Getting to the Roots: Early Life Risk Factors for Obesity and Chronic Disease

Ann Bullock, MD
IHS Division of Diabetes Treatment and Prevention
“Giving every child the best start in life is crucial to reducing health inequalities across the life course. The foundations for virtually every aspect of human development—physical, intellectual and emotional—are laid in early childhood. What happens during these early years (starting in the womb) has lifelong effects on many aspects of health and well-being—from obesity, heart disease and mental health, to educational achievement and economic status. To have an impact on health inequalities we need to address the social gradient in children’s access to positive early experiences.”

Fair Society, Healthy Lives: Strategic Review of Health Inequalities in England Post-2010
Childhood Trauma Predicts Adult Health

- Children born in Helsinki, Finland between 1934-44
- 320 were evacuated abroad during WW II—separated from their parents
  - Average age at evacuation: 4.8 years old
  - Average duration of evacuation: 1.7 years
- 60 years later, compared with children not evacuated, evacuees were much more likely to have:
  - Heart disease (OR 2.0) and hypertension
  - Type 2 Diabetes (OR 1.4)
  - Depressive symptoms (OR 1.7)
- “This study is among the first to show that early life trauma predicts higher prevalence of cardiovascular disease and type 2 diabetes in late adulthood...”

Early Life Experience and the Brain

- Developing brain is remarkably shapeable and adaptable
- “The brain’s exquisite sensitivity to experience in early childhood allows traumatic experiences during infancy and childhood to impact all future emotional, behavioral, cognitive, social, and physiologic functioning.”

FIGURE 8-1 Human brain development. SOURCE: Charles A. Nelson, University of Minnesota. Reprinted with permission.
For diabetes risk, it matters what’s happened...

- To us as adults
  - Diet and exercise choices
    - Food of poor nutritional quality: another stimulus to overeat
  - Stress and trauma
- To us as children
  - Nutrition and Stress
- To us in the womb
  - Nutrition and stress
- To our parents
  - Nutrition and stress
- To our grandparents
  - Nutrition and stress

- “It is through epigenetic marks that environmental factors like diet, stress and prenatal nutrition can make an imprint on genes that is passed from one generation to the next.” *Time* 1/18/10
International Diabetes Federation

Conference on Type 2 Diabetes Etiologies

2002

1. Genetics
2. Fetal Origins
3. Lifestyle
4. Stress
1. Genetics

- **Genes Inherited**
  - It does matter what genes we inherit
    - But proportion of predisposition explained for type 2 DM (5-10%) and BMI (1%) is small. 
      - NEJM 2010;363:2339-50
  - Only 15% of genes in cells “turned on” at any given time

- **Genes Expressed**
  - “Epigenetics”: the “on/off switches” for genes
    - reaction to the environment
    - not always reversible if at key developmental stage of life
    - heritable—some are passed to next generation
      - How the experiences of one generation help prepare the next
    - we know the body’s “on/off switches”: DNA methylation, histone acetylation, microRNA
Epigenetics

- No longer “nature vs. nurture”—nurture affects nature
  - Rat pups raised by nurturing mothers
    - Gene which affects stress hormone receptors “turned on”
    - Grow up to be stress resilient
  - Rat pups raised by neglectful mothers
    - Gene which affects stress hormone receptors “turned off”
    - Grow up to be very stress reactive
  - Same process has now been shown in humans

- Epigenetics and Diabetes
  - Epigenetic mechanisms play important role in DM predisposition
    - Gene imprinting comes from both parents
  - Risk of dying from diabetes strongly related to grandparents’ nutritional status
2. Fetal Origins

- Alcohol/Drugs
- Nutrition
- Smoking
- Maternal Diabetes
- Toxic/Infectious Exposures
- Maternal Low Birth Weight
- Maternal Stress/Mental Health
  - Mother’s own Childhood
  - Current/Prenatal
Low Birth Weight (SGA) and Preterm

- Babies can be either/both SGA and Preterm
  - they both are strongly associated with that baby’s later risk for chronic disease

  *Diabetes* 2009;58:523-526

- Maternal stressful life events during 1st trimester ↑ risk of preterm birth (OR 2.4) and SGA

  *Am J Obstet Gynecol* 2010;203:34.e1-8
FIG. 7. The physiological mechanisms underlying the programming of the separate and combined elements of the metabolic syndrome

Restricted substrate supply during embryogenesis, organogenesis and fetal life

- Substrate Restriction
  - Decreased O₂, glucose, amino acids etc
  - Amino acid balance: homocysteine/glycine

- Changes in Organ Development and Growth
  - Decreases in cell number, organ growth, fetal growth
  - Decreased vasculogenesis, angiogenesis
  - Premature differentiation of functional capacity

- Insulin synthetic/secretory capacity
- Hepatic glucose production
- Skeletal muscle mass
- Cardiac and renal functional capacity
- HPA activity

Maternal and/or fetal neuroendocrine adaptations

- Decreased anabolic hormones (Insulin, IGFs, thyroid hormones, GH/PRL)
- Increased stress hormones (Glucocorticoids, catecholamines)

Programmed Set points in Physiological Systems

- Cardiovascular, renal, metabolic, HPA, etc
- Altered neuroendocrine regulation of energy balance homeostasis, growth etc

Increased nutrient supply in neonatal, postnatal or adult life

- Increased insulin sensitivity – muscle, adipocyte
- Increased appetite
- Catch up growth

- Visceral obesity, increased circulating FFAs
- Hepatic glucose intolerance

- Obesity
  - Insulin resistance – hepatocyte, muscle
  - Decreased insulin synthetic/secretory capacity

- Decreased GFR
- Increased intravascular volume
- Increased vascular reactivity
- Hypertension
- Cardiac Hypertrophy

Type 2 Diabetes
Obesity
CVS Disease

doi:10.1152/physrev.00053.2003
**In utero Risks for Later Type 2 Diabetes**

- Fetuses of obese mothers develop insulin resistance *in utero*
  - “…maternal obesity creates a significant risk for the next generations with metabolic compromise already apparent at birth.”
    - *Diabetes Care* 2009;32:1076-1080

- Maternal diet during pregnancy epigenetically affects child’s adiposity at age 9 yrs
  - *Diabetes* 2011;60:1528-1534

- Inverse relationship between birth weight and risk of diabetes
  - *JAMA* 2008;300:2886-2897

- Rapid weight gain in first 3 months of life associated with ↑CVD and diabetes risk factors by early adulthood
  - *JAMA* 2009;301:2234-2242

- Low birth weight is related to nephron number and future risk of kidney disease
“Fetal Programming of Type 2 Diabetes”

- “...intrauterine environment may modify gene expression permanently. ...They might also be inherited transgenerationally, affecting the health of future generations. ...During intrauterine life, there are waves of epigenomic modification, intimately associated with growth and development, and opportunities galore for environmental factors to influence these processes. A fetus thus programmed travels a path of limited options.”

  *Diabetes Care* 2007;30:2754-5

- “It is important to understand that the story is not about birth weight but about fetal programming, and that intergenerational prevention of type 2 diabetes (primordial prevention) will need to target maternal nutrition and metabolism. ...Prevention of fetal programming of diabetes will need to concentrate on the health of young girls.”

  *Diabetes Care* 2010;33:1146-8
3. Lifestyle

Overeating as an *Adaptive* Response

- **Food Insecurity:**
  - Prevalence of overweight in women ↑’s as food insecurity ↑
    - *Journal of Nutrition.* 2001;131:1738-1745
  - Pregnancy: food insecurity assoc with pregravid obesity, ↑ gest wt gain, and gest diabetes
    - *J Am Diet Assoc* 2010;110:692-701
  - 42% of households below poverty level are food insecure, 21% of households w/children
    - *NEJM* 2010;363:6-9

- **Carbohydrates affect brain serotonin levels**

- **“Comfort Foods” ↓ HPA axis stress response**
  - *Proc Natl Acad Sci* 2003;100:11696-11701
4. Stress

- **Chronic exposure to Intimate Partner Violence almost doubles (OR 1.8) risk of obesity at age 5 years.**
  
  *Arch Pediatr Adolesc Med 2010;164:540-546*

- **Childhood SES associated with later type 2 DM and Obesity**
  
  *BMC Public Health 2010;10:525*

- **Toddlers who showed insecure attachment to their mothers at age 2 had a 30% increased risk of obesity by age 4 ½**
  
  *Arch Pediatr Adolesc Med 2011;165:235-242*
“As the twig is bent, so the tree inclines”

- Adverse Childhood Experiences (ACE) Study

--Overall Exposure: 86% (among 7 tribes)

<table>
<thead>
<tr>
<th></th>
<th>Non-Native</th>
<th>Native</th>
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</thead>
<tbody>
<tr>
<td>Physical Abuse-M</td>
<td>30%</td>
<td>40%</td>
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<tr>
<td>Physical Abuse-F</td>
<td>27</td>
<td>42</td>
</tr>
<tr>
<td>Sexual Abuse-M</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Sexual Abuse-F</td>
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<td>31</td>
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<tr>
<td>Emotional Abuse</td>
<td>11</td>
<td>30</td>
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<tr>
<td>Household ETOH</td>
<td>27</td>
<td>65</td>
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<tr>
<td>Four or More ACEs</td>
<td>6</td>
<td>33</td>
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</table>

ACEs and Adult Health

- **ACE Score ≥4**
  - 4-12 x risk for alcoholism, drug abuse, depression and suicide attempt
  - 2-4 x risk for smoking, teen pregnancy, STDs, multiple sexual partners
  - 1.4-1.6 x risk for severe obesity
  - Strong graded relationship at all levels of ACEs for almost all outcomes, including heart disease


- **Nurse’s Health Study II: Childhood abuse**
  - dose-response associations (HR ≤1.69) with risk of diabetes in adult women
  - only partly explained by their ↑ BMI

  *Am J Prev Med 2010;39:529-536*
What is the average ACE score of:

--the children in your community?

--their parents?

What is your ACE score?
Stress in Children

- Positive
  - Normal/necessary part of healthy development
    - First day with new caregiver; immunization
  - Brief increases in heart rate and stress hormones

- Tolerable
  - More severe, longer lasting stressor
    - Loss of a loved one, natural disaster, injury
  - If buffered by relationship with supportive adult(s), brain and body can recover

- Toxic
  - Strong, frequent, prolonged adversity
    - Abuse, neglect, caregiver mental illness, poverty
  - If no adult support, can disrupt brain and organ development long-term

Center on the Developing Child, Harvard Univ.
“Childhood Trauma…

- “…is probably our nation’s single most important public health challenge…
  - …chronic maltreatment has pervasive effects on the development of mind and brain.
  - Developmental trauma sets the stage for unfocused responses to subsequent stress, leading to dramatic increases in the use of medical, correctional, social, and mental health services.”

- Complex trauma/toxic stress
  - e.g. abuse; neglect; exposure to DV, community violence; poverty; caregiver mental health problems
  - worse when caregiver is source of trauma or even just if they are unable to help child process traumatic experiences

## Sidebar 1: Domains of Impairment in Children Exposed to Complex Trauma

<table>
<thead>
<tr>
<th>I. Attachment</th>
<th>IV. Dissociation</th>
<th>VI. Cognition</th>
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</thead>
<tbody>
<tr>
<td>Problems with boundaries</td>
<td>Distinct alterations in states of</td>
<td>Difficulties in attention regulation and</td>
</tr>
<tr>
<td>Distrust and suspiciousness</td>
<td>consciousness</td>
<td>executive functioning</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Amnesia</td>
<td>Lack of sustained curiosity</td>
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<tr>
<td>Interpersonal difficulties</td>
<td>Depersonalization and derealization</td>
<td>Problems with processing novel</td>
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<tr>
<td>Difficulty attuning to other people's</td>
<td>Two or more distinct states of</td>
<td>information</td>
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<tr>
<td>emotional states</td>
<td>consciousness</td>
<td>Problems focusing on and completing</td>
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<tr>
<td>Difficulty with perspective taking</td>
<td>Impaired memory for state-based events</td>
<td>tasks</td>
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<td>Problems with object constancy</td>
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<td>Difficulty planning and anticipating</td>
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<td>Problems understanding responsibility</td>
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<td>Learning difficulties</td>
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<td>Problems with language development</td>
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<td>Problems with orientation in time and</td>
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<td>space</td>
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<tr>
<td>II. Biology</td>
<td>V. Behavioral control</td>
<td>VII. Self-concept</td>
</tr>
<tr>
<td>Sensorimotor developmental problems</td>
<td>Poor modulation of impulses</td>
<td>Lack of a continuous, predictable sense</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Self-destructive behavior</td>
<td>of self</td>
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<tr>
<td>Problems with coordination, balance,</td>
<td>Aggression toward others</td>
<td>Poor sense of separateness</td>
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<tr>
<td>body tone</td>
<td>Pathological self-soothing behaviors</td>
<td>Disturbances of body image</td>
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<tr>
<td>Somatization</td>
<td>Sleep disturbances</td>
<td>Low self-esteem</td>
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<tr>
<td>Increased medical problems across a wide</td>
<td>Eating disorders</td>
<td>Shame and guilt</td>
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<tr>
<td>span (e.g., pelvic pain, asthma, skin</td>
<td>Substance abuse</td>
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<td>problems, autoimmune disorders,</td>
<td>Excessive compliance</td>
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<td>pseudoseizures)</td>
<td>Oppositional behavior</td>
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<td></td>
<td>Difficulty understanding and complying</td>
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<tr>
<td></td>
<td>with rules</td>
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<tr>
<td>III. Affect regulation</td>
<td>Reenactment of trauma in behavior or</td>
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<tr>
<td>Difficulty with emotional self-regulation</td>
<td>play (e.g., sexual, aggressive)</td>
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<tr>
<td>Difficulty labeling and expressing</td>
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<td>feelings</td>
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<tr>
<td>Problems knowing and describing</td>
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<td>internal states</td>
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<tr>
<td>Difficulty communicating wishes and needs</td>
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Seeds planted for the next generation

Prenatal/Early Life
Nutrition

Poverty

Prenatal Substance Use/Abuse

Child Abuse/Neglect

Quality of Early Life Relationships

Epi/Genetics

Seeds planted for the next generation

Alcohol Use

Drug Abuse

Violence

Traumatized Parenting

Depression

Diabetes

Obesity

Heart Disease

Emotional Responses

Overeating

Physiologic/Behavioral Ability to Respond to Life Stressors
Reducing Prenatal and Early Life Risk Factors for Obesity and Chronic Disease
Parenting is Key

- 2-3x ↑ risk for anxiety and disruptive behavior disorders and major depression in children of depressed parents
- Treating the mothers’ depression reduces symptoms in both mothers and children

*JAMA* 2006;295:1389-1398

- Maternal warmth buffers the effects of low early-life SES on pro-inflammatory signaling in adulthood.

*Molecular Psychiatry* 2010;doi:10.1038/mp.2010.53
Prenatal/Early Life Home Visiting

- One of the key evidence-based interventions proven to improve the life trajectories of low income women and children
  - Positive effects now shown up to age 19 yrs

- If home visiting were a medication, it would be malpractice not to provide it

- Tribal Maternal, Infant & Early Childhood Home Visiting Program
  - Administered by ACF
  - 18 tribes/T.O.’s now funded to provide home visiting
Nurse-Family Partnership

- Example of an evidence-based home visiting program
- Works with vulnerable first-time mothers living in poverty—starting early in pregnancy thru child’s 2nd birthday
- Goals: Improve prenatal care, quality of parenting and life prospects for mothers by partnering them with a registered nurse.
Academic Achievement

Grades 1-3, Age 9—Memphis
(Born to low-resource mothers)

<table>
<thead>
<tr>
<th>Nonparticipants</th>
<th>Nurse-Family Partnership Participants</th>
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Reading and Math Achievement Test Scores (percentiles)

Preschool Language Scale

Age 4—Denver
(Born to low-resource mothers)

<table>
<thead>
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Total Language Score

Source: Reproduced with permission from *Pediatrics*, Vol. 120, e838, Copyright © 2007 by the AAP.

Source: Reproduced with permission from *Pediatrics*, Vol. 114, 1565, Copyright © 2004 by the AAP.
Days Hospitalized for Injuries
Birth to age 2—Memphis

Months Between Births
Between first and second child
(by first child’s fifth birthday)—Memphis

Source: JAMA, 1997, Vol. 278, 650, Copyright © 1997, American Medical Association. All rights reserved.

Source: JAMA, 2000, Vol. 283, 1987, Copyright © 2000, American Medical Association. All rights reserved.
Months Receiving Welfare Assistance (AFDC)
Birth through age 5—Memphis

Nonparticipants
Nurse-Family Partnership Participants

Source: JAMA, 2000, Vol. 283, 1987, Copyright © 2000, American Medical Association. All rights reserved.

Months Receiving Food Stamps
Birth through age 5—Memphis

Nonparticipants
Nurse-Family Partnership Participants

Source: JAMA, 2000, Vol. 283, 1987, Copyright © 2000, American Medical Association. All rights reserved.
Monetary Benefits

Lower-risk families
- $7,271
- $9,151

Higher-risk families
- $7,271

Net present value dollars per child 2003

- Increased participant income (net of welfare loss)
- Reduction in tangible crime losses
- Savings to government
- Cost

Source: 2005 RAND Corporation Study
‘Weaving a safety net so tight that no child slips through’

- Map out all the programs/services already in a community—there’s more than we think
  - Look for gaps
  - Look for overlap
  - What can be realigned to better cover the gaps?
  - What new components are needed?

- All programs need to be talking to each other
  - Tribal, federal, state, county, private
  - Social services, medical, mental health, schools

- …and have a common, unifying vision
The start of one tribe’s map

**Preconception- Pregnancy- Childhood-Adolescence**

- School Food Programs
- WIC
- Breastfeeding support
- “Backpack Foods”
- Teen Pregnancy Support
- Zero-to-Three Court Referral Program, Healthy Parenting curriculum
- Mental Health: Parent Child Interaction Therapy, Parenting groups, Trauma Tx
- Coping Skills classes: emotions, finances
- Home Visiting
- Teen Education and Family Nights
- Cherokee Choices: Mentoring, coping skills, exercise, healthy foods
- Head Start/Parents as Teachers
- Language immersion program
- Prenatal Dental Program
- Pediatric dentist
- Renew tribal traditional pregnancy/child-rearing practices
What can we do—right now?

- Alleviate food insecurity/provide *good* nutrition
- Home visiting interventions
- Teach parenting and coping skills
- Screen for/treat depression and substance abuse
- Intervene in adverse childhood experiences
- Strengthen traditional values, worldviews and practices
  - Especially to care for pregnant women, children and young parents
  - Take the “long view”—good things that happen now may take several generations to show their full benefit
- Change *ourselves*
  - See patients more clearly—their resilience is amazing
  - See that *everything* relates to health—and vice versa
    - Need to develop new partnerships to strengthen the “web”
“Dance with Desire to Make the World Well”