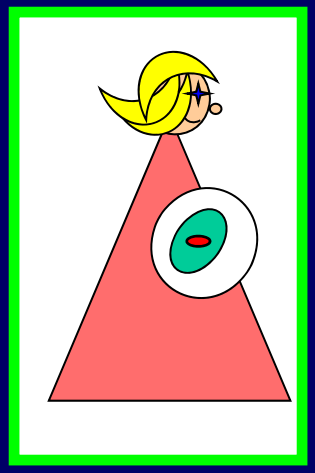
# Developmental Origins of Chronic Disease



## You Are What Your Mother & Grandmother Ate: Transgenerational Influences

Oregon LifeCourse Network
June 7, 2013

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Nephrology & Hypertension
OHSU Heart Research Center

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# Biology of Developmental Programming

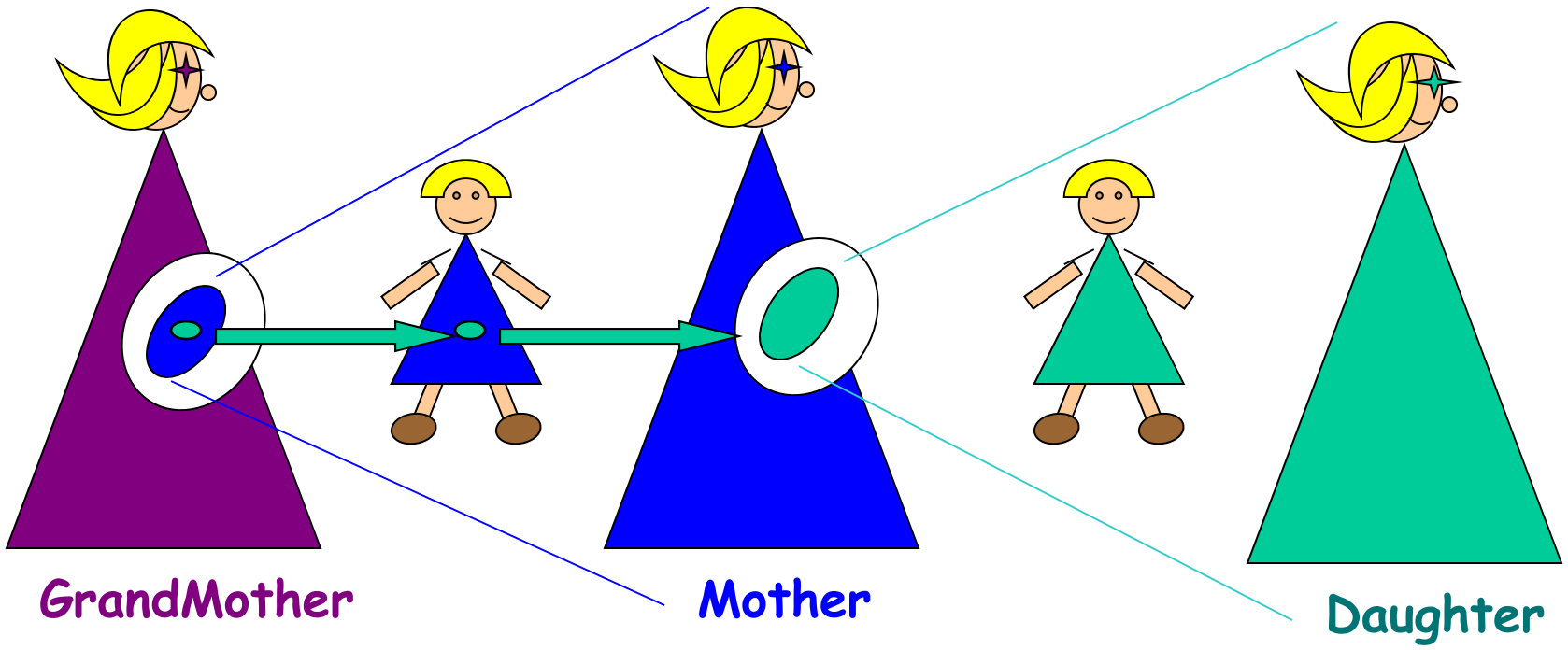
## OUTLINE

- What is “Developmental Origins of Health & Disease”?
- 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
- Obesity Programs Obesity: A crisis in progress

# We Are What We Eat -

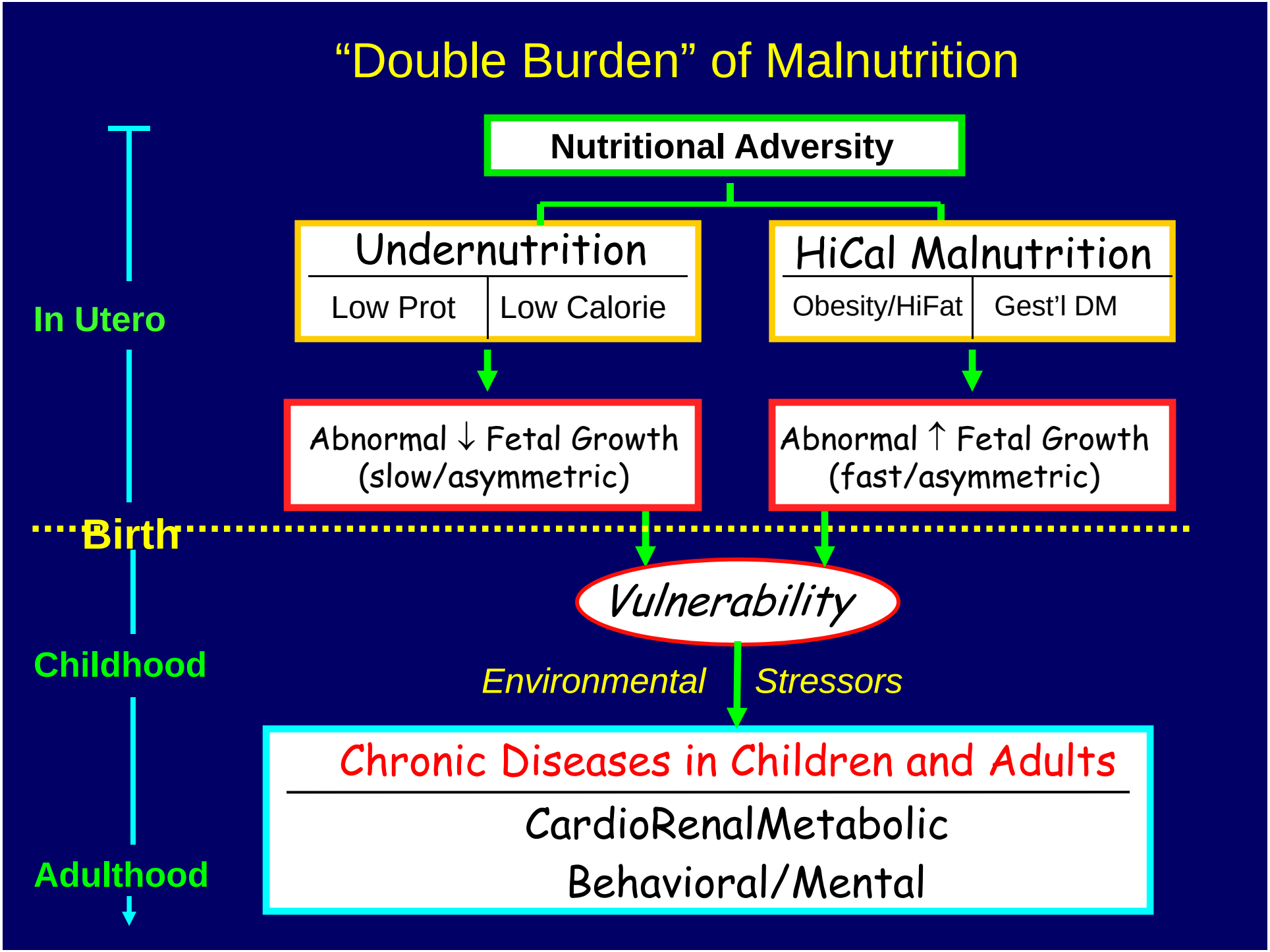
## And so are our kids & grand-kids !

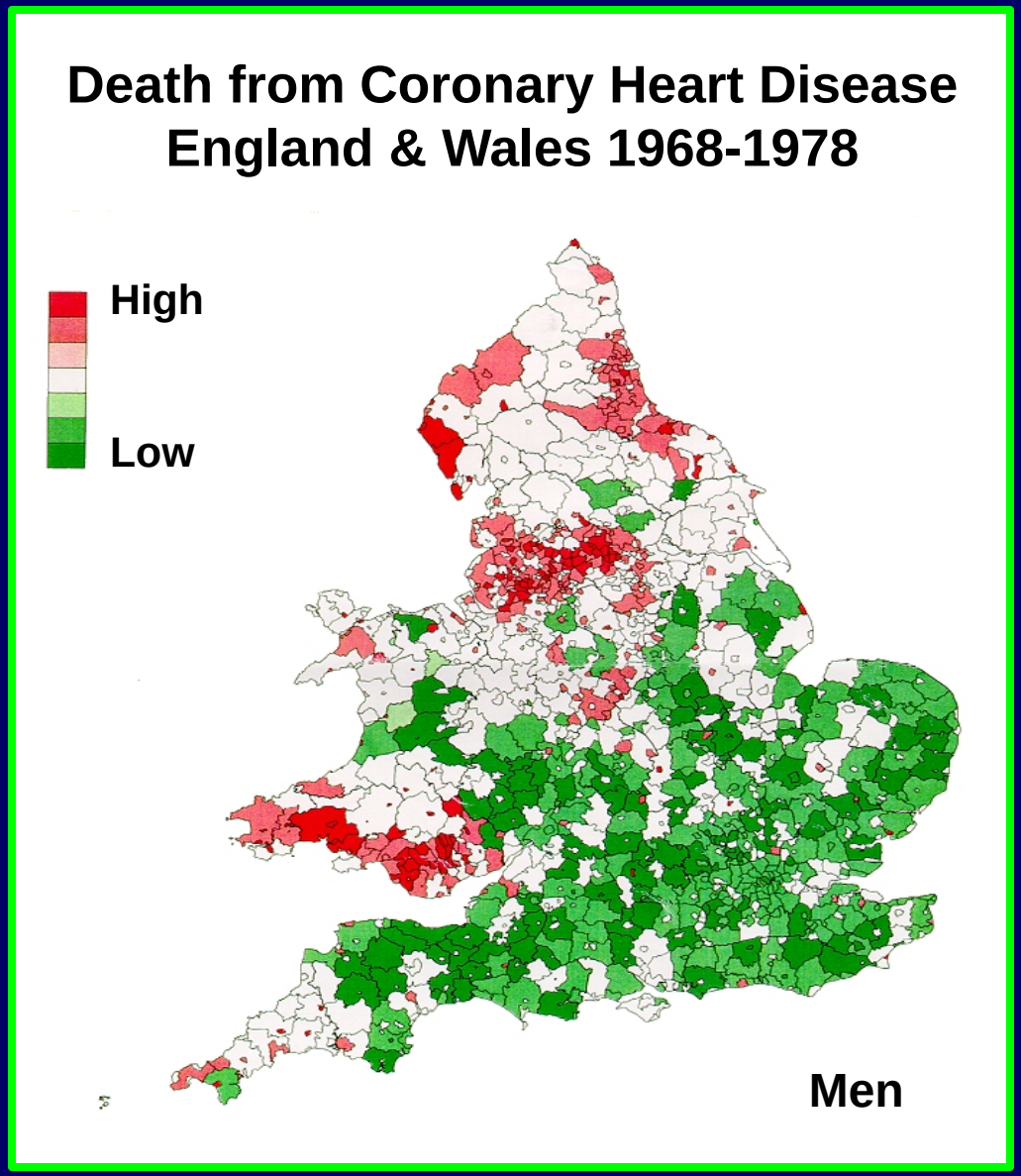
Nutritional Life of the Egg is Trans-Generational



# What is 'Developmental Origins of Health and Disease'?

- Concept: biologic capacity of normal *developing* organisms to be *durably* changed by environmental exposures without change in the inherited genome
- Process: 'developmental programming'
- Exposures: nutrients, $O_2$, chemicals, toxins
- Mechanisms: substrate deficits; epigenetic changes
- Pathways : $\Delta$ organ structure (permanent)
  $\Delta$ cell/organ function ($\pm$ reversible)
  $\Delta$ regulatory system setpoints
- Impact: **Vulnerability** to development of chronic disease in later life


"Double Burden" of Malnutrition
Nutritional Adversity
Undernutrition
Low Prot
Low Calorie
HiCal Malnutrition
Obesity/HiFat
Gest'l DM
In Utero
Abnormal ↓ Fetal Growth
(slow/asymmetric)
Abnormal ↑ Fetal Growth
(fast/asymmetric)
Birth
Vulnerability
Childhood
Environmental
Stressors
Chronic Diseases in Children and Adults
CardioRenalMetabolic
Behavioral/Mental
Adulthood




# 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 Developmental 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, calories)

# 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 stressors become *biologically* embedded within a population
  - developmentally-based health disparities can be transmitted to future generations

# The Barker Hypothesis
# Developmental Origins of Disease

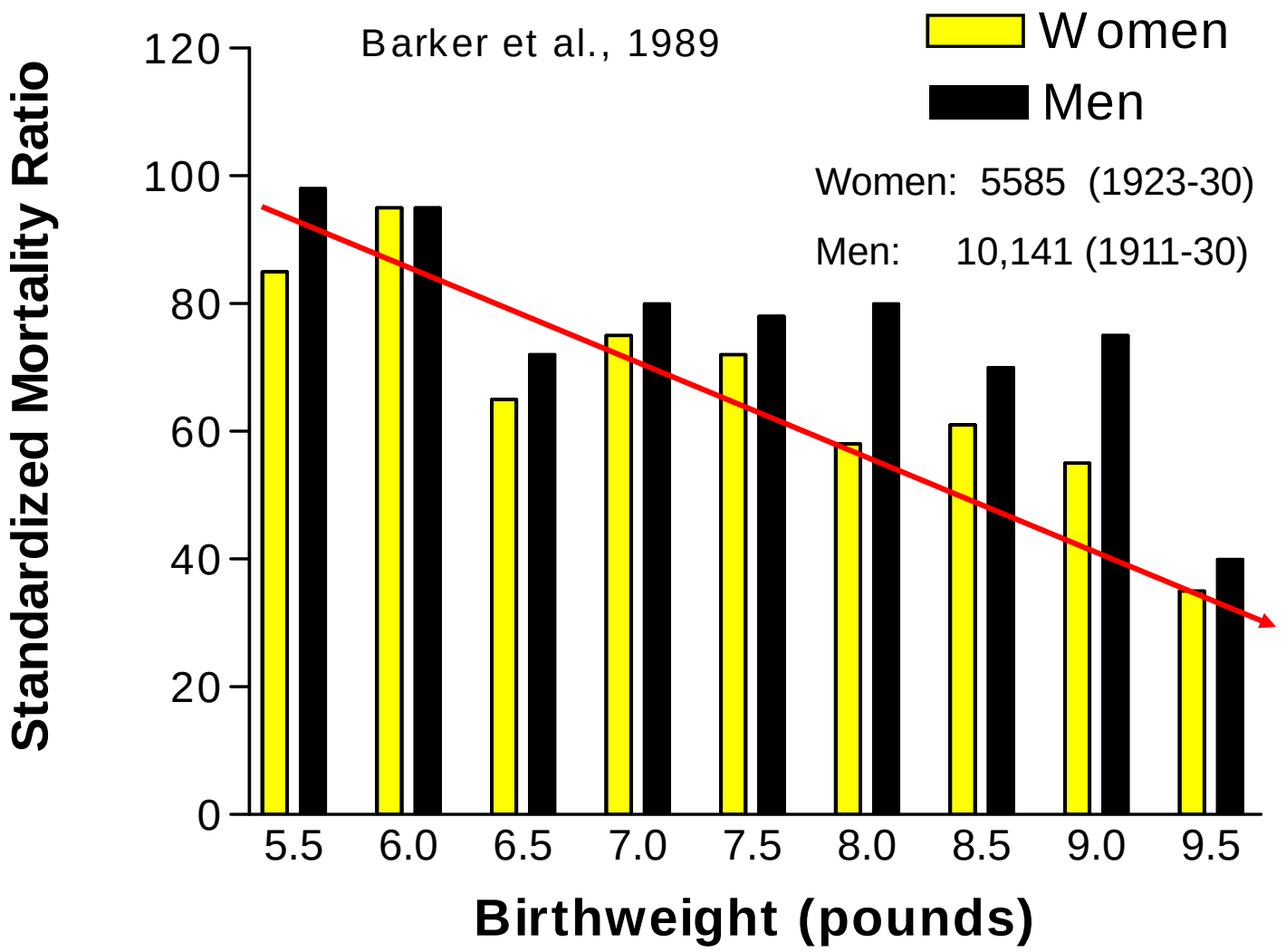
## Lessons from Cohort Studies

## The British Cohorts

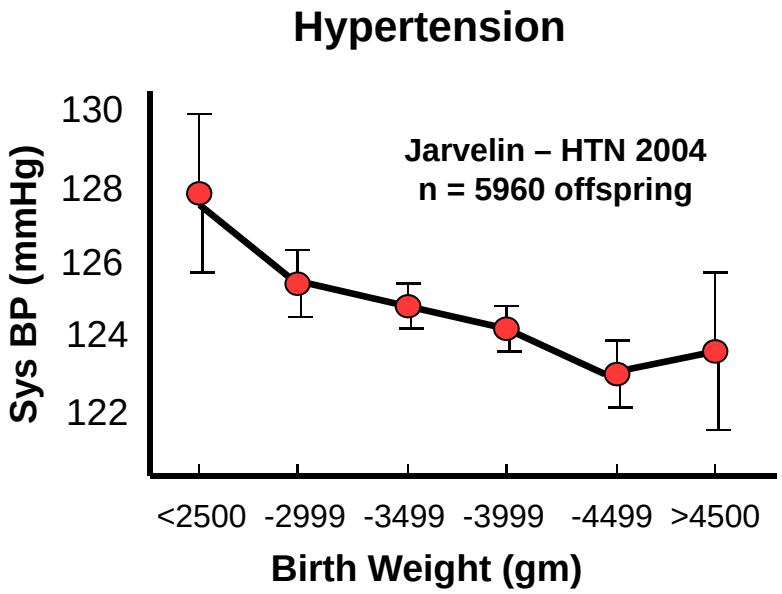
- Small English villages
- Two time points: Birth
  50+ yrs

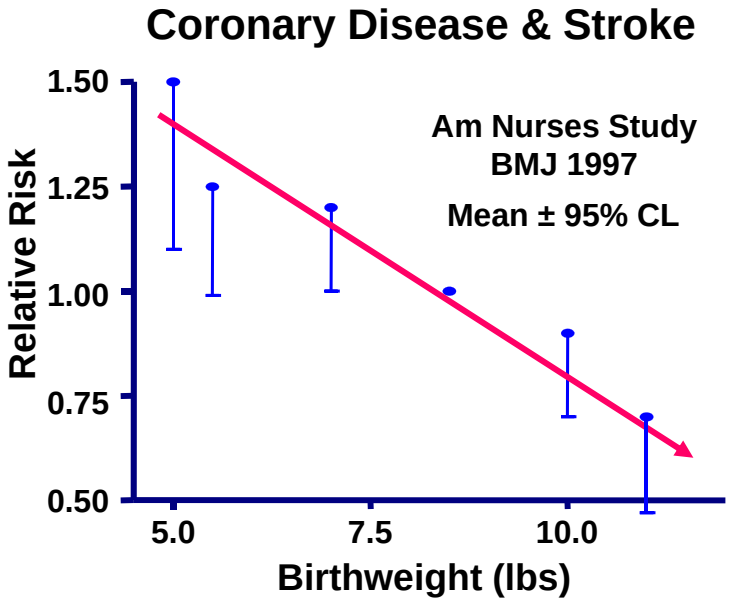
**Poor Fetal Growth Increases Risk of Chronic Disease in Later Life**

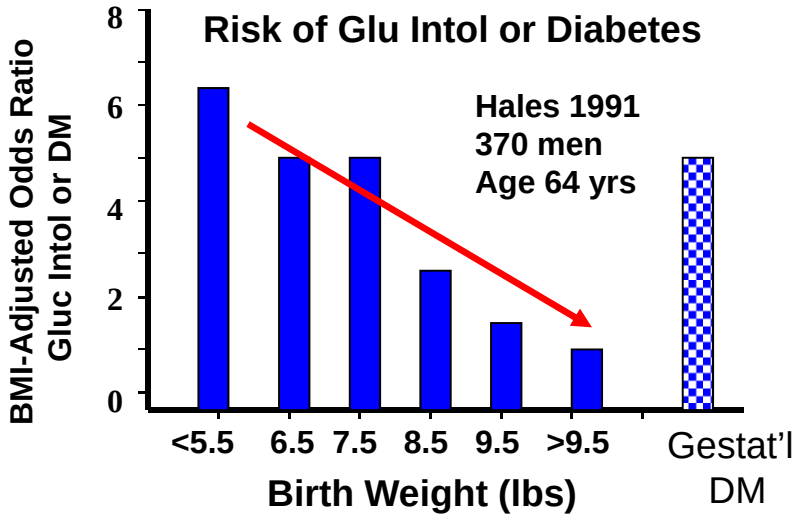
# The Effect of Term Birthweight on Mortality



# Poor Fetal growth → Increased Risk of Disease

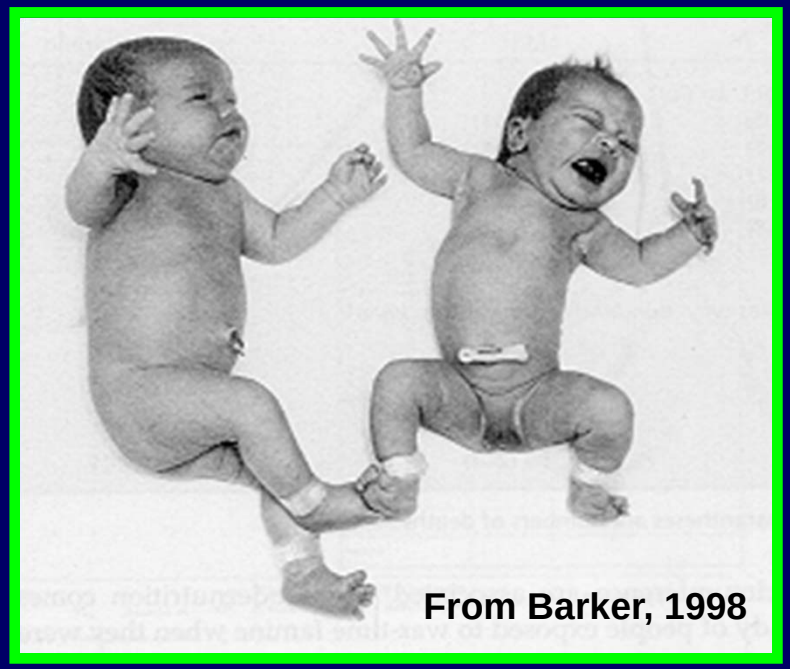


# Birth Weight is Crude Surrogate for Fetal Growth

## Asymmetric Growth Restriction

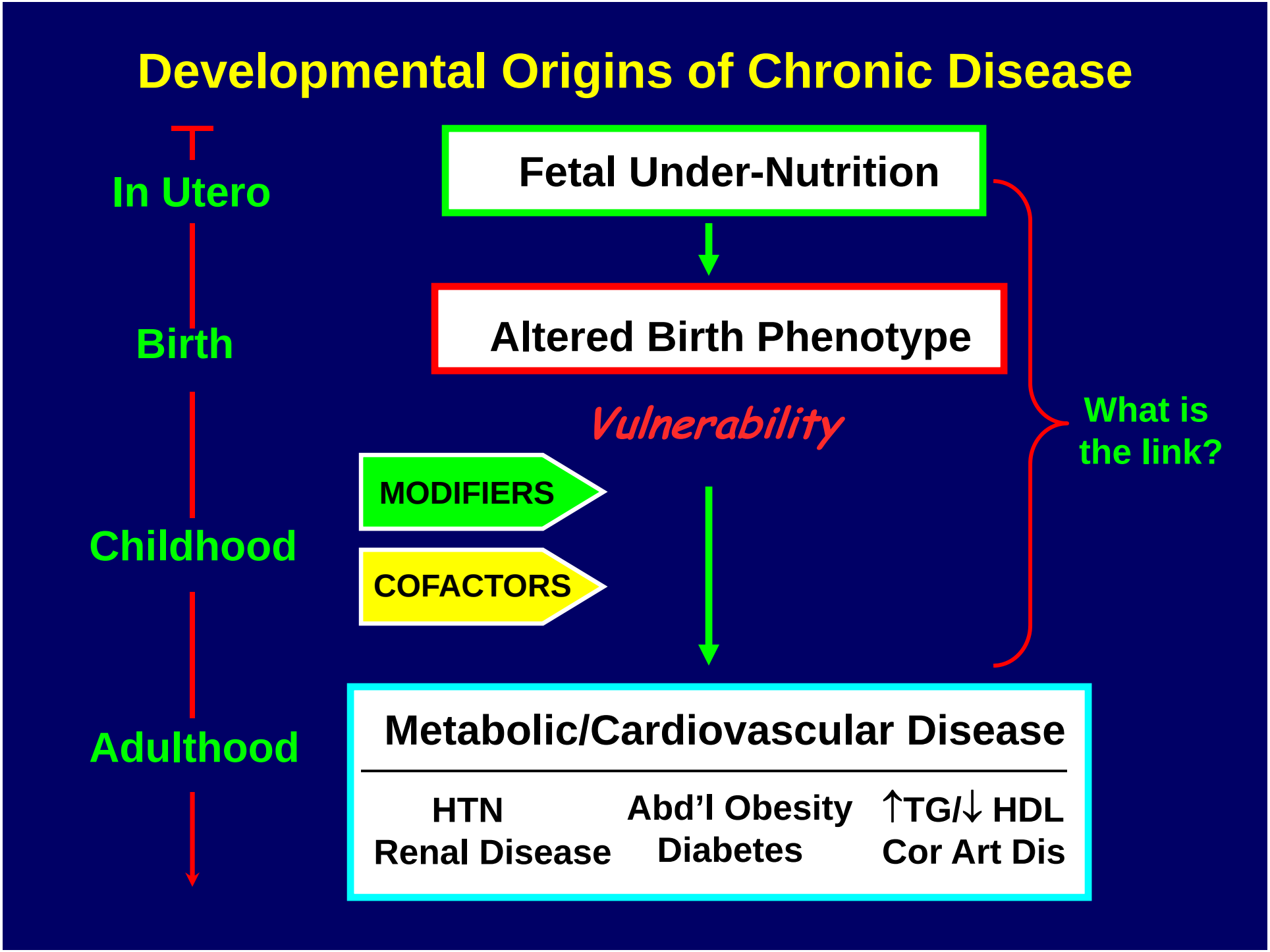


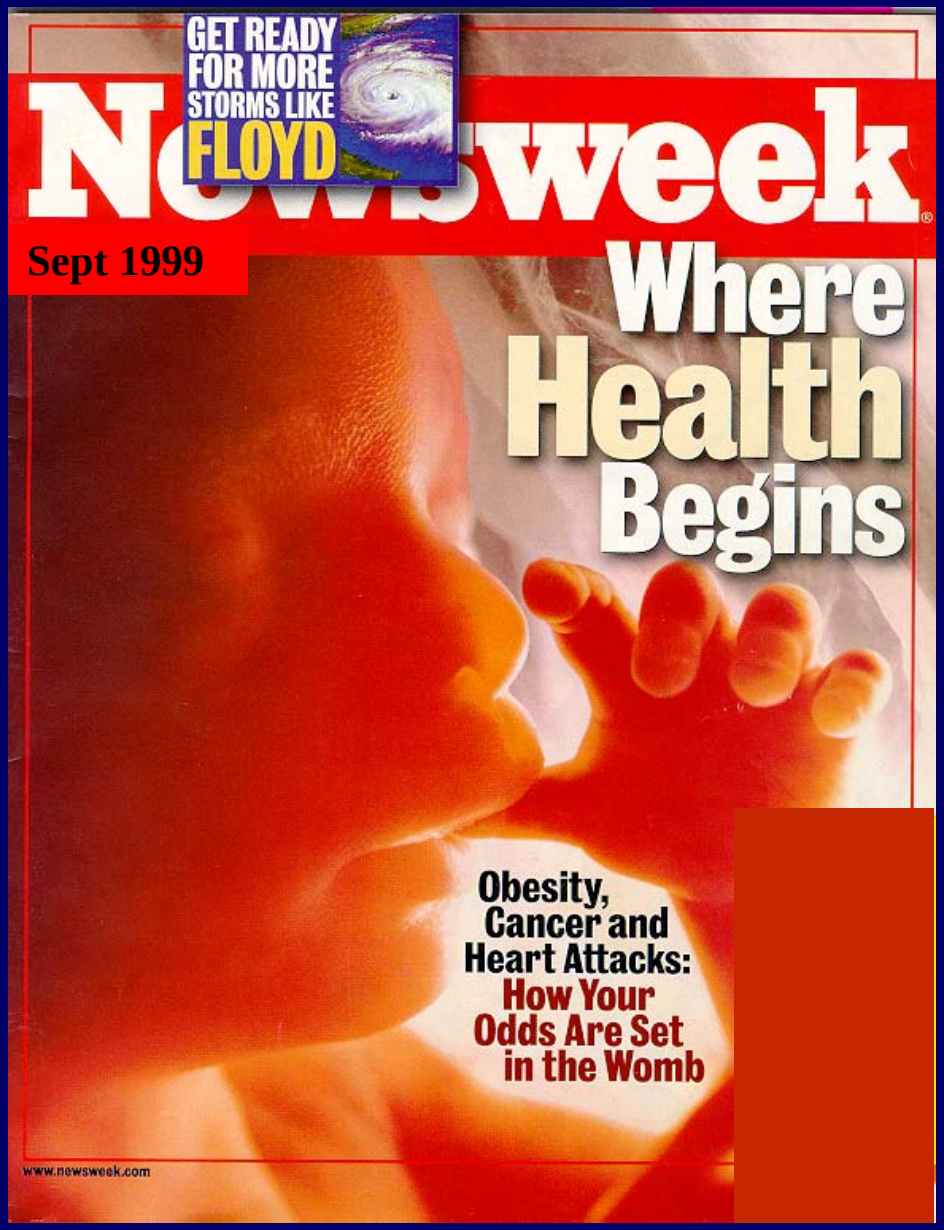
From Barker, 1998

- Thin (↓ Wt:Ht ratio)
- Fetal blood flow redistribution
  - ↓ kidney, liver, pancreas
  - ↓ abdom'l girth
  - Heart/brain 'sparing'
- Low arm circumference
  - ( ↓ muscle mass)

## May Occur with Normal Birth Weight!

# Developmental Origins of Chronic Disease






# Developmental Origins of Chronic Disease

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

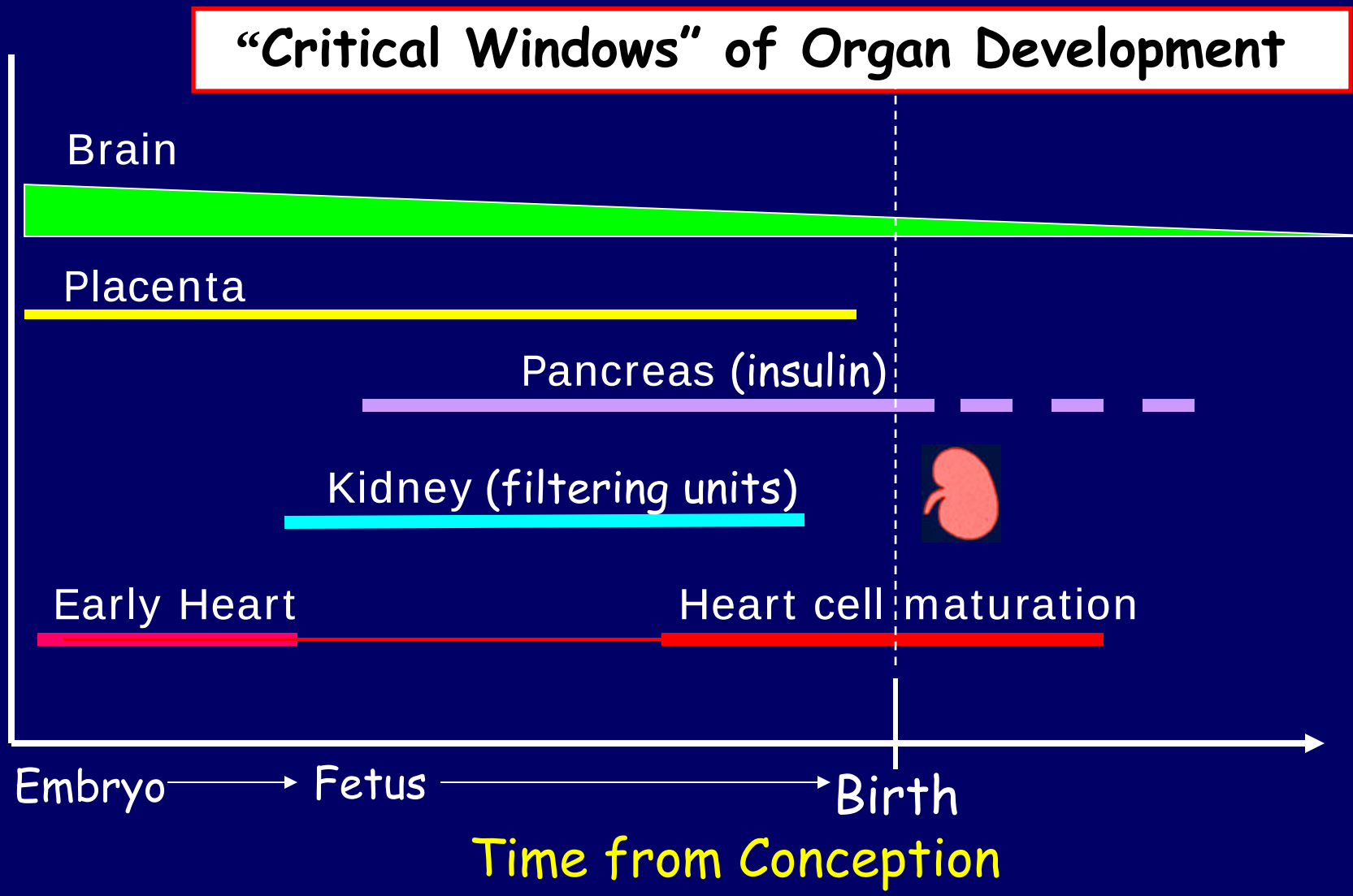
# Developmental Origins of Disease

## Pathways of Nutritional Programming

- Altered organ structure/function
- Altered homeostatic system setpoints
- Adverse interactions of prenatal vulnerabilities with postnatal stressors

# Pathways of Nutritional Programming

## Altered Organ Structure/Function

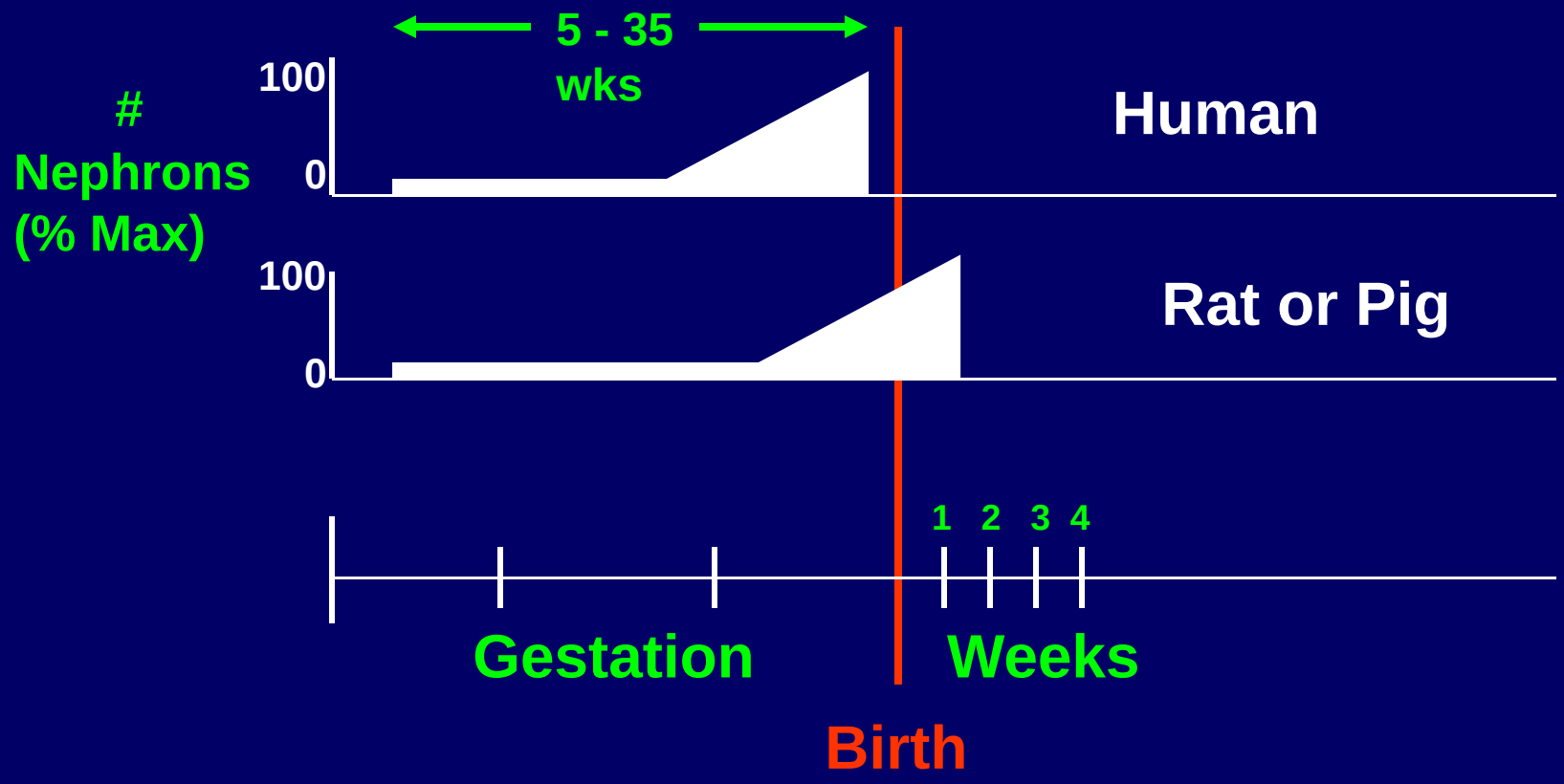


# Pathways of Nutritional Programming

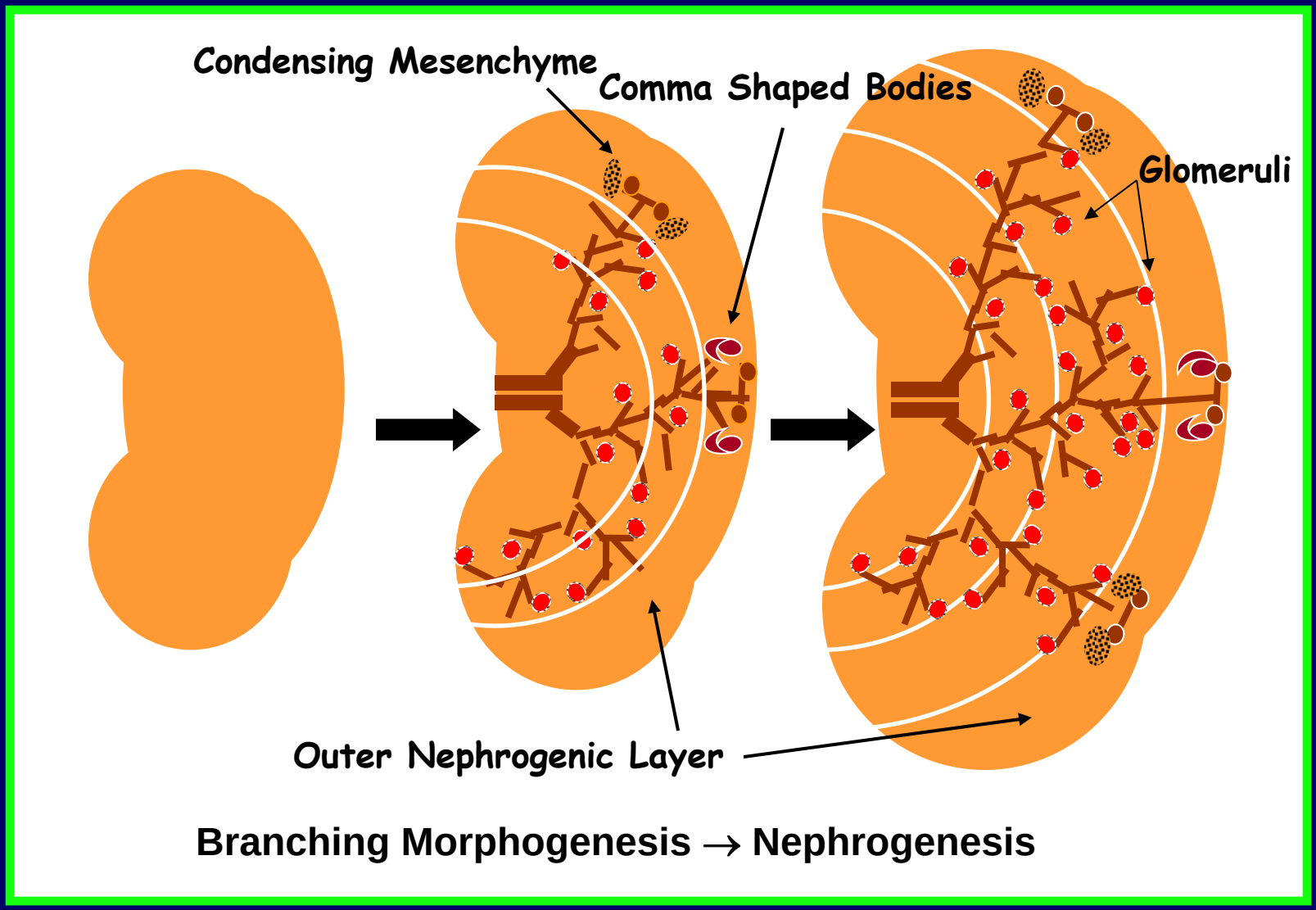
## Structural Deficits → ↓ # Functional Units

| | | |
|---|---|---|
| Kidney | ↓ Nephron # | HTN, renal risk |
| Pancreas | ↓ Islet β cell # | Δ Insulin secretion |
| Muscle | ↓ muscle mass | ↓ Basal met rate<br>↓ Exercise capacity<br>↓ Insulin sensitivity |
| Heart | ↓ myocyte # | ↑ Risk CHF |
| Liver | ↓ lobule, cell # | Δ lipid/protein metab. |
| Vascular | ↓ microvasc dens | ↑ vasc resistance<br>↑ ischemia risk |

# Time Course of Renal Development

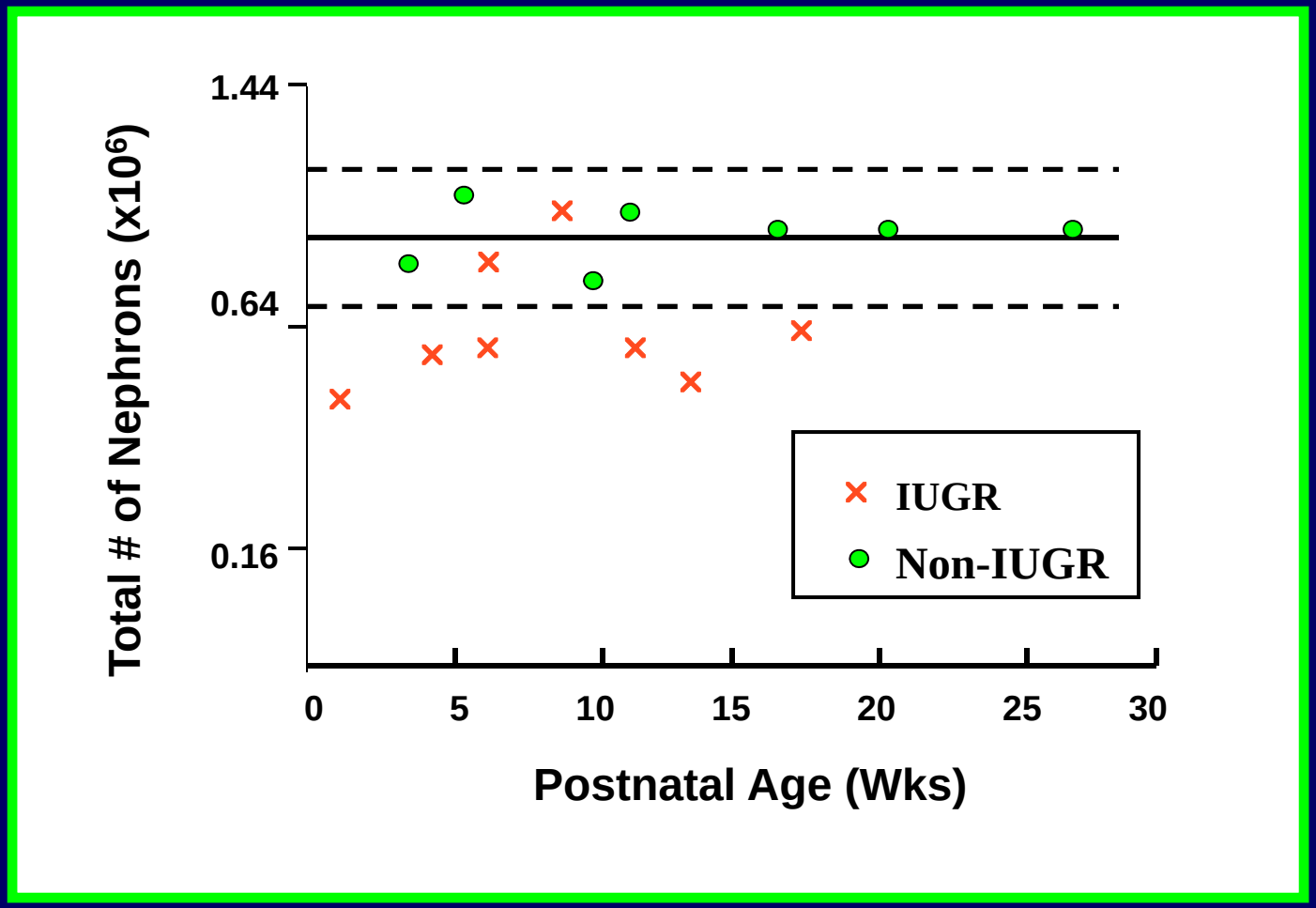


# New Nephrons Form in Concentric Layers during Gestation




**Branching Morphogenesis → Nephrogenesis**

# Reduced Glomerular # in Human IUGR




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

# Developmental Origins of HTN

## Pathways of Nutritional Programming

- Altered Organ Structure → Δ Function
  - Kidney: ↓ nephron number
- Altered Homeostatic Setpoints
  - Energy Balance: "thrifty phenotype"
- Interactions of prenatal vulnerabilities with postnatal stressors

# Altered Homeostatic System Setpoints in Programmed Offspring

## Enhanced Response to Postnatal Environment

- Sympathetic nervous system hyperactivity
- Renin/AngII system hyperactivity
- Stress hyperreactivity: HPA Axis
- Oxidative Stress/Inflammatory responses
- Immune hyperactivity (asthma, allergies)
- Energy homeostasis: Fat, glucose/insulin metabolism, appetite regulation

# Altered Homeostatic System Setpoints in Programmed Offspring

## Hyperreactive Cardiovascular Responses in Normotensive Low-Birth Wt Children

- ↑ Cold Pressor Test[1]
- ↑ Psychological stress responses[2,3]
  - mental arithmetic
  - public speaking
- ↓ Flow-dependent vasodilation[4]

**Stress Hyperactivity Predicts Later Hypertension**

[1] Nichols 2005; [2] Matthews 2004; [3] Ward 2004; [4] Leeson 1997

# Altered Energy Homeostasis in Programmed Offspring

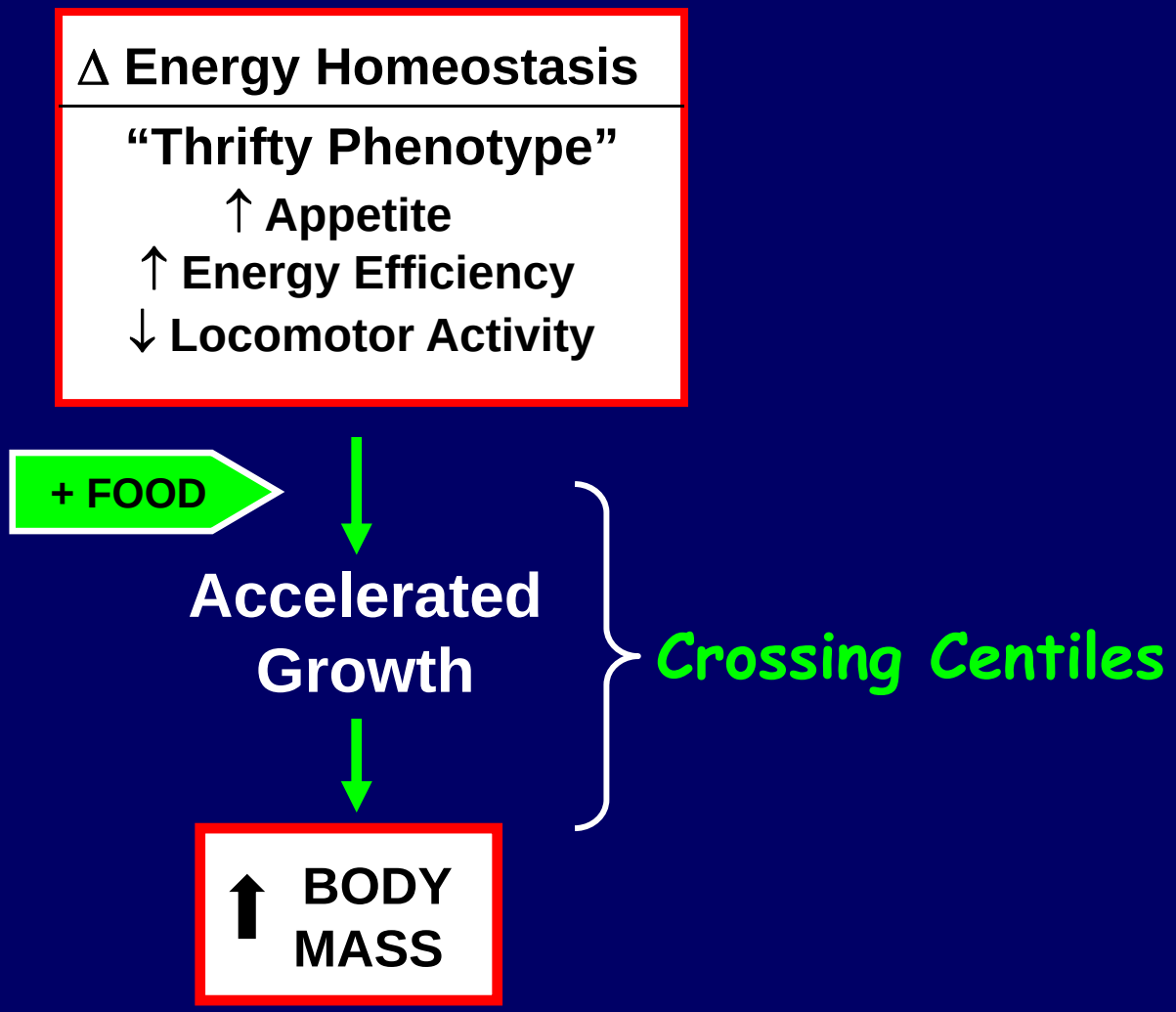
## "The Thrifty Phenotype"

- The fetus adapts to nutrient deficit by *permanently*
  - ↑'g energy utilization efficiency
  - ↑'g 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"

## Asymmetric Growth Restriction



# What is the Impact of Thrifty Phenotype?

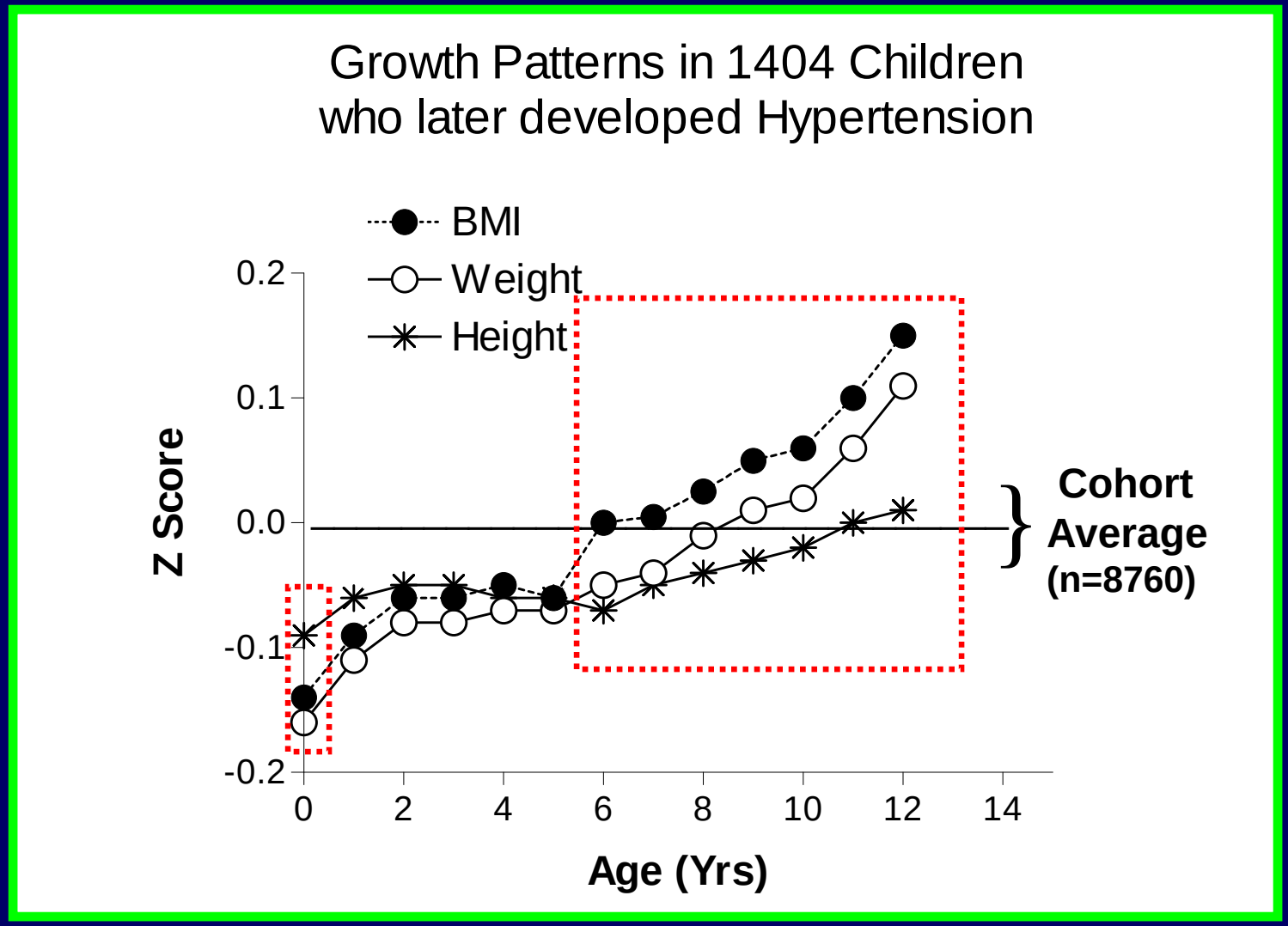
## Lessons from Cohort Studies

### The Helsinki Cohorts

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

Accelerated Postnatal Growth Enhances Risk of Chronic Disease in Later Life

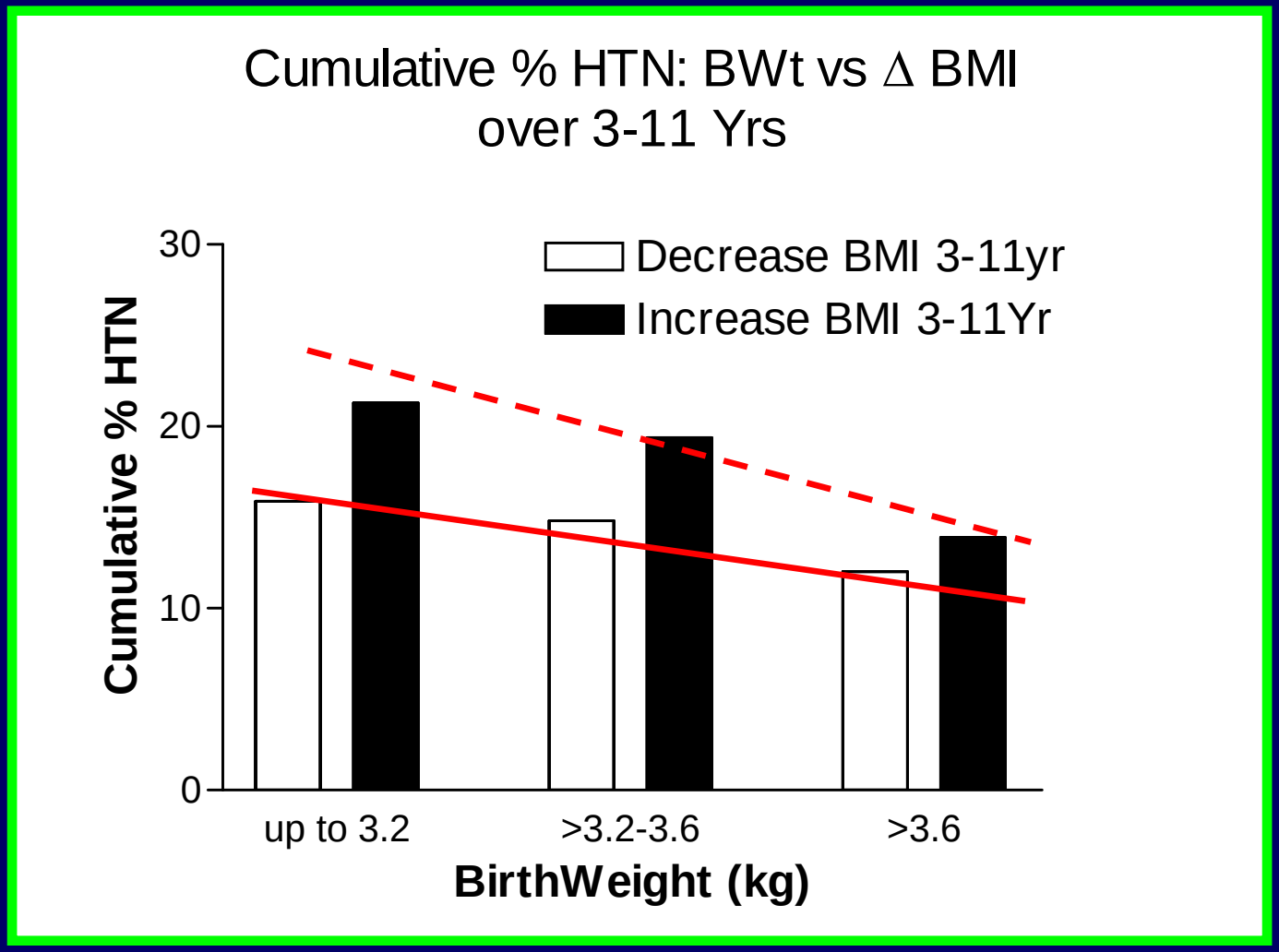
# Early Growth Patterns Predict Adult HTN




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

# Rapid Childhood Growth Predicts HTN

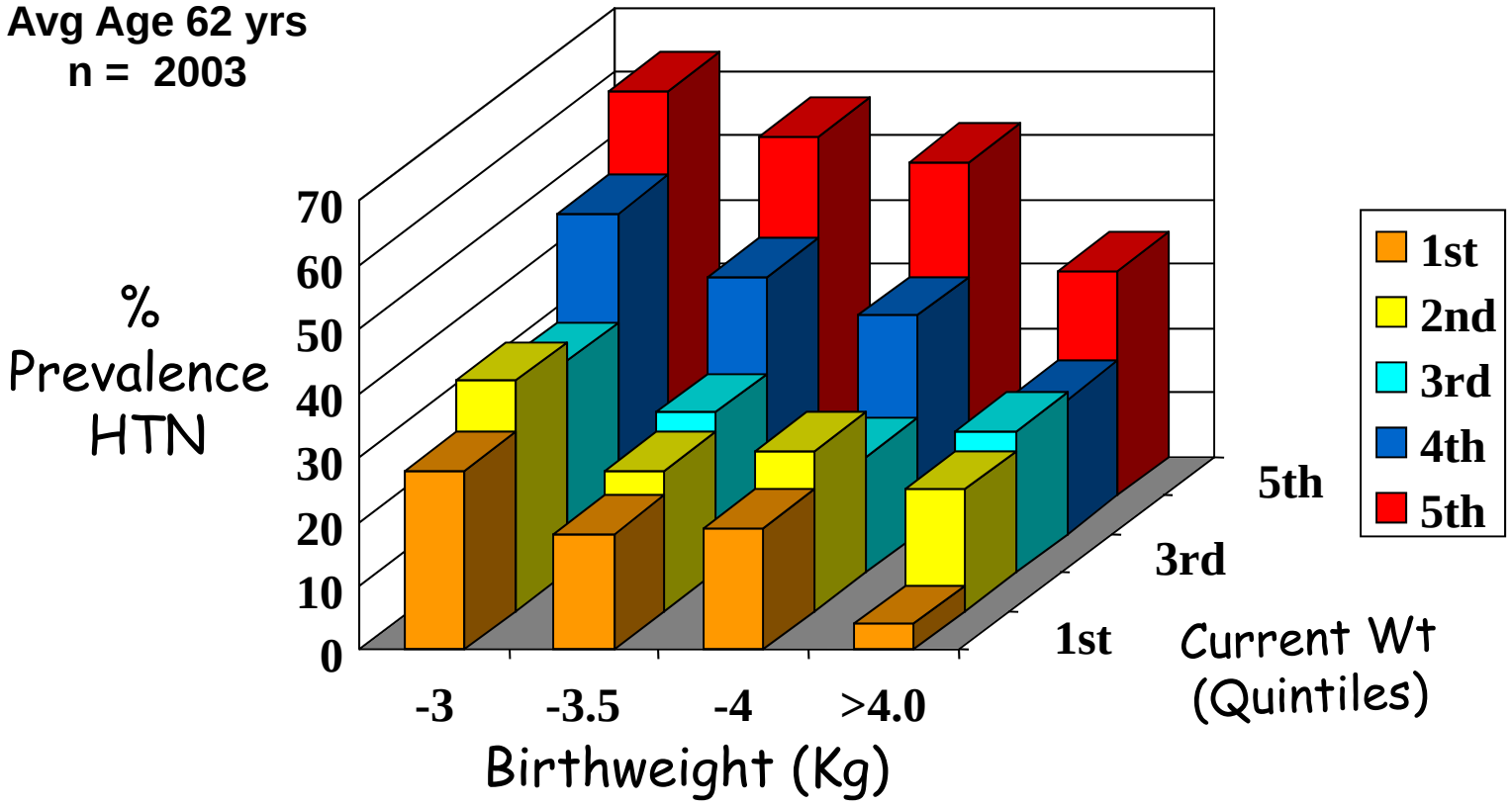
## Helsinki Cohort




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

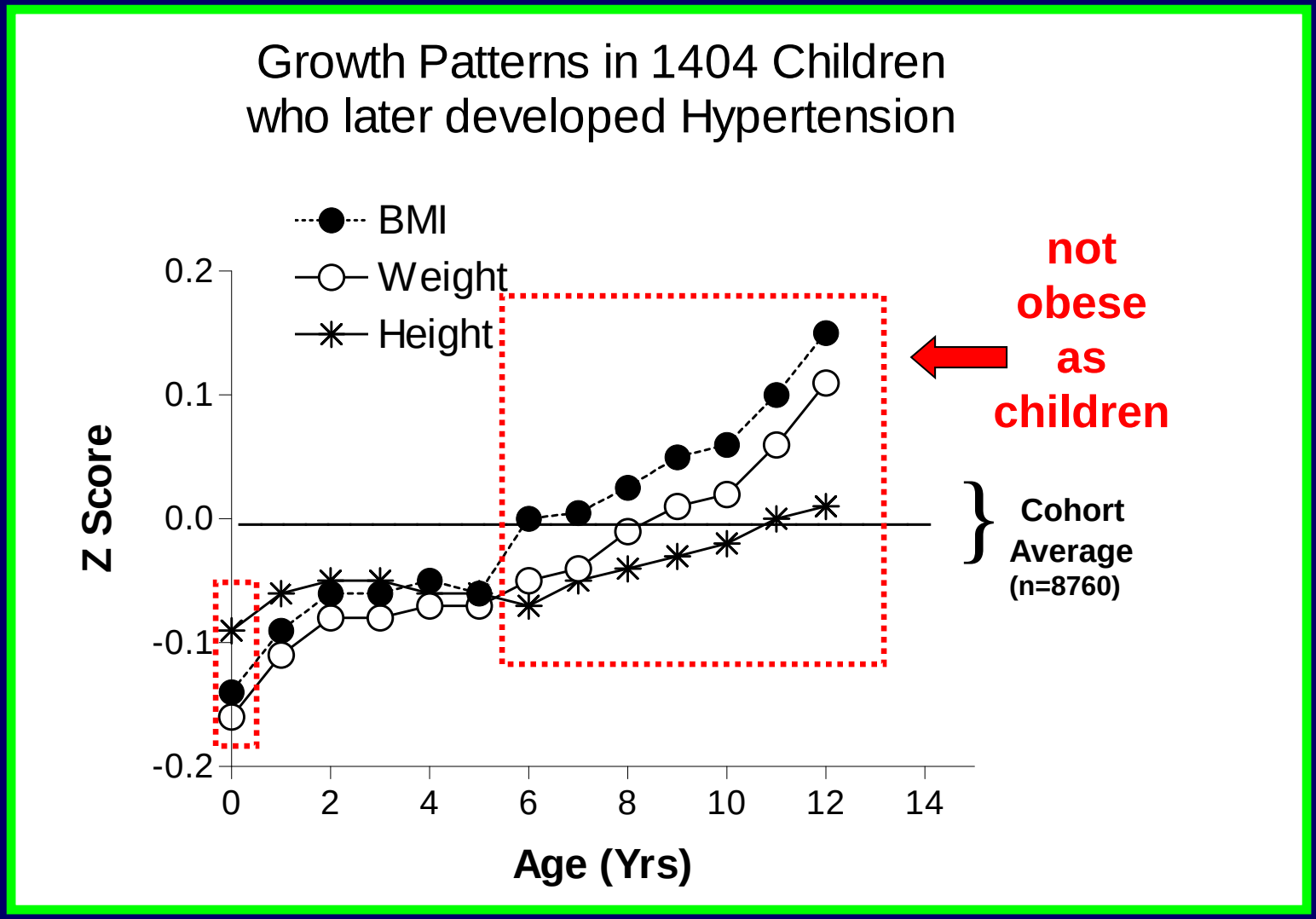
# Rapid Childhood Growth Predicts HTN & Enhances BirthWeight Effect

## Helsinki Cohort: Random Sample



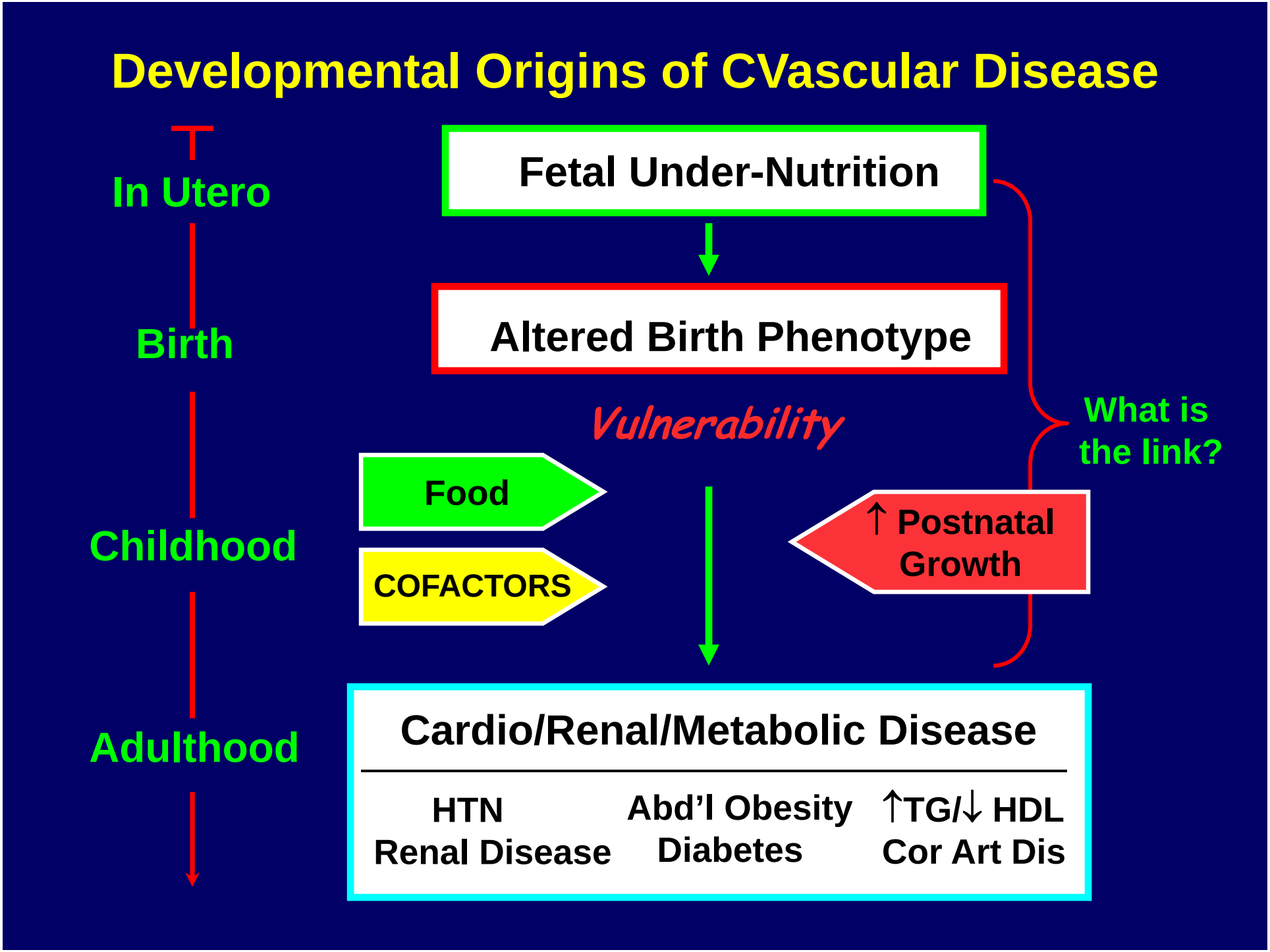

Eriksson et al. Hypertension 49: 2007

# Early Growth Patterns Predict Adult HTN




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

# Developmental Origins of CVascular Disease



# Developmental Origins of HTN

## Pathways of Nutritional Programming

- Altered Organ Structure ⟶ Δ Function

  Kidney: ↓ nephron number

- Altered Homeostatic Setpoints

  Energy Balance: “thrifty phenotype”

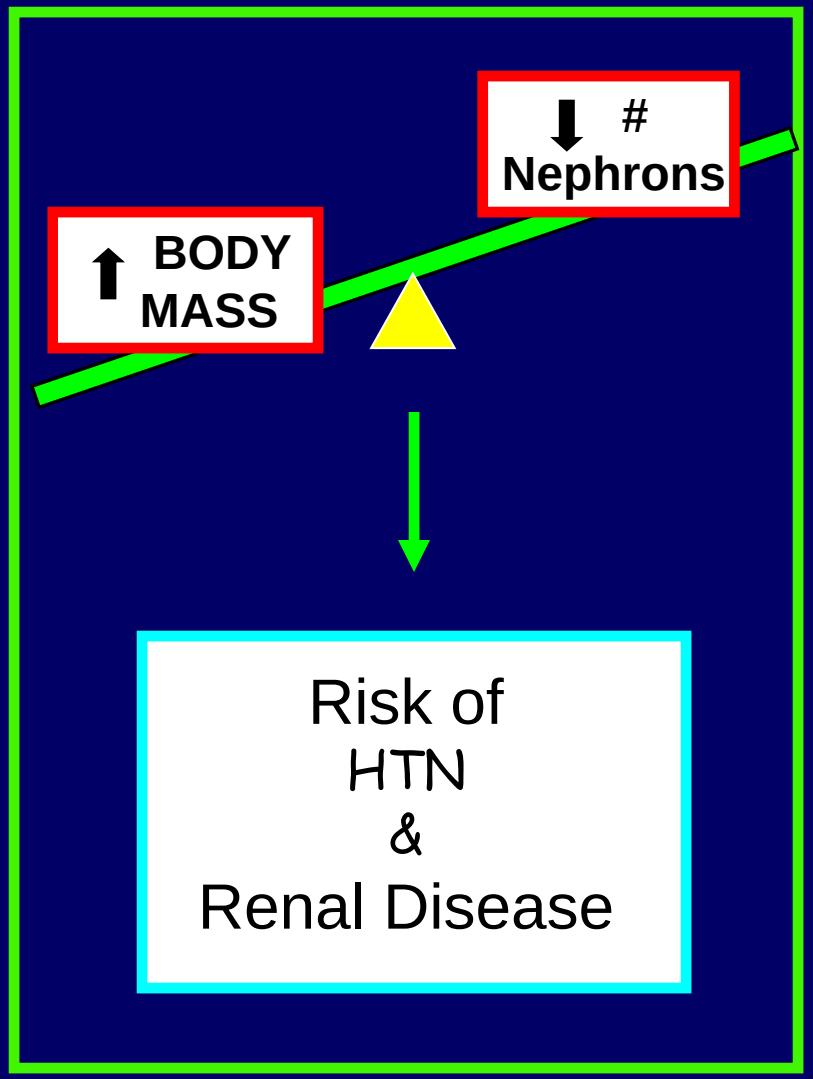
- Adverse interactions of prenatal vulnerabilities with postnatal stressors

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

## Low Nephron Number ?

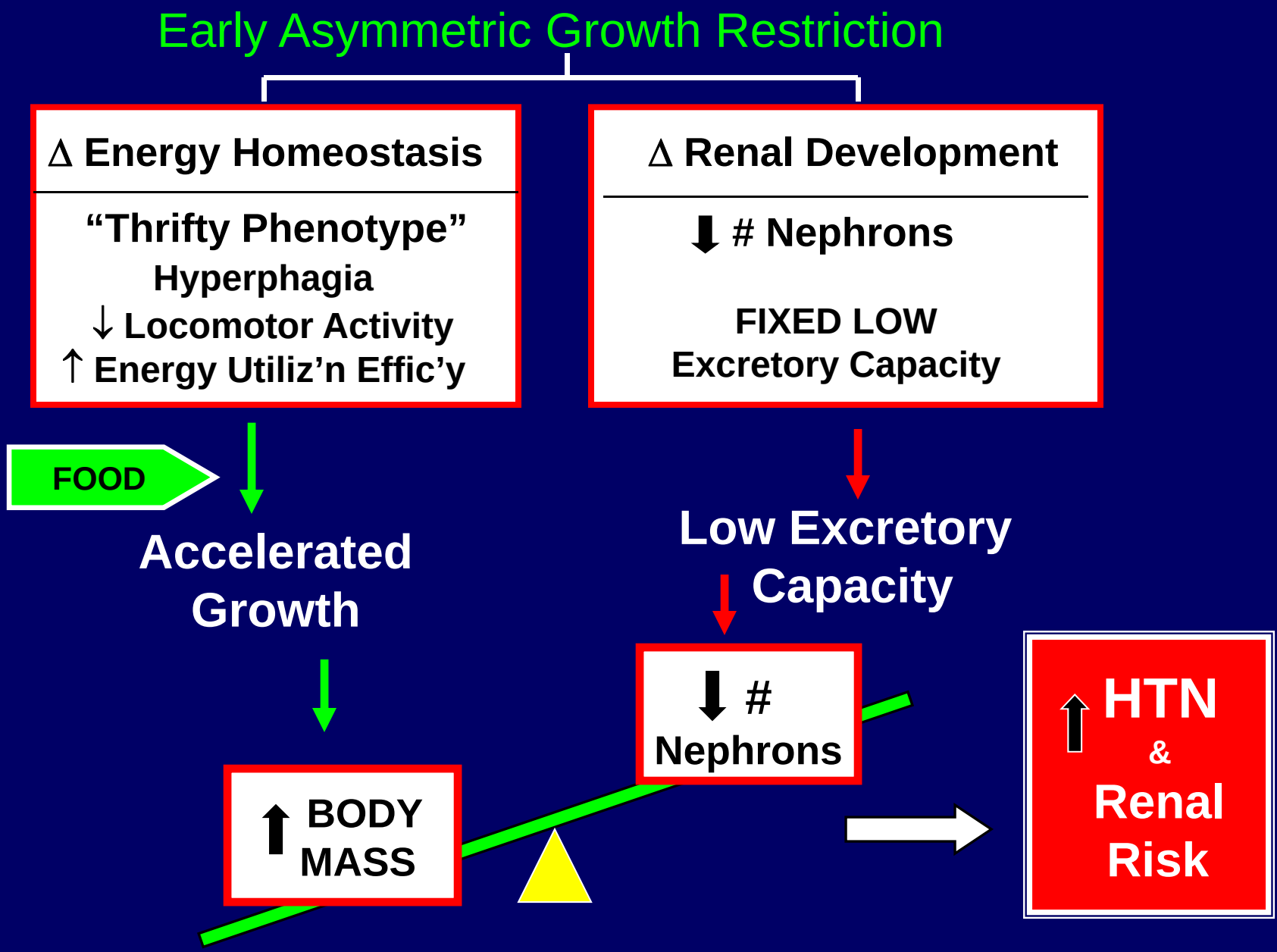
[1]Am J HTN 1988 1:335-47;
[2]Am J Kid Dis 1994 23: 171

## Nephron Dosing

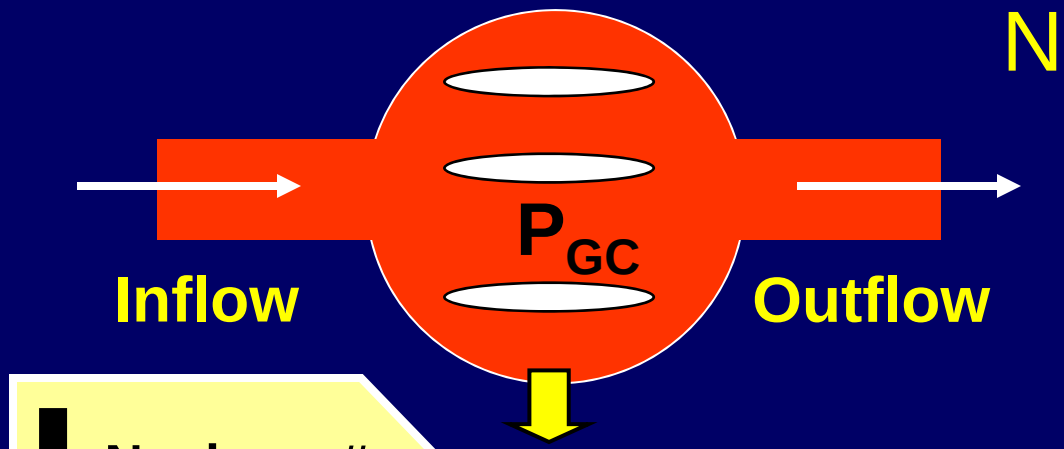



**Brenner Hypothesis[1,2]**

# Programming Pathways: Mismatch

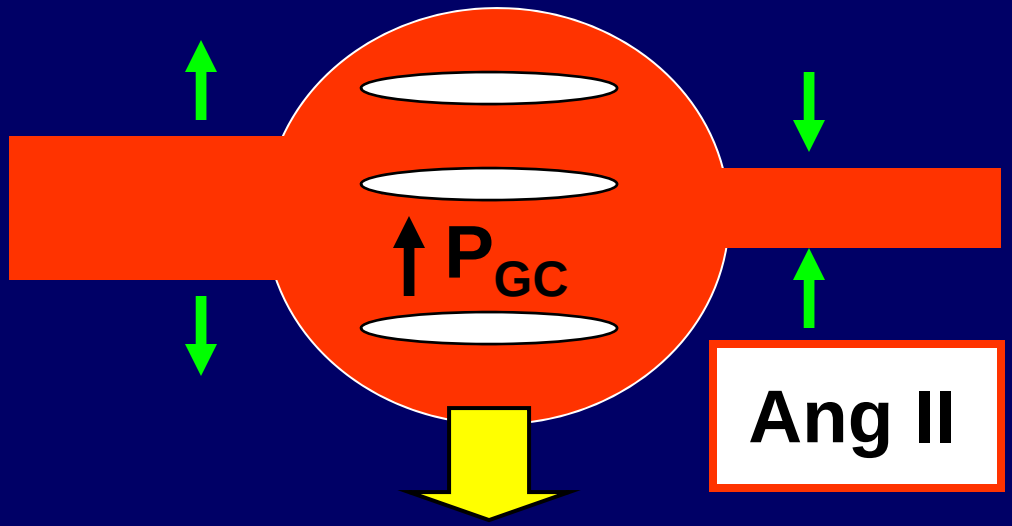


# Nephron Response to Excretory Overload




Nephron #
Body Mass

SNGFR

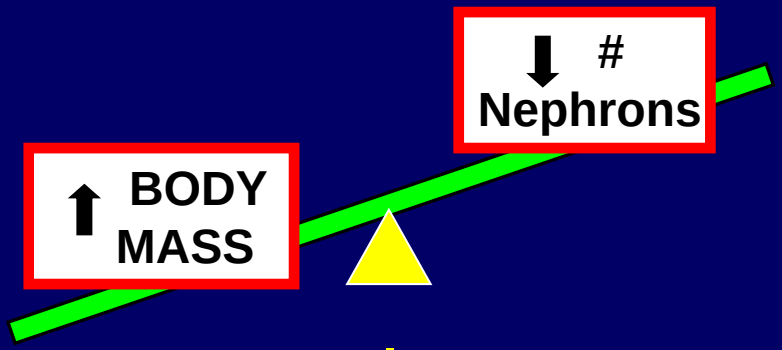


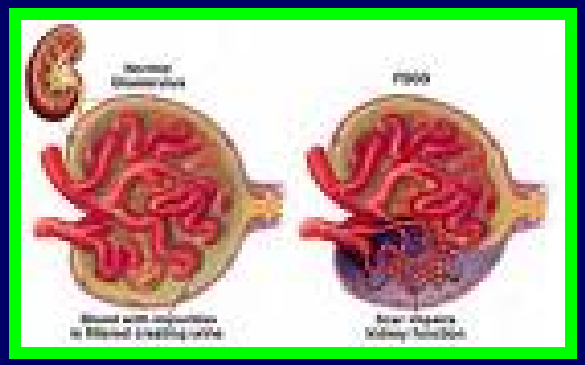

SNGFR

Increase glomerular capillary pressure ($P_{GC}$)

Increase single-nephron GFR

## Mismatch



Focal Glomerular Sclerosis (FSGS)

Progressive nephron loss; Fewer and fewer functional nephrons

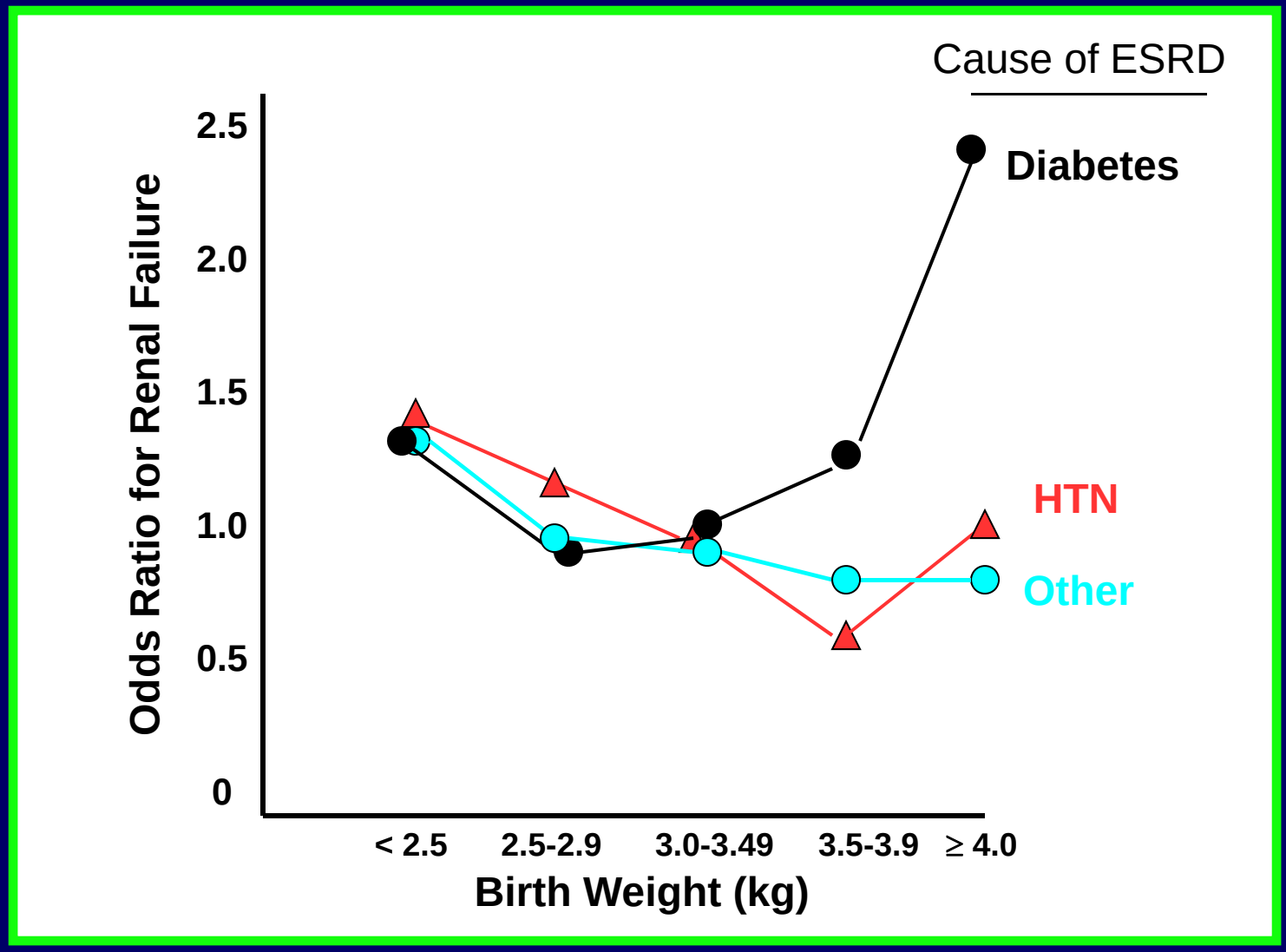
HTN

**Chronic Kidney Disease (CKD)**
**Reduced GFR (late stage)**

**High Cardiovascular Risk**

**END STAGE RENAL DISEASE (ESRD)**
**Dialysis or Transplant**

# Poor Fetal Growth Affects ESRD Risk




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

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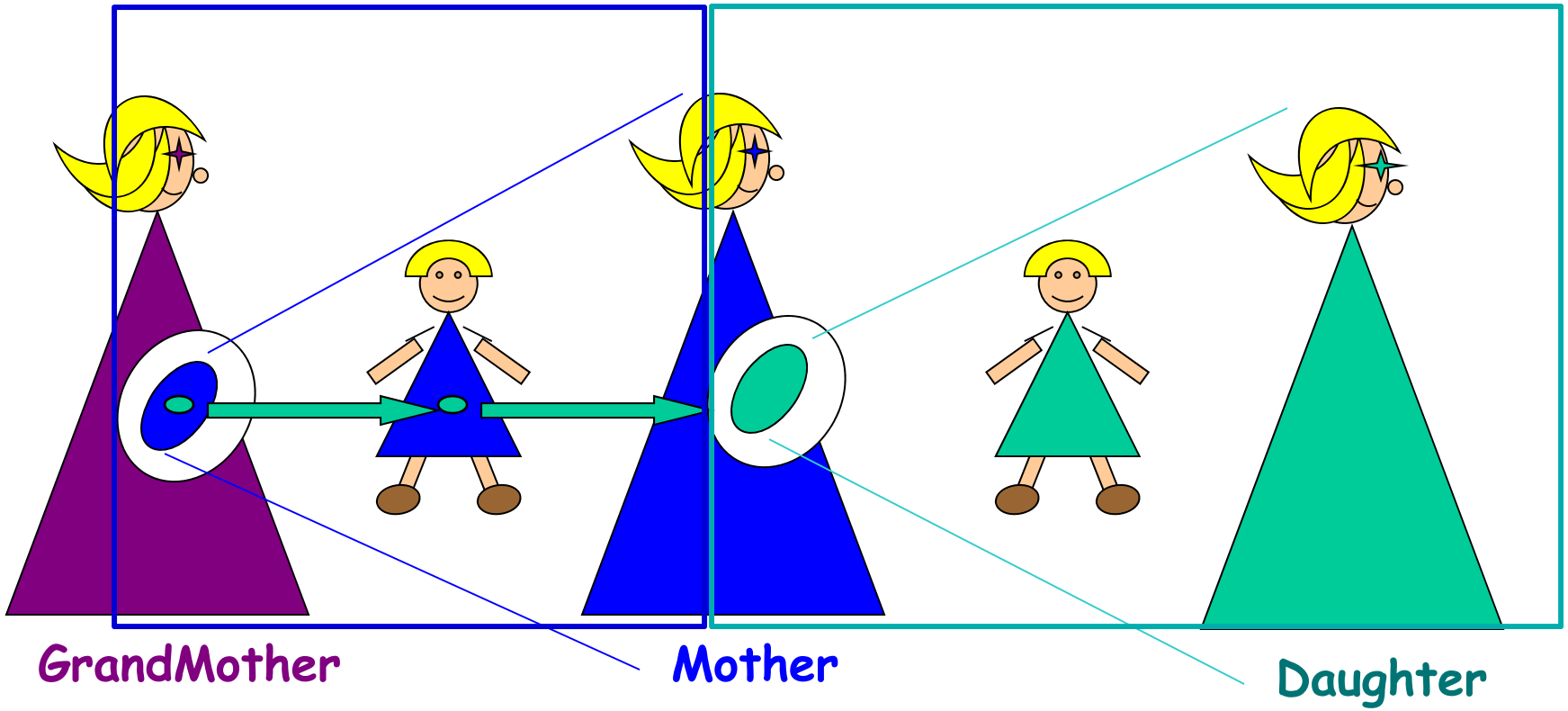
# Transgenerational Transmission of Programmed Changes

Nutritional Life of the Egg is Trans-Generational



# Transgenerational Transmission

## More Lessons from Cohort Studies

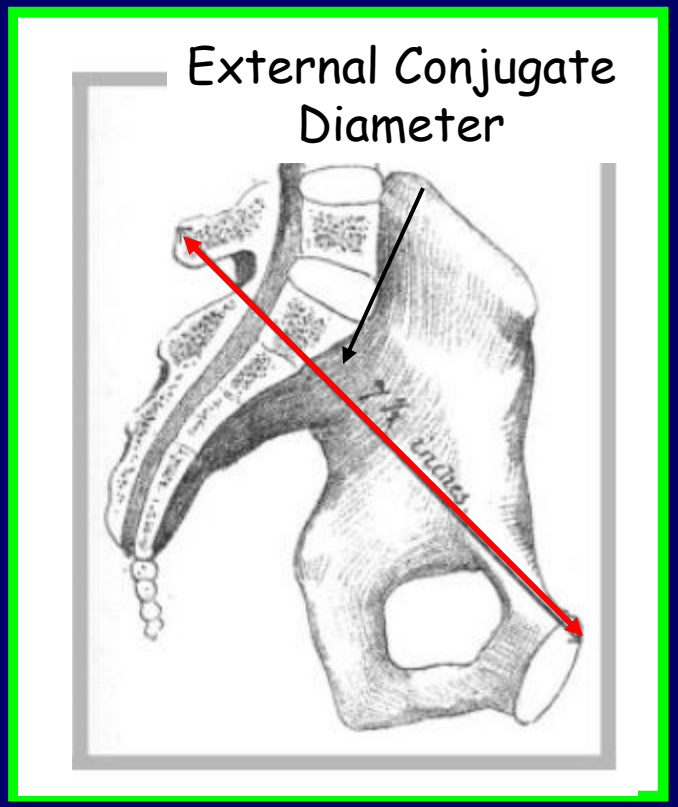
### The Helsinki Cohorts

- Finnish public health records
- Maternal pelvic dimensions
- Annual growth data from birth-15 yrs
- Adult Outcomes: random sampling of cohort members at avg age 62 yrs

Programmed abnormalities can be transmitted to the next generation

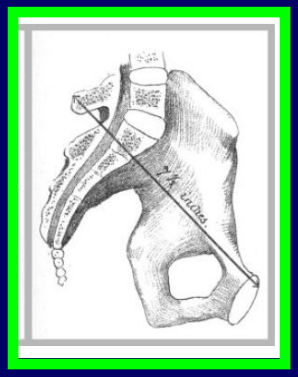
# Maternal Anterior-Posterior Pelvic Dimension Reflects Mom's Early-Life Nutrition

- Set in infancy
- Reflects fetal/infant nutrition (Vit D)
- Flatter pelvis indicates fetal/neonatal undernutrition



# Mother's Early-Life Nutrition Affects *Future* Offspring Disease Risk

## Mother's Pelvis



Flatter ant-posterior Pelvic diameter ≅ fetal/neonatal undernutrition

## Daughter's Outcome

- **Short at birth**
- **Slow growth as child**
- **Overweight as adult**
- **Late-onset HTN**

**Barker et al. Hypertension 50: December 2008**

# Transgenerational Transmission of Disease Risk

**Adult**
**Pelvic A-P Diam**

OUTCOMES at
62 yrs

HTN
Obesity

**Poor Growth**
**3-15 yrs**

**Poor Nutrition**
**Conceptn -2 yrs**

**Short at**
**Birth**

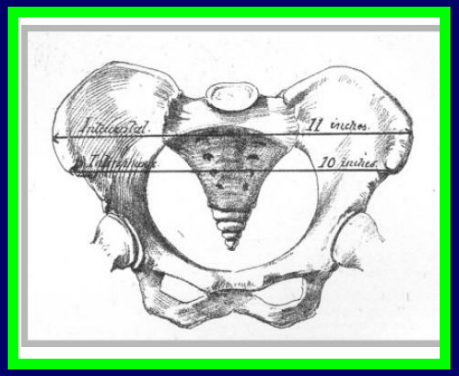
GrandMother

Mother

Daughter

# Transgenerational Transmission

## Mother's Pelvis




Wide, rounded
(? Hi estrogens)

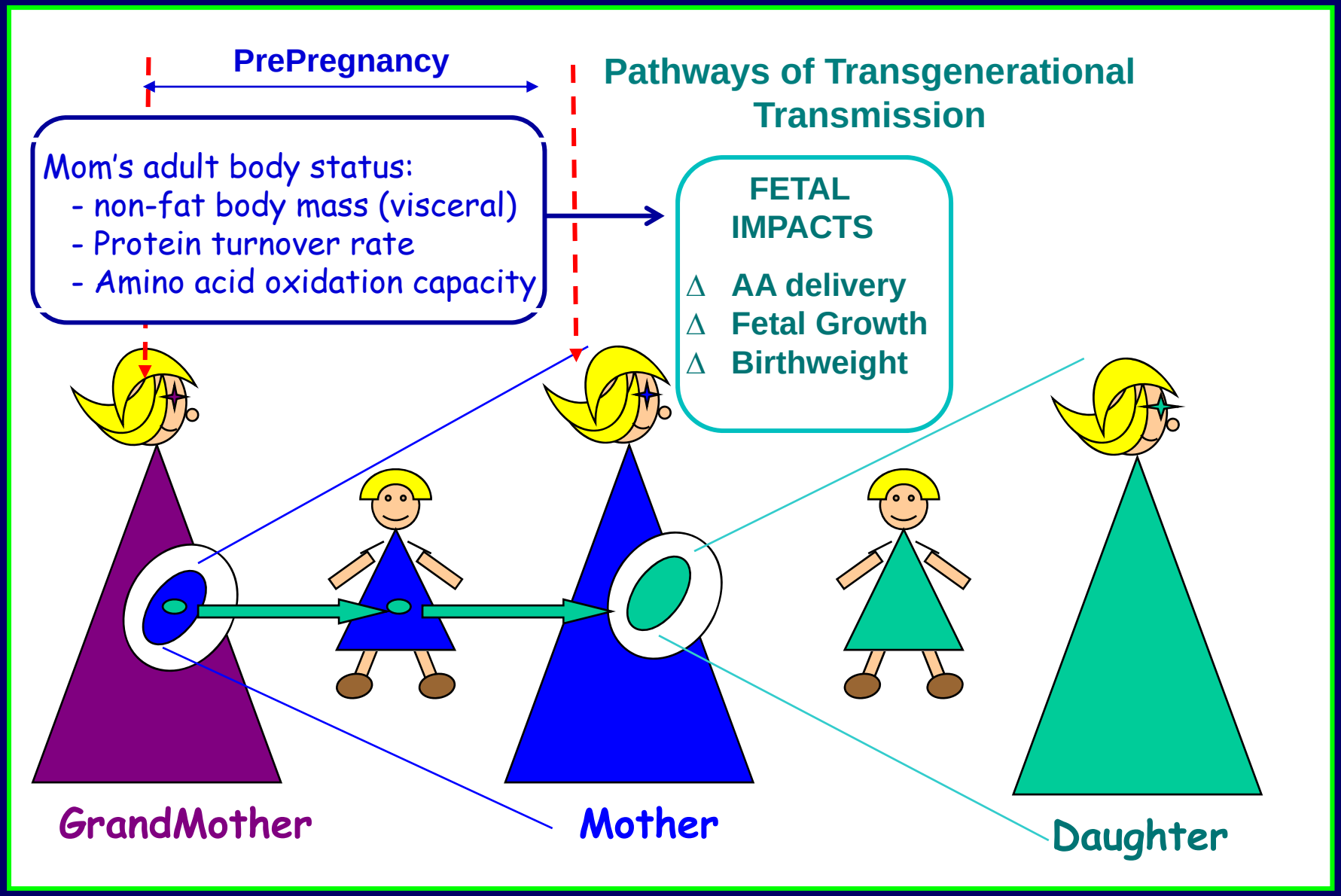
## Daughter's Outcome

Breast, Ovarian Cancer

**Hi maternal estrogen acts on developing fetal breast cells in utero ?**

**Mom's delayed puberty prolongs estrogen exposure of oocytes ?**

# Mom's Body Status Alters Future Fetal Nutrition



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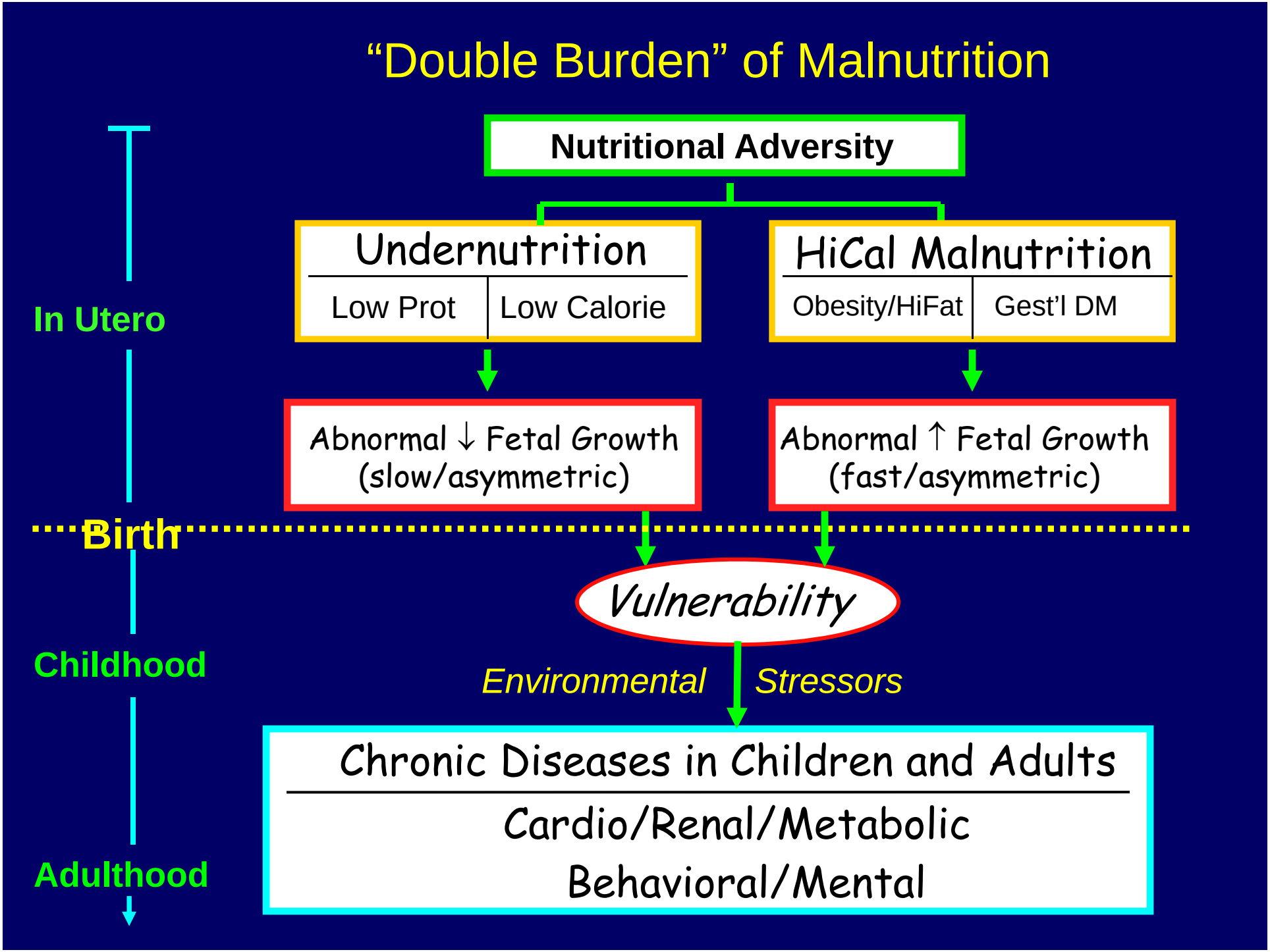
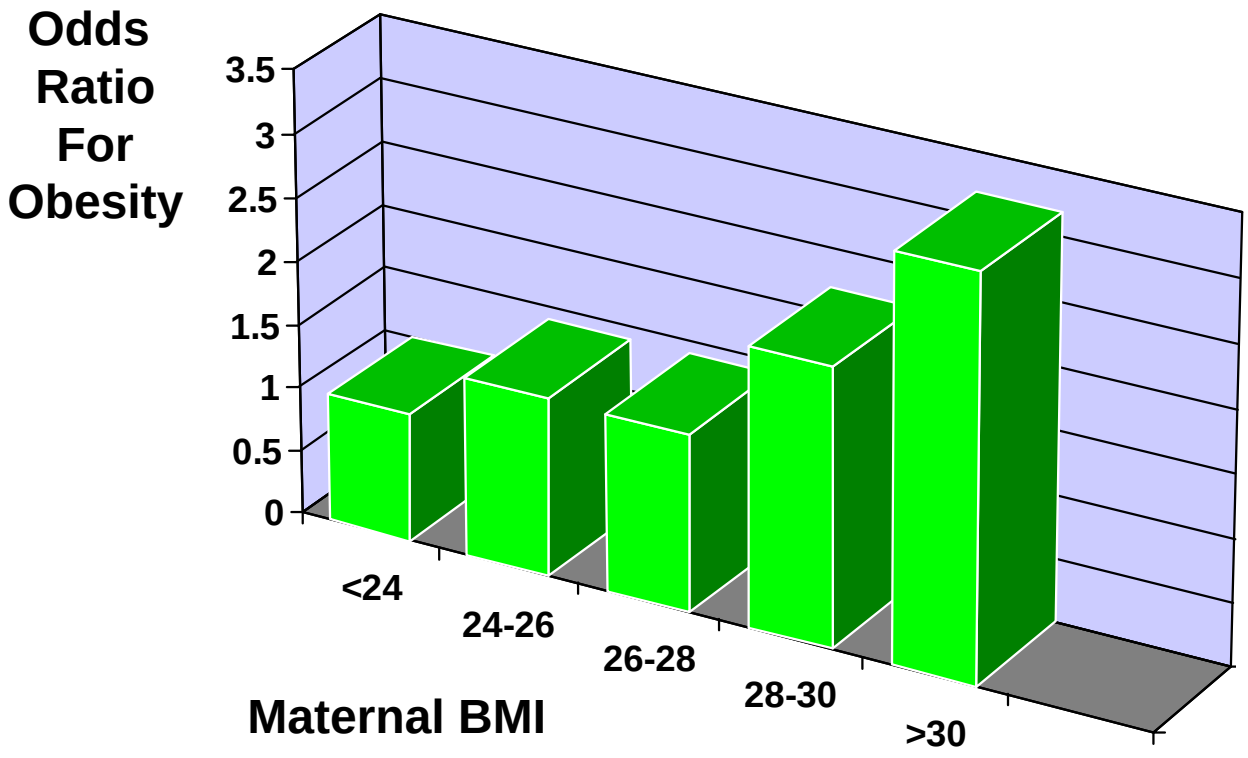
# "Double Burden" of Malnutrition



# Obesity Risk in Offspring following Fetal Overnutrition

## Maternal Obesity/High Energy Diet



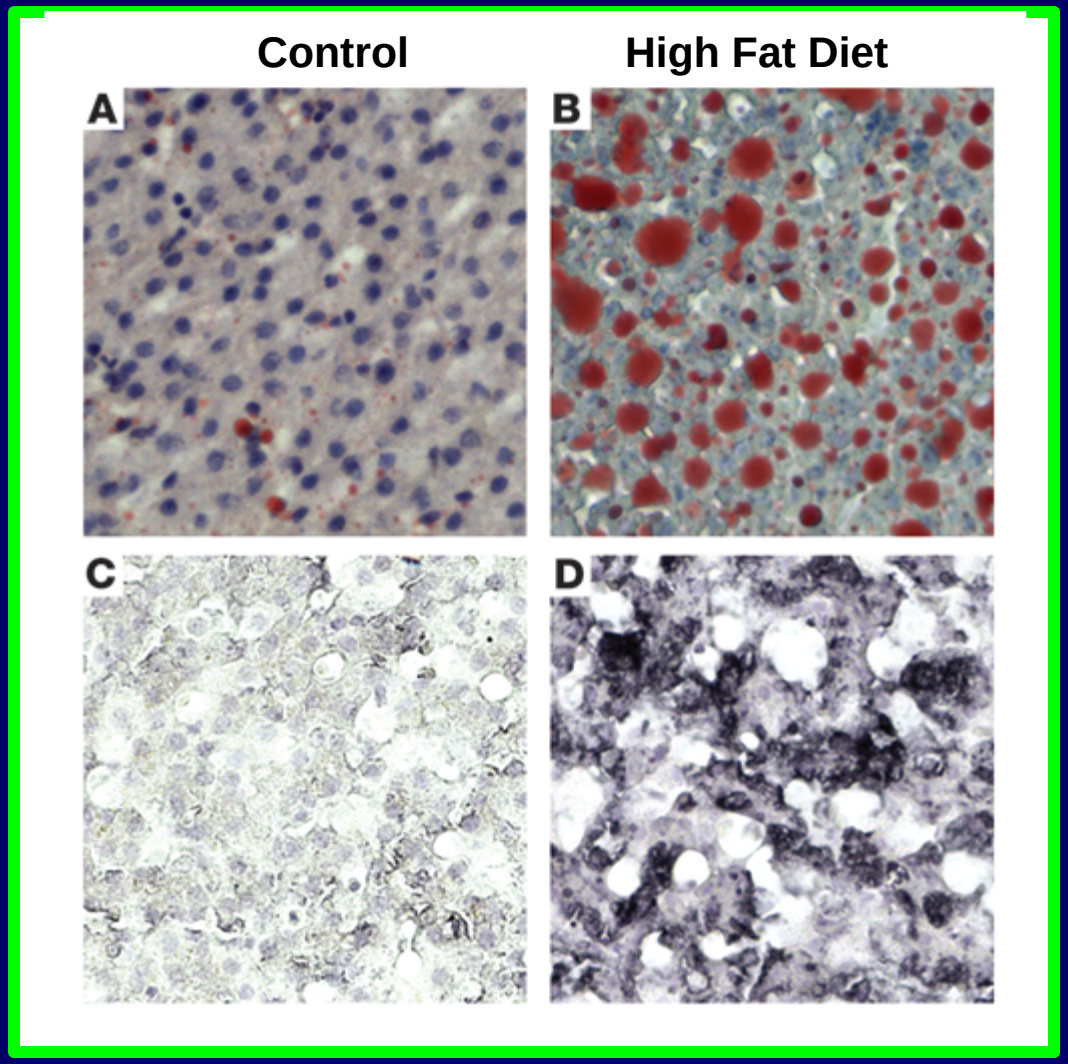

Eriksson J et al Internatl J Obesity 2001

# Maternal Hi Fat Diet/Obesity Programming Effects in Monkey Offspring

- Fetal/Neonatal Liver:
  - Lipotoxicity, inflammation, oxidative stress
  - Non-alcoholic fatty liver disease (neonate)
- Fetal Brain:
  - Inflammation
  - Δ neural appetite circuits, reward centers
- Postnatal Behaviors:
  - Hyperphagia
  - Preference for hi fat/sweet/salty food
  - Rapid infant growth rate
  - Early excess adiposity (age 6 mo)
  - Early onset puberty
  - ↑ 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



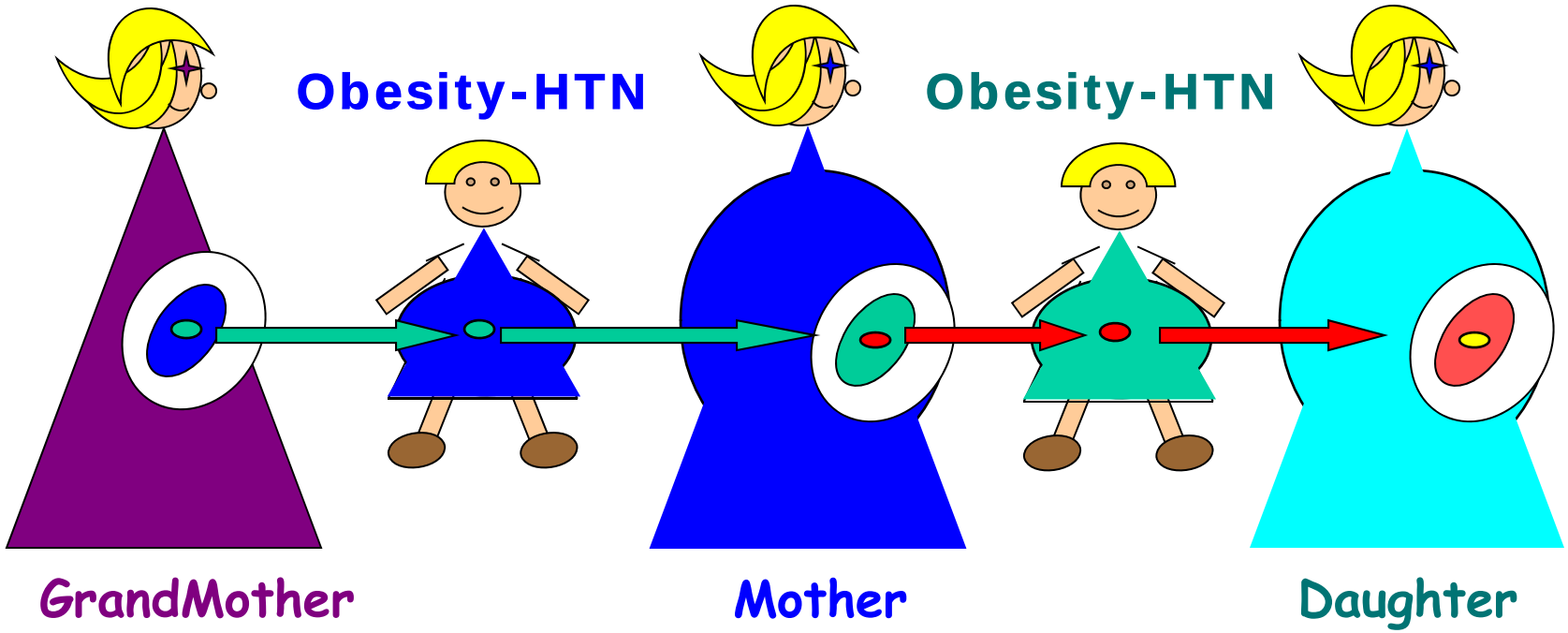

**Triglyceride Staining**

**Oxidative Stress Staining**

**McCurdy et al, J Clin Investigation, 2009**

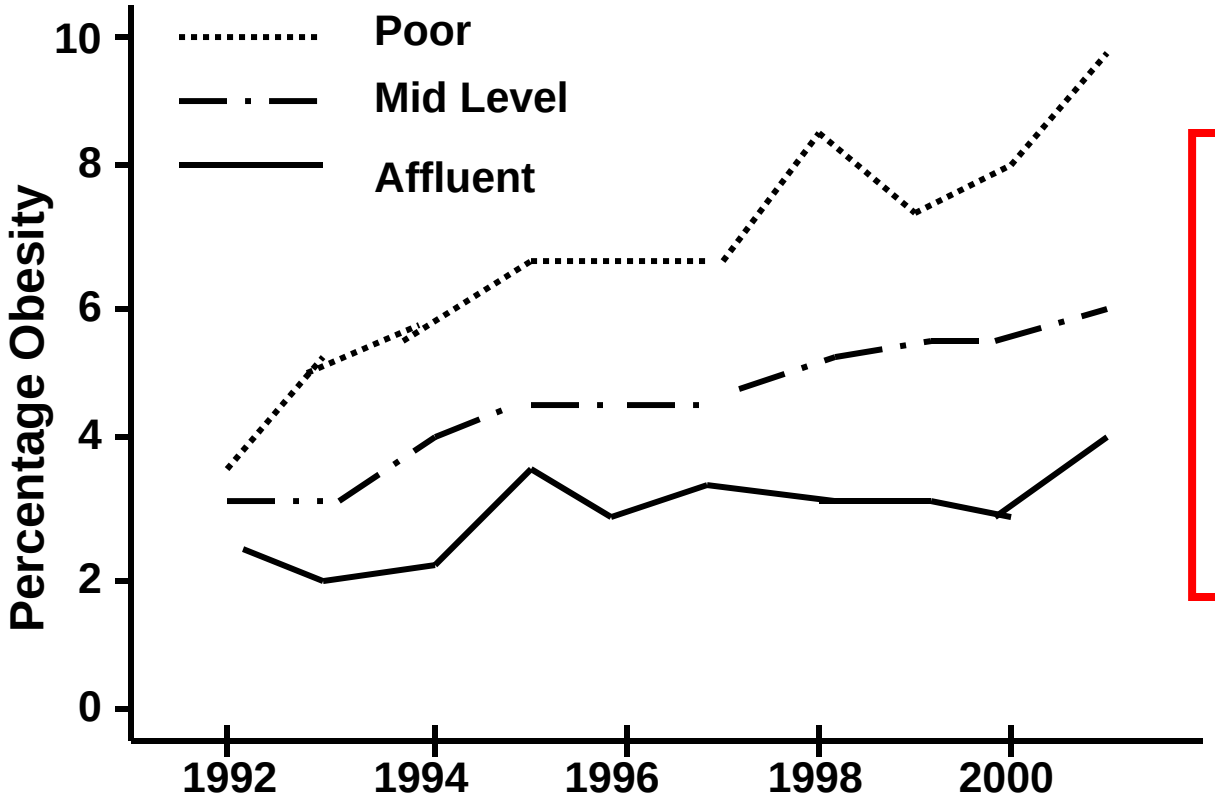
# Obesity-Hypertension in Children/Adolescents

## Transgenerational Transmission



# Rising Prevalence of Maternal Obesity

## Impact of Neighborhood Socio-Economic Status




**Accelerating rate of increase**

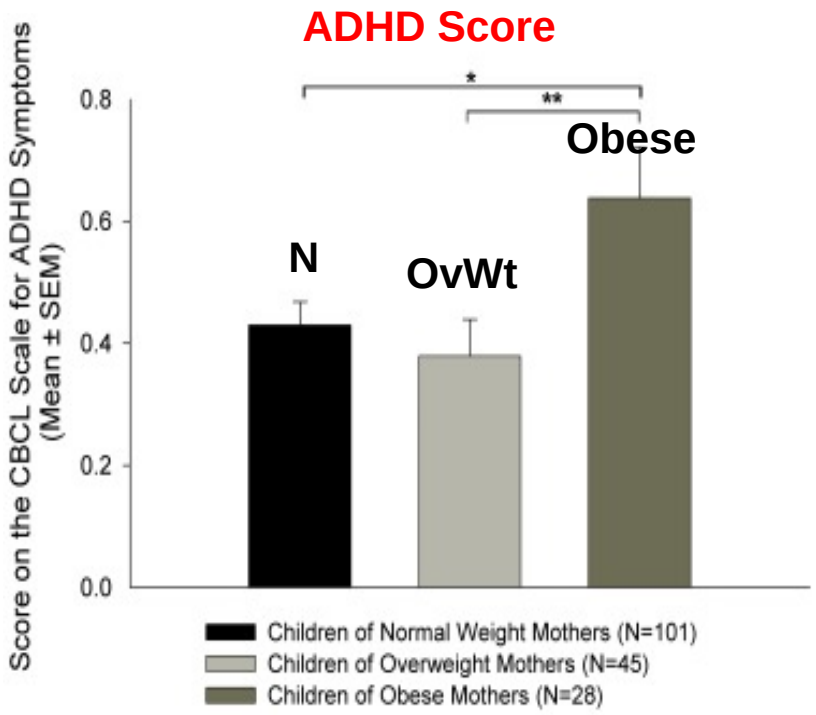
**Projected for 2010: 22% obesity**

**OHSU 2010: 40%**

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

# Maternal Obesity & Risk of Behavioral Dysfunction

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

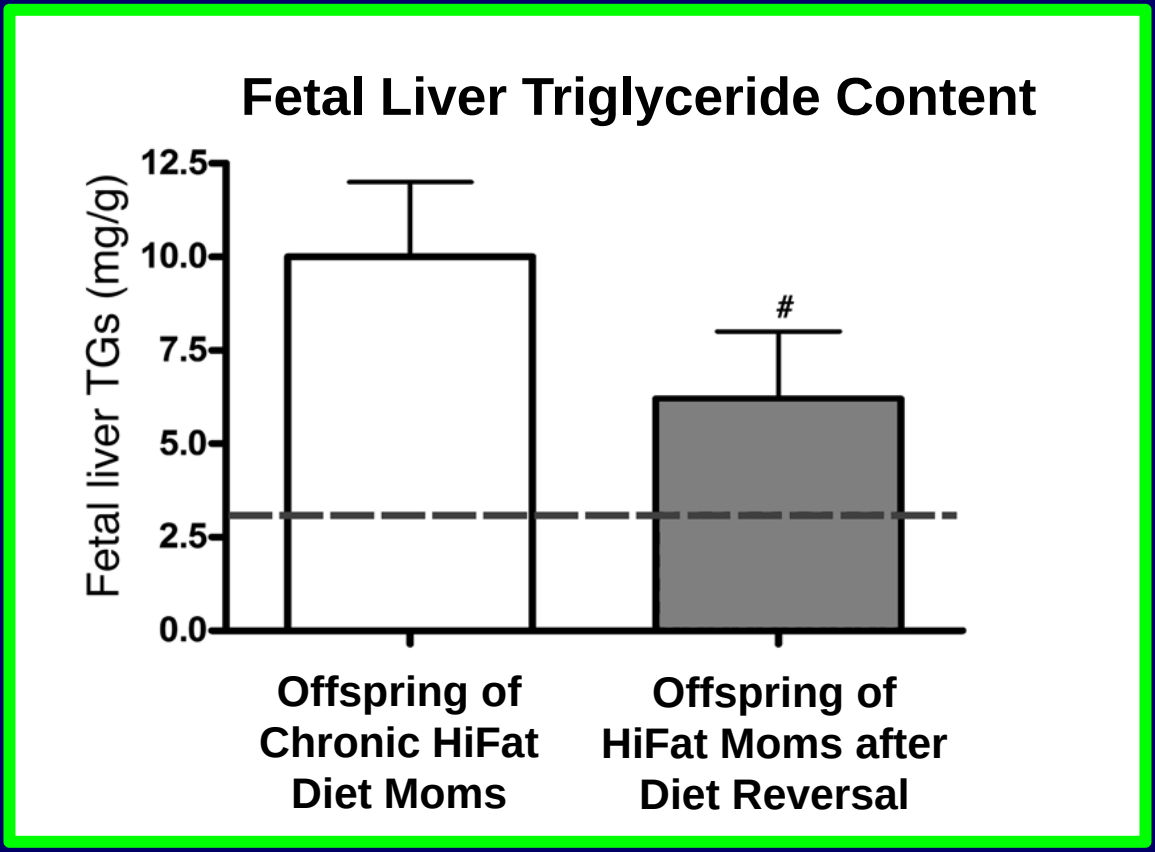




Buss C et al. PLoS One, June 2012

# Chronic Hi-Fat Diet Monkey Model

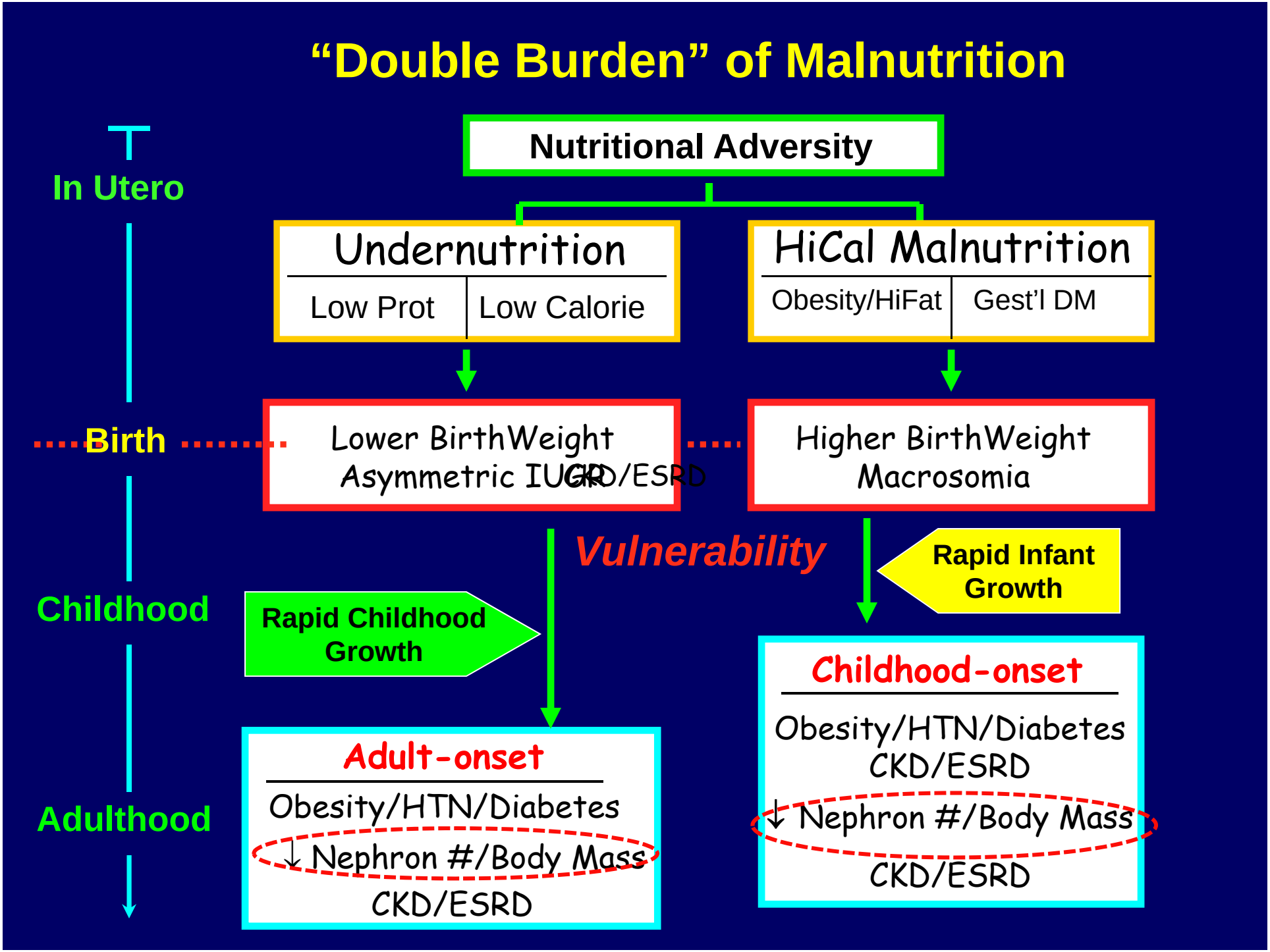
## Partial Improvement by HiFat Diet Reversal despite Persistent Maternal Obesity



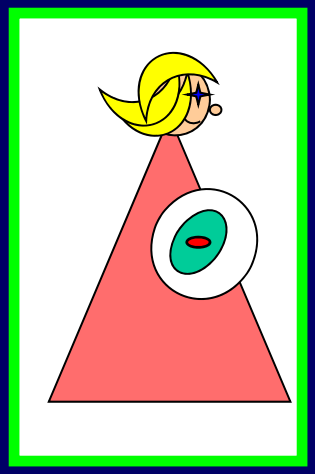

### Other Features Improved

- Liver inflammation
- Brain Inflammation
- Melanocortin Fxn

**McCurdy et al, J Clin Investigation, 2009**


"Double Burden" of Malnutrition
In Utero
Nutritional Adversity
Undernutrition
Low Prot
Low Calorie
HiCal Malnutrition
Obesity/HiFat
Gest'l DM
Birth
Lower BirthWeight
Asymmetric IUGR
CKD/ESRD
Higher BirthWeight
Macrosomia
Vulnerability
Rapid Infant Growth
Childhood
Rapid Childhood Growth
Childhood-onset
Obesity/HTN/Diabetes
CKD/ESRD
↓ Nephron #/Body Mass
CKD/ESRD
Adulthood
Adult-onset
Obesity/HTN/Diabetes
↓ Nephron #/Body Mass
CKD/ESRD

# What Do We DO About All This??



## Think Trans-generational

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

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

# What Do We DO About All This??

## Act Now: Nutrition

- Focus on girls, mothers and mothers-to-be
- Community-based research to define safe & effective interventions
- Harness the village:
  - change our food culture
  - change our school culture
  - change our corporate Agric. and food processing cultures

# THE BOB & CHARLEE MOORE INSTITUTE for NUTRITION & 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**

## A CONVERSATION

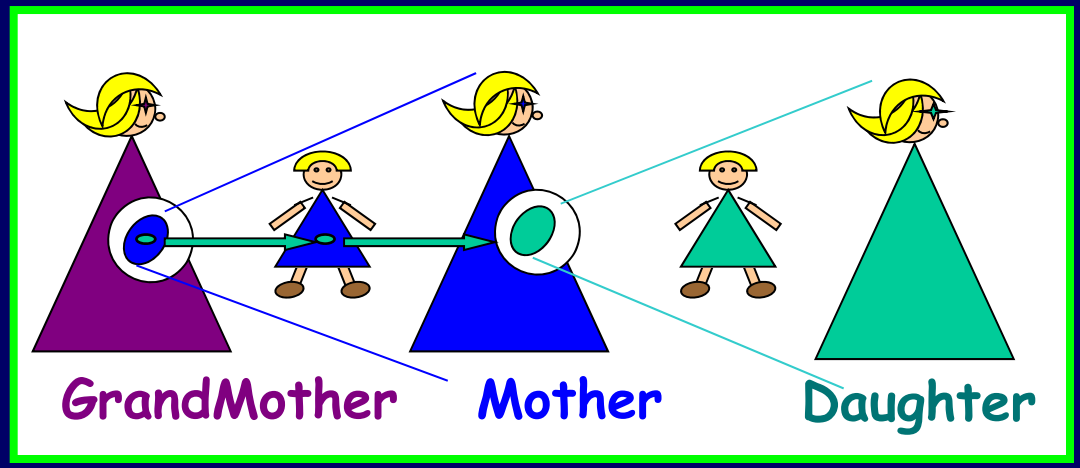
# DOHaD: Implications for Practice

## Harnessing the Power of the Science

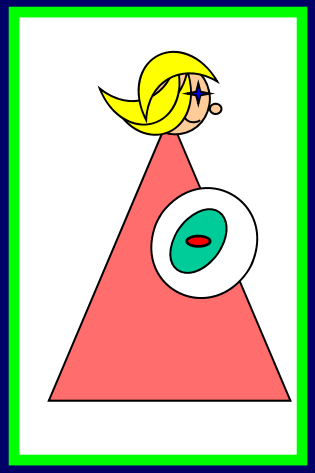
I. Patient/Client Education (life stage-specific)

II. Professional Training (multi-level)

III. Public Policy Advocacy



# Developmental Origins of Chronic Disease



## You Are What Your Mother & Grandmother Ate: Transgenerational Influences

Pediatric Nutrition Symposium
March 2013


Susan P. Bagby, MD

Professor of Medicine & Physiology
Nephrology & Hypertension
OHSU Heart Research Center

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

Bob & Charlee Moore Institute for Nutrition & Wellness