early Life Programming of Diabetes and Obesity:

Placental Health
High Fat Diet Impairs Placental Health in Primates

Increased Vascular Impedance. Reduced Diastolic Flow

↑ Placental infarctions
↑ Placental inflammation
Early Life Programming of Diabetes and Obesity:

Inflammation
Fetal Liver Fat Accumulation/Lipotoxicity in Offspring of Monkey Mom’s on Chronic High Fat Diet
McCurdy et al, J Clin Investigation. 2009
Maternal Obesity/Overnutrition leading to Childhood Disease

MATERNAL OBESITY, OVERNUTRITION
↑ INFLAMMATION
↑ INSULIN RESISTANCE
↑ II-1, II-6, TNF-a, MCP-1

Fetal Lipid Exposure
↑ LIPOLYSIS
↑ VLDL SECRETION

Reprogramming of Metabolic Gene Targets:
↑ FETAL INFLAMMATION?
↑ INFLAMMATION
↑ INSULIN RESISTANCE

↑ HEPATIC LIPIDS

SKELETAL MUSCLE
ADIPOSE TISSUE
BRAIN
PANCREAS

↑ RISK:
• NAFLD
• INSULIN RESISTANCE
• OBESITY
• HYPERPHAGIA
• DIABETES
Early Life Programming of Diabetes and Obesity: Effect of Weight Loss
Maternal Fetal Outcomes after Bariatric Surgery – High Blood Pressure and Blood Sugar

20 cohort studies, ~ 2.8 million subjects, 8364 of whom had bariatric surgery
Maternal Fetal Outcomes after Bariatric Surgery – Larger Birth Weights

20 cohort studies, ~ 2.8 million subjects, 8364 of whom had bariatric surgery

![Graph showing odds ratios for Macrosomia, Large babies, and SGA with control groups in analysis matched for pre-surg BMI and pre-preg BMI.](image-url)
Maternal Fetal Outcomes after Bariatric Surgery – Birth Issues

20 cohort studies, ~ 2.8 million subjects, 8364 of whom had bariatric surgery
Maternal Weight Loss From Biliopancreatic Diversion Prevents Transmission of Obesity to Children

• N=113 women
• BPD with pylorus-preserving sleeve gastrectomy ("duodenal switch")
• Mean BMI decreased from 48 to 31 kg/m²
### Maternal Weight Loss From Biliopancreatic Diversion Prevents Transmission of Obesity to Children (con’t)


<table>
<thead>
<tr>
<th>Weight Group</th>
<th>Before BPD (n = 45)</th>
<th>After BPD (n = 172)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight, n (%)</td>
<td>16 (36)</td>
<td>98 (57*)</td>
<td>Increase</td>
</tr>
<tr>
<td>Overweight, n (%)a</td>
<td>9 (20)</td>
<td>28 (16)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Obese, n (%)b</td>
<td>18 (40)</td>
<td>33 (19)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Severe Obese, n (%)c</td>
<td>11 (24)</td>
<td>23 (13)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Underweight, n (%)</td>
<td>2 (4.4)</td>
<td>13 (7.5)</td>
<td>Level</td>
</tr>
</tbody>
</table>

a Overweight + obese among BMS versus AMS: $P = 0.006$.
b Obese among BMS versus AMS: $P = 0.005$.
c Severe obese among BMS versus AMS: $P = 0.04$.
* Same as general population.
Summary

• Both maternal undernutrition (low birth weight) and over (mal) nutrition (increased birth rate) contribute to increased risk for obesity and diabetes.

• Evidence supports independent effects of both body weight and maternal diet on offspring risk.

• Proposed mechanisms include
  • Metabolic programming
  • Epigenetics
  • Altered placental health
  • Inflammatory mediators

• Implications are for a “feed forward,” transgenerational potentiation of obesity and T2DM.

• Preliminary data support benefits of maternal weight loss.