Early Life Nutrition and Diabetes
In-Utero Stressors and Vulnerability for Chronic Disease

Indian Health Service Diabetes Group
October 2014

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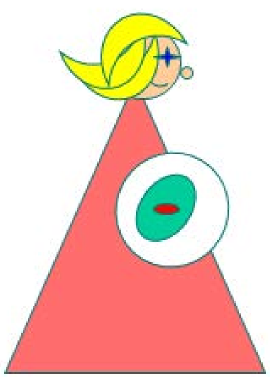


OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

What is ‘Developmental Programming’?

Basis: Biologic capacity of normal *developing* organisms to be *durably* changed by environmental exposures without change in the inherited genome.

Exposures: Nutrients, stress, O2, chemicals/toxins

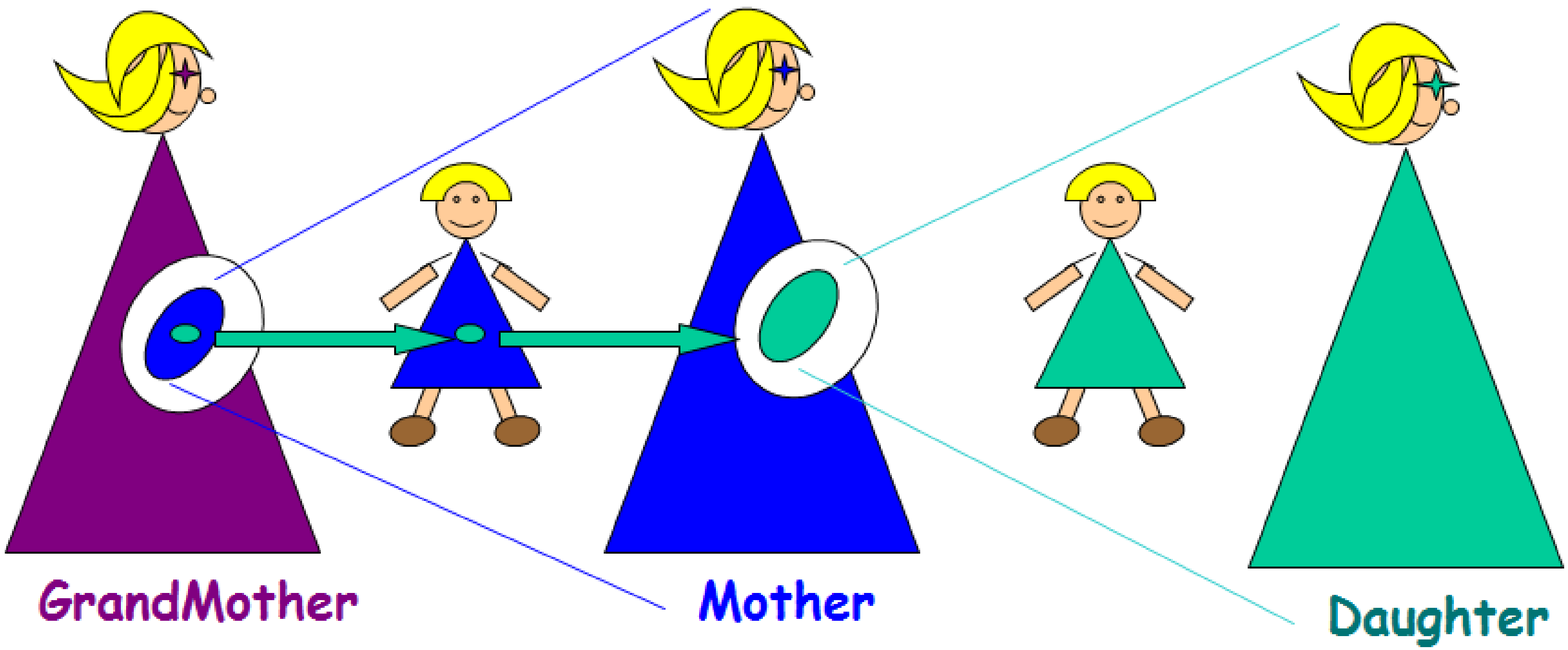
Mechanisms: Change in organ structure/function, change in gene expression via epigenetics

Susceptibility: Fetus>>infant>>child>>teen>>adult

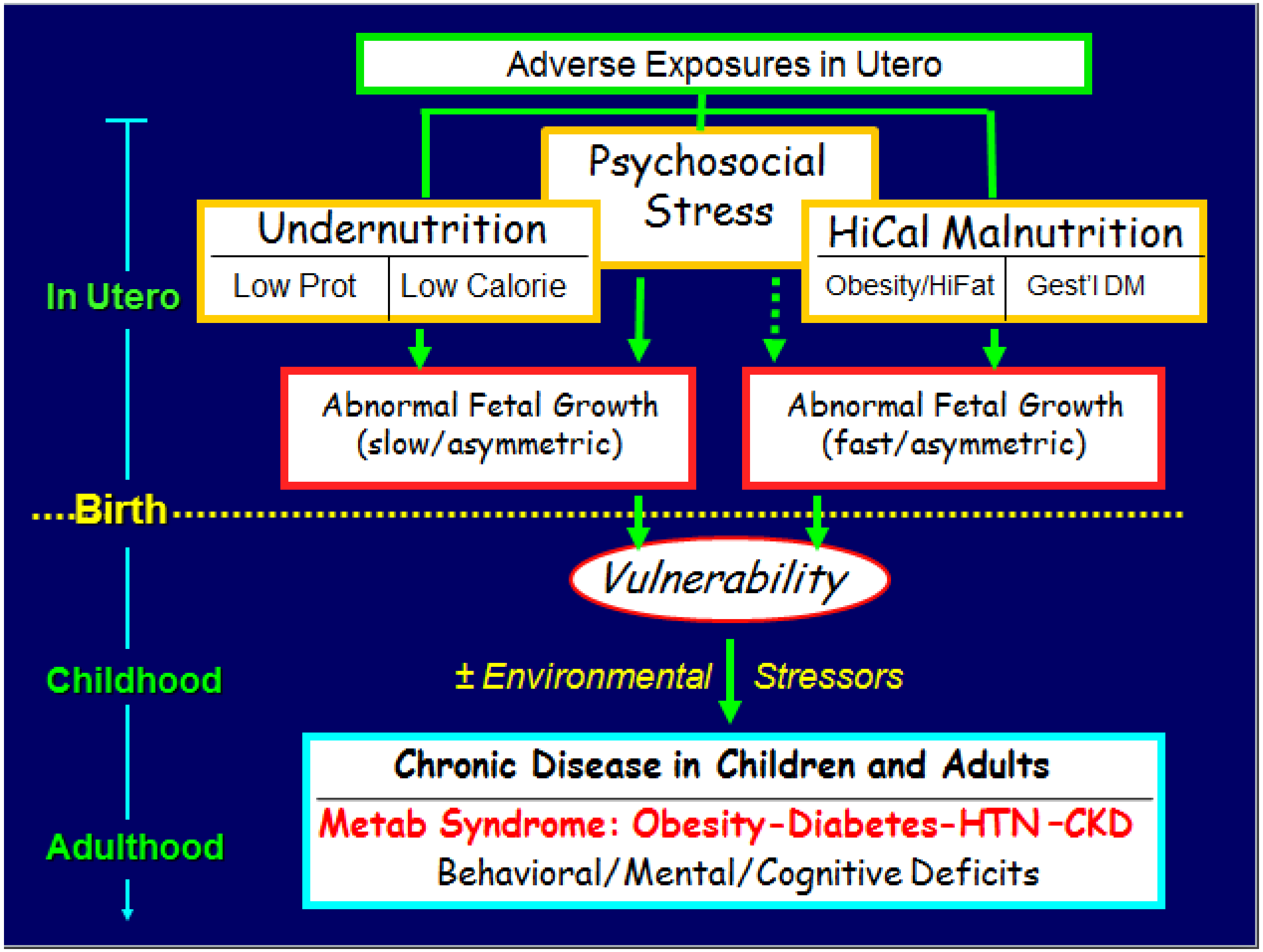
Impact: **Vulnerability** to development of chronic disease later in life.

We Are What We Eat – And So Are Our Kids & Grand-Kids

Nutritional Life of the Egg is Trans-Generational



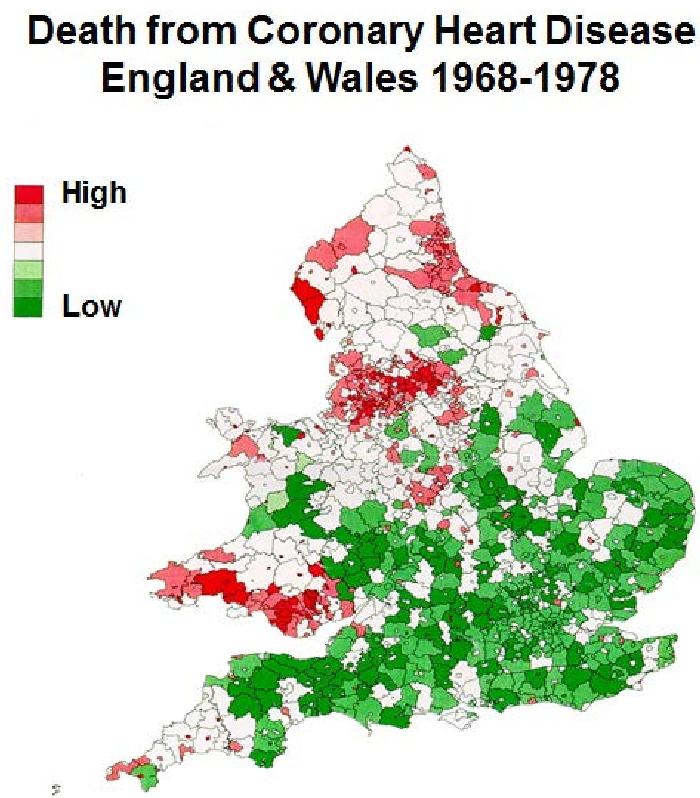
Adverse Exposures in Utero



Biology of Developmental Programming Outline

- The Origins of Developmental Origins: A Paradox
- Evolving History: Lessons from Cohort Studies
- Biological Pathways of Disease Vulnerability
  - Change in organ structure
  - Change in homeostatic system setpoints
  - Interactions of prenatal and postnatal exposures
- Transgenerational Transmission of Disease Risk
  - Mom’s early-life undernutrition affects future baby
  - Mom preconception obesity affects future baby

The Origins of Developmental Origins
Socioeconomic Health Disparity



Red areas:
- poor land
- sparse food
- Urban poverty

Green areas:
- rich land
- abundant food
- Non-$ wealth

Neonatal Mortality in early 1900's has identical pattern

Gardner MJ et al. 1984 Atlas of mortality from selected diseases in England and Wales, 1968-78. John Wiley, Chichester.

History of Development Programming "The Paradox"

- Everyone 'knew' that Coronary Artery Disease was a disease of societal *affluence*.
- How then can Coronary Mortality be tracking with socioeconomic disadvantage?

Answer: Babies developing in adverse conditions are uniquely susceptible to negative impacts of affluence (hi animal protein, fat, sugar, calories) on chronic disease risk

A Link to Health Disparity

Developmental Programming

- First recognized because it led to socioeconomically-based health disparity
- Is a major ***mechanism*** by which
  - SE/psychosocial disadvantage becomes *biologically embe*dded within a population
  - developmentally-based health disparities can be transmitted to future generations

The Barker Hypothesis
Developmental Origins of Disease

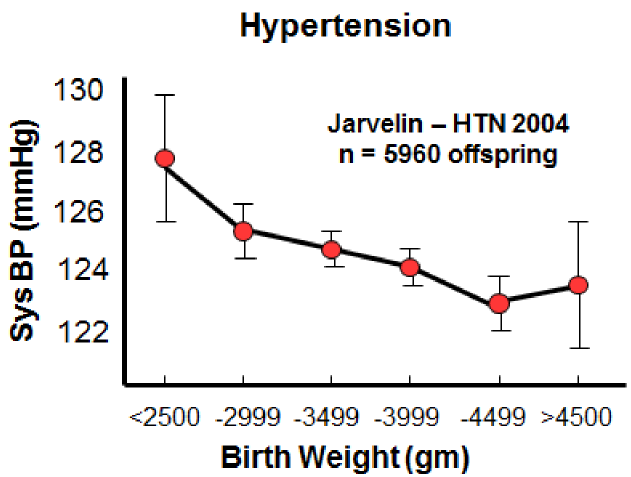
Lessons from Cohort Studies

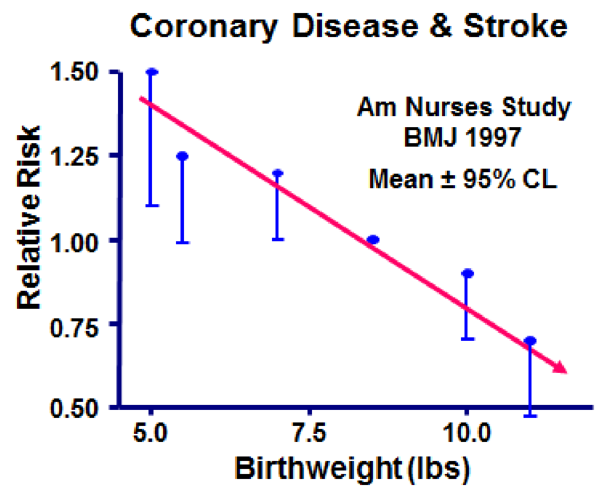
The British Cohorts

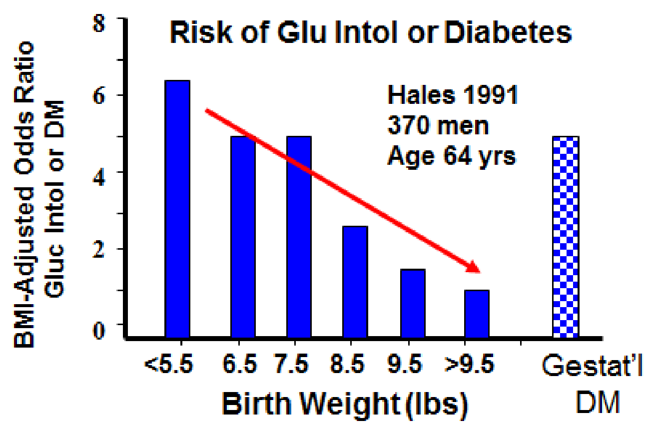
- Small English Villages
- Two time points: Birth
  50+ years

Poor Fetal Growth Increase Risk of Chronic Disease Later in Life

Poor Fetal Growth - Increased Risk of Disease

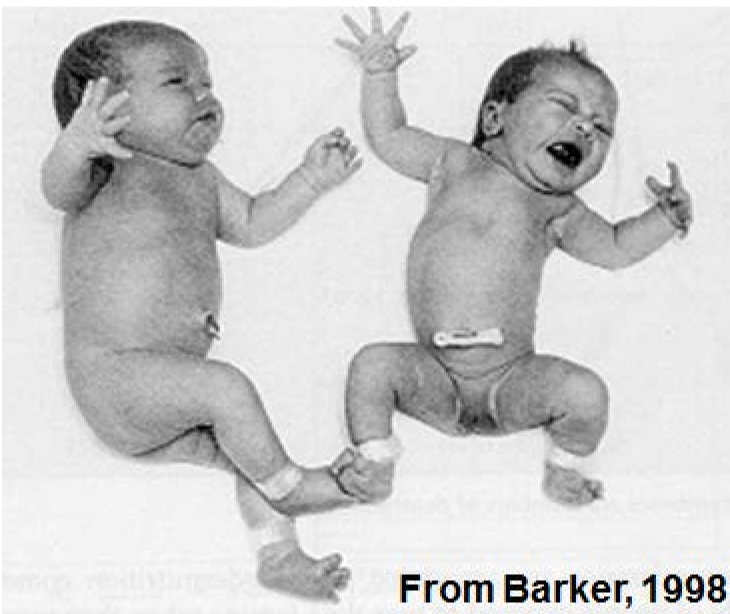






Birth Weight is Crude Surrogate for Fetal Growth

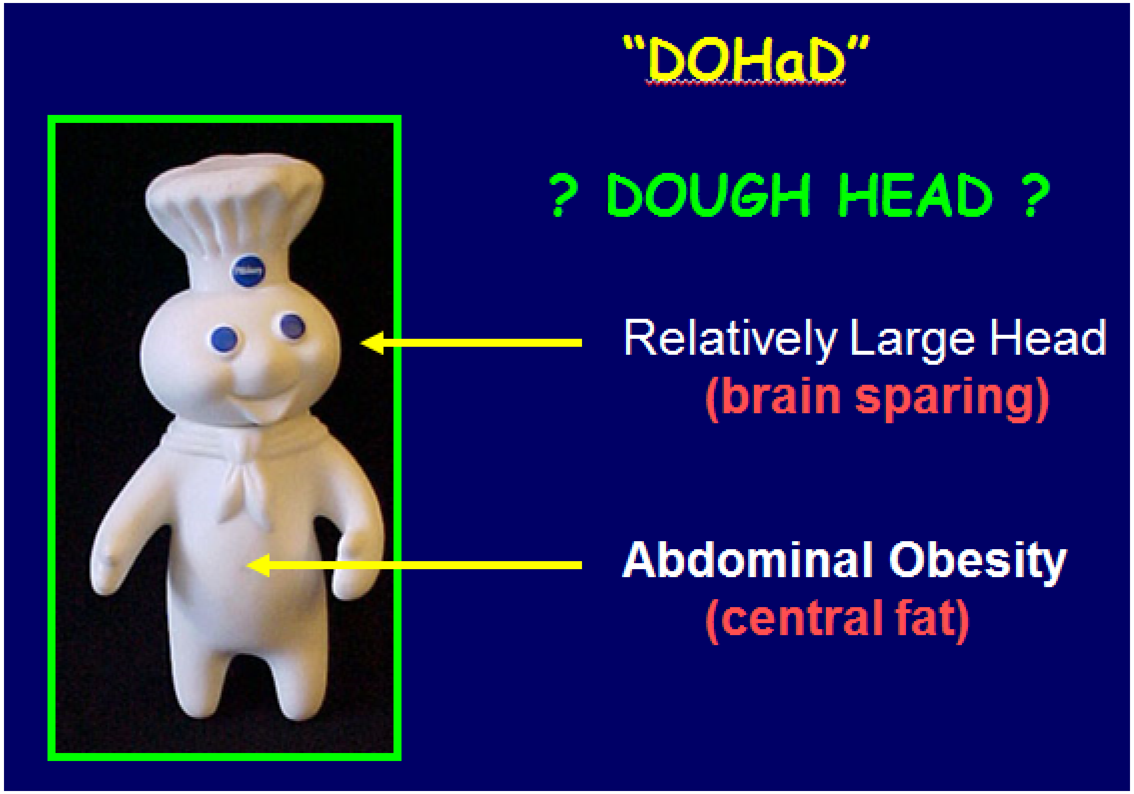
Asymmetric Growth Restriction



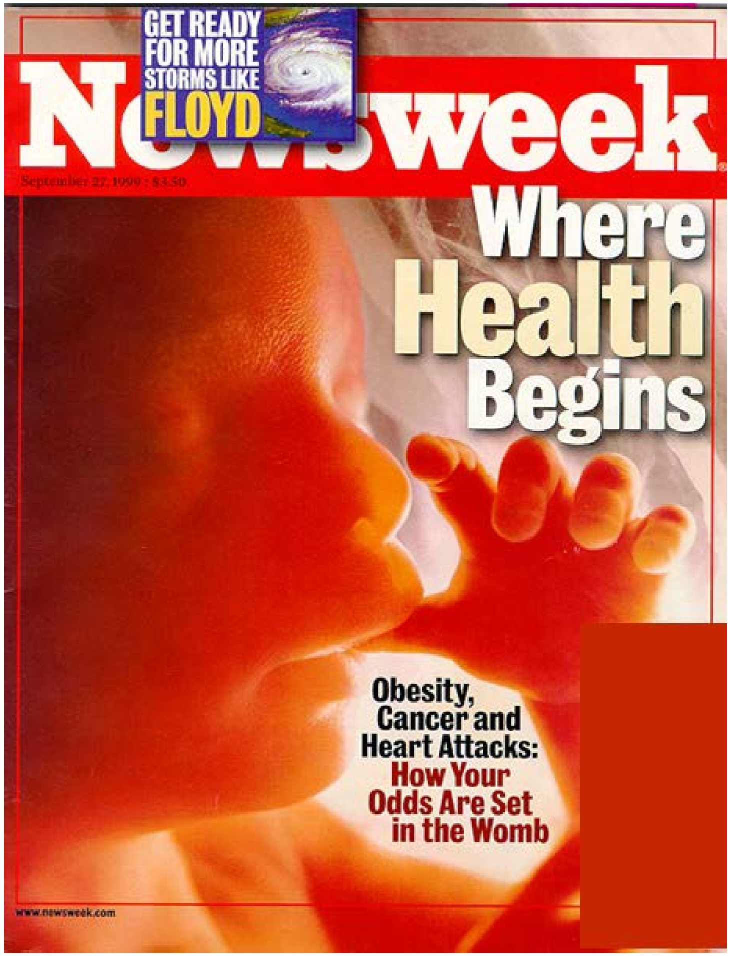
- Thin (Low weight to height ratio)
- Fetal blood flow redistribution
  - Low kidney, lover pancreas
  - Low abdominal girth
  - Heart/brain 'sparing'
- Low arm circumference (low muscle mass)

May Occur with Normal Birth Weight!

Developmental Origins of Health & Disease



Developmental Origins of Chronic Disease



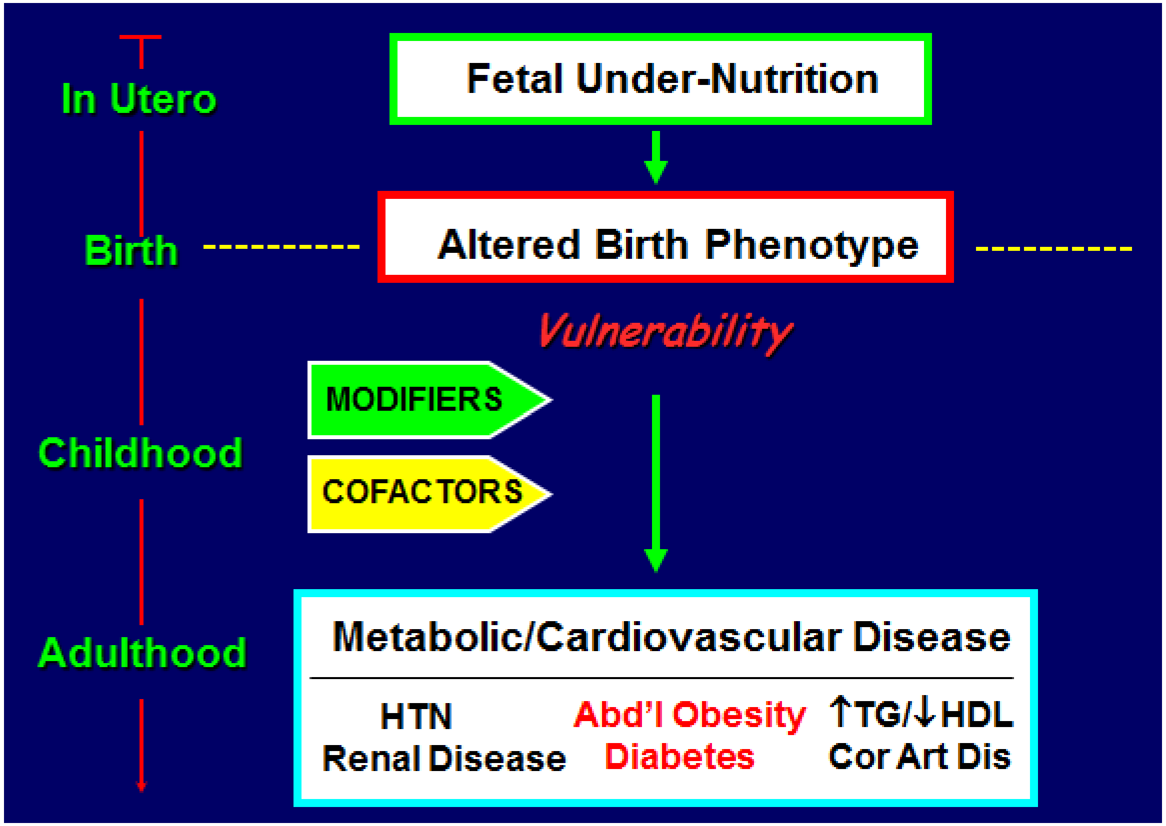
- Obesity
- Type II Diabetes
- Hypertension
- Kidney Disease
- Dyslipidemia
- Ischemic Heart Disease
- Osteoporosis
- Asthma/Allergies
- Depression, Anxiety
- ADHD, Schizophrenia
- Breast, Ovarian, & Lung Cancers

Developmental Origins of Disease

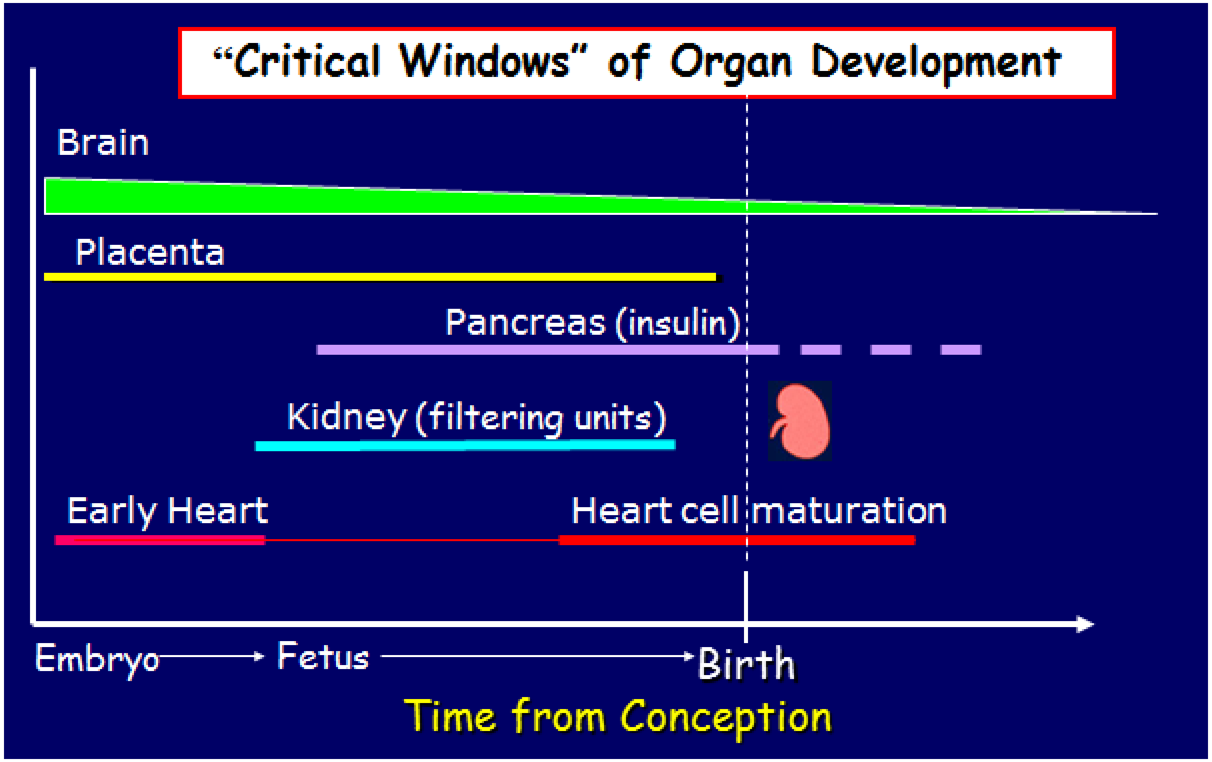
Pathways of Nutritional Programming

- Altered organ structure during development
- Altered regulatory system function
- Adverse interaction of prenatal vulnerabilities with postnatal stressors

Programming by Maternal-Fetal Undernutrition



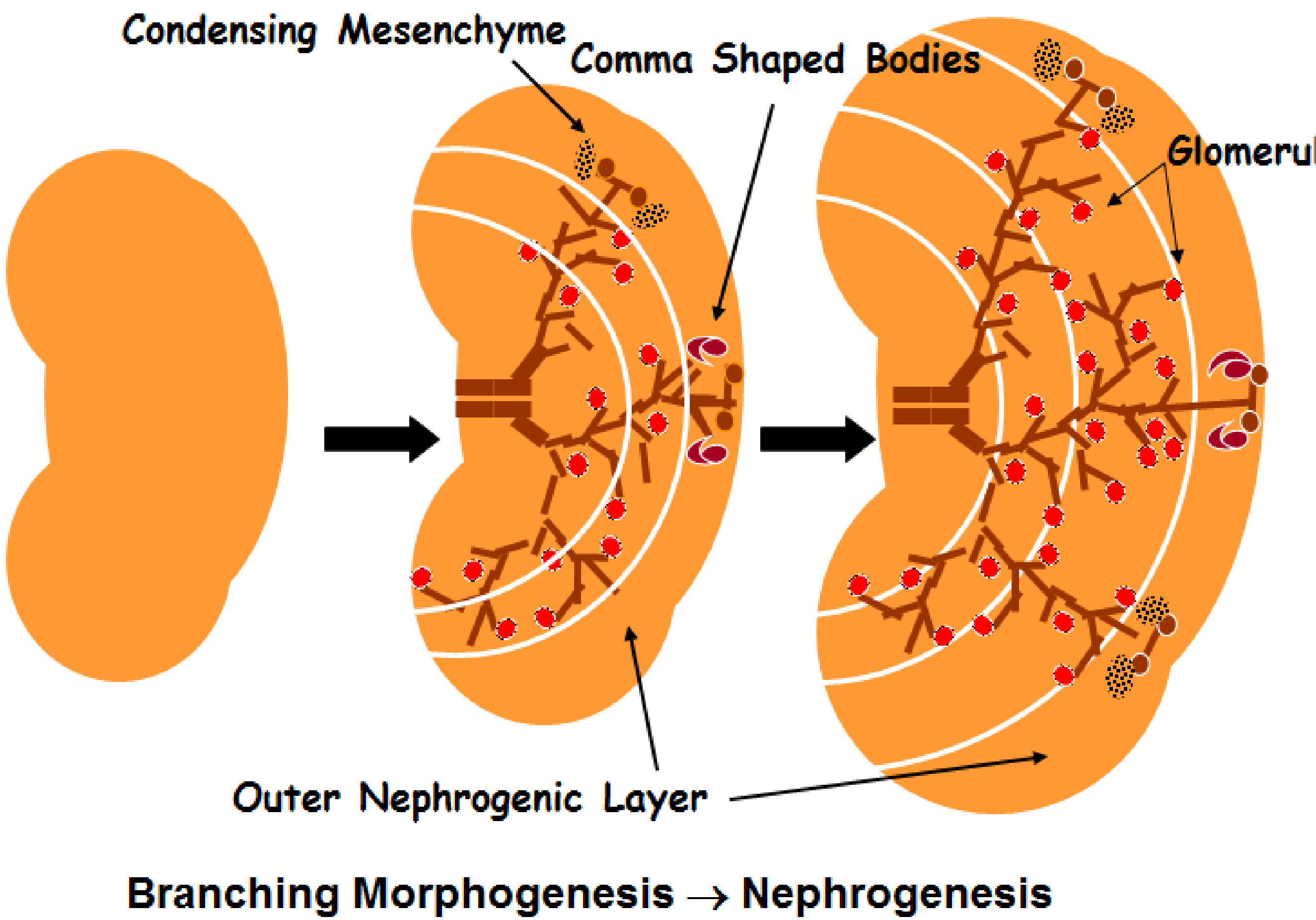
Pathways of Nutritional Programming
Altered Organ Structure/Function



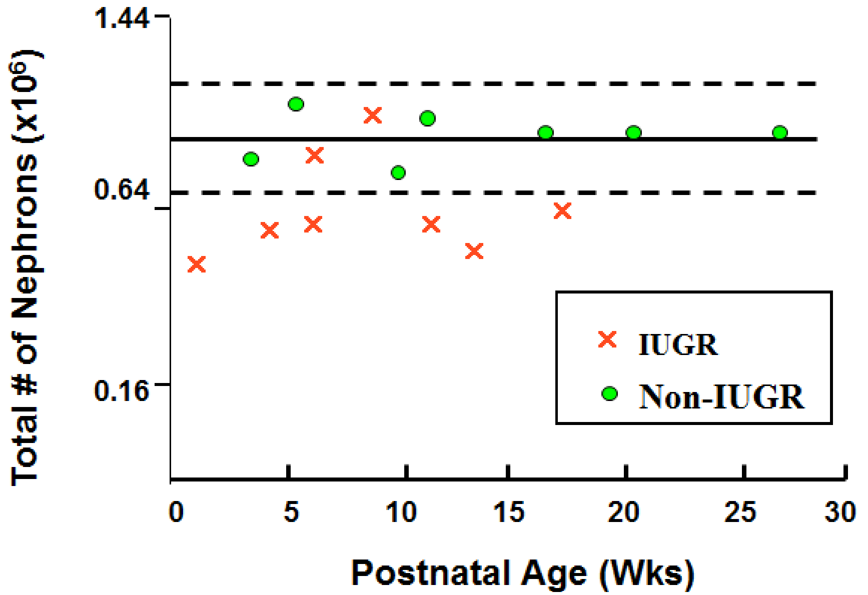
Pathways of Nutritional Programming
Structural Deficits – Decreased Number Functional Units

Kidney	Decreased Nephron Number	HTN, renal disease
Pancreas	Decreased Iselt ß cell Number	Change Insulin secretion
Muscle	Decrease muscle mass	Decreased Basal met rate Decreased exercise capacity Decreased insulin sensitivity
Heart	Decreased myocyte number	Increased Risk CHF
Liver	Decreased lobule, cell number	Change lipid/protein metab
Vascular	Decreased microvasc dens	Increased vasc resistance
Brain	Change nerural circuits	Increased appetite, HPA axis

New Nephrons Form in Concentric Layers During Gestation



Reduced Glomerular Number in Human IUGR



Hinchliffe et al, Br J Ob Gyn 99: 296, 1992

Developmental Origins of HTN Pathways of Nutritional Programming

- Altered Organ Structure during Development
  - **Kidney: Decreased nephron number**
- Altered Regulatory System Function
  - Energy Balance: “thrifty phenotype”
- Interaction of prenatal vulnerabilities with postnatal stressors

Altered Regulatory System Function in Programmed Offspring

Enhanced Responses to Postnatal Environment*

- Stress hyperreactivity: HPA Axis, cortisol
- Sympathetic nervous system hyperactivity
- Oxidative stress/Inflammatory responses
- Immune hyperactivity (asthma, allergies)
- Change energy homeostasis: Fat, glucose/insulin metabolism, appetite regulation

*Shown with all 3 major programming forces

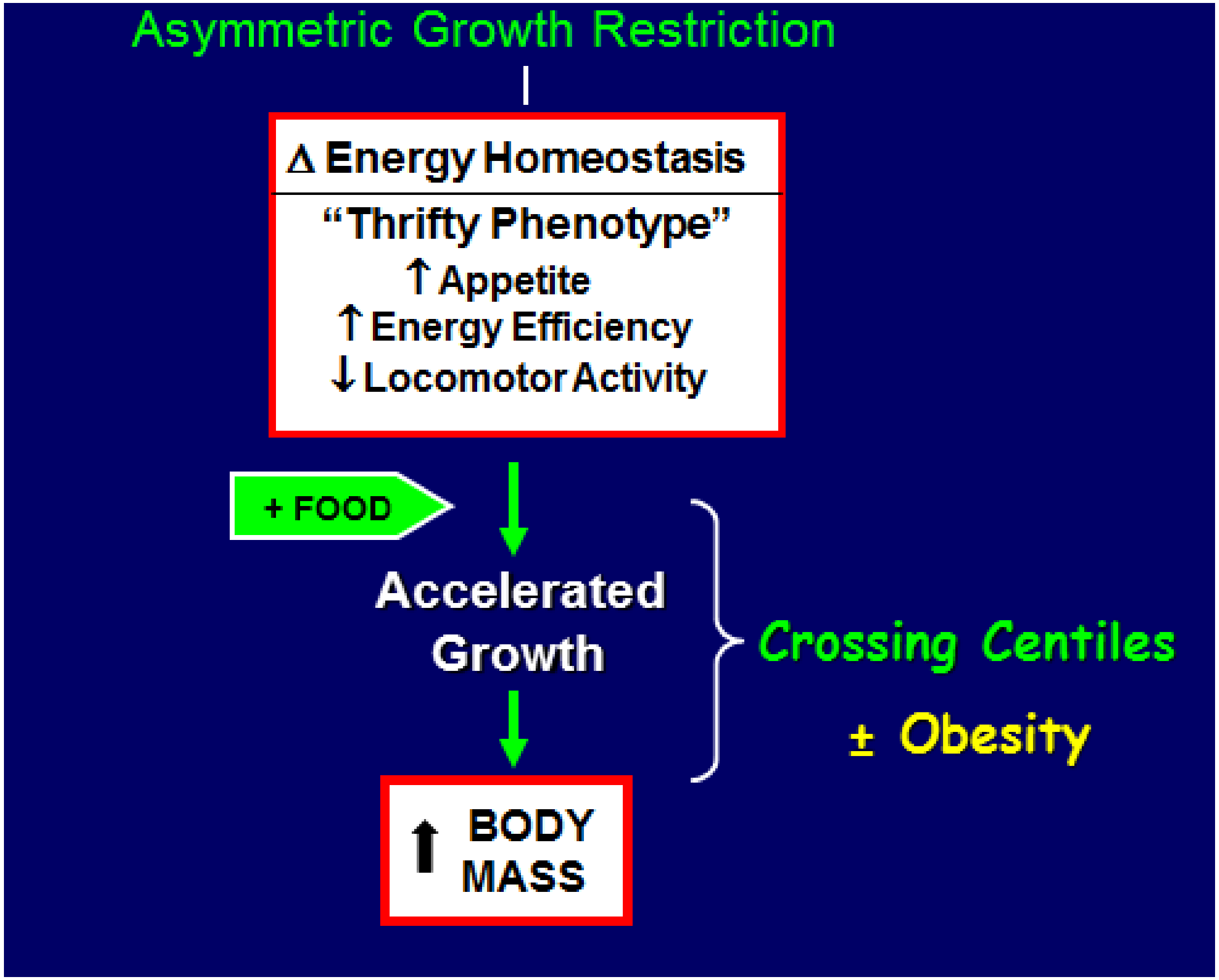
Altered Energy Homeostasis in Programmed Offspring

“The Thrifty Phenotype”

- The fetus adapts to nutrient deficit by permanently
  - Increasing energy utilization efficiency
  - Increasing appetite – promoting circuits
  - Promoting survival in utero
- These permanent adaptations:
  - Enhance postnatal tolerance to famine
  - Impair ability to handle nutrient excess
- Example: “Rural-to-Urban Transition”

Hales & Barker, 2001

"The Thrifty Phenotype"



What is the Impact of Thrifty Phenotype?

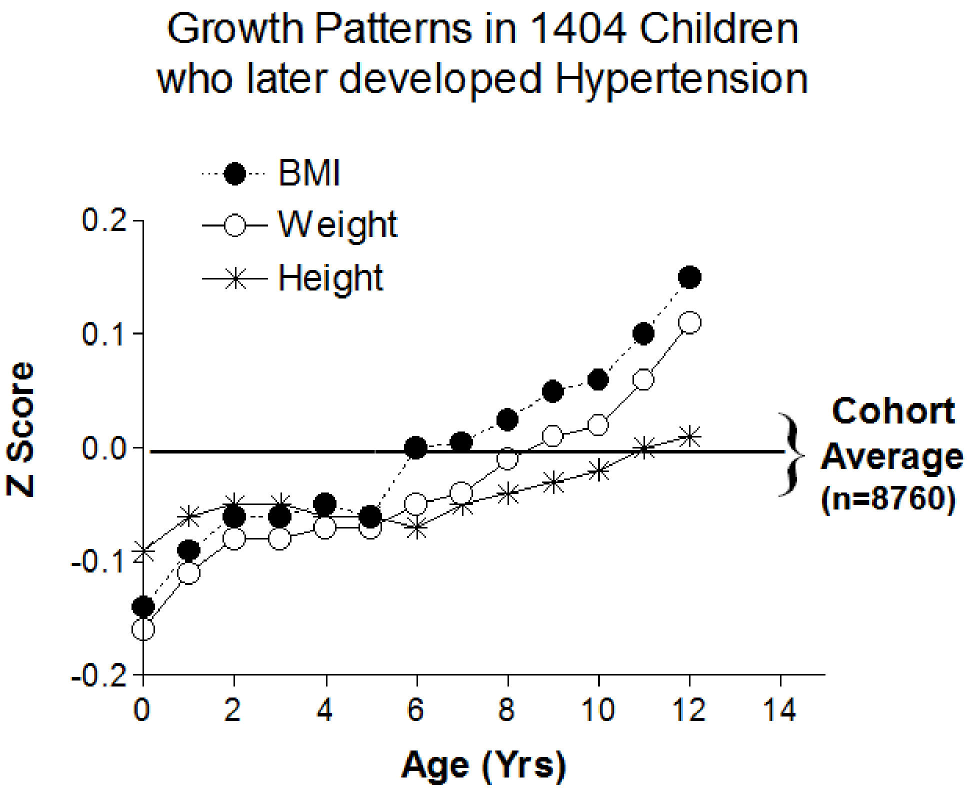
Lessons from Cohort Studies

The Helsinki Cohorts

- Finnish public health records
- Annual child growth data: birth – 15 years
- Adult Outcomes: med Rx, hospital records

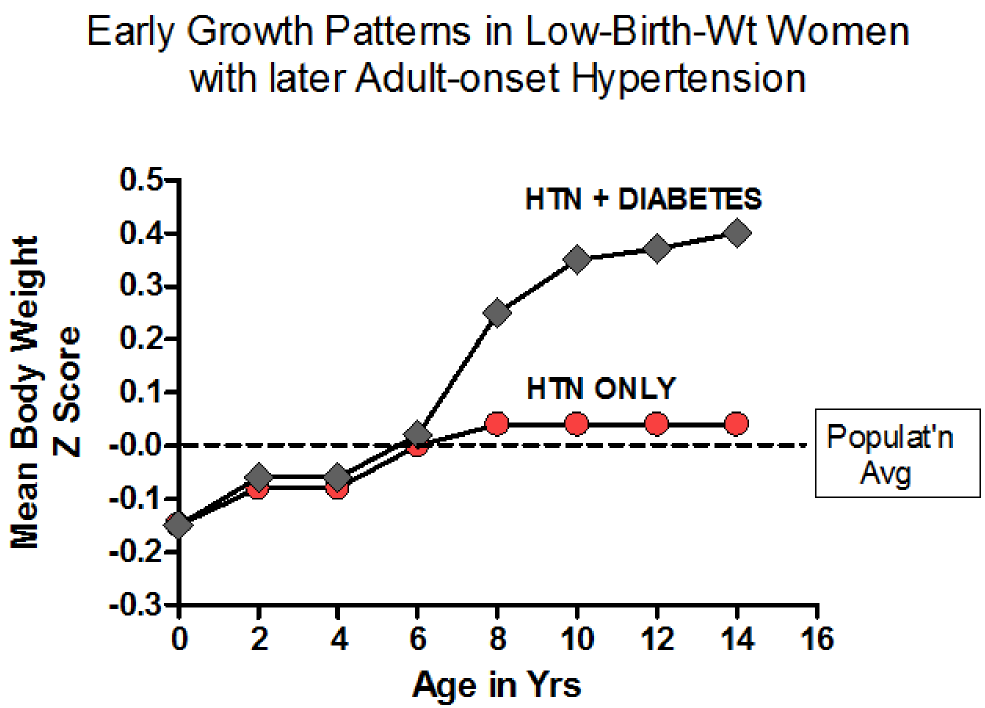
Accelerated Postnatal Growth Enhances Risk of Chronic Disease Later in Life

Rapid Early Growth Predicts Adult HTN



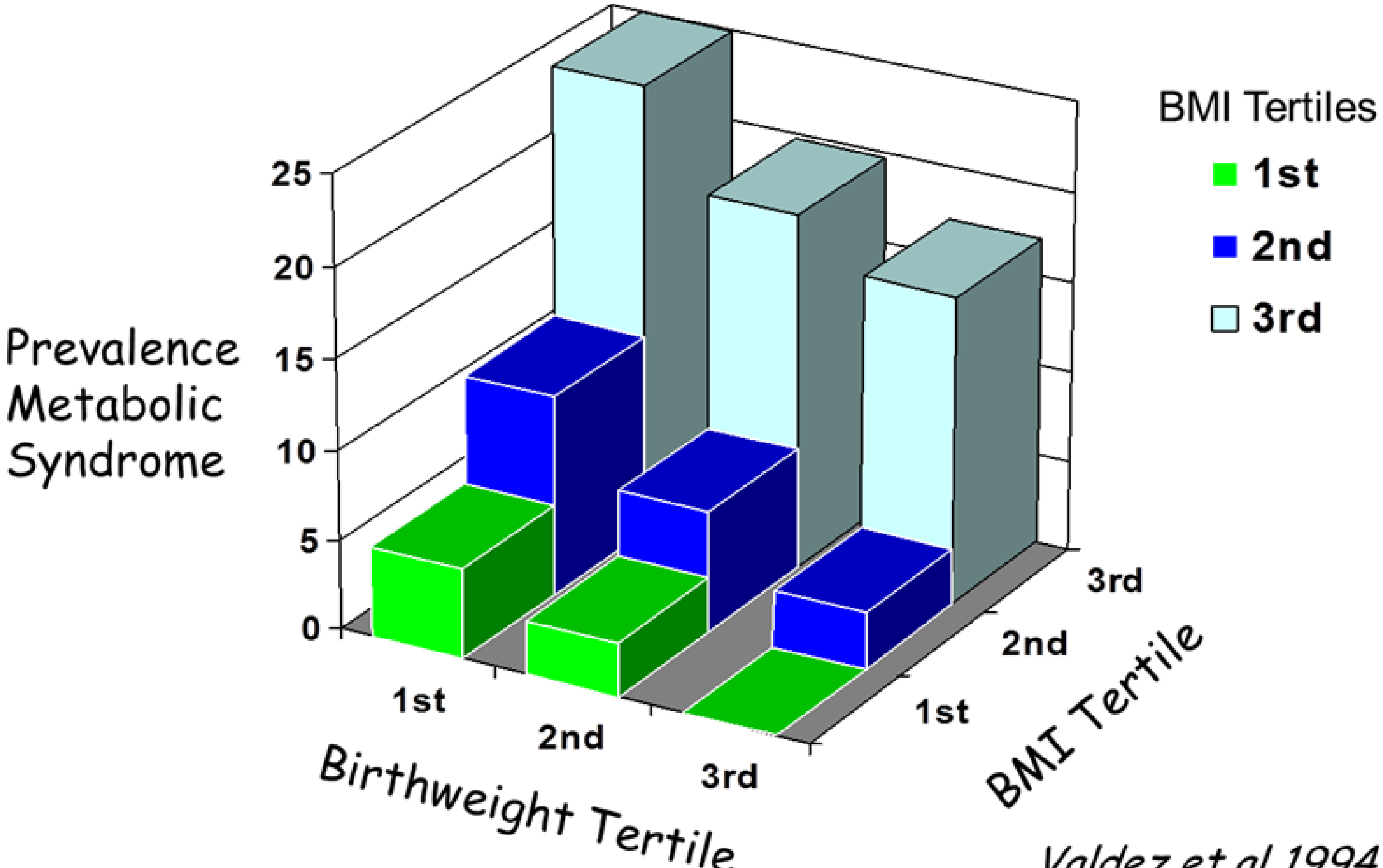
Barker et al. J HTN 20: 1951, 2002

Rapid Early Growth Patterns Predict Adult HTN ± Diabetes



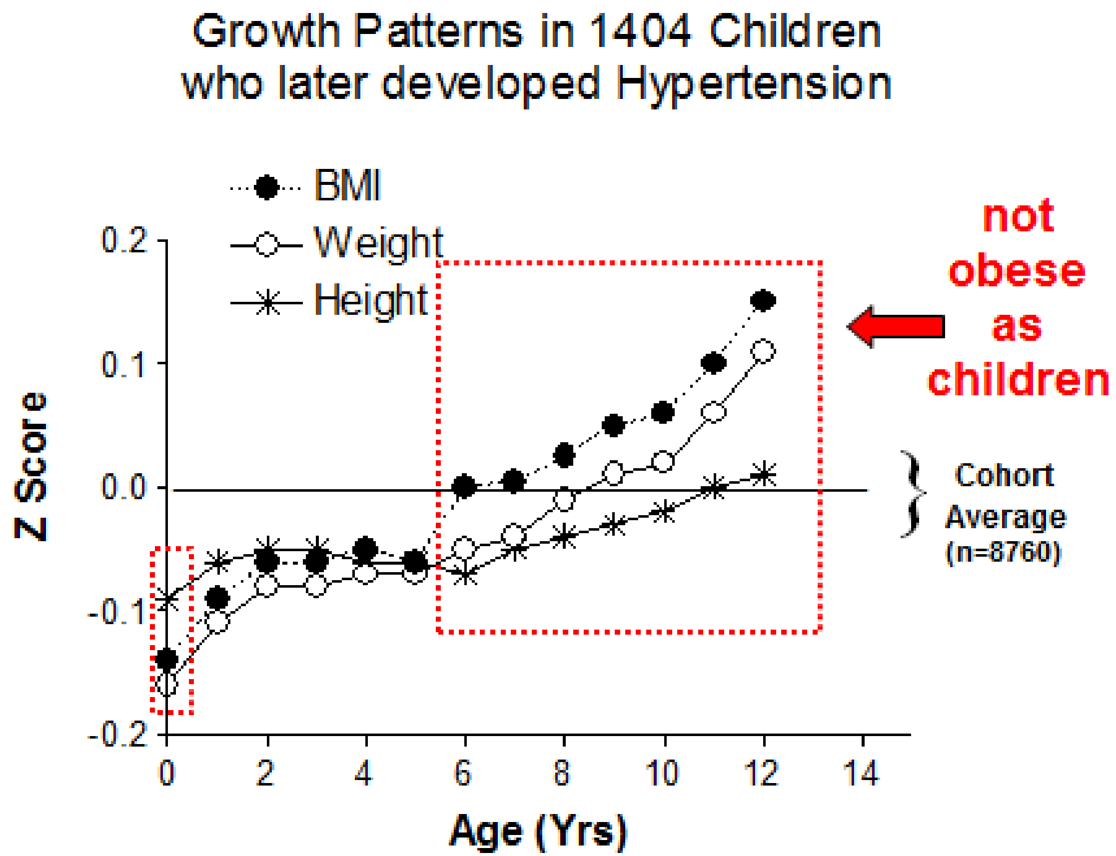
Eriksson et al, Hypertension 2000

Prevalence of Metabolic Syndrome Crossing Percentiles Enhances Disease



Valdez et al 1994

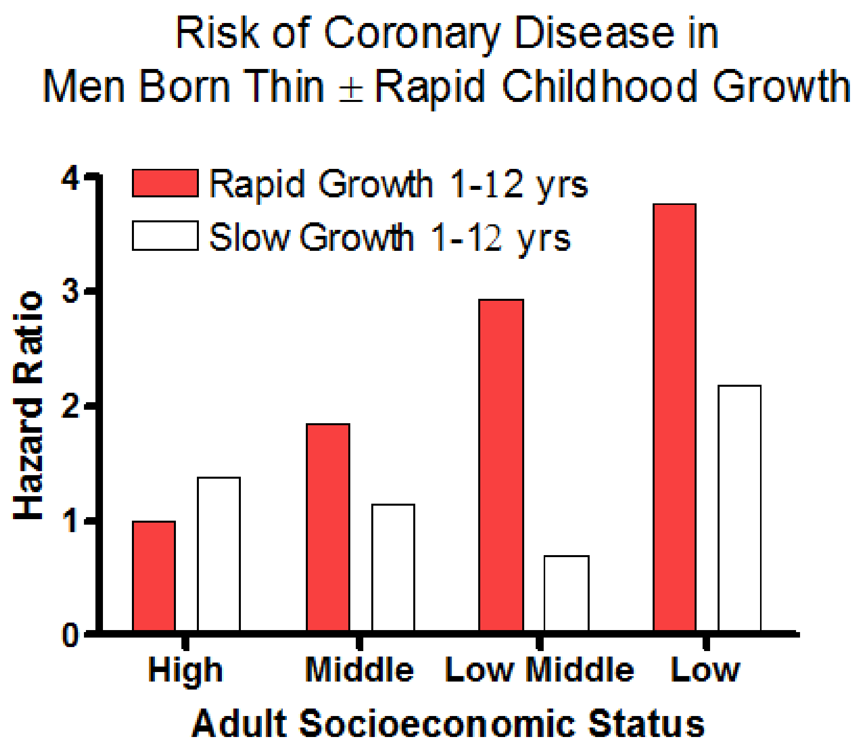
Early Growth Patterns Predict Adult HTN



Barker et al. J HTN 20: 1951, 2002.

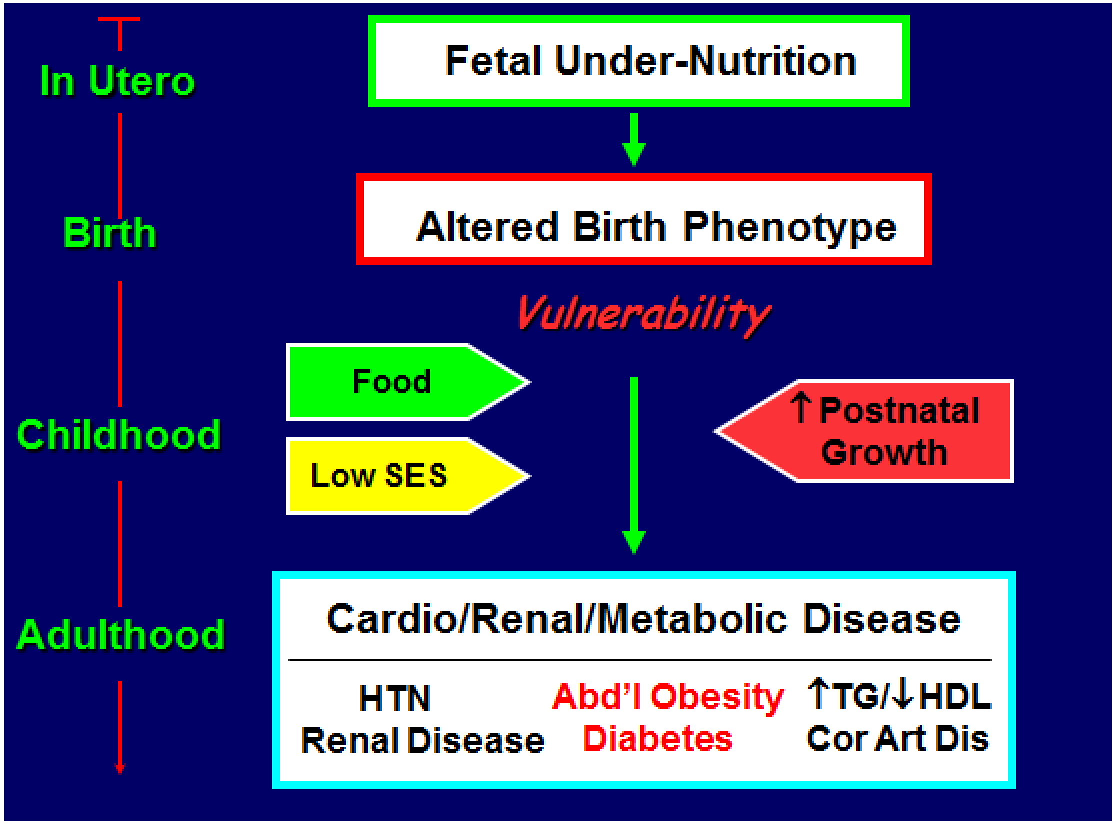
Adverse Impact of Accelerated Growth

Born Small + Rapid Childhood Growth



Ericksson et al 2001

Developmental Origins of Cvascular Disease



Developmental Origins of HTN

Pathways of Nutritional Programming

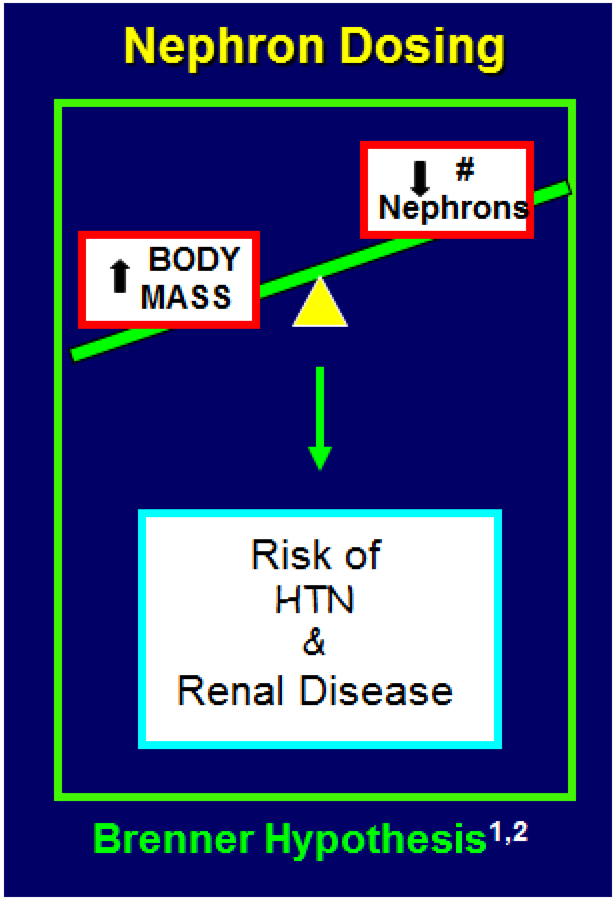
- Altered Organ Structure – Change Function
  - **Kidney: Decreased nephron number**
- Altered Homeostatic Setpoint
  - **Energy Balance: "thrifty phenotype"**
- Adverse interaction of prenatal vulnerabilities with postnatal stressors

What Conveys Risk of HTN-Renal Disease in Lower Birth-Weight Offspring?

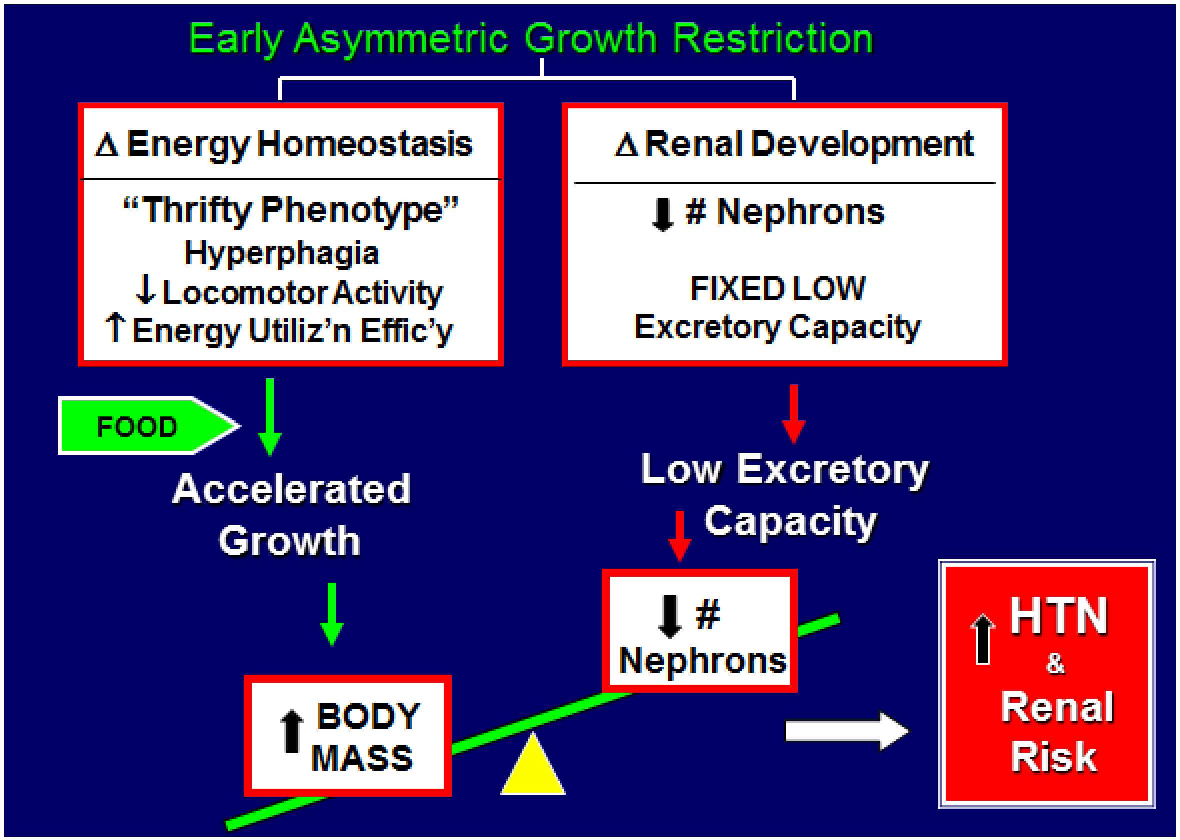
Low Nephron Number?

1Am J HTN 1988 1:335-47;

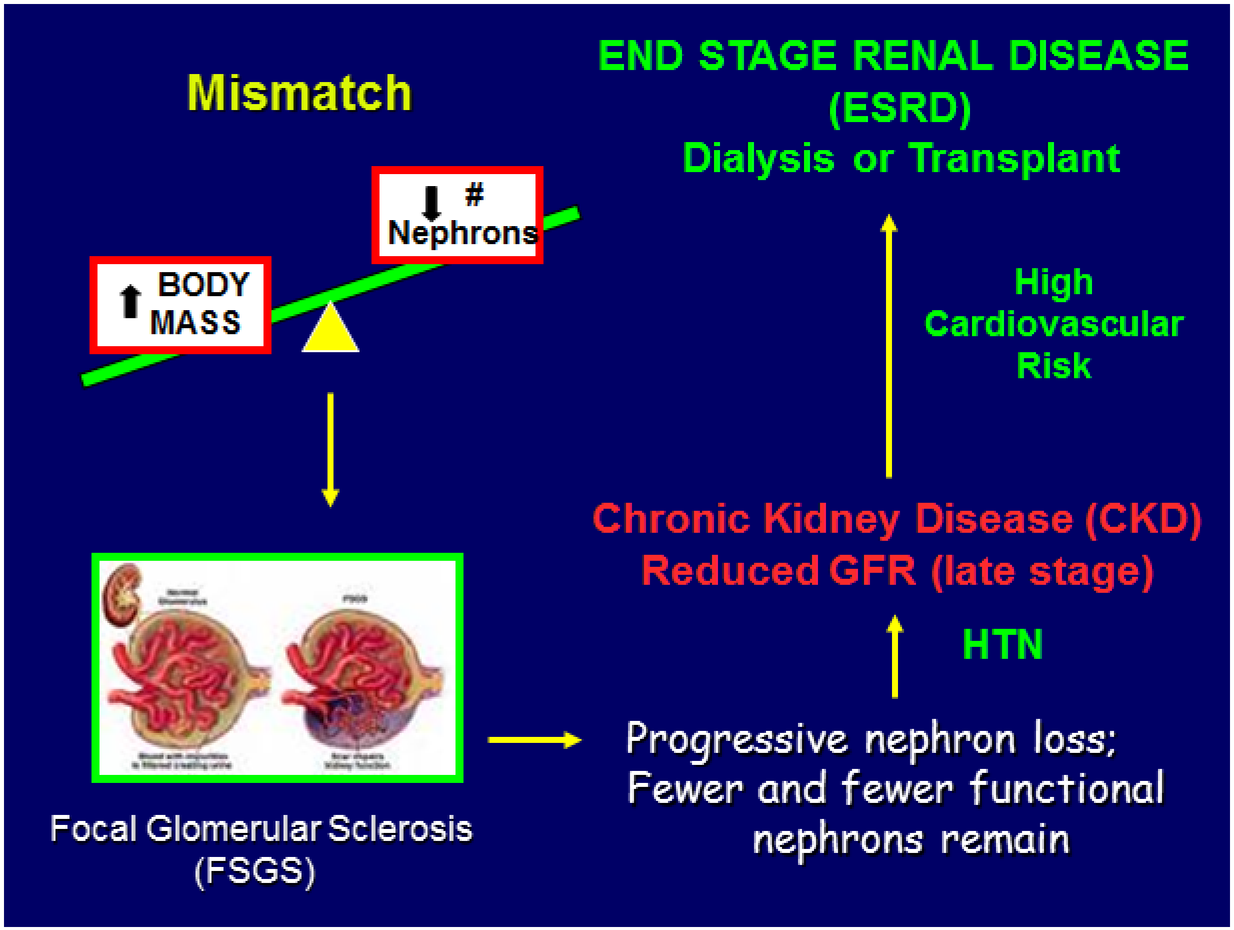
2Am J Kid Dis 1994 23: 171



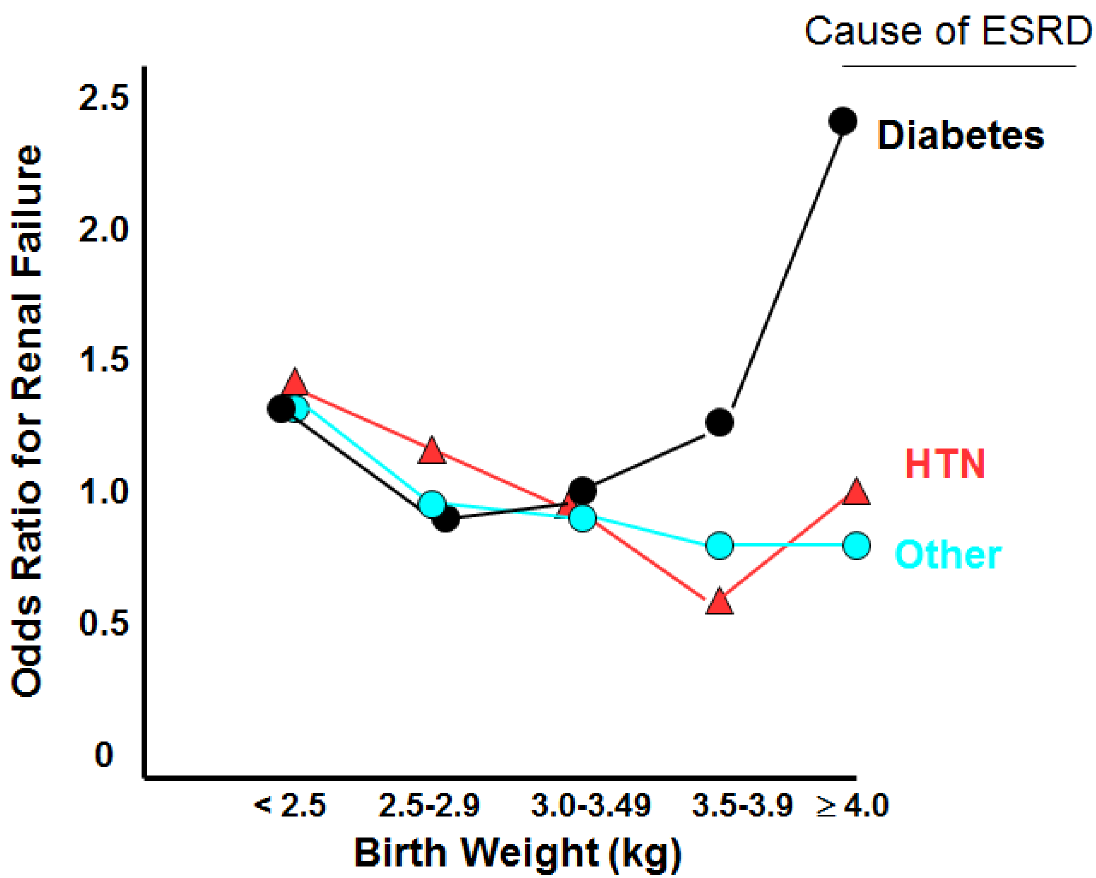
Programming Pathways: Mismatch



Mismatch


Mismatch
END STAGE RENAL DISEASE
(ESRD)
Dialysis or Transplant
Nephrons
BODY MASS
High Cardiovascular Risk
Chronic Kidney Disease (CKD)
Reduced GFR (late stage)
HTN
Progressive nephron loss;
Fewer and fewer functional nephrons remain
Focal Glomerular Sclerosis
(FSGS)

Poor Fetal Growth Affects ESRD Risk



Adapted from : Lackland D et al. Arch Intern Med, 2000

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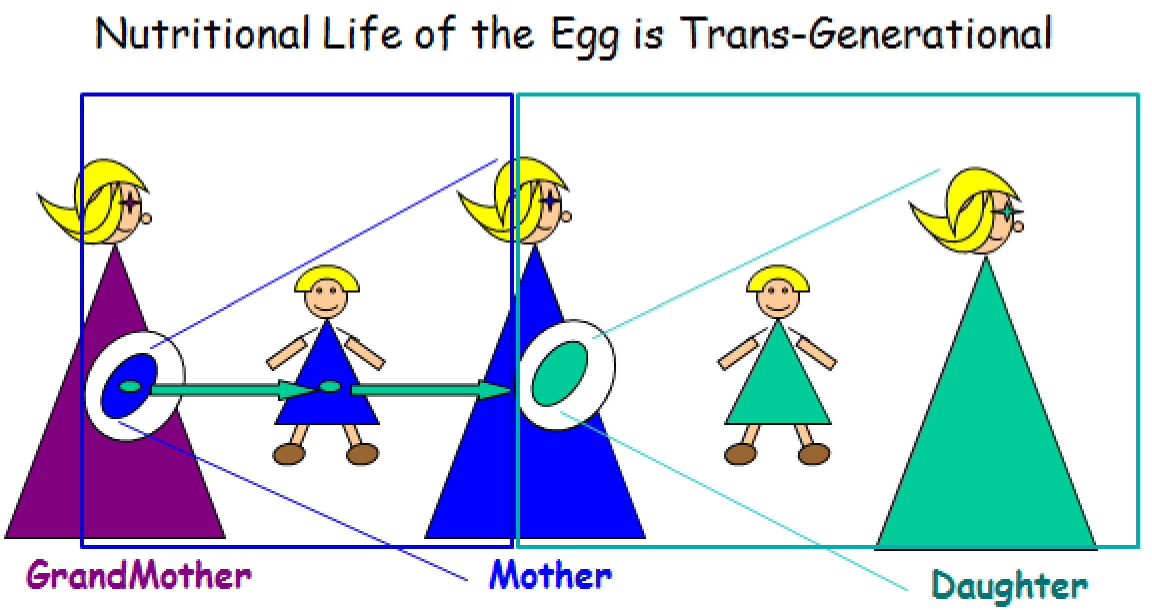
Transgenerational Transmission of Programmed Changes



Transgenerational Transmission of Programmed Disease Risk

A Mother's Lifetime Preconception Exposures Impacts ***Future*** Pregnancies

- **Undernutrition** in mom's early life:
  - Limits metabolic capacity to nurture future fetus
    - increased Amino Acid oxidation
    - reduced protein turnover rate
  - Impairs future fetal, childhood growth
    Links with offspring hypertension, obesity
- **Undernutrition** in the preconceptual period
  - Links with hypertension in adult offspring

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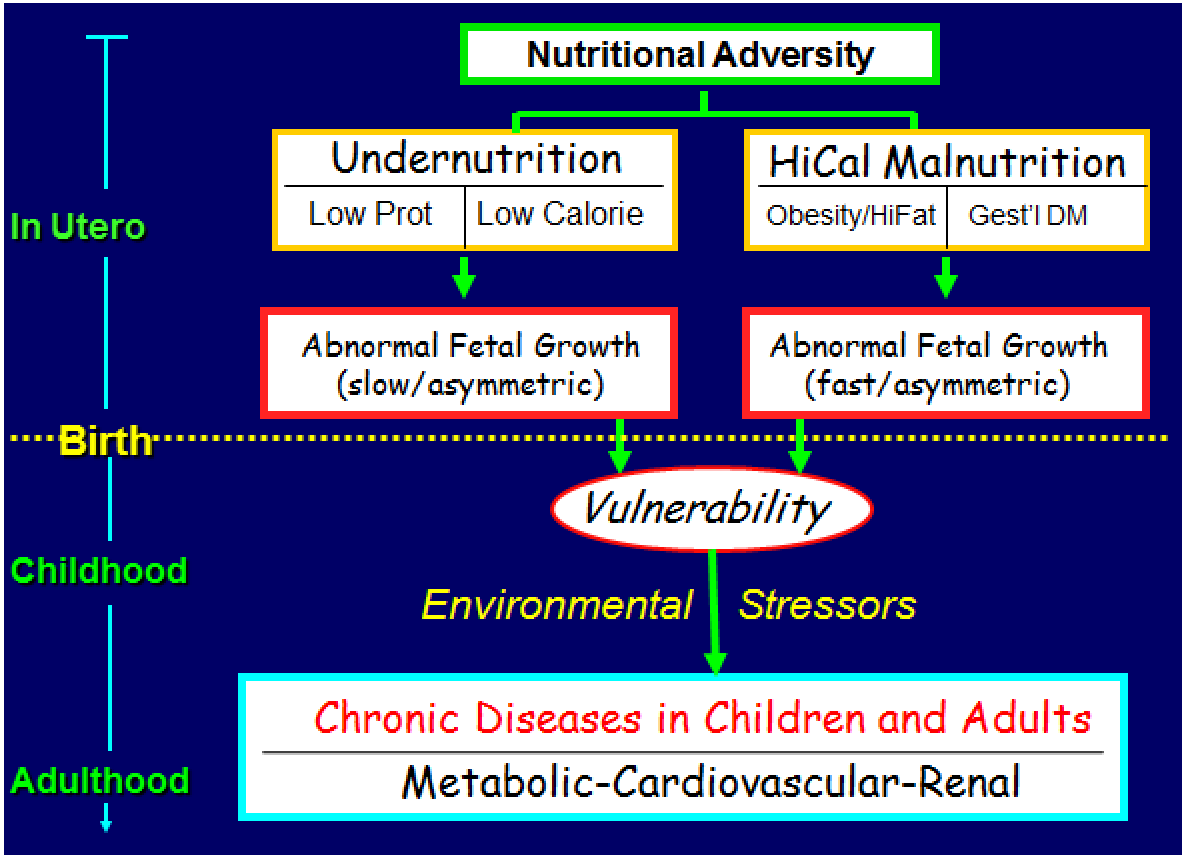
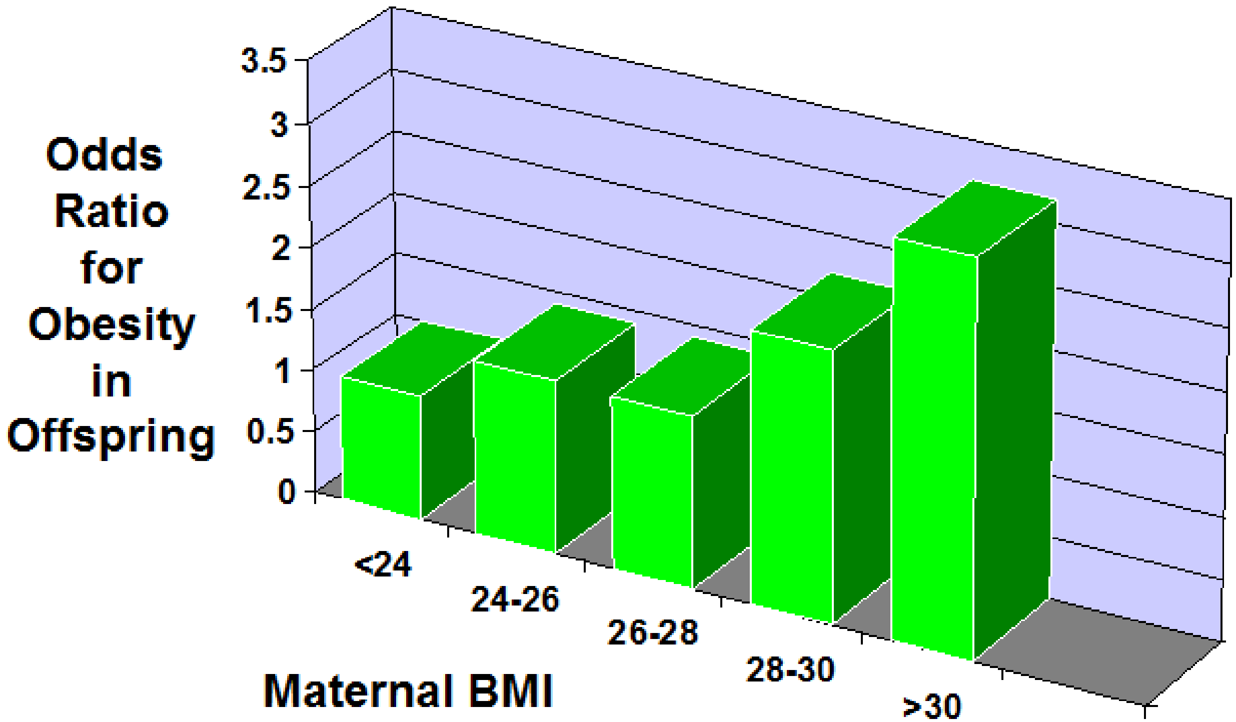
“Double Burden” of Malnutrition



Obesity Risk in Offspring of Obese Mothers
Maternal Obesity/High Energy Diet



Eriksson J et al Internatl J Obesity 2001

Consequence of Maternal Obesity for Offspring

Obstetric Risks

- Pre-Eclampsia
- Gestational DM
- Prematurity
- Congenital malformations

Offspring Outcomes

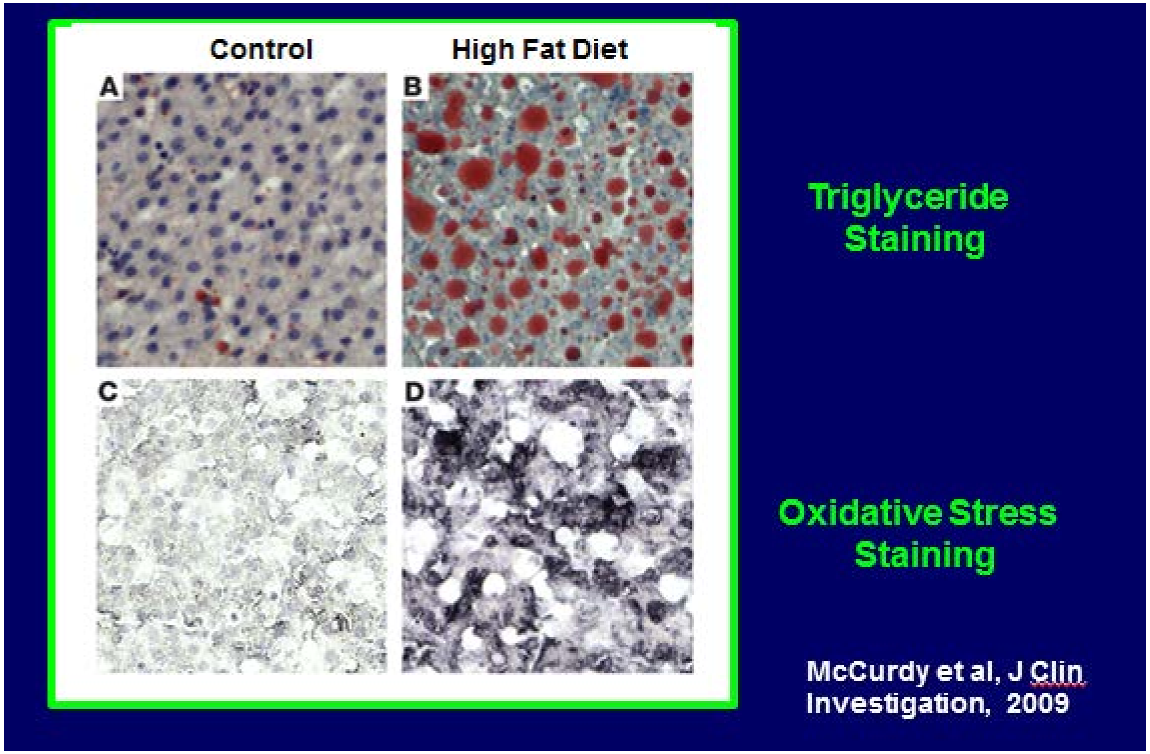
- LGA/Macrosomia
- IUGR
- Insulin resistance
- Rapid infant growth
- Early-onset obesity
- Early-hypertension
- Early-diabetes

Maternal Hi Fat Diet/Obesity
Programming Effects in Monkey Offspring

- Fetal/Neonatal **Liver**:
  - Fat deposition (hepatic 'lipotoxicity')
  - Inflammation, oxidative stress
  - Fatty liver disease (neonate)
- Fetal **Brain**:
  - Inflammation
  - Change neural appetite circuits, reward center setpoints
- Postnatal **Behaviors**:
  - Increased appetite (hyperphagia)
  - Preference for hi fat/sweet/salty food
  - Accelerated infant growth rate
  - Early excess adiposity (age 6 mo)
  - Early onset puberty
  - Increased Anxiety (females)/Aggression (males)

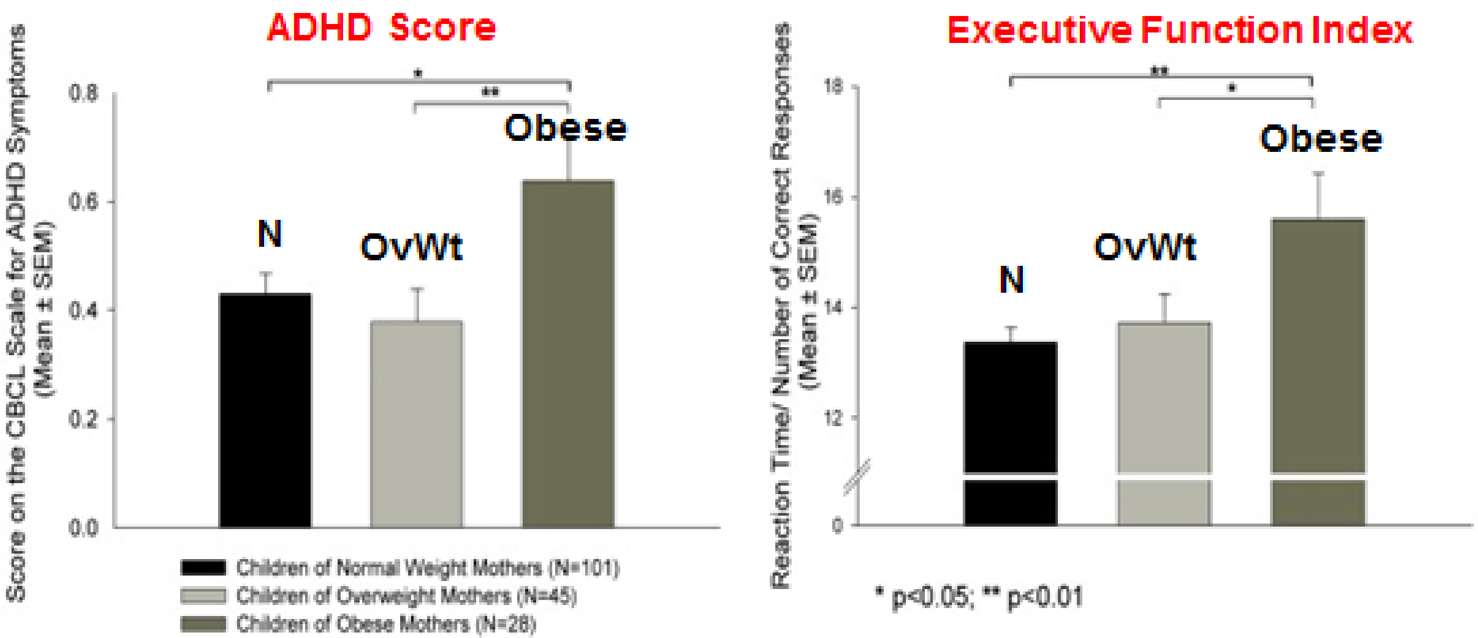
Grove K et al: Non-human primate model (ONPRC)

Fetal Liver Fat Accumulation/Lipotoxicity in Offspring of Monkey Mom's on Chronic High Fat Diet



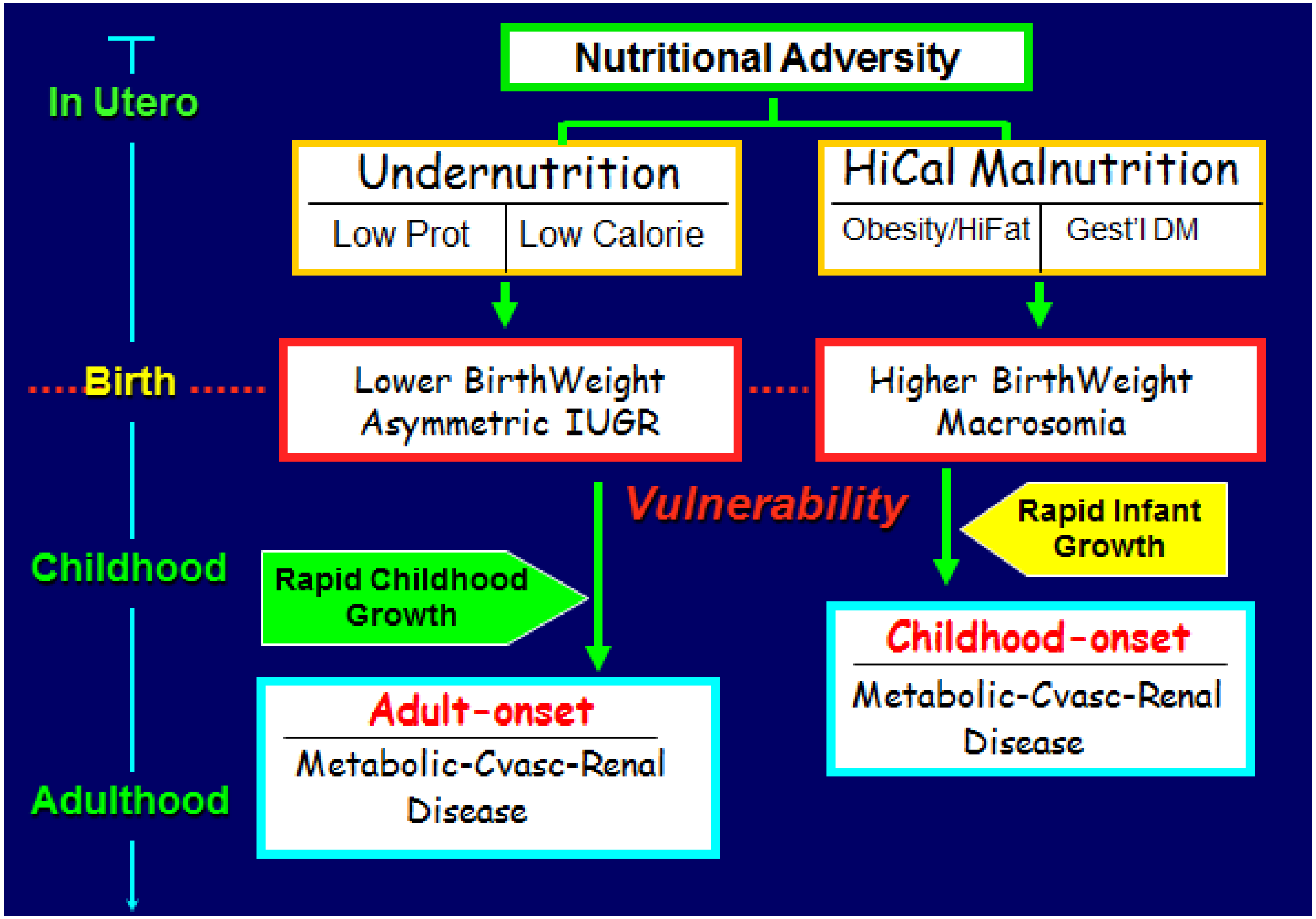
Maternal Obesity & Risk of Behavioral Dysfunction

Children's ADHD and Executive Function Scores
Based on Mother's Body Mass Index

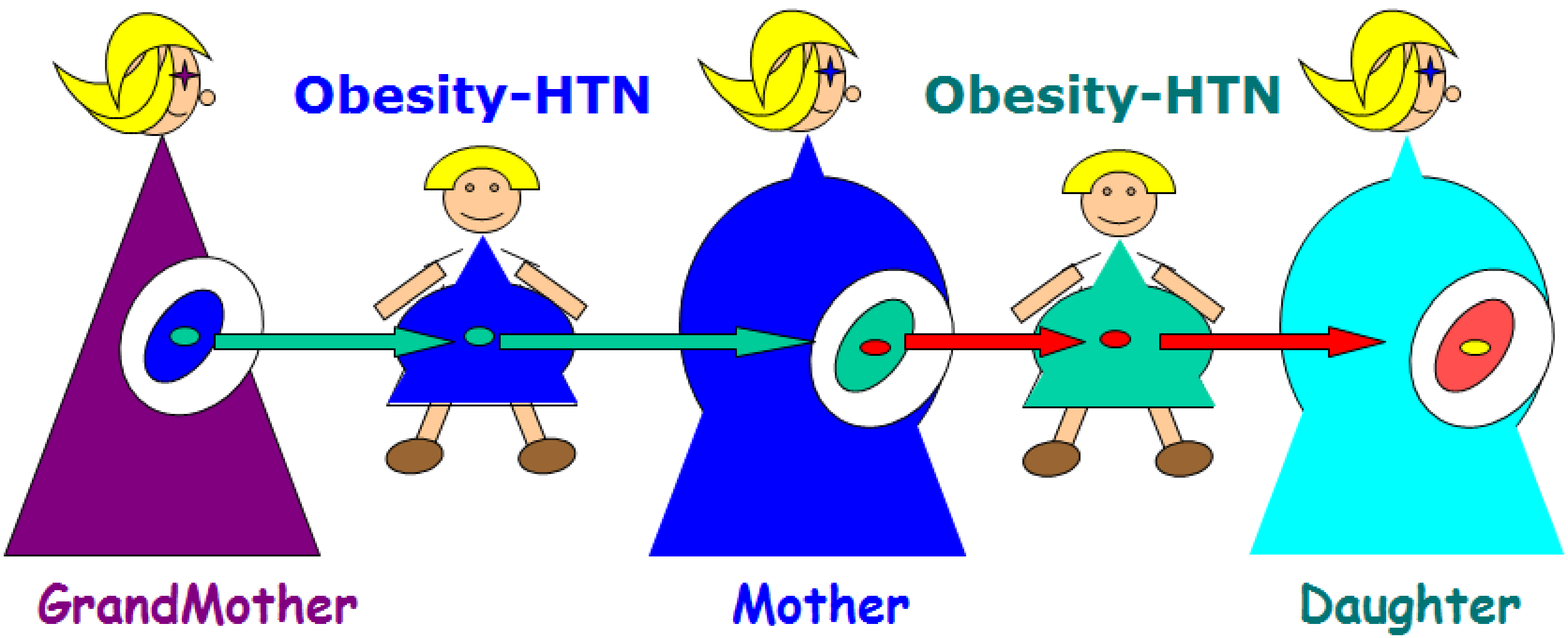


Buss C et al. PLoS One, June 2012

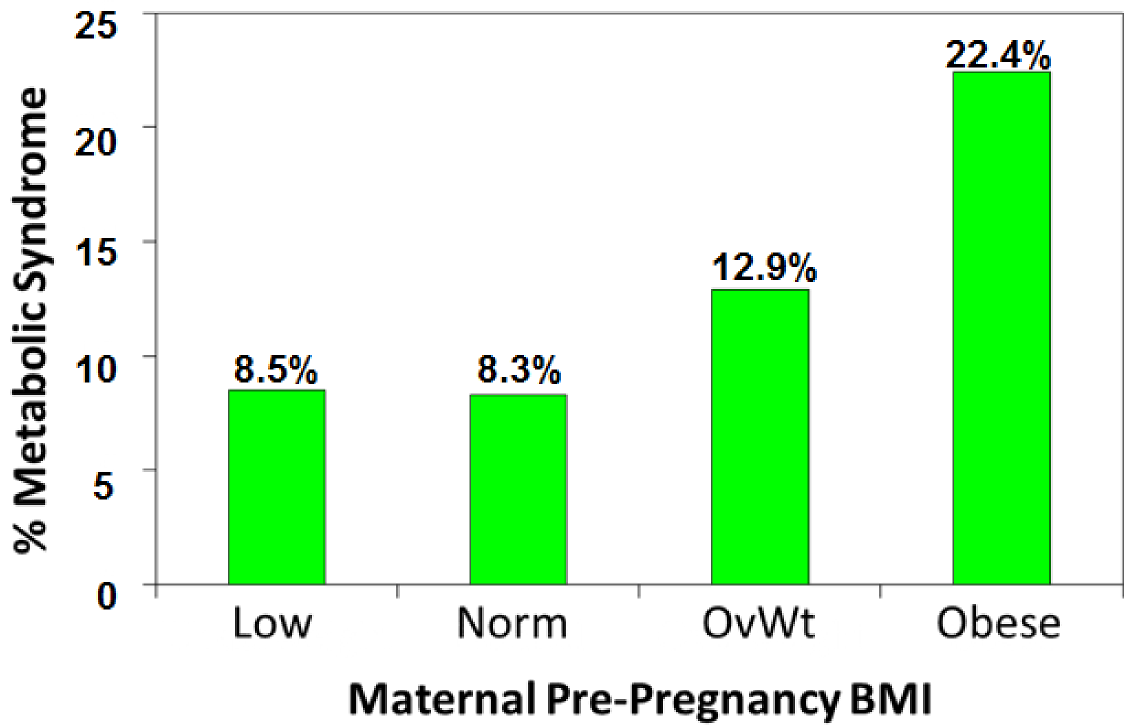
"Double Burden" Malnutrition



Obesity-Hypertension in Children/Adolescents
Transgenerational Transmission

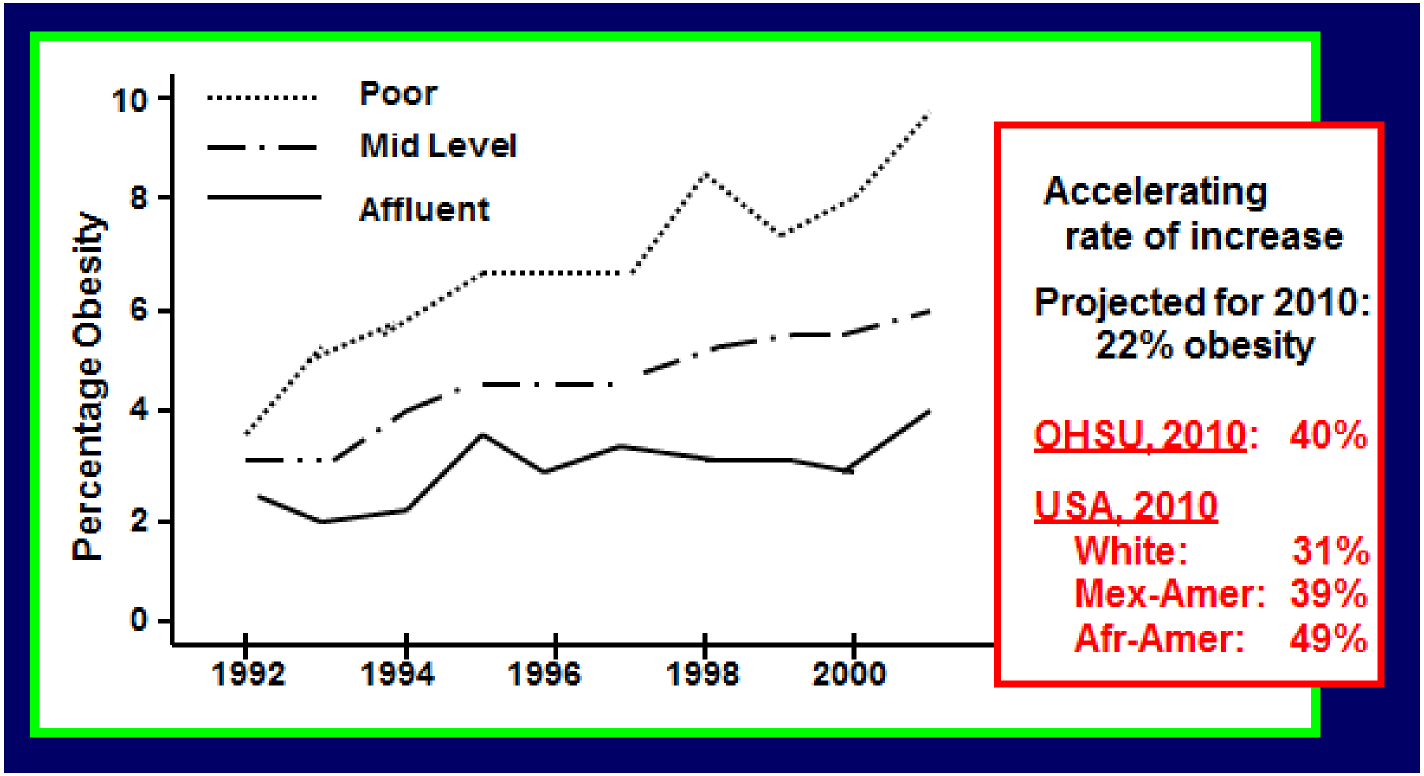


Metabolic Syndrome in 6 Year Old Offspring Predicted by Maternal Pre-Pregnancy BMI



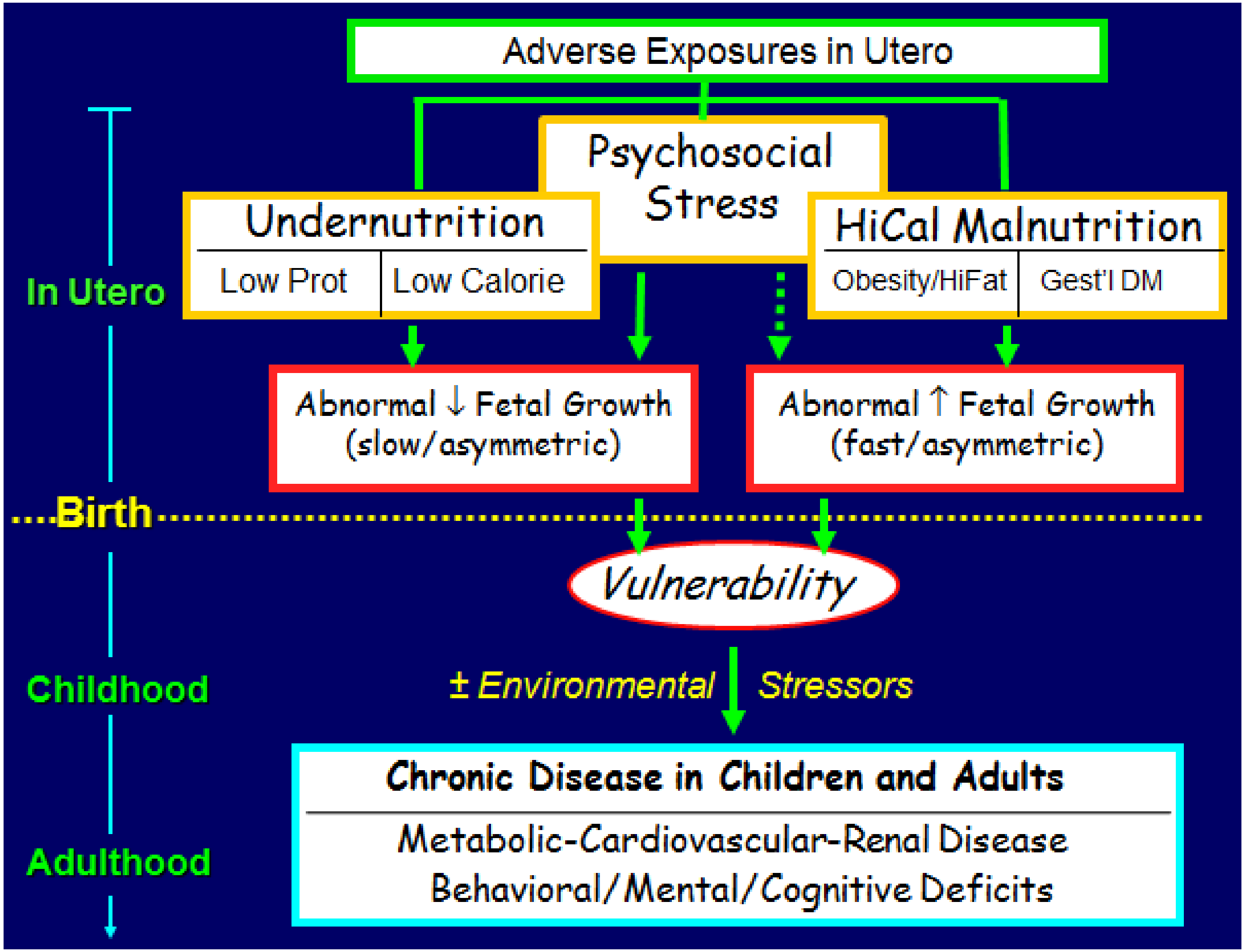
The Generation R Study: Hypertension 2014;63:683-691

Rising Prevalence of Maternal Obesity
Impact of Neighborhood Socio-Economic Status



Sellstrom E et al, BMC Pregnancy and Childbirth, Sweden, 2009

Adverse Exposures in Utero



What Do We Do About All This??

Think Trans-generational

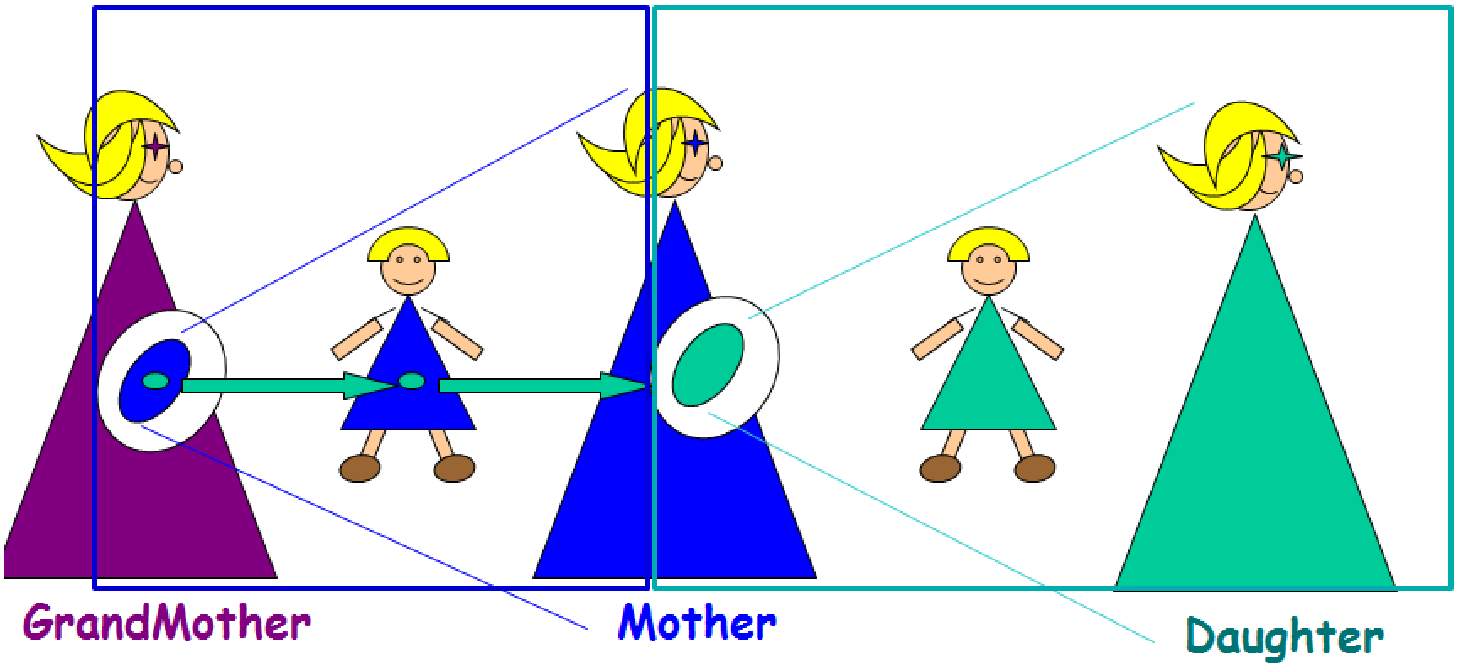
A girl is a **mother** form the time of her own mother's conception.

A mother is the biological bridge to the health of future generations.

Transgenerational Transmission of Programmed Changes

Key Populations at Risk:

Young girls, moms-to-be, pregnant women, young families



Protecting Future Generations

It Takes a Village...

Crucial Elements

- Healthy food choices for girls, young women, young families
- Support from husbands, partners, community
- Renewal of food wisdom in family, community, schools
- Regulation of inappropriate marketing to youth
- Restore “FOOD VALUE” - Put our $$ in our youth’s mouths

The Bob & Charlee Moore Institute for Nutrition and Wellness

Mission

To reduce the prevalence of chronic diseases across the lifespan

- In current and future generations
- Via promoting healthy, nutrient-rich whole-food diets in early life
  - Before conception
  - During pregnancy and lactation
  - In infancy and early childhood

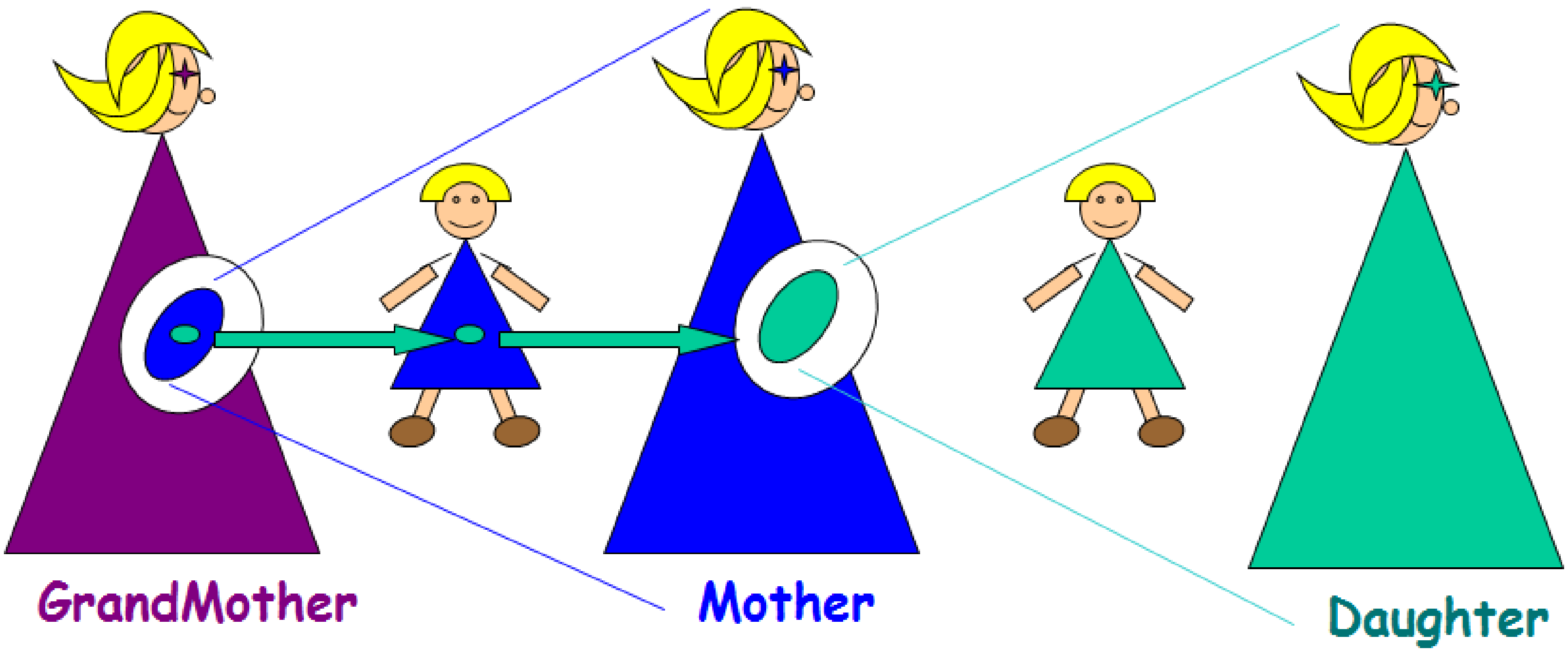
The Power of Partnership

Identifying At-Risk Groups
Practical Suggestions for Clinicians

- Include at-risk babies, children, moms, families
- Document obstetric history in chart
  - Mom: obesity, hi fat diet, GDM, preeclampsia
  - Offspring: birth wt/length, prematurity, gest’l age
- Track infant/childhood size, growth rate
- Recognize growth centile crossing as indicator of metabolic stress, higher disease risk
- At-risk children need regular monitoring
  - BP monitoring/tracking
  - Referrals for food insecurity, for obesity
  - Family referrals for nutrition education

We Are What We Eat – And So Are Our Kids & Grand-kids

Transgenerational Transmission of Chronic Disease Risk



Maternal Stress Causes Stress-Hyperactivity in Programmed Offspring

Enhanced Reactivity to Postnatal Environment

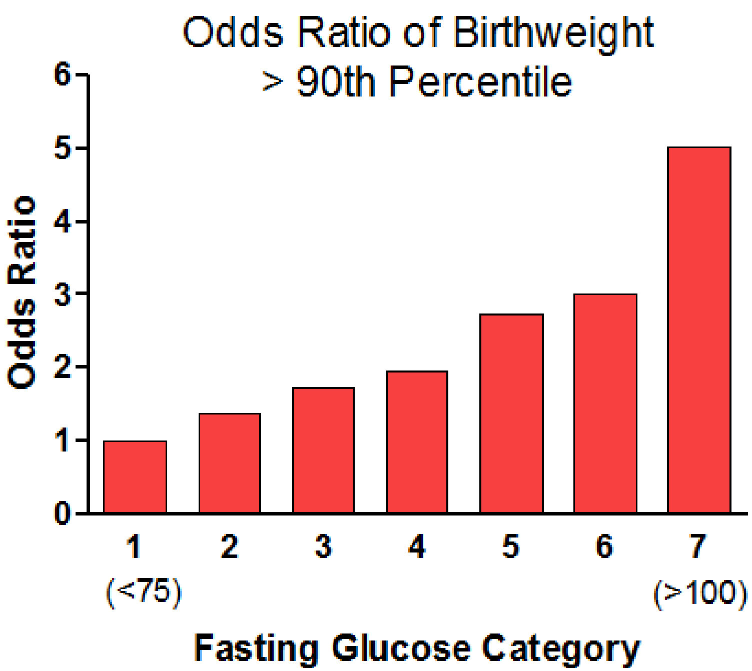
Maternal Stress: poverty, discrimination, fear, perceived lack of control

Offspring Phenotype:

- Low birth weight (due to hi fetal cortisol)
- Increased cortisol response to pain, social stress, public speaking
- Impaired cognition (verbal, memory)
- Increased aggression, rule-breaking, ADHD
- Increased metabolic dysfunction

Review: Reynolds R. Psychoneuroendocrinology 38: 2013

Maternal Glucose Elevations Convey Graded Offspring Risk in **NonDiabetic** Pregnancy



The HAPO Study. NEJM May 2008

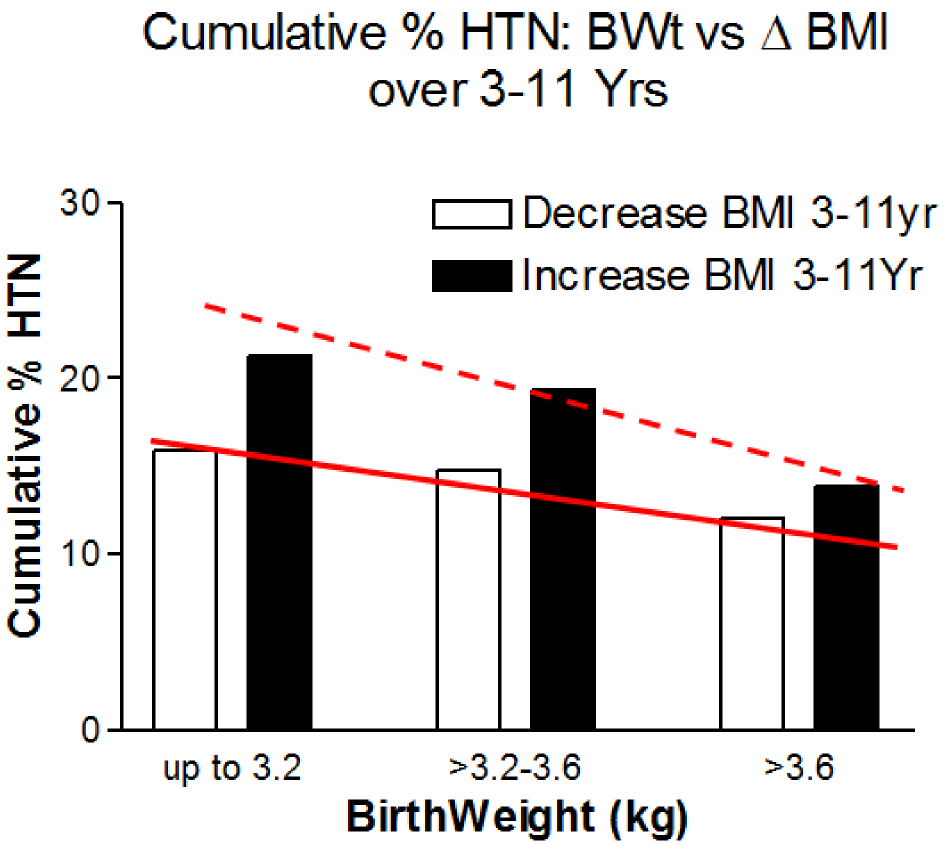
- 25,505 pregnant women
- Tested 24-32 weeks

Outcomes

Graded increase in:

- LGA babies
- Cord blood C-peptide
- Primary C-Section
- Neonatal hypoGly

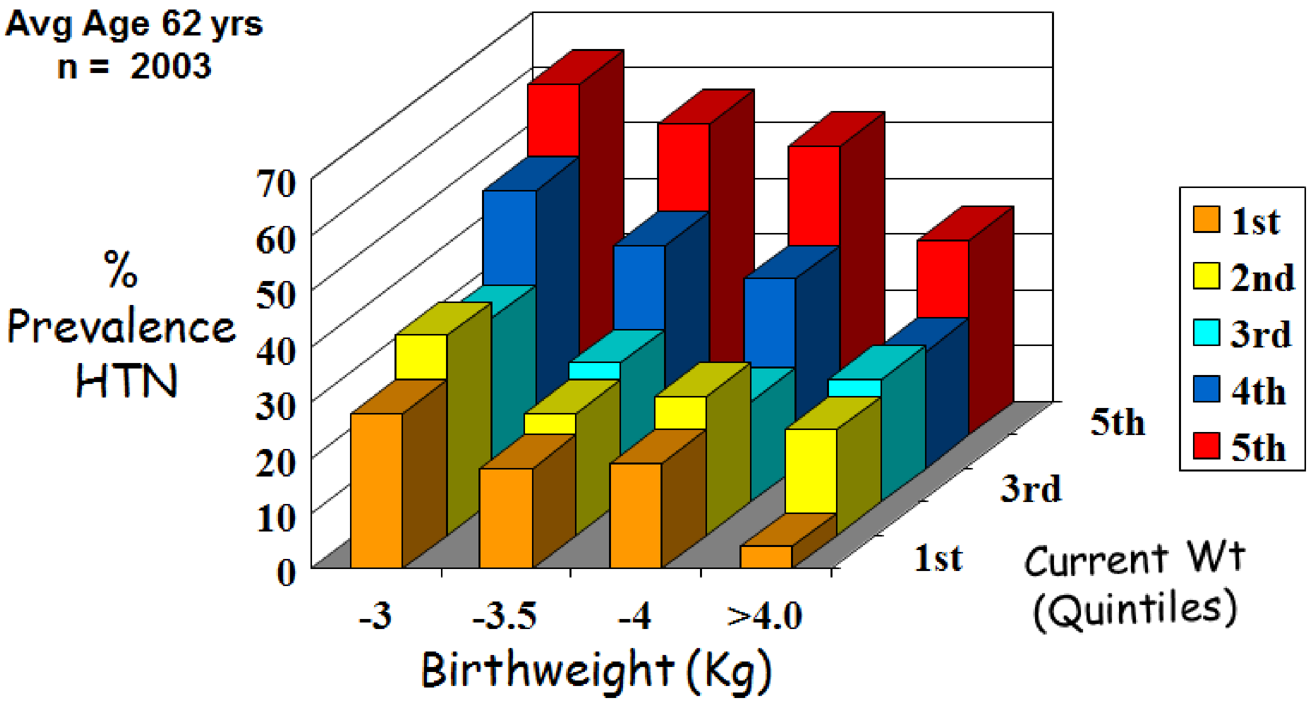
Rapid Childhood Growth Predicts HTN Helsinki Cohort



Barker et al. J HTN 20: 1951, 2002.

Rapid Childhood Growth Predicts HNT & Enhances Birth Weight Effects

Helsinki Cohort: Random Sample



Eriksson et al. Hypertension 49: 2007